Clinical Practice Guidelines

PSA Testing and Early Management of Test-detected Prostate Cancer

Guidelines for health professionals

TECHNICAL REPORT

Prostate Cancer Foundation of Australia

Cancer Council Australia

Date published: 20 January 2016

Disclaimer

This document should be read in conjunction with the *Clinical Practice Guidelines for PSA Testing and Early Management of Test-Detected Prostate Cancer*.

Suggested citation

Prostate Cancer Foundation of Australia and Cancer Council Australia PSA Testing Guidelines Expert Advisory Panel. Technical Report for Clinical Practice Guidelines for PSA Testing and Early Management of Test-Detected Prostate Cancer. Prostate Cancer Foundation of Australia and Cancer Council Australia, Sydney (2015).

These guidelines and associated documentation (i.e. Administrative and Technical Reports) can accessed and downloaded at:
http://wiki.cancer.org.au/australia/Guidelines:PSA_Testing

Contents

Introduction

This *Technical Report* accompanies the *Clinical Practice Guidelines for PSA Testing and Early Management of Test-Detected Prostate Cancer*, developed by Prostate Cancer Foundation of Australia and Cancer Council Australia.

It outlines the guideline development process and methodology, lists the clinical questions, provides all accompanying NHMRC Statement Forms, the detailed technical report for each PICO question and the quality assessment tools.

Guideline development process

The following description of the guideline development process appears in *Appendix 1* in the Clinical Practice Guidelines for PSA Testing and Early Management of Test-Detected Prostate Cancer.

A1.1 Introduction

Prostate Cancer Foundation of Australia (PCFA) initiated the process to develop a clinical practice guideline for PSA testing and management of test-detected prostate cancer. This guideline is a collaborative project between PCFA and Cancer Council Australia.

Development began in November 2012 after NHMRC agreed to consider approving the guideline, provided it were to be developed according to NHMRC procedures and requirements. To better describe the scope of the guideline, the title was changed to *Clinical practice guidelines for PSA testing and early management of test-detected prostate cancer*. Financial support for the guideline project was provided by PCFA with Cancer Council Australia contributing in kind resources of their guideline development team.

A1.2 Guideline development group

Following a consultation process with key stakeholders involved in cancer control and clinical care delivery, including the Urological Society of Australia and New Zealand (USANZ) and the Royal College of Pathologists of Australasia (RCPA), PCFA invited a multidisciplinary group of relevant experts to develop a clinical guideline for PSA testing and clinical care immediately following test-detected prostate cancer. This was to ensure that representatives from all specialities and disciplines involved in the diagnosis and management of prostate cancer were represented. Two consumer representatives were also invited to be part of the Expert Advisory Panel (EAP) (see *Appendix 2*).

PCFA and Cancer Council Australia appointed a steering committee. The Project Steering Committee was responsible for the overall management and strategic leadership of the guideline development process. The Project Steering Committee ensured that all deliverables agreed in the project plan were delivered to acceptable standards in accordance with NHMRC requirements.

A project team based at Cancer Council Australia conducted the systematic reviews, comprising of systematic literature searches, literature screening against pre-determined inclusion and exclusion criteria and critical evaluation and data extraction of the included literature. The project team was responsible for liaising with the EAP members in regards to content development and content review and compiling the document.

The clinical practice guideline was developed according to the procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines.[1] The development program was designed to meet the scientific rigour required by the standard for developing high quality, evidence-based clinical practice guidelines. A series of NHMRC resources and handbooks[2-10] guided the process and outlined the major steps and expectations involved in developing guidelines. These documents provided the definitions and protocols for developing research questions and search strategies, conducting systematic literature reviews, summarising and assessing the relevant literature and finally, formulating and grading the recommendations. They also included checklists and templates created to satisfy designated standards of quality and process.

At its initial meeting the Guidelines Expert Advisory Panel developed clinical questions. The questions were allocated to specific Guidelines Expert Advisory Panel members to act as lead authors according to their areas of expertise. Each lead author team was able to co-opt additional experts, who were not part of the Expert Advisory Panel, as co-authors for their allocated questions. These question-specific groups are referred to as Question Specific Working Parties in this guideline document. The Project Steering Committee assessed the suggestion of any additional co-authors including their declaration of interest (see *Appendix 6*).

A1.3 Steps in preparing clinical practice guidelines to NHMRC criteria

For every question the below steps were followed:

1. Develop a structured clinical question (PICO question)
2. Search for existing relevant guidelines and systematic reviews
3. Process if relevant clinical practice guideline was identified or not

3a If no relevant clinical practice guideline was found	**3b If a relevant clinical practice guideline was found and assessed as suitable for adaption**
Check if an existing systematic review of high quality exists and can be used to inform the systematic review process	Conduct systematic literature review update for the question of the existing clinical practice guideline
Develop the systematic review protocol and systematic literature search strategy for each PICO question	Screen literature update results against pre-defined inclusion and exclusion criteria
Conduct the systematic literature search according to protocol	Conduct critical appraisal and data extraction of each new included article
Screen literature results against pre-defined inclusion and exclusion criteria	Update evidence table of evidence review of existing guideline with new literature update results
Conduct critical appraisal and data extraction of each included article	

4. Summarise the relevant data
5. Assess if meta-analysis should be undertaken

5a If meta-analysis is decided to be undertaken as part of the systematic review	**5b No meta-analysis**
Formulate rationale for meta-analysis	Continue with step 6
Select studies for inclusion	
Extract data	
Perform statistical analysis	
Present results	

6. Assess the body of evidence and formulate recommendations
7. Write the content narrative

A1.3.1 Developing a structured clinical question

A wide range of questions was proposed for research. The questions focused on diagnosis, prognosis, risk and interventions. All proposed questions were reviewed on the basis of their purpose, scope and clinical importance to the target audience and were structured according to the PICO (populations, interventions, comparisons, outcomes) framework (see *Appendix 3*). The Question Specific Working Parties provided the systematic review team with feedback to refine the PICO questions.

A1.3.2 Search for existing relevant guidelines and systematic reviews

For each PICO question, the National Guideline Clearinghouse (http://guideline.gov) the Guidelines Resource Centre (www.cancerview.ca) as well as the scoping search for the PICO question were scanned for relevant clinical practice guidelines that could potentially be suitable for adaption.

If an existing guideline was identified, the guideline was assessed for adaption according to the ADAPTE process. If suitable, the guideline systematic review was adapted as outlined in *A1.3.7*.

Relevant guidelines that did not meet the criteria for adaption were checked for systematic reviews that could be used as a source of relevant references to inform the systematic review process for the PICO question. Full systematic reviews were then performed as outlined in *A1.3.3- A1.3.6*.

A1.3.3 Developing a systematic search strategy

For each PICO question, systematic literature search strategies were developed by the technical team.

Most searches were directed to prostate cancer as a generic base. Searches were limited or widened as necessary according to the PICO structure using keywords or MESH and subject terms. Systematic search strategies were derived from these terms for each included electronic databases. The included standard databases searched were Medline, Embase, Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects and Health Technology Assessment for all questions. The psychosocial questions also included CINAHL and PsycINFO databases to retrieve relevant literature.

A1.3.4 Conducting the systematic literature search according to protocol

Clinical practice guidelines should be based on systematic identification and synthesis of the best available scientific evidence.[2] For each clinical question, that required a systematic literature review, literature searches were conducted systematically with the literature cut-off date of 1 March 2014. The following electronic databases were part of the systematic literature search strategy:

- *Medline*: bibliographic references and abstracts to articles in a range of languages on topics such as clinical medical information and biomedicine, and including the allied health fields, biological and physical sciences
- *EMBASE*: major pharmacological and biomedical database indexing drug information from 4550 journals published in 70 countries
- *Database of Abstracts of Reviews of Effects and Health Technology Assessment:* contains details of systematic reviews that evaluate the effects of healthcare interventions and the delivery and organisation of health services

- *The Cochrane Database of Systematic Reviews*: contains systematic reviews of primary research in human health care and health policy, and are internationally recognised as the highest standard in evidence-based health care
- *CINAHL*: bibliographic references and abstracts to journal articles, book chapters, pamphlets, audiovisual materials, software, dissertations, critical paths, and research instruments on topics including nursing and allied health, biomedicine, consumer health, health sciences librarianship, behavioural sciences, management, and education
- *Psychinfo*: Bibliographic references and abstracts to journal articles, book chapters, dissertations and technical reports on psychology; social, clinical, cognitive and neuropsychology; psychiatry, sociology, anthropology and education, with source material from a wide range of languages.

A search filter to retrieve relevant literature considering Aboriginal and Torres Strait Islander peoples was added to each question.

Additional relevant papers from reference lists and, where appropriate, clinical trial registries, were also identified for retrieval as part of the snowballing process.

The full detailed systematic literature search strategy for every clinical question is fully documented in the technical report of the question (see *Technical report*).

A1.3.5 Screening of literature results against pre-defined inclusion and exclusion criteria

Part of the systematic review process is to screen all retrieved literature results against the pre-defined inclusion and exclusion criteria in two stages.

a) First screen

During the first screening round, the titles and abstracts of all retrieved literature were screened by one or two reviewers. All irrelevant, incorrect and duplicates were removed.

b) Second screen

A second screen was undertaken based on the full article. Two reviewers assessed each article for inclusion against the pre-defined inclusion and exclusion criteria for each question. In the case of a disagreement between the reviewers, a third independent reviewer assessed the article against the inclusion and exclusion criteria. Articles that met the inclusion criteria were forwarded for quality assessment and data extraction.

A1.3.6 Critical appraisal and data extraction of each included article

Two assessors independently assessed the risk of bias of each of the included studies using a study design specific assessment tool and where necessary pre-specified criteria (see *Technical report* for all quality assessment tools). Any disagreements were adjudicated by a third reviewer.

For all included articles, the relevant data was extracted and summarised in study characteristics and evidence tables. Each data extraction was checked by a second assessor. These tables are included in the technical report for each question (see *Technical report*).

A1.3.7 Guideline adaption for PICO questions 8.1, 8.2 and 9 (NICE)

For clinical questions 8.1, 8.2, and 9 (NICE), the National Institute for Health and Care Excellence (NICE) guideline[11] for the management of prostate cancer was identified as potentially relevant and

were assessed for potential adaption. The ADAPTE process[12] (particularly steps 2.2–2.5) was followed to establish if the guidelines were suitable for adaption.

To be considered for adaptation or adoption for this guideline, an existing guideline must:

- be assessed using the AGREE instrument for the domains rigour, clarity and editorial independence
- score at least 70% for each of these domains
- address PICO question(s) sufficiently similar to the PICO question(s) asked by the relevant working party (i.e. Do the recommendation(s) answer our question(s)?).

In the first instance, the NICE guidelines were assessed by four independent assessors using the three domains: rigour of development, clarity of presentation and editorial independence of the AGREE II instrument. The NICE guidelines scored 84.4% in the domain rigour of development, 76% in the domain clarity of presentation and 85.4% in the domain of editorial independence. The lead authors for PICO questions 8.1, 8.2 and 9 (NICE) were then approached by the systematic review team to verify that the PICO question addressed in the existing NICE guideline was suitable and relevant.

The systematic review team then updated the NICE systematic reviews to 1 March 2014 for the questions to be adapted. The literature was searched using the NICE literature search strategies and the results were screened against inclusion and exclusion derived from the NICE evidence review (see *A1.3.5*). Included studies were assessed for quality and data extraction (see *A1.3.6*). The evidence tables from the NICE guidelines were updated with the study results from the updated literature review and included in the technical report for the relevant PICO question. The term "Updated NICE systematic review" is used in the narrative of these guideline questions to refer to the studies identified in the literature update of the NICE systematic review.

A1.3.8 Meta-analysis for clinical question 7

For clinical question 7, a meta-analysis was conducted as part of the systematic review. The meta-analysis rationale was formulated. The relevant data was extracted from the studies included in the systematic review. The statistical analysis was conducted and the results presented. The analysis used logistic regression with generalised estimating equation adjustment to account for multiple (sometimes one but mostly two or more) biopsy components analysed from each man (using the patient identifier as the panel variable). The technical report for this question details the steps followed and includes the meta-analysis results.

A1.3.9 Summary of the relevant data

For each outcome examined, the results, level of the evidence, the risk of bias due to study design, and the relevance of the evidence for each included study were documented a body of evidence table.

Each question was addressed by a systematic review resulting in a systematic review report. All systematic review reports are published in the technical report of the guidelines. Levels of evidence are shown below.

Table A1. Designations of levels of evidence according to type of research question (NHMRC, 2009)

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Source: National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009. (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

A1.3.10 Assess the body of evidence and formulate recommendations

The technical report for each question was forwarded to each question-specific author team. The author teams in collaboration with the systematic review team (who conducted the systematic reviews and provided the technical reports) assessed the body of evidence and completed the NHMRC Evidence Statement form to record the volume of the evidence, its consistency, clinical

impact, generalisability and applicability and developed evidence statements (see *Technical report*). The process is described in *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines* (2009).[10]

Following grading of the body of evidence and development of evidence statements, expert authors were asked to formulate evidence-based recommendations that related to the summarised body of evidence. The method of grading recommendations is shown in Table A2.

Table A2. Grading of recommendations

Component of Recommendation	**Recommendation Grade**			
	A **Excellent**	**B** **Good**	**C** **Satisfactory**	**D** **Poor**
Volume of evidence[1**]	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	One or two level II studies with a low risk of bias or a systematic review/several level III studies with a low risk of bias	One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	Level IV studies, or level I to III studies/systematic reviews with a high risk of bias
Consistency[2**]	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population for the guideline	Population/s studied in the body of evidence are similar to the target population for the guideline	Population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population[3]	Population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

1 Level of evidence determined from level of evidence criteria

2 If there is only one study, rank this component as 'not applicable'

3 For example, results in adults that are clinically sensible to apply children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer

** For a recommendation to be graded A or B, the volume and consistency of evidence must also be graded either A or B.

Source: National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009. (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

The overall recommendations grade are shown in Table A3.

Table A3. Overall recommendation grades

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Source: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009. (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

In addition to developing evidence-based recommendations as a result of the systematic review for a question, expert authors could also draft consensus-based recommendations in the absence of evidence after having performed a systematic review, or practice points, when a matter was outside the scope of the search strategy for the systematic review. The NHMRC approved recommendation types and definitions are shown in Table A4.

Table A4. NHMRC approved recommendation types and definitions

Type of recommendation	Definition
Evidence-based recommendation	A recommendation based on the best available evidence identified by a systematic review of evidence.
Consensus-based recommendation	A recommendation based on clinical expertise, expert opinion and available evidence, and formulated using a consensus process, after a systematic review of the evidence found insufficient evidence on which to base a recommendation.
Practice point	A point of guidance to support the evidence-based recommendations, based on expert opinion and formulated by a consensus process, on a subject outside the scope of the systematic reviews.

Source: National Health and Medical Research Council. Procedures and requirements for meeting the NHMRC standard for clinical practice guidelines. Melbourne: National Health and Medical Research Council, 2011

A1.3.11 Writing the content

For each question, the assigned lead authors were asked to draft their guideline chapter using the following format:

- general introduction to the clinical question
- background to the clinical question, including its clinical importance and historical evidence, where relevant
- review of the evidence, including the number, quality and findings of studies identified by the systematic review
- evidence summary in tabular form including evidence statements, levels of evidence of included studies, and reference citations
- evidence-based recommendation(s) and corresponding grade(s), consensus-based recommendations and practice points
- implications for implementation of the recommendations, including possible effects on usual care, organisation of care, and any resource implications
- discussion, including unresolved issues, relevant studies currently underway, and future research priorities
- references.

The content draft was then reviewed by all Question Specific Working Party members. The draft documents underwent several iterations until agreement between the members of the Question Specific Working Parties on these drafts was reached.

A1.4 Review of the draft chapters

The complete draft guideline document with all draft chapters was circulated to the Guidelines Expert Advisory Panel. The whole group was asked to review the content and submit feedback. Members were asked to submit further suggestions on consensus-based recommendation and practice points.

A face-to-face meeting with all Expert Advisory Panel members was held to review and finalise the draft guidelines for public consultation. Prior to this meeting, the latest iteration draft guidelines were circulated. All panellists were asked to review the content, individual recommendations and practice points in detail, and to identify and note any controversies and points to be discussed at the group meeting. During the meeting, each recommendation and practice point was tabled as an agenda point. Each was reviewed and approved by consensus, which was reached by voting. The Expert Advisory Panel Chairperson nominated a particular recommendation/practice point to be reviewed and the panellists had the opportunity to discuss any issues and suggest revisions to recommendations and practice points. Each recommendation and practice point was approved once the eligible panellists (excluding representatives of the funding bodies and panellists who cannot vote due to conflict of interest) have reached consensus.

A1.5 Public consultation

A complete draft of the guideline was sent out for public consultation from 4 December 2014 to 16 January 2015. The public consultation of the guideline was launched at the joint meeting day of the

Union for International Cancer Control (UICC) World Cancer Congress and the Clinical Oncology Society of Australia (COSA) Annual Scientific meeting held on 4 December 2014 in Melbourne. The aim of this was to give the draft guidelines significant exposure to the international as well as the Australian cancer community. Submissions were invited from the general public and professional societies and groups and other relevant stakeholders. The consultation was publicised by advertisement in a national newspaper, and by contacting professional societies and groups, consumer groups and other relevant stakeholders.

All feedback on the draft received during the consultation period in Australia was compiled and sent to the relevant Question Specific Working Party to review their draft content, assessing and considering the submitted comments. Each additional submitted paper during public consultation was be assessed by the methodologist team against the systematic review protocol. Another face-to-face meeting was organised amongst the EAP to review all public consultation comments and the amended content. Subsequent changes to the draft were agreed by consensus, based on consideration of the evidence. The same consensus process that was followed during the face to face EAP meeting prior to public consultation was followed again. All changes resulting from the public consultation submission reviews were documented and made accessible once the guidelines are published.

A final independent review of experts in their fields was conducted before the final draft was submitted to NHMRC Council. Any further suggestions by the independent expert reviewers will be integrated in the final draft and then submitted to NHMRC Council for approval.

A1.6 Organisations formally endorsed the guidelines

[[ENDORSEMENT TO BE CONFIRMED FOLLOWING COMPLETION OF THE GUIDELINES]]

The following medical colleges and professional bodies will be approached to endorse the guideline:

- Australian College of Rural and Remote Medicine (ACRRM)
- Medical Oncology Group of Australia Incorporated (MOGA)
- Royal College of Pathologists of Australia (RCPA)
- Royal Australian College of Physicians (RACP) – Adult Health Division
- Royal Australian College of Physicians – Australian Chapter of Palliative Medicine (AChPM, RACP)
- Royal Australian College of Physicians – Australian Faculty of Public Health Medicine (AFPHM, RACP)
- Royal Australian College of Surgeons (RACS)
- Royal Australian College of General Practitioners (RACGP)
- Royal Australian and New Zealand College of Radiologists (RANZCR)
- Urological Society of Australia and New Zealand (USANZ).

A1.7 Dissemination and implementation

PCFA and Cancer Council Australia will take the lead in disseminating the guideline in Australia and are following a multi-strategy approach for the dissemination and implementation of the guideline, as this has shown to positively influence guideline uptake.[13, 14]

This will include a campaign to raise awareness of the new guidelines that incorporates organised media coverage through multiple outlets and an official launch at an international conference. The guideline will be distributed directly to relevant professional and other interested groups and through meetings, national and international conferences, and other professional development and continuing medical education (CME) events. A significant effort will be made to have the guideline introduced to senior undergraduate medical students and to encourage the relevant learned colleges to support the guideline and to foster their integration into hospital and community practice through resident and registrar education activities.

The guideline will be made available as a print publication, which can be ordered from PCFA and Cancer Council Australia. In addition, the guideline will also be made available as an online guideline via the Cancer Council Australia Cancer Guidelines Wiki. The online guideline version increases availability as well as accessibility, and usage will be tracked and analysed with a web analytics solution. Interlinking and listing the guidelines on national and international guideline portal is an important part of the digital dissemination strategy. Important Australian health websites, such as EviQ and healthdirect Australia will be approached to link to the online guideline. The guideline will also to be listed on national and international guideline portals such as Australia's Clinical Practice Guidelines Portal, Guidelines International Network guidelines library and National Guidelines Clearinghouse. The Cancer Guidelines Wiki is a responsive website that is optimised for mobile and desktop access. When accessing the guidelines with a mobile and tablet device, an icon can be easily added to the homescreen of mobile devices, offering easy mobile access.

In addition, the final guideline document will be launched via email alert to professional organisations, interested groups and clinical experts in the field, directing them via URL link to the online guideline and all associated resources. Future promotion will be conducted through print and social media campaigns as well as disseminating the guideline through further meetings, national and international conferences and other CME events. Local expert leaders will be identified and approached to facilitate dissemination and act as champions for the guidelines.

As part of the online guideline, online learning modules are planned to be developed to reinforce the guidelines content knowledge for participants, thus support guideline implementation and uptake. Programs will be developed using QStream (http://qstream.com/company/brain-science), a clinically proven online education method that was originally developed by Harvard Medical School. QStream programs have shown to improve knowledge acquisition in a number of randomised trials with medical practitioners.[15-20]

The Cancer Guidelines Wiki is based on semantic web technology, so the guidelines are available in a machine-readable format, which offers the possibility to easily integrate the guideline content with systems and web applications used in the Australian healthcare context.

Use of the guidelines as part of core curriculum in specialty exams will be encouraged. It is recognised that a planned approach is necessary to overcome specific barriers to implementation in particular settings and to identify appropriate incentives to encourage uptake of guideline recommendations. Implementation of the guidelines will require a combination of effective strategies and may include further CME initiatives and interactive learning, the development and promotion of computer-assisted decision aids and electronic decision-support systems, and the creation of audit and other clinical tools.

To support the implementation of this guideline a decision aid for men considering having a PSA test, and men who have had a positive PSA test result and are considering watchful waiting or active surveillance instead of immediate treatment are going to be developed.

A1.8 Future updates

The incoming literature updates will continue to be monitored for each systematic review question. If there is strong evidence emerging in a specific area of PSA testing, the Expert Advisory Panel will be reconvened to assess if this warrants a guideline update (full or partly). It is recommended for this guidelines to be updated after 3 years.

References

1. National Health and Medical Research Council. Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines. Melbourne: National Health and Medical Research Council; 2011.

2. National Health and Medical Research Council. A guide to the development, evaluation and implementation of clinical practice guidelines. Canberra: Commonwealth of Australia; 1999.

3. National Health and Medical Research Council. How to review the evidence: Systematic identification and review of scientific literature. Canberra: Commonwealth of Australia; 1999.

4. National Health and Medical Research Council. How to present evidence for consumers: Preparation of consumer publications. Canberra: Commonwealth of Australia; 1999.

5. National Health and Medical Research Council. How to prepare and present evidence-based information for consumers of health services: A literature review. Canberra: Commonwealth of Australia; 1999.

6. National Health and Medical Research Council. How to put evidence into practice: Implementation and dissemination strategies. Canberra, Commonwealth of Australia; 2000.

7. National Health and Medical Research Council. How to use the evidence: Assessment and application of scientific evidence. Canberra: Commonwealth of Australia; 2000.

8. National Health and Medical Research Council. How to compare the costs and benefits: evaluation of the economic evidence. Canberra: Commonwealth of Australia; 2001.

9. National Health and Medical Research Council. Using socioeconomic evidence in clinical practice guidelines. Canberra: Commonwealth of Australia; 2002.

10. National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. 2009. Canberra: Commonwealth of Australia.

11. National Collaborating Centre for Cancer. Prostate cancer: diagnosis and treatment. National Collaborating Centre for Cancer; 2014.

12. The ADAPTE Collaboration. The ADAPTE Process. Resource Toolkit for Guideline Adaptation. Version 2.0. 2009. Available from: http://www.g-i-n.net. 2014.

13. National Institute of Clinical Studies. Do guidelines make a difference to health outcomes? Melbourne: NICS; 2006.

14. Francke A, Smit M, de Veer A, Mistiaen P. Factors influencing the implementation of clinical guidelines for health care professionals: A systematic meta-review. BMC Med Inform Decis Mak. 2008: 8; 38.

15. Kerfoot B, Baker H, Koch M, Connelly D, Joseph D, Ritchey M. Randomized controlled trial of spaced education to US and Canadian urology residents. J Urol 2007;177(1481-1487).

16. Kerfoot B, DeWolf W, Masser B, Church P, Federman D. Spaced education improves the retention of clinical knowledge by medical students: randomized controlled trail. Med Educ 2007;41(23-31).

17. Kerfoot B, Armstrong E, O'Sullivan P. Interactive spaced education to teach the physical examination: A randomized controlled trial. J Gen Intern Med 2008;23(7):973-978.

18. Kerfoot B. Learning benefits of online spaced education persist for two years. J Urol 2009;181(6):2671-2673.

19. Kerfoot B, Kearney M, Connelly D, Ritchey M. Interactive spaced education to assess and improve knowledge of clinical practice guidelines: A randomized controlled trial. Ann Surg 2009;249(5):744-749.

20. Kerfoot B, Brotschi E. Online spaced education to teach urology to medical students: A multi-institutional randomized trial. Amer J Surg 2009;197(1):89-95.

List of clinical questions

Question No.	Clinical Question	Corresponding PICO Question(s)
Risk		
1	What risk factors can identify Australian men who are at high risk of prostate cancer or death from prostate cancer? Suggested risk factors include: - Family history	**1:** For Australian men, has a family history of prostate cancer been shown to be reliably associated with a 2.0-fold or greater increase in risk of occurrence of or death from prostate cancer when compared to men who do not have a family history of prostate cancer?
Testing		
2	What methods of decision support for men about PSA testing increase men's capacity to make an informed decision for or against testing?	**2:** In men without evidence of prostate cancer does a decision support intervention or decision aid compared with usual care improve knowledge, decisional satisfaction, decision-related distress and decisional uncertainty about PSA testing for early detection of prostate cancer?
3	In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what should be the PSA testing strategies (age to start, level at which to declare a test abnormal and frequency of subsequent testing if the PSA level is normal) for men at average risk of prostate cancer and how should they be modified, if at all, for men at high risk of prostate cancer?	**3.1:** For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what PSA testing strategies (with or without DRE), compared with no PSA testing or other PSA testing strategies, reduce prostate cancer specific mortality or the incidence of metastases at diagnosis and offer the best balance of benefits to harms of testing? **3.2**: For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what PSA testing strategies with or without DRE perform best in detecting any prostate cancer or high grade prostate cancer diagnosed in biopsy tissue? **3.3:** For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer does a PSA level measured at a particular age in men assist with determining the recommended interval to the next PSA test?
4	How best can DRE be used, if at all, in association with PSA testing?	**4:** For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what is the incremental value of performing a digital rectal examination (DRE) in

		addition to PSA testing in detecting any prostate cancer?
5	What age or health status criteria should be used to identify men who would be unlikely to live long enough to benefit from PSA testing and who, in consequence, would not be offered PSA testing?	**5:** For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer, how many years after the start of PSA testing is the benefit of PSA testing apparent?
6	In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what tests for prostate cancer should be offered in addition to a PSA test? Candidate tests include: free-to total PSA % PSA velocity Prostate health index Repeated total PSA	**Free-to-total PSA %** **6.1 a:** For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring free-to-total PSA percentage improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single total PSA result above 3.0 ng/mL? **6.1 b:** For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring free-to-total PSA percentage improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL? **PSA velocity** **6.2 a:** For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring PSA velocity improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single elevated total PSA result above 3.0 ng/mL? **6.2 b:** For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring PSA velocity improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL?

		Prostate Health Index (PHI) **6.3 a:** For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring the Prostate Health Index (PHI) improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single elevated total PSA result above 3.0 ng/mL? **6.3 b:** For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring the Prostate Health Index (PHI) improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single elevated total PSA result above 3.0 ng/mL? **Repeated total PSA** **6.4:** For asymptomatic men with initial total PSA above 3.0 ng/mL, does repeating the total PSA test and using an initial and repeat total PSA above 3.0 ng/mL as the indication for biopsy, improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL as the indication for biopsy?
Prostate biopsy and multiparametric MRI		
7	What constitutes an adequate prostate biopsy?	**7:** For men undergoing an initial prostate biopsy how many biopsy cores, which pattern of biopsy sampling sites and which approach constitute an adequate prostate biopsy?
8	If prostate cancer is not found in an adequate biopsy what if any additional steps should be taken and what recommendations should be made regarding the strategy for subsequent PSA testing?	**8.1:** In men who have been referred with suspected prostate cancer, what are the prognostic factors that determine the need for further investigation following a prior negative biopsy? **8.2:** In men with suspected prostate cancer whose initial TRUS biopsy is negative, what should be the next investigation(s)?

Active surveillance		
9	What should be the criteria for choosing active surveillance in preference to definitive treatment to offer as primary management to men who have a positive prostate biopsy?	**9:** For men with biopsy-diagnosed prostate cancer, for which patients (based on diagnostic, clinical and other criteria) does active surveillance achieve equivalent or better outcomes in terms of length and quality of life than definitive treatment?
10	What is the best monitoring protocol for active surveillance and what should be the criteria for intervention?	**10:** For men with biopsy-diagnosed prostate cancer following an active surveillance protocol, which combination of monitoring tests, testing frequency and clinical or other criteria for intervention achieve the best outcomes in terms of length and quality of life?
Watchful waiting		
11	What should be the criteria for choosing watchful waiting in preference to definitive treatment to offer as primary management to men who have a positive prostate biopsy?	**11:** For men with biopsy-diagnosed prostate cancer, for which patients (based on diagnostic, clinical and other criteria) does watchful waiting achieve equivalent or better outcomes in terms of length and quality of life than definitive treatment?
12	What is the best monitoring protocol for watchful waiting and what should be the criteria for intervention?	**12:** For men with biopsy-diagnosed prostate cancer following a watchful waiting protocol, which combination of monitoring tests, testing frequency and clinical or other criteria for intervention achieve the best outcomes in terms of length and quality of life?

Completed NHRMC Evidence Statement Forms

[Compiled pages 21-163]

Systematic review reports

[PDFs from page 164-1063]

Quality assessment tools

[PDF page 1064-1092]

List of abbreviations

[PDF page 1093]

Date published: 20 January 2016

Disclaimer

This document should be read in conjunction with the *Clinical Practice Guidelines for PSA Testing and Early Management of Test-Detected Prostate Cancer*.

Suggested citation

Prostate Cancer Foundation of Australia and Cancer Council Australia PSA Testing Guidelines Expert Advisory Panel. Technical Report for Clinical Practice Guidelines for PSA Testing and Early Management of Test-Detected Prostate Cancer. Prostate Cancer Foundation of Australia and Cancer Council Australia, Sydney (2015).

These guidelines and associated documentation (i.e. Administrative and Technical Reports) can accessed and downloaded at:
http://wiki.cancer.org.au/australia/Guidelines:PSA_Testing

Contents

Introduction

This *Technical Report* accompanies the *Clinical Practice Guidelines for PSA Testing and Early Management of Test-Detected Prostate Cancer*, developed by Prostate Cancer Foundation of Australia and Cancer Council Australia.

It outlines the guidelines development process and methodology, lists the clinical questions, provides all accompanying NHMRC Statement Forms, the detailed technical report for each PICO question and the quality assessment tools.

Guidelines development process

The following description of the guidelines development process appears in *Appendix 1* in the *Clinical Practice Guidelines for PSA Testing and Early Management of Test-Detected Prostate Cancer*.

A1.1 Introduction

Prostate Cancer Foundation of Australia (PCFA) initiated the process to develop clinical practice guidelines for PSA testing and management of test-detected prostate cancer. These guidelines are a collaborative project between PCFA and Cancer Council Australia.

Development began in November 2012 after NHMRC agreed to consider approving the guidelines, provided it were to be developed according to NHMRC procedures and requirements. To better describe the scope of the guidelines, the title was changed to *Clinical practice guidelines for PSA testing and early management of test-detected prostate cancer*. Financial support for the guidelines project was provided by PCFA with Cancer Council Australia contributing in kind resources of their guidelines development team.

A1.2 Guidelines development group

Following a consultation process with key stakeholders involved in cancer control and clinical care delivery, including the Urological Society of Australia and New Zealand (USANZ) and the Royal College of Pathologists of Australasia (RCPA), PCFA invited a multidisciplinary group of relevant experts to develop clinical guidelines for PSA testing and clinical care immediately following test-detected prostate cancer. This was to ensure that representatives from all specialities and disciplines involved in the diagnosis and management of prostate cancer were represented. Two consumer representatives were also invited to be part of the Expert Advisory Panel (EAP) (see *Appendix 2*).

PCFA and Cancer Council Australia appointed a steering committee. The Project Steering Committee was responsible for the overall management and strategic leadership of the guidelines development process. The Project Steering Committee ensured that all deliverables agreed in the project plan were delivered to acceptable standards in accordance with NHMRC requirements.

A project team based at Cancer Council Australia conducted the systematic reviews, comprising of systematic literature searches, literature screening against pre-determined inclusion and exclusion criteria and critical evaluation and data extraction of the included literature. The project team was responsible for liaising with the EAP members in regards to content development and content review and compiling the document.

The clinical practice guidelines were developed according to the procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines.[1] The development program was designed to meet the scientific rigour required by the standard for developing high quality, evidence-based clinical practice guidelines. A series of NHMRC resources and handbooks[2-10] guided the process and outlined the major steps and expectations involved in developing guidelines. These documents provided the definitions and protocols for developing research questions and search strategies, conducting systematic literature reviews, summarising and assessing the relevant literature and finally, formulating and grading the recommendations. They also included checklists and templates created to satisfy designated standards of quality and process.

At its initial meeting the Guidelines Expert Advisory Panel developed clinical questions. The questions were allocated to specific Guidelines Expert Advisory Panel members to act as lead authors according to their areas of expertise. Each lead author team was able to co-opt additional experts, who were not part of the Expert Advisory Panel, as co-authors for their allocated questions. These question-specific groups are referred to as Question Specific Working Parties in this guidelines document. The Project Steering Committee assessed the suggestion of any additional co-authors including their declaration of interest (see *Appendix 6*).

A1.3 Steps in preparing clinical practice guidelines to NHMRC criteria

For every question the below steps were followed:

1. Develop a structured clinical question (PICO question)
2. Search for existing relevant guidelines and systematic reviews
3. Process if relevant clinical practice guideline was identified or not

3a If no relevant clinical practice guideline was found	**3b If a relevant clinical practice guideline was found and assessed as suitable for adaption**
Check if an existing systematic review of high quality exists and can be used to inform the systematic review process	Conduct systematic literature review update for the question of the existing clinical practice guideline
Develop the systematic review protocol and systematic literature search strategy for each PICO question	Screen literature update results against pre-defined inclusion and exclusion criteria
Conduct the systematic literature search according to protocol	Conduct critical appraisal and data extraction of each new included article
Screen literature results against pre-defined inclusion and exclusion criteria	Update evidence table of evidence review of existing guideline with new literature update results
Conduct critical appraisal and data extraction of each included article	

4. Summarise the relevant data
5. Assess if meta-analysis should be undertaken

5a If meta-analysis is decided to be undertaken as part of the systematic review	**5b No meta-analysis**
Formulate rationale for meta-analysis	Continue with step 6
Select studies for inclusion	
Extract data	
Perform statistical analysis	
Present results	

6. Assess the body of evidence and formulate recommendations
7. Write the content narrative

A1.3.1 Developing a structured clinical question

A wide range of questions was proposed for research. The questions focused on diagnosis, prognosis, risk and interventions. All proposed questions were reviewed on the basis of their purpose, scope and clinical importance to the target audience and were structured according to the PICO (populations, interventions, comparisons, outcomes) framework (see *Appendix 3*). The Question Specific Working Parties provided the systematic review team with feedback to refine the PICO questions.

A1.3.2 Search for existing relevant guidelines and systematic reviews

For each PICO question, the National Guideline Clearinghouse (http://guideline.gov) the Guidelines Resource Centre (www.cancerview.ca) as well as the scoping search for the PICO question were scanned for relevant clinical practice guidelines that could potentially be suitable for adaption.

If an existing guideline was identified, the guideline was assessed for adaption according to the ADAPTE process. If suitable, the guideline systematic review was adapted as outlined in *A1.3.7*.

Relevant guidelines that did not meet the criteria for adaption were checked for systematic reviews that could be used as a source of relevant references to inform the systematic review process for the PICO question. Full systematic reviews were then performed as outlined in *A1.3.3- A1.3.6*.

A1.3.3 Developing a systematic search strategy

For each PICO question, systematic literature search strategies were developed by the technical team.

Most searches were directed to prostate cancer as a generic base. Searches were limited or widened as necessary according to the PICO structure using keywords or MESH and subject terms. Systematic search strategies were derived from these terms for each included electronic databases. The included standard databases searched were Medline, Embase, Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects and Health Technology Assessment for all questions. The psychosocial questions also included CINAHL and PsycINFO databases to retrieve relevant literature.

A1.3.4 Conducting the systematic literature search according to protocol

Clinical practice guidelines should be based on systematic identification and synthesis of the best available scientific evidence.[2] For each clinical question, that required a systematic literature review, literature searches were conducted systematically with the literature cut-off date of 1 March 2014. The following electronic databases were part of the systematic literature search strategy:

- *Medline*: bibliographic references and abstracts to articles in a range of languages on topics such as clinical medical information and biomedicine, and including the allied health fields, biological and physical sciences
- *EMBASE*: major pharmacological and biomedical database indexing drug information from 4550 journals published in 70 countries
- *Database of Abstracts of Reviews of Effects and Health Technology Assessment:* contains details of systematic reviews that evaluate the effects of healthcare interventions and the delivery and organisation of health services

- *The Cochrane Database of Systematic Reviews*: contains systematic reviews of primary research in human health care and health policy, and are internationally recognised as the highest standard in evidence-based health care
- *CINAHL*: bibliographic references and abstracts to journal articles, book chapters, pamphlets, audiovisual materials, software, dissertations, critical paths, and research instruments on topics including nursing and allied health, biomedicine, consumer health, health sciences librarianship, behavioural sciences, management, and education
- *Psychinfo*: Bibliographic references and abstracts to journal articles, book chapters, dissertations and technical reports on psychology; social, clinical, cognitive and neuropsychology; psychiatry, sociology, anthropology and education, with source material from a wide range of languages.

A search filter to retrieve relevant literature considering Aboriginal and Torres Strait Islander peoples was added to each question.

Additional relevant papers from reference lists and, where appropriate, clinical trial registries, were also identified for retrieval as part of the snowballing process.

The full detailed systematic literature search strategy for every clinical question is fully documented in the technical report of the question (see *Technical report*).

A1.3.5 Screening of literature results against pre-defined inclusion and exclusion criteria

Part of the systematic review process is to screen all retrieved literature results against the pre-defined inclusion and exclusion criteria in two stages.

a) First screen

During the first screening round, the titles and abstracts of all retrieved literature were screened by one or two reviewers. All irrelevant, incorrect and duplicates were removed.

b) Second screen

A second screen was undertaken based on the full article. Two reviewers assessed each article for inclusion against the pre-defined inclusion and exclusion criteria for each question. In the case of a disagreement between the reviewers, a third independent reviewer assessed the article against the inclusion and exclusion criteria. Articles that met the inclusion criteria were forwarded for quality assessment and data extraction.

A1.3.6 Critical appraisal and data extraction of each included article

Two assessors independently assessed the risk of bias of each of the included studies using a study design specific assessment tool and where necessary pre-specified criteria (see *Technical report* for all quality assessment tools). Any disagreements were adjudicated by a third reviewer.

For all included articles, the relevant data was extracted and summarised in study characteristics and evidence tables. Each data extraction was checked by a second assessor. These tables are included in the technical report for each question (see *Technical report*).

A1.3.7 Guideline adaption for PICO questions 8.1, 8.2 and 9 (NICE)

For clinical questions 8.1, 8.2, and 9 (NICE), the National Institute for Health and Care Excellence (NICE) guideline[11] for the management of prostate cancer was identified as potentially relevant and

were assessed for potential adaption. The ADAPTE process[12] (particularly steps 2.2–2.5) was followed to establish if the guidelines were suitable for adaption.

To be considered for adaptation or adoption for these guidelines, an existing guideline must:

- be assessed using the AGREE instrument for the domains rigour, clarity and editorial independence
- score at least 70% for each of these domains
- address PICO question(s) sufficiently similar to the PICO question(s) asked by the relevant working party (i.e. Do the recommendation(s) answer our question(s)?).

In the first instance, the NICE guidelines were assessed by four independent assessors using the three domains: rigour of development, clarity of presentation and editorial independence of the AGREE II instrument. The NICE guidelines scored 84.4% in the domain rigour of development, 76% in the domain clarity of presentation and 85.4% in the domain of editorial independence. The lead authors for PICO questions 8.1, 8.2 and 9 (NICE) were then approached by the systematic review team to verify that the PICO question addressed in the existing NICE guideline was suitable and relevant.

The systematic review team then updated the NICE systematic reviews to 1 March 2014 for the questions to be adapted. The literature was searched using the NICE literature search strategies and the results were screened against inclusion and exclusion derived from the NICE evidence review (see *A1.3.5*). Included studies were assessed for quality and data extraction (see *A1.3.6*). The evidence tables from the NICE guidelines were updated with the study results from the updated literature review and included in the technical report for the relevant PICO question. The term "Updated NICE systematic review" is used in the narrative of these guidelines questions to refer to the studies identified in the literature update of the NICE systematic review.

A1.3.8 Meta-analysis for clinical question 7

For clinical question 7, a meta-analysis was conducted as part of the systematic review. The meta-analysis rationale was formulated. The relevant data was extracted from the studies included in the systematic review. The statistical analysis was conducted and the results presented. The analysis used logistic regression with generalised estimating equation adjustment to account for multiple (sometimes one but mostly two or more) biopsy components analysed from each man (using the patient identifier as the panel variable). The technical report for this question details the steps followed and includes the meta-analysis results.

A1.3.9 Summary of the relevant data

For each outcome examined, the results, level of the evidence, the risk of bias due to study design, and the relevance of the evidence for each included study were documented a body of evidence table.

Each question was addressed by a systematic review resulting in a systematic review report. All systematic review reports are published in the technical report of the guidelines. Levels of evidence are shown below.

Table A1. Designations of levels of evidence according to type of research question (NHMRC, 2009)

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Source: National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009. (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

A1.3.10 Assess the body of evidence and formulate recommendations

The technical report for each question was forwarded to each question-specific author team. The author teams in collaboration with the systematic review team (who conducted the systematic reviews and provided the technical reports) assessed the body of evidence and completed the NHMRC Evidence Statement form to record the volume of the evidence, its consistency, clinical

impact, generalisability and applicability and developed evidence statements (see *Technical report*). The process is described in *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines* (2009).[10]

Following grading of the body of evidence and development of evidence statements, expert authors were asked to formulate evidence-based recommendations that related to the summarised body of evidence. The method of grading recommendations is shown in Table A2.

Table A2. Grading of recommendations

Component of Recommendation	**Recommendation Grade**			
	A **Excellent**	**B** **Good**	**C** **Satisfactory**	**D** **Poor**
Volume of evidence[1]**	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	One or two level II studies with a low risk of bias or a systematic review/several level III studies with a low risk of bias	One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	Level IV studies, or level I to III studies/systematic reviews with a high risk of bias
Consistency[2]**	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population for the guideline	Population/s studied in the body of evidence are similar to the target population for the guideline	Population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population[3]	Population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

1 Level of evidence determined from level of evidence criteria

2 If there is only one study, rank this component as 'not applicable'

3 For example, results in adults that are clinically sensible to apply children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer

** For a recommendation to be graded A or B, the volume and consistency of evidence must also be graded either A or B.

Source: National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009. (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

The overall recommendations grade are shown in Table A3.

Table A3. Overall recommendation grades

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Source: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009. (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

In addition to developing evidence-based recommendations as a result of the systematic review for a question, expert authors could also draft consensus-based recommendations in the absence of evidence after having performed a systematic review, or practice points, when a matter was outside the scope of the search strategy for the systematic review. The NHMRC approved recommendation types and definitions are shown in Table A4.

Table A4. NHMRC approved recommendation types and definitions

Type of recommendation	Definition
Evidence-based recommendation	A recommendation based on the best available evidence identified by a systematic review of evidence.
Consensus-based recommendation	A recommendation based on clinical expertise, expert opinion and available evidence, and formulated using a consensus process, after a systematic review of the evidence found insufficient evidence on which to base a recommendation.
Practice point	A point of guidance to support the evidence-based recommendations, based on expert opinion and formulated by a consensus process, on a subject outside the scope of the systematic reviews.

Source: National Health and Medical Research Council. Procedures and requirements for meeting the NHMRC standard for clinical practice guidelines. Melbourne: National Health and Medical Research Council, 2011

A1.3.11 Writing the content

For each question, the assigned lead authors were asked to draft their guidelines chapter using the following format:

- general introduction to the clinical question
- background to the clinical question, including its clinical importance and historical evidence, where relevant
- review of the evidence, including the number, quality and findings of studies identified by the systematic review
- evidence summary in tabular form including evidence statements, levels of evidence of included studies, and reference citations
- evidence-based recommendation(s) and corresponding grade(s), consensus-based recommendations and practice points
- implications for implementation of the recommendations, including possible effects on usual care, organisation of care, and any resource implications
- discussion, including unresolved issues, relevant studies currently underway, and future research priorities
- references.

The content draft was then reviewed by all Question Specific Working Party members. The draft documents underwent several iterations until agreement between the members of the Question Specific Working Parties on these drafts was reached.

A1.4 Review of the draft chapters

The complete draft guidelines document with all draft chapters was circulated to the Guidelines Expert Advisory Panel. The whole group was asked to review the content and submit feedback. Members were asked to submit further suggestions on consensus-based recommendation and practice points.

A face-to-face meeting with all Expert Advisory Panel members was held to review and finalise the draft guidelines for public consultation. Prior to this meeting, the latest iteration draft guidelines were circulated. All panellists were asked to review the content, individual recommendations and practice points in detail, and to identify and note any controversies and points to be discussed at the group meeting. During the meeting, each recommendation and practice point was tabled as an agenda point. Each was reviewed and approved by consensus, which was reached by voting. The Expert Advisory Panel Chairperson nominated a particular recommendation/practice point to be reviewed and the panellists had the opportunity to discuss any issues and suggest revisions to recommendations and practice points. Each recommendation and practice point was approved once the eligible panellists (excluding representatives of the funding bodies and panellists who cannot vote due to conflict of interest) have reached consensus.

A1.5 Public consultation

A complete draft of the guidelines was sent out for public consultation from 4 December 2014 to 16 January 2015. The public consultation of the guidelines was launched at the joint meeting day of the

Union for International Cancer Control (UICC) World Cancer Congress and the Clinical Oncology Society of Australia (COSA) Annual Scientific meeting held on 4 December 2014 in Melbourne. The aim of this was to give the draft guidelines significant exposure to the international as well as the Australian cancer community. Submissions were invited from the general public and professional societies and groups and other relevant stakeholders. The consultation was publicised by advertisement in a national newspaper, and by contacting professional societies and groups, consumer groups and other relevant stakeholders.

All feedback on the draft received during the consultation period in Australia was compiled and sent to the relevant Question Specific Working Party to review their draft content, assessing and considering the submitted comments. Each additional submitted paper during public consultation was be assessed by the methodologist team against the systematic review protocol. Another face-to-face meeting was organised amongst the EAP to review all public consultation comments and the amended content. Subsequent changes to the draft were agreed by consensus, based on consideration of the evidence. The same consensus process that was followed during the face to face EAP meeting prior to public consultation was followed again. All changes resulting from the public consultation submission reviews were documented and made accessible once the guidelines are published.

A final independent review of experts in their fields was conducted before the final draft was submitted to NHMRC Council. Any further suggestions by the independent expert reviewers will be integrated in the final draft and then submitted to NHMRC Council for approval.

A1.6 Organisations formally endorsing the guidelines

The following medical colleges and professional bodies were approached to endorse the guideline:

- Australian College of Rural and Remote Medicine (ACRRM)
- Medical Oncology Group of Australia Incorporated (MOGA)
- Royal College of Pathologists of Australia (RCPA)
- Royal Australian College of Physicians (RACP) – Adult Health Division
- Royal Australian College of Physicians – Australian Chapter of Palliative Medicine (AChPM, RACP)
- Royal Australian College of Physicians – Australian Faculty of Public Health Medicine (AFPHM, RACP)
- Royal Australian College of Surgeons (RACS)
- Royal Australian College of General Practitioners (RACGP)
- Royal Australian and New Zealand College of Radiologists (RANZCR)
- Urological Society of Australia and New Zealand (USANZ).

A1.7 Dissemination and implementation

PCFA and Cancer Council Australia will take the lead in disseminating the guidelines in Australia and are following a multi-strategy approach for the dissemination and implementation of the guidelines, as this has shown to positively influence guidelines uptake.[13, 14]

This will include a campaign to raise awareness of the new guidelines that incorporates organised media coverage through multiple outlets and an official launch at an international conference. The guidelines will be distributed directly to relevant professional and other interested groups and through meetings, national and international conferences, and other professional development and continuing medical education (CME) events. A significant effort will be made to have the guidelines introduced to senior undergraduate medical students and to encourage the relevant learned colleges to support the guidelines and to foster their integration into hospital and community practice through resident and registrar education activities.

The guidelines will be made available as a print publication, which can be ordered from PCFA and Cancer Council Australia. In addition, the guidelines will also be made available as online guidelines via the Cancer Council Australia Cancer Guidelines Wiki. The online guidelines version increases availability as well as accessibility, and usage will be tracked and analysed with a web analytics solution. Interlinking and listing the guidelines on national and international guidelines portal is an important part of the digital dissemination strategy. Important Australian health websites, such as EviQ and healthdirect Australia will be approached to link to the online guidelines. The guidelines will also to be listed on national and international guidelines portals such as Australia's Clinical Practice Guidelines Portal, Guidelines International Network guidelines library and National Guidelines Clearinghouse. The Cancer Guidelines Wiki is a responsive website that is optimised for mobile and desktop access. When accessing the guidelines with a mobile and tablet device, an icon can be easily added to the homescreen of mobile devices, offering easy mobile access.

In addition, the final guidelines document will be launched via email alert to professional organisations, interested groups and clinical experts in the field, directing them via URL link to the online guidelines and all associated resources. Future promotion will be conducted through print and social media campaigns as well as disseminating the guidelines through further meetings, national and international conferences and other CME events. Local expert leaders will be identified and approached to facilitate dissemination and act as champions for the guidelines.

As part of the online guidelines, online learning modules are planned to be developed to reinforce the guidelines content knowledge for participants, thus support guidelines implementation and uptake. Programs will be developed using QStream (http://qstream.com/company/brain-science), a clinically proven online education method that was originally developed by Harvard Medical School. QStream programs have shown to improve knowledge acquisition in a number of randomised trials with medical practitioners.[15-20]

The Cancer Guidelines Wiki is based on semantic web technology, so the guidelines are available in a machine-readable format, which offers the possibility to easily integrate the guidelines content with systems and web applications used in the Australian healthcare context.

Use of the guidelines as part of core curriculum in specialty exams will be encouraged. It is recognised that a planned approach is necessary to overcome specific barriers to implementation in particular settings and to identify appropriate incentives to encourage uptake of guidelines recommendations. Implementation of the guidelines will require a combination of effective strategies and may include further CME initiatives and interactive learning, the development and promotion of computer-assisted decision aids and electronic decision-support systems, and the creation of audit and other clinical tools.

To support the implementation of these guidelines a decision aid for men considering having a PSA test, and men who have had a positive PSA test result and are considering watchful waiting or active surveillance instead of immediate treatment are going to be developed.

A1.8 Future updates

The incoming literature updates will continue to be monitored for each systematic review question. If there is strong evidence emerging in a specific area of PSA testing, the Expert Advisory Panel will be reconvened to assess if this warrants a guidelines update (full or partly). It is recommended for these guidelines to be updated after 3 years.

References

1. National Health and Medical Research Council. Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines. Melbourne: National Health and Medical Research Council; 2011.

2. National Health and Medical Research Council. A guide to the development, evaluation and implementation of clinical practice guidelines. Canberra: Commonwealth of Australia; 1999.

3. National Health and Medical Research Council. How to review the evidence: Systematic identification and review of scientific literature. Canberra: Commonwealth of Australia; 1999.

4. National Health and Medical Research Council. How to present evidence for consumers: Preparation of consumer publications. Canberra: Commonwealth of Australia; 1999.

5. National Health and Medical Research Council. How to prepare and present evidence-based information for consumers of health services: A literature review. Canberra: Commonwealth of Australia; 1999.

6. National Health and Medical Research Council. How to put evidence into practice: Implementation and dissemination strategies. Canberra, Commonwealth of Australia; 2000.

7. National Health and Medical Research Council. How to use the evidence: Assessment and application of scientific evidence. Canberra: Commonwealth of Australia; 2000.

8. National Health and Medical Research Council. How to compare the costs and benefits: evaluation of the economic evidence. Canberra: Commonwealth of Australia; 2001.

9. National Health and Medical Research Council. Using socioeconomic evidence in clinical practice guidelines. Canberra: Commonwealth of Australia; 2002.

10. National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. 2009. Canberra: Commonwealth of Australia.

11. National Collaborating Centre for Cancer. Prostate cancer: diagnosis and treatment. National Collaborating Centre for Cancer; 2014.

12. The ADAPTE Collaboration. The ADAPTE Process. Resource Toolkit for Guideline Adaptation. Version 2.0. 2009. Available from: http://www.g-i-n.net. 2014.

13. National Institute of Clinical Studies. Do guidelines make a difference to health outcomes? Melbourne: NICS; 2006.

14. Francke A, Smit M, de Veer A, Mistiaen P. Factors influencing the implementation of clinical guidelines for health care professionals: A systematic meta-review. BMC Med Inform Decis Mak. 2008: 8; 38.

15. Kerfoot B, Baker H, Koch M, Connelly D, Joseph D, Ritchey M. Randomized controlled trial of spaced education to US and Canadian urology residents. J Urol 2007;177(1481-1487).

16. Kerfoot B, DeWolf W, Masser B, Church P, Federman D. Spaced education improves the retention of clinical knowledge by medical students: randomized controlled trail. Med Educ 2007;41(23-31).

17. Kerfoot B, Armstrong E, O'Sullivan P. Interactive spaced education to teach the physical examination: A randomized controlled trial. J Gen Intern Med 2008;23(7):973-978.

18. Kerfoot B. Learning benefits of online spaced education persist for two years. J Urol 2009;181(6):2671-2673.

19. Kerfoot B, Kearney M, Connelly D, Ritchey M. Interactive spaced education to assess and improve knowledge of clinical practice guidelines: A randomized controlled trial. Ann Surg 2009;249(5):744-749.

20. Kerfoot B, Brotschi E. Online spaced education to teach urology to medical students: A multi-institutional randomized trial. Amer J Surg 2009;197(1):89-95.

List of clinical questions

Question No.	Clinical Question	Corresponding PICO Question(s)
Risk		
1	What risk factors can identify Australian men who are at high risk of prostate cancer or death from prostate cancer? Suggested risk factors include: - Family history	**1:** For Australian men, has a family history of prostate cancer been shown to be reliably associated with a 2.0-fold or greater increase in risk of occurrence of or death from prostate cancer when compared to men who do not have a family history of prostate cancer?
Testing		
2	What methods of decision support for men about PSA testing increase men's capacity to make an informed decision for or against testing?	**2:** In men without evidence of prostate cancer does a decision support intervention or decision aid compared with usual care improve knowledge, decisional satisfaction, decision-related distress and decisional uncertainty about PSA testing for early detection of prostate cancer?
3	In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what should be the PSA testing strategies (age to start, level at which to declare a test abnormal and frequency of subsequent testing if the PSA level is normal) for men at average risk of prostate cancer and how should they be modified, if at all, for men at high risk of prostate cancer?	**3.1:** For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what PSA testing strategies (with or without DRE), compared with no PSA testing or other PSA testing strategies, reduce prostate cancer specific mortality or the incidence of metastases at diagnosis and offer the best balance of benefits to harms of testing? **3.2**: For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what PSA testing strategies with or without DRE perform best in detecting any prostate cancer or high grade prostate cancer diagnosed in biopsy tissue? **3.3:** For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer does a PSA level measured at a particular age in men assist with determining the recommended interval to the next PSA test?
4	How best can DRE be used, if at all, in association with PSA testing?	**4:** For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what is the incremental value of performing a digital rectal examination (DRE) in

		addition to PSA testing in detecting any prostate cancer?
5	What age or health status criteria should be used to identify men who would be unlikely to live long enough to benefit from PSA testing and who, in consequence, would not be offered PSA testing?	**5:** For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer, how many years after the start of PSA testing is the benefit of PSA testing apparent?
6	In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what tests for prostate cancer should be offered in addition to a PSA test? Candidate tests include: free-to total PSA % PSA velocity Prostate health index Repeated total PSA	**Free-to-total PSA %** **6.1 a:** For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring free-to-total PSA percentage improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single total PSA result above 3.0 ng/mL? **6.1 b:** For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring free-to-total PSA percentage improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL? **PSA velocity** **6.2 a:** For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring PSA velocity improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single elevated total PSA result above 3.0 ng/mL? **6.2 b:** For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring PSA velocity improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL?

		Prostate Health Index (PHI) **6.3 a:** For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring the Prostate Health Index (PHI) improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single elevated total PSA result above 3.0 ng/mL? **6.3 b:** For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring the Prostate Health Index (PHI) improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single elevated total PSA result above 3.0 ng/mL? **Repeated total PSA** **6.4:** For asymptomatic men with initial total PSA above 3.0 ng/mL, does repeating the total PSA test and using an initial and repeat total PSA above 3.0 ng/mL as the indication for biopsy, improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL as the indication for biopsy?
Prostate biopsy and multiparametric MRI		
7	What constitutes an adequate prostate biopsy?	**7:** For men undergoing an initial prostate biopsy how many biopsy cores, which pattern of biopsy sampling sites and which approach constitute an adequate prostate biopsy?
8	If prostate cancer is not found in an adequate biopsy what if any additional steps should be taken and what recommendations should be made regarding the strategy for subsequent PSA testing?	**8.1:** In men who have been referred with suspected prostate cancer, what are the prognostic factors that determine the need for further investigation following a prior negative biopsy? **8.2:** In men with suspected prostate cancer whose initial TRUS biopsy is negative, what should be the next investigation(s)?

Active surveillance		
9	What should be the criteria for choosing active surveillance in preference to definitive treatment to offer as primary management to men who have a positive prostate biopsy?	**9:** For men with biopsy-diagnosed prostate cancer, for which patients (based on diagnostic, clinical and other criteria) does active surveillance achieve equivalent or better outcomes in terms of length and quality of life than definitive treatment?
10	What is the best monitoring protocol for active surveillance and what should be the criteria for intervention?	**10:** For men with biopsy-diagnosed prostate cancer following an active surveillance protocol, which combination of monitoring tests, testing frequency and clinical or other criteria for intervention achieve the best outcomes in terms of length and quality of life?
Watchful waiting		
11	What should be the criteria for choosing watchful waiting in preference to definitive treatment to offer as primary management to men who have a positive prostate biopsy?	**11:** For men with biopsy-diagnosed prostate cancer, for which patients (based on diagnostic, clinical and other criteria) does watchful waiting achieve equivalent or better outcomes in terms of length and quality of life than definitive treatment?
12	What is the best monitoring protocol for watchful waiting and what should be the criteria for intervention?	**12:** For men with biopsy-diagnosed prostate cancer following a watchful waiting protocol, which combination of monitoring tests, testing frequency and clinical or other criteria for intervention achieve the best outcomes in terms of length and quality of life?

NHMRC Evidence Statement for clinical question 1: What risk factors can identify Australian men who are at high risk of prostate cancer or death from prostate cancer? Suggested risk factors include:

Family history

***PICO Question 1**: For Australian men, has a family history of prostate cancer been shown to be reliably associated with a 2.0-fold or greater increase in risk of occurrence of or death from prostate cancer when compared to men who do not have a family history of prostate cancer?*		**Report body of evidence tables**
1. Evidence base *(number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)*		
Twelve papers were included in the systematic review: 2 used linked population-wide data from Sweden (Gronberg 1996,1999); 6 used the Swedish Family Cancer Database (Bratt 2010, Brandt 2010,2012, Frank 2014, Hemminki 2011, Kharazmi 2012); 1 each used linked data from Utah in the US (Kerber 2005), Southern Sweden (Bratt 1997), Iceland (Eldon 2003) and Finland (Matikainen 2001). All of the 11 retrospective cohort studies (level III-2 evidence) that reported the risk of incident prostate cancer were of low quality with high risk of bias due to inadequate length of follow-up for the diagnosis of prostate cancer and none adequately controlled for potential confounding, notably with respect to PSA testing history that may be influenced by a positive family history. One nested case-control study (level II evidence) was also low quality with high risk of bias for similar reasons. Three of the retrospective cohort studies also reported the risk of death from prostate cancer and due to an inadequate length of follow-up were deemed to be low quality with a high risk of bias. **Grade D**	A	**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
	B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable') See body of evidence tables in report – results and p value (95% CI)*		
<u>Risk of prostate cancer diagnosis</u> Within levels of family history, the results are very consistent. Two studies	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**

that assessed family history in third degree relatives, reported standardised incidence ratios (SIRs) or risk ratios (RRs) of approximately 1.2 with 95% confidence intervals (CIs) including 1 or the lower limit close to 1. For family history in second degree relatives, the same two studies reported SIRs/RRs of 1.3-1.4 and 1.7 (with a lower confidence limit below 1) when the affected relative was diagnosed at a younger age (<68 years). Generally the SIR/RR was greater than 2.0 for affected first degree relatives. The main variation in these estimates was higher values for diagnosis at a younger age and lower values for diagnosis at an older age for either the affected family member or the man at risk. Risk also increased as the number of affected family members increased. <u>Prostate cancer mortality</u> There is reasonable consistency in the overall association between family history in a first degree relative and prostate cancer mortality with hazard ratios (HR) or Standardised Mortality Ratios (SMRs) ranging from around 2.0 to 2.75. Quite large associations were seen for multiple family members affected, especially at younger age. **Grade B**	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**

3. Clinical impact *See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Prostate cancer diagnosis and death are patient-relevant clinical outcomes (rated 1). <u>Risk of prostate cancer diagnosis</u> The magnitude of the association for family history for a second or third degree relative was either not clinically relevant (<2.0) or consistent with no association (95% CI includes 1). Generally the results for first degree relatives were clinically relevant (RR>2.0) for diagnosis at younger age of the family member or man at risk. Stronger associations were also observed for multiple family members contributing to the family history. <u>Prostate cancer mortality</u> The majority of studies found a clinically important increased risk of death	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**

from prostate cancer due to prostate cancer in first degree relatives (HR>2.0 and 95% CIs included only clinically important values). **Grade B**		
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*		
None of the studies were conducted in Australia and the largest body of evidence relates to Sweden. Generalisability will be affected by a number of factors including the use of PSA testing for screening asymptomatic men, genetic factors and prostate cancer treatment that may impact on mortality. All of these vary across the countries in which the studies were conducted and Australia. **Grade C**	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
This is difficult to judge as the association between family history and prostate cancer risk is potentially dependent on the effect of family history on PSA testing which in turn affects diagnosis of prostate cancer. The period of observation for diagnosis of prostate cancer preceded the PSA testing era (up to 1990) for only one of the studies. The association between family history and prostate cancer risk may be affected to some degree by increased PSA testing in the exposed group. Bratt (2010) reported stronger associations between family history and diagnosis of Stage 1c prostate cancer (which is detected after a PSA test) and diagnosis closer to the time of that of the family member (within 1 year). Therefore the applicability of the evidence is limited due to possible differences in PSA testing activity across different settings. **Grade C**	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*

The major factor in interpreting the evidence is the potential association between PSA testing and family history. None of the studies addressed this directly. One study reported that the risk of PSA detected prostate cancer (Stage 1c) was higher for men with a family history and that diagnosis of prostate cancer increased soon after the family member was diagnosed suggesting increased PSA testing in the exposed group.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	B	Substantial
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

Evidence statement:

Indicate any dissenting opinions

Risk of prostate cancer diagnosis

Men with a first-degree relative (father or brother) diagnosed with prostate cancer had approximately double the risk of being diagnosed with prostate cancer than men without this family history. This relative risk was higher for younger men, those whose first-degree relative was diagnosed at a younger age, and those with multiple first-degree relatives diagnosed with prostate cancer.

While there was some inconsistency across studies, the relative risk was less than 2 for those aged approximately 75–80 years or over.

The relative risk was 1.3 - 1.4 lower for men with only second- or third-degree relatives diagnosed with prostate cancer.

Uncontrolled confounding by PSA testing is likely to bias estimates of relative risk of prostate cancer incidence upwards.

Risk of death from prostate cancer

Men with a first-degree relative (father or brother) who was diagnosed with prostate cancer had a 2- to 3- fold increased risk of dying from prostate cancer compared with men without this family history.

For an asymptomatic man with a family history of prostate cancer in a first-degree relative, the risk of death from prostate cancer was greater if multiple first-degree relatives were affected, if his first-degree relative was diagnosed at a younger age, or if he was diagnosed at a younger age.

Compared with no family history, the relative risk of death from prostate cancer was 6- to 10- fold greater if multiple first-degree relatives were diagnosed with prostate cancer (two or three brothers, or two brothers and father), or if the brother and father had died from prostate cancer.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION**
No direct recommendations were formulated based on this evidence because it serves to identify risk, not to evaluate the effects of interventions to manage this risk. This evidence on risk informed the recommendations in *Chapter 2. PSA testing*.	

CONSENSUS-BASED RECOMMENDATION *If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.*
PRACTICE POINT *Points of guidance used to support evidence-based recommendations, where the subject matter is outside of the scope of search strategy, and which were formulated based on expert opinion using a consensus process*.

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*
The degree to which increased PSA testing of asymptomatic men with a family history of prostate cancer contributes to, or explains, their observed increased risk of a diagnosis of prostate cancer is unknown.

Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	**Not applicable**
Are there any resource implications associated with implementing this recommendation?	**Not applicable**
Will the implementation of this recommendation require changes in the way care is currently organised?	**Not applicable**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**Not applicable**

Chapter 2.1

NHMRC Evidence Statement Form for Clinical Question 2: *What methods of decision support for men about PSA testing increase men's capacity to make an informed decision for or against testing?*

<table>
<tr><td colspan="2">PICO Question 2: In men without evidence of prostate cancer does a decision support intervention or decision aid compared with usual care improve knowledge, decisional satisfaction, decision-related distress and decisional uncertainty about PSA testing for early detection of prostate cancer?</td><td>Report body of evidence tables</td></tr>
<tr><td colspan="3">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td rowspan="4">A total of 13 RCTs, 8 at high risk of bias and 5 at moderate risk of bias, examined the impact of decision support. Six studies compared a decision aid with information only (2 moderate risk of bias, 4 high risk of bias), 2 studies compared a decision aid with usual care (both high risk of bias) and 5 studies compared a decision aid with no intervention (2 high risk of bias, 3 moderate risk of bias).

All 13 reported the outcome of knowledge.

Ten of 13 studies considered the outcome of decisional conflict/distress. Six studies compared a decision aid with information only (4 high risk of bias, 2 moderate risk of bias), 1 study compared a decision aid with usual care (high risk of bias) and 3 studies compared a decision aid with no intervention (2 high risk of bias, 1 moderate risk of bias).

Four of the 13 studies considered decisional uncertainty. Three studies compared a decision aid with information only (2 high risk of bias, 1 moderate risk of bias), and 1 compared a decision aid with no intervention (moderate risk of bias).

Five of the 13 studies considered decisional satisfaction. Four studies compared a decision aid with information only (3 high risk of bias, 1 moderate risk of bias) and 1 compared two types of decision aids with usual care (high risk of bias).

Grade C</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias</td></tr>
<tr><td>D</td><td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td></tr>
<tr><td colspan="3">2. Consistency (if only one study was available, rank this component as 'not applicable') See body of evidence tables in report – results and p value (95% CI)</td></tr>
<tr><td rowspan="2">For the outcome of knowledge 11 of the 13 RCTs demonstrated a significant improvement in patient knowledge with a decision aid. One study only reported changes in knowledge within the intervention (significant improvement). Of the two studies that reported no significant</td><td>A</td><td>All studies consistent</td></tr>
<tr><td>B</td><td>Most studies consistent and inconsistency can be explained</td></tr>
</table>

changes in knowledge, one compared an entertainment approach to decision support and to an audio booklet. In this study the arms differed only in the decision aid arm having a values exercise and so this result may be due to the similarity of the information in each. The other study reporting no significant difference compared a decision aid with tailored information versus non-tailored information. **Grade B** **For the outcome of decisional conflict/distress** 7 of the 10 RCTs demonstrated a significant reduction in decisional conflict/distress with a decision aid. Three studies reported no changes in decisional conflict/distress between intervention and comparison. The first study that reported no changes in decisional conflict compared a decision counselling session to information only. In that study, participants in both study arms had the opportunity to discuss the issue of prostate cancer screening with their physician. This may have provided participants in both study arms the opportunity to allay any concerns with their physician. The second study that reported no changes in decisional conflict compared the use of a decision aid to no information about prostate cancer. Uptake of the decision aid was 30% amongst participants randomised to it. The final study reporting no significant difference in decisional conflict/distress compared men receiving a tailored decision aid to a non-tailored decision aid. **Grade B** **For the outcome of decisional uncertainty** 3 of the 4 RCTs demonstrated no difference between a decision aid and information only in reducing decisional uncertainty. Only one study, which compared a decision aid to no information, demonstrated a significant increase in decisional uncertainty. **Grade C** **For the outcome of decisional satisfaction** 3 of the 5 RCTs demonstrated a significant increase in decisional satisfaction with use of a decision aid. Of these three studies, one identified a short-term increase in decisional satisfaction, which was not evident at long-term follow-up (>12 months). Studies that did not demonstrate a significant benefit compared decision aids with audio booklet, leaflet or video. **Grade C**	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**
3. Clinical impact *See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results*		

varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)		
For the outcomes of knowledge, decisional distress and decisional satisfaction, clinical impact was variable across studies. Size of effect ratings in studies that found significant differences within the domain of knowledge ranged from (1) *"A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant benefit of the intervention."* to (3) *"The confidence interval does not include any clinically important benefits BUT does not include possible harm".* The size of effect rating in studies that found significant differences within the domain of decisional distress was assessed as (3) – *"The confidence interval does not include any clinically important benefits BUT does not include possible harm."* Size of effect ratings in studies that found significant differences within the domain of decisional satisfaction ranged from (1) *"A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant benefit of the intervention."*; to (2) *"The confidence interval includes clinically important and unimportant benefits BUT does not include possible harm."*; to (3) *"The confidence interval does not include any clinically important benefits BUT does not include possible harm".* **For the outcome of decisional uncertainty**, clinical impact was not assessed as there was no evidence of benefit reported in the studies. **Grade C**	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*		
Studies were undertaken with populations from the US, UK and Australia with some US studies including Hispanic and African American populations. The evidence is generalisable to well men in Western countries who are considering PSA testing with some reservations in considering how effective these interventions may be for men with low levels of education and low literacy; from a non-English speaking background; or other minority or cultural groups (e.g. Aboriginal and Torres Strait Islander populations).	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

Grade B		

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*

Application of the findings will require that the specific decision support interventions implemented in the respective RCTs are made widely and freely accessible for use in primary care and to the general public. This will require resourcing in the community and primary care setting. Four of the studies require discussion, or 'coaching', with a practice-nurse or health educator, which will only be available in clinical practices with such infrastructure. Three of the studies adopted web-based interventions, which would require a 'basic' level of computer literacy from patients. Health literacy and language barriers will require consideration across different settings. Geographic barriers to health services will also need to be considered in rural/regional settings. **Grade B**	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*

Because of the clinical heterogeneity between studies in terms of how outcomes were measured, pooling of published data for meta-analyses was not possible. Such outcomes may be pooled using a standardised mean difference; however, this method assumes that the differences in standard deviations among studies reflect differences in measurement scales and not real differences in variability among study populations [Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org]. This assumption is problematic in this review, given the heterogeneity between study participants. Additionally, comparisons differed, the design and implementation of the interventions were varied, and controls ranged from provision of generic information to no intervention. As a result a descriptive analysis of all studies was performed, given the possible impact of this clinical heterogeneity in pooling such diverse data.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	C	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats

5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

Evidence statement: *Indicate any dissenting opinions*

Use of a decision support intervention/decision aid, compared with usual care or minimally enhanced usual care, improved men's knowledge about the benefits and harms of PSA testing.

Use of a decision support intervention/decision aid, compared with usual care or minimally enhanced usual care, decreased the decisional conflict/distress men experienced when considering the benefits and harms of PSA testing.

Use of a decision support intervention/decision aid, compared with usual care or minimally enhanced usual care, improved men's satisfaction with their choice about whether or not to undertake a PSA test.

Use of a decision support intervention/decision aid, compared with usual care or minimally enhanced usual care, had no demonstrable benefit on the decisional uncertainty men experienced when considering the benefits and harms of PSA testing.

RECOMMENDATION	**GRADE OF RECOMMENDATION**
What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.	C

Offer evidence-based decisional support to men considering whether or not to have a PSA test, including the opportunity to discuss the benefits and harms of PSA testing before making the decision.

PRACTICE POINT

If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation (practice point) can be given.

Familiarity with the NHMRC fact sheet *PSA testing for prostate cancer in asymptomatic men. Information for health practitioners*,* which summarises evidence on the benefits and harms of PSA testing, should help health practitioners to accurately inform men about PSA testing.

* National Health and Medical Research Council. [PDF document on web]. Last updated 2014; Available from: https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/men4d_psa_testing_asymptomatic_men_140304.pdf.

Table 2: Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*

Table 3: Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care? Decision aids are not currently used routinely in primary care when discussing PSA testing. Usual care will need to incorporate the use of decision aids, either as part of the consultation with the main clinician (e.g. GP), a separate consultation with the primary care nurse (e.g. practice nurse) or health educator, or self-directed engagement with a decision aid. Community-wide strategies will be needed to increase public awareness of decision aids for PSA testing and to improve accessibility.	**YES**
Are there any resource implications associated with implementing this recommendation? Decision aids are produced across a variety of modalities, yet not all are readily accessible. It will be necessary to ensure that decision aids are available in primary care and to the community. Health professionals will need appropriate training in the use of these aids. For example, coaching or counselling of patients is a component of some decision aids.	**YES**
Will the implementation of this recommendation require changes in the way care is currently organised? Greater public awareness of existing decision aids will be required and community wide strategies to improve accessibility. Other decision aids incorporate a practice-nurse or health educator to 'coach' men. This type of decision aid will require incorporating a training program on PSA testing and counselling across nursing/health science courses, or up-skilling of existing professionals with the appropriate skills and knowledge as part of implementation.	**YES**
Are the guideline development group aware of any barriers to the implementation of this recommendation? Perceived lack of accessibility of decision aids by health professionals and consumers may be a barrier to its implementation. If the use of decision aids is to be incorporated into consultations in general practice, limited GP time may also be a barrier for implementation. These barriers may be potentially overcome by providing greater infrastructure and partnerships between primary practice, community care and peak bodies (e.g. the Royal Australian College of General Practitioners, Cancer Council Australia).	**YES**

Chapter 2.2

NHMRC Evidence Statement for clinical question 3: In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what should be the PSA testing strategies (age to start, level at which to declare a test abnormal and frequency of subsequent testing if the PSA level is normal) for men at average risk of prostate cancer and how should they be modified, if at all, for men at high risk of prostate cancer?

<table>
<tr><td colspan="2">PICO Question 3.1: For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what PSA testing strategies (with or without DRE), compared with no PSA testing or other PSA testing strategies, reduce prostate cancer specific mortality or the incidence of metastases at diagnosis and offer the best balance of benefits to harms of testing?</td><td>Body of evidence tables in Q4.1 report on RCT evidence and Q4.1 report on modelling evidence</td></tr>
<tr><td colspan="3">Evidence from randomized controlled trials</td></tr>
<tr><td colspan="3">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td rowspan="4">Four Level II studies and one Level III-1 (pseudo-randomized) study compared PSA testing with no PSA testing and reported mortality from prostate cancer as outcome. Each used a different PSA testing protocol. There were no randomised studies comparing different PSA testing protocols. Two Level II studies (PLCO and ERSPC) were at moderate risk of bias; the remaining studies were at high risk of bias. The ERSPC incorporated the results from 7 different centres including study core-group participants from Goteborg.
Three level I studies included most or all of these studies. These Level I studies were not included in the systematic review as none addressed the key question: “…what PSA testing strategies with or without DRE compared to no PSA testing or other PSA testing strategies reduce prostate cancer specific mortality or the incidence of metastases at diagnosis”.
Grade C
Two level II studies and one Level III-1 study reported results for metastatic prostate cancer at diagnosis as outcome. All were judged to be at high risk of bias.
Grade D</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or
II studies with a moderate risk of bias</td></tr>
<tr><td>D</td><td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td></tr>
</table>

2. Consistency *(if only one study was available, rank this component as 'not applicable') See body of evidence tables in report – results and p value (95% CI)*		
For prostate cancer mortality as outcome The ERSPC RCT showed a decreased relative risk (RR) of prostate cancer mortality of 0.79 (0.68 – 0.91) for screening men aged 55-69 years at a median follow-up of 11 years. Different ERSPC centres had different screening protocols with PSA testing every 4 years from 55 to 74 years of age and PSA ≥3.0ng/mL the indication for biopsy predominating. Within ERSPC a number of different screening protocols resulted in decreased prostate cancer mortality. At the Swedish centre (Goteborg) screening every 2 years until age 70 years with PSA ≥ 3.0 ng/mL from 1999 and ≥2.5 ng/mL from 2005 resulted in a decrease in prostate cancer mortality, RR 0.56 (0.39 – 0.82); as did screening every 4 years until age 75 years with PSA ≥ 4.0 or DRE+ or TRUS+ from 1993 to 1996 and PSA ≥ 3.0 ng/mL alone from 1997 at the Netherlands (Rotterdam) centre, RR 0.71 (0.52 – 0.96). Four other centres showed decreases in prostate cancer mortality. Only the smallest centre (N = 2,197 in Spain), which screened every 4 years for 12 years or until aged 75 years with PSA > 3.0ng/mL an indication for biopsy, showed no reduction in prostate cancer mortality, RR 2.15 (0.19 – 23.77). The 95% confidence intervals for the results of these ERSPC component studies substantially overlapped. The PLCO study (the other large study), which screened men aged 55-74 years annually for 6 years with a PSA level > 4.0ng/ml or abnormal DRE (first 4 years) as indications for biopsy and had a median follow-up of 11.5 years, did not observe a decrease in prostate cancer mortality, RR 1.09 (0.87 – 1.36). There were, however, high levels of prior PSA testing in participants, high levels of continuing PSA testing in men in the control arm and high levels of non-compliance with recommendation for biopsy all of which may have masked a benefit of this particular protocol. The pseudo randomised trial and the 2 earlier lower quality RCTs found no benefit for screening protocols dependant on DRE and TRUS as well as PSA (intention to treat analyses). The results of the ERSPC component studies show substantially similar results for PSA testing strategies varying with respect to age at commencement, 50 or 55 years, age at cessation, 69 or 74 years, frequency, every 2 or 4 years, and PSA threshold for biopsy, ≥3ng/mL or ≥4ng/mL. Together, they provide reasonably consistent evidence that PSA testing within this strategy range reduces prostate cancer mortality. While the lower RR for the Swedish centre (Goteborg) may indicate a greater effect for testing every two years from 50 years of age, collectively the ERSPC component studies provide only weak evidence that efficacy varied within their testing-strategy range. **Grade D**	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**

For metastatic prostate cancer at diagnosis as outcome Two of the three relevant studies reported a lower risk of metastatic prostate cancer at diagnosis in the intervention arm than in the control arm with RRs of 0.87 (0.66-1.14) PLCO (Screened annually from 55 years of age for 6 years PSA > 4.0ng/mL + DRE for 4 years) and 0.50 (0.41-0.62) ERSPC (Screened every 2 or 4 years from 50 or 55 years of age for ≥ 12 years or until 70 or 75 years of age, PSA ≥ 3.0 or 4.0ng/mL ± DRE). The third, the Norrkoping study (Screened every 3 years for 12 years from 50 years of age, DRE only first and second screens, DRE + PSA > 4.0ng/mL third and fourth screens) reported an RR of 1.12 (0.63-1.99). The RRs in the four ERSPC component centres included in the analysis varied between 0.40 and 0.59. There is moderately consistent evidence that PSA testing within the strategy range of these studies reduces incidence of metastatic prostate cancer at diagnosis. The apparently lower RR for the ERSPC than the PLCO and Norrkoping studies might indicate superiority of the PSA testing strategies used in the four component studies analysed, which differed from the PLCO and Norrkoping studies mainly in use of a PSA threshold for biopsy of ≥3ng/mL not ≥4 ng/mL. **Grade C**	NA	**Not applicable (one study only)**
3. Clinical impact *See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the*		

study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)		
There is lack of consistency among all relevant Level-II-evidence studies in the direction and size of clinical effects of PSA testing. This evaluation of clinical impact is based on ERSPC results since they are thought to be the most reliable. In men 55-69 years of age offered PSA testing every 2-4 years with a PSA threshold for biopsy of ≥3ng/mL, ERSPC reported the prostate cancer mortality rate ratio after a median 11 years of follow-up to be 0.79 (95% CI, 0.68 to 0.91; P=0.001) relative to men not offered PSA testing (Schroder et al 2012a). ERSPC estimated also that 1,005 men would need to be invited to testing and 37 would need to have prostate cancer diagnosed (NND) to prevent one death from prostate cancer. It is probable, however, that the prostate cancer mortality reduction due to testing has been underestimated and the NND overestimated because of the comparatively short follow-up and the inclusion of prostate cancer mortality experience from the beginning of testing in the analysis (Hanley et al 2011). **Grade C** Hanley JA. Measuring mortality reductions in cancer screening trials. Epidemiol Rev. 2011;33:36-45.	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*		
Study populations were located in the USA, Canada and continental western Europe. Study results, therefore, are generalisable to populations of men of predominantly western European ethnic origin and living in high income countries. Generalisability to men of lower socioeconomic status, non-English speaking background in Australia and Aboriginal and Torres Strait Islander populations, however, is uncertain. **Grade B**	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
PSA testing is already widespread in older Australian men, available annually with Medicare subsidy and has annual coverage of men 45-74 years of age in Australian that is not dissimilar to coverage of women in the relevant target age groups by Pap tests and screening mammography. **Grade A**	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Evidence from modelling studies		
1. Evidence base *(number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)*		
There were three modelling studies that met the inclusion criteria: one based on the MISCAN model of cancer screening (Heijnsdijk et al 2009, Heijnsdijk et al 2012) and two based on the Fred Hutchinson Cancer Research Center (FHCRC) microsimulation model of prostate cancer screening (Gulati et al 2013, Pataky et al 2014). In each the estimated benefit of screening on prostate cancer mortality was derived from results of the ERSPC Study. Each model was expertly assessed as to its strengths and limitations across the domains of specifications: natural history, screening or triage recommendations and behaviours, diagnostic pathways, invasive cancer (survival, treatment) and costs (reference to rating scale). The strengths of both models were considered to outweigh their limitations and both were found to adequately simulate prostate cancer incidence and mortality with the caveats that neither model incorporated realistic screening behaviours and the health outcomes presented for the MISCAN prostate cancer model were not adequately discounted in the assessment of quality adjusted life years gained or lost. Two modelling studies examined the outcomes of PSA testing for moderate and high risk men compared with low risk men (Howard et al 2009; Martin et al 2013). One was neither calibrated nor validated. It was developed to help individuals make informed decisions regarding PSA screening and as a result, although some assumptions that were made are appropriate for this context, they are not adequate for modelling population screening effectiveness (Howard 2009). As a result this model was considered inadequate for the purpose of assessing testing effectiveness and as such was not considered further. In the other model only prostate cancer mortality not the natural history parameters were calibrated (Martin 2013). **Grade – NA (NHMRC levels of evidence do not currently encompass modelling studies)**	A	**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
	B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable') See body of evidence tables in report – results and p value (95% CI)*		
Prostate cancer deaths Between the 3 models, 47 different PSA testing protocols varying in PSA threshold, testing frequency and testing age range were modelled from which the outcomes of probability of one or more false positive (FP) PSA test, probability of death from prostate cancer prevented; mean months of life gained per man tested; number of prostate cancers needed to diagnose to prevent one death from prostate cancer (NND) and mean months of life gained per man diagnosed as a result of testing could be derived.	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**

Martin showed that for higher risk men PSA testing resulted in higher number of lives saved compared with men at average risk. This study did not compare the effects of different testing protocols in higher risk men. **Metastatic disease at diagnosis** From Heijnsdijk 2009 using the MISCAN model it was possible to derive data on the effects of different testing protocols on the probability of metastatic disease at diagnosis. Neither of the other modelling studies addressed this outcome. **Quality adjusted life years** Using a PSA threshold of 3.0ng/mL every four years from 55 to 69 years of age across the lifetime of men offered testing was associated with a loss of 1.9 QALY per 1000 men offered testing (Pataky et al 2014). The MISCAN model, however, using an unspecified PSA threshold and quite different utility obtained a more favourable result for QALYs, +41 per 1,000 men offered testing (Heijnsdijk et al 2012). These findings are inconsistent. **NA – (Differences in the sets of screening protocols assessed by the studies make consistency impossible to evaluate meaningfully)**	NA	**Not applicable (one study only)**
3. Clinical impact *See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Prostate cancer deaths These modelled outcome estimates provide a basis for selecting the protocol that, on present evidence, achieves the best balance between the benefit of prevented prostate cancer deaths, and the harms of PSA testing, such as the probability of ≥1 FP and, inversely, the outcome of mean months of life gained per man diagnosed. The latter reflects the expectation life of gained by each man diagnosed with and treated for prostate cancer as a result of PSA testing. It is strongly influenced by the probability of over-diagnosis; the more men there are over-diagnosed, the more there are to "share" the expectation of extension of life with men who actually experience the extension due to early diagnosis and treatment of a cancer that would otherwise have killed them. In general terms and as would expected as modelled probability that death from prostate cancer is prevented increases probability of <u>≥</u>1 FP increases and the mean months of life gained per man diagnosed falls due to the increasing number needed to diagnose to prevent a death from prostate cancer. Thus the clinical impact of each testing protocol assessed by these models depends on the balance between these three parameters	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**

and no single statement of clinical impact can be made for each model. In practical terms, therefore, it would be appropriate to attribute to the models the clinical impact of the RCTs on which they are based. **Grade C** **Metastatic disease at diagnosis** Testing every 4 years from ages 55 to 70 years using a PSA threshold of 3.0ng/mL was associated with a reduction of 2.1 men undergoing palliative therapy for metastatic disease at diagnosis at a cost of 150 additional unnecessary biopsies per 1000 men tested. Extending the testing age range to 75 years or increasing the frequency of testing to annually resulted in modest increases in the reduction of metastatic disease at diagnosis accompanied by increases in the number of additional unnecessary biopsies. This study did not model PSA levels of 4.0ng/mL or age percentiles as thresholds for biopsy or report life years or months of life gained. **Quality adjusted life years** The quite inconsistent results of the two studies addressing this outcome prevents any judgement as to its clinical significance.		

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*		
The MISCAN studies were based in the Dutch population and calibrated mainly to Dutch and other European data; participation in testing was assumed at 100% in Heijnsdijk et al (2009) and 80% in Heijnsdijk et al (2013). The FHCRC studies were based primarily in the US population, although Pataky et al used initial treatment data for British Columbia, and were calibrated to US data: while not explicitly stated, it is thought that both assumed 100% screening participation. None were directly generalisable to the Australian population as none were developed and calibrated for the Australian context, or validated in Australia. **Grade B**	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
PSA testing is already widespread in older Australian men, available annually with Medicare subsidy and has annual coverage of men 45-74 years of age in Australian that is not dissimilar to coverage of women in the relevant target age	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**

groups by Pap tests and screening mammography. **Grade A**	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

RCTs

Present evidence is inconsistent as to whether PSA testing affects the risk of dying from prostate cancer (NHMRC 2014). The major inconsistency lies in the difference in findings between the two largest and most recent studies, one of which, ERSPC, found that PSA testing (mainly without DRE) reduced mortality from prostate cancer (RR 0.79, 0.68-0.91) while the other, PLCO (two thirds with DRE), did not (RR 1.09, 0.87-1.36). There is, though, consistency among the findings of individual ERSPC centres. There is concern, too, about the accuracy of the PLCO findings because of the high level of prior PSA testing in men recruited to the study, the high level of continuing PSA testing in men in the control group and the high level of non-compliance with recommendations for biopsy. While these important factors are documented only for one ERSPC centre (and are more favourable for that centre than PLCO), they appear less likely to have influenced ERSPC results given that all of them would have tended to produce bias towards a "no protective effect" finding. Therefore, reliance was placed on the ERSPC finding of a modest effect of PSA testing in reducing prostate cancer mortality in formulating guideline recommendations for this Key Question. This position gains some support from the consistent evidence that PSA testing reduces risk of prostate cancer that was metastatic at diagnosis. While such a finding could be simply a result of lead-time bias, additional evidence suggests that this is not so. The cumulative risk of prostate cancer metastases has remained lower out to 12 years of follow-up in men who had PSA testing than in men who did not in ERSPC centres that collected this follow-up information (Schroder et al 2012b).

While protocols followed by the ERSPC centres varied, all centres included men 55-69 years of age (the core group on which ERSPC's most recent analysis has been primarily based), all had a recommended screening interval of 4 years except Sweden (2 years), a majority adopted a PSA cut-off of $\geq$3ng/mL without DRE from the beginning or from the second screening round (having begun with $\geq$4ng/mL + DRE + TRUS) (the minority continued with a cut-off of $\geq$4ng/mL and a policy of triaging lower values, 2.5 or 3.0 to 3.9ng/mL, using DRE or % free PSA alone or DRE + TRUS) and cessation of testing at 70-75 years of age. Therefore, ERSPC results can be taken as indicative of the outcome of a policy of 2 to 4 yearly testing of men 55-69 years of age, referring men for biopsy when total PSA was $\geq$3ng/mL and ceasing screening at 70 -75 years of age. The published results of different ERSPC centres generally give little indication of differences in effect from variation in testing policy. It is plausible however to infer superiority of the Swedish centre's policy: broadly, testing from 50 years of age at 2-year intervals, a PSA cut-off of 2.9ng/mL (1999-2004) and cessation of screening at 70 years of age. This inference is made from the size of the relative risk from the Swedish study, RR 0.56 (0.38-0.83), the upper 95% confidence bound of which is just a little above the ERSPC RR point estimate of 0.79 and, correspondingly, the greater difference in cumulative hazard of death from prostate cancer (Nelson-Aalen method) to 14 years between intervention and control groups in the Swedish study, -0.0039, and the ERSPC as a whole, -0.0024 (estimates made from Figure 3 in Hugosson et al 2010 and Figure 2 in Schroder et al 2012a). In addition, the RR of prostate cancer death in the Gøteborg centre was the same, whether based on the full study population tested at age 50–69 years (RR 0.56; 95% CI 0.39–0.82), or its ERSPC core group members tested at age 55–69 years (RR 0.56; 95% CI 0.38–0.83).

Modelling Studies *PSA testing protocols*

In considering the information provided by the modelling studies, for each study the modelled protocol that was most nearly the same as that of the ERSPC or the Goteborg study was chosen as the base protocol with which other protocols were compared with respect to probability that prostate cancer death is prevented, probability a man would have $\geq$1 FP and the mean months of life gained per man diagnosed. Modelled protocols were considered as alternatives to

the ERSPC or Goteborg study testing protocols if they appeared to offer an improvement in the balance of benefit to harm, as reflected in changes in these variables. In this context increase in probability that prostate cancer death is prevented indicates benefit, increase in % ≥1 FP reflects harm and mean months of life gained per man diagnosed reflects the balance of benefit from lengthened life to the harm from over-diagnosis.

Modelling Studies *Modification of protocol for high risk men*

Martin et al (2013) compared estimated cost per QALY of PSA testing using a single protocol in low, intermediate and high risk men. It provides no information that could be used to inform modification of a PSA testing protocol for high risk men.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	**Rating**	**Description**
1. Evidence base		
RCTs	**C** (mortality) **D** (metastases at diagnosis)	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias Level IV studies or Level I to III studies/SRs with a high risk of bias
Modelling studies	NA	NHMRC levels of evidence do not currently encompass modelling studies
2. Consistency		
RCTs	**D** (mortality) **C** (metastases at diagnosis)	Evidence is inconsistent Some inconsistency, reflecting genuine uncertainty around question
Modelling studies	NA	Differences in the sets of screening protocols assessed by the studies make consistency impossible to evaluate meaningfully
3. Clinical impact		
RCTs	**C**	Moderate
Modelling studies	**C**	Moderate
4. Generalisability		
RCTs	**B**	Evidence directly generalisable to target population with some caveats
Modelling studies	**B**	Evidence directly generalisable to target population with some caveats
5. Applicability		

RCTs	**A**	Evidence directly applicable to Australian healthcare context
Modelling studies	**A**	Evidence directly applicable to Australian healthcare context

Evidence statement: *Indicate any dissenting opinions*

RCTs

For men aged 55–69 years without a prostate cancer diagnosis or symptoms that might indicate prostate cancer, prostate cancer-specific mortality was reduced by PSA testing every 2–4 years using total PSA > 3.0 ng/mL as the threshold for biopsy. The reduction in mortality may be greater in men aged 50-69 years offered testing every 2 years.

Modelling studies

While the modelling studies were not considered to provide evidence independent of the empirical data on which they were based, they offer a guide to how changes in specific parameters (age, testing interval and threshold for biopsy) affect the balance of benefits to harms. Modelled comparisons suggested that change in starting age from 55 to 50 years and a reduction in testing interval from 4 years to 2 years increases the number of prostate cancer deaths prevented by 18 per 10,000 men at an additional cost in overdiagnosed cancers of 1%; that is, an extra 5.6 overdiagnosed cancers per extra prostate cancer death prevented. There is also a reduction in mean months of life gained per man diagnosed of 10.2 months, but the mean months of life gained per man diagnosed for the protocol starting at 50 years of age and testing every 2 years remains reasonably high at 34.1 months.

Modelled comparisons also suggested that the number of over-diagnosed cancers per prostate cancer death prevented in men tested at ages 70–74 (7.0 to 9.0 in three relevant protocols) when testing ended at 74 years instead of 69 years was substantially more than the average number of over-diagnosed cancers per prostate cancer death prevented when testing only from 50 to 69 years (3.2 to 4.1 for the same protocols). The mean months of life gained per man diagnosed with testing at ages 70–74 was also about one third less than the average when testing only to 69 years.

A modelled comparison of testing 2-yearly with testing 4-yearly (with age held constant at 50–74 years and threshold constant at ≥ 3.0 ng/mL) estimated a 0.13 percentage-point gain in the probability of prostate cancer death prevented at the expense of a 0.7 percentage-point increase in the probability of ≥ 1 false positive test, a 0.7 percentage-point increase in the probability of over-diagnosis of prostate cancer, and a 0.5 month reduction in the mean months of life gained per man diagnosed with prostate cancer.

Modelled comparisons suggested there was little benefit gained from starting regular testing at age 40 rather than at age 50 (an increase of 0.02 to 0.04 percentage points in the probability that prostate cancer death is prevented).

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION** C

For men at average risk of prostate cancer who have been informed of the benefits and harms of testing and who decide to undergo regular testing for prostate cancer, offer PSA testing every 2 years from age 50 to age 69, and offer further investigation if total PSA is greater than 3.0 ng/mL.

CONSENSUS-BASED RECOMMENDATION *If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.*
If the necessary data become available and the required processes put in place to ensure effective implementation, consider replacing > 3.0 ng/mL with > 95th percentile for age as the criterion for further investigation.
PRACTICE POINT *Points of guidance used to support evidence-based recommendations, where the subject matter is outside of the scope of search strategy, and which were formulated based on expert opinion using a consensus process*.

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*

Implementation of recommendation

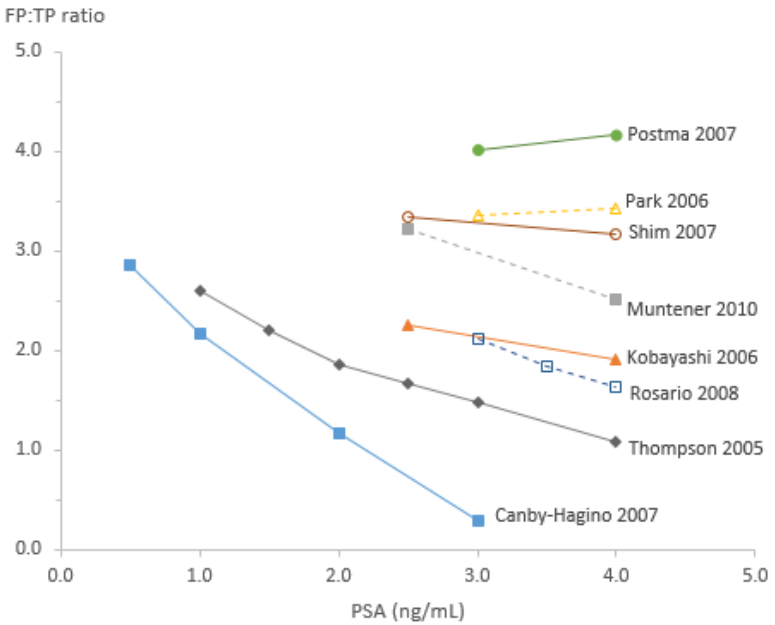
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care? Despite a recommendation by the Royal College of Pathologists of Australasia to repeat PSA testing at intervals of 2 years or 4 years, depending on the result, it is probable that many men currently having PSA testing are tested annually. Therefore, the recommendation to offer PSA testing every 2 years in men aged 50–69 years who wish to undergo testing after being informed of the risks and potential benefits could lead to less frequent testing and fewer false positive tests.	**YES**
Are there any resource implications associated with implementing this recommendation? Implementation of the recommendation for a 2-year interval between PSA tests for men aged 50–69 years who wish to undergo testing could reduce the costs of testing, reduce the frequency of false positive tests and reduce consequent investigation and its cost.	**YES**
Will the implementation of this recommendation require changes in the way care is currently organised? Ideally, reliable information on 95th percentiles of PSA for individual years of age or age groups not wider than 5 years will be required and routinely reported for PSA tests on men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer.	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

NHMRC Evidence Statement for clinical question 3: *In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what should be the PSA testing strategies (age to start, level at which to declare a test abnormal and frequency of subsequent testing if the PSA level is normal) for men at average risk of prostate cancer and how should they be modified, if at all, for men at high risk of prostate cancer?"*

<table>
<tr><td colspan="2">PICO Question 3.2: For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what PSA testing strategies with or without DRE perform best in detecting any prostate cancer or high grade prostate cancer diagnosed in biopsy tissue?</td><td colspan="2">Report body of evidence tables</td></tr>
<tr><td colspan="4">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td colspan="2" rowspan="3">Eight level III-2 studies at moderate risk of bias comparing the performance characteristics of PSA thresholds less than or equal to 4.0 ng/ml met the inclusion criteria.
In one study, the placebo arm of the Prostate Cancer Prevention Trial (PCPT), men were biopsied regardless of PSA level or DRE enabling comparisons of sensitivity and specificity at different PSA thresholds (Thompson et al.,2005). Potential verification bias was considered in the PCPT study and shown not to be an issue (Thompson 2005).
In 6 studies men were biopsied if their PSA levels exceeded specified thresholds (Park et al., 2006; Rosario et al., 2008, Muntener et al., 2010, Kobayashi et al., 2006, Shim et al.,2007 and the ERSPC (Schroder et al.,2012; Postma et al., 2007, Roobol et al., 2013; Kilpelainen et al., 2011)) and in one study men with a</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias</td></tr>
</table>

family history of prostate cancer and a PSA below a PSA threshold were biopsied; in this study no data was available for screen positives(Canby–Higano 2007). These studies provided estimates only of increases in cancers detected (true positives) and unnecessary biopsies (false positives) with decreasing PSA thresholds. Calibration could be inferred for 2 studies (Shim 2007; Park 2006). Two studies did not report the PSA assay used (Rosario 2008; Muntener 2010). Six studies (Thompson 2005; Kobayashi 2006; Rosario 2008; Park 2006: Muntener 2010; ERSPC (Gosselaar 2008)) reported cancer yield stratified by Gleason Score. **Grade D**	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable') See body of evidence tables in report – results and p value (95% CI)*		
Comparisons between studies in terms of absolute numbers were limited due to differing biopsy protocols, populations and PSA assays and their calibration and thus this review focuses on the effects of varying thresholds within studies. In all 8 studies lowering the PSA threshold increased cancer detection at a cost of increased unnecessary biopsies. The FP:TP ratio appeared to increase by about 1 as the PSA cut-off was reduced from 4ng/mL to 2ng/ml and, more rapidly, by about 1 again as the cut-off was reduced from 2ng/mL to 1ng/mL. The FP:TP ratio varied across the studies from 1.1 to 4.2 at a PSA cut-off of 4ng/mL (Figure 1).	A	**All studies consistent**

Figure 1. Plots of the FP:TP ratios at each PSA cut-off level in the 8 studies reviewed.



Grade B

B	**Most studies consistent and inconsistency can be explained**
C	**Some inconsistency, reflecting genuine uncertainty around question**
D	**Evidence is inconsistent**
NA	**Not applicable (one study only)**

3. Clinical impact *See body of evidence tables in report - p value (95% CI), size of effect and relevance of evidence (Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Greatest weight was given to the PCPT (Thompson 2005) as it provided the most complete data, and the ERSPC (Postma 2007) as it reported data for a multiply screened cohort. **Lowering the PSA threshold from 4.0 to 3.0ng/mL** resulted in 2.17 to 3.77 additional unnecessary biopsies for every additional cancer detected (Postma 2007; Park 2006; Rosario 2008; Thompson 2005): The value of 3.77 was based on 14 additional cancers detected and 52 additional unnecessary biopsies per 1000 men screened in the Rotterdam component of the ERSPC (Postma 2007). The value 2.17 was accompanied by an 11.7 percentage point increase in sensitivity based on 26 additional cancers detected per 1000 men screened, and a 7.1 percentage point decrease in specificity based on and 56 additional unnecessary biopsies per 1000 men screened in the placebo arm of the PCPT (Thompson 2005). For men aged over 69 years the gains in sensitivity were greater for a similar decrease in specificity (Thompson 2005). **Lowering the PSA threshold from 3.0 to 2.0ng/mL** resulted in a further 20.4 percentage point increase in sensitivity and a 14.2 percentage point decrease in specificity with 2.48 additional unnecessary biopsies for every additional cancer detected (Thompson 2005). Similar effects were seen in a cohort of men with PSA less than 4.0 ng/mL and a family history of prostate cancer (Canby–Higano 2007). **Lowering the threshold from 4.0 to 2.5 ng/mL or from 3.0 to 2.5 ng/m**L resulted in 2.26 and 2.39 additional unnecessary biopsies for every additional cancer detected respectively (Thompson 2005). **Modification by cancer grade and patient's age** The sensitivity for detecting higher-grade (Gleason score >6) cancers increased by 17.2 percentage points when the PSA threshold was lowered from 4.0 ng/mL to 3.0ng/mL, and this increase was greater than that for the detection of any cancer (Thompson 2005).The increase in sensitivity for detection of higher grade cancers was even higher for men over 69 years of age, 23.0 percentage points. In contrast a reduction from 3.0 to 2.0 ng/mL did not result in greater increases in sensitivity for higher grade disease (Thompson 2005). **Grade D**	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*		
The most complete data came from control participants in the US PCPT (Thompson 2005) in which eligible participants had PSA levels of 3.0 ng/mL or less, a normal DRE and a American Urological Association symptom score less than 20 prior to screening. These specifications may limit the generalizability to a general population of men. **Grade B**	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
As PSA measurements vary with assay type and calibration, the absolute values for PSA measurements in the PCPT (Thompson 2005) may not be directly applicable to the Australian context. In Australia over 95% of laboratories use the WHO calibration and the most commonly used assays are the Roche and Abbott assays. In the PCPT Hybritech PSA assays were used and how these assays were calibrated was not reported. **Grade C**	A	**Evidence directly applicable to Australian**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	D	Slight/Restricted
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

Evidence statement: *Indicate any dissenting opinions* As the PSA threshold for referral to biopsy was reduced from 4.0 ng/mL the ratio of false positive to true positive tests increased. The rate of increase in this ratio appeared to become greater as the threshold PSA level was progressively reduced. Thus, any reduction made in PSA threshold from 4.0 ng/mL was accompanied by an increasingly adverse trade-off of more true positive tests (greater sensitivity) for more false positive tests (lower specificity).	
RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION**
Recommendation is unchanged from that in PICO 1: For men at average risk of prostate cancer who have been informed of the benefits and harms of testing and who decide to undergo regular testing for prostate cancer, offer PSA testing every 2 years from age 50 to age 69, and offer further investigation if total PSA is greater than 3.0 ng/mL.	

CONSENSUS-BASED RECOMMENDATION *If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.*
PRACTICE POINT *Points of guidance used to support evidence-based recommendations, where the subject matter is outside of the scope of search strategy, and which were formulated based on expert opinion using a consensus process*.

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*

Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	**NO**
Are there any resource implications associated with implementing this recommendation?	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

NHMRC Evidence Statement for clinical question 3: *In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what should be the PSA testing strategies (age to start, level at which to declare a test abnormal and frequency of subsequent testing if the PSA level is normal) for men at average risk of prostate cancer and how should they be modified, if at all, for men at high risk of prostate cancer?*

<table>
<tr><td colspan="2">PICO Question 3.3: For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer does a PSA level measured at a particular age in men assist with determining the recommended interval to the next PSA test?</td><td>Report body of evidence tables</td></tr>
<tr><td colspan="3">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td rowspan="4">Two level III-2 studies reported the risk of prostate cancer mortality for PSA levels at ages less than 56 years. One was a retrospective cohort study of participants in the Copenhagen City Heart study (Orsted 2012). This study was at moderate risk of bias for PSA levels at ages 45-49 and 50-54 years and at high risk of bias for PSA levels at ages less than 45 years. The second study was the larger Malmo Preventive Study (Vickers 2013). This study was at high risk of bias. It used a consisted of a respective cohort design to assess of the risk associated with PSA levels at age 51-55 years, and a nested case-control design to assess the risk associated with PSA levels at 37.5 – 42.5 years and 45- 49 years. For the latter design absolute risk was calculated using imputed data and the imputation was validated in the cohort group.

This review focussed on men from ~40 to 55 years of age at testing and a maximum of 20 years follow-up since its primary purpose was to obtain data relevant to PSA testing over about a 20 year period from first testing. In the Danish study blood was sampled in 1981-1983 and PSA testing introduced into clinical practice in Denmark in 1995 thus informal PSA screening was unlikely to have affected 10 year risks of prostate cancer mortality. In the Swedish study blood was sampled from 1974 to 1984 for the case control study and 1980 – 1990 for the cohort study. On the basis of Swedish PSA testing data the authors assumed that screening rates remained low (up to 5%) up until 1998, (8 years prior to end of study) and therefore that it was unlikely that any informal or opportunistic screening could have substantively affected prostate cancer mortality 15 and 20 years after PSA measurement. Thus inferences about prostate cancer mortality in relation to prior PSA test values in these studies may be invalid for follow-up periods beyond 10-20 years. Given their retrospective designs baseline PSA levels could not have affected prostate cancer diagnosis in either of these studies.
Grade D</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or
II studies with a moderate risk of bias</td></tr>
<tr><td>D</td><td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td></tr>
</table>

2. Consistency *(if only one study was available, rank this component as 'not applicable') See body of evidence tables in report – results and p value (95% CI)*		
Both studies showed that as the baseline PSA level rose the risk of prostate cancer mortality rose. The risk increased with increased age range for the same PSA level (Orsted 2012) and baseline PSA levels rose with baseline age (Vickers 2013). Comparison of cumulative risk increases to 10 years in Orsted et al (2012) and to 15 years in Vickers et al (2013) within comparable age groups and comparable PSA bands indicates that the increases are similar but a little higher in Vickers et al as would be expected from the longer follow-up. **Grade B**	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**

3. Clinical impact *See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There is no intervention as such in the studies covered by this evidence review. Therefore, there is no clinical impact to be assessed. **Grade – NA (not applicable)**	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*		
Danish and Swedish populations (not primarily high risk populations) who were followed up primarily in the pre PSA era when more effective radical treatments may have been less readily available or offered than in Australia today. However given that these are populations of European origin, as a majority of Australians are, and the studies relate primarily to the natural history of a disease in relation to a risk indicator, they may reasonably be taken to represent the evolution of prostate cancer risk in Australia in relation to PSA levels measured on blood taken prior to the beginning of use of PSA for the early detection of prostate cancer. In principle, this is still the expected risk of prostate cancer in the absence of PSA testing. **Grade C**	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Given the present extent of PSA testing for early detection of prostate cancer in Australia, this body of evidence has the potential to inform specification of	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**

PSA testing protocols that achieve a better balance of benefits to harms than there is likely to be in present testing practice. **Grade B**	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *Indicate here any other factors that you took into account when assessing the evidence base for example, issues that might cause the group to downgrade or upgrade the recommendation.*

No other factors were considered in this context.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	NA	Not applicable. The evidence does not address the efficacy of an intervention
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

Evidence statement: *Indicate any dissenting opinions*

In men 37.5–42.5 years of age, absolute differences in cumulative risk for prostate cancer between men with PSA levels in the top quarter and the top 10% of the PSA distribution and men with PSA levels in the bottom quarter of the distribution were small at 15 years of follow-up (+0.1% and +0.5%) and a little more at 20 years of follow-up (+0.2% and +0.8%).

In men 45–49 years of age, these differences were greater (+0.2% and +0.7%) at 15 years of follow-up and more so at 20 years of follow-up (+0.9% and +2.2%). They were greater again in men 51–55 years of age: 1.5% and 3.1% at 15 years and 2.4% and 5.1% at 20 years.

RRs for prostate cancer death in men in the highest quarter and highest tenth of PSA, relative to men in the lowest quarter, out to 20 and 25 years of follow-up after an index PSA test varied little by age when the blood for PSA testing was taken.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION**

Recommendation is unchanged from that in PICO 3.1: For men at average risk of prostate cancer who have been informed of the benefits and harms of testing and who decide to undergo regular testing for prostate cancer, offer PSA testing every 2 years from age 50 to age 69, and offer further investigation if total PSA is greater than 3.0 ng/mL.

CONSENSUS-BASED RECOMMENDATION *If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.*
Do not offer PSA testing at age 40 years to predict risk of prostate cancer death
For men younger than 50 years who are concerned about their risk for prostate cancer, have been informed of the benefits and harms of testing and who wish to undergo regular testing for prostate cancer, offer testing every 2 years from age 45 to age 69 years. If initial PSA is at or below the 75th percentile for age, advise no further testing until age 50. If initial PSA is above the 75th percentile for age, but at or below the 95th percentile for age, reconfirm the offer of testing every 2 years. If a PSA test result before age 50 years is greater than the 95th percentile for age, offer further investigation. Offer testing from 50 years of age according to the protocol for all other men who are at average risk of prostate cancer
Advise men 70 years or older who have been informed of the benefits and harms of testing and who wish to start or continue regular testing that the harms of PSA testing may be greater than the benefits of testing in men of their age.

For men whose risk of prostate cancer is estimated to be at least 2.5–3 times higher than average due to the presence of risk factors (e.g. a brother diagnosed with prostate cancer, particularly if younger than 60 years at diagnosis), and who decide to undergo testing after being informed of the benefits and harms, offer testing every 2 years from age 45–69 years.

For men whose risk of prostate cancer is estimated to be at least 9–10 times higher than average due to the presence of risk factors (e.g. father and two brothers diagnosed with prostate cancer), and who decide to undergo testing after being informed of the benefits and harms, offer testing every 2 years from age 40–69 years.

If initial PSA is at or below the 75th percentile for age, advise no further testing until age 50.

If initial PSA is above the 75th percentile for age, but at or below the 95th percentile for age, reconfirm the offer of testing every 2 years.

If a PSA test result before age 50 years is greater than 95th percentile for age, offer further investigation.

Offer testing from 50 years of age according to the protocol for men who are at average risk of prostate cancer.

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*
None

Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	**YES**
Are there any resource implications associated with implementing this recommendation? Some additional PSA testing	**YES**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? Accurate estimates of 95th percentile of PSA required for individual years of age in the 40s	**YES**

Chapter 2.3

NHMRC Evidence Statement for clinical question 4: *How best can DRE be used, if at all, in association with PSA testing?*

<table>
<tr><td colspan="2">PICO Question 4: For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what is the incremental value of performing a digital rectal examination (DRE) in addition to PSA testing in detecting any prostate cancer?</td><td>Report body of evidence tables</td></tr>
<tr><td colspan="3">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td rowspan="4">A systematic search identified 5 studies at moderate risk of bias. However, only one study (Thompson 2007) subjected all men to biopsy and was of sufficient size to provide reliable estimates of differences in sensitivity and specificity when using DRE as an additional indication for biopsy. This key study was generally well conducted but with uncertainty about whether of DRE, PSA tests and pathologist review of biopsy specimens were performed blind.

All five studies reported the difference in true and false positives that would result from using both DRE and PSA as biopsy indications compared with using PSA only. Four of these reported cancer yield stratified by Gleason Score. The fifth study was included as it had used a biopsy scheme of 12 cores and the population consisted of healthy screening volunteers.
The PSA cut-off for biopsy was greater than (or) 4.0 ng/ml in all five studies. One study (Thompson 2007) also provided data on lower cut-offs (>3.5, >3.0, >2.5, >2.0 ng/ml), however, respective information on Gleason Score was not available.
In three studies men underwent 6-monthly or annual screening, whereas two studies reported data from a single set of tests only.
Grade D</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias</td></tr>
<tr><td>D</td><td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td></tr>
<tr><td colspan="3">2. Consistency (if only one study was available, rank this component as ‘not applicable’) See body of evidence tables in report – results and p value (95% CI)</td></tr>
</table>

Thompson is the key large study, which showed an incremental gain of DRE in addition to PSA testing, but at a cost of nearly twice the number of false positives. The other studies are in rough agreement in terms of direction and magnitude of accuracy of the incremental gain, though differences in verification and testing frequency prevent pooling and limit direct comparison. The number of false positives for every additional cancer detected is even higher in these studies. This is also true for detection of higher-grade cancers. **Grade C**	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**
3. Clinical impact *See body of evidence tables in report - p value (95% CI), size of effect and relevance of evidence (Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The clinical impact is a moderate increase in detection of any prostate cancer with a greater increase in false positives. The key study estimated an incremental gain from DRE over PSA (at a cut-off of 3.0 ng/ml): a relative	A	**Very large**
	B	**Substantial**
	C	**Moderate**

sensitivity increase of 12% but with a specificity decline of 7%. In absolute numbers per 1000 men repeatedly screened this would mean 26 more cancers found but with 52 more false positives going for biopsy At a PSA cut-off of 4.0 ng/ml the increase in sensitivity and decline in specificity was similar at 14% and 7% respectively, with an additional 30 more cancers detected and an additional 58 more unnecessary biopsies per 1000 men screened. At this cut-off detection of GS>7 cancers was shown to increase by 3 per 1000 with 85 more false positives. The proportions of additional cancers detected by DRE with GS>7 ranged from 3.3% to 13.6% and with GS>6 from 23.2% (Thompson 2007) to 34.0% (Fowler 2000). This was a slightly lower percentage of higher-grade cancers when compared to cancers detected by a PSA-only protocol. However, it nonetheless meant a 25.4% (GS>7) or 15.0% (GS>6) increase in sensitivity for detecting higher-grade disease with a concurrent reduction in specificity of 8.6% (GS>7) or 8.5% (GS>6). **Grade C**	D	**Slight/Restricted**

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*

There are modest differences across populations which may alter the absolute increase in detection. In particular, the men in the study were over 55 years old (and would have a higher incidence) who had an initial PSA < 3.0 ng/mL (and would have a lower incidence). **Grade B**	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
A key caveat would be that the use of DRE in Australian general practice is likely to have lower accuracy than in the trial setting of the key study as those performing DREs in the Thompson study may have benefited from specific training and had greater experience in performing DRE compared to primary care givers performing DRE in Australia. **Grade C**	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*		
EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*		
Component	**Rating**	**Description**
1. Evidence base	D	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	C	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

Evidence statement: *Indicate any dissenting opinions*

There is evidence from one large moderate-quality study that the addition of DRE to PSA testing provided an incremental gain in prostate cancers detected, but at a cost of two or more extra false positives per cancer detected. The study also showed that similar gains could be made by lowering the PSA threshold. DRE accuracy is likely to be lower outside the trial setting of this study.

The sensitivity for detecting high-grade cancers was increased when DRE was added to PSA testing. However, the gain in detecting higher-grade cancers by adding DRE was generally not greater than that for lower-grade cancers.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION** C
In asymptomatic men interested in undergoing testing for early diagnosis of prostate cancer, digital rectal examination is not recommended as a routine addition to PSA testing in the primary care setting.	

CONSENSUS-BASED RECOMMENDATION

If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.

PRACTICE POINT

Points of guidance used to support evidence-based recommendations, where the subject matter is outside of the scope of search strategy, and which were formulated based on expert opinion using a consensus process.

- Although DRE is not recommended as a routine test for men who, after advice, wish to be tested for the presence of prostate cancer, it will still be an important part of the man's assessment on referral to a urologist or other specialist for further assessment prior to consideration for biopsy.

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*

Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care? Current guidelines for preventive care in general practice recommend both DRE and PSA for men who choose to undergo prostate cancer screening after being fully informed of the risks, benefits and uncertainties. Therefore, implementation of this recommendation would alter current practice.	**YES**
Are there any resource implications associated with implementing this recommendation? Implementation of this recommendation would have no significant resource implications. It may slightly reduce the consultation time for men attending primary care.	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? No barriers to the implementation of this recommendation are foreseen.	**NO**

Chapter 2.4

NHMRC Evidence Statement for clinical question 5: *What age or health status criteria should be used to identify men who would be unlikely to live long enough to benefit from PSA testing and who, in consequence, would not be offered PSA testing?"*

<table>
<tr><td colspan="2">PICO Question 5: For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer, how many years after the start of PSA testing is the benefit of PSA testing apparent?</td><td>Report body of evidence tables</td></tr>
<tr><td colspan="3">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td rowspan="4">One Level II study (ERSPC) in which men were screened either every 2 or 4 years reported mortality from prostate cancer as outcome by time since screening began; as did two component studies of ERSPC (Rotterdam and Gøteborg). This study is at moderate risk of bias; cause of death was determined blind to the screening or control status of the deceased however participants were not blinded to the intervention.
Grade C

One Level II study (Gøteborg Study, a component of ERSPC) reported mortality from prostate cancer as outcome by time since screening ended. This study is at high risk of bias as it is unclear whether allocation of cause of death after screening ended was done blind to the screening or control status of the deceased.
Grade D</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or
II studies with a moderate risk of bias</td></tr>
<tr><td>D</td><td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td></tr>
<tr><td colspan="3">2. Consistency (if only one study was available, rank this component as 'not applicable') See body of evidence tables in report – results and p value (95% CI)</td></tr>
<tr><td>For mortality by time since screening began
The ERSPC (Schroder et al 2012) found little evidence that PSA testing reduced mortality up to 7 years after testing began, RR 0.92 (95% CI 0.73-1.18); thereafter, there was, evidence of a reduction in mortality at 8-9 years after testing began, RR 0.74 (95% CI 0.55-0.99), which was stronger again at 10-11 years after, RR 0.62 (0.45-0.85). The ERSPC and its Rotterdam (Roobol et al 2013 and Gøteborg</td><td>A</td><td>All studies consistent</td></tr>
</table>

(Hugosson et al 2010)) components have published plots of cumulative hazard of death from prostate cancer in screening and control arms by time since randomization (Nelson–Aalen method). Reading from these plots, the systematic review team estimated that divergence of the cumulative hazards was first evident at 7 years in the ERSPC in men 55-69 years, Gøteborg men 50-69 years and Rotterdam men 55-74 years, and at 6 years in Rotterdam men 55-69 years. **Grade A** **For mortality by time since screening ended** The Gøteborg study reported relative risk of death from prostate cancer by time since testing ended, and suggested that the lower mortality from prostate cancer in the intervention group was no longer evident after 9-12 years. However the relative risk estimates were imprecise: RRs were 0.47 (0.17-1.20) 3-6 years after testing ended; 0.51 (0.18-1.33) 6-9 years after; and 1.35 (0.39-4.78) 9-12 years after (RRs and 95% CIs estimated from data in Table 3 of Grenabo Bergdahl et al 2013 **Not applicable** (one study only)	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**

3. Clinical impact *See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
An estimate of the number of years after the start of PSA testing until the benefit of PSA testing is apparent might be used clinically to caution against PSA testing a man who, because of his age, health status or both is unlikely to live this long. The potential benefits of use of such an estimate are avoidance of prostate biopsy and prostate cancer diagnosis and, perhaps, treatment and its common adverse effects, principally urinary incontinence and erectile dysfunction under circumstances in which development of avoidable metastatic prostate cancer and death from prostate cancer is unlikely. The potential harms, which might arise if the estimate is too high or estimated life expectancy too low, are a period of life with metastatic prostate cancer and, perhaps, death from prostate cancer	A	**Very large**

that might have been avoided if testing had been offered. The potential benefits are best reflected in the rate of diagnosis of prostate cancer that would be avoided by not offering first testing or routine re-testing when expectation of life is lower than the estimated number of years until benefit is apparent. Estimates of the rate of diagnosis of extra prostatic cancers due to testing (extra above those that would have been diagnosed in the absence of screening) have been taken from the results of a recent modelling study (Pataky et al 2014, supplementary table A1) and are summarised in the following table.	B	**Substantial**
	C	**Moderate**

	First test*	Subsequent tests†	
Age at first PSA	One test only	Tests every 2 years to 74	Tests every 4 years to 74 years
50 years	0.06/1,000	2.8/1,000	4.3/1,000
60 years	2.2/1,000	4.3/1,000	Not estimated
70 years	9.2/1,000	Not estimated	Not estimated

*Incidence of extra prostate cancers diagnosed in comparison with no PSA testing with a PSA threshold for biopsy ≤3ng/ml

†Average incidence of extra prostate cancers diagnosed in comparison with no PSA testing per PSA test subsequent to the first PSA test with a PSA threshold for biopsy ≤3ng/ml

While limited in their scope, these rates are indicative of the burden of prostate cancer that men would experience if they were first tested, or continued to be tested, when they were unlikely to live long enough to gain benefit from being tested.

Equally, however, there could be benefits lost if men were not tested and lived more than 7 years. The ERSPC estimated, for men 55-69 years of age, that 8-9 years after first testing the rate of prostate cancer death in men tested at 55-69 years of age was 0.20/1,000 man years (95% CI 0-0.40/1,000) less than in untested men of this age (Schroder et al 2012a).

Thus, for example, it can be estimated that a man who forewent a first PSA test at 60 years of age on the basis of a life expectancy of 7 years or less and lived for 9 years would avoid a 2.2/1,000 chance of having been diagnosed with PSA-detected prostate cancer in this period but gain a 0.4/1,000 chance of dying from prostate cancer during his eighth or ninth year after foregoing the test.

In summary, the clinical impact of not PSA testing men unlikely to survive long enough to gain benefit from it is

D	**Slight/Restricted**

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*

Study populations were located in continental western Europe. Study results, therefore, are generalisable to populations of men of predominantly of western European ethnic origin and living in high income countries. Generalisability to men of lower socioeconomic status, non-English speaking background and Aboriginal and Torres	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**

Strait Islander populations, however, is uncertain. **Grade B**	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*

PSA testing is already widespread in older Australian men, available annually with Medicare subsidy and has annual coverage of men 45-74 years of age in Australia that is not dissimilar to coverage of women in the relevant target age groups by Pap tests and screening mammography. However, organised screening as evaluated in the cited level II trials is different to PSA testing as performed in Australia where mass population screening is not recommended nor practised. Importantly, although it is tempting to attribute the high level of testing to opportunistic screening, the extent that selective screening, albeit at different levels of patient engagement, is practised is uncertain. **Grade C**	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*

There is consistent evidence overall in the ERSPC, and in its Rotterdam and Gøteborg components that the observed lower mortality from prostate cancer in the PSA testing intervention group than the control group was evident at 6-7 years after testing began. Lower quality evidence from the Gøteborg study (wider confidence intervals and higher risk of bias) suggests that the lower mortality from prostate cancer in the intervention group was no longer evident 9-12 years after testing ended.

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	B	Substantial

4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

Evidence statement: *Indicate any dissenting opinions*

For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer, a reduction in the risk of death from prostate cancer was apparent at 6–7 years after the start of PSA testing.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION** C

Since any mortality benefit from early diagnosis of prostate cancer due to PSA testing is not seen in less than 6-7 years from testing, PSA testing is not recommended for men who are unlikely to live another 7 years.

CONSENSUS-BASED RECOMMENDATION *If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.*

PRACTICE POINT

Points of guidance used to support evidence-based recommendations, where the subject matter is outside of the scope of search strategy, and which were formulated based on expert opinion using a consensus process.

- When discussing the benefits and harms of PSA testing with older men or those with a potentially fatal chronic illness, explain each of the following:
    - Testing can only be expected to prevent prostate cancer death that would have occurred more than 7 years in the future.
    - If prostate cancer is diagnosed after the test, medium- to long-term quality of life may be better due to diagnosis and treatment of a cancer that could have become advanced in less than 7 years.
    - If prostate cancer is diagnosed after the test, quality of life in the immediate short term may be poorer due to the harmful effects of treatment.

- The percentage of men of a given age, and average health status for their age, who are expected to live for another 7 years is as shown in the table below:

Age	Percentage of men remaining alive after 7 years
50	97%
55	96%
60	94%
65	91%
70	85%
75	74%
80	57%
85	37%
90	19%

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*
None

Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care? Implementation of the recommendation would require clinicians to consider life expectancy whenever they offer a PSA test. Current Australian guidelines for disease prevention in primary care advise that men with a life expectancy of less than 10 years are at reduced risk of dying from prostate cancer. Reducing the estimate of the life expectancy at which a PSA test may have benefit from 10 years to 7 years may increase the number of men tested. However, it is not possible to predict whether there would be a net increase, reduction or no change in the number of men tested, because it not known whether all clinicians routinely discuss life expectancy when providing information about the risks and potential benefits of PSA testing, or the accuracy of life expectancy estimates in practice.	**YES**
Are there any resource implications associated with implementing this recommendation? Implementation of this recommendation would have no significant resource implications.	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? No barriers to the implementation of this recommendation are foreseen.	**NO**

Chapter 2.5

NHMRC Evidence Statement Form for Clinical Question 6: In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what tests for prostate cancer should be offered in addition to a PSA test? Candidate tests include:

Free-to-total PSA %

PSA velocity

Prostate health index

Repeated total PSA

<table>
<tr><td colspan="2">PICO Question 6.1 Free-to-total PSA:
6.1a. For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring free-to-total PSA percentage improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single total PSA result above 3.0 ng/mL?</td><td>Report body of evidence tables</td></tr>
<tr><td colspan="3">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td rowspan="4">Four prospective level lll-2 studies were identified that examined the effect on diagnostic accuracy of using f/t PSA% in addition to a tPSA test to detect prostate cancer in men with tPSA levels below 4.0 ng/mL. All included men aged 55 to 65 years; one study included men as young as 35 years and other included men up to the age of 79 years. Three of the studies performed sextant biopsies (Makinen 2001, Rowe 2005 and Uzzo 2003) while Ishidoya 2008 used 12-core biopsy. All were at risk of bias as the reference standard was not reportedly blinded.
The Uzzo 2003 study looked at the addition of f/t PSA% to the combination of either a tPSA >4.0ng/mL or an abnormal DRE in a group of men at higher risk of prostate cancer (African-American; or white with at least one first-degree or two or more second-degree relatives diagnosed with prostate cancer or tested positive for the BRCA1 gene). The other three studies examined f/t PSA% in performance in screening study participants.
Grade D</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias</td></tr>
<tr><td>D</td><td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td></tr>
<tr><td colspan="3">2. Consistency (if only one study was available, rank this component as ‘not applicable’) See body of evidence tables in report – results and p value (95% CI)</td></tr>
<tr><td rowspan="2">All studies found that using f/t PSA% at tPSA levels below the tPSA threshold of 4 ng/mL detected additional cancers however the numbers of extra unnecessary biopsies varied depending on f/t PSA% threshold, population and the tPSA range in which the f/t PSA% test</td><td>A</td><td>All studies consistent</td></tr>
<tr><td>B</td><td>Most studies consistent and inconsistency can be explained</td></tr>
</table>

was used. In a Japanese study (Ishidoya 2008)) of men aged 50 – 79 years using a f/t PSA% threshold of <12% for men with a tPSA of 2.0 – 4.0 ng/mL increased detection by approximately 10% at an incremental cost of 2.1 extra unnecessary biopsies for each additional cancers diagnosed. These results were not considered generalizable to Australian screening populations as the cancer detection rate for men with a tPSA greater than 4.0ng/mL was 43.1%. A Finnish study of participants in screening trial aged 55 to 67 years found that using a f/t PSA % threshold of <16% for men with a tPSA of 3.0 – 4.0 ng/mL increased detection by approximately 10% at an incremental cost of 3.9 extra unnecessary biopsies for each additional cancers diagnosed (Makinen (2001). The cancer detection rate in this study was 24.5% for a tPSA cut-off of 4.0ng/mL which was more typical of screening populations however this study was not directly relevant to testing protocols using a tPSA threshold of 3.0ng/mL as it did not did not seek to improve on the sensitivity at tPSA levels below 3.0 ng/mL. Rowe 2005 found that if a tPSA of threshold of 3.0 ng/mL were used for men with a tPSA of 1.1 – 2.99 ng/mL adding a f/t PSA% ratio of ≤20% resulted in 7 unnecessary biopsies for every cancer detected however this study did not report the corresponding relative increase in sensitivity. The study by Uzzo (2003) showed a particularly favourable incremental benefit with the use of f/t PSA%. By using a f/t PSA% cut-off of <27% when PSA is between 2.0 to 4.0 ng/L, 133% more cancers could be diagnosed with an incremental FP/TP ratio of 0.92. The most likely reason for the inconsistency of the benefit is the higher risk of cancer detection in that group of men reflected by the high cancer detection rate in that study (52.5%). These men were also younger than in the other studies including biopsied men with an age range of 41 to 69 years. **Grade C**	**C**	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**
3. Clinical impact *See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
For men with tPSA of 2.0 – 4.0 ng/mL between the ages of 50 to 79 years with a normal PSA, adding f/t PSA% with a threshold of ratio of <12% could increase detection by 10% at a cost of 2 extra unnecessary biopsies for each additional cancers diagnosed.	A	**Very large**
	B	**Substantial**
	C	**Moderate**

For men at high risk of prostate cancer between the age of 41 to 69 with a normal PSA, adding a f/t PSA% with a threshold ratio of <27%, could double the cancer detection rate with less than one unnecessary biopsy for every cancer detected. **Grade B**	D	**Slight/Restricted**

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*

The results of Ishidoya (2008) was not considered generalizable to Australian screening populations as the cancer detection rate for men with a tPSA greater than 4.0ng/mL was 43.1%. Makinen (2001) did not specifically address the tPSA range below 3 ng/mL. The Uzzo (2003) findings were for a high risk cohort of men aged 41 to 69 years at biopsy. In Australia, men with a family history of prostate cancer are often tested below the age of 50 years. **Grade C**	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*

Current reimbursement schedules for f/t PSA% ratio allow for the use of the ratio with tPSA levels down to the 2.0 ng/mL levels used in the Uzzo (2003) study. The typical threshold for flagging increased risk is typically a f/t PSA% below 10% rather than below 27% used in the Uzzo (2003) study. **Grade B**	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*

There were no studies that directly addressed the effect on sensitivity when using a tPSA threshold of 3.0 ng/mL, however three of the four studies included the application of f/t PSA% ratio for tPSA levels between 2.0 and 3.0 ng/L.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	B	Substantial
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

Evidence statement:

A study in men aged 41–69 years at high risk of prostate cancer (African American, family history of prostate cancer, or positive for BRCA1 gene), found that the use of free-to-total PSA < 27% as the criterion for biopsy in those with total PSA between 2.0 and 4.0 ng/mL, more than doubled the number of cancers detected, compared with the use of a total PSA threshold of 4.0 ng/mL alone, and resulted in approximately one extra unnecessary biopsy for each additional cancer detected.

One study in in a screening population found that the additional biopsy criterion of low free-to-total PSA (< 12%) for men with a total PSA of 2.0–4.0 ng/mL increased prostate cancer detection by approximately 10% and resulted in two extra biopsies per additional prostate cancer detected, compared with the use of a single biopsy indication of a total PSA > 4.0 ng/mL. The results of this study may not be generalisable to the Australian population, because a high cancer detection rate was observed with a total PSA threshold of 4.0 ng/mL.

In a second study in a screening population the use of a free-to-total PSA% threshold of < 16% for men with a total PSA of 3.0–4.0 ng/mL increased detection by approximately 10%, at an incremental cost of 3.9 extra unnecessary biopsies for each additional cancer diagnosed. However, this study was not directly relevant as it did not seek to improve on the sensitivity at total PSA levels below 3.0 ng/mL.

A third study in a screening population reported an increase in prostate cancer detection when using free-to-total PSA% as an additional indication for biopsy however the actual increase in sensitivity with the addition of the free-to-total PSA% test was not reported.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION** D
For men aged 45–69 years whose risk of prostate cancer is at least double the average risk and with total PSA 2.0–3.0 ng/mL, consider offering prostate biopsy if free-to-total PSA is less than 25%.	

CONSENSUS-BASED RECOMMENDATION *If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.*
PRACTICE POINT *Points of guidance used to support evidence-based recommendations, where the subject matter is outside of the scope of search strategy, and which were formulated based on expert opinion using a consensus process*.

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*

Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care? The interpretation of free-to-total PSA% below 25% in high risk men with PSA levels between 2.0 – 3.0 ng/mL is not currently a routine approach.	**YES**
Are there any resource implications associated with implementing this recommendation?	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

NHMRC Evidence Statement Form for Clinical Question 6: In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what tests for prostate cancer should be offered in addition to a PSA test? Candidate tests include:

Free-to-total PSA %

PSA velocity

Prostate health index

Repeated total PSA

<table>
<tr><td colspan="2">PICO Question: 6.2 PSA velocity

6.2a: For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring PSA velocity improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single elevated total PSA result above 3.0 ng/mL?</td><td>Report body of evidence tables</td></tr>
<tr><td colspan="3">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td rowspan="4">No studies were found that examined the ability of PSA velocity measurements to detect additional cancers in asymptomatic men with tPSA levels less than or equal to 3 ng/mL

Grade : Not applicable</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias</td></tr>
<tr><td>D</td><td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td></tr>
<tr><td colspan="3">2. Consistency (if only one study was available, rank this component as ‘not applicable’) See body of evidence tables in report – results and p value (95% CI)</td></tr>
<tr><td rowspan="5">Not applicable</td><td>A</td><td>All studies consistent</td></tr>
<tr><td>B</td><td>Most studies consistent and inconsistency can be explained</td></tr>
<tr><td>C</td><td>Some inconsistency, reflecting genuine uncertainty around question</td></tr>
<tr><td>D</td><td>Evidence is inconsistent</td></tr>
<tr><td>NA</td><td>Not applicable (one study only)</td></tr>
<tr><td colspan="3">3. Clinical impact See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)</td></tr>
<tr><td>Not applicable</td><td>A</td><td>Very large</td></tr>
</table>

	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*		
Not applicable	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Not applicable	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	N/A	Not applicable
2. Consistency	N/A	Not applicable
3. Clinical impact	N/A	Not applicable
4. Generalisability	N/A	Not applicable
5. Applicability	N/A	Not applicable

Evidence statement:	
There was no evidence for whether or not measuring the PSA velocity of men with a PSA less than or equal to 3.0 ng/mL improves the detection of prostate cancer, compared with PSA alone.	
RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION** N/A
No evidence based recommendations possible	

CONSENSUS-BASED RECOMMENDATION *If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.*
Do not use PSA velocity as an adjunct to total PSA testing in determining whether or not to offer prostate biopsy, except in the context of research conducted to assess its utility for this purpose.
PRACTICE POINT *Points of guidance used to support evidence-based recommendations, where the subject matter is outside of the scope of search strategy, and which were formulated based on expert opinion using a consensus process*.

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*
There a very few studies with Grade III evidence largely because the data used for PSA velocity calculation were inappropriate and similarly the tPSA assays used were not described and often raised the issue of analytical bias affecting velocity calculations in individual men. PSA kinetics include linear estimations of rise (PSA velocity) and exponential estimations of rise (PSA doubling time and PSA % change) which are not equivalent.

Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	NO
Are there any resource implications associated with implementing this recommendation?	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation?	NO

NHMRC Evidence Statement Form for Clinical Question 6: In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what tests for prostate cancer should be offered in addition to a PSA test? Candidate tests include:

Free-to total PSA %

PSA velocity

Prostate health index

Repeated total PSA

<table>
<tr><td colspan="2">PICO question 6.3 Prostate Health Index (PHI):
6.3a: For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring the Prostate Health Index (PHI) improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single elevated total PSA result above 3.0 ng/mL?</td><td>Report body of evidence tables</td></tr>
<tr><td colspan="3">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td rowspan="4">No studies were found that examined the role of the PHI test in improving prostate cancer detection amongst men a PSA test result below the threshold of 3.0 ng/mL, and as low as 2.0 ng/mL.

Grade: Not applicable</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias</td></tr>
<tr><td>D</td><td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td></tr>
<tr><td colspan="3">2. Consistency (if only one study was available, rank this component as ‘not applicable’) See body of evidence tables in report – results and p value (95% CI)</td></tr>
<tr><td rowspan="5">Not applicable</td><td>A</td><td>All studies consistent</td></tr>
<tr><td>B</td><td>Most studies consistent and inconsistency can be explained</td></tr>
<tr><td>C</td><td>Some inconsistency, reflecting genuine uncertainty around question</td></tr>
<tr><td>D</td><td>Evidence is inconsistent</td></tr>
<tr><td>NA</td><td>Not applicable (one study only)</td></tr>
<tr><td colspan="3">3. Clinical impact See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the</td></tr>
</table>

study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)		
Not applicable	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*		
Not applicable	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Not applicable	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	N/A	Not applicable

2. Consistency	N/A	Not applicable
3. Clinical impact	N/A	Not applicable
4. Generalisability	N/A	Not applicable
5. Applicability	N/A	Not applicable

Evidence statement:

There was no evidence for whether or not PHI testing men with a PSA less than or equal to 3.0 ng/mL improves the detection of prostate cancer, compared with PSA alone.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION** N/A
No evidence based recommendations possible	

CONSENSUS-BASED RECOMMENDATION

If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.

Do not use the PHI test as an adjunct to total PSA testing in determining whether or not to offer prostate biopsy, except in the context of research conducted to assess its utility for this purpose.

PRACTICE POINT

Points of guidance used to support evidence-based recommendations, where the subject matter is outside of the scope of search strategy, and which were formulated based on expert opinion using a consensus process.

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*
There is some evidence from observational studies that PHI predicts biopsy positivity better than either tPSA or f/tPSA, however further research is required into the incremental role of PHI to improve sensitivity in men with PSA below 3.0 ng/mL. Further research is also required into the role of PHI to incrementally improve sensitivity compared to combined tPSA and f/t PSA% strategies.

Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	**NO**
Are there any resource implications associated with implementing this recommendation?	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

NHMRC Evidence Statement Form for Clinical Question 6: In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what tests for prostate cancer should be offered in addition to a PSA test?

Free-to-total PSA %

PSA velocity

Prostate health index

Repeated total PSA

<table>
<tr><td colspan="2">PICO Question 6.1 Free-to-total PSA:
6.1b: For asymptomatic men with an initial total PSA above 3.0 ng/mL does measuring free-to-total PSA percentage improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL?</td><td>Report body of evidence tables</td></tr>
<tr><td colspan="3">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td rowspan="4">A total of 14 level III-2 studies were identified that met the inclusion criteria. Eight studies reported f/t PSA% value in men with a tPSA level within proximity to the threshold of 3.0 ng/mL, three studies used age-specific tPSA thresholds and 2 studies provided sub group analyses for men with tPSA 4 – 10 ng/mL who were older than 69 years. All were at risk of bias.
Most studies found that tPSA alone resulted in approximately 3 to 5 unnecessary biopsies for each prostate cancer detected which is not dissimilar to the positive predictive value (PPV) of 25% reported in the ERSCP study.
The studies covered a wide range of populations with ages ranging from 50 to 70 years, and over.
Grade D</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias</td></tr>
<tr><td>D</td><td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td></tr>
<tr><td colspan="3">2. Consistency (if only one study was available, rank this component as ‘not applicable’) See body of evidence tables in report – results and p value (95% CI)</td></tr>
<tr><td rowspan="3">The majority of studies did not compare the area under the ROC curve. Of the two studies that did, neither (Egawa 2002; Kobayashi 2005) found any statistically significant difference. Kobayashi (2005) was one of the smallest cohort numbers (n=139, with 31 cancers) and Egawa (2002) did not report their cancer detection rate.</td><td>A</td><td>All studies consistent</td></tr>
<tr><td>B</td><td>Most studies consistent and inconsistency can be explained</td></tr>
<tr><td>C</td><td>Some inconsistency, reflecting genuine uncertainty around question</td></tr>
</table>

The studies found that lowering the f/t PSA% threshold improved specificity and lowered the sensitivity. For men with tPSAs below 4.0 ng/mL 5 studies used thresholds that maintained at least 90% sensitivity compared to tPSA alone; 18% to 31% (4 studies a minimum of 25 to 31%) reducing the number of unnecessary biopsies by 3.8, 4.0, 6.0, 9.7 ,12.5 or 26 for each cancer missed. The variation in the f/t PSA% ratio that maintained at least 90% sensitivity and the number of unnecessary biopsies prevented per cancer missed for the threshold of 25% may be due to standardisation issues with both tPSA and f/t PSA% during the period 1997 – 2006. Safarinejad (2006) was an outlier amongst these studies reporting that 26 biopsies could be avoided for each cancer missed at high sensitivity at the lower threshold of f/t PSA% < 18%. The study was small (n=167) with 30 cancers detected and there may be possible population or cancer risk differences in Iran. The three studies that used age related tPSA thresholds (Reissigl retrospective and prospective studies 1996, 1997) found that a f/t PSA% threshold of 22% results in up to 21 biopsies that can be avoided for each cancer missed. This may be related to the often higher age related tPSA thresholds (2.5 / 3.5 / 4.5 / 6.5 ng/nL) used in these studies. Improved specificity at higher tPSA levels was also supported by the Lubholdt (2001) study that included men with tPSA levels from 4.0 - 10.0 ng/mL. This study specifically reported that in men aged over 69 years, at least 32 biopsies could be avoided for each cancer missed. This is of interest, because these older men will more often have higher tPSA levels (> 4.0 ng/mL), without the presence of prostate cancer. The Catalona (1998) study also looked at older men (70 – 74 years) but found a much lower improvement in unnecessary biopsies avoided (4.4) for each cancer missed. For men with a tPSA of 4.0 - 10.0 ng/mL the Catalona (1998) study represents a high risk cohort with 43.8% cancer detection rate while the Lubholdt (2001) study has a much lower cancer detection rate (14.7%) closer to the cancer detection rate in screening studies. **Grade C**	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**
3. Clinical impact *See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Maintaining over 90% sensitivity but avoiding approximately 4 to 12 biopsies for each cancer missed implies a substantial advantage to also applying a f/t PSA% threshold of 25% or more when tPSA is above a threshold in the proximity of 3.0 ng/mL.	A	**Very large**
	B	**Substantial**
	C	**Moderate**

This benefit is even greater when applied to tPSA levels 4.0 to 10.0 ng/mL, in men >69 years. **Grade B**	D	**Slight/Restricted**
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*		
The populations studied are similar to Australian men and address the over 50 age group. The substantial numbers of older men (60 to 69 years or more) being tested are more likely to have tPSA levels above 3.0 ng/mL and more likely to benefit from f/t PSA% testing. Of particular relevance is the single study that used a tPSA threshold of 3ng/mL and less than 4.0ng/mL. For men in this screening population using a f/t PSA% threshold of 26% as an indication for biopsy missed 7.4% of cancer with 12.5 false positives avoided per each cancer missed **Grade A**	**A**	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The use of f/t PSA% is reimbursable in Australia and in common usage when tPSA levels are elevated. The f/t PSA% decision thresholds used are either <10% or <25%. The latter cut-off, supported by the body of evidence, maintains 90% sensitivity. **Grade B**	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*		

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	B	Substantial
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

Evidence statement:

In populations of men without a diagnosis of prostate cancer or symptoms that suggest prostate cancer, and with total PSA levels of 3.0–4.0 ng/mL, using a free-to-total PSA threshold of 26% as an indication for biopsy missed 7.4% of cancers, with 12.5 false positives avoided per each cancer missed.

In populations of men without a diagnosis of prostate cancer or symptoms that suggest prostate cancer, and total PSA levels between 2.0 and 4.0 ng/mL, using free-to-total PSA thresholds from 25% to 31% as indications for biopsy maintained a sensitivity of at least 90%, with 3.8-12.5 false positives avoided per cancer missed.

In populations of men aged over 69 years without a diagnosis of prostate cancer or symptoms that suggest prostate cancer, with a total PSA of 4.0–10.0 ng/mL and a cancer detection rate of 15%, using a free-to-total PSA threshold of 22% as an indication for biopsy maintained over 90% sensitivity and avoided 32 false positives per missed cancer.

There is very little evidence for whether free-to-total PSA% improves specificity in men aged under 50 years. Studies that reported free-to-total PSA% thresholds with acceptable sensitivity either did not include men under 50, or included only a small proportion.

RECOMMENDATION	**GRADE OF RECOMMENDATION**
What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.	D

For those with initial total PSA greater than 3.0 ng/mL and up to 5.5 ng/mL, measure free-to-total PSA percentage at the same time as repeating total PSA.

CONSENSUS-BASED RECOMMENDATION *If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.*

For men aged 50–69 years with initial total PSA greater than 3.0 ng/mL who have undergone repeat total PSA and free-to-total PSA percentage tests at follow-up 1–3 months later, offer prostate biopsy:

- if repeat total PSA is greater than 5.5 ng/mL, regardless of free-to-total PSA percentage
- if repeat total PSA is greater than 3.0 ng/mL and less than or equal to 5.5 ng/mL **and** free-to-total PSA is below 25%.

For men aged 50–69 years with a previous total PSA test result greater than 3.0 ng/mL who are not offered prostate biopsy (or do not accept prostate biopsy when offered) after follow-up PSA testing, explain that there is a small chance of missing a significant cancer and advise them to return for PSA testing within 2 years.

PRACTICE POINT

Points of guidance used to support evidence-based recommendations, where the subject matter is outside of the scope of search strategy, and which were formulated based on expert opinion using a consensus process.

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*
It is uncertain how repeat total PSA and free-to-total PSA% work together in avoiding unnecessary biopsies while maintaining sensitivity. Furthermore it is not known how these diagnostic changes impact on clinical outcomes.

Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care? The use of f/tPSA% is in common usage when tPSA levels are elevated. The f/tPSA% decision thresholds used are either <10% or <25%. Implementation of these recommendations would not require changes in the way care is currently organised.	**NO**
Are there any resource implications associated with implementing this recommendation? Offering a f/tPSA% test if tPSA is greater than 3.0 ng/mL will reduce the number of biopsies.	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

NHMRC Evidence Statement Form for Clinical Question 6: In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what tests for prostate cancer should be offered in addition to a PSA test? Candidate tests include:

Free-to-total PSA %

PSA velocity

Prostate health index

Repeated total PSA

<table>
<tr><td colspan="3">PICO Question 6.2 PSA velocity:

6.2b: For asymptomatic men with an initial total PSA above 3.0 ng/mL does measuring PSA velocity improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single elevated total PSA result above 3.0 ng/mL?</td><td>Report body of evidence tables</td></tr>
<tr><td colspan="4">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td rowspan="4">One level lll-2 study investigated the benefit of determining PSA velocity (determined by a minimum of 3 total PSA measurements over a maximum of a 4 years period using the same assay) in selecting men for biopsy where the initial total PSA level was elevated. This study was determined to be at risk of bias using QUADAS-ll tool, and is a prospective study reporting diagnostic accuracy of PSA velocity and other diagnostic markers (Djavan 1999). This study used a PSA level of ≥2.5 ng/mL as the indication for prostate biopsy. If the initial sextant biopsy was negative, the biopsy procedure was repeated six weeks later with sextant plus two transitional zone biopsies.

Grade D</td><td>A</td><td colspan="2">One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td colspan="2">One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td colspan="2">One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias</td></tr>
<tr><td>D</td><td colspan="2">Level IV studies or Level I to III studies/SRs with a high risk of bias</td></tr>
<tr><td colspan="4">2. Consistency (if only one study was available, rank this component as ‘not applicable’) See body of evidence tables in report – results and p value (95% CI)</td></tr>
<tr><td rowspan="4">The addition of PSA velocity to total PSA did not appear to improve diagnostic performance for men with a total PSA of 2.5-4.0 ng/mL. Djavan 1999 found that for these men the area under the ROC graph for PSA velocity was significantly less than that for total PSA which was in turn</td><td>A</td><td colspan="2">All studies consistent</td></tr>
<tr><td>B</td><td colspan="2">Most studies consistent and inconsistency can be explained</td></tr>
<tr><td>C</td><td colspan="2">Some inconsistency, reflecting genuine uncertainty around question</td></tr>
<tr><td>D</td><td colspan="2">Evidence is inconsistent</td></tr>
</table>

significantly less than that for free to total PSA. Also, using a PSA velocity threshold that missed 20% of cancers (80% relative sensitivity) only approximately 27% of unnecessary biopsies (27% relative specificity) would have been avoided. It is unclear in this study as to how many men were included in the PSA velocity analyses and small numbers may explain weak performance. **Grade N/A**	NA	**Not applicable (one study only)**
3. Clinical impact *See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Djavan 1999 reported diagnostic performance data that indicated using PSA velocity cut-offs that resulting in relative sensitivities of 5 and 10% resulted in low specificities; missing 20% of cancers only achieved a relative specificity of approximately 27%. **Grade D**	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*		
The results of the single study were derived from an Austrian population with a mean age 67 years. It would therefore be generally applicable to similar population in Australia. **Grade A**	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
PSA velocity is used in a limited fashion in Australia and very few laboratories or GP's are familiar with the calculations or its use. Furthermore, reimbursement guidelines only allow one tPSA to be reimbursed each calendar year implying that it would take at least three	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**

years to estimate a reliable PSA velocity or doubling time. **Grade C**	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	One level III-2 study at risk of bias
2. Consistency	N/A	One study only
3. Clinical impact	D	Slight/Restricted
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

Evidence statement:

In a single level III-2 study, the use of PSA velocity to increase the specificity at PSA levels in the range of 2.5 to 4.0 ng/mL reduced sensitivity to an unacceptable degree.

RECOMMENDATION	GRADE OF RECOMMENDATION
What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.	D

Measurement of PSA velocity is not recommended to increase specificity of a total PSA test result of 3.0 ng/ml or greater.

CONSENSUS-BASED RECOMMENDATION *If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.*
PRACTICE POINT *Points of guidance used to support evidence-based recommendations, where the subject matter is outside of the scope of search strategy, and which were formulated based on expert opinion using a consensus process*.

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*
There a very few studies with Grade III evidence largely because the data used for PSA velocity calculation were inappropriate and similarly the tPSA assays used were not described and often raised the issue of analytical bias affecting velocity calculations in individual men. PSA kinetics include linear estimations of rise (PSA velocity) and exponential estimations of rise (PSA doubling time and PSA % change) which are not equivalent.

Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	NO
Are there any resource implications associated with implementing this recommendation?	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation?	NO

NHMRC Evidence Statement Form for Clinical Question 6: In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what tests for prostate cancer should be offered in addition to a PSA test? Candidate tests include:

Free-to-total PSA %

PSA velocity

Prostate health index

Repeated total PSA

<table>
<tr><td colspan="2">PICO question 6.3 Prostate Health Index (PHI):

6.3b: For asymptomatic men with an initial total PSA above 3.0 ng/mL does measuring the Prostate Health Index (PHI) improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single elevated total PSA result above 3.0 ng/mL?</td><td>Report body of evidence tables</td></tr>
<tr><td colspan="3">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td rowspan="4">No studies were found that examined the role of PHI to improve specificity for men with elevated PSA above the threshold of 3.0 ng/mL, and up to 5.5 ng/mL.

Grade Not applicable</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias</td></tr>
<tr><td>D</td><td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td></tr>
<tr><td colspan="3">2. Consistency (if only one study was available, rank this component as ‘not applicable’) See body of evidence tables in report – results and p value (95% CI)</td></tr>
<tr><td rowspan="5">Not applicable</td><td>A</td><td>All studies consistent</td></tr>
<tr><td>B</td><td>Most studies consistent and inconsistency can be explained</td></tr>
<tr><td>C</td><td>Some inconsistency, reflecting genuine uncertainty around question</td></tr>
<tr><td>D</td><td>Evidence is inconsistent</td></tr>
<tr><td>NA</td><td>Not applicable (one study only)</td></tr>
<tr><td colspan="3">3. Clinical impact See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)</td></tr>
<tr><td rowspan="2">Not applicable</td><td>A</td><td>Very large</td></tr>
<tr><td>B</td><td>Substantial</td></tr>
</table>

	C	**Moderate**
	D	**Slight/Restricted**
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*		
Not applicable	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Not applicable	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*

The review was specifically concerning the incremental use of PHI to improve specificity above the PSA threshold of 3.0 ng/mL. The review also included research within the PSA range of 2.0 to 5.5 ng/mL justified by the analytical and biological variability of PSA including the chronological variations of PSA with increasing age. The most common reason for excluding studies was PHI was unclear or inappropriate indications for biopsy.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	N/A	Not applicable
2. Consistency	N/A	Not applicable
3. Clinical impact	N/A	Not applicable
4. Generalisability	N/A	Not applicable
5. Applicability	N/A	Not applicable

Evidence statement:
There was no evidence for whether or not PHI testing improves the specificity of PSA testing in men with an elevated PSA up to 5.5 ng/mL, compared with PSA alone.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION** N/A
No evidence based recommendations possible	

CONSENSUS-BASED RECOMMENDATION *If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.*
Do not use the PHI test to increase specificity of a total PSA test result of 3.0 ng/mL or greater, except in the context of research conducted to assess its utility for this purpose.
PRACTICE POINT *Points of guidance used to support evidence-based recommendations, where the subject matter is outside of the scope of search strategy, and which were formulated based on expert opinion using a consensus process*.

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*
There is some evidence from observational studies that PHI predicts biopsy positivity better than either tPSA or f/tPSA, however further research is required into the incremental role of PHI to incrementally improve specificity in men with tPSA above 3.0 ng/mL. Further research is also required into the role of PHI to incrementally improve specificity compared to combined tPSA and f/t PSA% strategies.

Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	**NO**
Are there any resource implications associated with implementing this recommendation?	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

NHMRC Evidence Statement Form for Clinical Question 6: In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what tests for prostate cancer should be offered in addition to a PSA test? Candidate tests include:

Free-to-total PSA %

PSA velocity

Prostate health index

Repeated total PSA

<table>
<tr><td colspan="2">PICO Question 6.4: For asymptomatic men with initial total PSA above 3.0 ng/mL, does repeating the total PSA test and using an initial and repeat total PSA above 3.0 ng/mL as the indication for biopsy, improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL as the indication for biopsy?</td><td>Report body of evidence tables</td></tr>
<tr><td colspan="3">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td rowspan="4">Two level lll-2 studies were identified that met the inclusion criteria. Both studies were prospective (Boddy 2005, Rosario 2008) and used a 8-10 core biopsy scheme, which is more in line with current practice. Indications for biopsy were initial tPSA levels above age-specific cut-offs (Boddy 2005), and >or= to 3.0ng/ml (Rosario 2008).
Boddy 2005 did not indicate the interval between PSA measurements, and Rosario 2008 reported a median of 50 days (interquartile range 33-69). All studies were considered to be at risk of bias.
Grade D</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias</td></tr>
<tr><td>D</td><td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td></tr>
<tr><td colspan="3">2. Consistency (if only one study was available, rank this component as ‘not applicable’) See body of evidence tables in report – results and p value (95% CI)</td></tr>
<tr><td rowspan="4">Both studies found that if the PSA was lower or normalised on the second measurement, the number of negative biopsies could be reduced. However, in both studies, limiting biopsy to men with normalised or lower tPSA levels resulted in missed cancers. In the largest study of 4,102 men Rosario 2008 found that if men were not biopsied because their tPSA had normalised to < 3.0 ng/mL 8.6% of all cancer and 4% of higher-grade cancer would have been missed and if men were not biopsied because their tPSA was 30% or 20% less, 5.9% and 11.3% of cancers would have been missed. Boddy (2005) using age-specific PSA thresholds, biopsying only</td><td>A</td><td>All studies consistent</td></tr>
<tr><td>B</td><td>Most studies consistent and inconsistency can be explained</td></tr>
<tr><td>C</td><td>Some inconsistency, reflecting genuine uncertainty around question</td></tr>
<tr><td>D</td><td>Evidence is inconsistent</td></tr>
</table>

those with tPSA levels remaining elevated missed 6.0% of cancers. **Grade A**	NA	**Not applicable (one study only)**

3. Clinical impact *See body of evidence tables in report - p value (95% CI), size of effect and relevance of evidence (Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

The studies indicate that either normalisation of the PSA level or a 10, 20 or 30% reduction in the total PSA level could reduce the need to perform a biopsy however, this benefit is offset by the inability to demonstrate that cancer is not present. Using these strategies the rate of unnecessary biopsies could be reduced by 20.4% using a PSA cut-off of 3.0 ng./mL, and by 14.0 or 22.8% in men whose PSA had not dropped by 30 or 20% respectively but this had to be balanced against a cancer missed rate from 5.9 -11.3%. The largest study showed the greatest benefit to harm ratios for repeat total PSA testing: the ratio of avoided unnecessary biopsies to missed cancers was 4.26 if only men whose tPSA levels did not drop at least 20% were biopsied, 4.99 if only men with PSA levels that did not normalise or whose tPSA levels did not drop at least 30% were biopsied. In a cohort of men aged 45-79 years with a tPSA above age specific cut-off the ratio of avoided unnecessary biopsies to missed cancers was 3.2 if only men whose tPSA levels did not normalise were biopsied. (Boddy) **Grade C**	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*

The body of evidence is generalizable to the current clinical settings as repeat PSA estimations may be undertaken when the PSA level is close to the threshold used for biopsy. **Grade A**	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*

The observations if substantiated would be generalizable to the Australian population. Current national reimbursement schedules allow a repeat PSA to be reimbursed when PSA is abnormal. **Grade A**	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	C	Moderate
4. Generalisability	A	Evidence directly generalizable to target population
5. Applicability	A	Evidence directly applicable to the Australian health care context

Evidence statement: *Indicate any dissenting opinions*

In men with an initial total PSA ≥ 3.0 ng/mL who underwent a second total PSA test within 1–3 months after the initial test, referring to biopsy only those men whose total PSA failed to normalise or reduce by 30% on the repeat total PSA test missed 8.6% and 5.9% of cancers, respectively, and avoided 4.99 unnecessary biopsies per cancer missed. The use of an age-specific threshold, and referring to biopsy only those whose total PSA did not normalise on repeat total PSA, missed 6% of cancers and resulted in a ratio of unnecessary biopsies to missed cancers of 3.20.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION** D
For men aged 50–69 years with initial total PSA greater than 3.0 ng/mL, offer repeat PSA within 1–3 months.	

CONSENSUS-BASED RECOMMENDATION *If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.*

For men aged 50–69 years with initial total PSA greater than 3.0 ng/mL who have undergone repeat total PSA and free-to-total PSA percentage tests at follow-up 1–3 months later, offer prostate biopsy:

- if repeat total PSA is greater than 5.5 ng/mL, regardless of free-to-total PSA percentage
- if repeat total PSA is greater than 3.0 ng/mL and less than or equal to 5.5 ng/mL **and** free-to-total PSA is below 25%.

For men aged 50–69 years with a previous total PSA test result greater than 3.0 ng/mL who are not offered prostate biopsy (or do not accept prostate biopsy when offered) after follow-up PSA testing, explain that there is a small chance of missing a significant cancer and advise them to return for PSA testing within 2 years.

PRACTICE POINT

Points of guidance used to support evidence-based recommendations, where the subject matter is outside of the scope of search strategy, and which were formulated based on expert opinion using a consensus process.

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*
Larger and better designed studies are needed examining other markers as well as and in combination with repeat PSA and determining the most appropriate time between the repeat tPSA measurement. It is uncertain how repeat total PSA and free-to-total PSA% work together in avoiding unnecessary biopsies while maintaining sensitivity. Furthermore it is not known how these diagnostic changes impact on clinical outcomes.

Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	**NO**
Are there any resource implications associated with implementing this recommendation? Offering a repeat tPSA test will increase the number of PSA estimations and reduce the number of biopsies.	**YES**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? As long as the definition of an elevated PSA remains a PSA above the age related reference limit, there are no barriers in current reimbursement rules.	**NO**

Chapter 3.1

NHMRC Evidence Statement Form for clinical question 7: What constitutes an adequate biopsy?

<table>
<tr><td colspan="2">PICO Question 7: For men undergoing an initial prostate biopsy how many biopsy cores, which pattern of biopsy sampling sites and which approach constitute an adequate prostate biopsy?</td><td>Report body of evidence tables and patient-level regression analysis</td></tr>
<tr><td colspan="3">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td rowspan="3">A published systematic review and a patient-level regression analysis of studies published subsequent to this systematic review formed the basis of the current review.
The published systematic review/meta-analysis by Eichler et al. was at low risk of bias and included 87 randomised controlled trials (RCTs) and “sequential sampling” studies (SS).
The review of the literature published thereafter led to inclusion of 22 studies that reported the outcome detection of prostate cancer: 4 RCTs (all high risk of bias), 15 SS studies (3 moderate, 12 high risk of bias) and 3 RCTs that provided comparative data from a RCT design and also from</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias</td></tr>
</table>

a SS design in the intervention arm (all high risk of bias). A patient-level regression analysis of nineteen of these studies, which provided sufficient information, was performed to assess the effect of number and location of cores, and of transrectal or transperineal approach on cancer detection. Nine studies published after the Eichler systematic review literature cut-off reported **detection of Gleason Score (GS) >6 cancer**: 4 RCTs with high risk of bias, 2 SS studies with moderate risk of bias and 3 SS studies with high risk of bias. Sufficient information for performing a patient-level regression analysis was available from 6 of these studies. Data on **adverse events** was derived from 12 RCTs (4 included in Eichler systematic review, 8 published subsequently): 10 of these reported the effect of number and location of cores, and two reported the effect of transrectal vs. transperineal approach (all high risk of bias). A patient-level regression analysis was not performed due to the diversity in reporting. There were no studies examining concordance (i.e. agreement between the biopsy and post-prostatectomy pathology in individual patients). **Grade A**	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable') See body of evidence tables in report – results and p value (95% CI)*		
Detection of prostate cancer Inspection of point estimates and their confidence intervals revealed inconsistencies between some primary studies. These were explicable by small study size, particularly between cohorts in the RCTs. The published systematic review showed that biopsy schemes of the 5-region biopsies with 18 or more cores showed the highest cancer yield in comparison to the standard sextant scheme. For other included studies with this biopsy pattern but with fewer cores, the cancer yield was lower. There was, however, no statistically significant difference between the 18+ schemes and 10-12-core schemes that included the lateral and medial peripheral zones (LPZ and MPZ).	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**

The patient-level regression analysis performed with the updated systematic review showed a linear increase in the log odds of cancer detection with increased biopsy number and confirmed the importance of the additional sampling of the lateral peripheral zone. For a given biopsy pattern, the 24-core biopsy had a diagnostic yield of 56.9% compared to 45.6% for a 12-core biopsy when the 6-core biopsy was predicted to yield 40%. **Detection of Gleason Score >6 cancer** Patient-level regression analysis suggested that for a given number of cores, extended biopsy schemes do not increase the relative likelihood of finding low-grade cancer (but increasing the number of cores for a given biopsy pattern does increase the chance of detecting cancer). Results regarding number of cores and biopsy pattern for GS>6 cancers were similar to those for all cancer. This was also true when this comparison was restricted to the six studies in which results for detection of GS>6 cancers were reported. The published systematic review did not examine this outcome. **Transrectal vs. transperineal biopsy** Patient-level regression analysis revealed that there is little evidence to suggest that the transrectal approach is more or less likely to detect all cancer than the transperineal approach after accounting for differences in regions from which cores were taken and number of cores. However, there was significant variation in the study methods and the method of transperineal biopsy (from ultrasound directed to biopsy using a template and ultrasound probe). This was not assessable for GS>6 cancers because all GS>6 studies used the transrectal approach. The published systematic review did not examine this comparison. **Adverse events** The sequential studies cannot discriminate between adverse events due to particular biopsy numbers or sites. The RCTs showed varying or unclear reporting of methods or period of follow-up. The published systematic review did not demonstrate a systematic pattern of increasing adverse events with an increasing number of cores taken, but was not able to evaluate the impact of poor reporting of adverse events. **Grade B**		

3. Clinical impact *See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Patient-level regression analysis of the studies indicated that for any given biopsy region or set of regions, men who had 24 cores taken had nearly double the odds of having cancer detected than men who had 6 cores taken (OR=1.98 [95%CI[1.52, 2.58]), that there appeared to be a linear relationship between biopsy core number and the log odds of cancer detection, that extra sampling should be directed at the peripheral zone of the prostate and that the relative increases in yield from increasing core numbers is similar for higher-grade cancers (GS >6) and all cancers (although for the latter there would inevitably be higher absolute numbers). Evidence on adverse events is limited and there is no consistent demonstrated increase in serious adverse events related to core number. This would require further high quality studies. The improvement in cancer detection has the potential to reduce the risk of adverse events by precluding the need for repeat biopsy. **Grade B**	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*		
Most studies were conducted on men within the target age range for PSA testing. None of the studies were from Australian populations. Mean or median PSA levels were available for all studies included in the patient-level regression analysis. Three studies included a group of patients with very high PSA values (>50mg/L) with a very high likelihood of advanced prostate cancer which would be outside a prospective screening range for early prostate cancer. **Grade B**	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Biopsy regimes of 24 cores are already practised by many urologists. If more widely applied there would be some modest increases in time taken for the procedure and a modest increase in pathology costs.	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**

Grade B	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*

Component	Rating	Description
1. Evidence base	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	B	Substantial
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

Evidence statement: *Indicate any dissenting opinions*

Detection of prostate cancer:

Increasing biopsy core number improves cancer yield; as the number of cores increases, the yield increases. A patient-level regression analysis showed that:

- for any given biopsy region or set of regions, men who have 24 cores taken had nearly double the odds of having cancer detected than men who had 6 cores taken
- the 24-core biopsy had a clinically significant greater diagnostic yield of 56.9%, compared with 45.6% for a 12–core biopsy and an expected yield of 40% for a 6-core biopsy.

For a given number of cores, taking samples from the peripheral zones (i.e. LPZ and/or MPZ) yielded more cancers than the transitional zone.

There is insufficient evidence to determine if the transperineal approach is superior to the transrectal approach in detecting cancer.

Detection of cancer with Gleason Score >6:

The relative increases in yield from increasing core numbers was similar for higher-grade cancers (Gleason score > 6) and all cancers.

Overall, the evidence did not show that, for a given number of cores, sampling regions in addition to the peripheral zones (i.e. LPZ and/or MPZ) led to either an increase or a decrease in yield of cancers with Gleason score > 6.

There is insufficient evidence to determine if the transperineal approach is superior to the transrectal approach in detecting GS>6 cancers.

Adverse events:

Evidence on adverse events is limited.

Differences in adverse event rates were not consistently associated with the number of core biopsies or with the biopsy pattern.

There is insufficient evidence to determine whether the transperineal approach is consistently associated with a lower rate of adverse events than the transrectal approach.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION** **B**
Take 21-24 cores in initial biopsies for the diagnosis of prostate cancer. In addition to the sextant biopsies, direct 15-18 additional biopsies to the peripheral zones of the prostate.	

CONSENSUS-BASED RECOMMENDATION

If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.

PRACTICE POINT

Points of guidance used to support evidence-based recommendations, where the subject matter is outside of the scope of search strategy, and which were formulated based on expert opinion using a consensus process.

- Before offering biopsy after an elevated total PSA test result, take into account a man's family history of prostate cancer (see Chapter 1. *Risk*) and the results of further investigations (see 2.5 *Testing with variants of PSA to improve sensitivity after an initial total PSA ≤ 3.0 ng/mL* and 2.6 *Testing with variants of PSA or repeat PSA testing to improve specificity after an initial total PSA > 3.0 ng/mL*).

- Transrectal and transperineal biopsy approaches are both acceptable with respect to rates of cancer detection. The approach taken should be based on the man's wishes, the surgeon's experience, risk of sepsis and other morbidity, and practical issues such as cost and access to the necessary facilities.

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*
Further high quality studies would be needed to resolve the issues of transrectal vs. transperineal biopsy for cancer detection, adverse outcomes and comparability with subsequent prostatectomy findings. Only few studies reported data on complication rates for various biopsy schemes, which was difficult to evaluate and included data mainly on immediate rather than long-term complications with little information on follow-up patterns.

Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care? While already adopted by some urologists, smaller numbers of biopsies are routinely collected by others.	**YES**
Are there any resource implications associated with implementing this recommendation? Small increase in time needed to perform biopsies. Modest increase in pathology costs. No changes to equipment. Implementation of this recommendation may result in prostate biopsy becoming a procedure that is mainly performed in operating theatres and with general anaesthesia.	**YES**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

Chapter 3.2

NHMRC Evidence Statement Form for Clinical Question 8: If prostate cancer is not found in an adequate biopsy what if any additional steps should be taken and what recommendations should be made regarding the strategy for subsequent PSA testing?

NICE question 8.1: *In men who have been referred with suspected prostate cancer, what are the prognostic factors that determine the need for further investigation following a prior negative biopsy?* Question adopted from NICE 2014 guidelines - UK National Institute for Health and Care Excellence's (NICE's) January 2014 Clinical Guideline for Prostate cancer: diagnosis and treatment (National Collaborating Centre for Cancer 2014).		**Report body of evidence tables and NICE guidelines evidence review (**National Collaborating Centre for Cancer. Draft Evidence Review for Update of Clinical Guidelines 58 Prostate cancer: diagnosis and treatment http://www.nice.org.uk/guidance/cg175/evidence/cg175-prostate-cancer-appendix-m2)
1. Evidence base *(number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)*		
NICE review of studies of prognostic factors at initial negative biopsy that may predict prostate cancer at re-biopsy NICE reviewed 25 studies of age, 27 of PSA level, 18 of free-to-total PSA (ftPSA), nine of PSA density, ten of PSA velocity, 18 of DRE, 12 of prostatic intraepithelial neoplasia (PIN) or high grade prostatic intraepithelial neoplasia (HGPIN), six of atypical small acinar proliferation (ASAP), one of atypical glands suspicious for carcinoma (AGSC), 12 of biomarker PCA3, two of family history, and one of ethnicity assessed at initial biopsy as prognostic for prostate cancer at re-biopsy. All were either level II or level III prognostic or diagnostic accuracy studies. The NICE review rated one study as of moderate quality and the remainder as of low or very low quality; the main weaknesses being that the prognostic factor of interest influenced whether patient underwent repeat biopsy in many of the studies and that many of the models did not include important confounding factors such as age, free-to-total PSA, and prostate volume. **Grade D** **Studies found on repeating NICE review search strategy and published after the cut-off date for the NICE review and before 1st March 2014** One additional level II and two level III prognostic or diagnostic accuracy studies were found (ElShafei et al 2013; Gittelman et al 2013; Stewart et al 2013). All were judged to be at high risk of bias in predicting prostate cancer at re-biopsy. The one study that assessed diagnostic accuracy (of one prognostic factor, gene methylation status; Stewart et al 2013) was judged to be at risk of bias in this assessment. The prognostic factors assessed by these three studies were: ElShafei et al (2013) – Age, PSA, ftPSA, PSAd, PIN, HGPIN, ASAP, family history, ethnicity; Gittleman et al (2013) – Age, family history, ethnicity; Stewart et al (2013) – Age, PSA, DRE, HGPIN, DNA methylation.	A	**One or more level I studies with a low risk of bias or several level II studies with a low risk of bias**
	B	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias**
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**

Grade D		
2. Consistency *(if only one study was available, rank this component as 'not applicable') See body of evidence tables in report – results and p value (95% CI)*		
Age The NICE review found odds ratios (ORs) of 1.01-1.10 per year increase in age in 14 studies of the relationship of age (as a continuous variable) with prostate cancer at re-biopsy examined in multivariate models that adjusted for potential confounders such as different PSA measures, HGPIN, ASAP, DRE and prostate volume; three were statistically significant (p<0.05). This review found three additional studies that reported results from multivariate models, two with ORs of 1.01 per year of age as a continuous variable, p>0.05 in each case (Gittelman et al 2013 and Stewart et al 2013), and one with an OR of 1.47 (95%CI 1.10-1.97) for comparison of the 75th with 25th percentiles of age as a continuous variable (ElShafei et al 2013). There is consistent evidence of a weak positive association between age and detection of cancer at re-biopsy. **Grade B** **Total PSA at first biopsy** The NICE review found ORs of 0.93-1.04 per ng/mL increase in PSA in 14 studies of the relationship of PSA as a continuous variable with prostate cancer at re-biopsy examined in multivariate models; three were statistically significant. Two studies reported multivariate adjusted results for PSA in categories; none were statistically significant. Sensitivity and specificity were not consistent for similar PSA levels between six studies and showed no clear trend with increasing cut-off level. One additional study reported a multivariate adjusted OR of 1.59 for a PSA of <10 relative to ≥10 ng/mL (p=0.18; Stewart et al 2013). A second additional study did not report multivariate adjusted results for PSA (ElShafei et al 2013). In summary there is moderately consistent evidence of a weak positive association between total PSA and detection of cancer at re-biopsy. Test performance characteristics were not consistent. **Grade C** **Ratio of free PSA to total PSA (ftPSA) at first biopsy** The NICE review found odds ratios (ORs) of 0.87-1.40 per unit increase in ftPSA in 8 studies of the relationship of ftPSA as a continuous variable with prostate cancer at re-biopsy examined in multivariate models; four were statistically significant (3 for an inverse association and 1 for a direct association). Three studies reported multivariate adjusted ORs comparing categories of ftPSA; in each case the OR was <1 for the higher category relative to the lower category but none was statistically significant. Sensitivity and specificity were not consistent for similar ftPSA levels between five studies and showed no clear trend with increasing cut-off level. One additional study did not report multivariate adjusted results for ftPSA (ElShafei et al 2013). In summary there was inconsistent evidence of an inverse association of ftPSA with cancer at re-biopsy. Test performance characteristics were not consistent.	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**

Grade D **PSA density (PSAd) at first biopsy** The NICE review found statistically significant results in 4 of 5 studies of the relationship of PSAd as a continuous or categorical variable with prostate cancer at re-biopsy examined in multivariate models. Where reported the ORs were 1.005 (95%CI 0.998-1.012) per unit of PSAd as a continuous variable and 2.3 (95% CI 1.4-4.0) and 2.34 (p=0.012) for a PSAd of >0.15 relative to less than this value. Test performance characteristics were reported for only one study (sensitivity 66%, specificity 60%). One additional study did not report multivariate adjusted results for PSAd (ElShafei et al 2013). In summary, there was moderately consistent evidence of a positive association of PSAd with cancer at re-biopsy in five studies. **Grade C** **PSA velocity (PSAv) at first biopsy** The NICE review found statistically significant results in 3 of 5 studies of the relationship of PSAv as a continuous or categorical variable with prostate cancer at re-biopsy examined in multivariate models. Where reported the ORs were 1.34 (95%CI 1.03-1.74) and 1.58 (95%CI 1.06-2.35) per unit of PSAv as a continuous variable. Sensitivity and specificity showed no clear trend with increasing cut-off level and demonstrated low overall diagnostic accuracy in four studies. There were no additional studies of PSAv. In summary, there was moderately consistent evidence of a positive association of PSAv with cancer at re-biopsy in five studies. Test performance characteristics were not consistent. **Grade C** **DRE at first biopsy** The NICE review found odds ratios (ORs) of 0.4-6.75 for abnormal relative to normal DRE in 13 studies of its relationship with prostate cancer at re-biopsy examined in multivariate models; five were statistically significant with ORs of 2.63-4.61 (reported for only three of the five studies). Eight studies reported low overall diagnostic accuracy; most reporting low sensitivity (0-55.9% with six <30%) but high specificity (56.3-95.9% with five >85%). One additional study found an OR of 1.36 (p=0.30) from a multivariate model (Stewart et al 2013). In summary there is inconsistent evidence of positive association between abnormal DRE and detection of cancer at re-biopsy. There was moderately consistent evidence of low sensitivity and high specificity. **Grade C** **High grade prostatic intraepithelial neoplasia (HGPIN) at first biopsy**		

The NICE review found eight studies of HGPIN with multivariate models that reported ORs of 0.13 to 3.2 for prostate cancer at re-biopsy (there was, though, only one study with an OR <1); four were statistically significant. Five studies reported inconsistent test performance characteristics of the presence of HGPIN at initial biopsy. The NICE review also found two studies of PIN, which reported univariate results only; one reported a statistically significant association of PIN with prostate cancer at re-biopsy and the other did not. Two additional studies reported ORs of 1.87 (1.23-2.85) (ElShafei et al 2013) and 1.25 (p=0.5; Stewart et al 2013) for the association of HGPIN with prostate cancer at re-biopsy. There was moderately consistent evidence for the association of HGPIN with cancer at re-biopsy. Test performance was inconsistent. **Grade C** **Atypical small acinar proliferation (ASAP)/atypical glands suspicious for carcinoma (AGSC) at first biopsy** The NICE review found five studies that examined the relationship between the presence of atypical small acinar proliferation/atypical glands suspicious for carcinoma and the risk of prostate cancer at re-biopsy in multivariate models. All reported statistically significant associations (p<0.05). One study that was reported twice (more participants in the second report) reported multivariate adjusted OR of 20.7 (95% CI 4.45-96.4; p<0.001) in the first report and 17.7 (p<0.001) in the second. The other four studies reported ORs ranging between 2.97 and 3.65. Two studies that assessed diagnostic accuracy for the presence of atypical small acinar proliferation/atypical glands suspicious for carcinoma at initial biopsy both reported low sensitivity but high specificity. The updated review found one additional study that examined the relationship between the presence of atypical small acinar proliferation/atypical glands suspicious for carcinoma and the risk of prostate cancer at re-biopsy. It reported an OR of 1.92 (95% CI 1.07-3.46). **Grade A** **PCA3 at first biopsy** The NICE review found three studies that reported multivariate adjusted associations of PCA3 with prostate cancer at re-biopsy; the association was statistically significant in each case. One study reported an OR of 1.02 (95%CI 1.00-1.03) per unit of PCA3 as a continuous variable; another, an OR of 3.01 (95%CI 1.74-5.23) for a PCA3 value of >30 relative to <30; and another, ORs of 9.44 (95%CI 5.15-17.31) and 9.29 (95%CI 5.11-16.89) respectively for PCA3 cut-offs at 39 and 50. Sensitivity and specificity were not consistent in a total of 12 studies in which it had been measured and showed no clear trend with increasing cut-off level; indicating low overall diagnostic accuracy. No additional studies addressed PCA3. There was consistent evidence in three studies for the association of PCA3 with prostate cancer at re-biopsy. Test performance was inconsistent.		

Grade C

DNA methylation in first biopsy
One additional study reported on the association with prostate cancer on re-biopsy of hypermethylation of three marker genes combined, *GSTP1, APC and RASSF1*, evaluated in tissue from the first biopsy (Stewart et al 2013). The OR for cancer on re-biopsy was 3.17, 95%CI 1.81-5.53, adjusted for age, PSA, DRE, and histopathology of first biopsy (benign, atypical cells, HGPIN). The sensitivity of the test was 68% and specificity 64%.
Grade NA

Family history of prostate cancer
Both of two studies included in the NICE review found family history to be a significant predictor of prostate cancer at re-biopsy in multivariate models (OR of 3.1, 95%CI 1.2-8.0, reported from one study). Two additional studies observed ORs of 1.33 (95%CI 0.81-2.18) (ElShafei et al 2013) and 0.92 (95%CI 0.50-1.72) (Gittelman et al 2013) in multivariate models. There was inconsistent evidence in four studies of an association of family history with prostate cancer on re-biopsy.
Grade D

Ethnicity
The NICE review reported on one study, which found an OR of 0.8 (95%CI 0.4-1.6) for prostate cancer at re-biopsy in those of Caucasian ethnic origin relative to those of other ethnic origins in a multivariate model. Two additional studies observed ORs of 1.21 (95%CI 0.63-2.31) (ElShafei et al 2013) and 0.58 (95%CI 0.23-1.45) (Gittelman et al 2013) in US men of black ethnicity relative to non-black in multivariate models. There was consistent evidence in three studies of lack of association of ethnicity with prostate cancer on re-biopsy.
Grade C

3. Clinical impact *See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

Prognostic factors **Grade B** ASAP	A	**Very large**
	B	**Substantial**
	C	**Moderate**

Grade C DRE, ASGC **Grade D** Age, PSA, ftPSA, PSAd, PSAv, HGPIN, PCA3, DNA methylation, family history, ethnicity	D	**Slight/Restricted**

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*

The NICE review noted that there were six studies (16%) in which there were differences between the study populations and patients likely to be tested in practice. Two of the additional studies were done in US populations (both including African American men, 13.5% of population in ElShafei et al 2013 and 8.4% in Gittelman et al 2013), and the third was done in the UK and Belgium. **Grade B**	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*

Most of the prognostic factors studied are likely to be measured in Australian men having an initial prostate biopsy for suspected prostate cancer. **Grade B**	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*

The NICE guideline development group (GDG) noted that it considered the outcome of diagnostic accuracy to be the most important as it would show which prognostic factors were significant predictors of cancer. The GDG also took specific account of the following limitations of the evidence when making its recommendations: the time between biopsies was unclear in many studies and sometimes more than 1 year; several studies excluded important potential confounding factors from their statistical models; the way tests were performed and the way results were interpreted was poorly reported; and the reference standard depended on the index test result for several studies.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level II to Level III studies/SRs with a high risk of bias

2. Consistency	A-D	A – All studies consistent – ASAP B – Most studies consistent and inconsistency can be explained – age C – Some inconsistency, reflecting genuine uncertainty around question – total PSA, PSA density, PSA velocity, DRE, HGPIN, PCA3, ethnicity D – Evidence is inconsistent – ftPSA, family history NA – Not applicable (one study only) – AGSC, DNA methylation
3. Clinical impact	B-D	B – Substantial – ASAP C – Moderate – DRE, ASGC D – Slight/restricted – Age, PSA, ftPSA, PSAd, PSAv, HGPIN, PCA3, DNA methylation, family history, ethnicity
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

Evidence statement:

Age: There is consistent evidence that each additional year of age at an initial negative biopsy predicts a 1-10% greater risk of prostate cancer at re-biopsy.

Ethnicity: There is consistent evidence in three studies (two including African American men) that ethnicity at an initial negative biopsy is not associated with prostate cancer at re-biopsy.**Family history of prostate cancer**: There is inconsistent evidence in four studies that family history of prostate cancer at an initial negative biopsy is associated with risk of prostate cancer at re-biopsy.**DRE:** There is moderately consistent evidence that an abnormal DRE at an initial negative biopsy predicts a higher risk of prostate cancer at re-biopsy, with high specificity but low sensitivity.

Total PSA: There is little evidence that a higher total PSA at an initial negative prostate biopsy predicts a higher risk of prostate cancer at re-biopsy.

Ratio of free to total PSA: There is inconsistent evidence that a higher f/t PSA% at an initial negative prostate biopsy predicts a lower risk of prostate cancer at re-biopsy.

PSA density: A moderately consistent association of PSA density at an initial negative biopsy with risk of prostate cancer at re-biopsy is rendered uncertain by the few studies that adjusted for possible confounding and incomplete reporting of key results.

PSA velocity: A moderately consistent association of PSA velocity at an initial negative biopsy with risk of prostate cancer at re-biopsy is rendered uncertain by the few studies that adjusted for possible confounding and incomplete reporting of key results.

Atypical small acinar proliferation: There is consistent evidence that a finding of ASAP at an initial negative biopsy predicts with high specificity but low sensitivity a higher risk of prostate cancer at re-biopsy.

High-grade PIN: There is moderately consistent evidence that high-grade PIN at an initial negative biopsy predicts a higher risk of prostate cancer at re-biopsy, but with low diagnostic accuracy.

PCA3: The three studies that adjusted for potential confounding found significantly positive associations of PCA3 at an initial negative biopsy with prostate cancer at re-biopsy. However, the sensitivity and specificity PCA3 for prostate cancer at re-biopsy were not consistent in 12 studies in which they were measured and showed no clear trend with increasing cut-off level.

DNA methylation: The only available study found that methylation of three marker genes in tissue from an initial negative biopsy was a moderately strong predictor of prostate cancer at re-biopsy.

The additional studies identified in the update review (those published after the NICE systematic review and before 1 March 2014) did not materially alter the evidence on which the recommendations in the NICE guideline were based. Therefore we have chosen to adapt the NICE 2014 recommendations with minimal changes. The NICE guideline recommended that clinicians should advise men whose initial biopsy is negative for prostate cancer that there is still a risk that prostate cancer is present, and that the risk is higher if any of the following conditions apply: the initial biopsy showed high-grade prostatic intraepithelial neoplasia, the initial biopsy showed atypical small acinar proliferation, or their digital rectal examination before the initial biopsy was abnormal.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION** **D**
Advise men whose initial biopsy is negative for prostate cancer that they should continue to be followed up. Monitor more closely for those with abnormal findings on pre-biopsy digital rectal examination, and for those whose biopsy findings included either atypical small acinar proliferation or high-grade prostatic intra-epithelial neoplasia. In addition to further PSA testing and digital rectal examination, consider prostate imaging with investigations that can help to localise the site of cancer within the prostate, and repeat biopsy using a targeted approach.	
CONSENSUS-BASED RECOMMENDATION *If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.*	
None.	
PRACTICE POINTS *Points of guidance used to support evidence-based recommendations, where the subject matter is outside of the scope of search strategy, and which were formulated based on expert opinion using a consensus process*.	
None.	

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*
The predictive value of histopathological features reported by the pathologist reviewing the initial biopsy.

Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care? Implementation of the recommendations for advising men with a negative initial biopsy about their risk of prostate cancer would not necessitate significant changes to usual care.	**NO**
Are there any resource implications associated with implementing this recommendation? Implementation of the recommendations for advising men with a negative initial biopsy about their risk of prostate cancer would not have any important resource implications.	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised? Implementation of the recommendations for advising men with a negative initial biopsy about their risk of prostate cancer would not necessitate significant change the way care is organised.	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

No barriers to the implementation of these recommendations are envisaged.	

NHMRC Evidence Statement Form for Clinical Question 8: If prostate cancer is not found in an adequate biopsy what if any additional steps should be taken and what recommendations should be made regarding the strategy for subsequent PSA testing?

<table>
<tr><td colspan="2">NICE question 8.2: In men with suspected prostate cancer whose initial TRUS biopsy is negative, what should be the next investigation(s)?

Question adopted from NICE 2014 guidelines - UK National Institute for Health and Care Excellence's (NICE's) January 2014 Clinical Guideline for Prostate cancer: diagnosis and treatment (National Collaborating Centre for Cancer 2014).</td><td colspan="2">Report body of evidence tables and NICE guidelines evidence review (National Collaborating Centre for Cancer. Draft Evidence Review for Update of Clinical Guidelines 58 Prostate cancer: diagnosis and treatment http://www.nice.org.uk/guidance/cg175/evidence/cg175-prostate-cancer-appendix-m2)</td></tr>
<tr><td colspan="4">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td colspan="2" rowspan="4">NICE review: NICE systematically reviewed studies reporting the diagnostic yield of the following after a negative prostate biopsy: review of initial biopsy, repeat TRUS biopsy, multiparametric MRI-targeted biopsy, extended/saturation transrectal or transperineal biopsy, enhanced ultrasound targeted biopsy, and elastography targeted biopsy.

The NICE systematic review included case series (level IV evidence) as well as comparative studies. The primary comparison of different types of investigations, that being MRI targeted rebiopsy and saturation biopsies, was drawn from a meta-regression analysis of essentially case series (level IV evidence) data (Nelson et al 2013). Evidence on multiparametric MRI targeted biopsy in addition to standard biopsy came from a systematic review (Mowatt et al 2013) which included case series studies and four additional recent studies. These four recent studies, included three sequential sampling studies (Arsov et al 2012, Portalez et al 2012, Vourganti et al 2012) of level II evidence and one case series study of level IV evidence (Lee et al 2012). Evidence on extended/saturation biopsy came from 35 case series level IV studies and four cohort studies. NICE systematically reviewed 7 studies on repeat standard TRUS biopsy including data from control arms of cohort studies (level IV evidence) and five studies including 3 case series that reported on the use of contrast enhanced ultrasound. One study compared elastosonography rebiopsy and contrast enhanced ultrasound rebiopsy however no relevant data could be extracted. Another study compared the initial diagnosis (performed by consultant pathologists) with a reference standard diagnosis by consultant pathologists with a special interest in uropathology. NICE assessed the risk of bias using the QUADAS-2 checklist. Namely, risk of bias in patient selection (was the sample representative, was the selection</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or
II studies with a moderate risk of bias</td></tr>
<tr><td>D</td><td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td></tr>
</table>

criteria clearly described) and risk of bias in the index test (was the repeat biopsy protocol described in sufficient detail). Risk of bias was deemed as low in the majority of studies. **Grade D** **NICE review update:** The literature search was extended to include studies published up to 1st March 2014. The update review was restricted to studies that directly compared different post negative biopsy investigations, i.e. sequential sampling studies or randomised controlled trials (level II evidence). Eight additional level II evidence sequential sampling studies were found (Salomon *et al* 2014; Abd-Alazeez *et al* 2014; Costa *et al* 2013; Tang *et al* 2013; Sonn *et al* 2013; Pepe *et al* 2013; Cornelis *et al* 2013; Yerram *et al* 2012). One study examined the addition of real-time elastography targeted biopsies to TRUS biopsy (Salomon *et al* 2014), while the other studies examined the addition of multiparametric MRI (including 3T MRI) targeted prostate biopsy to random or systematic biopsy. For consistency, we extracted data from studies in the NICE systematic review, including three of the four level II mpMRI studies (Lee *et al* 2012; Portalez *et al* 2012; Vourganti *et al* 2012). All eight update studies were judged to be at moderate risk of bias using a modified QUADAS-2 quality appraisal tool. **Grade C**		
2. Consistency *(if only one study was available, rank this component as 'not applicable') See body of evidence tables in report – results and p value (95% CI)*		
Based on the meta-regression by Nelson *et al* 2013, the NICE review reported an estimated prostate cancer detection of 37.6% using MRI targeted biopsy in addition to non-targeted biopsy, 36.8% detection rate using transperineal saturation biopsy and 30.0% detection rate using transrectal saturation biopsy. **Multiparametric MRI targeted biopsy** The NICE review reported that the Mowatt *et al* 2013 systematic review estimated 4-21% of cancers would be missed if only men with mpMRI lesion(s) were re-biopsied. The three additional studies included in the NICE review showed that the addition of mpMRI targeted biopsies to standard biopsies improved cancer detection rates by 14.3% to 42.6% points. Six of the seven more recent studies reported in the NICE update review, showed more modest improvements of 5.1% to 26.3% points. One of the most recent studies showed no improvement (Abd-Alazeez *et al* 2014). The variability in the magnitude of these improvements may be in part explained by the variation in the extent of the standard biopsy (6-32 biopsy cores), type of mpMRI and number of targeted cores, and also the study	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**

size. **Grade B** **Extended/saturation biopsy** NICE found that cancer detection rate appears to increase with the number of re-biopsy cores, although there is variability between studies in the reported rates. Their findings are based on the pooling of results from primarily case series studies; pooled cancer detection rates were approximately 20% for repeat TRUS biopsy (10-12 biopsy cores), 20% for TRUS extended biopsy (12-14 biopsy cores), 30% for TRUS saturation biopsy (median of 24 biopsy cores) and 40% for transperineal saturation biopsy (median of 29 biopsy cores). The pooled proportion of detected cancers considered clinically significant (according to the individual study definitions) was 27% for repeat TRUS 10-12 biopsy cores, 60% for TRUS extended biopsy, 57% for TRUS saturation biopsy, and 62% for transperineal saturation biopsy. **Grade C** **Enhanced ultrasound targeted biopsy** NICE reported a cancer detection rate of 30% (13/44) for Power Doppler enhanced ultrasound based on pooled data from two small studies (Remzi *et al* 2004, Morelli *et al* 2009) and a rate of 20.8% (117/562) for Colour Doppler enhanced ultrasound based on pooled data from two studies. Taverna *et al* 2011 compared Colour Doppler ultrasound with or without SonoVue against TRUS grey-scale 13-core systematic biopsy sampling, finding no differences in cancer detection rates between groups (29% verse 28% verse 31%). **Grade C** **Elastography targeted biopsy** NICE included one small study published as an abstract only which did not report any comparative information (Morelli *et al* 2009). One study identified in the NICE update reported an 8.2% point improvement (31.4% vs 39.2%) with the addition of elastography in a group of 449 patients (Salomon *et al* 2014).		

Grade NA **Review of initial biopsy** NICE reported that a study of 2516 non-screened men found that 1.2% of biopsies initially classified as benign were changed to cancer on review, 1.5% of biopsies with an initial HGPIN diagnosis were changed to cancer on review and for biopsies an initial diagnosis of suspicious for malignancy the figure was 4.9% (Oxley *et al* 2011). Of those biopsies which were initially positive, 0.4% were changed to benign and 0.1% to suspicious. **Grade NA**		

3. Clinical impact *See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

Multiparametric MRI targeted biopsy Adding mpMRI targeted biopsies to standard biopsies improved cancer detection rates by 0% to 5.1% points when compared with standard biopsies with >20 cores (Abd-Alazeez *et al* 2014; Pepe *et al* 2013) and by 6.4% to 14.3% using various different or unspecified types of mpMRI in 4 of 5 studies compared with 12 core biopsy (Sonn *et al* 2013; Cornelis *et al* 2013; Yerram *et al* 2012; Vourganti *et al* 2012) In the fifth study using a 12 core standard biopsy, the improvement was 42.6% using T2W + DWI mpMRI (Lee *et al* 2012). **Grade B** **Enhanced ultrasound targeted biopsy** NICE reported that the one study examining the effect of adding enhanced ultrasound (Colour Doppler) targeted biopsy to a TRUS grey-scale 13-core systematic biopsy, found a 2-3% point improvement (Taverna *et al* 2011). **Grade D** **Saturation or extended biopsy** Increasing the number of biopsy cores increased cancer detection rates. Transrectal 12-14 core biopsies had cancer detection rates of 15% to 25%, whereas transrectal saturation biopsies (median core number ~24) had cancer detection rates of 11%-45% and transperineal saturation biopsies (median core number ~28) reported cancer detection rates of 23%-72%. The NICE review also pooled data for complications related to repeat saturation biopsy. The most common complication was haematuria, occurring in 8.8% of men undergoing transrectal saturation biopsy and 23.4% of	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**

men undergoing transperineal biopsy. Rectal bleeding was a complication in 1.2% of men undergoing transrectal biopsy. Urinary retention was more common amongst men undergoing transperineal saturation biopsy (6.8%) whereas acute prostatitis was more common amongst men undergoing transrectal biopsy (3.9%). **Grade C** **Elastography targeted biopsy** The addition of elastography targeted biopsies to a TRUS 10 core biopsy increased cancer detection rate by 8.2% points (Morelli *et al* 2009). **Grade D** **Review of initial biopsy** Review of initial biopsy reclassified 1.2% of benign biopsies as cancerous and 0.4% of positive biopsies were reclassified to benign (Oxley *et al* 2011). **Grade C**		

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*		
Nearly one third of the included studies were from US/Canadian populations with, no more 25% of the included men African American. The remainder of the studies were predominantly from European countries, with only 4 studies from Asian countries. **Grade C**	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Applicability relates directly to the availability of MRI facilities, expertise in interpretation of findings and the ability to pay for the investigations. At present, prostate MRI is not reimbursed by Medicare, although this may change. Detailed cost-benefit analyses are awaited to help guide endorsement. **Grade B**	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*		
Availability and affordability, especially for non-insured patients, may change in the future.		
EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*		
Component	**Rating**	**Description**
1. Evidence base	C, D	C – One or two Level III studies with low risk of bias or Level I or II studies with a moderate risk of bias – Update of the NICE review D – Level IV studies or Level I to III studies/SRs with a high risk of bias – NICE review
2. Consistency	B, C, NA	B – Most studies consistent and inconsistency can be explained – Multiparametric MRI targeted biopsy, C – Some inconsistency, reflecting genuine uncertainty around question – Extended/saturation biopsy, Enhanced ultrasound biopsy NA – Not applicable (one study only) – Elastography and review of initial biopsy
3. Clinical impact	B, C, D	B – Substantial – Multiparametric MRI targeted biopsy C – Moderate – Extended/saturation biopsy, Review of initial biopsy D – Slight/Restricted – Enhanced ultrasound targeted biopsy, Elastography targeted biopsy
4. Generalisability	C	Evidence not directly generalizable to the target population but could be sensibly applied
5. Applicability	B	Evidence applicable to Australian healthcare context with caveats

Evidence statement:

Multiparametric MRI targeted biopsy

Studies included in the NICE systematic review found that compared with 12 core biopsy protocols adding multiparametric MRI (T2W+ DWI +DCE) targeted biopsies improved cancer detection rates by 14.3 % points and adding T2W + DWI multiparametric MRI improved cancer detection rates by 42.6 percentage points.

For men with positive findings on multi parametric MRI , adding multiparametric MRI targeted biopsies to 12-core biopsies improved cancer detection rates by 6.4 , 10.1, 14.3 and 45.2 percentage points.

A single study from the updated NICE systematic review showed that a repeat saturation biopsy on its own had a cancer detection rate of 35.9%. Adding 3–4 multiparametric MRI targeted biopsies increased the cancer detection rate by an additional 5.1 percentage points.

Enhanced ultrasound targeted biopsy

Studies included in the NICE systematic review found that adding enhanced ultrasound targeted biopsy to a TRUS grey-scale schematic biopsy resulted in cancer detection rates similar to those using the TRUS grey-scale schematic biopsy method alone.

Saturation or extended biopsy

Studies included in the NICE systematic review found that increasing the number of biopsy cores increased cancer detection rates. Transrectal 12-14 core biopsies had a cancer detection rate of 15-25%. Transrectal saturation biopsies had a cancer detection rate of 11-45%, and transperineal saturation biopsies had a cancer detection rate of 23-72%. The most common complication was haematuria reported in 8.8% of men undergoing transrectal saturation biopsy and 23.4% of men undergoing transperineal biopsy.

Elastography targeted biopsy

Studies included in the NICE systematic review found no relevant evidence.

NICE update review found that the addition of elastography-targeted biopsies to a TRUS 10-core biopsy increased cancer detection rate by 8.2 percentage points.

Review of initial biopsy

A study included in the NICE systematic review found that review of initial biopsy reclassified 1.2% of benign biopsies as cancerous and 0.4% of positive biopsies to benign.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION **D**
Consider multiparametric MRI (using T2- and diffusion-weighted imaging) for men with a negative transrectal ultrasound-guided biopsy to determine whether another biopsy is needed. Do not offer another biopsy if the multiparametric MRI (using T2- and diffusion-weighted imaging) is negative, unless any of the following risk factors are present: • atypical small acinar proliferation on initial biopsy • abnormal digital rectal examination before the initial biopsy • high-grade prostatic intra-epithelial neoplasia on initial biopsy	
CONSENSUS-BASED RECOMMENDATION *If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given***.**	
None.	
PRACTICE POINTS *Points of guidance used to support evidence-based recommendations, where the subject matter is outside of the scope of search strategy, and which were formulated based on expert opinion using a consensus process*.	
• Multiparametric MRI should be used only in centres with experienced radiologists appropriately trained in the use of multiparametric MRI to aid urologists in the management of individual patients. • Clinicians and other staff performing multiparametric MRI should do so in accordance with appropriate standards and guidelines for its use. • The recommendations for multiparametric MRI apply only to its use in patients who have already undergone biopsy. Primary healthcare professionals should not order multiparametric MRI in the initial investigation of suspected prostate cancer in men with raised PSA levels. • Advise patients not undergoing repeat biopsy after a normal multiparametric MRI that there is a 10-15% chance of missing a significant cancer and that further follow-up is recommended. • For men at average risk for prostate cancer whose initial biopsy is negative for prostate cancer, and who have a life expectancy of less than 7 years (e.g. due to their age or due to other illness), advise that no further action is recommended unless they develop symptoms that suggest prostate cancer.	

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*
The following issues remain unresolved: • Whether the transrectal and transperineal biopsy approaches differ according to effectiveness in cancer detection, comparability of biopsy findings with subsequent prostatectomy findings, or rates of adverse outcomes • Comparative complication rates for various biopsy schemes. Few studies reported complication rates for various biopsy schemes and these were mainly immediate outcomes. Data for long-term follow-up findings were difficult to match to biopsy pattern. • The role of multiparametric MRI, given that it cannot identify all prostate tumours, including all clinically significant tumours.

Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care? The use of multiparametric MRI after an initial biopsy would affect the patient's pathway through the healthcare system and would alter the way clinical decisions are made about further biopsies.	**YES**
Are there any resource implications associated with implementing this recommendation? Implementation of the recommendation for the use of multiparametric MRI would lead to an increase in referrals for this imaging procedure before clinical decisions are made about further biopsies and would therefore increase the cost of care, but may reduce the number of further biopsies. If a man chooses to have multiparametric MRI after a negative biopsy, this will incur significant costs, which may not be offset by the reduced need for biopsies.	**YES**

Will the implementation of this recommendation require changes in the way care is currently organised? Implementation of the recommendations for advising men with a negative initial biopsy about their risk of prostate cancer would not necessitate significant change the way care is organised.	**NO**
Is the guideline development group aware of any barriers to the implementation of this recommendation? At present, facilities for performing multiparametric MRI and expertise in its interpretation are limited to major metropolitan centres. The cost of this imaging procedure may be a deterrent for some men. There is currently no Medicare Item number for multiparametric MRI in assessment of the prostate. However, the Prostate Cancer Foundation of Australia is collaborating with the Australian Government Department of Health, the Urological Society of Australia and New Zealand, and The Royal Australian and New Zealand College of Radiologists to establish item numbers for multiparametric MRI.	**YES**

Chapter 4

Evidence Statement Form for Clinical Question 9: What should be the criteria for choosing active surveillance in preference to definitive treatment offer as primary management to men who have a positive prostate biopsy?

<table>
<tr><td colspan="2">PICO Question 9: For men with biopsy diagnosed prostate cancer, for which patients (based on diagnostic, clinical and other criteria) does active surveillance achieve equivalent or better outcomes in terms of length and quality of life than definitive treatment?

NICE question: Which men with localised prostate cancer should be offered active surveillance?</td><td>Report body of evidence tables and evidence review for NICE Guidelines (National Collaborating Centre for Cancer. Draft Evidence Review for Update of Clinical Guidelines 58 Prostate cancer: diagnosis and treatment accessed 29/01/14 - . final version accessed 18/11/14 http://www.nice.org.uk/guidance/cg175/evidence/cg175-prostate-cancer-appendix-m2)</td></tr>
<tr><td colspan="3">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td rowspan="4">NICE review regarding men with localised prostate cancer that should be offered active surveillance, reviewed 4 analyses from 3 studies, one was considered moderate quality (Selvadurai et al. 2013) and the others of low (Khatami et al. 2007) or very low quality (Khatami et al. 2009, Klotz et al. 2010). All studies reported results with end points of cessation of active surveillance and did not report overall survival, prostate cancer specific mortality or quality of life.
Grade D

A further 3 cohort studies were examined. These studies reported mortality and quality of life data between men on surveillance and immediate treatment. All were considered of low quality and at high risk of bias (Holmström et al. 2010, Kakehi et al. 2008, Sun et al. 2012).
Grade D</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or
II studies with a moderate risk of bias</td></tr>
<tr><td>D</td><td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td></tr>
<tr><td colspan="3">2. Consistency (if only one study was available, rank this component as ‘not applicable’) See body of evidence tables in report – results and p value (95% CI)</td></tr>
<tr><td rowspan="2">NICE review analysed factors such as PSA velocity, PSA level at diagnosis, PSA density, free-to-total PSA ratio, PSA doubling time, total cancer length at biopsy, tumour</td><td>A</td><td>All studies consistent</td></tr>
<tr><td>B</td><td>Most studies consistent and inconsistency can be explained</td></tr>
</table>

volume, Gleason score at diagnosis, clinical stage at diagnosis and expression of the biomarker Ki67. All studies reported conflicting results for all parameters and inconsistent results. **Grade D** The additional studies demonstrated similar prostate cancer specific survivals for men on active surveillance. In one study (Kakehi *et al.* 2008) men with PSA ≤20 ng/mL, clinical stage T1c prostate cancer, 1-2 cores involved and Gleason ≤6, did not demonstrate any difference in prostate cancer specific mortality. A second study (Holmström *et al*. 2010) included men with PSA <20 ng/mL, Gleason ≤ 6, with T1-2 cancer demonstrated an increased prostate cancer mortality in those men undergoing active surveillance (0.7% vs 0.9%, p > 0.05). Overall risk of cancer death was low, including those men with Gleason score ≤6, PSA ≤20 ng/mL and clinical stage T1-2 tumours (Sun *et al.* 2012). **Grade C**	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**

3. Clinical impact *See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

NICE review demonstrated one study (Selvadurai *et al.* 2013) with a PSA velocity of >1 ng/mL/year was predictive of progressing off active surveillance (p <0.001). Conflicting results were obtained with regards to PSA density, free-to-total PSA ratio, Gleason score at diagnosis and clinical stage at diagnosis. Whilst one study (Klotz *et al.* 2010) found patients with PSA doubling time of <3 years to have 8.5 times greater risk of biochemical progression, the absolute level of the PSA doubling time (e.g. 0-1,1-2 or 2-3 years) was not predictive. Other studies did not confirm PSA doubling time as a factor for progression. **Grade C**	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*

There were significant differences between study populations in this review.	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**

Grade D	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*

Most of the factors measured here would be routinely measured in Australian men who are being considered for active surveillance. **Grade B**	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*

None.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	**D**	Level I to III studies with a high risk of bias
2. Consistency	**C**	C - Some inconsistency, reflecting genuine uncertainty around question
	D	D - NICE review - Evidence is inconsistent
3. Clinical impact	**C**	Moderate
4. Generalisability	**D**	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability	**B**	Evidence applicable to Australian healthcare context with few caveats

Evidence statement:

Three cohort studies reported similar prostate cancer-specific survival rates for men aged 41-80 years with prostate cancer managed by active surveillance. In men aged ≥ 66 years with early prostate cancer with PSA ≤ 20 ng/mL, clinical stage T1-2, and Gleason score ≤ 6, active surveillance was associated with a similarly low risk of death due to prostate cancer as immediate definitive treatment.

A systematic review of studies that followed men undergoing active surveillance found conflicting and inconsistent results for the effects of various baseline parameters including PSA velocity, PSA level at diagnosis, PSA density, free-to-total PSA%, PSA doubling time, total cancer length at biopsy, tumour volume, Gleason score at diagnosis, clinical stage at diagnosis, and Ki67 expression. However, PSA velocity > 1.0 ng/mL/year predicted progression from active surveillance to definitive treatment ($p < 0.001$) in one study.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION** **C**

Offer active surveillance to men with prostate cancer if all the following criteria are met:

- PSA ≤ 20 ng/mL
- clinical stage T1-2
- Gleason score 6.

CONSENSUS-BASED RECOMMENDATION

If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.

Consider offering active surveillance to men with prostate cancer if all the following criteria are met:

- PSA ≤ 10.0 ng/mL
- clinical stage T1-2a
- Gleason score ≤ (3 + 4 = 7) and pattern 4 component < 10% after pathological review.

For men aged less than 60 years, consider offering active surveillance based on the above criteria, provided that the man understands that treatment in these circumstances may be delayed rather than avoided.

Consider offering definitive treatment for:

- men with clinical stage T2b-c prostate cancer
- men with biopsy-diagnosed prostate cancer with PSA 10.0–20.0 ng/mL who do not meet the other criteria for active surveillance.

If the man strongly prefers active surveillance, offer repeat biopsy to ensure that disease classification is accurate.

Consider offering definitive treatment to men aged less than 60 years with either of the following:

- clinical stage T2b-c prostate cancer
- PSA 10.0–20.0 ng/mL and biopsy-diagnosed prostate cancer which does not meet the other criteria for active surveillance.

If the man strongly prefers active surveillance, offer repeat biopsy.

PRACTICE POINTS

Advise men with prostate cancer who have PSA ≤ 20 ng/mL, clinical stage T1-2, and Gleason score 6 that, if they choose active surveillance, their risk of death due to prostate cancer over the next 10 years would be low, and would probably be no greater than if they were to choose immediate definitive treatment.

When considering active surveillance, take into account other factors that may be associated with risk of future pathological progression but for which evidence is inconsistent (e.g. total cancer length at biopsy, tumour volume, PSA doubling time < 3 years and PSA density).

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*
There are several unresolved issues about identifying men in whom active surveillance is likely to achieve the optimal balance of benefits and harms. These include: • difficulty in estimating life expectancy. • the safety of active surveillance in men diagnosed with Gleason 7 (3+4) cancer • the role of multiparametric MRI in selecting men for active surveillance • the role of new biomarkers including genomic and epigenetic panels in selecting men for active surveillance • the safety of active surveillance in men younger than 60 years.

Table 3: Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This*	
Will this recommendation result in changes in usual care? No changes to the way care is currently organised would be required for implementation of the recommendations about which men with early prostate cancer should be offered active surveillance. If this results in more men being offered active surveillance, increased capacity for follow-up clinics and PSA testing facilities may be required.	**NO**
Are there any resource implications associated with implementing this recommendation? Implementation of this recommendation would have no significant implications for resourcing.	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised? Implementation of this recommendation would not require changes in the way care is currently organised.	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? No barriers to the implementation of these recommendations are envisaged.	**NO**

NHMRC Evidence Statement Form for Clinical Question 10: What is the best monitoring protocol for active surveillance and what should be the criteria for intervention?

<table>
<tr><td colspan="2">PICO Question 10: For men with biopsy-diagnosed prostate cancer following an active surveillance protocol, which combination of monitoring tests, testing frequency, and clinical or other criteria for intervention achieve the best outcomes in terms of length and quality of life?</td><td>Report body of evidence tables</td></tr>
<tr><td colspan="3">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td rowspan="4">No studies directly compared different monitoring protocols. The groups randomly allocated watchful waiting in these three studies all used 6 monthly testing (clinical examination and PSA) for the first year or two, following by annual testing thereafter. More extensive radiography testing was performed annually or less frequently, and in the event of suspected disease progression.

No studies directly compared different triggers for intervention. All three studies reported initial of treatment following symptomatic or metastatic progression. Treatment varied between studies, and included androgen deprivation therapy or TURP to treat ureteric obstruction.

Grade D</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias</td></tr>
<tr><td>D</td><td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td></tr>
<tr><td colspan="3">2. Consistency (if only one study was available, rank this component as ‘not applicable’) See body of evidence tables in report – results and p value (95% CI)</td></tr>
<tr><td rowspan="5">All studies reported similar monitor protocols or triggers for intervention, with similar mortality or quality of life outcomes.

Grade N/A</td><td>A</td><td>All studies consistent</td></tr>
<tr><td>B</td><td>Most studies consistent and inconsistency can be explained</td></tr>
<tr><td>C</td><td>Some inconsistency, reflecting genuine uncertainty around question</td></tr>
<tr><td>D</td><td>Evidence is inconsistent</td></tr>
<tr><td>NA</td><td>Not applicable (one study only)</td></tr>
<tr><td colspan="3">3. Clinical impact See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be</td></tr>
</table>

determined)		
All studies do not report sufficient direct evident to address this question. **Grade N/A**	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*		
All studies do not report sufficient direct evident to address this question. **Grade N/A**	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
All studies do not report sufficient direct evident to address this question. **Grade N/A**	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*

None.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description

1. Evidence base	D	Level I to III studies with a high risk of bias
2. Consistency	N/A	Insufficient evidence in the literature to address this.
3. Clinical impact	N/A	Insufficient evidence in the literature to address this.
4. Generalisability	N/A	Insufficient evidence in the literature to address this.
5. Applicability	N/A	Insufficient evidence in the literature to address this.

Evidence statement:

No studies were found that compared different active surveillance monitoring protocols.

RECOMMENDATION	**GRADE OF RECOMMENDATION**
What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.	N/A

No evidence based recommendation possible.

CONSENSUS-BASED RECOMMENDATION *If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.*

For men with prostate cancer managed by an active surveillance protocol, offer monitoring with PSA measurements every 3 months, and a physical examination including digital rectal examination every 6 months.

Offer a reclassification repeat prostate biopsy within 6–12 months of starting an active surveillance protocol.

Offer repeat biopsies every 2–3 years, or earlier as needed to investigate suspected disease progression: offer repeat biopsy and/or multiparametric MRI (in specialised centres) if PSA doubling time is less than 2–3 years or clinical progression is detected on digital rectal examination.

During active surveillance, offer definitive treatment if pathological progression is detected on biopsy, or if the patient prefers to proceed to intervention.

PRACTICE POINT

Points of guidance used to support evidence-based recommendations, where the subject matter is outside of the scope of search strategy, and which were formulated based on expert opinion using a consensus process.

In centres where staff have skills and experience in the use of multiparametric MRI for prostate examination, consider using it to help identify foci of potentially higher-grade disease, aid targeting at reclassification biopsies and aid determination of interval tumour growth. Clinicians and other staff performing multiparametric MRI should refer to appropriate standards and guidelines for its use.

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*
There are also several unresolved issues about patient monitoring while on active surveillance and triggers for intervention. These include: • the frequency of PSA measurement and repeat biopsy while on active surveillance. • the role of multiparametric MRI in predicting prostate cancer progression, which might affect the way care is organised and have resource implications. • the role of PSA doubling time as a trigger for intervention, given the multiple non-malignant causes of a variable and rising PSA levels. • the potential role of new genomic and epigenetic markers in selecting men for continued active surveillance. To date, the use of such indicators remains experimental and is not considered standard of care. • quality-of-life outcomes of different active surveillance protocols.

Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care? Implementation of the recommendations for monitoring protocols during active surveillance may result in an increase in biopsies.	**NO**
Are there any resource implications associated with implementing this recommendation? The use of multiparametric MRI would be associated with additional costs. Biopsies performed within monitoring protocols may be associated with indirect additional costs, including the cost of pathological examination, given that the recommendation for biopsy (see Chapter 3) requires a taking higher number of cores than is current practice for some urologists. However, biopsy-related costs may be offset if the monitoring protocol were to result in fewer biopsies.	**YES**
Will the implementation of this recommendation require changes in the way care is currently organised? Implementation of this recommendation would not require changes in the way care is currently organised.	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? No barriers to the implementation of these recommendations are envisaged.	**NO**

Chapter 5

NHMRC Evidence Statement for Clinical Question 11: What should be the criteria for choosing watchful waiting in preference to definitive treatment offer as primary management to men who have a positive prostate biopsy?

<table>
<tr><td colspan="2">PICO Question 11: For men with biopsy-diagnosed prostate cancer, for which patients (based on diagnostic, clinical and other criteria) does watchful waiting achieve equivalent or better outcomes in terms of length and quality of life than definitive treatment?</td><td colspan="2">Report body of evidence tables</td></tr>
<tr><td colspan="4">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td colspan="2" rowspan="4">Two level II studies reported on development of distant metastases, mortality from all causes and mortality from prostate cancer as outcomes. Both these studies, SPCG-4 (Bill-Axelson et al 2012) and PIVOT (Wilt et al 2011), were judged to be at moderate risk of bias with respect to mortality outcomes.
Grade C

Two level II studies reported on aspects of quality of life as outcomes. Both SPCG-4 and PIVOT were judged to be at high risk of bias with respect to quality of life outcomes.
Grade D

One level II study reported on adverse events occurring within 30 days of surgery in men randomly assigned to radical prostatectomy and having it. This study, PIVOT, was judged to be at high risk of bias with respect to surgical adverse events outcomes.
Grade D</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or
II studies with a moderate risk of bias</td></tr>
<tr><td>D</td><td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td></tr>
<tr><td colspan="4">2. Consistency (if only one study was available, rank this component as ‘not applicable’) See body of evidence tables in report – results and p value (95% CI)</td></tr>
<tr><td colspan="2" rowspan="5">For all causes mortality, prostate cancer mortality and distant metastases as outcomes.
Based on 695 men with early stage, low or intermediate grade prostate cancer diagnosed from 1989 to 1999 and randomised to immediate radical prostatectomy (RP) or to watchful waiting (WW), SPCG-4 reported an HR of 0.75 (0.61-0.92) for all-cause mortality favouring RP in an intention-to-treat analysis done after a median 12.8 years of follow-up. Of men randomised to RP, 84.7% had RP and of those randomised to WW, 13.2% had definitive therapy. The HR for death from prostate cancer was 0.62 (0.44-0.87) and the HR for development of distant metastases was 0.59 (0.45 to 0.79). Results were also analysed in strata of age at diagnosis and risk of a poor cancer outcome (low risk = PSA <10ng/mL and either Gleason score <7 or a WHO cancer grade 1). Impact of RP appeared to be confined to or greater in younger men (HR 0.52 <65y, 0.98 ≥65y all-cause mortality; 0.49 <65y, 0.83 ≥65y prostate cancer</td><td>A</td><td>All studies consistent</td></tr>
<tr><td>B</td><td>Most studies consistent and inconsistency can be explained</td></tr>
<tr><td>C</td><td>Some inconsistency, reflecting genuine uncertainty around question</td></tr>
<tr><td>D</td><td>Evidence is inconsistent</td></tr>
<tr><td>NA</td><td>Not applicable (one study only)</td></tr>
</table>

mortality; 0.47 <65y, 0.77 ≥65y distant metastases) and greater in men with low risk cancer (HR 0.62 all-cause mortality, 0.53 prostate cancer mortality, 0.43 distant metastases; results for high risk cancer not reported). Based on 731 men with early stage prostate cancer of any grade diagnosed between 1994 and 2002 and randomised to immediate radical prostatectomy (RP) or to watchful waiting (WW), PIVOT reported an HR of 0.88 (0.71-1.08) for all-cause mortality favouring RP in an intention-to-treat analysis done after a median 10.0 years of follow-up. Of men randomised to RP, 77.2% had RP and 85.4% had definitive therapy and of those randomised to WW, 10.1% had undergone RP and 20.4% had definitive therapy. The HR for death from prostate cancer was 0.63 (0.36-1.09) and the HR for development of bony metastases was 0.40 (0.22 to 0.70). Results were also analysed in strata of age at diagnosis, race, comorbidity, performance status, PSA level, Gleason score and tumour risk (based on PSA, stage and biopsy findings). Impact of RP appeared to be limited to or greater in men with PSA >10ng/mL (HR 0.67 >10ng/mL, 1.03 ≤10 all-cause mortality; HR 0.36 >10ng/mL, 0.92 ≤10 prostate cancer mortality; RR 0.28 >10ng/mL, 0.58 ≤10 bony metastases) and men with high or intermediate risk disease, although the latter may be due to inclusion of PSA in the risk algorithm since there was little difference in RP effect between Gleason score categories (<7, ≥7). There was also little evidence that effect of RP differed by age at diagnosis or any other stratification variable. These two studies are consistent in their evidence that in men with early stage prostate cancer there is higher all-causes and prostate cancer mortality and a higher rate of development of distant metastases in men randomised to WW than in men randomised to RP. They were not consistent, however, in the strata of personal and disease characteristics in which apparently beneficial effects of RP were observed. In particular, whereas SPCG-4 observed an apparently greater reduction in mortality from all causes and from prostate cancer, and in rate of development of distant metastases, in men with low risk cancer (PSA <10ng/mL and either Gleason score <7 or a WHO cancer grade 1) randomised to RP, PIVOT observed an apparently greater reduction in all three of these outcomes in men with a PSA > 10ng/mL randomised to RP. **Grade D** (for patient or disease characteristics influencing difference in outcomes between treatment groups) **Grade A** (for difference in outcomes between treatment groups)		

For aspects of quality of life as outcomes In both SPCG-4 (at mean of 4.1 and median of 12.2 years after randomisation) and PIVOT (~ 2 years after randomisation) there were significantly greater prevalence rates of urinary incontinence, erectile dysfunction and associated distress in men randomised to RP than in men randomised to WW (Steineck et al 2002; Johansson et al 2011; Wilt et al 2012). In PIVOT, prevalence of bowel dysfunction was not different between the randomised groups at ~2 years after randomisation (Wilt et al 2012). In SPCG-4, anxiety, depression, wellbeing and patient assessed quality of life were similar between the two groups at 4.1 (mean) and 12.2 (median) years after randomisation (Steineck et al 2002; Johansson et al 2011). These studies provide consistent evidence of greater rates of urinary incontinence and associated distress and erectile dysfunction and associated distress in men randomised to RP than in men randomised to WW at least up to a mean of 4.1 years after randomisation. **Not applicable** (patient or disease characteristics influencing difference in outcomes between treatment groups not reported) **Grade A** (for lack of difference in outcomes between treatment groups) Consistency with respect to bowel dysfunction, psychological symptoms, wellbeing and quality of life cannot be assessed (one study only for each). **For adverse events occurring within 30 days of surgery** Based on 280 patients, cumulative incidence ranged from 4.3% for wound infection, 2.5-2.1% for urinary tract infection, additional surgical repair needed, bleeding requiring transfusion and urinary catheter present at >30 days, 1.1% for bowel injury requiring repair and 0.4% for death (1 death) (Wilt et al 2012). Consistency with respect to perioperative complications cannot be assessed (one study only) **Not applicable**		

3. Clinical impact *See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The HRs for death from prostate cancer were 0.62 (0.44-0.87) at a median 12.8 years of follow-up (SPCG-4) and 0.63 (0.36-1.09) at a median 10.0 years of follow-up in men randomised to RP relative to those randomised to WW. The HRs for distant metastases (SPCG-4) or bony metastases (PIVOT) were 0.59 (0.45 to 0.79) and 0.40 (0.22 to 0.70) respectively. These reductions in prostate cancer mortality and distant metastases represent a substantial clinical benefit. There was also moderate clinical harm. There were statistically significant ($p<0.05$) absolute risk differences in favour of WW over RP of -33% to -9% for urinary incontinence and associated distress and -37% to -15% for erectile dysfunction or distress at means of ~2 to 4.1 years after randomisation (PIVOT and SPCG-4) and, respectively, -32% to -13% for urinary incontinence and associated distress and -4% to -12% for erectile dysfunction or distress at a median of 12.2 years after randomisation (SPCG-4). There were, however, no material differences between RP and WW in anxiety, depression, wellbeing and patient assessed quality of life at 4.1 (mean) and 12.2 (median) years after randomisation in the one study that assessed them (SPCG-4). **Grade B**	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*		
There are a number of ways in which the SPCG-4 and PIVOT study populations differ from Australian men diagnosed with prostate cancer today. SPCG-4 was conducted in Sweden and enrolled patients from 1989 to 1999; 11% of men were randomised without a biopsy or only on cytology and the core biopsy technique was recognised to be less sensitive than more recent techniques (Bill-Axelson et al 2011). PIVOT was conducted in the USA from 1994 to 2002 (the "early PSA era") and prostate cancer diagnoses in it were based on fewer cores than is usual today (Wilt et al 2012). Just over thirty percent of PIVOT patients were African American men, who have a much higher incidence of prostate cancer (223.9/100,000 in 2007-2011 in the 18 SEER areas of the USA; SEER Cancer Statistics Review 1975-2011, http://seer.cancer.gov/ accessed 25/05/14) than White men in the USA (White Hispanics 120.7/100,000; White non-Hispanics 143.2/100,000). Both SPCG-4 and PIVOT participants had higher PSA levels than are usual today (up to 50ng/mL in SPCG-4 and 10% of men with PSA levels greater that 20ng/mL in PIVOT) and the contribution that PSA testing made to detection of cancer in study patients was lower in both	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

SPCG-4 (12% with T1c cancers) and PIVOT (50% T1c) than it is in Australia today. The fact, though, that the results of these two studies are quite similar suggests that differences in prevalence of PSA detection of diagnosed prostate cancer, diagnostic accuracy and ethnic composition of the population do not greatly limit generalizability of these results to Australian men. **Grade B**		

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*

The evidence is based on studies that applied a watchful waiting approach to men who had prostate cancer that was potentially curable (early stage) by immediate definitive (radical) treatment. This approach would be clinically acceptable in Australia today only when applied to men who had refused radical therapy or to men who because of their age or health status were unlikely to survive long enough to benefit from definitive treatment of a PSA-detected prostate cancer. Therefore it is of limited applicability. **Grade C**	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*

None.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description	
1. Evidence base	C	Mortality	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Quality of life	Level I to III studies with a high risk of bias
	D	Adverse events	Level I to III studies with a high risk of bias
2. Consistency	A	Mortality	All studies consistent (for difference in outcomes between treatment groups)
	D		Evidence is inconsistent (for patient or disease characteristics influencing difference in outcomes between treatment groups)
	A	Quality of Life	All evidence is consistent (for lack of difference in outcomes between treatment groups)
	N/A		Not applicable (patient or disease characteristics influencing difference in outcomes between treatment groups not reported)
3. Clinical impact	B	Substantial	
4. Generalisability	B	Evidence directly generalisable to target population with some caveats	
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats	

Evidence statement:

The studies were inconsistent in patient selection and in their findings on effects of age and risk of cancer progression (as assessed at diagnosis) on observed differences in rates of all-cause mortality, prostate cancer-specific mortality and prostate cancer metastases between men offered radical prostatectomy and men offered watchful waiting. In the one study that reported on race, comorbidity and performance status, these factors were not associated with differences in clinical outcomes between treatment groups.

In men with early stage prostate cancer of any grade, watchful waiting was associated with higher rates of distant metastases and death due to prostate cancer, compared with radical prostatectomy. However, watchful waiting was associated with lower rates of erectile dysfunction, urinary incontinence and distress than radical prostatectomy. Despite these differences, rates of anxiety, depression, wellbeing and patient-assessed quality of life did not differ between men who receive watchful waiting and those who receive radical prostatectomy, according to data from follow-up of 4.1 years (mean) and 12.2 years (median) from diagnosis.

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE OF RECOMMENDATION** **C**
For men with potentially curable prostate cancer who are considering watchful waiting, advise that: • the risk of developing more advanced prostate cancer and dying from it is higher with watchful waiting than with immediate definitive treatment • watchful waiting is unlikely to diminish wellbeing and quality of life in the medium-to-long term.	

CONSENSUS-BASED RECOMMENDATION *If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.*
Offer watchful waiting to men diagnosed with potentially curable prostate cancer who, for reasons other than prostate cancer, are unlikely to live for more than another 7 years. Offer watchful waiting to men diagnosed with potentially curable prostate cancer who choose not to accept potentially curative therapy when it is offered to them.
PRACTICE POINT *Points of guidance used to support evidence-based recommendations, where the subject matter is outside of the scope of search strategy, and which were formulated based on expert opinion using a consensus process*.
None

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*
The optimal criteria for choosing watchful waiting have not been identified. Emerging research may provide more information on the relative contribution of prostate cancer and other illness to cause of death among men undergoing watchful waiting. A study published after the systematic reviews were completed for this guideline reported that 200 of the 347 men in the radical prostatectomy group and 247 of the 348 in the watchful waiting group died during median of 13.4 years follow-up. Death was due to prostate cancer in 99 men assigned to watchful waiting and 63 men assigned to radical prostatectomy (p = 0.001).

Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This*	
Will this recommendation result in changes in usual care? Implementation of this recommendation would not require any changes in the way care is currently organised.	**NO**
Are there any resource implications associated with implementing this recommendation? Implementation of this recommendation would have no significant implications for resourcing.	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised? Implementation of this recommendation would not require changes in the way care is currently organised.	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? No barriers to the implementation of this recommendation are envisaged.	**NO**

NHMRC Evidence Statement Form for Clinical Question 12: What is the best monitoring protocol for watchful waiting and what should be the criteria for intervention?

<table>
<tr><td colspan="2">PICO Question 12: For men with biopsy-diagnosed prostate cancer following a watchful waiting protocol, which combination of monitoring tests, testing frequency and clinical or other criteria for intervention achieve the best outcomes in terms of length and quality of life?</td><td>Report body of evidence tables</td></tr>
<tr><td colspan="3">1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)</td></tr>
<tr><td rowspan="4">No studies directly compared different monitoring protocols. The groups randomly allocated watchful waiting in these three studies all used 6 monthly testing (clinical examination and PSA) for the first year or two, following by annual testing thereafter. More extensive radiography testing was performed annually or less frequently, and in the event of suspected disease progression.

No studies directly compared different triggers for intervention. All three studies reported initial of treatment following symptomatic or metastatic progression. Treatment varied between studies, and included androgen deprivation therapy or TURP to treat ureteric obstruction.

Grade D</td><td>A</td><td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td></tr>
<tr><td>B</td><td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td></tr>
<tr><td>C</td><td>One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias</td></tr>
<tr><td>D</td><td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td></tr>
<tr><td colspan="3">2. Consistency (if only one study was available, rank this component as ‘not applicable’) See body of evidence tables in report – results and p value (95% CI)</td></tr>
<tr><td rowspan="5">All studies reported similar monitor protocols or triggers for intervention, with similar mortality or quality of life outcomes.

Grade: N/A</td><td>A</td><td>All studies consistent</td></tr>
<tr><td>B</td><td>Most studies consistent and inconsistency can be explained</td></tr>
<tr><td>C</td><td>Some inconsistency, reflecting genuine uncertainty around question</td></tr>
<tr><td>D</td><td>Evidence is inconsistent</td></tr>
<tr><td>NA</td><td>Not applicable (one study only)</td></tr>
<tr><td colspan="3">3. Clinical impact See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)</td></tr>
</table>

All studies do not report sufficient direct evident to address this question. **Grade: N/A**	A	**Very large**
	B	**Substantial**
	C	**Moderate**
	D	**Slight/Restricted**

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report*		
All studies do not report sufficient direct evident to address this question. **Grade: N/A**	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
All studies do not report sufficient direct evident to address this question. **Grade: N/A**	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*

None.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	No studies directly compared different monitoring protocols or different triggers for intervention.
2. Consistency	N/A	All studies do not report sufficient direct evident to address this question.
3. Clinical impact	N/A	All studies do not report sufficient direct evident to address this question.

4. Generalisability	N/A	All studies do not report sufficient direct evident to address this question.
5. Applicability	N/A	All studies do not report sufficient direct evident to address this question.

Evidence statement:

No studies were found that directly compared different watchful waiting protocols.

RECOMMENDATION	**GRADE OF RECOMMENDATION**
What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.	N/A

No evidence based recommendation possible.

CONSENSUS-BASED RECOMMENDATION

If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.

For all men choosing watchful waiting, discuss the purpose, duration, frequency and location of follow-up with the man and, if he wishes, with his partner or carers. Source: adapted from [UK] National Collaborating Centre for Cancer (2014)[8]

Specialists should consider referring men without advanced incurable prostate cancer back to their general practitioners for follow-up in primary care according to a protocol the specialist suggests and/or these guidelines.

If there is no evidence of significant disease progression (as indicated by 3–4 monthly PSA levels over 1 year and absence of relevant symptoms), continue monitoring by 6-monthly PSA levels.

If there is evidence of significant disease progression (that is, relevant symptoms and/or rapidly-rising PSA level), refer to a member of the treating team (urologist, medical oncologist or radiation oncologist) for review.

PRACTICE POINT

Points of guidance used to support evidence-based recommendations, where the subject matter is outside of the scope of search strategy, and which were formulated based on expert opinion using a consensus process.

For men whose prostate cancer is advanced and is not curable with local treatments, follow guidelines for the management of locally advanced or metastatic prostate cancer. If no treatment is offered or accepted, monitor clinically and by PSA testing and reconsider androgen deprivation therapy if any of the following occur:

- symptomatic local disease progression
- symptomatic or proven metastasis
- a PSA doubling time of < 3 months, based on at least three measurements over a minimum of 6 months (this should warrant consideration of further clinical investigations).

Unresolved issues

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*
There is no high-quality evidence on which to base protocols for watchful waiting.

Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care? Implementation of this recommendation would not require any changes in the way care is currently organised.	**NO**
Are there any resource implications associated with implementing this recommendation? Implementation of this recommendation would have no significant implications for resourcing.	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised? Implementation of this recommendation would not require changes in the way care is currently organised.	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? No barriers to the implementation of this recommendation are envisaged	**NO**

Systematic review reports

Systematic review report for question 1

Clinical Question 1: *"What risk factors can identify Australian men who are at high risk of prostate cancer or death from prostate cancer? Suggested risk factors include: Family history"*

PICO Question 1: *For Australian men, has a family history of prostate cancer been shown to be reliably associated with a 2.0-fold or greater increase in risk of occurrence of or death from prostate cancer when compared to men who do not have a family history of prostate cancer?*

Population	Exposure	Comparator/Reference group	Outcomes
Men without a diagnosis or symptoms suggestive of prostate cancer	Presence of a family history of prostate cancer	No known family history of prostate cancer	Prostate cancer diagnosis Prostate cancer mortality

1. Methods

1.1. Guidelines

This question does not lead to a recommendation and as a result searches for guidelines were not undertaken.

1.2. Literature Search

As it was anticipated that for this question there would be a large volume of literature already well established by the 1990s, the search was performed in two stages.

In the first stage searches were undertaken to identify relevant systematic reviews or meta-analyses for inclusion or, if they did not meet the inclusion criteria, to be used as a means of identifying potentially relevant articles. Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases from 1990 up until 1st March 2014 were searched using text terms and, where available, database specific subject headings. Each database was searched for articles dealing with prostate cancer. For the Medline and Embase databases, family history search terms and a meta-analysis/systematic review filter were added to the prostate cancer search.

In the second stage to identify recently published relevant articles that may not have been included in systematic reviews, the Medline and Embase searches were run without the meta-analysis/systematic review filter from 1st January 2010. This date was chosen as a recent, comprehensive meta-analysis was identified with a literature search cut-off in 2010. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 added to the relevant database after February 2014. Alerts were checked until July 2014. To identify studies which considered

Aboriginal and Torres Strait Islander (ATSI) peoples, these searches were then coupled with search terms for ATSI peoples and the databases searched from 1990 until 1st March 2014.
A complete list of the terms used for all search strategies are included as Appendix A. Reference lists of all relevant articles were checked for potential additional articles.

1.3. Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Aetiology/risk factor	
Study design	Cohort studies, or Nest case-control studies, or Systematic reviews of above	Case-control studies
Population	Men without a diagnosis or symptoms suggestive of prostate cancer	High-risk populations e.g. African Americans or Population subgroups e.g. smokers other than specific age groups
Exposure	Independently confirmed family history of prostate cancer including first-degree, second-degree relative, brother or father diagnosed with prostate cancer	Did not specify degree of family history i.e. only examined 'family history'
Comparator/ Reference group	No known family history of prostate cancer, including no first-degree relative diagnosed with prostate cancer and general male population	Studies comparing men with prostate cancer with men with benign prostate hyperplasia
Outcomes	Independently confirmed Diagnosis of prostate cancer Prostate cancer mortality	Reported only a specific cancer stage, metastatic disease, prostate cancer survival or a specific Gleason score range
Language	English	
Publication period	After 31st December 1989 and before1st March 2014	

- Conference proceedings identified by the search literature searches were included if they met the inclusion criteria.

2. Results

2.1. Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the systematic review. The systematic/meta-analyses searches identified 1,834 citations: the Medline search identified 1,167 citations, the Embase search 667 citations and the search of the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment database no additional citations. Titles and abstracts were examined and 15 articles were retrieved for a more detailed evaluation, of which 5 were systematic reviews or meta-analyses. None of these met the inclusion criteria for the current systematic review. Reference lists from the excluded systematic reviews were used to identify relevant primary studies and 18 articles were collected for more detailed evaluation. Seven articles met the inclusion criteria and were included in the review.

The searches to identify recently published relevant articles that may not have been included in systematic reviews, identified 3,204 citations: the Medline search identified 1,197 citations, and the Embase search 2,007 citations. Titles and abstracts were examined and 27 articles were retrieved for a more detailed evaluation, of which 5 articles met the inclusion criteria and were included in the review. No additional articleswere identified from their reference lists supporting the decision to rely on systematic reviews to identify relevant articles published prior to 2010.

A total of 7 studies reported in 12 articles met the inclusion criteria for the current systematic review.

For ATSI men the incidence of prostate cancer is lower than that for non-ATSI men and the rates of prostate cancer specific mortality are similar (AIHW 2013). No studies were found that examined family history of prostate cancer as a risk factor for prostate cancer incidence or mortality among ATSI men.

The retrieved articles that were not included and the reason for their exclusion are documented in Appendix C. In summary, the main reasons for exclusion were exposure or outcome self–reported, narrative reviews or commentaries rather than primary reports, no relevant comparisons and more mature data published.

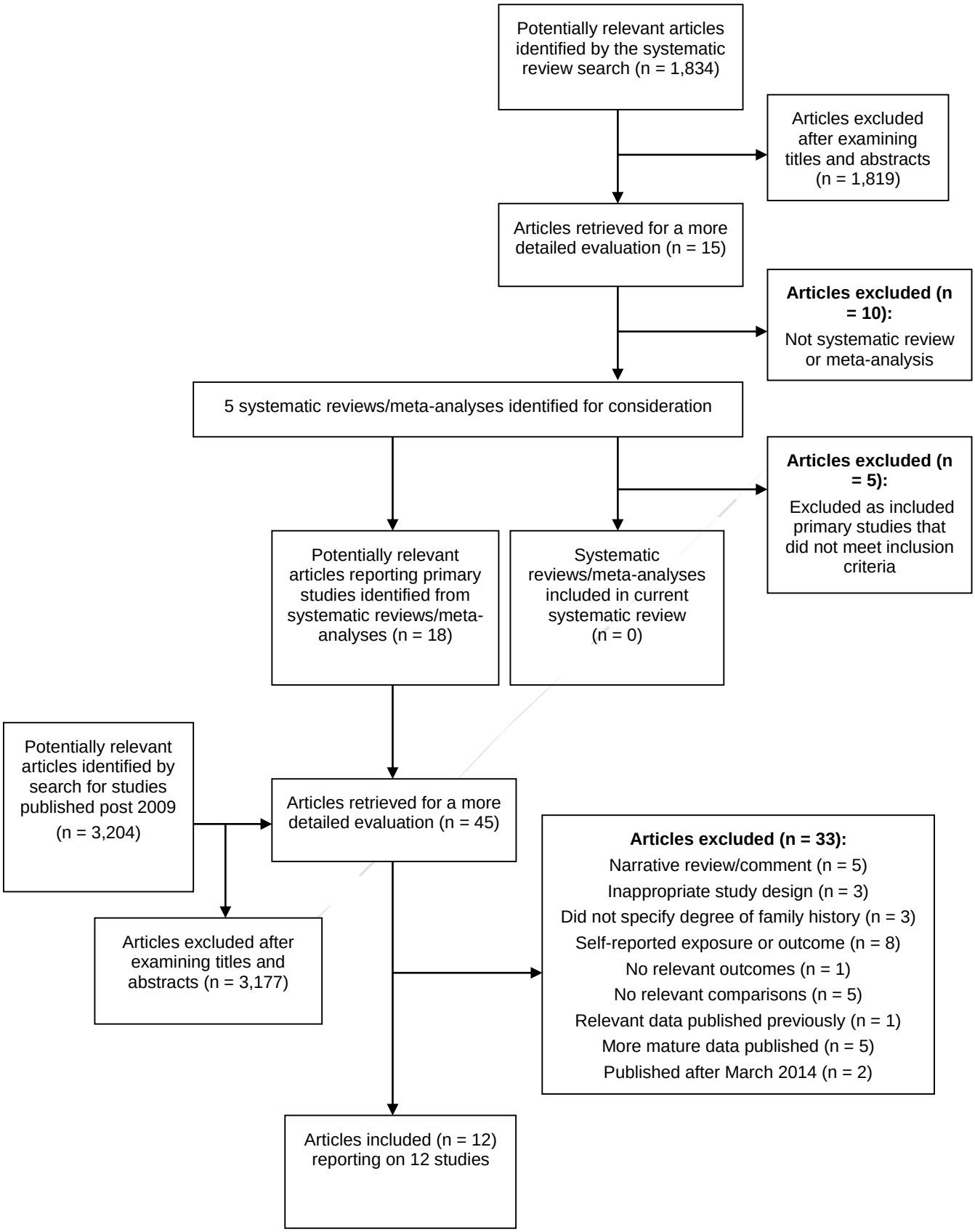


Figure 1. Process of inclusion and exclusion of studies

2.2. Study Characteristics

Characteristics of included studies are described in Table 1.

Table 1: Characteristics of cohort and nested case-control studies examining family history of prostate cancer as a strong risk factor for prostate cancer

Study	Study design	Population and databases	Exposure	Comparator	Outcome	Comments
Prostate cancer incidence						
Bratt 2010 (Sweden)	Retrospective cohort	Male population of Sweden Prostate Cancer Database Sweden (PCBaSe): population-based database containing data for all Swedish men diagnosed with prostate cancer between 1996 and 2006 and registered in the National Prostate Cancer Register (NPCR). Data for each man was obtained by linkages with the Swedish Cancer Register, the Register of Total Population, the Multi-Generation Register (MGR) and the Census databases The Swedish MGR was used to identify the brothers and father of each man in the PCBaSe	A **brother** diagnosed with prostate cancer between 01/01/1996 and 31/12/2006 and registered on the NPCR (index person) and a father identified on the MGR Excluded brothers diagnosed prior to 1996, who had died or emigrated before the date of diagnosis of the index patient N exposed = 22,511 A **brother** diagnosed with prostate cancer as above and **father** diagnosed with prostate cancer recorded in the Swedish Cancer Register prior to men entering the study N exposed not reported	Male population of Sweden	Diagnosis of prostate cancer recorded on the NPCR NCPR covers 98% of prostate cancers on the Swedish Cancer Register	If more than one brother diagnosed with prostate cancer the brother with the earlier diagnosis was designated the index case Follow-up of exposed men was from the date of prostate cancer diagnosis of index case till date of prostate cancer diagnosis, death, emigration or 31/12/2006 (whichever came first) For men with 2 brothers diagnosed with prostate cancer, a second follow-up started at the date of diagnosis of their second brother Analyses considered age (5-year groups) and calendar time (1-year groups) Fathers were not followed-up for prostate cancer diagnosis Pre-1999 (before cancer incidence rose steeply in Sweden) men with risk exposure had greater risk of cancer of any grade and T1c

						compared with general population
Bratt 1997 (Sweden)	Retrospective cohort	Male population of southern healthcare region of Sweden All men diagnosed with prostate cancer before the age of 51 years between 1958 and 1994 identified in the population-based Swedish Cancer Register Medical records of each man checked to ensure accuracy of diagnosis Census registers held by parish authorities used to identify first-degree relatives	A first-degree relative(s) (son, brother or father) diagnosed with prostate cancer before the age of 51 years between 1958 and 1994 recorded in the Swedish Cancer Register N exposed = 216	Male population of southern healthcare region of Sweden	*Exposed:* Diagnosis of prostate cancer between 1958 and June 1996 recorded on the Swedish Cancer Register *Not exposed:* Data from South Swedish Regional Tumour Registry	Follow-up of exposed men from January 1958 until June 1996 using Swedish Cancer Register, Census and Cause of Death Register Analyses considered age (5-year groups) and calendar time (1-year groups)
Brandt 2010 & 2012; Frank 2014; Hemminki 2011; Kharazmi 2012 (Sweden)	Retrospective cohort	All Swedish men born after 1932 with linkage in Swedish Family-Cancer Database to both parents Aged <75 years (Brandt 2010, Hemminki 2011) N = 3.9 million men Aged <77 years (Brandt 2012; Kharazmi 2012) Aged <79 years (Frank 2014) The nationwide Swedish Family-Cancer Database was created by linkage of information from the Multi-Generation Register (MGR), national censuses, Swedish	**Brother(s) diagnosed** with prostate cancer between 1961 and 2006 recorded in the Swedish Cancer Registry **Father diagnosed** with prostate cancer between 1961 and 2006 recorded in the Swedish Cancer Registry **Brother(s) and father diagnose**d with prostate cancer between 1961 and 2006 recorded in the Swedish Cancer Registry **Father died of** prostate cancer between 1961 and 2006 recorded in the Swedish Causes of Death Registry	**No brother or father with diagnosis** of prostate cancer between 1961 and 2006 recorded in the Swedish Cancer Registry **Father with no diagnosis** of prostate cancer between 1961 and 2006 recorded in the Swedish Cancer Registry	Diagnosis of prostate cancer between 1961 and 2006 (Brandt 2010; Hemminki 2011), 2008 (Brandt 2012; Kharazmi 2012), 2010 (Frank 2014) recorded on the Swedish Cancer Registry	Follow-up from birth, immigration or 01/01/1961 (whichever came last) Censoring events for diagnosis were death, emigration, 31/12/2006 (Brandt 2010; Hemminki 2011), 31/12/2008 (Brandt 2012; Kharazmi 2012), end of 2010 (Frank 2014), absence at census (Brandt 2010; Hemminki 2011;Brandt 2012), and diagnosis of other cancer Exposure began at start of study regardless of when family members were

		Cancer Registry and death notifications Swedish Cancer Registry has coverage of cancer registrations of close to 90%	**Brother(s) diagnosed** with prostate cancer between 1961 and 2008 recorded in the Swedish Cancer Registry **Father diagnosed** with prostate cancer between 1961 and 2008 recorded in the Swedish Cancer Registry	**Male population** of Sweden (Brandt 2012**)**		diagnosed with prostate cancer. This definition of period of risk has been shown to result in estimates similar to those defining the period of risk as starting from the date of relative's diagnosis Analyses considered age, SES, calendar period and region (Brandt 2010; Hemminki 2011; Brandt 2012). Kharazmi 2012 also adjusted for father's age at start and end of follow-up For men diagnosed after 2002 there was no difference between sporadic and familial cancers in terms of stage distribution and in particular T1c (Brandt 2010)
			Father diagnosed with prostate cancer between 1961 and 2008 recorded in the Swedish Cancer Registry	**Father with no diagnosis** of prostate cancer between 1961 and 2008 recorded in the Swedish Cancer Registry		
			First-degree relative diagnosed with prostate cancer between 1961 and 2010 recorded in the Swedish Cancer Registry	**No first-degree or second-degree relative with diagnosis** of prostate cancer or in situ prostate cancer between 1961 and 2010 recorded in the Swedish Cancer Registry		
Eldon 2003 (Iceland)	Retrospective cohort	Male population of Iceland Men diagnosed with prostate cancer between 1983 and 1987 in the population-based Icelandic Cancer Registry Mean age at diagnosis = 74.4 years Excluded men diagnosed at autopsy or by death certificates only, with histopathology other than adenocarcinoma or with unknown stage of prostate cancer Icelandic Cancer Registry has complete coverage on cancer incidence in Iceland	First-degree relative(s) (father, brothers or sons), second-degree or third-degree relative(s) diagnosed with prostate cancer between 1983 and 1987, recorded in the Icelandic Cancer Registry First-degree relatives N = 1,832 Second-degree relatives N = 5,604 Third-degree relatives N = 10,649	Male population of Iceland	Diagnosis of prostate cancer between 1955 and 1999 recorded on the Icelandic Cancer Registry	Analyses considered age and calendar year

		Record linkage of population-based genealogical database and cancer registry used to identify index case's family up to and including third-degree relatives	A first-degree relative(s) (father, brothers or sons), diagnosed with prostate cancer between 1983 and 1987, who died of prostate cancer N = 784			
Gronberg 1996 & 1999 (Sweden)	Retrospective cohort	Male population of Sweden All men diagnosed with histologically confirmed prostate cancer between 1959 and 1963 in the population-based Swedish Cancer Register Parish office records used to identify children	Father diagnosed with prostate cancer between 1959 and 1963, recorded in the Swedish Cancer Register Excluded men with diagnoses that were not histologically or cytologically confirmed and men for whom personal identification code, or no record on Causes of Death Register (1952 onwards) or National Population Register (died before 1952 or emigrated before 1990 – Gronberg 1996) N exposed = 5,496 (Gronberg 1996) 5,595/5,717 (unclear - Gronberg 1999)	Male population of Sweden	Diagnosis of prostate cancer between 1958 to 1990 (Gronberg 1996) or 1995 (Gronberg 1999), recorded on the Swedish Cancer Register	Assumed those without vital status or immigration status either died before 1952 or had emigrated from Sweden before 1990 Follow-up calculated from 01/01/1958 to the date of death or 31/12/1990 (Gronberg 1996) Analyses considered age (5-year groups) and calendar time (1-year groups) (Gronberg 1996) Follow-up of participants from birth to prostate cancer diagnosis, emigration or 31/12/1994 (whichever came first) (Gronberg 1999)
Kerber 2005 (USA)	Nested case-control	Male descendants of Mormon pioneers of Utah born between 1870 and 1984 Utah population database was created from the "family group sheets" Utah Mormons were encouraged to submit to Genealogical Society of Utah covering men born between	A first-degree relative(s) (son, brother or father) of 11,573 men diagnosed with prostate cancer (cases) between 1966 and 1996 recorded in the Utah Cancer Registry A second-degree relative(s) (not specified) diagnosed	Relative of 11,572 men randomly selected and matched to 11,573 cases according to age (years), place of birth (Utah, Idaho or other) and presence in risk set at time of diagnosis and not diagnosed with prostate cancer at time of matching	Diagnosis of prostate cancer recorded on Utah Cancer Registry between 1966 and 1996	Vital status follow-up either a death record (death certificate or genealogical data), an HCFA record placing them in Utah between 1966 and 2000, or current Utah driver's license Followed from 1966 or birth if born after 1966 until diagnosed or censored

		1800 and 1970 and linked to Utah birth certificate data, Utah Department of Health, the statewide Utah Cancer Registry (1966 onwards), Utah driver license data and State death certificates (1903-1999) and Health Care Finance Administration (HCFA) records	with prostate cancer between 1966 and 1996 recorded in the Utah Cancer Registry	Included men diagnosed with prostate cancer after their case		If more than 1 brother had prostate cancer each was treated as a separate case and the risk among all siblings for each case tabulated separately and variance estimated using Huber–White sandwich method which is robust to non–independence of observations
Matikainen 2001 (Finland)	Retrospective cohort	Male population of Finland All men diagnosed with prostate cancer at an age of 60 years or less and men diagnosed with prostate cancer at an age greater than 60 years from 3 hospital regions of Finland, between 1988 and 1993 and in the nationwide population-based Finnish Cancer Registry Parish and local authority records used to identify sons, brothers and fathers up until 1967	Father, brother or son diagnosed with prostate cancer between 1988 and 1993 recorded in the Finnish Cancer Registry	Male population of Finland	Diagnosis of prostate cancer between 1953 to 1997 recorded on the Finnish Cancer Registry	Follow-up for father of men diagnosed with prostate cancer started at date of birth of son or 01/01/1953 (whichever came later) Follow-up for brothers and sons started at their date of birth or 01/01/1953 (whichever was later) Follow-up ended at death, emigration or 31/12/1997 (whichever came first) Follow-up excluded 1988 – 1993 as those diagnosed in this period determined the exposure Analyses considered age and calendar period
Prostate cancer mortality						
Brandt 2010 & 2012; Hemminki 2011 (Sweden)	Retrospective cohort	All Swedish men born after 1932 with linkage in Swedish Family-Cancer Database to both parents Aged <75 years (Brandt 2010, Hemminki 2011) N = 3.9 million men	**Brother(s) diagnosed** with prostate cancer **Father diagnosed** with prostate cancer **Brother(s) and father diagnosed** with prostate cancer	**No brother or father** recorded as **diagnosed** with prostate cancer between 1961 and 2006 on the Swedish Cancer Registry	Prostate cancer death between 1961 and 2006 (Brandt 2010; Hemminki 2011), 2008 (Brandt 2012) recorded on Swedish Causes of Death Register	Follow-up from birth, immigration or 01/01/1961 (whichever came last) Censoring events for prostate cancer death were emigration, 31/12/2006 (Brandt 2010: Hemminki

	Aged <77 years (Brandt 2012) The nationwide Swedish Family-Cancer Database was created by linkage of information from the Multi-Generation Register (MGR), national censuses, Swedish Cancer Registry and death notifications Swedish Cancer Registry has coverage of cancer registrations of close to 90%	Between 1961 and 2006 and recorded in the Swedish Cancer Registry **Brother(s) died of** prostate cancer **Father died of** prostate cancer **Brother(s) and father died of** prostate cancer Between 1961 and 2006 recorded on Swedish Causes of Death Register			2011), 31/12/2008 (Brandt 2012), absence at census and death from other causes Exposure began at start of study regardless of when familial cancer(s) diagnosed which has been shown to result in similar estimates as starting exposure from the date of relative's diagnosis Analyses considered age, SES, calendar period and region
		Father died of prostate cancer between 1961 and 2006 recorded in the Swedish Causes of Death Registry before diagnosis	**Father not** recorded as **diagnosed with** or **died from** prostate cancer between 1961 and 2006 on the Swedish Cancer Registry (Hemminki 2011)		
		Brother died of prostate cancer **Father died of** prostate cancer Between 1961 and 2008 recorded in the Swedish Causes of Death Registry	**Male population** of Sweden (Brandt 2012)		

MGR = Multi-Generation Register; NPCR = National Prostate Cancer Register; PCBaSe = Prostate Cancer Database Sweden; SES = socioeconomic status

2.3. Study quality

Methodological quality of included cohort studies is described in Tables 2 – 5.
Methodological quality of included nested case-control studies is described in Tables 6 and 7.

Table 2: Risk of bias for the outcome **prostate cancer diagnosis** in the included **cohort** studies (n = 11)

Quality Category	N (%)
Selection of the exposed and non-exposed cohorts	
Low risk of bias	10 (90.9)
Moderate risk of bias	1 (9.1)
High risk of bias	0 (0)
Measurement of exposure	
Low risk of bias	4 (36.4)
Moderate risk of bias	7 (63.6)
High risk of bias	0 (0)
Measurement of outcome	
Low risk of bias	11 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Was outcome of interest absent at the time to which the exposure refers?	
Low risk of bias	11 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Was follow-up long enough for outcome to occur?	
Low risk of bias	0 (0)
High risk of bias	11 (100)
Participation rate	
Low risk of bias	11 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Completeness of follow-up	
Low risk of bias	9 (81.8)
Moderate risk of bias	0 (0)
High risk of bias	2 (18.2)
Accuracy of dates of outcome or censoring	
Low risk of bias	11 (100)
Moderate risk of bias	0 (0)
Difference in follow-up between exposed and non-exposed	
Low risk of bias	11 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Difference in missing data for exposure between those with or without the outcome	
Low risk of bias	11 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Comparability of exposed and non-exposed cohorts with respect to potentially important confounding variables	
Low risk of bias	0 (0)
Moderate risk of bias	10 (90.9)

High risk of bias	1 (9.1)
Covariates are appropriately included in statistical analysis models	
Low risk of bias	11 (100)
High risk of bias	0 (0)

Table 3: Risk of bias for the outcome of **prostate cancer diagnosis** in the included **cohort** studies (n = 11)

	Brandt 2010	**Brandt 2012**	**Bratt 1997**	**Bratt 2010**	**Eldon 2003**	**Frank 2014**	**Gronberg 1996**	**Gronberg 1999**	**Hemminki 2011**	**Kharazmi 2011**	**Matikainen 2001**
Selection of the exposed and non-exposed cohorts	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Moderate
Measurement of exposure[1]	Low	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Low	Low	Moderate
Measurement of outcome	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Was outcome of interest absent at the time to which the exposure refers?	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Was follow-up long enough for outcome to occur as a consequence of measured exposure? [2]	High	High	High	High	High	High	High	High	High	High	High
Participation rate	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Completeness of follow-up[3]	Low	Low	High	Low	High	Low	Low	Low	Low	Low	Low
Accuracy of dates of outcome or censoring	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Difference in follow-up between exposed and non-exposed	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Difference in missing data for exposure between those with or without the outcome	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low

Comparability of exposed and non-exposed cohorts with respect to potentially important confounding variables[4]	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	High	Moderate	Moderate	Moderate
Covariates are appropriately included in statistical analysis models	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Overall risk of bias	**High**	**High**	**High**	**High**	**High**	**High**	**High**	**High**	**High**	**High**	**High**
Overall quality rating	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**

[1] Rated at moderate risk of bias when general population was the comparator as over 5% of the population (USA and Scandinavia) have a family history of prostate cancer

[2] Adequate follow-up if follow-up until age 75 years for diagnosis

[3] For Swedish studies if censored for immigration assumed used Register of Total Population if method of ascertaining emigration not described

[4] Age, race (USA only), socioeconomic status or occupation or education, PSA testing history or annual medical check, and calendar time were pre-specified as potentially important confounders for prostate cancer diagnosis

Key to overall rating
High risk of bias – high risk of bias in any domain
Moderate risk of bias – moderate or low risk of bias in all domains
Low risk of bias – all domains low risk of bias

Table 4: Risk of bias for the outcome **prostate cancer mortality** in the included **cohort** studies (n = 3)

Quality Category	N (%)
Selection of the exposed and non-exposed cohorts	
Low risk of bias	3 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Measurement of exposure	
Low risk of bias	2 (66.7)
Moderate risk of bias	1 (33.3)
High risk of bias	0 (0)
Measurement of outcome	
Low risk of bias	3 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Was outcome of interest absent at the time to which the exposure refers?	
Low risk of bias	3 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Was follow-up long enough for outcome to occur as a consequence of measured exposure?	
Low risk of bias	0 (0)
High risk of bias	3 (100)
Participation rate	
Low risk of bias	3 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Completeness of follow-up	
Low risk of bias	3 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Accuracy of dates of outcome or censoring	
Low risk of bias	3 (100)
Moderate risk of bias	0 (0)
Difference in follow-up between exposed and non-exposed	
Low risk of bias	3 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Difference in missing data for exposure between those with or without the outcome	
Low risk of bias	3 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Comparability of exposed and non-exposed cohorts with respect to potentially important confounding variables	
Low risk of bias	3 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Covariates are appropriately included in statistical analysis models	
Low risk of bias	3 (100)

High risk of bias	0 (0)

Table 5: Risk of bias for the outcome of **prostate cancer mortality** of the included **cohort** studies (n = 3)

	Brandt 2010	**Brandt 2012**	**Hemminki 2011**
Selection of the exposed and non-exposed cohorts	Low	Low	Low
Measurement of exposure[1]	Low	Moderate	Low
Measurement of outcome	Low	Low	Low
Was outcome of interest absent at the time to which the exposure refers?	Low	Low	Low
Was follow-up long enough for outcome to occur as a consequence of measured exposure?[2]	High	High	High
Participation rate	Low	Low	Low
Completeness of follow-up[3]	Low	Low	Low
Accuracy of dates of outcome or censoring	Low	Low	Low
Difference in follow-up between exposed and non-exposed	Low	Low	Low
Difference in missing data for exposure between those with or without the outcome	Low	Low	Low
Comparability of exposed and non-exposed cohorts with respect to potentially important confounding variables[4]	Low	Low	Low
Covariates are appropriately included in statistical analysis models	Low	Low	Low
Overall risk of bias	**High**	**High**	**High**
Overall quality rating	**Low**	**Low**	**Low**

[1] Rated at moderate risk of bias when general population was the comparator as over 5% of the population (USA and Scandinavia) have a family history of prostate cancer

[2] Adequate follow-up if follow-up until age 85 years for prostate cancer mortality

[3] For Swedish studies if censored for immigration assumed used Register of Total Population if method of ascertaining emigration not described

[4] Age, race (USA only), socioeconomic status or occupation or education and calendar time were pre-specified as potentially important confounders for prostate cancer mortality

Key to overall rating
High risk of bias – high risk of bias in any domain
Moderate risk of bias – moderate or low risk of bias in all domains
Low risk of bias – all domains low risk of bias

Table 6: Risk of bias for the outcome **prostate cancer diagnosis** of the included **nested case-control** studies (n = 1)

Quality Category	N (%)
Sources of cases and controls	
Low risk of bias	1 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Selection of cases and controls	
Low risk of bias	1 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Definition of cases	
Low risk of bias	1 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Definition of controls	
Low risk of bias	1 (100)
Moderate risk of bias	0 (0)
Was outcome of interest likely to have been absent at the time to which the exposure refers?	
Low risk of bias	1 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Was follow-up long enough for outcome to occur?	
Low risk of bias	0 (0)
High risk of bias	1 (100)
Measurement of exposure	
Low risk of bias	1 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Was the same method used to measure exposure in cases and controls?	
Low risk of bias	1 (100)
High risk of bias	0 (0)
Participation rate in cohort	
Low risk of bias	1 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Participation (response) rate for cases	
Low risk of bias	0 (0)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Not applicable	1 (100)
Participation (response) rate for controls	
Low risk of bias	0 (0)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Not applicable	1 (100)

Difference in participation rate (response rate) between cases and controls	
Low risk of bias	0 (0)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Not applicable	1 (100)
Completeness of follow-up of cohort	
Low risk of bias	0 (0)
Moderate risk of bias	0 (0)
High risk of bias	1 (100)
Accuracy of dates of outcome or censoring	
Low risk of bias	1 (100)
Moderate risk of bias	0 (0)
Difference in follow-up between exposed and non-exposed members of cohort	
Low risk of bias	1 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Difference in missing data for exposure between cases and controls	
Low risk of bias	1 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Comparability of exposed and non-exposed cohorts with respect to potentially important confounding variables	
Low risk of bias	0 (0)
Moderate risk of bias	0 (0)
High risk of bias	1 (100)
Analysis appropriate to design	
Low risk of bias	0 (0)
High risk of bias	1 (100)
Covariates are appropriately included in statistical analysis models	
Low risk of bias	1 (100)
High risk of bias	0 (0)

Table 7: Risk of bias for the outcome **prostate cancer diagnosis** of the included **nested case-control** studies (n = 1)

	Kerber 2005
Sources of cases and controls	Low
Selection of cases and controls	Low
Definition of cases	Low
Definition of controls	Low
Was outcome of interest likely to have been absent at the time to which the exposure refers?	Low
Was follow-up long enough for outcome to occur?[1]	High
Measurement of exposure	Low
Was the same method used to measure exposure in cases and controls?	Low
Participation rate in cohort	Low
Participation (response) rate for cases	N/A
Participation (response) rate for controls	N/A
Difference in participation rate (response rate) between cases and controls	N/A
Completeness of follow-up of cohort	High
Accuracy of dates of outcome or censoring	Low
Difference in follow-up between exposed and non-exposed members of cohort	Low
Difference in missing data for exposure between cases and controls	Low
Comparability of exposed and non-exposed cohorts with respect to potentially important confounding variables[2]	High
Analysis appropriate to design	High
Covariates are appropriately included in statistical analysis models	Low
Risk of bias	**High**
Overall quality rating	**Low**

[1] *Adequate follow-up if follow-up until age 75 years for diagnosis*

[2] *Age, race (USA only), socioeconomic status or occupation or education, PSA testing history or annual medical check, and calendar time were pre-specified as potentially important confounders for prostate cancer diagnosis*

Key to overall rating
High risk of bias – high risk of bias in any domain
Moderate risk of bias – moderate or low risk of bias in all domains – no high risk domains
Low risk of bias – all domains low risk of bias – no moderate or high risk domains

2.4. Study Results

Prostate cancer diagnosis (Table 8)

Prostate cancer mortality (Table 9)

I PROSTATE CANCER INCIDENCE

Table 8: Risk of prostate cancer diagnosis for relatives of men with prostate cancer: cohort and nested case-control studies

Study	Outcome Definition	Outcome metric	Exposure	No exposure	p value	Size of effect (95%CI)
First-degree relative vs no first or second -degree relative diagnosed with prostate cancer/ male relative not diagnosed with prostate cancer/general population						
Kerber 2005	Prostate cancer diagnosis		NR	NR	NR	RR[i^] = 2.1 (1.9 – 2.2)
Frank 2014	Prostate cancer diagnosis	n	11,967	NR	NR	SIR[k] = 2.44 (2.40 – 2.49)
Eldon 2003	Prostate cancer diagnosis	n	109	63.4[n]	NR	SIR = 1.72 (1.28 – 2.34)
	Exposure = First-degree relative diagnosed aged < 68 years	n	29	12.4[n]	NR	SIR = 2.42 (1.25 – 4.68)
Matikainen 2001	*Exposure = First-degree relative diagnosed at age*					
	< 55 years	n	10	3.8[o]	<0.05	SIR = 2.61 (1.25 – 4.80)
	55 – 60 years	n	42	17.2[o]	<0.001	SIR = 2.44 (1.76 – 3.29)
	61 – 69 years	n	38	14.0[o]	<0.001	SIR = 2.71 (1.92 – 3.71)
	70 – 79 years	n	30	26.0[o]	NS	SIR = 1.15 (0.78 – 1.64)
	≥ 80 years	n	34	18.6[o]	<0.01	SIR = 1.83 (1.27 – 2.55)
Bratt 1997	Prostate cancer diagnosis	n	16	11.0[c]	0.17	SIR = 1.43 (0.82 – 2.33)
	Age at diagnosis < 70 years	n	7	2.1[c]	0.006	SIR = 3.37 (1.36 – 6.94)
	< 80 years	n	11	6.1[c]	0.06	SIR = 1.80 (0.90 – 3.21)
First-degree relative died of prostate cancer vs general population						
Eldon 2003	Prostate cancer diagnosis	n	50	23.4[n]	NR	SIR = 2.17 (1.34 – 3.53)
Father vs no father/no brother or father diagnosed with prostate cancer/ general population						

Brandt 2010 & 2012; Kharazmi 2012	Prostate cancer diagnosis	n	5,555	31,323	NR	HR[l] = 2.3 (2.2 – 2.4)
	Exposure = father diagnosed at age					
	< 40 years	n	0	31,323	-	-
	40 – 49 years	n	7	31,323	NR	HR[l] = 5.2 (2.5 – 10.9)
	50 – 59 years	n	168	31,323	NR	HR[l] = 3.3 (2.8 – 3.8)
	60 – 69 years	n	1,234	31,323	NR	HR[l] = 2.9 (2.8 – 3.1)
	70 – 79 years	n	2,580	31,323	NR	HR[l] = 2.4 (2.3 – 2.4)
	80 – 89 years	n	1,465	31,323	NR	HR[l] = 1.9 (1.8 – 2.0)
	≥ 90 years	n	101	31,323	NR	HR[l] = 1.3 (1.1 – 1.6)
	Prostate cancer diagnosis	n	5,571	NR	NR	SIR[i] = 2.28 (2.22 – 2.34)
	Exposure = father only	n	3,636	21,028[f]	<0.0001	HR[e] = 2.12 (2.05 – 2.20)
	Age at diagnosis < 55 years	n	438	1,639[f]	<0.0001	HR[e] = 2.93 (2.64 – 3.25)
	55 – 64 years	n	2,075	10,969[f]	<0.0001	HR[e] = 2.22 (2.12 – 2.33)
	65 – 74 years	n	1,123	8,420[f]	<0.0001	HR[e] = 1.78 (1.68 – 1.90)
Gronberg 1996 & 1999	Prostate cancer diagnosis	n	302	177.84[b]	NR	SIR = 1.70 (1.51 – 1.90)
	Age at diagnosis 45 – 49 years	n	3	0.89[b]	NS	SIR = 3.38 (0.68 – 9.88)
	50 – 54 years	n	9	4.00[b]	NR	SIR = 2.25 (1.03 – 4.27)
	55 – 59 years	n	31	13.38[b]	NR	SIR = 2.32 (1.57 – 3.29)
	60 – 64 years	n	51	30.76[b]	NR	SIR = 1.66 (1.23 – 2.18)
	65 – 69 years	n	85	45.62[b]	NR	SIR = 1.86 (1.49 – 2.30)
	70 – 74 years	n	72	46.57[b]	NR	SIR = 1.55 (1.21 – 1.95)
	75 – 79 years	n	37	26.25[b]	NS	SIR = 1.41 (0.99 – 1.94)
	≥ 80 years	n	14	10.37[b]	NS	SIR = 1.35 (0.74 – 2.27)
	Exposure = father diagnosed aged < 70 years	n	34	NR	NR	SIR = 2.27 (1.57 – 3.17)
					<0.001	RR[d] = 2.68 (2.15 – 3.34)
	Exposure = father diagnosed aged 70 – 79 years	n	165	NR	NR	SIR = 1.92 (1.64 – 2.23)
					<0.001	RR[d] = 1.93 (1.70 – 2.19)
	Exposure = father diagnosed aged ≥ 80 years	n	103	NR	NR	SIR = 1.34 (1.09 – 1.62)
					<0.001	RR[d] = 1.56 (1.32 – 1.83)
Father **died of** prostate cancer vs father not diagnosed with prostate cancer						

Hemminki 2011	Prostate cancer diagnosis	n	2,311	20,763	NR	HR[g] = 2.30 (2.20 – 2.40)
Brother(s) vs no no brother or father diagnosed with prostate cancer/general population						
Brandt 2010 & 2012	Prostate cancer diagnosis	n	3,112	NR	NR	SIR[i] = 3.25 (3.13 – 3.36)
	Exposure = 1 brother only	n	1,377	21,028[f]	<0.0001	HR[e] = 2.96 (2.80 – 3.13)
	Age at diagnosis < 55 years	n	96	1,639[f]	<0.0001	HR[e] = 4.41 (3.59 – 5.42)
	55 – 64 years	n	753	10,969[f]	<0.0001	HR[e] = 3.15 (2.92 – 3.39)
	65 – 74 years	n	528	8,420[f]	<0.0001	HR[e] = 2.56 (2.34 – 2.79)
	Exposure = brother(s) only diagnosed at age					
	< 60 years	n	379	21,028[f]	<0.0001	HR[e] = 3.94 (3.56 – 4.36)
	60 – 64 years	n	483	21,028[f]	<0.0001	HR[e] = 3.01 (2.75 – 3.29)
	65 – 74 years	n	515	21,028[f]	<0.0001	HR[e] = 2.46 (2.25 – 2.69)
	Exposure = 2 brothers only	n	144	21,028[f]	<0.0001	HR[e] = 7.71 (6.54 – 9.08)
	Age at diagnosis < 55 years	n	5	1,639[f]	<0.0001	HR[e] = 5.90 (2.45 –14.20)
	55 – 64 years	n	83	10,969[f]	<0.0001	HR[e] = 8.93 (7.19 – 11.08)
	65 – 74 years	n	56	8,420[f]	<0.0001	HR[e] = 6.49 (4.99 – 8.43)
	Exposure = 2 brothers only at least one of which diagnosed aged < 60 years	n	67	21,028[f]	<0.0001	HR[e] = 8.79 (6.92 – 11.18)
	Exposure = 3 brothers only	n	28	21,028[f]	<0.0001	HR[e] = 17.74 (12.26 – 25.67)
	Exposure = 3 brothers only at least one of which diagnosed aged < 60 years	n	23	21,028[f]	<0.0001	HR[e] = 24.35 (16.18 – 36.64)
Bratt 2010	Prostate cancer diagnosis					
	Exposure = 1 brother	n	1,022	329[b]	NR	SIR = 3.1 (2.9 – 3.3)
	Exposure = 2 brothers	n	77	7[b]	NR	SIR = 11 (8.7 – 14)
Brother(s) + father vs no father or brother diagnosed with prostate cancer/general population						

Brandt 2010	Prostate cancer diagnosis					
	Exposure = father + 1 brother	n	402	21,028[f]	<0.0001	HR[e] = 5.51 (5.00 – 6.09)
	Age at diagnosis < 55 years	n	47	1,639[f]	<0.0001	HR[e] = 11.32 (8.47 – 15.13)
	55 – 64 years	n	250	10,969[f]	<0.0001	HR[e] = 6.48 (5.72 – 7.35)
	65 – 74 years	n	105	8,420[f]	<0.0001	HR[e] = 3.46 (2.85 – 4.19)
	Exposure = father + 1 brother at least one of which diagnosed aged < 60 years	n	160	21,028[f]	<0.0001	HR[e] = 7.63 (6.53 – 8.92)
	Exposure = father + 2 brothers	n	36	21,028[f]	<0.0001	HR[e] = 8.51 (6.13 – 11.80)
	Exposure = father + 2 brothers at least one of which diagnosed aged < 60 years	n	21	21,028[f]	<0.0001	HR[e] = 10.86 (7.08 – 16.66)
Bratt 2010	Prostate cancer diagnosis					
	Exposure = father + 1 brother	n	225	43[b]	NR	SIR = 5.3 (4.6 – 6.0)
	Exposure = father + 2 brothers	n	14	1.4[b]	NR	SIR = 9.7 (5.3 – 16)
Second-degree relative vs male relative not diagnosed with prostate cancer/general population						
Eldon 2003	Prostate cancer diagnosis	n	85	67.6[n]	NS	SIR = 1.25 (0.91 – 1.72)
	Exposure = Second-degree relative diagnosed aged < 68 years	n	32	18.5[n]	NS	SIR = 1.68 (0.96 – 2.96)
Kerber 2005	Prostate cancer diagnosis		NR	NR	NR	RR[i^] = 1.4 (1.3 – 1.5)
Third-degree relative vs male relative not diagnosed with prostate cancer/general population						
Eldon 2003	Prostate cancer diagnosis	n	241	197.8[n]	NR	SIR = 1.22 (1.01 – 1.47)
	Exposure = Third-degree relative diagnosed aged < 68 years	n	58	51.0[n]	NS	SIR = 1.14 (0.78 – 1.65)
Kerber 2005	Prostate cancer diagnosis		NR	NR	NR	RR[i^] = 1.2 (1.1 – 1.2)

CI = confidence interval; HR = hazard ratio; NR = not reported; NS = not statistically significantly different; RR = risk ratio; SIR = standardised incidence ratio

^ Nested case-control study - comparator may include some men with first-degree relatives diagnosed with prostate cancer

[b] Expected number for corresponding ages and calendar periods in the Swedish population

[c] Expected number for corresponding ages and calendar periods in the southern Swedish population

[d] Risk ratio calculated using log-linear model Swedish population as comparator

[e] Hazard ratio calculated using Cox regression with socioeconomic status, calendar period and region included as covariates

[f] Non-exposure = men with no brothers or father diagnosed with prostate cancer

[g] Hazard ratio calculated using Cox model with age as underlying time scale and socioeconomic status, calendar period and region included as covariates

[i] SIR standardised for age, calendar year, socioeconomic status and region

[j] RR estimated by proportional hazards methods adjusting for year of birth

[k] SIR standardised for age, calendar year and socioeconomic status

[l] Hazard ratio calculated using Cox regression adjusted for age, period, socioeconomic status, region, father's age at start and end of follow-up, admission to hospital for obesity, chronic obstructive pulmonary disease and alcohol

[m] RR estimated using Mantel-Haenszel method and adjusted for age

[n] Expected number for corresponding ages and calendar periods in the Icelandic population

[o] Expected number for corresponding ages and calendar periods in the Finnish population

II PROSTATE CANCER MORTALITY

Table 9: Risk of prostate cancer mortality for relatives of men with prostate cancer: cohort study results

Study	Outcome Definition	Outcome metric	Exposure	No exposure	p value	Size of effect (95%CI)
Father vs no brother or father diagnosed with prostate cancer						
Brandt 2010	Prostate cancer mortality					
	Exposure = father only	n	306	2,113[f]	<0.0001	HR[e] = 1.81 (1.61 – 2.04)
	Exposure = father only diagnosed at age < 60 years	n	7	2,113[f]	0.06	HR[e] = 2.06 (0.98 – 4.32)
Father **died of** prostate cancer vs no father/no father or brother diagnosed with prostate cancer/general population						
Brandt 2010 & 2012; Hemminki 2011	Prostate cancer mortality	n	280	NR[b]	NR	SMR[i] = 2.04 (1.81 – 2.29)
		n	202	2,113[f]	<0.0001	HR[e] = 2.08 (1.80 – 2.41)
		n	206	2,082[h]	NR	HR[g] = 2.03 (1.76 – 2.35)
Brother(s) vs no brother or father diagnosed with prostate cancer						
Brandt 2010	Prostate cancer mortality					
	Exposure = 1 brother only	n	139	2,113[f]	<0.0001	HR[e] = 2.75 (2.32 – 3.26)
	Exposure = 1 brother only diagnosed at age < 60 years	n	32	2,113[f]	<0.0001	HR[e] = 3.27 (2.31 – 4.64)
	Exposure = 2 brothers only	n	15	2,113[f]	<0.0001	HR[e] = 6.29 (3.79 – 10.46)
	Exposure = 3 brothers only	n	2	2,113[f]	0.003	HR[e] = 8.12 (2.03 – 32.50)
Brother **died of** prostate cancer vs no brother or father diagnosed with prostate cancer/general population						
Brandt 2010 & 2012	Prostate cancer mortality	n	36	NR[b]	NR	SMR[i] = 2.75 (1.93 – 3.80)
		n	15	2,113[f]	0.002	HR[e] = 2.30 (1.38 – 3.81)
Brother(s) + father vs no father or brother diagnosed with prostate cancer						
Brandt 2010	Prostate cancer mortality					
	Exposure = father and 1 brother only	n	24	2,113[f]	<0.0001	HR[e] = 2.96 (1.98 – 4.43)
	Exposure = father and 2 brothers	n	5	2,113[f]	<0.0001	HR[e] = 9.74 (4.05 –23.43)
Brother + father **died of** prostate cancer vs no father or brother diagnosed with prostate cancer						
Brandt 2010	Prostate cancer mortality	n	4	2,113[f]	<0.0001	HR[e] = 6.86 (2.57 – 18.28)

CI = confidence interval; HR = hazard ratio; NR = not reported; NS = not statistically significantly different; SMR = standardised mortality ratio

[b] Expected number based on the Swedish population rates

[e] Hazard ratio calculated using Cox regression with socioeconomic status, calendar period and region included as covariates

[f] Non-exposure = no brothers or father diagnosed with prostate cancer

[g] Hazard ratio calculated using Cox model with age as underlying time scale and socioeconomic status, calendar period and region included as covariates

[h] Non-exposure = no fathers diagnosed with prostate cancer

[i] SMR standardised for age, calendar year, socioeconomic status and region

2.5. Body of Evidence

I PROSTATE CANCER DIAGNOSIS

Name of study	Study type	Population	Level of evidence *	Quality of evidence **	Risk of bias	Results summary		p value (95% CI)	Size of the effect rating*	Relevance of evidence*
FAMILY HISTORY OF PROSTATE CANCER										
Third-degree relative vs male relative not diagnosed with prostate cancer/general population										
Eldon 2003	Retrospective cohort	Male population of Iceland	III-2	Low	High	Prostate cancer diagnosis	SIR = 1.22	NR (1.01 – 1.47)	3	1
						Exposure subgroup = Relative diagnosed aged <68 years	SIR = 1.14	NS (0.78 – 1.65)	4	
Kerber 2005	Nested case-control	Male descendants of Mormon pioneers of Utah born between 1870 and 1984	II	Low	High	Prostate cancer diagnosis	RR = 1.2	NR (1.1 – 1.2)	3	1
Second-degree relative vs male relative not diagnosed with prostate cancer/general population										
Eldon 2003	Retrospective cohort	Male population of Iceland	III-2	Low	High	Prostate cancer diagnosis	SIR = 1.25	NS (0.91 – 1.72)	4	1
						Exposure subgroup = Relative diagnosed aged <68 years	SIR = 1.68	NS (0.96 – 2.96)	4	

Kerber 2005	Nested case-control	Male descendants of Mormon pioneers of Utah born between 1870 and 1984	II	Low	High	Prostate cancer diagnosis	RR = 1.4	NR (1.3 – 1.5)	3	1
First-degree relative vs no first or second -degree relative diagnosed with prostate cancer/ male relative not diagnosed with prostate cancer/general population										
Kerber 2005	Nested case-control	Male descendants of Mormon pioneers of Utah born between 1870 and 1984	II	Low	High	Prostate cancer diagnosis	RR = 2.1	NR (1.9 – 2.2)	2	1
Frank 2014	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer diagnosis	SIR = 2.44	NR (2.40 – 2.49)	1	1
Eldon 2003	Retrospective cohort	Male population of Iceland	III-2	Low	High	Prostate cancer diagnosis *Exposure subgroup = Relative diagnosed aged <68 years*	SIR = 1.72 SIR = 2.42	NR (1.28 – 2.34) NR (1.25 – 4.68)	2 2	1
Matikainen 2001	Retrospective cohort	Male population of Finland	III-2	Low	High	Prostate cancer diagnosis *Exposure subgroup = Relative diagnosed aged*: <55 years 55 – 60 years 61 – 69 years 70 – 79 years ≥80 years	 SIR = 2.61 SIR = 2.44 SIR = 2.71 SIR = 1.15 SIR = 1.83	 <0.05 (1.25 – 4.80) <0.001 (1.76 – 3.29) <0.001 (1.92 – 3.71) NS (0.78 – 1.64) <0.01 (1.27 – 2.55)	 2 2 2 4 2	1
Bratt 1997	Retrospective cohort	Male population of southern healthcare	III-2	Low	High	Prostate cancer diagnosis *Exposure subgroup = Relative diagnosed aged <51 years* Overall	 SIR = 1.43	 0.17 (0.82 – 2.33)	 3	1

		region of Sweden				Men diagnosed at age: <70 years <80 years	 SIR = 3.37 SIR = 1.80	 0.006 (1.36 – 6.94) 0.06 (0.90 – 3.21)	 2 3	
First-degree relative **died of** prostate cancer vs general population										
Eldon 2003	Retrospective cohort	Male population of Iceland	III-2	Low	High	Prostate cancer diagnosis	SIR = 2.17	NR (1.34 – 3.53)	2	1
Father vs no father/no brother or father diagnosed with prostate cancer/ general population										
Brandt 2010 & 2012; Kharazmi 2012	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer diagnosis *Exposure subgroup = Father diagnosed aged*: 40 – 49 years 50 – 59 years 60 – 69 years 70 – 79 years 80 – 89 years ≥90 years *Exposure subgroup = Only father diagnosed* Overall Men diagnosed at age: <55 years 55 – 64 years 65 – 74 years	SIR = 2.28 HR = 2.3 HR = 5.2 HR = 3.3 HR = 2.9 HR = 2.4 HR = 1.9 HR = 1.3 HR = 2.12 HR = 2.93 HR = 2.22 HR = 1.78	NR (2.22 – 2.34) NR (2.2 – 2.4) NR (2.5 – 10.9) NR (2.8 – 3.8) NR (2.8 – 3.1) NR (2.3 – 2.4) NR (1.8 – 2.0) NR (1.1 – 1.6) <0.0001 (2.05 – 2.20) <0.0001 (2.64 – 3.25) <0.0001 (2.12 – 2.33) <0.0001 (1.68 – 1.90)	1 1 1 1 1 1 2 3 1 1 1 3	1
Gronberg 1996 & 1999	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer diagnosis Overall Men diagnosed at age: 45 – 49 years 50 – 54 years 55 – 59 years 60 – 64 years	 SIR = 1.70 SIR = 3.38 SIR = 2.25 SIR = 2.32 SIR = 1.66	 NR (1.51 – 1.90) NS (0.68 – 9.88) NR (1.03 – 4.27) NR (1.57 – 3.29) NR (1.23 – 2.18)	 3 4 2 2 2	1

						65 – 69 years	SIR = 1.86	NR (1.49 – 2.30)	2		
						70 – 74 years	SIR = 1.55	NR (1.21 – 1.95)	3		
						75 – 79 years	SIR = 1.41	NS (0.99 – 1.94)	4		
						≥80 years	SIR = 1.35	NS (0.74 – 2.27)	4		
						Exposure subgroup = Father diagnosed aged:					
						<70 years	1990 follow-up	SIR = 2.27	NR (1.57 – 3.17)	2	
							1994 follow-up	RR = 2.68	<0.001 (2.15 – 3.34)	1	
						70–79 years	1990 follow-up	SIR = 1.92	NR (1.64 – 2.23)	2	
							1994 follow-up	RR = 1.93	<0.001 (1.70 – 2.19)	2	
						≥80 years	1990 follow-up	SIR = 1.34	NR (1.09 – 1.62)	3	
							1994 follow-up	RR = 1.56	<0.001 (1.32 – 1.83)	3	
Father **died of** prostate cancer vs father not diagnosed with prostate cancer											
Hemminki 2011	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer diagnosis		HR = 2.30	NR (2.20 – 2.40)	1	1
Brother(s) vs no brother or father diagnosed with prostate cancer/general population											
Brandt 2010 & 2012	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer diagnosis		SIR = 3.25	NR (3.13 – 3.36)	1	1
						Exposure subgroup = At least one brother diagnosed aged:					
						<60 years		HR = 3.94	<0.0001 (3.56 – 4.36)	1	
						60 – 64 years		HR = 3.01	<0.0001 (2.75 – 3.29)	1	
						65 – 74 years		HR = 2.46	<0.0001 (2.25 – 2.69)	1	
One brother vs no brother or father diagnosed with prostate cancer/general population											
Brandt 2010	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer diagnosis					1
						Overall		HR = 2.96	<0.0001 (2.80 – 3.13)	1	
						Men diagnosed at age:					
						<55 years		HR = 4.41	<0.0001 (3.59 – 5.42)	1	
						55 – 64 years		HR = 3.15	<0.0001 (2.92 – 3.39)	1	
						65 – 74 years		HR = 2.56	<0.0001 (2.34 – 2.79)	1	

Bratt 2010	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer diagnosis	SIR = 3.1	NR (2.9 – 3.3)	1	1
Two brothers vs no brother or father diagnosed with prostate cancer/general population										
Brandt 2010	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer diagnosis Overall Men diagnosed at age: <55 years 55 – 64 years 65 – 74 years *Exposure subgroup = At least one brother diagnosed aged < 60 years*	 HR = 7.71 HR = 5.90 HR = 8.93 HR = 6.49 HR = 8.79	 <0.0001 (6.54 – 9.08) <0.0001 (2.45 – 14.20) <0.0001 (7.19 – 11.08) <0.0001 (4.99 – 8.43) <0.0001 (6.92 – 11.18)	 1 1 1 1 1	1
Bratt 2010	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer diagnosis	SIR = 11	NR (8.7 – 14)	1	1
Three brothers vs no brother or father diagnosed with prostate cancer										
Brandt 2010	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer diagnosis *Exposure subgroup = At least one brother diagnosed aged < 60 years*	HR = 17.74 HR = 24.35	<0.0001 (12.26 – 25.67) <0.0001 (16.18 – 36.64)	1 1	1
Father **and** one brother vs no father or brother diagnosed with prostate cancer/general population										
Brandt 2010	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer diagnosis Overall Men diagnosed at age: <55 years 55 – 64 years 65 – 74 years *Exposure subgroup = At least one relative diagnosed* aged < 60 years	 HR = 5.51 HR = 11.32 HR = 6.48 HR = 3.46	 <0.0001 (5.00 – 6.09) <0.0001 (8.47 – 15.13) <0.0001 (5.72 – 7.35) <0.0001 (2.85 – 4.19)	 1 1 1 1	1

							HR = 7.63	<0.0001 (6.53 – 8.92)	1	
Bratt 2010	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer diagnosis	SIR = 5.3	NR (4.6 – 6.0)	1	1
Father **and** two brothers vs no father or brother diagnosed with prostate cancer/ general population										
Brandt 2010	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer diagnosis *Exposure subgroup = At least one relative diagnosed* aged < 60 years	HR = 8.51 HR = 10.86	<0.0001 (6.13 – 11.80) <0.0001 (7.08 – 16.66)	1 1	1
Bratt 2010	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer diagnosis	SIR = 9.7	NR (5.3 – 16)	1	1

CI = confidence interval; HR = hazard ratio; NR = not reported; NS = not statistically significantly different; RR = risk ratio; SIR = standardised incidence ratio

**Refer to appendix B for detailed explanations of rating scores; ** See Tables 2 – 3 and 6 – 7 for quality appraisals*

II PROSTATE CANCER MORTALITY

Name of study	Study type	Population	Level of evidence *	Quality of evidence**	Risk of bias	Results summary		p value (95% CI)	Size of the effect rating*	Relevance of evidence*
FAMILY HISTORY OF PROSTATE CANCER										
Father vs no brother or father diagnosed with prostate cancer										
Brandt 2010	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer mortality *Exposure subgroup = Father diagnosed aged* < 60 years	HR = 1.81 HR = 2.06	<0.0001 (1.61 – 2.04) 0.06 (0.98 – 4.32)	2 4	1
Father **died of** prostate cancer vs no father/ no father or brother diagnosed with prostate cancer/general population										
Brandt 2010 & 2012; Hemminki 2011	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer mortality Follow up to 2006 Follow up to 2008	HR = 2.03 HR = 2.08 SMR = 2.04	NR (1.76 – 2.35) <0.001 (1.80 – 2.41) NR (1.81 – 2.29)	2 2 2	1
Brother vs no brother or father diagnosed with prostate cancer										

Brandt 2010	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer mortality *Exposure subgroups* *One brother only* *One brother only diagnosed at age <60 years*	 HR = 2.75 HR = 3.27	 <0.0001 (2.32 – 3.26) <0.0001 (2.31 – 4.64)	 1 1	1
Brothers vs no brother or father diagnosed with prostate cancer										
Brandt 2010	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer mortality *Exposure subgroups:* *2 brothers only* *3 brothers only*	 HR = 6.29 HR = 8.12	 <0.0001 (3.79 – 10.46) 0.003 (2.03 – 32.50)	 1 1	1
Brother **died of** prostate cancer vs no brother or father diagnosed with prostate cancer										
Brandt 2010 & 2012	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer mortality Follow up to 2006 Follow up to 2008	 HR = 2.30 SMR = 2.75	 0.002 (1.38 – 3.81) NR (1.93 – 3.80)	 1 1	1
Brother(s) **and** father vs no father or brother diagnosed with prostate cancer										
Brandt 2010	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer mortality *Exposure subgroups:* *Father + 1 brother only* *Father + 2 brothers*	 HR = 2.96 HR = 9.74	 <0.0001 (1.98 – 4.43) <0.0001 (4.05 – 23.43)	 1 1	1
Brother **and** father **died of** prostate cancer vs no father or brother diagnosed with prostate cancer										
Brandt 2010	Retrospective cohort	Male population of Sweden	III-2	Low	High	Prostate cancer mortality	HR = 6.86	<0.0001 (2.57 – 18.28)	1	1

CI = confidence interval; HR = hazard ratio; NR = not reported; SMR = standardised mortality ratio

**Refer to appendix B for detailed explanations of rating scores; ** See Table 4 – 5 for quality appraisals*

References: Included Studies

1. Brandt A, Bermejo JL, Sundquist J, Hemminki K. Age-specific risk of incident prostate cancer and risk of death from prostate cancer defined by the number of affected family members. Eur Urol 2010; 58(2):275-280.

2. Brandt A, Sundquist J, Hemminki K. Risk for incident and fatal prostate cancer in men with a family history of any incident and fatal cancer. Ann Oncol 2012; 23(1):251-256.

3. Bratt O, Kristoffersson U, Lundgren R, Olsson H. The risk of malignant tumours in first-degree relatives of men with early onset prostate cancer: a population-based cohort study. Eur J Cancer 1997; 33(13):2237-2240.

4. Bratt O, Garmo H, Adolfsson J, Bill-Axelson A, Holmberg L, Lambe M et al. Effects of prostate-specific antigen testing on familial prostate cancer risk estimates. J Natl Cancer Inst 2010; 102(17):1336-1343.

5. Eldon BJ, Jonsson E, Tomasson J, Tryggvadottir L, Tulinius H. Familial risk of prostate cancer in Iceland. BJU Int 2003; 92(9):915-919.

6. Frank C, Fallah M, Ji J, Sundquist J, Hemminki K. The population impact of familial cancer, a major cause of cancer. International Journal of Cancer 2014; 134(8):1899-1906.

7. Gronberg H, Damber L, Damber JE. Familial prostate cancer in Sweden. A nationwide register cohort study. Cancer 1996; 77(1):138-143.

8. Gronberg H, Wiklund F, Damber JE. Age specific risks of familial prostate carcinoma: a basis for screening recommendations in high risk populations. Cancer 1999; 86(3):477-483.

9. Hemminki K, Sundquist J, Brandt A. Familial mortality and familial incidence in cancer. J Clin Oncol 2011; 29(6):712-718.

10. Kerber RA, O'Brien E. A cohort study of cancer risk in relation to family histories of cancer in the Utah population database. Cancer 2005; 103(9):1906-1915.

11. Kharazmi E, Fallah M, Sundquist K, Hemminki K. Familial risk of early and late onset cancer: nationwide prospective cohort study. BMJ 2012; 345:e8076.

12. Matikainen MP, Pukkala E, Schleutker J, Tammela TL, Koivisto P, Sankila R et al. Relatives of prostate cancer patients have an increased risk of prostate and stomach cancers: a population-based, cancer registry study in Finland. Cancer Causes Control 2001; 12(3):223-230.

3. Appendices

Appendix A: Search strategies used

For Medline database: Search terms used to identify systematic reviews and meta-analysis

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	exp pedigree/
5	exp heredity/
6	exp family health/
7	disease susceptibility/
8	medical history taking/
9	(brother$ or father$ or sibling$ or relative$ or hereditary).tw.
10	(famil$ adj3 (history or cluster$ or aggreg$ or associate$ or member$ or risk$ or factor$)).tw.
11	4 or 5 or 6 or 7 or 8 or 9 or 10
12	3 and 11
13	limit 12 to (english language and humans and yr="1990-current")
14	meta-analysis/
15	review literature/
16	meta-analy$.tw.
17	metaanal$.tw.
18	(systematic$ adj4 (review$ or overview$)).mp.
19	meta-analysis.pt.
20	review.pt.
21	review.ti.
22	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23	case report/
24	letter.pt.
25	historical article.pt.
26	23 or 24 or 25
27	22 not 26
28	13 and 27

The systematic review filter used was based on the Centre for Reviews and Dissemination strategy 2.2 *published in Lee et al, (2012) An optimal search filter for retrieving systematic reviews and meta-analyses* ***BMC Medical Research Methodology 12*:*51***.

Search terms used to identify papers published after 2010

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	exp pedigree/
5	exp heredity/
6	exp family health/
7	exp disease susceptibility/
8	exp medical history taking/
9	(famil$ adj3 (history or cluster$ or aggreg$ or associat$ or member$ or risk$ or factor$)).tw.
10	(hereditary adj3 (history or cluster$ or aggreg$ or associat$ or risk$ or factor$)).tw.
11	((brother$ or father$ or sibling$ or relative$ or uncle$) adj5 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$))).tw.
12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	3 and 12
14	limit 13 to (english language and humans and yr="2010-current")

ATSI search terms used:

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database:

Search terms used to identify systematic reviews and meta-analysis

#	Searches
1	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neopla* OR metast* OR adeno*)
2	'prostate cancer'/exp OR 'prostate cancer'
3	1 or 2
4	'family history'/exp
5	'cancer susceptibility'/exp
6	'heredity'/de
7	brother* OR father* OR sibling* OR relative* OR hereditary
8	famil* NEAR/3 (history OR cluster* OR aggreg* OR associat* OR member* OR risk* OR factor*)
9	4 OR 5 OR 6 OR 7 OR 8
10	[embase]/lim AND [1990-2014]/py AND [english]/lim AND [humans]/lim
11	3 AND 9 AND 10
12	'systematic review'/exp OR 'systematic review'
13	'meta analysis'/exp OR 'meta analysis'
14	meta NEXT/1 analys*
15	search*
16	review* NEAR/2 systematic*
17	12 OR 13 OR 14 OR 15 OR 16
18	11 AND 17

Search terms used to identify papers published after 2010

#	Searches
1	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neopla* OR metast* OR adeno*)
2	'prostate cancer'/exp OR 'prostate cancer'
3	1 or 2
4	'family history'/exp
5	'cancer susceptibility'/exp
6	famil* NEAR/3 (history OR cluster* OR aggreg* OR associat* OR member* OR risk* OR factor*)
7	hereditary NEAR/3 (history OR cluster* OR aggreg* OR associat* OR risk* OR factor*)
8	(brother* OR father* OR sibling* OR relative* OR uncle*) NEAR/5 prostat*
9	4 or 5 or 6 or 7 or 8
10	[embase]/lim AND [2010-2014]/py AND [english]/lim AND [humans]/lim
11	3 and 9 and 10
12	'genetic polymorphism'/exp

13	11 not 12

ATSI search terms used:

#	Searches
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

For Cochrane Database of Systematic Reviews – The Cochrane Library:
Title, abstracts, keywords: “prostate”

For Database of Abstracts of Reviews of Effects and Health Technology Assessment database (via OvidSP):

#	Searches
1	exp Prostatic Neoplasms/
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
3	1 or 2

Appendix B:

Level of Evidence rating criteria – Risk factor studies

Level	Study design
I	Meta-analysis or a systematic review of level II studies
II	Prospective cohort studies
III-1	All or none
III-2	Retrospective cohort studies
III-3	Case-control studies
IV	Cross-sectional studies or case series

According to the standards of the National Health and Medical Research Council

Size of Effect Rating

Rating	Clinical Importance of Benefit
1	A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant benefit of the intervention.
2	The confidence interval includes clinically important and unimportant benefits BUT does not include possible harm.
3	The confidence interval does not include any clinically important benefits BUT does not include possible harm.
4	The range of estimates defined by the confidence interval includes clinically important benefits BUT is also compatible with no effect or a harmful effect.
5	The range of estimated defined by the confidence interval does not include any clinically important benefits AND is also compatible with no effect or a harmful effect.
6	Not assessable. Statistical significance (p value or CI) not reported and cannot be calculated from the data

Points for considering the size of effect:
i) The size of the effect is important because it relates to the clinical importance of the effect
ii) The size of the effect and the certainty with which it is known should both be assessed
iii) Wherever relevant and possible, the size of the effect should be expressed in both relative and absolute terms (i.e. as relative risks and absolute risk reductions or NNT for a range of baseline risks)

As a guide where there is no confidence interval:
1: Point estimate is clinically important and p value ≤ 0.01. Assume narrow confidence interval that is unlikely to include clinically unimportant effects
2: Point estimate is clinically important and 0.01 < p value < 0.05. Assume wide confidence interval and therefore may include clinically unimportant results
3: Point estimate is not clinically important and p < 0.05. Assume confidence interval does not include clinically important effects
4/5: Difference not statistically significant (p > 0.05). CI will be compatible with no effect but may also include clinically important effects or a harmful effect
6: Not assessable. Statistical significance (p value or CI) not reported and cannot be calculated from the data

Adapted from table 1.7 of: National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra: NHMRC; 2000.
http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp69.pdf

Relevance of the Evidence

Rating	Relevance
1	Evidence of an effect on patient-relevant clinical outcomes including benefits and harms, quality of life and survival.
2	Evidence of an effect on a surrogate outcome* that has been shown to be predictive of patient-relevant outcomes for the same intervention.
3	Evidence of an effect on proven surrogate outcomes but for a different intervention.
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population.
5	Evidence confined to unproven surrogate outcomes.

**'surrogate outcome' refers to reasonable indicators of whether there has been some effect (e.g. blood pressure measurements or levels of serum cholesterol)*

Points for considering patient-relevant outcomes:
i) The goal of decision making in health care is to choose the intervention(s) (which may include doing nothing) that is (are) most likely to deliver the outcomes that patients find desirable.
ii) Surrogate outcomes (such as blood pressure measurements or levels of serum cholesterol) may be reasonable indicators of whether there has been some effect. However, they should not be the basis for clinical decisions unless they reliably predict an effect on the way the patient feels, otherwise they will not be of interest to the patient or their carers.
iii) All possible outcomes that are of most interest to patients (particularly harms) should be identified and evaluated.

Adapted from table 1.10 of: National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra: NHMRC; 2000.
http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp69.pdf

Appendix C: Excluded Studies

Study	Reason for Exclusion
Albright 2012	No relevant comparisons
Bishop 1997	Narrative review/comment
Brandt 2010	Inappropriate study design
Bratt 2007	Narrative review/comment
Bratt 2002	Narrative review/comment
Bratt 2000	Narrative review/comment
Bruner 2003	Systematic review – not all included studies meet inclusion criteria
Cannon-Albright 1994	No relevant comparisons
Cerhan 1999	Self-reported family history of prostate cancer or prostate cancer diagnosis
Chen 2008	Self-reported family history of prostate cancer or prostate cancer diagnosis
Colloca 2011	Narrative review/comment
Cunningham 2003	Self-reported family history of prostate cancer or prostate cancer diagnosis
Cussenot 1998	Narrative review/comment
Damber 1999	Narrative review/comment
Dong 2001	More mature data published
Elshafei 2013	Self-reported family history of prostate cancer or prostate cancer diagnosis
Gil-Bazo 2014	Inappropriate study design
Goldgar 1994	More mature data published
Hemminki 2012	Narrative review/comment
Hemminki 2008	No relevant outcomes
Hemminki 2002a	More mature data published
Hemminki 2002b	More mature data published
Hemminki 2000	More mature data published
Hodgson 2013	Narrative review/comment
Jansson 2012	Relevant data published previously
Johns 2003	Systematic review – included studies have since published more mature data
Kalish 2000	Did not specify degree of family history
Kicinski 2011	Systematic review – not all included studies meet inclusion criteria
Kral 2011	Narrative review/comment
Liang 2013	No relevant comparisons
Madersbacher 2011	Narrative review/comment
Mai 2010	No relevant comparisons
Makinen 2002	Self-reported family history of prostate cancer or prostate cancer diagnosis
McLellan 1995	Systematic review – not all included studies meet inclusion criteria
Monroe 1995	No relevant comparisons
Muller 2013	Did not specify degree of family history
Narod 1995	Self-reported family history of prostate cancer or prostate cancer diagnosis
Noe 2008	Narrative review/comment

Park 2009	Did not specify degree of family history
Pienta 1993	Narrative review/comment
Randazzo 2014	Published after March 2014
Rodriguez 1997	Self-reported family history of prostate cancer or prostate cancer diagnosis
Romero 2013	Self-reported family history of prostate cancer or prostate cancer diagnosis
Roobol 2009	Narrative review/comment
Stanford 2001	Narrative review/comment
Turati 2013	Inappropriate study design
Zeegers 2003	Systematic review – not all included studies meet inclusion criteria
Zoller 2014	Published after March 2014

References: Excluded Studies

1. Albright F, Teerlink C, Werner TL, Cannon-Albright LA. Significant evidence for a heritable contribution to cancer predisposition: a review of cancer familiality by site. BMC Cancer 2012; 12:138.

2. Bishop DT, Kiemeney LA. Family studies and the evidence for genetic susceptibility to prostate cancer. Semin Cancer Biol 1997; 8(1):45-51.

3. Brandt A, Bermejo JL, Sundquist J, Hemminki K. Familial risks of breast and prostate cancers: does the definition of the at risk period matter? Eur J Cancer 2010; 46(4):752-757.

4. Bratt O. Hereditary prostate cancer. BJU Int 2000; 85(5):588-598.

5. Bratt O. Hereditary prostate cancer: clinical aspects. J Urol 2002; 168(3):906-913.

6. Bratt O. What should a urologist know about hereditary predisposition to prostate cancer? BJU Int 2007; 99(4):743-747.

7. Bruner DW, Moore D, Parlanti A, Dorgan J, Engstrom P. Relative risk of prostate cancer for men with affected relatives: systematic review and meta-analysis. Int J Cancer 2003; 107(5):797-803.

8. Cannon-Albright LA, Thomas A, Goldgar DE, Gholami K, Rowe K, Jacobsen M et al. Familiality of cancer in Utah. Cancer Res 1994; 54(9):2378-2385.

9. Cerhan JR, Parker AS, Putnam SD, Chiu BC, Lynch CF, Cohen MB et al. Family history and prostate cancer risk in a population-based cohort of Iowa men. Cancer Epidemiol Biomarkers Prev 1999; 8(1):53-60.

10. Chen YC, Page JH, Chen R, Giovannucci E. Family history of prostate and breast cancer and the risk of prostate cancer in the PSA era. Prostate 2008; 68(14):1582-1591.

11. Colloca G, Venturino A. The evolving role of familial history for prostate cancer. Acta Oncol 2011; 50(1):14-24.

12. Cunningham GR, Ashton CM, Annegers JF, Souchek J, Klima M, Miles B. Familial aggregation of prostate cancer in African-Americans and white Americans. Prostate 2003; 56(4):256-262.

13. Cussenot O, Valeri A, Berthon P, Fournier G, Mangin P. Hereditary prostate cancer and other genetic predispositions to prostate cancer. Urol Int 1998; 60 Suppl 2:30-34.

14. Damber JE. Hereditary prostate cancer. Scand J Urol Nephrol Suppl 1999; 203:25-28.

15. Dong C, Hemminki K. Modification of cancer risks in offspring by sibling and parental cancers from 2,112,616 nuclear families. Int J Cancer 2001; 92(1):144-150.

16. Elshafei A, Moussa AS, Hatem A, Ethan V, Panumatrassamee K, Hernandez AV et al. Does positive family history of prostate cancer increase the risk of prostate cancer on initial prostate biopsy? Urology 2013; 81(4):826-830.

17. Gil-Bazo I, Castanon E, Fusco JP, Martin P, Zubiri L, Ceniceros L et al. Familial clustering of prostate cancer (Pca) cases in a nonselected south European population (sEp). J Clin Oncol 2014; 32(4).

18. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. J Natl Cancer Inst 1994; 86(21):1600-1608.

19. Hemminki K, Dong C. Familial prostate cancer from the family-cancer database. Eur J Cancer 2000; 36(2):229-234.

20. Hemminki K, Czene K. Age specific and attributable risks of familial prostate carcinoma from the family-cancer database. Cancer 2002; 95(6):1346-1353.

21. Hemminki K, Czene K. Attributable risks of familial cancer from the Family-Cancer Database. Cancer Epidemiol Biomarkers Prev 2002; 11(12):1638-1644.

22. Hemminki K, Ji J, Forsti A, Sundquist J, Lenner P. Concordance of survival in family members with prostate cancer. J Clin Oncol 2008; 26(10):1705-1709.

23. Hemminki K. Familial risk and familial survival in prostate cancer. World J Urol 2012; 30(2):143-148.

24. Hodgson S. Familial risk of early and late onset cancer. J R Coll Phys Edinburgh 2013; 43(2):134-135.

25. Jansson KF, Akre O, Garmo H, Bill-Axelson A, Adolfsson J, Stattin P et al. Concordance of tumor differentiation among brothers with prostate cancer. Eur Urol 2012; 62(4):656-661.

26. Johns LE, Houlston RS. A systematic review and meta-analysis of familial prostate cancer risk. BJU Int 2003; 91(9):789-794.

27. Kalish LA, McDougal WS, McKinlay JB. Family history and the risk of prostate cancer. Urology 2000; 56(5):803-806.

28. Kicinski M, Vangronsveld J, Nawrot TS. An epidemiological reappraisal of the familial aggregation of prostate cancer: a meta-analysis. PLoS One 2011; 6(10):e27130.

29. Kral M, Rosinska V, Student V, Grepl M, Hrabec M, Bouchal J. Genetic determinants of prostate cancer: a review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2011; 155(1):3-9.

30. Liang Y, Messer JC, Louden C, Jimenez-Rios MA, Thompson IM, Camarena-Reynoso HR. Prostate cancer risk prediction in a urology clinic in Mexico. Urologic Oncology 2013; 31(7):1085-1092.

31. Madersbacher S, Alcaraz A, Emberton M, Hammerer P, Ponholzer A, Schroder FH et al. The influence of family history on prostate cancer risk: implications for clinical management. BJU Int 2011; 107(5):716-721.

32. Mai PL, Wideroff L, Greene MH, Graubard BI. Prevalence of family history of breast, colorectal, prostate, and lung cancer in a population-based study. Public Health Genomics 2010; 13(7-8):495-503.

33. Makinen T, Tammela TL, Stenman UH, Maattanen L, Rannikko S, Aro J et al. Family history and prostate cancer screening with prostate-specific antigen. J Clin Oncol 2002; 20(11):2658-2663.

34. McLellan DL, Norman RW. Hereditary aspects of prostate cancer. CMAJ 1995; 153(7):895-900.

35. Monroe KR, Yu MC, Kolonel LN, Coetzee GA, Wilkens LR, Ross RK et al. Evidence of an X-linked or recessive genetic component to prostate cancer risk. Nat Med 1995; 1(8):827-829.

36. Muller RL, Faria EF, Carvalhal GF, Reis RB, Mauad EC, Carvalho AL et al. Association between family history of prostate cancer and positive biopsies in a Brazilian screening program. World Journal of Urology 2013; 31(5):1273-1278.

37. Narod SA, Dupont A, Cusan L, Diamond P, Gomez JL, Suburu R et al. The impact of family history on early detection of prostate cancer. Nat Med 1995; 1(2):99-101.

38. Noe M, Schroy P, Demierre MF, Babayan R, Geller AC. Increased cancer risk for individuals with a family history of prostate cancer, colorectal cancer, and melanoma and their associated screening recommendations and practices. Cancer Causes Control 2008; 19(1):1-12.

39. Park SY, Wilkens LR, Henning SM, Le ML, Gao K, Goodman MT et al. Circulating fatty acids and prostate cancer risk in a nested case-control study: the Multiethnic Cohort. Cancer Causes Control 2009; 20(2):211-223.

40. Pienta KJ, Esper PS. Risk factors for prostate cancer. Ann Intern Med 1993; 118(10):793-803.

41. Randazzo M, Beatrice J, Huber A, Grobholz R, Manka L, Recker F et al. The impact of family history on prostate cancer incidence and -aggressiveness in a population-based screening trial (ERSPC AARAU). J Urol 2014; 191(4):e814.

42. Rodriguez C, Calle EE, Miracle-McMahill HL, Tatham LM, Wingo PA, Thun MJ et al. Family history and risk of fatal prostate cancer. Epidemiology 1997; 8(6):653-657.

43. Romero FR, Romero AW, Almeida RM, Oliveira FC, Jr., Tambara FR. The significance of biological, environmental, and social risk factors for prostate cancer in a cohort study in Brazil. Int Braz J Urol 2012; 38(6):769-778.

44. Roobol MJ, Schroder FH, Crawford ED, Freedland SJ, Sartor AO, Fleshner N et al. A framework for the identification of men at increased risk for prostate cancer. J Urol 2009; 182(5):2112-2120.

45. Stanford JL, Ostrander EA. Familial prostate cancer. Epidemiol Rev 2001; 23(1):19-23.

46. Turati F, Edefonti V, Bosetti C, Ferraroni M, Malvezzi M, Franceschi S et al. Family history of cancer and the risk of cancer: a network of case-control studies. Annals of Oncology 2013; 24(10):2651-2656.

47. Zeegers MP, Jellema A, Ostrer H. Empiric risk of prostate carcinoma for relatives of patients with prostate carcinoma: a meta-analysis. Cancer 2003; 97(8):1894-1903.

48. Zoller B, Li X, Sundquist J, Sundquist K. Familial transmission of prostate, breast and colorectal cancer in adoptees is related to cancer in biological but not in adoptive parents: A nationwide family study. Eur J Cancer 2014; 50(13):2319-2327.

Systematic review report for question 2

Clinical Question 2: *"What methods of decision support for men about PSA testing increase men's capacity to make an informed decision for or against testing?"*

PICO Question 2: *"In men without evidence of prostate cancer does a decision support intervention or decision aid compared with usual care improve knowledge, decisional satisfaction, decision-related distress and decisional uncertainty about PSA testing for early detection of prostate cancer?"*

Population	Intervention	Comparator	Outcomes
Men without evidence of prostate cancer considering a PSA test	Decision support intervention,	Usual care	Knowledge Decisional satisfaction Decision-related distress Decisional uncertainty

1. METHODS

1.1. Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption guidelines had to be evidence based and meet the pre-specified criteria of scores of greater or equal to 70% for the domains rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

1.2. Literature Search

Medline, Embase, CINAHL, PsycINFO, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases, were searched from 1990, using text terms and, where available, database specific subject headings. Each database was searched for articles dealing with prostate cancer. In Medline, Embase, CINAHL and PsycINFO databases the prostate cancer search was coupled with a search for decision support interventions or decision aids and database-specific filters for identifying randomized controlled trials and systematic reviews/meta-analyses of randomized controlled trials. To identify studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples. A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for Medline, CINAHL, PsycINFO and Embase searches to identify relevant articles published before 1st March 2014 which were either published after the initial search was completed and/or added to the relevant database after the search was completed. Alerts were checked until July 2014. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched regularly up until April 2014 for relevant reviews published after the initial search. Reference lists of all relevant articles were checked for potential additional articles.

1.3. Inclusion Criteria

Selection criteria	**Inclusion criteria**
Study type	Intervention
Study design	Randomised controlled trial (RCT) Systematic reviews or meta-analyses of RCTs
Population	Men (average or high risk) without evidence of prostate cancer considering a PSA test
Intervention	Decision support intervention/decision aid or tailored information (including risk communication) about PSA testing for early detection of prostate cancer
Comparator	Usual care including no information or non-tailored generic information about PSA testing for early detection of prostate cancer
Outcomes	Knowledge Decisional satisfaction including feeling informed Decision-related distress including: decisional conflict, anxiety Decisional uncertainty
Language	English
Publication period	After 31st December 1989 and before1st March 2014

Conference proceedings identified by the literature searches were included if they met the inclusion criteria.

1.4. Definitions

Decision support intervention/decision aid

Interventions designed to help people make specific and deliberative choices among options (including the status quo) by providing (at the minimum):

1. Information on the options and outcomes relevant to a person's health status and
2. Implicit methods to clarify values.
   The aid also may have included:
3. Information on the disease/condition; costs associated with options; probabilities of outcomes tailored to personal health risk factors;
4. An explicit values clarification exercise;
5. Information on other's opinions; a personalised recommendation on the basis of clinical characteristics and expressed preferences; and
6. Guidance or coaching in the steps of making and communicating decisions with others.
   (Stacey et al., 2011)

Tailored information

An intervention through which information is given to patients or individuals at risk of developing cancer where

1. The main objective of the information is to inform people about cancer risks, screening options, cancer genetic counselling and DNA testing;
2. The information is delivered by computer (e.g. CD-ROM or internet) or as printed material (e.g. letter or leaflet);
3. The information is tailored based on more than one variable using algorithms.
   (Albada et al., 2009)

Non-tailored information

Providing information on risks and benefits of testing in a screening context or discussion of risks and benefits of different options in a treatment context but does not include tailoring for the individual and does not include specific decision making advice about strategies such as in particular weighing up pros and cons or consideration of personal values.

2. RESULTS

2.1. Guidelines

Only one set of guidelines was identified (Wolf, A.: American Cancer Society Guideline for the Early Detection of Prostate Cancer – Update 2010, CA: A Cancer Journal for Clinicians) that contained potentially relevant recommendations. These recommendations were not adopted as these guidelines did not meet the pre-specified AGREE II criteria for adoption and the recommendations did not specifically address the clinical question; it highlighted the importance of informed and shared decision making, and recommended core elements of information that should be provided to patients, but did not mention what methods should be used.

2.2. Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the systematic review. The combined Medline and PsycINFO search identified 707 citations, the Embase search 210 citations, the CINAHL search 17 citations, the search of the Cochrane Database of Systematic Reviews 59 citations, the Database of Abstracts of Reviews of Effects search 282 citations and the search of the Health Technology Assessment database identified an additional 216 citations, resulting in a total of 1,491 citations. Titles and abstracts were examined and 70 articles were retrieved for a more detailed evaluation. An additional 10 potential citations were identified from the reference list of retrieved articles.

Thirteen (13) studies reported in as many articles met the inclusion criteria and were included in the review. There were no studies of Aboriginal and/or Torres Strait Islander men that met the inclusion criteria.

The retrieved articles that were not included and the reasons for their exclusion are documented in Appendix C. In summary, most articles were excluded because they had used an inappropriate study design, had included men/patients with a history of prostate cancer, or were not limited to prostate cancer/PSA testing, had not used an appropriate intervention or control group, or had not examined the relevant outcomes of knowledge, decisional satisfaction, decision-related distress or decisional uncertainty.

Studies were only included if sufficient information was available to determine whether the intervention met the criteria of the above-mentioned definitions. In particular, for decision aids the method for clarifying men's values about undergoing the PSA test had to be described adequately. Studies examining the effect of a decision aid that did not meet these criteria or those that provided insufficient information to allow for assessment of adequacy of the decision aid were excluded.

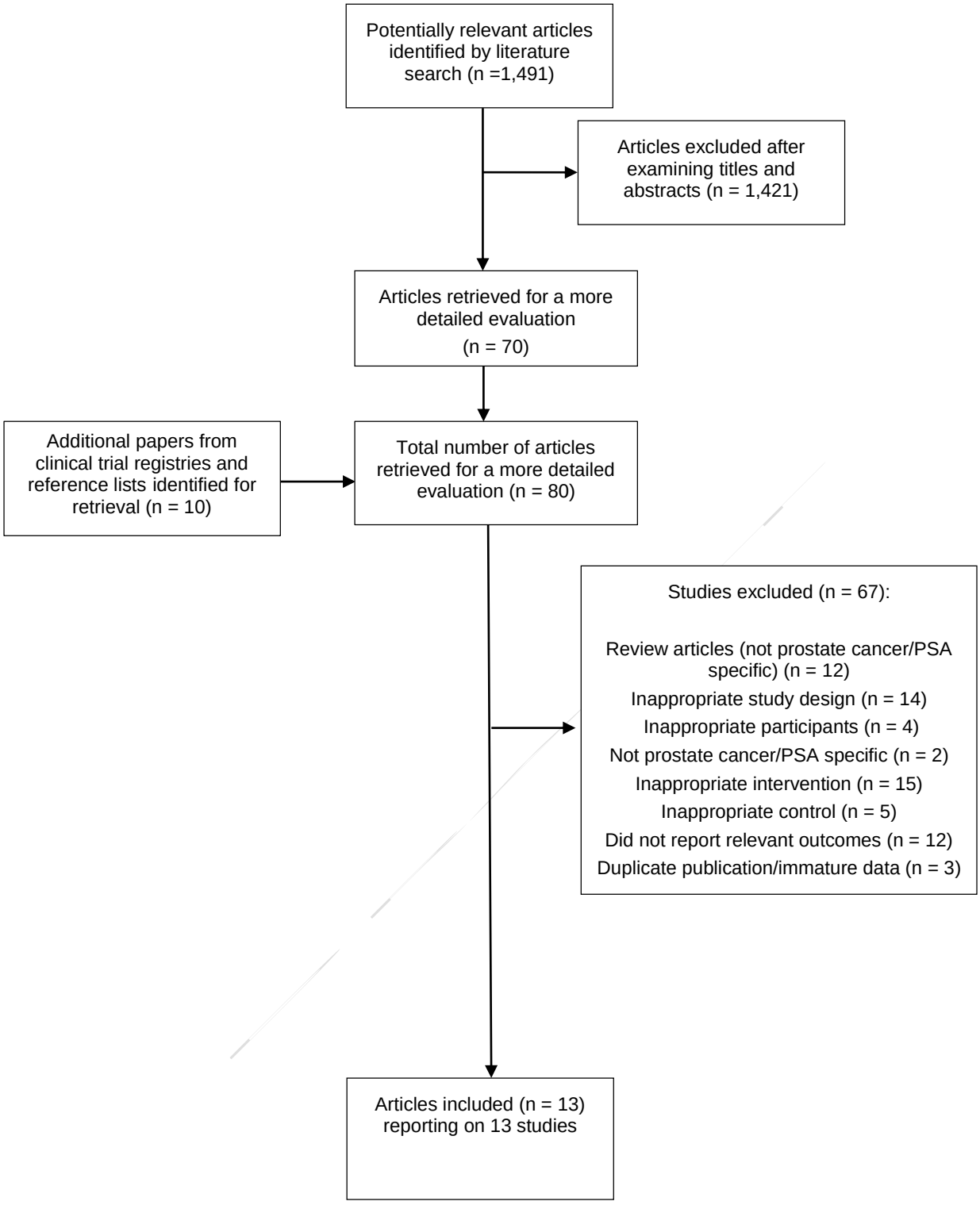


Figure 1. Process of inclusion and exclusion of studies

2.3. Study Characteristics

Characteristics of included studies are described in Table 1.

Table 1. Studies examining decision support interventions for improving the outcomes of knowledge, decisional satisfaction, decisional conflict and decisional uncertainty in men considering undergoing PSA testing

Study	Participants	Design	Intervention	Comparison	Outcomes	Comments
Decision aid vs. information only						
Gattellari 2003 (Australia)	Consecutive male patients not diagnosed with prostate cancer, sufficiently fluent in English recruited from 13 GP practices in Sydney aged 40-70 years (mean age 54.0) N = 248	RCT (multi-centre)	**Decision aid** *Booklet* (published) containing information on prostate cancer incidence, mortality, treatments and their side effects, and the pros and cons of PSA test; implicit methods to clarify values N = 126	**Usual care** *Government pamphlet* advising men of Australian government policy on PSA screening (published in 1996, not available for review) N = 122	*Knowledge* about prostate cancer, risk factors and evidence for screening and treatment *Decisional Conflict – Factors contributing to Decisional Uncertainty* (post-test only) *Decisional Uncertainty* (post-test only) *Perceived ability to make an informed choice* *Worry* about developing or dying from prostate cancer *Estimates of lifetime risks* of prostate cancer incidence and death *Interest in having PSA test* in next 12 months *Attitude* towards screening outcomes were assessed before consultation via pre-test questionnaires and via post-test questionnaires that were mailed 3 days after receiving information Follow-up 86.29%	Study powered to detect a mean difference of 0.35 between groups in Decisional Conflict scores (1-β=0.80 and α=0.05) Unsure as to whether any adjustments were made for baseline values in statistical analyses; 40% of men receiving intervention and 33% of men receiving usual care had had a prior PSA screening test;

Gattellari 2005 (Australia)	Community sample of men aged 50-70 years (mean age 58.1) without a history of prostate cancer, fluent in English, selected randomly from white-pages telephone directory (29 contiguous postcodes in Sydney), enrolled if interested in receiving information about PSA screening N = 421	R C T	**Decision Aid** *Booklet* including information and statistics on life-time and age-specific risks of developing/ dying from prostate cancer, family history as a risk factor, test accuracy, benefits/risk of harm from treatment, treatment-related complications; flow chart outlining the consequences of screening; values clarification exercise N = 140	**Standard Care** *Leaflet* brief information about the type of screening tests, chance of false positive result N = 140 <u>or</u> **Video** with information about the natural history of prostate cancer, test accuracy and treatment options; showing a man with a family history of prostate cancer and an older man, both weighing up the pros and cons of PSA "screening"; no values clarification exercise N = 141	*Knowledge* about efficacy of PSA screening, test accuracy, controversy about screening, nature of prostate cancer, risk factors, treatment-related issues *Decisional Conflict - Factors contributing to Decisional Uncertainty* (post-test only) *Decisional Uncertainty* (post-test only) *Perceived ability to make informed choice* Self-perceived *worry* about developing prostate cancer *Men's views* towards PSA screening *Decisional control preferences* *Propensity to undergo PSA screening* during the next 12 months *Likelihood of accepting a doctor's recommendation* to undergo PSA screening Scenario-based assessment of the *appropriateness of two different approaches to PSA screening* in general practice *Men's perceptions of GP fault* regarding adverse consequences of screening decisions Outcomes assessed at pre- and post-test telephone interviews; information mailed within 3 days of pre-test interview, participants contacted after ≥7 days after mailing (median number of days between pre-/post-test interview = 21 days) Follow-up = 93.57% (booklet) 97.87% (video) 97.14% (leaflet)	Sample of 300 considered sufficient to detect a difference of 20% between groups in dichotomous categorical outcomes (assuming a power of 80%, α=0.05, and to detect differences regarding items with continuous scores (Decisional Conflict) No baseline scores of Decisional Conflict; more men in the booklet group were living as married (82.1% vs. 68.6%) and less were divorced/separated (5.7% vs. 13.6%) a second experimental intervention (video) did not meet criteria for a decision aid

Myers 2011 (USA)	Males aged 50-69 years with no history of prostate cancer or benign prostatic hyperplasia, who had not had a PSA test in the preceding 11 months, recruited from two primary care practice sites in Philadelphia N = 313	R C T	**Enhanced Intervention** *Brochure* on prostate cancer and screening *Decision counselling session* eliciting factors that were likely to influence the participant's screening decision along with their relative influence and strength; computed each participant's decision preference score (direction, strength) with a pre-programmed algorithm and verified participant agreement with the preference *Discussion* of prostate cancer screening with physician N = 156	**Standard Intervention** *Brochure* on prostate cancer and screening *Practice quality assessment survey* *Discussion* of prostate cancer screening with physician N = 157	*Knowledge* about prostate cancer, implications of abnormal test results and controversy about screening *Decisional Conflict* (endpoint only) *Participant perceptions about prostate cancer screening* *Informed Decision Making* *Participant Social Desirability Response Set* *Prostate cancer screening use* *Preferred role in decision making* Outcomes assessed at baseline and endpoint telephone surveys; brochure sent to all participants following baseline survey; endpoint telephone survey 7 days after office visit Follow-up = 91.37%	Determined that a total sample size of 310 provided 83% power to detect an effect size of 0.4 standard deviations on the knowledge and decisional conflict scales (based on the use of a two-sided α of 0.05) Degree of clustering effects among participants seen by the same physician negligible – did not account for clustering in analyses (unsure if physicians' ability to discuss PSA screening differed between groups)
Volk 2008 (USA)	Patients aged 50-70 years if not African-American, and 40-70 years if African-American, without a history of prostate cancer, who visited one of two clinics for non-acute care (general medicine clinic – low health literacy site, university-affiliated family medicine clinic – high health literacy site) 37.1% (low-literacy)/74.5% (high literacy) had undergone previous PSA test N = 149 (low-literacy)	R C T	**Entertainment-based multimedia Decision Aid** *Didactic soap-opera episodes* with the ethnicity of the main character tailored to the viewer; interactive learning modules about basic facts about the prostate, risk factors, screening tests, treatment options for prostate cancer, complications of prostate cancer treatment; values clarification exercise ("pick who is most like you") N = 76 (low-literacy) N = 148 (high-literacy)	**Audio booklet** *Booklet* with same factual learner content presented with illustrations and text; no interactivity, no values clarification exercise N = 73 (low-literacy) N = 153 (high-literacy)	*Knowledge of prostate cancer and screening* *Decisional Conflict* *Acceptability of the decision aids* *Engagement with the entertainment-based aid* *Patient involvement* in health-care decision making (Patient Self-Advocacy Scale) Baseline questionnaire (and post-intervention surveys) administered on the day of intervention, follow-up assessment by telephone/mail two weeks later Follow-up = 56.38% (low-literacy/knowledge) 59.73% (low-literacy/dec. conflict) 79.40% (high-literacy)	Target sample size of 75 subjects per group to detect a "moderate" effect size when comparing the two groups on the knowledge measure Significant differences of baseline values between those who were and were not lost to follow-up; Patients who completed follow-up were older, more likely to have a family history of prostate cancer and to have had a previous PSA test, and were possibly more interested in screening than those who did not – decrease in decisional

	N = 301 (high-literacy)					conflict of low-literacy patients may have been overestimated
Watts 2013 (Australia)	Men aged 40-79 years (mean age 55.9) with at least one first- or second-degree relative with a previous diagnosis of prostate cancer, who were proficient in English, able to give informed consent and who had not been diagnosed with prostate cancer themselves recruited via advertisements in newspapers, a radiobroadcast, electronic newsletters, an online link to the study website, and by mailing of a study package to prostate cancer patients to give to their male relatives N = 138	RCT	**Tailored online Decision Aid** information about (familial) prostate cancer, prevention, diagnosis, treatment of prostate cancer, types and possible outcomes of screening (with PSA test), diagnosis of prostate cancer by biopsy or ultrasound, treatment of prostate cancer including side effects; specifically targeted towards an Australian audience; included a values clarification exercise: interactive personal worksheet regarding pros and cons of screening, two example worksheets completed by hypothetical men in a similar situation; included individually tailored statistics about men's chances of being diagnosed or dying from prostate cancer within the next 10 years, with and without annual screening, based on a combination of age and number of first- and/or second-degree relatives previously diagnosed with prostate cancer; N = 69	**Non-tailored materials** online educational materials about prostate cancer screening with identical information to that of decision aid, but without individually tailored statistics, worksheets N = 69	*Knowledge* of pros and cons of PSA testing, inheritance and relevance of family history, chances of being diagnosed with or dying of prostate cancer *Accuracy of perceived risk of developing prostate cancer* *Decisional Conflict* *Decision Regret (12 months after intervention)* *Inclination toward having a PSA test* *Screening behaviour* questionnaires completed by patients prior to, immediately after and 12 months after being requested to read online information Follow-up = 65.2%	Target sample size of 64 participants in each group provided 80% power to detect a 0.5 effect size difference (medium effect size) in decisional conflict between groups
Williams 2013 (USA)	English speaking men aged 40-70 years (mean age 54.9) with no history of prostate cancer, who had been pre-registered for prostate cancer	RCT	**Decision Aid Booklet** Information on the leading causes of death among men, accuracy of the PSA test and diagnostic procedures and treatments for prostate cancer;	**Usual Care Booklet** Short fact sheet with information about who is recommended for testing, how to interpret	*Knowledge* of prostate cancer symptoms, risk factors, natural history, the PSA controversy, false positive/negative results *Decisional Conflict*	80% power to detect small effect sizes (0.13-0.27; two-tailed, $p<0.05$) when comparing groups on knowledge and decisional

	screening at Georgetown University Medical Center or registered for free screening programs at Howard University Cancer Center at least 5 days before recruitment; 73.8% previously tested for prostate cancer N = 543		values clarification section (10-item tool - "Does this sound like you?") N = 272	results, limitations of testing N = 271	*Satisfaction with Decision* *Screening outcomes* Intervention materials mailed 5-10 days before scheduled screening date (Home condition) or distributed at visit (Clinic condition); baseline interview at time of randomisation (T0), T1 assessment at 2 months, T2 assessment at 13 months Follow-up = 82.69% (T1) 70.17% (T2 - knowledge)	conflict at the T1 assessment Additional analyses for "Home" and "Clinic" conditions – no relevant comparisons reported
Decision aid vs. "usual care" (undefined)						
Partin 2004 (USA)	Male veterans aged 50+ years (mean age 68.4) without evidence of prostate cancer, who had scheduled primary care appointments at one of four Veterans Affairs medical facilities in the Midwest of the USA ~70% of participants had undergone previous PSA test N = 768	RCT	**Video** Presenting the risks and benefits of screening, showing two physicians discussing their differing opinions about the value of the PSA test, and a patient explaining how he feels about screening; patients encouraged to consider which outcomes would most influence their decision to be screened, and to discuss their preferences with their doctor N = 384	**Usual Care** "and whatever decision-making support was provided in routine appointments" N = 384	*Knowledge* about risk factors for and the natural history of prostate cancer, treatment efficacy and complications, (expert disagreement about) PSA accuracy *Patient participation in prostate cancer screening decision making* *Screening preference* *PSA testing rates* Materials mailed 2 weeks prior to, phone surveys conducted 1 week after doctor's appointment Follow-up = 77.86%	No sample size calculations reported Only 56% of participants reported looking at intervention materials mailed to them (additional "per protocol" analysis performed); No assessment of pre-test knowledge

Taylor 2013 (USA)	Male primary care outpatients aged 45-70 years (mean age 56.9) with no history of prostate cancer who had had an outpatient appointment in the previous 24 months at one of three Washington DC medical facilities 86% of participants had been screened for prostate cancer 73% had discussed screening with physician N = 1893	RCT	**1. Web-based Decision Aid** information about prostate cancer risk factors, tests and treatment options including risks and possible outcomes, an encouragement to discuss screening with physician and resources for further information; interactive values clarification tool N = 631 **2. Print-based Decision Aid** same content as website except no video testimonials, voice-over, graphics or pop-up definitions, values clarification not interactive N = 630	**Usual care** not defined N = 632	*Knowledge* about prostate cancer risk factors, testing and the controversy surrounding testing, and natural history, prostate cancer treatment efficacy and complications, *Decisional conflict* *Satisfaction with decision* *Prostate cancer testing rates* Printed materials or study URL details mailed after randomisation Knowledge and decisional conflict measured at baseline (prior to randomisation), 1 month and 13 months after randomisation Decisional satisfaction measured at 1 month and 13 months after randomisation Follow-up = 88.75% at 1 month 82.57% at 13 months	Assuming 500 participants per arm and a significance level of 0.05, the 3 pairwise comparisons (web vs. usual care, print vs. usual care, web vs. print) had 80% power to detect effect sizes as small as 0.17 standard deviations for the continuous outcomes Web arm had higher incidence of individual cancer history No data on intervention uptake

Decision aid vs. no information about prostate cancer/PSA testing						
Allen 2010 (USA)	Male permanent employees working ≥20 hours per week, aged ≥45 years recruited from work sites (= unit of randomisation, individuals = unit of measurement) 45.9% of participants had had a previous PSA test N = 12 sites (= clusters) N = 2615 eligible N = 1195 selected N = 812 consented to participate	Randomized cluster trial	Access to a **Computer-based Decision Aid** with interactive video and audio components; information about prostate cancer and screening, probabilities of potential outcomes, exercises to elucidate values, guidance about the development of a plan that will facilitate progress toward the chosen option; tailored on three characteristics: personal risk (calculated using an algorithm), individual ratings of the pros and cons of screening, and decisional consistency; available on computers at workplace for a minimum of 15 days during the 3-month intervention N = 6 sites N = 398	**Non-Intervention** N = 6 sites N = 414	*Knowledge* of prostate cancer prevalence, risk factors, screening modalities, diagnostic procedures and treatment-related complications, recognition of the PSA test *Decisional Conflict* *Decisional status* (readiness to make a decision) *Decision self-efficacy* (confidence in one's ability to participate in decision making to the extent desired) *Consistency between values and screening decision* *Preference for control in decision making* All outcomes assessed at baseline (before intervention) and at 3-month follow-up (intervention made available at worksites for four weeks; final surveys administered 1-1½ months after intervention) Follow-up = 77.0%	Sample size had 79% power (assuming a type one error of 0.05) when the coefficient of variation (ratio of SD to mean) was 1.2 Only 30% of men in intervention group used the decision aid Exclusion of men with a history of prostate cancer not explicitly stated; Men in intervention arm younger, lower income, more educated; Older men had more Decisional Conflict
Chan 2011 (USA)	Hispanic men aged ≥40 years (mean age 60.9) with no history of prostate cancer recruited from all senior social and housing centres in El Paso (Texas, US) (44% had undergone previous PSA tests) N = 25 centres (= clusters) N = 321 men	Randomized cluster trial	**Group Discussions** Facilitated by "promotores" using a script and slides with video clips of role models to trigger discussion; objectives: to improve knowledge of prostate cancer (including personal risk, treatment, characteristics of PSA testing and follow-up procedures) self-efficacy relating to health decisions, and outcome expectations about informed decision making N = 12 clusters	**Video** about type 2 diabetes with discussion about the same topic N = 13 clusters N = 160	*Knowledge* about prostate cancer, PSA and biopsy accuracy, treatment complications, uncertainty whether testing saves lives *Ease of making a decision* *Desired level of participation in decision making* *Beliefs about decision-making for screening Intention to be screened* Outcomes assessed before and after the intervention, after the	Sample size calculations assumed an intra-class correlation of 0.01; to detect an effect size of 0.44 SD units in knowledge planned for a total of 160 men per condition

	Recruitment rate not reported		N = 161 men		control intervention only (surveys administered by "promotores") Follow-up = 98.75%	
Evans 2010 (UK)	Men aged 50-75 who could read English, use a computer, were not seriously ill, and whose records did not indicate that they had previously had prostate cancer or a PSA test, recruited at 25 GP practices in South Wales (UK) N = 382	RCT	**1) Web-based Decision Aid ("Prosdex")** Information about prostate cancer and PSA testing, informed decision making; encouraging users to weigh the pros and cons of testing; deliberation tool to visualise attitudes towards PSA testing; aimed to encourage informed decision making N = 129 **2) Paper Version** Same content as website N = 126	**Control** No intervention N = 127 A second control group (N = 132) completed questionnaires only at follow-up, but comparisons were not relevant	*Knowledge* of prostate cancer and PSA *Decisional Conflict* *Anxiety* *Attitude toward PSA testing* *Behaviour* (intention to undergo PSA testing) *Uptake of PSA test* Outcomes measured by completion of an online-questionnaire immediately after the intervention, and again 6 months after randomisation Follow-up = 45.55% at 6 months (72.77% immediately after intervention)	*Web-based vs. control*: power of 87% to detect a 20% improvement in knowledge No assessment of pre-intervention knowledge, anxiety, decisional conflict
Lepore 2012 (USA)	Men of black African descent aged 45-70 years (mean age 55.0) without a history of prostate cancer, who had not had a prostate cancer test in the 12 months before enrolment, were accessible by telephone and who had a primary care physician, selected from a list of health insurance beneficiaries of a healthcare workers' union in the New York City area (response rate = 78.5%) 45.9% had undergone a previous PSA test N = 490	RCT	**Decision Support Intervention** *Print education material* *Discussions* with a health educator (telephone calls - one initial, one follow-up call to address any further questions); values clarification exercise addressing men's knowledge, values and decision conflict and increased their ability and motivation to talk with a physician about testing; informed about the perception of prostate cancer testing among other men and medical experts, provided a source of support during their decision-making process N = 244	**Attention Control** *Educational pamphlet* *Tailored telephone education* to increase knowledge of and adherence to guidelines related to fruit and vegetable intake N = 246	*Knowledge* about prostate cancer testing, risk factors, epidemiology, treatment effectiveness and side effects (pre- and post-test) *Decisional Conflict* (post-test) *Anxiety* (pre- and post-test) *Verified physician visit to discuss testing* *Testing intention, Benefits-to-risk Ratio of testing, and Verified PSA testing* *Congruence* Pre-test survey by telephone, pamphlets mailed to participants immediately after randomisation, telephone calls within one month; post-test data collection 8 months after randomisation (2 years for other non-relevant outcomes)	Assumed an effect size of 0.30, which required a sample size of 350 to achieve a 80% power (α=0.05) >50% of men had previously talked about prostate cancer with their physician, 40% recalled a prostate cancer test being recommended; Nearly a quarter had had a PSA test in the preceding 12 months, but did not report this upon enrolment (exclusion criterion)

					Follow-up = 88%	
Sherid an 2012 (USA)	Men aged 40-80 years with no prior history of prostate cancer or evidence of a serious medical illness recruited from one of two practices in North Carolina (one academic, one community practice) from weekly schedules of participating physicians N = 130	RCT x 2	**Video-based Decision Aid + Coaching Session + Brochure** ***Trial 1:*** *Video* showing four men engaged in a discussion about prostate cancer screening with their doctor; objectives: to provide core information needed for informed decision making, to model the process of deciding whether or not to be screened, and to help men begin to clarify their values and make a decision *Coaching session* by trained health counsellors to answer additional questions, help men further clarify their values and to prepare men to discuss prostate cancer screening with their doctor; included a process in which men rated and then ranked the relative importance of several factors in their decision making *Brochure* reinforcing information given about characteristics of prostate cancer, risk factors for and treatment options (incl. side effects) for prostate cancer, characteristics of the PSA test ***Trial 2*** ("Men's Health"): Trial 1 intervention with additional information on cardiovascular disease screening and colon cancer screening N = 60	**Attention Control** *Video* on highway-safety N = 70	*Knowledge* of the benign natural history of most prostate cancers, the high likelihood of side effects with treatments delivered for prostate cancer detected by PSA screening *Decisional Uncertainty* (pre-intervention only) *Perception that prostate cancer screening requires a decision* *Participation in decision-making* *Intent for PSA screening* *Patient reported PSA screening after clinical visit* *Actual PSA screening rates* randomisation, intervention/control delivered ~1 hour before office visit; knowledge measured just before and immediately after office visit Follow-up = 98.46%	No power calculations Combination of data from two trials after no difference in the patient outcomes between the two was found ("accounting for the random effects of practices as is done in meta-analysis") Uncertainty subscale of Decisional Conflict Scale used only at baseline; Baseline knowledge, patient characteristics not taken into account (large differences between groups) when assessing knowledge, as did not alter outcome by >10%

Study quality

Methodological quality of included studies is described in Tables 2 – 3.

Table 2. Summary of methodological quality of included randomised controlled trials (n = 13)

Quality Category	N (%)
I. Was the study double-blinded?	
2 = Reasonably certain double-blind (e.g. identical placebo)	1 (07.7)
1 = Single-blind, objective outcomes	10 (76.9)
0 = Not blinded, not reported	2 (15.4)
II. Concealment of treatment allocation schedule	
2 = Adequately concealed (e.g. central randomisation)	6 (46.2)
1 = Inadequately concealed (e.g. sealed envelopes)	2 (15.4)
0 = No concealment, not reported	5 (38.5)
III. Inclusion of all randomised participants in analysis of majority of outcomes (i.e. ITT)	
2 = No exclusions, survival analysis used	3 (23.1)
1 = Exclusions not likely to cause bias	3 (23.1)
0 = Too many exclusions, not reported	7 (53.8)
IV. Generation of allocation sequences*	
1 = Adequate (e.g. computer random number generator)	8 (61.5)
0 = Inadequate, not reported	5 (38.5)

** not considered when calculating the overall evidence quality rating*
ITT = intention-to-treat

Table 3. Methodological quality of included studies (n = 13)

	Blinding	Allocation concealment	Inclusion of all participants (ITT)	Generation of allocation sequence*	Overall rating
Allen 2010	1	0	0	1	Low
Chan 2011	1	2	2	1	Medium
Evans 2010	1	2	0	0	Low
Gattellari 2003	2	0	1	0	Low
Gattellari 2005	1	2	2	1	Medium
Lepore 2012	1	2	1	1	Medium
Myers 2011	1	1	1	0	Medium
Partin 2004	1	2	0	1	Low
Sheridan 2012	1	1	2	1	Medium
Taylor 2013	0	0	0	1	Low
Volk 2008	1	0	0	0	Low
Watts 2013	0	2	0	1	Low
Williams 2013	1	0	0	0	Low

* Not considered when calculating the overall evidence quality rating. Generation of allocation sequences was assessed to ensure trials were truly randomized and not pseudo-randomized and thus was not included in the overall risk of bias.

ITT = intention-to-treat

Key to overall quality rating
High quality: a review that received 2 for three main criteria (double-blinding, concealment of treatment allocation schedule, Inclusion of all randomised participants
in analysis (i.e. ITT))
Medium quality: Received 2 and/or 1 for all three main criteria
Low quality: Received 0 for all three criteria or 0 and 1 for all three criteria or received 0 for any of the three criteria

2.4. Study results

I. Effects of decision aids on knowledge (Table 4)

II. Effects of decision aids on decisional satisfaction (Table 5)

III. Effects of decision aids on decision-related distress (Table 6)

IV. Effects of decision aids on decisional uncertainty (Table 7)

Table 4. Results of studies examining effects of decision aids on **knowledge** about prostate cancer, risk factors and evidence for screening and treatment

Study	Outcome Definition	Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value	Follow up/ Timing
Decision aid vs. information only									
Gattellari 2003	*Knowledge* (10 items) Percentage items correctly answered	Mean (95% CI)	214[a]	50 (46-53)	45 (42-48)	NR	NR	0.049	>3 days
	Correct estimate of lifetime incidence of prostate cancer (within 10%)	Percentage (95% CI)	214[a]	57 (47-67)	17 (11-26)	NR	NR	<0.001	>3 days
	Correct estimate of lifetime mortality of prostate cancer (within 2%)	Percentage (95% CI)	214[a]	53 (43-63) N = 106[a]	4 (1-10) N = 108[a]	NR	NR	<0.001	>3 days
Gattellari 2005	*Knowledge* (14 items) Percentage items correctly answered	Mean (95% CI)	267	*Booklet* 57.2 (53.5-60.8) N = 131	*Leaflet* 42.2 (39.4-45.0) N = 136	NR	NR	<0.001[b]	>7 days
	Knowledge (14 items) Percentage items correctly answered	Mean (95% CI)	269	*Booklet* 57.2 (53.5-60.8) N = 131	*Video* 45.8 (42.7-48.8) N = 138	NR	NR	<0.001[b]	>7 days
Myers 2011	*Knowledge* (10 items) Change of Score (0-10) between baseline and endpoint	Mean (SD)	286	1.5 (2.1) N = 144	0.8 (0.49) N = 142	0.8[c]	0.5 - 1.2	0.001[d]	7 days
Volk 2008	*Knowledge* Score	NR	NR	NR	NR	NR	NR	NS	2 weeks
Watts 2013	*Knowledge* (10 items) Score (0-10)	Mean (SD)	137	6.6 (2.2) N = 68	6.4 (2.0) N = 69	NR	NR		before intervention
			99	8.6 (1.4) N = 47	7.8 (1.9) N = 52	NR	NR	0.88[s]	immediately after intervention
			89	8.2 (1.6) N = 42	8.1 (1.2) N = 47	NR	NR		12 months

	Accuracy of perceived risk of developing prostate cancer men classified as accurate[t]	Percentage	136	39.7 N = 68*	51.5 N = 68*				before intervention
			102	68.1 N = 47*	50.9 N = 55*	OR = 1.02	0.95 – 1.09	0.62[u]	immediately after intervention
			90	47.6 N = 42*	39.6 N = 48*				12 months
Williams 2013	*Knowledge* (16 items) Score	Mean	381	~10.4	~10.0	NR	NR	<0.05[e]	2 months
				~10.4	~10.1	NR	NR	<0.05[e]	13 months
Decision aid vs. "usual care" (undefined)									
Partin 2004	*Knowledge* (10 items) Index score = number of correct responses (0-10) – post-test	Mean (95% CI)	598	7.44 (7.22-7.65) N = 308	6.90 (6.68-7.13) N = 290	0.54[f]	NR	0.001[r]	<3 weeks
	PSA predictive value question	Adjusted percentage	598	28	22	NR	NR	>0.05[g]	<3 weeks
	Natural history question			63	54			≤0.05[g]	
	Treatment efficacy question			19	5			≤0.05[g]	
	Expert disagreement question			28	8			≤0.05[g]	
	men correctly answering			N = 308	N = 290				
Taylor 2013	*Knowledge* (18 items) Score (0 - 18)	Mean (SD)	1876	Web 10.4 (3.0)	Print	Control 10.4 (3.0)	NR	NR	0.78[n]	baseline
					10.4 (3.0)	10.4 (3.0)			0.98[n]	
			1656	13.5 (3.4)		11.1 (3.1)	2.26[q]	1.88 – 2.64	<0.001[o]	1 month
					13.5 (3.5)	11.1 (3.1)	2.40[q]	2.02 – 2.78	<0.001[o]	
			1550	12.6 (3.4) N = 497		11.0 (3.0) N = 544	1.46[q]	1.07 – 1.84	<0.001[o]	13 months
					12.7 (3.3) N = 509	11.0 (3.0) N = 544	1.54[q]	1.17 – 1.91	<0.001[o]	

Decision aid vs. no information about prostate cancer/PSA testing									
Allen 2010	*Knowledge* (14 questions) men with improved score at follow-up	Percentage	625	54	39	NR	NR	NR	3 months
	increase of score from baseline (percentage points)	Change in means		10 N = 291	4 N = 334	NR	NR	0.03[h]	
Chan 2011	*Knowledge* (12 item Index) number of correct responses	Mean (SD)	317	8.7 (3.3)	4.7 (3.0)	NR	NR	<0.001[i]	immediately after inter-vention
	"All experts agree that men should get annual PSA tests" men correctly answering	Percentage	317	23	3	NR	NR	<0.001[i]	immediately after inter-vention
	"Currently no one is sure that regular PSA testing will reduce the number of men who die from prostate cancer" men correctly answering	Percentage	317	62 N = 160	31 N = 157	NR	NR	<0.0001[p]	immediately after inter-vention
Evans 2010				*Prosdex*	*Paper*	*Control*			immediately after inter-vention
	Knowledge (12 items) Score (-12 to 12)	Mean	278	4.90 N = 89	5.40 N = 86	2.17 N = 103	0.70[j, k]	0.62 - 0.76	<0.001[k]
	Knowledge (12 items) (restricted to men with full data available at follow-up)	Mean	173	5.13 N = 48	5.79 N = 57	2.30 N = 69	NR	NR	NR	immediately after inter-vention
	Knowledge (12 items) – 6 months (restricted to men with full data available at follow-up)	Mean	173	3.70 N = 48	3.96 N = 57	2.80 N = 69	NR	NR	NR	6 months
Lepore 2012	*Knowledge* (14 items) correct answers	Mean percentage (SE)	431	61.6 (0.009) N = 215		54.7 (0.009) N = 216	NR	NR	<0.001[l] $F_{(1,426)}$ = 27.48	<8 months
Sheridan 2012	*Knowledge* (4 items) men correctly answering all items	Percentage	128	47 N = 58		13 N = 70	RR = 4.28[m]	2.30 - 6.45	NR	immediately after inter-vention

*~ Approximate (estimated from published figure); * Calculated by reviewers; CI = confidence interval, NR = not reported, NS = not statistically significantly different, SD = standard deviation*

[a] *Numbers relating to follow-up for all outcomes (no knowledge-specific numbers reported; categorical data indicates that these may vary)*

[b] *Post-hoc ANOVA with Tukey's honestly significance difference test to minimise type I errors from multiple comparisons*

[c] *Mean difference*

[d] *Adjusted for study site, participant's age, race, education, marital status, baseline knowledge*

[e] *Controlled for baseline score, age, having been screened in the previous year, race, site*

[f] *Difference in mean*

[g] *Multivariate logistic regression adjusted for baseline characteristics (mean age, marital status, education, ethnicity, overall health, comorbid conditions, prostate-specific items, AUA urinary symptom scale severity, medications)*

[h] *Adjusted linear regression indicating the average change in knowledge between follow-up and baseline controlling for age, race, income, education, marital status, family history of prostate cancer, previous PSA*

[i] *Accounted for baseline values, clustering*

[j] *U/mn = effect size derived from the Mann-Whitney U-statistic divided by the product of the two samples sizes, >0.5 means intervention group scored higher than control (0.5 = line of no effect)*

[k] *Prosdex group vs Control group*

[l] *Adjusted for 3 covariates (education, PSA claim prior to test, % correct at pre-test)*

[m] *Adjusted for random effects of physician and practice*

[n] *ANOVA for pairwise comparisons (analyses of variance)*

[o] *Generalised estimating equations for linear regression models controlled for baseline measures*

[p] *Calculated by reviewers using Chi-squared test*

[q] *Adjusted mean differences*

[r] *Unadjusted linear regression*

[s] *Random intercept linear mixed effects model adjusted for time x group*

[t] *Actual relative risk calculated based on participant-reported family history and average lifetime risk of prostate cancer of 1/9 (Australian Institute of Health and Welfare 2007)*

[u] *Population-averaged logistic generalized linear mixed effects model adjusted for time x group*

Table 5. Results of studies examining effects of decision aids on **decisional satisfaction**

Study	Outcome: Definition	Outcome: Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value	Follow up/ Timing
Decision aids vs. information only									
Gattellari 2003	*I feel I can make an informed choice about PSA testing*	Percentage (95% CI)	209			NR	NR	0.008	>3 days
	Strongly agree			16 (9-24)	15 (9-24)				
	Agree			74 (64-82)	53 (43-63)				
	Neither			6 (2-13)	16 (11-27)				
	Disagree			4 (1-10)	10 (6-18)				
	Strongly disagree			1 (0-6)	4 (1-10)				
				N = 103	N = 106				
Gattellari 2005	*I feel I can make an informed choice about PSA testing*	N (%)	405	*Booklet*	*Video*	*Leaflet*	NR	NR	0.10[a]	>7 days
	Strongly agree			27 (20.6)	14 (10.1)	19 (14.0)				
	Agree			91 (69.5)	107 (77.5)	105 (77.2)				
	Neither			6 (4.3)	6 (4.3)	5 (3.7)				
	Disagree			7 (5.3)	11 (8.0)	7 (5.1)				
	Strongly disagree			0 (0)	0 (0)	0 (0)				
				N = 131	N = 138	N = 136				
Volk 2008	*Decisional Conflict Scale – Informed Subscale* (3 items)	Mean (95% CI)					NR	NR	0.09[b]	2 weeks
	Subgroup: low-literacy		85	9.1	18.8					
	Score (higher scores indicate greater perception of being uninformed)			(0.9-17.2)	(11.2-26.3)					
				N = 39	N = 46					
	Subgroup: high-literacy		254	10.2	10.3		NR	NR	0.96[b]	2 weeks
	Score (higher scores indicate greater perception of being uninformed)			(7.5-12.9)	(7.8-12.8)					
				N = 116	N = 138					

	Decisional Conflict Scale – Effective Decision Subscale (4 items) Subgroup: high-literacy Score (higher scores indicate greater dissatisfaction)	Mean (95% CI)	257	11.0 (8.7-13.3) N = 120	12.7 (10.5-14.8) N = 137	NR	NR	0.30[b]	2 weeks
Watts 2013	*Decision Regret Scale* (5 items) Score (0-100; higher scores indicate greater regret)	Mean (SD)	78	11.7 (11.8) N = 35	15.1 (16.5) N = 43	NR	NR	<0.01[d]	12 months
	Subgroup: men who had not made a choice about PSA testing at baseline Score (0-100; higher scores indicate greater regret)	Mean (SD)	NR	11.7 (11.7)	31.4 (7.5)	NR	NR	NR	12 months
Decision aid vs. "usual care" (undefined)									
Taylor 2013	*Satisfaction With Decision Scale (*6 items) Score above median	Percentage	1537	*Web* *52.2*	*Print*	*Control* 45.5	OR 1.29	1.02 – 1.66	0.04[c]	1 month
	Subgroup: Men who had made a decision				*60.4*	45.5	1.79	1.41 – 2.29	<0.001[c]	
	High satisfaction (based on overall median (interquartile range)		1438	50.4 N = 464		49.8 N = 504	1.04	0.81 – 1.34	0.75[c]	13 months
					55.7 N = 470	49.8 N = 504	1.29	1.01 – 1.66	0.046[c]	

CI = confidence interval, NR = not reported;

[a] For comparison of 3 groups (chi-square)

[b] ANCOVA, adjusted for baseline scores

[c] Generalised estimating equations for logistic regression models

[d] Linear regression adjusted for baseline decisional conflict score, group, stage, education

Table 6. Results of studies examining effects of decision aids on **decision-related distress** (including decisional conflict, worry about screening/prostate cancer and anxiety)

Study	Outcome Definition	Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value	Follow up/ Timing
Decision aid vs. information only									
Gattellari 2003	*Decisional Conflict Scale - Factors Contributing to Uncertainty* (9 items) Score (higher scores indicate greater decisional uncertainty)	Mean (95% CI)	214[a]	21.6 (20.7-22.5) N = 106[a]	24.3 (23.4-25.2) N = 108[a]	NR	NR	<0.001	>3 days
	Worry about developing prostate cancer	Percentage (95% CI)	219			NR	NR	0.23	>3 days
	Not worried			38 (29-48)	25 (17-34)				
	A little			31 (23-41)	43 (33-52)				
	Moderately			21 (14-30)	23 (16-32)				
	Quite			6 (2-13)	6 (3-12)				
	Extremely worried			5 (2-11)	8 (4-16)				
				N = 106	N = 113				
	Worry about dying of prostate cancer	Percentage (95% CI)	213			NR	NR	0.058	>3 days
	Not worried			48 (38-58)	33 (25-43)				
	A little			30 (21-39)	37 (28-47)				
	Moderately			11 (6-19)	17 (10-25)				
	Quite			7 (3-14)	7 (3-14)				
	Extremely worried			5 (2-11)	6 (2-12)				
				N = 105	N = 108				
Gattellari 2005	*Decisional Conflict Scale - Factors Contributing to Uncertainty* (3 unspecified items) Score (3-15; higher scores indicate greater decisional conflict)	Mean (95% CI)	267	*Booklet* 6.1 (5.9-6.4) N = 131	*Leaflet* 6.6 (6.3-6.8) N = 136	NR	NR	0.03[b]	>7 days

	Decisional Conflict Scale - Factors Contributing to Uncertainty (3 unspecified items) Score (3-15; higher scores indicate greater decisional conflict)	Mean (95% CI)	269	*Booklet* 6.1 (5.9-6.4) N = 131	Video 6.4 (6.2-6.6) N = 138	NR	NR	0.35[b]	>7 days
	Worry about developing prostate cancer – post-test Not worried A little worried Moderately worried Quite worried Worried a lot	N (%)	504	*Booklet* 66 (50.4) 44 (33.6) 15 (11.5) 4 (3.1) 2 (1.5) N = 131	*Video* 57 (41.3) 54 (39.1) 24 (17.4) 1 (0.7) 2 (1.4) N = 138	*Leaflet* 62 (45.6) 43 (31.6) 26 (19.1) 4 (2.9) 1 (0.7) N = 136			0.37[o]	>7 days
Myers 2011	*Decisional Conflict Scale* (16 items – adapted version) Score (0-4; higher scores indicate greater decisional conflict)	Mean (SD)	286	0.29 (0.34) N = 144	0.32 (0.49) N = 142		-0.02[c]	-0.12 to 0.07	0.620[d]	7 days
Volk 2008	*Decisional Conflict Scale* (10 items – low-literacy version) Subgroup: low-literacy Score (0-100; higher scores indicate greater decisional conflict)	Mean (95% CI)	84	12.0 (5.0-18.9) N = 38	21.7 (15.4-28.0) N = 46		NR	NR	0.04[e]	2 weeks
	Decisional Conflict Scale (16 items) Subgroup: high-literacy Score (0-100; higher scores indicate greater decisional conflict)	Mean (95% CI)	239	12.7 (10.4-15.0) N = 108	15.0 (12.9-17.1) N = 131		NR	NR	0.15[e]	2 weeks
Watts 2013	*Decisional Conflict Scale* (10 items – low literacy version) Score (0-100; higher scores indicate	Mean (SD)	138	38.6 (31.1) N = 69	36.7 (30.2) N = 69		NR	NR		before intervention
			103	12.9 (18.8) N = 48	14.0 (18.8) N = 55		NR	NR	0.95[p]	immediately after intervention
			91	15.1 (19.4) N = 42	15.5 (20.9) N = 49		NR	NR		12 months

Williams 2013	*Decisional Conflict Scale* (10 items – low-literacy version)	Percentage	289	~28		~39	OR = 0.49	(0.26 – 0.91)	<0.05[f]	2 months
	Men with score greater than median			~39		~31	NR	NR	NS	13 months
Decision aid vs. "usual care" (undefined)										
Taylor 2013	*Decisional Conflict Scale* (10 items)	Mean		*Web*	*Print*	*Control*				baseline
	Score (0-100; higher scores indicate greater decisional conflict)	(SD)	1858	*24.8 (26.1)*		*25.8 (26.1)*			0.49[l]	
					24.6 (26.0)	*25.8 (26.1)*			0.41[l]	
			1652	12.7 (21.0)		20.0 (23.7)	-6.7[n]	-9.35 to -4.14	<0.001[m]	1 month
					12.2 (19.3)	20.0 (23.7)	-7.50[n]	-9.99 to -4.99	<0.001[m]	
			1558	11.4 (19.5) N = 499		15.0 (21.2) N = 546	-3.57[n]	-5.99 to -1.14	0.004[m]	13 months
					10.7 (16.9) N = 513	15.0 (21.2) N = 546	-4.08[n]	-6.37 to -1.80	<0.001[m]	
Decision aid vs. no information about prostate cancer/PSA testing										
Allen 2010	*Decisional Conflict Scale* (16 items)		625							3 months
	men with improved score at follow-up	Percentage		53		49	NR	NR	NR	
	decrease in score from baseline (percentage points)	Mean		11 N = 291		8 N = 334	NR	NR	0.09[g]	
Evans 2010	*Decisional Conflict Scale* (16 items)			*Prosdex*	*Paper*	*Control*				
	Score (0-100; higher scores indicate greater decisional conflict)	Mean	278	40.37 N = 89	38.49 N = 86	47.73 N = 103	0.32[h, i]	0.25 –0.40	<0.001[i]	immediately after intervention
	Spielberger State Anxiety Inventory (6 items short version) Score (higher scores indicate greater anxiety)	Mean	278	4.98 N = 89	4.78 N = 86	4.88 N = 103	0.50[h, i]	0.42 – 0.58	0.98[i]	immediately after intervention

Lepore 2012	*Decisional Conflict Scale* for low-literacy populations (three-level response category) [modified version: only 7 out of 16 items used (1-5,7,9)] Score (0-100; higher score indicates higher decisional conflict)	Mean (SE)	431	34.15 (1.639) N = 215	39.85 (1.636) N = 216	NR	NR	<0.05[j] $F_{(1,427)}$ = 6.05	<8 months
	Hospital Anxiety and Depression Scale (7 items) Score (0-21; higher scores indicate greater anxiety)	Mean (SE)	431	2.02 (0.147) N = 215	2.16 (0.146) N = 216	NR	NR	NS[k] $F_{(1,426)}$ = 0.42	<8 months

~ Approximate (estimated from published figure); *CI = confidence interval, NR = not reported, OR = Odds ratio; NS = not statistically significantly different, SD = standard deviation, SE = standard error,*

[a] *Numbers relating to follow-up for all outcomes (no decisional conflict-specific numbers reported; categorical data indicates that these may vary)*

[b] *Post-hoc ANOVA with Tukey's honestly significance difference test to minimise type I errors from multiple comparisons*

[c] *Mean difference*

[d] *Adjusted for study site, participant's age, race, education, marital status, baseline score*

[e] *ANCOVA, adjusted for baseline scores of decisional conflict*

[f] *Controlled for baseline score, age, having been screened in the previous year, race, site*

[g] *Adjusted linear regression indicating the average change in knowledge between follow-up and baseline controlling for age, race, income, education, marital status, family history of prostate cancer, previous PSA*

[h] *U/mn = effect size derived from the Mann-Whitney U-statistic divided by the product of the two samples sizes (<0.5 means intervention group scored lower than control, 0.5 = line of no effect)*

[i] *Prosdex group vs. Control group*

[j] *Adjusted for two covariates (education, any PSA claim prior to pre-test)*

[k] *Adjusted for two covariates (any PSA claim prior to test, state anxiety level at pre-test)*

[l] *Analyses of variance*

[m] *Generalised estimating equations for linear regression models controlled for baseline measures*

[n] *Adjusted mean differences*

[o] *Chi-square test*

[p] *Linear mixed effects model with random baseline measurements adjusted for time x group*

Table 7. Results of studies examining effects of decision aids on **decisional uncertainty**

Study	Outcome		N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value	Follow up/ Timing
	Definition	Measure							
Decision aid vs. information only									
Gattellari 2003	*Decisional Conflict Scale - Uncertainty Subscale* (3 items) Score (higher scores indicate greater uncertainty)	Mean (95% CI)	214[a]	8.1 (7.5-8.4) N = 106[a]	8.1 (7.2-8.7) N = 108[a]	NR	NR	0.93	>3 days
Gattellari 2005	*Decisional Conflict Scale - Uncertainty Subscale* (3 items) Score (3-15; higher scores indicate greater uncertainty) – post-test	Mean (95% CI)	405	Booklet 6.7 (6.3-7.1) N = 131	Video / Leaflet 6.5 / 6.5 (6.2-6.8) / (6.2-6.8) N = 138 / N = 136	NR	NR	0.56[b]	>7 days
Volk 2008	*Decisional Conflict Scale – Uncertainty Subscale* (3 items) Subgroup: low-literacy Score (higher scores indicate greater uncertainty)	Mean (95% CI)	87	5.8 (0.1-11.4) N = 39	6.8 (1.7-11.9) N = 48	NR	NR	0.80[c]	2 weeks
	Subgroup: high-literacy Score (higher scores indicate greater uncertainty)		256	14.3 (11.8-16.7) N = 120	16.5 (14.1-18.8) N = 136	NR	NR	0.20[c]	2 weeks
Decision aid vs. no information about prostate cancer/PSA testing									
Chan 2011	*Decisional Conflict Scale – Effective Decision Subscale: Ease of making a decision* (single item) "Is making the decision to be tested for prostate cancer easy for you?" - yes	Probability/ Percentage (95%CI)	317[d]	0.74 (0.70-0.77) N = 160[d]	0.87 (0.84-0.89) N = 157[d]	NR	NR	0.038[e]	imme-diately after inter-vention

CI = confidence interval, NR = not reported, SD = standard deviation;

[a]Numbers relating to follow-up for all outcomes (no decisional uncertainty-specific numbers reported; categorical data indicates that these may vary) [b]ANOVA with Tukey's honestly significance difference test to minimise type I errors from multiple comparisons [c]ANCOVA, adjusted for baseline scores [d]No outcome-specific numbers reported [e]Analysis accounted for baseline values, clustering

2.5. Body of Evidence

2.5.1. Knowledge

Name of study	Study type	N	Level of evidence *	Quality of evidence **	Risk of Bias	Results summary	p value (95% CI)	Relevance of evidence*
Decision aids vs. information only								
Gattellari 2003 *DA booklet*	RCT (multi-centre)	248	II	Low	High	Score - mean percentage items correctly answered D: 50 C: 45 Percentage men correctly estimating lifetime incidence of prostate cancer (within 10%) D: 57 C: 17 Percentage men correctly estimating lifetime mortality of prostate cancer (within 2%) D: 53 C: 4	 0.049 <0.001 <0.001	2
Gattellari 2005 *DA booklet*	RCT	421	II	Medium	Moderate	Score – mean percentage items correctly answered D: 57.2 C1: 42.2 D: 57.2 C2: 45.8	 <0.001 <0.001	2
Myers 2011 *Brochure* *+ decision counselling session* *+ discussion with physician*	RCT	313	II	Medium	Moderate	Mean change of score D: 1.5 C: 0.8 (Mean difference: 0.8 (0.5-1.2))	0.001	2
Volk 2008 *Entertainment-based DA*	RCT	149 + 301	II	Low	High	Score NR	NS	2
Watts 2013 *Online DA*	RCT	138	II	Low	High	Mean score D: 6.6 C: 6.4 - before intervention D: 8.6 C: 7.8 - immediately after intervention	0.88	2

						D: 8.2 C: 8.1 - 12 months after intervention Percentage men with accurate perception of risk of developing prostate cancer D: 39.7 C: 51.5 - before intervention D: 68.1 C: 50.9 - immediately after intervention D: 47.6 C: 39.6 - 12 months after intervention	0.62	2
Williams 2013 *DA booklet*	RCT	543	II	Low	High	Mean score D: ~10.4 C: ~10.0 - 2 months after intervention D: ~10.4 C: ~10.1 - 13 months after intervention	 <0.05 <0.05	2
Decision aid vs. "usual care" (undefined)								
Partin 2004 *Video*	RCT	768	II	Low	High	Mean score D: 7.44 C: 6.90 (Difference in mean: 0.54)	0.001	2
Taylor 2013 *Web-based DA*	RCT	1263	II	Low	High	Mean score D: 13.5 C: 11.1 (adjusted mean difference 2.26) - 1 month after intervention D: 12.6 C: 11.0 (adjusted mean difference 1.46) - 13 months after intervention	 <0.001 (1.88 – 2.64) <0.001 (1.07 – 1.84)	2
Print-based DA	RCT	1262	II	Low	High	Mean score D: 13.5 C: 11.1 (adjusted mean difference 2.40) - 1 month after intervention D: 12.7 C: 11.0 (adjusted mean difference 1.54) - 13 months after intervention	 <0.001 (2.02 – 2.78) <0.001 (1.17 – 1.91)	2
Decision aid vs. no information about prostate cancer/PSA testing								
Allen 2010 *Computer-based DA*	Rando-mized cluster trial	812	II	Low	High	Change in mean score D: 10 C: 4	0.03	2
Chan 2011 *Group discussions*	Rando-mized	321	II	Medium	Moderate	Mean score D: 8.7 C: 4.7	 <0.001	2

	cluster trial					Percentage men correctly identifying the controversy around PSA testing D: 23 C: 3 D: 62 C: 31	<0.001 <0.001	
Evans 2010 *Web-based DA* (=D1)	RCT	382	II	Low	High	Mean score D1 (Web-based): 4.9 C: 2.17	<0.001	2
Lepore 2012 *Print education material* *+ discussion with health educator*	RCT	490	II	Medium	Moderate	Mean percentage of correct answers D: 61.6 C: 54.7	<0.001	2
Sheridan 2012 *Video-based DA* *+ coaching session* *+ brochure*	RCT x 2	130	II	Medium	Moderate	Percentage men correctly answering all items D: 47 C: 13 (RR = 4.28 (2.30-6.45))	NR	2

C = control group; DA/D = decision aid; NR = not reported; NS = not statistically significantly different; RCT = randomized controlled trial; RR = risk ratio;
** refer to appendix B for detailed explanations of rating scores; ** see Table 3 for quality appraisals;*

2.5.2. Decisional Satisfaction

Name of study	Study type	N	Level of evidence*	Quality of evidence**	Risk of Bias	Results summary	p value (95% CI)	Relevance of evidence*
Decision aids vs. information only								
Gattellari 2003 *DA booklet*	RCT (multi-centre)	248	II	Low	High	Percentage men believing they can make an informed choice D: 90 C: 68	0.008	1
Gattellari 2005 *DA booklet*	RCT	421	II	Medium	Moderate	Men believing they can make an informed choice	0.10	1
Volk 2008 Entertainment -based DA	RCT	149 + 301	II	Low	High	Mean score (DCS: Informed subscale) - low-literacy subgroup D: 9.1 C: 18.8 Mean score (DCS: Informed subscale) - high-literacy subgroup D: 10.2 C: 10.3 Mean score (DCS: Effective decision subscale) - high-literacy subgroup D: 11.0 C: 12.7	0.09 0.96 0.30	1
Watts 2013 *Online DA*	RCT	138	II	Low	High	Decision Regret Score D: 11.7 C: 15.1	<0.01	1
Decision aids vs. "usual care" (undefined)								
Taylor 2013 *Web-based DA*	RCT	1263	II	Low	High	Percentage highly satisfied based on SDS score - subgroup: men who had made a decision D: 52.2 C: 45.5 (OR = 1.29) - 1 month after intervention D: 50.4 C: 49.8 (OR = 1.04) - 13 months after intervention	 0.04 (1.02 – 1.66) 0.75 (0.81 – 1.34)	1
Print-based DA	RCT	1262	II	Low	High	Percentage highly satisfied based on SDS score - subgroup: men who had made a decision D:60.4 C: 45.5 (OR = 1.79) - 1 month after intervention D: 55.7 C: 49.8 (OR = 1.29) - 13 months after intervention	 <0.001 (1.41 – 2.29) 0.046 (1.01 – 1.66)	1

C = control group; DA/D = decision aid; DCS = Decisional Conflict Scale; OR = odds ratio; RCT = randomized controlled trial; SDS = Satisfaction with Decision Scale;

** refer to appendix B for detailed explanations of rating scores; ** see Table 3 for quality appraisals*

2.5.3. Decision-related Distress

Name of study	Study type	N	Level of evidence*	Quality of evidence**	Risk of Bias	Results summary	p value (95% CI)	Relevance of evidence*
Decision aids vs. information only								
Gattellari 2003 *DA booklet*	RCT (multi-centre)	248	II	Low	High	Mean score (DCS: Factors contributing to uncertainty) D: 21.6 C: 24.3 Worry about developing prostate cancer Worry about dying from prostate cancer	 <0.001 0.23 0.058	1
Gattellari 2005 *DA booklet*	RCT	421	II	Medium	Moderate	Mean score (DCS: Factors contributing to uncertainty) D: 6.1 C1: 6.6 D: 6.1 C2: 6.4 Worry about developing prostate cancer	 0.03 0.35 0.37	1
Myers 2011 *Brochure* *+ decision counselling session* *+ discussion with physician*	RCT	313	II	Medium	Moderate	Mean score (DCS) D: 0.29 C: 0.32 (Mean difference -0.02 (-0.12 to 0.07)	 0.620	1
Volk 2008 *Entertainment-based DA*	RCT	149 + 301	II	Low	High	Mean score (DCS) – low-literacy subgroup D: 12.0 C: 21.7 Mean score (DCS) – high-literacy subgroup D: 12.7 C: 15.0	 0.04 0.15	1
Watts 2013 *Online DA*	RCT	138	II	Low	High	Mean Score (DCS) D: 38.6 C: 36.7 - before intervention D: 12.9 C: 14.0 - immediately after intervention D: 15.1 C: 15.5 - 12 months after intervention	0.95	1

Williams 2013 *DA booklet*	RCT	543	II	Low	High	Percentage men with decisional conflict – 2 months after intervention D: ~28 C: ~39 OR = 0.49 Percentage men with decisional conflict – 13 months after intervention D: ~39 C: ~31	<0.05 (0.26 – 0.91) NS	1
Decision aid vs. "usual care"								
Taylor 2013 *Web-based DA*	RCT	1263	II	Low	High	Mean score (DCS) 1 month after intervention D: 12.7 C: 20.0 (adjusted mean difference -6.7) 13 months after intervention D: 11.4 C: 15.0 (adjusted mean difference -3.57)	<0.001 (-9.35 to -4.14) 0.004 (-5.99 to -1.14)	1
Print-based DA	RCT	1262	II	Low	High	Mean score (DCS) 1 month after intervention D:12.2 C: 20.0 (adjusted mean difference -7.50) 13 months after intervention D: 10.7 C: 15.0 (adjusted mean difference -4.08)	<0.001 (-9.99 to -4.99) 0.001 (-6.37 to -1.80)	1
Decision aid vs. no information about prostate cancer/PSA testing								
Allen 2010 *Computer-based DA*	Rando-mized cluster trial	812	II	Low	High	Mean decrease in score (DCS) D: 11 C: 8	0.09	1
Evans 2010 *Web-based DA*	RCT	382	II	Low	High	Mean score (DCS) D1 (Web-based): 40.37 C: 47.73 Mean score (SSAI) D1 (Web-based): 4.98 C: 4.88	<0.001 0.98	1
Lepore 2012 *Print education material*	RCT	490	II	Medium	Moderate	Mean score (DCS) D: 34.15 C: 39.85 Mean score (HADS) D: 2.02 C: 2.16	<0.05 NS	1

+ discussion with health educator								

C = control group; DA/D = decision aid; DCS = Decisional Conflict Scale; HADS = Hospital Anxiety and Depression Scale; NS = not statistically significantly different; RCT = randomized controlled trial; SSAI = Spielberger State Anxiety Inventory;
** refer to appendix B for detailed explanations of rating scores; ** see Table 3 for quality appraisals;*

2.5.4. Decisional Uncertainty

Name of study	Study type	N	Level of evidence*	Quality of evidence**	Risk of Bias	Results summary	p value (95% CI)	Relevance of evidence*
Decision aids vs. information only								
Gattellari 2003 *DA booklet*	RCT (multi-centre)	248	II	Low	High	Mean score D: 8.1 C: 8.1	0.93	1
Gattellari 2005 *DA booklet*	RCT	421	II	Medium	Moderate	Mean score D: 6.7 C1: 6.5 C2: 6.5	0.56	1
Volk 2008 *Entertainment-based DA*	RCT	149 + 301	II	Low	High	Mean score – low-literacy subgroup D: 5.8 C: 6.8 Mean score – high-literacy subgroup D: 14.3 C: 16.5	0.80 0.20	1
Decision aid vs. no information about prostate cancer/PSA testing								
Chan 2011 *Group discussions*	Rando-mized cluster trial	321	II	Medium	Moderate	Probability of ease of making a decision D: 0.74 C: 0.87	0.038	1

C = control group; DA/D = decision aid; RCT = randomized controlled trial;
** refer to appendix B for detailed explanations of rating scores; ** see Table 3 for quality appraisals;*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the NHMRC evidence statement for

2.6. References: Included studies

(1) Allen JD, Othus MK, Hart A, Jr., Tom L, Li Y, Berry D et al. A randomized trial of a computer-tailored decision aid to improve prostate cancer screening decisions: results from the take the wheel trial. *Cancer Epidemiology, Biomarkers & Prevention* 2010; 19(9):2172-2186.

(2) Chan EC, McFall SL, Byrd TL, Mullen PD, Volk RJ, Ureda J et al. A community-based intervention to promote informed decision making for prostate cancer screening among Hispanic American men changed knowledge and role preferences: a cluster RCT. *Patient Education & Counseling* 2011; 84(2):e44-e51.

(3) Evans R, Joseph-Williams N, Edwards A, Newcombe RG, Wright P, Kinnersley P et al. Supporting informed decision making for prostate specific antigen (PSA) testing on the web: an online randomized controlled trial. *Journal of Medical Internet Research* 2010; 12(3):e27.

(4) Gattellari M, Ward JE. Does evidence-based information about screening for prostate cancer enhance consumer decision-making? A randomised controlled trial.[Erratum appears in J Med Screen. 2004;11(4):211]. *Journal of Medical Screening* 2003; 10(1):27-39.

(5) Gattellari M, Ward JE. A community-based randomised controlled trial of three different educational resources for men about prostate cancer screening. *Patient Education & Counseling* 2005; 57(2):168-182.

(6) Lepore SJ, Wolf RL, Basch CE, Godfrey M, McGinty E, Shmukler C et al. Informed decision making about prostate cancer testing in predominantly immigrant Black men: A randomized controlled trial. *Annals of Behavioral Medicine* 2012; 44(3):320-330.

(7) Myers RE, Daskalakis C, Kunkel EJ, Cocroft JR, Riggio JM, Capkin M et al. Mediated decision support in prostate cancer screening: a randomized controlled trial of decision counseling. *Patient Education & Counseling* 2011; 83(2):240-246.

(8) Partin MR, Nelson D, Radosevich D, Nugent S, Flood AB, Dillon N et al. Randomized trial examining the effect of two prostate cancer screening educational interventions on patient knowledge, preferences, and behaviors. *Journal of General Internal Medicine* 2004; 19(8):835-842.

(9) Sheridan SL, Golin C, Bunton A, Lykes JB, Schwartz B, McCormack L et al. Shared decision making for prostate cancer screening: the results of a combined analysis of two practice-based randomized controlled trials. *BMC Med Inform Decis Mak* 2012; 12:130.

(10) Taylor KL, Williams RM, Davis K, Luta G, Penek S, Barry S et al. Decision making in prostate cancer screening using decision aids vs usual care: a randomized clinical trial. *JAMA Internal Medicine* 2013; 173(18):1704-1712.

(11) Volk RJ, Jibaja-Weiss ML, Hawley ST, Kneuper S, Spann SJ, Miles BJ et al. Entertainment education for prostate cancer screening: a randomized trial among primary care patients with low health literacy. *Patient Education & Counseling* 2008; 73(3):482-489.

(12) Watts KJ, Meiser B, Wakefield CE, Barratt AL, Howard K, Cheah BC et al. Online Prostate Cancer Screening Decision Aid for At-Risk Men: A Randomized Trial. *Health Psychol* 2013. Advance online publication. doi: 10.1037/a0034405

(13) Williams RM, Davis KM, Luta G, Edmond SN, Dorfman CS, Schwartz MD et al. Fostering informed decisions: A randomized controlled trial assessing the impact of a decision aid among men registered to undergo mass screening for prostate cancer. *Patient Educ Couns* 2013; 91:329-336.

APPENDICES

Appendix A: Search strategies used

For Medline and PsycINFO databases (via OvidSP):

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	exp Prostatic Neoplasms/
3	1 or 2
4	randomized controlled trial.pt.
5	controlled clinical trial.pt.
6	placebo.ab.
7	randomi?ed.ab.
8	randomly.ab.
9	trial.ab.
10	groups.ab.
11	4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp animals/ not humans.sh.
13	11 not 12
14	decision making/ or choice behavior/ or consensus/ or negotiating/ or uncertainty/
15	exp decision support techniques/
16	Educational Technology/
17	decision$.tw.
18	(choic$ or preference$).tw.
19	communication package.tw.
20	14 or 15 or 16 or 17 or 18 or 19
21	health education/ or consumer health information/ or patient education as topic/
22	*Health Knowledge, Attitudes, Practice/
23	*client education/ or *health education/
24	informed consent.tw,hw.
25	patient.tw,hw.
26	consumer.tw,hw.
27	21 or 22 or 23 or 24 or 25 or 26
28	20 and 27
29	((patient$ or consumer? or men or man) adj1 (decision$ or choice$ or preference? or participation$)).tw.
30	((personal or individual) adj1 (decision$ or choice$ or preference? or participation$)).tw.
31	decision aid.tw.

32	shared decision making.tw.
33	informed choice.tw.
34	29 or 30 or 31 or 32 or 33
35	28 or 34
36	3 and 13 and 35

Used the Cochrane sensitivity maximizing filter for identifying randomized controlled trials (http://handbook.cochrane.org, accessed 20/02/2013) Decision aid search terms based on those used by Stacey D, Bennett CL, Barry MJ, Col NF, Eden KB, Holmes-Rovner M et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2011;(10):CD001431.

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database:

#	Searches
1	'decision aid'
2	'decision support'
3	'shared decision making'
4	'informed choice'
5	(patient* OR consumer* OR men* OR personal OR interpersonal OR individual) next/1 (decision* OR choice* OR preference* OR participation)
6	1 OR 2 OR 3 OR 4 OR 5
7	'decision making'/exp
8	'patient decision making'/exp
9	'decision support system'/exp
10	'decision theory'/exp
11	'educational technology'/exp
12	decision*
13	7 OR 8 OR 9 OR 10 OR 11 OR 12
14	'patient attitude'/exp
15	'health behavior'/de OR 'attitude to health'/de OR 'behavioral risk factor surveillance system'/de OR 'health belief'/de OR 'risk reduction'/de
16	'health education'/de OR 'health literacy'/de OR 'patient education'/de OR 'preoperative education'/de OR 'psychoeducation'/de
17	'informed consent'/de OR 'informed consent'
18	'patient'/de OR patient
19	'consumer'/de OR consumer

20	14 OR 15 OR 16 OR 17 OR 18 OR 19
21	rct
22	'randomized controlled trial'/de
23	'randomized controlled trial' OR 'randomised controlled trial' OR 'randomized controlled trials' OR 'randomised controlled trials'
24	'random allocation'
25	'randomly allocated'
26	'randomization'/de
27	allocated near/2 random
28	'double blind procedure'/de
29	'single blind procedure'/de
30	single next/1 blind*
31	double next/1 blind*
32	(treble OR triple) next/1 blind*
33	placebo*
34	'placebo'/de
35	'prospective study'/de
36	'crossover procedure'/de
37	'clinical trial'/de
38	21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37
39	'case study'/de
40	'case report'
41	'abstract report'/de
42	'letter'/de
43	39 OR 40 OR 41 OR 42
44	38 NOT 43
45	'prostate cancer'/exp
46	prostat* near/3 (cancer* OR carcinoma* OR malignan* OR tumo?r OR neoplas* OR metast* OR adeno*)
47	45 OR 46
48	13 AND 20
49	6 OR 48
50	44 AND 47 AND 49
51	50 AND [humans]/lim AND [english]/lim AND [1990-3000]/py NOT [medline]/lim

Used the SIGN filter for identifying randomized controlled trials (www.sign.ac.uk/methodology/filters.html#systematic accessed 20/02/2013)

ATSI search terms used

#	Searches
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

For CINAHL database:

#	Searches
S39	S24 AND S27 AND S38
S38	S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37
S37	TX allocat* random*
S36	(MM "Crossover Design") OR (MM "Quasi-Experimental Studies") OR (MM "Experimental Studies")
S35	(MM "Placebos")
S34	TX placebo*
S33	TX random* allocat*
S32	TX randomi* control* trial*
S31	TX ((single OR double OR triple OR treble) N1 blind*)
S30	TX clinic* N1 trial*
S29	PT Clinical trial
S28	(MH "Clinical Trials+")
S27	S25 OR S26
S26	TX (prostat* N3 (cancer* OR carcinoma* OR malignan* or tumo#r* OR neoplas* OR metast* OR adeno*))
S25	(MM "Prostatic Neoplasms")
S24	S18 OR S23
S23	S19 OR S20 OR S21 OR S22
S22	TX informed choice
S21	TX decision aid*
S20	TX shared decision making
S19	TX ((patient* OR consumer* or men* OR personal OR interpersonal OR individual) N1 (decision* OR choice* OR preference OR participation))
S18	S7 AND S17
S17	S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
S16	"consumer" OR (MM "Consumers")
S15	"patient" OR (MM "Patients")
S14	TX informed consent
S13	(MH "Consent+")
S12	(MM "Health Knowledge") OR (MM "Professional Knowledge")

S11	(MM "Patient Education") OR (MM "Preoperative Education")
S10	(MM "Health Education")
S9	(MM "Consumer Participation")
S8	(MH "Health Behavior+")
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6
S6	(MM "Educational Technology")
S5	TX decision*
S4	TX (choice* OR preference*)
S3	(MM "Help Seeking Behavior")
S2	(MM "Information Seeking Behavior")
S1	(MM "Decision Making, Patient") OR (MM "Decision Making") OR (MM "Decision Support Techniques")

Used database filters for English language, dates from 01/01/1990 to 31/12/2013, and to exclude any records from Medline

ATSI search terms used

#	**Searches**
S5	S1 AND S4
S4	S2 OR S3
S3	TX (aborigin* OR indigenous OR torres strait islander*)
S2	(MH “Aborigines+”)
S1	TX Australia*

For Cochrane Database of Systematic Reviews – The Cochrane Library:

Title, abstracts, keywords: “prostate”

For Database of Abstracts of Reviews of Effects and Health Technology Assessment database (via OvidSP):

#	**Searches**
1	exp Prostatic Neoplasms/
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
3	1 or 2

Appendix B:

Level of Evidence rating criteria – Intervention studies

Level	**Study design**
I	Meta-analysis or a systematic review of level II studies

II	Randomised controlled trial or a phase III/IV clinical trial
III-1	Pseudo-randomised controlled trial or a meta-analysis/systematic review of level III-1 studies
III-2	Comparative study with concurrent controls: - Phase II clinical trial - Non-randomised, experimental trial9 - Controlled pre-test/post-test study - Adjusted indirect comparisons - Interrupted time series with a control group - Cohort study - Case-control study or a meta-analysis/systematic review of level III-2 studies
III-3	A comparative study without concurrent controls: - Phase I clinical trial - Historical control study - Two or more single arm study10 - Unadjusted indirect comparisons - Interrupted time series without a parallel control group or a meta-analysis/systematic review of level III-3 studies
IV	Case series with either post-test or pre-test/post-test outcomes or a meta-analysis/systematic review of level IV studies

According to the standards of the National Health and Medical Research Council

Relevance of the evidence

Rating	Relevance
1	Evidence of an effect on patient-relevant clinical outcomes including benefits and harms, quality of life and survival.
2	Evidence of an effect on a surrogate outcome* that has been shown to be predictive of patient-relevant outcomes for the same intervention.
3	Evidence of an effect on proven surrogate outcomes but for a different intervention.
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population.
5	Evidence confined to unproven surrogate outcomes.

**'surrogate outcome' refers to reasonable indicators of whether there has been some effect (e.g. blood pressure measurements or levels of serum cholesterol)*

Points for considering patient-relevant outcomes:
i) The goal of decision making in health care is to choose the intervention(s) (which may include doing nothing) that is (are) most likely to deliver the outcomes that patients find desirable
ii) Surrogate outcomes (such as blood pressure measurements or levels of serum cholesterol) may be reasonable indicators of whether there has been some effect. However, they should not be the basis for clinical decisions unless they reliably predict an effect on the way the patient feels; otherwise they will not be of interest to the patient or their carers
iii) All possible outcomes that are of most interest to patients (particularly harms) should be identified and evaluated

Adapted from table 1.10: National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra: NHMRC; 2000. http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp69.pdf

Study	Reason for Exclusion
Albada 2009	(Review) not prostate cancer-specific
Avery 2008	Not a RCT or systematic review/meta-analysis of RCTs; no relevant outcomes
Barry 2010	(Review) not PSA screening-specific
Bowles 2013	(Review) not prostate cancer-specific
Chan 2003	No relevant outcomes (opinions about how information should be presented)
Cunich 2011	No relevant outcomes (evaluation of a decision-support tool)
Davison 1999	Intervention did not meet criteria for definition of a decision aid
Davison 2007	Included patients with prostate cancer
Dorfman 2010	No relevant outcomes (evaluation of a decision-support tool/medium)
Driscoll 2008	No adequate control (same as intervention but with additional information given)
Edwards 2013	(Review) not PSA testing specific (except for one non-relevant outcome)
Ellison 2008	Not a RCT or systematic review/meta-analysis of RCTs (“quasi-experimental”); no adequate control [“usual care decision aid” that “met the standards for developing decision aids” (Cochrane Review O’Connor 2001 – Stacey 2012)]
Evans 2005	(Review) not all included studies met inclusion criteria, e.g. definition of “decision aid”
Evans 2007a	Protocol, preliminary results only, see Evans 2010 (included)
Evans 2007b	Not a RCT or systematic review/meta-analysis of RCTs, no relevant outcomes
Flood 1996	Not a RCT or systematic review/meta-analysis of RCTs (quasi-randomized)
Fox 2006	(Review) not prostate cancer-specific
Frosch 2001	Included men with previous history of “cancer”; no adequate control
Frosch 2003	Included men with previous history of “cancer”; no adequate control
Frosch 2008	Included men with previous history of “cancer”; no adequate control
Hewitson 2005	(Review) not all included studies met inclusion criteria, e.g. definition of decision aid
Holt 2009	No adequate control (comparison of two decision aids, control also decision aid, “spiritual” vs. “non-spiritual”)
Ilic 2008	Intervention did not meet criteria for definition of a decision aid, no adequate control (no difference in content of interventions – testing mode of delivery)
James 2011	Not prostate cancer-specific
Jimbo 2013	(Systematic review) not prostate cancer-specific
Jones 2008	Not a RCT or systematic review/meta-analysis of RCTs; no relevant outcomes
Joseph-Williams 2010	Not a RCT or systematic review/meta-analysis of RCTs (no adequate control)
Kerns 2008	No adequate control (compared relevant outcomes, but between resident/faculty groups, not intervention/no intervention)
Kripalani 2007	No relevant outcomes
Krist 2007	Insufficient information available to determine whether intervention met criteria for definition of a decision aid
Leader 2012	No relevant outcomes

Linder 2012	No relevant outcomes (validation of a tool using data from Volk 2008)
McCormack 2009	Not a RCT or systematic review/meta-analysis of RCTs
Meade 2003	Not a RCT or systematic review/meta-analysis of RCTs (no adequate control)
Meiser 2011	No relevant outcomes (abstract only, but confirmed by analysing full text article – Wakefield 2010)
Myers 1999	No relevant outcomes
Myers 2005a	(Review) no relevant outcomes
Myers 2005b	Not a RCT or systematic review/meta-analysis of RCTs; no relevant outcomes
O'Brien 2009	(Review) not prostate cancer-specific
Partin 2006	Same data as Partin 2004 (included) - slightly different focus (not relevant)
Penson 2010	Editorial comment, preliminary results only; see Evans 2010 (included)
Pignone 2013	No adequate control
Rubel 2010	Intervention did not meet criteria for definition of a decision aid – same intervention as Stephens 2010
Ruthman 2004	Not a RCT or systematic review/meta-analysis of RCTs (quasi-experimental, no randomisation)
Sajid 2012	(Review) not PSA testing specific, review only
Salkeld 2013	Insufficient information available to determine adequacy of control ("active comparator" decision aid); abstract only
Schapira 2000	Intervention did not meet criteria for definition of a decision aid
Sheridan 2004	Not prostate cancer-specific
Stacey 2011	(Review) not PSA testing-specific
Stacey 2014	(Review) not PSA testing-specific
Stephens 2010	Intervention did not meet criteria for definition of a decision aid – same intervention as Rubel 2010
Taylor 2002	Not a RCT or systematic review/meta-analysis of RCTs (no adequate control)
Taylor 2006	Insufficient information available to determine whether the intervention met criteria for definition of a decision aid
Taylor 2010	Insufficient information available to determine whether the intervention met criteria for definition of a decision aid
Van Vugt 2010	Not a RCT or systematic review/meta-analysis of RCTs (no adequate control)
Volk 1999	Insufficient information available to determine whether the intervention met criteria for definition of a decision aid
Volk 2003	Insufficient information available to determine whether the intervention met criteria for definition of a decision aid – follow-up of Volk 1999
Volk 2007	(Review) not all included studies met inclusion criteria, e.g. definition of decision aid
Wakefield 2010	No relevant outcomes (see Meiser 2011)
Walling 2004	No relevant outcomes; included men with diagnosis of prostate cancer
Watson 2006	Insufficient information available to determine whether the intervention met criteria for definition of a decision aid
Watts 2011	Duplicate publication (more mature data available, see Watts 2013 - included)

Wheeler 2011	Not a RCT or systematic review/meta-analysis of RCTs (“debate”)
Williams-Piehota 2008	Not a RCT or systematic review/meta-analysis of RCTs, no adequate control
Wilt 2001	Intervention did not meet criteria for definition of a decision aid
Wolf 1996	No relevant outcomes
Woolf 2005	No relevant results (preliminary data for Krist 2007)

References: Excluded studies

(1) Albada A, Ausems MG, Bensing JM, van DS. Tailored information about cancer risk and screening: a systematic review. *Patient Educ Couns* 2009; 77(2):155-171.

(2) Avery KN, Blazeby JM, Lane JA, Neal DE, Hamdy FC, Donovan JL. Decision-making about PSA testing and prostate biopsies: a qualitative study embedded in a primary care randomised trial. *European Urology* 2008; 53(6):1186-1193.

(3) Barry MJ. Shared decision making supported by patient decision aids for prostate cancer screening and treatment. *Psicooncologia* 2010; 7(2-3):257-267.

(4) Bowles B, Schwartz M, Marteau T. Enhancing Informed Choice to Undergo Health Screening: A Systematic Review. *American Journal of Health Behavior* 2013; 37(3):351-359.

(5) Chan EC, Haynes MC, O'Donnell FT, Bachino C, Vernon SW. Cultural sensitivity and informed decision making about prostate cancer screening. *Journal of Community Health* 2003; 28(6):393-405.

(6) Cunich M, Salkeld G, Dowie J, Henderson J, Bayram C, Britt H et al. Integrating evidence and individual preferences using a web-based multi-criteria decision analytic tool: an application to prostate cancer screening. *The Patient: Patient-Centered Outcomes Research* 2011; 4(3):153-162.

(7) Davison BJ, Kirk P, Degner LF, Hassard TH. Information and patient participation in screening for prostate cancer. *Patient Education & Counseling* 1999; 37(3):255-263.

(8) Davison BJ, Degner L, Gleave M, Goldenberg L. Providing individualized information utilizing a computerized decision support intervention. *Oncology Nursing Forum* 2007; 34(1):205-206.

(9) Dorfman CS, Williams RM, Kassan EC, Red SN, Dawson DL, Tuong W et al. The development of a web- and a print-based decision aid for prostate cancer screening. *BMC Medical Informatics & Decision Making* 2010; 10:12.

(10) Driscoll DL, Rupert DJ, Golin CE, McCormack LA, Sheridan SL, Welch BM et al. Promoting prostate-specific antigen informed decision-making. Evaluating two community-level interventions. *Am J Prev Med* 2008; 35(2):87-94.

(11) Edwards AG, Naik G, Ahmed H, Elwyn GJ, Pickles T, Hood K et al. Personalised risk communication for informed decision making about taking screening tests. *Cochrane Database Syst Rev* 2013; 2:CD001865.

(12) Ellison GL, Weinrich SP, Lou M, Xu H, Powell IJ, Baquet CR. A randomized trial comparing web-based decision aids on prostate cancer knowledge for African-American men. *Journal of the National Medical Association* 2008; 100(10):1139-1145.

(13) Evans R, Edwards A, Brett J, Bradburn M, Watson E, Austoker J et al. Reduction in uptake of PSA tests following decision aids: systematic review of current aids and their evaluations. *Patient Educ Couns* 2005; 58(1):13-26.

(14) Evans R, Elwyn G, Edwards A, Newcombe R, Kinnersley P, Wright P et al. A randomised controlled trial of the effects of a web-based PSA decision aid, Prosdex. Protocol. *BMC Fam Pract* 2007; 8:58.

(15) Evans R, Elwyn G, Edwards A, Watson E, Austoker J, Grol R. Toward a model for field-testing patient decision-support technologies: A qualitative field-testing study. *Journal of Medical Internet Research* 2007; 9(3):13-22.

(16) Flood AB, Wennberg JE, Nease RF, Jr., Fowler FJ, Jr., Ding J, Hynes LM. The importance of patient preference in the decision to screen for prostate cancer. Prostate Patient Outcomes Research Team. *Journal of General Internal Medicine* 1996; 11(6):342-349.

(17) Fox R. Informed choice in screening programmes: do leaflets help? A critical literature review. *J Public Health (Oxf)* 2006; 28(4):309-317.

(18) Frosch DL, Kaplan RM, Felitti V. The evaluation of two methods to facilitate shared decision making for men considering the prostate-specific antigen test. *Journal of General Internal Medicine* 2001; 16(6):391-398.

(19) Frosch DL, Kaplan RM, Felitti VJ. A randomized controlled trial comparing internet and video to facilitate patient education for men considering the prostate specific antigen test. *Journal of General Internal Medicine* 2003; 18(10):781-787.

(20) Frosch DL, Bhatnagar V, Tally S, Hamori CJ, Kaplan RM. Internet patient decision support: a randomized controlled trial comparing alternative approaches for men considering prostate cancer screening. *Archives of Internal Medicine* 2008; 168(4):363-369.

(21) Hewitson P, Austoker J. Part 2: Patient information, informed decision-making and the psycho-social impact of prostate-specific antigen testing. *BJU Int* 2005; 95 Suppl 3:16-32.

(22) Holt CL, Wynn TA, Litaker MS, Southward P, Jeames S, Schulz E. A comparison of a spiritually based and non-spiritually based educational intervention for informed decision making for prostate cancer screening among church-attending African-American men. *Urologic Nursing* 2009; 29(4):249-258.

(23) Ilic D, Egberts K, McKenzie JE, Risbridger G, Green S. Informing men about prostate cancer screening: a randomized controlled trial of patient education materials. *Journal of General Internal Medicine* 2008; 23(4):466-471.

(24) James KM, Cowl CT, Tilburt JC, Sinicrope PS, Robinson ME, Frimannsdottir KR et al. Impact of direct-to-consumer predictive genomic testing on risk perception and worry among patients receiving routine care in a preventive health clinic. *Mayo Clinic Proceedings* 2011; 86(10):933-940.

(25) Jimbo M, Rana GK, Hawley S, Holmes-Rovner M, Kelly-Blake K, Nease DE, Jr. et al. What is lacking in current decision aids on cancer screening? *CA Cancer J Clin* 2013; 63(3):193-214.

(26) Jones R, Williams I, Steeves R. Decision-making issues with prostate cancer screening among African Americans. *Oncology Nursing Forum* 2008; 35(3):487.

(27) Joseph-Williams N, Evans R, Edwards A, Newcombe RG, Wright P, Grol R et al. Supporting informed decision making online in 20 minutes: an observational web-log study of a PSA test decision aid. *Journal of Medical Internet Research* 2010; 12(2):e15.

(28) Kerns JW, Krist AH, Woolf SH, Flores SK, Johnson RE. Patient perceptions of how physicians communicate during prostate cancer screening discussions: a comparison of residents and faculty. *Family Medicine* 2008; 40(3):181-187.

(29) Kripalani S, Sharma J, Justice E, Justice J, Spiker C, Laufman LE et al. Low-literacy interventions to promote discussion of prostate cancer: a randomized controlled trial.[Erratum appears in Am J Prev Med. 2008 Mar;34(3):270 Note: Jacobson, Terry A [added]]. *Am J Prev Med* 2007; 33(2):83-90.

(30) Krist AH, Woolf SH, Johnson RE, Kerns JW. Patient education on prostate cancer screening and involvement in decision making. *Ann Fam Med* 2007; 5(2):112-119.

(31) Leader A, Daskalakis C, Braddock CH, III, Kunkel EJ, Cocroft JR, Bereknyei S et al. Measuring informed decision making about prostate cancer screening in primary care. *Medical Decision Making* 2012; 32(2):327-336.

(32) Linder SK, Swank PR, Vernon SW, Morgan RO, Mullen PD, Volk RJ. Is a prostate cancer screening anxiety measure invariant across two different samples of age-appropriate men? *BMC Medical Informatics & Decision Making* 2012; 12:52.

(33) McCormack L, Williams-Piehota P, Bann C. Behind Closed Doors: What Happens when Patients and Providers Talk about Prostate-Specific Antigen Screening?: Survey of the Effects of a Community-Based Intervention. *Patient* 2009; 2(3):191-201.

(34) Meade CD, Calvo A, Rivera MA, Baer RD. Focus groups in the design of prostate cancer screening information for Hispanic farmworkers and African American men. *Oncology Nursing Forum* 2003; 30(6):967-975.

(35) Meiser B, Mann GJ, Watts KJ, Wakefield CE, Sansom-Daly U, Barratt A et al. Prostate cancer screening decision aid. *Fam Cancer* 2011; 10:S93-S94.

(36) Myers RE, Chodak GW, Wolf TA, Burgh DY, McGrory GT, Marcus SM et al. Adherence by African American men to prostate cancer education and early detection. *Cancer* 1999; 86(1):88-104.

(37) Myers RE. Decision counseling in cancer prevention and control. *Health Psychology* 2005; 24(4:Suppl):Suppl-7.

(38) Myers RE, Daskalakis C, Cocroft J, Kunkel EJ, Delmoor E, Liberatore M et al. Preparing African-American men in community primary care practices to decide whether or not to have prostate cancer screening. *Journal of the National Medical Association* 2005; 97(8):1143-1154.

(39) O'Brien MA, Whelan TJ, Villasis-Keever M, Gafni A, Charles C, Roberts R et al. Are cancer-related decision aids effective? A systematic review and meta-analysis. *J Clin Oncol* 2009; 27(6):974-985.

(40) Partin MR, Nelson D, Flood AB, Friedemann-Sanchez G, Wilt TJ. Who uses decision aids? Subgroup analyses from a randomized controlled effectiveness trial of two prostate cancer screening decision support interventions. *Health Expectations* 2006; 9(3):285-295.

(41) Penson DF. Supporting informed decision making for prostate specific antigen (PSA) testing on the web: An online randomized controlled trial. *J Urol* 2011; 185(6):2158-2159.

(42) Pignone MP, Howard K, Brenner AT, Crutchfield TM, Hawley ST, Lewis CL et al. Comparing 3 techniques for eliciting patient values for decision making about prostate-specific antigen screening: A randomized controlled trial. *JAMA Intern Med* 2013; 173(5):362-368.

(43) Rubel SK, Miller JW, Stephens RL, Xu Y, Scholl LE, Holden EW et al. Testing the effects of a decision aid for prostate cancer screening. *Journal of Health Communication* 2010; 15(3):307-321.

(44) Ruthman JL, Ferrans CE. Efficacy of a video for teaching patients about prostate cancer screening and treatment. *American Journal of Health Promotion* 2004; 18(4):292-295.

(45) Sajid S, Kotwal AA, Dale W. Interventions to improve decision making and reduce racial and ethnic disparities in the management of prostate cancer: a systematic review. *J Gen Intern Med* 2012; 27(8):1068-1078.

(46) Salkeld G, Cunich M, Dowie J, Howard K, Mann G, Patel M. The role of personalized choice: A randomized controlled trial of an online decision aid for prostate cancer screening. *J Urol* 2013; 189(4):e511.

(47) Schapira MM, VanRuiswyk J. The effect of an illustrated pamphlet decision-aid on the use of prostate cancer screening tests. *Journal of Family Practice* 2000; 49(5):418-424.

(48) Sheridan SL, Harris RP, Woolf SH. Shared decision making about screening and chemoprevention. a suggested approach from the U.S. Preventive Services Task Force. *Am J Prev Med* 2004; 26(1):56-66.

(49) Stacey D, Bennett CL, Barry MJ, Col NF, Eden KB, Holmes-Rovner M et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev* 2011;(10):CD001431.

(50) Stacey D, Legare F, Col NF, Bennett CL, Barry MJ, Eden KB et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev* 2014; 1:CD001431.

(51) Stephens RL, Xu Y, Volk RJ, Scholl LE, Kamin SL, Holden EW et al. Influence of a patient decision aid on decisional conflict related to PSA testing: a structural equation model. *Health Psychology* 2008; 27(6):711-721.

(52) Taylor KL, Shelby R, Kerner J, Redd W, Lynch J. Impact of undergoing prostate carcinoma screening on prostate carcinoma-related knowledge and distress. *Cancer* 2002; 95(5):1037-1044.

(53) Taylor KL, Davis JL, III, Turner RO, Johnson L, Schwartz MD, Kerner JF et al. Educating African American men about the prostate cancer screening dilemma: a randomized intervention. *Cancer Epidemiology, Biomarkers & Prevention* 2006; 15(11):2179-2188.

(54) Taylor KL. Decision making in prostate cancer screening. *Cancer Prev Res* 2010; 3(12):5.

(55) van Vugt HA, Roobol MJ, Venderbos LD, Joosten-van ZE, Essink-Bot ML, Steyerberg EW et al. Informed decision making on PSA testing for the detection of prostate cancer: an evaluation of a leaflet with risk indicator. *European Journal of Cancer* 2010; 46(3):669-677.

(56) Volk RJ, Cass AR, Spann SJ. A randomized controlled trial of shared decision making for prostate cancer screening. *Archives of Family Medicine* 1999; 8(4):333-340.

(57) Volk RJ, Spann SJ, Cass AR, Hawley ST. Patient education for informed decision making about prostate cancer screening: a randomized controlled trial with 1-year follow-up. *Annals of Family Medicine* 2003; 1(1):22-28.

(58) Volk RJ, Hawley ST, Kneuper S, Holden EW, Stroud LA, Cooper CP et al. Trials of Decision Aids for Prostate Cancer Screening. A Systematic Review. *Am J Prev Med* 2007; 33(5):428-434.

(59) Wakefield CE, Watts KJ, Meiser B, Sansom-Daly U, Barratt A, Mann GJ. Development and pilot testing of an online screening decision aid for men with a family history of prostate cancer. 83[1], 64-72. 2011. Ref Type: Generic

(60) Walling AM, Maliski S, Bogorad A, Litwin MS. Assessment of content completeness and accuracy of prostate cancer patient education materials. *Patient Education & Counseling* 2004; 54(3):337-343.

(61) Watson E, Hewitson P, Brett J, Bukach C, Evans R, Edwards A et al. Informed decision making and prostate specific antigen (PSA) testing for prostate cancer: a randomised controlled trial exploring the impact of a brief patient decision aid on men's knowledge, attitudes and intention to be tested. *Patient Education & Counseling* 2006; 63(3):367-379.

(62) Watts KJ, Wakefield CE, Meiser B, Sansom-Daly U, Barratt A, Patel MI et al. A tailored online screening decision aid for men with a family history of prostate cancer: Development, pilot-testing and evaluation. *Asia-Pac J Clin Oncol* 2011; 7:109.

(63) Wheeler DC, Szymanski KM, Black A, Nelson DE. Applying strategies from libertarian paternalism to decision making for prostate specific antigen (PSA) screening. *BMC Cancer* 2011; 11:148.

(64) Williams-Piehota PA, McCormack LA, Treiman K, Bann CM. Health information styles among participants in a prostate cancer screening informed decision-making intervention. *Health Education Research* 2008; 23(3):440-453.

(65) Wilt TJ, Paul J, Murdoch M, Nelson D, Nugent S, Rubins HB. Educating men about prostate cancer screening. A randomized trial of a mailed pamphlet. *Eff Clin Pract* 2001; 4(3):112-120.

(66) Wolf AM, Nasser JF, Wolf AM, Schorling JB. The impact of informed consent on patient interest in prostate-specific antigen screening. *Archives of Internal Medicine* 1996; 156(12):1333-1336.

(67) Woolf SH, Krist AH, Johnson RE, Stenborg PS. Unwanted control: how patients in the primary care setting decide about screening for prostate cancer. *Patient Educ Couns* 2005; 56(1):116-124.

Systematic review report for question 3.1 (randomised controlled trials)

Clinical Question 3: *In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what should be the PSA testing strategies (age to start, level at which to declare a test abnormal and frequency of subsequent testing if the PSA level is normal) for men at average risk of prostate cancer and how should they be modified, if at all, for men at high risk of prostate cancer?*

PICO 3.1: *For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what PSA testing strategies (with or without DRE), compared with no PSA testing or other PSA testing strategies, reduce prostate cancer specific mortality or the incidence of metastases at diagnosis and offer the best balance of benefits to harms of testing?*

Population	Intervention	Comparator	Outcomes
Men without a prior history of prostate cancer or symptoms that might indicate prostate cancer	A PSA testing strategy with or without digital rectal examination (DRE)	No PSA testing or another testing strategy	Prostate cancer-specific mortality Incidence of metastatic disease at diagnosis

Strategy for PICO 1

The NHMRC recently reviewed the evidence for prostate cancer screening https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/men4a_psa_evidence_report_140519.pdf. The NHMRC review identified 5 systematic reviews with a "good" quality rating. These systematic reviews identified 4 randomised controlled trials and one pseudo-randomised controlled trial comparing prostate screening with no screening. Each trial used a different screening protocol. The systematic reviews included in the NHMRC review reported that there were no trials comparing different screening protocols however scoping searches indicated that there were published models comparing different PSA screening protocols. As a result this PICO question was approached in two stages:

Stage 1: **Randomised or pseudo-randomised controlled trials** included in the NHMRC systematic review were used to identify PSA testing strategies found to reduce prostate cancer-specific mortality or the incidence of metastases at diagnosis when compared to no PSA testing.

Stage 2: Modelling studies that compared the benefits and harms of different PSA screening protocols, and of screening in higher risk populations were identified by a systematic search of the literature. To compare different protocols, the benefits and harms of protocols closest to those shown in randomised controlled trials to reduce prostate cancer-

specific mortality or the incidence of metastases at diagnosis, were compared to those of other PSA testing strategies.

For simplicity each stage was the subject of a separate systematic review.

This report deals with the first stage – randomised and pseudo-randomised controlled trials.

1. Methods

1.1 Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption guidelines had to be evidence based and meet the pre-specified criteria of scores of greater or equal to 70% for the domains rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

1.2 Literature Search

In 2013 the NHMRC evaluated the evidence for prostate cancer screening (NHMRC 2013a). This evidence evaluation identified 5 systematic reviews which were rated as "good" quality:

- New Zealand Guidelines Group (2009)
- Djulbegovic M et al. (2010)
- Lin K et al. (2011) and Chou R et al. (2011)
- Lumen N et al. (2012)
- Ilic D et al. (2013).

These systematic reviews sought to determine whether prostate cancer screening decreased prostate cancer mortality. They did not seek to determine which specific screening protocols reduced prostate cancer mortality or the incidence of metastases at diagnosis, the PICO question that the current systematic review addresses. However as part of their review process the systematic reviews identified trials assessing different screening protocols. As a result they were used to identify relevant articles published up until 2012 -- the year when the NHMRC systematic review searches were undertaken. Literature searches were then run to identify relevant articles published from 2012 until 1st March 2014.

Specifically, the literature search was performed in two steps:

1. The NHMRC systematic review and the systematic reviews listed above were considered to comprehensively search the literature for trials of screening strategies and as such were used to identify potentially relevant articles up until 2012, the year the searches for the NHMRC systematic review and the most recent systematic

review (Ilic et al., 2013) were undertaken. All references of the randomised controlled trials included in the NHMRC technical report, (National Health and Medical Research Council 2013b) and the five systematic reviews were collected.

2. The literature was then searched from 2012 onwards to identify more recent publications of the trials already identified and any new trials using modifications of the search strategies used in the most recent systematic review (Ilic et al., 2013) and the NHMRC systematic review (NHMRC 2013b).

Literature Search for trials published from 2012 onwards

Medline, Embase, CENTRAL, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched. Medline, Embase and CENTRAL databases were searched from 2012 onwards. Each database was searched for articles dealing with prostate cancer. In Medline, Embase and CENTRAL databases prostate cancer search terms were coupled with search terms for PSA screening and randomised controlled trial filters based on those used by Ilic et al., 2013 and in the NHMRC systematic review (NHMRC 2013b). To identify studies that considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples. A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014, which were either published after the initial search was completed and/or added to the relevant database after the search was completed. Alerts were checked until July 2014. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched regularly up until April 2014 for relevant reviews published after the initial search. Reference lists of all relevant articles were checked for potential additional articles.

References

National Health and Medical Research Council (2013a). *Prostate-Specific Antigen (PSA) testing in asymptomatic men: Evidence Evaluation Report.* Canberra: National Health and Medical Research Council. Published July 2013

New Zealand Guidelines Group (2009) Cancer control strategy guidance completion: update of evidence for prostate-specific antigen (PSA) testing in asymptomatic men. Wellington: Ministry of Health

Djulbegovic M et al. (2010) Screening for prostate cancer: Systematic review and meta-analysis of randomised controlled trials. *BMJ* 3412:c4543

Lin K et al. (2011) Prostate-specific antigen-based screening for prostate cancer: An evidence update for the US Preventative Services Task Force. *Evidence synthesis no. 90. AHRQ publication no.12-05160-EF-1.* Rockville, MD: Agency for Healthcare Research and Quality

Chou R et al. (2011) Screening for prostate cancer: A review of the evidence for the US Preventative Services Task Force. *Ann Intern Med 155:*762 -77

Lumen N et al. (2012) Population screening for prostate cancer: an overview of available studies and meta-analysis. *Int J Urol* 19:100-108

Ilic D et al. (2013) Screening for prostate cancer. *Cochrane Database of Systematic Reviews*, Issue 1. Art. No.: CD004720. DOI: 10.1002/14651858.CD004720.pub3.

National Health and Medical Research Council (2013b). *Prostate-Specific Antigen (PSA) testing in asymptomatic men: Technical Report.* Canberra: National Health and Medical Research Council.

1.3 Inclusion Criteria

Selection criteria	Inclusion criteria
Study type	Intervention
Study design	Randomised or pseudo-randomised controlled trial
Population	Men without a prior history of prostate cancer or symptoms that might indicate prostate cancer
Intervention	PSA testing strategy with or without digital rectal examination (DRE)
Comparator	No PSA testing or another PSA testing strategy
Outcomes	Prostate cancer-specific mortality, or Incidence of metastatic disease at diagnosis
Language	English
Publication period	After 31st December 1989 and before1st March 2014

The current review sought to identify screening protocols that were potentially efficacious, i.e. showed evidence of reducing prostate cancer mortality. As a result it focused on the actual trials and the protocols used, rather than systematic reviews and meta-analyses and as each trial used a different screening protocol pooling of data was not appropriate.

2. Results

2.1. Guidelines

Eighteen guidelines were identified that contained potentially relevant recommendations regarding PSA testing protocols and four guidelines were identified that considered screening protocols for higher risk men. These recommendations were not adopted as they either were not based on a systematic review, did not meet the pre-specified AGREE II criteria for adoption, or the recommendations did not specifically address the clinical question. These guidelines and the reason why they were not adopted are listed in Appendix C.

In Australia the Royal College of Pathologists of Australasia has consensus based position statements regarding PSA testing (http://www.rcpa.edu.au/Library/College-Policies/Position-Statements/Prostate-Specific-Antigen-Testing-Age-related-inte, accessed 20/10/14).

"The response to an initial test should be:

a. *If the total PSA level is at or above 10 µg/L, the patient should either have the PSA confirmed in 4 weeks and be referred if the result is confirmed or be immediately referred for specialist management.*
b. *If the total PSA level is abnormal (above 97.5% age-related, method-specific reference limit) but below 10 µg/L, the PSA should be confirmed in 4 weeks including an estimation of the free-to-total PSA ratio (F/T PSA ratio). If confirmed and/or the result of the F/T PSA ratio is <10%, the patient should be immediately referred for specialist management.*
c. *If the PSA level is normal, but above the age-related median, the patient should be reassured that their result is normal and be re-tested in 2 years.*
d. *If the PSA level is not above the age-related median, the patient should be reassured that their risk is low and be re-tested in 4 years."*

In 2012 the Royal Australian College of General Practitioners recommended as a practice point (no good evidence available) that general practitioners respond to requests for screening by high risk men by informing them of the risks and benefits of screening (Guidelines for Preventative Activities in General Practice 8th edition, (2012) The Royal Australian College of General Practitioners).

2.2. Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the current systematic review. The NHMRC systematic review identified 5 systematic reviews rated as "good" quality. From these systematic reviews 22 potentially relevant articles were identified for retrieval.

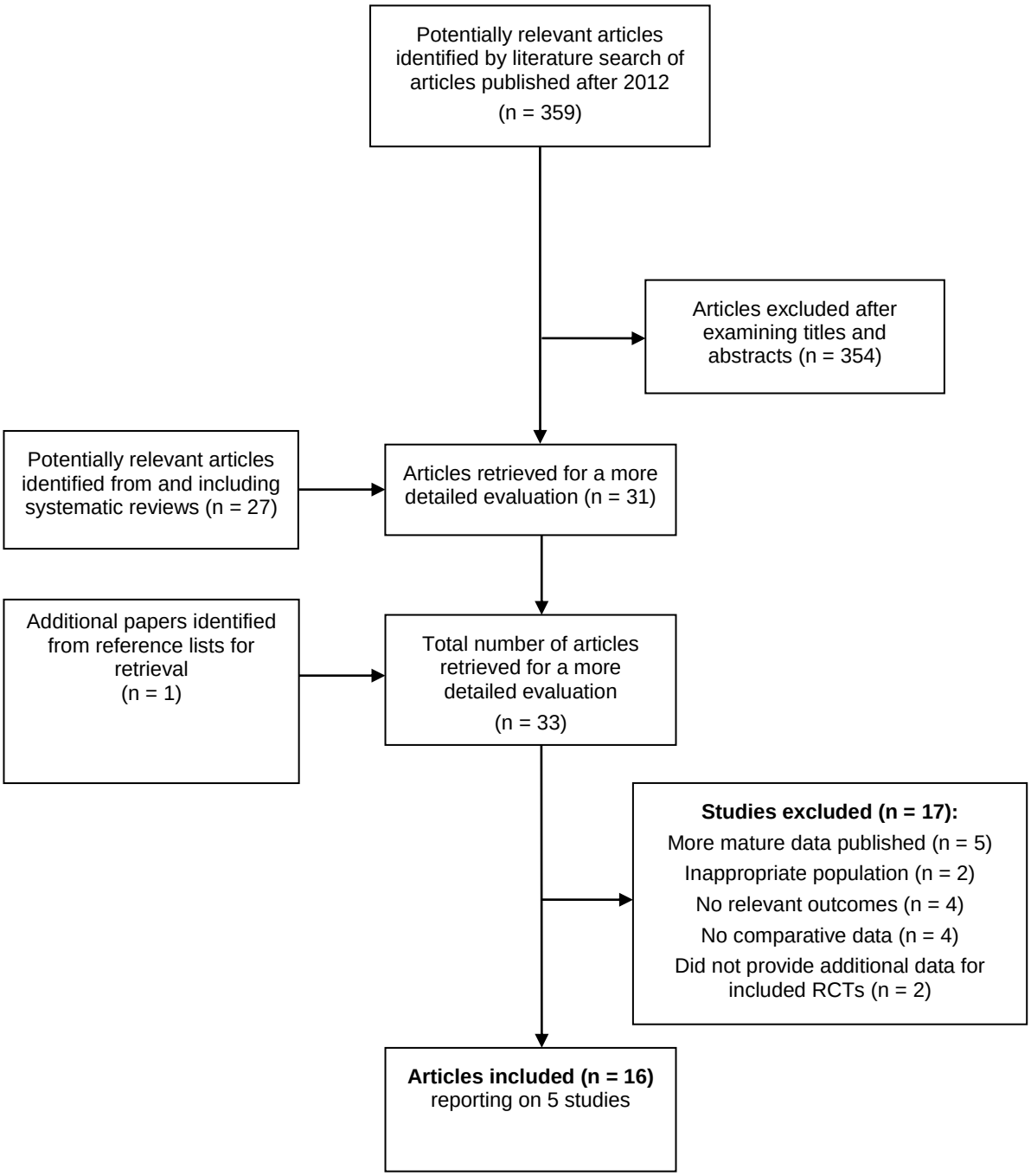
The Medline search from 2012 onwards identified 116 citations, the Embase search from 2012 onwards 216 citations, the CENTRAL search from 2012 onwards 12 citations and the search of the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases identified an additional 15 potentially relevant citations, resulting in a total of 359 citations. Titles and abstracts were examined and 5 additional articles were retrieved for a more detailed evaluation. A further additional potential citation was identified from the reference list of retrieved articles.

Five trials reported in 13 articles met the inclusion criteria. They were population-based screening trials and each compared a screening strategy with no screening. They did not examine the effects of a given screening protocol in higher risk populations. One study did not provide an intention to treat analysis (Labrie 2004). Intention to treat analyses of these data were conducted by three of the systematic reviews (Ilic 2013, Djulbegovic 2010 and Lumen 2012) identified by the NHMRC systematic review and these results were included in the current review.

The systematic reviews included in the NHMRC review reported that there were no trials comparing different screening protocols and the 2012 onwards literature searches found no trials comparing different screening protocols. No relevant studies of ATSI men were identified.

The retrieved articles that were not included and the reason for their exclusion are documented in Appendix C. In summary, the reasons for exclusion were an inappropriate population, no relevant outcomes reported or more mature data had been published.

Figure 1. Process of inclusion and exclusion of studies



2.3. Study Characteristics

Characteristics of included studies are described in Table 1.

Table 1: Characteristics of studies examining PSA testing strategies ± DRE compared to no PSA testing in reducing prostate cancer-specific mortality and/or incidence of metastases at diagnosis

Study	Design	Participants	Intervention	Comparison	Relevant Outcomes	Comments
Andriole 2012 & 2009 (USA) *Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)* *NCT00002540*	RCT 10 study centres 1993 – 2001	Men aged 55 – 74 years with no previous personal history of prostate, lung or colorectal cancer Excluded men: • Currently receiving treatment for cancer except non-melanoma skin cancer • Who have had previous surgical removal of the entire prostate, one lung or the entire colon • Who have participated in another cancer screening or primary prevention study • Who have used finasteride in the previous 6 months From April 1995, men reporting more than one PSA blood test and any lower gastrointestinal diagnostic procedure in the previous 3 years were also excluded **N = 76,685**	**Annual PSA** testing for **6 years** and annual **DRE** for the first **4 years** **PSA cut-off: >4.0ng/mL** Participants with PSA >4.0ng/mL or a suspicious DRE were advised to seek diagnostic evaluation Screening completed in October 2006 Compliance rate for PSA testing and DRE were 85% and 86%, respectively 31.5% of men with PSA >4.0ng/mL or suspicious DRE underwent prostate biopsy within 1 year of screening (2005) **N = 38,340**	**Opportunistic screening** Usual care – Included opportunistic screening when a test was requested by the participant or recommended by a doctor 40% of participants underwent PSA testing in first year 52% of participants underwent PSA testing in sixth year DRE rates ranged from 41 – 46% **N = 38,345**	**Primary outcome:** Prostate cancer-specific mortality ascertained through periodic linkage to the National Death Index Vital status known for 57% of participants at 13 years (2012); 92% of participants at 10 years (2012); 98% of participants at 7 years (2009) Median follow-up = 11.5 years (2009) Metastatic disease at diagnosis; 13 years follow-up	Follow-up till 31/12/2009 or to 13 years from trial entry Approximately 44% of participants had at least 1 PSA test within the year of randomisation and 55% of participants had at least 1 DRE in the 3 years prior to recruitment: this will have selected out some potential participants who would otherwise have had prostate cancer diagnosed in the trial Treatment distributions similar for stage II between arms

Schroder 2012a & b: Grenabo Bergdahl 2013, Bokhorst 2014, Hugosson 2010, Kilpelainen 2013, Roobol 2013, (The Netherlands, Belgium, Sweden, Finland, Italy, Spain and Switzerland) *The European Randomised Study of Screening for Prostate Cancer (ERSPC)* *ISRCTN49127736*	RCT 7 European countries	Men aged 50 – 74 years with no previous personal history of prostate cancer identified in population registries **N = 182,160** Core age group: 55 – 69 years old Median age = 60.1 years **N = 162,388**	Invited to screening for prostate cancer Different screening protocols in different countries Screened at 4 year intervals until age 75 (5/7 countries) PSA test only (5/7 countries) Sextant biopsy recommended for all men with positive test; lateralised sextant biopsies from June 1996 82.6% screened at least once **N = 72,891** Diagnosed with prostate cancer N = 6,963 63.6% surgery or radiotherapy 23.0% watchful waiting 8.8% ADT only as primary treatment	Not invited to screening for prostate cancer **N = 89,352** 39.6% underwent one or more PSA test in the period after randomisation until end of 2008 (Rotterdam cohort only) Diagnosed with prostate cancer N = 5,396 59.2% surgery or radiotherapy, 16.0% watchful waiting, 19.6% ADT only as primary treatment	**Primary outcome:** Prostate cancer-specific mortality; prostate cancer death if clinical evidence of metastatic disease in absence of unrelated cause of death – determined by examining medical records of all men diagnosed with prostate cancer (even at autopsy) who had died regardless of official cause of death, or after validation, on the basis of official causes of death Metastatic disease at diagnosis; it was detected in control arm by 6-monthly chart reviews and includes men with PSA >100ng/mL in absence of imaging reports Median follow-up = 11.0 years (2009)	Follow-up till 31/12/2008 Unclear as to whether centralised randomisation at all Centres Study powered for analysis of core age group 85.9% of men with positive test underwent biopsy Authors state little difference in treatments for prostate cancer between arms after adjustment for disease stage, tumour grade and age

The Netherlands (Rotterdam)				
Men aged 55 – 74 years without any previous prostate cancer diagnosis; randomised after consent given between 1993 and 2000 **N = 41,902** Core age group 55 – 69 years old Median age = 61.7 years **N = 34,833**	*1993 – 1995* PSA + DRE + TRUS PSA cut-off **≥ 4ng/mL** *1995 – 1997* PSA (Hybritech Tandem-E) only PSA cut-off **≥ 4ng/mL** If PSA 1.0 – 3.9ng/mL DRE + TRUS *1997 onwards* **PSA** only PSA cut-off **≥ 3ng/mL** (Hybritech Tandem-E until 2000 when replaced by Access version) 2004 WHO calibration Test interval = **4 years** Sextant biopsy 1993 – 1996 screen one year after benign biopsy Men screened until age 75 **N = 17,443** 94.6% screened at least once	Not offered testing **N = 17,390**	Study database linked to Dutch Cancer Registry and Statistics Netherlands databases Median follow-up = 11.1 years (2012)	Not designed as stand-alone trial Centralised randomisation Prostatectomy first treatment option for localised disease in both arms GPs encouraged to refer men with positive biopsy to regional urology centres (whether intervention or control) 89.8% of men with positive test underwent biopsy
Belgium (Antwerp)				
Men aged 55 – 74 years without any previous prostate cancer diagnosis; randomised after consent given between 1991 and 2003 Core age group 55 – 69 years old Median age = 63.0 years	Invited to attend Oncological Centre Antwerp *1992 – 1994* PSA + DRE + TRUS PSA cut-off **≥ 10ng/mL** *1995 – 1997* PSA + DRE + TRUS PSA cut-off **≥ 4ng/mL** *1998* **PSA** only PSA cut-off **≥ 4ng/mL** *1999 onwards* PSA cut-off **≥ 3ng/mL** Test interval = **4 years** (first interval between screens up to 7 years) Screening discontinued after 3 rounds TRUS guided biopsy	Referred to own GP for routine check-up which could include DRE as this is considered general practice for older men in Belgium	Median follow-up = 12.1 years	Men diagnosed with prostate cancer decided with GP on treatment 71.1% of men with positive test underwent biopsy

	Men screened until age 75			
N = 8,562	**N = 4,307** 90.7% screened at least once	**N = 4,255**		
Sweden (Goteborg)				
Men aged 50 – 65 years without any previous prostate cancer diagnosis identified from population registries randomised 31/12/1994 before consent given	**PSA only** PSA cut-off: *1995 – 1998* **≥ 3.0/3.4ng/mL** (Prostatus assay - nominal value /WHO corrected value) *1999 – 2004* PSA cut-off **≥ 2.5/2.9 ng/mL** (Prostatus assay-nominal value /WHO corrected value) *2005 onwards* **≥ 2.5 ng/mL** (WHO calibration) Test interval = **2 years** Above cut-off: further examination by urologist including DRE, TRUS and laterally-directed sextant biopsy Men with PIN or ASAP re-biopsied until screening round 5 Only men with PSA ≥1.0ng/mL on second screen invited to undergo third screen Men with PSA ≥ 7ng/mL and no cancer on biopsy were PSA tested 6 months later at screening rounds 1 & 2	Received a letter in 1995 stating they belonged to a control group for a cancer study	Deaths ascertained by linkage with National Population Register 4 times a years Median follow-up = 14.0 years for core age group	78% of entire cohort reached the maximum follow-up period of 14 years Last date of follow-up was date of death or emigration or 31st December 2008 86.6% of men in core group and 93% of entire cohort with positive test underwent biopsy Men not previously exposed to screening
Median age = 56 years **N = 19,904**	Men screened until age 70	**N = 9,952** (50 – 69 years old)		
Core age group 55 – 69 years old Median age = 59.7 years **N = 11,852**	**N = 9,952** (50 – 69 years old) **N = 5,901** (core age group)	**N = 5,951** (core age		

	76.0% screened at least once	group)		
Finland (Helsinki and Tampere)				
Men aged 55, 59, 63 and 67 years at recruitment without any previous prostate cancer diagnosis identified from population registries randomised before consent given 1996 – 1999 Core age group 55 – 69 years old Median age = 58.7 years **N = 80,379**	**PSA only** PSA cut-off **≥ 4.0ng/mL** (Hybritech Tandem-E) Test interval = **4 years** Above cut-off: referred to local urology clinic for examination including DRE, TRUS and biopsy in 1996 – 1998 PSA 3.0 – 3.9ng/mL: referred for DRE with abnormal DRE trigger for biopsy. In 1999 DRE replaced by free-to-total PSA with ratio ≤16% trigger for biopsy Treated as per established guidelines including watchful waiting for small, well-differentiated tumours (1987 consensus guidelines) Sextant biopsy with directed biopsy for focal lesions replaced in 2002 by 10 – 12 core biopsies depending on prostate volume and specifically targeting apex Screening discontinued after 3 screening rounds or until age 71 **N = 31,970** 74.4% screened at least once	Not contacted **N = 48,409**	Information on cancer incidence and deaths obtained from Finnish Cancer Registry and Statistics Finland respectively Median follow-up = 11.0 years (2012)	Followed up until death, emigration or closing date 91.1% of men with positive test underwent biopsy

Italy (Florence)				
Men aged 55 – 74 years without any previous prostate cancer diagnosis identified from population registries randomised before consent given 1996 – 2000	**PSA (Hybritech Tandem-R) only** PSA cut-off **≥ 4.0ng/mL** Test interval = **4 years** Above cut-off: DRE, TRUS and biopsy PSA 2.5 – 3.9ng/mL: DRE + TRUS followed by biopsy if abnormalities present Transperineal sextant biopsies with directed biopsy for focal lesions	Not described	Median follow-up = 10.7 years	62.5% of men with positive test underwent biopsy
Core age group 55 – 69 years old Median age = 61.8 years **N = 14,517**	Men screened until age 75 **N = 7,266** 78.9% screened at least once	**N = 7,251**		
Spain (Getafe-Madrid)				
Men aged 55 – 74 years without any previous prostate cancer diagnosis randomised after consent given 1996 – 1999	**PSA only** PSA cut-off **≥ 3.0ng/mL** Test interval = **4 years** Above cut-off: TRUS guided biopsy; sextant TRUS biopsies with directed biopsy for focal lesions Screening discontinued after 3 screening rounds Men screened until age 75	Not described	Median follow-up = 10.7 years	74.3% of men with positive test underwent biopsy
Core age group 55 – 69 years old Median age = 60.4 years **N = 2,197**	**N = 1,056** 100% screened at least once	**N = 1,141**		

		Switzerland (Aarau)				
		Men aged 55 – 69 years without any previous prostate cancer diagnosis randomised after consent given 1998 – 2003 Core age group 55 – 69 years old Median age = 61.1 years **N = 9,903**	**PSA only** PSA cut-off **>3.0ng/mL** OR PSA 1.0 – 3.0ng/mL + free-to-total PSA ratio <20% (Abbott AxSym assay until June 2000, Hybritech assay from July 2000) Test interval = **4 years** Above cut-off: DRE + TRUS guided biopsy; sextant TRUS biopsies with directed biopsy for focal lesions Men screened until age 75 **N = 4,948** 96.9% screened at least once	Not described **N = 4,955**	Median follow-up = 8.2 years	79.9% of men with positive test underwent biopsy
Sandblom 2004 & 2011 (Sweden) *Norrkoping Study* *ISRCTN06342431*	Pseudo-RCT	All men aged 50 – 69 years residing in the city of Norrkoping in 1987, identified through the national population register. Every 6th man in order by date of birth allocated to screening. Unclear as to whether excluded men with previous diagnosis of prostate cancer **N = 9,026**	**DRE ± PSA** PSA cut-off **>4ng/mL** Test interval = **3 years** DRE only for first (1987) and second (1990) screenings PSA + DRE for third (1993) and fourth (1996) screenings For fourth screening only men aged ≤ 69 years were invited for rescreening Participants with a suspicious DRE or PSA >4ng/mL underwent fine needle aspiration biopsy with a sextant distribution Screening discontinued after 4 screening rounds **N = 1,494** 78% underwent initial screening	Not contacted Screening for prostate cancer unknown **N = 7,532**	**Primary outcome:** Prostate cancer-specific mortality determined by linkage to South-East Region Prostate Cancer Register and Central Death Register Cause of death determined by blinded review of medical records of all deceased; 20 years Maximum follow-up = 20 years Median follow -up = 75 months Metastatic disease at diagnosis; 12 years follow-up	Started 1987 Follow-up till 31/12/2008 for mortality; 31/12/1999 for metastatic disease incidence at diagnosis All men who remained in Sweden were followed-up for mortality Both screened and control men managed by the same urology unit 98.1% of men with positive test underwent biopsy

			59.9% underwent third screening with PSA test 48 localised cancer diagnosed of which only 21 were treated with curative intention			
Kjellman 2009 (Sweden) *Stockholm Study*	RCT	All men aged 55 – 70 years identified through the national population register as residing in the catchment area of the Stockholm South Hospital Excluded men with a previous diagnosis of prostate cancer Screened men were a random sample who gave consent after selection for screening arm **N = 26,602**	**Single screening** PSA + DRE + TRUS PSA cut-off **>10ng/mL** PSA 7.0 – 10ng/mL: underwent second TRUS Participant with PSA > 10ng/mL underwent quadrant biopsy Participants with abnormal DRE or TRUS underwent TRUS guided biopsy **N = 2,400** 74% underwent screening 4.6% (3/65) screen detected cancers detected by PSA levels +/- repeated TRUS 41/65 men diagnosed with prostate cancer were offered treatment with curative intent	Not contacted Screening for prostate cancer unknown **N = 24,202**	Prostate cancer-specific mortality Ascertained through the Cause of Death Registry Sensitivity = 100% Specificity = 92% Maximum 15 years of follow-up (1988 – 2003) Median follow-up = 12.9 years	Trial began in 1988 Follow-up from start of study until death, or end of study in 2003 Unknown % of men with positive test underwent biopsy Unable to retrieve files of original randomised population so the population was reconstructed with the help of Statistics Sweden; it included an additional 602 men. All intervention men could be identified in it.

Labrie 2004 (Canada) *Quebec Prospective Randomised Controlled Trial*	RCT	Men aged 45 – 80 years registered in the electoral roll of the Quebec city area Excluded men: • With a previous diagnosis of prostate cancer • Who had undergone previous prostate cancer screening and were referred to the study clinic for consultation Randomised before consent given **N = 46,486**	Test interval = **1 year** *First visit* **PSA (Hybritech Tandem-R) + DRE** Participants with PSA **>3.0ng/mL** and/or abnormal DRE underwent TRUS except for first 1,002 participants who underwent PSA test, DRE and TRUS *Subsequent visits* **PSA only** Participants with PSA **>3.0ng/mL** underwent TRUS unless PSA was >3.0ng/mL at a previous visit and PSA had not increased by more than 20% over previously measured or predicted PSA levels Biopsy at judgment of radiologist if hypoechoic image seen, abnormal DRE or measured PSA greater than predicted PSA (dependent on prostate volume) Duration of screening unclear **N = 31,133 invited to screen** 7,348 (23.6%) screened Median age = 60 years Median delay between invitation and screening = 3.19 years	Not invited to screening for prostate cancer Followed according to current medical practice Level of contamination could not be assessed **N = 15,353 not invited to screen** 14,231 (92.7%) not screened at clinic Median age = 59 years	Prostate cancer-specific mortality Ascertained through the Death Registry of the Health Department of the Province of Quebec Maximum 11 years of follow-up (1988 – 1999)	Trial began in 1988 Follow-up for men in screening arm was from first visit at the screening centre till 31/12/1999 Follow-up for men in non-screening arm was from 15/11/1988 till 31/12/1999 No intention-to-treat analysis Three of the systematic reviews (Ilic 2013, Djulbegovic 2010 and Lumen 2012 provided intention to treat analyses of the data for this study and these results were included in the current review.

ADT = androgen deprivation therapy; ASAP = atypical small acinar proliferation; DRE = digital rectal examination; ERSPC = the European Randomised Study of Screening for Prostate Cancer; PIN = prostatic intraepithelial neoplasia; PSA = prostate specific antigen; RCT = randomised controlled trial; TRUS = transrectal ultrasonography of the prostate; WHO = World Health Organisation

2.4. Study Quality

Methodological quality of included randomised controlled trials is described in Tables 2 – 5.
Methodological quality of included pseudo-randomised controlled trials is described in Tables 6 – 8.

Table 2: Methodological quality of included RCTs for outcome **prostate cancer-specific mortality** (n = 9, 4 RCTs reported in 10 publications, 2 of which, Andriole et al., 2012 and 2009, used identical methodology and population)

Quality Category	**N (%)**
1. Was the study double-blinded?	
2 = Reasonably certain double-blind (e.g. identical placebo)	0 (0)
1 = Single-blind, objective outcomes	7 (77.8)
0 = Not blinded, not reported	2 (22.2)
2. Concealment of treatment allocation schedule	
2 = Adequately concealed (e.g. central randomisation)	6 (66.7)
1 = Inadequately concealed (e.g. sealed envelopes)	1 (11.1)
0 = No concealment, not reported	2 (22.2)
3. Inclusion of all randomised participants in analysis of majority of outcomes (i.e. ITT)	
2 = No exclusions, survival analysis used	7 (77.8)
1 = Exclusions not likely to cause bias	1 (11.1)
0 = Too many exclusions, not reported	1 (11.1)
4. Generation of allocation sequences	
1 = Adequate (e.g. computer random number generator)	7 (77.8)
0 = Inadequate, not reported	2 (22.2)

ITT = intention-to-treat

Table 3: Methodological quality of included RCTs for outcome **prostate cancer-specific mortality** (4 RCTs reported in 10 publications)

Trials/Publications	Blinding	Allocation concealment	Inclusion of all participants (ITT)	Generation of allocation sequence*	**Overall Rating**	**Risk of bias**
Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)						
Andriole 2012 and 2009	1	2	1	1	**Medium**	**Moderate**
The European Randomised Study of Screening for Prostate Cancer (ERSPC)						
Bokhorst 2014	1	2	2	1	**Medium**	**Moderate**
Grenabo Bergdahl 2013	0	2	2	1	**Low**	**High**
Hugosson 2010	1	2	2	1	**Medium**	**Moderate**
Kilpelainen 2013	1	2	2	1	**Medium**	**Moderate**
Roobol 2013	1	2	2	1	**Medium**	**Moderate**
Schroder 2012a	1	1	2	1	**Medium**	**Moderate**
Stockholm Study						
Kjellman 2009	1	0	2	0	**Low**	**High**
Quebec Prospective Randomised Controlled Trial						
Labrie 2004	0	0	0	0	**Low**	**High**

ITT = intention-to-treat

* Not considered when calculating the overall evidence quality rating - Generation of allocation sequences was assessed to ensure trials were truly randomized and not pseudo-randomized and thus was not included in the overall risk of bias

Key to overall quality rating

High quality: a study that received 2 for three main criteria (double-blinding, concealment of treatment allocation schedule, inclusion of all randomised participants in analysis (i.e. ITT))

Medium quality: received 2 and/or 1 for all three main criteria

Low quality: received 0 for all three criteria or 0 and 1 for all three criteria or received 0 for any of the three criteria

Table 4: Methodological quality of included RCTs for outcome **metastatic disease at diagnosis** (n = 2)

Quality Category	**N (%)**
1. Was the study double-blinded?	
2 = Reasonably certain double-blind (e.g. identical placebo)	0 (0)
1 = Single-blind, objective outcomes	1 (50.0)
0 = Not blinded, not reported	1 (50.0)
2. Concealment of treatment allocation schedule	
2 = Adequately concealed (e.g. central randomisation)	1 (50.0)
1 = Inadequately concealed (e.g. sealed envelopes)	1 (50.0)
0 = No concealment, not reported	0 (0)
3. Inclusion of all randomised participants in analysis of majority of outcomes (i.e. ITT)	
2 = No exclusions, survival analysis used	0 (0)
1 = Exclusions not likely to cause bias	0 (0)
0 = Too many exclusions, not reported	2 (100)
4. Generation of allocation sequences	
1 = Adequate (e.g. computer random number generator)	2 (100)
0 = Inadequate, not reported	0 (0)

ITT = intention-to-treat

Three of the systematic reviews (Ilic 2013, Djulbegovic 2010 and Lumen 2012) provided intention to treat analyses of the data for the Labrie 2004 study and these results were included in the current review. These systematic reviews had been assessed as being of good methodological quality in the NHMRC systematic review. As the actual meta-analyses and systematic reviews were not used in the current review further assessment of the methodological quality of these systematic reviews was not considered relevant.

Table 5: Methodological quality of included RCTs for outcome **metastatic disease at diagnosis** (2 RCTs)

Trials/Publications	Blinding	Allocation concealment	Inclusion of all participants (ITT)	Generation of allocation sequence*	**Overall Rating**	**Risk of bias**
Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)						
Andriole 2012	1	2	0	1	**Low**	**High**
The European Randomised Study of Screening for Prostate Cancer (ERSPC)						
Schroder 2012b	0	1	0	1	**Low**	**High**

ITT = intention-to-treat

* Not considered when calculating the overall evidence quality rating - Generation of allocation sequences was assessed to ensure trials were truly randomized and not pseudo-randomized and thus was not included in the overall risk of bias

Key to overall quality rating

High quality: a study that received 2 for three main criteria (double-blinding, concealment of treatment allocation schedule, inclusion of all randomised participants in analysis (i.e. ITT))

Medium quality: received 2 and/or 1 for all three main criteria

Low quality: received 0 for all three criteria or 0 and 1 for all three criteria or received 0 for any of the three criteria

.

Table 6: Methodological quality of included **pseudo-RCTs** for outcome **prostate cancer-specific mortality** (n = 1)

Quality Category	**N (%)**
I. Subject selection	
2 = Representative of eligible patients	1 (100)
1 = Selected group	0 (0)
0 = Highly selected or not described	0 (0)
II. Measurement of outcomes – outcome measures blind to technology used?	
2 = Yes	0 (0)
1 = No, but objective measures used	1 (100)
0 = No or not described (issues of blinding not described, subjective measurements used (e.g. QOL, pain, hospital length of stay), blinding not possible (e.g. different treatment schedules))	0 (0)
III. Comparability of groups on demographic characteristics and clinical features	
2 = Comparable	0 (0)
1 = Not comparable but adjusted analysis used	1 (100)
0 = Not comparable and not adjusted for differences	0 (0)
IV. Completeness of follow-up – follow-up complete and all patients included in the analysis?	
2 = Yes (follow-up >95% or intention to treat)	1 (100)
1 = Reasonable follow-up of all groups (>80% subjects included)	0 (0)
0 = No or not described (considerable drop outs, differential drop out in intervention and control groups, or no information provided)	0 (0)

Table 7: Methodological quality of included **pseudo-RCTs** for outcome **metastatic disease at diagnosis** (n = 1)

Quality Category	**N (%)**
I. Subject selection	
2 = Representative of eligible patients	1 (100)
1 = Selected group	0 (0)
0 = Highly selected or not described	0 (0)
II. Measurement of outcomes – outcome measures blind to technology used?	
2 = Yes	0 (0)
1 = No, but objective measures used	0 (0)
0 = No or not described (issues of blinding not described, subjective measurements used (e.g. QOL, pain, hospital length of stay), blinding not possible (e.g. different treatment schedules))	1 (100)
III. Comparability of groups on demographic characteristics and clinical features	
2 = Comparable	1 (100)
1 = Not comparable but adjusted analysis used	0 (0)
0 = Not comparable and not adjusted for differences	0 (0)
IV. Completeness of follow-up – follow-up complete and all patients included in the analysis?	
2 = Yes (follow-up >95% or intention to treat)	0 (0)
1 = Reasonable follow-up of all groups (>80% subjects included)	0 (0)
0 = No or not described (considerable drop outs, differential drop out in intervention and control groups, or no information provided)	1 (100)

Table 8: Methodological quality of included **pseudo-randomised controlled trials** (1 trial, 2 publications)

Trial/Publications	Outcome	Subject selection	Measurement of outcomes	Demographic characteristics comparability	Follow-up	**Overall rating**	**Risk of bias**
Norrkoping Study							
Sandblom 2011	Prostate cancer-specific mortality	2	1	1	2	**Medium**	**Moderate**
Sandblom 2004	Metastatic disease at diagnosis	2	0	2	0	**Low**	**High**

Key to overall quality rating
High quality: A study that received 2 for all quality criteria
Medium quality: Received 2 and 1 for all quality criteria
Low quality: Received 0 for all quality criteria or 1 and 0 for all quality criteria or received 0 for any of the quality criteria

2.5. Study Results

I PROSTATE CANCER-SPECIFIC MORTALITY

Table 9: Results of studies examining PSA testing strategies ± DRE compared to no PSA testing on prostate cancer-specific mortality

Study	Outcome	N	Intervention	Control	p value	RR (95% CI)	Follow-up duration
PLCO Andriole 2012 & 2009	Prostate cancer-specific mortality: *cumulative deaths per 10,000 person-years*	76,685	3.7	3.4	NS	1.09 (0.87 – 1.36)	13 years
			2.7	2.4	NS	1.11 (0.83 – 1.50)	10 years
			2.1	2.0	NS	1.05 (0.73 – 1.51)	8 years
			2.0	1.7	NS	1.13 (0.75 – 1.70)	7 years
			1.6	1.6	NS	1.03 (0.64 – 1.65)	6 years
			1.4	1.2	NS	1.13 (0.64 – 1.98)	5 years
	Subgroup analysis:						
	Age at randomisation						
	55 – 64 years	NR	2.35	1.97	NS	1.19 (0.83 – 1.72)	13 years
	65 – 74 years	NR	6.17	6.02	NS	1.02 (0.77 – 1.37)	
	*Modified Charlson score**						
	0	NR	3.47	3.48	NS	1.00 (0.76 – 1.31)	
	≥ 1	NR	3.78	3.41	NS	1.11 (0.72 – 1.71)	
	Number of pre-trial PSA tests#						
	0	NR	4.21	3.57	NS	1.18 (0.85 – 1.64)	
	≥ 1	NR	3.14	3.09	NS	1.02 (0.71 – 1.46)	

ERSPC Schroder 2012a, Roobol 2013, Bokhorst 2014, Kilpelainen 2013, Hugosson 2010, Grenabo Bergdahl 2013	Prostate cancer-specific mortality: *deaths per 10,000 person-years*						Median 11 years
	Overall (core age group)	162,388	3.9	5.0	0.001	0.79 (0.68 – 0.91)[1,2,3,4]	
	Overall (all ages)	182,160	4.2	5.0	0.005	0.83 (0.72 – 0.94)[1,2]	
	Study years 1 – 9 (core age group)	NR	3.1	3.7	NS	0.85 (0.71 – 1.03)[1,2]	
	Study years 8 – 9 (core age group)	NR	5.8	7.8	0.04	0.74 (0.55 – 0.99)[1,2]	
	Study years 10 – 11 (core age group)	NR	5.7	9.2	0.003	0.62 (0.45 – 0.85)[1,2]	
	Study years 1 – 11 (core age group)	NR	3.5	4.4	0.003	0.79 (0.67 – 0.92)[1,2]	
	Study years ≥ 12 (core age group)	NR	9.4	11.6	NS	0.80 (0.56 – 1.13)[1,2]	
	Subgroup analysis						
	Age at randomisation (exploratory analysis)						
	≤ 54 years	NR	0.9	1.4	NS	0.65 (0.23 – 1.83)[1,2]	
	55 – 59 years	NR	2.5	3.0	NS	0.81 (0.62 – 1.05)[1,2]	
	60 – 64 years	NR	4.7	5.2	NS	0.92 (0.71 – 1.18)[1,2]	
	65 – 69 years	NR	6.2	9.5	NR	0.67 (0.53 – 0.86)[1,2]	
	≥ 70 years	NR	13.3	11.3	NS	1.18 (0.81 – 1.72)[1,2]	
	Centre						
	Belgium (core age group)	8,562	4.6	5.3	NS	0.86 (0.48 – 1.52)[1]	12.1 years
	Finland (core age group)	80,379	4.2	4.7	NS	0.89 (0.72 – 1.09)[1]	11.0 years
	Italy (core age group)	14,517	2.6	3.1	NS	0.86 (0.46 – 1.58)[1]	10.7 years
	Netherlands (core age group)	34,833	3.7	5.2	NR	0.71 (0.52 – 0.96)[1]	11.1 years
					0.004	0.68 (0.53 – 0.89)[5]	13.0 years
	Spain (core age group)	2,197	1.8	0.8	NS	2.15 (0.19 – 23.77)[1]	10.7 years
	Switzerland (core age group)	9,903	2.3	2.6	NS	0.89 (0.36 – 2.20)[1]	8.2 years

	Sweden (core age group)	11,852	5.3	9.5	NR	0.56 (0.38 – 0.83)[1]	14.0 years
	Sweden – men without prostate cancer at end of screening period (entire Goteborg cohort – men aged 50 – 69)	13,423					
	3 – 6 years after end of screening		0.17	0.36	NR	0.43[6]	4.8 – 4.9 years after end of screening
	6 – 9 years after end of screening		0.29	0.56	NR	0.46[6]	
	9 – 12 years after end of screening		0.62	0.46	NR	1.2[6]	
	Cumulative hazard (%)						
	Overall (55 – 69 years) 14 years post randomization	162,388	~0.65	~0.89	NR	NR	11 years
	Sweden (**50** – 69 years) 14 years post randomization	19,904	0.50	0.90	0.002	0.56 (0.39 – 0.82)[1]	14.0 years
	Netherlands (55 – **74** years)	41,902	NR	NR	0.042	0.80 (0.65 – 0.99)[1]	12.8 years
	Finland (55 – 69 years) 12 years post randomisation	80,144	0.47	0.55	0.10	0.85 (0.69 – 1.04)[7]	12.0 years
	Deaths per 1,000 men						
	Netherlands (core age group)		5.5	8.1	NR	0.68 (0.53 – 0.89)[5]	13.0 years
Norrkoping Study Sandblom 2011	Prostate cancer-specific mortality: *deaths per men screened/non-screened*	9,026	30/1,494	130/7,532	NS	1.16 (0.78 – 1.73)	20 years maximum
Stockholm Study Kjellman 2009	Prostate cancer-specific mortality: *deaths per 1,000 person-years (95%CI)*	27,146	1.72 (1.32 – 2.26)	1.57 (1.44 – 1.71)	NS	1.10 (0.83 – 1.46)[8]	15 years maximum
Quebec Study Labrie 2004	Prostate cancer-specific mortality: *deaths per person-years*	21,579	NR	NR	0.047	0.49 (0.25 – 0.99)[9]	7.93 years maximum

CI = confidence interval; ERSPC = European Randomised Study of Screening for Prostate Cancer; NR = not reported; NS = not statistically significantly different; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RR = relative risk

*Assessed a subgroup of Charlson score comorbidities: 0 = no comorbidities; ≥1 = one or more comorbid conditions

[#] Number of PSA tests in the 3-year period before entry into the study

~Estimated by systematic review team from published figure

[1] Poisson regression analysis used to calculate rate ratios

[2] Adjusted according to centre

[3] RR = 0.71 (95% CI 0.58 – 0.86; p = 0.001) when adjusted for selection bias and non-compliance

[4] Risk reduction remained significant omitting each centre one at a time

[5] Binary analysis

[6] Fine and Gray competing risk analysis

[7] Cox proportional hazards analysis

[8] Poisson regression analysis used to calculate rate ratios and adjusted for attained age

[9] Not intention-to-treat analysis. Risk ratio and 95% confidence interval for prostate cancer mortality using intention-to-treat analysis = 1.01 (0.76 - 1.33) calculated by Djulbegovic 2010, Ilic et al., 2013, Lumen et al 2012 from data by Labrie et al 2004

II METASTATIC DISEASE AT DIAGNOSIS

Table 10: Results of studies examining PSA testing strategies ± DRE compared to no PSA testing on metastatic disease at diagnosis

Study	Outcome	N	Intervention	Control	p value	RR (95% CI)	Follow-up duration
PLCO Andriole 2012	Stage IV prostate cancer at diagnosis: *cumulative diagnoses per 10,000 person-years*	76,685	2.4	2.8	0.31	0.87 (0.66 – 1.14)	13 years
ERSPC Schroder 2012b	Metastatic disease at diagnosis including PSA >100ng/mL in absence of imaging report: *number of men*	76,813 (4 centres)	121	280	<0.0001	0.50 (0.41 – 0.62)	Median 12 years
	Subgroup analysis						
	Finland	20,225	27	83	<0.0001	0.59	12.9 years
	Netherlands	34,833	54	114	<0.0001	0.50	12.0 years
	Sweden	11,852	35	70	<0.0001	0.52	14.9 years
	Switzerland	9,903	5	13	<0.079	0.40	9.1 years
Norrkoping Study Sandblom 2004	Metastatic disease at diagnosis: *number of men (%)*	9,026	14 (0.94)	63 (0.84)	NR	OR = 1.12 (0.63 – 1.99)†	12 years

CI = confidence interval; ERSPC = European Randomised Study of Screening for Prostate Cancer; NR = not reported; OR = odds ratio; PSA = prostate specific antigen; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RR = relative risk;

† Calculated by the systematic review team using the log-transformation method (WinPepi - http://www.brixtonhealth.com/pepi4windows.html).

‡ Calculated by the systematic review team using Fisher's exact test (WinPepi - http://www.brixtonhealth.com/pepi4windows.html). Mid-P confidence intervals were chosen.

2.6. Body of Evidence

I PROSTATE CANCER-SPECIFIC MORTALITY

Name of study	Study type	N	Level of evidence *	Quality of evidence **	Risk of bias	Results summary			Size of effect (RR)	p value	95% CI	Relevance of evidence*
PSA (± DRE) Screening vs Opportunistic Screening												
Screened **annually** for **6** years PSA **> 4.0ng/mL**+ **DRE** (for 4 years)												
PLCO *Andriole 2012 & 2009* Follow-up (median): 11.5 years	RCT	76,685	II	Medium	Moderate	***Cumulative deaths per 10,000 person-years***						1
						13 years follow-up	S: 3.7	C: 3.4				
						10 years follow-up	S: 2.7	C: 2.4	1.09	NS	0.87 – 1.36	
						8 years follow-up	S: 2.1	C: 2.0	1.11	NS	0.83 – 1.50	
						7 years follow-up	S: 2.0	C: 1.7	1.05	NS	0.73 – 1.51	
						6 years follow-up	S: 1.6	C: 1.6	1.13	NS	0.75 – 1.70	
						5 years follow-up	S: 1.4	C: 1.2	1.03	NS	0.64 – 1.65	
									1.13	NS	0.64 – 1.98	
						Subgroup analysis						
						Age (years):						
						55 – 64	S: 2.35	C: 1.97				
						65 – 74	S: 6.17	C: 6.02	1.19	NS	0.83 – 1.72	
						Modified Charlson score[#]:			1.02	NS	0.77 – 1.37	
						0	S: 3.47	C: 3.48				
						≥1	S: 3.78	C: 3.41	1.00	NS	0.76 – 1.31	
						Number of pre-trial PSA tests[##]:			1.11	NS	0.72 – 1.71	
						0	S: 4.21	C:3.57				
						≥1	S: 3.14	C:3.09	1.18	NS	0.85 – 1.64	
									1.02	NS	0.71 – 1.46	
PSA (± DRE) Screening vs No Screening												

Screened every **2 or 4 years** for ≥12 years or until 75 years of age PSA **≥ 3.0 or 4.0ng/mL** ± DRE												
ERSPC (overall) *Bokhorst 2014, Hugosson 2010, Kilpelainen 2013, Roobol 2013, Schroder 2012a*	RCT	182,160 Ages 55 - 69 years 162,388	II	Medium	Moderate	***Deaths per 10,000 person-years***						1
						Overall (ages 50 – 75)	S: 4.2	C: 5.0	0.83[2,3]	0.005	0.72 – 0.94	
						Overall (ages 55 – 69)	S: 3.9	C: 5.0	0.79[2,3,6,7]	0.001	0.68 – 0.91	
						Study years 1 – 9	S: 3.1	C: 3.7		NS	0.71 – 1.03	
						Study years 8 – 9	S: 5.8	C: 7.8	0.85[2,3]	0.04	0.55 – 0.99	
						Study years 10 – 11	S: 5.7	C: 9.2	0.74[2,3]	0.003	0.45 – 0.85	
						Study years 1 – 11	S: 3.5	C: 4.4	0.62[2,3]	0.003	0.67 – 0.92	
						Study years ≥ 12	S: 9.4	C: 11.6	0.79[2,3]	NS	0.56 – 1.13	
									0.80[2,3]			
						Cumulative hazard (%) 14 years post randomisation						
						Overall (ages 55 – 69) 11 years median follow-up	S: 65	C: 89	NR	NR	NR	
						Subgroup analysis *Age (years) (exploratory analysis)*						
						≤ 54	S: 0.9	C: 1.4	0.65[2,3]	NS	0.23 – 1.83	
						55 – 59	S: 2.5	C: 3.0	0.81[2,3]	NS	0.62 – 1.05	
						60 – 64	S: 4.7	C: 5.2	0.92[2,3]	NS	0.71 – 1.18	
						65 – 69	S: 6.2	C: 9.5	0.67[2,3]	NR	0.53 – 0.86	
						≥ 70	S: 13.3	C:11.3	1.18[2,3]	NS	0.81 – 1.72	
Screened every **4 years** until 75 years of age *1993 – 1995* PSA ≥ 4ng/mL + DRE + TRUS *1995 – 1997* PSA ≥ 4ng/mL with ancillary DRE + TRUS for PSA 1.0 – 3.9ng/mL *1997 onwards* PSA ≥ 3ng/mL only												
ERSPC **The Netherlands**	RCT	41,902 Ages 55 - 69 years 34,833	II	Medium	Moderate	***Deaths per 10,000 person-years***						1
						Overall (ages 55 – 69)						
						11.1 years median follow-up	S: 3.7	C: 5.2	0.71[2]	NR	0.52 – 0.96	
						13.0 years median follow-up	NR	NR	0.68[4]	0.004	0.53 – 0.89	
						Cumulative hazard (%)						

						Overall (ages 55 – 74) 12.8 years median follow-up	NR	NR	0.80[2]	0.042	0.65 – 0.99	
Screened every **4 years** for **12 years** or until 75 years of age *1992 – 1994* PSA ≥ 10ng/mL + DRE + TRUS *1995 – 1997* PSA ≥ 4ng/mL + DRE + TRUS *1998* PSA only cut-off ≥ 4ng/mL *1999 onwards* PSA cut-off ≥ 3ng/mL												
***ERSPC* Belgium**	RCT	Ages 55 – 69 years 8,562	II	NA	NA	***Deaths per 10,000 person-years*** Overall (ages 55 – 69) 12.1 years median follow-up	S: 4.6	C: 5.3	0.86[2]	NS	0.48 – 1.52	1
Screened every **2 years** until 70 years of age *1995 – 1998* PSA ≥ **3.0ng/mL** *1999 – 2004* PSA ≥ 2.9ng/mL *2005 onwards* PSA ≥ 2.5ng/mL												
***ERSPC* Sweden (Goteborg)**	RCT	19,904 Ages 55 – 69 years 11,852	II	Medium	Moderate	***Deaths per 10,000 person-years*** Overall (ages 55 – 69) 14.0 years median follow-up ***Cumulative hazard (%) 14 years post randomisation*** Overall (ages 50 – 69) 14.0 years median follow-up	S: 5.3 S: 0.50	C: 9.5 C: 0.90	0.56[2] 0.56[2]	NR 0.002	0.38 – 0.83 0.39 – 0.82	1
Screened every **4 years** for **12 years** or until 71 years of age *1996 – 1998* PSA **≥ 4ng/mL** with ancillary DRE for PSA 3.0 – 3.9ng/mL *1999 onwards* ancillary free-to-total PSA ratio (≤16% trigger for biopsy) for PSA 3.0 - 3.9ng/mL												
***ERSPC* Finland**	RCT	Ages 55 – 69 years 80,379 80,144	II	Medium	Moderate	***Deaths per 10,000 person-years*** Overall (ages 55 – 69) 11.0 years median follow-up ***Cumulative hazard (%) 12 years post randomisation*** Overall (ages 55 – 69) 12.0 years median follow-up	S: 4.2 S:0.47	C: 4.7 C:0.55	0.89[2] 0.85[9]	NS 0.10	0.72 – 1.09 0.69 – 1.04	1
Screened every **4 years** until 75 years of age												

PSA **≥ 4ng/mL** with ancillary DRE + TRUS for PSA 2.5 – 3.9ng/mL											
ERSPC **Italy**	RCT	Ages 55 – 69 years 14,517	II	NA	NA	***Deaths per 10,000 person-years*** Overall (ages 55 – 69) 10.7 years median follow-up	S: 2.6	C: 3.1	0.89[2]	NS	0.46 – 1.58	1
Screened every **4 years** for **12 years** or until 75 years of age PSA **≥ 3ng/mL**											
ERSPC **Spain**	RCT	Ages 55 – 69 years 2,197	II	NA	NA	***Deaths per 10,000 person-years*** Overall (ages 55 – 69) 10.7 years median follow-up	S: 1.8	C: 0.8	2.15[2]	NS	0.19 – 23.8	1
Screened every **4 years** until 75 years of age PSA **> 3ng/mL** with ancillary free-to-total PSA for PSA 1.0 – 3.0ng/mL											
ERSPC **Switzerland**	RCT	Ages 55 – 69 years 9,903	II	NA	NA	***Deaths per 10,000 person-years*** Overall (ages 55 – 69) 8.2 years median follow-up	S: 2.3	C: 2.6	0.89[2]	NS	0.36 – 2.20	1
Screened **once** PSA **> 10ng/mL** + DRE + TRUS with second TRUS for PSA 7.0 – 10.0ng/mL											
Stockholm Study Kjellman 2009	RCT	27,146	II	Low	High	***Deaths per 1,000 person-years (95% CI)*** 12.9 years median follow-up S: 1.72 (1.32 – 2.26) C: 1.57 (1.44 – 1.71)			1.10[5]	NS	0.83 – 1.46	1
Screened **annually** PSA **> 3.0ng/mL** + DRE ± TRUS for first screening and TRUS if PSA **> 3.0ng/mL** for subsequent screenings Biopsy if abnormal TRUS or DRE or measured PSA greater than predicted PSA (dependent on prostate volume)											
Quebec Study Labrie 2004	RCT	21,579	II	Low	High	***Deaths per men-years*** Maximum follow-up = 7.9 years S: NR C: NR			0.49[10]	0.047	0.25 – 0.99	1

DRE (± PSA) Screening vs No Screening										
Screened every **3 years** for **12** years **DRE** only first and second screens DRE + PSA **> 4.0ng/mL** third and fourth screens										
Norrkoping Study Sandblom 2011	Pseudo -RCT	9,026	III-1	Medium	Moderate	***Deaths per men screened/non-screened*** 75 months median follow-up S: 30/1,494 C: 130/7,532	1.16	NS	0.78 – 1.73	1

C = control group; CI = confidence interval; DRE = digital rectal examination; ERSPC = the European Randomised Study of Screening for Prostate Cancer; NR = not reported; NS = not statistically significantly different; PLCO = Prostate, Lung Colorectal and Ovarian Cancer Screening Trial; PSA = prostate specific antigen; RCT = randomised controlled trial; RR = relative risk; S = screening group; TRUS = transrectal ultrasonography of the prostate

NA = not accessible as only included data from Schroder 2012 which did not describe randomisation protocols at each of the 7 centres – for the Rotterdam, Goteborg and Finnish centres some data was identified from articles specifically for those centres that described the randomisation protocol at those centres

**Refer to appendix B for detailed explanations of rating scores; ** see Tables 2-3, 6 and 8 for quality appraisals*

[#] Assessed a subgroup of Charlson score comorbidities: 0 = no comorbidities; ≥1 = one or more comorbid conditions

[##] Number of PSA tests in the 3-year period before entry into the study

[1] Results are for core age group unless otherwise stated

[2] Poisson regression analysis used to calculate relative risks

[3] Adjusted according to centre

[4] Binary analysis

[5] Poisson regression analysis used to calculate relative risk and adjusted for attained age

[6] RR = 0.71 (95% CI 0.58 – 0.86; P = 0.001) when adjusted for selection bias and non-compliance

[7] Risk reduction remained significant omitting each centre one at a time

[8] Fine and Gray competing risk analysis

[9] Cox proportional hazards analysis

[10] Not intention to treat analysis. Risk ratio and 95% confidence interval for prostate cancer mortality) using intention to treat analysis = 1.01 (0.76 - 1.33 calculated by Djulbegovic 2010, Ilic et al., 2013, Lumen et al 2012 from data by Labrie et al 2004

II METASTATIC OR STAGE IV PROSTATE CANCER AT DIAGNOSIS

Name of study	Study type	N	Level of evidence *	Quality of evidence **	Risk of bias	Results summary	Size of effect (RR)	p value	95% CI	Relevance of evidence*
PSA (± DRE) Screening vs Opportunistic Screening										
Screened **annually** for 6 years PSA **> 4.0ng/mL** + **DRE** for 4 years										
PLCO Andriole 2012 Follow-up: 13 years	RCT	76,685	II	Low	High	**<u>Stage IV prostate cancer at diagnosis</u>** *Cumulative diagnoses per 10,000 person-years* S: 2.4 C: 2.8	0.87	0.31	0.66 – 1.14	1
PSA (± DRE) Screening vs No Screening										
Screened every **2 or 4 years** for ≥ 12 years or until 75 years of age PSA **≥ 3.0 or 4.0ng/mL** ± DRE										
ERSPC Schroder 2012b (4 centres) Follow-up (median): 13 years	RCT	76,813	II	Low	High	**<u>Metastatic disease at diagnosis</u> including PSA >100ng/mL in absence of imaging report** *Number of men* S: 121 C: 280	0.50	< 0.0001	0.41 – 0.62	1
Screened every **4 years** for **12 years** or until 71 years of age *<u>1996 – 1998</u>* PSA **≥ 4ng/mL** with ancillary DRE for PSA 3.0 – 3.9ng/mL *<u>1999 onwards</u>* ancillary free-to-total PSA ratio (≤16% trigger for biopsy) for PSA 3.0 – 3.9ng/mL										
ERSPC **Finland** Follow-up (median): 12.9 years	RCT	20,225	II	Low	High	S: 27 C: 83	0.59	<0.0001	NR	1

Screened every **4 years** until 75 years of age *1993 – 1995* PSA ≥ 4ng/mL + DRE + TRUS *1995 – 1997* PSA ≥ 4ng/mL with ancillary DRE + TRUS for PSA 1.0 – 3.9ng/mL *1997 onwards* PSA ≥ 3ng/mL only											
ERSPC **The Netherlands** Follow-up (median): 12.0 years	RCT	34,833	II	Low	High	S: 54	C: 114	0.50	<0.0001	NR	1
Screened every **2 years** until 70 years of age *1995 – 1998* PSA ≥ **3.0ng/mL** *1999 – 2004* PSA ≥ 2.9ng/mL *2005 onwards* PSA ≥ 2.5ng/mL											
ERSPC **Sweden (Goteborg)** Follow-up (median): 14.9 years	RCT	11,852	II	Low	High	S: 35	C: 70	0.52	<0.0001	NR	1
Screened every **4 years** until 75 years of age PSA **> 3ng/mL** with ancillary free-to-total PSA for PSA 1.0 – 3.0ng/mL											
ERSPC **Switzerland** Follow-up (median): 9.1 years	RCT	9,903	II	Low	High	S: 5	C: 13	0.40	0.079	NR	1
DRE (± PSA) Screening vs No Screening											
Screened every **3 years** for **12** years **DRE** only first and second screens DRE + PSA **> 4.0ng/mL** third and fourth screens											
Sandblom 2004 *Norrkoping Study* Follow-up 12 years	Pseudo - RCT	9,026	III-1	Low	High	**Metastatic disease at diagnosis** *Number of men (% men in arm)* S: 14 (0.94)	C: 63 (0.84)	1.12	NR	0.63 – 1.99	1

C = control group; CI = confidence interval; DRE = digital rectal examination; ERSPC = the European Randomised Study of Screening for Prostate Cancer; NR = not reported; OR = odds ratio; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PSA = prostate specific antigen; RCT = randomised controlled trial; RR = relative risk; S = screening group

**Refer to appendix B for detailed explanations of rating scores; ** See Tables 4-5 and 7-8 for quality appraisals*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the NHMRC evidence statement form.

References: Included Studies

1. Andriole GL, Crawford ED, Grubb RL, III, Buys SS, Chia D, Church TR et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009; 360(13):1310-1319.

2. Andriole GL, Crawford ED, Grubb RL, III, Buys SS, Chia D, Church TR et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. J Natl Cancer Inst 2012; 104(2):125-132.

3. Bokhorst LP, Bangma CH, van Leenders GJ, Lous JJ, Moss SM, Schroder FH et al. Prostate-specific antigen-based prostate cancer screening: reduction of prostate cancer mortality after correction for nonattendance and contamination in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. Eur Urol 2014; 65(2):329-336.

4. Grenabo Bergdahl A, Holmberg E, Moss S, Hugosson J. Incidence of prostate cancer after termination of screening in a population-based randomised screening trial. Eur Urol 2013; 64(5):703-709.

5. Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. Lancet Oncol 2010; 11(8):725-732.

6. Kilpelainen TP, Tammela TL, Malila N, Hakama M, Santti H, Maattanen L et al. Prostate cancer mortality in the Finnish randomized screening trial. Journal of the National Cancer Institute 2013; 105(10):719-725.

7. Kjellman A, Akre O, Norming U, Tornblom M, Gustafsson O. 15-year followup of a population based prostate cancer screening study. J Urol 2009; 181(4):1615-1621.

8. Labrie F, Candas B, Cusan L, Gomez JL, Belanger A, Brousseau G et al. Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. Prostate 2004; 59(3):311-318.

9. Roobol MJ, Kranse R, Bangma CH, Van Leenders AGJL, Blijenberg BG, Van Schaik RHN et al. Screening for prostate cancer: Results of the Rotterdam section of the European randomized study of screening for prostate cancer. Eur Urol 2013; 64(4):530-539.

10. Sandblom G, Varenhorst E, Lofman O, Rosell J, Carlsson P. Clinical consequences of screening for prostate cancer: 15 years follow-up of a randomised controlled trial in Sweden. Eur Urol 2004; 46(6):717-723.

11. Sandblom G, Varenhorst E, Rosell J, Lofman O, Carlsson P. Randomised prostate cancer screening trial: 20 year follow-up. BMJ 2011; 342:d1539.

12. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012; 366(11):981-990.

13. Schroder FH, Hugosson J, Carlsson S, Tammela T, Maattanen L, Auvinen A et al. Screening for prostate cancer decreases the risk of developing metastatic disease: findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC). Eur Urol 2012; 62(5):745-752.

References for systematic reviews with intention to treat results for Quebec Study

1. Djulbegovic M, Beyth RJ, Neuberger MM, Stoffs TL, Vieweg J, Djulbegovic B et al. Screening for prostate cancer: systematic review and meta-analysis of randomised controlled trials. BMJ 2010; 341:c4543.

2. Ilic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. Cochrane Database Syst Rev 2013; 1:CD004720.

3. Lumen N, Fonteyne V, De MG, Ost P, Villeirs G, Mottrie A et al. Population screening for prostate cancer: an overview of available studies and meta-analysis. Int J Urol 2012; 19(2):100-108.

3. Appendices

Appendix A: Search strategies used

For Medline database:

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	prostate-specific antigen/
5	prostate specific antigen.tw,mp.
6	PSA.mp,tw.
7	4 or 5 or 6
8	exp mass screening/
9	"early detection of cancer"/
10	screen$.mp,tw.
11	8 or 9 or 10
12	clinical trial.pt.
13	random$.mp.
14	((single or double) adj3 (blind$ or mask$)).mp,tw.
15	placebo$.mp,tw.
16	12 or 13 or 14 or 15
17	3 and 7 and 11 and 16
18	limit 17 to (english language and humans and yr="2012-current")

Modification of search strategies used by Ilic et al 2013. Cochrane Database of Systematic Reviews. Issue 1. Art. No.: CD004720 and National Health and Medical Research Council (2013b). Prostate-Specific Antigen (PSA) testing in asymptomatic men: Technical Report. Canberra: National Health and Medical Research Council.

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database:

#	Searches
1	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neopla* OR metast* OR adeno*)
2	'prostate cancer'/exp
3	1 OR 2
4	'prostate specific antigen'/exp
5	'prostate specific antigen':de,ab,ti OR psa:de,ab,ti
6	'prostate specific antigen' OR psa
7	4 OR 5 OR 6
8	'mass screening'/exp
9	'screening test'/exp
10	'early diagnosis'/exp
11	screen*
12	8 OR 9 OR 10 OR 11
13	'clinical trial'
14	'clinical trial':de
15	random*
16	random*:ab,ti
17	(single OR double) NEAR/3 (blind* OR mask*)
18	((single OR double) NEAR/3 (blind* OR mask*)):ab,ti
19	placebo*
20	placebo:ab,ti
21	13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20
22	[embase]/lim AND [2012-2014]/py AND [english]/lim AND [humans]/lim
23	3 AND 7 AND 12 AND 21 AND 22

Modification of search strategies used by Ilic et al 2013. Cochrane Database of Systematic Reviews. Issue 1. Art. No.: CD004720 and National Health and Medical Research Council (2013b). Prostate-Specific Antigen (PSA) testing in asymptomatic men: Technical Report. Canberra: National Health and Medical Research Council.

ATSI search terms used

#	Searches
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

For CENTRAL database:

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	Prostate-Specific Antigen/
5	prostate specific antigen.tw,mp.
6	psa.tw,mp.
7	4 or 5 or 6
8	exp mass screening/
9	"early detection of cancer"/
10	screen$.mp,tw.
11	8 or 9 or 10
12	clinical trial.pt.
13	random$.mp.
14	((single or double) adj3 (blind$ or mask$)).mp,tw.
15	placebo$.mp,tw.
16	12 or 13 or 14 or 15
17	3 and 7 and 11 and 16
18	limit 17 to (yr="2012-current")

Modification of search strategies used by Ilic et al 2013. Cochrane Database of Systematic Reviews. Issue 1. Art. No.: CD004720 and National Health and Medical Research Council (2013b).

For Cochrane Database of Systematic Reviews – The Cochrane Library:
Title, abstracts, keywords: “prostate”

For Database of Abstracts of Reviews of Effects and Health Technology Assessment database (via OvidSP):

#	Searches
1	exp Prostatic Neoplasms/
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
3	1 or 2

Appendix B:

Level of Evidence rating criteria – Intervention studies

Level	Study design
I	Meta-analysis or a systematic review of level II studies
II	Randomised controlled trial or a phase III/IV clinical trial
III-1	Pseudo-randomised controlled trial or a meta-analysis/systematic review of level III-1 studies
III-2	Comparative study with concurrent controls: - Phase II clinical trial - Non-randomised, experimental trial9 - Controlled pre test/post test study - Adjusted indirect comparisons - Interrupted time series with a control group - Cohort study - Case-control study or a meta-analysis/systematic review of level III-2 studies
III-3	A comparative study without concurrent controls: - Phase I clinical trial - Historical control study - Two or more single arm study10 - Unadjusted indirect comparisons - Interrupted time series without a parallel control group or a meta-analysis/systematic review of level III-3 studies
IV	Case series with either post-test or pre-test/post-test outcomes or a meta-analysis/systematic review of level IV studies

According to the standards of the National Health and Medical Research Council

Relevance of the Evidence

Rating	Relevance
1	Evidence of an effect on patient-relevant clinical outcomes including benefits and harms, quality of life and survival.
2	Evidence of an effect on a surrogate outcome* that has been shown to be predictive of patient-relevant outcomes for the same intervention.
3	Evidence of an effect on proven surrogate outcomes but for a different intervention.
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population.
5	Evidence confined to unproven surrogate outcomes.

**'surrogate outcome' refers to reasonable indicators of whether there has been some effect (e.g. blood pressure measurements or levels of serum cholesterol)*

Points to considering patient-relevant outcomes:
i) The goal of decision making in health care is to choose the intervention(s) (which may include doing nothing) that is (are) most likely to deliver the outcomes that patients find desirable
ii) Surrogate outcomes (such as blood pressure measurements or levels of serum cholesterol) may be reasonable indicators of whether there has been some effect. However, they should not be the basis for clinical decisions unless they reliably predict an effect on the way the patient feels; otherwise they will not be of interest to the patient or their carers
iii) All possible outcomes that are of most interest to patients (particularly harms) should be identified and evaluated

Adapted from table 1.10: National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra: NHMRC; 2000. http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp69.pdf

Appendix C:

Potentially relevant guidelines identified and reason why not adopted

Year	Organisation	Title	Reason why not adopted
2010	American Cancer Society	American Cancer Society Guideline for the Early Detection of Prostate Cancer	Did not meet pre-specified AGREE II criteria for adoption
2008	American College of Preventive Medicine	Screening for Prostate Cancer in U.S. Men: ACPM Position Statement on Preventive Practice	Did not meet pre-specified AGREE II criteria for adoption
2013	American College of Physicians	Screening for prostate cancer – guidance statement	Did not meet pre-specified AGREE II criteria for adoption
2012	American Society of Clinical Oncology	Screening for Prostate Cancer with Prostate-Specific Antigen Testing: American Society of Clinical Oncology Provisional Clinical Opinion	Did not meet pre-specified AGREE II criteria for adoption
2013	American Urological Association	Early Detection of Prostate Cancer: AUA Guideline	Did not meet pre-specified AGREE II criteria for inclusion
2014	European Association of Urology	Guidelines on Prostate Cancer	Did not specifically address clinical question as to which screening protocol to use
2011	Canadian Urological Association	Prostate Cancer Screening: Canadian guidelines	Did not meet pre-specified AGREE II criteria for adoption
2013	European Society for Medical Oncology	ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Consensus based
2010	Japanese Urological Association	Japanese Urological Association Guidelines on prostate-specific antigen-based screening for prostate cancer in 2010	Not based on a systematic review
2013	Prostate Cancer World Congress	Melbourne Consensus Statement on Prostate Cancer Testing	Consensus based
2008	National Academy of Clinical Biochemistry	National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for Use of Tumor Markers in Testicular, Prostate, Colorectal, Breast, and Ovarian Cancers	Not based on a systematic review
2010	National Health Service	Prostate Cancer Risk Management Programme: PSA testing in asymptomatic men	Consensus based
2012	NCCN	Prostate cancer early detection version 2.2012	Not based on a systematic review

2009	New Zealand Guidelines Group	Suspected cancer in primary care: Guidelines for investigation, referral and reducing ethnic disparities	Not based on a systematic review
2012	Royal Australian College of General Practitioners	Guidelines for preventive activities in general practice	Not based on a systematic review
2012	Royal College of Pathologists of Australasia	Prostate specific antigen testing: Age-related interpretation in early prostate cancer detection	Consensus based
2012	University of Michigan Health System	Cancer Screening	Did not meet pre-specified AGREE II criteria for adoption
2012	US Preventive Services Task Force	Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement	Did not specifically address clinical question as to which screening protocol to use

Excluded Studies

Study	Reason for Exclusion
Andriole 2005	No comparative data
Aus 2006	More mature data published
Carlsson 2010	Inappropriate population
Crawford 2011	More mature data published
Grenabo Bergdahl 2009	No comparative data
Johnson 2006	No relevant outcomes
Kerkhof 2010	More mature data published
Kilpelainen 2010	No relevant outcomes
Kilpelainen 2011	No relevant outcomes
Lin 2011	Did not provide original or additional data for RCTs included for Q4.1
New Zealand Guidelines Group 2009	Did not provide original or additional data for RCTs included for Q4.1
Pinsky 2012	Inappropriate population
Raaijmakers 2002	No comparative data
Roobol 2009	More mature data published
Schroder 2009	More mature data published
Taylor 2004	No relevant outcomes
Zhu 2011	No comparative data

References: Excluded Studies

1. Andriole GL, Levin DL, Crawford ED, Gelmann EP, Pinsky PF, Chia D et al. Prostate Cancer Screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: findings from the initial screening round of a randomized trial. J Natl Cancer Inst 2005; 97(6):433-438.

2. Aus G, Bergdahl S, Lodding P, Lilja H, Hugosson J. Prostate cancer screening decreases the absolute risk of being diagnosed with advanced prostate cancer--results from a prospective, population-based randomized controlled trial. Eur Urol 2007; 51(3):659-664.

3. Carlsson SV, Holmberg E, Moss SM, Roobol MJ, Schroder FH, Tammela TL et al. No excess mortality after prostate biopsy: results from the European Randomized Study of Screening for Prostate Cancer. BJU Int 2011; 107(12):1912-1917.

4. Crawford DE, Grubb R, Black A, Andriole GL, Chen M-H, Izmirlian G et al. Comorbidity and mortality results from a randomized prostate cancer screening trial. J Clin Oncol 2011; 29(4): 355-361.

5. Grenabo Bergdahl A, Aus G, Lilja H, Hugosson J. Risk of dying from prostate cancer in men randomized to screening: differences between attendees and nonattendees. Cancer 2009; 115(24):5672-5679.

6. Johnson DB. The effects of an abnormal cancer screening test on health related quality of life. International Journal of Cancer Research 2006; 2(3):277-289.

7. Kerkhof M, Roobol MJ, Cuzick J, Sasieni P, Roemeling S, Schroder FH et al. Effect of the correction for noncompliance and contamination on the estimated reduction of metastatic prostate cancer within a randomized screening trial (ERSPC section Rotterdam). Int J Cancer 2010; 127(11):2639-2644.

8. Kilpelainen TP, Tammela TL, Maattanen L, Kujala P, Stenman UH, Ala-Opas M et al. False-positive screening results in the Finnish prostate cancer screening trial. Br J Cancer 2010; 102(3):469-474.

9. Kilpelainen TP, Tammela TL, Roobol M, Hugosson J, Ciatto S, Nelen V et al. False-positive screening results in the European randomized study of screening for prostate cancer. Eur J Cancer 2011; 47(18):2698-2705.

10. Lin K, Croswell JM, Koenig H, Lam C, Maltz A. Prostate-specific antigen-based screening for prostate cancer: an evidence update for the U.S. preventive services task force. Evidence synthesis no.90. 2011. Rockville, MD, Agency for Healthcare Research and Quality.

11. New Zealand Guidelines Group. Cancer control strategy guidance completion: update of evidence for prostate-specific antigen (PSA) testing in asymptomatic men. 2009. Wellington, Ministry of Health.

12. Pinsky PF, Black A, Parnes HL, Grubb R, David CE, Miller A et al. Prostate cancer specific survival in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Cancer Epidemiol 2012; 36(6):e401-e406.

13. Raaijmakers R, Kirkels WJ, Roobol MJ, Wildhagen MF, Schroder FH. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. Urology 2002; 60(5):826-830.

14. Roobol MJ, Kerkhof M, Schroder FH, Cuzick J, Sasieni P, Hakama M et al. Prostate cancer mortality reduction by prostate-specific antigen-based screening adjusted for nonattendance and contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). Eur Urol 2009; 56(4):584-591.

15. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009; 360(13):1320-1328.

16. Taylor KL, Shelby R, Gelmann E, McGuire C. Quality of life and trial adherence among participants in the prostate, lung, colorectal, and ovarian cancer screening trial. J Natl Cancer Inst 2004; 96(14):1083-1094.

17. Zhu X, van Leeuwen PJ, Bul M, Bangma CH, Roobol MJ, Schroder FH. Identifying and characterizing "escapes"-men who develop metastases or die from prostate cancer despite screening (ERSPC, section Rotterdam). Int J Cancer 2011; 129(12):2847-2854.

Systematic review report for question 3.1 (modelling studies)

Clinical Question 3: *In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what should be the PSA testing strategies (age to start, level at which to declare a test abnormal and frequency of subsequent testing if the PSA level is normal) for men at average risk of prostate cancer and how should they be modified, if at all, for men at high risk of prostate cancer?*

PICO 3.1: *For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what PSA testing strategies (with or without DRE), compared with no PSA testing or other PSA testing strategies, reduce prostate cancer specific mortality or the incidence of metastases at diagnosis and offer the best balance of benefits to harms of testing?*

Population	Intervention	Comparator	Outcomes
Men without a history of prostate cancer or symptoms that might indicate prostate cancer	Any specified PSA testing strategy	Any other specified PSA testing strategy, or no PSA testing in cohorts of men at different risk of prostate cancer	Modelled outcomes of PSA testing: • prostate cancer deaths prevented • months or years of life gained reduction in metastatic disease at diagnosis • false positive tests • overdiagnosis of prostate cancer • number needed to diagnose • quality adjusted life years gained

Strategy for PICO 1

The NHMRC recently reviewed the evidence for prostate cancer screening https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/men4a_psa_evidence_report_140519.pdf. The NHMRC review identified 5 systematic reviews with a "good" quality rating. These systematic reviews identified 4 randomised controlled trials and one pseudo-randomized trial of prostate comparing screening with no screening. Each trial used a different screening protocol. The systematic reviews included in the NHMRC review reported that there were no trials that compared different screening protocols however scoping searches indicated that there were published models comparing different PSA screening protocols. As a result this PICO question was approached in two stages:

Stage 1: **Randomised or pseudo-randomised controlled trials** included in the NHMRC systematic review were used to identify PSA testing strategies found to reduce prostate cancer-specific mortality or the incidence of metastases at diagnosis when compared to no PSA testing.

Stage 2: Modelling studies that compared the benefits and harms of different PSA screening protocols and of screening in higher risk populations were identified by a systematic search of the literature. To compare different protocols, the benefits and harms of protocols closest to those shown in randomised controlled trials to reduce prostate cancer-specific mortality or the incidence of metastases at diagnosis, were then compared to those of other PSA testing strategies.

For simplicity each stage was the subject of a separate systematic review.

This report deals with the second stage – the modelling studies.

1. Methods – modelling studies

1.1 Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption guidelines had to be evidence based and meet the pre-specified criteria of scores of greater or equal to 70% for the rigour of development, clarity of presentation and editorial independence domains of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

1.2 Literature Search for modelling studies

Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases from 1990 were searched using text terms and, where available, database specific subject headings. Each database was searched for articles dealing with prostate cancer. In Medline and Embase databases, the prostate cancer search terms were coupled with search terms for PSA testing models. Scoping searches identified a key modelling study by Gulati et al 2013 which compared a number of screening protocols. Web of Science was searched for citations of this article that might be relevant. To identify studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples. A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 which were either published after the initial search was completed and/or added to the relevant database after the search was completed. Alerts were checked until July 2014. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched regularly up until April 2014 for relevant reviews published after the initial search. Reference lists of all relevant articles were checked for potential additional articles.

1.3 Inclusion Criteria

Selection criteria	Inclusion criteria
Study type	Modelling
Study design	Validated state-transition models with European Randomized Study of Screening for Prostate Cancer (ERSPC) (2009 or later) data as input data for screening survival benefit *
Population	Included men without a history of prostate cancer or symptoms that might indicate prostate cancer
Intervention	A specified PSA testing strategy
Comparator	Another PSA testing strategy, or

	No PSA testing in cohorts of men at different risk of prostate cancer
Outcomes	Reports both harms and benefits • prostate cancer deaths prevented • months or years of life gained • reduction in metastatic disease at diagnosis • increase in false positive tests • Increase in overdiagnosis of prostate cancer or number needed to diagnose to prevent a death or quality adjusted life years gained
Language	English
Publication period	After 31st December 1989 and before1st March 2014

**Models of screening are based on the assumption that screening detects cancers at an earlier stage and that this earlier detection delivers a benefit in terms of decreasing mortality. To ensure that the models reflected/could replicate the best available trial estimate of a screening benefit to be included a model had to be validated against ERSPC screening benefit results i.e. if the model is used to simulate the control and intervention arms in the ERSPC trial, the screening benefit outputs obtained from the model have to be similar to those actually observed in ERSPC.*

2. Results

2.1. Guidelines

Eighteen guidelines were identified that contained potentially relevant recommendations regarding PSA testing protocols and four guidelines were identified that considered screening protocols for higher risk men. These recommendations were not adopted as they either were not based on a systematic review, did not meet the pre-specified AGREE II criteria for adoption, or the recommendations did not specifically address the clinical question. These guidelines and the reason why they were not adopted are listed in Appendix C.

In Australia the Royal College of Pathologists of Australasia has consensus based position statements regarding PSA testing (http://www.rcpa.edu.au/Library/College-Policies/Position-Statements/Prostate-Specific-Antigen-Testing-Age-related-inte, accessed 20/10/14):

"The response to an initial test should be:

a. *If the total PSA level is at or above 10 µg/L, the patient should either have the PSA confirmed in 4 weeks and be referred if the result is confirmed or be immediately referred for specialist management.*
b. *If the total PSA level is abnormal (above 97.5% age-related, method-specific reference limit) but below 10 µg/L, the PSA should be confirmed in 4 weeks including an estimation of the Free to Total PSA ratio (F/T PSA ratio). If confirmed and/or the result of the F/T PSA ratio is <10%, the patient should be immediately referred for specialist management.*
c. *If the PSA level is normal, but above the age-related median, the patient should be reassured that their result is normal and be re-tested in 2 years.*
d. *If the PSA level is not above the age-related median, the patient should be reassured that their risk is low and be re-tested in 4 years."*

In 2012 the Royal Australian College of General Practitioners recommended as a practice point (no good evidence available) that general practitioners respond to requests for screening by high risk men by informing them of the risks and benefits of screening (Guidelines for Preventative Activities in General Practice 8th edition, (2012) The Royal Australian College of General Practitioners).

2.2. Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the systematic review. The Medline search identified 654 citations, the Embase search 707 citations and the Web of Science search 9 citations resulting in a total of 1,370 citations. The search of the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment database identified no additional citations. Titles and abstracts were examined and 16 articles were retrieved for a more detailed evaluation. An additional 20 potential citations were identified from the reference list of retrieved articles.

Four models reported in 6 articles (two models with 2 publications each) met the inclusion criteria and were included in the review. There were no studies of ATSI men that met the inclusion criteria.

The retrieved articles that were not included and the reason for their exclusion are documented in Appendix C. The two main reasons for exclusion were that they did not compare different PSA screening protocols or examine screening for higher risk men, or did not incorporate ERSPC data for survival benefit.

Figure 1

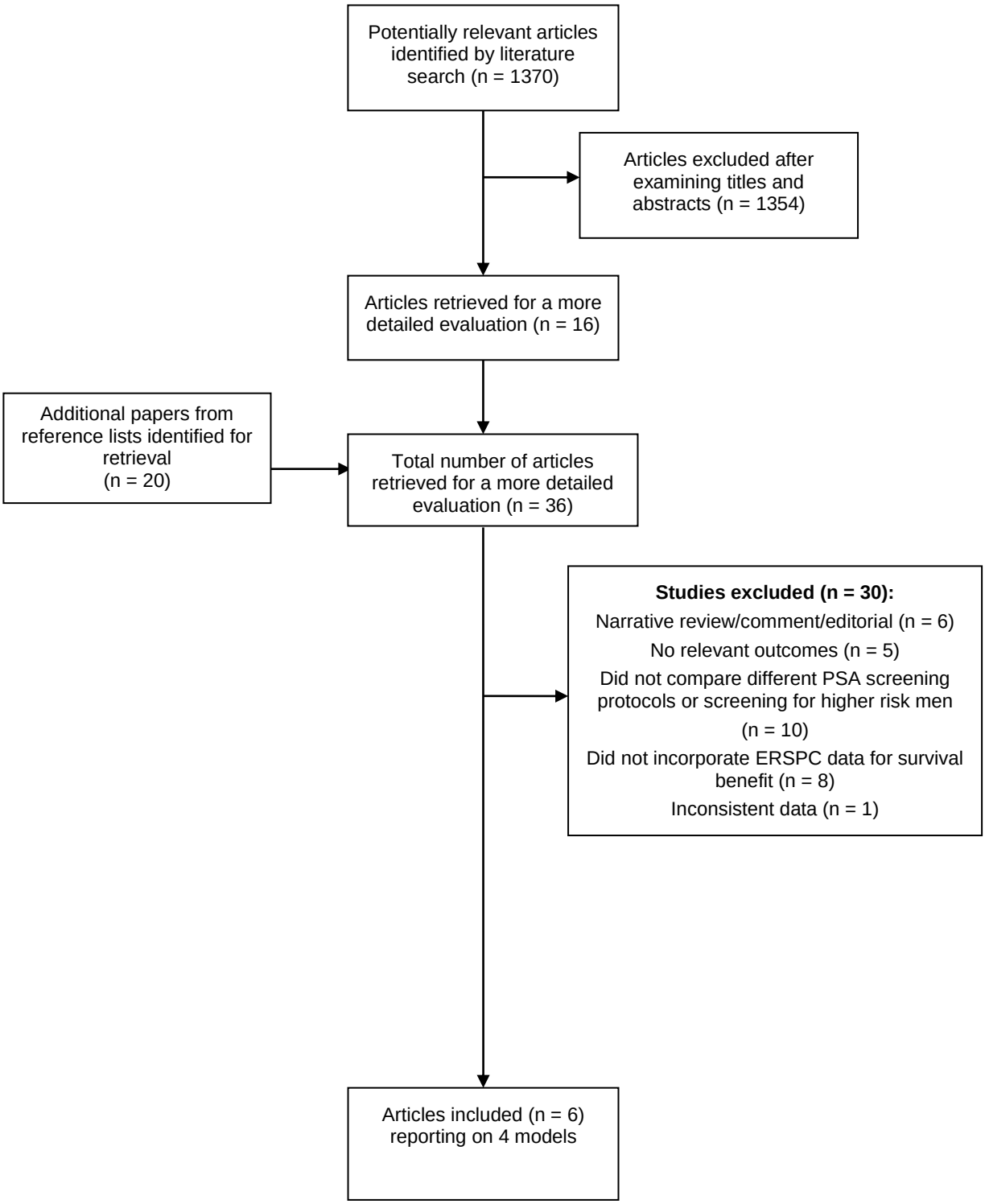


Figure 1. Process of inclusion and exclusion of studies

2.3. Study Characteristics

Characteristics of included studies are described in Tables 1 – 2.

Table 1: Characteristic of included studies and their state-transition models comparing different PSA screening protocols.

Model	FHCRC PSAPC micro-simulation model*	MISCAN micro-simulation semi-Markov model**
Included studies	Gulati 2013 Pataky 2014	Heijnsdijk 2009 Heijnsdijk 2012
Natural history model	**PSA level based state-transition model** *Incidence component* based on two parts: 1. PSA growth model • Pre-onset PSA dependent on age • Post-onset PSA dependent on age and grade 2. Disease progression model • Risk of disease onset dependant on age • Risk of metastatic disease and clinical diagnosis dependant on PSA levels *Mortality* component based on disease specific survival and other cause mortality • Disease-specific survival dependant on age, stage (local-regional or distant) and Gleason score (2 – 7 vs 8 – 10) at diagnosis and primary treatment in the case of local-regional cancers	**State-transition model** • 18 disease states defined by T stage, metastatic status and Gleason score • Disease onset dependent on age • In each state the cancer may progress, be screen-detected or be clinically diagnosed • Time spent in a stage and transition to another stage dependent on the current stage and in most cases age • Transition from local-regional to metastatic also dependent on Gleason score
Assumptions and inputs	**Incidence** PSA growth curves (pre- and post-onset) derived from PCPT and PLCO Biopsy compliance as in PLCO Assumed that: • biopsy sensitivity increased over time with uptake of extended biopsy (Eichler) from 53% in 1985 to 80% in 1990 (sextant) to 96% in 2000 (extended) • disease incidence remains at 1987 pre-PSA levels in absence of screening **Mortality – Stage shift model** Assumed that: • in the absence of screening or treatment age- and stage-	**Incidence** Assumed screening attendance 100% (Heijnsdijk 2009) and 80% (Heijnsdijk 2012) PSA test and subsequent biopsy modelled as a single test PSA test sensitivity dependent on stage and Gleason score (Heijnsdijk 2012) Screen positive biopsy rate calculated using predicted number of diagnoses and PPV value of 22.3% and 35.8% from screened and control arms of ERSPC (Heijnsdijk 2009) **Mortality – Cure model** Assumed that: • in the absence of screening or treatment age- and stage-specific

	specific survival remained at 1983-1986 levels for men in SEER 9 who did not receive curative treatment • screening detects local-regional disease that would have been diagnosed at a distant stage in absence of screening *Gulati 2013* assumed that: • effects of prostate cancer screening on prostate cancer survival corresponded to a **28% reduction in prostate cancer mortality after 11 years** using ERSPC protocol • survival benefit for radical prostatectomy or radiotherapy treatment for men with local-regional disease of 0.62 compared with conservative management on the basis of CaPSURE and SPCG-4 results *Pataky 2014* assumed that: • men detected at the earlier stage with screening have a prostate cancer mortality reduction consistent with ERSPC results • survival benefits for radical prostatectomy and radiotherapy with or without ADT and ADT alone for men with local-regional disease compared with conservative management those estimated by Etzioni 2012 on the basis of CaPSURE and SPCG-4 results *Gulati 2013* used initial treatment patterns by age, year, stage (M0 vs M1) and grade derived from SEER 9 2005 data *Pataky 2014* used initial treatment patterns derived from British Columbia data	survival remained at 1983-1986 levels for men in SEER 9 who did not receive curative treatment • a fraction of the screen detected local-regional cancers are cured because they are treated earlier • all men diagnosed with non-metastatic prostate cancer underwent prostatectomy, radiotherapy or active surveillance • all men with metastatic disease underwent palliative therapy which had no survival benefit • survival benefit for radical prostatectomy for men with local-regional disease of 0.65 compared with conservative management on the basis of SPCG-4 results and that radiotherapy provided the same benefit • conservative management resulted in baseline survival rates Survival of unscreened untreated men diagnosed with local-regional disease based on Gleason score and Albertsen 2004 data Survival of men with metastatic disease based on SEER data Included treatment rates for active surveillance within 7 years of diagnosis based on results of Klotz 2010 Initial treatment patterns for men with local-regional disease by age, stage and Gleason score based on ERSPC Rotterdam and Goteborg data (2000 – 2006)
Calibration	*Gulati 2013* The PSA growth model calibrated using serial PSA data from the control group of the PCPT Model prostate cancer incidence and risk of transition from one disease state to the next calibrated for USA population using age (50 – 84), year (1975 – 2000), stage (local-regional or distant) and grade (Gleason score 2 – 7 vs 8 – 10) specific incidence from SEER 9. Simulated PSA screening histories based on PSA testing data from SEER-Medicare database were used to account for opportunistic PSA testing from 1987 Baseline survival for unscreened and untreated patients calibrated using SEER 9 data in 1983 – 1986. *Pataky 2014* Natural history parameters estimated for the US model (Gulati 2013) were not changed. Appropriate adjustments (documented in the appendix) made to compensate for various factors.	*Heijnsdijk 2009* Model prostate cancer incidence and risk of transition from one disease state to the next calibrated for Dutch population using results of first 2 rounds of ERSPC Rotterdam trial age (55 – 74), age specific from 1991 in Netherlands Cancer Registry and stage distribution data from Rotterdam Cancer Registry 1992 – 1993 *Heijnsdijk 2012* Time spent in a stage, risk of transition from one disease stage to the next and stage-specific test sensitivities calibrated using results of ERSPC Rotterdam trial age (55 – 74) from 1994 to 2006 and ERSPC Goteborg up to 2004, incidence and stage distribution in the Netherlands from 1991 to 1993 incidence in Netherlands from 1992 to 2002, and incidence in Sweden in 1990 Cure rate for local-regional cancers detected earlier with screening calibrated to obtain a relative mortality reduction at 11 years follow-up with screening with 4 year intervals of 29% as observed in the ERSPC trial

External validation population	*Gulati 2013* Prostate cancer incidence component validated using data by stage for men aged 50 – 84 years in 2001 – 2005 in the USA (included all of the calibration population) Prostate cancer mortality component validated by simulating the ERSPC using screening protocol of 4 yearly screening with threshold of PSA > 3.0ng/mL for men aged 55 – 69 years after 11 years follow-up *Pataky 2014* Prostate cancer incidence component validated using incidence data from the British Columbia Cancer Registry for men aged 50 – 84 years from 1970 – 2005 Prostate cancer mortality component validated using prostate cancer mortality data for patients aged 50 – 84 years diagnosed since 1970 observed from the British Columbia Cancer Registry	*Heijnsdijk 2012* Model predicted prostate cancer mortality in the Dutch population in 1992 – 2002 compared with the observed counts.
Simulated population	*Gulati 2013* 100 million contemporary men in USA aged 40 years *Pataky 2014* Men in British Columbia aged 40 years in 2000 until age 90 or death	*Heijnsdijk 2009* 100,000 men with age distribution according to the European Standard Population 2003 *Heijnsdijk 2012* Men aged 0 – 100 years from 2010 – 2110 with age distribution according to the European Standard Population
Utility estimates for QALY	1.0 Healthy/screening 0.90 Long term treatment effects 0.88 Short term treatment effects 0.90 Untreated symptomatic disease 0.85 Distant disease 0.50 End of life	1.0 More than 10 years after prostatectomy or radiotherapy for local-regional disease 0.95 1 – 10 years after prostatectomy or radiotherapy for local-regional disease (does not take into account possible recent treatment improvements) 0.60 Receiving palliative therapy

ADT = androgen deprivation therapy; CaPSURE = Cancer of the Prostate Strategic Urologic Research Endeavor; ERSPC = European Randomized Study of Screening for Prostate Cancer; FHCRC = Fred Hutchinson Cancer Research Center; M0 = no metastatic disease; M1 = metastatic disease; NCHS = National Center for Health Statistics; PCPT = Prostate Cancer Prevention Trial; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; PPV = positive predictive value; PSAPC = PSA-Prostate Cancer; QALY = quality-adjusted life-years; SEER 9 = Surveillance, Epidemiology, and End Results – 9 areas; SPCG-4 = Scandinavian Prostate Cancer Group Study 4

* Details of FHCRC model extracted from previous publications regarding this model (Etzioni 2012, Gulati 2010 and 2012), as well as included studies Gulati 2013 and Pataky 2014.

** Details of MISCAN model extracted from previous publications regarding this model (Draisma 2003 and 2009, Wever 2011 and 2012), as well as included studies Heijnsdijk 2009 and 2012.

Table 2: Characteristics of included studies and their state-transition models comparing PSA screening vs no screening in populations with different risks of prostate cancer

Study - Model	Howard 2009 – Markov model	Martin 2012 – Decision model incorporating a Markov process
Natural history model	No model described	**State-transition model** • No prostate cancer, undetected asymptomatic prostate cancer, screen-detected prostate cancer and non-screen-detected prostate cancer – distinguishes between screen-detected and non-screen-detected cancers
Screening	Annual PSA screening commencing at age 40 years	Screening every 4 years from age 50 years with PSA threshold for biopsy of 4ng/mL
Assumptions and inputs	**Assumed:** • 100% screening in screening cohort • 0% screening in non-screening cohort • Underlying risk of prostate cancer continued to rise as per 1983 to 1988 • Proportions of men diagnosed with localised and non-localised disease similar in Australia and the Netherlands • Proportional increase with screening in incidence and decrease in prostate cancer mortality was consistent across risk groups • All men with positive test underwent biopsy • PSA test sensitivity and specificity the same for all risk categories • All men diagnosed accepted effective treatment • Screening and subsequent effective treatment conferred a mortality benefit • With screening there was no mortality benefit at 7 years and a mortality benefit of 0.8 at 9 years (ERSPC, Schroder 2009) • Mortality benefit declined linearly once screening stops **Incidence** based on: • Australian age-specific incidence rates from 1982 – 1988 for incidence for unscreened men • ERSPC data based on pre-1993 Dutch data for proportions of localised and non-localised cancers for unscreened men (Draisma 2003) • ERSPC data (Schroder 2009) – applied to incidence in unscreened men to calculate incidence in screened men • ERSPC screening round-specific proportions data for proportions of localised and non-localised cancers for screened men (Draisma 2003)	**Incidence** based on: • Incidence rates of screen-detected and non-screen-detected prostate cancer in ERSPC trial and age-adjusted using Australian age-specific incidence • PSA threshold of 4.0ng/mL having sensitivity of 44% and specificity of 92% based on nested case-control study within the Vasterbotten Intervention Project cohort, Umea, Sweden **Mortality** based on: • Prostate cancer mortality rates for screen-detected cancer and non-screen-detected cancer derived from risk profiles of men with prostate cancer in the ERSPC • Prognosis of men who have undergone prostatectomy (model by Eggener 2011) • Prognosis of men who have undergone conservative management (Albertsen 2005 data)

	applied to unscreened incidence • Annual age-specific incidence rates for unscreened men aged 40 – 59 years and ERSPC data for men aged 60 – 79 years used to estimate interval cancers **Mortality** based on: • Australian age-specific prostate cancer mortality rates in 2005 for prostate cancer mortality rates for unscreened men adjusted for age-specific proportion of men undergoing PSA test derived from 1995 Medicare data • ERSPC relative risk of prostate cancer mortality of 0.8 with screening (Schroder 2009) applied to rates for unscreened men to calculate prostate cancer mortality amongst screened men • ABS age-specific mortality data for all-cause mortality Proportions in risk categories based on Australian data (Staples 2003) Numbers of biopsies by age estimated from ERSPC data (PPV = 0.241, Schroder 2009)	
Calibration	Not reported	Prostate cancer mortality rates for screened and non-screened calibrated against results of ERSPC trial resulting in a relative risk of prostate cancer mortality for men with screen-detected prostate cancer of 0.87
External validation population	Not reported	Not reported
Simulated population	2 cohorts – one screen and one unscreened	1,000,000 men aged 50 years
Prostate cancer risk	Low: No first-degree relatives affected by prostate cancer 2.5 x low risk (one affected first-degree relative) 5 x low risk (two or more affected first-degree relatives) Derived from Staples 2003, Bruner 2003, Zeegers 2003 and expert opinion	Average: age-adjusted and based on men enrolled in ERSPC 2 x average risk 5 x average risk
Utility estimates for QALY	Not relevant – did not report QALY	0.95 After diagnosis and treatment 0.50 12 months prior to death from prostate cancer

ABS = Australian Bureau of Statistics; ERSPC = European Randomized Study of Screening for Prostate Cancer; QALY = quality-adjusted life-years

2.4. Study Quality

Methodological quality of included models is described in Tables 3 – 8.

Table 3: Domain 1. Specifications

Model	Framework			
	Structure	**Data sources/parameters**	**Calibration and/or Validation**	**Uncertainty/sensitivity analysis**
Fred Hutchinson	Strengths: Decision problem, target population, time-frame, discount rate for costs and benefits, currency and perspective clearly defined. Limitations: ICER threshold not specified.	Not relevant	Not relevant	Not relevant
MISCAN	Strengths: Decision problem, target population and time-frame clearly defined. Limitations: Discount rates not used and ICER threshold not specified.	Not relevant	Not relevant	Not relevant
Martin	Strengths: Decision problem, target population, discount rate for costs and benefits, currency and perspective clearly defined. Limitations: Not clear about the time frame and indicative ICER threshold not specified.	Not relevant	Not relevant	Not relevant
Howard	Strengths: Decision problem, target population and benefits clearly defined. Limitations: Discussion required on discounting benefits (no. of cases, deaths)	Not relevant	Not relevant	Not relevant

ICER = International Centre for Economic Research

Table 4: Domain 2. Natural history

	Framework			
Model	**Structure**	**Data sources/parameters**	**Calibration and/or Validation**	**Uncertainty/sensitivity analysis**
Fred Hutchinson	Strengths: PSA levels explicitly modelled, preclinical and clinical stages modelled, other cause mortality included. Limitations: No risk factors included, no recurrence of disease after treatment modelled.	Strengths: Data sources documented and the sources are relevant (Prostate Cancer Prevention Trial (PCPT) and Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial). Limitations: None.	Strengths: Data sources clearly defined and carefully considered. Independent validation performed. Limitations: Although predictive validation was not performed, this is not considered as a major limitation.	Strengths: Multi-way sensitivity analysis performed on unobservable natural history parameters. Limitations: One-way sensitivity analysis was not performed.
MISCAN	Strengths: Preclinical and clinical stages modelled and other cause mortality included. Limitations: No risk factors included, no recurrence of disease after treatment modelled.	Strengths: Data sources documented and the sources are relevant (Rotterdam section of the European Randomised study of Screening for Prostate Cancer [ERSPC]). Limitations: None.	Strengths: Data sources clearly defined and carefully considered. Independent validation performed Limitations: Although predictive validation was not performed, this is not considered as a major limitation.	Strengths: None Limitations: No sensitivity analysis performed on natural history parameters.
Martin	Strengths: Preclinical and clinical stages modelled and other cause mortality included. Limitations: Natural history does not include stage of disease and Gleason score.	Strengths: Data sources documented and the sources are relevant. Limitations: None.	Strengths: None. Limitations: No calibration or validation performed.	Strengths: One-way sensitivity analysis performed on the rates of developing non-screen detected and screen-detectable prostate cancer. Limitations: No sensitivity analysis performed on the rates of symptomatic detection of prostate cancer.
Howard	Strengths: Preclinical and clinical stages modelled and other cause mortality included. Risk based on family history modelled. Limitations: Natural history does not include stage of disease and Gleason score.	Strengths: Data sources documented and the sources are relevant. Limitations: None.	Strengths: None. Limitations: No calibration or validation performed.	Strengths: None. Limitations: No sensitivity analysis performed.

Table 5: Domain 3. Screening/triage recommendations & behaviours

	Framework			
Model	**Structure**	**Data sources/parameters†**	**Calibration and/or Validation†**	**Uncertainty/sensitivity analysis**
Fred Hutchinson	Strengths: Different screening age and intervals modelled. Limitations: Although unsatisfactory test results were not modelled, this is not considered as a major limitation.	Strengths: None. Limitations: Realistic screening behaviour was not modelled.	Strengths: None Limitations: Calibration and validation of screening behaviour was not performed.	Strengths: None Limitations: No sensitivity analysis performed on screening compliance assumptions.
MISCAN	Strengths: Different screening age and intervals modelled. Limitations: Although unsatisfactory test results were not modelled, this is not considered as a major limitation.	Strengths: None. Limitations: Realistic screening behaviour was not modelled.	Strengths: None Limitations: Not clear whether calibration and/or validation of screening behaviour was performed.	Strengths: One-way sensitivity analysis was performed on screening attendance. Limitations: No multi-way sensitivity analysis performed on screening compliance assumptions.
Martin	Strengths: One screening interval modelled. Limitations: Screening age range (age at starting and stopping screening) not specified.	Not relevant	Strengths: None Limitations: Calibration and/or validation of screening behaviour was not performed.	Strengths: None Limitations: No sensitivity analysis performed on screening compliance assumptions.
Howard	Strengths: Screening age and interval modelled. Limitations: Although realistic assumption on screening behaviour not modelled, this is not considered as a major limitation given the study aim (decision making at individual level).	Not relevant	Strengths: None Limitations: Calibration and/or validation of screening behaviour was not performed.	Strengths: None Limitations: No sensitivity analysis performed on screening compliance assumptions.

†If a model did not incorporate the relevant structure, quality assessment against data sources/parameters and calibration and/or validation framework was classified as not relevant.

Table 6: Domain 4. Diagnostic pathways

	Framework			
Model	**Structure**	**Data sources/parameters†**	**Calibration and/or Validation**	**Uncertainty/sensitivity analysis**
Fred Hutchinson	Strengths: Different management for abnormal results by age and PSA level. Test (biopsy) characteristics well specified. Limitations: Details on active surveillance not clearly defined.	Strengths: Biopsy compliance and test characteristics from PLCO and systematic review, respectively. Limitations: Not relevant.	Strengths: Data sources clearly defined and carefully considered. Limitations: Independent validation not performed. Although predictive validation was not performed, this is not considered as a major limitation.	Strengths: None Limitations: No sensitivity analysis performed on biopsy compliance rates and test characteristics.
MISCAN	Strengths: Different management for abnormal results by age. Test (PSA test and biopsy combined) characteristics well specified. Limitations: Details on active surveillance not clearly defined.	Strengths: Test characteristics from the ERSPC. Limitations: Not relevant.	Strengths: None. Limitations: Calibration and/or validation not performed.	Strengths: None Limitations: No sensitivity analysis performed on biopsy compliance rates and test characteristics.
Martin	Strengths: PSA test sensitivity and specificity were specified. Limitations: Biopsy sensitivity not modelled. Management of abnormal test results not specified.	Strengths: PSA test characteristics obtained from a relevant source. Limitations: Not relevant.	Strengths: None. Limitations: Calibration and/or validation not performed.	Strengths: One-way sensitivity performed on PSA test sensitivity. Limitations: Sensitivity analysis not performed on biopsy sensitivity.
Howard	Strengths: PSA test positivity was specified. Limitations: Biopsy sensitivity not modelled. Management of abnormal test results not specified.	Strengths: PSA test characteristics obtained from a relevant source. Limitations: Not relevant.	Strengths: None. Limitations: Calibration and/or validation not performed.	Strengths: None Limitations: No sensitivity analysis performed on test characteristics.

†If a model did not incorporate the relevant structure, quality assessment against data sources/parameters and calibration and/or validation framework was classified as not relevant.

ERSPC = European Randomized Study of Screening for Prostate Cancer; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

Table 7: Domain 5. Invasive cancer (survival, treatment)

Model	Framework			
	Structure	**Data sources/parameters**	**Calibration and/or Validation**	**Uncertainty/sensitivity analysis**
Fred Hutchinson	Strengths: Age, stage, Gleason score and treatment (loco-regional cancers) specific survival. Limitations: None.	Strengths: Data sources documented and the sources are relevant (SEER) Limitations: None	Strengths: Data sources clearly defined and carefully considered. Limitations: Although predictive validation was not performed, this is not considered as a major limitation.	Strengths: Effect of screening impact on mortality reduction. Limitations: Not clear what sensitivity analysis method was used (one-way vs multi-way).
MISCAN	Strengths: Age, stage, Gleason score and treatment (loco-regional cancers) specific survival. Limitations: None.	Strengths: Data sources documented and the sources are relevant (SEER, longitudinal study) Limitations: None	Strengths: Data sources clearly defined and carefully considered. Limitations: Although predictive validation was not performed, this is not considered as a major limitation.	Strengths: None Limitations: No sensitivity analysis performed on survival parameters.
Martin	Strengths: None, although death from other causes modelled. Limitations: Age, stage, Gleason score and treatment specific survival not modelled.	Strengths: None. Limitations: Age, stage, Gleason score and treatment specific survival not modelled.	Strengths: Mortality was calibrated to the ERSPC data. Limitations: Validation not performed.	Strengths: One-way sensitivity analysis performed on annual rates of prostate cancer mortality. Limitations: No multi-way sensitivity analysis performed.
Howard	Strengths: None, although death from other causes modelled. Limitations: Age, stage, Gleason score and treatment specific survival not modelled.	Strengths: None. Limitations: Age, stage, Gleason score and treatment specific survival not modelled.	Strengths: None. Limitations: Calibration and/or validation not performed.	Strengths: One-way sensitivity analysis was performed on the RR of mortality reduction. Limitations: No multi-way sensitivity analysis performed.

ERSPC = European Randomized Study of Screening for Prostate Cancer; RR = risk ratio; SEER = Surveillance, Epidemiology, and End Results

Table 8: Domain 6. Costs

Model	Framework			
	Structure†	**Data sources/parameters†**	**Calibration and/or Validation‡**	**Uncertainty/sensitivity analysis†**
Fred Hutchinson	Strengths: Appropriate for perspective chosen. Unit costs used and all relevant costs captured. Limitations: None.	Strengths: Cost data obtained from appropriate sources. Limitations: None.	Not relevant	Strengths: Sensitivity analysis was performed on screening and treatment costs, and discount rate. Limitations: Not clear what sensitivity analysis method was used (one-way vs multi-way).
MISCAN	Strengths: Appropriate for perspective chosen. Unit costs used and all relevant costs captured. Limitations: Costs not discounted.	Strengths: Cost data obtained from appropriate sources. Limitations: None.	Not relevant	Strengths: None. Limitations: No sensitivity analysis performed.
Martin	Strengths: Appropriate for perspective chosen. Unit costs used and all relevant costs captured. Limitations: None.	Strengths: Cost data obtained from appropriate sources. Limitations: None.	Not relevant	Strengths: Sensitivity analysis was performed on screening and treatment costs. Limitations: No sensitivity analysis on discount rate. No multi-way sensitivity analysis performed.
Howard	Not relevant	Not relevant	Not relevant	Not relevant

†If a model specification did not consider costs, quality assessment against structure, data sources/parameters and calibration and/or validation framework was classified as not relevant.

‡Costs are not part of calibration and/or validation exercise.

2.5. Study Results

Benefits (lives saved) and harms

Comparison of different PSA screening protocols:

- Benefits **(lives saved)** and harms (Table 9)
- Benefits (**decreased metastatic disease at diagnosis**) and harms (Table 10)

Comparison of PSA screening vs no screening for higher risk men:

- Benefits **(lives saved)** and harms (Table 11)

Table 9: Comparison of different PSA screening protocols; benefits **(lives saved)** and harms

Fred Hutchinson Cancer Research Centre model												
Gulati 2013	*Lifetime probability (%) for contemporary men aged 40 years or more in the USA*											
Criteria for biopsy referral	Screening interval	≥1 FP	Over-diagnosis	Lives saved	Mean time of life saved	NND	Life years gained[#] (discounted)	Quality adjusted life years gained[#] (discounted)	Difference % FP*	Difference % over-diagnosis*	Difference % life saved*	Difference NND*
*Screening age **50 – 69** years*												
PSA >2.5ng/mL	2 years	23	2	0.49	0.7	4.12	NR	NR	Reference			
PSA >2.5ng/mL	Annual	27	2.9	0.61	0.82	4.75	NR	NR	4	0.9	0.12	0.63
PSA >4.0ng/mL	2 years	14	1.3	0.41	0.61	3.11	NR	NR	-9	-0.7	-0.08	-1.01
PSA >4.0ng/mL	Annual	17	1.8	0.51	0.73	3.58	NR	NR	-6	-0.2	0.02	-0.54
PSA >4.0ng/mL or vPSA >0.35ng/mL per year	2 years	20	1.8	0.47	0.67	3.85	NR	NR	-3	-0.2	-0.02	-0.27
PSA >4.0ng/mL or vPSA >0.35ng/mL per year	Annual	40	3.7	0.65	0.85	5.67	NR	NR	17	1.7	0.16	1.55
PSA >95th percentile for age	Annual	14	1.5	0.48	0.71	3.2	NR	NR	-9	-0.5	-0.01	-0.92
*Screening age **40 – 69** years*												
PSA >2.5ng/mL	2 years	24	2.2	0.52	0.72	4.2	NR	NR	1	0.2	0.03	0.08
PSA >2.5ng/mL	Annual	27	3.1	0.63	0.84	4.85	NR	NR	4	1.1	0.14	0.73
PSA >4.0ng/mL	2 years	15	1.4	0.43	0.64	3.18	NR	NR	-8	-0.6	-0.06	-0.94
PSA >4.0ng/mL	Annual	17	2	0.54	0.75	3.66	NR	NR	-6	0	0.05	-0.46
PSA >4.0ng/mL or vPSA >0.35ng/mL per year	2 years	21	1.9	0.5	0.71	3.9	NR	NR	-2	-0.1	0.01	-0.22
PSA >4.0ng/mL or vPSA >0.35ng/mL per year	Annual	41	3.9	0.67	0.89	5.77	NR	NR	18	1.9	0.18	1.65
PSA >95th percentile for age**	2 years	13	1.3	0.42	0.63	2.99	NR	NR	-10	-0.7	-0.07	-1.13

PSA >95th percentile for age**	Annual	15	1.7	0.51	0.73	3.29	NR	NR	-8	-0.3	0.02	-0.83
*Screening age **50 – 74** years*												
PSA >2.5ng/mL	2 years	29	3.8	0.69	0.84	5.51	NR	NR	6	1.8	0.2	1.39
PSA >2.5ng/mL	Annual	31	4.7	0.78	0.94	6.01	NR	NR	8	2.7	0.29	1.89
PSA >4.0ng/mL	2 years	20	2.7	0.61	0.77	4.34	NR	NR	-3	0.7	0.12	0.22
PSA >4.0ng/mL	Annual	21	3.3	0.7	0.86	4.7	NR	NR	-2	1.3	0.21	0.58
PSA >4.0ng/mL	Annual (2 years if PSA level <2.5ng/mL)	21	3.3	0.7	0.86	4.7	NR	NR	-2	1.3	0.21	0.58
PSA >4.0ng/mL or vPSA >0.35ng/mL per year	2 years	26	3.4	0.67	0.82	5.07	NR	NR	3	1.4	0.18	0.95
PSA >4.0ng/mL or vPSA >0.35ng/mL per year	Annual	44	5.5	0.81	0.96	6.84	NR	NR	21	3.5	0.32	2.72
PSA >95th percentile for age**	2 years	14	1.7	0.51	0.7	3.32	NR	NR	-9	-0.3	0.02	-0.8
PSA >95th percentile for age**	Annual	15	2.3	0.61	0.81	3.71	NR	NR	-8	0.3	0.12	-0.41
*Screening age **40 – 74** years*												
PSA >2.5ng/mL	2 years	29	4	0.71	0.85	5.58	NR	NR	6	2	0.22	1.46
PSA >2.5ng/mL	Annual	32	4.9	0.81	0.96	6.08	NR	NR	9	2.9	0.32	1.96
PSA >2.5ng/mL or vPSA >0.35ng/mL per year	Annual (5 years if age<50yrs and PSA level <1ng/mL)	44	6	0.85	1	7.08	NR	NR	21	4	0.36	2.96
PSA >4.0ng/mL	2 years	20	2.8	0.64	0.78	4.42	NR	NR	-3	0.8	0.15	0.3
PSA >4.0ng/mL	Annual	22	3.5	0.72	0.88	4.79	NR	NR	-1	1.5	0.23	0.67
PSA >4.0ng/mL or vPSA >0.35ng/mL per year	2 years	26	3.6	0.69	0.84	5.13	NR	NR	3	1.6	0.2	1.01
PSA >4.0ng/mL or vPSA >0.35ng/mL per year	Annual	45	5.8	0.84	1	6.9	NR	NR	22	3.8	0.35	2.78

PSA >95th percentile for age**	2 years	14	1.8	0.54	0.73	3.39	NR	NR	-9	-0.2	0.05	-0.73
PSA >95th percentile for age**	Annual	16	2.4	0.64	0.83	3.78	NR	NR	-7	0.4	0.15	-0.34
*Screening age **45 – 74** years*												
PSA >4.0ng/mL	2 years (5 years if PSA level < median for age)	19	2.4	0.58	0.75	4.09	NR	NR	-4	0.4	0.09	-0.03
Pataky 2014	*Counts per 100 men for British Columbian men aged 40+ years in 2000 until age 90 or death*											
*Screening age **55 – 69** years*												
PSA ≥3.0ng/mL^^	4 years	15.5	1.1	0.37	NR	2.99	4.1 (1.17)	- 0.19 (-0.43)	Reference			
*Screening age **50 – 69** years*												
PSA ≥3.0ng/mL^^	2 years	19.1	2.1	0.55	NR	3.79	5.9 (1.66)	-0.95 (-0.93)	3.6	1	0.18	0.8
*Screening age **55 – 74** years*												
PSA ≥3.0ng/mL^^	2 years	21.7	2.9	0.64	NR	4.57	6.2 (1.70)	-1.32 (-1.05)	6.2	1.8	0.27	1.58
*Screening age **50 – 74** years*												
PSA ≥3.0ng/mL^^	4 years	21.8	2.5	0.55	NR	4.57	5.4 (1.48)	-0.33 (-0.60)	6.3	1.4	0.18	1.58
PSA ≥3.0ng/mL^^	2 years	22.5	3.2	0.68	NR	4.71	6.6 (1.84)	-1.11 (-1.04)	7	2.1	0.31	1.72
PSA ≥3.0ng/mL^^	2 years if PSA > median for age 4 years if PSA ≤ median for age	22.5	3.2	0.68	NR	4.73	6.6 (1.84)	-1.11 (-1.04)	7	2.1	0.31	1.74
PSA ≥3.0ng/mL up to age 69 years and PSA ≥4.0ng/mL for men aged ≥ 70 years^^	4 years	15	1.4	0.44	NR	3.28	4.7 (1.34)	0.23 (-0.40)	-0.5	0.3	0.07	0.29
PSA ≥3.0ng/mL up to age 69 years and PSA ≥4.0ng/mL for men aged ≥ 70 years^^	2 years	17.4	2.3	0.6	NR	3.86	6.2 (1.72)	-0.25 (-0.67)	1.9	1.2	0.23	0.87
*Screening age **60 – 74** years*												
PSA ≥3.0ng/mL^^	2 years	22.1	3.2	0.63	NR	4.97	5.7 (1.51)	-1.42 (-1.03)	6.6	2.1	0.26	1.98
*Screening age **40 – 74** years*												
PSA ≥3.0ng/mL^^	2 years	22.8	3.4	0.7	NR	4.86	6.7 (1.87)	-0.81 (-0.96)	7.3	2.3	0.33	1.87
*Screening age **50** years*												

PSA ≥3.0ng/mL^^	Single screen	0.2	0.008	0.01	NR	0.68	0.2 (0.09)	-0.06 (-0.05)	-15.3	-1.1	-0.36	-2.31
*Screening age **60** years*												
PSA ≥3.0ng/mL^^	PSA ≤ median single screen PSA > median second screen at age 65 years	11.8	0.6	0.25	NR	2.62	2.7 (0.77)	0.16 (-0.26)	-3.7	-0.5	-0.12	-0.37
PSA ≥3.0ng/mL^^	Single screen	6.9	0.2	0.12	NR	1.95	1.5 (0.45)	0.02 (-0.15)	-8.6	-0.9	-0.25	-1.04
*Screening age **70** years*												
PSA ≥3.0ng/mL^^	Single screen	15.3	0.9	0.18	NR	5.09	1.4 (0.34)	-0.12 (-0.12)	-0.2	-0.2	-0.19	2.1
MISCAN model												
Heijnsdijk 2012	*Counts per 100 men over the life time of men aged 0 – 100 years with distribution according to the European Standard Population over period 2010 – 2110*											
*Screening age **55 – 69** years*												
Not specified^	4 years	36.7	2.9	0.6	NR	5	5.2	4.1	Reference			
Not specified^	1 year	44.8	4.5	0.9	NR	5	7.3	5.6	8.1	1.6	0.3	0
*Screening age **55 – 74** years*												
Not specified^	1 year	57.3	7.2	1.1	NR	7	8.2	5.6	20.6	4.3	0.5	2
*Screening age **55** years*												
Not specified^	Single screen	21.9	0.2	0.1	NR	2	1.2	1.2	-14.8	-2.7	-0.5	-3
*Screening age **60** years*												
Not specified^	Single screen	25.3	0.8	0.2	NR	4	2.2	1.9	-11.4	-2.1	-0.4	-1
*Screening age **65** years*												
Not specified^	Single screen	30.3	1.9	0.3	NR	6	2.5	1.7	-6.4	-1	-0.3	1

FP = false positive; NND = additional number needed to detect to prevent one prostate cancer death; NR = not reported; vPSA = PSA velocity

* Difference from reference protocol calculated by systematic review team from published data

**95th percentiles were 2.5, 3.5, 4.5 and 6.5ng/mL for ages 40 – 49, 50 – 59, 60 – 69 and 70 – 74 years, respectively

^^ Assumed PSA threshold of 3.0 = PSA ≥3.0ng/mL (ERSPC) and PSA threshold of 4.0 = PSA ≥4.0ng/mL

Base case undiscounted

^ Stage (clinical T stage and Gleason score) specific test sensitivities

Table 10: Comparison of different PSA screening protocols; benefits (**decreased metastatic disease at diagnosis**) and harms

MISCAN model					
Heijnsdijk 2009	*Counts per 100 men with age distribution according to the European Standard Population over period 2008 – 2033*				
Criteria for biopsy referral	Screening interval	FP*	Reduction in metastatic disease at diagnosis *	Difference FP*	Difference metastatic disease at diagnosis reduction*
*Screening age **55 – 70** years*					
PSA ≥3.0ng/mL	4 years	15.0	0.21	Reference	
PSA ≥3.0ng/mL	2 years	18.1	0.26	3.1	0.05
PSA ≥3.0ng/mL	1 year	18.6	0.27	3.6	0.06
*Screening age **55 – 75** years*					
PSA ≥3.0ng/mL	4 years	23.0	0.30	8.0	0.09

FP = false positive

* Calculated by systematic review team from published data

Table 11: Comparison of PSA screening vs no screening in populations with different risks of prostate cancer: benefits **(lives saved)** and harms

Screening protocol	Risk	FP due to PSA testing	% interval cancers in screening arm	Additional cancers detected due to PSA testing*	Prostate cancer mortality		Prostate cancer deaths prevented by screening *	NND**	Quality adjusted life years gained – discounted*
					Screened	Non-screened			
Martin 2013 *Lifelong counts per 1,000 Australian men*									
PSA test from age **50 years** every **four years** with biopsy at 4.0ng/mL	Average	580	33.1	79.08	37.55	45.35	7.8	10.1	7.40
	2 x average	510	33.4	116.15	65.83	82.16	16.33	7.1	22.74
	5 x average	370	34.1	120.41	117.63	163.38	45.75	2.6	90.14
Howard 2009 *Counts per 1,000 Australian men aged 40 – 69 years (FPs and diagnoses) and from age 40 – 85 years (prostate cancer mortality)*									
PSA test from age **40 – 69 years annually** with test positivity estimated from ERSPC	Low	104.2	NR	35.0	27.9	29.9	2.0	17.5	NR
	2.5 x low	255.3	NR	85.2	67.6	72.3	4.7	18.1	NR
	5.0 x low	494.4	NR	163.1	128.5	137.1	8.6	19.0	NR
Counts per 1,000 Australian men aged 40 – 49 years (FPs and diagnoses) and from age 40 – 85 years (prostate cancer mortality)									
PSA test from age **40 – 49 years annually** with test positivity estimated from ERSPC	Low	0.9	NR	0.3	27.9	29.9	2.0	NR	NR
	2.5 x low	2.3	NR	0.7	67.6	72.3	4.7	NR	NR
	5.0 x low	4.6	NR	1.5	128.5	137.1	8.6	NR	NR
Counts per 1,000 Australian men aged 50 – 59 years (FPs and diagnoses) and from age 50 – 85 years (prostate cancer mortality)									
PSA test from age **50 – 59 years annually** with test positivity estimated from ERSPC for men previously tested from age 40	Low	16.4	NR	5.2	28.4	30.5	2.1	NR	NR
	2.5 x low	40.7	NR	13.0	68.9	73.7	4.8	NR	NR
	5.0 x low	80.8	NR	25.5	131.1	139.9	8.8	NR	NR
Counts per 1,000 Australian men aged 60 – 69 years (FPs and diagnoses) and from age 60 – 85 years (prostate cancer mortality)									
PSA test from age **60 – 69 years**	Low	16.4	NR	29.5	29.3	31.3	2.0	NR	NR

annually with test positivity estimated from ERSPC for men previously tested from age 40	2.5 x low	40.7	NR	71.5	71.0	75.8	4.8	NR	NR
	5.0 x low	80.8	NR	136.1	135.1	143.9	8.8	NR	NR
Counts per 1,000 Australian men aged 70 – 79 years (FPs and diagnoses) and from age 70 – 85 years (prostate cancer mortality)									
PSA test from age **40 – 79 years annually** with test positivity estimated from ERSPC	Low	211.4	NR	33.8	26.2	31.6	5.4	NR	NR
	2.5 x low	500.5	NR	79.3	63.7	76.5	12.8	NR	NR
Subgroup of men undergoing PSA testing from age 70 – 79 years	5.0 x low	916.3	NR	142.7	122.3	145.5	23.2	NR	NR

FP = false positive; ERSPC = European Randomized Study for Screening of Prostate Cancer; NND = additional number needed to detect to prevent one prostate cancer death; NR = not reported;

* Calculated by systematic review team from published data

** Number of extra diagnoses due to screening/number of prostate cancer deaths prevented

2.6. Body of Evidence

Levels of evidence: Modelling studies are not covered by the NHMRC Evidence Hierarchy. As a result, levels of evidence cannot be ascribed to modelling studies. The published methodology for each model is described in Tables 1 – 2 model characteristics.

Quality assessment: The quality of the models was assessed using a recently developed tool that assessed the models (structure and data sources/parameters) and their application (calibration and/or validation, uncertainty/sensitivity) over 6 domains (Tables 3 **–** 8). Currently this tool does not have a system assessing the overall risk of bias of a model and as a result it was not possible to rate the overall risk of bias or study quality. The strengths and limitations of each of the models and their applicability to the Australian context are discussed in the content template.

Clinical significance of size of effects are addressed in the assessment of clinical impact in the NHMRC evidence statement form

Relevance of evidence = 1 Please see Appendix B - Evidence of an effect on patient-relevant clinical outcomes including benefits and harms, quality of life and survival.

I Different Protocols

Table 12: Modelled outcomes of a range of PSA testing protocols sorted in order by probability of death from prostate cancer prevented reported by **Heijnsdijk et al 2012**

Protocol specifications				Outcomes					
No.	PSA testing age range	Criteria for biopsy referral	Interval between PSA tests	Probability of ≥1 FP %	Probability of over-diagnosis %	Probability that prostate cancer death is prevented %	Mean months of life gained per man tested	NND	Mean months of life gained per man diagnosed
1	55 **–** 74	~3ng/mL	1 year	57.3	7.2	1.10	0.98[2]	7	12.8
2	55 **–** 69	~3ng/mL	1 year	44.8	4.5	0.90	0.88[2]	5	19.5
28 ~ERSPC protocol	55 **–** 69	~3ng/mL	4 years	36.7	2.9	0.60	0.62[2]	5	20.8

˜ Approximate

[2] Estimated by the review team using the following approach: life years gained (undiscounted) per 100 men tested multiplied by 12 and divided by 100.

ERSPC = European Randomized Study of Screening for Prostate Cancer; FP = false positive; NND = additional number needed to detect to prevent one prostate cancer death

Mean months of life gained per man diagnosed = Mean months of life gained per man whose death from prostate cancer was prevented by testing divided by the NND (calculated as mean months of life gained per man tested divided by probability that prostate cancer death is prevented % multiplied by 100 and the result divided by the NND).

Table 13: Modelled outcomes of a range of PSA testing protocols sorted in order by probability of death from prostate cancer prevented reported by **Pataky et al 2014**

Protocol specifications				Outcomes					
No.	PSA testing age range	Criteria for biopsy referral	Interval between PSA tests	Probability of ≥1 FP %	Probability of over-diagnosis %	Probability that prostate cancer death is prevented %	Mean months of life gained per man tested	NND	Mean months of life gained per man diagnosed
10	40 – 74	PSA ≥3.0ng/mL	2 years	22.8	3.4	0.70	0.81[2]	4.86	23.8
15	50 – 74	PSA ≥3.0ng/mL	2 years	22.5	3.2	0.68	0.80[2]	4.71	25.0
16	50 – 74	PSA ≥3.0ng/mL	2 years if PSA > median for age; 4 years if PSA < median for age	22.5	3.2	0.68	0.80[2]	4.73	24.9
20	55 – 74	PSA ≥3.0ng/mL	2 years	21.7	2.9	0.64	0.74[2]	4.57	25.3
23	60 – 74	PSA ≥3.0ng/mL	2 years	22.1	3.2	0.63	0.69[2]	4.97	22.0
29	50 – 74	PSA ≥3.0ng/mL up to age 69 years and PSA ≥4.0ng/mL for men aged ≥ 70 years	2 years	17.4	2.3	0.60	0.74[2]	3.86	32.0
31	50 – 74	PSA ≥3.0ng/mL	4 years	21.8	2.5	0.55	0.64[2]	4.57	25.5
32 Goteborg protocol	50 – 69	PSA ≥3.0ng/mL	2 years	19.1	2.1	0.55	0.71[2]	3.79	34.1
43	50 – 74	PSA ≥3.0ng/mL up to age 69 years and PSA ≥4.0ng/mL for men aged ≥ 70 years	4 years	15	1.4	0.44	0.57[2]	3.28	39.5
47	55 – 69	PSA ≥3.0ng/mL	4 years	15.5	1.1	0.37	0.49[2]	2.99	44.3

[2] Estimated by the review team using the following approach: life years gained (undiscounted) per 100 men tested multiplied by 12 and divided by 100.

FP = false positive; NND = additional number needed to detect to prevent one prostate cancer death

Mean months of life gained per man diagnosed = Mean months of life gained per man whose death from prostate cancer was prevented by testing divided by the NND (calculated as mean months of life gained per man tested divided by probability that prostate cancer death is prevented % multiplied by 100 and the result divided by the NND).

Table 14: Modelled outcomes of a range of PSA testing protocols sorted in order by probability of death from prostate cancer prevented reported by **Gulati et al 2013**

Protocol specifications				Outcomes[1]					
No.	PSA testing age range	Criteria for biopsy referral	Interval between PSA tests	Probability of ≥1 FP %	Probability of over-diagnosis %	Probability that prostate cancer death is prevented %	Mean months of life gained per man tested	NND	Mean months of life gained per man diagnosed
3	40 – 74	PSA >2.5ng/mL or vPSA >0.35ng/mL per year	Annual (5 years if age<50yrs and PSA level <1ng/mL)	44	6	0.85	1.00	7.08	16.6
4	40 – 74	PSA >4.0ng/mL or vPSA >0.35ng/mL per year	Annual	45	5.8	0.84	1.00	6.90	17.3
5	50 – 74	PSA >4.0ng/mL or vPSA >0.35ng/mL per year	Annual	44	5.5	0.81	0.96	6.84	17.3
6	40 – 74	PSA >2.5ng/mL	Annual	32	4.9	0.81	0.96	6.08	19.5
7	50 – 74	PSA >2.5ng/mL	Annual	31	4.7	0.78	0.94	6.01	20.1
8	40 – 74	PSA >4.0ng/mL	Annual	22	3.5	0.72	0.88	4.79	25.5
9	40 – 74	PSA >2.5ng/mL	2 years	29	4	0.71	0.85	5.58	21.5
11	50 – 74	PSA >4.0ng/mL	Annual	21	3.3	0.70	0.86	4.70	26.1
12	50 – 74	PSA >4.0ng/mL	Annual (2 years if PSA level <2.5ng/mL)	21	3.3	0.70	0.86	4.70	26.1
13	50 – 74	PSA >2.5ng/mL	2 years	29	3.8	0.69	0.84	5.51	22.1
14	40 – 74	PSA >4.0ng/mL or vPSA >0.35ng/mL per year	2 years	26	3.6	0.69	0.84	5.13	23.7

17	40 – 69	PSA >4.0ng/mL or vPSA >0.35ng/mL per year	Annual	41	3.9	0.67	0.89	5.77	23.0
18	50 – 74	PSA >4.0ng/mL or vPSA >0.35ng/mL per year	2 years	26	3.4	0.67	0.82	5.07	24.1
19	50 – 69	PSA >4.0ng/mL or vPSA >0.35ng/mL per year	Annual	40	3.7	0.65	0.85	5.67	23.1
21	40 – 74	PSA >4.0ng/mL	2 years	20	2.8	0.64	0.78	4.42	27.6
22	40 – 74	PSA >95th percentile for age[3]	Annual	16	2.4	0.64	0.83	3.78	34.3
24	40 – 69	PSA >2.5ng/mL	Annual	27	3.1	0.63	0.84	4.85	27.5
25	50 – 69	PSA >2.5ng/mL	Annual	27	2.9	0.61	0.82	4.75	28.3
26	50 – 74	PSA >4.0ng/mL	2 years	20	2.7	0.61	0.77	4.34	29.1
27	50 – 74	PSA >95th percentile for age[3]	Annual	15	2.3	0.61	0.81	3.71	35.8
30	45 – 74	PSA >4.0ng/mL	2 years (5 years if PSA level < median for age)	19	2.4	0.58	0.75	4.09	31.6
33	40 – 69	PSA >4.0ng/mL	Annual	17	2	0.54	0.75	3.66	37.9
34	40 – 74	PSA >95th percentile for age[3]	2 years	14	1.8	0.54	0.73	3.39	39.9
35	40 – 69	PSA >2.5ng/mL	2 years	24	2.2	0.52	0.72	4.20	33.0
36	50 – 69	PSA >4.0ng/mL	Annual	17	1.8	0.51	0.73	3.58	40.0
37	40 – 69	PSA >95th percentile for age[3]	Annual	15	1.7	0.51	0.73	3.29	43.5
38	50 – 74	PSA >95th percentile for age[3]	2 years	14	1.7	0.51	0.70	3.32	41.3

39	40 – 69	PSA >4.0ng/mL or vPSA >0.35ng/mL per year	2 years	21	1.9	0.50	0.71	3.90	36.4
40 ~Goteborg protocol	50 – 69	PSA >2.5ng/mL	2 years	23	2	0.49	0.70	4.12	34.7
41	50 – 69	PSA >95th percentile for age[3]	Annual	14	1.5	0.48	0.71	3.20	46.2
42	50 – 69	PSA >4.0ng/mL or vPSA >0.35ng/mL per year	2 years	20	1.8	0.47	0.67	3.85	37.0
44	40 – 69	PSA >4.0ng/mL	2 years	15	1.4	0.43	0.64	3.18	46.8
45	40 – 69	PSA >95th percentile for age[3]	2 years	13	1.3	0.42	0.63	2.99	50.2
46	50 – 69	PSA >4.0ng/mL	2 years	14	1.3	0.41	0.61	3.11	47.8

˜ Approximate

FP = false positive; NND = additional number needed to detect to prevent one prostate cancer death; vPSA = PSA velocity

Mean months of life gained per man diagnosed = Mean months of life gained per man whose death from prostate cancer was prevented by testing divided by the NND (calculated as mean months of life gained per man tested divided by probability that prostate cancer death is prevented % multiplied by 100 and the result divided by the NND).

[3]95th percentiles were 2.5, 3.5, 4.5 and 6.5ng/mL for ages 40-49, 50-59, 60-69 and 70-74 years, respectively.

II PSA screening vs no screening for higher risk men

Please see table 11

References: Included studies

1. Gulati R, Gore JL, Etzioni R. Comparative effectiveness of alternative prostate-specific antigen--based prostate cancer screening strategies: model estimates of potential benefits and harms. Ann Intern Med 2013; 158(3):145-153.

2. Heijnsdijk EA, der KA, Wever EM, Draisma G, Roobol MJ, de Koning HJ. Overdetection, overtreatment and costs in prostate-specific antigen screening for prostate cancer. Br J Cancer 2009; 101(11):1833-1838.

3. Heijnsdijk EA, Wever EM, Auvinen A, Hugosson J, Ciatto S, Nelen V et al. Quality-of-life effects of prostate-specific antigen screening. N Engl J Med 2012; 367(7):595-605.

4. Howard K, Barratt A, Mann GJ, Patel MI. A model of prostate-specific antigen screening outcomes for low- to high-risk men: information to support informed choices. Arch Intern Med 2009; 169(17):1603-1610.

5. Martin AJ, Lord SJ, Verry HE, Stockler MR, Emery JD. Risk assessment to guide prostate cancer screening decisions: a cost-effectiveness analysis. Med J Aust 2013; 198(10):546-550.

6. Pataky R, Gulati R, Etzioni R, Black P, Chi KN, Coldman AJ et al. Is prostate cancer screening cost-effective? A microsimulation model of prostate-specific antigen-based screening for British Columbia, Canada. Int J Cancer 2014; 135(4):939-947.

3. Appendices

Appendix A: Search strategies used

For Medline database:

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	prostate-specific antigen/
5	prostate specific antigen.tw,mp.
6	PSA.mp,tw.
7	4 or 5 or 6
8	exp mass screening/
9	"early detection of cancer"/
10	screen$.mp,tw.
11	8 or 9 or 10
12	exp Models, Theoretical/
13	exp Computer Simulation/
14	(model$ or simulat$ or microsimulat$ or micro-simulat$ or MISCAN).mp,tw.
15	12 or 13 or 14
16	3 and 7 and 11 and 15
17	limit 16 to (english language and humans and yr="1990-current")

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database:

#	Searches
1	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neopla* OR metast* OR adeno*)
2	'prostate cancer'/exp
3	1 OR 2
4	'prostate specific antigen'/exp
5	'prostate specific antigen':de,ab,ti OR psa:de,ab,ti
6	'prostate specific antigen' OR psa
7	4 OR 5 OR 6
8	'mass screening'/exp
9	'screening test'/exp
10	'early diagnosis'/exp
11	screen*
12	8 OR 9 OR 10 OR 11
13	'model'/exp
14	'computer simulation'/exp
15	model* OR simulat* OR microsimulat* OR MISCAN
16	model*:ab,ti OR simulat*:ab,ti OR microsimulat*:ab,ti OR MISCAN:ab,ti
17	13 OR 14 OR 15 OR 16
18	[embase]/lim AND [1990-2014]/py AND [english]/lim AND [humans]/lim
19	3 AND 7 AND 12 AND 17 AND 18

ATSI search terms used

#	Searches
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

For Cochrane Database of Systematic Reviews – The Cochrane Library:
Title, abstracts, keywords: “prostate”

For Database of Abstracts of Reviews of Effects and Health Technology Assessment database (via OvidSP):

#	Searches
1	exp Prostatic Neoplasms/
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
3	1 or 2

Appendix B:

Relevance of the Evidence

Rating	Relevance
1	Evidence of an effect on patient-relevant clinical outcomes including benefits and harms, quality of life and survival.
2	Evidence of an effect on a surrogate outcome* that has been shown to be predictive of patient-relevant outcomes for the same intervention.
3	Evidence of an effect on proven surrogate outcomes but for a different intervention.
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population.
5	Evidence confined to unproven surrogate outcomes.

**'surrogate outcome' refers to reasonable indicators of whether there has been some effect (e.g. blood pressure measurements or levels of serum cholesterol)*

Points to considering patient-relevant outcomes:
i) The goal of decision making in health care is to choose the intervention(s) (which may include doing nothing) that is (are) most likely to deliver the outcomes that patients find desirable
ii) Surrogate outcomes (such as blood pressure measurements or levels of serum cholesterol) may be reasonable indicators of whether there has been some effect. However, they should not be the basis for clinical decisions unless they reliably predict an effect on the way the patient feels; otherwise they will not be of interest to the patient or their carers
iii) All possible outcomes that are of most interest to patients (particularly harms) should be identified and evaluated

Adapted from table 1.10: National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra: NHMRC; 2000. http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp69.pdf

Appendix C:

Potentially relevant guidelines identified and reason why not adopted

Year	Organisation	Title	Reason why not adopted
2010	American Cancer Society	American Cancer Society Guideline for the Early Detection of Prostate Cancer	Did not meet pre-specified AGREE II criteria for adoption
2008	American College of Preventive Medicine	Screening for Prostate Cancer in U.S. Men: ACPM Position Statement on Preventive Practice	Did not meet pre-specified AGREE II criteria for adoption
2013	American College of Physicians	Screening for prostate cancer – guidance statement	Did not meet pre-specified AGREE II criteria for adoption
2012	American Society of Clinical Oncology	Screening for Prostate Cancer with Prostate-Specific Antigen Testing: American Society of Clinical Oncology Provisional Clinical Opinion	Did not meet pre-specified AGREE II criteria for adoption
2013	American Urological Association	Early Detection of Prostate Cancer: AUA Guideline	Did not meet pre-specified AGREE II criteria for inclusion
2011	Canadian Urological Association	Prostate Cancer Screening: Canadian guidelines	Did not meet pre-specified AGREE II criteria for adoption
2014	European Association of Urology	Guidelines on Prostate Cancer	Did not specifically address clinical question as to which screening protocol to use
2013	European Society for Medical Oncology	ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Consensus based
2010	Japanese Urological Association	Japanese Urological Association Guidelines on prostate-specific antigen-based screening for prostate cancer in 2010	Not based on a systematic review
2013	Prostate Cancer World Congress	Melbourne Consensus Statement on Prostate Cancer Testing	Consensus based
2008	National Academy of Clinical Biochemistry	National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for Use of Tumor Markers in Testicular, Prostate, Colorectal, Breast, and Ovarian Cancers	Not based on a systematic review
2010	National Health Service	Prostate Cancer Risk Management Programme: PSA testing in asymptomatic men	Consensus based
2012	NCCN	Prostate cancer early detection version 2.2012	Not based on a systematic review
2009	New Zealand Guidelines Group	Suspected cancer in primary care: Guidelines for investigation, referral and reducing ethnic disparities	Not based on a systematic review
2012	Royal Australian College of	Guidelines for preventive activities in general	Not based on a systematic review

	General Practitioners	practice	
2012	Royal College of Pathologists of Australasia	Prostate specific antigen testing: Age-related interpretation in early prostate cancer detection	Consensus based
2012	University of Michigan Health System	Cancer Screening	Did not meet pre-specified AGREE II criteria for adoption
2012	US Preventive Services Task Force	Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement	Did not specifically address clinical question as to which screening protocol to use

Excluded Studies

Study	Reason for Exclusion
Albers 2013	Narrative review/comment/editorial
Concato 2013	Narrative review/comment/editorial
Dosoretz 2012	Did not compare different PSA screening protocols or screening for higher risk men
Draisma 2009	Did not compare different PSA screening protocols or screening for higher risk men
Draisma 2006	Did not compare different PSA screening protocols or screening for higher risk men
Draisma 2003	No relevant outcomes
Etzioni 2013a	Narrative review/comment/editorial
Etzioni 2013b	Narrative review/comment/editorial
Etzioni 2013c	Data inconsistent with data from same model
Etzioni 2012	Did not compare different PSA screening protocols or screening for higher risk men
Etzioni 2008	Did not compare different PSA screening protocols or screening for higher risk men
Etzioni 1999	Did not incorporate ERSPC data for survival benefit
Etzioni 1996	Did not incorporate ERSPC data for survival benefit
Gulati 2014	Did not compare different PSA screening protocols or screening for higher risk men
Gulati 2012	Did not compare different PSA screening protocols or screening for higher risk men
Gulati 2011	Did not compare different PSA screening protocols or screening for higher risk men
Gulati 2010	No relevant outcomes
Kobayashi 2007	No relevant outcomes
Labrecque 2013	Narrative review/comment/editorial
Loeb 2014	Narrative review/comment/editorial
Nichol 2012	No relevant outcomes
Ross 2005	Did not incorporate ERSPC data for survival benefit
Ross 2000	Did not incorporate ERSPC data for survival benefit
Underwood 2013	Did not incorporate ERSPC data for survival benefit
Underwood 2012	Did not incorporate ERSPC data for survival benefit
Wever 2012	No relevant outcomes
Wever 2011	Did not compare different PSA screening protocols or screening for higher risk men
Wever 2010	Did not compare different PSA screening protocols or screening for higher risk men
Wu 2012	Did not incorporate ERSPC data for survival benefit
Zhang 2012	Did not incorporate ERSPC data for survival benefit

References: Excluded Studies

1. Albers P, Arsov C. Re: Comparative effectiveness of alternative prostate specific antigen-based prostate cancer screening strategies: model estimates of potential benefits and harms. European Urology 2013; 64:682.

2. Concato J. Probability, uncertainty, and prostate cancer. Ann Intern Med 2013; 158(3):211-212.

3. Dosoretz AP, Lester-Coll NH, Yu JB. A decision analysis to assess the value of prostate cancer screening: A shift in focus from prostate cancer-specific mortality to distant metastasis-free survival. Int J Radiat Oncol Biol Phys 2012; 84(3):S57.

4. Draisma G, Boer R, Otto SJ, van der Cruijsen IW, Damhuis RA, Schroder FH et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 2003; 95(12):868-878.

5. Draisma G, Postma R, Schroder FH, van der Kwast TH, de Koning HJ. Gleason score, age and screening: modeling dedifferentiation in prostate cancer. Int J Cancer 2006; 119(10):2366-2371.

6. Draisma G, Etzioni R, Tsodikov A, Mariotto A, Wever E, Gulati R et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. J Natl Cancer Inst 2009; 101(6):374-383.

7. Etzioni R, Shen Y, Petteway JC, Brawer MK. Age-specific prostate-specific antigen: a reassessment. Prostate Suppl 1996; 7:70-77.

8. Etzioni R, Cha R, Cowen ME. Serial prostate specific antigen screening for prostate cancer: a computer model evaluates competing strategies. J Urol 1999; 162:741-748.

9. Etzioni R, Tsodikov A, Mariotto A, Szabo A, Falcon S, Wegelin J et al. Quantifying the role of PSA screening in the US prostate cancer mortality decline. Cancer Causes Control 2008; 19(2):175-181.

10. Etzioni R, Gulati R, Tsodikov A, Wever EM, Penson DF, Heijnsdijk EA et al. The prostate cancer conundrum revisited: treatment changes and prostate cancer mortality declines. Cancer 2012; 118(23):5955-5963.

11. Etzioni R, Gulati R, Mallinger L, Mandelblatt J. Influence of study features and methods on overdiagnosis estimates in breast and prostate cancer screening. Ann Intern Med 2013; 158(11):831-838.

12. Etzioni R, Gulati R. Response: Reading between the lines of cancer screening trials: using modeling to understand the evidence. Med Care 2013; 51(4):304-306.

13. Etzioni R, Durand-Zaleski I, Lansdorp-Vogelaar I. Evaluation of new technologies for cancer control based on population trends in disease incidence and mortality. J Natl Cancer Inst Monogr 2013; 2013(46):117-123.

14. Gulati R, Inoue L, Katcher J, Hazelton W, Etzioni R. Calibrating disease progression models using population data: a critical precursor to policy development in cancer control. Biostatistics 2010; 11(4):707-719.

15. Gulati R, Mariotto AB, Chen S, Gore JL, Etzioni R. Long-term projections of the harm-benefit trade-off in prostate cancer screening are more favorable than previous short-term estimates. J Clin Epidemiol 2011; 64(12):1412-1417.

16. Gulati R, Tsodikov A, Wever EM, Mariotto AB, Heijnsdijk EA, Katcher J et al. The impact of PLCO control arm contamination on perceived PSA screening efficacy. Cancer Causes Control 2012; 23(6):827-835.

17. Gulati R, Inoue LY, Gore JL, Katcher J, Etzioni R. Individualized estimates of overdiagnosis in screen-detected prostate cancer. J Natl Cancer Inst 2014; 106(2):djt367.

18. Kobayashi T, Goto R, Ito K, Mitsumori K. Prostate cancer screening strategies with re-screening interval determined by individual baseline prostate-specific antigen values are cost-effective. Eur J Surg Oncol 2007; 33(6):783-789.

19. Labrecque M, Aprikian A. Alternative prostate cancer screening strategies. Ann Intern Med 2013; 158(10):778.

20. Loeb S, Bjurlin MA, Nicholson J, Tammela TL, Penson DF, Carter HB et al. Overdiagnosis and Overtreatment of Prostate Cancer. Eur Urol 2014; 65(6):1046-1055.

21. Nichol MB, Wu J, Huang J, Denham D, Frencher SK, Jacobsen SJ. Cost-effectiveness of Prostate Health Index for prostate cancer detection. BJU Int 2012; 110(3):353-362.

22. Ross KS, Carter HB, Pearson JD, Guess HA. Comparative efficiency of prostate-specific antigen screening strategies for prostate cancer detection. JAMA 2000; 284(11):1399-1405.

23. Ross KS, Guess HA, Carter HB. Estimation of treatment benefits when PSA screening for prostate cancer is discontinued at different ages. Urology 2005; 66(5):1038-1042.

24. Underwood DJ, Zhang J, Denton BT, Shah ND, Inman BA. Simulation optimization of PSA-threshold based prostate cancer screening policies. Health Care Manag Sci 2012; 15(4):293-309.

25. Underwood DJ, Zhang J, Denton BT, Shah ND, Inman BA. Note on "simulation optimization of PSA-threshold based prostate cancer screening policies". Health Care Manag Sci 2013; 16(4):377-378.

26. Wever EM, Draisma G, Heijnsdijk EA, Roobol MJ, Boer R, Otto SJ et al. Prostate-specific antigen screening in the United States vs in the European Randomized Study of Screening for Prostate Cancer-Rotterdam. J Natl Cancer Inst 2010; 102(5):352-355.

27. Wever EM, Draisma G, Heijnsdijk EA, de Koning HJ. How does early detection by screening affect disease progression? Modeling estimated benefits in prostate cancer screening. Med Decis Making 2011; 31(4):550-558.

28. Wever EM, Hugosson J, Heijnsdijk EA, Bangma CH, Draisma G, de Koning HJ. To be screened or not to be screened? Modeling the consequences of PSA screening for the individual. Br J Cancer 2012; 107(5):778-784.

29. Wu GH, Auvinen A, Yen AM, Hakama M, Tammela TL, Stenman UH et al. The impact of interscreening interval and age on prostate cancer screening with prostate-specific antigen. Eur Urol 2012; 61(5):1011-1018.

30. Zhang J, Denton BT, Balasubramanian H, Shah ND, Inman BA. Optimization of PSA screening policies: a comparison of the patient and societal perspectives. Med Decis Making 2012; 32(2):337-349.

Systematic review report for question 3.2

Clinical Question 3: ***"****In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what should be the PSA testing strategies (age to start, level at which to declare a test abnormal and frequency of subsequent testing if the PSA level is normal) for men at average risk of prostate cancer and how should they be modified, if at all, for men at high risk of prostate cancer?"*

PICO 3.2: *For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what PSA testing strategies with or without DRE perform best in detecting any prostate cancer or high grade prostate cancer diagnosed in biopsy tissue?*

Population	Index test 1	Index test 2	Reference standard	Outcomes
Men without a history of prostate cancer or symptoms that indicate prostate cancer	PSA test using one threshold	PSA test using a lower threshold	Prostate biopsy	Diagnostic performance

1. Methods

1.1. Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption guidelines had to be evidence based and meet the pre-specified criteria of scores of greater or equal to 70% for the domains rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

1.2. Literature Search

Scoping searches indicated a vast literature. Preliminary searches indicated that in order to maximise sensitivity, broad search terms would be required resulting in an unmanageable number of titles of low specificity. Searches could not be narrowed by using filters for diagnostic studies as such filters are not recommended (http://srdta.cochrane.org/handbook-dta-reviews, accessed 04/11/2014). As part of the scoping process, recent guidelines and systematic reviews were examined. Furthermore, on examination of relevant references cited in these guidelines and systematic reviews it became apparent that papers with relevant data may not be identified on the basis of their titles and abstracts and thus could be missed when

from scanning titles and abstracts in standard medical publication databases. As a result, multiple search strategies were used to identify potentially relevant articles.

Examination of recent guidelines and their systematic reviews identified a pivotal study, the Prostate Cancer Prevention Trial (PCPT) in which all men were biopsied regardless of PSA levels, enabling the calculation of the specificity and sensitivity of different PSA thresholds. The Web of Science database was searched in February 2014 for citations of the two relevant references for this study, Thompson et al., 2004 and Thompson et al., 2005.

Two guidelines were identified that systematically reviewed the performance characteristics of the total PSA test, the American Cancer Society (ACS) guidelines as reported by Wolf 2010 and the American Urological Association (AUA) guidelines. The NHMRC, as part of their evaluation of the evidence for PSA testing of asymptomatic men, reviewed the performance characteristics of the total PSA test in a non-systematic manner. All relevant references from the AUA systematic reviews (provided by the AUA), the Wolf 2010 publication (systematic reviews not accessible) and the NHMRC review were collected.

The AUA reviewed the literature up until February 2013. To identify relevant articles published after this date and any relevant systematic reviews, Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched from 2013 using text terms and, where available, database specific subject headings. Each database was searched for articles dealing with prostate cancer. In Medline and Embase databases the searches were based on those used by the AUA, coupling prostate cancer terms with both PSA and detection terms.

The large prostate cancer screening trials, the European Randomised Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) were also considered possible sources of relevant data. As a result Medline and Embase databases were searched for publications for these trials.

To identify studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014, which were either published after the initial search was completed and/or added to the relevant database after the search was completed. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched regularly up until April 2014 for relevant reviews published after the initial search. Alerts were checked until July 2014. A complete list of the terms used for all search strategies are included as Appendix A.

Reference lists of all relevant articles were checked for potential additional articles.

References

1. Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL et al. Early detection of Prostate Cancer: AUA Guideline. American Urological Association approved 2013 http://www.auanet.org/common/pdf/education/clinical-guidance/Prostate-Cancer-Detection.pdf

2. National Health and Medical Research Council (2013a). Prostate-Specific Antigen (PSA) testing in asymptomatic men: Evidence Evaluation Report. Canberra: National Health and Medical Research Council. Published July 2013

3. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med 2004; 350(22):2239-2246.

4. Thompson IM, Ankerst DP, Chi C, Lucia MS, Goodman PJ, Crowley JJ et al. Operating characteristics of prostate-specific antigen in men with an initial PSA level of 3.0 ng/ml or lower. JAMA 2005; 294(1):66-70.

5. Wolf AMD, Wender RC, Etzioni RB, Thompson IM, D'Amico AV, Volk RJ et al. American Cancer Society Guideline for the Early Detection of Prostate Cancer Update 2010 CA Cancer J Clin 2010; 60:70–98.

1.3. Inclusion and exclusion criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Diagnostic performance	
Study design	Fully paired diagnostic study, or Paired randomised cohort study	Diagnostic case-control studies or studies of diagnostic yield
Population	Men without a history of prostate cancer or symptoms that indicate prostate cancer who have undergone prostate biopsy	Included men with prostate cancer or some other urologic disease e.g. bladder cancer or men undergoing a particular treatment e.g. finasteride
Index test 1	PSA test with threshold ≤ 4.1ng/mL	
Index test 2	PSA test with a lower threshold	
Reference standard	Prostate biopsy less than 1 year after a PSA test (assumed if men presenting for biopsy) Minimum of 8 biopsy cores unless all participants underwent biopsy regardless of PSA level in which case a minimum of 6 biopsy cores *	
Indications for biopsy^	No indications for biopsy - all men underwent biopsy regardless of PSA level or result of any other test or Index test 2 is one of the indications for biopsy	Indications for biopsy not precisely defined Only a non-random subgroup of men with PSA levels below index test 1 levels and index 2 test levels were biopsied
Outcomes	For the diagnosis of prostate cancer, prostate cancer Gleason Score >7 or prostate cancer Gleason score > 6 • Absolute accuracy if all participants regardless of screen test results	

	underwent biopsy or, if the results were adjusted for verification bias, otherwise • Comparative accuracy as assessed by the number additional false positives for each additional true positive **	
Language	English	
Publication period	After 31st December 1989 and before1st March 2014	

* In this review an adequate biopsy was pre-specified as ≥ 12-core biopsy however initial searches found that if studies were restricted to those using ≥12-core biopsy no studies met the inclusion criteria for this question as most PSA performance studies were undertaken when 6-core and later 8-core biopsies were considered adequate. As a result a pragmatic approach was taken; the inclusion criteria were broadened to include studies in which the biopsy had a minimum of 8 cores. An exception was made for studies in which men underwent biopsy regardless of PSA levels and thus provided absolute diagnostic accuracy as these studies were so rare; in the case of these studies only, studies that employed a 6-core (sextant) biopsy were included. The inadequate nature of the biopsies was taken into account when assessing the risk of bias.

^To be included studies needed to provide data enabling the comparison of at least 2 different PSA thresholds. When comparing 2 different PSA thresholds the best evidence is derived from studies in which all men with PSA levels above the given thresholds undergo biopsy. If one of the indications for biopsy requires both a PSA level above a PSA threshold and a positive result in another test then only a subgroup of men with PSA above this threshold will be biopsied and the results will not truly reflect the diagnostic performance of that PSA threshold. An example of this is when an indication for biopsy is dependent on the result of an ancillary test at lower PSA levels. As a result, studies in which the only comparisons possible were with a subgroup of the men with PSA levels above a given threshold ie in which the indications for biopsy above that PSA level required that a group of these men be positive for another test, for example the they had been triaged using another test, were excluded . For these reasons studies in which the indications for biopsy were unclear or vague were also excluded.

**Verification bias is a major issue when assessing the diagnostic performance of tests for prostate cancer as men normally do not undergo biopsy unless they are test positive. As a result most studies examining diagnostic performance of test s for prostate cancer are only able to report numbers of true positives and false positives. Where there is a comparison of two index tests in the same patient and where one index test is purely adding additional test positives to another index test, as when the PSA threshold is lowered, this data can be used to calculate the difference in true positives and the difference in false positives and the number of additional false positives for each additional cancer detected; findings that will not be subject to verification bias.

Conference proceedings identified by the search literature searches were included if they met the inclusion criteria.

In the systematic review of the effects of different PSA testing protocols on prostate cancer mortality for the current guidelines, one study was identified that showed a decrease in prostate cancer mortality with PSA testing, the European Randomised Study of Screening for Prostate Cancer (ERSPC). As a result it was decided to compare PSA performance

characteristics in this study with the studies that met the above inclusion criteria. The ERSPC trial did not meet the inclusion criteria above as only men with an elevated PSA were biopsied and the biopsy was a sextant biopsy, thus additional inclusion criteria were drafted specific for publications from the ERSPC trial. To maximise comparability with the pivotal study, PCPT, which examined PSA performance in a routinely screened population, performance in the initial ERSPC screening round was not included.

Inclusion criteria for publications from the ERSPC trial.

Selection criteria	**Inclusion criteria**	**Exclusion criteria**
Study type	Diagnostic performance	
Study design	Cohort in which men with PSA above a certain level underwent prostate biopsy	Diagnostic case-control studies or studies of diagnostic yield
Population	Participants in the ERSPC screening arm from all centres except France combined , or the Rotterdam or Goteborg centres (centres that individually showed a significant reduction in prostate cancer mortality with screening) who have undergone prostate biopsy	
Index test 1	PSA test with threshold ≤ 3.0 ng/mL	
Reference standard	Prostate biopsy	
Outcomes	Diagnostic performance for all screening rounds combined or for individual screening rounds other than the initial screening round Diagnosis of prostate cancer, prostate cancer Gleason Score >7 or prostate cancer Gleason score > 6 True positives and false positives Relative accuracy as assessed by the number additional false positives for each additional true positive if comparison of 2 thresholds possible	Diagnostic performance in first screening round
Language	English	
Publication period	After 31st December 1989 and before1st March 2014	

2. Results

2.1. Guidelines

Eighteen guidelines contained recommendations as to which screening protocol to use including two that systematically reviewed the diagnostic performance of PSA as a test to detect prostate cancer. These recommendations were not adopted as they either were not based on a systematic review, did not meet the pre-specified AGREE II criteria for adoption, or the recommendations did not specifically address the clinical question. These guidelines and the reason why they were not adopted are listed in Appendix C.

In Australia the Royal College of Pathologists of Australasia has consensus-based position statements regarding PSA testing (http://www.rcpa.edu.au/Library/College-Policies/Position-Statements/Prostate-Specific-Antigen-Testing-Age-related-inte, accessed 20/10/2014).

"The response to an initial test should be:

a. *If the total PSA level is at or above 10 µg/L, the patient should either have the PSA confirmed in 4 weeks and be referred if the result is confirmed or be immediately referred for specialist management.*
b. *If the total PSA level is abnormal (above 97.5% age-related, method-specific reference limit) but below 10 µg/L, the PSA should be confirmed in 4 weeks including an estimation of the free-to-total PSA ratio (F/T PSA ratio). If confirmed and/or the result of the F/T PSA ratio is <10%, the patient should be immediately referred for specialist management.*
c. *If the PSA level is normal, but above the age-related median, the patient should be reassured that their result is normal and be re-tested in 2 years.*
d. *If the PSA level is not above the age-related median, the patient should be reassured that their risk is low and be re-tested in 4 years."*

2.2. Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the systematic review. The Web of Science search yielded 1,207 citations. The Medline searches identified 412 citations, the Embase search an additional 739 citations and the search of the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment database identified an additional 15 citations resulting in a total of 2,373 citations. Titles and abstracts were examined and 168 articles were retrieved for a more detailed evaluation. 43 potentially relevant articles were identified for retrieval from the AUA guidelines systematic review, the ACS guidelines publication, the NHMRC review and other guidelines. An additional 15 potential citations were identified from the reference list of retrieved articles resulting in a total of 226 retrieved articles.

Database or Source	Number of Citations	Number of Articles Collected	Number of Articles Included
Other guidelines (Scoping)	Not applicable	8	2
Web of Science	1,207	55	4
AUA systematic review	Not applicable	23	1
Wolf systematic review	Not applicable	8	2
NHMRC evidence evaluation	Not applicable	4	0
AUA update - Medline	128	7	0
AUA update - Embase	375	3	0
ERSPC - Medline	222	81	6
ERSPC - Embase	281	10	0
PLCO - Medline	62	8	0
PLCO – Embase	83	3	0
Cochrane Database of Systematic Reviews, DARE and HTA	15	1	0
Snowballing	Not applicable	15	0

Eight studies reported in 15 articles met the inclusion criteria and were included in the review. There were no studies of ATSI men that met the inclusion criteria.

The retrieved articles that were not included and the reason for their exclusion are documented in Appendix C. In summary, the main reasons for exclusion were inappropriate population, no comparison of PSA performance at 2 or more thresholds ≤4.1ng/mL (and not ERSPC study) and did not report any relevant outcomes.

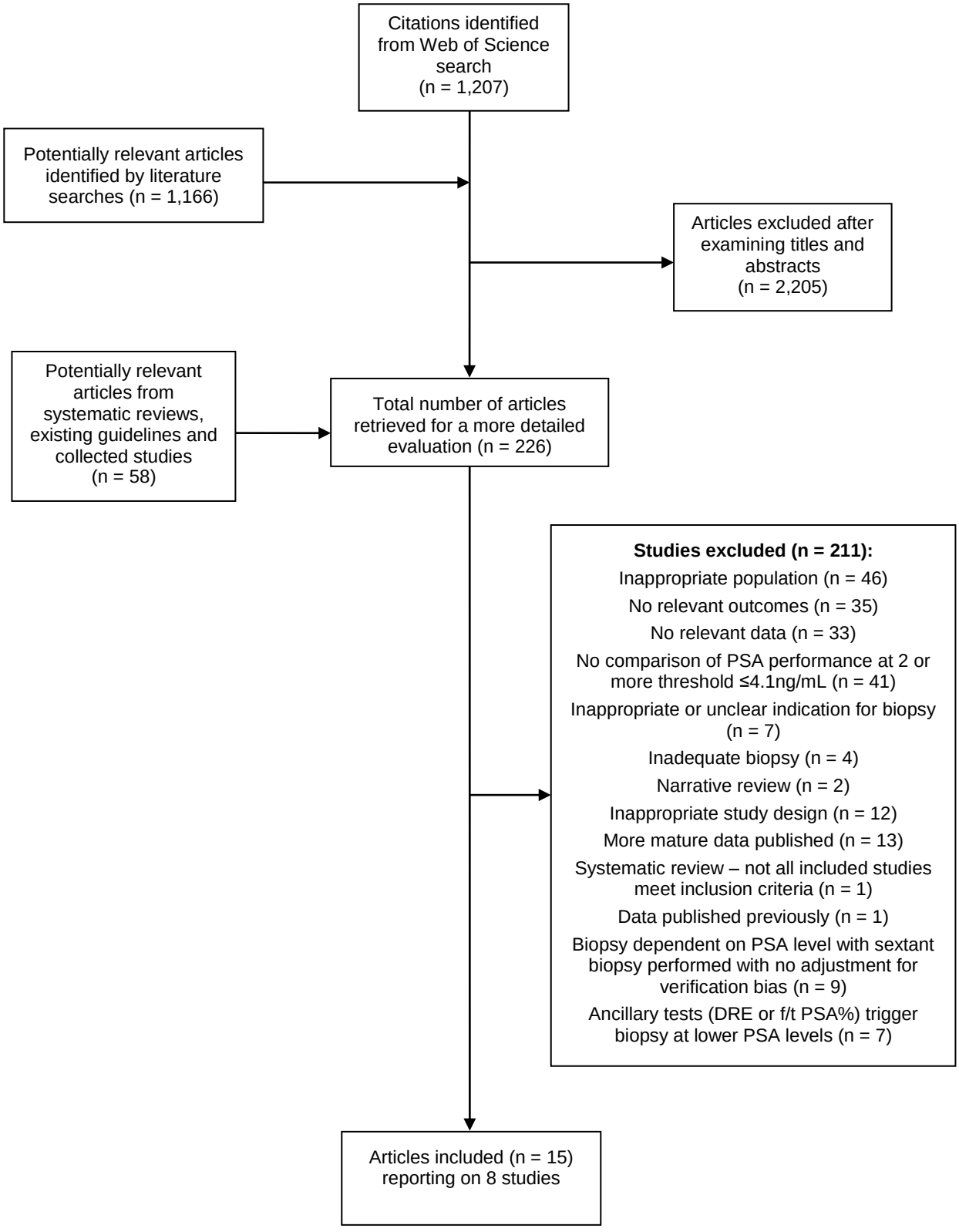


Figure 1. Process of inclusion and exclusion of studies

2.3. Study Characteristics

Characteristics of included studies are described in Table 1.

Table 1: Characteristics of fully paired studies comparing the performance characteristics of 2 PSA thresholds for the detection of prostate cancer

Study	Participants	Biopsy	Indication for biopsy	PSA test	PSA threshold comparison/s	Relevant Outcomes	Comments
PCPT Thompson 2005 (USA)	Participants in placebo arm of PCPT (1993 – 2003) At enrolment: aged ≥55, PSA ≤3.0ng/mL, normal DRE, AUA symptom score <20 N = 9,459	6 cores minimum (84.5% of men biopsied with PSA <4.0ng/mL underwent sextant biopsy) Biopsy within 1 year of PSA test	PSA >4.0 ng/ml or suspicious DRE at 7 annual checks then regardless of PSA level or DRE after 7 years follow-up Men who underwent biopsy N = 5,587 (65.2%) 47.1% aged ≥ 70 years	**Hybritech** Tandem E assay 1993 – 2000 **Hybritech** Access assay 2000 – 2003 Measured in a central laboratory (Esoterix CA)	1.1 (>1.0) vs 1.6 (>1.5) vs 2.1 (>2.0) vs 2.6 (>2.5) vs 3.1 (>3.0) vs 4.1 (>4.0) ng/mL	Prostate cancer detection Gleason score > 7 disease Gleason score > 6 disease	Pre-screened cohort Authors adjusted for verification bias by imputing missing data. The areas under the curve were almost identical for verified patients and after verification bias adjustment
PCPT Thompson 2006	***Subgroup*** with 2 PSA tests in 3 years prior to biopsy N = 5,519				1.1 (>1.0) vs 2.1 (>2.0) vs 3.1 (>3.0) vs 4.1 (>4.0) ng/mL	Prostate cancer detection Gleason score > 6 disease	
PCPT Thompson 2004	***Subgroup*** with PSA level ≤4.0 ng/mL and no history of abnormal DRE in previous 7 years N = 3,568	Biopsy within 90 days of PSA test	Men who underwent biopsy N = 2,950 (82.7%)		0.6 (>0.5) vs 1.1 (>1.0) vs 2.1 (>2.0) vs 3.1 (>3.0) ng/mL	Prostate cancer detection Gleason score > 6 disease	Sensitivity and specificity restricted to cut-off values <4.0ng/mL
Canby-Hagino 2007 (USA)	Male participants in the SABOR study with a family history (first or second degree relative) of prostate cancer, PSA ≤4.0ng/mL and normal DRE, who were willing to undergo prostate biopsy (2003 – 2006) N = 87 Median age = 57.8 – 60.9	10 – 12 cores	Regardless of PSA level	**Bayer**-Cendaur Chemoluminescent assay 2003 – 2005; Beckman (**Hybritech**) ICMA 2005 –2006	0.5 vs 1.0 vs 2.0 vs 3.0ng/mL	Prostate cancer detection	Pre-screened cohort Single institution?

	years						
Kobayashi 2006 (Japan)	Men presenting mainly with LUTS who underwent prostate biopsy (2001 – 2004), aged ≤70 years and with PSA levels 2.5 – 10.0ng/mL N = 182 Median age = 62.5 – 65 years	10 cores	PSA ≥ 2.0ng/mL or abnormal DRE	**Hybritech** Tandem-R assay	2.5 vs 4.1ng/mL	Prostate cancer detection Gleason score > 7 disease Gleason score > 6 disease	Biopsy referral cohort Single institution 82.5% of men with PSA 2.5 – 4.0ng/mL biopsied 91.1% of men with PSA 4.1 – 10.0ng/mL biopsied
Muntener 2010 (Switzerland)	Men referred for prostate check-up who underwent biopsy (1999 – 2004), aged ≤75 years and with PSA levels 2.5 – 10.0ng/mL and normal DRE N = 506 Median age = 63 years	8 cores Biopsy repeated 4 – 6 weeks later if first biopsy negative 24.5% with initial negative biopsy did not undergo second biopsy	PSA ≥ 2.5ng/mL	**Not reported**	2.5 vs 4.0ng/mL	Prostate cancer detection Gleason score > 6 disease	Retrospective biopsy referral cohort Single institution Men that did not undergo second biopsy after an initial negative biopsy did not differ in age and PSA level from the cohort of men with either a positive biopsy or 2 negative biopsies
Park 2006 (Korea)	Men undergoing prostate biopsy, with PSA levels 3.0 – 10.0ng/mL and normal DRE N = 579 Mean age = 61.6 – 63.2 years Subgroup with normal TRUS N = 450 Mean age = 61.9 – 62.5 years	12 cores; 16 cores if prostate >50cm^3	PSA ≥3.0ng/mL regardless of DRE or TRUS findings	Izotop immunoradiometric assay (calibrated against WHO standard)	3.0 vs 4.1ng/mL	Prostate cancer detection Gleason score > 6 disease	Biopsy referral cohort Single institution
ProtecT Rosario 2008 (UK)	Participants in ProtecT Study aged 50 – 70 years undergoing prostate biopsy 2002 – 2006, with initial PSA	10 cores	PSA 3.0 – 19.9ng/mL regardless of DRE findings	**Not reported** All laboratories participants in the	3.0 vs 3.5 vs 4.0ng/mL	Prostate cancer detection Gleason score > 6 disease	Men referred for biopsy as a result of PSA screening 9 centres

	levels ≥3.0ng/mL N = 4,102 Median age = 62.2 years			UK National External Quality Assessment Service (UK NEQAS) programme for PSA testing			
Shim 2007 (Korea)	Men with no history of prostate cancer undergoing initial prostate biopsy, aged 45 – 79 years and with PSA levels 2.5 – 19.9ng/mL N = 913 Men with normal DRE N = 721 Median age = 66 years	Median 12 cores Biopsy within 3 months of PSA test	PSA >2.5ng/mL or abnormal DRE	Izotop immunoradiometric assay (calibrated against **WHO standard**)	2.5 vs 4.0ng/mL	Prostate cancer detection	Retrospective biopsy referral cohort 3 hospitals?
ERSPC Schroder 2012 (7 European countries)	Men aged 50 – 74 years with no previous personal history of prostate cancer identified in population registries and randomised to screening arm of ERSPC N = 82,816 *Core age group:* 55 – 69 years old Median age = 60.1 years N = 72,891	Sextant biopsy	Primarily PSA ≥3ng/mL	Primarily **Hybritech** assay systems; Tandem-E, Tandem-R or Access assays	PSA ≥ ~3ng/mL	Prostate cancer detection	82.6% screened at least once 85.9% of men with positive test underwent biopsy Median follow-up = 11.0 years
	The Netherlands (Rotterdam)						
Roobol 2013, Gosselaar 2008, Postma 2007	Men aged 55 – 74 years without any previous prostate cancer diagnosis and randomised to screening arm of ERSPC N = 21,206 *Core age group*: 55 – 69 years Median age = 61.7 years	Sextant biopsy	*<u>1993 – 1997</u>* PSA ≥4ng/mL screening round 1 *<u>1997 onwards</u>* PSA ≥3ng/mL remainder of screening round 1, and rounds 2, 3 and 4 Calibration changed to	**Hybritech** Tandem-E assay until January 2000 when replaced by the Access version	PSA ≥ 3ng/mL	Prostate cancer detection Gleason score > 7 disease Gleason score > 6 disease Gleason score < 7 disease	89.8% of screen positive men underwent biopsy Median follow-up = 11.1 years

	N = 17,443 Maximum of 4 screening rounds		WHO calibration in 2004 Test interval = **4 years**				
	Sweden (Goteborg)						
Kilpelainen 2011, Vickers 2009	Men aged 50 – 64 years without any previous prostate cancer diagnosis and randomised to screening arm of ERSPC Median age = 56 years N = 9,957 *Core age group*: 55 – 69 years Median age = 59.7 years N = 5,901 Maximum of 7 screening rounds	Sextant biopsy	Screening rounds 1 and 2 PSA ≥3.0ng/mL (**3.4ng/mL** WHO corrected value) Screening rounds 3-5 PSA ≥2.5ng/mL (**2.9ng/mL** WHO corrected value) Screening rounds 6-7 PSA ≥ **2.5ng/mL** (WHO calibration) Test interval = **2 years**	DELFIA Prostatus total/free PSA assay – WHO calibrated since 2004	2.9 vs 3.4ng/mL 2.9 vs 2.5ng/mL	Prostate cancer detection Gleason score > 7 disease Gleason score > 6 disease Gleason score < 7 disease	Men not previously exposed to screening 86.6% of men in core age group and 93% of entire cohort with positive test underwent biopsy Men with PSA <1.0ng/mL at invitation round 2 not invited to third invitation round Median follow-up = 14.0 years

~ Approximately; AUA = American Urologic Association; DRE = digital rectal examination; ERSPC = European Randomised Study of Screening for Prostate Cancer; f/t PSA = percentage free PSA; LUTS = lower urinary tract symptoms; PCPT = Prostate Cancer Prevention Trial; ProtecT = Prostate Testing for Cancer and Treatment; PSA = prostate specific antigen; SABOR = San Antonio Center of Biomarkers of Risk of Prostate Cancer; TRUS = transrectal ultrasound; WHO = World Health Organisation

2.4. Study quality

Assessment of risk of bias of included diagnostic studies is described in Tables 2 – 3.

Table 2: Methodological quality of studies containing relevant diagnostic performance data (n = 13, 8 studies reported in 15 publications, 3 of which, Thompson 2004, 2005 and 2006, used identical methodology and population)

Quality Category	N (%)
I. Selection of participants	
Low risk of bias	13 (100)
High risk of bias	0 (0)
Unclear risk of bias	0 (0)
II. Index test 1	
Low risk of bias	13 (100)
High risk of bias	0 (0)
Unclear risk of bias	0 (0)
III. Index test 2	
Low risk of bias	8 (61.5)
High risk of bias	0 (0)
Unclear risk of bias	0 (0)
Not applicable	5 (38.5)
IV. Reference standard	
Low risk of bias	0 (0)
High risk of bias	11 (84.6)
Unclear risk of bias	2 (15.4)
Not applicable	0 (0)
V. Flow and timing	
Low risk of bias	13 (100)
High risk of bias	0 (0)
Unclear risk of bias	0 (0)
Not applicable	0 (0)

Table 3: Assessment of risk of bias in individual included diagnostic studies (8 studies reported in 15 publications)

	Patient selection	Index test 1	Index test 2	Reference standard*	Flow and timing - *Sensitivity and specificity*	Flow and timing** - *True positives and false positives*	Overall risk of bias
Canby-Hagino 2007	Low	Low	Low	High	Low	Low	At risk
European Randomised Study of Screening for Prostate Cancer							
Schroder 2012 (7 centres combined)	Low	Low	NA	High	NA	Low	At risk
Gosselaar 2008 (Rotterdam)	Low	Low	NA	High	NA	Low	At risk
Roobol 2013 (Rotterdam)	Low	Low	NA	High	NA	Low	At risk
Postma 2007 (Rotterdam)	Low	Low	Low	High	NA	Low	At risk
Kilpelainen 2011 (Gotegorg)	Low	Low	NA	High	NA	Low	At risk
Vickers 2009 (Goteborg)	Low	Low	NA	High	NA	Low	At risk
Kobayashi 2006	Low	Low	Low	High	NA	Low	At risk
Muntener 2010	Low	Low	Low	High	NA	Low	At risk
Park 2006	Low	Low	Low	Unclear	NA	Low	At risk
Rosario 2008	Low	Low	Low	High	NA	Low	At risk
Shim 2007	Low	Low	Low	Unclear	NA	Low	At risk
Prostate Cancer Prevention Trial							
Thompson 2004, 2005 & 2006	Low	Low	Low	High	Low	Low	At risk

NA = not applicable

***** *Adequate reference standard pre-specified as biopsy ≥12 cores*

****** *Appropriate interval between index test(s) and reference standard pre-specified as less than 1 year – for biopsy referral cohorts where interval was not stated, assumed to be less than 1 year*

Key to overall rating

Low risk of bias: A study rated at low risk of bias for all domains

At risk of bias: A study rated at high or unclear risk of bias for one or more domains

2.5. Study Results

I Prostate cancer detection (Tables 4 – 5)

II Gleason score > 7 prostate cancer detection (Tables 6 – 7)

III Gleason score > 6 prostate cancer detection (Tables 8 – 9)

IV Gleason score 2 – 6 prostate cancer detection (Table 10)

I PROSTATE CANCER DETECTION

Table 4: Results of studies examining performance characteristics of different PSA thresholds with respect to prostate cancer detection

PSA threshold	Screen positive biopsied (No.)	TP (No.)	FP (No.)	FP/TP	Screen negative biopsied (No.)	TN (No.)	FN (No.)	Sensitivity	Specificity	DOR	Youden's Index	ΔFP/ ΔTP	PPV (%)
Kobayashi 2006	N = 182	(men with PSA 2.5 – 10.0ng/mL)											
PSA ≥2.5	182	56	126	2.25								2.5 vs 4.1: 2.81*****	30.77*
PSA >4.0	102	35	67	1.91									34.31*
Muntener 2010	N = 506	(men with normal DRE and PSA 2.5 – 10.0ng/mL)											
PSA ≥2.5	506	120	386	3.22								2.5 vs 4.0: 4.78*****	23.72*
PSA ≥4.0	292	83	209	2.52									28.43*
Park 2006	N = 579	(men with normal DRE and PSA 3.0 – 10.0ng/mL)											
PSA ≥3.0	579	133	446	3.35								3.0 vs 4.1: 3.07*****	22.97*
PSA >4.0	469	106	363	3.42									22.60*
*Subgroup analysis – **men with normal TRUS***	N = 450												
PSA ≥3.0	450	92	358	3.89								3.0 vs 4.1: 2.86*****	20.44*
PSA >4.0	365	70	295	4.21									19.18*
ProtecT Rosario 2008	N = 4,102	(men with PSA 3.0 – 19.9ng/mL)											
PSA ≥3.0	4,102	1,318	2,784	2.11								3.0 vs 3.5: 3.46***** 3.0 vs 4.0: 3.21*****	32.13*
PSA ≥3.5	3,122	1,098	2,024	1.84								3.5 vs 4.0: 2.91*****	35.17*
PSA ≥4.0	2,403	914	1,489	1.63									38.04*
Shim 2007	N = 721	(men with normal DRE and PSA 2.5 – 20.0ng/mL)											
PSA ≥2.5	721	166	555	3.34								2.5 vs 4.0: 5.5*****	23.02*
PSA ≥4.0	643	154	489	3.18									23.95*
PCPT Thompson 2005	N = 5,587	All screen negatives and positives biopsied											

PSA >1.0	3,687*	1,022*	2,665*	2.61	NR	NR	NR	83.4	38.9	0.22*	1.1 vs 1.6: 4.29 1.1 vs 2.1: 3.88 1.1 vs 2.6: 3.50 1.1 vs 3.1: 3.32 1.1 vs 4.1: 3.11	27.72*
PSA >1.5	2,623*	821*	1,802*	2.20	NR	NR	NR	67.0	58.7	0.257*	1.6 vs 2.1: 3.40 1.6 vs 2.6: 3.01 1.6 vs 3.1: 2.86 1.6 vs 4.1: 2.69	31.30*
PSA >2.0	1,844*	644*	1,200*	1.86	NR	NR	NR	52.6	72.5	0.25*	2.1 vs 2.6: 2.54 2.1 vs 3.1: 2.48 2.1 vs 4.1: 2.37	34.92*
PSA >2.5	1,320*	496*	824*	1.66	NR	NR	NR	40.5	81.1	0.216*	2.6 vs 3.1: 2.39 2.6 vs 4.1: 2.26	37.58*
PSA >3.0	974*	394*	580*	1.47	NR	NR	NR	32.2	86.7	0.189*	3.1 vs 4.1: 2.17	40.45*
PSA >4.0	521*	251*	270*	1.08	NR	NR	NR	20.5	93.8	0.14*		48.18*
*Subgroup analyses – **men aged <70 years** at biopsy N = 2,956*												
PSA >1.0	NR	NR	NR		NR	NR	NR	82.6	43.2	0.258*		
PSA >1.5	NR	NR	NR		NR	NR	NR	66.6	62.0	0.286*		
PSA >2.0	NR	NR	NR		NR	NR	NR	54.8	72.8	0.276*		
PSA >2.5	NR	NR	NR		NR	NR	NR	45.1	80.8	0.259*		
PSA >3.0	NR	NR	NR		NR	NR	NR	37.3	85.0	0.22*		
PSA >4.0	NR	NR	NR		NR	NR	NR	27.7	91.7	0.19*		
*Subgroup analyses – **men aged ≥70 years** at biopsy N = 2,631*												
PSA >1.0	NR	NR	NR		NR	NR	NR	81.4	37.6	0.19*		
PSA >1.5	NR	NR	NR		NR	NR	NR	68.3	55.1	0.23*		
PSA >2.0	NR	NR	NR		NR	NR	NR	53.9	68.5	0.22*		
PSA >2.5	NR	NR	NR		NR	NR	NR	42.0	78.3	0.20*		
PSA >3.0	NR	NR	NR		NR	NR	NR	34.3	85.2	0.195*		
PSA >4.0	NR	NR	NR		NR	NR	NR	21.1	92.9	0.14*		

PCPT Thompson 2006 N = 5,519 All screen negatives and positives biopsied													
PSA >1.0	3,556	994	2,562	2.58	1,963	1,746	217	82.08*	40.53*	3.12*	0.226*	1.1 vs 2.1: 3.87* 1.1 vs 3.1: 3.46* 1.1 vs 4.1: 3.21*	27.95*
PSA >2.0	1,916	657	1,259	1.92	3,603	3,049	554	54.25*	70.78*	2.87*	0.25*	2.1 vs 3.1: 2.78* 2.1 vs 4.1: 2.59*	34.29*
PSA >3.0	1,141	452	689	1.52	4,378	3,619	759	37.33*	84.01*	3.13*	0.21*	3.1 vs 4.1: 2.33*	39.61*
PSA >4.0	631	299	332	1.11	4,888	3,976	912	24.69*	92.29*	3.93*	0.17*		47.39*
PCPT Thompson 2004 All screen negatives biopsied *Subgroup analyses –* ***men with PSA ≤ 4.0ng/mL and normal DRE in previous 7 years*** *N = 2,950*													
PSA >0.5	2,464	417	2,047	4.91								0.6 vs 1.1: 8.89* 0.6 vs 2.1: 6.16* 0.6 vs 3.1: 5.22*	16.92*
PSA >1.0	1,673	337	1,336	3.96								1.1 vs 2.1: 4.87* 1.1 vs 3.1: 4.19*	20.14*
PSA >2.0	675	167	508	3.04								2.1 vs 3.1: 3.19*	24.74*
PSA >3.0	193	52	141	2.71									26.94*
Canby-Hagino 2007 All screen negatives (PSA 0 – 4.0 ng/mL) biopsied N = 87 ***Men with a family history of prostate cancer***													
PSA ≥0.5	77	20	57	2.85								0.5 vs 1.0: 6.67* 0.5 vs 2.0: 5.38* 0.5 vs 3.0: 4.23*	25.97*
PSA ≥1.0	54	17	37	2.18								1.0 vs 2.0: 4.6* 1.0 vs 3.0: 3.5*	31.48*
PSA ≥2.0	26	12	14	1.17								2.0 vs 3.0: 2.4*	46.15*
PSA ≥3.0	9	7	2	0.29									77.78*

**Calculated by systematic review team from published data*

∆FP/ ∆TP = difference in false positives/difference in true positives; DOR = diagnostic odds ratio (TP/FN x TN/FP); DRE = digital rectal examination; FN = false negatives; FP = false positives; NR = not reported; PCPT = Prostate Cancer Prevention Trial; PPV = positive predictive value = TP/ screen positive biopsied; ProtecT = Prostate Testing for Cancer and Treatment; PSA = prostate specific antigen; sensitivity = TP/(TP+FN); specificity = TN/(TN+FP); TN = true negatives; TP = true positives; Youden's Index = (sensitivity + specificity – 1)

Table 5: Results of studies reporting performance characteristics with respect to prostate cancer detection of various PSA thresholds used in the screening arm of the **European Randomised Study of Screening for Prostate Cancer** (ERSPC) which showed a cancer mortality benefit for prostate cancer screening

PSA threshold	Cohort (reference)	N screened	Screen positive biopsied (No.)	TP (No.)	FP (No.)	FP/TP	ΔFP/ΔTP	PPV (%)	NND
ERSPC – 7 centres									
Overall – Screening rounds combined – 11.0 years median follow-up (Schroder 2012)									
~3.0ng/mL	Ages 50 – 74 years	82,816	22,699	5,455	17,244	3.16		24.03*	NR
	Core age group	72,891	19,646	4,757	14,889	3.13		24.21*	33
ERSPC – Rotterdam									
Individual screening rounds – 12.8 years median follow-up (rounds 3 and 4)									
	Ages 55 – 74 years								
≥3.0ng/mL	Round 2 (Postma 2007)	12,520	2,211	441	1,770	4.01		19.95*	NR
≥4.0ng/mL	Round 2 (Postma 2007)	12,520	1,381	267	1,114	4.17	3.0 vs 4.0: 3.77*	19.33*	
≥3.0ng/mL	Round 3 (Roobol 2013)	7,609	1,384	279	1,105	3.96		20.16*	NR
≥3.0ng/mL	Round 4 (Roobol 2013)	3,106	557	132	425	3.22		23.70*	NR
ERSPC – Goteborg									
Individual screening rounds – 13.5 years median follow-up (Kilpelainen 2011)									
	Ages 50 – 64 years								
≥3.4ng/mL	Round 2	5,260	512	111	401	3.61		21.68*	NR
≥2.9ng/mL	Round 4[#]	4,622	629	133	496	3.73		21.14*	NR
≥2.9ng/mL	Round 5	4,114	546	111	435	3.92		20.33*	NR
≥2.5ng/mL	Round 6	3,475	614	147	467	3.18		23.94*	NR

[#]Did not include round 3 as men with PSA <1.0ng/mL at invitation round 2 not invited to third invitation round

**Calculated by systematic review team from published data*

ΔFP/ ΔTP = difference in false positives/difference in true positives; FP = false positives; NND = numbers needed to detect to prevent one prostate cancer death; NR = not reported; PPV = positive predictive value = TP/ screen positive biopsied; PSA = prostate specific antigen; TP = true positives

II GLEASON SCORE > 7 PROSTATE CANCER DETECTION

Table 6: Results of studies examining performance characteristics of different PSA thresholds with respect to Gleason Score >7 prostate cancer detection

PSA threshold	Screen positive biopsied (No.)	TP (No.)	FP (No.)	FP/TP	Screen negative biopsied (No.)	TN (No.)	FN (No.)	Sensitivity	Specificity	Youden's Index	ΔFP/ ΔTP	PPV (%)
PCPT Thompson 2005 N = 5,575 All screen negatives and positives biopsied												
PSA >1.0	3,591	54*	3,537*	65.50	NR	NR	NR	94.7	35.9	0.306*	1.1 vs 1.6: 323.67 1.1 vs 2.1: 331 1.1 vs 2.6: 240.33 1.1 vs 3.1: 165.93 1.1 vs 4.1: 117.44	1.50*
PSA >1.5	2,617	51*	2,566*	50.31	NR	NR	NR	89.5	53.5	0.430*	1.6 vs 2.1: 342 1.6 vs 2.6: 198.67 1.6 vs 3.1: 126.5 1.6 vs 4.1: 89.32	1.95*
PSA >2.0	1,931	49*	1,882*	38.41	NR	NR	NR	86.0	65.9	0.519*	2.1 vs 2.6: 127 2.1 vs 3.1: 83.4 2.1 vs 4.1: 64.05	2.54*
PSA >2.5	1,419	45*	1,374*	30.53	NR	NR	NR	78.9	75.1	0.540*	2.6 vs 3.1: 54.33 2.6 vs 4.1: 48.31	3.17*
PSA >3.0	1,087	39*	1,048*	26.87	NR	NR	NR	68.4	81.0	0.494*	3.1 vs 4.1: 44.7	3.59*
PSA >4.0	630	29*	601*	20.72	NR	NR	NR	50.9	89.1	0.400*		4.60*
*Subgroup analyses – **men aged <70 years at biopsy** N = 2,950*												
PSA >1.0	NR	NR	NR		NR	NR	NR	96.3	38.0	0.343*		
PSA >1.5	NR	NR	NR		NR	NR	NR	96.3	56.4	0.527*		
PSA >2.0	NR	NR	NR		NR	NR	NR	92.6	67.6	0.602*		

PSA >2.5	NR	NR	NR		NR	NR	NR	88.9	75.9	0.648*	
PSA >3.0	NR	NR	NR		NR	NR	NR	74.1	80.8	0.549*	
PSA >4.0	NR	NR	NR		NR	NR	NR	59.3	88.1	0.474*	
*Subgroup analyses – **men aged ≥70 years** at biopsy N = 2,625*											
PSA >1.0	NR	NR	NR		NR	NR	NR	93.3	33.6	0.269*	
PSA >1.5	NR	NR	NR		NR	NR	NR	83.3	50.2	0.335*	
PSA >2.0	NR	NR	NR		NR	NR	NR	80	64.0	0.440*	
PSA >2.5	NR	NR	NR		NR	NR	NR	70	74.2	0.442*	
PSA >3.0	NR	NR	NR		NR	NR	NR	63.3	81.3	0.446*	
PSA >4.0	NR	NR	NR		NR	NR	NR	43.3	90.1	0.334*	
Kobayashi 2006	N = 182		(men with PSA 2.5 – 10.0 ng/mL)								
PSA ≥ 2.5	182	1	181	181						2.5 vs 4.1: 80/0*****	0.55*
PSA >4.0	102	1	101	101							0.98*

**Calculated by systematic review team from published data*

∆FP/ ∆TP = difference in false positives/difference in true positives; DOR = diagnostic odds ratio (TP/FN x TN/FP); FN = false negatives; FP = false positives; NR = not reported; PCPT = Prostate Cancer Prevention Trial; PPV = positive predictive value = TP/ screen positive biopsied; PSA = prostate specific antigen; sensitivity = TP/(TP+FN); specificity = TN/(TN+FP); TN = true negatives; TP = true positives; Youden's Index = (sensitivity + specificity – 1

Table 7: Results of studies reporting performance characteristics with respect to detection of prostate cancer with Gleason Score >7 of various PSA thresholds used in the screening arm of the European Randomised Study of Screening for Prostate Cancer (ERSPC) which showed a cancer mortality benefit for prostate cancer screening

PSA threshold	Cohort	N screened	Screen positive biopsied (No.)	TP (No.)	FP (No.)	FP/TP	PPV (%)
ERSPC – Rotterdam							
Individual screening rounds 2 and 3 (Gosselaar 2008)							
	Ages 55 – 74 years						
≥3.0ng/mL	Round 2	12,533	2,220	16	2,204	137.75	0.72*
≥3.0ng/mL	Round 3	5,625	971	7	964	137.71	0.72*
ERSPC – Goteborg							
Screening rounds 2 – 6 combined (Vickers 2009)							
≥3.4, 2.9 or 2.5ng/mL	Ages 50 – 64 years Men undergoing initial biopsy at screening rounds 2 – 6	NR	1,241	8	1,233	154.13	0.64*

**Calculated by systematic review team from published data*

∆FP/ ∆TP = difference in false positives/difference in true positives; FP = false positives; NND = numbers needed to detect to prevent one prostate cancer death; NR = not reported; PPV = positive predictive value = TP/ screen positive biopsied; PSA = prostate specific antigen; TP = true positives

III GLEASON SCORE > 6 PROSTATE CANCER DETECTION

Table 8: Results of studies examining performance characteristic of different PSA thresholds with respect to Gleason Score > 6 prostate cancer detection

PSA threshold	Screen positive biopsied (No.)	TP (No.)	FP (No.)	FP/TP	Screen negative biopsied (No.)	TN (No.)	FN (No.)	Sensitivity	Specificity	DOR	Youden's Index	∆FP/ ∆TP	PPV (%)
Muntener 2010	N = 506	(men with normal DRE and PSA 2.5 – 10.0ng/mL)											
PSA ≥2.5	506	28	478	17.07								2.5 vs 4.0: 52.5*	5.53*
PSA ≥4.0	292	24	268	11.17									8.22*
Kobayashi 2006	N = 182	(men with PSA 2.5 – 10.0ng/mL)											
PSA ≥2.5	182	12	170	14.17								2.5 vs 4.1: 19.0*****	6.59*
PSA >4.0	102	8	94	11.75									7.84*
Park 2006	N = 579	(men with normal DRE and PSA 3.0 – 10.0ng/mL)											
PSA ≥3.0	579	50	529	10.58								3.0 vs 4.1: 11.22*****	8.64*
PSA >4.0	469	41	428	10.44									8.74*
*Subgroup analysis – **men with normal TRUS***	N = 450												
PSA ≥3.0	450	35	415	11.86								3.0 vs 4.1: 11.14*****	7.78*
PSA >4.0	365	28	337	12.04									7.67*
ProtecT Rosario 2008	N = 4,102	(men with PSA 3.0 – 19.9ng/mL)											
PSA ≥3.0	4,102	366	3,736	10.21								3.0 vs 3.5: 28.70***** 3.0 vs 4.0: 21.36*****	8.92*
PSA ≥3.5	3,122	333	2,789	8.38								3.5 vs 4.0: 15.72*****	10.67*
PSA ≥4.0	2,403	290	2,113	7.29									12.07*

PCPT Thompson 2005 N = 5,575 All screen negatives and positives biopsied												
PSA >1.0	3,587	232*	3,355*	14.46	NR	NR	NR	92.8	37.0	0.298*	1.1 vs 1.6: 45.14 1.1 vs 2.1: 37.53 1.1 vs 2.6: 32.88 1.1 vs 3.1: 27.41 1.1 vs 4.1: 21.54	6.47*
PSA >1.5	2,618	211*	2,407*	11.41	NR	NR	NR	84.4	54.8	0.392*	1.6 vs 2.1: 30.27 1.6 vs 2.6: 26.88 1.6 vs 3.1: 21.85 1.6 vs 4.1: 17.04	8.06*
PSA >2.0	1,930	189*	1,741*	9.21	NR	NR	NR	75.6	67.3	0.429*	2.1 vs 2.6: 23.33 2.1 vs 3.1: 17.73 2.1 vs 4.1: 13.73	9.79*
PSA >2.5	1,419	168*	1,251*	7.45	NR	NR	NR	67.2	76.5	0.437*	2.6 vs 3.1: 12.83 2.6 vs 4.1: 10.72	11.84*
PSA >3.0	1,087	144*	943*	6.55	NR	NR	NR	57.6	82.3	0.399*	3.1 vs 4.1: 9.53	13.25*
PSA >4.0	634	101*	533*	5.28	NR	NR	NR	40.4	90.0	0.304*		15.93*
*Subgroup analyses – **men aged <70 years at biopsy** N = 2,950*												
PSA >1.0	NR	NR	NR		NR	NR	NR	92.7	39.1	0.318*		
PSA >1.5	NR	NR	NR		NR	NR	NR	84.7	57.7	0.424*		
PSA >2.0	NR	NR	NR		NR	NR	NR	75.0	68.9	0.439*		
PSA >2.5	NR	NR	NR		NR	NR	NR	66.1	77.1	0.432*		
PSA >3.0	NR	NR	NR		NR	NR	NR	54.0	81.8	0.358*		
PSA >4.0	NR	NR	NR		NR	NR	NR	42.7	89.0	0.317*		
*Subgroup analyses – **men aged ≥70 years** at biopsy N = 2,625*												
PSA >1.0	NR	NR	NR		NR	NR	NR	92.9	34.6	0.275*		
PSA >1.5	NR	NR	NR		NR	NR	NR	84.1	51.5	0.356*		
PSA >2.0	NR	NR	NR		NR	NR	NR	76.2	65.5	0.417*		
PSA >2.5	NR	NR	NR		NR	NR	NR	68.3	75.8	0.441*		
PSA >3.0	NR	NR	NR		NR	NR	NR	61.1	82.9	0.440*		

PSA >4.0	NR	NR	NR		NR	NR	NR	38.1	91.2		0.293*		
PCPT Thompson 2006 N = 5,519 All screen negatives and positives biopsied													
PSA >1.0	3,556	238	3,318	13.94	1,963	1,944	19	92.61*	36.94*	7.34*	0.296*	1.1 vs 2.1: 37.14* 1.1 vs 3.1: 26.76* 1.1 vs 4.1: 20.67*	6.69*
PSA >2.0	1,916	195	1,721	8.83	3,603	3,541	62	75.88*	67.29*	6.47*	0.432*	2.1 vs 3.1: 16.61* 2.1 vs 4.1: 12.97*	10.18*
PSA >3.0	1,141	151	990	6.56	4,378	4,272	106	58.75*	81.19*	6.15*	0.399*	3.1 vs 4.1: 9.63*	13.23*
PSA >4.0	631	103	528	5.13	4,888	4,734	154	40.08*	90.00*	6.00*	0.301*		16.32*
PCPT Thompson 2004 All screen negatives biopsied *Subgroup analyses –* ***men with PSA ≤4.0ng/mL and normal DRE in previous 7 years*** *N = 2,950*													
PSA >0.5	2,464	63	2,401	38.11								0.6 vs 1.1: 97.88* 0.6 vs 2.1: 62.89* 0.6 vs 3.1: 44.42*	2.56*
PSA >1.0	1,673	55	1,618	29.42								1.1 vs 2.1: 48.9* 1.1 vs 3.1: 34.24*	3.29*
PSA >2.0	675	35	640	18.29								2.1 vs 3.1: 20.91*	5.19*
PSA >3.0	193	13	180	13.85									6.74*

**Calculated by systematic review team from published data*

∆FP/ ∆TP = difference in false positives/difference in true positives; DOR = diagnostic odds ratio (TP/FN x TN/FP); DRE = digital rectal examination; FN = false negatives; FP = false positives; NR = not reported; PCPT = Prostate Cancer Prevention Trial; PPV = positive predictive value = TP/ screen positive biopsied; ProtecT = Prostate Testing for Cancer and Treatment; PSA = prostate specific antigen; sensitivity = TP/(TP+FN); specificity = TN /(TN+FP); TN = true negatives; TP = true positives; TRUS = transrectal ultrasound; Youden's Index = (sensitivity + specificity – 1)

Table 9: Results of studies reporting performance characteristics with respect to detection of prostate cancer with Gleason Score >6 of various PSA thresholds used in the screening arm of the European Randomised Study of Screening for Prostate Cancer (ERSPC) which showed a cancer mortality benefit for prostate cancer screening

PSA threshold	Cohort	N screened	Screen positive biopsied (No.)	TP (No.)	FP (No.)	FP/TP	PPV (%)
ERSPC – Rotterdam							
Individual screening rounds 2 and 3 (Gosselaar 2008)							
	Ages 55 – 74 years						
≥3.0ng/mL	Round 2	12,533	2,220	98	2,122	21.65	4.41*
≥3.0ng/mL	Round 3	5,625	971	31	940	30.32	3.19*
ERSPC – Goteborg							
Screening rounds 2 - 6 combined (Vickers 2009)							
3.4, 2.9 or 2.5 ng/mL	Ages 50 – 64 years Men undergoing initial biopsy at screening rounds 2 – 6	NR	1,241	45	1,196	26.58	3.63*

**Calculated by systematic review team from published data*

∆FP/ ∆TP = difference in false positives/difference in true positives; FP = false positives; NR = not reported; PPV = positive predictive value = TP/ screen positive biopsied; PSA = prostate specific antigen; TP = true positives

IV GLEASON SCORE 2 – 6 PROSTATE CANCER DETECTION

Table 10: Results of studies reporting performance characteristics with respect to detection of prostate cancer with Gleason Score 2 – 6 of various PSA thresholds used in the screening arm of the European Randomised Study of Screening for Prostate Cancer (ERSPC) which showed a cancer mortality benefit for prostate cancer screening

PSA threshold	Cohort	N screened	Screen positive biopsied (No.)	TP (No.)	FP (No.)	FP/TP	PPV
ERSPC – Rotterdam							
Individual screening rounds 2 and 3 (Gosselaar 2008)							
	Ages 55 – 74 years						
≥3.0ng/mL	Round 2	12,533	2,220	343	1,877	5.47	15.45
≥3.0ng/mL	Round 3	5,625	971	154	817	5.31	15.86
ERSPC – Goteborg							
Screening rounds 2 - 6 combined (Vickers 2009)							
3.4, 2.9 or 2.5ng/mL	Ages 50 – 64 years Men undergoing initial biopsy at screening rounds 2 – 6	NR	1,241	269	972	3.61	21.68

**Calculated by systematic review team from published data*

∆FP/ ∆TP = difference in false positives/difference in true positives; FP = false positives; NR = not reported; PPV = positive predictive value = TP/ screen positive biopsied; PSA = prostate specific antigen; TP = true positives

2.6. Body of Evidence

I PROSTATE CANCER DETECTION

Name of study	Participants	Number biopsied	Level of evidence *	Risk of bias**	PSA threshold/s (ng/mL)	ΔFP/ ΔTP	FP/TP	Sensitivity	Specificity	DOR	Youden's Index
Biopsy independent of screening result											
PCPT Thompson 2005	Pre-screened men **any PSA level**	5,587	III-2	At risk	> 1.0		2.61	83.4	38.9		0.22
					> 1.0 vs > 1.5	4.29					
					> 1.0 vs > 2.0	3.88					
					> 1.0 vs > 2.5	3.50					
					> 1.0 vs > 3.0	3.32					
					> 1.0 vs > 4.0	3.11					
					> 1.5		2.20	67.0	58.7		0.26
					> 1.5 vs > 2.0	3.40					
					> 1.5 vs > 2.5	3.01					
					> 1.5 vs > 3.0	2.86					
					> 1.5 vs > 4.0	2.69					
					> 2.0		1.86	52.6	72.5		0.25
					> 2.0 vs > 2.5	2.54					
					> 2.0 vs > 3.0	2.48					
					> 2.0 vs > 4.0	2.37					
					> 2.5		1.66	40.5	81.1		0.22
					> 2.5 vs > 3.0	2.39					
					> 2.5 vs > 4.0	2.26					
					> 3.0		1.47	32.2	86.7		0.19
					> 3.0 vs > 4.0	2.17					
					> 4.0		1.08	20.5	93.8		0.14

	Subgroup – **men aged <70 years**	2,956			> 1.0			82.6	43.2		0.26
					> 1.5			66.6	62.0		0.29
					> 2.0			54.8	72.8		0.28
					> 2.5			45.1	80.8		0.26
					> 3.0			37.3	85.0		0.22
					> 4.0			27.7	91.7		0.19
	Subgroup – **men aged ≥70 years**	2,631			> 1.0			81.4	37.6		0.19
					> 1.5			68.3	55.1		0.23
					> 2.0			53.9	68.5		0.22
					> 2.5			42.0	78.3		0.20
					> 3.0			34.3	85.2		0.20
					> 4.0			21.1	92.9		0.14
PCPT Thompson 2006	*Subgroup* – men with **2 PSA tests in 3 years** prior to biopsy	5,519	III-2	At risk	> 1.0		2.58	82.08	40.53	3.12	0.23
					> 1.0 vs > 2.0	3.87					
					> 1.0 vs > 3.0	3.46					
					> 1.0 vs > 4.0	3.21					
					> 2.0		1.92	54.25	70.78	2.87	0.25
					> 2.0 vs > 3.0	2.78					
					> 2.0 vs > 4.0	2.59					
					> 3.0		1.52	37.33	84.01	3.13	0.21
					> 3.0 vs > 4.0	2.33					
					> 4.0		1.11	24.69	92.29	3.93	0.17
PCPT Thompson 2004	*Subgroup* – men with **PSA ≤4.0 ng/mL and normal DRE in past 7 years**	2,950	III-2	At risk	> 0.5		4.91				
					> 0.5 vs > 1.0	8.89					
					> 0.5 vs > 2.0	6.16					
					> 0.5 vs > 3.0	5.22					
					> 1.0		3.96				
					> 1.0 vs > 2.0	4.87					
					> 1.0 vs > 3.0	4.19					
					> 2.0		3.04				
					> 2.0 vs > 3.0	3.19					
					>3.0		2.71				

Canby-Hagino 2007	Men with **family history** of prostate cancer and **PSA ≤4.0ng/mL**	87	III-2	At risk	≥ 0.5		2.85
					≥ 0.5 vs ≥ 1.0	6.67	
					≥ 0.5 vs ≥ 2.0	5.38	
					≥ 0.5 vs ≥ 3.0	4.23	
					≥ 1.0		2.18
					≥ 1.0 vs ≥ 2.0	4.6	
					≥ 1.0 vs ≥ 3.0	3.5	
					≥ 2.0		1.17
					≥ 2.0 vs ≥ 3.0	2.4	
					≥ 3.0		0.29
Biopsy dependent on screening result							
ERSPC *7 centres combined* Schroder 2012	Primarily men with PSA **≥3.0ng/mL**		III-2	At risk			
	Age at initial screening						
	50 – 74 years	22,699			~3.0		3.16
	55 – 69 years	19,646			~3.0		3.13
Rotterdam centre Postma 2007, Roobol 2013	Men with PSA **≥3.0 ng/mL**		III-2	At risk			
	Age at initial screening						
	50 – 74 years						
	Screening round 2	2,211			≥ 3.0		4.01
					≥ 3.0 vs ≥ 4.0	3.77	
					≥ 4.0		4.17
	Screening round 3	1,384			≥ 3.0		3.96
	Screening round 4	557			≥ 3.0		3.22
Goteborg centre Kilpelainen 2011	Men with PSA **≥2.5 ng/mL**		III-2	At risk			
	Age at initial screening						
	50 – 64 years						
	Screening round 2	512			≥ 3.4		3.61
	Screening round 4	629			≥ 2.9		3.73

	Screening round 5	546			≥ 2.9		3.92
	Screening round 6	614			≥ 2.5		3.18
Kobayashi 2006	Men with PSA **2.5 – 10.0 ng/mL**	182	III-2	At risk	≥ 2.5 ≥ 2.5 vs > 4.0 >4.0	2.81	2.25 1.91
Shim 2007	Men with **normal DRE** and PSA **2.5 – 20.0 ng/mL**	721	III-2	At risk	≥ 2.5 ≥ 2.5 vs ≥ 4.0 ≥ 4.0	5.5	3.34 3.18
Muntener 2010	Men with **normal DRE** and PSA **2.5 – 10.0 ng/mL**	506	III-2	At risk	≥ 2.5 ≥ 2.5 vs ≥ 4.0 ≥ 4.0	4.78	3.22 2.52
Rosario 2008	Men with PSA **3.0 – 19.9 ng/mL**	4,102	III-2	At risk	≥ 3.0 ≥ 3.0 vs ≥ 3.5 ≥ 3.0 vs ≥ 4.0 ≥ 3.5 ≥ 3.5 vs ≥ 4.0 ≥ 4.0	3.46 3.21 2.91	2.11 1.84 1.63
Park 2006	Men with **normal DRE** and PSA **3.0 – 10.0 ng/mL**	579	III-2	At risk	≥ 3.0 ≥ 3.0 vs > 4.0 > 4.0	3.07	3.35 3.42
	Subgroup – men with **normal TRUS**	450			≥ 3.0 ≥ 3.0 vs > 4.0 > 4.0	2.86	3.89 4.21

ΔFP/ ΔTP = difference in false positives/difference in true positives; DOR = diagnostic odds ratio (TP/FN x TN/FP); DRE = digital rectal examination; ERSPC = European Randomised Study of Screening for Prostate Cancer; FP = false positives; PCPT = Prostate Cancer Prevention Trial; PSA = prostate specific antigen; TP = true positives; TRUS = trans-rectal ultrasound; Youden's Index = (sensitivity + specificity – 1)

Shaded data = includes or compares data for total PSA threshold of 3.0 ng/mL

**Refer to appendix B for detailed explanations of rating scores; **See Tables 2-3 for risk of bias assessment*

II GLEASON SCORE > 7 PROSTATE CANCER DETECTION

Name of study	Participants	Number biopsied	Level of evidence*	Risk of bias**	PSA threshold/s (ng/mL)	ΔFP/ ΔTP	FP/TP	Sensitivity	Specificity	Youden's Index
Biopsy independent of screening result										
PCPT Thompson 2005	Pre-screened men **any PSA level**	5,575	III-2	At risk	> 1.0		65.50	94.7	35.9	0.31
					> 1.0 vs > 1.5	323.7				
					> 1.0 vs > 2.0	331.0				
					> 1.0 vs > 2.5	240.3				
					> 1.0 vs > 3.0	165.9				
					> 1.0 vs > 4.0	117.4				
					> 1.5		50.31	89.5	53.5	0.43
					> 1.5 vs > 2.0	342.0				
					> 1.5 vs > 2.5	198.7				
					> 1.5 vs > 3.0	126.5				
					> 1.5 vs > 4.0	89.3				
					> 2.0		38.41	86.0	65.9	0.52
					> 2.0 vs > 2.5	127.0				
					> 2.0 vs > 3.0	83.4				
					> 2.0 vs > 4.0	64.1				
					> 2.5		30.53	78.9	75.1	0.54
					> 2.5 vs > 3.0	54.3				
					> 2.5 vs > 4.0	48.3				
					> 3.0		26.87	68.4	81.0	0.49
					> 3.0 vs > 4.0	44.7				
					> 4.0		20.72	50.9	89.1	0.40
	Subgroup - **men aged <70 years**	2,950			> 1.0			96.3	38.0	0.34
					> 1.5			96.3	56.4	0.53
					> 2.0			92.6	67.6	0.60
					> 2.5			88.9	75.9	0.65
					> 3.0			74.1	80.8	0.55
					> 4.0			59.3	88.1	0.47

	Subgroup – **men aged ≥70 years**	2,625			> 1.0 > 1.5 > 2.0 > 2.5 > 3.0 > 4.0		93.9 83.3 80 70 63.3 43.3	33.6 50.2 64.0 74.2 81.3 90.1	0.27 0.34 0.44 0.44 0.45 0.33
Biopsy dependent on screening result									
ERSPC *Rotterdam centre* Gosselaar 2008	Men with PSA **≥3.0 ng/mL** Age at initial screening 50 – 74 years Screening round 2 Screening round 3	 2,220 971	III-2	At risk	 ≥ 3.0 ≥ 3.0		 137.8 137.7		
Kobayashi 2006	Men with PSA **2.5 – 10.0ng/mL**	182	III-2	At risk	≥ 2.5 ≥ 2.5 vs > 4.0 > 4.0	80/0	181 101		

ΔFP/ ΔTP = difference in false positives/ difference in true positives; ERSPC = European Randomised Study of Screening for Prostate Cancer; FP = false positives; PCPT = Prostate Cancer Prevention Trial; PSA = prostate specific antigen; TP = true positives; Youden's Index = (sensitivity + specificity – 1)

Shaded data = includes or compares data for total PSA threshold of 3.0 ng/mL
**Refer to appendix B for detailed explanations of rating scores; **See Tables 2-3 for risk of bias assessment*

III GLEASON SCORE > 6 PROSTATE CANCER DETECTION

Name of study	Participants	Number biopsied	Level of evidence *	Risk of bias**	PSA threshold/s (ng/mL)	ΔFP/ ΔTP	FP/TP	Sensitivity	Specificity	DOR	Youden's Index
Biopsy independent of screening result											
PCPT Thompson 2005	Pre-screened men **any PSA level**	5,575	III-2	At risk	> 1.0		14.46	92.8	37.0		0.30
					> 1.0 vs > 1.5	45.14					
					> 1.0 vs > 2.0	37.53					
					> 1.0 vs > 2.5	32.88					
					> 1.0 vs > 3.0	27.41					
					> 1.0 vs > 4.0	21.54					
					> 1.5		11.41	84.4	54.8		0.39
					> 1.5 vs > 2.0	30.27					
					> 1.5 vs > 2.5	26.88					
					> 1.5 vs > 3.0	21.85					
					> 1.5 vs > 4.0	17.04					
					> 2.0		9.21	75.6	67.3		0.43
					> 2.0 vs > 2.5	23.33					
					> 2.0 vs > 3.0	17.73					
					> 2.0 vs > 4.0	13.73					
					> 2.5		7.45	67.2	76.5		0.44
					> 2.5 vs > 3.0	12.83					
					> 2.5 vs > 4.0	10.72					
					> 3.0		6.55	57.6	82.3		0.40
					> 3.0 vs > 4.0	9.53					
					> 4.0		5.28	40.4	90.0		0.30
	Subgroup – **men aged <70 years**	2,950			> 1.0			92.7	39.1		0.32
					> 1.5			84.7	57.7		0.42
					> 2.0			75.0	68.9		0.44
					> 2.5			66.1	77.1		0.43
					> 3.0			54.0	81.8		0.36
					> 4.0			42.7	89.0		0.32

	Subgroup – **men aged ≥70 years**	2,625			> 1.0			92.9	34.6		0.28
					> 1.5			84.1	51.5		0.36
					> 2.0			76.2	65.5		0.42
					> 2.5			68.3	75.8		0.44
					> 3.0			61.1	82.9		0.44
					> 4.0			38.1	91.2		0.29
PCPT Thompson 2006	*Subgroup* – men with **2 PSA tests in 3 years** prior to biopsy	5,519	III-2	At risk	> 1.0		13.94	92.61	36.94	7.34	0.30
					> 1.0 vs > 2.0	37.14					
					> 1.0 vs > 3.0	26.76					
					> 1.0 vs > 4.0	20.67					
					> 2.0		8.83	75.88	67.29	6.47	0.43
					> 2.0 vs > 3.0	16.61					
					> 2.0 vs > 4.0	12.97					
					> 3.0		6.56	58.75	81.19	6.15	0.40
					> 3.0 vs > 4.0	9.63					
					> 4.0		5.13	40.08	90.00	6.00	0.30
PCPT Thompson 2004	*Subgroup* – men with **PSA ≤4.0 ng/mL and normal DRE in past 7 years**	2,950	III-2	At risk	> 0.5		38.11				
					> 0.5 vs > 1.0	97.88					
					> 0.5 vs > 2.0	62.89					
					> 0.5 vs > 3.0	44.42					
					> 1.0		29.42				
					> 1.0 vs > 2.0	48.9					
					> 1.0 vs > 3.0	34.24					
					> 2.0		18.29				
					> 2.0 vs > 3.0	20.91					
					> 3.0		13.85				
Biopsy dependent on screening result											
ERSPC *Rotterdam centre* Gosselaar 2008	Men with PSA **≥3.0 ng/mL**		III-2	At risk							
	Age at initial screening										
	50 – 74 years										
	Screening round 2	2,220			≥ 3.0		21.65				
	Screening round 3	971			≥ 3.0		30.32				

Kobayashi 2006	Men with PSA **2.5 – 10.0ng/mL**	182	III-2	At risk	≥ 2.5		14.17
					≥ 2.5 vs > 4.0	19.0	
					>4.0		11.75
Muntener 2010	Men with **normal DRE** and PSA **2.5 – 10.0ng/mL**	506	III-2	At risk	≥ 2.5		17.07
					≥ 2.5 vs ≥ 4.0	52.5	
					≥ 4.0		11.17
Rosario 2008	Men with **normal DRE** and PSA **3.0 – 19.9ng/mL**	4,102	III-2	At risk	≥ 3.0		10.21
					≥ 3.0 vs ≥ 3.5	28.70	
					≥ 3.0 vs ≥ 4.0	21.36	
					≥ 3.5		8.38
					≥ 3.5 vs ≥ 4.0	15.72	
					≥ 4.0		7.29
Park 2006	Men with **normal DRE** and PSA **3.0 – 10.0ng/mL**	579	III-2	At risk	≥ 3.0		10.58
					≥ 3.0 vs > 4.0	11.22	
					> 4.0		10.44
	Subgroup – men with **normal TRUS**	450			≥ 3.0		11.86
					≥ 3.0 vs > 4.0	11.14	
					> 4.0		12.04

∆FP/ ∆TP = difference in false positives/ difference in true positives; DOR = diagnostic odds ratio (TP/FN x TN/FP); DRE = digital rectal examination; ERSPC = European Randomised Study of Screening for Prostate Cancer; FP = false positives; PCPT = Prostate Cancer Prevention Trial; PSA = prostate specific antigen; TP = true positives; TRUS = trans-rectal ultrasound; Youden's Index = (sensitivity + specificity – 1)

Shaded data = includes or compares data for total PSA threshold of 3.0 ng/mL
**Refer to appendix B for detailed explanations of rating scores; ** see Tables 2-3 for risk of bias assessment*

IV GLEASON SCORE < 6 PROSTATE CANCER DETECTION

Name of study	Participants	Number biopsied	Level of evidence*	Risk of bias**	PSA threshold/s (ng/mL)	∆FP/ ∆TP	FP/TP
Biopsy dependent on screening result							
ERSPC	Men with PSA **≥3.0 ng/mL**		III-2	At risk of bias			
Rotterdam centre	Age at initial screening						
	50 – 74 years						
Gosselaar 2008	Screening round 2	2,220			≥ 3.0		5.47
	Screening round 3	971			≥ 3.0		5.31

∆FP/ ∆TP = difference in false positives/ difference in true positives; ERSPC = European Randomised Study of Screening for Prostate Cancer; FP = false positives; PSA = prostate specific antigen; TP = true positives;

Shaded data = includes or compares data for total PSA threshold of 3.0 ng/mL
**Refer to appendix B for detailed explanations of rating scores; ** see Tables 2-3 for risk of bias assessment*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the NHMRC evidence statement form.

Assessment of the relevance of the evidence in terms of whether the outcomes of diagnostic performance studies were directly relevant to the patient or whether they were surrogate outcomes was not assessed as it was not considered relevant to diagnostic performance studies.

References: Included studies

1. Canby-Hagino E, Hernandez J, Brand TC, Troyer DA, Higgins B, Ankerst DP et al. Prostate cancer risk with positive family history, normal prostate examination findings, and PSA less than 4.0 ng/mL. Urology 2007; 70(4):748-752.

2. Gosselaar C, Roobol MJ, Roemeling S, Schroder FH. The role of the digital rectal examination in subsequent screening visits in the European randomized study of screening for prostate cancer (ERSPC), Rotterdam. Eur Urol 2008; 54(3):581-588.

3. Kilpelainen TP, Tammela TL, Roobol M, Hugosson J, Ciatto S, Nelen V et al. False-positive screening results in the European randomized study of screening for prostate cancer. Eur J Cancer 2011; 47(18):2698-2705.

4. Kobayashi T, Mitsumori K, Kawahara T, Nishizawa K, Ogura K, Ide Y. Prostate cancer detection among men with prostate specific antigen levels of 2.5 to 4.0 ng/ml in a Japanese urological referral population. J Urol 2006; 175(4):1281-1285.

5. Muntener M, Kunz U, Eichler K, Puhan M, Schmid DM, Sulser T et al. Lowering the PSA threshold for prostate biopsy from 4 to 2.5 ng/ml: influence on cancer characteristics and number of men needed to biopt. Urol Int 2010; 84(2):141-146.

6. Park HK, Hong SK, Byun SS, Lee SE. T1c prostate cancer detection rate and pathologic characteristics: comparison between patients with serum prostate-specific antigen range of 3.0 to 4.0 ng/mL and 4.1 to 10.0 ng/mL in Korean population. Urology 2006; 68(1):85-88.

7. Postma R, Schroder FH, van Leenders GJ, Hoedemaeker RF, Vis AN, Roobol MJ et al. Cancer detection and cancer characteristics in the European Randomized Study of Screening for Prostate Cancer (ERSPC)--Section Rotterdam. A comparison of two rounds of screening. Eur Urol 2007; 52(1):89-97.

8. Roobol MJ, Kranse R, Bangma CH, van Leenders AG, Blijenberg BG, van Schaik RH et al. Screening for prostate cancer: results of the Rotterdam section of the European randomized study of screening for prostate cancer. Eur Urol 2013; 64(4):530-539.

9. Rosario DJ, Lane JA, Metcalfe C, Catto JW, Dedman D, Donovan JL et al. Contribution of a single repeat PSA test to prostate cancer risk assessment: experience from the ProtecT study. Eur Urol 2008; 53(4):777-784.

10. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012; 366(11):981-990.

11. Shim HB, Lee SE, Park HK, Ku JH. Digital rectal examination as a prostate cancer-screening method in a country with a low incidence of prostate cancer. Prostate Cancer Prostatic Dis 2007; 10(3):250-255.

12. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med 2004; 350(22):2239-2246.

13. Thompson IM, Ankerst DP, Chi C, Lucia MS, Goodman PJ, Crowley JJ et al. Operating characteristics of prostate-specific antigen in men with an initial PSA level of 3.0 ng/ml or lower. JAMA 2005; 294(1):66-70.

14. Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, Lucia MS et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. J Natl Cancer Inst 2006; 98(8):529-534.

15. Vickers AJ, Wolters T, Savage CJ, Cronin AM, O'Brien MF, Pettersson K et al. Prostate-specific antigen velocity for early detection of prostate cancer: result from a large, representative, population-based cohort. Eur Urol 2009; 56(5):753-760.

3. Appendices

Appendix A: Search strategies used

For Medline database:

Updated AUA

#	Searches
1	exp prostate specific antigen/
2	exp *prostatic neoplasms/di
3	((prostate or prostatic) adj2 (cancer$ or neoplas$ or carcinoma$ or adenocarcinoma$) adj3 (diagnosis or incidence or screening or detect$)).mp.
4	2 or 3
5	exp cohort studies/
6	exp retrospective study/
7	exp prospective study/
8	exp comparative study/
9	exp clinical trial/
10	(case adj control$ adj (study or studies or analysis or analyses)).mp.
11	((control$ or randomized) adj2 (study or studies or trial or trials)).mp.
12	exp practice guideline/
13	exp randomized controlled trials as topic/
14	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	1 and 4 and 14
16	limit 15 to (english language and humans and yr="2013-current")

ERSPC + PSA

#	Searches
1	prostate-specific antigen/
2	PSA.mp,tw.
3	(prostate specific antigen or prostate-specific antigen).tw,mp.
4	1 or 2 or 3
5	ERSPC.mp,tw.
6	'european randomi?ed study of screening for prostate cancer'.mp,tw.
7	5 or 6
8	4 and 7
9	limit 8 to (english language and humans and yr="1990-current")

PLCO + PSA

#	Searches
1	prostate-specific antigen/
2	PSA.mp,tw.
3	(prostate specific antigen or prostate-specific antigen).tw,mp.
4	1 or 2 or 3
5	PLCO.tw,mp.
6	('the prostate, lung, colorectal and ovarian cancer screening trial').mp,tw.
7	5 or 6
8	4 and 7
9	limit 8 to (english language and humans and yr="1990-current")

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database:

Updated AUA

#	Searches
1	'prostate specific antigen'/exp
2	'prostate cancer'/exp/mj/dm_di
3	(('prostate cancer' OR 'prostate carcinoma' OR 'prostatic neoplasm') NEAR/3 (diagnosis OR incidence OR screening OR detect*)):de,ab,ti
4	('prostate cancer' OR 'prostate carcinoma' OR 'prostatic neoplasm') NEAR/3 (diagnosis OR incidence OR screening OR detect*)
5	2 OR 3 OR 4
6	'cohort analysis'/exp
7	'retrospective study'/exp
8	'prospective study'/exp
9	'comparative study'/exp
10	'clinical trial'/exp
11	'practice guideline'/exp
12	'randomized controlled trial (topic)'/exp
13	'controlled study'/exp
14	(('case control' OR 'case controls') NEAR/1 (study OR studies OR analysis OR analyses)):de,ab,ti
15	('case control' OR 'case controls') NEAR/1 (study OR studies OR analysis OR analyses)
16	((control* OR randomised OR randomized) NEAR/2 (study OR studies OR trial OR trials)):de,ab,ti
17	(control* OR randomized OR randomised) NEAR/2 (study OR studies OR trial OR trials)
18	6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
19	1 AND 5 AND 18
20	[embase]/lim AND [2013-2014]/py AND [english]/lim AND [humans]/lim
21	19 AND 20

ERSPC + PSA

#	Searches
1	'prostate specific antigen':de
2	psa
3	'prostate specific antigen' OR 'prostate-specific antigen'
4	1 OR 2 OR 3
5	erspc
6	'european randomi?ed study of screening for prostate cancer'
7	5 OR 6
8	[embase]/lim AND [1990-2014]/py AND [english]/lim AND [humans]/lim
9	4 AND 7 AND 8

PLCO + PSA

#	Searches
1	'prostate specific antigen':de
2	psa
3	'prostate specific antigen' OR 'prostate-specific antigen'
4	1 OR 2 OR 3
5	plco
6	'prostate, lung, colorectal and ovarian cancer screening trial'
7	5 OR 6
8	[embase]/lim AND [1990-2014]/py AND [english]/lim AND [humans]/lim
9	4 AND 7 AND 8

ATSI search terms used

#	Searches
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

For Cochrane Database of Systematic Reviews – The Cochrane Library:
Title, abstracts, keywords: "prostate"

For Database of Abstracts of Reviews of Effects and Health Technology Assessment database (via OvidSP):

#	Searches
1	exp Prostatic Neoplasms/
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
3	1 or 2

Appendix B:

Level of Evidence rating criteria – Diagnostic accuracy studies

Level	Study design
I	Meta-analysis or a systematic review of level II studies
II	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation
III-1	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation
III-2	A comparison with reference standard that does not meet the criteria required for level II and III-1 evidence
III-3	Diagnostic case-control study
IV	Study of diagnostic yield (no reference standard)

According to the standards of the National Health and Medical Research Council

Appendix C:

Potentially relevant guidelines identified and reason why not adopted

Year	Organisation	Title	Reason why not adopted
2010	American Cancer Society	American Cancer Society Guideline for the Early Detection of Prostate Cancer	Did not meet pre-specified AGREE II criteria for adoption
2008	American College of Preventive Medicine	Screening for Prostate Cancer in U.S. Men: ACPM Position Statement on Preventive Practice	Did not meet pre-specified AGREE II criteria for adoption
2013	American College of Physicians	Screening for prostate cancer – guidance statement	Did not meet pre-specified AGREE II criteria for adoption
2012	American Society of Clinical Oncology	Screening for Prostate Cancer with Prostate-Specific Antigen Testing: American Society of Clinical Oncology Provisional Clinical Opinion	Did not meet pre-specified AGREE II criteria for adoption
2013	American Urological Association	Early Detection of Prostate Cancer: AUA Guideline	Did not meet pre-specified AGREE II criteria for inclusion
2011	Canadian Urological Association	Prostate Cancer Screening: Canadian guidelines	Did not meet pre-specified AGREE II criteria for adoption
2014	European Association of Urology	Guidelines on Prostate Cancer	Did not specifically address clinical question as to which screening protocol to use
2013	European Society for Medical Oncology	ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Consensus based
2010	Japanese Urological Association	Japanese Urological Association Guidelines on prostate-specific antigen-based screening for prostate cancer in 2010	Not based on a systematic review
2013	Prostate Cancer World Congress	Melbourne Consensus Statement on Prostate Cancer Testing	Consensus based
2008	National Academy of Clinical Biochemistry	National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for Use of Tumor Markers in Testicular, Prostate, Colorectal, Breast, and Ovarian Cancers	Not based on a systematic review
2010	National Health Service	Prostate Cancer Risk Management Programme: PSA testing in asymptomatic men	Consensus based
2012	NCCN	Prostate cancer early detection version 2.2012	Not based on a systematic review
2009	New Zealand Guidelines Group	Suspected cancer in primary care: Guidelines for	Not based on a systematic review

		investigation, referral and reducing ethnic disparities	
2012	Royal Australian College of General Practitioners	Guidelines for preventive activities in general practice	Not based on a systematic review
2012	Royal College of Pathologists of Australasia	Prostate specific antigen testing: Age-related interpretation in early prostate cancer detection	Consensus based
2012	University of Michigan Health System	Cancer Screening	Did not meet pre-specified AGREE II criteria for adoption
2012	US Preventive Services Task Force	Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement	Did not specifically address clinical question as to which screening protocol to use

Excluded Studies

Study	Reason for Exclusion
Abdrabo 2011	Inappropriate population
Ahyai 2008	Inappropriate population
Al-Azab 2007	Inappropriate population
Andriole 2012	Biopsy dependent on PSA level with sextant biopsy performed with no adjustment for verification bias
Andriole 2009	Biopsy dependent on PSA level with sextant biopsy performed with no adjustment for verification bias
Andriole 2005	Biopsy dependent on PSA level with sextant biopsy performed with no adjustment for verification bias
Aragona 2005	Ancillary tests (DRE or F/T PSA) trigger biopsy at lower PSA levels
Aus 2007	More mature data published
Aus 2005	No relevant outcomes
Auvinen 2009	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Babaian 2006	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Bangma 1995	Inappropriate population
Barocas 2013	Biopsy dependent on PSA level with sextant biopsy performed with no adjustment for verification bias
Beemsterboer 1999	No relevant data
Benecchi 2008	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Berenguer 2003	No relevant data
Boevee 2010	No relevant outcomes
Bokhorst 2014	No relevant outcomes
Bokhorst 2012	Inappropriate population
Botelho 2012	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Bratslavsky 2008	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Bul 2011	Inadequate biopsy
Bunker 2002	Inappropriate population
Carlsson 2011	No relevant outcomes
Carter 1997	Inappropriate or unclear indications for biopsy
Catalona 2011	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Catalona 2003	Inappropriate or unclear indications for biopsy
Catalona 2000	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Catalona 1997	Inappropriate population
Chavan 2009	Inappropriate population
Chiang 2009	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Chun 2006	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Ciatto 2003	No relevant data
Connolly 2008	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Crawford 2012	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Crawford 2011	Inappropriate study design
Crawford 2008	Narrative review

Crawford 2006	Biopsy dependent on PSA level with sextant biopsy performed with no adjustment for verification bias
Croswell 2009	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
De Koning 2002	No relevant data
Djavan 2002	Inappropriate population
Djavan 1998	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Eggener 2008	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Elliott 2008	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Etzioni 2004	Inappropriate study design
Eyre 2009	Inappropriate population
Finne 2010	No relevant data
Finne 2008	Inappropriate study design
Finne 2002	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Finne 2000	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Gann 1995	Inappropriate study design
Gilbert 2005	Inappropriate population
Gomez-Guerra 2009	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Gosselaar 2009	Inappropriate population
Gosselaar 2008a	More mature data published
Gosselaar 2006	Inappropriate population
Grenabo Bergdahl 2013	No relevant outcomes
Grenabo Bergdahl 2009	More mature data published
Grubb 2008	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Guazzoni 2011	Indications for biopsy unclear
Hakama 2001	Inappropriate study design
Hanley 2010	No relevant outcomes
Harvey 2009	Systematic review – not all included studies meet inclusion criteria
Helzlsouer 1992	Inappropriate study design
Hernandez 2009	Inappropriate population
Hill 2013	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Holmstrom 2009	Inappropriate population
Hugosson 2010	No relevant data
Hugosson 2003	No relevant data
Ishidoya 2008	Ancillary tests (DRE or F/T PSA) trigger biopsy at lower PSA levels
Ishimura 2004	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Ito 1997	Inappropriate population
Jansen 2010	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Johnson 2006	Biopsy dependent on PSA level with sextant biopsy performed with no adjustment for verification bias
Karakiewicz 2005	Inappropriate population
Kerkhof 2010	No relevant outcomes
Khatami 2006	No relevant outcomes

Kilpelainen 2013	No relevant data
Kilpelainen 2012	No relevant data
Kilpelainen 2010	No relevant data
Kim 2010	Inappropriate population
Klein 2012	Inappropriate study design
Kobayashi 2003	Inappropriate population
Kranse 1999	No relevant data
Krumholtz 2002	Inappropriate population
Kwiatkowski 2004	No relevant data
Kwiatkowski 2003	No relevant data
Lane 2007	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Laurila 2010	More mature data published
Lazzeri 2013	Inappropriate population
Lee 2011	Inappropriate population
Lee 2006	Ancillary tests (DRE or F/T PSA) trigger biopsy at lower PSA levels
Leite 2008	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Liang 2010	Inappropriate study design
Loeb 2012a	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Loeb 2012b	No relevant outcomes
Loeb 2012c	No relevant outcomes
Loeb 2007	Inappropriate study design
Lucia 2008	Inappropriate population
Lujan 2006	No relevant data
Lynn 2000	Inappropriate population
Maattanen 2007	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Makinen 2004	No relevant data
Makinen 2003	No relevant data
Makinen 2002	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
McLernon 2006	Inappropriate or unclear indications for biopsy
Mistry 2003	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Moul 2007	Ancillary tests (DRE or F/T PSA) trigger biopsy at lower PSA levels
Na 2013	Ancillary tests (DRE or F/T PSA) trigger biopsy at lower PSA levels
Na 2012	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Nadler 2005	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Nelen 2010	No relevant data
Nelen 2003	No relevant data
Oesterling 1993	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Okihara 2006	No relevant outcomes
Otto 2010a	No relevant outcomes
Otto 2010b	No relevant data
Otto 2003	No relevant outcomes

Paez 2003	No relevant outcomes
Parekh 2006	Inappropriate population
Partin 2003	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Patel 2013	Inappropriate population
Paterson 2013	Inappropriate population
Pelzer 2005a	Inappropriate or unclear indications for biopsy
Pelzer 2005b	Inappropriate or unclear indications for biopsy
Pepe 2007	Ancillary tests (DRE or F/T PSA) trigger biopsy at lower PSA levels
Perdona 2013	Inappropriate population
Pinsky 2012	Inappropriate population
Pinsky 2007	Biopsy dependent on PSA level with sextant biopsy performed with no adjustment for verification bias
Pinsky 2005	Biopsy dependent on PSA level with sextant biopsy performed with no adjustment for verification bias
Prior 2010	Inappropriate population
Punglia 2003	Inadequate biopsy
Raaijmakers 2004a	No relevant data
Raaijmakers 2004b	More mature data published
Raaijmakers 2002	No relevant outcomes
Randazzo 2013	Inappropriate population
Reissigl 1997	Inappropriate population
Rietbergen 1998a	No relevant outcomes
Rietbergen 1998b	No relevant outcomes
Roddam 2007	No relevant outcomes
Roemeling 2007	No relevant outcomes
Roemeling 2006	No relevant outcomes
Roobol 2012a	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Roobol 2012b	No relevant outcomes
Roobol 2010a	Inadequate biopsy
Roobol 2010b	More mature data published
Roobol 2009	No relevant outcomes
Roobol 2007a	More mature data published
Roobol 2007b	No relevant outcomes
Roobol 2006	More mature data published
Roobol 2005	Inappropriate population
Roobol 2004a	Inappropriate population
Roobol 2004b	Inappropriate population
Roobol 2003	Inappropriate population
Rowe 2006	Inappropriate population
Rowe 2005	Inappropriate population
Ryden 2007	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Saito 2007	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL

Salami 2013	Inappropriate population
Scattoni 2013	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Schroder 2012	No relevant outcomes
Schroder 2010	No relevant outcomes
Schroder 2009a	More mature data published
Schroder 2009b	More mature data published
Schroder 2008a	Inappropriate study design
Schroder 2008b	No relevant outcomes
Schroder 2006	Inappropriate population
Schroder 2005	No relevant data
Schroder 2003	Narrative review
Schroder 2001	No relevant data
Schroder 2000	No relevant data
Schroder 1998	No relevant data
Schroder 1996	No relevant outcomes
Schroder 1995	No relevant outcomes
Seiler 2012	No relevant data
Seo 2007	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Shim 2007b	Ancillary tests (DRE or F/T PSA) trigger biopsy at lower PSA levels
Smith 1997	Inappropriate population
Sokoll 2010	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Spurgeon 2007	Inappropriate or unclear indications for biopsy
Standaert 1997	No relevant data
Stephan 2013a	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Stephan 2013b	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Sun 2007	Inappropriate population
Tang 2010	Inappropriate study design
Tanguay 2002	No relevant outcomes
Taylor 2004	Biopsy dependent on PSA level with sextant biopsy performed with no adjustment for verification bias
Thiesler 2007	Inappropriate population
Thompson 2006	Data published previously
Thompson 2003	No comparison of PSA performance at two or more thresholds ≤4.1ng/mL
Van Der Cruijsen-Koeter 2006	More mature data published
Van Der Cruijsen-Koeter 2005	More mature data published
Van Der Cruijsen-Koeter 2003	No relevant data
Van Der Kwast 2006	No relevant data
Van Leeuwen 2012	No relevant data
Van Leeuwen 2010a	No relevant outcomes
Van Leeuwen 2010b	No relevant outcomes
Van Leeuwen 2010c	No relevant data

Van Leeuwen 2009	Inappropriate population
Vickers 2010a	No relevant outcomes
Vickers 2010b	Inappropriate population
Vickers 2008	Inadequate biopsy
Villers 2003	No relevant data
Vis 2007	No relevant outcomes
Wallner 2013	Inappropriate study design
Wolters 2010	No relevant outcomes
Wolters 2009	More mature data published
Wolters 2008	No relevant outcomes
Wu 2004	Inappropriate population
Zhu 2011a	No relevant data
Zhu 2011b	No relevant data

References: Excluded Studies

1. Abdrabo AA, Fadlalla AI, Fadl-Elmula IM. Significance of serum total prostate specific antigen and digital rectal examination in the diagnosis of prostate cancer. Saudi Med J 2011; 32(11):1133-1136.

2. Ahyai SA, Graefen M, Steuber T, Haese A, Schlomm T, Walz J et al. Contemporary prostate cancer prevalence among T1c biopsy-referred men with a prostate-specific antigen level < or = 4.0 ng per milliliter. Eur Urol 2008; 53(4):750-757.

3. Al-Azab R, Toi A, Lockwood G, Kulkarni GS, Fleshner N. Prostate volume is strongest predictor of cancer diagnosis at transrectal ultrasound-guided prostate biopsy with prostate-specific antigen values between 2.0 and 9.0 ng/mL. Urology 2007; 69(1):103-107.

4. Andriole GL, Levin DL, Crawford ED, Gelmann EP, Pinsky PF, Chia D et al. Prostate Cancer Screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: findings from the initial screening round of a randomized trial. J Natl Cancer Inst 2005; 97(6):433-438.

5. Andriole GL, Crawford ED, Grubb RL, III, Buys SS, Chia D, Church TR et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009; 360(13):1310-1319.

6. Andriole GL, Crawford ED, Grubb RL, III, Buys SS, Chia D, Church TR et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. J Natl Cancer Inst 2012; 104(2):125-132.

7. Aragona F, Pepe P, Motta M, Saita A, Raciti G, La RP et al. Incidence of prostate cancer in Sicily: results of a multicenter case-findings protocol. Eur Urol 2005; 47(5):569-574.

8. Aus G, Damber JE, Khatami A, Lilja H, Stranne J, Hugosson J. Individualized screening interval for prostate cancer based on prostate-specific antigen level: results of a prospective, randomized, population-based study. Arch Intern Med 2005; 165(16):1857-1861.

9. Aus G, Bergdahl S, Lodding P, Lilja H, Hugosson J. Prostate cancer screening decreases the absolute risk of being diagnosed with advanced prostate cancer--results from a prospective, population-based randomized controlled trial. Eur Urol 2007; 51(3):659-664.

10. Auvinen A, Raitanen J, Moss S, de Koning HJ, Hugosson J, Tammela T et al. Test sensitivity in the European prostate cancer screening trial: results from Finland, Sweden, and the Netherlands. Cancer Epidemiol Biomarkers Prev 2009; 18(7):2000-2005.

11. Babaian RJ, Naya Y, Cheli C, Fritsche HA. The detection and potential economic value of complexed prostate specific antigen as a first line test. J Urol 2006; 175(3 Pt 1):897-901.

12. Bangma CH, Grobbee DE, Schroder FH. Volume adjustment for intermediate prostate-specific antigen values in a screening population. Eur J Cancer 1995; 31A(1):12-14.

13. Barocas DA, Grubb R, III, Black A, Penson DF, Fowke JH, Andriole G et al. Association between race and follow-up diagnostic care after a positive prostate cancer screening test in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer 2013; 119(12):2223-2229.

14. Beemsterboer PM, Kranse R, de Koning HJ, Habbema JD, Schroder FH. Changing role of 3 screening modalities in the European randomized study of screening for prostate cancer (Rotterdam). Int J Cancer 1999; 84(4):437-441.

15. Benecchi L, Pieri AM, Destro PC, Potenzoni M. Optimal measure of PSA kinetics to identify prostate cancer. Urology 2008; 71(3):390-394.

16. Berenguer A, Lujan M, Paez A, Santonja C, Pascual T. The Spanish contribution to the European Randomized Study of Screening for Prostate Cancer. BJU Int 2003; 92 Suppl 2:33-38.

17. Boevee SJ, Venderbos LD, Tammela TL, Nelen V, Ciatto S, Kwiatkowski M et al. Change of tumour characteristics and treatment over time in both arms of the European Randomized study of Screening for Prostate Cancer. Eur J Cancer 2010; 46(17):3082-3089.

18. Bokhorst LP, Zhu X, Bul M, Bangma CH, Schroder FH, Roobol MJ. Positive predictive value of prostate biopsy indicated by prostate-specific-antigen-based prostate cancer screening: trends over time in a European randomized trial*. BJU Int 2012; 110(11):1654-1660.

19. Bokhorst LP, Bangma CH, van Leenders GJ, Lous JJ, Moss SM, Schroder FH et al. Prostate-specific antigen-based prostate cancer screening: reduction of prostate cancer mortality after correction for nonattendance and contamination in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. Eur Urol 2014; 65(2):329-336.

20. Botelho F, Pina F, Figueiredo L, Cruz F, Lunet N. Does baseline total testosterone improve the yielding of prostate cancer screening? Eur J Cancer 2012; 48(11):1657-1663.

21. Bratslavsky G, Fisher HA, Kaufman RP, Jr., Voskoboynik D, Nazeer T, Mian BM. PSA-related markers in the detection of prostate cancer and high-grade disease in the contemporary era with extended biopsy. Urol Oncol 2008; 26(2):166-170.

22. Bul M, van Leeuwen PJ, Zhu X, Schroder FH, Roobol MJ. Prostate cancer incidence and disease-specific survival of men with initial prostate-specific antigen less than 3.0 ng/ml who are participating in ERSPC Rotterdam. Eur Urol 2011; 59(4):498-505.

23. Bunker CH, Patrick AL, Maharaj G, Keenan HA, Ramnarine S, Belle A et al. Prostate cancer risk is three-fold higher among men, aged 50-64, of African descent compared with men of Asian-Indian descent in Trinidad and Tobago. Ethn Dis 2002; 12(4):S3.

24. Carlsson SV, Holmberg E, Moss SM, Roobol MJ, Schroder FH, Tammela TL et al. No excess mortality after prostate biopsy: results from the European Randomized Study of Screening for Prostate Cancer. BJU Int 2011; 107(12):1912-1917.

25. Carter HB, Epstein JI, Chan DW, Fozard JL, Pearson JD. Recommended prostate-specific antigen testing intervals for the detection of curable prostate cancer. JAMA 1997; 277(18):1456-1460.

26. Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination. Enhancement of specificity with free PSA measurements. JAMA 1997; 277(18):1452-1455.

27. Catalona WJ, Partin AW, Slawin KM, Naughton CK, Brawer MK, Flanigan RC et al. Percentage of free PSA in black versus white men for detection and staging of prostate cancer: a prospective multicenter clinical trial. Urology 2000; 55(3):372-376.

28. Catalona WJ, Bartsch G, Rittenhouse HG, Evans CL, Linton HJ, Amirkhan A et al. Serum pro prostate specific antigen improves cancer detection compared to free and complexed prostate specific antigen in men with prostate specific antigen 2 to 4 ng/ml. J Urol 2003; 170(6 Pt 1):2181-2185.

29. Catalona WJ, Partin AW, Sanda MG, Wei JT, Klee GG, Bangma CH et al. A multicenter study of [-2]pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/ml prostate specific antigen range. J Urol 2011; 185(5):1650-1655.

30. Chavan PR, Chavan SV, Chavan NR, Trivedi VD. Detection rate of prostate cancer using prostate specific antigen in patients presenting with lower urinary tract symptoms: a retrospective study. J Postgrad Med 2009; 55(1):17-21.

31. Chiang IN, Chang SJ, Pu YS, Huang KH, Yu HJ, Huang CY. Comparison of 6- and 12-core prostate biopsy in Taiwanese men: impact of total prostate-specific antigen, prostate-specific antigen density and prostate volume on prostate cancer detection. Urol Int 2009; 82(3):270-275.

32. Chun FK, Perrotte P, Briganti A, Benayoun S, Lebeau T, Ramirez A et al. Prostate specific-antigen distribution in asymptomatic Canadian men with no clinical evidence of prostate cancer. BJU Int 2006; 98(1):50-53.

33. Ciatto S, Gervasi G, Frullini P, Zendron P, Zappa M. Specific features of the Italian section of the ERSPC. BJU Int 2003; 92 Suppl 2:30-32.

34. Connolly D, Black A, Murray LJ, Nambirajan T, Keane PF, Gavin A. The utility of prostate-specific antigen velocity thresholds in clinical practice: a population-based analysis. BJU Int 2008; 101(12):1507-1512.

35. Crawford ED, Pinsky PF, Chia D, Kramer BS, Fagerstrom RM, Andriole G et al. Prostate specific antigen changes as related to the initial prostate specific antigen: data from the prostate, lung, colorectal and ovarian cancer screening trial. J Urol 2006; 175(4):1286-1290.

36. Crawford ED, Abrahamsson PA. PSA-based screening for prostate cancer: how does it compare with other cancer screening tests? Eur Urol 2008; 54(2):262-273.

37. Crawford ED, Moul JW, Rove KO, Pettaway CA, Lamerato LE, Hughes A. Prostate-specific antigen 1.5-4.0 ng/mL: a diagnostic challenge and danger zone. BJU Int 2011; 108(11):1743-1749.

38. Crawford ED, Rove KO, Trabulsi EJ, Qian J, Drewnowska KP, Kaminetsky JC et al. Diagnostic performance of PCA3 to detect prostate cancer in men with increased prostate specific antigen: a prospective study of 1,962 cases. J Urol 2012; 188(5):1726-1731.

39. Croswell JM, Kramer BS, Kreimer AR, Prorok PC, Xu JL, Baker SG et al. Cumulative incidence of false-positive results in repeated, multimodal cancer screening. Ann Fam Med 2009; 7(3):212-222.

40. de Koning HJ, Auvinen A, Berenguer SA, Calais da SF, Ciatto S, Denis L et al. Large-scale randomized prostate cancer screening trials: program performances in the European Randomized Screening for Prostate Cancer trial and the Prostate, Lung, Colorectal and Ovary cancer trial. Int J Cancer 2002; 97(2):237-244.

41. Djavan B, Zlotta AR, Byttebier G, Shariat S, Omar M, Schulman CC et al. Prostate specific antigen density of the transition zone for early detection of prostate cancer. J Urol 1998; 160(2):411-418.

42. Djavan B, Remzi M, Zlotta A, Seitz C, Snow P, Marberger M. Novel artificial neural network for early detection of prostate cancer. J Clin Oncol 2002; 20(4):921-929.

43. Eggener SE, Yossepowitch O, Roehl KA, Loeb S, Yu X, Catalona WJ. Relationship of prostate-specific antigen velocity to histologic findings in a prostate cancer screening program. Urology 2008; 71(6):1016-1019.

44. Elliott CS, Shinghal R, Presti JC, Jr. The performance of prostate specific antigen, prostate specific antigen density and transition zone density in the era of extended biopsy schemes. J Urol 2008; 179(5):1756-1761.

45. Etzioni R, Falcon S, Gann PH, Kooperberg CL, Penson DF, Stampfer MJ. Prostate-specific antigen and free prostate-specific antigen in the early detection of prostate cancer: do combination tests improve detection? Cancer Epidemiol Biomarkers Prev 2004; 13(10):1640-1645.

46. Eyre SJ, Ankerst DP, Wei JT, Nair PV, Regan MM, Bueti G et al. Validation in a multiple urology practice cohort of the Prostate Cancer Prevention Trial calculator for predicting prostate cancer detection. J Urol 2009; 182(6):2653-2658.

47. Finne P, Finne R, Auvinen A, Juusela H, Aro J, Maattanen L et al. Predicting the outcome of prostate biopsy in screen-positive men by a multilayer perceptron network. Urology 2000; 56(3):418-422.

48. Finne P, Auvinen A, Aro J, Juusela H, Maattanen L, Rannikko S et al. Estimation of prostate cancer risk on the basis of total and free prostate-specific antigen, prostate volume and digital rectal examination. Eur Urol 2002; 41(6):619-626.

49. Finne P, Auvinen A, Maattanen L, Tammela TL, Ruutu M, Juusela H et al. Diagnostic value of free prostate-specific antigen among men with a prostate-specific antigen level of <3.0 microg per liter. Eur Urol 2008; 54(2):362-370.

50. Finne P, Fallah M, Hakama M, Ciatto S, Hugosson J, de KH et al. Lead-time in the European Randomised Study of Screening for Prostate Cancer. Eur J Cancer 2010; 46(17):3102-3108.

51. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. JAMA 1995; 273(4):289-294.

52. Gilbert SM, Cavallo CB, Kahane H, Lowe FC. Evidence suggesting PSA cutpoint of 2.5 ng/mL for prompting prostate biopsy: review of 36,316 biopsies. Urology 2005; 65(3):549-553.

53. Gomez-Guerra LS, Martinez-Fierro ML, Alcantara-Aragon V, Ortiz-Lopez R, Martinez-Villarreal RT, Morales-Rodriguez IB et al. Population based prostate cancer screening in north Mexico reveals a high prevalence of aggressive tumors in detected cases. BMC Cancer 2009; 9:91.

54. Gosselaar C, Roobol MJ, Roemeling S, de Vries SH, Cruijsen-Koeter I, van der Kwast TH et al. Screening for prostate cancer without digital rectal examination and transrectal ultrasound: results after four years in the European Randomized Study of Screening for Prostate Cancer (ERSPC), Rotterdam. Prostate 2006; 66(6):625-631.

55. Gosselaar C, Roobol MJ, Roemeling S, Wolters T, van Leenders GJ, Schroder FH. The value of an additional hypoechoic lesion-directed biopsy core for detecting prostate cancer. BJU Int 2008; 101(6):685-690.

56. Gosselaar C, Roobol MJ, van den Bergh RC, Wolters T, Schroder FH. Digital rectal examination and the diagnosis of prostate cancer--a study based on 8 years and three screenings within the European Randomized Study of Screening for Prostate Cancer (ERSPC), Rotterdam. Eur Urol 2009; 55(1):139-146.

57. Grenabo Bergdahl A, Aus G, Lilja H, Hugosson J. Risk of dying from prostate cancer in men randomized to screening: differences between attendees and nonattendees. Cancer 2009; 115(24):5672-5679.

58. Grenabo Bergdahl A, Holmberg E, Moss S, Hugosson J. Incidence of prostate cancer after termination of screening in a population-based randomised screening trial. Eur Urol 2013; 64(5):703-709.

59. Grubb RL, III, Pinsky PF, Greenlee RT, Izmirlian G, Miller AB, Hickey TP et al. Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian cancer screening trial: update on findings from the initial four rounds of screening in a randomized trial. BJU Int 2008; 102(11):1524-1530.

60. Guazzoni G, Nava L, Lazzeri M, Scattoni V, Lughezzani G, Maccagnano C, et al. Prostate-specific antigen (PSA) isoform p2PSA significantly improves the prediction of prostate cancer at initial extended prostate biopsies in patients with total PSA between 2.0 and 10 ng/mL: results of a prospective study in a clinical setting. Eur Urol 2011; 60(2):214-222.

61. Hakama M, Stenman UH, Aromaa A, Leinonen J, Hakulinen T, Knekt P. Validity of the prostate specific antigen test for prostate cancer screening: followup study with a bank of 21,000 sera in Finland. J Urol 2001; 166(6):2189-2191.

62. Hanley JA. Mortality reductions produced by sustained prostate cancer screening have been underestimated. J Med Screen 2010; 17(3):147-151.

63. Harvey P, Basuita A, Endersby D, Curtis B, Iacovidou A, Walker M. A systematic review of the diagnostic accuracy of prostate specific antigen. BMC Urol 2009; 9:14.

64. Helzlsouer KJ, Newby J, Comstock GW. Prostate-specific antigen levels and subsequent prostate cancer: potential for screening. Cancer Epidemiol Biomarkers Prev 1992; 1(7):537-540.

65. Hernandez DJ, Han M, Humphreys EB, Mangold LA, Taneja SS, Childs SJ et al. Predicting the outcome of prostate biopsy: comparison of a novel logistic regression-based model, the prostate cancer risk calculator, and prostate-specific antigen level alone. BJU Int 2009; 103(5):609-614.

66. Hill OT, Mason TJ, Schwartz SW, Foulis PR. Improving prostate cancer detection in veterans through the development of a clinical decision rule for prostate biopsy. BMC Urol 2013; 13:6.

67. Holmstrom B, Johansson M, Bergh A, Stenman UH, Hallmans G, Stattin P. Prostate specific antigen for early detection of prostate cancer: longitudinal study. BMJ 2009; 339:b3537.

68. Hugosson J, Aus G, Bergdahl S, Fernlund P, Frosing R, Lodding P et al. Population-based screening for prostate cancer by measuring free and total serum prostate-specific antigen in Sweden. BJU Int 2003; 92 Suppl 2:39-43.

69. Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. Lancet Oncol 2010; 11(8):725-732.

70. Ishidoya S, Ito A, Orikasa K, Kawamura S, Tochigi T, Kuwahara M et al. The outcome of prostate cancer screening in a normal Japanese population with PSA of 2-4 ng/ml and the free/total PSA under 12%. Jpn J Clin Oncol 2008; 38(12):844-848.

71. Ishimura T, Sakai I, Hara I, Eto H, Miyake H. Clinical outcome of transrectal ultrasound-guided prostate biopsy, targeting eight cores, for detecting prostate cancer in Japanese men. Int J Clin Oncol 2004; 9(1):47-50.

72. Ito K, Ichinose Y, Kubota Y, Imai K, Yamanaka H. Clinicopathological features of prostate cancer detected by transrectal ultrasonography-guided systematic six-sextant biopsy. Int J Urol 1997; 4(5):474-479.

73. Jansen FH, van Schaik RH, Kurstjens J, Horninger W, Klocker H, Bektic J et al. Prostate-specific antigen (PSA) isoform p2PSA in combination with total PSA and free PSA improves diagnostic accuracy in prostate cancer detection. Eur Urol 2010; 57(6):921-927.

74. Johnson DB. The effects of an abnormal cancer screening test on health related quality of life. International Journal of Cancer Research 2006; 2(3):277-289.

75. Karakiewicz PI, Benayoun S, Kattan MW, Perrotte P, Valiquette L, Scardino PT et al. Development and validation of a nomogram predicting the outcome of prostate biopsy based on patient age, digital rectal examination and serum prostate specific antigen. J Urol 2005; 173(6):1930-1934.

76. Kerkhof M, Roobol MJ, Cuzick J, Sasieni P, Roemeling S, Schroder FH et al. Effect of the correction for noncompliance and contamination on the estimated reduction of metastatic prostate cancer within a randomized screening trial (ERSPC section Rotterdam). Int J Cancer 2010; 127(11):2639-2644.

77. Khatami A, Aus G, Damber JE, Lilja H, Lodding P, Hugosson J. PSA doubling time predicts the outcome after active surveillance in screening-detected prostate cancer: results from the European randomized study of screening for prostate cancer, Sweden section. Int J Cancer 2006; 120(1):170-174.

78. Kilpelainen T, Tammela T, Maattanen L, Malila N, Hakama M, Stenman UH et al. Screening failures in Finland: Improving prostate cancer screening. European Urology Supplements 2012; 11(1):e152.

79. Kilpelainen TP, Tammela TL, Maattanen L, Kujala P, Stenman UH, Ala-Opas M et al. False-positive screening results in the Finnish prostate cancer screening trial. Br J Cancer 2010; 102(3):469-474.

80. Kilpelainen TP, Tammela TL, Malila N, Hakama M, Santti H, Maattanen L et al. Prostate cancer mortality in the Finnish randomized screening trial. J Natl Cancer Inst 2013; 105(10):719-725.

81. Kim HS, Jeon SS, Choi JD, Kim W, Han DH, Jeong BC et al. Detection rates of nonpalpable prostate cancer in Korean men with prostate-specific antigen levels between 2.5 and 4.0 ng/mL. Urology 2010; 76(4):919-922.

82. Klein RJ, Hallden C, Gupta A, Savage CJ, Dahlin A, Bjartell A et al. Evaluation of multiple risk-associated single nucleotide polymorphisms versus prostate-specific antigen at baseline to predict prostate cancer in unscreened men. Eur Urol 2012; 61(3):471-477.

83. Kobayashi T, Kamoto T, Isogawa Y, Kinoshita H, Terai A, Habuchi T et al. Ratio of prostate specific antigen minor molecular forms-to-total prostate specific antigen is constant regardless of the pathological condition of the prostate. J Urol 2003; 169(1):121-124.

84. Kranse R, Beemsterboer P, Rietbergen J, Habbema D, Hugosson J, Schroder FH. Predictors for biopsy outcome in the European Randomized Study of Screening for Prostate Cancer (Rotterdam region). Prostate 1999; 39(4):316-322.

85. Krumholtz JS, Carvalhal GF, Ramos CG, Smith DS, Thorson P, Yan Y et al. Prostate-specific antigen cutoff of 2.6 ng/mL for prostate cancer screening is associated with favorable pathologic tumor features. Urology 2002; 60(3):469-473.

86. Kwiatkowski M, Huber A, Stamm B, Lehmann K, Wernli M, Hafeli A et al. Features and preliminary results of prostate cancer screening in Canton Aargau, Switzerland. BJU Int 2003; 92 Suppl 2:44-47.

87. Kwiatkowski M, Huber A, Moschopulos M, Lehmann K, Wernli M, Hafeli A et al. Prostate cancer screening: results of a prospective trial in Canton Aargau, Switzerland. Swiss Med Wkly 2004; 134(39-40):580-585.

88. Lane JA, Howson J, Donovan JL, Goepel JR, Dedman DJ, Down L et al. Detection of prostate cancer in unselected young men: prospective cohort nested within a randomised controlled trial. BMJ 2007; 335(7630):1139.

89. Laurila M, van der Kwast T, Bubendorf L, di LS, Pihl CG, Ciatto S et al. Detection rates of cancer, high grade PIN and atypical lesions suspicious for cancer in the European Randomized Study of Screening for Prostate Cancer. Eur J Cancer 2010; 46(17):3068-3072.

90. Lazzeri M, Haese A, De La Taille A, Palou Redorta J, McNicholas T, Lughezzani G et al. Serum isoform [-2]proPSA derivatives significantly improve prediction of prostate cancer at initial biopsy in a total PSA range of 2-10 ng/ml: A multicentric european study. Eur Urol 2013; 63(6):986-994.

91. Lee BH, Moussa AS, Li J, Fareed K, Jones JS. Percentage of free prostate-specific antigen: implications in modern extended scheme prostate biopsy. Urology 2011; 77(4):899-903.

92. Lee SE, Byun SS, Park HK, Shim HB, Ku JH. Detection of prostate cancer at low and intermediate serum prostate-specific antigen levels in a country with a low incidence of prostate cancer. Jpn J Clin Oncol 2006; 36(6):376-380.

93. Leite KR, Srougi M, Dall'Oglio MF, Sanudo A, Camara-Lopes LH. Histopathological findings in extended prostate biopsy with PSA < or = 4 ng/mL. Int Braz J Urol 2008; 34(3):283-290.

94. Liang Y, Ankerst DP, Sanchez M, Leach RJ, Thompson IM. Body mass index adjusted prostate-specific antigen and its application for prostate cancer screening. Urology 2010; 76(5):1268-6.

95. Loeb S, Nadler RB, Roehl KA, Antenor JA, Catalona WJ. Risk of prostate cancer for young men with a prostate specific antigen less than their age specific median. J Urol 2007; 177(5):1745-1748.

96. Loeb S, Metter EJ, Kan D, Roehl KA, Catalona WJ. Prostate-specific antigen velocity (PSAV) risk count improves the specificity of screening for clinically significant prostate cancer. BJU Int 2012; 109(4):508-513.

97. Loeb S, van den Heuvel S, Zhu X, Bangma CH, Schroder FH, Roobol M. Complications on repeat versus initial prostate biopsy in a randomized screening trial. J Urol 2012; 187(4S):e149.

98. Loeb S, Zhu X, Schroder FH, Roobol MJ. Long-term radical prostatectomy outcomes among participants from the European Randomized Study of Screening for Prostate Cancer (ERSPC) Rotterdam. BJU Int 2012; 110(11):1678-1683.

99. Lucia MS, Darke AK, Goodman PJ, La Rosa FG, Parnes HL, Ford LG et al. Pathologic characteristics of cancers detected in The Prostate Cancer Prevention Trial: implications for prostate cancer detection and chemoprevention. Cancer Prev Res (Phila) 2008; 1(3):167-173.

100. Lujan M, Paez A, Pascual C, Angulo J, Miravalles E, Berenguer A. Extent of prostate-specific antigen contamination in the Spanish section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Eur Urol 2006; 50(6):1234-1240.

101. Lynn NN, Collins GN, Brown SC, Brooman PJ. Comparative analysis of the role of prostate specific antigen parameters in clinical practice. The Prostate Journal 2000; 2(4):205-210.

102. Maattanen L, Hakama M, Tammela TL, Ruutu M, Ala-Opas M, Juusela H et al. Specificity of serum prostate-specific antigen determination in the Finnish prostate cancer screening trial. Br J Cancer 2007; 96(1):56-60.

103. Makinen T, Tammela TL, Stenman UH, Maattanen L, Rannikko S, Aro J et al. Family history and prostate cancer screening with prostate-specific antigen. J Clin Oncol 2002; 20(11):2658-2663.

104. Makinen T, Tammela TL, Hakama M, Stenman UH, Rannikko S, Aro J et al. Tumor characteristics in a population-based prostate cancer screening trial with prostate-specific antigen. Clin Cancer Res 2003; 9(7):2435-2439.

105. Makinen T, Tammela TL, Stenman UH, Maattanen L, Aro J, Juusela H et al. Second round results of the Finnish population-based prostate cancer screening trial. Clin Cancer Res 2004; 10(7):2231-2236.

106. McLernon DJ, Donnan PT, Gray M, Weller D, Sullivan F. Receiver operating characteristics of the prostate specific antigen test in an unselected population. J Med Screen 2006; 13(2):102-107.

107. Mistry K, Cable G. Meta-analysis of prostate-specific antigen and digital rectal examination as screening tests for prostate carcinoma. J Am Board Fam Pract 2003; 16(2):95-101.

108. Moul JW, Sun L, Hotaling JM, Fitzsimons NJ, Polascik TJ, Robertson CN et al. Age adjusted prostate specific antigen and prostate specific antigen velocity cut points in prostate cancer screening. J Urol 2007; 177(2):499-503.

109. Na R, Jiang H, Kim ST, Wu Y, Tong S, Zhang L et al. Outcomes and trends of prostate biopsy for prostate cancer in Chinese men from 2003 to 2011. PLoS One 2012; 7(11):e49914.

110. Na R, Wu Y, Xu J, Jiang H, Ding Q. Age-specific prostate specific antigen cutoffs for guiding biopsy decision in Chinese population. PLoS One 2013; 8(6):e67585.

111. Nadler RB, Loeb S, Roehl KA, Antenor JA, Eggener S, Catalona WJ. Use of 2.6 ng/ml prostate specific antigen prompt for biopsy in men older than 60 years. J Urol 2005; 174(6):2154-7, discussion.

112. Nelen V, Thys G, Neels H, Neetens I, Coebergh JW, Dourcy-Belle-Rose B et al. ERSPC: features and preliminary results from the Antwerp study centre. BJU Int 2003; 92 Suppl 2:17-21.

113. Nelen V, Thys G, Hermans A, D'Hooge K, Dourcy-Belle-Rose B, Coebergh JW et al. Interval cancers in the Antwerp European randomised study of screening for prostate cancer study, using a 6 year screening interval. Eur J Cancer 2010; 46(17):3090-3094.

114. Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA et al. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. JAMA 1993; 270(7):860-864.

115. Okihara K, Ukimura O, Nakamura T, Ushijima S, Mizutani Y, Kawauchi A et al. Complexed PSA improves prostate cancer detection: results from a multicenter Japanese clinical trial. Urology 2006; 67(2):328-332.

116. Otto SJ, van der Cruijsen IW, Liem MK, Korfage IJ, Lous JJ, Schroder FH et al. Effective PSA contamination in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. Int J Cancer 2003; 105(3):394-399.

117. Otto SJ, van Leeuwen PJ, Hoekstra JW, Merckelbach JW, Blom JH, Schroder FH et al. Blinded and uniform causes of death verification in cancer screening: a major influence on the outcome of a prostate cancer screening trial? Eur J Cancer 2010; 46(17):3061-3067.

118. Otto SJ, Moss SM, Maattanen L, Roobol M, Zappa M, Nelen V et al. PSA levels and cancer detection rate by centre in the European Randomized Study of Screening for Prostate Cancer. Eur J Cancer 2010; 46(17):3053-3060.

119. Paez A, Lujan M, Raaijmakers R, Berenguer A. Four-year prostate-specific antigen progression in the non-cancer population of the European Randomized Study of Screening for Prostate Cancer. BJU Int 2003; 92 Suppl 2:84-87.

120. Parekh DJ, Ankerst DP, Higgins BA, Hernandez J, Canby-Hagino E, Brand T et al. External validation of the Prostate Cancer Prevention Trial risk calculator in a screened population. Urology 2006; 68(6):1152-1155.

121. Partin AW, Brawer MK, Bartsch G, Horninger W, Taneja SS, Lepor H et al. Complexed prostate specific antigen improves specificity for prostate cancer detection: results of a prospective multicenter clinical trial. J Urol 2003; 170(5):1787-1791.

122. Patel S, Issa MM, El-Galley R. Evaluation of novel formula of PSA, age, prostate volume, and race in predicting positive prostate biopsy findings. Urology 2013; 81(3):602-606.

123. Paterson AL, Sut MK, Khan AR, Sharma HK. Prostatic biopsies in selected men aged 75 years and older guide key clinical management decisions. Int Urol Nephrol 2013; 45(6):1539-1544.

124. Pelzer AE, Tewari A, Bektic J, Berger AP, Frauscher F, Bartsch G et al. Detection rates and biologic significance of prostate cancer with PSA less than 4.0 ng/mL: observation and clinical implications from Tyrol screening project. Urology 2005; 66(5):1029-1033.

125. Pelzer AE, Volgger H, Bektic J, Berger AP, Rehder P, Bartsch G et al. The effect of percentage free prostate-specific antigen (PSA) level on the prostate cancer detection rate in a screening population with low PSA levels. BJU Int 2005; 96(7):995-998.

126. Pepe P, Panella P, Savoca F, Cacciola A, D'Arrigo L, Dibenedetto G et al. Prevalence and clinical significance of prostate cancer among 12,682 men with normal digital rectal examination, low PSA levels (< or =4 ng/ml) and percent free PSA cutoff values of 15 and 20%. Urol Int 2007; 78(4):308-312.

127. Perdona S, Bruzzese D, Ferro M, Autorino R, Marino A, Mazzarella C et al. Prostate health index (phi) and prostate cancer antigen 3 (PCA3) significantly improve diagnostic accuracy in patients undergoing prostate biopsy. Prostate 2013; 73(3):227-235.

128. Pinsky PF, Andriole GL, Kramer BS, Hayes RB, Prorok PC, Gohagan JK. Prostate biopsy following a positive screen in the prostate, lung, colorectal and ovarian cancer screening trial. J Urol 2005; 173(3):746-750.

129. Pinsky PF, Crawford ED, Kramer BS, Andriole GL, Gelmann EP, Grubb R et al. Repeat prostate biopsy in the prostate, lung, colorectal and ovarian cancer screening trial. BJU Int 2007; 99(4):775-779.

130. Pinsky PF, Black A, Parnes HL, Grubb R, David CE, Miller A et al. Prostate cancer specific survival in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Cancer Epidemiol 2012; 36(6):e401-e406.

131. Prior C, Guillen-Grima F, Robles JE, Rosell D, Fernandez-Montero JM, Agirre X et al. Use of a combination of biomarkers in serum and urine to improve detection of prostate cancer. World J Urol 2010; 28(6):681-686.

132. Punglia RS, D'Amico AV, Catalona WJ, Roehl KA, Kuntz KM. Effect of verification bias on screening for prostate cancer by measurement of prostate-specific antigen. N Engl J Med 2003; 349(4):335-342.

133. Raaijmakers R, Kirkels WJ, Roobol MJ, Wildhagen MF, Schrder FH. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. Urology 2002; 60(5):826-830.

134. Raaijmakers R, Blijenberg BG, Finlay JA, Rittenhouse HG, Wildhagen MF, Roobol MJ et al. Prostate cancer detection in the prostate specific antigen range of 2.0 to 3.9 ng/ml: value of percent free prostate specific antigen on tumor detection and tumor aggressiveness. J Urol 2004; 171(6 Pt 1):2245-2249.

135. Raaijmakers R, Wildhagen MF, Ito K, Paez A, de Vries SH, Roobol MJ et al. Prostate-specific antigen change in the European Randomized Study of Screening for Prostate Cancer, section Rotterdam. Urology 2004; 63(2):316-320.

136. Randazzo M, Seiler D, Beatrice J, Baumgartner M, Huber A, Grobholz R et al. Prostate specific antigen (PSA)-pyramid in men with low range PSA: Prostate cancer incidence and mortality-a plea for risk-based prostate cancer

screening strategy in the European randomized study of screening for prostate cancer (ERSPC), AARAU. J Urol 2013; 189(4):e793.

137. Reissigl A, Bartsch G. Prostate-specific antigen as a screening test. The Austrian experience. Urol Clin North Am 1997; 24(2):315-321.

138. Rietbergen JB, Kranse R, Hoedemaeker RF, Kruger AE, Bangma CH, Kirkels WJ et al. Comparison of prostate-specific antigen corrected for total prostate volume and transition zone volume in a population-based screening study. Urology 1998; 52(2):237-246.

139. Rietbergen JB, Kruger AE, Hoedemaeker RF, Bangma CH, Kirkels WJ, Schroder FH. Repeat screening for prostate cancer after 1-year followup in 984 biopsied men: clinical and pathological features of detected cancer. J Urol 1998; 160(6 Pt 1):2121-2125.

140. Roddam AW, Hamdy FC, Allen NE, Price CP. The impact of reducing the prostate-specific antigen threshold and including isoform reflex tests on the performance characteristics of a prostate-cancer detection programme. BJU Int 2007; 100(3):514-517.

141. Roemeling S, Kranse R, Vis AN, Gosselaar C, van der Kwast TH, Schroder FH. Metastatic disease of screen-detected prostate cancer : characteristics at diagnosis. Cancer 2006; 107(12):2779-2785.

142. Roemeling S, Roobol MJ, Otto SJ, Habbema DF, Gosselaar C, Lous JJ et al. Feasibility study of adjustment for contamination and non-compliance in a prostate cancer screening trial. Prostate 2007; 67(10):1053-1060.

143. Roobol MJ, Kirkels WJ, Schroder FH. Features and preliminary results of the Dutch centre of the ERSPC (Rotterdam, the Netherlands). BJU Int 2003; 92 Suppl 2:48-54.

144. Roobol MJ, Kranse R, de Koning HJ, Schroder FH. Prostate-specific antigen velocity at low prostate-specific antigen levels as screening tool for prostate cancer: results of second screening round of ERSPC (ROTTERDAM). Urology 2004; 63(2):309-313.

145. Roobol MJ, van der Cruijsen IW, Schroder FH. No reason for immediate repeat sextant biopsy after negative initial sextant biopsy in men with PSA level of 4.0 ng/mL or greater (ERSPC, Rotterdam). Urology 2004; 63(5):892-897.

146. Roobol MJ, Roobol DW, Schroder FH. Is additional testing necessary in men with prostate-specific antigen levels of 1.0 ng/mL or less in a population-based screening setting? (ERSPC, section Rotterdam). Urology 2005; 65(2):343-346.

147. Roobol MJ, Schroder FH, Kranse R. A comparison of first and repeat (four years later) prostate cancer screening in a randomized cohort of a symptomatic men aged 55-75 years using a biopsy indication of 3.0 ng/ml (results of ERSPC, Rotterdam). Prostate 2006; 66(6):604-612.

148. Roobol MJ, Grenabo A, Schroder FH, Hugosson J. Interval cancers in prostate cancer screening: comparing 2- and 4-year screening intervals in the European Randomized Study of Screening for Prostate Cancer, Gothenburg and Rotterdam. J Natl Cancer Inst 2007; 99(17):1296-1303.

149. Roobol MJ, Zappa M, Maattanen L, Ciatto S. The value of different screening tests in predicting prostate biopsy outcome in screening for prostate cancer data from a multicenter study (ERSPC). Prostate 2007; 67(4):439-446.

150. Roobol MJ, Kerkhof M, Schroder FH, Cuzick J, Sasieni P, Hakama M et al. Prostate cancer mortality reduction by prostate-specific antigen-based screening adjusted for nonattendance and contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). Eur Urol 2009; 56(4):584-591.

151. Roobol MJ, Schroder FH, van LP, Wolters T, van den Bergh RC, van Leenders GJ et al. Performance of the prostate cancer antigen 3 (PCA3) gene and prostate-specific antigen in prescreened men: exploring the value of PCA3 for a first-line diagnostic test. Eur Urol 2010; 58(4):475-481.

152. Roobol MJ, Steyerberg EW, Kranse R, Wolters T, van den Bergh RC, Bangma CH et al. A risk-based strategy improves prostate-specific antigen-driven detection of prostate cancer. Eur Urol 2010; 57(1):79-85.

153. Roobol MJ, Schroder FH, Hugosson J, Jones JS, Kattan MW, Klein EA et al. Importance of prostate volume in the European Randomised Study of Screening for Prostate Cancer (ERSPC) risk calculators: results from the prostate biopsy collaborative group. World J Urol 2012; 30(2):149-155.

154. Roobol MJ, Heus I, de Bekker-Grob E, Bangma C, Schroder F, Steyerberg E. Prostate cancer disease progression and mortality after radical prostatectomy or external beam radiotherapy: results from the ERSPC, section Rotterdam. J Urol 2012; 187(4S):e402.

155. Rowe EW, Laniado ME, Walker MM, Patel A. Prostate cancer detection in men with a 'normal' total prostate-specific antigen (PSA) level using percentage free PSA: a prospective screening study. BJU Int 2005; 95(9):1249-1252.

156. Rowe EW, Laniado ME, Walker MM, Anup P. Incidental acute prostatic inflammation is associated with a lower percentage of free prostate-specific antigen than other benign conditions of the prostate: a prospective screening study. BJU Int 2006; 97(5):1039-1042.

157. Ryden L, Egevad L, Ekman P, Hellstrom M. Prevalence of prostate cancer at different levels of serum prostate-specific antigen (PSA) and different free: total PSA ratios in a consecutive series of men referred for prostate biopsies. Scand J Urol Nephrol 2007; 41(4):302-307.

158. Saito S. Prostate-specific antigen cut-off point of 2.5 ng/mL and increasing the number of prostate biopsies results in the detection of curable prostate cancer even in Japanese population. Int J Urol 2007; 14(8):709-712.

159. Salami SS, Schmidt F, Laxman B, Regan MM, Rickman DS, Scherr D et al. Combining urinary detection of TMPRSS2: ERG and PCA3 with serum PSA to predict diagnosis of prostate cancer. Urol Oncol Semin Orig Invest 2013; 31(5):566-571.

160. Scattoni V, Lazzeri M, Lughezzani G, De Luca S, Passera R, Bollito E et al. Head-to-head comparison of prostate health index and urinary PCA3 for predicting cancer at initial or repeat biopsy. J Urol 2013; 190(2):496-501.

161. Schroder FH, Denis LJ, Kirkels W, de Koning HJ, Standaert B. European randomized study of screening for prostate cancer. Progress report of Antwerp and Rotterdam pilot studies. Cancer 1995; 76(1):129-134.

162. Schroder FH, Damhuis RA, Kirkels WJ, de Koning HJ, Kranse R, Nijs HG et al. European randomized study of screening for prostate cancer - the Rotterdam pilot studies. Int J Cancer 1996; 65:145-151.

163. Schroder FH, van der Maas P, Beemsterboer P, Kruger AB, Hoedemaeker R, Rietbergen J et al. Evaluation of the digital rectal examination as a screening test for prostate cancer. Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 1998; 90(23):1817-1823.

164. Schroder FH, van dC-K, I, de Koning HJ, Vis AN, Hoedemaeker RF, Kranse R. Prostate cancer detection at low prostate specific antigen. J Urol 2000; 163(3):806-812.

165. Schroder FH, Roobol-Bouts M, Vis AN, van der Kwast T, Kranse R. Prostate-specific antigen-based early detection of prostate cancer--validation of screening without rectal examination. Urology 2001; 57(1):83-90.

166. Schroder FH, Denis LJ, Roobol M, Nelen V, Auvinen A, Tammela T et al. The story of the European Randomized Study of Screening for Prostate Cancer. BJU Int 2003; 92 Suppl 2:1-13.

167. Schroder FH, Raaijmakers R, Postma R, van der Kwast TH, Roobol MJ. 4-year prostate specific antigen progression and diagnosis of prostate cancer in the European Randomized Study of Screening for Prostate Cancer, section Rotterdam. J Urol 2005; 174(2):489-494.

168. Schroder FH, Roobol MJ, van der Kwast TH, Kranse R, Bangma CH. Does PSA velocity predict prostate cancer in pre-screened populations? Eur Urol 2006; 49(3):460-465.

169. Schroder FH, Bangma CH, Roobol MJ. Is it necessary to detect all prostate cancers in men with serum PSA levels <3.0 ng/ml? A comparison of biopsy results of PCPT and outcome-related information from ERSPC. Eur Urol 2008; 53(5):901-908.

170. Schroder FH, Kattan MW. The comparability of models predicting the risk of a positive prostate biopsy with prostate-specific antigen alone: A systematic review. Eur Urol; 54:274-290.

171. Schroder FH, Roobol MJ, Andriole GL, Fleshner N. Defining increased future risk for prostate cancer: evidence from a population based screening cohort. J Urol 2009; 181(1):69-74.

172. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009; 360(13):1320-1328.

173. Schroder FH, van den Bergh RC, Wolters T, van Leeuwen PJ, Bangma CH, van der Kwast TH et al. Eleven-year outcome of patients with prostate cancers diagnosed during screening after initial negative sextant biopsies. Eur Urol 2010; 57(2):256-266.

174. Schroder FH, Hugosson J, Carlsson S, Tammela T, Maattanen L, Auvinen A et al. Screening for prostate cancer decreases the risk of developing metastatic disease: findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC). Eur Urol 2012; 62(5):745-752.

175. Seiler D, Randazzo M, Isbam H, Chun F, Ahyai S, Huber A et al. Long-term risk assessment of prostate cancer diagnosis in men with initial PSA-values <1.0ng/mL; results from the Swiss arm of the European Randomized Study of Screening for Prostate Cancer (ERSPC). J Urol 2012; 187(4S):e402.

176. Seo HK, Chung MK, Ryu SB, Lee KH. Detection rate of prostate cancer according to prostate-specific antigen and digital rectal examination in Korean men: a nationwide multicenter study. Urology 2007; 70(6):1109-1112.

177. Shim HB, Lee SE, Park HK, Ku JH. Histological diagnosis of prostate cancer in Korean men aged 70-79 years. Jpn J Clin Oncol 2007; 37(10):782-787.

178. Smith DS, Humphrey PA, Catalona WJ. The early detection of prostate carcinoma with prostate specific antigen: the Washington University experience. Cancer 1997; 80(9):1852-1856.

179. Sokoll LJ, Sanda MG, Feng Z, Kagan J, Mizrahi IA, Broyles DL et al. A prospective, multicenter, National Cancer Institute Early Detection Research Network study of [-2]proPSA: improving prostate cancer detection and correlating with cancer aggressiveness. Cancer Epidemiol Biomarkers Prev 2010; 19(5):1193-1200.

180. Spurgeon SE, Mongoue-Tchokote S, Collins L, Priest R, Hsieh YC, Peters LM et al. Assessment of prostate-specific antigen doubling time in prediction of prostate cancer on needle biopsy. Urology 2007; 69(5):931-935.

181. Standaert B, Denis L. The European Randomized Study of Screening for Prostate Cancer: an update. Cancer 1997; 80(9):1830-1834.

182. Stephan C, Vincendeau S, Houlgatte A, Cammann H, Jung K, Semjonow A. Multicenter evaluation of [-2]proprostate-specific antigen and the prostate health index for detecting prostate cancer. Clin Chem 2013; 59(1):306-314.

183. Stephan C, Jung K, Semjonow A, Schulze-Forster K, Cammann H, Hu X et al. Comparative assessment of urinary prostate cancer antigen 3 and TMPRSS2:ERG gene fusion with the serum [-2]proprostate-specific antigen-based prostate health index for detection of prostate cancer. Clin Chem 2013; 59(1):280-288.

184. Sun L, Moul JW, Hotaling JM, Rampersaud E, Dahm P, Robertson C et al. Prostate-specific antigen (PSA) and PSA velocity for prostate cancer detection in men aged <50 years. BJU Int 2007; 99(4):753-757.

185. Tang P, Sun L, Uhlman MA, Polascik TJ, Freedland SJ, Moul JW. Baseline PSA as a predictor of prostate cancer-specific mortality over the past 2 decades: Duke University experience. Cancer 2010; 116(20):4711-4717.

186. Tanguay S, Begin LR, Elhilali MM, Behlouli H, Karakiewicz PI, Aprikian AG. Comparative evaluation of total PSA, free/total PSA, and complexed PSA in prostate cancer detection. Urology 2002; 59(2):261-265.

187. Taylor KL, Shelby R, Gelmann E, McGuire C. Quality of life and trial adherence among participants in the prostate, lung, colorectal, and ovarian cancer screening trial. J Natl Cancer Inst 2004; 96(14):1083-1094.

188. Thiesler T, Trinkler F, Horcic M, Willi N, Cathomas G, Hailemariam S. Patients with low prostate-specific antigen levels (< or =4 ng/ml) would benefit from a twelve-core biopsy protocol for prostate cancer detection. Urol Int 2007; 78(4):318-322.

189. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG et al. The influence of finasteride on the development of prostate cancer. N Engl J Med 2003; 349(3):215-224.

190. Thompson IM, Chi C, Ankerst DP, Goodman PJ, Tangen CM, Lippman SM et al. Effect of finasteride on the sensitivity of PSA for detecting prostate cancer. J Natl Cancer Inst 2006; 98(16):1128-1133.

191. van der Cruijsen-Koeter IW, van der Kwast TH, Schroder FH. Interval carcinomas in the European Randomized Study of Screening for Prostate Cancer (ERSPC)-Rotterdam. J Natl Cancer Inst 2003; 95(19):1462-1466.

192. van der Cruijsen-Koeter IW, Vis AN, Roobol MJ, Wildhagen MF, de Koning HJ, van der Kwast TH et al. Comparison of screen detected and clinically diagnosed prostate cancer in the European randomized study of screening for prostate cancer, section rotterdam. J Urol 2005; 174(1):121-125.

193. van der Cruijsen-Koeter IW, Roobol MJ, Wildhagen MF, van der Kwast TH, Kirkels WJ, Schroder FH. Tumor characteristics and prognostic factors in two subsequent screening rounds with four-year interval within prostate cancer screening trial, ERSPC Rotterdam. Urology 2006; 68(3):615-620.

194. van der Kwast TH, Ciatto S, Martikainen PM, Hoedemaeker R, Laurila M, Pihl CG et al. Detection rates of high-grade prostate cancer during subsequent screening visits. Results of the European Randomized Screening Study for Prostate Cancer. Int J Cancer 2006; 118(10):2538-2542.

195. van Leeuwen PJ, Connolly D, Gavin A, Roobol MJ, Black A, Bangma CH et al. Prostate cancer mortality in screen and clinically detected prostate cancer: estimating the screening benefit. Eur J Cancer 2010; 46(2):377-383.

196. van Leeuwen PJ, Kranse R, Hakulinen T, Roobol MJ, de Koning HJ, Bangma CH et al. Disease-specific mortality may underestimate the total effect of prostate cancer screening. J Med Screen 2010; 17(4):204-210.

197. van Leeuwen PJ, Connolly D, Tammela TL, Auvinen A, Kranse R, Roobol MJ et al. Balancing the harms and benefits of early detection of prostate cancer. Cancer 2010; 116(20):4857-4865.

198. van Leeuwen PJ, Roobol MJ, Kranse R, Zappa M, Carlsson S, Bul M et al. Towards an optimal interval for prostate cancer screening. Eur Urol 2012; 61(1):171-176.

199. van Leeuwen PJ, van den Bergh R, Wolters T, Schroder F, Roobol M. Screening: should more biopsies be taken in larger prostates? BJU Int 2009; 104(7):919-924.

200. Vickers AJ, Cronin AM, Aus G, Pihl CG, Becker C, Pettersson K et al. A panel of kallikrein markers can reduce unnecessary biopsy for prostate cancer: data from the European Randomized Study of Prostate Cancer Screening in Goteborg, Sweden. BMC Med 2008; 6:19.

201. Vickers AJ, Cronin AM, Roobol MJ, Hugosson J, Jones JS, Kattan MW et al. The relationship between prostate-specific antigen and prostate cancer risk: the Prostate Biopsy Collaborative Group. Clin Cancer Res 2010; 16(17):4374-4381.

202. Vickers AJ, Cronin AM, Aus G, Pihl CG, Becker C, Pettersson K et al. Impact of recent screening on predicting the outcome of prostate cancer biopsy in men with elevated prostate-specific antigen: data from the European Randomized Study of Prostate Cancer Screening in Gothenburg, Sweden. Cancer 2010; 116(11):2612-2620.

203. Villers A, Malavaud B, Rebillard X, Bataille V, Iborra F. ERSPC: features and preliminary results of France. BJU Int 2003; 92 Suppl 2:27-29.

204. Vis AN, Roemeling S, Kranse R, Schroder FH, van der Kwast TH. Should we replace the Gleason score with the amount of high-grade prostate cancer? Eur Urol 2007; 51(4):931-939.

205. Wallner LP, Frencher SK, Hsu JW, Chao CR, Nichol MB, Loo RK et al. Changes in serum prostate-specific antigen levels and the identification of prostate cancer in a large managed care population. BJU Int 2013; 111(8):1245-1252.

206. Wolters T, Roobol MJ, Schroder FH, van der Kwast TH, Roemeling S, van der Cruijsen-Koeter IW et al. Can non-malignant biopsy features identify men at increased risk of biopsy-detectable prostate cancer at re-screening after 4 years? BJU Int 2008; 101(3):283-288.

207. Wolters T, Roobol MJ, Bangma CH, Schroder FH. Is prostate-specific antigen velocity selective for clinically significant prostate cancer in screening? European Randomized Study of Screening for Prostate Cancer (Rotterdam). Eur Urol 2009; 55(2):385-392.

208. Wolters T, Roobol MJ, Steyerberg EW, van den Bergh RC, Bangma CH, Hugosson J et al. The effect of study arm on prostate cancer treatment in the large screening trial ERSPC. Int J Cancer 2010; 126(10):2387-2393.

209. Wu TT, Huang JK. The clinical usefulness of prostate-specific antigen (PSA) level and age-specific PSA reference ranges for detecting prostate cancer in Chinese. Urol Int 2004; 72(3):208-211.

210. Zhu X, van Leeuwen PJ, Bul M, Otto SJ, de Koning HJ, Bangma CH et al. Disease-specific survival of men with prostate cancer detected during the screening interval: results of the European randomized study of screening for prostate cancer-Rotterdam after 11 years of follow-up. Eur Urol 2011; 60(2):330-336.

211. Zhu X, van Leeuwen PJ, Bul M, Bangma CH, Roobol MJ, Schroder FH. Identifying and characterizing "escapes"-men who develop metastases or die from prostate cancer despite screening (ERSPC, section Rotterdam). Int J Cancer 2011; 129(12):2847-2854.

Systematic review report for question 3.3

Clinical Question 3: *In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what should be the PSA testing strategies (age to start, level at which to declare a test abnormal and frequency of subsequent testing if the PSA level is normal) for men at average risk of prostate cancer and how should they be modified, if at all, for men at high risk of prostate cancer?*

PICO Question 3.3: For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer does a PSA level measured at a particular age in men assist with determining the recommended interval to the next PSA test?

Population	Exposure	Comparator	Outcomes
Men not known to have a prostate cancer diagnosis or to have symptoms that might indicate prostate cancer	Higher PSA level at ages less than 56 years	Lower PSA level at ages less than 56 years	Prostate cancer-specific mortality

1. METHODS

1.1. Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption guidelines had to be evidence based and meet the pre-specified criteria of scores of greater or equal to 70% for the domains rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

1.2. Literature search

Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched from 1990 using text terms and, where available, database-specific subject headings. Each database was searched for articles dealing with prostate cancer. In Medline and Embase databases the prostate cancer search was coupled with a search for baseline PSA. To identify studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples search terms for ATSI peoples were then added to the searches. A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 which were either published after the initial search was completed and/or added to the relevant database after the search was completed. Alerts were checked until July 2014. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched regularly up until April 2014 for relevant reviews

published after the initial search. Reference lists of all relevant articles were checked for potential additional articles.

1.3. Inclusion Criteria

Selection criteria	Inclusion criteria
Study type	Aetiology/risk factor
Study design	Prospective or retrospective cohort studies, case-control studies nested within a cohort study or case-cohort studies
Population	Men not known to have a prostate cancer diagnosis or to have symptoms that might indicate prostate cancer at the time of baseline PSA measurement
Exposure	Higher PSA level at ages less than 56 years whose subsequent management was not altered as a result of their PSA level
Comparator	Lower PSA level at ages less than 56 years
Outcomes	Prostate cancer-specific mortality stratified by age at blood collection (at least two different age strata)
Language	English
Publication period	After 31st December 1989 and before1st March 2014

Conference proceedings identified by the search literature searches were included if they met the inclusion criteria.

2. RESULTS

2.1. Guidelines

Eleven guidelines contained potentially relevant recommendations. These recommendations were not adopted as they either were not based on a systematic review, did not meet the pre-specified AGREE II criteria for adoption, or the recommendations did not specifically address the clinical question. These guidelines and the reason why they were not adopted are listed in Appendix C.

In Australia the Royal College of Pathologists of Australasia has consensus based position statements regarding PSA testing (http://www.rcpa.edu.au/Library/College-Policies/Position-Statements/Prostate-Specific-Antigen-Testing-Age-related-inte, accessed 20/10/14):

"PSA testing should begin at age 40 in order to provide a baseline estimate of the risk of prostate cancer being found at an older age."

In 2012 the Royal Australian College of General Practitioners recommended as a practice point (no good evidence available) that general practitioners respond to requests for screening by high risk men by informing them of the risks and benefits of screening (Guidelines for Preventative Activities in General Practice 8th edition, (2012) The Royal Australian College of General Practitioners).

In 2013 at the Prostate Cancer World Congress in Melbourne a consensus statement was issued by a group of leading prostate cancer experts from around the world as part of the Melbourne Consensus Statement (Murphy al., (2013) The Melbourne Consensus Statement on the early detection of prostate cancer. *BJU International* **113:**186-188):
"*Baseline PSA testing for men in their 40s is useful for predicting the future risk of prostate cancer and its aggressive forms"*

2.2. Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the systematic review. The Medline search identified 6,896 citations, the Embase search an additional 6,009 citations, the search of the Cochrane Database of Systematic Reviews 59 citations, the Database of Abstracts of Reviews of Effects 282 citations and the Health Technology Assessment database 216 citations, resulting in a total of 13,462 citations. Titles and abstracts were examined and 208 articles were retrieved for a more detailed evaluation. An additional 18 potential citations were identified from the reference lists of retrieved articles.

Two studies reported in two articles met the inclusion criteria and were included in the review. There were no studies of Aboriginal and/or Torres Strait Islander men that met the inclusion criteria.

The retrieved articles that were not included and the reason for their exclusion are documented in Appendix C. In summary, the main reasons for exclusion were; did not report original data, altered subsequent management as a result of baseline PSA levels and no comparison of baseline PSA levels.

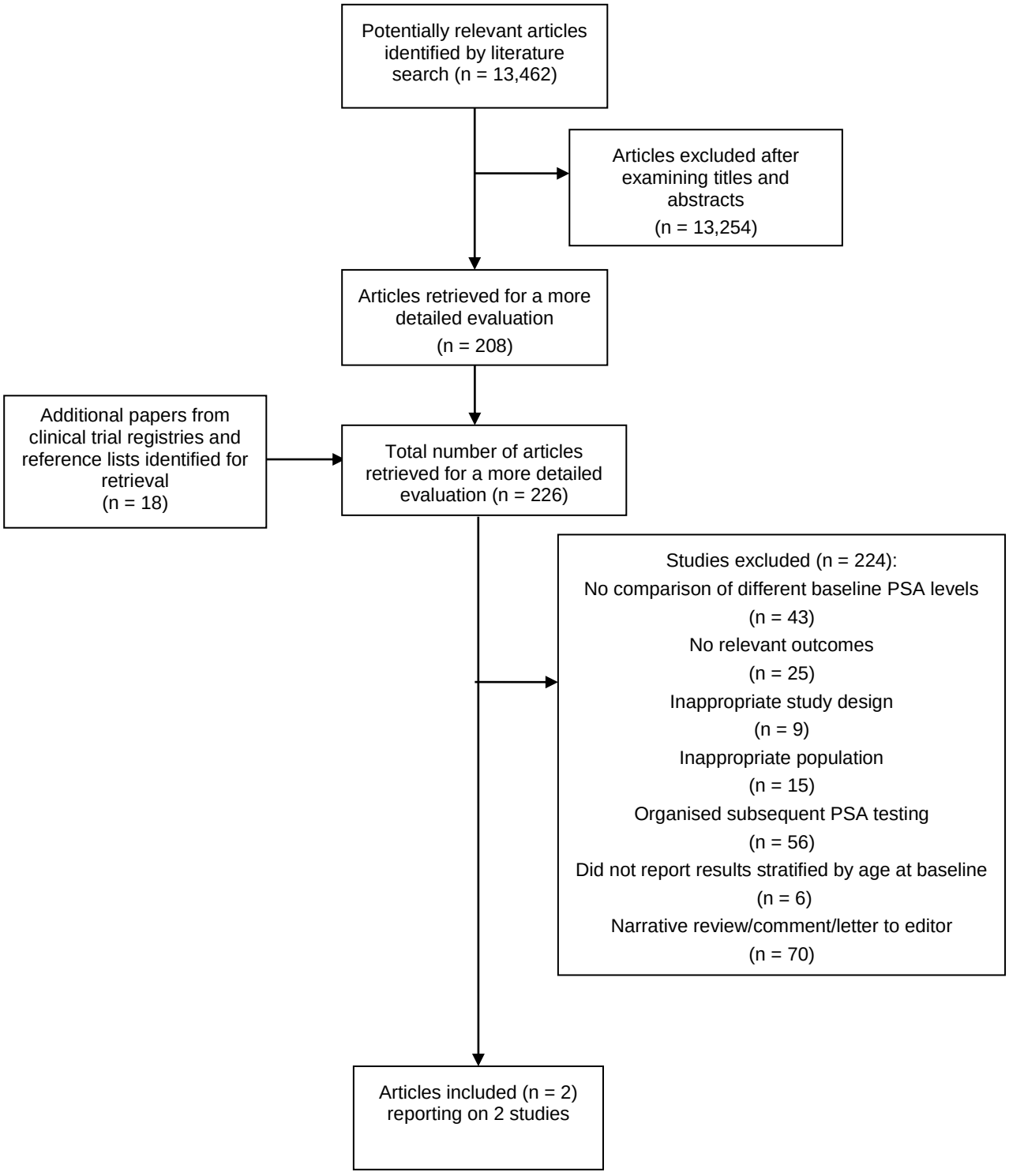


Figure 1. Process of inclusion and exclusion of studies

2.3. Study Characteristics

Characteristics of included studies are described in Tables 1 and 2.

Table 1: Characteristics of studies examining different baseline PSA levels as a risk factor for prostate cancer mortality: **cohort studies**

Study	Cohort participants	Study design	Exposure	Outcomes	Comments
Ørsted 2012 (Denmark)	Men aged 20 – 94 years selected randomly from the Danish Central Person Register and examined between 1981-1983 in the Copenhagen City Heart Study Median age at baseline (IQR): 58 (49 **–** 69) years N = 4,349	Retrospective cohort	Total PSA level at age **<45 years** Total PSA level at age **45 – 49** years Total PSA level at age **50 – 54** years Total PSA measured in plasma stored at -20ºC for up to 27 **–** 29 years using the ADIVIA Centaur XP Immunoassay (Siemens), traceable to the WHO (90:10) 96/670 PSA standard and the same auto-analyser operated by the same laboratory technician	Prostate cancer-specific mortality as recorded in Danish Causes of Death Registry, which records date and causes for all deaths in Denmark reported by hospitals and general practitioners Median follow-up 18 years Range = 0.5 **–** 28 years Follow-up 100% (2 individuals lost until 1999)	Individual patients followed from study entry until prostate cancer death, death due to other causes, emigration, or 31st December 2008, whichever came first 21 men emigrated, 2,914 died from other causes PSA testing introduced into clinical practice in Denmark in 1995 Number of men aged <45,45 **–** 49 and 50 **–** 54 years at baseline not reported Laboratory technician blinded to disease status
Vickers 2013 *Malmö Preventive Project* (Sweden)	Men aged 27 – 52 years invited for a baseline health examination who provided a blood sample between 1974 and 1984 and a subsequent blood sample approximately six years later. Men aged **51 – 55** years at second venepuncture N = 4,063	Retrospective cohort	Total PSA level at age **51 – 55** years Total PSA measured in EDTA plasma stored at -20ºC for up to 26 years (storage shown not to significantly affect measurements) using the Prostatus free/total PSA assay	Prostate cancer-specific mortality according to: an independent review of the medical charts of men diagnosed with prostate cancer who subsequently died or the Cause of Death Registry before 31st December 2006 Chart and registry cause of death had a concordance of 82% N < 162	Follow-up until 31st December 2006 otherwise not described Men not given recommendations to undergo early screening for prostate cancer; Assumed PSA screening rates remained low (up to 5%) during the period of interest (1998, 8 years prior to end of study), and therefore that it was unlikely that any informal or opportunistic screening in Malmö could have substantively affected estimates

IQR = interquartile range; PSA = prostate specific antigen; WHO = World Health Organization.

Table 2: Characteristics of studies examining different baseline PSA levels as a risk factor for prostate cancer mortality: **nested case-control studies**

Study	Cohort participants	Study design	Cases	Controls	Exposures	Comments
Vickers 2013 *Malmö Preventive Project* (Sweden)	Men aged 27 – 52 years invited for a baseline health examination who provided a blood sample between 1974 and 1984 Men aged **37.5 – 42.5** years at baseline N = 3,979 Men aged **45 – 49** years at baseline N = 10,357	Nested case-control	Men who had died from prostate cancer according to: an independent review of medical charts of men diagnosed with prostate cancer who subsequently died or the Cause of Death Registry before 31st December 2006 Chart and registry cause of death had a concordance of 82% N < 162	Three controls selected at random from participants who were event-free at the time at which the index case event occurred Matched by age and date of venepuncture within 3 months (or up to 2 years if unavailable)	Total PSA level at age 37.5 – 42.5 years Total PSA level at age 45 – 49 years Total PSA measured in EDTA plasma stored at -20ºC for a maximum of 32 years (storage shown not to significantly affect measurements) using the Prostatus free/total PSA assay	Men not given recommendations to undergo early screening for prostate cancer Assumed PSA screening rates remained low (up to 5%) during the period of interest (1998, 8 years prior to end of study), and therefore that it was unlikely that any informal or opportunistic screening in Malmö could have substantively affected estimates Imputed baseline PSA levels for unmatched controls whose PSA levels were not measured. Imputation validated in cohort aged 51 – 55 years at second PSA test

PSA = prostate specific antigen

2.4. Study quality

Methodological quality of included cohort studies is described in Tables 3 and 4.

Methodological quality of included nested case-control studies is described in Table 5 and 6.

Table 3: Assessment of risk of bias of included **cohort** studies (n = 2)

Quality Category	N (%)
Selection of the exposed and non-exposed cohorts	
Low risk of bias	2 (100.0)
Moderate risk of bias	-
High risk of bias	-
Measurement of exposure	
Low risk of bias	1 (50.0)
Moderate risk of bias	1 (50.0)
High risk of bias	-
Measurement of outcome	
Low risk of bias	1 (50.0)
Moderate risk of bias	1 (50.0)
High risk of bias	-
Was outcome of interest absent at the time to which the exposure refers?	
Low risk of bias	2 (100.0)
Moderate risk of bias	-
High risk of bias	-
Was follow-up long enough for outcome to occur?	
Low risk of bias	2 (100.0)
High risk of bias	-
Participation rate	
Low risk of bias	2 (100.0)

Moderate risk of bias	-
High risk of bias	-
Completeness of follow-up	
Low risk of bias	1 (50.0)
Moderate risk of bias	-
High risk of bias	1 (50.0)
Difference in follow-up between exposed and non-exposed	
Low risk of bias	2 (100.0)
Moderate risk of bias	-
High risk of bias	-
Accuracy of dates of outcome or censoring	
Low risk of bias	2 (100.0)
Moderate risk of bias	-
Difference in missing data for exposure between those with or without the outcome	
Low risk of bias	2 (100.0)
Moderate risk of bias	-
High risk of bias	-
Comparability of exposed and non-exposed cohorts with respect to potentially important confounding variables	
Low risk of bias	1 (50.0)
Moderate risk of bias	-
High risk of bias	1 (50.0)
Covariates are appropriately included in statistical analysis models	
Low risk of bias	2 (100.0)
High risk of bias	-

Table 4: Assessment of risk of bias of included **cohort** studies (n = 2)

	Orsted 2012	**Vickers 2013**
Selection of the exposed and non-exposed cohorts	Low	Low
Measurement of exposure	Low	Moderate
Measurement of outcome	Moderate	Low
Was outcome of interest absent at the time to which the exposure refers?	Low	Low
Was follow-up long enough for outcome to occur?	Low	Low
Participation rate	Low	Low
Completeness of follow-up	Low	High
Difference in follow-up between exposed and non-exposed	Low	Low
Accuracy of dates of outcome or censoring	Low	Low
Difference in missing data for exposure between those with or without the outcome	Low	Low
Comparability of exposed and non-exposed cohorts with respect to potentially important confounding variables*	High for age <45 years Moderate	Low
Covariates are appropriately included in statistical analysis models	Low	Low
Overall Risk of bias	**High** for age <45 years **Moderate**	**High**
Overall quality rating	**Low** for age <45 years **Moderate**	**Low**

**pre-specified confounding variable is age*

Key to overall rating
High risk of bias – high risk of bias in any domain
Moderate risk of bias – moderate or low risk of bias in all domains
Low risk of bias – all domains low risk of bias

Table 5: Assessment of risk of bias of included **nested case-control** studies (n = 1)

Quality Category	**N (%)**
Selection of the exposed and non-exposed cohorts	
Low risk of bias	1 (100.0)
Moderate risk of bias	-
High risk of bias	-
Selection of cases and controls	
Low risk of bias	1 (100.0)
Moderate risk of bias	-
High risk of bias	-
Measurement of exposure	
Low risk of bias	-
Moderate risk of bias	1 (100.0)
High risk of bias	-
Temporality of exposure	
Low risk of bias	1 (100.0)
Moderate risk of bias	-
High risk of bias	-
Was the same method used to measure exposure in cases and controls?	
Low risk of bias	1 (100.0)
High risk of bias	-
Definition of cases	
Low risk of bias	1 (100.0)
Moderate risk of bias	-
High risk of bias	-
Definition of controls	
Low risk of bias	1 (100.0)
Moderate risk of bias	-
Was outcome of interest likely to have been absent at the time to which the exposure refers?	
Low risk of bias	1 (100.0)
Moderate risk of bias	-
High risk of bias	-
Was follow-up long enough for outcome to occur?	
Low risk of bias	1 (100.0)
High risk of bias	-
Participation rate in cohort	
Low risk of bias	1 (100.0)
Moderate risk of bias	-
High risk of bias	-
Not application	-
Participation (response) rate for cases	
Low risk of bias	-
Moderate risk of bias	-

High risk of bias	-
Not applicable	1 (100.0)
Participation (response) rate for controls	
Low risk of bias	-
Moderate risk of bias	-
High risk of bias	-
Not applicable	1 (100.0)
Difference in participation rate (response rate) between cases and controls	
Low risk of bias	-
Moderate risk of bias	-
High risk of bias	-
Not applicable	1 (100.0)
Completeness of follow-up of cohort	
Low risk of bias	-
Moderate risk of bias	-
High risk of bias	1 (100.0)
Difference in follow-up between exposed and non-exposed members of cohort	
Low risk of bias	1 (100.0)
Moderate risk of bias	-
High risk of bias	-
Accuracy of dates of outcome or censoring	
Low risk of bias	1 (100.0)
Moderate risk of bias	-
Difference in missing data for exposure between cases and controls	
Low risk of bias	1 (100.0)
Moderate risk of bias	-
High risk of bias	-
Comparability of exposed and non-exposed cohorts with respect to potentially important confounding variables	
Low risk of bias	1 (100.0)
Moderate risk of bias	-
High risk of bias	-
Analysis appropriate to design	
Low risk of bias	1 (100.0)
High risk of bias	-
Covariates are appropriately included in statistical analysis models	
Low risk of bias	1 (100.0)
High risk of bias	-

Table 6: Assessment of risk of bias of included **nested case-control** studies (n = 1)

	Vickers 2013
Selection of the exposed and non-exposed cohorts	Low
Selection of cases and controls	Low
Measurement of exposure	Moderate
Temporality of exposure	Low
Was the same method used to measure exposure in cases and controls?	Low
Definition of cases	Low
Definition of controls	Low
Was outcome of interest likely to have been absent at the time to which the exposure refers?	Low
Was follow-up long enough for outcome to occur?	Low
Participation rate in cohort	Low
Participation (response) rate for cases	N/A
Participation (response) rate for controls	N/A
Difference in participation rate (response rate) between cases and controls	N/A
Completeness of follow-up of cohort	High
Difference in follow-up between exposed and non-exposed members of cohort	Low
Accuracy of dates of outcome or censoring	Low
Difference in missing data for exposure between cases and controls	Low
Comparability of exposed and non-exposed cohorts with respect to potentially important confounding variables*	Low
Analysis appropriate to design	Low
Covariates are appropriately included in statistical analysis models	Low
Overall quality rating	**Low**
Risk of bias	**High**

**pre-specified confounding variable is age*

Key to overall rating
High risk of bias – high risk of bias in any domain
Moderate risk of bias - moderate or low risk of bias in all domains – no high risk domains
Low risk of bias – all domains low risk of bias – no moderate or high risk domains

2.5. Study Results

Table 7: Risk of prostate cancer death with baseline PSA level for men aged 55 years or younger: **cohort** and **nested case-control** studies

Study	Age at baseline (years)	Follow-up	N	PSA threshold or range (ng/mL)	Absolute risk of prostate cancer mortality (95% CI)
Cohort studies					
Ørsted 2012	<45	10 year risk	NR	≤1.0	0.3%*
				>1.0 – 2.0	0.6%*
				>2.0 – 3.0	1.5%*
				>3.0 – 4.0	1.7%*
				>4.0 – 10.0	2.4%*
				>10.0	9.8%*
	45 – 49	10 year risk	NR	≤1.0	0.4%*
				>1.0 – 2.0	1.0%*
				>2.0 – 3.0	2.4%*
				>3.0 – 4.0	2.6%*
				>4.0 – 10.0	3.9%*
				>10.0	16%*
	50 – 54	10 year risk	NR	≤1.0	0.5%*
				>1.0 – 2.0	1.3%*
				>2.0 – 3.0	3.2%*
				>3.0 – 4.0	3.5%*
				>4.0 – 10.0	5.1%*
				>10.0	20%*
Vickers 2013 *Malmo project*	51 – 55	15 years	4,063	≤0.53 (lowest quarter)	0.33 (0.11 – 1.02)%
				≤0.85 (below median)	0.22 (0.08 – 0.59)%
				0.85 – 1.4 (second quarter)	0.66 (0.30 – 1.47)%
				≥1.4 (highest quarter)	1.80 (1.12 – 2.88)%

				≥2.4 (highest 10th)	3.38 (1.97 – 5.75)%
		20 years		≤0.53 (lowest quarter)	0.57 (0.24 – 1.36)%
				≤0.85 (below median)	0.47 (0.24 – 0.94)%
				0.85 – 1.4 (second quarter)	1.67 (0.99 – 2.81)%
				≥1.4 (highest quarter)	2.98 (2.05 – 4.33)%
				≥2.4 (highest 10th)	5.68 (3.74 – 8.59)%
		25 years		≤0.53 (lowest quarter)	0.94 (0.44 – 2.02)%
				≤0.85 (below median)	0.80 (0.45 – 1.42)%
				0.85 – 1.4 (second quarter)	2.09 (1.30 – 3.35)%
				≥1.4 (highest quarter)	5.07 (3.70 – 6.93)%
				≥2.4 (highest 10th)	9.03 (6.34 – 12.78)%
Nested case-control					
Vickers 2013 *Malmo project*	37.5 – 42.5	15 years	3,979	≤0.42 (lowest quarter)	0.10 (0.01 – 0.69)^%
				below median	NR
				0.61 – 0.90 (second quarter)	0
				≥0.90 (highest quarter)	0.22 (0.04 – 0.90)^%
				≥1.30 (highest 10th)	0.60 (0.09 – 2.39)^%
		20 years		≤0.42 (lowest quarter)	0.10 (0.01 – 0.69)^%
				below median	NR
				0.61 – 0.90 (second quarter)	0
				≥0.90 (highest quarter)	0.34 (0.08 – 1.05)^%
				≥1.30 (highest 10th)	0.90 (0.21 – 2.79)^%
		25 years		≤0.42 (lowest quarter)	0.10 (0.01 – 0.69)^%
				below median	NR
				0.61 – 0.90 (second quarter)	0.16 (0.01 - 0.97) ^%
				≥0.90 (highest quarter)	0.70 (0.26 – 1.61)^%
				≥1.30 (highest 10th)	1.23 (0.35 – 3.26)^%
	45 – 49	15 years	10,357	≤0.44 (lowest quarter)	0.08 (0.01 – 0.30)^%

		≤0.68 (below median)	0.04 (0.01 – 0.16)^%
		0.68 – 1.10 (second quarter)	<0.01 (<0.01 – 0.07)^%
		≥1.10 (highest quarter)	0.31 (0.13 – 0.66)^%
		≥1.60 (highest 10th)	0.74 (0.31 – 1.57)^%
	20 years	≤0.44 (lowest quarter)	0.24 (0.09 – 0.54)^%
		≤0.68 (below median)	0.17 (0.08 – 0.34)^%
		0.68 – 1.10 (second quarter)	0.24 (0.09 – 0.56)^%
		≥1.10 (highest quarter)	1.18 (0.75 – 1.77)^%
		≥1.60 (highest 10th)	2.42 (1.48 – 3.75)^%
	25 years	≤0.44 (lowest quarter)	0.52 (0.26 – 0.96)^%
		≤0.68 (below median)	0.55 (0.35 – 0.83)^%
		0.68 – 1.10 (second quarter)	0.72 (0.40 – 1.21)^%
		≥1.10 (highest quarter)	2.67 (1.97 – 3.54)^%
		≥1.60 (highest 10th)	5.14 (3.63 – 7.04)^%

**Estimated using regression coefficients from a Poisson regression model*

^ estimated using imputed data

CI = confidence interval; NR = not reported;

2.6. Body of Evidence

I PROSTATE CANCER MORTALITY

Study	Study design	Level of evidence *	Risk of bias**	Age at baseline (years)	Follow-up	N	Baseline PSA threshold or range (ng/mL)	Prostate cancer mortality		Relevance of evidence*
								Absolute risk (95% CI)	Increment in absolute risk (%)	
Orsted 2012	Retrospective cohort	III-2	High	<45	10 year risk	NR	≤1.0 >1.0 – 2.0 >2.0 – 3.0 >3.0 – 4.0 >4.0 – 10.0 >10.0	0.3% 0.6% 1.5% 1.7% 2.4% 9.8%	Reference 0.3 1.2 1.4 2.1 9.5	1
Vickers 2013 *Malmo Preventive Project*	Nested case-control within retrospective cohort	III-2	High	37.5 – 42.5	15 years	3,979	≤0.42 (lowest quarter) below median 0.61 – 0.90 (second quarter) ≥0.90 (highest quarter) ≥1.30 (highest 10th)	0.10 (0.01 – 0.69)% NR 0 0.22 (0.04 – 0.90)% 0.60 (0.09 – 2.39)%	Reference - -0.10 0.12 0.50	1
					20 years		≤0.42 (lowest quarter) below median 0.61 – 0.90 (second quarter) ≥0.90 (highest quarter) ≥1.30 (highest 10th)	0.10 (0.01 – 0.69)% NR 0 0.34 (0.08 – 1.05)% 0.90 (0.21 – 2.79)%	Reference NR -0.10 0.24 0.80	1
					25 years		≤0.42 (lowest quarter) below median 0.61 – 0.90 (second quarter) ≥0.90 (highest quarter) ≥1.30 (highest 10th)	0.10 (0.01 – 0.69)% NR 0.16 (0.01 - 0.97)% 0.70 (0.26 – 1.61)% 1.23 (0.35 – 3.26)%	Reference NR 0.06 0.60 1.13	1
Orsted 2012	Retrospective cohort	III-2	Moderate	45 – 49	10 year risk	NR	≤1.0 >1.0 – 2.0 >2.0 – 3.0 >3.0 – 4.0 >4.0 – 10.0 >10.0	0.4% 1.0% 2.4% 2.6% 3.9% 16%	Reference 0.6 2.0 2.2 3.5 15.6	1
Vickers 2013 *Malmo Preventive*	Nested case-control within retrospective cohort	III-2	High	45 – 49	15 years	10,357	≤0.44 (lowest quarter) ≤0.68 (below median) 0.68 – 1.10 (second quarter) ≥1.10 (highest quarter)	0.08 (0.01 – 0.30)% 0.04 (0.01 – 0.16)% <0.01 (<0.01 – 0.07)% 0.31 (0.13 – 0.66)% 0.74 (0.31 – 1.57)%	Reference -0.04 -0.072 0.23 0.66	1

Project							≥1.60	(highest 10th)		
					20 years		≤0.44 ≤0.68 0.68 – 1.10 ≥1.10 ≥1.60	(lowest quarter) (below median) (second quarter) (highest quarter) (highest 10th)	0.24 (0.09 – 0.54)% 0.17 (0.08 – 0.34)% 0.24 (0.09 – 0.56)% 1.18 (0.75 – 1.77)% 2.42 (1.48 – 3.75)%	Reference -0.07 0 0.94 2.18	1
					25 years		≤0.44 ≤0.68 0.68 – 1.10 ≥1.10 ≥1.60	(lowest quarter) (below median) (second quarter) (highest quarter) (highest 10th)	0.52 (0.26 – 0.96)% 0.55 (0.35 – 0.83)% 0.72 (0.40 – 1.21)% 2.67 (1.97 – 3.54)% 5.14 (3.63 – 7.04)%	Reference 0.03 0.20 2.15 4.62	1
Orsted 2012	Retrospective cohort	III-2	Moderate	50 – 54	10 year risk	NR	≤1.0 >1.0 – 2.0 >2.0 – 3.0 >3.0 - 4.0 >4.0 - 10.0 >10.0		0.5% 1.3% 3.2% 3.5% 5.1% 20%	Reference 0.8 2.7 3.0 4.6 19.5	1
Vickers 2013 *Malmo Preventive Project*	Retrospective Cohort	III-2	High	51 – 55	15 years	4,063	≤0.53 ≤0.85 0.85 – 1.4 ≥1.4 ≥2.4	(lowest quarter) (below median) (second quarter) (highest quarter) (highest 10th)	0.33 (0.11 – 1.02)% 0.22 (0.08 – 0.59)% 0.66 (0.30 – 1.47)% 1.80 (1.12 – 2.88)% 3.38 (1.97 – 5.75)%	Reference -0.11 0.33 1.47 3.05	1
					20 years		≤0.53 ≤0.85 0.85 – 1.4 ≥1.4 ≥2.4	(lowest quarter) (below median) (second quarter) (highest quarter) (highest 10th)	0.57 (0.24 – 1.36)% 0.47 (0.24 – 0.94)% 1.67 (0.99 – 2.81)% 2.98 (2.05 – 4.33)% 5.68 (3.74 – 8.59)%	Reference -0.10 1.10 2.41 5.11	1
					25 years		≤0.53 ≤0.85 0.85 – 1.4 ≥1.4 ≥2.4	(lowest quarter) (below median) (second quarter) (highest quarter) (highest 10th)	0.94 (0.44 – 2.02)% 0.80 (0.45 – 1.42)% 2.09 (1.30 – 3.35)% 5.07 (3.70 – 6.93)% 9.03 (6.34 – 12.78)%	Reference -0.14 1.15 4.13 8.09	1

AR = absolute risk; NR = not reported; PSA = prostate-specific antigen;

** refer to appendix B for detailed explanations of rating scores; ** see tables 3-6 for results of quality appraisals;*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the NHMRC evidence statement form.

2.7. References of included studies

(1) Orsted DD, Nordestgaard BG, Bojesen SE. Prostate-specific antigen and long-term prediction of prostate cancer incidence and mortality in the general population. J Clin Oncol 2012;30(5).

(2) Vickers AJ, Ulmert D, Sjoberg DD, Bennette CJ, Bjork T, Gerdtsson A, et al. Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long term risk of metastasis: case-control study. BMJ 2013;346:f2023.

APPENDICES

Appendix A: Search strategies used

For Medline database:

#	Searches
1	(baseline or initial$ or first or single or early).tw.
2	(young* or youth or unscreened or nonscreened or non-screened).tw.
3	Prostate-Specific Antigen/
4	(PSA or (prostate adj1 specific adj1 antigen)).tw.
5	1 or 2
6	3 or 4
7	5 and 6
8	(diagnos* or detect*).tw.
9	(risk$ or susceptib$ or predict$ or associat$ or subsequent$ or long-term).tw
10	exp risk factors/ or exp risk assessment/
11	8 or 9 or 10
12	7 and 11
13	Early Diagnosis/ or Early Detection of Cancer/
14	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
15	prostate cancer.mp. or exp Prostatic Neoplasms/
16	14 or 15
17	13 and 16
18	12 or 17
19	18 not (psoriatic or brachytherapy or salvage or cryotherapy or gene or focal or polymorphism$ or ablation or radiotherapy or radiation or castration).ti.
20	limit 19 to (english language and humans and yr="1990 -Current")

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database:

#	Searches
1	early or single or baseline or initial* or first
2	young* or ‘youth’/exp or unscreened or 'non screened' or nonscreened
3	'prostate specific antigen'/exp
4	'psa' or 'prostate specific antigen'
5	1 or 2
6	3 or 4
7	5 and 6
8	'cancer diagnosis'/syn or diagnos* or detect*
9	risk* or susceptib* or predict* or associat* or subsequent* or 'long term'
10	'risk factor'/exp or 'risk assessment'/exp
11	8 or 9 or 10
12	7 and 11
13	'cancer screening'/exp or 'early diagnosis'/exp
14	prostat* near/3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or metast* or adeno*)
15	'prostate cancer'/exp and [humans]/lim
16	14 or 15
17	13 and 16
18	12 or 17
19	18 not (brachytherapy:ti or salvage:ti or cryotherapy:ti or gene:ti or focal:ti or polymorphism$:ti or ablation:ti or radiotherapy:ti or radiation:ti or castration:ti or 'psoriatic arthritis'/exp)
20	19 and [humans]/lim and [english]/lim and [embase]/lim and [1990-3000]/py not [medline]/lim

ATSI search terms used

#	Searches
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

For Cochrane Database of Systematic Reviews – The Cochrane Library:

Title, abstracts, keywords: “prostate”

For Database of Abstracts of Reviews of Effects and Health Technology Assessment database (via OvidSP):

#	Searches
1	exp Prostatic Neoplasms/
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
3	1 or 2

Appendix B:

Level of Evidence rating criteria – Risk factor studies (Aetiology)

Level	Study design
I	Meta-analysis or a systematic review of level II studies
II	Prospective cohort studies
III-1	All or none
III-2	Retrospective cohort studies
III-3	Case-control studies
IV	Cross-sectional studies or case series

According to the standards of the National Health and Medical Research Council

Case-control studies nested within a prospective cohort study were considered Level II evidence and are referred to as "nested case-control" studies.

Case-control studies nested within a retrospective cohort study were considered Level III-2 evidence and are referred to as "nested case-control" studies.

Relevance of the evidence

Rating	Relevance
1	Evidence of an effect on patient-relevant clinical outcomes including benefits and harms, quality of life and survival.
2	Evidence of an effect on a surrogate outcome* that has been shown to be predictive of patient-relevant outcomes for the same intervention.
3	Evidence of an effect on proven surrogate outcomes but for a different intervention.
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population.
5	Evidence confined to unproven surrogate outcomes.

**'surrogate outcome' refers to reasonable indicators of whether there has been some effect (e.g. blood pressure measurements or levels of serum cholesterol)*

Points to considering patient-relevant outcomes:
i) The goal of decision making in health care is to choose the intervention(s) (which may include doing nothing) that is (are) most likely to deliver the outcomes that patients find desirable
ii) Surrogate outcomes (such as blood pressure measurements or levels of serum cholesterol) may be reasonable indicators of whether there has been some effect. However, they should not be the basis for clinical decisions unless they reliably predict an effect on the way the patient feels; otherwise they will not be of interest to the patient or their carers
iii) All possible outcomes that are of most interest to patients (particularly harms) should be identified and evaluated

Adapted from table 1.10: National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra: NHMRC; 2000. http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp69.pdf

Appendix C:

Potentially relevant guidelines identified and reason why not adopted

Year	Organisation	Title	Reason why not adopted
2010	American Cancer Society	American Cancer Society Guideline for the Early Detection of Prostate Cancer	Did not meet pre-specified AGREE II criteria for adoption
2008	American College of Preventive Medicine	Screening for Prostate Cancer in U.S. Men: ACPM Position Statement on Preventive Practice	Did not meet pre-specified AGREE II criteria for adoption
2013	American College of Physicians	Screening for prostate cancer – guidance statement	Did not meet pre-specified AGREE II criteria for adoption
2011	Canadian Urological Association	Prostate Cancer Screening: Canadian guidelines	Did not meet pre-specified AGREE II criteria for adoption
2014	European Association of Urology	Guidelines on Prostate Cancer	Not based on an available systematic review
2013	European Society for Medical Oncology	ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Consensus based
2010	Japanese Urological Association	Japanese Urological Association Guidelines on prostate-specific antigen-based screening for prostate cancer in 2010	Not based on a systematic review
2013	Prostate Cancer World Congress	Melbourne Consensus Statement on Prostate Cancer Testing	Consensus based
2012	NCCN	Prostate cancer early detection version 2.2012	Not based on a systematic review
2012	Royal College of Pathologists of Australasia	Prostate specific antigen testing: Age-related interpretation in early prostate cancer detection	Consensus based
2012	University of Michigan Health System	Cancer Screening	Did not meet pre-specified AGREE II criteria for adoption

Excluded Studies

Study	Reason for exclusion
Alibhai 2004	Narrative review/comment/letter to editor (no original data)
Altwein 1999	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Aly 2011	Inappropriate population (included only men who underwent biopsy)
Andriole 2012	No comparison of different baseline PSA levels
Antenor 2004	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Arsov 2013	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Aus 2004	Inappropriate population (included only men who underwent biopsy)
Aus 2005	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Bartoletti 2009	Narrative review/comment/letter to editor (no original data)
Bartsch 2001	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Beemsterboer 2000	No comparison of different baseline PSA levels
Bergdahl 2009	No comparison of different baseline PSA levels
Berger 2005	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Berger 2007	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Berglund 2000	No relevant outcomes
Bohnen 2007	No relevant outcomes
Bokhorst 2012	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Boergermann 2009	No relevant outcomes
Botchorishvili 2009	Narrative review/comment/letter to editor (no original data)
Botelho 2012	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Brawer 1998	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Bretton 1994	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Brewster 1994	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Briganti 2014	Narrative review/comment/letter to editor (no original data)
Bul 2011	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Bul 2011 (abstract)	Duplicate publication
Canby-Hagino 2007	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Candas 2006	Organised subsequent PSA testing (alteration of

	management depending on baseline PSA levels)
Carroll 2011	Narrative review/comment/letter to editor (no original data)
Carter 1992	No comparison of different baseline PSA levels
Carter 1997	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Carter 2000	Narrative review/comment/letter to editor (no original data)
Carter 2006	No comparison of different baseline PSA levels
Catalona 2003	Inappropriate population (included only men who underwent biopsy)
Catalona 2004	Narrative review/comment/letter to editor (no original data)
Carlsson 2010	No comparison of different baseline PSA levels
Carlsson 2012	Narrative review/comment/letter to editor (no original data)
Carlsson 2013	Inappropriate population (included only men diagnosed with prostate cancer)
Connolly 2008	No relevant outcomes
Crawford 2006	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Crawford 2011	Did not report results stratified by age at baseline
DeAntoni 1997	Narrative review/comment/letter to editor (no original data)
Draisma 2009	No comparison of different baseline PSA levels
Eggener 2008	No comparison of different baseline PSA levels
Etzioni 2004	No relevant outcomes
Fang 2001	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Faria 2012	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Finne 2008	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Fleshner 2009	Narrative review/comment/letter to editor (no original data)
Foulkes 1995	Narrative review/comment/letter to editor (no original data)
Friedrich 2011	Narrative review/comment/letter to editor (no original data)
Gann 1995	Did not report results stratified by age at baseline
Gilligan 2009	Narrative review/comment/letter to editor (no original data)
Giri 2009	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Glass 2013	Narrative review/comment/letter to editor (no original data)
Gomella 2011	Narrative review/comment/letter to editor (no original data)
Greene 2009	Narrative review/comment/letter to editor (no original data)
Gretzer 2002	Narrative review/comment/letter to editor (no original data)
Gretzer 2003	Narrative review/comment/letter to editor (no original data)
Hakama 2001	Inappropriate population
Haines 2013	Narrative review/comment/letter to editor (no original data)
Harris 1997	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)

Heidenreich 2013	Narrative review/comment/letter to editor (no original data)
Helzlsouer 1992	No relevant outcomes
Heyns 2011	No relevant outcomes
Hobbs 2013	Narrative review/comment/letter to editor (no original data)
Hoedemaeker 2001	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Hoffman 2012	No comparison of different baseline PSA levels
Holmberg 2010	Narrative review/comment/letter to editor (no original data)
Holmstrom 2009	No relevant outcomes
Hugosson 2003	No comparison of different baseline PSA levels
Hugosson 2004	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Hugosson 2010	No comparison of different baseline PSA levels
Illic 2009	Narrative review/comment/letter to editor (no original data)
Ito 2000	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Ito 2001	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Ito 2003	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Ito 2003	No comparison of different baseline PSA levels
Ito 2004 a	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Ito 2004 b	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
JUA guideline 2010	Narrative review/comment/letter to editor (no original data)
Kane 1992	No relevant outcomes
Katz 2013	Narrative review/comment/letter to editor (no original data)
Kawamura 2011	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Kettermann 2010	No comparison of different baseline PSA levels
Kilpelainen 2013	No comparison of different baseline PSA levels
Kim 2011	Inappropriate population (only included men who underwent biopsy)
Kim 2013	No comparison of different baseline PSA levels
Kitagawa 2014	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Kirby 2004	Narrative review/comment/letter to editor (no original data)
Kirby 2009	Narrative review/comment/letter to editor (no original data)
Kjellman 2009	No comparison of different baseline PSA levels (Stockholm RCT single-intervention screening vs. no screening)
Klein 2012	Inappropriate study design
Kobayashi 2005	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Kuller 2004	Did not report results stratified by age at baseline

Kundu 2005	No comparison of different baseline PSA levels
Labrecque 2013	Narrative review/comment/letter to editor (no original data)
Labrie 2004	No comparison of different baseline PSA levels
Lamb 2011	Narrative review/comment/letter to editor (no original data)
Lane 2007	Inappropriate study design
Larsen 2013	Inappropriate population
Leach 2012	Narrative review/comment/letter to editor (no original data)
Legler 1998	No comparison of different baseline PSA levels
Lilja 2007	No relevant outcomes
Lilja 2008	Narrative review/comment/letter to editor (no original data)
Lilja 2011	No relevant outcomes
Lippi 2013	Narrative review/comment/letter to editor (no original data)
Liu 2013	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Lodding 1998	No comparison of different baseline PSA levels
Loeb 2006	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Loeb 2007 a	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Loeb 2007 b	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Loeb 2009	Narrative review/comment/letter to editor (no original data)
Loeb 2012 a	Narrative review/comment/letter to editor (no original data)
Loeb 2012 b	Narrative review/comment/letter to editor (no original data)
Louria 2005	Narrative review/comment/letter to editor (no original data)
Marberger 2012	Narrative review/comment/letter to editor (no original data)
Marsland 2011	Narrative review/comment/letter to editor (no original data)
Marta 2013	Narrative review/comment/letter to editor (no original data)
Martin 2008	Inappropriate population (included only men diagnosed with prostate cancer)
McGreevy 2006	No relevant outcomes
McKenzie 2011	Narrative review/comment/letter to editor (no original data)
McKenzie 2013	Narrative review/comment/letter to editor (no original data)
Melia 2005	Narrative review/comment/letter to editor (no original data)
Mian 2010	Narrative review/comment/letter to editor (no original data)
Miller 2012	Narrative review/comment/letter to editor (no original data)
Miller 2013	Narrative review/comment/letter to editor (no original data)
Miner 2010	Narrative review/comment/letter to editor (no original data)
Mitka 2009	Narrative review/comment/letter to editor (no original data)
Mitra 2010	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Mizusawa 2011	Inappropriate study design (included only men diagnosed with prostate cancer)

Moul 2003	Narrative review/comment/letter to editor (no original data)
Murphy 2014	Narrative review/comment/letter to editor (no original data)
Neal 2010	Narrative review/comment/letter to editor (no original data)
Nordstrom 2013	No relevant outcomes
Oesterling 1993	No relevant outcomes
Ohi 2008	No relevant outcomes
Paez 2003	No relevant outcomes
Park 2012	No relevant outcomes
Petrylak 2007	Narrative review/comment/letter to editor (no original data)
Pienta 2009	Narrative review/comment/letter to editor (no original data)
Pinsky 2012	No comparison of different baseline PSA levels
Postma 2004	Inappropriate population (included only men diagnosed with prostate cancer)
Preston 2000	No relevant outcomes
Ranasinghe 2014	No comparison of different baseline PSA levels
Randazzo 2013	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Raviv 1996	Inappropriate population (include only men with PIN)
Rees 2010	Narrative review/comment/letter to editor (no original data)
Reissigl 1996	No comparison of different baseline PSA levels
Reissigl 1997	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Rhodes 2012	No comparison of different baseline PSA levels
Richardson 1997	Narrative review/comment/letter to editor (no original data)
Rogers 2010	Narrative review/comment/letter to editor (no original data)
Roobol 2004	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Roobol 2007	No comparison of different baseline PSA levels
Roobol 2010	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Roobol 2011	No comparison of different baseline PSA levels
Roobol 2012	No comparison of different baseline PSA levels
Roobol 2013 a	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Roobol 2013 b	No comparison of different baseline PSA levels
Roobol 2013 c	Narrative review/comment/letter to editor (no original data)
Rosario 2008	Inappropriate study design
Rundle 2013	No comparison of different baseline PSA levels
Sammon 2013	Narrative review/comment/letter to editor (no original data)
Sarma 2014	Narrative review/comment/letter to editor (no original data)
Savage 2010	No relevant outcomes
Sawada 2013	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)

Schaeffer 2009	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Schroder 2005	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Schroder 2008	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Schroder 2009	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Schroder 2011	Narrative review/comment/letter to editor (no original data)
Schroder 2012 a	No comparison of different baseline PSA levels
Schroder 2012 b	No comparison of different baseline PSA levels
Scosyrev 2012	No comparison of different baseline PSA levels
Seiler 2012	No comparison of different baseline PSA levels
Smith 1996	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Smith 1997	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Squires 2007	Narrative review/comment/letter to editor (no original data)
Stattin 2011	No comparison of different baseline PSA levels
Stenman 2005	Narrative review/comment/letter to editor (no original data)
Steuber 2008	Narrative review/comment/letter to editor (no original data)
Strope 2010	Narrative review/comment/letter to editor (no original data)
Strope 2012	Narrative review/comment/letter to editor (no original data)
Sun 2007	Inappropriate study design
Tang 2010	Inappropriate study design
Tang 2012	No relevant outcomes
Tairman 2006	Narrative review/comment/letter to editor (no original data)
Thompson 2005	No relevant outcomes
Thompson 2010	Narrative review/comment/letter to editor (no original data)
Törnblom 1999	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Törnblom 2004	Did not report results stratified by age at baseline
Uchida 2000	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Ulmert 2008	No relevant outcomes
Uozumi 2002	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Van der Cruijsen-Koeter 2003	No comparison of different baseline PSA levels
Van der Cruijsen-Koeter 2006	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Van Leeuwen 2010	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Van Leeuwen 2012	No comparison of different baseline PSA levels
Van Vugt 2011	No comparison of different baseline PSA levels

Vashi 1997	Narrative review/comment/letter to editor (no original data)
Vickers 2007 predictive	No relevant outcomes
Vickers 2007 long-term	Inappropriate population
Vickers 2009	Inappropriate study design
Vickers 2010 a	Inappropriate study design
Vickers 2010 b	Inappropriate population
Vickers 2011	No comparison of different baseline PSA levels
Vickers 2012	Narrative review/comment/letter to editor (no original data)
Vickers 2014	Inappropriate population
Vis 2002	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Vukotic 2005	Inappropriate population (included only men who underwent biopsy)
Wallner 2013 a	No comparison of different baseline PSA levels
Wallner 2013 b	Systematic review of case control-studies (inappropriate study design)
Walsh 2010	Narrative review/comment/letter to editor (no original data)
Weight 2013	Organised subsequent PSA testing (alteration of management depending on baseline PSA levels)
Welch 2005	Inappropriate study design (“modelling”)
Whittemore 1995	No comparison of different baseline PSA levels
Whittemore 2005	Did not report results stratified by age at baseline (stratified by age at diagnosis)
Wright 2002	No relevant outcomes
Yli-Hemminki 2013	No comparison of different baseline PSA levels
Zeliadt 2010	No comparison of different baseline PSA levels
Zhao 2010	Inappropriate population (included only men who underwent biopsy)
Zhu 2012 a	No comparison of different baseline PSA levels
Zhu 2012 b	Narrative review/comment/letter to editor (no original data)

References: Excluded Studies

(1) Updated Japanese Urological Association Guidelines on prostate-specific antigen-based screening for prostate cancer in 2010. Int J Urol 2010 Oct;17(10):830-8.

(2) Alibhai SMH. What is the prevalence of prostate cancer among men with low prostate-specific antigen levels? Can Med Assoc J 2004;171(6):572.

(3) Altwein JE, Luboldt HA. Results of a screening program in Germany for early detection of early prostate cancer. Prostate Cancer Prostatic Dis 1999;2(SUPPL. 2):S15-S18.

(4) Aly M, Wiklund F, Xu J, Isaacs WB, Eklund M, D'Amato M, et al. Polygenic risk score improves prostate cancer risk prediction: results from the Stockholm-1 cohort study. Eur Urol 2011 Jul;60(1):21-8.

(5) Andriole GL, Crawford ED, Grubb RL, III, Buys SS, Chia D, Church TR, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. Journal of the National Cancer Institute 2012 Jan 18;104(2):125-32.

(6) Antenor JA, Han M, Roehl KA, Nadler RB, Catalona WJ. Relationship between initial prostate specific antigen level and subsequent prostate cancer detection in a longitudinal screening study. J Urol 2004 Jul;172(1):90-3.

(7) Arsov C, Becker N, Hadaschik BA, Hohenfellner M, Herkommer K, Gschwend JE, et al. Prospective randomized evaluation of risk-adapted prostate-specific antigen screening in young men: The PROBASE trial. Eur Urol 2013;64(6):873-5.

(8) Aus G, Becker C, Franzen S, Lilja H, Lodding P, Hugosson J. Cumulative prostate cancer risk assessment with the aid of the free-to-total prostate specific antigen ratio. Eur Urol 2004 Feb;45(2):160-5.

(9) Aus G, Damber JE, Khatami A, Lilja H, Stranne J, Hugosson J. Individualized screening interval for prostate cancer based on prostate-specific antigen level: results of a prospective, randomized, population-based study. Archives of Internal Medicine 2005 Sep 12;165(16):1857-61.

(10) Bartoletti R. Prostate-specific antigen dynamics and prostate cancer diagnosis. Eur Urol 763 20;56(5):761-2.

(11) Bartsch G, Horninger W, Klocker H, Reissigl A, Oberaigner W, Schonitzer D, et al. Prostate cancer mortality after introduction of prostate-specific antigen mass screening in the Federal State of Tyrol, Austria. Urology 2001 Sep;58(3):417-24.

(12) Beemsterboer PM, de Koning HJ, Kranse R, Trienekens PH, van der Maas PJ, Schroder FH. Prostate specific antigen testing and digital rectal examination before and during a randomized trial of screening for prostate cancer: European randomized study of screening for prostate cancer, Rotterdam. J Urol 2000 Oct;164(4):1216-20.

(13) Bergdahl AG, Aus G, Lilja H, Hugosson J. Risk of dying from prostate cancer in men randomized to screening: differences between attendees and nonattendees. Cancer 2009 Dec 15;115(24):5672-9.

(14) Berger AP, Deibl M, Steiner H, Bektic J, Pelzer A, Spranger R, et al. Longitudinal PSA changes in men with and without prostate cancer: assessment of prostate cancer risk. Prostate 2005 Aug 1;64(3):240-5.

(15) Berger AP, Deibl M, Strasak A, Bektic J, Pelzer AE, Klocker H, et al. Large-scale study of clinical impact of PSA velocity: long-term PSA kinetics as method of differentiating men with from those without prostate cancer. Urology 2007 Jan;69(1):134-8.

(16) Berglund G, Nilsson P, Eriksson KF, Nilsson JA, Hedblad B, Kristenson H, et al. Long-term outcome of the Malmo preventive project: mortality and cardiovascular morbidity. J Intern Med 2000 Jan;247(1):19-29.

(17) Bohnen AM, Groeneveld FP, Bosch JL. Serum prostate-specific antigen as a predictor of prostate volume in the community: the Krimpen study. Eur Urol 1652 Mar;51(6):1645-52.

(18) Bokhorst LP, Zhu X, Bul M, Bangma CH, Schroder FH, Roobol MJ. Positive predictive value of prostate biopsy indicated by prostate-specific-antigen-based prostate cancer screening: trends over time in a European randomized trial*. BJU Int 2012 Dec;110(11):1654-60.

(19) Borgermann C, vom DF, Swoboda A, Ketteniss O, Becker M, Rubben H. PSA quo vadis? It is reasonable to start with prostate-specific antigen testing at the age of 40! Cancer Epidemiology, Biomarkers & Prevention 2011 Jun;20(6):1190-5.

(20) Botchorishvili G, Matikainen MP, Lilja H. Early prostate-specific antigen changes and the diagnosis and prognosis of prostate cancer. [Review] [91 refs]. Current Opinion in Urology 2009 May;19(3):221-6.

(21) Botelho F, Pina F, Figueiredo L, Cruz F, Lunet N. Does baseline total testosterone improve the yielding of prostate cancer screening? Eur J Cancer 2012 Jul;48(11):1657-63.

(22) Brawer MK, Meyer GE, Letran JL, Bankson DD, Morris DL, Yeung KK, et al. Measurement of complexed PSA improves specificity for early detection of prostate cancer. Urology 1998 Sep;52(3):372-8.

(23) Bretton PR. Prostate-specific antigen and digital rectal examination in screening for prostate cancer: a community-based study. Southern Medical Journal 1994 Jul;87(7):720-3.

(24) Brewster SF, Kemple T, MacIver AG, Astley JP, Gingell JC. The Bristol prostate cancer pilot screening study--a 3-year follow-up. British Journal of Urology 1994 Nov;74(5):556-8.

(25) Briganti A, Suardi N, Gallina A, Abdollah F, Novara G, Ficarra V, et al. Predicting the risk of bone metastasis in prostate cancer. Cancer Treat Rev 2014;40(1):3-11.

(26) Bul M, van Leeuwen PJ, Zhu X, Schroder FH, Roobol MJ. Prostate cancer incidence and disease-specific survival of men with initial prostate-specific antigen less than 3.0 ng/ml who are participating in ERSPC Rotterdam. Eur Urol 2011 Apr;59(4):498-505.

(27) Bul M, van Leeuwen PJ, Zhu X, Schroder FH, Roobol MJ. Prostate cancer incidence and disease-specific survival in men participating in the ERSPC with an initial PSA less than 3.0 ng/mL. J Clin Oncol 2011;29(7).

(28) Canby-Hagino E, Hernandez J, Brand TC, Troyer DA, Higgins B, Ankerst DP, et al. Prostate cancer risk with positive family history, normal prostate examination findings, and PSA less than 4.0 ng/mL. Urology 2007 Oct;70(4):748-52.

(29) Candas B, Labrie F, Gomez JL, Cusan L, Chevrette E, Levesque J, et al. Relationship among initial serum prostate specific antigen, prostate specific antigen progression and prostate cancer detection at repeat screening visits. J Urol 516 Jul;175(2):510-6.

(30) Carlsson S, Vickers AJ, Roobol M, Eastham J, Scardino P, Lilja H, et al. Prostate cancer screening: facts, statistics, and interpretation in response to the US Preventive Services Task Force Review. J Clin Oncol 2012 Jul 20;30(21):2581-4.

(31) Carlsson S, Maschino A, Schroder F, Bangma C, Steyerberg EW, van der Kwast T, et al. Predictive value of four kallikrein markers for pathologically insignificant compared with aggressive prostate cancer in radical prostatectomy specimens: Results from the European randomized study of screening for prostate cancer section Rotterdam. Eur Urol 2013;64(5):693-9.

(32) Carlsson SV, Holmberg E, Moss SM, Roobol MJ, Schroder FH, Tammela TL, et al. No excess mortality after prostate biopsy: results from the European Randomized Study of Screening for Prostate Cancer. BJU Int 2011 Jun;107(12):1912-7.

(33) Carroll PR, Whitson JM, Cooperberg MR. Serum prostate-specific antigen for the early detection of prostate cancer: always, never, or only sometimes? J Clin Oncol 2011 Feb 1;29(4):345-7.

(34) Carter HB, Pearson JD, Metter EJ, Brant LJ, Chan DW, Andres R, et al. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. JAMA 1992 Apr 22;267(16):2215-20.

(35) Carter HB, Epstein JI, Chan DW, Fozard JL, Pearson JD. Recommended prostate-specific antigen testing intervals for the detection of curable prostate cancer. JAMA 1997 May 14;277(18):1456-60.

(36) Carter HB. A PSA threshold of 4.0 ng/mL for early detection of prostate cancer: the only rational approach for men 50 years old and older. Urology 2000 Jun;55(6):796-9.

(37) Carter HB, Ferrucci L, Kettermann A, Landis P, Wright EJ, Epstein JI, et al. Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. J Natl Cancer Inst 2006 Nov 1;98(21):1521-7.

(38) Catalona WJ, Bartsch G, Rittenhouse HG, Evans CL, Linton HJ, Amirkhan A, et al. Serum pro prostate specific antigen improves cancer detection compared to free and complexed prostate specific antigen in men with prostate specific antigen 2 to 4 ng/ml. J Urol 2003 Dec;170(6:Pt 1):t-5.

(39) Catalona WJ. Prostate cancer screening. BJU Int 2004 Nov;94(7):964-6.

(40) Connolly D, Black A, Gavin A, Keane PF, Murray LJ. Baseline prostate-specific antigen level and risk of prostate cancer and prostate-specific mortality: diagnosis is dependent on the intensity of investigation. Cancer Epidemiology, Biomarkers & Prevention 2008 Feb;17(2):271-8.

(41) Crawford ED, Pinsky PF, Chia D, Kramer BS, Fagerstrom RM, Andriole G, et al. Prostate specific antigen changes as related to the initial prostate specific antigen: data from the prostate, lung, colorectal and ovarian cancer screening trial. J Urol 1290 20;175(4):1286-90.

(42) Crawford ED, Moul JW, Rove KO, Pettaway CA, Lamerato LE, Hughes A. Prostate-specific antigen 1.5-4.0 ng/mL: a diagnostic challenge and danger zone. BJU Int 2011 Dec;108(11):1743-9.

(43) DeAntoni EP. Age-specific reference ranges for PSA in the detection of prostate cancer. [Review] [57 refs]. Oncology (Williston Park) 485;11(4):475-82.

(44) Draisma G, Etzioni R, Tsodikov A, Mariotto A, Wever E, Gulati R, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. J Natl Cancer Inst 2009 Mar 18;101(6):374-83.

(45) Eggener SE, Yossepowitch O, Roehl KA, Loeb S, Yu X, Catalona WJ. Relationship of prostate-specific antigen velocity to histologic findings in a prostate cancer screening program. Urology 2008 Jun;71(6):1016-9.

(46) Etzioni R, Falcon S, Gann PH, Kooperberg CL, Penson DF, Stampfer MJ. Prostate-specific antigen and free prostate-specific antigen in the early detection of prostate cancer: do combination tests improve detection? Cancer Epidemiology, Biomarkers & Prevention 2004 Oct;13(10):1640-5.

(47) Fang J, Metter EJ, Landis P, Chan DW, Morrell CH, Carter HB. Low levels of prostate-specific antigen predict long-term risk of prostate cancer: results from the Baltimore Longitudinal Study of Aging. Urology 2001 Sep;58(3):411-6.

(48) Faria EF, Carvalhal GF, dos Reis RB, Tobias-Machado M, Vieira RA, Reis LO, et al. Use of low free to total PSA ratio in prostate cancer screening: detection rates, clinical and pathological findings in Brazilian men with serum PSA levels <4.0 ng/mL. BJU Int 2012 Dec;110(11:Pt B):t-7.

(49) Finne P, Auvinen A, Maattanen L, Tammela TL, Ruutu M, Juusela H, et al. Diagnostic value of free prostate-specific antigen among men with a prostate-specific antigen level of <3.0 microg per liter. Eur Urol 2008 Aug;54(2):362-70.

(50) Fleshner NE, Lawrentschuk N. Risk of developing prostate cancer in the future: overview of prognostic biomarkers. [Review] [48 refs][Erratum appears in Urology. 2010 Sep;76(3):771]. Urology 2009 May;73(5:Suppl):Suppl-7.

(51) Foulkes W. Detection of prostate cancer. Recent evidence suggests screening may be justified in high risk younger men. BMJ 1995 Apr 29;310(6987):1139-40.

(52) Friedrich MJ. Debate continues on use of PSA testing for early detection of prostate cancer. JAMA 2011 Jun 8;305(22):2273-5.

(53) Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. JAMA 1995 Jan 25;273(4):289-94.

(54) Gilligan T. The new data on prostate cancer screening: what should we do now? Cleveland Clinic Journal of Medicine 2009 Aug;76(8):446-8.

(55) Giri VN, Egleston B, Ruth K, Uzzo RG, Chen DY, Buyyounouski M, et al. Race, genetic West African ancestry, and prostate cancer prediction by prostate-specific antigen in prospectively screened high-risk men. Cancer Prevention Research 2009 Mar;2(3):244-50.

(56) Glass AS, Cary KC, Cooperberg MR. Risk-based prostate cancer screening: Who and how? Curr Urol Rep 2013;14(3):192-8.

(57) Gomella LG, Liu XS, Trabulsi EJ, Kelly WK, Myers R, Showalter T, et al. Screening for prostate cancer: the current evidence and guidelines controversy. [Review]. Canadian Journal of Urology 2011 Oct;18(5):5875-83.

(58) Greene KL, Albertsen PC, Babaian RJ, Carter HB, Gann PH, Han M, et al. Prostate specific antigen best practice statement: 2009 update. J Urol 2009 Nov;182(5):2232-41.

(59) Gretzer MB, Partin AW. PSA levels and the probability of prostate cancer on biopsy. European Urology, Supplement 2002;1(6):21-7.

(60) Gretzer MB, Partin AW. PSA markers in prostate cancer detection. [Review] [92 refs]. Urologic Clinics of North America 2003 Nov;30(4):677-86.

(61) Haines IE. Prostate-specific antigen screening for prostate cancer and the risk of overt metastatic disease at presentation : analysis of trends over time. Cancer 2013 Mar 1;119(5):1113.

(62) Hakama M, Stenman UH, Aromaa A, Leinonen J, Hakulinen T, Knekt P. Validity of the prostate specific antigen test for prostate cancer screening: followup study with a bank of 21,000 sera in Finland. J Urol 2001;166(6):2189-91.

(63) Harris CH, Dalkin BL, Martin E, Marx PC, Ahmann FR. Prospective longitudinal evaluation of men with initial prostate specific antigen levels of 4.0 ng./ml. or less. J Urol 1997 May;157(5):1740-3.

(64) Heidenreich A, Abrahamsson PA, Artibani W, Catto J, Montorsi F, Van Poppel H, et al. Early detection of prostate cancer: European association of urology recommendation. Eur Urol 2013;64(3):347-54.

(65) Helzlsouer KJ, Newby J, Comstock GW. Prostate-specific antigen levels and subsequent prostate cancer: potential for screening.[Reprint in Am J Epidemiol. 2008 Oct 1;168(7):841-4; PMID: 18820278]. Cancer Epidemiology, Biomarkers & Prevention 1992 Nov;1(7):537-40.

(66) Heyns CF, Fisher M, Lecuona A, Van der Merwe A. Should baseline PSA testing be performed in men aged 40 to detect those aged 50 or less who are at risk of aggressive prostate cancer? South African Medical Journal 2011 Sep;Suid-Afrikaanse(9):642-4.

(67) Hobbs FDR. Commentary: Last and icebergs - spotting the iceberg doesn't predict its scale, even after 50 years. Int J Epidemiol 2013;42(6):1615-7.

(68) Hoedemaeker RF, van der Kwast TH, Boer R, de Koning HJ, Roobol M, Vis AN, et al. Pathologic features of prostate cancer found at population-based screening with a four-year interval. Journal of the National Cancer Institute 2001 Aug 1;93(15):1153-8.

(69) Hoffman RM. Periodic PSA-based screening in men 55 to 69 years of age reduced prostate cancer mortality. Ann Intern Med 2012;157(2):JC2-JC4.

(70) Holmberg L, Akre O. Screening for prostate cancer: defining critical issues. Acta Oncologica 2011 Jun;50:Suppl-3.

(71) Holmstrom B, Johansson M, Bergh A, Stenman UH, Hallmans G, Stattin P. Prostate specific antigen for early detection of prostate cancer: longitudinal study. BMJ 2009;339:b3537.

(72) Hugosson J, Aus G, Lilja H, Lodding P, Pihl CG, Pileblad E. Prostate specific antigen based biennial screening is sufficient to detect almost all prostate cancers while still curable. J Urol 2003 May;169(5):1720-3.

(73) Hugosson J, Aus G, Lilja H, Lodding P, Pihl CG. Results of a randomized, population-based study of biennial screening using serum prostate-specific antigen measurement to detect prostate carcinoma. Cancer 2004 Apr 1;100(7):1397-405.

(74) Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P, et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. Lancet Oncol 2010 Aug;11(8):725-32.

(75) Ilic D, Green S. Prostate specific antigen for detecting early prostate cancer. BMJ 2009;339:b3572.

(76) Ito K, Kubota Y, Suzuki K, Shimizu N, Fukabori Y, Kurokawa K, et al. Correlation of prostate-specific antigen before prostate cancer detection and clinicopathologic features: evaluation of mass screening populations. Urology 2000 May;55(5):705-9.

(77) Ito K, Kubota Y, Yamamoto T, Suzuki K, Fukabori Y, Kurokawa K, et al. Long term follow-up of mass screening for prostate carcinoma in men with initial prostate specific antigen levels of 4.0 ng/ml or less. Cancer 2001 Feb 15;91(4):744-51.

(78) Ito K, Yamamoto T, Ohi M, Takechi H, Kurokawa K, Suzuki K, et al. Possibility of re-screening intervals of more than one year in men with PSA levels of 4.0 ng/ml or less. Prostate 2003 Sep 15;57(1):8-13.

(79) Ito K, Yamamoto T, Ohi M, Kurokawa K, Suzuki K, Yamanaka H. Free/total PSA ratio is a powerful predictor of future prostate cancer morbidity in men with initial PSA levels of 4.1 to 10.0 ng/mL. Urology 2003 Apr;61(4):760-4.

(80) Ito K, Yamamoto T, Suzuki K, Kurokawa K, Yamanaka H. The risk of rapid prostate specific antigen increase in men with baseline prostate specific antigen 2.0 ng/ml or less. J Urol 2004 Feb;171(2:Pt 1):t-60.

(81) Ito K, Raaijmakers R, Roobol M, Wildhagen M, Yamanaka H, Schroder FH. Prostate carcinoma detection and increased prostate-specific antigen levels after 4 years in Dutch and Japanese males who had no evidence of disease at initial screening. Cancer 2005 Jan 15;103(2):242-50.

(82) Kane RA, Littrup PJ, Babaian R, Drago JR, Lee F, Chesley A, et al. Prostate-specific antigen levels in 1695 men without evidence of prostate cancer. Findings of the American Cancer Society National Prostate Cancer Detection Project. Cancer 1992 Mar 1;69(5):1201-7.

(83) Katz MH. Can we stop ordering prostate-specific antigen screening tests? JAMA Internal Medicine 2013 May 27;173(10):847-8.

(84) Kawamura S, Tochigi T, Kuwahara M. Every three years PSA screening is sufficient to detect almost all prostate cancers while still curable in men with baseline PSA less than 2.1ng/mL: Findings of a longitudinal study in Natori, Japan. Urology 2011;78(3):S45.

(85) Kettermann AE, Ferrucci L, Trock BJ, Metter EJ, Loeb S, Carter HB. Interpretation of the prostate-specific antigen history in assessing life-threatening prostate cancer. BJU Int 1290 Feb;106(9):1284-90.

(86) Kilpelainen TP, Tammela TL, Malila N, Hakama M, Santti H, Maattanen L, et al. Prostate cancer mortality in the Finnish randomized screening trial. Journal of the National Cancer Institute 2013 May 15;105(10):719-25.

(87) Kim HW, Ko YH, Kang SH, Lee JG. Predictive factors for prostate cancer in biopsy of patients with prostate-specific antigen levels equal to or less than 4 ng/ml. Korean J Urol 2011;52(3):166-71.

(88) Kim YM, Park S, Kim J, Park S, Lee JH, Ryu DS, et al. Role of prostate volume in the early detection of prostate cancer in a cohort with slowly increasing prostate specific antigen. Yonsei Medical Journal 2013 Sep;54(5):1202-6.

(89) Kirby R, Fitzpatrick J. Prostate-specific antigen testing for the early detection of prostate cancer. BJU Int 2004 Nov;94(7):966-7.

(90) Kirby R. Early detection the key to prostate cancer. Practitioner 2009 Feb 21;253(1715):17-8.

(91) Kitagawa Y, Ueno S, Izumi K, Kadono Y, Konaka H, Mizokami A, et al. Cumulative probability of prostate cancer detection in biopsy according to free/total PSA ratio in men with total PSA levels of 2.1-10.0 ng/ml at population screening. Journal of Cancer Research & Clinical Oncology 2014 Jan;140(1):53-9.

(92) Kjellman A, Akre O, Norming U, Tornblom M, Gustafsson O. 15-year followup of a population based prostate cancer screening study. J Urol 2009 Apr;181(4):1615-21.

(93) Klein RJ, Hallden C, Gupta A, Savage CJ, Dahlin A, Bjartell A, et al. Evaluation of multiple risk-associated single nucleotide polymorphisms versus prostate-specific antigen at baseline to predict prostate cancer in unscreened men. Eur Urol 2012 Mar;61(3):471-7.

(94) Kobayashi D, Takahashi O, Fukui T, Glasziou PP. Optimal prostate-specific antigen screening interval for prostate cancer. Annals of Oncology 2012 May;23(5):1250-3.

(95) Kuller LH, Thomas A, Grandits G, Neaton JD, Multiple Risk Factor Intervention Trial Research Group. Elevated prostate-specific antigen levels up to 25 years prior to death from prostate cancer. Cancer Epidemiology, Biomarkers & Prevention 2004 Mar;13(3):373-7.

(96) Kundu SD, Grubb RL, Roehl KA, Antenor JA, Han M, Catalona WJ. Delays in cancer detection using 2 and 4-year screening intervals for prostate cancer screening with initial prostate specific antigen less than 2 ng/ml. J Urol 2005 Apr;173(4):1116-20.

(97) Labrecque M, Aprikian A. Alternative prostate cancer screening strategies. Ann Intern Med 2013 May 21;158(10):778.

(98) Labrie F, Candas B, Cusan L, Gomez JL, Belanger A, Brousseau G, et al. Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. Prostate 2004 May 15;59(3):311-8.

(99) Lamb DS, Delahunt B, Nacey JN. Revised status of PSA testing in the early detection and treatment of prostate cancer. New Zealand Medical Journal 2011 Nov 4;124(1345):13-5.

(100) Lane JA, Howson J, Donovan JL, Goepel JR, Dedman DJ, Down L, et al. Detection of prostate cancer in unselected young men: prospective cohort nested within a randomised controlled trial. BMJ 2007 Dec 1;335(7630):1139.

(101) Larsen SB, Brasso K, Iversen P, Christensen J, Christiansen M, Carlsson S, et al. Baseline prostate-specific antigen measurements and subsequent prostate cancer risk in the Danish Diet, Cancer and Health cohort. Eur J Cancer 2013 Sep;49(14):3041-8.

(102) Leach R, Thompson IM. The dilemma of prostate-specific antigen testing. Archives of Internal Medicine 2012 Jun 11;172(11):835-6.

(103) Legler JM, Feuer EJ, Potosky AL, Merrill RM, Kramer BS. The role of prostate-specific antigen (PSA) testing patterns in the recent prostate cancer incidence decline in the United States. Cancer Causes & Control 1998 Oct;9(5):519-27.

(104) Lilja H, Ulmert D, Bjork T, Becker C, Serio AM, Nilsson JA, et al. Long-term prediction of prostate cancer up to 25 years before diagnosis of prostate cancer using prostate kallikreins measured at age 44 to 50 years. J Clin Oncol 2007 Feb 1;25(4):431-6.

(105) Lilja H, Ulmert D, Vickers AJ. Prostate-specific antigen and prostate cancer: prediction, detection and monitoring. Nat Rev Cancer 2008 Apr;8(4):268-78.

(106) Lilja H, Cronin AM, Dahlin A, Manjer J, Nilsson PM, Eastham JA, et al. Prediction of significant prostate cancer diagnosed 20 to 30 years later with a single measure of prostate-specific antigen at or before age 50. Cancer 2011 Mar 15;117(6):1210-9.

(107) Lippi G, Mattiuzzi C, Cervellin G. Prostate-specific antigen for prostate cancer screening: a different strategy should be planned. JAMA Internal Medicine 2013 Mar 11;173(5):392.

(108) Liu M, Wang JY, Su HX, Wan G, Zhu L, Wang XM. A longitudinal study of PSA and its influential factors in a cohort of Chinese men with initial PSA levels less than 4 ng ml(-1). Asian Journal of Andrology 2013 Jul;15(4):483-6.

(109) Lodding P, Aus G, Bergdahl S, Frosing R, Lilja H, Pihl CG, et al. Characteristics of screening detected prostate cancer in men 50 to 66 years old with 3 to 4 ng./ml. Prostate specific antigen. J Urol 1998 Mar;159(3):899-903.

(110) Loeb S. Use of baseline prostate-specific antigen measurements to personalize prostate cancer screening. Eur Urol 876 Jul;61(5):875-6.

(111) Loeb S, Roehl KA, Antenor JA, Catalona WJ, Suarez BK, Nadler RB. Baseline prostate-specific antigen compared with median prostate-specific antigen for age group as predictor of prostate cancer risk in men younger than 60 years old. Urology 2006 Feb;67(2):316-20.

(112) Loeb S, Nadler RB, Roehl KA, Antenor JA, Catalona WJ. Risk of prostate cancer for young men with a prostate specific antigen less than their age specific median. J Urol 2007 May;177(5):1745-8.

(113) Loeb S, Roehl KA, Catalona WJ, Nadler RB. Prostate specific antigen velocity threshold for predicting prostate cancer in young men. J Urol 2007 Mar;177(3):899-902.

(114) Loeb S, Schaeffer EM. Risk factors, prevention and early detection of prostate cancer. Primary Care; Clinics in Office Practice 2009 Sep;36(3):603-21.

(115) Loeb S, Carter HB, Catalona WJ, Moul JW, Schroder FH. Baseline prostate-specific antigen testing at a young age. [Review]. Eur Urol 2012 Jan;61(1):1-7.

(116) Louria DB. The likelihood that PSA detection of early prostate cancers is associated with high mortality. Archives of Internal Medicine 2005 Mar 28;165(6):702.

(117) Marberger M, Barentsz J, Emberton M, Hugosson J, Loeb S, Klotz L, et al. Novel approaches to improve prostate cancer diagnosis and management in early-stage disease. BJU Int 2012 Mar;109:Suppl-7.

(118) Marsland T, Arena F, Yeilding A, Glode M, Ellis L, Yu J, et al. Perspective on...the new PSA screening recommendations. Oncology (Williston Park) 1190 20;25(12):1183-8.

(119) Marta GN, Hanna SA, Fernandes da Silva JL, Carvalho HA. Screening for prostate cancer: an updated review. [Review]. Expert Review of Anticancer Therapy 2013 Jan;13(1):101-8.

(120) Martin NE, Chen MH, Catalona WJ, Loeb S, Roehl KA, D'Amico AV. The influence of serial prostate-specific antigen (PSA) screening on the PSA velocity at diagnosis. Cancer 2008 Aug 15;113(4):717-22.

(121) McGreevy K, Rodgers K, Lipsitz S, Bissada N, Hoel D. Impact of race and baseline PSA on longitudinal PSA. International Journal of Cancer 2006 Apr 1;118(7):1773-6.

(122) McKenzie P, Delahunt B, deVoss K, Ross B, Tran H, Sikaris K. Prostate specific antigen testing for the diagnosis of prostate cancer. Pathology 2011 Aug;43(5):403.

(123) McKenzie PR, Delahunt B, Kench JG, Ross B, Lam Q, deVoss K, et al. Prostate specific antigen testing: age-related interpretation in early prostate cancer detection. Pathology 2013 Jun;45(4):343-5.

(124) Melia J. Part 1: The burden of prostate cancer, its natural history, information on the outcome of screening and estimates of ad hoc screening with particular reference to England and Wales. [Review] [97 refs]. BJU Int 2005 Apr;95:Suppl-15.

(125) Mian BM. Prostate cancer screening and mortality: comparison of recent randomized controlled clinical trials. Urologic Oncology 2010 May;28(3):233-6.

(126) Miller AB. New data on prostate-cancer mortality after PSA screening. New England Journal of Medicine 2012 Mar 15;366(11):1047-8.

(127) Miller AB, Harvey BJ. Data to support PSA screening for younger men lacking. CMAJ Canadian Medical Association Journal 2013 Mar 5;185(4):325.

(128) Miner MM, Seftel AD. Erectile dysfunction and testosterone screening with prostate specific antigen screening at age 40: are these three gender specific determinants additive for overall men's heath and do they improve traditional non-gender specific determinants to lessen cardiovascular risk and all-cause mortality?. [Review]. International Journal of Clinical Practice 2010 Dec;64(13):1754-62.

(129) Mitka M. Urology group: prostate screening should be offered beginning at age 40. JAMA 2009 Jun 24;301(24):2538-9.

(130) Mitra AV, Bancroft EK, Barbachano Y, Page EC, Foster CS, Jameson C, et al. Targeted prostate cancer screening in men with mutations in BRCA1 and BRCA2 detects aggressive prostate cancer: preliminary analysis of the results of the IMPACT study. BJU Int 2011 Jan;107(1):28-39.

(131) Mizusawa H, Mimura Y, Domen T, Koizumi K, Oguchi T, Kikuchi T. Clinical analysis of patients with prostate cancer who initially demonstrated a markedly elevated prostate specific antigen level. Urology 2011;78(3):S326.

(132) Moul JW. Population screening for prostate cancer and emerging concepts for young men. [Review] [123 refs]. Clinical Prostate Cancer 2003 Sep;2(2):87-97.

(133) Murphy DG, Ahlering T, Catalona WJ, Crowe H, Crowe J, Clarke N, et al. The Melbourne Consensus Statement on the early detection of prostate cancer. BJU Int 2014;113(2):186-8.

(134) Neal DE. PSA testing for prostate cancer improves survival--but can we do better? Lancet Oncology 2010 Aug;11(8):702-3.

(135) Nordstrom T, Aly M, Clements MS, Weibull CE, Adolfsson J, Gronberg H. Prostate-specific antigen (PSA) testing is prevalent and increasing in Stockholm County, Sweden, Despite no recommendations for PSA screening: results from a population-based study, 2003-2011. Eur Urol 2013 Mar;63(3):419-25.

(136) Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, et al. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. JAMA 1993 Aug 18;270(7):860-4.

(137) Ohi M, Ito K, Yamamoto T, Miyakubo M, Takechi H, Kubota Y, et al. Changes in baseline PSA levels in Japanese men from 1988 to 2003. Urology 2008 Jul;72(1):95-8.

(138) Paez A, Lujan M, Raaijmakers R, Berenguer A, ERSPC. Four-year prostate-specific antigen progression in the non-cancer population of the European Randomized Study of Screening for Prostate Cancer. BJU Int 2003 Dec;92:Suppl-7.

(139) Park KK, Lee SH, Choi YD, Chung BH. Optimal baseline prostate-specific antigen level to distinguish risk of prostate cancer in healthy men between 40 and 69 years of age. Journal of Korean Medical Science 2012 Jan;27(1):40-5.

(140) Petrylak DP. Risk Factors for the Development of Bone Metastases in Prostate Cancer. Eur Urol Suppl 2007;6(11):677-82.

(141) Pienta KJ. Critical appraisal of prostate-specific antigen in prostate cancer screening: 20 years later. [Review] [83 refs][Erratum appears in Urology. 2010 Sep;76(3):771]. Urology 2009 May;73(5:Suppl):Suppl-20.

(142) Pinsky PF, Black A, Parnes HL, Grubb R, David CE, Miller A, et al. Prostate cancer specific survival in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Cancer Epidemiology 2012 Dec;36(6):e401-e406.

(143) Postma R, Roobol M, Schroder FH, van der Kwast TH. Potentially advanced malignancies detected by screening for prostate carcinoma after an interval of 4 years. Cancer 2004 Mar 1;100(5):968-75.

(144) Preston DM, Levin LI, Jacobson DJ, Jacobsen SJ, Rubertone M, Holmes E, et al. Prostate-specific antigen levels in young white and black men 20 to 45 years old. Urology 2000 Nov 1;56(5):812-6.

(145) Ranasinghe W, Kim SP, Lawrentschuk N, Sengupta S, Hounsome L, Barber J, et al. Population based analysis of the trends of Prostate Specific Antigen (PSA) use in Australia. BJU Int 2013;111:90-1.

(146) Randazzo M, Seiler D, Beatrice J, Baumgartner M, Huber A, Grobholz R, et al. Prostate specific antigen (PSA)-pyramid in men with low range PSA: Prostate cancer incidence and mortality-a plea for risk-based prostate cancer screening strategy in the European randomized study of screening for prostate cancer (ERSPC), AARAU. J Urol 2013;189(4):e793.

(147) Raviv G, Zlotta AR, Janssen T, Descamps F, Vanegas JP, Verhest A, et al. Do prostate specific antigen and prostate specific antigen density enhance the detection of prostate carcinoma after initial diagnosis of prostatic intraepithelial neoplasia without concurrent carcinoma? Cancer 1996 May 15;77(10):2103-8.

(148) Rees J. PSA at 60 may predict risk of death from prostate cancer. Practitioner 2010 Oct;254(1733):5.

(149) Reissigl A, Klocker H, Pointner J, Fink K, Horninger W, Ennemoser O, et al. Usefulness of the ratio free/total prostate-specific antigen in addition to total PSA levels in prostate cancer screening. Urology 1996 Dec;48(6A:Suppl):Suppl-6.

(150) Reissigl A, Bartsch G. Prostate-specific antigen as a screening test. The Austrian experience. Urologic Clinics of North America 1997 May;24(2):315-21.

(151) Rhodes T, Jacobson DJ, McGree ME, St Sauver JL, Girman CJ, Lieber MM, et al. Longitudinal changes of benign prostate-specific antigen and [-2]proprostate-specific antigen in seven years in a community-based sample of men. Urology 2012 Mar;79(3):655-61.

(152) Richardson TD, Oesterling JE. Age-specific reference ranges for serum prostate-specific antigen. Urologic Clinics of North America 1997 May;24(2):339-51.

(153) Rogers CS. Perspective on prostate cancer screening. International Journal of Clinical Practice 2011 Jan;65(1):31-4.

(154) Roobol M, Semnojow A, Stephan C. Comparison of various risk calculators for prostate cancer. Urology 2011;78(3):S306-S307.

(155) Roobol MJ, Roobol DW, Schroder FH. Is additional testing necessary in men with prostate-specific antigen levels of 1.0 ng/mL or less in a population-based screening setting? (ERSPC, section Rotterdam). Urology 2005 Feb;65(2):343-6.

(156) Roobol MJ, Zappa M, Maattanen L, Ciatto S. The value of different screening tests in predicting prostate biopsy outcome in screening for prostate cancer data from a multicenter study (ERSPC). Prostate 2007 Mar 1;67(4):439-46.

(157) Roobol MJ, Steyerberg EW, Kranse R, Wolters T, van den Bergh RC, Bangma CH, et al. A risk-based strategy improves prostate-specific antigen-driven detection of prostate cancer. Eur Urol 2010 Jan;57(1):79-85.

(158) Roobol MJ, van Vugt HA, Loeb S, Zhu X, Bul M, Bangma CH, et al. Prediction of prostate cancer risk: the role of prostate volume and digital rectal examination in the ERSPC risk calculators. Eur Urol 2012 Mar;61(3):577-83.

(159) Roobol MJ, Zhu X, Schroder FH, van Leenders GJ, van Schaik RH, Bangma CH, et al. A Calculator for Prostate Cancer Risk 4 Years After an Initially Negative Screen: Findings from ERSPC Rotterdam. Eur Urol 2013 Apr;63(4):627-33.

(160) Roobol MJ, Kranse R, Bangma CH, Van Leenders AGJL, Blijenberg BG, Van Schaik RHN, et al. Screening for prostate cancer: Results of the Rotterdam section of the European randomized study of screening for prostate cancer. Eur Urol 2013;64(4):530-9.

(161) Roobol MJ, Bangma CH, Loeb S. Prostate-specific antigen screening can be beneficial to younger and at-risk men. CMAJ Canadian Medical Association Journal 2013 Jan 8;185(1):47-51.

(162) Rosario DJ, Lane JA, Metcalfe C, Catto JW, Dedman D, Donovan JL, et al. Contribution of a single repeat PSA test to prostate cancer risk assessment: experience from the ProtecT study. Eur Urol 2008 Apr;53(4):777-84.

(163) Rundle A, Neckerman KM, Sheehan D, Jankowski M, Kryvenko ON, Tang D, et al. A prospective study of socioeconomic status, prostate cancer screening and incidence among men at high risk for prostate cancer. Cancer Causes & Control 2013 Feb;24(2):297-303.

(164) Sammon JD, Sukumar S, Trinh QD. Prostate cancer screening and incidence: a question of causality. JAMA Internal Medicine 2013 Mar 11;173(5):392-3.

(165) Sarma AV, St Sauver JL, Jacobson DJ, McGree ME, Klee GG, Lieber MM, et al. Racial differences in longitudinal changes in serum prostate-specific antigen levels: the Olmsted County Study and the Flint Men's Health Study. Urology 2014 Jan;83(1):88-93.

(166) Savage CJ, Lilja H, Cronin AM, Ulmert D, Vickers AJ. Empirical estimates of the lead time distribution for prostate cancer based on two independent representative cohorts of men not subject to prostate-specific antigen screening. Cancer Epidemiology, Biomarkers & Prevention 2010 May;19(5):1201-7.

(167) Sawada K, Kitagawa Y, Ito K, Takeda Y, Mizokami A, Namiki M. Cumulative risk of developing prostate cancer in men with low ((less-than or equal to)2.0ng/mL) prostate-specific antigen levels: A population-based screening cohort study in Japan. Int J Urol 2013.

(168) Schaeffer EM, Carter HB, Kettermann A, Loeb S, Ferrucci L, Landis P, et al. Prostate specific antigen testing among the elderly--when to stop? J Urol 2009 Apr;181(4):1606-14.

(169) Schroder FH, Roobol MJ, Andriole GL, Fleshner N. Defining increased future risk for prostate cancer: evidence from a population based screening cohort. J Urol 1974 20;181(1):69-74.

(170) Schroder FH, Raaijmakers R, Postma R, van der Kwast TH, Roobol MJ. 4-year prostate specific antigen progression and diagnosis of prostate cancer in the European Randomized Study of Screening for Prostate Cancer, section Rotterdam. J Urol 2005 Aug;174(2):489-94.

(171) Schroder FH, Bangma CH, Roobol MJ. Is it necessary to detect all prostate cancers in men with serum PSA levels <3.0 ng/ml? A comparison of biopsy results of PCPT and outcome-related information from ERSPC. Eur Urol 2008 May;53(5):901-8.

(172) Schroder FH. Screening for prostate cancer. [Review]. Eur J Cancer 2011 Sep;47:Suppl-70.

(173) Schroder FH, Hugosson J, Carlsson S, Tammela T, Maattanen L, Auvinen A, et al. Screening for prostate cancer decreases the risk of developing metastatic disease: findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC). Eur Urol 2012 Nov;62(5):745-52.

(174) Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Prostate-cancer mortality at 11 years of follow-up.[Erratum appears in N Engl J Med. 2012 May 31;366(22):2137]. New England Journal of Medicine 2012 Mar 15;366(11):981-90.

(175) Scosyrev E, Wu G, Mohile S, Messing EM. Prostate-specific antigen screening for prostate cancer and the risk of overt metastatic disease at presentation: analysis of trends over time. Cancer 2012 Dec 1;118(23):5768-76.

(176) Seiler D, Randazzo M, Switzerland A, Isbarn H, Chun F, Ahyai S, et al. Long-term risk assessment of prostate cancer diagnosis in men with initial psa-values <1.0 ng/ml; results from the swiss arm of the european randomized study of screening for prostate cancer (ERSPC). J Urol 2012;187(4):e402.

(177) Smith DS, Catalona WJ, Herschman JD. Longitudinal screening for prostate cancer with prostate-specific antigen. JAMA 1996 Oct 23;276(16):1309-15.

(178) Smith DS, Humphrey PA, Catalona WJ. The early detection of prostate carcinoma with prostate specific antigen: the Washington University experience. Cancer 1997 Nov 1;80(9):1852-6.

(179) Squires N. Detection of prostate cancer in unselected young men: Prospective cohort nested within a randomized controlled trial. Ann Clin Biochem 2008;45(3):341.

(180) Stattin P, Holmstrom B, Carlsson S, Vickers A, Lilja H, Hanullkanon J, et al. Nation-wide, incidence-based analysis of prostate cancer mortality in counties with high versus low rates of PSA testing in Sweden. J Urol 2011;189(4):e792.

(181) Stenman UH, Abrahamsson PA, Aus G, Lilja H, Bangma C, Hamdy FC, et al. Prognostic value of serum markers for prostate cancer. Scand J Urol Nephrol 2005;39(SUPP. 216):64-81.

(182) Steuber T, O'Brien MF, Lilja H. Serum markers for prostate cancer: a rational approach to the literature. [Review] [71 refs]. Eur Urol 2008 Jul;54(1):31-40.

(183) Strope SA, Andriole GL. Improving prostate-specific antigen screening. J Clin Oncol 2010 May 20;28(15):2491-2.

(184) Strope SA, Andriole GL. Prostate-specific antigen-based risk assessment in younger men. Eur Urol 2012 Oct 9;61(1):8-9.

(185) Sun L, Moul JW, Hotaling JM, Rampersaud E, Dahm P, Robertson C, et al. Prostate-specific antigen (PSA) and PSA velocity for prostate cancer detection in men aged <50 years. BJU Int 2007 Apr;99(4):753-7.

(186) Tang P, Sun L, Uhlman MA, Polascik TJ, Freedland SJ, Moul JW. Baseline PSA as a predictor of prostate cancer-specific mortality over the past 2 decades: Duke University experience. Cancer 2010 Oct 15;116(20):4711-7.

(187) Tang P, Du W, Xie K, Fu J, Chen H, Yang W, et al. Characteristics of baseline PSA and PSA velocity in young men without prostate cancer: Racial differences. Prostate 2012 Feb 1;72(2):173-80.

(188) Tariman JD. Prostate cancer: screening and early detection. Advance for Nurse Practitioners 2006 Sep;14(9):20.

(189) Thompson IM, Ankerst DP, Chi C, Lucia MS, Goodman PJ, Crowley JJ, et al. Operating characteristics of prostate-specific antigen in men with an initial PSA level of 3.0 ng/ml or lower. JAMA 2005 Jul 6;294(1):66-70.

(190) Thompson IM, Ankerst DP, Tangen CM. Prostate-specific antigen, risk factors, and prostate cancer: confounders nestled in an enigma. Journal of the National Cancer Institute 2010 Sep 8;102(17):1299-301.

(191) Tornblom M, Norming U, Adolfsson J, Becker C, Abrahamsson PA, Lilja H, et al. Diagnostic value of percent free prostate-specific antigen: retrospective analysis of a population-based screening study with emphasis on men with PSA levels less than 3.0 ng/mL. Urology 1999 May;53(5):945-50.

(192) Tornblom M, Eriksson H, Franzen S, Gustafsson O, Lilja H, Norming U, et al. Lead time associated with screening for prostate cancer. Int J Cancer 2004 Jan 1;108(1):122-9.

(193) Uchida K, Takeshima H, Akaza H, Ono Y. Screening for prostate cancer using prostate-specific antigen alone as a first-line checkup parameter: results of the health checkup system. Japanese Journal of Clinical Oncology 2000 Feb;30(2):95-100.

(194) Ulmert D, Serio AM, O'Brien MF, Becker C, Eastham JA, Scardino PT, et al. Long-term prediction of prostate cancer: prostate-specific antigen (PSA) velocity is predictive but does not improve the predictive accuracy of a single PSA measurement 15 years or more before cancer diagnosis in a large, representative, unscreened population. J Clin Oncol 2008 Feb 20;26(6):835-41.

(195) Ulmert D, Cronin AM, Bjork T, O'Brien MF, Scardino PT, Eastham JA, et al. Prostate-specific antigen at or before age 50 as a predictor of advanced prostate cancer diagnosed up to 25 years later: a case-control study. BMC Med 2008;6:6.

(196) Uozumi J, Tokuda Y, Fujiyama C, Takagi N, Meiri H, Kuratomi K, et al. Annual PSA tests are not necessary for men with a PSA level below 2 ng/mL: findings of the Imari prostate cancer screening program. Int J Urol 2002 Jun;9(6):334-9.

(197) van der Cruijsen-Koeter IW, van der Kwast TH, Schroder FH. Interval carcinomas in the European Randomized Study of Screening for Prostate Cancer (ERSPC)-Rotterdam. Journal of the National Cancer Institute 2003 Oct 1;95(19):1462-6.

(198) van der Cruijsen-Koeter IW, Roobol MJ, Wildhagen MF, van der Kwast TH, Kirkels WJ, Schroder FH. Tumor characteristics and prognostic factors in two subsequent screening rounds with four-year interval within prostate cancer screening trial, ERSPC Rotterdam. Urology 2006 Sep;68(3):615-20.

(199) van Leeuwen PJ, Connolly D, Tammela TL, Auvinen A, Kranse R, Roobol MJ, et al. Balancing the harms and benefits of early detection of prostate cancer. Cancer 2010 Oct 15;116(20):4857-65.

(200) van Leeuwen PJ, Roobol MJ, Kranse R, Zappa M, Carlsson S, Bul M, et al. Towards an optimal interval for prostate cancer screening. Eur Urol 2012 Jan;61(1):171-6.

(201) van Vugt HA, Roobol MJ, Kranse R, Maattanen L, Finne P, Hugosson J, et al. Prediction of prostate cancer in unscreened men: external validation of a risk calculator. Eur J Cancer 2011 Apr;47(6):903-9.

(202) Vashi AR, Oesterling JE. Percent free prostate-specific antigen: entering a new era in the detection of prostate cancer. [Review] [52 refs]. Mayo Clinic Proceedings 1997 Apr;72(4):337-44.

(203) Vickers AJ, Ulmert D, Serio AM, Bjork T, Scardino PT, Eastham JA, et al. The predictive value of prostate cancer biomarkers depends on age and time to diagnosis: towards a biologically-based screening strategy. International Journal of Cancer 2007 Nov 15;121(10):2212-7.

(204) Vickers AJ, Wolters T, Savage CJ, Cronin AM, O'Brien MF, Pettersson K, et al. Prostate-specific antigen velocity for early detection of prostate cancer: result from a large, representative, population-based cohort. Eur Urol 2009 Nov;56(5):753-60.

(205) Vickers AJ, Cronin AM, Roobol MJ, Savage CJ, Peltola M, Pettersson K, et al. A four-kallikrein panel predicts prostate cancer in men with recent screening: data from the European Randomized Study of Screening for Prostate Cancer, Rotterdam. Clinical Cancer Research 2010 Jun 15;16(12):3232-9.

(206) Vickers AJ, Cronin AM, Bjork T, Manjer J, Nilsson PM, Dahlin A, et al. Prostate specific antigen concentration at age 60 and death or metastasis from prostate cancer: case-control study. BMJ 2010;341:c4521.

(207) Vickers AJ, Gupta A, Savage CJ, Pettersson K, Dahlin A, Bjartell A, et al. A panel of kallikrein marker predicts prostate cancer in a large, population-based cohort followed for 15 years without screening. Cancer Epidemiology, Biomarkers & Prevention 2011 Feb;20(2):255-61.

(208) Vickers AJ, Lilja H. Predicting prostate cancer many years before diagnosis: how and why? World Journal of Urology 2012 Apr;30(2):131-5.

(209) Vickers AJ, Sjoberg DD, Ulmert D, Vertosick E, Roobol MJ, Thompson I, et al. Empirical estimates of prostate cancer overdiagnosis by age and prostate-specific antigen. BMC Med 2014;12(1).

(210) Vis AN, Kranse R, Roobol M, van der Kwast TH, Schroder FH. Serendipity in detecting disease in low prostate-specific antigen ranges. BJU Int 2002 Mar;89(4):384-9.

(211) Vukotic V, Cerovic S, Kozomara M, Lazic M. The predictive value of PSA in diagnosis of prostate cancer in non screened population. Acta Chirurgica Iugoslavica 2005;52(4):81-7.

(212) Wallner LP, Frencher SK, Hsu JY, Chao CR, Loo RK, Jacobsen SJ. Changes in serum prostate specific antigen levels and the identification of prostate cancer in a large managed care population. Eur Urol Suppl 2012;11(1):e258-e258a.

(213) Wallner LP, Jacobsen SJ. Prostate-specific antigen and prostate cancer mortality: A systematic review. Am J Prev Med 2013;45(3):318-26.

(214) Walsh PC. Prostate specific antigen concentration at age 60 and death or metastasis from prostate cancer: Case-control study. J Urol 2011;185(5):1705.

(215) Weight CJ, Kim SP, Jacobson DJ, McGree ME, Karnes RJ, St.Sauver J. Men (aged 40-49 years) with a single baseline prostate-specific antigen below 1.0 ng/mL have a very low long-term risk of prostate cancer: Results from a prospectively screened population cohort. Urology 2013;82(6):1211-7.

(216) Welch HG, Schwartz LM, Woloshin S. Prostate-specific antigen levels in the United States: implications of various definitions for abnormal. J Natl Cancer Inst 2005 Aug 3;97(15):1132-7.

(217) Whittemore AS, Lele C, Friedman GD, Stamey T, Vogelman JH, Orentreich N. Prostate-specific antigen as predictor of prostate cancer in black men and white men. Journal of the National Cancer Institute 1995 Mar 1;87(5):354-60.

(218) Whittemore AS, Cirillo PM, Feldman D, Cohn BA. Prostate specific antigen levels in young adulthood predict prostate cancer risk: results from a cohort of Black and White Americans. J Urol 2005;174(3):872-6.

(219) Wright EJ, Fang J, Metter EJ, Partin AW, Landis P, Chan D, et al. Prostate specific antigen predicts the long-term risk of prostate enlargement: results from the Baltimore Longitudinal Study of Aging. J Urol 2487 Aug;167(6):2484-7.

(220) Yli-Hemminki TH, Laurila M, Auvinen A, Maattanen L, Huhtala H, Tammela TL, et al. Histological inflammation and risk of subsequent prostate cancer among men with initially elevated serum prostate-specific antigen (PSA) concentration in the Finnish prostate cancer screening trial. BJU Int 2013 Oct;112(6):735-41.

(221) Zeliadt SB, Hoffman RM, Etzioni R, Ginger VA, Lin DW. What happens after an elevated PSA test: the experience of 13,591 veterans. Journal of General Internal Medicine 2010 Nov;25(11):1205-10.

(222) Zhao Z, Zeng G. Increased serum level of early prostate cancer antigen is associated with subsequent cancer risk in men with high-grade prostatic intraepithelial neoplasia. Endocrine-Related Cancer 2010 Jun;17(2):505-12.

(223) Zhu X, van Leeuwen PJ, Holmberg E, Bul M, Carlsson S, Schroder FH, et al. Efficacy versus effectiveness study design within the European screening trial for prostate cancer: consequences for cancer incidence, overall mortality and cancer-specific mortality. Journal of Medical Screening 2012;19(3):133-40.

(224) Zhu X, Albertsen PC, Andriole GL, Roobol MJ, Schroder FH, Vickers AJ. Risk-based prostate cancer screening. [Review]. Eur Urol 2012 Apr;61(4):652-61.

Systematic review report for question 4

Clinical Question 4*: How best can DRE be used, if at all, in association with PSA testing?*

PICO Question 4: *For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what is the incremental value of performing a digital rectal examination (DRE) in addition to PSA testing in detecting any prostate cancer?*

Population	Index test 1	Index test 2	Reference standard	Outcomes
Men without a history of prostate cancer or symptoms that might indicate prostate cancer	PSA and DRE tests	PSA test only	Prostate biopsy	Diagnostic performance

1. Methods

1.1. Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption guidelines had to be evidence based and meet the pre-specified criteria of scores of greater or equal to 70% for the domains rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

1.2. Literature Search

Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched from 1990 using text terms and, where available, database-specific subject headings. Each database was searched for articles dealing with prostate cancer. In Medline and Embase databases the prostate cancer search was coupled with a search for prostate-specific antigen (PSA) and digital rectal examination (DRE). To identify studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples. A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 which were either published after the initial search was completed and/or added to the relevant database after the search was completed. Alerts were checked until July 2014. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were

searched regularly up until April 2014 for relevant reviews published after the initial search. Reference lists of all relevant articles were checked for potential additional articles.

1.3. **Inclusion Criteria**

Selection criteria	**Inclusion criteria**
Study type	Diagnostic performance
Study design	Fully paired diagnostic study, or Paired randomised cohort study
Population	Men without a history of prostate cancer or symptoms that indicate prostate cancer who have undergone prostate biopsy
Index test 1	PSA and DRE tests
Index test 2	PSA test only
Reference standard	Prostate biopsy
Indications for biopsy	No indications for biopsy - all men underwent biopsy regardless of PSA level or results of any other test or PSA test result is one of the indications for biopsy and DRE result is another indication for biopsy
Outcomes	For the diagnosis of prostate cancer, prostate cancer Gleason Score >7 or prostate cancer Gleason score > 6 • Absolute accuracy if all participants regardless of screen test results underwent biopsy or, if the results were adjusted for verification bias otherwise • Comparative accuracy as assessed by the number additional false positives for each additional true positive detected with the addition of DRE testing to PSA testing ** AND Results stratified by Gleason Score, unless: - biopsy scheme consisted of 8 or more cores*, and - participants were men undergoing screening
Language	English
Publication period	After 31st December 1989 and before1st March 2014

* In this review an adequate biopsy was pre-specified as ≥ 8-core biopsy however initial searches found that if studies were restricted to those using ≥8-core biopsy only one study met the inclusion criteria for this question as most studies were undertaken when 6-core biopsies were considered adequate. As a result a pragmatic approach was taken; the inclusion criteria were broadened to include studies which used biopsies with less than 8 cores in very specific circumstances: when results were stratified by Gleason Score and the study took place in a screening population, and the inadequacy of biopsies was taken into account when assessing the risk of bias.

**Verification bias is a major issue when assessing the diagnostic performance of tests for prostate cancer as men normally do not undergo biopsy unless they are test positive. As a result most studies examining diagnostic performance of adding DRE test to PSA testing are only able to report numbers of true positives and false positives. Where there is a comparison of two index tests in the same patient and where one index test is purely adding additional test positives to another index test, as when DRE is added to PSA testing, this data can be used to calculate the difference in true positives and the difference in false positives and the number of additional false positives for each additional cancer detected; findings that will not be subject to verification bias.

Conference proceedings identified by the search literature searches were included if they met the inclusion criteria.

2. Results

2.1. Guidelines

Eighteen guidelines were identified that contained potentially relevant recommendations. These recommendations were not adopted as they either were not based on a systematic review, did not meet the pre-specified AGREE II criteria for adoption, or the recommendations did not specifically address the clinical question. These guidelines and the reasons why they were not adopted are listed in Appendix C.

2.2. Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the systematic review. The Medline search identified 2,921 citations, the Embase search an additional 1,520 citations the search of the Cochrane Database of Systematic Reviews 59 citations, the Database of Abstracts of Reviews of Effects 282 citations and the Health Technology Assessment database 216 citations, resulting in a total of 4,998 citations. Titles and abstracts were examined and 176 articles were retrieved for a more detailed evaluation. An additional 36 potential citations were identified from the reference list of retrieved articles.

Five trials reported in five articles met the inclusion criteria and were included in the review. There were no studies of Aboriginal and/or Torres Strait Islander men that met the inclusion criteria.

The retrieved articles that were not included and the reason for their exclusion are documented in Appendix C. In summary, most articles were excluded because they used an inappropriate study design, not all of their participants underwent both DRE and PSA, their indications for biopsy were inappropriate or unclear, did not report relevant outcomes or original data, examined an inappropriate population, or used an inadequate biopsy scheme and did not report cancers detected stratified by e.g. Gleason scores.

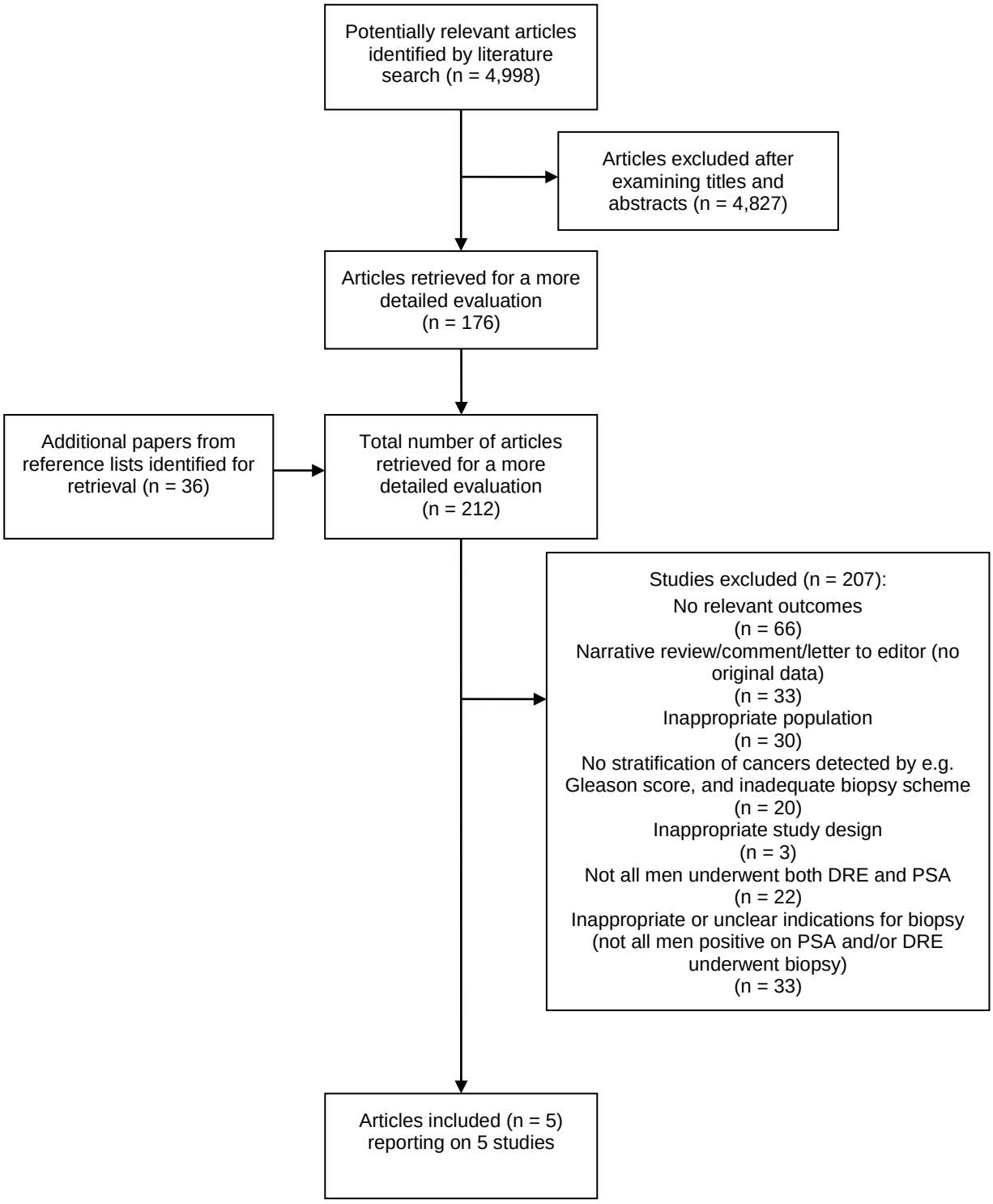


Figure 1: Process of inclusion and exclusion of studies

2.3. Study Characteristics

Characteristics of included studies are described in Table 1.

Table 1: Characteristics of studies reporting the incremental value of DRE in addition to PSA testing

Study	Design	Participants	Indications for biopsy	DRE	PSA test	Biopsy	Outcomes	Comments
Screening population, inadequate* biopsy scheme – biopsy regardless of PSA and DRE								
Thompson 2007 (USA) *PCPT*	Fully paired	Men **aged ≥55** years with PSA ≤3 ng/ml, normal DRE, no clinically significant coexisting conditions and an AUA symptom score <20 at enrolment randomly assigned to receive placebo in PCPT N = 5,947 (biopsied) N = 5,112 (analysed)	PSA >4.0 ng/ml or abnormal DRE Re-biopsy if DRE abnormal during subsequent years or PSA 1.5 times above level that prompted initial biopsy, or >10.0 ng/ml (most recent biopsy data analysed) Regardless of PSA level and DRE status after 7 years follow-up Men who underwent biopsy **N = 5,947** (62.9%)	Normal/ abnormal	Tandem E assay (1993-2000), Access assay (2000-2003) Performed in central laboratory	Within 1 year of PSA test and DRE Sextant biopsy recommended Reviewed by a central pathology laboratory and by pathologists at the study site	*Detection of prostate cancer* *Detection of GS>6 cancer* *Detection of GS>7 cancer*	Pre-screened cohort Annual screening with PSA and DRE for up to 7 years Biopsies rarely prompted by both PSA and DRE 221 study sites

"Screening population", adequate* biopsy scheme – biopsy of screen-positive men only								
Galić 2003 (Croatia)	Fully paired	Men **aged ≥50** years recruited from the community (2 villages) by the method of random choice Exclusion criteria: previously verified prostate cancer, (chronic) prostatitis, urinary tract infection; N = 88 (biopsied and analysed)	PSA >4.0 ng/ml and/or abnormal DRE Compliance with biopsy recommendation 94.6%	Normal/ suspect of cancer (induration, asymmetry, irregularity indicative of cancer) Performed by one urologist	PSA-RIACT radioimmuno-assay Samples collected prior to DRE	12 cores (6 apical, 6 basal), transperineal approach, ultrasound-guided	*Detection of prostate cancer*	
"Screening population", inadequate* biopsy scheme – biopsy of screen-positive men only								
Carvalhal 1999 (USA)	Fully paired	Black and white community volunteers **aged ≥50** years (mean age 60) without a history of elevated PSA, prostate biopsy or prostate surgery recruited between May 1991 and December 1997 via a press release asking healthy men to participate in a prostate cancer screening study Exclusion of men of Asian, Hispanic and other racial backgrounds N = 1,905 (biopsied due to abnormal DRE only and analysed)	PSA >4.0 ng/ml or suspicious DRE Compliance with biopsy recommendation (positive DRE) 70.5%	Suspicious for cancer (induration, asymmetry or irregularity) Performed by staff urologists or resident physicians	Tandem-E immuno-enzymatic PSA essay (Hybritech) Performed immediately before DRE	Quadrant and biopsies of suspicious lesions on ultrasound from 1989 to 1991 At least sextant biopsies after May 1995	*Detection of prostate cancer* *Detection of GS>7 cancer* Gleason grading system not uniformly used until 1992 – modified grading system: well, moderately, poorly differentiated disease documented as Gleason grades 2-4, 5-7, 8-10	Serial screening with PSA and DRE: 6-monthly if negative biopsy or patient refused biopsy annually if normal screening results PSA cut-off changed to >2.5 ng/ml after May 1995

Gomez-Guerra 2009 (Mexico)	Fully paired	Men **aged ≥40** years (mean age 61.9) who lived in the metropolitan area of Monterrey, Mexico screened in 2004, 2005 and 2006 in the primary health centres of a University Health Program No exclusion criteria Mean AUA Symptom Index score (range 0-35): 8.72 (moderate) Mean BMI: 28.0 **N = 55** (men biopsied and analysed)	PSA >4.0 ng/ml and/or abnormal DRE Compliance with biopsy recommendation 44.4%	Normal/ abnormal Performed by a urologist or urology resident		Transrectal TRUS-guided sextant biopsies (≥6 cores) Evaluated by two pathologists	*Detection of prostate cancer* *Detection of GS>5 cancer* *Detection of GS>6 cancer* *Detection of GS>7 cancer*	Majority of men had not had previous PSA tests or prostate biopsies
Referral population, inadequate* biopsy scheme – biopsy of screen-positive men only								
Fowler 2000 (USA)	Fully paired	Men with suspected prostate cancer due to an abnormal DRE or PSA ≥4.0 ng/ml who underwent a single prostate biopsy at a tertiary care facility **N = 2,256** Exclusion criteria: men who had undergone transurethral prostatic resection or open prostatectomy before biopsy; N = 2,256 (biopsied) N = 581 (biopsied due to abnormal DRE only) N = 536 (included in the analysis)	PSA ≥4.0 ng/ml and/or abnormal DRE	Suspicious for carcinoma (palpable induration, nodularity or asymmetry)	Blood specimens obtained on an outpatient basis before prostatic manipulation or biopsy Hybritech radioimmuno-assays	Sextant biopsies: 49.8% Sextant and transition zone biopsies: 34.3% 5-region technique: 15.9% (% of men analysed) Performed by urological personnel under ultrasound guidance	*Detection of prostate cancer* *Detection of GS>7 cancer*	

	White men (% of men analysed): 357 (66.7) Mean age of men analysed (SD): 65.1 (8.1)

*AUA = American Urological Association; BMI = Body Mass Index; GS = Gleason Score; PCPT = Prostate Cancer Prevention Trial; SD = standard deviation; * biopsy schemes with 8 or more cores considered adequate; ** determined by an independent data and safety monitoring committee to equalize recommended biopsy rates in the two groups;*

2.4. Risk of bias

Assessment of risk of bias of included diagnostic studies is described in Tables 2 and 3.

Table 2: Risk of bias of included diagnostic studies (n = 5)

Quality Category	N (%)
I. Selection of participants	
Low risk of bias	4 (80.0)
High risk of bias	-
Unclear risk of bias	1 (20.0)
II. Index test 1	
Low risk of bias	1 (20.0)
High risk of bias	-
Unclear risk of bias	4 (80.0)
III. Index test 2	
Low risk of bias	3 (60.0)
High risk of bias	-
Unclear risk of bias	2 (40.0)
Not applicable	-
IV. Reference standard	
Low risk of bias	-
High risk of bias	2 (40.0)
Unclear risk of bias	3 (60.0)
Not applicable	-
V. Flow and timing	
Low risk of bias	3 (60.0)
High risk of bias	2 (40.0)
Unclear risk of bias	-
Not applicable	-

Table 3: Risk of bias in individual included diagnostic studies (n = 5)

	Patient selection	Index test 1	Index test 2	Reference standard [a]	Flow and timing [b]	Overall Risk of bias
Carvalhal 1999	Low	Low	Low	Unclear	Low	**At risk**
Fowler 2000	Unclear	Unclear	Low	High	Low	**At risk**
Galić 2003	Low	Unclear	Low	Unclear	High	**At risk**
Gomez-Guerra 2009	Low	Unclear	Unclear	Unclear	Low	**At risk**
Thompson 2007	Low	Unclear	Unclear	High	High	**At risk**

[a.] An adequate biopsy was pre-specified as 12 or more cores; [b.] An appropriate interval was pre-specified as up to 1 year, for biopsy referral cohorts where the interval was not stated the interval was assumed to be less than one year

Key to overall rating
Low risk of bias: A study that received "low" for all domains
At risk of bias: Received "high" or "unclear" for one or more domains

2.5. Study Results

I. **Detection of prostate cancer (Table 4)**

II. **Detection of Gleason score >4 cancer (Table 5)**

III. **Detection of Gleason score >5 cancer (Table 6)**

IV. **Detection of Gleason score >6 cancer (Table 7)**

V. **Detection of Gleason score >7 cancer (Table 8)**

I DETECTION OF PROSTATE CANCER

Table 4: Results of studies reporting the incremental value of DRE in addition to PSA testing with respect to detection of prostate cancer

Biopsy indication	Screen positives biopsied (N)	TP (N)	FP (N)	ΔFP/ΔTP	PPV	Screen negatives biopsied (N)	FN (N)	TN (N)	Sensitivity (%)	Specificity (%)	DOR	Youden's Index
Screening population, inadequate biopsy scheme – biopsy regardless of PSA and DRE												
Thompson 2007 (PCPT)	N = 5,112					7 years of annual screening						
PSA >4.0	561	267	294		47.6	4,551	844	3,707	24.0	92.7	3.99	0.17
PSA >4.0 and/or DRE+	1,012	422	590	296/155 = **1.91**	41.7	4,100	689	3,411	38.0	85.3	3.54	0.23
PSA >3.0	973	389	584		40.0	4,139	722	3,417	35.0	85.4	3.15	0.20
PSA >3.0 and/or DRE+	1,376	524	852	268/135 = **1.99**	38.1	3,736	587	3,149	47.2	78.7	3.30	0.26
PSA >2.0	1,747	594	1,153		34.0	3,365	517	2,848	53.5	71.2	2.84	0.25
PSA >2.0 and/or DRE+	2,057	684	1,373	220/90 = **2.44**	33.3	3,055	427	2,628	61.6	65.7	3.07	0.27
"Screening population", adequate biopsy scheme – biopsy of screen-positive men only												
Galić 2003	N = 88						cross-sectional					
PSA >4.0	68	32	36		47.1	0	N/A	N/A	N/A	N/A	N/A	N/A
PSA >4.0 and/or DRE+	88	35	53	17/3 = **5.67**	39.8	0	N/A	N/A	N/A	N/A	N/A	N/A
"Screening population", inadequate biopsy scheme – biopsy of screen-positive men only												
Carvalhal 1999	N = 1,905 + men biopsied with PSA>4.0 and negative DRE (no data reported)						6-monthly to annual screening					
PSA >4.0	NR	NR	NR		NR	0	N/A	N/A	N/A	N/A	N/A	N/A
PSA >4.0 and/or DRE+	NR	NR	NR	1,661/244 = **6.81**	NR	0	N/A	N/A	N/A	N/A	N/A	N/A
Gomez-Guerra 2009	N = 55						annual screening for 3 years					
PSA >4.0	45	14	31		31.1	0	N/A	N/A	N/A	N/A	N/A	N/A
PSA >4.0 and/or DRE+	55	15	40	9/1 = **9.00**	27.3	0	N/A	N/A	N/A	N/A	N/A	N/A

Referral population, inadequate biopsy scheme – biopsy of screen-positive men only												
Fowler 2000	N = 2,256								single biopsy			
PSA ≥4.0	1,675	NR	NR		NR	0	N/A	N/A	N/A	N/A	N/A	N/A
PSA ≥4.0 and/or DRE+	2,256	NR	**NR**	433/103 = **4.20**	NR	0	N/A	N/A	N/A	N/A	N/A	N/A

ΔFP/ΔTP = difference in false positives/difference in true positives; DOR = diagnostic odds ratio = (TP/FN x TN/FP); FN = false negatives; FP = false positives; N/A = not applicable; PPV = positive predictive value; TN = true negatives; TP = true positives; Youden's Index = sensitivity + specificity – 1

II DETECTION OF GLEASON SCORE >4 CANCER

Table 5: Results of studies reporting the incremental value of DRE in addition to PSA testing with respect to detection of Gleason Score >4 cancer

Biopsy indication	Screen positives biopsied (N)	TP (N)	FP (N)	ΔFP/ΔTP	PPV	Screen negatives biopsied (N)	FN (N)	TN (N)	Sensitivity (%)	Specificity (%)	DOR	Youden's Index
screening population, inadequate biopsy scheme – biopsy regardless of PSA and DRE												
Carvalhal 1999	N = 1,905 + men biopsied with PSA>4.0 and negative DRE (no data reported)					6-monthly to annual screening						
PSA >4.0	NR	NR	NR		NR	0	N/A	N/A	N/A	N/A	N/A	N/A
PSA >4.0 and/or DRE+	NR	NR	NR	1,746/159 = **10.98**	NR	0	N/A	N/A	N/A	N/A	N/A	N/A
referral population, inadequate biopsy scheme – biopsy of screen-positive men only												
Fowler 2000	N = 2,256					single biopsy						
PSA ≥4.0	1,675	NR	NR		NR	0	N/A	N/A	N/A	N/A	N/A	N/A
PSA ≥4.0 and/or DRE+	2,256	NR	NR	446/90 = **4.96**	NR	0	N/A	N/A	N/A	N/A	N/A	N/A

ΔFP/ΔTP = difference in false positives/difference in true positives; DOR = diagnostic odds ratio = (TP/FN x TN/FP); FN = false negatives; FP = false positives; N/A = not applicable; PPV = positive predictive value; TN = true negatives; TP = true positives; Youden's Index = sensitivity + specificity – 1

III DETECTION OF GLEASON SCORE >5 CANCER

Table 6: Results of studies reporting the incremental value of DRE in addition to PSA testing with respect to detection of Gleason Score >5 cancer

Biopsy indication	Screen positives biopsied (N)	TP (N)	FP (N)	ΔFP/ΔTP	PPV	Screen negatives biopsied (N)	FN (N)	TN (N)	Sensitivity (%)	Specificity (%)	DOR	Youden's Index
"Screening population", inadequate biopsy scheme – biopsy of screen-positive men only												
Gomez-Guerra 2009	N = 55					annual screening for 3 years						
PSA >4.0	45	14	31		31.1	0	N/A	N/A	N/A	N/A	N/A	N/A
PSA >4.0 and/or DRE+	55	15	40	9/1 = **9.00**	27.3	0	N/A	N/A	N/A	N/A	N/A	N/A

ΔFP/ΔTP = difference in false positives/difference in true positives; DOR = diagnostic odds ratio = (TP/FN x TN/FP); FN = false negatives; FP = false positives; N/A = not applicable; PPV = positive predictive value; TN = true negatives; TP = true positives; Youden's Index = sensitivity + specificity – 1

IV DETECTION OF GLEASON SCORE >6 CANCER

Table 7: Results of studies reporting the incremental value of DRE in addition to PSA testing with respect to detection of Gleason Score >6 cancer

Biopsy indication	Screen positives biopsied (N)	TP (N)	FP (N)	ΔFP/ΔTP	PPV	Screen negatives biopsied (N)	FN (N)	TN (N)	Sensitivity (%)	Specificity (%)	DOR	Youden's Index
Screening population, inadequate biopsy scheme – biopsy regardless of PSA and DRE												
Thompson 2007 (PCPT) N = 5,101 (placebo arm)							7 years of annual screening					
PSA >4.0	557	94	463		16.9	4,544	146	4,398	39.2	90.5	6.12	0.30
PSA >4.0 and/or DRE+	1,006	130	876	413/36 = **11.47**	12.9	4,095	110	3,985	54.2	82.0	5.38	0.36
"Screening population", inadequate biopsy scheme – biopsy of screen-positive men only												
Gomez-Guerra 2009 N = 55							annual screening for 3 years					
PSA >4.0	45	13	32		28.9	0	N/A	N/A	N/A	N/A	N/A	N/A
PSA >4.0 and/or DRE+	55	14	41	9/1 = **9.00**	25.5	0	N/A	N/A	N/A	N/A	N/A	N/A
Referral population, inadequate biopsy scheme – biopsy of screen-positive men only												
Fowler 2000 N = 2,256							single biopsy					
PSA ≥4.0	1,675	NR	NR		NR	0	N/A	N/A	N/A	N/A	N/A	N/A
PSA ≥4.0 and/or DRE+	2,256	NR	NR	501/35 = **14.31**	NR	0	N/A	N/A	N/A	N/A	N/A	N/A

ΔFP/ΔTP = difference in false positives/difference in true positives; DOR = diagnostic odds ratio = (TP/FN x TN/FP); FN = false negatives; FP = false positives; N/A = not applicable; PPV = positive predictive value; TN = true negatives; TP = true positives; Youden's Index = sensitivity + specificity – 1

V DETECTION OF GLEASON SCORE >7 CANCER

Table 8: Results of studies reporting the incremental value of DRE in addition to PSA testing with respect to detection of Gleason Score >7 cancer

Biopsy indication	Screen positives biopsied (N)	TP (N)	FP (N)	ΔFP/ΔTP	PPV	Screen negatives biopsied (N)	FN (N)	TN (N)	Sensitivity (%)	Specificity (%)	DOR	Youden's Index
Screening population, inadequate biopsy scheme – biopsy regardless of PSA and DRE												
Thompson 2007 (PCPT)	N = 5,101			(placebo arm)					7 years of annual screening			
PSA >4.0	557	27	530		4.9	4,544	28	4,516	49.1	89.5	8.22	0.39
PSA >4.0 and/or DRE+	1,006	41	965	435/14 = **31.07**	4.1	4,095	14	4,081	74.5	80.9	12.38	0.55
"Screening population", inadequate biopsy scheme – biopsy of screen-positive men only												
Carvalhal 1999	N = 1,905 + men biopsied with PSA>4.0 and negative DRE (no data reported)						6-monthly to annual screening					
PSA >4.0	NR	NR	NR		NR	0	N/A	N/A	N/A	N/A	N/A	N/A
PSA >4.0 and/or DRE+	NR	NR	NR	1,897/8 = **237.13**	NR	0	N/A	N/A	N/A	N/A	N/A	N/A
Gomez-Guerra 2009	N = 55						annual screening for 3 years					
PSA >4.0	45	9	36		25.0	0	N/A	N/A	N/A	N/A	N/A	N/A
PSA >4.0 and/or DRE+	55	9	46	10/0 – **N/A**	19.6	0	N/A	N/A	N/A	N/A	N/A	N/A
Referral population, inadequate biopsy scheme – biopsy of screen-positive men only												
Fowler 2000	N = 2,256						single biopsy					
PSA ≥4.0	1,675	NR	NR		NR	0	N/A	N/A	N/A	N/A	N/A	N/A
PSA ≥4.0 and/or DRE+	2,256	NR	NR	522/14 = **37.29**	NR	0	N/A	N/A	N/A	N/A	N/A	N/A

ΔFP/ΔTP = difference in false positives/difference in true positives; DOR = diagnostic odds ratio = (TP/FN x TN/FP); FN = false negatives; FP = false positives; N/A = not applicable; PPV = positive predictive value; TN = true negatives; TP = true positives; Youden's Index = sensitivity + specificity – 1

2.6. Body of Evidence

Name of study	Study type	N	Level of evidence*	Risk of bias**	ΔFP/ΔTP	DOR	Youden's Index
Screening population, inadequate biopsy scheme – biopsy regardless of PSA and DRE							
Thompson 2007 *PSA **>4.0** +/ DRE+* *vs. PSA >4.0 only*	Fully paired	Placebo arm: N = 5,947 (biopsied) N = 5,112 (analysed)	III-2	At risk	Any cancer: 296/155 = **1.91** GS>6: 413/36 = **11.47** GS>7: 435/14 = **31.07**	Any cancer: PSA only: 3.99 PSA+/DRE: 3.54 GS>6: PSA only: 6.11 PSA+/DRE: 5.38 GS>7: PSA only: 8.22 PSA+/DRE: 12.38	Any cancer: PSA only: 0.17 PSA+/DRE: 0.23 GS>6: PSA only: 0.30 PSA+/DRE: 0.36 GS>7: PSA only: 0.39 PSA+/DRE: 0.55
Thompson 2007 *PSA **>3.0** +/ DRE+* *vs. PSA >3.0 only*	Fully paired	Placebo arm: N = 5,947 (biopsied) N = 5,112 (analysed)	III-2	At risk	Any cancer: 268/135 = **1.99**	Any cancer: PSA only: 3.15 PSA+/DRE: 3.30	Any cancer: PSA only: 0.20 PSA+/DRE: 0.26
Thompson 2007 *PSA **>2.0** +/ DRE+* *vs. PSA >2.0 only*	Fully paired	Placebo arm: N = 5,947 (biopsied) N = 5,112 (analysed)	III-2	At risk	Any cancer: 220/90 = **2.44**	Any cancer: PSA only: 2.84 PSA+/DRE: 3.07	Any cancer: PSA only: 0.25 PSA+/DRE: 0.27
"Screening population", adequate biopsy scheme – biopsy of screen-positive men only							
Galić 2003 *PSA >4.0 +/ DRE+* *vs. PSA >4.0 only*	Fully paired	N = 88 (biopsied and analysed)	III-2	At risk	Any cancer: 17/3 = **5.67**	N/A	N/A
"Screening population", inadequate biopsy scheme – biopsy of screen-positive men only							
Carvalhal 1999 *PSA >4.0 +/ DRE+* *vs. PSA >4.0 only*	Fully paired	N = 1,905 (biopsied due to abnormal DRE only and analysed)	III-2	At risk	Any cancer: 1,661/244 = **6.81** GS>4: 1,746/159 = **10.98** GS>7: 1,897/8 = **237.13**	N/A	N/A
Gomez-Guerra 2009 *PSA >4.0 +/ DRE+* *vs. PSA >4.0 only*	Fully paired	N = 55 (biopsied and analysed)	III-2	At risk	Any cancer: 9/1 = **9.00** GS>5: 9/1 = **9.00** GS>6: 9/1 = **9.00** GS>7: **10/0**	N/A	N/A
Referral population, inadequate biopsy scheme – biopsy of screen-positive men only							

Fowler 2000 *PSA ≥4.0 +/ DRE+ vs. PSA ≥4.0 only*	Fully paired	N = 581 (biopsied due to abnormal DRE only) N = 536 (analysed)	III-2	At risk	Any cancer: 433/103 = **4.20** GS>4: 446/90 = **4.96** GS>6: 501/35 = **14.31** GS>7: 522/14 = **37.29**	N/A	N/A

** Refer to appendix B for detailed explanations of rating scores; ** See tables 2 and 3 for assessment of risk of bias*

∆FP/∆TP = difference in false positives/difference in true positives; DOR = diagnostic odds ratio = (TP/FN x TN/FP); DRE = digital rectal examination; GS = Gleason Score; PSA = prostate-specific antigen; Youden's Index = sensitivity + specificity – 1;

Clinical significance of size of effect is addressed in the assessment of clinical impact in the NHMRC evidence statement form.

Assessment of the relevance of the evidence in terms of whether the outcomes were directly relevant to the patient or surrogate outcomes was not assessed as it was not considered relevant to diagnostic performance studies.

2.7. References of included studies

1. Carvalhal GF, Smith DS, Mager DE, Ramos C, Catalona WJ. Digital rectal examination for detecting prostate cancer at prostate specific antigen levels of 4 ng./ml. or less. *J Urol* 1999; 161(3):835-839.

2. Fowler JE JR, Bigler SA, Farabaugh PB, Wilson SS. Prostate cancer detection in Black and White men with abnormal digital rectal examination and prostate specific antigen less than 4 ng./ml. *J Urol* 2000; 164(6):1961-1963.

3. Galic J, Karner I, Cenan L, Tucak A, Hegedus I, Pasini J et al. Comparison of digital rectal examination and prostate specific antigen in early detection of prostate cancer. *Collegium Antropologicum* 2003; 27:Suppl-6.

4. Gomez-Guerra LS, Martinez-Fierro ML, Alcantara-Aragon V, Ortiz-Lopez R, Martinez-Villarreal RT, Morales-Rodriguez IB et al. Population based prostate cancer screening in north Mexico reveals a high prevalence of aggressive tumors in detected cases. *BMC Cancer* 2009; 9:91.

5. Thompson IM, Tangen CM, Goodman PJ, Lucia MS, Parnes HL, Lippman SM et al. Finasteride improves the sensitivity of digital rectal examination for prostate cancer detection. *J Urol* 2007; 177(5):1749-1752.

APPENDICES

Appendix A: Search strategies used

For Medline database:

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	(digital adj1 rectal adj1 exam$).mp.
5	(DRE or 'rectal exam$' or 'physical exam$' or palpabl$ or nonpalpabl$ or palpation or 'prostate exam$').mp.
6	Digital Rectal Examination/
7	(clinical$ adj2 (detect$ or diagnos$ or exam$)).mp.
8	4 or 5 or 6 or 7
9	('prostate specific antigen' or PSA).tw.
10	Prostate-Specific Antigen/
11	9 or 10
12	3 and 8 and 11
13	limit 12 to (english language and humans and yr="1990 -Current")

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database:

#	Searches
1	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR metast* OR adeno*)
2	'prostate cancer'/exp
3	1 OR 2
4	'digital rectal examination' OR 'digital rectal exam' OR 'digital rectal examinations' OR 'digital rectal exams'
5	prostate NEAR/1 exam* OR rectal near/1 exam* OR physical near/1 exam OR dre OR palpabl* OR nonpalpabl* OR palpation OR impalpabl*
6	'digital rectal examination'/exp
7	(clinical OR clinically) NEAR/2 (detect* OR diagnos* OR exam*)
8	4 OR 5 OR 6 OR 7

9	'prostate specific antigen' OR psa
10	'prostate specific antigen'/exp
11	9 OR 10
12	3 AND 8 AND 11
13	12 NOT [medline]/lim AND [humans]/lim AND [english]/lim AND [embase]/lim AND [1990-3000]/py

ATSI search terms used

#	**Searches**
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

For Cochrane Database of Systematic Reviews – The Cochrane Library:

Title, abstracts, keywords: “prostate”

For Database of Abstracts of Reviews of Effects and Health Technology Assessment database (via OvidSP):

#	**Searches**
1	exp Prostatic Neoplasms/
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
3	1 or 2

Appendix B:

Level of Evidence rating criteria – Diagnostic accuracy studies

Level	Study design
I	Meta-analysis or a systematic review of level II studies
II	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation
III-1	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation
III-2	A comparison with reference standard that does not meet the criteria required for level II and III-1 evidence
III-3	Diagnostic case-control study
IV	Study of diagnostic yield (no reference standard)

According to the standards of the National Health and Medical Research Council

Appendix C:

Potentially relevant guidelines identified and reason why not adopted

Year	Organisation	Title	Reason why not adopted
2010	American Cancer Society	American Cancer Society Guideline for the Early Detection of Prostate Cancer	Did not meet pre-specified AGREE II criteria for adoption
2008	American College of Preventive Medicine	Screening for Prostate Cancer in U.S. Men: ACPM Position Statement on Preventive Practice	Did not meet pre-specified AGREE II criteria for adoption
2013	American College of Physicians	Screening for prostate cancer – guidance statement	Did not meet pre-specified AGREE II criteria for adoption
2013	American Urological Association	Early Detection of Prostate Cancer: AUA Guideline	Did not meet pre-specified AGREE II criteria for inclusion
2011	Canadian Urological Association	Prostate Cancer Screening: Canadian guidelines	Did not meet pre-specified AGREE II criteria for adoption
2014	European Association of Urology	Guidelines on Prostate Cancer	Did not meet pre-specified AGREE II criteria for adoption
2008	National Academy of Clinical Biochemistry	National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for Use of Tumor Markers in Testicular, Prostate, Colorectal, Breast, and Ovarian Cancers	Not based on a systematic review
2012	NCCN	Prostate cancer early detection version 2.2012	Not based on a systematic review
2009	New Zealand Guidelines Group	Suspected cancer in primary care: Guidelines for investigation, referral and reducing ethnic disparities	Not based on a systematic review
2012	Royal Australian College of General Practitioners	Guidelines for preventive activities in general practice	Not based on a systematic review

Excluded studies

Study	Reason for Exclusion
Agalliu 2007	No relevant outcomes
Ahmed 2011	No relevant outcomes
Akdas 1995	No relevant outcomes (methods of calculating diagnostic outcomes unclear)
Al Rumaihi 2013	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Alibhai 2004	Narrative review/comment/letter to editor (no original data)
Allhoff 1993	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Altwein 1999	Not all men underwent both DRE and PSA
Andriole 2005	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Argyropoulos 2005	Inappropriate population
Arratia-Maqueo 2010	Not all men underwent both DRE and PSA
Aziz 1993	Narrative review/comment/letter to editor (no original data)
Babaian 1991 a	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Babaian 1991 b	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Babaian 1992	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Babaian 1993	Inappropriate population
Babaian 2001	Not all men underwent both DRE and PSA
Baden 2011	No relevant outcomes
Bangma 1995 a	No relevant outcomes
Bangma 1995 b	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Bangma 1995 c	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Bangma 1997	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Bare 1993	Inappropriate population
Basler 1998	Narrative review/comment/letter to editor (no original data)
Beemsterboer 1999	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Beemsterboer 2000	No relevant outcomes
Benson 1993	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Bentvelsen 1993	Narrative review/comment/letter to editor (no original data)
Berger 1993	Narrative review/comment/letter to editor (no original data)
Bergstralh 2007	Not all men underwent both DRE and PSA
Borden 2006	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)

Boulos 2001	No relevant outcomes (no number of additional FP reported)
Bozeman 2005	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Brett 1998	Not all men underwent both DRE and PSA
Bretton 1994	Inappropriate population (indication for biopsy unclear)
Bruno 2007	No relevant outcomes
Bunting 2002	Narrative review/comment/letter to editor (no original data)
Candas 2000	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Canto 2002	Narrative review/comment/letter to editor (no original data)
Carroll 2001	Narrative review/comment/letter to editor (no original data)
Carter 1997	No relevant outcomes
Catalona 1991	Inappropriate population
Catalona 1993	No relevant outcomes (no separate data reported for DRE)
Catalona 1994	Inappropriate population (stratified results only reported for men who underwent prostatectomy)
Catalona 1997	No relevant outcomes
Chen 1996	No relevant outcomes
Chevil 2012	No relevant outcomes
Chong 2001	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Chu 1994	Narrative review/comment/letter to editor (no original data)
Chu 2011	No relevant outcomes
Chun 2006	No relevant outcomes
Clements 1997	Narrative review/comment/letter to editor (no original data)
Coley 1995	Narrative review/comment/letter to editor (no original data)
Coley 1997	Narrative review/comment/letter to editor (no original data)
Concato 2006	No relevant outcomes
Cooner 1993	Narrative review/comment/letter to editor (no original data)
Cooner 2002	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Crawford 1996	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Crawford 1999	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
DeAntoni 1997	Narrative review/comment/letter to editor (no original data)
Djulbegovic 2010	No relevant outcomes (systematic review)
Douville 1996	Narrative review/comment/letter to editor (no original data)
Drago 1992	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Ellis 1994	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Estham 1991	Inappropriate population
El-Galley 1995	Inappropriate population

Fiella 1996	Inappropriate population
Foo 2013	No relevant outcomes
Friedman 1991	Inappropriate study design
Gann 1995	No relevant outcomes
Gerber 1993	No relevant outcomes
Giri 2007	No relevant outcomes
Glass 2013	Narrative review/comment/letter to editor (no original data)
Gohji 1995	Inappropriate population
Gore 2001	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Gosselaar 2007	Not all men underwent both DRE and PSA
Gosselaar 2008	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Gosselaar 2009	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Gretzer 2002	Narrative review/comment/letter to editor (no original data)
Grubb 2008	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Gustafsson 1992	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Haid 1994	Inappropriate population
Hamilton 2005	Inappropriate population
Hattangadi 2012	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Higashihara 1996	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Hoedmaeker 1997	Inappropriate population
Hoffman 2000	Not all men underwent both DRE and PSA (systematic review)
Hoogendam 1999	Not all men underwent both DRE and PSA (systematic review)
Hugosson 2003	No relevant outcomes
Imai 1994	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Imai 1995	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Issa 2006	Inappropriate population
Ito 2001	No relevant outcomes (no separate data for DRE)
Jacobsen 1998	Inappropriate study design
Karakiewicz 2005	No relevant outcomes (no separate data for DRE)
Kawakami 2008	Inappropriate population
Killian 1990	Narrative review/comment/letter to editor (no original data)
Kim 2011	Not all men underwent both DRE and PSA
Kirby 1994	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Kranse 1999	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme

Lane 2007	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Lee 1992	Narrative review/comment/letter to editor (no original data)
Liang 2011	No relevant outcomes
Lin 1998	No relevant outcomes
Littrup 1992	Narrative review/comment/letter to editor (no original data)
Littrup 1994	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Littrup 1995	Narrative review/comment/letter to editor (no original data)
Loeb 2006	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Loeb 2009	Narrative review/comment/letter to editor (no original data)
Lodding 1998	Not all men underwent both DRE and PSA
Lopez-Saez 2004	No relevant outcomes
Lopez-Saez 2007	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Louria 1992	Narrative review/comment/letter to editor (no original data)
Maattanen 1999	Not all men underwent both DRE and PSA
Maattanen 2007	Not all men underwent both DRE and PSA
Makinen 2001	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Marta 2013	Narrative review/comment/letter to editor (no original data)
Meeks 2009	Inappropriate population
Mettlin 1991	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Mettlin 1993 a	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Mettlin 1993 b	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Mettlin 1996	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Mettlin 1997	No relevant outcomes
Mistry 2003	No relevant outcomes
Mizusawa 2011	Inappropriate population
Mohamed 2013	Not all men underwent both DRE and PSA
Montironi 2000	Narrative review/comment/letter to editor (no original data)
Morgentaler 2006	Inappropriate population
Muris 1993	Not all men underwent both DRE and PSA (systematic review)
Nadler 2005	No relevant outcomes
Nam 2006	Inappropriate study design
Ng 2005	Inappropriate population
Ngo 2011	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Nightingale 1994	Narrative review/comment/letter to editor (no original data)
Nishio 2003	No relevant outcomes

Norming 1991	No relevant outcomes
Oesterling 1992	No relevant outcomes
Oesterling 1995	Inappropriate population
Ohori 1995	Inappropriate population
Ojewola 2012	No relevant outcomes
Okada 2010	No relevant outcomes
Okotie 2007	Inappropriate population (men who underwent prostatectomy)
Olson 1994	Not all men underwent both DRE and PSA
Ouzaid 2012	No relevant outcomes
Park 2011	No relevant outcome (no separate data for DRE)
Pedersen 1990	No relevant outcomes
Perrin 1991	Not all men underwent both DRE and PSA
Petrillo 2013	No relevant outcomes
Philip 2005	No relevant outcomes
Pinsky 2005	No relevant outcomes
Polascik 1999	Narrative review/comment/letter to editor (no original data)
Potter 2001	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Quinlan 2007	No relevant outcomes (no number of additional FP reported)
Reissigl 1996	No relevant outcomes
Reissigl 1997 a	No relevant outcomes
Reissigl 1997 b	Not all men underwent both DRE and PSA
Richie 1993	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Richie 1994	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Rietbergen 1997	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Roberts 2000	Inappropriate population
Roobol 2003	Narrative review/comment/letter to editor (no original data)
Roobol 2006	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Roobol 2011	Not all men underwent both DRE and PSA
Roobol 2012	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Rowe 2005	No relevant outcomes (no separate data for DRE)
Ryden 2007	Not all men underwent both DRE and PSA
Sandblom 2011	No relevant outcomes
Schmidt 1992	Narrative review/comment/letter to editor (no original data)
Schroder 1996	Inappropriate population
Schröder 1998	Inappropriate population (for outcome of cancer detection stratified by Gleason Score)
Schröder 2000	No relevant outcomes (no separate data for DRE)
Schröder 2001	No relevant outcomes (no separate data for DRE)

Schröder 2003	Narrative review/comment/letter to editor (no original data)
Selley 1997	Narrative review/comment/letter to editor (no original data)
Seo 2007	Inappropriate population
Shaida 2009	No relevant outcomes
Shapiro 1994	No relevant outcomes
Shigemura 2008	No relevant outcomes
Shim 2007	No relevant outcomes
Shimizu 1995	No relevant outcomes (no separate data for DRE)
Singh 2003	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Slawin 1995	Narrative review/comment/letter to editor (no original data)
Small 1993	Narrative review/comment/letter to editor (no original data)
Smith 1997	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Song 2005	Inappropriate population
Spencer 1993	No relevant outcomes
Stenman 1994	No relevant outcomes
Stone 1994	Not all men underwent both DRE and PSA
Thompson 2004	More current data available (Thompson 2007 – included)
Thompson 2005	No relevant outcomes
Thompson 2006 a	No relevant outcomes
Thompson 2006 b	No relevant outcomes
Tornblom 1999	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Uchida 2000	Not all men underwent both DRE and PSA
Van Cangh 1996	No relevant outcomes
Van der Bergh 2008	No relevant outcomes
Van der Cruijsen-Koeter 2005	No relevant outcomes
Van der Cruijsen-Koeter 2011	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Van Vugt 2011	No relevant outcomes
Van Vugt 2012	No relevant outcomes
Vickers 2013	No relevant outcomes
Vis 2001	No relevant outcomes (no separate data for DRE)
Vis 2002	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Walz 2008	No relevant outcomes (no separate data for DRE)
Weinmann 2005	Not all men underwent both DRE and PSA
Yamamoto 1994	Inappropriate population
Yamamoto 2001	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Yu 1998	Inappropriate population

References of excluded studies

1. Agalliu I, Weiss NS, Lin DW, Stanford JL. Prostate cancer mortality in relation to screening by prostate-specific antigen testing and digital rectal examination: a population-based study in middle-aged men. *Cancer Causes & Control* 2007; 18(9):931-937.

2. Ahmed M. Prostate cancer diagnosis in a resource-poor setting: the changing role of digital rectal examination. *Tropical Doctor* 2011; 41(3):141-143.

3. Akdas A, Tarcan T, Turkeri L, Cevik I, Biren T, Gurmen N. The diagnostic accuracy of digital rectal examination, transrectal ultrasonography, prostate-specific antigen (PSA) and PSA density in prostate carcinoma. *British Journal of Urology* 1995; 76(1):54-56.

4. Al Rumaihi K, Al Jalham K, Younes N, Majzoub AA, Shokeir AA. The role of an abnormal prostate-specific antigen level and an abnormal digital rectal examination in the diagnosis of prostate cancer: A cross-sectional study in Qatar. *Arab J Urol* 2013; 11(4):355-361.

5. Alibhai SMH. What is the prevalence of prostate cancer among men with low prostate-specific antigen levels? *Can Med Assoc J* 2004; 171(6):572.

6. Allhoff EP, Liedke SG, Gonnermann O, Stief CG, Jonas U, Schneider B. Efficient pathway for early detection of prostate cancer concluded from a 5-year prospective study. *World Journal of Urology* 1993; 11(4):201-205.

7. Altwein JE, Luboldt HA. Results of a screening program in Germany for early detection of early prostate cancer. *Prostate Cancer Prostatic Dis* 1999; 2(SUPPL. 2):S15-S18.

8. Andriole GL, Levin DL, Crawford ED, Gelmann EP, Pinsky PF, Chia D et al. Prostate Cancer Screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: findings from the initial screening round of a randomized trial. *J Natl Cancer Inst* 2005; 97(6):433-438.

9. Argyropoulos A, Doumas K, Farmakis A, Aristas O, Kontogeorgos G, Lykourinas M. Characteristics of patients with stage T1b incidental prostate cancer. *Scand J Urol Nephrol* 2005; 39(4):289-293.

10. Arratia-Maqueo JA, Cortes-Gonzalez JR, Garza-Cortes R, Gomez-Guerra LS. Prospective study of prostate cancer's detection rate at our hospital in Northeast Mexican patients with PSA values between 2.6 y 4 ng/ml. *Archivos Espanoles de Urologia* 2010; 63(4):287-290.

11. Aziz DC, Barathur RB. Prostate-specific antigen and prostate volume: a meta-analysis of prostate cancer screening criteria. *J Clin Lab Anal* 1993; 7(5):283-292.

12. Babaian RJ, Miyashita H, Evans RB, von Eschenbach AC, Ramirez EI. Early detection program for prostate cancer: results and identification of high-risk patient population. *Urology* 1991; 37(3):193-197. (a)

13. Babaian RJ, Camps JL. The role of prostate-specific antigen as part of the diagnostic triad and as a guide when to perform a biopsy. *Cancer* 1991; 68(9):2060-2063. (b)

14. Babaian RJ, Mettlin C, Kane R, Murphy GP, Lee F, Drago JR et al. The relationship of prostate-specific antigen to digital rectal examination and transrectal ultrasonography. Findings of the American Cancer Society National Prostate Cancer Detection Project. *Cancer* 1992; 69(5):1195-1200.

15. Babaian RJ, Dinney CP, Ramirez EI, Evans RB. Diagnostic testing for prostate cancer detection: less is best. *Urology* 1993; 41(5):421-425.

16. Babaian RJ, Johnston DA, Naccarato W, Ayala A, Bhadkamkar VA, Fritsche HA HAJ. The incidence of prostate cancer in a screening population with a serum prostate specific antigen between 2.5 and 4.0 ng/ml: relation to biopsy strategy. *J Urol* 2001; 165(3):757-760.

17. Baden J, Adams S, Astacio T, Jones J, Markiewicz J, Painter J et al. Predicting prostate biopsy result in men with prostate specific antigen 2.0 to 10.0 ng/ml using an investigational prostate cancer methylation assay. *J Urol* 2011; 186(5):2101-2106.

18. Bangma CH, Grobbee DE, Schroder FH. Volume adjustment for intermediate prostate-specific antigen values in a screening population. *European Journal of Cancer* 1995; 31A(1):12-14. (a)

19. Bangma CH, Kranse R, Blijenberg BG, Schroder FH. The value of screening tests in the detection of prostate cancer. Part I: Results of a retrospective evaluation of 1726 men. *Urology* 1995; 46(6):773-778. (b)

20. Bangma CH, Kranse R, Blijenberg BG, Schroder FH. The value of screening tests in the detection of prostate cancer. Part II: Retrospective analysis of free/total prostate-specific analysis ratio, age-specific reference ranges, and PSA density. *Urology* 1995; 46(6):779-784. (c)

21. Bangma CH, Rietbergen JB, Kranse R, Blijenberg BG, Petterson K, Schroder FH. The free-to-total prostate specific antigen ratio improves the specificity of prostate specific antigen in screening for prostate cancer in the general population. *J Urol* 1997; 157(6):2191-2196.

22. Bare R, Hart L, McCullough DL. Correlation of prostate-specific antigen and prostate-specific antigen density with outcome of prostate biopsy. *Urology* 1994; 43(2):191-196.

23. Basler JW, Thompson IM. Lest we abandon digital rectal examination as a screening test for prostate cancer. *Journal of the National Cancer Institute* 1998; 90(23):1761-1763.

24. Beemsterboer PM, Kranse R, de Koning HJ, Habbema JD, Schroder FH. Changing role of 3 screening modalities in the European randomized study of screening for prostate cancer (Rotterdam). *International Journal of Cancer* 1999; 84(4):437-441.

25. Beemsterboer PM, de Koning HJ, Kranse R, Trienekens PH, van der Maas PJ, Schroder FH. Prostate specific antigen testing and digital rectal examination before and during a randomized trial of screening for prostate cancer: European randomized study of screening for prostate cancer, Rotterdam. *J Urol* 2000; 164(4):1216-1220.

26. Benson MC, McMahon DJ, Cooner WH, Olsson CA. An algorithm for prostate cancer detection in a patient population using prostate-specific antigen and prostate-specific antigen density. *World Journal of Urology* 1993; 11(4):206-213.

27. Bentvelsen FM, Schroder FH. Modalities available for screening for prostate cancer. *Eur J Cancer* 1993; 29A(6):804-811.

28. Berger NS. Prostate cancer: screening and early detection update. [Review] [25 refs]. *Seminars in Oncology Nursing* 1993; 9(3):180-183.

29. Bergstralh EJ, Roberts RO, Farmer SA, Slezak JM, Lieber MM, Jacobsen SJ. Population-based case-control study of PSA and DRE screening on prostate cancer mortality. *Urology* 2007; 70(5):936-941.

30. Borden LS, Jr., Wright JL, Kim J, Latchamsetty K, Porter CR. An abnormal digital rectal examination is an independent predictor of Gleason > or =7 prostate cancer in men undergoing initial prostate biopsy: a prospective study of 790 men. *BJU International* 2007; 99(3):559-563.

31. Boulos MTB, Rifkin MD, Ross J. Should prostate-specific antigen or prostate-specific antigen density be used as the determining factor when deciding which prostates should undergo biopsy during prostate ultrasound. *Ultrasound Q* 2001; 17(3):177-180.

32. Bozeman CB, Carver BS, Caldito G, Venable DD, Eastham JA. Prostate cancer in patients with an abnormal digital rectal examination and serum prostate-specific antigen less than 4.0 ng/mL. *Urology* 2005; 66(4):803-807.

33. Brett TD. An analysis of digital rectal examination and serum-prostate-specific antigen in the early detection of prostate cancer in general practice. *Fam Pract* 1998; 15(6):529-533.

34. Bretton PR. Prostate-specific antigen and digital rectal examination in screening for prostate cancer: a community-based study. *Southern Medical Journal* 1994; 87(7):720-723.

35. Bruno JJ, Armenakas NA, Fracchia JA. Influence of prostate volume and percent free prostate specific antigen on prostate cancer detection in men with a total prostate specific antigen of 2.6 to 10.0 ng/ml. *J Urol* 2007; 177(5):1741-1744.

36. Bunting PS. Screening for prostate cancer with prostate-specific antigen: beware the biases. *Clin Chim Acta* 2002; 315(1-2):71-97.

37. Candas B, Cusan L, Gomez JL, Diamond P, Suburu RE, Levesque J et al. Evaluation of prostatic specific antigen and digital rectal examination as screening tests for prostate cancer. *Prostate* 2000; 45(1):19-35.

38. Canto EI, Slawin KM. Early management of prostate cancer: how to respond to an elevated PSA?. [Review] [70 refs]. *Annual Review of Medicine* 2002; 53:355-368.

39. Carroll P, Coley C, McLeod D, Schellhammer P, Sweat G, Wasson J et al. Prostate-specific antigen best practice policy--part I: early detection and diagnosis of prostate cancer. *Urology* 2001; 57(2):217-224.

40. Carter HB, Epstein JI, Chan DW, Fozard JL, Pearson JD. Recommended prostate-specific antigen testing intervals for the detection of curable prostate cancer. *JAMA* 1997; 277(18):1456-1460.

41. Catalona WJ, Smith DS, Ratliff TL, Dodds KM, Coplen DE, Yuan JJ et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer.[Erratum appears in N Engl J Med 1991 Oct 31;325(18):1324]. *New England Journal of Medicine* 1991; 324(17):1156-1161.

42. Catalona WJ, Smith DS, Ratliff TL, Basler JW. Detection of organ-confined prostate cancer is increased through prostate-specific antigen-based screening. *JAMA* 1993; 270(8):948-954.

43. Catalona WJ, Richie JP, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. *J Urol* 1994; 151(5):1283-1290.

44. Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination. Enhancement of specificity with free PSA measurements. *JAMA* 1997; 277(18):1452-1455.

45. Chen YT, Luderer AA, Thiel RP, Carlson G, Cuny CL, Soriano TF. Using proportions of free to total prostate-specific antigen, age, and total prostate-specific antigen to predict the probability of prostate cancer. *Urology* 1996; 47(4):518-524.

46. Chevli KK, Duff M, Yu C, Capuder B, Elshafei A, Malczewski S et al. Urinary pca 3 as a predictor for prostate cancer in a cohort of 1928 men undergoing initial prostate biopsy. *J Urol* 2012; 187(4):e489.

47. Chong WL, Sahabudin RM, Teh GC, Woo SY, Lim TC, Khairullah A. The role of DRE in the diagnosis of prostate carcinoma. *Medical Journal of Malaysia* 2001; 56(2):167-173.

48. Chu DI, De NC, Gerber L, Thomas JA, Calloway EE, Albisinni S et al. Predictive value of digital rectal examination for prostate cancer detection is modified by obesity. *Prostate Cancer & Prostatic Diseases* 2011; 14(4):346-353.

49. Chu TM. Prostate-specific antigen in screening of prostate cancer. [Review] [43 refs]. *Journal of Clinical Laboratory Analysis* 1994; 8(5):323-326.

50. Chun FK, Perrotte P, Briganti A, Benayoun S, Lebeau T, Ramirez A et al. Prostate specific-antigen distribution in asymptomatic Canadian men with no clinical evidence of prostate cancer. *BJU International* 2006; 98(1):50-53.

51. Clements R. Has ultrasonography a role in screening for prostatic cancer?. [Review] [43 refs]. *European Radiology* 1997; 7(2):217-223.

52. Coley CM, Barry MJ, Fleming C, Wasson JH, Fahs MC, Oesterling JE. Should Medicare provide reimbursement for prostate-specific antigen testing for early detection of prostate cancer? Part II: Early detection strategies. *Urology* 1995; 46(2):125-141.

53. Coley CM, Barry MJ, Fleming C, Mulley AG. Early detection of prostate cancer. Part I: Prior probability and effectiveness of tests. The American College of Physicians. *Ann Intern Med* 1997; 126(5):394-406.

54. Concato J, Wells CK, Horwitz RI, Penson D, Fincke G, Berlowitz DR et al. The effectiveness of screening for prostate cancer: a nested case-control study. *Archives of Internal Medicine* 2006; 166(1):38-43.

55. Cooner WH. Prostate-specific antigen coordinated with digital rectal examination and transrectal ultrasonography in the detection of prostate cancer. *World Journal of Urology* 1993; 11(4):214-217.

56. Cooner WH, Mosley BR, Rutherford CL, Jr., Beard JH, Pond HS, Terry WJ et al. Prostate cancer detection in a clinical urological practice by ultrasonography, digital rectal examination and prostate specific antigen. 1990. *J Urol* 2002; 167(2:Pt 2):t-73.

57. Crawford ED, DeAntoni EP, Etzioni R, Schaefer VC, Olson RM, Ross CA. Serum prostate-specific antigen and digital rectal examination for early detection of prostate cancer in a national community-based program. The Prostate Cancer Education Council. *Urology* 1996; 47(6):863-869.

58. Crawford ED, Leewansangtong S, Goktas S, Holthaus K, Baier M. Efficiency of prostate-specific antigen and digital rectal examination in screening, using 4.0 ng/ml and age-specific reference range as a cutoff for abnormal values. *Prostate* 1999; 38(4):296-302.

59. DeAntoni EP. Age-specific reference ranges for PSA in the detection of prostate cancer. *Oncology (Williston Park)* 1997; 11(4):475-82, 485.

60. Djulbegovic M, Beyth RJ, Neuberger MM, Stoffs TL, Vieweg J, Djulbegovic B et al. Screening for prostate cancer: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2010; 341:c4543.

61. Douville P, Cembrowski G. DRE-PSA data revisited: PSA sampling should precede DREs. *Archives of Internal Medicine* 1996; 156(12):1352-1353.

62. Drago JR, York JP. Prostate-specific antigen, digital rectal examination, and transrectal ultrasound in predicting the probability of cancer. *Journal of Surgical Oncology* 1992; 49(3):172-175.

63. Eastham JA, May R, Robertson JL, Sartor O, Kattan MW. Development of a nomogram that predicts the probability of a positive prostate biopsy in men with an abnormal digital rectal examination and a prostate-specific antigen between 0 and 4 ng/mL. *Urology* 1999; 54(4):709-713.

64. el-Galley RE, Petros JA, Sanders WH, Keane TE, Galloway NT, Cooner WH et al. Normal range prostate-specific antigen versus age-specific prostate-specific antigen in screening prostate adenocarcinoma. *Urology* 1995; 46(2):200-204.

65. Ellis WJ, Chetner MP, Preston SD, Brawer MK. Diagnosis of prostatic carcinoma: the yield of serum prostate specific antigen, digital rectal examination and transrectal ultrasonography. *J Urol* 1994; 152(5:Pt 1):t-5.

66. Filella X, Molina R, Ballesta AM, Gil MJ, Allepuz C, Rioja LA. Value of PSA (prostate-specific antigen) in the detection of prostate cancer in patients with urological symptoms. Results of a multicentre study. *European Journal of Cancer* 1996; 32A(7):1125-1128.

67. Foo SL, Lim J, Tham TM, Wong TB, Ong TA. The detection rate of prostate cancer using Prostate Specific Antigen (PSA) and Digital Rectal Examination (DRE) in Sabah. *J Univ Malaya Med Cent* 2013; 16(SPECIAL):77-78.

68. Friedman GD, Hiatt RA, Quesenberry CP, Jr., Selby JV. Case-control study of screening for prostatic cancer by digital rectal examinations. *Lancet* 1991; 337(8756):1526-1529.

69. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. *JAMA* 1995; 273(4):289-294.

70. Gerber GS, Thompson IM, Thisted R, Chodak GW. Disease-specific survival following routine prostate cancer screening by digital rectal examination. *JAMA* 1993; 269(1):61-64.

71. Giri VN, Beebe-Dimmer J, Buyyounouski M, Konski A, Feigenberg SJ, Uzzo RG et al. Prostate cancer risk assessment program: a 10-year update of cancer detection. *J Urol* 1924; 178(5):1920-1924.

72. Glass AS, Cary KC, Cooperberg MR. Risk-based prostate cancer screening: who and how? *Curr Urol Rep* 2013; 14(3):192-198.

73. Gohji K, Okamoto M, Morisue K, Fujii A. Usefulness of digital rectal examination, serum prostate-specific antigen, transrectal ultrasonography and systematic prostate biopsy for the detection of organ-confined prostate cancer. *International Journal of Urology* 1995; 2(2):116-120.

74. Gore JL, Shariat SF, Miles BJ, Kadmon D, Jiang N, Wheeler TM et al. Optimal combinations of systematic sextant and laterally directed biopsies for the detection of prostate cancer. *J Urol* 2001; 165(5):1554-1559.

75. Gosselaar C, Roobol MJ, Roemeling S, van der Kwast TH, Schroder FH. Screening for prostate cancer at low PSA range: the impact of digital rectal examination on tumor incidence and tumor characteristics. *Prostate* 2007; 67(2):154-161.

76. Gosselaar C, Roobol MJ, Roemeling S, Schroder FH. The role of the digital rectal examination in subsequent screening visits in the European randomized study of screening for prostate cancer (ERSPC), Rotterdam. *Eur Urol* 2008; 54(3):581-588.

77. Gosselaar C, Roobol MJ, van den Bergh RCN, Wolters T, Schroder FH. Digital Rectal Examination and the Diagnosis of Prostate Cancer-a Study Based on 8 Years and Three Screenings within the European Randomized Study of Screening for Prostate Cancer (ERSPC), Rotterdam. *Eur Urol* 2009; 55(1):139-147.

78. Gretzer MB, Partin AW. PSA levels and the probability of prostate cancer on biopsy. *Eur Urol* 2002; Supplements 1:21-27.

79. Grubb RL, III, Pinsky PF, Greenlee RT, Izmirlian G, Miller AB, Hickey TP et al. Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian cancer screening trial: update on findings from the initial four rounds of screening in a randomized trial. *BJU International* 2008; 102(11):1524-1530.

80. Gustafsson O, Norming U, Almgard LE, Fredriksson A, Gustavsson G, Harvig B et al. Diagnostic methods in the detection of prostate cancer: a study of a randomly selected population of 2,400 men. *J Urol* 1992; 148(6):1827-1831.

81. Haid M, Rabin D, King KM, Feinstein CM, Janson KL, Levine SR et al. Digital rectal examination, serum prostate specific antigen, and prostatic ultrasound: how effective is this diagnostic triad? *Journal of Surgical Oncology* 1994; 56(1):32-38.

82. Hamilton W, Sharp DJ, Peters TJ, Round AP. Clinical features of prostate cancer before diagnosis: a population-based, case-control study. *British Journal of General Practice* 2006; 56(531):756-762.

83. Hattangadi JA, Chen MH, D'Amico AV. Early detection of high-grade prostate cancer using digital rectal examination (DRE) in men with a prostate-specific antigen level of <2.5 ng/mL and the risk of death. *BJU International* 2012; 110(11):1636-1641.

84. Higashihara E, Nutahara K, Kojima M, Okegawa T, Miura I, Miyata A et al. Significance of free prostate-specific antigen and gamma-seminoprotein in the screening of prostate cancer. *Prostate - Supplement* 1996; 7:40-47.

85. Hoedemaeker RF, Rietbergen JB, Kranse R, van der Kwast TH, Schroder FH. Comparison of pathologic characteristics of T1c and non-T1c cancers detected in a population-based screening study, the European Randomized Study of Screening for Prostate Cancer. *World J Urol* 1997; 15(6):339-345.

86. Hoffman RM, Clanon DL, Littenberg B, Frank JJ, Peirce JC. Using the free-to-total prostate-specific antigen ratio to detect prostate cancer in men with nonspecific elevations of prostate-specific antigen levels. *J Gen Intern Med* 2000; 15(10):739-748.

87. Hoogendam A, Buntinx F, de Vet HC. The diagnostic value of digital rectal examination in primary care screening for prostate cancer: a meta-analysis. *Fam Pract* 1999; 16(6):621-626.

88. Hugosson J, Aus G, Lilja H, Lodding P, Pihl CG, Pileblad E. Prostate specific antigen based biennial screening is sufficient to detect almost all prostate cancers while still curable. *J Urol* 2003; 169(5):1720-1723.

89. Imai K, Ichinose Y, Kubota Y, Yamanaka H, Sato J, Saitoh M et al. Clinical significance of prostate specific antigen for early stage prostate cancer detection. *Jpn J Clin Oncol* 1994; 24(3):160-165.

90. Imai K, Ichinose Y, Kubota Y, Yamanaka H, Sato J. Diagnostic significance of prostate specific antigen and the development of a mass screening system for prostate cancer. *J Urol* 1995; 154(3):1085-1089.

91. Issa MM, Zasada W, Ward K, Hall JA, Petros JA, Ritenour CW et al. The value of digital rectal examination as a predictor of prostate cancer diagnosis among United States Veterans referred for prostate biopsy. *Cancer Detection & Prevention* 2006; 30(3):269-275.

92. Ito K, Kubota Y, Yamamoto T, Suzuki K, Fukabori Y, Kurokawa K et al. Long term follow-up of mass screening for prostate carcinoma in men with initial prostate specific antigen levels of 4.0 ng/ml or less. *Cancer* 2001; 91(4):744-751.

93. Jacobsen SJ, Bergstralh EJ, Katusic SK, Guess HA, Darby CH, Silverstein MD et al. Screening digital rectal examination and prostate cancer mortality: a population-based case-control study. *Urology* 1998; 52(2):173-179.

94. Karakiewicz PI, Benayoun S, Kattan MW, Perrotte P, Valiquette L, Scardino PT et al. Development and validation of a nomogram predicting the outcome of prostate biopsy based on patient age, digital rectal examination and serum prostate specific antigen. *J Urol* 2005; 173(6):1930-1934.

95. Kawakami S, Koga F, Fujii Y, Saito K, Yamamoto S, Tatokoro M et al. History of malignancy is a predictor of prostate cancer detection: incorporation into a pre-biopsy nomogram. *International Journal of Urology* 2008; 15(12):1055-1060.

96. Killian CS, Chu TM. Prostate-specific antigen: questions often asked. [Review] [84 refs]. *Cancer Investigation* 1990; 8(1):27-37.

97. Kim HW, Ko YH, Kang SH, Lee JG. Predictive factors for prostate cancer in biopsy of patients with prostate-specific antigen levels equal to or less than 4 ng/ml. *Korean J Urol* 2011; 52(3):166-171.

98. Kirby RS, Kirby MG, Feneley MR, McNicholas T, McLean A, Webb JA. Screening for carcinoma of the prostate: a GP based study. *Br J Urol* 1994; 74(1):64-71.

99. Kranse R, Beemsterboer P, Rietbergen J, Habbema D, Hugosson J, Schroder FH. Predictors for biopsy outcome in the European Randomized Study of Screening for Prostate Cancer (Rotterdam region). *Prostate* 1999; 39(4):316-322.

100. Lane JA, Howson J, Donovan JL, Goepel JR, Dedman DJ, Down L et al. Detection of prostate cancer in unselected young men: prospective cohort nested within a randomised controlled trial. *BMJ* 2007; 335(7630):1139.

101. Lee F, Littrup PJ. The role of digital rectal examination, transrectal ultrasound, and prostate specific antigen for the detection of confined and clinically relevant prostate cancer. [Review] [23 refs]. *Journal of Cellular Biochemistry - Supplement* 1992; 16H:69-73.

102. Liang Y, Ankerst DP, Ketchum NS, Ercole B, Shah G, Shaughnessy JD, Jr. et al. Prospective evaluation of operating characteristics of prostate cancer detection biomarkers. *J Urol* 2011; 185(1):104-110.

103. Lin DW, Gold MH, Ransom S, Ellis WJ, Brawer MK. Transition zone prostate specific antigen density: lack of use in prediction of prostatic carcinoma. *J Urol* 1981; 160(1):77-81.

104. Littrup PJ, Lee F, Mettlin C. Prostate cancer screening: current trends and future implications. *CA: a Cancer Journal for Clinicians* 1992; 42(4):198-211.

105. Littrup PJ, Kane RA, Mettlin CJ, Murphy GP, Lee F, Toi A et al. Cost-effective prostate cancer detection. Reduction of low-yield biopsies. Investigators of the American Cancer Society National Prostate Cancer Detection Project. *Cancer* 1994; 74(12):3146-3158.

106. Littrup PJ, Sparschu R. Transrectal ultrasound and prostate cancer risks. *Cancer* 1995; 75:1805-1813.

107. Lodding P, Aus G, Bergdahl S, Frosing R, Lilja H, Pihl CG et al. Characteristics of screening detected prostate cancer in men 50 to 66 years old with 3 to 4 ng./ml. Prostate specific antigen. *J Urol* 1998; 159(3):899-903.

108. Loeb S, Gonzalez CM, Roehl KA, Han M, Antenor JA, Yap RL et al. Pathological characteristics of prostate cancer detected through prostate specific antigen based screening. *J Urol* 2006; 175(3:Pt 1):t-6.

109. Loeb S, Schaeffer EM. Risk factors, prevention and early detection of prostate cancer. *Primary Care; Clinics in Office Practice* 2009; 36(3):603-621.

110. Lopez-Saez JB, Otero M, Senra-Varela A, Ojea A, Saez Martin JL, Duran Munoz B et al. Prospective observational study to assess value of prostate cancer diagnostic methods. *J Diagn Med Sonogr* 2004; 20(6):383-393.

111. Lopez-Saez JB, Otero M, Villar MD, Penuelas AL, Navarro PR, Moreira PG et al. Diagnostic methods in the detectiion of prostate cancer: Prospective observational study. *Curr Med Imaging Rev* 2007; 3(1):27-35.

112. Louria DB. Is digital screening for prostatic cancer effective? *Bulletin of the New York Academy of Medicine* 1992; 68(4):470-475.

113. Maattanen L, Auvinen A, Stenman UH, Rannikko S, Tammela T, Aro J et al. European randomized study of prostate cancer screening: first-year results of the Finnish trial. *Br J Cancer* 1999; 79(7-8):1210-1214.

114. Maattanen L, Hakama M, Tammela TL, Ruutu M, Ala-Opas M, Juusela H et al. Specificity of serum prostate-specific antigen determination in the Finnish prostate cancer screening trial. *British Journal of Cancer* 2007; 96(1):56-60.

115. Makinen T, Tammela TL, Hakama M, Stenman UH, Rannikko S, Aro J et al. Prostate cancer screening within a prostate specific antigen range of 3 to 3.9 ng./ml.: a comparison of digital rectal examination and free prostate specific antigen as supplemental screening tests. *J Urol* 2001; 166(4):1339-1342.

116. Marta GN, Hanna SA, Fernandes da Silva JL, Carvalho HA. Screening for prostate cancer: an updated review. *Expert Rev Anticancer Ther* 2013; 13(1):101-108.

117. Meeks JJ, Loeb S, Helfand BT, Kan D, Smith ND, Catalona WJ. Characteristics of prostate cancers detected at prostate specific antigen levels less than 2.5 ng/ml. *J Urol* 2518; 181(6):2515-2518.

118. Mettlin C, Lee F, Drago J, Murphy GP. The American Cancer Society National Prostate Cancer Detection Project. Findings on the detection of early prostate cancer in 2425 men. *Cancer* 1991; 67(12):2949-2958.

119. Mettlin C, Murphy GP, Ray P, Shanberg A, Toi A, Chesley A et al. American Cancer Society--National Prostate Cancer Detection Project. Results from multiple examinations using transrectal ultrasound, digital rectal examination, and prostate specific antigen. *Cancer* 1993; 71(3:Suppl):Suppl-8. (a)

120. Mettlin C. The status of prostate cancer early detection. [Review] [20 refs]. *Cancer* 1993; 72(3:Suppl):Suppl-5. (b)

121. Mettlin C, Murphy GP, Babaian RJ, Chesley A, Kane RA, Littrup PJ et al. The results of a five-year early prostate cancer detection intervention. Investigators of the American Cancer Society National Prostate Cancer Detection Project. *Cancer* 1996; 77(1):150-159.

122. Mettlin CJ, Murphy GP, Babaian RJ, Chesley A, Kane RA, Littrup PJ et al. Observations on the early detection of prostate cancer from the American Cancer Society National Prostate Cancer Detection Project. *Cancer* 1997; 80(9):1814-1817.

123. Mistry K, Cable G. Meta-analysis of prostate-specific antigen and digital rectal examination as screening tests for prostate carcinoma. *Journal of the American Board of Family Practice* 2003; 16(2):95-101.

124. Mizusawa H, Mimura Y, Domen T, Koizumi K, Oguchi T, Kikuchi T. Clinical analysis of patients with prostate cancer who initially demonstrated a markedly elevated prostate specific antigen level. *Urology* 2011; 78(3):S326.

125. Mohamed ZK, Dominguez-Escrig J, Vasdev N, Bharathan B, Greene D. The prognostic value of transrectal ultrasound guided biopsy in patients over 70 years old with a prostate specific Antigen (PSA) level (less-than or equal to)15 ng/ml and normal digital rectal examination: A 10-year prospective follow-up study of 427 consecutive patients. *Urol Oncol Semin Orig Invest* 2013; 31(8):1489-1496.

126. Montironi R, Mazzucchelli R, Algaba F, Bostwick DG, Krongrad A. Prostate-specific antigen as a marker of prostate disease. [Review] [63 refs]. *Virchows Archiv* 2000; 436(4):297-304.

127. Morgentaler A, Luis Rhoden E. Prevalence of prostate cancer among hypogonadal men with prostate-specific antigen levels of 4.0 ng/mL or less. *Adult Urology* 2006; 68:1263-1267.

128. Muris JW, Starmans R, Wolfs GG, Pop P, Knottnerus JA. The diagnostic value of rectal examination. *Fam Pract* 1993; 10(1):34-37.

129. Nadler RB, Loeb S, Roehl KA, Antenor JA, Eggener S, Catalona WJ. Use of 2.6 ng/ml prostate specific antigen prompt for biopsy in men older than 60 years. *J Urol* 2157; 174(6):2154-2157.

130. Nam RK, Toi A, Trachtenberg J, Klotz LH, Jewett MA, Emami M et al. Making sense of prostate specific antigen: improving its predictive value in patients undergoing prostate biopsy. *J Urol* 2006; 175(2):489-494.

131. Ng TK, Vasilareas D, Mitterdorfer AJ, Maher PO, Lalak A. Prostate cancer detection with digital rectal examination, prostate-specific antigen, transrectal ultrasonography and biopsy in clinical urological practice. *BJU International* 2005; 95(4):545-548.

132. Ngo TC, Turnbull BB, Lavori PW, Presti JC, Jr. The prostate cancer risk calculator from the Prostate Cancer Prevention Trial underestimates the risk of high grade cancer in contemporary referral patients. *J Urol* 2011; 185(2):483-487.

133. Nightingale SL. PSA test is approved for use in conjunction with digital rectal examination as aid in prostate cancer detection. *J AM MED ASSOC* 1994; 272(15):1160.

134. Nishio R, Furuya Y, Nagakawa O, Fuse H. Metastatic prostate cancer with normal level of serum prostate-specific antigen. *Int Urol Nephrol* 2003; 35(2):189-192.

135. Norming U, Gustafsson O, Nyman CR, Almgard LE, Fredriksson A, Gustafsson G et al. Digital rectal examination versus transrectal ultrasound in detection of prostate cancer. Preliminary results from a study of a randomly selected population. *Acta Oncologica* 1991; 30(2):277-279.

136. Oesterling JE. Prostate-specific antigen and diagnosing early malignancies of the prostate. [Review] [42 refs]. *Journal of Cellular Biochemistry - Supplement* 1992; 16H:31-43.

137. Oesterling JE, Jacobsen SJ, Cooner WH. The use of age-specific reference ranges for serum prostate specific antigen in men 60 years old or older. *J Urol* 1995; 153(4):1160-1163.

138. Ohori M, Dunn JK, Scardino PT. Is prostate-specific antigen density more useful than prostate-specific antigen levels in the diagnosis of prostate cancer? *Urology* 1995; 46(5):666-671.

139. Ojewola RW, Tijani KH, Jeje EA, Anunobi CC, Ogunjimi MA, Ezenwa EV et al. Is extended biopsy protocol justified in all patients with suspected prostate cancer? *Nigerian Journal of Clinical Practice* 2012; 15(3):315-319.

140. Okada K, Okihara K, Kitamura K, Mikami K, Ukimura O, Kawauchi A et al. Community-based prostate cancer screening in Japan: predicting factors for positive repeat biopsy. *International Journal of Urology* 2010; 17(6):541-547.

141. Okotie OT, Roehl KA, Han M, Loeb S, Gashti SN, Catalona WJ. Characteristics of prostate cancer detected by digital rectal examination only. *Urology* 2007; 70(6):1117-1120.

142. Olson MC, Posniak HV, Fisher SG, Flisak ME, Salomon CG, Flanigan RC et al. Directed and random biopsies of the prostate: indications based on combined results of transrectal sonography and prostate-specific antigen density determinations. *AJR* 1994; American(6):1407-1411.

143. Ouzaid I, Yates D, Hupertan V, Mozer P, Chartier-Kastler E, Bitker MO et al. A direct comparison of the diagnostic accuracy of three prostate cancer nomograms designed to predict the likelihood of a positive initial transrectal biopsy. *J Urol* 2012; 187(4):e589.

144. Park JY, Yoon S, Park MS, Cho DY, Park HS, Moon dG et al. Initial biopsy outcome prediction in Korean patients-comparison of a noble web-based Korean prostate cancer risk calculator versus prostate-specific antigen testing. *Journal of Korean Medical Science* 2011; 26(1):85-91.

145. Pedersen KV, Carlsson P, Varenhorst E, Lofman O, Berglund K. Screening for carcinoma of the prostate by digital rectal examination in a randomly selected population. *BMJ* 1990; 300(104):1-4.

146. Perrin P, Maquet JH, Bringeon G, Devonec M. Screening for prostate cancer. Comparison of transrectal ultrasound, prostate specific antigen and rectal examination. *British Journal of Urology* 1991; 68(3):263-265.

147. Petrillo A, Fusco R, Setola SV, Ronza FM, Granata V, Petrillo M et al. Multiparametric MRI for prostate cancer detection: Performance in patients with prostate-specific antigen values between 2.5 and 10 ng/mL. *J Magn Reson Imaging* 2013.

148. Philip J, Dutta RS, Ballal M, Foster CS, Javle P. Is a digital rectal examination necessary in the diagnosis and clinical staging of early prostate cancer? *BJU International* 2005; 95(7):969-971.

149. Pinsky PF, Andriole GL, Kramer BS, Hayes RB, Prorok PC, Gohagan JK. Prostate biopsy following a positive screen in the prostate, lung, colorectal and ovarian cancer screening trial. *J Urol* 2005; 173(3):746-750.

150. Polascik TJ, Oesterling JE, Partin AW. Prostate specific antigen: a decade of discovery--what we have learned and where we are going. *J Urol* 1999; 162(2):293-306.

151. Potter SR, Horniger W, Tinzl M, Bartsch G, Partin AW. Age, prostate-specific antigen, and digital rectal examination as determinants of the probability of having prostate cancer. *Urology* 2001; 57(6):1100-1104.

152. Quinlan MR, Teahan S, Mulvin D, Quinlan DM. Is digital rectal examination still necessary in the early detection of prostate cancer? *Irish Journal of Medical Science* 2007; 176(3):161-163.

153. Reissigl A, Klocker H, Pointner J, Fink K, Horninger W, Ennemoser O et al. Usefulness of the ratio free/total prostate-specific antigen in addition to total PSA levels in prostate cancer screening. *Urology* 1996; 48(6A Suppl):62-66.

154. Reissigl A, Horninger W, Fink K, Klocker H, Bartsch G. Prostate carcinoma screening in the county of Tyrol, Austria: experience and results. *Cancer* 1997; 80(9):1818-1829. (a)

155. Reissigl A, Pointner J, Horninger W, Strasser H, Mayersbach P, Klocker H et al. PSA-based screening for prostate cancer in asymptomatic younger males: pilot study in blood donors. *Prostate* 1997; 30(1):20-25. (b)

156. Richie JP, Catalona WJ, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC et al. Effect of patient age on early detection of prostate cancer with serum prostate-specific antigen and digital rectal examination. *Urology* 1993; 42(4):365-374.

157. Richie JP, Kavoussi LR, Ho GT, Vickers MA, O'Donnell MA, St LD et al. Prostate cancer screening: role of the digital rectal examination and prostate-specific antigen. *Annals of Surgical Oncology* 1994; 1(2):117-120.

158. Rietbergen JB, Kranse R, Kirkels WJ, de Koning HJ, Schroder FH. Evaluation of prostate-specific antigen, digital rectal examination and transrectal ultrasonography in population-based screening for prostate cancer: improving the efficiency of early detection. *British Journal of Urology* 1997; 79:Suppl-63.

159. Roberts RO, Bergstralh EJ, Lieber MM, Jacobsen SJ. Digital rectal examination and prostate-specific antigen abnormalities at the time of prostate biopsy and biopsy outcomes, 1980 to 1997. *Urology* 2000; 56(5):817-822.

160. Roobol MJ, Kirkels WJ, Schroder FH. Features and preliminary results of the Dutch centre of the ERSPC (Rotterdam, the Netherlands). *BJU Int* 2003; 92 Suppl 2:48-54.

161. Roobol MJ, Schroder FH, Kranse R, ERSPC R. A comparison of first and repeat (four years later) prostate cancer screening in a randomized cohort of a symptomatic men aged 55-75 years using a biopsy indication of 3.0 ng/ml (results of ERSPC, Rotterdam). *Prostate* 2006; 66(6):604-612.

162. Roobol MJ, Semjonow A, Bangma CH. Performance of the european randomized study of screening for prostate cancer (ERSPC) risk calculator for high grade PC in a clinical setting and the additional value of the prostate health index (PHI). *Clin Chem Lab Med* 2011; 49:S268.

163. Roobol MJ, van Vugt HA, Loeb S, Zhu X, Bul M, Bangma CH et al. Prediction of prostate cancer risk: the role of prostate volume and digital rectal examination in the ERSPC risk calculators. *Eur Urol* 2012; 61(3):577-583.

164. Rowe EW, Laniado ME, Walker MM, Patel A. Prostate cancer detection in men with a 'normal' total prostate-specific antigen (PSA) level using percentage free PSA: a prospective screening study. *BJU International* 2005; 95(9):1249-1252.

165. Ryden L, Egevad L, Ekman P, Hellstrom M. Prevalence of prostate cancer at different levels of serum prostate-specific antigen (PSA) and different free: total PSA ratios in a consecutive series of men referred for prostate biopsies. *Scandinavian Journal of Urology & Nephrology* 2007; 41(4):302-307.

166. Sandblom G, Varenhorst E, Rosell J, Lofman O, Carlsson P. Randomised prostate cancer screening trial: 20 year follow-up. *BMJ* 2011; 342:d1539.

167. Schmidt JD. Clinical diagnosis of prostate cancer. [Review] [29 refs]. *Cancer* 1992; 70(1:Suppl):Suppl-4.

168. Schroder FH, Damhuis RA, Kirkels WJ, de Koning HJ, Kranse R, Nus HG et al. European randomized study of screening for prostate cancer--the Rotterdam pilot studies. *International Journal of Cancer* 1996; 65(2):145-151.

169. Schroder FH, van der Maas P, Beemsterboer P, Kruger AB, Hoedemaeker R, Rietbergen J et al. Evaluation of the digital rectal examination as a screening test for prostate cancer. Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. *Journal of the National Cancer Institute* 1998; 90(23):1817-1823.

170. Schroder FH, van dC-K, I, de Koning HJ, Vis AN, Hoedemaeker RF, Kranse R. Prostate cancer detection at low prostate specific antigen. *J Urol* 2000; 163(3):806-812.

171. Schroder FH, Roobol-Bouts M, Vis AN, van der Kwast T, Kranse R. Prostate-specific antigen-based early detection of prostate cancer--validation of screening without rectal examination. *Urology* 2001; 57(1):83-90.

172. Schroder FH, Denis LJ, Roobol M, Nelen V, Auvinen A, Tammela T et al. The story of the European Randomized Study of Screening for Prostate Cancer. *BJU Int* 2003; 92 Suppl 2:1-13.

173. Selley S, Donovan J, Faulkner A, Coast J, Gillatt D. Diagnosis, management and screening of early localised prostate cancer. [Review] [432 refs]. *Health Technology Assessment (Winchester, England)* 1997; 1(2):i-96.

174. Seo HK, Chung MK, Ryu SB, Lee KH, Korean Urological Oncologic Society Prostate Cancer Study Group. Detection rate of prostate cancer according to prostate-specific antigen and digital rectal examination in Korean men: a nationwide multicenter study. *Urology* 2007; 70(6):1109-1112.

175. Shaida N, Jones CM, Ravindranath N, Malone PR. The chances of subsequent cancer detection in patients with a PSA > 20 ng/ml and an initial negative biopsy. *Thescientificworldjournal* 2009; 9:343-348.

176. Shapiro A, Lebensart PD, Pode D, Bloom RA. The clinical utility of transrectal ultrasound and digital rectal examination in the diagnosis of prostate cancer. *British Journal of Radiology* 1994; 67(799):668-671.

177. Shigemura K, Arakawa S, Yamanaka K, Yasui N, Matsubara S, Iwamoto T et al. Potential predictive factors of positive prostate biopsy in the Japanese population. *International Urology & Nephrology* 2008; 40(1):91-96.

178. Shim HB, Lee SE, Park HK, Ku JH. Digital rectal examination as a prostate cancer-screening method in a country with a low incidence of prostate cancer. *Prostate Cancer & Prostatic Diseases* 2007; 10(3):250-255.

179. Shimizu TS, Uchida T, Satoh J, Imai K, Yamanaka H. Prostate-specific antigen in mass screening for carcinoma of the prostate. *International Journal of Urology* 1995; 2(4):257-260.

180. Singh R, Cahill D, Popert R, O'Brien TS. Repeating the measurement of prostate-specific antigen in symptomatic men can avoid unnecessary prostatic biopsy. *BJU International* 2003; 92(9):932-935.

181. Slawin KM, Ohori M, Dillioglugil O, Scardino PT. Screening for prostate cancer: an analysis of the early experience. [Review] [52 refs]. *CA: a Cancer Journal for Clinicians* 1995; 45(3):134-147.

182. Small EJ. Prostate cancer: who to screen, and what the results mean. [Review] [16 refs]. *Geriatrics* 1935; 48(12):28-30.

183. Smith DS, Humphrey PA, Catalona WJ. The early detection of prostate carcinoma with prostate specific antigen: the Washington University experience. *Cancer* 1997; 80(9):1852-1856.

184. Song JM, Kim CB, Chung HC, Kane RL. Prostate-specific antigen, digital rectal examination and transrectal ultrasonography: a meta-analysis for this diagnostic triad of prostate cancer in symptomatic korean men. *Yonsei Medical Journal* 2005; 46(3):414-424.

185. Spencer JA, Alexander AA, Gomella L, Matteucci T, Goldberg BB. Clinical and US findings in prostate cancer: patients with normal prostate-specific antigen levels. *Radiology* 1993; 189(2):389-393.

186. Stenman UH, Hakama M, Knekt P, Aromaa A, Teppo L, Leinonen J. Serum concentrations of prostate specific antigen and its complex with alpha 1-antichymotrypsin before diagnosis of prostate cancer. *Lancet* 1994; 344(8937):1594-1598.

187. Stone NN, DeAntoni EP, Crawford FD. Screening for prostate cancer by digital rectal examination and prostate- specific antigen: Results of Prostate Cancer Awareness Week, 1989-1992. *Urology* 1994; 44(6 SUPPL.):18-25.

188. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter.[Erratum appears in N Engl J Med. 2004 Sep 30;351(14):1470]. *New England Journal of Medicine* 2004; 350(22):2239-2246.

189. Thompson IM, Ankerst DP, Chi C, Lucia MS, Goodman PJ, Crowley JJ et al. Operating characteristics of prostate-specific antigen in men with an initial PSA level of 3.0 ng/ml or lower. *JAMA* 2005; 294(1):66-70.

190. Thompson IM, Chi C, Ankerst DP, Goodman PJ, Tangen CM, Lippman SM et al. Effect of finasteride on the sensitivity of PSA for detecting prostate cancer. *J Natl Cancer Inst* 2006; 98(16):1128-1133. (a)

191. Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, Lucia MS et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. *Journal of the National Cancer Institute* 2006; 98(8):529-534. (b)

192. Tornblom M, Norming U, Adolfsson J, Becker C, Abrahamsson PA, Lilja H et al. Diagnostic value of percent free prostate-specific antigen: retrospective analysis of a population-based screening study with emphasis on men with PSA levels less than 3.0 ng/mL. *Urology* 1999; 53(5):945-950.

193. Uchida K, Takeshima H, Akaza H, Ono Y. Screening for prostate cancer using prostate-specific antigen alone as a first-line checkup parameter: results of the health checkup system. *Japanese Journal of Clinical Oncology* 2000; 30(2):95-100.

194. Van Cangh PJ, De NP, De VL, Sauvage P, Tombal B, Lorge F et al. Free to total prostate-specific antigen (PSA) ratio improves the discrimination between prostate cancer and benign prostatic hyperplasia (BPH) in the diagnostic gray zone of 1.8 to 10 ng/mL total PSA. *Urology* 1996; 48(6A Suppl):67-70.

195. van den Bergh RC, Roobol MJ, Wolters T, van Leeuwen PJ, Schroder FH. The Prostate Cancer Prevention Trial and European Randomized Study of Screening for Prostate Cancer risk calculators indicating a positive prostate biopsy: a comparison. *BJU International* 2008; 102(9):1068-1073.

196. van der Cruijsen-Koeter IW, Vis AN, Roobol MJ, Wildhagen MF, de Koning HJ, van der Kwast TH et al. Comparison of screen detected and clinically diagnosed prostate cancer in the European randomized study of screening for prostate cancer, section rotterdam. *J Urol* 2005; 174(1):121-125.

197. van der Cruijsen-Koeter IW, Roobol MJ, Wildhagen MF, van der Kwast TH, Kirkels WJ, Schroder FH. Tumor characteristics and prognostic factors in two subsequent screening rounds with four-year interval within prostate cancer screening trial, ERSPC Rotterdam. *Urology* 2006; 68(3):615-620.

198. van Vugt HA, Roobol MJ, Kranse R, Maattanen L, Finne P, Hugosson J et al. Prediction of prostate cancer in unscreened men: external validation of a risk calculator. *European Journal of Cancer* 2011; 47(6):903-909.

199. van Vugt HA, Kranse R, Steyerberg EW, van der Poel HG, Busstra M, Kil P et al. Prospective validation of a risk calculator which calculates the probability of a positive prostate biopsy in a contemporary clinical cohort. *European Journal of Cancer* 2012; 48(12):1809-1815.

200. Vickers AJ, Sjoberg D, Ankerst DP, Tangen CM, Goodman PJ, Thompson IM. The prostate cancer prevention trial (PCPT) risk calculator and the relationship between PSA and biopsy outcome. *J Urol* 2012; 187(4):e492-e493.

201. Vis AN, Hoedemaeker RF, Roobol M, van der Kwast TH, Schroder FH. Tumor characteristics in screening for prostate cancer with and without rectal examination as an initial screening test at low PSA (0.0-3.9 ng/ml). *Prostate* 2001; 47(4):252-261.

202. Vis AN, Kranse R, Roobol M, van der Kwast TH, Schroder FH. Serendipity in detecting disease in low prostate-specific antigen ranges. *BJU International* 2002; 89(4):384-389.

203. Walz J, Haese A, Scattoni V, Steuber T, Chun FK, Briganti A et al. Percent free prostate-specific antigen (PSA) is an accurate predictor of prostate cancer risk in men with serum PSA 2.5 ng/mL and lower. *Cancer* 2008; 113(10):2695-2703.

204. Weinmann S, Richert-Boe KE, Van Den Eeden SK, Enger SM, Rybicki BA, Shapiro JA et al. Screening by prostate-specific antigen and digital rectal examination in relation to prostate cancer mortality: a case-control study.[Erratum appears in Epidemiology. 2005 Jul;16(4):515]. *Epidemiology* 2005; 16(3):367-376.

205. Yamamoto M, Hibi H, Miyake K. Role of prostate-specific antigen and digital rectal examination in the detection of prostate cancer. *International Journal of Urology* 1994; 1(1):74-77.

206. Yamamoto T, Ito K, Ohi M, Kubota Y, Suzuki K, Fukabori Y et al. Diagnostic significance of digital rectal examination and transrectal ultrasonography in men with prostate-specific antigen levels of 4 NG/ML or less. *Urology* 2001; 58(6):994-998.

207. Yu HJ, Lai MK. The usefulness of prostate-specific antigen (PSA) density in patients with intermediate serum PSA level in a country with low incidence of prostate cancer. *Urology* 1998; 51(5A:Suppl):Suppl-30.

Systematic review report for question 5

Clinical Question 5: "*What age or health status criteria should be used to identify men who would be unlikely to live long enough to benefit from PSA testing and who, in consequence, would not be offered PSA testing?"*

PICO 5: *For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer how many years after the start of PSA testing is the benefit of PSA testing apparent?*

Population	Intervention	Comparator	Outcomes
Men without a prior history of prostate cancer or symptoms that might indicate prostate cancer	PSA testing strategy with or without digital rectal examination (DRE)	No PSA testing	Time until reduction in prostate cancer mortality as a result of PSA testing is apparent

1. Methods

1.1. Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption guidelines had to be evidence based and meet the pre-specified criteria of scores of greater or equal to 70% for the domains rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

1.2. Literature Search

The systematic review for this question drew on the results of the literature searches for the PICO:

For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what PSA testing strategies with or without DRE compared to no PSA testing or other PSA testing strategies reduce prostate cancer-specific mortality or the incidence of metastases at diagnosis?

These literature searches identified trials comparing the effects of prostate cancer testing with no testing on prostate cancer mortality.

In brief, systematic reviews published up until 2013 and identified by the NHMRC systematic review (National Health and Medical Research Council 2013) were used to identify relevant trials published up until 2012, and Medline, Embase and CENTRAL databases were searched for relevant randomised controlled trials published from 2012 onwards. In each database prostate cancer search terms were coupled with search terms for PSA testing or screening and randomised controlled trial filters. To identify studies that considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI

peoples. A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles before 1st March 2014 which were either published after the initial search was completed and/or added to the relevant database after the search was completed. Alerts were checked until July 2014. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched regularly up until April 2014 for relevant reviews published after the initial search. Reference lists of all relevant articles were checked for potential additional articles.

The trials identified by this search that showed a reduction in prostate cancer mortality with PSA testing were included in this systematic review.

1.3. Inclusion Criteria

Selection criteria	**Inclusion criteria**
Study type	Intervention
Study design	Randomised or pseudo-randomised controlled trials demonstrating a reduction in prostate cancer mortality as a result of PSA testing when compared with no testing^
Population	Men without a prior history of prostate cancer or symptoms that might indicate prostate cancer
Intervention	PSA testing with or without digital rectal examination (DRE)
Comparator	No PSA testing
Outcomes	Time until reduction in prostate cancer mortality as a result of PSA testing is apparent
Language	English
Publication period	After 31st December 1989 and before1st March 2014

^ There is an inevitable delay between the application of a test to detect cancer early and any reduction in cancer mortality as a consequence of the test. As a result testing people with a life expectancy less than the time it takes for a reduction in cancer mortality associated with the test to become apparent will offer no benefit and may expose them to short-term harms that flow from the test. Therefore, to identify those unlikely to live long enough to benefit from PSA testing, this review examines the trials in which PSA testing reduced prostate cancer mortality to determine when this benefit is first apparent, and is, in consequence, restricted to studies that showed a reduction in prostate cancer mortality with PSA testing.

Conference proceedings identified by the search literature searches were included if they met the inclusion criteria.

References

National Health and Medical Research Council (2013). *Prostate-Specific Antigen (PSA) testing in asymptomatic men: Evidence Evaluation Report.* Canberra: National Health and Medical Research Council. Published July 2013

2. Results

2.1. Guidelines

Ten guidelines were identified that contained potentially relevant recommendations as to which men should not be tested for prostate cancer. These recommendations were not adopted as they either were not based on a systematic review or did not meet the pre-specified AGREE II criteria for adoption. These guidelines and the reasons why they were not adopted are listed in Appendix C.

The Royal College of Pathologists of Australasia noted in its consensus-based position statements regarding PSA testing (http://www.rcpa.edu.au/Library/College-Policies/Position-Statements/Prostate-Specific-Antigen-Testing-Age-related-inte, accessed 20/10/14) that "*PSA testing has no proven value in the management of prostate cancer in men over the age of 70 years when men of these ages often have co-morbidities that are likely to be of greater clinical significance than the risk of prostate cancer*."

In 2013 at the Prostate Cancer World Congress in Melbourne a consensus statement was issued by a group of leading prostate cancer experts from around the world as part of the Melbourne Consensus Statement (Murphy al., (2013) The Melbourne Consensus Statement on the early detection of prostate cancer. *BJU International* **113:**186-188):
"Older men in good health with a > 10-year life expectancy should not be denied PSA testing based on their age"

2.2. Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the current systematic review. The NHMRC systematic review identified 5 "good" systematic reviews. These systematic reviews identified 21 potentially relevant articles for retrieval.

The Medline search from 2012 onwards identified 116 citations, the Embase search from 2012 onwards 216 citations, the CENTRAL search from 2012 onwards 12 citations and the search of the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases identified an additional 15 potentially relevant citations, resulting in a total of 359 citations. Titles and abstracts were examined and 5 additional articles were retrieved for a more detailed evaluation. A further additional potential citation was identified from the reference list of retrieved articles.

One trial, a population–based screening trial reported in 4 articles met the inclusion criteria and was included in the current review. There were no studies of ATSI men that met the inclusion criteria.

The retrieved articles that were not included and the reason for their exclusion are documented in Appendix C. In summary, the main reasons for exclusion were reduction in prostate cancer mortality as a result of testing for prostate cancer not found, no relevant outcomes reported and no comparative data reported.

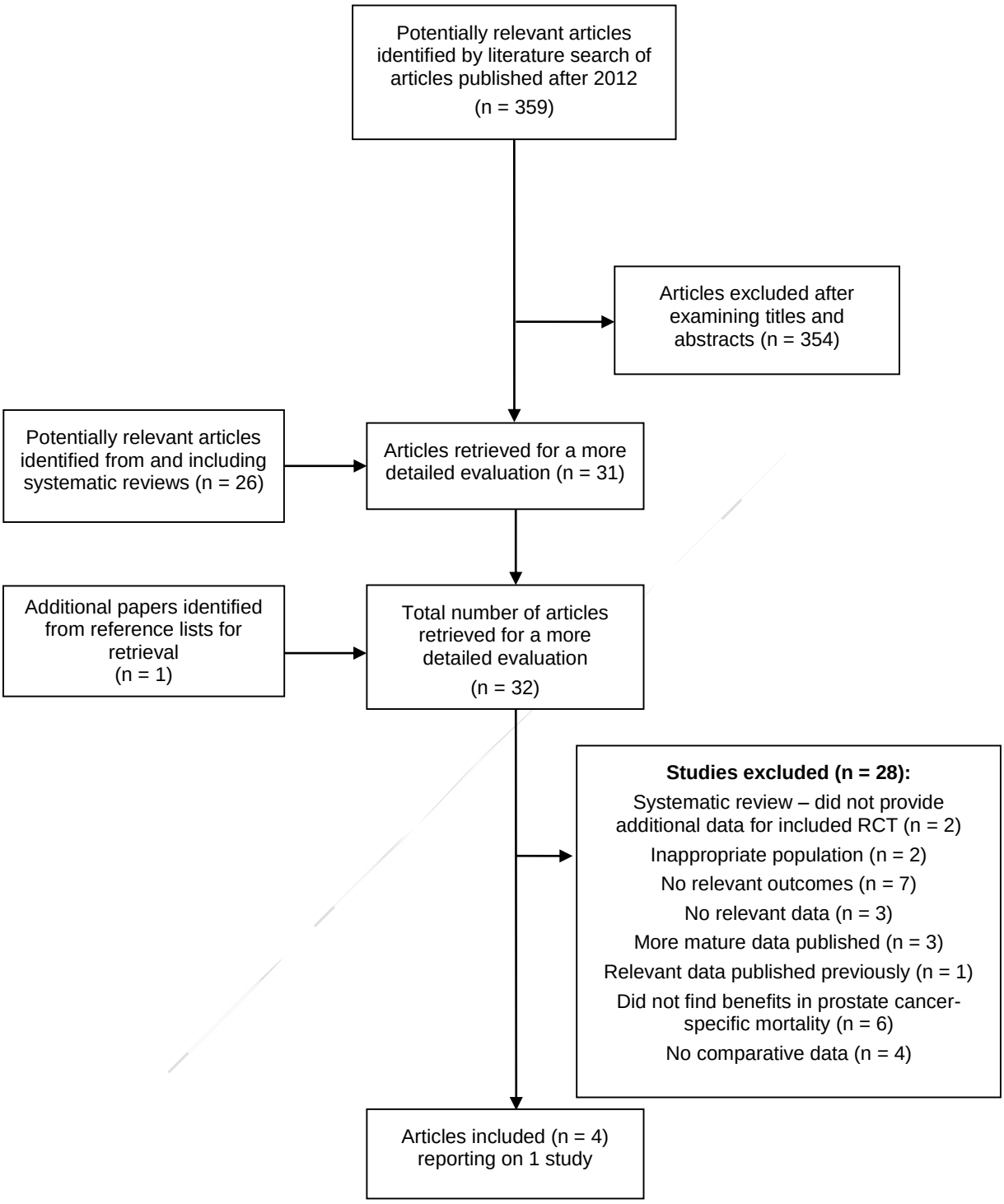


Figure 1. Process of inclusion and exclusion of studies

2.3. Study Characteristics

Characteristics of included studies are described in Table 1.

Table 1: Characteristics of studies examining PSA testing strategies ± DRE compared to no PSA testing that showed a significant reduction in prostate cancer-specific mortality with PSA testing

Study	Design	Participants	Intervention	Comparison	Relevant Outcomes	Comments
The European Randomised Study of Screening for Prostate Cancer (ERSPC) Schroder 2012, Grenabo Bergdahl 2013, Hugosson 2010, Roobol 2013, (The Netherlands, Belgium, Sweden, Finland, Italy, Spain and Switzerland) *ISRCTN49127736*	RCT	Men aged 50 – 74 years with no previous personal history of prostate cancer identified from population registries **N = 182,160** Core age group: 55 – 69 years old Median age = 60.1 years **N = 162,388**	Invited to screening for prostate cancer Different screening protocols in different countries Screened at 4 year intervals until age 75 (5/7 countries) PSA test only (5/7 countries) Sextant biopsy recommended for all men with positive test; lateralised sextant biopsies from June 1996 82.6% screened at least once **N = 72,891** Diagnosed with prostate cancer N = 6,963 63.6% surgery or radiotherapy 23.0% watchful waiting 8.8% ADT only as primary treatment	Not invited to screening for prostate cancer **N = 89,352** 39.6% underwent one or more PSA test in the period after randomisation until end of 2008 (Rotterdam cohort only) Diagnosed with prostate cancer N = 5,396 59.2% surgery or radiotherapy 16.0% watchful waiting 19.6% ADT only as primary treatments	**Primary outcome:** Prostate cancer-specific mortality, prostate cancer death if clinical evidence of metastatic disease in absence of unrelated cause of death - determined by examining medical records of all men diagnosed with prostate cancer (even at autopsy) who had died regardless of official cause of death, or after validation, on the basis of official causes of death **Prostate cancer-specific mortality RR (95% CI):** • Core age group **0.79 (0.68 – 0.91)** • Entire group aged 50 – 74 years **0.83 (0.72 – 0.94)** Median follow-up = 11.0 years (2009)	Follow-up till 31/12/2008 Unclear as to whether centralised randomisation at all centres Study powered for analysis of core age group 85.9% of men with positive test underwent biopsy Authors state little difference in treatments for prostate cancer per arm after adjustment for disease stage, tumour grade or age Contamination data only available for a portion of Rotterdam cohort

The Netherlands (Rotterdam) centre				
Men aged 55 – 74 years without any previous prostate cancer diagnosis randomised after consent given between 1993 and 2000 **N = 41,902** Core age group 55 – 69 years old Median age = 61.7 years **N = 34,833**	*<u>1993 – 1995</u>* PSA + DRE + TRUS PSA cut-off ≥ **4ng/mL** *<u>1995 – 1997</u>* PSA (Hybritech Tandem-E) only PSA cut-off ≥ **4ng/mL** PSA 1.0 – 3.9ng/mL = DRE + TRUS *<u>1997 onwards</u>* **PSA** only PSA cut-off ≥ **3ng/mL** Test interval = **4 years** Sextant biopsy 1993 – 1996 screen one year after benign biopsy Men screened until 75 years of age **N = 17,443** 94.6% screened at least once	Not offered testing **N = 17,390**	Study database linked to Dutch Cancer Registry and Statistics Netherlands databases yearly **Prostate cancer-specific mortality** for core age group at 13 years of follow-up RR (95% CI) = **0.68 (0.53 – 0.89)** Cumulative hazard for prostate cancer of the entire cohort aged 55 – 74 years RR (95% CI) = **0.80 (0.65 – 0.99)** Median follow-up = 12.8 years (2013)	Not designed as stand-alone trial Centralised randomisation Prostatectomy first treatment option for localised disease in screening and control arms GPs encouraged to refer men with positive biopsy to regional urology centres (whether intervention or control) 89.8% of men with positive test underwent biopsy

	Sweden (Goteborg) centre				
	Men aged 50 – 65 years without any previous prostate cancer diagnosis identified from population registries randomised on 31/12/1994 before consent given Median age = 56 years **N = 19,904** Core age group 55 – 69 years old Median age = 59.7 years **N = 11,852**	**PSA only** PSA cut-off: *1995 – 1998* **≥ 3.0/3.4ng/mL** (using Prostatus assay/WHO calibrated value) *1999 – 2004* PSA cut-off **≥ 2.9 ng/mL** (WHO calibration) *2005 onwards* **≥ 2.5 ng/mL** (WHO calibration) Test interval = **2 years** Above cut-off: further examination by urologist including DRE, TRUS and laterally-directed sextant biopsy Men with PIN or ASAP re-biopsied until screening round 5 Only men with PSA ≥1.0ng/mL on second screen invited to undergo third screen Men with PSA ≥ 7ng/mL PSA tested 6 months later at screening rounds 1 & 2 Men screened until 70 years of age **N = 9,952** (50-69 years old) **N = 5,901** (core age group) 76.0% screened at least once	Received a letter in 1995 stating they belonged to a control group for a cancer study **N = 9,952** (50-69 years old) **N = 5,951** (core age group)	Deaths ascertained by linkage with National Population Register 4 times a years **Prostate cancer-specific mortality** for core age group at 14 years of follow-up RR (95% CI) = **0.56 (0.38 – 0.83)** Cumulative hazard for prostate cancer of the entire cohort aged 50 – 69 years at 14 years of follow-up RR (95% CI) = **0.56 (0.39 – 0.82)** Median follow-up = 14.0 years for core age group	78% of entire cohort reached the maximum follow-up period of 14 years Last date of follow-up was date of death or emigration or 31st December 2008 86.6% of men in core group and 93% of entire cohort with positive test underwent biopsy Men not previously exposed to screening

ADT = androgen deprivation therapy; ASAP = atypical small acinar proliferation; DRE = digital rectal examination; ERSPC = the European Randomised Study of Screening for Prostate Cancer; PIN = prostatic intraepithelial neoplasia; PSA = prostate specific antigen; RCT = randomised controlled trial; TRUS = transrectal ultrasonography of the prostate; WHO = World Health Organisation

2.4. Study Quality

Methodological quality of included randomised controlled trials is described in Tables 2 – 3.

Table 2: Methodological quality of included randomised controlled trials (n = 4)

Quality Category	N (%)
I. Was the study double-blinded?	
2 = Reasonably certain double-blind (e.g. identical placebo)	0 (0)
1 = Single-blind, objective outcomes	3 (75.0)
0 = Not blinded, not reported	1 (25.0)
II. Concealment of treatment allocation schedule	
2 = Adequately concealed (e.g. central randomisation)	3 (75.0)
1 = Inadequately concealed (e.g. sealed envelopes)	1 (25.0)
0 = No concealment, not reported	0 (0)
III. Inclusion of all randomised participants in analysis of majority of outcomes (i.e. ITT)	
2 = No exclusions, survival analysis used	4 (100)
1 = Exclusions not likely to cause bias	0 (0)
0 = Too many exclusions, not reported	0 (0)
IV. Generation of allocation sequences	
1 = Adequate (e.g. computer random number generator)	4 (100)
0 = Inadequate, not reported	0 (0)

ITT = intention-to-treat

Table 3: Methodological quality of included RCT (4 publications, 1 trial)

	Blinding	Allocation concealment	Inclusion of all participants (ITT)	Generation of allocation sequence*	**Overall Rating**	**Risk of bias**
Grenabo Bergdahl 2013	0	2	2	1	**Low**	**High**
Hugosson 2010	1	2	2	1	**Medium**	**Moderate**
Roobol 2013	1	2	2	1	**Medium**	**Moderate**
Schroder 2012	1	1	2	1	**Medium**	**Moderate**

* Not considered when calculating the overall evidence quality rating - Generation of allocation sequences was assessed to ensure trials were truly randomized and not pseudo-randomized and thus was not included in the overall risk of bias

ITT = intention-to-treat

Key to overall quality rating
High quality: a study that received 2 for three main criteria (double-blinding, concealment of treatment allocation schedule, inclusion of all randomised participants in analysis (i.e. ITT))
Medium quality: received 2 and/or 1 for all three main criteria
Low quality: received 0 for all three criteria or 0 and 1 for all three criteria or received 0 for any of the three criteria

2.5. Study Results

Table 4: Results of RCTs examining PSA testing strategies ± DRE compared to no PSA testing that showed a significant reduction in prostate cancer-specific mortality with PSA testing

Study	Outcome	N	Intervention	Control	p value	RR (95% CI)	Follow-up duration
ERSPC Schroder 2012, Roobol 2013, Hugosson 2010, Grenabo Bergdahl 2013	**Prostate cancer-specific mortality**						
	Overall – all centres – men aged 55-69 years at randomisation						
	Deaths per 10,000 person-years						
	1 – 7 years follow-up	NR	2.4	2.6	0.53	0.92 (0.73 – 1.18)†	
	8 – 9 years follow-up	NR	5.8	7.8	0.04	0.74 (0.55 – 0.99)[1,2]	
	10 – 11 years follow-up	NR	5.7	9.2	0.003	0.62 (0.45 – 0.85)[1,2]	
	≥ 12 years follow-up	NR	9.4	11.6	0.21	0.80 (0.56 – 1.13)[1,2]	
	1 – 9 years follow-up	NR	3.1	3.7	0.09	0.85 (0.71 – 1.03)[1,2]	
	1 – 11 years follow-up	NR	3.5	4.4	0.003	0.79 (0.67 – 0.92)[1,2]	
	Cumulative hazard estimates[4]						Median
	Time from randomisation until screening and control arm estimates start to diverge	162,243				~ 7 years*	11 years
	The Netherlands (Rotterdam) centre						
	Time from randomisation until screening and control arm estimates start to diverge						
	Prostate cancer mortality cumulative hazard estimates[4]						Median
	Men aged 55 – 74 years at randomisation	41,902				~ 7 years*	12.8 years
	Men aged 55 – 69 years at randomisation	34,833				~ 6 years*	
	Sweden (Goteborg) centre						
	Time from randomisation until screening and control arm estimates start to diverge	19,904				~ 7 years*	Median 14 years
	Prostate cancer mortality cumulative hazard estimates[4] – men aged 50 – 69 years at randomisation						

Prostate cancer-specific mortality: *deaths per 10,000 person-years* ***from end of screening***	13,423				
Subgroup analysis - Men without prostate cancer at end of screening period -					
3 – 6 years after end of screening	17	36	NS	0.43[3] 0.47 (0.17 – 1.20)‡	Medians 4.8 & 4.9 years after end of screening
6 – 9 years after end of screening	29	56	NS	0.46[3] 0.51 (0.18 – 1.33)‡	
9 – 12 years after end of screening	62	46	NS	1.2[3]1.35 (0.39 – 4.78)‡	

CI = confidence interval; ERSPC = the European Randomised Study of Screening for Prostate Cancer; NR = not reported; NS = not statistically significantly different; RR = relative risk;

* Estimated by the systematic review team from published graphs
† Calculated by the systematic review team from data in Table 3 of Schroder et al 2013 using WinPepi (http://www.brixtonhealth.com/pepi4windows.html). Mid-P confidence intervals were chosen.
‡ Calculated by the systematic review team from data in Table 3 of Grenabo Bergdahl et al 2013 using WinPepi (http://www.brixtonhealth.com/pepi4windows.html). Mid-P confidence intervals were chosen.

~ Approximately
[1] Poisson regression analysis used to calculate rate ratios
[2] Adjusted according to centre
[3] Fine and Grey competing risk analysis
[4] Nelson-Aalen method

2.5 Body of Evidence

I Prostate cancer-specific mortality at times after randomisation

Name of study	Study type	N	Level of evidence *	Quality of evidence **	Risk of bias	Results summary	Size of effect (RR)	p value	95% CI	Relevance of evidence*
ERSPC **(Overall)** *Schroder 2012*	RCT	162,243	II	Medium	Moderate	**Prostate cancer-specific mortality** ***Deaths per 10,000 person-years*** Men aged 55-69 years at randomisation 1 – 7 years follow-up S: 2.4 C: 2.6 1 – 9 years follow-up S: 3.1 C: 3.7 8 – 9 years follow-up S: 5.8 C: 7.8 10 – 11 years follow-up S: 5.7 C: 9.2 1 – 11 years follow-up S: 3.5 C: 4.4 ≥ 12 years follow-up S: 9.4 C: 11.6 ***Cumulative hazard estimates*** [1] Time from randomisation until screening and control arm estimates start to diverge Men aged 55 – 69 years at randomisation ~ 7 years	0.92 0.85 0.74 0.62 0.79 0.80	NS NS 0.04 0.003 0.003 NS	0.73 – 1.18 0.71 – 1.03 0.55 – 0.99 0.45 – 0.85 0.67 – 0.92 0.56 – 1.13	1
ERSPC **The Netherlands (Rotterdam)** *Roobol 2013*	RCT	34,833 41,902	II	Medium	Moderate	Time from randomisation until screening and control arm estimates start to diverge Men aged 55 – 69 years at randomisation ~ 6 years Men aged 55 – 74 years at randomisation ~ 7 years				1
ERSPC **Sweden (Goteborg)** *Hugosson 2010*	RCT	19,904	II	Medium	Moderate	Time from randomisation until screening and control arm estimates start to diverge Men aged 50 – 69 years at randomisation ~ 7 years				1

Subgroup	13,423	Low	High	**Deaths per 10,000 person-years**		**RR**	**p value**	**95% CI**	
Men without prostate cancer at end of screening period				3 – 6 years after end of screening	S: 17 C: 36	0.43	NS	0.17 – 1.20	
						0.47			
				6 – 9 years after end of screening	S: 29 C: 56	0.46	NS	0.18 – 1.33	1
Grenabo Bergdahl 2013						0.51			
				9 – 12 years after end of screening	S: 62 C: 46	1.2	NS	0.39 – 4.78	
						1.35			

C = control group; CI = confidence interval; ERSPC = the European Randomised Study of Screening for Prostate Cancer; NS = not statistically significantly different; RCT = randomised controlled trial; RR = relative risk; S = screening group

**Refer to Appendix B for detailed explanations of rating scores; ** see Tables 2 – 3 for quality appraisals*

~ Approximately
[1] Nelson- Aalen method

Clinical significance of size of effect is addressed in the assessment of clinical impact in the NHMRC evidence statement form.

References: Included studies

1. Grenabo Bergdahl A, Holmberg E, Moss S, Hugosson J. Incidence of prostate cancer after termination of screening in a population-based randomised screening trial. Eur Urol 2013; 64(5):703-709.

2. Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. Lancet Oncol 2010; 11(8):725-732.

3. Roobol MJ, Kranse R, Bangma CH, Van Leenders AGJL, Blijenberg BG, Van Schaik RHN et al. Screening for prostate cancer: Results of the Rotterdam section of the European randomized study of screening for prostate cancer. Eur Urol 2013; 64(4):530-539.

4. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012; 366(11):981-990.

3. Appendices

Appendix A: Search strategies used

For Medline database:

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	Prostate-Specific Antigen/
5	prostate specific antigen.tw,mp.
6	psa.tw,mp.
7	4 or 5 or 6
8	exp mass screening/
9	"early detection of cancer"/
10	screen$.mp,tw.
11	8 or 9 or 10
12	clinical trial.pt.
13	random$.mp.
14	((single or double) adj3 (blind$ or mask$)).mp,tw.
15	placebo$.mp,tw.
16	12 or 13 or 14 or 15
17	3 and 7 and 11 and 16
18	limit 17 to (english language and humans and yr="2012-current")

Modification of search strategies used by Ilic et al 2013. Cochrane Database of Systematic Reviews. Issue 1. Art. No.: CD004720 and National Health and Medical Research Council (2013b). Prostate-Specific Antigen (PSA) testing in asymptomatic men: Technical Report. Canberra: National Health and Medical Research Council.

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database:

#	Searches
1	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neopla* OR metast* OR adeno*)
2	'prostate cancer'/exp
3	1 OR 2
4	'prostate specific antigen'/exp
5	'prostate specific antigen':de,ab,ti OR psa:de,ab,ti
6	'prostate specific antigen' OR psa
7	4 OR 5 OR 6
8	'mass screening'/exp
9	'screening test'/exp
10	'early diagnosis'/exp
11	screen*
12	8 OR 9 OR 10 OR 11
13	'clinical trial'
14	'clinical trial':de
15	random*
16	random*:ab,ti
17	(single OR double) NEAR/3 (blind* OR mask*)
18	((single OR double) NEAR/3 (blind* OR mask*)):ab,ti
19	placebo*
20	placebo:ab,ti
21	13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20
22	[embase]/lim AND [2012-2014]/py AND [english]/lim AND [humans]/lim
23	3 AND 7 AND 12 AND 21 AND 22

Modification of search strategies used by Ilic et al 2013. Cochrane Database of Systematic Reviews. Issue 1. Art. No.: CD004720 and National Health and Medical Research Council (2013b). Prostate-Specific Antigen (PSA) testing in asymptomatic men: Technical Report. Canberra: National Health and Medical Research Council.

ATSI search terms used

#	Searches
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

For CENTRAL database:

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	Prostate-Specific Antigen/
5	prostate specific antigen.tw,mp.
6	psa.tw,mp.
7	4 or 5 or 6
8	exp mass screening/
9	"early detection of cancer"/
10	screen$.mp,tw.
11	8 or 9 or 10
12	clinical trial.pt.
13	random$.mp.
14	((single or double) adj3 (blind$ or mask$)).mp,tw.
15	placebo$.mp,tw.
16	12 or 13 or 14 or 15
17	3 and 7 and 11 and 16
18	limit 17 to (yr="2012-current")

Modification of search strategies used by Ilic et al 2013. Cochrane Database of Systematic Reviews. Issue 1. Art. No.: CD004720 and National Health and Medical Research Council (2013b).

For Cochrane Database of Systematic Reviews – The Cochrane Library:
Title, abstracts, keywords: “prostate”

For Database of Abstracts of Reviews of Effects and Health Technology Assessment database (via OvidSP):

#	Searches
1	exp Prostatic Neoplasms/
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
3	1 or 2

Appendix B:

Level of Evidence rating criteria – Intervention studies

Level	Study design
I	Meta-analysis or a systematic review of level II studies
II	Randomised controlled trial or a phase III/IV clinical trial
III-1	Pseudo-randomised controlled trial or a meta-analysis/systematic review of level III-1 studies
III-2	Comparative study with concurrent controls: - Phase II clinical trial - Non-randomised, experimental trial9 - Controlled pre-test/post-test study - Adjusted indirect comparisons - Interrupted time series with a control group - Cohort study - Case-control study or a meta-analysis/systematic review of level III-2 studies
III-3	A comparative study without concurrent controls: - Phase I clinical trial - Historical control study - Two or more single arm study10 - Unadjusted indirect comparisons - Interrupted time series without a parallel control group or a meta-analysis/systematic review of level III-3 studies
IV	Case series with either post-test or pre-test/post-test outcomes or a meta-analysis/systematic review of level IV studies

According to the standards of the National Health and Medical Research Council

Relevance of the Evidence

Rating	Relevance
1	Evidence of an effect on patient-relevant clinical outcomes including benefits and harms, quality of life and survival.
2	Evidence of an effect on a surrogate outcome* that has been shown to be predictive of patient-relevant outcomes for the same intervention.
3	Evidence of an effect on proven surrogate outcomes but for a different intervention.
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population.
5	Evidence confined to unproven surrogate outcomes.

**'surrogate outcome' refers to reasonable indicators of whether there has been some effect (e.g. blood pressure measurements or levels of serum cholesterol)*

Points for considering patient-relevant outcomes:
i) The goal of decision making in health care is to choose the intervention(s) (which may include doing nothing) that is (are) most likely to deliver the outcomes that patients find desirable.
ii) Surrogate outcomes (such as blood pressure measurements or levels of serum cholesterol) may be reasonable indicators of whether there has been some effect. However, they should not be the basis for clinical decisions unless they reliably predict an effect on the way the patient feels, otherwise they will not be of interest to the patient or their carers.
iii) All possible outcomes that are of most interest to patients (particularly harms) should be identified and evaluated.

Adapted from table 1.10 of: National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra: NHMRC; 2000. http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp69.pdf

Appendix C:

Potentially relevant guidelines identified and reason why not adopted

Year	Organisation	Title	Reason why not adopted
2010	American Cancer Society	American Cancer Society Guideline for the Early Detection of Prostate Cancer	Did not meet pre-specified AGREE II criteria for adoption
2008	American College of Preventive Medicine	Screening for Prostate Cancer in U.S. Men: ACPM Position Statement on Preventive Practice	Did not meet pre-specified AGREE II criteria for adoption
2013	American College of Physicians	Screening for prostate cancer – guidance statement	Did not meet pre-specified AGREE II criteria for adoption
2012	American Society of Clinical Oncology	Screening for Prostate Cancer with Prostate-Specific Antigen Testing: American Society of Clinical Oncology Provisional Clinical Opinion	Did not meet pre-specified AGREE II criteria for adoption
2013	American Urological Association	Early Detection of Prostate Cancer: AUA Guideline	Did not meet pre-specified AGREE II criteria for inclusion
2013	European Association of Urology	Guidelines on Prostate Cancer	Did not meet pre-specified AGREE II criteria for inclusion
2013	European Society for Medical Oncology	ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Consensus based
2013	Prostate Cancer World Congress	Melbourne Consensus Statement on Prostate Cancer Testing	Consensus based
2012	Royal College of Pathologists of Australasia	Prostate specific antigen testing: Age-related interpretation in early prostate cancer detection	Consensus based
2012	University of Michigan Health System	Cancer Screening	Did not meet pre-specified AGREE II criteria for adoption

Excluded Studies

Study	Reason for Exclusion
Andriole 2005	No comparative data
Andriole 2009	Did not find benefits in prostate cancer-specific mortality
Andriole 2012	Did not find benefits in prostate cancer-specific mortality
Aus 2006	No relevant outcomes
Bergdahl 2009	No comparative data
Bokhorst 2014	Relevant data previously published
Carlsson 2011	Inappropriate population
Djulbegovic 2010	No relevant data
Ilic 2013	No relevant data
Johnson 2006	No relevant outcomes
Kerkhof 2010	More mature data published
Kilpelainen 2010	No relevant outcomes
Kilpelainen 2011	No relevant outcomes
Kilpelainen 2013	Did not find benefits in prostate cancer-specific mortality
Kjellman 2009	Did not find benefits in prostate cancer-specific mortality
Labrie 2004	Did not find benefits in prostate cancer-specific mortality
Lin 2011	Systematic review – did not provide additional data for included RCTs
Lumen 2012	No relevant data
New Zealand Guidelines Group 2009	Systematic review – did not provide additional data for included RCTs
Pinsky 2012	Inappropriate population
Raaijmakers 2002	No comparative data
Roobol 2009	More mature data published
Sandblom 2004	No relevant outcomes
Sandblom 2011	Did not find benefits in prostate cancer-specific mortality
Schroder 2009	More mature data published
Schroder 2012	No relevant outcomes
Taylor 2004	No relevant outcomes
Zhu 2011	No comparative data

References: Excluded Studies

1. Andriole GL, Levin DL, Crawford ED, Gelmann EP, Pinsky PF, Chia D et al. Prostate Cancer Screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: findings from the initial screening round of a randomized trial. J Natl Cancer Inst 2005; 97(6):433-438.
2. Andriole GL, Crawford ED, Grubb RL, III, Buys SS, Chia D, Church TR et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009; 360(13):1310-1319.
3. Andriole GL, Crawford ED, Grubb RL, III, Buys SS, Chia D, Church TR et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. J Natl Cancer Inst 2012; 104(2):125-132.
4. Aus G, Bergdahl S, Lodding P, Lilja H, Hugosson J. Prostate cancer screening decreases the absolute risk of being diagnosed with advanced prostate cancer--results from a prospective, population-based randomized controlled trial. Eur Urol 2007; 51(3):659-664.
5. Bokhorst LP, Bangma CH, van Leenders GJLH, Lous JJ, Moss SM, Schroder FH et al. Prostate-specific Antigen-Based Prostate Cancer Screening: Reduction of Prostate Cancer Mortality After Correction for Nonattendance and Contamination in the Rotterdam Section of the European Randomized Study of Screening for Prostate Cancer. Eur Urol 2013.
6. Carlsson SV, Holmberg E, Moss SM, Roobol MJ, Schroder FH, Tammela TL et al. No excess mortality after prostate biopsy: results from the European Randomized Study of Screening for Prostate Cancer. BJU Int 2011; 107(12):1912-1917.
7. Djulbegovic M, Beyth RJ, Neuberger MM, Stoffs TL, Vieweg J, Djulbegovic B et al. Screening for prostate cancer: systematic review and meta-analysis of randomised controlled trials. BMJ 2010; 341:c4543.
8. Grenabo Bergdahl A, Aus G, Lilja H, Hugosson J. Risk of dying from prostate cancer in men randomized to screening: differences between attendees and nonattendees. Cancer 2009; 115(24):5672-5679.
9. Ilic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. Cochrane Database Syst Rev 2013; 1:CD004720.
10. Johnson DB. The effects of an abnormal cancer screening test on health related quality of life. International Journal of Cancer Research 2006; 2(3):277-289.
11. Kerkhof M, Roobol MJ, Cuzick J, Sasieni P, Roemeling S, Schroder FH et al. Effect of the correction for noncompliance and contamination on the estimated reduction of metastatic prostate cancer within a randomized screening trial (ERSPC section Rotterdam). Int J Cancer 2010; 127(11):2639-2644.
12. Kilpelainen TP, Tammela TL, Maattanen L, Kujala P, Stenman UH, Ala-Opas M et al. False-positive screening results in the Finnish prostate cancer screening trial. Br J Cancer 2010; 102(3):469-474.
13. Kilpelainen TP, Tammela TL, Roobol M, Hugosson J, Ciatto S, Nelen V et al. False-positive screening results in the European randomized study of screening for prostate cancer. Eur J Cancer 2011; 47(18):2698-2705.
14. Kilpelainen TP, Tammela TL, Malila N, Hakama M, Santti H, Maattanen L et al. Prostate cancer mortality in the Finnish randomized screening trial. Journal of the National Cancer Institute 2013; 105(10):719-725.
15. Kjellman A, Akre O, Norming U, Tornblom M, Gustafsson O. 15-year followup of a population based prostate cancer screening study. J Urol 2009; 181(4):1615-1621.
16. Labrie F, Candas B, Cusan L, Gomez JL, Belanger A, Brousseau G et al. Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. Prostate 2004; 59(3):311-318.
17. Lin K, Croswell JM, Koenig H, Lam C, Maltz A. Prostate-specific antigen-based screening for prostate cancer: an evidence update for the U.S. preventive services task force. Evidence synthesis no.90. 2011. Rockville, MD, Agency for Healthcare Research and Quality. Ref Type: Report

18. Lumen N, Fonteyne V, De MG, Ost P, Villeirs G, Mottrie A et al. Population screening for prostate cancer: an overview of available studies and meta-analysis. Int J Urol 2012; 19(2):100-108.
19. New Zealand Guidelines Group. Cancer control strategy guidance completion: update of evidence for prostate-specific antigen (PSA) testing in asymptomatic men. 2009. Wellington, Ministry of Health. Ref Type: Report
20. Pinsky PF, Black A, Parnes HL, Grubb R, David CE, Miller A et al. Prostate cancer specific survival in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Cancer Epidemiol 2012; 36(6):e401-e406.
21. Raaijmakers R, Kirkels WJ, Roobol MJ, Wildhagen MF, Schrder FH. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. Urology 2002; 60(5):826-830.
22. Roobol MJ, Kerkhof M, Schroder FH, Cuzick J, Sasieni P, Hakama M et al. Prostate cancer mortality reduction by prostate-specific antigen-based screening adjusted for nonattendance and contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). Eur Urol 2009; 56(4):584-591.
23. Sandblom G, Varenhorst E, Lofman O, Rosell J, Carlsson P. Clinical consequences of screening for prostate cancer: 15 years follow-up of a randomised controlled trial in Sweden. Eur Urol 2004; 46(6):717-723.
24. Sandblom G, Varenhorst E, Rosell J, Lofman O, Carlsson P. Randomised prostate cancer screening trial: 20 year follow-up. BMJ 2011; 342:d1539.
25. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009; 360(13):1320-1328.
26. Schroder FH, Hugosson J, Carlsson S, Tammela T, Maattanen L, Auvinen A et al. Screening for prostate cancer decreases the risk of developing metastatic disease: findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC). Eur Urol 2012; 62(5):745-752.
27. Taylor KL, Shelby R, Gelmann E, McGuire C. Quality of life and trial adherence among participants in the prostate, lung, colorectal, and ovarian cancer screening trial. J Natl Cancer Inst 2004; 96(14):1083-1094.
28. Zhu X, van Leeuwen PJ, Bul M, Bangma CH, Roobol MJ, Schroder FH. Identifying and characterizing "escapes"-men who develop metastases or die from prostate cancer despite screening (ERSPC, section Rotterdam). Int J Cancer 2011; 129(12):2847-2854.

Systematic review report for question 6.1a

Clinical Question 6: In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what tests for prostate cancer should be offered in addition to a PSA test?

Candidate tests include:

Free-to-total PSA % (f/tPSA%)

PSA velocity

Prostate health index

Repeated total PSA

PICO Question 6.1:

6.1a: For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring free-to-total PSA percentage improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single total PSA result above 3.0 ng/mL?

6.1b: For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring free-to-total PSA percentage improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL?

This review addresses part (a) of the above PICO -

For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring free-to-total PSA percentage improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single total PSA result above 3.0 ng/mL?

Population	Index Test 1	Index Test 2	Reference standard	Outcomes
Men without prostate cancer diagnosis or symptoms that might indicate prostate cancer	Total PSA > 3.0 ng/mL **or** abnormal f/tPSA% test	Total PSA >3.0 ng/mL only	Prostate biopsy	Diagnostic performance

1. Methods

1.1 Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption guidelines had to be evidence based and meet the pre-specified criteria of scores of greater or equal to 70% for the domains rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

1.2 Literature Search

Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched from 1990 using text terms and, where available, database specific subject headings. Each database was searched for articles dealing with prostate cancer. In Medline and Embase databases the prostate cancer search was combined with a search for free/total PSA ratio. To identify studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples. A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 added to the relevant database after February 2014. Alerts were checked until July 2014. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched regularly up until April 2014 for relevant reviews published after the initial search. Reference lists of all relevant articles were checked for potential additional articles.

1.3 Inclusion and Exclusion Criteria

Selection criteria	**Inclusion criteria**	**Exclusion criteria**
Study type	Diagnostic performance	Predictive accuracy
Study design	Fully paired diagnostic study, or Paired randomised cohort study	Diagnostic case-control or studies of diagnostic yield
Population	Men without prostate cancer diagnosis or symptoms that might indicate prostate cancer, who had undergone prostate biopsy or TURP and at least 80% of those undergoing biopsy had undergone an initial rather than a repeat prostate biopsy	- Included men with prostate cancer or some other urologic disease e.g. bladder cancer or men undergoing a particular treatment e.g. finasteride. - Restricted to men who only had an abnormal DRE and/or abnormal TRUS. - Included men whose cancer status was not based on biopsy or TURP pathology
Index test 1	An abnormal f/tPSA% regardless of total PSA level or an elevated initial total PSA as separate indications for biopsy	- Bloods were drawn for f/t PSA% test after biopsy. - Stated blood not frozen or analysed on the day that was collected or if thawed and refrozen. - Used total PSA thresholds which were greater than 4.0 ng/mL* and not age-specific reference upper limits. - Did not use a commercial total PSA test e.g. Hybritech, Immulite, Abbott, Roche, Bayer or pre 1996 and did not describe tPSA assay used. - Used Chugai, CISbio, Dainippon, Dianon, Eiken E plate or Mitsui gamma-SM-MP f/tPSA %test.
Index test 2	An elevated initial total PSA alone as the indication for biopsy	
Reference standard	Prostate biopsy which included 6 or more cores or TURP	
Indications for biopsy	Include a total PSA level above thresholds of 4.0 ng/mL or less, or age-specific reference upper limits Or an abnormal f/tPSA% result	Indications for biopsy not precisely defined and no subgroup analysis for men with PSA >4.0 ng/mL^
Outcomes	Accuracy relative to using total PSA test alone**:	

	- Additional cancer (true positives) detected. - Additional unnecessary biopsies (false positives). - Additional unnecessary biopsies per additional cancer detected.	
Language	English	
Publication period	After 31st December 1989 and before1st March 2014	

TURP = transurethral resection of the prostate

**Verification bias is a major issue when assessing the diagnostic performance of tests for prostate cancer as men normally do not undergo biopsy unless they are test positive. As a result most studies examining the performance of tests in diagnosing prostate cancer are only able to report numbers of true positives and false positives. Where there is a comparison of two index tests in the same patient and where one index test is purely adding additional test positives to the other index test, as when f/tPSA% is used to test men with PSA levels below the PSA threshold, this data can be used to calculate the difference in true positives and the difference in false positives and the number of additional false positives for each additional cancer detected; findings that will not be subject to verification bias.

^If indications for biopsy not reported assumed that all men with PSA >4.0 ng/mL were offered biopsy due to the elevated total PSA result alone.

*This question focuses on a total PSA threshold of 3.0 ng/mL. However, studies using a total PSA threshold of up to 4.0 ng/mL were also included as the day-to-day biological variability in a man's PSA level of 15% means that, for a man with an average level of 3.0 ng/mL, the levels on consecutive days can be as high as 3.9 ng/mL (upper 95th percentile).

Conference proceedings identified by the search literature searches were included if they met the inclusion criteria.

2. Results

2.1 Guidelines

Two guidelines were identified that contained recommendations regarding free-to-total PSA and prostate cancer detection. These recommnedations were not adopted as they were either consensus based or not based on a systematic review and thus did not meet the pre-specified AGREE II criteria for adoption. These guidelines and the reason why they were not adopted are listed in Appendix C.

In Australia, the Royal College of Pathologists of Australasia has consensus based recommendations regarding the role of percentage free-to-total PSA to improve specificity (http://www.rcpa.edu.au/Library/College-Policies/Position-Statements/Prostate-Specific-Antigen-Testing-Age-related-inte, accessed 20/10/14).

3. Notes regarding follow up PSA testing;

a. A breakdown of how much of the Total PSA is present as Free PSA (e.g. Free to Total PSA ratio) improves the specificity of PSA testing and should be used in confirmatory and follow up testing of men when the initial PSA is above the age related median but not above10 µg/L (which of itself is sufficient to indicate high risk).

2.2 Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the systematic review. The Medline search identified 1,300 citations and the Embase search an additional 1,656 citations. The search of the Cochrane Database of Systematic Reviews 59 citations, the Database of Abstracts of Reviews of Effects 282 citations and the Health Technology Assessment database identified an additional 216 citations, resulting in a total of 3,513 citations. Titles and abstracts were examined and 382 articles were retrieved for a more detailed evaluation.

A total of 4 articles met the inclusion criteria for part A of the PICO and were included in the review. There were no studies of ATSI men that met the inclusion criteria.

The retrieved articles that were not included for part B of the PICO and the reason for their exclusion are documented in Appendix C. In summary, the main reasons for exclusion were inappropriate or unclear indications for biopsy, inappropriate population including studies with participants with elevated total PSA levels (studies that met inclusion criteria for part A of the PICO), and no extractable data.

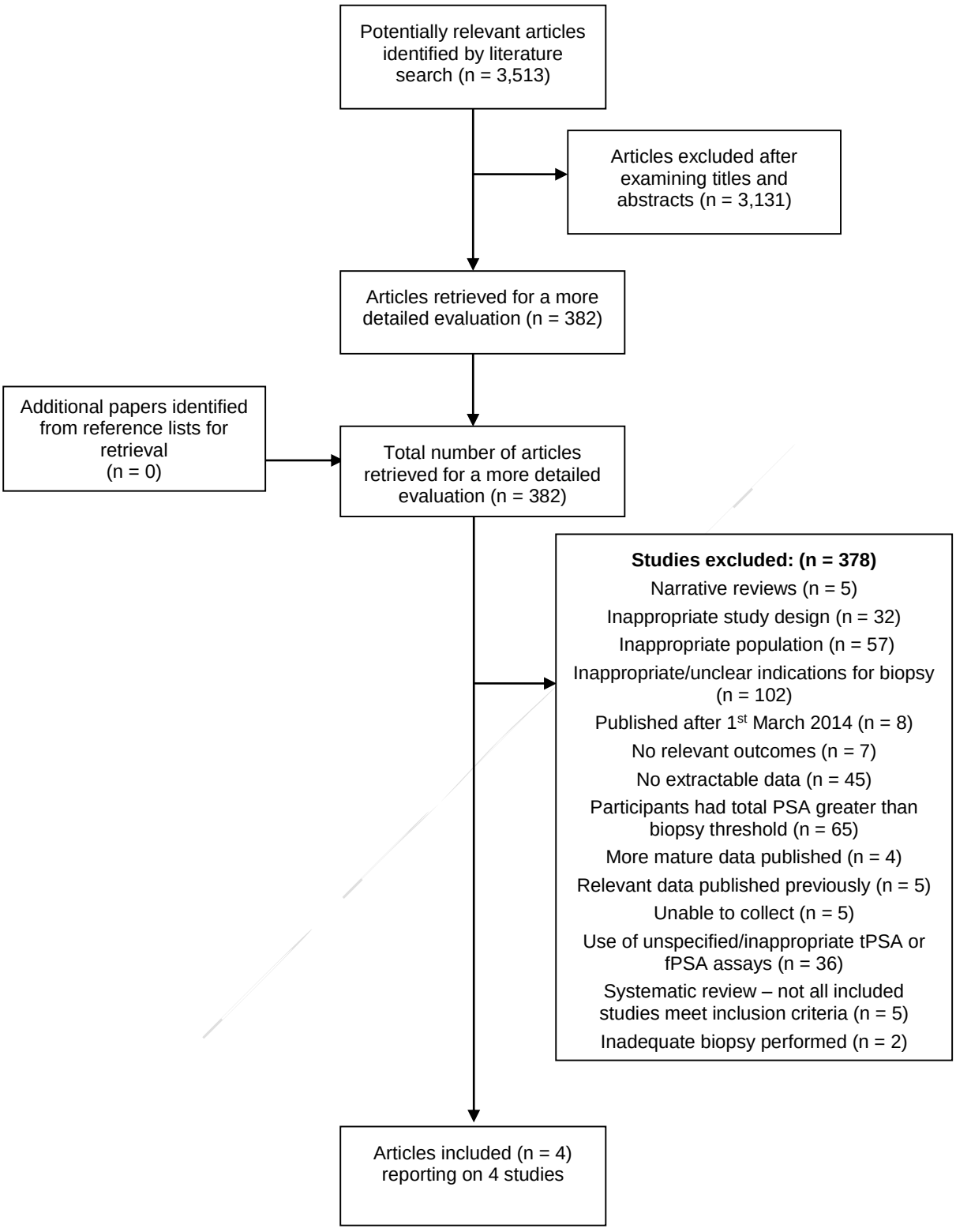


Figure 1. Process of inclusion and exclusion of studies

2.3 Study Characteristics

Table 1: Characteristics of studies comparing performance characteristics of tPSA or f/t PSA% with those of tPSA alone as indication for biopsy

Study	Design	Participants	Indication for biopsy	Biopsy	Blood collection and processing	tPSA assay	fPSA assay	Comments
tPSA >4.0 ng/mL or **tPSA 2.0-4.0 ng/mL and f/t PSA% ≤12%** *vs* tPSA >4.0 ng/mL								
Ishidoya 2008 (Japan)	Prospective multicentre	Male volunteers participating in the Northern Japan f/t PSA% PSA Screening Project **N = 332** biopsied Aged 50-79 years	tPSA >4.0 ng/mL or tPSA 2.0-4.0 ng/mL and f/t PSA% ≤12%	12-core biopsy	Serum samples collected in each community and measured 3-5 hours after collection	Architect Abbott total PSA assay Calibration not described	Architect Abbott free PSA assay Calibration not described	DRE not part of screening protocol Diagnoses made by central pathologist
tPSA ≥4.0 ng/mL or **tPSA 3.0-3.9 ng/mL and f/t PSA% <16%** *vs* tPSA ≥4.0 ng/mL								
Makinen 2001 (Finland)	Prospective	Men enrolled in the screening arm of Finnish prostate cancer screening trial in 1999 and referred for biopsy according to protocol 2 **N = 537** biopsied Aged 55-67 years	tPSA ≥4.0 ng/mL or tPSA 3.0-3.9 ng/mL and f/t PSA% <16% (= protocol 2)	Sextant biopsy	Blood collection, processing and storage conditions not described	Hybritech total PSA assay Calibration not described	ProStatus free-to-total PSA assay Calibration not described	
tPSA ≥4.0 ng/ml or **tPSA 1.1-3.99 ng/mL and f/t PSA% ≤20%** *vs* tPSA ≥4.0 ng/ml								
Rowe 2005 (UK)	Prospective	Men recruited into a screening study via six general practices N = 115 biopsied in the tPSA range 1.1-3.99 ng/mL	tPSA ≥4.0 ng/mL or tPSA 1.1-3.99 ng/mL and f/t PSA% ≤20%	Sextant biopsy for men with prostate volume ≤ 30 mL 8-core if 30-40 mL 14-core if >40 mL	Serum separated and snap-frozen in liquid nitrogen within 3 hours of collection	Beckman Coulter Access total PSA assay Calibration not described	Beckman Coulter Access free PSA assay Calibration not described	98% of biopsies taken by one operator, all histology reported by one pathologist
tPSA >4.0 ng/mL or abnormal DRE or **tPSA 2.0-4.0 ng/mL and f/t PSA% <27%** *vs* tPSA >4.0 ng/mL or abnormal DRE								
Uzzo 2003 (USA)	Prospective	Asymptomatic **high-risk men*** with no history of prostate cancer, BPH or PIN evaluated in a prostate cancer risk	tPSA >4.0 ng/mL or abnormal DRE	Sextant biopsy from 10/1996 to 10/2000	Blood drawn before biopsy	Abbott AxSYM assay from 1996 to May 2000	Abbott AxSYM assay from 1996 to May 2000	Pathologic examina- tion reviewed by an experienced

		assessment programme between October 1996 and April 2002 **N = 40** biopsied	or tPSA 2.0-4.0 ng/mL and f/t PSA% <27%	10- to 12-core five-region biopsy from 10/2000 to 04/2002		Hybritech total PSA assays from May 2000 to April 2002 (with parallel testing with AxSYM for internal validation) Calibration not described	Hybritech free PSA assays from May 2000 to April 2002 (with parallel testing with AxSYM for internal validation) Calibration not described	uropathologist and at intradepartmental conferences when indicated

BPH = benigh prostatic hyperplasia; DRE = digital rectal examination; fPSA = free prostate specific antigen; f/t PSA% = percentage free-to-total prostate apecific antigen; PIN = prostatic interepithelial neoplasia; PSA = prostate specific antigen; tPSA = total prostate specific antigen;

** African-American; or white with at least one first-degree or two or more second-degree relatives diagnosed with prostate cancer or tested positive for the BRCA1 gene*

2.4 Quality Appraisal

Table 2: Assessment of risk of bias of included diagnostic studies (n = 4)

Quality Category	N (%)
I. Selection of participants	
Low risk of bias	3 (75.0)
High risk of bias	-
Unclear risk of bias	1 (25.0)
II. Index test 1	
Low risk of bias	-
High risk of bias	-
Unclear risk of bias	4 (100)
III. Index test 2	
Low risk of bias	4 (100)
High risk of bias	-
Unclear risk of bias	-
IV. Reference standard	
Low risk of bias	-
High risk of bias	3 (75.0)
Unclear risk of bias	1 (25.0)
V. Flow and timing	
Low risk of bias	-
High risk of bias	3 (75.0)
Unclear risk of bias	1 (25.0)

Table 3: Assessment of risk of bias in individual included diagnostic studies (n = 4)

	Patient selection	Index test 1	Index test 2	Reference standard [a]	Flow and timing [b]	Overall risk of bias
Ishidoya 2008	Unclear	Unclear	Low	Unclear	High	**At risk**
Makinen 2001	Low	Unclear	Low	High	Unclear	**At risk**
Rowe 2005	Low	Unclear	Low	High	High	**At risk**
Uzzo 2003	Low	Unclear	Low	High	High	**At risk**

[a.] *An adequate biopsy was pre-specified as 12 or more cores;*
[b.] *An appropriate interval was pre-specified as up to 1 year, for biopsy referral cohorts where the interval was not stated the interval was assumed to be less than one year*

Key to overall rating

Low risk of bias: A study rated at “low” risk of bias for all domains

At risk of bias: A study rated “high” or “unclear” risk of bias for one or more domains

2.5 Study Results

Table 4: Results of studies comparing performance characteristics of tPSA and/or f/t PSA% with those of tPSA alone with respect to prostate cancer detection

Study	Men biopsied (N)	CDR (%)	*tPSA and/or f/t PSA%*			*tPSA*				*tPSA or f/t PSA% vs. tPSA*		
			f/t PSA% threshold (%)	TP (N)	FP (N)	tPSA threshold (ng/mL)	tPSA sensitivity* (%)	TP (N)	FP (N)	Additional cancers detected ΔTP	Additional unnecessary biopsies ΔFP	ΔFP/ΔTP
Ishidoya 2008	332	41.6	≤12	138	194	>4.0	88.4	122	161	16	33	2.06
Makinen 2001	537	24.0	<16	129	408	≥4.0	89.9	116	357	13	51	3.92
Rowe 2005	NR	NR	≤20	NR	NR	≥4.0	NR	NR	NR	13	102	7.85
	NR	NR	≤20	NR	NR	≥3.5	NR	NR	NR	12	94	7.83
	NR	NR	≤20	NR	NR	≥3.0	NR	NR	NR	12	85	7.08
	NR	NR	≤20	NR	NR	≥2.5	NR	NR	NR	9	74	9.33
	NR	NR	≤20	NR	NR	≥2.0	NR	NR	NR	5	50	10.0
Uzzo 2003	40	52.5	<27	21	19	>4.0	42.9	9	8	12	11	0.92

ΔFP = difference in false positives; ΔTP = difference in true positives; CDR = cancer detection rate (cancers detected/all men biopsied); FP = false positives (unnecessary biopsies); f/t PSA% = percentage free-to-total prostate apecific antigen; NR = not reported; PSA = prostate specific antigen; tPSA = total prostate specific antigen; TP = true positives (cancers detected);

**relative to using tPSA and/or f/tPSA as biopsy indication*

2.6 Body of Evidence

Study	Study type	N biop-sied	CDR (%)	Biopsy core number	Level of evidence *	Risk of bias**	tPSA threshold	Additional f/t PSA% criteria for biopsy	Additional cancers detected ΔTP	Additional unnecessary biopsies ΔFP	ΔFP/ ΔTP
Ishidoya 2008	Prospective multicentre	332	41.6	12	III-2	At risk	>4.0 ng/mL	**tPSA 2.0-4.0** ng/mL and f/t PSA% **≤12**%	16	33	2.06
Makinen 2001	Prospective	537	24.0	6	III-2	At risk	≥4.0 ng/mL	**tPSA 3.0-3.9** ng/mL and f/t PSA% **<16**%	13	51	3.92
Rowe 2005	Prospective	115 with tPSA 1.1-3.99 and f/t PSA% ≤20%	NR	6 if PV ≤30 mL 8 if 30-40 mL 14 if >40 mL	III-2	At risk	≥4.0 ng/mL	**tPSA 1.1-3.99** ng/mL and f/t PSA% **≤20**%	13	102	7.85
							≥3.5 ng/mL	**tPSA 1.1-3.5** ng/mL and f/t PSA% **≤20**%	12	94	7.83
							≥3.0 ng/mL	**tPSA 1.1-3.0** ng/mL and f/t PSA% **≤20**%	12	85	7.08
							≥2.5 ng/mL	**tPSA 1.1-2.5** ng/mL and f/t PSA% **≤20**%	9	74	9.33
							≥2.0 ng/mL	**tPSA 1.1-2.0** ng/mL and f/t PSA% **≤20**%	5	50	10.0
Uzzo 2003 ***High risk men***	Prospective	40	52.5	6 from 10/1996 to 10/2000 10 -12 from 10/2000 to 04/2002	III-2	At risk	**>4.0** ng/mL (or abnormal DRE)	**tPSA 2.0-4.0** ng/mL and f/t PSA% **<27**%	12	11	0.92

ΔFP = difference in false positives relative to tPSA (or DRE) as only biopsy indication(s); ΔTP = difference in true positives relative to tPSA (or DRE) as only biopsy indication(s); CDR = cancer detection rate; DRE = digital rectal examination; f/t PSA% = percentage free-to-total prostate apecific antigen; NR = not reported; PV = prostate volume; tPSA = total prostate specific antigen

** Refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for quality appraisals;*

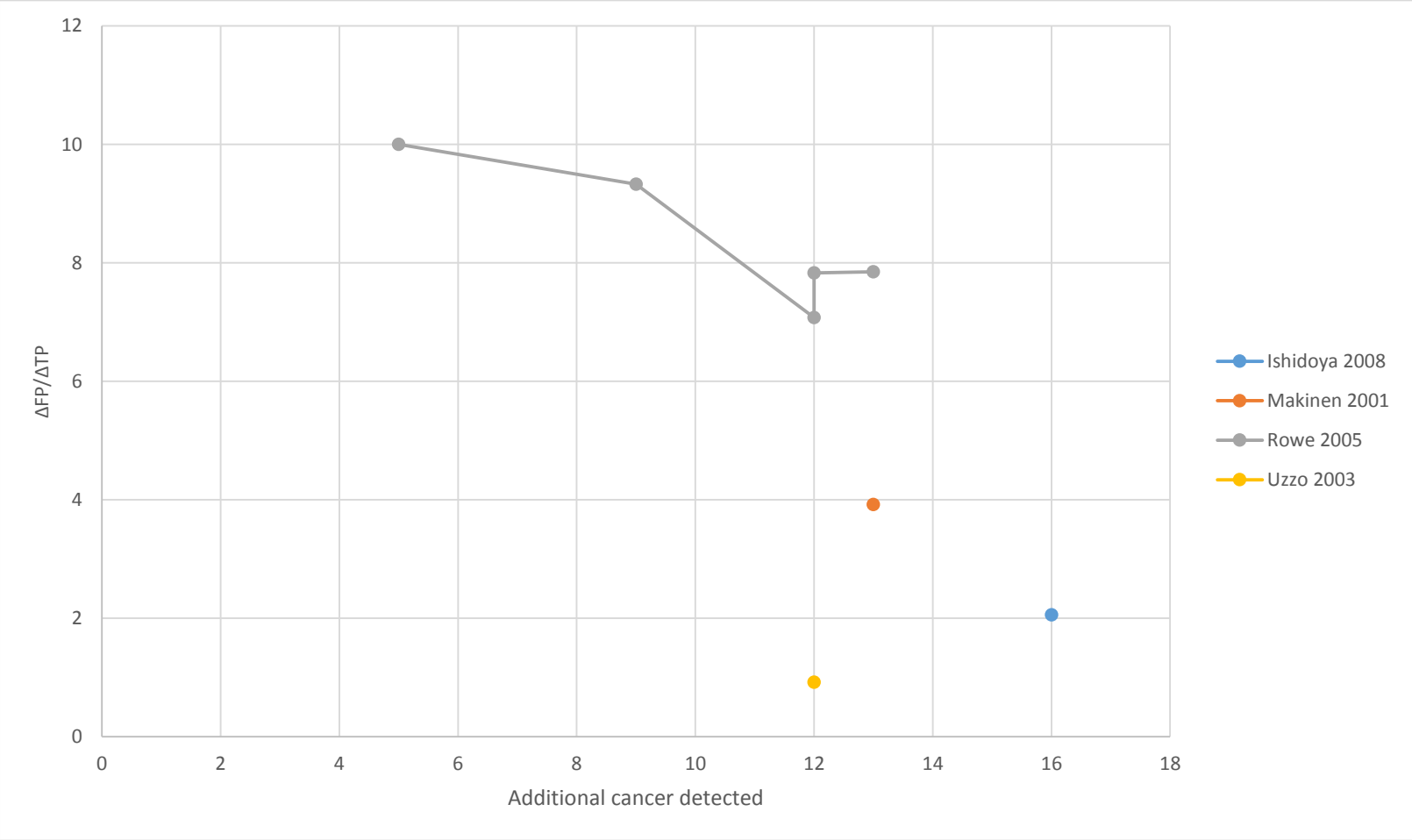


Figure 2. Diagnostic outcome of studies that investigated the use of f/t PSA% to increase sensitivity in detecting prostate cancers compared with tPSA alone

Clinical significance of size of effect is addressed in the assessment of clinical impact in the NHMRC evidence statement form.

Assessment of the relevance of the evidence in terms of whether the outcomes were directly relevant to the patient or surrogate outcomes was not assessed as it was not considered relevant to diagnostic performance studies.

References: Included studies

1. Ishidoya S, Ito A, Orikasa K, Kawamura S, Tochigi T, Kuwahara M et al. The outcome of prostate cancer screening in a normal Japanese population with PSA of 2-4 ng/ml and the free/total PSA under 12%. Japanese Journal of Clinical Oncology 2008; 38(12):844-848.
2. Makinen T, Tammela TL, Hakama M, Stenman UH, Rannikko S, Aro J et al. Prostate cancer screening within a prostate specific antigen range of 3 to 3.9 ng./ml.: a comparison of digital rectal examination and free prostate specific antigen as supplemental screening tests. J Urol 2001; 166(4):1339-1342.
3. Rowe EW, Laniado ME, Walker MM, Patel A. Prostate cancer detection in men with a 'normal' total prostate-specific antigen (PSA) level using percentage free PSA: a prospective screening study. BJU International 2005; 95(9):1249-1252.
4. Uzzo RG, Pinover WH, Horwitz EM, Parlanti A, Mazzoni S, Raysor S et al. Free prostate-specific antigen improves prostate cancer detection in a high-risk population of men with a normal total PSA and digital rectal examination. Urology 2003; 61(4):754-759.

APPENDICES

Appendix A: Search strategies used

For Medline database:

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	(free adj2 (total PSA or total prostate specific antigen or PSA or prostate specific antigen)).mp.
5	(f adj2 (tPSA or total PSA or total prostate specific antigen)).mp.
6	(ratio adj2 free to total adj2 (PSA or prostate specific antigen)).mp.
7	(derivative$ adj2 (PSA or prostate specific antigen)).mp.
8	(%fPSA or fPSA or FTPSA or f?tPSA or f tPSA or f t PSA).mp.
9	4 or 5 or 6 or 7 or 8
10	3 and 9
11	salvage.mp.
12	bisphosphonates.mp. or diphosphonates/
13	cryotherapy.mp.
14	brachytherapy.mp.
15	focal therapy.mp.
16	androgen deprivation.mp.
17	biochemical recurrence.mp.
18	biochemical relapse.mp.
19	biochemical disease.mp.
20	biochemical failure.mp.
21	active surveillance.mp.
22	(castrate resistant or castrate resistance).mp.
23	(hormone resistant or hormone resistance).mp.
24	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25	10 not 24
26	limit 25 to (english language and humans and yr="1990-current")

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database

#	Searches
1	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neopla* OR metast* OR adeno*)
2	'prostate cancer'/exp
3	1 OR 2
4	[embase]/lim AND [1990-2014]/py AND [english]/lim AND [humans]/lim
5	salvage:ab OR chemotherapy:ab OR bisphosphonate*:ab OR brachytherapy:ab OR cryotherapy:ab OR recurrence:ab OR relapse:ab OR castration:ab
6	%fpsa OR fpsa OR ftpsa OR 'f/tpsa' OR 'f/t psa' OR 'f tpsa' OR 'f t psa'
7	free NEAR/2 ('total psa' OR 'total prostate specific antigen' OR psa OR 'prostate specific antigen')
8	f NEAR/2 (tpsa OR 'total psa' OR 'total prostate specific antigen')
9	('free/total' OR 'free to total') NEAR/2 (psa OR 'prostate specific antigen')
10	derivative* NEAR/2 (psa OR 'prostate specific antigen')
11	6 OR 7 OR 8 OR 9 OR 10
12	3 AND 4 AND 11
13	12 NOT 5

ATSI search terms used

#	Searches
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

For Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment database

#	Searches
1	(prostat$ adj3 (cancer$ OR carcinoma$ OR malignan$ OR tumo?r$ OR neoplas$ OR metastas$ OR adeno$)).tw

APPENDIX B:

Level of Evidence rating criteria – Diagnostic accuracy studies

Level	Study design
I	Meta-analysis or a systematic review of level II studies
II	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation
III-1	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation
III-2	A comparison with reference standard that does not meet the criteria required for level II and III-1 evidence
III-3	Diagnostic case-control study
IV	Study of diagnostic yield (no reference standard)

According to the standards of the National Health and Medical Research Council

Appendix C:

Potentially relevant guidelines identified and reason why not adopted

Year	Organisation	Title	Reason why not adopted
2008	National Academy of Clinical Biochemistry	National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for Use of Tumor Markers in Testicular, Prostate, Colorectal, Breast, and Ovarian Cancers	Not based on a systematic review
2012	Royal College of Pathologists of Australasia	Prostate specific antigen testing: Age-related interpretation in early prostate cancer detection	Consensus based

Excluded studies

Study	Reason for Exclusion
Agnihotri 2014	Inappropriate population
Agyei-Frempong 2008	Inappropriate population
Akdas 1997	Inappropriate population
Alivizatos 1996	Inappropriate population – part a
Amirrasouli 2010	No extractable data
Auprich 2011	Inappropriate population
Auvinen 1996	Inappropriate population – part a
Auvinen 2004	No extractable data
Babaian 1998	Inappropriate population
Bajramovic 2012	Inappropriate or unclear indications for biopsy
Baltaci 2003	Inappropriate population
Bangma 1995	More mature data published
Bangma 1997a	More mature data published
Bangma 1997b	Inappropriate population – part a
Bartoletti 1997	Inappropriate population – part a
Barutcuoglu 2009	Inappropriate population – part a
Basso 2000	Inappropriate population
Becker 2000 a	Inappropriate study design
Becker 2000 b	Inappropriate population – part a
Becker 2003	Inappropriate population – part a
Benecchi 2006	Inappropriate population
Benecchi 2011	Inappropriate or unclear indications for biopsy
Bjork 1996	Inappropriate study design
Blijenberg 2001	Inappropriate study design
Boegemann 2013	Inappropriate or unclear indications for biopsy
Borgermann 2009	Inappropriate population – part a
Bratslavsky 2008	No extractable data

Brawer 1998	Inappropriate population - part a
Brawer 2000	Use of unspecified or inappropriate tPSA or fPSA assays
Bruno 2007	Use of unspecified or inappropriate tPSA or fPSA assays
Canto 2004	No extractable data
Carlson 1998	Use of unspecified or inappropriate tPSA or fPSA assays
Carter 1997	Inappropriate population
Castaldo 1997	Inappropriate population
Catalona 1998	Inappropriate population – part a
Catalona 1999	Inappropriate population – part a
Catalona 2000	Inappropriate population – part a
Catalona 2000	Inappropriate population – part a
Catalona 2003	Inappropriate population – part a
Catalona 2011	Inappropriate or unclear indications for biopsy
Catalona 2004	Inappropriate or unclear indications for biopsy
Catalona 1997	More mature data published
Catalona 1995	Inappropriate population
Chakraborty 2012	Use of unspecified or inappropriate tPSA or fPSA assays
Chen 1996	Use of unspecified or inappropriate tPSA or fPSA assays
Chi-Fai 2012a	Use of unspecified or inappropriate tPSA or fPSA assays
Chi-Fai 2012b	Inappropriate population
Ciatto 2001	Inappropriate population – part a
Ciatto 2004	Inappropriate or unclear indications for biopsy
Ciatto 2006	Inappropriate population – part a
Ciatto 2008	Inappropriate population – part a
Collins 1999	No extractable data
Correale 1996	Inappropriate population
Dadkhah 2010	Use of unspecified or inappropriate tPSA or fPSA assays
Dalva 1999	Inappropriate population – part a
De la Taille 2011	Use of unspecified or inappropriate tPSA or fPSA assays
De la Taille 1998	No extractable data
De Luca 2013	Inappropriate or unclear indications for biopsy
Demura 1996	Use of unspecified or inappropriate tPSA or fPSA assays
Dincel 1999	Inappropriate population – part a
Djavan 2002	No extractable data
Djavan 1998	Inappropriate population – part a
Djavan 1999a	Inappropriate or unclear indications for biopsy
Djavan 1999b	No relevant outcomes
Djavan 1999c	Relevant data published previously
Dowell 1996	Unable to collect
Eekers 2008	Inappropriate or unclear indications for biopsy

Egawa 1997	Inappropriate study design
Egawa 2002 a	Inappropriate population – part a
Egawa 2002 b	Inappropriate population – part a
Elabbady 2006	No extractable data
Elgamal 1996	Use of unspecified or inappropriate tPSA or fPSA assays
Ellison 2002	Inappropriate population
El-Shafei 2012	Inappropriate population
Emara 2013	Inappropriate or unclear indications for biopsy
Erol 2014	No extractable data
Eskicorapei 2006	Inappropriate or unclear indications for biopsy
Espana 1998	Inappropriate population – part a
Etzioni 2004	Inappropriate population
Ezenwa 2012	Inappropriate population
Faria 2010	Inappropriate population – part a
Faria 2012	Relevant data published previously
Ferreira 2005	Use of unspecified or inappropriate tPSA or fPSA assays
Ferro 2013a	Inappropriate or unclear indications for biopsy
Ferro 2013b	Use of unspecified or inappropriate tPSA or fPSA assays
Ferro 2012	Inappropriate or unclear indications for biopsy
Filella 1995	Inappropriate population
Filella 1997a	Inappropriate study design
Filella 1997b	Inappropriate study design
Filella 1999	Inappropriate study design
Filella 2000	No extractable data
Filella 2001	Inappropriate population
Filella 2004 a	More mature data published
Filella 2004 b	Inappropriate population – part a
Filella 2007	Inappropriate study design
Filella 2014	Published after March 2014
Fillee 2011	No relevant outcomes
Finne 2000	Inappropriate population – part a
Finne 2002	Inappropriate population – part a
Finne 2004	No extractable data
Finne 2008	No extractable data
Fischer 2005	Inappropriate study design
Foj 2014	Published after March 2014
Fowler 2000	Use of unspecified or inappropriate tPSA or fPSA assays
Froehner 2009	Inappropriate or unclear indications for biopsy
Froehner 2006	Inappropriate population
Froschermaier 1996	Inappropriate study design

Fuchsova 2014	Published after March 2014
Furuya 200	Inappropriate study design
Ganguly 2013	Inappropriate or unclear indications for biopsy
Gann 2002	Inappropriate study design
Ghalia 1996	Inappropriate study design
Gilson 1997	Inappropriate study population
Gion 1998	Inappropriate population – part a
Gion 2000	No extractable data
Gjengsto 2005	Inappropriate or unclear indications for biopsy
Gregorio 2007	Inappropriate study population
Guazzoni 2011	Inappropriate or unclear indications for biopsy
Gulkesen 2010	Inappropriate or unclear indications for biopsy
Haese 2013	Inappropriate or unclear indications for biopsy
Haese 2002	Inappropriate or unclear indications for biopsy
Haese 2001	Unable to collect
Haese 1997	Inappropriate or unclear indications for biopsy
Han 2000	Systematic review – not all included studies meet inclusion criteria
Hara 2006	Inappropriate or unclear indications for biopsy
Haroun 2011	No extractable data
Herrmann 2004	No extractable data
Higashihara 1996a	Inadequate biopsy performed
Higashihara 1996b	Inadequate biopsy performed
Hofer 2000	Inappropriate population – part a
Hoffman 2000	Systematic review – not all included studies meet inclusion criteria
Horninger 2004	No extractable data
Horninger 2002	Inappropriate or unclear indications for biopsy
Horninger 1998	Inappropriate or unclear indications for biopsy
Huang 2014	Published after March 2014
Hugosson 2003	Inappropriate population – part a
Iqbal 2005	Inappropriate study population
Ismail 2002	Use of unspecified or inappropriate tPSA or fPSA assays
Im 2004	Inappropriate population – part a
Ito 2013	Inappropriate or unclear indications for biopsy
Ito 2003	Inappropriate or unclear indications for biopsy
Jain 2002	Narrative review
Jansen 2010	No extractable data
Jeong 2008	Use of unspecified or inappropriate tPSA or fPSA assays
Jitendra 2003	Unable to collect
Jung 2001	No extractable data
Jung 2000	Inappropriate study population

Jung 2001	Inappropriate study population
Jung 1996	Inappropriate study design
Jung 1999	Inappropriate study design
Jung 1998	Inappropriate or unclear indications for biopsy
Junker 1997	Inappropriate study design
Kang 2006	Use of unspecified or inappropriate tPSA or fPSA assays
Kapoor 2006	Unable to collect
Khan 2003	Inappropriate population – part a
Khan 2004	No extractable data
Kikuchi 2000	Use of unspecified or inappropriate tPSA or fPSA assays
Kitagawa 2014	Inappropriate or unclear indications for biopsy
Klingler 1998	Inappropriate population – part a
Kobayashi 2004	No relevant outcomes
Kobayashi 2005 a	Inappropriate population
Kobayashi 2005 b	Inappropriate population – part a
Kobori 2008	Inappropriate or unclear indications for biopsy
Kocer 2013	Inappropriate or unclear indications for biopsy
Kochansko-Dziurowicz 1999	No extractable data
Kochansko-Dziurowicz 1998	Inappropriate population
Koliakos 2000	Use of unspecified or inappropriate tPSA or fPSA assays
Kral 2011	No relevant outcomes
Kravchick 2005	Inappropriate population – part a
Kurita 1998	Use of unspecified or inappropriate tPSA or fPSA assays
Kuriyama 1998a	Inappropriate population
Kuriyama 1998b	Inappropriate or unclear indications for biopsy
Kuriyama 1999	Use of unspecified or inappropriate tPSA or fPSA assays
Kwiatkowski 2004	No extractable data
Kwiatkowski 1998	Inappropriate population
Lazzeri 2014	No relevant outcomes
Lazzeri 2013a	Inappropriate or unclear indications for biopsy
Lazzeri 2013b	Inappropriate or unclear indications for biopsy
Lazzeri 2013c	Inappropriate or unclear indications for biopsy
Lazzeri 2012	Inappropriate population
Lazzeri 2011	Inappropriate or unclear indications for biopsy
Lee 2006	Systematic review – not all included studies meet inclusion criteria
Lee 2011	Inappropriate population – part a
Lein 2005	Inappropriate or unclear indications for biopsy
Lein 2003	Inappropriate or unclear indications for biopsy
Lein 2001a	Inappropriate or unclear indications for biopsy
Lein 2001b	Inappropriate study design

Lein 2000	Inappropriate population
Leung 1997	Inappropriate population – part a
Li 2005	No extractable data
Li 1999	Inappropriate study design
Liang 2011	Inappropriate population
Liao 2001	Inappropriate population – part a
Lieberman 1999	Inappropriate population
Lista 2012	Inappropriate or unclear indications for biopsy
Ljesevic 2014	Published after March 2014
Lodding 1998	Inappropriate population – part a
Lopez-Saez 2007	No extractable data
Lopez-Saez 2004	No extractable data
Luboldt 2001	Inappropriate population – part a
Lucarelli 2012	Inappropriate study design
Luderer 1995	Use of unspecified or inappropriate tPSA or fPSA assays
Lughezzani 2012	Inappropriate or unclear indications for biopsy
Lynn 2000	Inappropriate population – part a
Maattanen 2007	No extractable data
Maeda 1998	Inappropriate or unclear indications for biopsy
Maeda 1999	Inappropriate population – part a
Magklara 1999	Inappropriate study design
Mankoo 2013	Narrative review
Marley 1996	Inappropriate or unclear indications for biopsy
Martin 2006	No extractable data
Martin 2004	Inappropriate population
Martinez-Pineiro 2004	Inappropriate population – part a
Matsuyama 2000	Use of unspecified or inappropriate tPSA or fPSA assays
Masters 1998	Inappropriate population – part a
McArdle 2004	No extractable data
McNicholas 2013a	Inappropriate or unclear indications for biopsy
McNicholas 2013b	Inappropriate or unclear indications for biopsy
Mearini 2014	Unable to collect
Mettlin 1999	Inappropriate or unclear indications for biopsy
Michielsen 2004	Use of unspecified or inappropriate tPSA or fPSA assays
Miele 2001	Inappropriate population
Mikolajczyk 2004	Inappropriate or unclear indications for biopsy
Milicevic 2014	No relevant outcomes
Milkovic 2010	No extractable data
Milkovic 2007	Inappropriate or unclear indications for biopsy
Miller 2001	Inappropriate or unclear indications for biopsy

Minardi 2001	Inappropriate population – part a
Miotto 2004	Use of unspecified or inappropriate tPSA or fPSA assays
Mitchell 2001	Inappropriate or unclear indications for biopsy
Miyake 2001	Inappropriate population – part a
Miyakubo 2009	Inappropriate or unclear indications for biopsy
Moon 2000	Use of unspecified or inappropriate tPSA or fPSA assays
Moon 1999	Use of unspecified or inappropriate tPSA or fPSA assays
Morote 1997 a	Inappropriate population
Morote 1997 b	Inappropriate population – part a
Morote 1999	Inappropriate population – part a
Morote 2002	Inappropriate population – part a
Mungan 2007	No extractable data
Murphy 1996	Inappropriate population
Na 2013	No extractable data
Na 2012	Use of unspecified or inappropriate tPSA or fPSA assays
Nakano 2005	Inappropriate or unclear indications for biopsy
Naya 2005	Inappropriate or unclear indications for biopsy
Naya 2002	Inappropriate or unclear indications for biopsy
Ng 2014	Inappropriate population – part a
Ochiai 2013	Use of unspecified or inappropriate tPSA or fPSA assays
Ohori 1998	Use of unspecified or inappropriate tPSA or fPSA assays
Okegawa 2000a	No extractable data
Okegawa 2000b	No extractable data
Okegawa 2000c	Inappropriate population – part a
Okihara 2001	Inappropriate population – part a
Okihara 2004	Inappropriate population – part a
Okihara 2011	Use of unspecified or inappropriate tPSA or fPSA assays
Okihara 2002	No extractable data
Oliver 2004	No extractable data
Onur 2003	Inappropriate population
Oremek 2003	Inappropriate study design
Ozdal 2004	Inappropriate or unclear indications for biopsy
Ozen 2001	Inappropriate population – part a
Ozveri 2001	Inappropriate population
Parsons 2004	Inappropriate or unclear indications for biopsy
Partin 2003	Inappropriate or unclear indications for biopsy
Partin 1996a	Inappropriate or unclear indications for biopsy
Partin 1996b	Narrative review
Patel 2000	Inappropriate population
Pelekanos 2008	No extractable data

Pelzer 2005	Inappropriate or unclear indications for biopsy
Pepe 2007	Inappropriate or unclear indications for biopsy
Perdona 2013	Inappropriate or unclear indications for biopsy
Perdona 2012a	Inappropriate or unclear indications for biopsy
Perdona 2012b	No extractable data
Pfister 2005	No extractable data
Ploussard 2010	Inappropriate population
Pourmand 2013	Inappropriate or unclear indications for biopsy
Prestigiacomo 1997	Use of unspecified or inappropriate tPSA or fPSA assays
Prestigiacomo 1996	Inappropriate study design
Prestigiacomo 1995	Inappropriate study design
Raaijmakers 2004	Inappropriate population – part a
Rafi 2003	Inappropriate or unclear indications for biopsy
Randazzo 2014	Published after March 2014
Recker 1998a	Inappropriate study design
Recker 1998b	Inappropriate study design
Reissigl 1996	Inappropriate population – part a
Reissigl 1997a	Relevant data published previously
Reissigl 1997a	Relevant data published previously
Reissigl 1997c	Inappropriate population – part a
Reiter 1999	Inappropriate study design
Reiter 1997	Inappropriate population
Reiter 1996	Inappropriate population
Roddam 2005	Systematic review – not all included studies meet inclusion criteria
Roehl 2002	Inappropriate population – part a
Roehrborn 1996	Inappropriate population
Rowe 2006	Inappropriate population – part a
Saavedra 2013	Inappropriate or unclear indications for biopsy
Safarinejad 2006	Inappropriate population – part a
Saika 2002	Inappropriate or unclear indications for biopsy
Sakai 2004	Inappropriate study design
Sanda 2013	No extractable data
Santotoribio 2014	Published after March 2014
Sasaki 2014	Published after March 2014
Sasaki 2013a	Use of unspecified or inappropriate tPSA or fPSA assays
Sasaki 2013b	Inappropriate study design
Sasaki 2012	Inappropriate study design
Sasaki 2000	Inappropriate population
Scattoni 2013a	No extractable data
Scattoni 2013b	Inappropriate or unclear indications for biopsy

Scorilas 2003	Inappropriate or unclear indications for biopsy
Segawa 2003	No extractable data
Semjonow 2011	Inappropriate or unclear indications for biopsy
Serdar 2002	No extractable data
Shao 2000	Inappropriate study design
Skrepetis 2001	Inappropriate or unclear indications for biopsy
Smrkolj 2013	Inappropriate or unclear indications for biopsy
Sokoll 2008	Inappropriate or unclear indications for biopsy
Sokoll 2003	Inappropriate or unclear indications for biopsy
Sokoll 2010	Inappropriate population – part a
Southwick 2001	Narrative review
Sozen 2005	Inappropriate population
Stamey 2000	Inappropriate or unclear indications for biopsy
Stangelberger 2007	Narrative review
Stattin 2001	Inappropriate population
Stephan 2013a	Inappropriate or unclear indications for biopsy
Stephan 2013b	Inappropriate or unclear indications for biopsy
Stephan 2013c	Inappropriate population
Stephan 2013d	Inappropriate or unclear indications for biopsy
Stephan 2012	Inappropriate or unclear indications for biopsy
Stephan 2011	Inappropriate or unclear indications for biopsy
Stephan 2005	Inappropriate population
Steuber 2007	Inappropriate population
Strittmatter 2011	Inappropriate or unclear indications for biopsy
Szalay 2011	Inappropriate study design
Tamimi 2010	No extractable data
Tanguay 2002	Inappropriate or unclear indications for biopsy
Tello 2001	Inappropriate or unclear indications for biopsy
Thakur 2003	Inappropriate or unclear indications for biopsy
Thiel 1996	Use of unspecified or inappropriate tPSA or fPSA assays
Topolcan 2012	Inappropriate or unclear indications for biopsy
Tornblom 1999	Inappropriate or unclear indications for biopsy
Toubert 1996	Use of unspecified or inappropriate tPSA or fPSA assays
Trinkler 1998	Inappropriate population
Trygg 1997	Inappropriate population
Van Cangh 1996a	Inappropriate population
Van Cangh 1996b	Inappropriate or unclear indications for biopsy
Vashi 1997	Inappropriate or unclear indications for biopsy
Veltri 1999	Inappropriate or unclear indications for biopsy
Veneziano 2005	Inappropriate population – part a

Vessella 2000	Inappropriate population – part a
Vickers 2009	No extractable data
Vilanova 2011	No extractable data
Vincendeau 2011	Inappropriate or unclear indications for biopsy
Vogl 1997	Inappropriate or unclear indications for biopsy
Vukotic 2005	Inappropriate or unclear indications for biopsy
Wald 2000	Inappropriate population
Walz 2008	Inappropriate or unclear indications for biopsy
Wang 2006	Systematic review – not all included studies meet inclusion criteria
Wang 2004	Inappropriate population
Wang 1999	No relevant outcomes
Wechsel 1997	Inappropriate study design
Wesseling 2003	Inappropriate population
Wians 2002	Inappropriate or unclear indications for biopsy
Winkler 2004	Inappropriate or unclear indications for biopsy
Wolff 1997	Inappropriate or unclear indications for biopsy
Wolff 1996	Inappropriate or unclear indications for biopsy
Wu 2000	Inappropriate or unclear indications for biopsy
Wu 1998	Inappropriate population
Wymenga 2000	Inappropriate population – part a
Yamamoto 2008	Inappropriate or unclear indications for biopsy
Yang 2005	Use of unspecified or inappropriate tPSA or fPSA assays
Yeniyol 2001	Inappropriate or unclear indications for biopsy
Yokomizo 2009	Inappropriate population – part a
Yoshida 1999	Inappropriate or unclear indications for biopsy
Zambon 2012	Inappropriate or unclear indications for biopsy
Zhang 2000a	Inappropriate or unclear indications for biopsy
Zhang 2000b	Relevant data previously published
Zhang 1999	No extractable data
Zhao 2007	Inappropriate or unclear indications for biopsy
Zheng 2008	Use of unspecified or inappropriate tPSA or fPSA assays

References: Excluded Studies

(1) Agnihotri S, Mittal RD, Ahmad S, Mandhani A. Free to total serum prostate specific antigen ratio in symptomatic men does not help in differentiating benign from malignant disease of the prostate. Indian J Urol 2014;30(1):28-32.

(2) Agyei-Frempong MT, Frempong NYF, Aboah K, Boateng KA. Correlation of serum free/total prostate specific antigen ratio with histological features for differential diagnosis of prostate cancer. J Med Sci (Pakistan) 2008;8(6):540-6.

(3) Akdas A, Cevik I, Tarcan T, Turkeri L, Dalaman G, Emerk K. The role of free prostate-specific antigen in the diagnosis of prostate cancer. Br J Urol 1997 Jun;79(6):920-3.

(4) Alivizatos G, Deliveliotis C, Mitropoulos D, Raptides G, Louras G, Karayiannis A, et al. Does free to total ratio of prostate-specific antigen alter decision-making on prostatic biopsy? Urology 1996 Dec;48(6A):71-5.

(5) Amirrasouli H, Kazerouni F, Sanadizade M, Sanadizade J, Kamalian N, Jalali M, et al. Accurate cut-off point for free to total prostate-specific antigen ratio used to improve differentiation of prostate cancer from benign prostate hyperplasia in Iranian population. Urology Journal 2010;7(2):99-104.

(6) Auprich M, Augustin H, Budaus L, Kluth L, Mannweiler S, Shariat SF, et al. A comparative performance analysis of total prostate-specific antigen, percentage free prostate-specific antigen, prostate-specific antigen velocity and urinary prostate cancer gene 3 in the first, second and third repeat prostate biopsy. BJU Int 2012 Jun;109(11):1627-35.

(7) Auvinen A, Tammela T, Stenman UH, Uusi-Erkkila I, Leinonen J, Schroder FH, et al. Screening for prostate cancer using serum prostate-specific antigen: a randomised, population-based pilot study in Finland. British Journal of Cancer 1996 Aug;74(4):568-72.

(8) Auvinen A, Maattanen L, Finne P, Stenman U-H, Aro J, Juusela H, et al. Test sensitivity of prostate-specific antigen in the Finnish randomised prostate cancer screening trial. Int J Cancer 2004;111(6):940-3.

(9) Babaian RJ, Fritsche HA, Zhang Z, Zhang KH, Madyastha KR, Barnhill SD. Evaluation of prostAsure index in the detection of prostate cancer: a preliminary report. Urology 1998 Jan;51(1):132-6.

(10) Bajramovic S, Junuzovic D. Optimal marker for reduction of unnecessary prostate biopsies. Urology 2012;80(3):S279.

(11) Baltaci S, Aksoy H, Turkolmez K, Elhan AH, Ozden E, Gogus O. Use of percent free prostate-specific antigen density to improve the specificity for detecting prostate cancer in patients with normal rectal examinations and intermediate prostate-specific antigen levels. Urol Int 2003;70(1):36-41.

(12) Bangma CH, Kranse R, Blijenberg BG, Schroder FH. The value of screening tests in the detection of prostate cancer. Part I: Results of a retrospective evaluation of 1726 men. Urology 1995 Dec;46(6):773-8.

(13) Bangma CH, Kranse R, Blijenberg BG, Schroder FH. Free and total prostate-specific antigen in a screened population. Br J Urol 1997 May;79(5):756-62. (a)

(14) Bangma CH, Rietbergen JB, Kranse R, Blijenberg BG, Petterson K, Schroder FH. The free-to-total prostate specific antigen ratio improves the specificity of prostate specific antigen in screening for prostate cancer in the general population. J Urol 1997 Jun;157(6):2191-6. (b)

(15) Bartoletti R, D'Agata A, Travaglini F, Cappelli G, Agostini S, Barbagli G, et al. Free to total prostatic specific antigen ratio as a new diagnostic tool in prostatic carcinoma. Anticancer Res 1997 Mar;17(2B):1297-301.

(16) Barutcuoglu B, Bozdemir AE, Ertan Y, Kabaroglu C, Tamsel S, Hekimgil M, et al. Performance of total prostate specific antigen and free prostate specific antigen ratio for screening prostate cancer in a Turkish population. Turk J Cancer 2009;39(1):18-25.

(17) Basso D, Fogar P, Piva MG, Navaglia F, Mazza S, Prayer-Galetti T, et al. Total PSA, free PSA/total PSA ratio, and molecular PSA detection in prostate cancer: which is clinically effective and when? Urology 2000 May;55(5):710-5.

(18) Becker C, Piironen T, Pettersson K, Bjork T, Wojno KJ, Oesterling JE, et al. Discrimination of men with prostate cancer from those with benign disease by measurements of human glandular kallikrein 2 (HK2) in serum. J Urol 2000 Jan;163(1):311-6. (a)

(19) Becker C, Piironen T, Pettersson K, Hugosson J, Lilja H. Clinical value of human glandular kallikrein 2 and free and total prostate-specific antigen in serum from a population of men with prostate-specific antigen levels 3.0 ng/mL or greater. Urology 2000 May;55(5):694-9. (b)

(20) Becker C, Piironen T, Pettersson K, Hugosson J, Lilja H. Testing in serum for human glandular kallikrein 2, and free and total prostate specific antigen in biannual screening for prostate cancer. J Urol 2003 Oct;170:1169-74.

(21) Benecchi L. Optimum PSA reflex-range. Archivio Italiano di Urologia, Andrologia 2006 Jun;78(2):44-8.

(22) Benecchi L, Potenzoni M, Pastizzaro CD, Uliano N, Pieri AM. Value of longitudinal percent free PSA in prostate cancer diagnosis. J Urol 2011;185(4S):e809.

(23) Bjork T, Piironen T, Pettersson K, Lovgren T, Stenman UH, Oesterling JE, et al. Comparison of analysis of the different prostate-specific antigen forms in serum for detection of clinically localized prostate cancer. Urology 1996 Dec;48(6):882-8.

(24) Blijenberg BG, Yurdakul G, Van Zelst BD, Bangma CH, Wildhagen MF, Schroder FH. Discordant performance of assays for free and total prostate-specific antigen in relation to the early detection of prostate cancer. BJU Int 2001 Oct;88(6):545-50.

(25) Boegemann M, Vincendeau S, Stephan C, Houlgatte A, Krabbe L-M, Semjonow A, et al. Use of [-2]proPSA and prostate health index (phi) to improve the diagnostic accuracy of prostate cancer compared to t-PSA and %f-PSA in young men (65 years old). J Clin Oncol 2013;31(15).

(26) Borgermann C, Swoboda A, Luboldt HJ, vom DF, Rubben H. The f/t-PSA ratio in diagnosis of in-patients and out-patients: a unitary cutoff value is not useful! World Journal of Urology 2009 Oct;27(5):581-5.

(27) Bratslavsky G, Fisher HA, Kaufman RP, Jr., Voskoboynik D, Nazeer T, Mian BM. PSA-related markers in the detection of prostate cancer and high-grade disease in the contemporary era with extended biopsy. Urol Oncol 2008 Mar;26(2):166-70.

(28) Brawer MK, Meyer GE, Letran JL, Bankson DD, Morris DL, Yeung KK, et al. Measurement of complexed PSA improves specificity for early detection of prostate cancer. Urology 1998 Sep;52(3):372-8.

(29) Brawer MK, Cheli CD, Neaman IE, Goldblatt J, Smith C, Schwartz MK, et al. Complexed prostate specific antigen provides significant enhancement of specificity compared with total prostate specific antigen for detecting prostate cancer. J Urol 2000 May;163(5):1476-80.

(30) Bruno JJ, Armenakas NA, Fracchia JA. Influence of prostate volume and percent free prostate specific antigen on prostate cancer detection in men with a total prostate specific antigen of 2.6 to 10.0 ng/ml. J Urol 2007 May;177(5):1741-4.

(31) Canto EI, Singh H, Shariat SF, Kadmon D, Miles BJ, Wheeler TM, et al. Effects of systematic 12-core biopsy on the performance of percent free prostate specific antigen for prostate cancer detection. J Urol 2004 Sep;172(3):900-4.

(32) Carlson GD, Calvanese CB, Partin AW. An algorithm combining age, total prostate-specific antigen (PSA), and percent free PSA to predict prostate cancer: results on 4298 cases. Urology 1998 Sep;52(3):455-61.

(33) Carter HB, Partin AW, Luderer AA, Metter EJ, Landis P, Chan DW, et al. Percentage of free prostate-specific antigen in sera predicts aggressiveness of prostate cancer a decade before diagnosis. Urology 1997 Mar;49(3):379-84.

(34) Castaldo G, Cecere G, di F, V, Prezioso D, d'Armiento M, Salvatore F. Prostate-specific antigen (protein and mRNA) analysis in the differential diagnosis and staging of prostate cancer. Clin Chim Acta 1997 Sep 8;265(1):65-76.

(35) Catalona WJ, Smith DS, Wolfert RL, Wang TJ, Rittenhouse HG, Ratliff TL, et al. Evaluation of percentage of free serum prostate-specific antigen to improve specificity of prostate cancer screening. JAMA 1995 Oct 18;274(15):1214-20.

(36) Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination. Enhancement of specificity with free PSA measurements. JAMA 1997 May 14;277(18):1452-5.

(37) Catalona WJ, Partin AW, Slawin KM, Brawer MK, Flanigan RC, Patel A, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. JAMA 1998 May 20;279(19):1542-7.

(38) Catalona WJ, Partin AW, Finlay JA, Chan DW, Rittenhouse HG, Wolfert RL, et al. Use of percentage of free prostate-specific antigen to identify men at high risk of prostate cancer when PSA levels are 2.51 to 4 ng/mL and digital rectal examination is not suspicious for prostate cancer: an alternative model. Urology 1999 Aug;54(2):220-4.

(39) Catalona WJ, Southwick PC, Slawin KM, Partin AW, Brawer MK, Flanigan RC, et al. Comparison of percent free PSA, PSA density, and age-specific PSA cutoffs for prostate cancer detection and staging. Urology 2000 Aug 1;56(2):255-60. (a)

(40) Catalona WJ, Partin AW, Slawin KM, Naughton CK, Brawer MK, Flanigan RC, et al. Percentage of free PSA in black versus white men for detection and staging of prostate cancer: a prospective multicenter clinical trial. Urology 2000 Mar;55(3):372-6. (b)

(41) Catalona WJ, Bartsch G, Rittenhouse HG, Evans CL, Linton HJ, Amirkhan A, et al. Serum pro prostate specific antigen improves cancer detection compared to free and complexed prostate specific antigen in men with prostate specific antigen 2 to 4 ng/ml. J Urol 2003 Dec;170(6:Pt 1):t-5.

(42) Catalona WJ, Bartsch G, Rittenhouse HG, Evans CL, Linton HJ, Horninger W, et al. Serum pro-prostate specific antigen preferentially detects aggressive prostate cancers in men with 2 to 4 ng/ml prostate specific antigen. J Urol 2004 Jun;171:2239-44.

(43) Catalona WJ, Partin AW, Sanda MG, Wei JT, Klee GG, Bangma CH, et al. A multicenter study of [-2]pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/ml prostate specific antigen range.[Erratum appears in J Urol. 2011 Jul;186(1):354]. J Urol 2011 May;185(5):1650-5.

(44) Chakraborty L, Ahmed AN, Paul BK, Haque A, Ara A, Nabi S, et al. Comparative study of total prostate specific antigen and free to total prostate specific antigen ratio in the diagnosis of prostate cancer. Mymensingh Medical Journal: MMJ 2012 Jan;21(1):98-102.

(45) Chen YT, Luderer AA, Thiel RP, Carlson G, Cuny CL, Soriano TF. Using proportions of free to total prostate-specific antigen, age, and total prostate-specific antigen to predict the probability of prostate cancer. Urology 1996 Apr;47(4):518-24.

(46) Chi-Fai N, Peter KFC, Ny L, Hc L, Kim WML, Eddie S, et al. Comparison of free-to-total PSA ratio, p2psa-to-free PSA ratio and Prostate Health Index (Phi) in the prediction of prostate biopsy outcome in patients who have serum psa level between 4 to 10 Ng/ Ml receiving first transrectal ultrasound guided biopsy. Int J Urol 2012;19:253.

(47) Chi-Fai N, Peter KFC, Ny L, Hc L, Kim WML, Eddie S, et al. To assess the role of total PSA, free-tototal PSA and prostate health index (PHI) in the differentiation of high and low grade prostate cancer in patients with serum PSA level between 4 to 10 ng/ml. Int J Urol 2012;19:278.

(48) Ciatto S, Bonardi R, Lombardi C, Cappelli G, Castagnoli A, D'Agata A, et al. Predicting prostate biopsy outcome by findings at digital rectal examination, transrectal ultrasonography, PSA, PSA density and free-to-total PSA ratio in a population-based screening setting. International Journal of Biological Markers 2001 Jul;16(3):179-82.

(49) Ciatto S, Rubeca T, Confortini M, Pontenani G, Lombardi C, Zendron P, et al. Free to total PSA ratio is not a reliable predictor of prostate biopsy outcome. Tumori 2004 May;90(3):324-7.

(50) Ciatto S, Rubeca T, Franceschini R, Trevisiol C, Confortini M, Pontenani G, et al. On the clinical usefulness of the free-to-total prostate-specific antigen ratio. International Journal of Biological Markers 2006 Jan;21(1):1-5.

(51) Ciatto S, Rubeca T, Martinelli F, Pontenani G, Lombardi C, Di LS. PSA doubling time as a predictor of the outcome of random prostate biopsies prompted by isolated PSA elevation in subjects referred to an outpatient biopsy facility in a routine clinical scenario. International Journal of Biological Markers 2008 Jul;23(3):187-91.

(52) Collins GN, Alexandrou K, Wynn-Davies A, Mobley S, O'reilly PH. Free prostate-specific antigen 'in the field': a useful adjunct to standard clinical practice. BJU Int 1999 Jun;83(9):1000-2.

(53) Correale M, Pagliarulo A, Donatuti G, Sturda F, Capobianco AM, Stigliani V, et al. Preliminary clinical evaluation of free/total PSA ratio by the IMMULITE system. International Journal of Biological Markers 1996 Jan;11(1):24-8.

(54) Dadkhah F, Safarinejad MR, Amini E, Lashay AR, Baghayee A. Utility of prostate specific antigen density and free to total prostate specific antigen ratio for detecting prostate cancer in Iranian men: A prospective study of 187 cases. Curr Urol 2010;4(1):1-5.

(55) Dalva I, Akan H, Yildiz O, Telli C, Bingol N. The clinical value of the ratio of free prostate specific antigen to total prostate specific antigen. International Urology & Nephrology 1999;31(5):675-80.

(56) De La Taille A, Houlgatte A, Houdelette P, Goluboff ET, Berlizot P, Ricordel I. Influence of free-to-total prostate specific antigen variability on the early diagnosis of prostate cancer: a comparative study of three immunoassays. Br J Urol 1998 Sep;82(3):389-92.

(57) De La Taille A, Irani J, Graefen M, Chun F, de RT, Kil P, et al. Clinical evaluation of the PCA3 assay in guiding initial biopsy decisions. J Urol 2011 Jun;185(6):2119-25.

(58) De LS, Parziale A, Caccia P, Cavallini A, Faraone N, Giargia E, et al. Comparison of prostate health index, urinary pca3 assay and % free PSA in predicting prostate cancer at first biopsy. Anticancer Res 2013;33(5):2277-8.

(59) Demura T, Shinohara N, Tanaka M, Enami N, Chiba H, Togashi M, et al. The proportion of free to total prostate specific antigen: a method of detecting prostate carcinoma. Cancer 1996 Mar 15;77(6):1137-43.

(60) Dincel C, Caskurlu T, Tasci AI, Cek M, Sevin G, Fazlioglu A. Prospective evaluation of prostate specific antigen (PSA), PSA density, free-to-total PSA ratio and a new formula (prostate malignancy index) for detecting prostate cancer and preventing negative biopsies in patients with normal rectal examinations and intermediate PSA levels. International Urology & Nephrology 1999;31(4):497-509.

(61) Djavan B, Zlotta AR, Byttebier G, Shariat S, Omar M, Schulman CC, et al. Prostate specific antigen density of the transition zone for early detection of prostate cancer. J Urol 1998;160(2):411-8.

(62) Djavan B, Zlotta A, Kratzik C, Remzi M, Seitz C, Schulman CC, et al. PSA, PSA density, PSA density of transition zone, free/total PSA ratio, and PSA velocity for early detection of prostate cancer in men with serum PSA 2.5 to 4.0 ng/mL. Urology 1999 Sep;54(3):517-22.

(63) Djavan B, Zlotta AR, Remzi M, Ghawidel K, Bursa B, Hruby S, et al. Total and transition zone prostate volume and age: how do they affect the utility of PSA-based diagnostic parameters for early prostate cancer detection? Urology 1999 Nov;54(5):846-52.

(64) Djavan B, Remzi M, Zlotta AR, Seitz C, Wolfram R, Hruby S, et al. Combination and multivariate analysis of PSA-based parameters for prostate cancer prediction. Techniques in Urology 1999 Jun;5(2):71-6.

(65) Djavan B, Remzi M, Zlotta AR, Ravery V, Hammerer P, Reissigl A, et al. Complexed prostate-specific antigen, complexed prostate-specific antigen density of total and transition zone, complexed/total prostate-specific antigen ratio, free-to-total prostate-specific antigen ratio, density of total and transition zone prostate-specific antigen: results of the prospective multicenter European trial. Urology 2002 Oct;60(4A):4-9.

(66) Dowell B, Friese J, Dunlop C, Booker M, Weigand R, Barnes W, et al. Free/Total PSA Ratios in an early detection study. KLIN LABOR 1996;42(6):521-3.

(67) Eekers DB, Laschet A, de GM, Roelofs E, Kester A, Delaere K, et al. Why determine only the total prostate-specific antigen, if the free-to-total ratio contains the information? Annals of Clinical Biochemistry 2008 May;45(Pt:3):270-4.

(68) Egawa S, Soh S, Ohori M, Uchida T, Gohji K, Fujii A, et al. The ratio of free to total serum prostate specific antigen and its use in differential diagnosis of prostate carcinoma in Japan. Cancer 1997 Jan 1;79(1):90-8.

(69) Egawa S, Suyama K, Takashima R, Kuwao S, Baba S. Probability of prostate cancer at various levels of per cent free prostate specific antigen in Japanese men with total PSA of 4.1-10.0 ng/ml. Prostate Cancer & Prostatic Diseases 2002;5(2):115-8. (a)

(70) Egawa S, Suyama K, Matsumoto K, Kuwao S, Baba S. Prospective evaluation of prostate cancer detection by prostate specific antigen related parameters: comparison in serum and plasma samples. J Urol 2002 Jan;167(1):97-102. (b)

(71) El-Shafei A, Zaytoun O, Vargo E, Li J, Berglund R, Gong M, et al. PSA slope as a predictor of prostate cancer & high grade cancer on repeat biopsy. J Urol 2012;187(4):e774.

(72) Elabbady AA, Khedr MM. Free/total PSA ratio can help in the prediction of high gleason score prostate cancer in men with total serum prostate specific antigen (PSA) of 3-10 ng/ml. International Urology & Nephrology 2006;38(3-4):553-7.

(73) Elgamal AA, Cornillie FJ, Van Poppel HP, Van de Voorde WM, McCabe R, Baert LV. Free-to-total prostate specific antigen ratio as a single test for detection of significant stage T1c prostate cancer. J Urol 1996;156(3):1042-7.

(74) Ellison L, Cheli CD, Bright S, Veltri RW, Partin AW. Cost-benefit analysis of total, free/total, and complexed prostate-specific antigen for prostate cancer screening. Urology 2002 Oct;60(4A):42-6.

(75) Emara A, Maiti R, Bott S, Khan S, Nedas T, Hindley R. Validation of PSA free to total ratio and PSA density against template biopsies of prostate. J Urol 2013;189(4):e909.

(76) Erol B, Gulpinar MT, Bozdogan G, Ozkanli S, Onem K, Mungan G, et al. The cutoff level of free/total prostate specific antigen (f/t PSA) ratios in the diagnosis of prostate cancer: A validation study on a Turkish patient population in different age categories. Kaohsiung J Med Sci 2014.

(77) Eskicorapci SY, Ozkara HA, Onder E, Akdogan B, Erkan I, Ciliv G, et al. Serum ribonuclease activity in the diagnosis of prostate cancer in men with serum prostate-specific antigen levels between 2.5 and 20 ng/mL. Clinical Biochemistry 2006 Apr;39(4):363-6.

(78) Espana F, Royo M, Martinez M, Enguidanos MJ, Vera CD, Estelles A, et al. Free and complexed prostate specific antigen in the differentiation of benign prostatic hyperplasia and prostate cancer: studies in serum and plasma samples. J Urol 1998 Dec;160:2081-8.

(79) Etzioni R, Falcon S, Gann PH, Kooperberg CL, Penson DF, Stampfer MJ. Prostate-specific antigen and free prostate-specific antigen in the early detection of prostate cancer: do combination tests improve detection? Cancer Epidemiology, Biomarkers & Prevention 2004 Oct;13(10):1640-5.

(80) Ezenwa EV, Tijani KH, Jeje EA, Soriyan OO, Ogunjimi MA, Ojewola RW, et al. The value of percentage free prostate specific antigen (PSA) in the detection of prostate cancer among patients with intermediate levels of total PSA (4.0-10.0 ng/mL) in Nigeria. Arab J Urol 2012;10(4):394-401.

(81) Faria EF, Carvalhal GF, Vieira RAC, Silva TB, Mauad EC, Carvalho AL. Program for prostate cancer screening using a mobile unit: Results from Brazil. Urology 2010;76(5):1052-7.

(82) Faria EF, Carvalhal GF, dos Reis RB, Tobias-Machado M, Vieira RA, Reis LO, et al. Use of low free to total PSA ratio in prostate cancer screening: detection rates, clinical and pathological findings in Brazilian men with serum PSA levels <4.0 ng/mL. BJU Int 2012 Dec;110(11b):E653-E657.

(83) Ferreira MD, Koff WJ. Assessment of serum level of prostate-specific antigen adjusted for the transition zone volume in early detection of prostate cancer. International Braz J Urol 146 20;31(2):137-45.

(84) Ferro M, Bruzzese D, Perdona S, Mazzarella C, Marino A, Sorrentino A, et al. Predicting prostate biopsy outcome: prostate health index (phi) and prostate cancer antigen 3 (PCA3) are useful biomarkers. Clin Chim Acta 2012 Aug 16;413(15-16):1274-8.

(85) Ferro M, Bruzzese D, Perdona S, Marino A, Mazzarella C, Perruolo G, et al. Prostate Health Index (Phi) and Prostate Cancer Antigen 3 (PCA3) Significantly Improve Prostate Cancer Detection at Initial Biopsy in a Total PSA Range of 2-10 ng/ml. PLoS ONE 2013;8(7).

(86) Ferro M, Marino A, Gargiulo L, Cosimato V, Mazzarella C, Perruolo G, et al. Increasing prostate cancer detection by a model including prostate health index (PHI) and prostate cancer antigen 3 (PCA3). Anticancer Res 2013;33(5):2275-6.

(87) Filella X, Alcover J, Molina R, Gimenez N, Rodriguez A, Jo J, et al. Clinical usefulness of free PSA fraction as an indicator of prostate cancer. Int J Cancer 1995 Dec 11;63(6):780-4.

(88) Filella X, Alcover J, Molina R, Rodriguez A, Carretero P, Ballesta AM. Clinical evaluation of free PSA/total PSA (prostate-specific antigen) ratio in the diagnosis of prostate cancer. European Journal of Cancer 1997 Jul;33(8):1226-9.

(89) Filella X, Alcover J, Molina R, Rodriguez A, Carretero P, Ballesta AM. Free and total PSA in the diagnosis of prostate cancer. Tumour Biology 1997;18(6):332-40.

(90) Filella X, Alcover J, Quinto L, Molina R, Bosch-Capblanch X, Carretero P, et al. Evaluation of a multivariate prostate-specific antigen and percentage of free prostate-specific antigen logistic regression model in the diagnosis of prostate cancer. Tumour Biology 1999 Nov;20(6):312-8.

(91) Filella X, Alcover J, Molina R, Corral JM, Carretero P, Ballesta AM. Measurement of complexed PSA in the differential diagnosis between prostate cancer and benign prostate hyperplasia. Prostate 2000 Feb 15;42(3):181-5.

(92) Filella X, Alcover J, Manuel CJ, Molina R, Beardo P, Ballesta AM. Free to complexed PSA ratio in differentiating benign prostate hyperplasia from prostate cancer. Anticancer Res 2001;21(5):3717-20.

(93) Filella X, Truan D, Alcover J, Gutierrez R, Molina R, Coca F, et al. Complexed prostate-specific antigen for the detection of prostate cancer. Anticancer Res 2004 Nov;24(6):4181-5. (a)

(94) Filella X, Truan D, Alcover J, Quinto L, Molina R, Luque P, et al. Comparison of several combinations of free, complexed, and total PSA in the diagnosis of prostate cancer in patients with urologic symptoms. Urology 2004;63(6):1100-3. (b)

(95) Filella X, Alcover J, Molina R, Luque P, Corral JM, Auge JM, et al. Usefulness of proprostate-specific antigen in the diagnosis of prostate cancer. Anticancer Res 2007 Jan;27(1B):607-10.

(96) Filella X, Foj L, Auge JM, Molina R. Evaluation of the P2PSA and prostate health index to improve prostate cancer detection. Tumor Biol 2014;35:S13.

(97) Fillee C, Philippe M, Tombal B. Clinical evaluation of prostate health indexin a general population in order to detect prostate cancer. Clin Chem Lab Med 2011;49:S237.

(98) Finne P, Zhang WM, Auvinen A, Leinonen J, Maattanen L, Rannikko S, et al. Use of the complex between prostate specific antigen and alpha 1-protease inhibitor for screening prostate cancer. J Urol 2000 Dec;164(6):1956-60.

(99) Finne P, Auvinen A, Aro J, Juusela H, Maattanen L, Rannikko S, et al. Estimation of prostate cancer risk on the basis of total and free prostate-specific antigen, prostate volume and digital rectal examination. European Urology 2002;41(6):619-26.

(100) Finne P, Finne R, Bangma C, Hugosson J, Hakama M, Auvinen A, et al. Algorithms based on prostate-specific antigen (PSA), free PSA, digital rectal examination and prostate volume reduce false-positive PSA results in prostate cancer screening. Int J Cancer 2004 Aug 20;111(2):310-5.

(101) Finne P, Auvinen A, Maattanen L, Tammela TL, Ruutu M, Juusela H, et al. Diagnostic value of free prostate-specific antigen among men with a prostate-specific antigen level of <3.0 microg per liter. European Urology 2008 Aug;54(2):362-70.

(102) Fischer K, Loertzer H, Fornara P. The use of complexed PSA for the early detection of prostate cancer. Anticancer Res 2005 May;25(3A):1591-6.

(103) Foj L, Mila M, Mengual L, Luque P, Alcaraz A, Jimenez W, et al. Real-time PCR PCA3 assay is a useful test measured in urine to improve prostate cancer detection. Clin Chim Acta 2014;435:53-8.

(104) Fowler JE, Jr., Sanders J, Bigler SA, Rigdon J, Kilambi NK, Land SA. Percent free prostate specific antigen and cancer detection in black and white men with total prostate specific antigen 2.5 to 9.9 ng./ml. J Urol 2000 May;163(5):1467-70.

(105) Froehner M, Hakenberg OW, Koch R, Schmidt U, Meye A, Wirth MP. Comparison of the clinical value of complexed PSA and total PSA in the discrimination between benign prostatic hyperplasia and prostate cancer. Urol Int 2006;76(1):27-30.

(106) Froehner M, Buck LM, Koch R, Hakenberg OW, Wirth MP. Derivatives of prostate-specific antigen as predictors of incidental prostate cancer. BJU Int 2009 Jul;104(1):25-8.

(107) Froschermaier SE, Pilarsky CP, Wirth MP. Clinical significance of the determination of noncomplexed prostate-specific antigen as a marker for prostate carcinoma. Urology 1996 Apr;47(4):525-8.

(108) Fuchsova R, Topolcan O, Windrichova J, Hora M, Kucera R, Dolejsova O. Serum levels of markers in early detection of prostate cancer. Tumor Biol 2014;35:S30.

(109) Furuya Y, Akakura K, Ito H. Value of free-to-total prostate-specific antigen ratio for detection and staging of prostate cancer. Int J Clin Oncol 2000;5(1):8-11.

(110) Ganguly R, Narula A. Can free PSA/total PSA ratio predict the outcome of prostate biopsy? J Pathol 2013;231:S43.

(111) Gann PH, Ma J, Catalona WJ, Stampfer MJ. Strategies combining total and percent free prostate specific antigen for detecting prostate cancer: a prospective evaluation. J Urol 2002 Jun;167(6):2427-34.

(112) Ghalia AHA, Khalifa A, El-Gharib AM. Comparison between serum total PSA, free PSA levels and free/total PSA index in detecting prostatic carcinoma. CANCER MOL BIOL 1996;3(6):937-44.

(113) Gilson G, Lamy S, Humbel RL. First clinical results with Enzymun-Test for free PSA. Anticancer Res 1997 Jul;17(4B):2861-4.

(114) Gion M, Mione R, Barioli P, Barichello M, Zattoni F, Prayer-Galetti T, et al. Percent free prostate-specific antigen in assessing the probability of prostate cancer under optimal analytical conditions. Clinical Chemistry 1998 Dec;44(12):2462-70.

(115) Gion M, Mione R, Barioli P, Barichello M, Zattoni F, Prayer-Galetti T, et al. Clinical evaluation of percent free prostate-specific antigen using the AxSYM system in the best analytical scenario. European Urology 2000 Apr;37(4):460-9.

(116) Gjengsto P, Paus E, Halvorsen OJ, Eide J, Akslen LA, Wentzel-Larsen T, et al. Predictors of prostate cancer evaluated by receiver operating characteristics partial area index: a prospective institutional study. J Urol 2005 Feb;173(2):425-8.

(117) Gregorio EP, Grando JP, Saqueti EE, Almeida SH, Moreira HA, Rodrigues MA. Comparison between PSA density, free PSA percentage and PSA density in the transition zone in the detection of prostate cancer in patients with serum PSA between 4 and 10 ng/mL. International Braz J Urol 2007 Mar;33(2):151-60.

(118) Guazzoni G, Nava L, Lazzeri M, Scattoni V, Lughezzani G, Maccagnano C, et al. Prostate-specific antigen (PSA) isoform p2PSA significantly improves the prediction of prostate cancer at initial extended prostate biopsies in patients with total PSA between 2.0 and 10 ng/ml: results of a prospective study in a clinical setting. European Urology 2011 Aug;60(2):214-22.

(119) Gulkesen KH, Koksal IT, Bilge U, Saka O. Comparison of methods for prediction of prostate cancer in Turkish men with PSA levels of 0-10 ng/mL. Journal of B 2010 Jul;15(3):537-42.

(120) Haese A, Graefen M, Noldus J, Hammerer P, Huland E, Huland H. Prostatic volume and ratio of free-to-total prostate specific antigen in patients with prostatic cancer or benign prostatic hyperplasia. J Urol 1997 Dec;158(6):2188-92.

(121) Haese A, Partin AW. New serum tests for the diagnosis of prostate cancer. Drugs Today 2001;37(9):607-16.

(122) Haese A, Dworschack RT, Partin AW. Percent free prostate specific antigen in the total prostate specific antigen 2 to 4 ng./ml. range does not substantially increase the number of biopsies needed to detect clinically significant prostate cancer compared to the 4 to 10 ng./ml. range. J Urol 2002 Aug;168(2):504-8.

(123) Haese A, Lazzeri M, De La Taille A, Palou J, McNicholas T, Scattoni V, et al. Serum isoform [(plus or minus)2]propsa derivates (%P2PSA and PHI) significantly improves the prediction of prostate cancer at initial biopsy in a TPSA range 2-10 NG/ML. A multicentric european study. J Urol 2013;189(4):e913-e914.

(124) Han M, Potter SR, Partin AW. The role of free prostate-specific antigen in prostate cancer detection. [Review] [40 refs]. Current Urology Reports 2000 May;1(1):78-82.

(125) Hara N, Kitamura Y, Saito T, Komatsubara S. Total and free prostate-specific antigen indexes in prostate cancer screening: value and limitation for Japanese populations. Asian J Androl 2006 Jul;8(4):429-34.

(126) Haroun AA, Hadidy AS, Awwad ZM, Nimri CF, Mahafza WS, Tarawneh ES. Utility of free prostate specific antigen serum level and its related parameters in the diagnosis of prostate cancer. Saudi Journal of Kidney Diseases & Transplantation 2011 Mar;22(2):291-7.

(127) Herrmann W, Stockle M, Sand-Hill M, Hubner U, Herrmann M, Obeid R, et al. The measurement of complexed prostate-specific antigen has a better performance than total prostate-specific antigen. Clin Chem Lab Med 2004;42(9):1051-7.

(128) Higashihara E, Nutahara K, Kojima M, Okegawa T, Miura I, Miyata A, et al. Significance of serum free prostate specific antigen in the screening of prostate cancer. J Urol 1996;156(6):1964-8.

(129) Higashihara E, Nutahara K, Kojima M, Okegawa T, Miura I, Miyata A, et al. Significance of free prostate-specific antigen and gamma-seminoprotein in the screening of prostate cancer. Prostate - Supplement 1996;7:40-7.

(130) Hofer C, Sauerstein P, Wolter C, Scholz M, Hartung R, Breul J. Value of free prostate-specific antigen (Hybritech Tandem-R) in symptomatic patients consulting the urologist. Urol Int 2000;64(1):18-23.

(131) Hoffman RM, Clanon DL, Littenberg B, Frank JJ, Peirce JC. Using the free-to-total prostate-specific antigen ratio to detect prostate cancer in men with nonspecific elevations of prostate-specific antigen levels. Journal of General Internal Medicine 2000 Oct;15(10):739-48.

(132) Horninger W, Reissigl A, Klocker H, Rogatsch H, Fink K, Strasser H, et al. Improvement of specificity in PSA-based screening by using PSA-transition zone density and percent free PSA in addition to total PSA levels. Prostate 1998;37(3):133-7.

(133) Horninger W, Cheli CD, Babaian RJ, Fritsche HA, Lepor H, Taneja SS, et al. Complexed prostate-specific antigen for early detection of prostate cancer in men with serum prostate-specific antigen levels of 2 to 4 nanograms per milliliter. Urology 2002 Oct;60(4:Suppl 1):Suppl-5.

(134) Horninger W, Berger A, Pelzer A, Klocker H, Oberaigner W, Schonitzer D, et al. Screening for prostate cancer: updated experience from the Tyrol study. Current Urology Reports 2004 Jun;5(3):220-5.

(135) Huang M, Lin Y, Xu A, Uhlman M, Deng X, Lin X, et al. Percent free prostate-specific antigen does not improve the effectiveness of prostate cancer detection in Chinese men with a prostate-specific antigen of 2.5-20.0 ng/ml: A multicenter study. Med Oncol 2014;31(4).

(136) Hugosson J, Aus G, Bergdahl S, Fernlund P, Frosing R, Lodding P, et al. Population-based screening for prostate cancer by measuring free and total serum prostate-specific antigen in Sweden. BJU Int 2003 Dec;92(Suppl 2):39-43.

(137) Im YJ, Kim JW, Hong SJ, Chung BH. Proper cut-off value of free to total PSA ratio for detection of prostate cancer in Korean men. Yonsei Medical Journal 2004 Oct 31;45(5):873-8.

(138) Iqbal N, Chaughtai N. Evaluation of the diagnostic use of free prostate specific antigen/total prostate specific antigen ratio in detecting prostate cancer. JPMA - Journal of the Pakistan Medical Association 2005 Aug;55(8):318-20.

(139) Ismail AH, Pollak M, Behlouli H, Tanguay S, Begin LR, Aprikian AG. Insulin-like growth factor-1 and insulin-like growth factor binding protein-3 for prostate cancer detection in patients undergoing prostate biopsy. J Urol 2002 Dec;168(6):2426-30.

(140) Ito K, Yamamoto T, Ohi M, Kurokawa K, Suzuki K, Yamanaka H. Free/total PSA ratio is a powerful predictor of future prostate cancer morbidity in men with initial PSA levels of 4.1 to 10.0 ng/mL. Urology 2003 Apr;61(4):760-4.

(141) Ito K, Miyakubo M, Sekine Y, Koike H, Matsui H, Shibata Y, et al. Diagnostic significance of [-2]pro-PSA and prostate dimension-adjusted PSA-related indices in men with total PSA in the 2.0-10.0 ng/mL range. World Journal of Urology 2013 Apr;31(2):305-11.

(142) Jain S, Bhojwani AG, Mellon JK. Improving the utility of prostate specific antigen (PSA) in the diagnosis of prostate cancer: The use of PSA derivatives and novel markers. Postgrad Med J 2002;78(925):646-50.

(143) Jansen FH, van Schaik RH, Kurstjens J, Horninger W, Klocker H, Bektic J, et al. Prostate-specific antigen (PSA) isoform p2PSA in combination with total PSA and free PSA improves diagnostic accuracy in prostate cancer detection. European Urology 2010 Jun;57(6):921-7.

(144) Jeong IG, Lee KH, Korean Urological Oncologic Society Prostate Cancer Study Group. Percent free prostate specific antigen does not enhance the specificity of total prostate specific antigen for the detection of prostate cancer in Korean men 50 to 65 years old: a prospective multicenter study. J Urol 2008 Jan;179(1):111-6.

(145) Jitendra N, Sandhu MS, Khuller GK, Sharma SK. Role of the ratio of free to total prostate specific antigen (PSA) in the diagnosis of prostate cancer. JMS J Med Soc 2003;17(1):3-7.

(146) Jung K, Stephan C, Lein M, Henke W, Schnorr D, Brux B, et al. Analytical performance and clinical validity of two free prostate-specific antigen assays compared. Clinical Chemistry 1996 Jul;42(7):1026-33.

(147) Jung K, Meyer A, Lein M, Rudolph B, Schnorr D, Loening SA. Ratio of free-to-total prostate specific antigen in serum cannot distinguish patients with prostate cancer from those with chronic inflammation of the prostate. J Urol 1998 May;159(5):1595-8.

(148) Jung K, Brux B, Lein M, Knabich A, Sinha P, Rudolph B, et al. Determination of alpha1-antichymotrypsin-PSA complex in serum does not improve the differentiation between benign prostatic hyperplasia and prostate cancer compared with total PSA and percent free PSA. Urology 1999 Aug;53(6):1160-7.

(149) Jung K, Elgeti U, Lein M, Brux B, Sinha P, Rudolph B, et al. Ratio of free or complexed prostate-specific antigen (PSA) to total PSA: which ratio improves differentiation between benign prostatic hyperplasia and prostate cancer? Clinical Chemistry 2000 Jan;46(1):55-62.

(150) Jung K, Stephan C, Elgeti U, Lein M, Brux B, Kristiansen G, et al. Molecular forms of prostate-specific antigen in serum with concentrations of total prostate-specific antigen <4 (mu)g/L: Are they useful tools for early detection and screening of prostate cancer? Int J Cancer 2001;93(5):759-65.

(151) Jung K, Stephan C, Lein M, Brux B, Sinha P, Schnorr D, et al. Receiver-operating characteristic as a tool for evaluating the diagnostic performance of prostate-specific antigen and its molecular forms--What has to be considered? Prostate 2001 Mar 1;46(4):307-10.

(152) Junker R, Brandt B, Zechel C, Assmann G. Comparison of prostate-specific antigen (PSA) measured by four combinations of free PSA and total PSA assays. Clinical Chemistry 1997 Sep;43(9):1588-94.

(153) Kang SH, Bae JH, Park HS, Yoon DK, Moon DG, Kim JJ, et al. Prostate-specific antigen adjusted for the transition zone volume as a second screening test: a prospective study of 248 cases. Int J Urol 2006 Jul;13(7):910-4.

(154) Kapoor N, Jain R, Surange S, Bhardwaj VK, Srivastava A. Prostate specific antigen ratio: for diagnosis and assessment of aggressiveness of malignancy of prostate.[Erratum appears in Indian J Pathol Microbiol. 2006 Jul;49(3):476]. Indian Journal of Pathology & Microbiology 2006 Apr;49(2):178-81.

(155) Khan MA, Partin AW, Rittenhouse HG, Mikolajczyk SD, Sokoll LJ, Chan DW, et al. Evaluation of proprostate specific antigen for early detection of prostate cancer in men with a total prostate specific antigen range of 4.0 to 10.0 ng/ml. J Urol 2003 Sep;170(3):723-6.

(156) Khan MA, Sokoll LJ, Chan DW, Mangold LA, Mohr P, Mikolajczyk SD, et al. Clinical utility of proPSA and "benign" PSA when percent free PSA is less than 15%. Urology 2004 Dec;64(6):1160-4.

(157) Kikuchi E, Nakashima J, Ishibashi M, Ohigashi T, Asakura H, Tachibana M, et al. Prostate specific antigen adjusted for transition zone volume: the most powerful method for detecting prostate carcinoma. Cancer 2000 Aug 15;89(4):842-9.

(158) Kitagawa Y, Ueno S, Izumi K, Kadono Y, Konaka H, Mizokami A, et al. Cumulative probability of prostate cancer detection in biopsy according to free/total PSA ratio in men with total PSA levels of 2.1-10.0 ng/ml at population screening. J Cancer Res Clin Oncol 2014 Jan;140(1):53-9.

(159) Klingler HC, Woo H, Rosario D, Cutinha PE, Anderson J, Ward AM, et al. The value of prostate specific antigen (PSA) density and free: total PSA ratio in selecting patients with a normal digital rectal examination and intermediate total PSA levels for further investigation. Br J Urol 1998 Sep;82(3):393-7.

(160) Kobayashi T, Nishizawa K, Ogura K, Mitsumori K, Ide Y. Detection of prostate cancer in men with prostate-specific antigen levels of 2.0 to 4.0 ng/mL equivalent to that in men with 4.1 to 10.0 ng/mL in a Japanese population. Urology 2004 Apr;63(4):727-31.

(161) Kobayashi T, Kamoto T, Nishizawa K, Mitsumori K, Ogura K, Ide Y. Prostate-specific antigen (PSA) complexed to alpha1-antichymotrypsin improves prostate cancer detection using total PSA in Japanese patients with total PSA levels of 2.0-4.0 ng/mL. BJU Int 2005 Apr;95(6):761-5. (a)

(162) Kobayashi T, Kawahara T, Nishizawa K, Ogura K, Mitsumori K, Ide Y. Volume-adjusted prostate-specific antigen (PSA) variables in detecting impalpable prostate cancer in men with PSA levels of 2-4 ng/mL: transabdominal measurement makes a significant contribution. BJU Int 2005 Jun;95(9):1245-8. (b)

(163) Kobori Y, Kitagawa Y, Mizokami A, Komatsu K, Namiki M. Free-to-total prostate-specific antigen (PSA) ratio contributes to an increased rate of prostate cancer detection in a Japanese population screened using a PSA level of 2.1-10.0 ng/ml as a criterion. Int J Clin Oncol 2008;13(3):229-32.

(164) Kocer D, Karakukcu C, Karaman H, Tasdemir A, Ali EM. PSA-based parameters and their diagnostic performances in patients with prostate cancer and benign prostatic hyperplasia. Turk J Biochem 2013;38(1):37-42.

(165) Kochanska-Dziurowicz AA, Mielniczuk MR, Stojko A, Kaletka J. The clinical utility of measuring free-to-total prostate-specific antigen (PSA) ratio and PSA density in differentiating between benign prostatic hyperplasia and prostate cancer. Br J Urol 1998 Jun;81(6):834-8.

(166) Kochanska-Dziurowicz AA, Mielniczuk M, Kaletka J, Teneta L. Evaluation of prostate specific antigen (t-PSA and f-PSA) in blood serum in screening research on prostate cancer. Med Sci Monit 1999;5(5):870-3.

(167) Koliakos G, Chatzivasiliou D, Dimopoulos T, Trachana V, Paschalidou K, Galiamoutsas V, et al. The significance of PSA/IGF-1 ratio in differentiating benign prostate hyperplasia from prostate cancer. Disease Markers 2000;16(3-4):143-6.

(168) Kral M, Hradil D, Grepl M, Hrabec M, Petrek M, Kolar Z, et al. Prostate Health Index (PHI) in patients with prostate cancer and with BPH. Eur Urol Suppl 2011;10(9):647.

(169) Kravchick S, Peled R, Dorfman D, Agulansky L, Ben-Dor D, Cytron S. Predictive criteria for prostate cancer detection in men with serum PSA concentration of 2.0 to 4.0 ng/mL. Urology 2005 Sep;66(3):542-6.

(170) Kurita Y, Terada H, Masuda H, Suzuki K, Fujita K. Prostate specific antigen (PSA) value adjusted for transition zone volume and free PSA (gamma-seminoprotein)/PSA ratio in the diagnosis of prostate cancer in patients with intermediate PSA levels. Br J Urol 1998 Aug;82(2):224-30.

(171) Kuriyama M, Ueno K, Uno H, Kawada Y, Akimoto S, Noda M, et al. Clinical evaluation of serum prostate-specific antigen-alpha1-antichymotrypsin complex values in diagnosis of prostate cancer: a cooperative study. Int J Urol 1998 Jan;5(1):48-54.

(172) Kuriyama M, Kawada Y, Arai Y, Maeda H, Egawa S, Koshiba K, et al. Significance of free to total PSA ratio in men with slightly elevated serum PSA levels: a cooperative study. Japanese Journal of Clinical Oncology 1998 Nov;28(11):661-5.

(173) Kuriyama M, Uno H, Watanabe H, Yamanaka H, Saito Y, Shida K. Determination of reference values for total PSA, F/T and PSAD according to prostatic volume in japanese prostate cancer patients with slightly elevated serum PSA levels. Japanese Journal of Clinical Oncology 1999 Dec;29(12):617-22.

(174) Kwiatkowski M, Huber A, Moschopulos M, Lehmann K, Wernli M, Hafeli A, et al. Prostate cancer screening: results of a prospective trial in Canton Aargau, Switzerland. Swiss Medical Weekly 2004 Oct 2;134(39-40):580-5.

(175) Kwiatkowski MK, Recker F, Piironen T, Pettersson K, Otto T, Wernli M, et al. In prostatism patients the ratio of human glandular kallikrein to free PSA improves the discrimination between prostate cancer and benign hyperplasia within the diagnostic "gray zone" of total PSA 4 to 10 ng/mL. Urology 1998 Sep;52(3):360-5.

(176) Lazzeri M. Prostate cancer: The Prostate Health Index (PHI) may guide diagnostic and treatment. Tumor Biol 2011;32:S40.

(177) Lazzeri M, Briganti A, Scattoni V, Lughezzani G, Larcher A, Gadda GM, et al. Serum index test %[-2]proPSA and Prostate Health Index are more accurate than prostate specific antigen and %fPSA in predicting a positive repeat prostate biopsy. J Urol 2012 Oct;188(4):1137-43.

(178) Lazzeri M, Lughezzani G, Lista G, Larcher A, Cestari A, Buffi N, et al. Clinical performance of serum isoform [-2]proPSA (p2PSA) and its derivatives, namely %p2PSA and PHI (Prostate Health Index) in men with family history of prostate cancer. Results from a multicentric European study (PROMEtheuS project). Eur Urol Suppl 2013;12(1):e848-e849.

(179) Lazzeri M, Haese A, Abrate A, De La Taille A, Redorta JP, McNicholas T, et al. Clinical performance of serum prostate-specific antigen isoform [-2]proPSA (p2PSA) and its derivatives, %p2PSA and the prostate health index (PHI), in men with a family history of prostate cancer: results from a multicentre European study, the PROMEtheuS project. BJU Int 2013 Aug;112(3):313-21.

(180) Lazzeri M, Haese A, De La Taille A, Palou RJ, McNicholas T, Lughezzani G, et al. Serum isoform [-2]proPSA derivatives significantly improve prediction of prostate cancer at initial biopsy in a total PSA range of 2-10 ng/ml: a multicentric European study. European Urology 2013 Jun;63(6):986-94.

(181) Lazzeri M, Abrate A, Lughezzani G, Gadda GM, Freschi M, Mistretta F, et al. Relationship of chronic histologic prostatic inflammation in biopsy specimens with serum isoform [-2]proPSA (p2PSA), %p2PSA, and prostate health index in men with a total prostate-specific antigen of 4-10 ng/ml and normal digital rectal examination. Urology 2014 Mar;83(3):606-12.

(182) Lee BH, Moussa AS, Li J, Fareed K, Jones JS. Percentage of free prostate-specific antigen: implications in modern extended scheme prostate biopsy. Urology 2011 Apr;77(4):899-903.

(183) Lee R, Localio AR, Armstrong K, Malkowicz SB, Schwartz JS, Free PSA Study Group. A meta-analysis of the performance characteristics of the free prostate-specific antigen test. Urology 2006 Apr;67(4):762-8.

(184) Lein M, Jung K, Elgeti U, Brux B, Sinha P, Schnorr D, et al. Ratio of alpha 1-antichymotrypsin--prostate specific antigen to total prostate specific antigen in prostate cancer diagnosis. Anticancer Res 2000 Nov;20(6D):4997-5001.

(185) Lein M, Jung K, Hammerer P, Graefen M, Semjonow A, Stieber P, et al. A multicenter clinical trial on the use of alpha1-antichymotrypsin-prostate-specific antigen in prostate cancer diagnosis. Prostate 2001 May 1;47(2):77-84.

(186) Lein M, Jung K, Elgeti U, Petras T, Stephan C, Brux B, et al. Comparison of the clinical validity of free prostate-specific antigen, alpha-1 antichymotrypsin-bound prostate-specific antigen and complexed prostate-specific antigen in prostate cancer diagnosis. European Urology 2001 Jan;39(1):57-64.

(187) Lein M, Kwiatkowski M, Semjonow A, Luboldt HJ, Hammerer P, Stephan C, et al. A multicenter clinical trial on the use of complexed prostate specific antigen in low prostate specific antigen concentrations. J Urol 2003 Oct;170(4:Pt 1):t-9.

(188) Lein M, Semjonow A, Graefen M, Kwiatkowski M, Abramjuk C, Stephan C, et al. A multicenter clinical trial on the use of (-5, -7) pro prostate specific antigen. J Urol 2005 Dec;174(6):2150-3.

(189) Leung HY, Lai LC, Day J, Thomson J, Neal DE, Hamdy FC. Serum free prostate-specific antigen in the diagnosis of prostate cancer. Br J Urol 1997 Aug;80(2):256-9.

(190) Li W, Ren Y, Mee V, Wong PY. Prostate-specific antigen ratio correlates with aggressiveness of histology grades of prostate cancer. Clinical Biochemistry 1999 Feb;32(1):31-7.

(191) Li X-M, Zhang L, Li J, Li Y, Wang H-L, Ji G-Y, et al. Measurement of serum zinc improves prostate cancer detection efficiency in patients with PSA levels between 4 ng/mL and 10 ng/mL. Asian J Androl 2005;7(3):323-8.

(192) Liang Y, Ankerst DP, Ketchum NS, Ercole B, Shah G, Shaughnessy JD, Jr., et al. Prospective evaluation of operating characteristics of prostate cancer detection biomarkers. J Urol 2011 Jan;185(1):104-10.

(193) Liao CH, Liu SP, Pu YS, Huang CY, Yu HJ, Chen J. Effect of percent free prostate-specific antigen measurement on improving the specificity of serum prostate-specific antigen testing in Taiwanese patients. Journal of the Formosan Medical Association 2001 Feb;100(2):113-9.

(194) Lieberman S. Can percent free prostate-specific antigen reduce the need for prostate biopsy? Effective Clinical Practice 1999 Nov;2(6):266-71.

(195) Lista G, Lughezzani G, Lazzeri M, Scattoni V, Nava L, Centemero A, et al. Isoform [-2]proPSA (p2PSA) and its derivates, %p2PSA and PHI values differ between BPH, ASAP, HG-PIN and PCa in a set of contemporary men undergoing prostate biopsy. Eur Urol Suppl 2012;11(1):e910-e910a.

(196) Ljesevic S, Joksimovic D, Stojadinovic D, Nedeljkovic T. The role of F/T(%) ratio for differential diagnosis between benign prostatic hyperplasia and prostatic carcinoma in patient at the clinical center of Kragujevac in Serbia. Tumor Biol 2014;35:S47.

(197) Lodding P, Aus G, Bergdahl S, Frosing R, Lilja H, Pihl CG, et al. Characteristics of screening detected prostate cancer in men 50 to 66 years old with 3 to 4 ng./ml. Prostate specific antigen. J Urol 1998 Mar;159(3):899-903.

(198) Lopez-Saez J-B, Otero M, Senra-Varela A, Ojea A, Saez Martin JL, Duran MB, et al. Prospective observational study to assess value of prostate cancer diagnostic methods. J Diagn Med Sonogr 2004;20(6):383-93.

(199) Lopez-Saez J-B, Otero M, Villar MD, Penuelas AL, Navarro PR, Moreira PG, et al. Diagnostic methods in the detectiion of prostate cancer: Prospective observational study. Curr Med Imaging Rev 2007;3(1):27-35.

(200) Luboldt HJ, Swoboda A, Borgermann C, Fornara P, Rubben H, Early Detection Project Group of the German Society of Urology. Clinical usefulness of free PSA in early detection of prostate cancer. Onkologie 2001 Feb;24(1):33-7.

(201) Lucarelli G, Fanelli M, Larocca AMV, Germinario CA, Rutigliano M, Vavallo A, et al. Serum sarcosine increases the accuracy of prostate cancer detection in patients with total serum PSA less than 4.0 ng/ml. Prostate 2012;72(15):1611-21.

(202) Luderer AA, Chen YT, Soriano TF, Kramp WJ, Carlson G, Cuny C, et al. Measurement of the proportion of free to total prostate-specific antigen improves diagnostic performance of prostate-specific antigen in the diagnostic gray zone of total prostate-specific antigen. Urology 1995 Aug;46(2):187-94.

(203) Lughezzani G, Lazzeri M, Scattoni V, Larcher A, Gadda G, Nava L, et al. Clinical cut-offs of isoform [-2]proPSA (p2PSA) derivatives, namely %p2PSA and PHI (Prostate Health Index) for guiding biopsy decision in Caucasian population. Eur Urol Suppl 2012;11(1):e909-e909a.

(204) Lynn NNK, Collins GN, Alexandrou K, Brown SCW, Brooman PJC, O'reilly PH. Comparative analysis of the role of prostate specific antigen parameters in clinical practice. Prostate J 2000;2(4):205-10.

(205) Maattanen L, Hakama M, Tammela TL, Ruutu M, Ala-Opas M, Juusela H, et al. Specificity of serum prostate-specific antigen determination in the Finnish prostate cancer screening trial. British Journal of Cancer 2007 Jan 15;96(1):56-60.

(206) Maeda H, Arai Y, Okubo K, Aoki Y, Okada T, Maekawa S. Value of the free to total prostate specific antigen ratio and prostate specific antigen density for detecting prostate cancer in Japanese patients. Int J Urol 1998 Jul;5(4):343-8.

(207) Maeda H, Arai Y, Aoki Y, Okubo K, Okada T, Maekawa S. Complexed prostate-specific antigen and its volume indexes in the detection of prostate cancer. Urology 1999 Aug;54(2):225-8.

(208) Magklara A, Scorilas A, Catalona WJ, Diamandis EP. The combination of human glandular kallikrein and free prostate-specific antigen (PSA) enhances discrimination between prostate cancer and benign prostatic hyperplasia in patients with moderately increased total PSA. Clinical Chemistry 1999 Nov;45(11):1960-6.

(209) Mankoo K. ProPSA and the Prostate H ealth index in the role of prostate cancer diagnosis. Where are they now? A review of the current literature. BJU Int 2013;112(Suppl 1):3.

(210) Marley GM, Miller MC, Kattan MW, Zhao G, Patton KP, Vessella RL, et al. Free and complexed prostate-specific antigen serum ratios to predict probability of primary prostate cancer and benign prostatic hyperplasia. Urology 1996 Dec;48(6A):16-22.

(211) Martin BJ, Finlay JA, Sterling K, Ward M, Lifsey D, Mercante D, et al. Early detection of prostate cancer in African-American men through use of multiple biomarkers: human kallikrein 2 (hK2), prostate-specific antigen (PSA), and free PSA (fPSA). Prostate Cancer & Prostatic Diseases 2004;7(2):132-7.

(212) Martin BJ, Cheli CD, Sterling K, Ward M, Pollard S, Lifsey D, et al. Prostate specific antigen isoforms and human glandular kallikrein 2--which offers the best screening performance in a predominantly black population? J Urol 2006 Jan;175(1):104-7.

(213) Martinez-Pineiro L, Garcia Mediero JM, Gonzalez GP, Tabernero A, Lozano D, Lopez-Tello JJ, et al. Probability of prostate cancer as a function of the percentage of free prostate-specific antigen in patients with a non-suspicious rectal examination and total prostate-specific antigen of 4-10 ng/ml. World Journal of Urology 2004 Jun;22(2):124-31.

(214) Masters JG, Keegan PE, Hildreth AJ, Greene DR. Free/total serum prostate-specific antigen ratio: how helpful is it in detecting prostate cancer? Br J Urol 1998 Mar;81(3):419-23.

(215) Matsuyama H, Baba Y, Yamakawa G, Yamamoto N, Naito K. Diagnostic value of prostate-specific antigen-related parameters in discriminating prostate cancer. Int J Urol 2000 Nov;7(11):409-14.

(216) McArdle PA, Pollock MA, Wallace AM, McMillan DC, Crooks JE, Underwood MA. Comparison of total, complexed and free prostate-specific antigens and their ratios in the detection of prostate cancer in a non-screened population. Annals of Clinical Biochemistry 2004 May;41:201-6.

(217) McNicholas T, Lazzeri M, Haese A, De La Taille A, Palou J, Lughezzani G, et al. Serum isoform [-2]proPSA (p2PSA) and its derivatives, namely %p2PSA and PHI (prostate health index) in men younger than 60 years of age for prediction of prostate cancer. Results from a multicentric european study (prometheus project). J Urol 2013;189(4):e790.

(218) McNicholas T, Lazzeri M, Haese A, De La Taille A, Palou J, Lughezzani G, et al. PHI (Prostate Health Index) and %p2PSA for prediction of prostate cancer in men younger than 60 years of age. A nested-case control study from PROpsa Multicentric European Study (PROMEtheuS project). Eur Urol Suppl 2013;12(1):e137-e138.

(219) Mearini L, Ferri C, Lazzeri M, Bini V, Nunzi E, Fiorini D, et al. Evaluation of Prostate-Specific Antigen Isoform p2PSA and Its Derivates, %p2PSA, Prostate Health Index and Prostate Dimension-Adjusted Related Index in the Detection of Prostate Cancer at First Biopsy: An Exploratory, Prospective Study. Urol Int 2014.

(220) Mettlin C, Chesley AE, Murphy GP, Bartsch G, Toi A, Bahnson R, et al. Association of free PSA percent, total PSA, age, and gland volume in the detection of prostate cancer. Prostate 1999 May 15;39(3):153-8.

(221) Michielsen DPJ, Braeckman JG, De Reijke TM, Vijverberg PLM, De La Rosette JJMC. Prediction of free PSA, PSA density and PSA density transition zone in the outcome of sextant prostate biopsies in patients with total PSA between 3 and 15 ng/ml. UroOncology 2004;4(2):71-6.

(222) Miele ME. Percent free PSA as an additional measure in a prostate cancer screen. Clinical Laboratory Science 2001;14(2):102-7.

(223) Mikolajczyk SD, Catalona WJ, Evans CL, Linton HJ, Millar LS, Marker KM, et al. Proenzyme forms of prostate-specific antigen in serum improve the detection of prostate cancer. Clinical Chemistry 2004 Jun;50(6):1017-25.

(224) Milicevic N, Mrcela M, Lukic I, Mandic S, Horvat V, Galic J. Comparison between clinical significance of serum proinflammatory protein interleukin-6 and classic tumor markers total PSA, free PSA and free/total PSA prior to prostate biopsy. Collegium Antropologicum 2014 Mar;38(1):147-50.

(225) Milkovic B, Hadzi-Djokic J, Dzamic Z, Pejcic T. The significance of TPSA, free to total PSA ratio and PSA density in prostate carcinoma diagnostics. Acta Chirurgica Iugoslavica 2007;54(4):105-7.

(226) Milkovic B, Dzamic Z, Pejcic T, Kajmakovic B. (F/T)/PSAD ratio determination according to the prostate volume with the patients in Serbia. Eur Urol Suppl 2010;9(6):601.

(227) Miller MC, O'Dowd GJ, Partin AW, Veltri RW. Contemporary use of complexed PSA and calculated percent free PSA for early detection of prostate cancer: impact of changing disease demographics. Urology 2001 Jun;57(6):1105-11.

(228) Minardi D, Galosi AB, Recchioni A, Giammarco L, Polito M, Muzzonigro G. Diagnostic accuracy of percent free prostate-specific antigen in prostatic pathology and its usefulness in monitoring prostatic cancer patients. Urol Int 2001;67(4):272-82.

(229) Miotto A, Jr., Srougi M, Brito GA, Leite KM, Nesrallah AJ, Ortiz V. Value of various PSA parameters for diagnosing prostate cancer in men with normal digital rectal examination. International Braz J Urol 2004 Mar;30(2):109-13.

(230) Mitchell ID, Croal BL, Dickie A, Cohen NP, Ross I. A prospective study to evaluate the role of complexed prostate specific antigen and free/total prostate specific antigen ratio for the diagnosis of prostate cancer. J Urol 2001 May;165(5):1549-53.

(231) Miyake H, Hara S, Nomi M, Arakawa S, Kamidono S, Hara I. Value of prostate specific antigen (alpha)1-antichymotrypsin complex for the detection of prostate cancer in patients with a PSA level of 4.1-10.0 ng/mL: Comparison with PSA-related parameters. Int J Urol 2001;8(11):589-93.

(232) Miyakubo M, Ito K, Yamamoto T, Takechi H, Ohi M, Suzuki K. Proprostate-specific antigen: its usefulness in the era of multiple-core prostate biopsy. Int J Urol 2009 Jun;16(6):561-5.

(233) Moon DG, Cheon J, Kim JJ, Yoon DK, Koh SK. Prostate-specific antigen adjusted for the transition zone volume versus free-to-total prostate-specific antigen ratio in predicting prostate cancer. Int J Urol 1999 Sep;6(9):455-62.

(234) Moon DG, Yu JW, Lee JG, Kim JJ, Koh SK, Cheon J. The influence of prostate volume on the prostate-specific antigen (PSA) level adjusted for the transition zone volume and free-to-total PSA ratio: a prospective study. BJU Int 2000 Oct;86(6):670-4.

(235) Morote J, Raventos CX, Lorente JA, Lopez-Pacios MA, Encabo G, de T, I, et al. Comparison of percent free prostate specific antigen and prostate specific antigen density as methods to enhance prostate specific antigen specificity in early prostate cancer detection in men with normal rectal examination and prostate specific antigen between 4.1 and 10 ng./ml. J Urol 1997 Aug;158(2):502-4. (a)

(236) Morote J, Raventos CX, Lorente JA, Lopez-Pacios MA, Encabo G, de T, I, et al. Measurement of free PSA in the diagnosis and staging of prostate cancer. Int J Cancer 1997 May 29;71(5):756-9. (b)

(237) Morote J, Encabo G, Lopez M, de Torres IM. Individual variations of total and percent free serum prostatic specific antigen: could they change the indication of prostatic biopsy? Oncol Rep 1999 Jul;6(4):887-90.

(238) Morote J, Trilla E, Esquena S, Serrallach F, Abascal JM, Munoz A, et al. The percentage of free prostatic-specific antigen is also useful in men with normal digital rectal examination and serum prostatic-specific antigen between 10.1 and 20 ng/ml. European Urology 2002 Oct;42(4):333-7.

(239) Mungan AG, Erol B, Akduman B, Bozdogan G, Kiran S, Yesilli C, et al. Values for free/total prostate-specific antigen ratio as a function of age: necessity of reference validation in a Turkish population.[Erratum appears in Clin Chem Lab Med. 2007;45(11):1570]. Clinical Chemistry & Laboratory Medicine 2007;45(7):912-6.

(240) Murphy GP, Barren RJ, Erickson SJ, Bowes VA, Wolfert RL, Bartsch G, et al. Evaluation and comparison of two new prostate carcinoma markers. Free-prostate specific antigen and prostate specific membrane antigen.[Erratum appears in Cancer 1996 Oct 1;78(7):1524]. Cancer 1996 Aug 15;78(4):809-18.

(241) Na R, Jiang H, Kim ST, Wu Y, Tong S, Zhang L, et al. Outcomes and trends of prostate biopsy for prostate cancer in Chinese men from 2003 to 2011. PLoS ONE [Electronic Resource] 2012;7(11):e49914.

(242) Na R, Wu Y, Xu J, Jiang H, Ding Q. Age-specific prostate specific antigen cutoffs for guiding biopsy decision in Chinese population. PLoS ONE [Electronic Resource] 2013;8(6):e67585.

(243) Nakano Y, Okamura K, Takamura S, Okamoto N, Narishima M, Yoshino Y, et al. Measurement of prostate specific antigen complexed to alpha1-antichymotrypsin to avoid unnecessary biopsy in patients with serum prostate specific antigen levels 4-20 ng/mL. Int J Urol 2005 Aug;12(8):721-7.

(244) Naya Y, Stamey TA, Cheli CD, Partin AW, Sokoll LJ, Chan DW, et al. Can volume measurement of the prostate enhance the performance of complexed prostate-specific antigen? Urology 2002 Oct;60(4A):36-41.

(245) Naya Y, Fritsche HA, Bhadkamkar VA, Mikolajczyk SD, Rittenhouse HG, Babaian RJ. Evaluation of precursor prostate-specific antigen isoform ratios in the detection of prostate cancer. Urol Oncol 2005 Jan;23(1):16-21.

(246) Ng CF, Chiu PKF, Lam NY, Lam HC, Lee KWM, Hou SSM. The Prostate Health Index in predicting initial prostate biopsy outcomes in Asian men with prostate-specific antigen levels of 4-10 ng/mL. Int Urol Nephrol 2014;46(4):711-7.

(247) Ochiai A, Okihara K, Kamoi K, Oikawa T, Shimazui T, Murayama S, et al. Clinical utility of the prostate cancer gene 3 (PCA3) urine assay in Japanese men undergoing prostate biopsy. BJU Int 2013 May;111(6):928-33.

(248) Ohori M, Egawa S, Koshiba K. The utility of free to total PSA ratio for detecting prostate cancer in Japanese men with total PSA between 2.1 and 10 ng/ml. Urol Oncol 1998;4(3):80-5.

(249) Okegawa T, Noda H, Nutahara K, Higashihara E. Comparison of two investigative assays for the complexed prostate-specific antigen in total prostate-specific antigen between 4.1 and 10.0 ng/mL. Urology 2000 May;55(5):700-4. (a)

(250) Okegawa T, Kinjo M, Watanabe K, Noda H, Kato M, Miyata A, et al. The significance of the free-to-complexed prostate-specific antigen (PSA) ratio in prostate cancer detection in patients with a PSA level of 4.1-10.0 ng/mL. BJU Int 2000 Apr;85(6):708-14. (b)

(251) Okegawa T, Noda H, Nutahara K, Higashihara E. Comparisons of the various combinations of free, complexed, and total prostate-specific antigen for the detection of prostate cancer. European Urology 2000 Oct;38(4):380-7. (c)

(252) Okihara K, Fritsche HA, Ayala A, Johnston DA, Allard WJ, Babaian RJ. Can complexed prostate specific antigen and prostatic volume enhance prostate cancer detection in men with total prostate specific antigen between 2.5 And 4.0 Ng./Ml. J Urol 2001;165:1930-6.

(253) Okihara K, Cheli CD, Partin AW, Fritche HA, Chan DW, Sokoll LJ, et al. Comparative analysis of complexed prostate specific antigen, free prostate specific antigen and their ratio in detecting prostate cancer. J Urol 2002 Apr;167(5):2017-23.

(254) Okihara K, Ukimura O, Nakamura T, Mizutani Y, Kawauchi A, Naya Y, et al. Can complexed prostate specific antigen enhance prostate cancer detection in Japanese men? European Urology 2004 Jul;46(1):57-64.

(255) Okihara K, Ochiai A, Kamoi K, Miki T. Utility of PCA3 urine assay in Japanese men undergoing prostate biopsy. J Clin Oncol 2011;29(7).

(256) Oliver SE, Holly J, Peters TJ, Donovan J, Persad R, Gillatt D, et al. Measurement of insulin-like growth factor axis does not enhance specificity of PSA-based prostate cancer screening. Urology 2004 Aug;64(2):317-22.

(257) Onur R, Ilhan N, Orhan I, Ilhan N. Increased discrimination between benign prostatic hyperplasia and prostate cancer with equimolar total prostate specific antigen measurement. World Journal of Urology 2003 May;21(1):43-7.

(258) Oremek GM, Sapoutzis N, Eden F, Jonas D. Complexed PSA in routine diagnosis. Anticancer Res 2003 Mar;23(2A):975-7.

(259) Ozdal OL, Aprikian AG, Begin LR, Behlouli H, Tanguay S. Comparative evaluation of various prostate specific antigen ratios for the early detection of prostate cancer. BJU Int 2004;93(7):970-4.

(260) Ozen H, Aygun C, Ergen A, Sozen S, Aki FT, Uygur MC. Combined use of prostate-specific antigen derivatives decreases the number of unnecessary biopsies to detect prostate cancer. American Journal of Clinical Oncology 2001 Dec;24(6):610-3.

(261) Ozveri H, Cam K, Tarcan T, Turkeri L, Akdas A. Significance of free to total PSA ratio in men with normal digital rectal examination, normal transrectal ultrasonography, and intermediate total serum PSA levels. J B U ON 2001;6(1):79-82.

(262) Parsons JK, Brawer MK, Cheli CD, Partin AW, Djavan R. Complexed prostate specific antigen (PSA) reduces unnecessary prostate biopsies in the 2.6-4.0 ng/mL range of total PSA. BJU Int 2004 Jul;94(1):47-50.

(263) Partin AW, Carter HB. The use of prostate-specific antigen and free/total prostate-specific antigen in the diagnosis of localized prostate cancer. Urol Clin North Am 1996;23(4):531-40.

(264) Partin AW, Catalona WJ, Southwick PC, Subong EN, Gasior GH, Chan DW. Analysis of percent free prostate-specific antigen (PSA) for prostate cancer detection: influence of total PSA, prostate volume, and age. Urology 1996 Dec;48(6A):55-61.

(265) Partin AW, Brawer MK, Bartsch G, Horninger W, Taneja SS, Lepor H, et al. Complexed prostate specific antigen improves specificity for prostate cancer detection: results of a prospective multicenter clinical trial. J Urol 2003 Nov;170(5):1787-91.

(266) Patel D, White PA, Milford WA. A comparison of six commercial assays for total and free prostate specific antigen (PSA): the predictive value of the ratio of free to total PSA. BJU Int 2000 Apr;85(6):686-9.

(267) Pelekanos C, Beardi J, Jonas D, Oremek GM. Isoforms of PSA (prostate-specific antigen) in the diagnosis of prostate cancer. Clin Exp Med Lett 2008;49(1):23-5.

(268) Pelzer AE, Volgger H, Bektic J, Berger AP, Rehder P, Bartsch G, et al. The effect of percentage free prostate-specific antigen (PSA) level on the prostate cancer detection rate in a screening population with low PSA levels. BJU Int 2005 Nov;96(7):995-8.

(269) Pepe P, Panella P, Savoca F, Cacciola A, D'Arrigo L, Dibenedetto G, et al. Prevalence and clinical significance of prostate cancer among 12,682 men with normal digital rectal examination, low PSA levels (< or =4 ng/ml) and percent free PSA cutoff values of 15 and 20%. Urol Int 2007;78(4):308-12.

(270) Perdona S, Quarto G, Sorrentino D, De DR, Cariati F, Sorrentino A, et al. Phi and PCA3 significantly improve diagnostic accuracy in patients undergoing prostate biopsy. Anticancer Res 2012;32(5):1920.

(271) Perdona S, Quarto G, De DR, Sorrentino D, Ferro M, Altieri V, et al. Work-up in patients without a specific risk of prostate cancer (PSA (less-than or equal to)10 ng/ml): A multiparametric mri scoring system. Anticancer Res 2012;32(5):1892.

(272) Perdona S, Bruzzese D, Ferro M, Autorino R, Marino A, Mazzarella C, et al. Prostate health index (phi) and prostate cancer antigen 3 (PCA3) significantly improve diagnostic accuracy in patients undergoing prostate biopsy. Prostate 2013 Feb 15;73(3):227-35.

(273) Pfister C, Basuyau JP, Normandy Urological Association. Current usefulness of free/total PSA ratio in the diagnosis of prostate cancer at an early stage. World Journal of Urology 2005 Sep;23(4):236-42.

(274) Ploussard G, Haese A, Van PH, Marberger M, Stenzl A, Mulders PFA, et al. The prostate cancer gene 3 (PCA3) urine test in men with previous negative biopsies: Does free-to-total prostate-specific antigen ratio influence the performance of the PCA3 score in predicting positive biopsies? BJU Int 2010;106(8):1143-7.

(275) Pourmand G. Preventing unnecessary invasive cancer-diagnostic tests. Eur Urol Suppl 2013;12(6):163.

(276) Prestigiacomo AF, Stamey TA. Clinical usefulness of free and complexed PSA. Scandinavian Journal of Clinical and Laboratory Investigation Supplement 1995;221:32-4.

(277) Prestigiacomo AF, Lilja H, Pettersson K, Wolfert RL, Stamey TA. A comparison of the free fraction of serum prostate specific antigen in men with benign and cancerous prostates: the best case scenario. J Urol 1996 Aug;156:350-4.

(278) Prestigiacomo AF, Stamey TA. Can free and total prostate specific antigen and prostatic volume distinguish between men with negative and positive systematic ultrasound guided prostate biopsies? J Urol 1997 Jan;157(1):189-94.

(279) Raaijmakers R, Blijenberg BG, Finlay JA, Rittenhouse HG, Wildhagen MF, Roobol MJ, et al. Prostate cancer detection in the prostate specific antigen range of 2.0 to 3.9 ng/ml: value of percent free prostate specific antigen on tumor detection and tumor aggressiveness. J Urol 2004 Jun;171:2245-9.

(280) Rafi T, Sattar A, Asif N, Dawood MM, Aamir M, Rehman Z. The Comparison of Percent Free PSA with total PSA in the diagnosis of Prostate Cancer. J Pak Med Assoc 2003;53(6):233-6.

(281) Randazzo M, Beatrice J, Huber A, Grobholz R, Manka L, Recker F, et al. Future risk for intermediate or high risk prostate cancer in men with baseline PSA of 1-3ng/mL and low free-to-total PSA-ratio in a prospective population-based screening trial (ERSPC AARAU). J Urol 2014;191(4S):e815.

(282) Recker F, Kwiatkowski MK, Piironen T, Pettersson K, Lummen G, Wernli M, et al. The importance of human glandular kallikrein and its correlation with different prostate specific antigen serum forms in the detection of prostate carcinoma. Cancer 1998 Dec 15;83(12):2540-7.

(283) Recker F, Kwiatkowski MK, Piironen T, Pettersson K, Goepel M, Tscholl R. Free-to-total prostate-specific antigen (PSA) ratio improves the specificity for detecting prostate cancer in patients with prostatism and intermediate PSA levels. Br J Urol 1998 Apr;81(4):532-8.

(284) Reissigl A, Klocker H, Pointner J, Fink K, Horninger W, Ennemoser O, et al. Usefulness of the ratio free/total prostate-specific antigen in addition to total PSA levels in prostate cancer screening. Urology 1996 Dec;48(6A):62-6.

(285) Reissigl A, Klocker H, Pointner J, Ennemoser O, Falk M, Bartsch G. Improvement of prostate cancer screening by determination of the ratio free/total PSA in addition to PSA levels. Prostate 1997 Mar 1;30(4):243-7. (a)

(286) Reissigl A, Bartsch G. Prostate-specific antigen as a screening test. The Austrian experience. Urol Clin North Am 1997 May;24(2):315-21. (b)

(287) Reissigl A, Horninger W, Fink K, Klocker H, Bartsch G. Prostate carcinoma screening in the county of Tyrol, Austria: experience and results. Cancer 1997 Nov 1;80(9):1818-29. (c)

(288) Reiter W, Stieber P, Schmeller N, Nagel D, Pahl H, Mattes M, et al. Free PSA: A useful marker in the differential diagnosis of benign hyperplasia and cancer of the prostate? TUMOR DIAGN THER 1996;17(3):88-92.

(289) Reiter W, Stieber P, Schmeller N, Nagel D, Jansen HM, Schambeck C, et al. The ratio of free to total prostate specific antigen: an advantageous addition in the differential diagnosis of benign hyperplasia and cancer of the prostate? Anticancer Res 1997 Jul;17(4B):2987-91.

(290) Reiter W. The clinical value of the Enzymun-Test for total and free PSA--a multicentre evaluation. Anticancer Res 1999 Nov;19(6C):5559-62.

(291) Roddam AW, Duffy MJ, Hamdy FC, Ward AM, Patnick J, Price CP, et al. Use of prostate-specific antigen (PSA) isoforms for the detection of prostate cancer in men with a PSA level of 2-10 ng/ml: systematic review and meta-analysis. [Review] [96 refs]. European Urology 2005 Sep;48(3):386-99.

(292) Roehl KA, Antenor JA, Catalona WJ. Robustness of free prostate specific antigen measurements to reduce unnecessary biopsies in the 2.6 to 4.0 ng./ml. range. J Urol 2002 Sep;168(3):922-5.

(293) Roehrborn CG, Gregory A, McConnell JD, Sagalowsky AI, Wians FH, Jr. Comparison of three assays for total serum prostate-specific antigen and percentage of free prostate-specific antigen in predicting prostate histology. Urology 1996 Dec;48(6A):23-32.

(294) Rowe EW, Laniado ME, Walker MM, Anup P. Incidental acute prostatic inflammation is associated with a lower percentage of free prostate-specific antigen than other benign conditions of the prostate: a prospective screening study. BJU Int 2006 May;97(5):1039-42.

(295) Saavedra II, Konstantinidis C, Celma A, Agreda F, Placer J, Planas J, et al. PSA kinetics does not predict prostate cancer in men subjected to prostate biopsy. J Urol 2013;189(4):e789.

(296) Safarinejad MR. Population-based screening for prostate cancer by measuring free and total serum prostate-specific antigen in Iran. Annals of Oncology 2006 Jul;17(7):1166-71.

(297) Saika T, Tsushima T, Nasu Y, Kusaka N, Miyaji Y, Takamoto H, et al. Prostate specific antigen complexed to alpha-1-antichymotrypsin in patients with intermediate prostate specific antigen levels. Cancer 2002 Mar 15;94(6):1685-91.

(298) Sakai I, Harada K, Hara I, Eto H, Miyake H. Limited usefulness of the free-to-total prostate-specific antigen ratio for the diagnosis and staging of prostate cancer in Japanese men. Int J Clin Oncol 2004 Feb;9(1):64-7.

(299) Sanda M, Wei J, Broyles D, Shin S, Partin A, Klee G, et al. Prostate health index (Phi) for reducing overdetection of indolent prostate cancer and unnecessary biopsy while improving detection of aggressive cancers. J Urol 2013;189(4):e843.

(300) Santotoribio JD, Garcia-De La Torre A, Canavate-Solano C, Arce-Matute F, Perez-Ramos S. LDH and %FPSA for diagnosis of prostate cancer. Tumor Biol 2014;35:S47.

(301) Sasaki M, Ishidoya S, Ito A, Saito H, Yamada S, Mitsuzuka K, et al. Low percentage of free prostate-specific antigen is a strong predictor of later detection of prostate cancer among men with serum levels of total PSA 4.0ng/mL or under. Urology 2013;82(3 Suppl 1):S69.

(302) Sasaki M, Ishidoya S, Ito A, Saito H, Shibuya D, Arai Y. Diagnostic value of free prostate-specific antigen among men with prostate-specific antigen 2.0 to 4.0ng/ml at screening cohort in Japan. J Urol 2012;187(4):e773-e774.

(303) Sasaki M. Pathological outcomes for patients with PSA 2.0-4.0 ng/mL and free/total PSA under 12% at prostate cancer screening in Japan. J Urol 2013;189(4):e795.

(304) Sasaki M, Ishidoya S, Ito A, Numahata K, Shibuya D, Arai Y. Early detection of clinically significant prostate cancer: Low free prostate-specific antigen levels as a criterion for prostate biopsy in patients with low total prostate-specific antigen levels. J Urol 2014;191(4):e715.

(305) Sasaki R, Habuchi T, Sato K, Akao T, Kakinuma H, Zhang LQ, et al. The clinical utility of measuring total PSA, PSA density, gamma-seminoprotein and gamma-seminoprotein/total PSA in prostate cancer prediction. Jpn J Clin Oncol 2000 Aug;30(8):337-42.

(306) Scattoni V, Lazzeri M, Lughezzani G, De LS, Passera R, Bollito E, et al. Comparison between PCA3 and phi specificty and sensitivity in predicting the presence of cancer at initial or repeat biopsy. Anticancer Res 2013;33(5):2293.

(307) Scattoni V, Lazzeri M, Lughezzani G, De LS, Passera R, Bollito E, et al. Head-to-head comparison of prostate health index and urinary PCA3 for predicting cancer at initial or repeat biopsy. J Urol 2013 Aug;190(2):496-501.

(308) Scorilas A, Plebani M, Mazza S, Basso D, Soosaipillai AR, Katsaros N, et al. Serum human glandular kallikrein (hK2) and insulin-like growth factor 1 (IGF-1) improve the discrimination between prostate cancer and benign prostatic hyperplasia in combination with total and %free PSA. Prostate 2003 Feb 15;54(3):220-9.

(309) Segawa N, Gohji K, Iwamoto Y, Ueda H, Katsuoka Y. Prostate cancer detection by prostate-specific antigen-related parameters. Hinyokika Kiyo - Acta Urologica Japonica 2003 Jul;49(7):405-10.

(310) Semjonow A, Bogemann M, Eminaga O, Hinkelammert R, Abbas M, Eltze E, et al. [-2] proPSA improves prediction of repeat prostate biopsy results. Urologe Ausg A 2011;50:73.

(311) Serdar MA, Oguz O, Olgun A, Seckin B, Ilgan S, Hasimi A, et al. Diagnostic approach to prostate cancer using total prostate specific antigen-based parameters together. Annals of Clinical & Laboratory Science 2002;32(1):22-30.

(312) Shao Y, Zhang Z-B. Evaluation of free-to-total prostate specific antigen ratio in the diagnosis of prostate cancer. Chin J Cancer Res 2000;12(2):114.

(313) Skrepetis K, Doumas K, Kiminas E, Davilas E, Lykourinas M. Clinical usefulness of free to total PSA in the detection of prostate cancer in men with total PSA of 2 to 4 ng/ml and normal prostate digital rectal examination. J B U ON 2001;6(1):83-5.

(314) Smrkolj T, Osredkar J. Performance of early prostate cancer antigen-2 (EPCA2), propsa, free PSA (FPSA) and prostate health index (PHI) in detection of prostatic carcinoma. Biochim Clin 2013;37:S196.

(315) Sokoll LJ, Chan DW, Mikolajczyk SD, Rittenhouse HG, Evans CL, Linton HJ, et al. Proenzyme psa for the early detection of prostate cancer in the 2.5-4.0 ng/ml total psa range: preliminary analysis. Urology 2003 Feb;61(2):274-6.

(316) Sokoll LJ, Wang Y, Feng Z, Kagan J, Partin AW, Sanda MG, et al. [-2]proenzyme prostate specific antigen for prostate cancer detection: a national cancer institute early detection research network validation study. J Urol 2008;180(2):539-43.

(317) Sokoll LJ, Sanda MG, Feng Z, Kagan J, Mizrahi IA, Broyles DL, et al. A prospective, multicenter, National Cancer Institute Early Detection Research Network study of [-2]proPSA: improving prostate cancer detection and correlating with cancer aggressiveness. Cancer Epidemiology, Biomarkers & Prevention 2010 May;19(5):1193-200.

(318) Southwick PC. The role of free PSA in the detection of prostate cancer. Lab Med 2001;32(5):259-63.

(319) Sozen S, Eskicorapci S, Kupeli B, Irkilata L, Altinel M, Ozer G, et al. Complexed prostate specific antigen density is better than the other PSA derivatives for detection of prostate cancer in men with total PSA between 2.5 and 20 ng/ml: results of a prospective multicenter study. European Urology 2005 Mar;47(3):302-7.

(320) Stamey TA, Yemoto CE. Examination of the 3 molecular forms of serum prostate specific antigen for distinguishing negative from positive biopsy: relationship to transition zone volume. J Urol 2000 Jan;163(1):119-26.

(321) Stangelberger A, Margreiter M, Seitz C, Djavan B. Prostate cancer screening markers. J Men's Health Gender 2007;4(3):233-44.

(322) Stattin P, Stenman UH, Riboli E, Hallmans G, Kaaks R. Ratios of IGF-I, IGF binding protein-3, and prostate-specific antigen in prostate cancer detection. Journal of Clinical Endocrinology & Metabolism 2001 Dec;86(12):5745-8.

(323) Stephan C, Stroebel G, Heinau M, Lenz A, Roemer A, Lein M, et al. The ratio of prostate-specific antigen (PSA) to prostate volume (PSA density) as a parameter to improve the detection of prostate carcinoma in PSA values in the range of < 4 ng/mL. Cancer 2005 Sep 1;104(5):993-1003.

(324) Stephan C, Vincendeau S, Houlgatte A, Semjonow A. Prostate health index (PHI) using [-2]Propsa improves detection of prostate cancer preferentially identifying aggressive cancers. Clin Chem Lab Med 2011;49:S269.

(325) Stephan C, Jung K, Semjonow A. Prospective head-to-head evaluation of [-2]proPSA, PCA3 and TMPRSS2:ERG in patients referred for prostate biopsy. Tumor Biol 2012;33:S49.

(326) Stephan C, Vincendeau S, Houlgatte A, Miller K, Semjonow A. [-2]proPSA and prostate health index (phi) improve detection of prostate cancer at initial and repeated biopsies in young men ((less-than or equal to) 60 year old) preferentially detecting clinically significant cancer. Eur Urol Suppl 2013;12(1):e853.

(327) Stephan C, Semjonow A, Boegemann M, Miller K, Friedersdorff F. Parallel measurement of urinary PCA3 and TMPRSS2:ERG with serum [-2]proPSA based Phi for prostate cancer detection. Urologe Ausg A 2013;52(1):119.

(328) Stephan C, Jung K, Semjonow A, Schulze-Forster K, Cammann H, Hu X, et al. Comparative assessment of urinary prostate cancer antigen 3 and TMPRSS2:ERG gene fusion with the serum [-2]proprostate-specific antigen-based prostate health index for detection of prostate cancer. Clinical Chemistry 2013 Jan;59(1):280-8.

(329) Stephan C, Vincendeau S, Houlgatte A, Cammann H, Jung K, Semjonow A. Multicenter evaluation of [-2]proprostate-specific antigen and the prostate health index for detecting prostate cancer. Clinical Chemistry 2013 Jan;59(1):306-14.

(330) Steuber T, Vickers A, Haese A, Kattan MW, Eastham JA, Scardino PT, et al. Free PSA isoforms and intact and cleaved forms of urokinase plasminogen activator receptor in serum improve selection of patients for prostate cancer biopsy. Int J Cancer 2007 Apr 1;120(7):1499-504.

(331) Strittmatter F, Stieber P, Nagel D, Fullhase C, Walther S, Stief CG, et al. Detection of prostate cancer with complexed PSA and complexed/total PSA ratio - is there any advantage? European Journal of Medical Research 2011 Oct 10;16(10):445-50.

(332) Szalay I, Bordas N, Pajor L, Farkas G, Salgo L. A new way in the early detection of prostate cancer: The [-2]pro prostate specific antigen. Clin Chem Lab Med 2011;49:S276.

(333) Tamimi W, Dafterdar R, Mansi M, Alsaad K, Alarifi SA. Complexed and total PSA in patients with benign prostatic hyperplasia and prostate cancer. British Journal of Biomedical Science 2010;67(4):184-8.

(334) Tanguay S, Begin LR, Elhilali MM, Behlouli H, Karakiewicz PI, Aprikian AG. Comparative evaluation of total PSA, free/total PSA, and complexed PSA in prostate cancer detection. Urology 2002 Feb;59(2):261-5.

(335) Tello FL, Prats CH, Gonzalez MD. Free and complexed prostate-specific antigen (PSA) in the early detection of prostate cancer. Clinical Chemistry & Laboratory Medicine 2001 Feb;39(2):116-20.

(336) Thakur V, Singh PP, Talwar M, Mukherjee U. Utility of free/total prostate specific antigen (f/t PSA) ratio in diagnosis of prostate carcinoma. Disease Markers 2003;19(6):287-92.

(337) Thiel RP, Oesterling JE, Wojno KJ, Partin AW, Chan DW, Carter HB, et al. Multicenter comparison of the diagnostic performance of free prostate-specific antigen. Urology 1996 Dec;48(6A):45-50.

(338) Topolcan O, Fuchsova R, Klecka J, Hora M, Vrzalova J. Tumor markers serum levels for early diagnosis of prostate cancer. Tumor Biol 2012;33:S47-S48.

(339) Tornblom M, Norming U, Adolfsson J, Becker C, Abrahamsson PA, Lilja H, et al. Diagnostic value of percent free prostate-specific antigen: retrospective analysis of a population-based screening study with emphasis on men with PSA levels less than 3.0 ng/mL. Urology 1999 May;53(5):945-50.

(340) Toubert ME, Guillet J, Chiron M, Meria P, Role C, Schlageter MH, et al. Percentage of free serum prostate-specific antigen: a new tool in the early diagnosis of prostatic cancer. European Journal of Cancer 1996 Nov;32A(12):2088-93.

(341) Trinkler FB, Schmid DM, Hauri D, Pei P, Maly FE, Sulser T. Free/total prostate-specific antigen ratio can prevent unnecessary prostate biopsies. Urology 1998 Sep;52(3):479-86.

(342) Trygg G, Pousette A, Ekengren J, Hahn RG. Free and total prostate-specific antigen serum concentrations do not help to detect prostate cancer in patients with urinary outlet obstruction. Br J Urol 1997;80(4):618-22.

(343) Van Cangh PJ, De NP, De VL, Sauvage P, Tombal B, Lorge F, et al. Free to total prostate-specific antigen (PSA) ratio improves the discrimination between prostate cancer and benign prostatic hyperplasia (BPH) in the diagnostic gray zone of 1.8 to 10 ng/mL total PSA. Urology 1996 Dec;48(6A):67-70.

(344) Van Cangh PJ, De NP, Sauvage P, Tombal B, Elsen M, Lorge F, et al. Free to total prostate-specific antigen (PSA) ratio is superior to total-PSA in differentiating benign prostate hypertrophy from prostate cancer. Prostate - Supplement 1996;7:30-4.

(345) Vashi AR, Wojno KJ, Henricks W, England BA, Vessella RL, Lange PH, et al. Determination of the "reflex range" and appropriate cutpoints for percent free prostate-specific antigen in 413 men referred for prostatic evaluation using the AxSYM system. Urology 1997 Jan;49(1):19-27.

(346) Veltri RW, Miller MC. Free/total PSA ratio improves differentiation of benign and malignant disease of the prostate: critical analysis of two different test populations. Urology 1999 Apr;53(4):736-45.

(347) Veneziano S, Pavlica P, Compagnone G, Martorana G. Usefulness of the (F/T)/PSA density ratio to detect prostate cancer. Urol Int 2005;74(1):13-8.

(348) Vessella RL, Lange PH, Partin AW, Chan DW, Sokoll LJ, Sasse EA, et al. Probability of prostate cancer detection based on results of a multicenter study using the AxSYM free PSA and total PSA assays. Urology 2000 Jun;55(6):909-14.

(349) Vickers AJ, Wolters T, Savage CJ, Cronin AM, O'Brien MF, Pettersson K, et al. Prostate-specific antigen velocity for early detection of prostate cancer: result from a large, representative, population-based cohort. European Urology 2009 Nov;56(5):753-60.

(350) Vilanova JC, Barcelo-Vidal C, Comet J, Boada M, Barcelo J, Ferrer J, et al. Usefulness of prebiopsy multifunctional and morphologic MRI combined with free-to-total prostate-specific antigen ratio in the detection of prostate cancer. AJR Am J Roentgenol 2011 Jun;196(6):W715-W722.

(351) Vincendeau S, Stephan C, Houlgatte A, Semjonow A. The beckman coulter prostate health index (PHI) Increases the specificity of detection of prostate cancer and reduces the number of negative biopsies. Clin Chem Lab Med 2011;49:S270.

(352) Vogl M, Muller MM, Holtl W. Clinical usefulness of percentage of free serum prostate specific antigen. Clin Chim Acta 1997 Feb 3;258(1):79-90.

(353) Vukotic V, Cerovic S, Kozomara M, Lazic M. The predictive value of PSA in diagnosis of prostate cancer in non screened population. Acta Chirurgica Iugoslavica 2005;52(4):81-7.

(354) Wald NJ, Watt HC, George L, Knekt P, Helzlsouer KJ, Tuomilehto J. Adding free to total prostate-specific antigen levels in trials of prostate cancer screening. British Journal of Cancer 2000 Feb;82(3):731-6.

(355) Walz J, Haese A, Scattoni V, Steuber T, Chun FK, Briganti A, et al. Percent free prostate-specific antigen (PSA) is an accurate predictor of prostate cancer risk in men with serum PSA 2.5 ng/mL and lower. Cancer 2008 Nov 15;113(10):2695-703.

(356) Wang TJ, Linton HJ, Payne J, Rittenhouse HG, Chan DW, Partin AW, et al. Generation of PSA-ACT-specific monoclonal antibodies and their application in a sandwich immunoassay. Hybridoma 1999 Dec;18(6):535-41.

(357) Wang Y, Sun G, Pan JG, Guo ZJ, Li T. Performance of tPSA and f/tPSA for prostate cancer in Chinese. A systematic review and meta-analysis. [Review] [16 refs]. Prostate Cancer & Prostatic Diseases 2006;9(4):374-8.

(358) Wang Z, Zhang P, Chong T, Zhao L. The clinical significance of percent free PSA in differentiating prostate cancer and benign prostate hyperplasia. Acad J Xi'An Jiaotong Univ 2004;16(1):75-7.

(359) Wechsel PH, Petri E, Bichler KH, Schreiber M. Free PSA in the detection of prostatic carcinoma. Anticancer Res 1997 Jul;17(4B):3015-8.

(360) Wesseling S, Stephan C, Semjonow A, Lein M, Brux B, Sinha P, et al. Determination of non-alpha1-antichymotrypsin-complexed prostate-specific antigen as an indirect measurement of free prostate-specific antigen: analytical performance and diagnostic accuracy. Clinical Chemistry 2003 Jun;49(6):887-94.

(361) Wians FH, Jr., Cheli CD, Balko JA, Bruzek DJ, Chan DW, Sokoll LJ. Evaluation of the clinical performance of equimolar- and skewed-response total prostate-specific antigen assays versus complexed and free PSA assays and their ratios in discriminating between benign prostatic hyperplasia and prostate cancer. Clin Chim Acta 2002 Dec;326(1-2):81-95.

(362) Winkler MH, Kulinskaya E, Gillatt DA. Prediction of prostate cancer in extended-field biopsies of the prostate. BJU Int 2004 Mar;93(4):516-21.

(363) Wolff JM, Borchers H, Effert PJ, Habib FK, Jakse G. Free-to-total prostate-specific antigen serum concentrations in patients with prostate cancer and benign prostatic hyperplasia. Br J Urol 1996 Sep;78(3):409-13.

(364) Wolff JM, Boeckmann W, Effert PJ, Habib FK, Jakse G. Increased discrimination between benign prostatic hyperplasia and prostate cancer through measurement of percentage free PSA. Anticancer Res 1997 Jul;17(4B):2993-4.

(365) Wu CT, Chuang CK, Chou CC, Chu SH, Chen HW, Chen CS, et al. The role of free to total prostate-specific antigen ratio for prostate cancer in screening patients with total serum levels between 4 and 20 ng/ml. Chang Gung Medical Journal 2000 Mar;23(3):142-8.

(366) Wu JT, Liu GH, Zhang P, Stephenson RA. Monitoring percent free PSA in serial specimens: improvement of test specificity, early detection, and identification of occult tumors. Journal of Clinical Laboratory Analysis 1998;12(1):26-31.

(367) Wymenga LF, Duisterwinkel FJ, Groenier K, Visser-van BP, Marrink J, Mensink HJ. Clinical implications of free-to-total immunoreactive prostate-specific antigen ratios. Scandinavian Journal of Urology & Nephrology 2000 Jun;34(3):181-7.

(368) Yamamoto S, Maruyama T, Kondoh N, Nojima M, Takiuchi H, Hirota S, et al. Diagnostic efficacy of free to total ratio of prostate-specific antigen and prostate-specific antigen velocity, singly and in combination, in detecting prostate cancer in patients with total serum prostate-specific antigen between 4 and 10 ng/ml. International Urology & Nephrology 2008;40(1):85-9.

(369) Yang CR, Su CK, Chiu KY, Ho HC, Ou YC, Cheng CL, et al. Free / total prostate specific antigen ratio for prostate cancer detection: a prospective blind study. Anticancer Res 2005 May;25(3c):2439-43.

(370) Yeniyol CO, Bozkaya G, Cavusoglu A, Arslan M, Karaca B, Ayder AR. The relation of prostate biopsy results and ratio of free to total PSA in patients with a total PSA between 4-20 ng/mL. International Urology & Nephrology 2001;33(3):503-6.

(371) Yokomizo Y, Miyoshi Y, Nakaigawa N, Makiyama K, Ogawa T, Yao M, et al. Free PSA/total PSA ratio increases the detection rate of prostate cancer in twelve-core biopsy. Urol Int 2009;82(3):280-5.

(372) Yoshida K, Honda M, Sumi S, Arai K, Suzuki S, Kitahara S. Levels of free prostate-specific antigen (PSA) can be selectively measured by heat treatment of serum: free/total-PSA ratios improve detection of prostate carcinoma. Clin Chim Acta 1999 Feb;280(1-2):195-203.

(373) Zambon CF, Prayer-Galetti T, Basso D, Padoan A, Rossi E, Secco S, et al. Effectiveness of the combined evaluation of KLK3 genetics and free-to-total prostate specific antigen ratio for prostate cancer diagnosis. J Urol 2012 Oct;188(4):1124-30.

(374) Zhang WM, Finne P, Leinonen J, Vesalainen S, Nordling S, Stenman UH. Measurement of the complex between prostate-specific antigen and alpha1-protease inhibitor in serum. Clinical Chemistry 1999 Jun;45:814-21.

(375) Zhang WM, Finne P, Leinonen J, Salo J, Stenman UH. Determination of prostate-specific antigen complexed to alpha(2)-macroglobulin in serum increases the specificity of free to total PSA for prostate cancer. Urology 2000 Aug 1;56(2):267-72.

(376) Zhang WM, Finne P, Leinonen J, Stenman UH. Characterization and determination of the complex between prostate-specific antigen and alpha 1-protease inhibitor in benign and malignant prostatic diseases. Scandinavian Journal of Clinical and Laboratory Investigation Supplement 2000;233:51-8.

(377) Zhao Z, Liu J, Li S, Shen W. Serum insulin-like growth factor I/free prostate specific antigen (IGF-I/fPSA) ratio enhances prostate cancer detection in men with total PSA 4.0-10.0 ng/ml. Journal of Surgical Oncology 2007 Jul 1;96(1):54-61.

(378) Zheng XY, Xie LP, Wang YY, Ding W, Yang K, Shen HF, et al. The use of prostate specific antigen (PSA) density in detecting prostate cancer in Chinese men with PSA levels of 4-10 ng/mL. Journal of Cancer Research & Clinical Oncology 2008 Nov;134(11):1207-10.

Systematic review report for questions 6.2a and 6.2b

Clinical Question 6: In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what tests for prostate cancer should be offered in addition to a PSA test?

Candidate tests include:

Free-to-total PSA %

PSA velocity

Prostate health index

Repeated total PSA

PICO question 6.2:

6.2a: For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring PSA velocity improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single elevated total PSA result above 3.0 ng/mL?

Population	Index Test 1	Index Test 2	Reference standard	Outcomes
Men without prostate cancer diagnosis or symptoms that might indicate prostate cancer	Total PSA > 3.0 ng/ml **or** abnormal PSA velocity	Total PSA >3.0 ng/mL only	Prostate biopsy	Diagnostic performance

6.2b: For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring PSA velocity improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL?

Population	Index Test 1	Index Test 2	Reference standard	Outcomes
Men without prostate cancer diagnosis or symptoms that might indicate prostate cancer	Total PSA >3.0 ng/mL **and** abnormal PSA velocity	Total PSA >3.0 ng/mL only	Prostate biopsy	Diagnostic performance

1. Methods

1.1 Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption guidelines had to be evidence based and meet the pre-specified criteria of scores of greater or equal to 70% for the domains rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

1.2 Literature Search

Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched from 1990 using text terms and, where available, database specific subject headings. Each database was searched for articles dealing with prostate cancer. In Medline and Embase databases the prostate cancer search was combined with a search for prostate-specific antigen (PSA) and PSA velocity (PSAV). To identify studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples. A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 added to the relevant database after February 2014. Alerts were checked until July 2014. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched regularly up until April 2014 for relevant reviews published after the initial search. Reference lists of all relevant articles were checked for potential additional articles.

1.3 PICO Question 6.2a - Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Diagnostic performance	Predictive accuracy
Study design	Fully paired diagnostic study, or paired randomised cohort study	Diagnostic case-control or studies of diagnostic yield
Population	Men without prostate cancer diagnosis or symptoms that might indicate prostate cancer, who had undergone prostate biopsy or TURP and at least 80% of those undergoing biopsy had undergone an initial rather than a repeat prostate biopsy	- Included men with prostate cancer or some other urologic disease e.g. bladder cancer or men undergoing a particular treatment e.g. finasteride. - Restricted to men who only had an abnormal DRE and/or abnormal TRUS. - Included men whose cancer status was not based on biopsy or TURP pathology.
Index test 1	An abnormal PSA velocity (regardless of total PSA level) **or** an elevated initial total PSA as separate indications for biopsy	- Less than 3 total PSA measurements used to calculate the PSA velocity. - Did not use a consistent assay for total PSA tests. - Evaluated multiple total PSA measurements that were <3 months apart or taken over a period >4 years for PSA velocity calculations. - Used total PSA thresholds which were greater than 4.0 ng/mL* and not age-specific reference upper limits. - Bloods were drawn for PSA velocity calculations after biopsy. - Did not use a commercial total PSA test (e.g. Hybritech, Immulite, Abbott, Roche, Bayer).
Index test 2	An elevated initial total PSA alone as the indication for biopsy	
Reference standard	Prostate biopsy which included 6 or more cores or TURP	
Indications for biopsy	- Indications for biopsy include a total PSA level above thresholds of 4.0	Indications for biopsy not precisely defined and no subgroup analysis for men with PSA >4.0 ng/mL^

	ng/mL or less, or age-specific reference upper limits. - Or an abnormal PSA velocity result.	
Outcomes	Accuracy relative to using total PSA test alone**: - Additional cancer (true positives) detected - Additional unnecessary biopsies (false positives) - Additional unnecessary biopsies per additional cancer detected	
Language	English	
Publication period	After 31st December 1989 and before 1st March 2014	

TURP = transurethral resection of the prostate

**Verification bias is a major issue when assessing the diagnostic performance of tests for prostate cancer as men normally do not undergo biopsy unless they are test positive. As a result most studies examining the performance of tests in diagnosing prostate cancer are only able to report numbers of true positives and false positives. Where there is a comparison of two index tests in the same patient and where one index test is purely adding additional test positives to the other index test, as when PSA velocity is used to test men with PSA levels below the PSA threshold, this data can be used to calculate the difference in true positives and the difference in false positives and the number of additional false positives for each additional cancer detected; findings that will not be subject to verification bias.

^ If indications for biopsy not reported assumed that all men with PSA >4.0 ng/mL were offered biopsy due to the elevated total PSA result alone.

* This question focuses on a total PSA threshold of 3.0 ng/mL. However, studies using a total PSA threshold of up to 4.0 ng/mL were also included as the day-to-day biological variability in a man's PSA level of 15% means that, for a man with an average level of 3.0 ng/mL, the levels on consecutive days can be as high as 3.9 ng/mL (upper 95th percentile).

Conference proceedings identified by the search literature searches were included if they met the inclusion criteria.

1.4 PICO Question 6.2b - Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Diagnostic performance	Predictive accuracy
Study design	Fully paired diagnostic study, or paired randomised cohort study	Diagnostic case-control or studies of diagnostic yield
Population	Men without prostate cancer diagnosis or symptoms that might indicate prostate cancer, who had an initial total PSA >2.0 ng/mL but <5.5 ng/mL, unless participants were at higher risk of prostate cancer, aged over 60 or there were subgroup analyses for age, risk or PSA level^^, and who had undergone prostate biopsy or TURP and at least 80% of those undergoing biopsy had undergone an initial rather than a repeat prostate biopsy	- Included men with prostate cancer or some other urologic disease e.g. bladder cancer or men undergoing a particular treatment e.g. finasteride. - Restricted to men who only had an abnormal DRE and/or abnormal TRUS. - Included men whose cancer status was not based on biopsy or TURP pathology.

Index test 1	An elevated initial total PSA **together with** an abnormal PSA velocity as a single indication for biopsy	- Less than 3 total PSA measurement used to calculate the PSA velocity. - Did not use a consistent assay for total PSA tests. - Evaluated multiple total PSA measurements that were < 3 months apart or taken over a period > 4 years for PSA velocity calculations. - Bloods were drawn for PSA velocity calculations after biopsy. - Used total PSA thresholds which were greater than 4.0 ng/mL^^ and not age-specific reference upper limits. - Did not use a commercial total PSA test (e.g. Hybritech, Immulite, Abbott, Roche, Bayer).
Index test 2	An elevated initial total PSA an indication for biopsy	
Reference standard	Prostate biopsy (or TURP) which included 6 or more cores	
Indications for biopsy	Indications for biopsy include a total PSA level above thresholds of 4.0 ng/mL or less, or age-specific reference upper limits	Indications for biopsy not precisely defined and no subgroup analysis for men with PSA >4.0 ng/mL^
Outcomes	Diagnostic performance relative** to using total PSA alone: - Relative specificity (% unnecessary biopsies avoided), - Relative sensitivity (% cancers detected missed), - Unnecessary biopsies avoided per cancer missed	
Language	English	
Publication period	After 31st December 1989 and before 1st March 2014	

TURP = transurethral resection of the prostate

**Verification bias is a major issue when assessing the diagnostic performance of tests for prostate cancer as men normally do not undergo biopsy unless they are test positive. As a result most studies examining the performance of tests in diagnosing prostate cancer are only able to report numbers of true positives and false positives. Where there is a comparison of two index tests in the same patient and where one index test is identifying a subgroup of those positive with the other index test so as to reduce the number of false positives, as when the PSA velocity is used to test men with PSA levels above the PSA threshold, this data can be used to calculate the decrease in true positives and relative sensitivity, the decrease in false positives and relative specificity and the number of unnecessary biopsies avoided (decrease in false positives) for each cancer missed (decrease in true positives); findings that will not be subject to verification bias.

^ If indications for biopsy not reported assumed that all men with PSA >4.0 ng/mL were offered biopsy due to the elevated total PSA result alone

^^ This question focuses on PSA velocity as a means to improve specificity for men with a total PSA level above 3.0 ng/mL. Because of the analytical and biological variability of total PSA, including the chronological rise in PSA in men in their sixties, this review focused on studies that used total PSA thresholds between 2.0 and 4.0 ng/mL or age-specific thresholds. Restricting the evidence to studies that used a total PSA threshold of 3.0 ng/mL would have limited the evidence and would not have taken into account analytical variation in the total PSA test over the last two decades.
Men with only slightly elevated levels are less likely to have prostate cancer and could benefit from attempts to improve specificity without compromising sensitivity, whereas men with higher PSA levels are more likely to have prostate cancer and for such men attempts to reduce unnecessary biopsies could compromise the

effectiveness of the recommended PSA testing strategy. As a result, studies using a single total PSA threshold were restricted to those whose participants had a total PSA ≤ 5.5 ng/mL unless there were analyses for older men (who are more likely not to have prostate cancer despite a total PSA > 5.5 ng/mL).

Conference proceedings identified by the search literature searches were included if they met the inclusion criteria.

2. Results

2.1 Guidelines

Three guidelines were identified that contained potentially relevant recommendations. These recommendations were not adopted as they either were not based on a systematic review or did not meet the pre-specified AGREE II criteria for adoption. These guidelines and the reason why they were not adopted are listed in Appendix C.

In Australia the Royal College of Pathologists of Australasia has consensus based recommendations regarding the role of PSA velocity in PSA testing (http://www.rcpa.edu.au/Library/College-Policies/Position-Statements/Prostate-Specific-Antigen-Testing-Age-related-inte, accessed 20/10/14).

3. Notes regarding follow up PSA testing;

> *b. An estimation of the rate of PSA rise should be considered in all follow up PSA testing. A PSA level that has doubled within 2 or 4 years is associated with a high risk and should be managed with immediate specialist referral or confirmatory testing followed by referral as indicated. Ideally, at least three PSA levels are required using the same method for a reliable estimation of PSA doubling time.*

2.2 Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the systematic review. The Medline search identified 1,584 citations and the Embase search an additional 2,053 citations. The search of the Cochrane Database of Systematic Reviews 59 citations, the Database of Abstracts of Reviews of Effects 282 citations and the Health Technology Assessment database identified an additional 216 citations, resulting in a total of 4,194 citations. Titles and abstracts were examined and 64 articles were retrieved for a more detailed evaluation. No additional potential citations were identified from the reference list of retrieved articles.

No articles met the inclusion criteria for question 6.2a and one article met the inclusion criteria for question 6.2b and was included in the review. There were no studies of ATSI men that met the inclusion criteria.

The retrieved articles that were not included and the reason for their exclusion are documented in Appendix C. In summary, the main reasons for exclusion were unclear or inappropriate data used to calculate PSA velocity for example velocity calculated using only 2 total PSA measures, the total PSA assay was not described or the population was inappropriate.

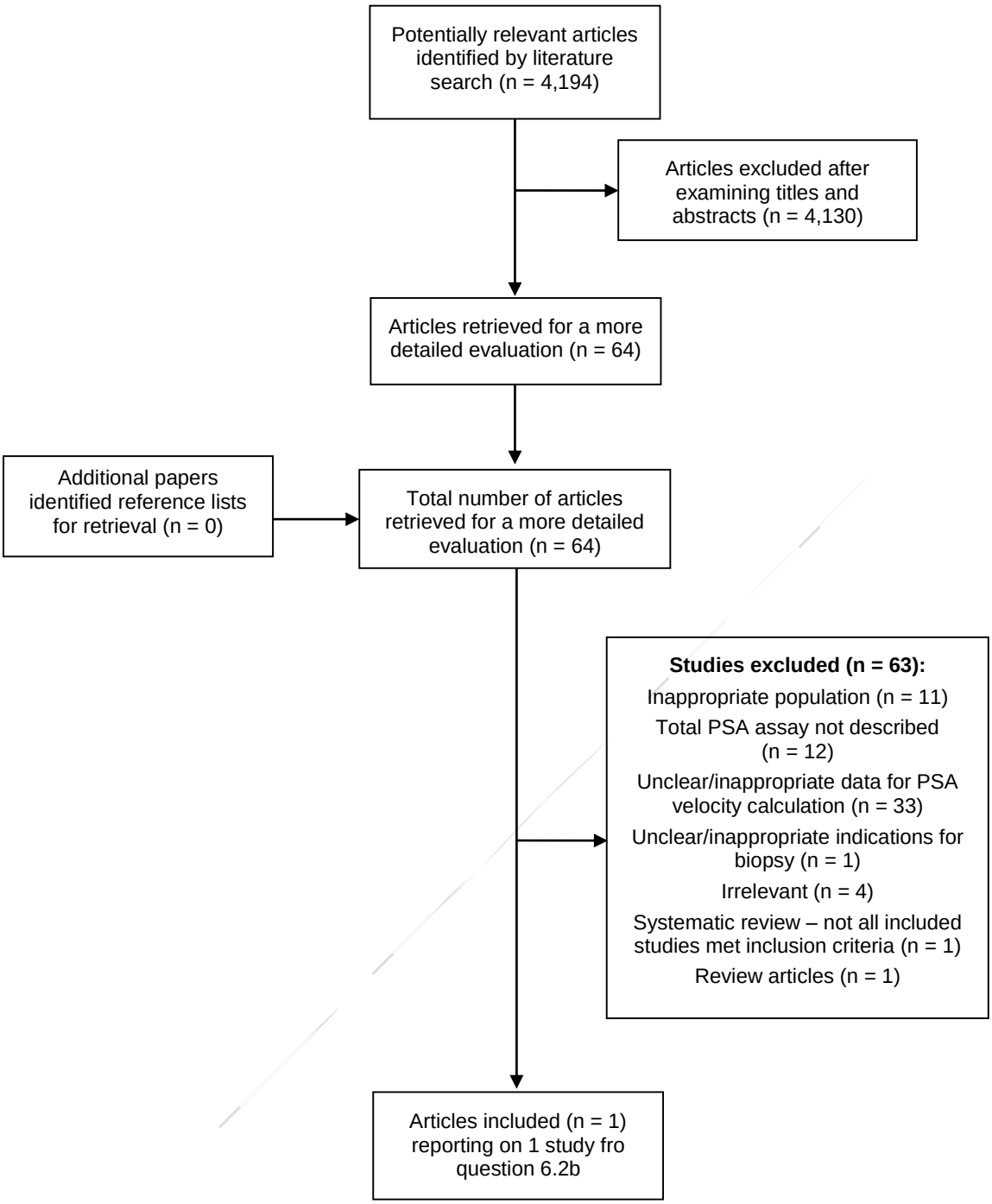


Figure 1. Process of inclusion and exclusion of studies.

2.3 Study Characteristics

Table 1: Characteristics of studies comparing performance characteristics of PSA velocity and total PSA with those of tPSA alone with respect to prostate cancer detection

Study	Design	Participants	Indication for Biopsy	Biopsy (Reference)	Blood collection/ processing/ storage	PSA assay (Index Test 1)	PSA Velocity (Index Test 2)	Comments
Djavan 1999 (Austria)	Diagnostic accuracy study	Men referred for either early cancer detection or for lower urinary symptoms between January 1997 and October 1998. **Exclusion Criteria:** prostate cancer, acute or chronic prostatitis, PIN, PSA > 4 ng/mL, urinary retention, previous catheter use, or a urinary tract infection **Age:** mean 67.1 years **Range:** 40 to 78 years **PSA:** 2.5-4.0 ng/mL **N = 273**	Total PSA ≥ 2.5 ng/mL	Transrectal ultrasound with systematic sextant needle biopsies and two additional transition zone biopsies. If the first biopsies were negative, within 6 weeks an additional set of sextant biopsies (+2 transition zone biopsies) was routinely performed to minimize sampling errors.	Not reported	Equimolar AxSYM PSA assay (Abbott Laboratories, Abbot Park, III)	PSAV based on PSA measurements (same assay) at 12-month intervals	Does not state how many men had PSAV data

PIN = prostatic intraepithelial neoplasia; PSA = prostate specific antigen; PSAV = prostate specific antigen velocity

2.4 Study Quality/Risk of Bias

Assessment of risk of bias of included diagnostic studies is described in Tables 2 and 3.

Table 2: Assessment of risk of bias for included study (n = 1)

Quality Category	N (%)
I. Selection of participants	
Low risk of bias	1 (100)
High risk of bias	-
Unclear risk of bias	-
II. Index test 1	
Low risk of bias	-
High risk of bias	1 (100)
Unclear risk of bias	-
III. Index test 2	
Low risk of bias	-
High risk of bias	-
Unclear risk of bias	1 (100)
IV. Reference standard	
Low risk of bias	-
High risk of bias	1 (100)
Unclear risk of bias	-
V. Flow and timing	
Low risk of bias	-
High risk of bias	-
Unclear risk of bias	1 (100)
Not applicable	-

Table 3: Assessment of risk of bias in individual included study (n = 1)

	Patient selection	Index test 1	Index test 2	Reference standard*	Flow and timing**	Overall Risk of bias
Djavan 1999	Low	High	Unclear	High	Unclear	At risk

** Adequate reference standard pre-specified as biopsy ≥12 cores.*

*** Appropriate interval between index test(s) and reference standard pre-specified as less than 1 year – for biopsy referral cohorts where interval was not stated, assumed to be less than 1 year*

Key to overall rating

Low risk of bias: A study that received low for all domains

At risk of bias: A study rated at high or unclear risk of bias for one or more domains

2.5 Study Results

PROSTATE CANCER DIAGNOSIS

Table 4: Results of study comparing diagnostic accuracy of PSA velocity and total PSA with total PSA alone

Study	Men biopsied with PSVD data (N)	Relative* sensitivity of PSAV	Relative* specificity of PSAV (% reduction in false positives)	AUC tPSA	AUC PSAV	p value
tPSA 2.5 – 4.0 ng/mL						
Djavan 1999 (Austria)	NR	95% 90% 80%	10.1%^ ~14%^ ~27%^	NR	NR	AUC significantly smaller for PSAV than for tPSA which was in turn significantly lower than the AUC for f/ tPSA%.

~ Approximate; * Relative to total PSA for the total PSA range specified; ^ estimated by review team from published receiver operator curve; AUC = area under the curve; f/t PSA% = free-to-total PSA; NR = not reported; PSAV = prostate specific antigen velocity; tPSA = total PSA.

2.6 Body of Evidence

Table 5: Diagnostic performance characteristics of PSA velocity and total PSA compared with those of total PSA alone – **prostate cancer diagnosis**

Study	Study type	N	Cancer detection rate	Level of evidence *	Risk of bias**	tPSA threshold	PSAV threshold	% cancers missed^^	% Unnecessary biopsies avoided ^^	ΔFP/ ΔTP	p value for AUC
tPSA 2.5 – 4.0 ng/mL											
Djavan 1999	Prospective **diagnostic** accuracy	273	24.2%	III-2	At risk	2.5 ng/mL	NR	5% 10% 20%	10.1^ ~14^ ~27^	NR	AUC significantly smaller for PSAV than for tPSA

* Refer to Appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^^ Relative to tPSA alone in tPSA range specified; ^ estimated by review team from published receiver operator curve; ΔFP = difference in false positives; ΔTP = difference in true positives; AUC = area under the curve; NR = not reported; PSAV = prostate specific antigen velocity; tPSA = total PSA.

Clinical significance of size of effect is addressed in the assessment of clinical impact in the NHMRC evidence statement form.

Assessment of the relevance of the evidence in terms of whether the outcomes were directly relevant to the patient or surrogate outcomes was not assessed as it was not considered relevant to diagnostic performance studies.

References: Included studies

1. Djavan B, Zlotta A, Kratzik C, Remzi M, Seitz C, Schulman CC, Marberger M. PSA, PSA density, PSA density of transition zone, free/total PSA ratio, and PSA velocity for early detection of prostate cancer in men with serum PSA 2.5 to 4.0 ng/mL. *Urology* 1999;54(3):517-22.

APPENDICES

Appendix A: Search strategies used

For Medline database:

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	exp Prostatic Neoplasms/
3	1 OR 2
4	(PSADT or PSAV or vPSA or PSA-DT).mp.
5	(PSA adj2 (velocity or 'doubling time' or dynamic$ or kinetic$ or slope$ or accelerat$ or inclin$)).mp.
6	(prostate specific antigen or prostate-specific antigen adj2 (velocity or 'doubling time' or dynamic$ or kinetic$ or slope$ or accelerat$ or inclin$)).mp.
7	((PSA or prostate specific antigen or prostate–specific antigen) adj4 (speed or rate$ or change$ or doubl$)).mp.
8	4 OR 5 OR 6 OR 7
9	salvage.mp.
10	(biochemical adj1 (recurrence or relapse or disease or failure)).mp.
11	active surveillance.mp.
12	((castrat$ or hormone) adj1 (resistant or resistance)).mp.
13	9 OR 10 OR 11 OR 12
14	3 AND 8
15	14 NOT 13
16	limit 15 to (english language and yr="1990 -Current")

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	exp prostate cancer/
3	1 OR 2
4	(PSADT or PSAV or vPSA or PSA-DT).mp.
5	(PSA adj2 (velocity or 'doubling time' or dynamic$ or kinetic$ or slope$ or accelerat$ or inclin$)).mp.
6	((prostate specific antigen or prostate-specific antigen) adj2 (velocity or 'doubling time' or dynamic$ or kinetic$ or slope$ or accelerat$ or inclin$)).mp.
7	((PSA or prostate specific antigen or prostate-specific antigen) adj4 (speed or rate$ or change$ or doubl$)).mp.
8	4 OR 5 OR 6 OR 7
9	salvage.mp.
10	(biochemical adj1 (recurrence or relapse or disease or failure)).mp.
11	active surveillance.mp.
12	((castrat$ or hormone) adj1 (resistant or resistance)).mp.
13	9 OR 10 OR 11 OR 12
14	3 AND 8
15	14 NOT 13
16	limit 15 to (english language and humans and yr="1990-current")
17	commentary/
18	case report/
19	letter.pt.
20	historical article.pt.
21	chemotherapy.mp.
22	editorial.pt.
23	17 OR 18 OR 19 OR 20 OR 21 OR 22
24	16 NOT 23

ATSI search terms used

#	Searches
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	(#1 AND #2) OR #3

For Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment database:

#	Searches
1	(prostat$ adj3 (cancer$ OR carcinoma$ OR malignan$ OR tumo?r$ OR neoplas$ OR metastas$ OR adeno$)).tw

Appendix B:

Level of Evidence rating criteria – Diagnostic accuracy studies

Level	Study design
I	Meta-analysis or a systematic review of level II studies
II	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation
III-1	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation
III-2	A comparison with reference standard that does not meet the criteria required for level II and III-1 evidence
III-3	Diagnostic case-control study
IV	Study of diagnostic yield (no reference standard)

According to the standards of the National Health and Medical Research Council

Appendix C:

Potentially relevant guidelines identified and reason why not adopted

Year	Organisation	Title	Reason why not adopted
2009	American Urological Association	Early Detection of Prostate Cancer: AUA Guideline	Did not meet pre-specified AGREE II criteria for inclusion
2013	European Society for Medical Oncology	ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Consensus based
2012	Royal Australian College of General Practitioners	Guidelines for preventive activities in general practice	Not based on a systematic review

Excluded Studies

Study	Reason for Exclusion
Auprich 2011	Inappropriate population (Study population had a prior negative biopsy)
Benecchi 2006	Inappropriate population (Study included men with rebiopsy, does not report initial biopsy separately)
Benecchi 2008	Inappropriate population (Study included men with rebiopsy, does not report initial biopsy separately)
Benecchi 2011	Inappropriate population (Study included men with rebiopsy, does not report initial biopsy separately)
Benecchi 2012	Total PSA (tPSA) assay not described (No information on type of tPSA test, does not specify indications for biopsy)
Benecchi 2013	Unclear/inappropriate data for PSA velocity (PSAV) calculation (Study included men with 2 tPSA measurements in PSAV calculation, does not specify indications for biopsy)
Berger 2005	Unclear/inappropriate data for PSAV calculation (Time period of tPSA measurements exceeds 4 years)
Berger 2007	Unclear/inappropriate data for PSAV calculation (Time period of tPSA measurements exceeds 4 years)
Bertaccini 2013	tPSA assay not described (No information on type of tPSA test, does not specify indications for biopsy)
Bittner 2009	Inappropriate population (Study population had a prior negative biopsy)
Carter 2006	Unclear/inappropriate data for PSAv calculation (Time period for of tPSA measurements exceeds 4 years)
Carter 2007	Inappropriate population (Study included men with 2 tPSA measurements in PSA velocity calculation)
Choi 2011	Unclear/inappropriate data for PSAV calculation (PSA velocity calculation only used 2 tPSA measurements)
Ciatto 2008	Unclear/inappropriate data for PSAV calculation (PSA velocity calculation only used 2 tPSA measurements)
Concato 2006	tPSA assay not described (No information on type of tPSA test)
Connolly 2007	tPSA assay not described (No information on type of tPSA test, does not specify indications for biopsy)
Connolly 2008	tPSA assay not described (No information on type of tPSA test, tPSA threshold for biopsy was greater than 10ng/mL)
Djavan 1998	Unclear/inappropriate indication for biopsy (Does not specify indications for biopsy)
Eggener 2008	Unclear/inappropriate data for PSAV calculation (PSA velocity calculation only used 2 tPSA measurements)
Fang 2002	Unclear/inappropriate data for PSAV calculation (Time period of tPSA measurements exceeds 4 years)
Hakimi 2012	tPSA assay not described (No information on type of tPSA test)
Haller 2012	Unclear/inappropriate data for PSAV calculation (Time period of tPSA measurements exceeds 4 years)

Harris 1997	Inappropriate population (Study included men that had not undergone initial biopsy)
Inman 2012	Unclear/inappropriate data for PSAV calculation (PSA velocity calculation only used 2 tPSA measurements)
Ito 2000	Unclear/inappropriate data for PSAV calculation (No information on number or time period of tPSA measurements for PSA velocity calculation, repeat biopsy patients included in analysis)
Ito 2002	Unclear/inappropriate data for PSAV calculation (Study included men with 2 tPSA measurements in PSA velocity calculation, no information on type of tPSA test)
Ito 2003	Unclear/inappropriate data for PSAV calculation (Study included men with 2 tPSA measurements in PSA velocity calculation, repeat biopsy patients included in analysis)
Jacobsen 2012	Unclear/inappropriate data for PSAV calculation (Time period of tPSA measurements exceeds 4 years)
Karnes 2014	Unclear/inappropriate data for PSAV calculation (PSA velocity calculation included tPSA measurements calculated after initial biopsy)
Kettermann 2010	tPSA assay not described (No information on type of tPSA test, does not specify indications for biopsy, time period of PSA measurements exceeds 4 years)
Kubota 2011	tPSA assay not described (No information on type of tPSA test or time period tPSA measurements were collected to calculate PSA velocity)
Loeb 2007a	Unclear/inappropriate data for PSAV calculation (PSA velocity calculation only used 2 tPSA measurements)
Loeb 2007b	Unclear/inappropriate data for PSAV calculation (Period of tPSA measurements for PSA velocity calculation too short)
Loeb 2008	Unclear/inappropriate data for PSAV calculation (Study included men with 2 tPSA measurements in PSA velocity calculation)
Loeb 2008	Inappropriate population (Not clear if all patients underwent biopsy)
Loeb 2011	Inappropriate population (Study included men that had not undergone initial biopsy)
Loeb 2012	Irrelevant(Does not calculate a suitable PSA dynamic quantity)
Miotto 2004	Irrelevant(Does not calculate PSA velocity in study cohort)
Moul 2007	Unclear/inappropriate data for PSAV calculation (Study included men with 2 tPSA measurements in PSA velocity calculation)
Mouraview 2008	Unclear/inappropriate data for PSAV calculation (Study included men with 2 tPSA measurements in PSA velocity calculation)
O'Brien 2010	Irrelevant (All men in study population had symptoms indicating prostate cancer)
Park 2012	Inappropriate population (All men in study population had prostate cancer, no information on type of tPSA test, does not specify indications for biopsy)
Punglia 2007	Unclear/inappropriate data for PSAV calculation (Study included men with 2 tPSA measurements in PSA velocity calculation, repeat biopsy patients included in analysis)
Rawson 2014	tPSA assay not described (No information on type of tPSA test, does not specify indications for biopsy)
Roobol 2014	Unclear/inappropriate data for PSAV calculation (PSA velocity calculation only used 2 tPSA measurements)
Saavedra 2013	tPSA assay not described (No information on type of tPSA test, does not specify indications for biopsy, time period of tPSA measurements exceeds 4 years)
Sarma 2014	Unclear/inappropriate data for PSAV calculation (Time period of tPSA measurements exceeds 4 years)
Shinmei 2012	tPSA assay not described (No information on type of tPSA test, repeat biopsy patients included in analysis)
Spurgeon 2007	Unclear/inappropriate data for PSAV calculation (Study included men with 2 tPSA measurements in PSAv calculation)
Takechi 2008	Inappropriate population (All men in study population had prostate cancer, PSA velocity calculation only used 2 tPSA measurements)
Tang 2011	Unclear/inappropriate data for PSAV calculation (Study included men with 2 tPSA measurements in PSAV calculation)
Tang 2012	Unclear/inappropriate data for PSAV calculation (Study included men with 2 tPSA measurements in PSAV calculation)
Thanigasalam 2009	Systematic review(No papers met our inclusion criteria)
Uozumi 2002	Irrelevant (No indication of a PSAV calculation)

Vickers 2009	Unclear/inappropriate data for PSAV calculation (Number of tPSA tests for PSA velocity calculation not provided, time period of tPSA measurements exceeds 4 years)
Vickers 2011	Unclear/inappropriate data for PSAV calculation (Time period of tPSA measurements for PSA velocity calculation exceeds 4 years)
Vickers 2013	Review Article
Wallner 2013	Unclear/inappropriate data for PSAV calculation (No indication 3 tPSA measurements were completed within 4 years. Not all men in study underwent biopsy)
Wolters 2009	Unclear/inappropriate data for PSAV calculation (PSAV calculation only used 2 tPSA measurements)
Yamamoto 2009	tPSA assay not described (No information on type of tPSA, number of tPSA tests for PSA velocity calculation not provided, test, does not specify indications for biopsy)
Yu 2007	Unclear/inappropriate data for PSAV calculation (No indication 3 tPSA measurements were completed within 4 years)
Zeliadt 2012	Unclear/inappropriate data for PSAV calculation (No indication 3 tPSA measurements were completed within 4 years. Not all men in study underwent biopsy. Does not specify indications for biopsy)
Zheng 2012	Unclear/inappropriate data for PSAV calculation (PSAV calculation only used 2 tPSA measurements

References: Excluded Studies

1. Auprich M, Augustin H, Budaus L, Kluth L, Mannweiler S, Shariat SF et al. A comparative performance analysis of total prostate-specific antigen, percentage free prostate-specific antigen, prostate-specific antigen velocity and urinary prostate cancer gene 3 in the first, second and third repeat prostate biopsy. *BJU International* 2012; 109(11):June.

2. Benecchi L. PSA velocity and PSA slope. *Prostate Cancer & Prostatic Diseases* 2006; 9(2):169-172.

3. Benecchi L, Pieri AM, Destro PC, Potenzoni M. Optimal measure of PSA kinetics to identify prostate cancer. *Urology* 2008; 71(3):390-394.

4. Benecchi L, Pieri AM, Pastizzaro CD, Potenzoni M. Evaluation of prostate specific antigen acceleration for prostate cancer diagnosis. *Journal of Urology* 2011; 185(3):821-826.

5. Benecchi L, Loeb S. Nomogram with "psa acceleration" predicting high grade prostate cancer. *Journal of Urology* 2012; Conference(var.pagings):April.

6. Benecchi L, Loeb S, Potenzoni M, Bocchi F, Russo F, Del BC. PSA velocity per prostate volume: A tool forprostate cancer diagnosis. *Journal of Urology* 2013; Conference(var.pagings):April.

7. Berger AP, Deibl M, Steiner H, Bektic J, Pelzer A, Spranger R et al. Longitudinal PSA changes in men with and without prostate cancer: assessment of prostate cancer risk. *Prostate* 2005; 64(3):240-245.

8. Berger AP, Deibl M, Strasak A, Bektic J, Pelzer AE, Klocker H et al. Large-scale study of clinical impact of PSA velocity: long-term PSA kinetics as method of differentiating men with from those without prostate cancer. *Urology* 2007; 69(1):134-138.

9. Bertaccini A, Giampaoli M, Manferrari F, Schiavina R, Marchiori D, Martorana G. Researching the more efficient model for calculating the PSA velocity in order to detect a prostate cancer: An explorative study. *Anticancer Research* 2013; Conference(var.pagings):May.

10. Bittner N, Merrick GS, Andreini H, Taubenslag W, Allen ZA, Butler WM et al. Prebiopsy PSA velocity not reliable predictor of prostate cancer diagnosis, Gleason score, tumor location, or cancer volume after TTMB. *Urology* 2009; 74(1):171-176.

11. Carter HB, Ferrucci L, Kettermann A, Landis P, Wright EJ, Epstein JI et al. Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. *Journal of the National Cancer Institute* 2006; 98(21):1521-1527.

12. Carter HB, Kettermann A, Ferrucci L, Landis P, Metter EJ. Prostate-specific antigen velocity risk count assessment: a new concept for detection of life-threatening prostate cancer during window of curability. *Urology* 2007; 70(4):685-690.

13. Choi SY, Chang IH, Kim YS, Kim TH, Kim W, Myung SC. Prostate specific antigen velocity per prostate volume: a novel tool for prostate biopsy prediction. *Urology* 2011; 78(4):874-879.

14. Ciatto S, Rubeca T, Martinelli F, Pontenani G, Lombardi C, Di LS. PSA doubling time as a predictor of the outcome of random prostate biopsies prompted by isolated PSA elevation in subjects referred to an outpatient biopsy facility in a routine clinical scenario. *International Journal of Biological Markers* 2008; 23(3):187-191.

15. Concato J, Wells CK. Prostate-specific antigen 'velocity' as a diagnostic test for prostate cancer. *Journal of Investigative Medicine* 2006; 54(7):November.

16. Connolly D, Black A, Murray LJ, Napolitano G, Gavin A, Keane PF. Methods of Calculating Prostate-Specific Antigen Velocity. *European Urology* 2007; 52(4):October.

17. Connolly D, Black A, Murray LJ, Nambirajan T, Keane PF, Gavin A. The utility of prostate-specific antigen velocity thresholds in clinical practice: a population-based analysis. *BJU International* 2008; 101(12):1507-1512.

18. Eggener SE, Yossepowitch O, Roehl KA, Loeb S, Yu X, Catalona WJ. Relationship of prostate-specific antigen velocity to histologic findings in a prostate cancer screening program. *Urology* 2008; 71(6):1016-1019.

19. Fang J, Metter EJ, Landis P, Carter HB. PSA velocity for assessing prostate cancer risk in men with PSA levels between 2.0 and 4.0 ng/ml. *Urology* 893; 59(6):889-893.

20. Hakimi AA, Agalliu I, Ho GY, Ghavamian R, Yu C, Kattan MW et al. Detection of prostate cancer in an ethnically diverse, disadvantaged population with multiple prostate specific antigen measurements before biopsy. *Journal of Urology* 2012; 187(4):April.

21. Haller H, El-Shafei A, Moussa A, Fareed K, Ramanathan R, Berglund R et al. Value of serial psa measurements for prostate cancer prediction on screening using a maximum likelihood estimation-prostate specific antigen (MLE-PSA) model. *Journal of Urology* 2012; Conference(var.pagings):April.

22. Harris CH, Dalkin BL, Martin E, Marx PC, Ahmann FR. Prospective longitudinal evaluation of men with initial prostate specific antigen levels of 4.0 ng./ml. or less. *Journal of Urology* 1997; 157(5):1740-1743.

23. Inman BA, Zhang J, Shah ND, Denton BT. An examination of the dynamic changes in prostate-specific antigen occurring in a population-based cohort of men over time. *BJU International* 2012; 110(3):375-381.

24. Ito K, Kubota Y, Suzuki K, Shimizu N, Fukabori Y, Kurokawa K et al. Correlation of prostate-specific antigen before prostate cancer detection and clinicopathologic features: evaluation of mass screening populations. *Urology* 2000; 55(5):705-709.

25. Ito K, Yamamoto T, Ohi M, Kubota Y, Fukabori Y, Kurokawa K et al. Usefulness of prostate-specific antigen velocity in screening for prostate cancer. *International Journal of Urology* 2002; 9(6):2002.

26. Ito K, Yamamoto T, Ohi M, Takechi H, Kurokawa K, Suzuki K et al. Natural history of PSA increase with and without prostate cancer. *Urology* 2003; 62(1):64-69.

27. Jacobsen SJ, Jacobson DJ, McGree ME, St Sauver JL, Klee GG, Girman CJ et al. Sixteen-year longitudinal changes in serum prostate-specific antigen levels: the olmsted county study. *Mayo Clinic Proceedings* 2012; 87(1):34-40.

28. Karnes RJ, Rawson L, MacKintosh R, Morrell C, Loeb S, Van Den Eeden S et al. Delay in a biopsy to allow for additional PSA testing often can eliminate the need for the biopsy. *Journal of Urology* 2014; Conference(var.pagings):April.

29. Kettermann AE, Ferrucci L, Trock BJ, Metter EJ, Loeb S, Carter HB. Interpretation of the prostate-specific antigen history in assessing life-threatening prostate cancer. *BJU International* 2010; 106(9):November.

30. Loeb S, Roehl KA, Catalona WJ, Nadler RB. Prostate specific antigen velocity threshold for predicting prostate cancer in young men. *Journal of Urology* 2007; 177(3):899-902.

31. Loeb S, Kettermann A, Ferrucci L, Landis P, Metter EJ, Carter HB. PSA doubling time versus PSA velocity to predict high-risk prostate cancer: data from the Baltimore Longitudinal Study of Aging. *European Urology* 2008; 54(5):1073-1080.

32. Loeb S, Roehl KA, Catalona WJ, Nadler RB. Is the utility of prostate-specific antigen velocity for prostate cancer detection affected by age? *BJU International* 2008; 101(7):817-821.

33. Loeb S, Carter HB, Schaeffer EM, Kettermann A, Ferrucci L, Metter EJ. Distribution of PSA velocity by total PSA levels: data from the Baltimore Longitudinal Study of Aging. *Urology* 2011; 77(1):143-147.

34. Loeb S, Metter EJ, Kan D, Roehl KA, Catalona WJ. Prostate-specific antigen velocity (PSAV) risk count improves the specificity of screening for clinically significant prostate cancer. *BJU International* 2012; 109(4):February.

35. Loeb S, Roehl KA, Nadler RB, Yu X, Catalona WJ. Prostate specific antigen velocity in men with total prostate specific antigen less than 4 ng/ml. *Journal of Urology* 2352; 178(6):2348-2352.

36. Miotto A, Jr., Srougi M, Brito GA, Leite KM, Nesrallah AJ, Ortiz V. Value of various PSA parameters for diagnosing prostate cancer in men with normal digital rectal examination. *International Braz J Urol* 2004; 30(2):109-113.

37. Mizutani K, Maeda S, Seike K, Shinohara Y, Iwata M. Pre-biopsy PSA kinetics in prostate cancer screening: Analysis of Toyota Motor Corporation employees Kubota Y1. *Urology* 2011; Conference(var.pagings):September.

38. Moul JW, Sun L, Hotaling JM, Fitzsimons NJ, Polascik TJ, Robertson CN et al. Age adjusted prostate specific antigen and prostate specific antigen velocity cut points in prostate cancer screening. *Journal of Urology* 503; 177(2):499-503.

39. Mouraviev V, Broadwater G, Sun L, Mayes JM, Moul JW, Polascik TJ. Can Prostate-Specific Antigen and Prostate-Specific Antigen Velocity Be Used for Prostate Cancer Screening in Men Older Than 70 Years? *Urology* 2008; 71(6):June.

40. O'Brien MF, Cronin AM, Fearn PA, Savage CJ, Smith B, Stasi J et al. Evaluation of prediagnostic prostate-specific antigen dynamics as predictors of death from prostate cancer in patients treated conservatively. *International Journal of Cancer* 2011; 128(10):2373-2381.

41. Park JJ, Chen MH, Loffredo M, D'Amico AV. Prostate-specific antigen velocity before and after elimination of factors that can confound the prostate-specific antigen level. *International Journal of Radiation Oncology, Biology, Physics* 2012; 82(3):1217-1221.

42. Punglia RS, Cullen J, McLeod DG, Chen Y, D'Amico AV. Prostate-specific antigen velocity and the detection of gleason score 7 to 10 prostate cancer. *Cancer* 2007; 110(9):1973-1978.

43. Rawson L, MacKintosh R, Morrell C, Karnes RJ, Loeb S, Van Den Eeden S et al. New analysis of PSA trends helps identify deadly cancers prior to biopsy. *Journal of Urology* 2014; Conference(var.pagings):April.

44. Roobol MJ, Kranse R, de Koning HJ, Schroder FH. Prostate-specific antigen velocity at low prostate-specific antigen levels as screening tool for prostate cancer: results of second screening round of ERSPC (ROTTERDAM). *Urology* 313; 63(2):309-313.

45. Saavedra II, Konstantinidis C, Celma A, Agreda F, Placer J, Planas J et al. PSA kinetics does not predict prostate cancer in men subjected to prostate biopsy. *Journal of Urology* 2013; Conference(var.pagings):April.

46. Sarma AV, St.Sauver JL, Jacobson DJ, McGree ME, Klee GG, Lieber MM et al. Racial differences in longitudinal changes in serum prostate-specific antigen levels: The Olmsted county study and the flint men's health study. *Urology* 2014; 83(1):January.

47. Shinmei S, Inoue S, Ohkuchi T, Yasukawa A. Assessment of prostate-specific antigen (PSA) kinetics in prediction of prostate cancer on prostate biopsy. *Urology* 2012; Conference(var.pagings):September.

48. Spurgeon SE, Mongoue-Tchokote S, Collins L, Priest R, Hsieh YC, Peters LM et al. Assessment of prostate-specific antigen doubling time in prediction of prostate cancer on needle biopsy. *Urology* 2007; 69(5):931-935.

49. Takechi H, Ito K, Yamamoto T, Miyakubo M, Ohi M, Suzuki K. Prostate-Specific Antigen Kinetics in Screen-Detected Prostate Cancer in Japan. *Urology* 2008; 72(5):November.

50. Tang P, Sun L, Uhlman MA, Robertson CN, Polascik TJ, Moul JW. Prostate-specific antigen velocity based risk-adapted discontinuation of prostate cancer screening in elderly men. *BJU International* 2011; 108(1):44-48.

51. Tang P, Du W, Xie K, Fu J, Chen H, Yang W et al. Characteristics of baseline PSA and PSA velocity in young men without prostate cancer: Racial differences. *Prostate* 2012; 72(2):01.

52. Thanigasalam R, Mancuso P, Tsao K, Rashid P. Prostate-specific antigen velocity (PSAV): A practical role for PSA? *ANZ Journal of Surgery* 2009; 79(10):October.

53. Uozumi J, Tokuda Y, Fujiyama C, Takagi N, Meiri H, Kuratomi K et al. Annual PSA tests are not necessary for men with a PSA level below 2 ng/mL: findings of the Imari prostate cancer screening program. *International Journal of Urology* 2002; 9(6):334-339.

54. Vickers AJ, Wolters T, Savage CJ, Cronin AM, O'Brien MF, Pettersson K et al. Prostate-specific antigen velocity for early detection of prostate cancer: result from a large, representative, population-based cohort. *European Urology* 2009; 56(5):753-760.

55. Vickers AJ, Savage C, O'Brien MF, Lilja H. Systematic review of pretreatment prostate-specific antigen velocity and doubling time as predictors for prostate cancer. *Journal of Clinical Oncology* 2009; 27(3):398-403.

56. Vickers AJ, Till C, Tangen CM, Lilja H, Thompson IM. An empirical evaluation of guidelines on prostate-specific antigen velocity in prostate cancer detection. *Journal of the National Cancer Institute* 2011; 103(6):462-469.

57. Vickers AJ. Counterpoint: Prostate-specific antigen velocity is not of value for early detection of cancer. *JNCCN Journal of the National Comprehensive Cancer Network* 2013; 11(3):01.

58. Wallner LP, Frencher SK, Hsu JW, Chao CR, Nichol MB, Loo RK et al. Changes in serum prostate-specific antigen levels and the identification of prostate cancer in a large managed care population. *BJU International* 2013; 111(8):1245-1252.

59. Wolters T, Roobol MJ, Bangma CH, Schroder FH. Is prostate-specific antigen velocity selective for clinically significant prostate cancer in screening? European Randomized Study of Screening for Prostate Cancer (Rotterdam). *European Urology* 2009; 55(2):385-392.

60. Yamamoto S, Maruyama T, Kondoh N, Nojima M, Takiuchi H, Hirota S et al. Diagnostic efficacy of free to total ratio of prostate-specific antigen and prostate-specific antigen velocity, singly and in combination, in detecting prostate cancer in patients with total serum prostate-specific antigen between 4 and 10 ng/ml. *International Urology & Nephrology* 2008; 40(1):85-89.

61. Yu X, Loeb S, Roehl KA, Han M, Catalona WJ. The association between total prostate specific antigen concentration and prostate specific antigen velocity. *Journal of Urology* 1301; 177(4):1298-1302.

62. Zeliadt SB, Buist DSM, Reid RJ, Grossman DC, Ma J, Etzioni R. Biopsy follow-up of prostate-specific antigen tests. *American Journal of Preventive Medicine* 2012; 42(1):January.

63. Zheng XY, Zhang P, Xie LP, You QH, Cai BS, Qin J. Prostate-specific antigen velocity (PSAV) and PSAV per initial volume (PSAVD) for early detection of prostate cancer in Chinese men. *Asian Pacific Journal of Cancer Prevention: Apjcp* 2012; 13(11):5529-5533.

Systematic review report for questions 6.3a and 6.3b

Clinical Question 6: In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what tests for prostate cancer should be offered in addition to a PSA test?

Candidate tests include:

Free-to total PSA %

PSA velocity

Prostate health index

Repeated total PSA

PICO question 6.3

6.3a: For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring the Prostate Health Index (PHI) improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single elevated total PSA result above 3.0 ng/mL?

Population	Index test 1	Index test 2	Reference standard	Outcomes
Men without prostate cancer diagnosis or symptoms that might indicate prostate cancer	Total PSA >3.0 ng/mL **or** abnormal PHI test	Total PSA >3.0 ng/mL only	Prostate biopsy	Diagnostic performance

6.3b: For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring the Prostate Health Index (PHI) improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single elevated total PSA result above 3.0 ng/mL?

Population	Index test 1	Index test 2	Reference standard	Outcomes
Men without prostate cancer diagnosis or symptoms that might indicate prostate cancer	Total PSA >3.0 ng/mL **and** abnormal PHI test	Total PSA >3.0 ng/mL only	Prostate biopsy	Diagnostic performance

1. Methods

1.1. Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption guidelines had to be evidence based and meet the pre-specified criteria of scores of greater or equal to 70% for the domains rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

1.2 Literature Search

Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched from 1990 using text terms and, where available, database-specific subject headings. Each database was searched for articles dealing with prostate cancer. In Medline and Embase databases the prostate cancer search was combined with a search for prostate-specific antigen (PSA) and the Prostate Health Index (PHI). To identify studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples. A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 added to the relevant database after February 2014. Alerts were checked until July 2014. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched regularly up until April 2014 for relevant reviews published after the initial search. Reference lists of all relevant articles were checked for potential additional articles.

1.3. PICO Question 6.3a - Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Diagnostic performance	Predictive accuracy
Study design	Fully paired diagnostic study, or paired randomised cohort study	Diagnostic case-control or studies of diagnostic yield
Population	Men without prostate cancer diagnosis or symptoms that might indicate prostate cancer, who had undergone prostate biopsy or TURP and at least 80% of those undergoing biopsy had undergone an initial rather than a repeat prostate biopsy	- Included men with prostate cancer or some other urologic disease e.g. bladder cancer or men undergoing a particular treatment e.g. finasteride. - Restricted to men who only had an abnormal DRE and/or abnormal TRUS. - Included men whose cancer status was not based on biopsy or TURP pathology.
Index test 1	An abnormal PHI test (regardless of total PSA level) **or** an elevated initial total PSA as separate indications for biopsy	- Bloods were drawn for tests after biopsy. - Used total PSA thresholds which were greater than 4.0 ng/mL* and not age-specific reference upper limits.
Index test 2	An elevated initial total PSA as the indication for biopsy	
Reference standard	Prostate biopsy which included 6 or more cores or TURP	
Indications for biopsy	- Indications for biopsy include a total PSA level above thresholds of 4.0 ng/mL or less, or age-specific reference upper limits. - Or an abnormal PHI result.	Indications for biopsy not precisely defined and no subgroup analysis for men with PSA >4.0 ng/mL^
Outcomes	Accuracy relative to using total PSA test alone**: - Additional cancer (true positives) detected - Additional unnecessary biopsies (false positives) - Additional unnecessary biopsies per additional cancer detected	
Language	English	
Publication period	After 31st December 1989 and before1st March 2014	

TURP = transurethral resection of the prostate

**Verification bias is a major issue when assessing the diagnostic performance of tests for prostate cancer as men normally do not undergo biopsy unless they are test positive. As a result most studies examining the performance of tests in diagnosing prostate cancer are only able to report numbers of true positives and false positives. Where there is a comparison of two index tests in the same patient and where one index test is purely adding additional test positives to the other index test, as when the PHI test is used to test men with PSA levels below the PSA threshold, this data can be used to calculate the difference in true positives and the difference in false positives and the number of additional false positives for each additional cancer detected; findings that will not be subject to verification bias.

^If indications for biopsy not reported assumed that all men with PSA >4.0 ng/mL were offered biopsy due to the elevated total PSA result alone.

*This question focuses on a total PSA threshold of 3.0 ng/mL. However, studies using a total PSA threshold of up to 4.0 ng/mL were also included as the day-to-day biological variability in a man's PSA level of 15% means that, for a man with an average level of 3.0 ng/mL, the levels on consecutive days can be as high as 3.9 ng/mL (upper 95th percentile).

Conference proceedings identified by the search literature searches were included if they met the inclusion criteria.

1.4. PICO Question 6.3b - Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Diagnostic performance	Predictive accuracy
Study design	Fully paired diagnostic study, or paired randomised cohort study	Diagnostic case-control or studies of diagnostic yield
Population	Men without prostate cancer diagnosis or symptoms that might indicate prostate cancer, who had an initial total PSA >2.0 ng/mL but <5.5 ng/mL, unless participants were at higher risk of prostate cancer, aged over 60 or there were subgroup analyses for age, risk or PSA level,^^ and who had undergone prostate biopsy or TURP and at least 80% of those undergoing biopsy had undergone an initial rather than a repeat prostate biopsy	- Included men with prostate cancer or some other urologic disease e.g. bladder cancer or men undergoing a particular treatment e.g. finasteride. - Restricted to men who only had an abnormal DRE and/or abnormal TRUS. - Included men whose cancer status was not based on biopsy or TURP pathology.
Index test 1	An elevated initial total PSA **together with** an abnormal PHI test as a single indication for biopsy	- Bloods were drawn for tests after biopsy. - Used total PSA thresholds which were greater than 4.0 ng/mL^^ and not age-specific reference upper limits.
Index test 2	An elevated initial total PSA an indication for biopsy	
Reference standard	Prostate biopsy which included 6 or more cores or TURP	
Indications for biopsy	Indications for biopsy include a total PSA level above thresholds of 4.0 ng/mL or less, or age-specific reference upper limits	Indications for biopsy not precisely defined and no subgroup analysis for men with PSA >4.0 ng/mL^
Outcomes	Diagnostic performance relative** to using total PSA alone: - Relative specificity (% unnecessary biopsies avoided). - Relative sensitivity (% cancers detected missed). - Unnecessary biopsies avoided per cancer missed.	
Language	English	
Publication period	After 31st December 1989 and before1st March 2014	

TURP = transurethral resection of the prostate

**Verification bias is a major issue when assessing the diagnostic performance of tests for prostate cancer as men normally do not undergo biopsy unless they are test positive. As a result most studies examining the performance of tests in diagnosing prostate cancer are only able to report numbers of true positives and false positives. Where there is a comparison of two index tests in the same patient and where one index test is identifying a subgroup of those positive with the other index test so as to reduce the number of false positives, as when the PHI test is used to test men with PSA levels above the PSA threshold, this data can be used to calculate the decrease in true positives and relative sensitivity, the decrease in false positives and relative specificity and the number of unnecessary biopsies avoided (decrease in false positives) for each cancer missed (decrease in true positives); findings that will not be subject to verification bias.

^If indications for biopsy not reported assumed that all men with PSA >4.0 ng/mL were offered biopsy due to the elevated total PSA result alone

^^This question focuses on the PHI test as a means to improve specificity for men with a total PSA level above 3.0 ng/mL. Because of the analytical and biological variability of total PSA, including the chronological rise in PSA in men in their sixties, this review focused on studies that used total PSA thresholds between 2.0 and 4.0 ng/mL or age-specific thresholds. Restricting the evidence to studies that used a total PSA threshold of

3.0 ng/mL would have limited the evidence and would not have taken into account analytical variation in the total PSA test over the last two decades.
Men with only slightly elevated levels are less likely to have prostate cancer and could benefit from attempts to improve specificity without compromising sensitivity, whereas men with higher PSA levels are more likely to have prostate cancer and for such men attempts to reduce unnecessary biopsies could compromise the effectiveness of the recommended PSA testing strategy. As a result, studies using a single total PSA threshold were restricted to those whose participants had a total PSA ≤ 5.5 ng/mL unless there were analyses for older men (who are more likely not to have prostate cancer despite a total PSA > 5.5 ng/mL).

Conference proceedings identified by the search literature searches were included if they met the inclusion criteria.

2. Results

2.1. Guidelines

No guidelines were identified that contained potentially relevant recommendations.

2.2. Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the systematic review. The Medline search identified 179 citations, the Embase search an additional 280 citations, the search of the Cochrane Database of Systematic Reviews 59 citations, the Database of Abstracts of Reviews of Effects 282 citations and the Health Technology Assessment database 216 citations, resulting in a total of 1,016 citations. Titles and abstracts were examined and 58 articles were retrieved for a more detailed evaluation. An additional 10 potential citations were identified from the reference list of retrieved articles.

None of the articles met the inclusion criteria. There were no studies of Aboriginal and/or Torres Strait Islander men that met the inclusion criteria.

The retrieved articles and the reason for their exclusion are documented in Appendix B. The major reasons for exclusion were unclear or inappropriate indications for biopsy, did not report relevant outcomes and did not report original data. Three studies met all of the inclusion criteria with the one exception that they included men with total PSA >5.5 ng/mL and had no subgroup analyses for men >60 years or at higher risk.

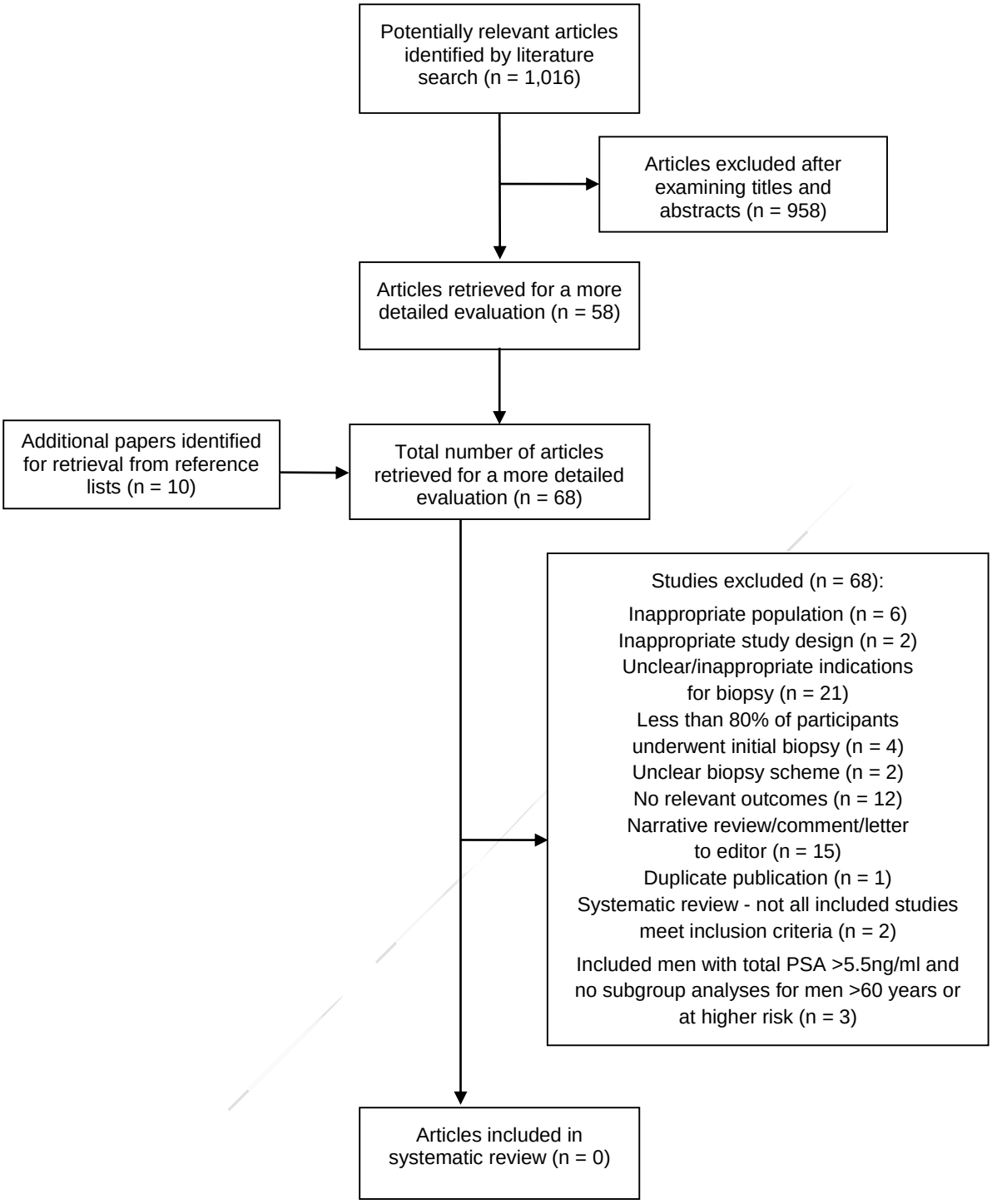


Figure 1. Process of inclusion and exclusion of studies

APPENDICES

Appendix A: Search strategies used

For Medline database:

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	(prostate health index or PHI).mp.
5	((isoform$ or proenzyme$) adj2 (PSA or prostate specific antigen)).mp.
6	(proPSA$ or pro PSA or pro-PSA$ or -2 proPSA or -2 pPSA or p2PSA or p2 PSA or %p2PSA or % p2PSA or %p2 PSA).mp.
7	(proprostate specific antigen$ or pro-prostate specific antigen$).mp.
8	((-2proenzyme or -2 proenzyme) adj2 (PSA or prostate specific antigen)).mp.
9	4 or 5 or 6 or 7 or 8
10	3 and 9
11	limit 10 to (english language and humans and yr="1990 -Current")

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database:

#	Searches
1	prostat* near/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR metast* OR adeno*))
2	'prostate cancer'/exp
3	1 or 2
4	‘prostate health index’ OR phi
5	‘propsa’ OR ‘pro psa’ OR ‘-2 propsa’ OR ‘-2 ppsa’ OR p2psa OR ‘p2 psa’ OR ‘%p2psa’ OR ‘% p2psa’
6	‘proprostate specific antigen’ OR ‘proprostate specific antigens’ OR ‘pro-prostate specific antigen’ OR ‘pro-prostate specific antigens’
7	(isoform* OR proenzyme*) NEAR/2 (psa OR ‘prostate specific antigen’)
8	4 or 5 or 6 or 7
9	3 and 8
10	9) AND [humans]/lim AND [english]/lim AND [embase]/lim AND [1990-3000]/py

ATSI search terms used

#	Searches
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

For Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment database:

#	Searches
1	(prostat$ adj3 (cancer$ OR carcinoma$ OR malignan$ OR tumo?r$ OR neoplas$ OR metastas$ OR adeno$)).tw

Appendix B: Excluded studies

Study	Reason for exclusion
Alvarez 2014	Narrative review/comment/letter to editor (no original data)
Bangma 2010	Narrative review/comment/letter to editor (no original data)
Bordas 2013	Unclear/inappropriate biopsy scheme
Bryant 2014	Narrative review/comment/letter to editor (no original data)
Cary 2013	Narrative review/comment/letter to editor (no original data)
Castelli 2010	Narrative review/comment/letter to editor (no original data)
Catalona 2003	No relevant outcomes
Catalona 2004	No relevant outcomes
Catalona 2010	Duplicate publication (full article Catalona 2011)
Catalona 2011	Less than 80% of participants underwent initial biopsy
Chi-Fai 2012 a	No relevant outcomes
Chi-Fai 2012 b	Inappropriate population
Chi-Fai 2012 c	Inappropriate population
De Vries 2005	No relevant outcomes
De Luca 2013	Unclear indications for biopsy
Ferro 2012	Included men with total PSA >5.5 ng/mL and no subgroup analyses for men >60 years or at higher risk
Ferro 2013	Unclear indications for biopsy
Filella 2007	No relevant outcomes
Filella 2013	Not all included studies meet inclusion criteria (systematic review)
Fillee 2011	Unclear biopsy scheme
Friedersdorff 2014	Unclear indications for biopsy
Guazzoni 2011	Included men with total PSA >5.5 ng/mL and no subgroup analyses for men >60 years or at higher risk
Guazzoni 2012	Inappropriate population
Haese 2013	Unclear indications for biopsy
Heidegger 2014	No relevant outcomes
Hori 2013	Not all included studies meet inclusion criteria (systematic review)
Ito 2013	Unclear indications for biopsy
Jansen 2009	Narrative review/comment/letter to editor (no original data)
Jansen 2010	Inappropriate indications for biopsy
Khan 2003	No relevant outcomes
Khan 2004	No relevant outcomes
Klecka 2011	Unclear indications for biopsy
Kral 2011	Inappropriate indications for biopsy (cut-off unclear)
Lazzeri 2011	Unclear indications for biopsy
Lazzeri 2013 a	Unclear indications for biopsy
Lazzeri 2013 b	Unclear indications for biopsy
Lazzeri 2013 c	Unclear indications for biopsy
Le 2010	Unclear indications for biopsy
Liang 2011	Inappropriate study design
Lista 2012	No relevant outcomes
Loeb 2008	Narrative review/comment/letter to editor (no original data)
Loeb 2013 a	Narrative review/comment/letter to editor (no original data)
Loeb 2013 b	Inappropriate study design
Loeb 2014	Narrative review/comment/letter to editor (no original data)
Lughezzani 2012 a	Less than 80% of participants underwent initial biopsy (33.5%)

Lughezzani 2012 b	Unclear indications for biopsy
Makarov 2009	Narrative review/comment/letter to editor (no original data)
McNicholas 2013	Unclear indications for biopsy
Miyakubo 2011	Unclear indications for biopsy
Ng 2014	Included men with total PSA >5.5 ng/mL and no subgroup analyses for men >60 years or at higher risk
Nogueira 2009	Narrative review/comment/letter to editor (no original data)
Perdona 2013	Unclear indications for biopsy
Roobol 2013	Unclear indications for biopsy
Sanda 2013	Inappropriate population (men with prostate cancer)
Scattoni 2013	Unclear indications for biopsy
Sokoll 2008	No relevant outcomes
Sokoll 2010	Unclear indications for biopsy
Sottile 2012	Inappropriate population
Stephan 2009	No relevant outcomes
Stephan 2013 a	Unclear indications for biopsy
Stephan 2013 b	Less than 80% of participants underwent initial biopsy (relevant data not reported separately)
Stephan 2013 c	Less than 80% of participants underwent initial biopsy (relevant data not reported separately)
Stephan 2014	Narrative review/comment/letter to editor (no original data)
Tefekli 2013	Narrative review/comment/letter to editor (no original data)
Tosoian 2010	Narrative review/comment/letter to editor (no original data)
Tosoian 2012	Inappropriate population
Vincendeau 2010	No relevant outcomes
Zhang 2012	Narrative review/comment/letter to editor (no original data)

References: Excluded Studies

1. Alvarez MA. Prostate cancer biomarkers. *Ultrasound Cln* 2014; 9(1):95-98.
2. Bangma CH, van Schaik RH, Blijenberg BG, Roobol MJ, Lilja H, Stenman UH. On the use of prostate-specific antigen for screening of prostate cancer in European Randomised Study for Screening of Prostate Cancer. *European Journal of Cancer* 2010; 46(17):3109-3119.
3. Bordas N, Szalay I, Farkas G, Salgo L. The diagnostic value of the [-2]propsa and PHI markers in the diagnosis of prostate cancer. *Biochim Clin* 2013; 37:S159.
4. Bryant RJ, Lilja H. Emerging PSA-based tests to improve screening. *Urol Clin North Am* 2014; 41(2):267-276.
5. Cary KC, Cooperberg MR. Biomarkers in prostate cancer surveillance and screening: Past, present, and future. *Ther Adv Urol* 2013; 5(6):318-329.
6. Castelli T, Cimino S, Magno C, Morgia G. Molecular markers for prostatic cancer. [Review] [139 refs]. *Frontiers in Bioscience* 2010; 2:641-656.
7. Catalona WJ, Bartsch G, Rittenhouse HG, Evans CL, Linton HJ, Amirkhan A et al. Serum pro prostate specific antigen improves cancer detection compared to free and complexed prostate specific antigen in men with prostate specific antigen 2 to 4 ng/mL. *J Urol* 2003; 170(6:Pt 1):t-5.
8. Catalona WJ, Bartsch G, Rittenhouse HG, Evans CL, Linton HJ, Horninger W et al. Serum pro-prostate specific antigen preferentially detects aggressive prostate cancers in men with 2 to 4 ng/mL prostate specific antigen. *J Urol* 2004; 171(6:Pt 1):t-44.
9. Catalona WJ, Sanda MG, Wei JT, Klee GG, Slawin KM, Marks LS. [-2]PROPSA in combination with PSA and free-PSA, using the Beckman Coulter access immunoassay systems improves prostate cancer detection relative to PSA and free PSA. A multi-center prospective clinical study. *The Journal of Urology* 2010; 183(4):e717.
10. Catalona WJ, Partin AW, Sanda MG, Wei JT, Klee GG, Bangma CH et al. A multicenter study of [-2]pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/mL prostate specific antigen range.[Erratum appears in J Urol. 2011 Jul;186(1):354]. *J Urol* 2011; 185(5):1650-1655.
11. Chi-Fai N, Peter KFC, Ny L, Hc L, Kim WML, Eddie S et al. Comparison of free-to-total PSA ratio, p2psa-to-free PSA ratio and Prostate Health Index (Phi) in the prediction of prostate biopsy outcome in patients who have serum psa level between 4 to 10 Ng/ Ml receiving first transrectal ultrasound guided biopsy. *Int J Urol* 2012; 19:253. (a)
12. Chi-Fai N, Peter KFC, Ny L, Hc L, Kim WML, Eddie S et al. Role of Prostate Health Index (Phi) for prostate cancer detection in patients with serum PSA level between 4 to 10 Ng/mL receiving first transrectal ultrasound guided biopsy. *Int J Urol* 2012; 19:253. (b)

13. Chi-Fai N, Peter KFC, Ny L, Hc L, Kim WML, Eddie S et al. To assess the role of total PSA, free-tototal PSA and prostate health index (PHI) in the differentiation of high and low grade prostate cancer in patients with serum PSA level between 4 to 10 ng/mL. *Int J Urol* 2012; 19:278. (c)

14. de Vries SH, Raaijmakers R, Blijenberg BG, Mikolajczyk SD, Rittenhouse HG, Schroder FH. Additional use of [-2] precursor prostate-specific antigen and "benign" PSA at diagnosis in screen-detected prostate cancer. *Urology* 2005; 65(5):926-930.

15. De LS, Parziale A, Caccia P, Cavallini A, Faraone N, Giargia E et al. Comparison of prostate health index, urinary pca3 assay and % free PSA in predicting prostate cancer at first biopsy. *Anticancer Res* 2013; 33(5):2277-2278.

16. Ferro M, Bruzzese D, Perdona S, Mazzarella C, Marino A, Sorrentino A, et al. Predicting prostate biopsy outcome: prostate health index (phi) and prostate cancer antigen 3 (PCA3) are useful biomarkers. Clinica Chimica Acta 2012 Aug 16;413(15-16):1274-8.

17. Ferro M, Bruzzese D, Perdona S, Marino A, Mazzarella C, Perruolo G et al. Prostate Health Index (Phi) and Prostate Cancer Antigen 3 (PCA3) significantly improve prostate cancer detection at initial biopsy in a total PSA range of 2-10 ng/mL. *PLoS ONE [Electronic Resource]* 2013; 8(7):e67687.

18. Filella X, Alcover J, Molina R, Luque P, Corral JM, Auge JM et al. Usefulness of proprostate-specific antigen in the diagnosis of prostate cancer. *Anticancer Res* 2007; 27(1 B):607-610.

19. Filella X, Gimenez N. Evaluation of [-2] proPSA and Prostate Health Index (phi) for the detection of prostate cancer: a systematic review and meta-analysis. [Review]. *Clinical Chemistry & Laboratory Medicine* 2013; 51(4):729-739.

20. Fillee C, Philippe M, Tombal B. Clinical evaluation of prostate health indexin a general population in order to detect prostate cancer. *Clin Chem Lab Med* 2011; 49:S237.

21. Friedersdorff F, Manus P, Miller K, Lein M, Jung K, Stephan C. Serum testosterone improves the accuracy of Prostate Health Index for the detection of prostate cancer. *Clin Biochem* 2014.

22. Guazzoni G, Nava L, Lazzeri M, Scattoni V, Lughezzani G, Maccagnano C, et al. Prostate-specific antigen (PSA) isoform p2PSA significantly improves the prediction of prostate cancer at initial extended prostate biopsies in patients with total PSA between 2.0 and 10 ng/mL: results of a prospective study in a clinical setting. European Urology 2011 Aug;60(2):214-22.

23. Guazzoni G, Lazzeri M, Nava L, Lughezzani G, Larcher A, Scattoni V et al. Preoperative prostate-specific antigen isoform p2PSA and its derivatives, %p2PSA and prostate health index, predict pathologic outcomes in patients undergoing radical prostatectomy for prostate cancer. *Eur Urol* 2012; 61(3):455-466.

24. Haese A, Lazzeri M, de la Taille A, Palou J, McNicholas T, Scattoni V et al. Serum isoform [(plus or minus)2]propsa derivates (%P2PSA and PHI) significantly improves the prediction of prostate cancer at

initial biopsy in a TPSA range 2-10 NG/ML. A multicentric european study. *J Urol* 2013; 189(4):e913-e914.

25. Heidegger I, Klocker H, Steiner E, Skradski V, Ladurner M, Pichler R et al. ProPSA is an early marker for prostate cancer aggressiveness. *Prostate Cancer Prostatic Dis* 2014; 17(1):70-74.

26. Hori S, Blanchet JS, McLoughlin J. From prostate-specific antigen (PSA) to precursor PSA (proPSA) isoforms: a review of the emerging role of proPSAs in the detection and management of early prostate cancer. [Review]. *BJU International* 2013; 112(6):717-728.

27. Ito K, Miyakubo M, Sekine Y, Koike H, Matsui H, Shibata Y et al. Diagnostic significance of [-2]pro-PSA and prostate dimension-adjusted PSA-related indices in men with total PSA in the 2.0-10.0 ng/mL range. *World Journal of Urology* 2013; 31(2):305-311.

28. Jansen FH, Roobol M, Jenster G, Schroder FH, Bangma CH. Screening for prostate cancer in 2008 II: the importance of molecular subforms of prostate-specific antigen and tissue kallikreins. [Review] [84 refs]. *European Urology* 2009; 55(3):563-574.

29. Jansen FH, van Schaik RH, Kurstjens J, Horninger W, Klocker H, Bektic J et al. Prostate-specific antigen (PSA) isoform p2PSA in combination with total PSA and free PSA improves diagnostic accuracy in prostate cancer detection. *European Urology* 2010; 57(6):921-927.

30. Khan MA, Partin AW, Rittenhouse HG, Mikolajczyk SD, Sokoll LJ, Chan DW et al. Evaluation of proprostate specific antigen for early detection of prostate cancer in men with a total prostate specific antigen range of 4.0 to 10.0 ng/mL. *J Urol* 2003; 170(3):723-726.

31. Khan MA, Sokoll LJ, Chan DW, Mangold LA, Mohr P, Mikolajczyk SD et al. Clinical utility of proPSA and "Benign" PSA when percent free PSA is less than 15%. *Urology* 2004; 64(6):1160-1164.

32. Klecka J, Behounek P, Topolcan O, Hora M, Fuchsova R, Karlikova M et al. Is pro PSA more cancer specific form of prostate specific antigen for the early detection of prostate cancer? *Urology* 2011; 78(3):S149-S150.

33. Kral M, Hradil D, Grepl M, Hrabec M, Petrek M, Kolar Z et al. Prostate Health Index (PHI) in patients with prostate cancer and with BPH. *Eur Urol Suppl* 2011; 10(9):647.

34. Lazzeri M. Prostate cancer: The Prostate Health Index (PHI) may guide diagnostic and treatment. *Tumor Biol* 2011; 32:S40.

35. Lazzeri M, Haese A, de la Taille A, Palou RJ, McNicholas T, Lughezzani G et al. Serum isoform [-2]proPSA derivatives significantly improve prediction of prostate cancer at initial biopsy in a total PSA range of 2-10 ng/mL: a multicentric European study. *European Urology* 2013; 63(6):986-994. (a)

36. Lazzeri M, Haese A, Abrate A, de la Taille A, Redorta JP, McNicholas T et al. Clinical performance of serum prostate-specific antigen isoform [-2]proPSA (p2PSA) and its derivatives, %p2PSA and the prostate health index (PHI), in men with a family history of prostate cancer: results from a multicentre European study, the PROMEtheuS project. *BJU International* 2013; 112(3):313-321. (b)

37. Lazzeri M. Impact of prostate health index on the management of patients with prostate cancer. *Biochim Clin* 2013; 37:s53. (c)

38. Le BV, Griffin CR, Loeb S, Carvalhal GF, Kan D, Baumann NA et al. [-2]Proenzyme prostate specific antigen is more accurate than total and free prostate specific antigen in differentiating prostate cancer from benign disease in a prospective prostate cancer screening study. *J Urol* 2010; 183(4):1355-1359.

39. Liang Y, Ankerst DP, Ketchum NS, Ercole B, Shah G, Shaughnessy JD, Jr. et al. Prospective evaluation of operating characteristics of prostate cancer detection biomarkers. *J Urol* 2011; 185(1):104-110.

40. Lista G, Lughezzani G, Lazzeri M, Scattoni V, Nava L, Centemero A et al. Isoform [-2]proPSA (p2PSA) and its derivates, %p2PSA and PHI values differ between BPH, ASAP, HG-PIN and PCa in a set of contemporary men undergoing prostate biopsy. *Eur Urol Suppl* 2012; 11(1):e910-e910a.

41. Loeb S, Catalona WJ. What to do with an abnormal PSA test. [Review] [45 refs]. *Oncologist* 2008; 13(3):299-305.

42. Loeb S. Prostate Health Index (PHI): golden bullet or just another prostate cancer marker? *European Urology* 2013; 63(6):995-996.

43. Loeb S, Sokoll LJ, Broyles DL, Bangma CH, van Schaik RH, Klee GG et al. Prospective multicenter evaluation of the Beckman Coulter Prostate Health Index using WHO calibration. *J Urol* 2013; 189(5):1702-1706.

44. Loeb S, Catalona WJ. The Prostate Health Index: A new test for the detection of prostate cancer. *Ther Adv Urol* 2014; 6(2):74-77.

45. Lughezzani G, Lazzeri M, Larcher A, Lista G, Scattoni V, Cestari A et al. Development and internal validation of a Prostate Health Index based nomogram for predicting prostate cancer at extended biopsy. *J Urol* 2012; 188(4):1144-1150. (a)

46. Lughezzani G, Lazzeri M, Scattoni V, Larcher A, Gadda G, Nava L et al. Clinical cut-offs of isoform [-2]proPSA (p2PSA) derivatives, namely %p2PSA and PHI (Prostate Health Index) for guiding biopsy decision in Caucasian population. *Eur Urol Suppl* 2012; 11(1):e909-e909a. (b)

47. Makarov DV, Loeb S, Getzenberg RH, Partin AW. Biomarkers for prostate cancer. [Review] [96 refs]. *Annual Review of Medicine* 2009; 60:139-151.

48. McNicholas T, Lazzeri M, Haese A, de la Taille A, Palou J, Lughezzani G et al. PHI (Prostate Health Index) and %p2PSA for prediction of prostate cancer in men younger than 60 years of age. A nested-case control study from PROpsa Multicentric European Study (PROMEtheuS project). *Eur Urol Suppl* 2013; 12(1):e137-e138.

49. Miyakubo M, Ito K, Yamamoto T, Suzuki K. Diagnostic significance of [-2]propsa, total and transition zone prostate volume adjusted PSA-related indices in Japanese men with total PSA in the 2.0 to 10.0 ng/mL range. *European Urology Supplements* 2011; 10(2):65.

50. Ng CF, Chiu PKF, Lam NY, Lam HC, Lee KWM, Hou SSM. The Prostate Health Index in predicting initial prostate biopsy outcomes in Asian men with prostate-specific antigen levels of 4-10 ng/mL. Int Urol Nephrol 2014;46(4):711-7.

51. Nogueira L, Corradi R, Eastham JA. Prostatic specific antigen for prostate cancer detection. [Review]. *International Braz J Urol* 530; 35(5):521-529.

52. Perdona S, Bruzzese D, Ferro M, Autorino R, Marino A, Mazzarella C et al. Prostate health index (phi) and prostate cancer antigen 3 (PCA3) significantly improve diagnostic accuracy in patients undergoing prostate biopsy. *Prostate* 2013; 73(3):227-235.

53. Roobol MJ, Nieboer D, Houlgatte A, Vincendeau S, Lazzeri M, Guazzoni G et al. Reducing unnecessary biopsies for suspicion of prostate cancer: Extension and validation of an ERSPC based risk calculator with Phi. *Eur Urol Suppl* 2013; 12(1):e139-e140.

54. Sanda M, Wei J, Broyles D, Shin S, Partin A, Klee G et al. Prostate health index (Phi) for reducing overdetection of indolent prostate cancer and unnecessary biopsy while improving detection of aggressive cancers. *J Urol* 2013; 189(4):e843.

55. Scattoni V, Lazzeri M, Lughezzani G, De LS, Passera R, Bollito E et al. Head-to-head comparison of prostate health index and urinary PCA3 for predicting cancer at initial or repeat biopsy. *J Urol* 2013; 190(2):496-501.

56. Sokoll LJ, Wang Y, Feng Z, Kagan J, Partin AW, Sanda MG et al. [-2]proenzyme prostate specific antigen for prostate cancer detection: a national cancer institute early detection research network validation study. *J Urol* 2008; 180(2):539-543.

57. Sokoll LJ, Sanda MG, Feng Z, Kagan J, Mizrahi IA, Broyles DL et al. A prospective, multicenter, National Cancer Institute Early Detection Research Network study of [-2]proPSA: improving prostate cancer detection and correlating with cancer aggressiveness. *Cancer Epidemiology, Biomarkers & Prevention* 2010; 19(5):1193-1200.

58. Sottile A, Ortega C, Berruti A, Mangioni M, Saponaro S, Polo A et al. A pilot study evaluating serum pro-prostate-specific antigen in patients with rising PSA following radical prostatectomy. *Oncol Lett* 2012; 3(4):819-824.

59. Stephan C, Kahrs AM, Cammann H, Lein M, Schrader M, Deger S et al. A [-2]proPSA-based artificial neural network significantly improves differentiation between prostate cancer and benign prostatic diseases. *Prostate* 2009; 69(2):198-207.

60. Stephan C, Vincendeau S, Houlgatte A, Cammann H, Jung K, Semjonow A. Multicenter evaluation of [-2]proprostate-specific antigen and the prostate health index for detecting prostate cancer. *Clin Chem* 2013; 59(1):306-314. (a)

61. Stephan C, Jung K, Semjonow A, Schulze-Forster K, Cammann H, Hu X et al. Comparative assessment of urinary prostate cancer antigen 3 and TMPRSS2:ERG gene fusion with the serum [-2]proprostate-

specific antigen-based prostate health index for detection of prostate cancer. *Clin Chem* 2013; 59(1):280-288. (b)

62. Stephan C, Vincendeau S, Houlgatte A, Miller K, Semjonow A. [-2]proPSA and prostate health index (phi) improve detection of prostate cancer at initial and repeated biopsies in young men ((less-than or equal to) 60 year old) preferentially detecting clinically significant cancer. *Eur Urol Suppl* 2013; 12(1):e853. (c)

63. Stephan C, Ralla B, Jung K. Prostate-specific antigen and other serum and urine markers in prostate cancer. *Biochim Biophys Acta Rev Cancer* 2014; 1846(1):99-112.

64. Tefekli A, Tunc M. Future prospects in the diagnosis and management of localized prostate cancer. [Review]. *Thescientificworldjournal* 2013; 2013:347263.

65. Tosoian J, Loeb S. PSA and beyond: the past, present, and future of investigative biomarkers for prostate cancer. [Review]. *Thescientificworldjournal* 2010; 10:1919-1931.

66. Tosoian JJ, Loeb S, Feng Z, Isharwal S, Landis P, Elliot DJ et al. Association of [-2]proPSA with biopsy reclassification during active surveillance for prostate cancer. *J Urol* 2012; 188(4):1131-1136.

67. Vincendeau S, Ramirez J, Durand X, Degline E, Houlgatte A. The Beckman Coulter Prostate Health Index (PHI) improves diagnostic accuracy in prostate cancer detection. *European Urology Supplements* 2010; 9(2):309.

68. Zhang MZ, Lu YP. From pro-prostate specific antigen, [-2]pro-prostate specific antigen to Beckman Coulter phi: the evolution of new biomarkers for early detection of prostatic carcinoma. *Chinese Medical Journal* 2012; 125(9):1643-1649.

Systematic review report for question 6.1b

Clinical Question 6: In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what tests for prostate cancer should be offered in addition to a PSA test?

Candidate tests include:

Free-to-total PSA % (f/tPSA%)

PSA velocity

Prostate health index

Repeat PSA

PICO Question 6.1:

6.1a: For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring free-to-total PSA percentage improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single total PSA result above 3.0 ng/mL?

6.1b: For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring free-to-total PSA percentage improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL?

This review addresses part (b) of the above PICO -

For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring free-to-total PSA percentage improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL?

Population	Index Test 1	Index Test 2	Reference Standard	Outcomes
Men without prostate cancer diagnosis or symptoms that might indicate prostate cancer	Total PSA >3.0 ng/mL **and** abnormal f/tPSA% test	Total PSA >3.0 ng/mL only	Prostate biopsy	Diagnostic performance

1. Methods

1.1 Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca). Excluded guidelines are documented in Appendix C.

To be considered for adoption guidelines had to be evidence based and meet the pre-specified criteria of scores of greater or equal to 70% for the domains rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

1.2 Literature Search

Medline (1/01/1990 – 1/03/2014), Embase (1/01/1990 – 1/03/2014), Cochrane Database of Systematic Reviews (2005 – 2014), Database of Abstracts of Reviews of Effects and Health Technology Assessment databases from 1990 were searched using text terms and, where available, database specific subject headings. Each database was searched for articles dealing with prostate cancer. In Medline and Embase databases the prostate cancer search was combined with a search for percentage free-to-total PSA (f/t PSA%). To identify studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples. A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 added to the relevant database after February 2014. Alerts were checked until July 2014. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched regularly up until April 2014 for relevant reviews published after the initial search. Reference lists of all relevant articles were checked for potential additional articles.

1.3 Inclusion and Exclusion Criteria

Selection criteria	**Inclusion criteria**	**Exclusion criteria**
Study type	Diagnostic performance	Predictive accuracy
Study design	Fully paired diagnostic study, or Paired randomised cohort study	Diagnostic case-control or studies of diagnostic yield
Population	Men without prostate cancer diagnosis or symptoms that might indicate prostate cancer, who had an initial total PSA >2.0 ng/mL but <5.5 ng/mL, unless participants were at higher risk of prostate cancer, aged over 60 or there were subgroup analyses for age, risk or PSA level^^, and who had undergone prostate biopsy or TURP and at least 80% of those undergoing biopsy had undergone an initial rather than a repeat prostate biopsy	- Included men with prostate cancer or some other urologic disease e.g. bladder cancer or men undergoing a particular treatment e.g. finasteride. - Restricted to men who only had an abnormal DRE and/or abnormal TRUS. - Included men whose cancer status was not based on biopsy or TURP pathology.
Index test 1	An elevated initial total PSA **together with** an abnormal f/tPSA% result as a single indication for biopsy	- Bloods were drawn for f/t PSA% test after biopsy. - Stated bloods not frozen or analysed on collection day or if thawed and refrozen. - Did not use a commercial total PSA test e.g. Hybritech, Immulite, Abbott, Roche, Bayer, or pre 1996 and did not describe total PSA assay used. - Used total PSA thresholds which were greater than 4.0 ng/mL* and not age-specific reference upper limits. - Used Chugai, CISbio, Dainippon, Dianon, Eiken E plate or Mitsui gamma-SM-MP f/tPSA% test.
Index test 2	An elevated initial total PSA alone an indication for biopsy	
Reference standard	Prostate biopsy which included 6 or more cores or TURP	

Indications for biopsy	Indications for biopsy include a total PSA level above thresholds of 4.0 ng/mL or less, or age-specific reference upper limits	Indications for biopsy not precisely defined and no subgroup analysis for men with PSA >4.0 ng/mL^
Outcomes	Diagnostic performance relative** to using total PSA alone: - Relative specificity (% unnecessary biopsies avoided) - Relative sensitivity (% cancers detected missed) - Unnecessary biopsies avoided per cancer missed	
Language	English	
Publication period	After 31st December 1989 and before1st March 2014	

TURP = transurethral resection of the prostate

**Verification bias is a major issue when assessing the diagnostic performance of tests for prostate cancer as men normally do not undergo biopsy unless they are test positive. As a result most studies examining the performance of tests in diagnosing prostate cancer are only able to report numbers of true positives and false positives. Where there is a comparison of two index tests in the same patient and where one index test is identifying a subgroup of those positive with the other index test so as to reduce the number of false positives, as when the f/tPSA% test is used to test men with PSA levels above the PSA threshold, this data can be used to calculate the decrease in true positives and relative sensitivity, the decrease in false positives and relative specificity and the number of unnecessary biopsies avoided (decrease in false positives) for each cancer missed (decrease in true positives); findings that will not be subject to verification bias.

^If indications for biopsy not reported assumed that all men with PSA >4.0 ng/mL were offered biopsy due to the elevated total PSA result alone.

^^This question focuses on f/tPSA% as a means to improve specificity for men with a total PSA level above 3.0 ng/mL. Because of the analytical and biological variability of total PSA, including the chronological rise in PSA in men in their sixties, this review focused on studies that used total PSA thresholds between 2.0 and 4.0 ng/mL or age-specific thresholds. Restricting the evidence to studies that used a total PSA threshold of 3.0 ng/mL would have limited the evidence and would not have taken into account analytical variation in the total PSA test over the last two decades.
Men with only slightly elevated levels are less likely to have prostate cancer and could benefit from attempts to improve specificity without compromising sensitivity, whereas men with higher PSA levels are more likely to have prostate cancer and for such men attempts to reduce unnecessary biopsies could compromise the effectiveness of the recommended PSA testing strategy. As a result, studies using a single total PSA threshold were restricted to those whose participants had a total PSA ≤ 5.5 ng/mL unless there were analyses for older men (who are more likely not to have prostate cancer despite a total PSA > 5.5 ng/mL).

Conference proceedings identified by the search literature searches were included if they met the inclusion criteria.

2. Results

2.1 Guidelines

Two guidelines were identified that contained recommendations regarding free-to-total PSA and prostate cancer detection. These recommnedations were not adopted as they were either consensus based or not based on a systematic review and thus did not meet the pre-specified AGREE II criteria for adoption. These guidelines and the reason why they were not adopted are listed in Appendix C.

In Australia, the Royal College of Pathologists of Australasia has consensus based recommendations regarding the role of percentage free-to-total PSA to improve specificity:

"The response to an initial test should be:

> *If the total PSA level is abnormal (above 97.5% age-related, method-specific reference limit) but below 10 µg/L, the PSA should be confirmed in 4 weeks including an estimation of the free-to-total PSA ratio (F/T PSA ratio). If confirmed and/or the result of the F/T PSA ratio is <10%, the patient should be immediately referred for specialist management.*

(http://www.rcpa.edu.au/Library/College-Policies/Position-Statements/Prostate-Specific-Antigen-Testing-Age-related-inte, accessed 20th October 2014).

2.2 Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the systematic review. The Medline search identified 1,300 citations, the Embase search an additional 1,656 citations. The search of the Cochrane Database of Systematic Reviews 59 citations, the Database of Abstracts of Reviews of Effects 282 citations and the Health Technology Assessment database identified an additional 216 citations, resulting in a total of 3,513 citations. Titles and abstracts were examined and 382 articles were retrieved for a more detailed evaluation.

A total of 13 articles reporting 14 studies (2 studies reported in 1 article) met the inclusion criteria for part (a) of the PICO and were included in the review. There were no studies of ATSI men that met the inclusion criteria.

The retrieved articles that were not included for part (a) of the PICO and the reason for their exclusion are documented in Appendix C. In summary, the main reasons for exclusion were inappropriate population, inappropriate or unclear indications for biopsy and no extractable data.

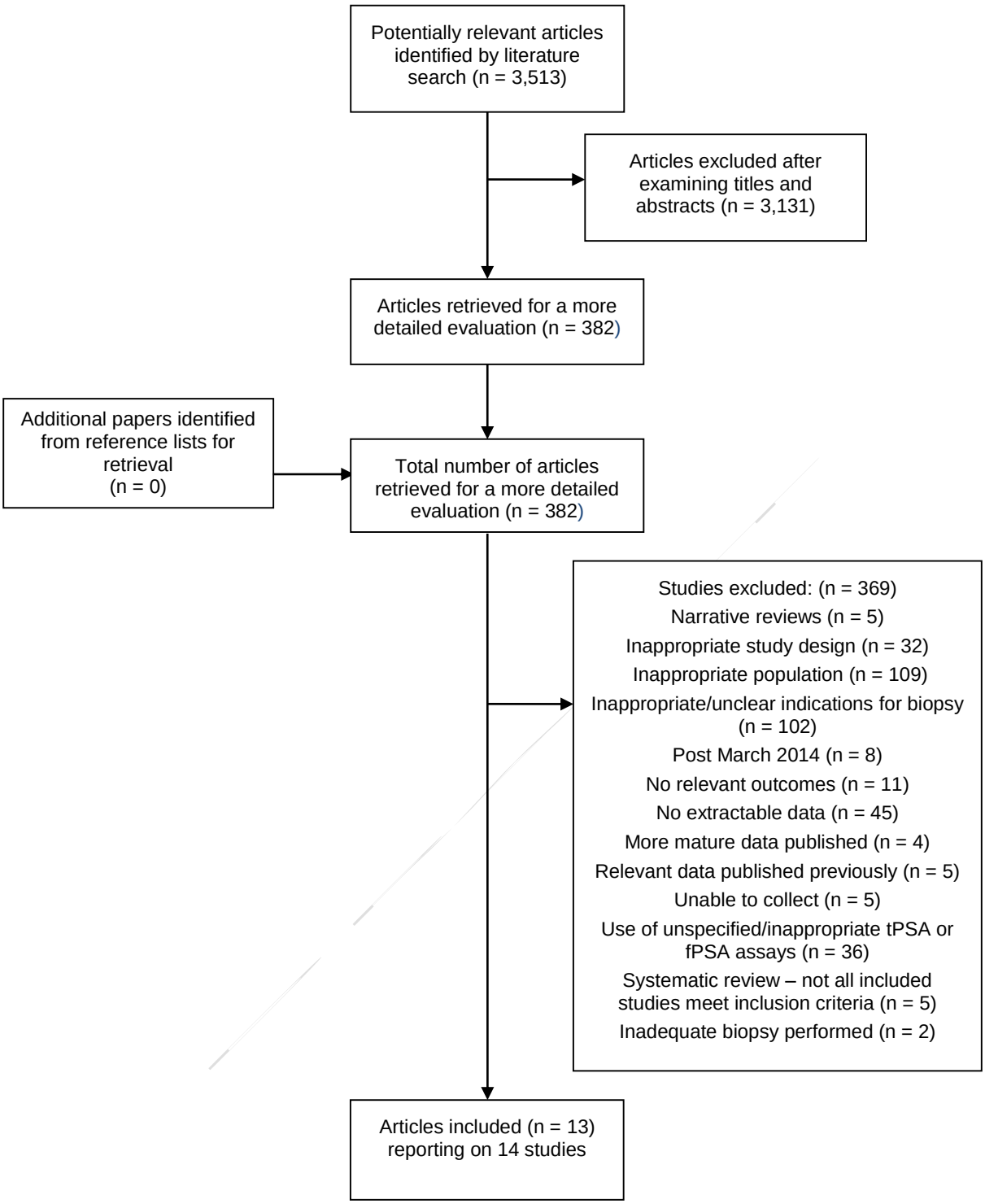


Figure 1. Process of inclusion and exclusion of studies

2.3 Study Characteristics

Table 1: Characteristics of studies comparing performance characteristics of tPSA and/or f/t PSA% with those of tPSA alone with respect to prostate cancer detection.

Study	Design	Participants	Indication for biopsy	Biopsy	Blood collection and processing	tPSA assay	fPSA assay	tPSA range assessed	Comments
Catalona 1998 (USA)	Prospective	Men attending prostate cancer screening between 1994 and 1996 and referred for biopsy Excluded men who had undergone treatment for prostatic disease or who had suspicious DRE N = 773 Aged 50 – 75 years Median age = 64 years 9% African American	Assume tPSA ≥4ng/mL	6 core TRUS biopsy	Serum samples were processed and refrigerated within 3 hours of collection Stored at 2-8°C if samples were to be assayed within 24 hours or -70°C for any time longer than 24 hours	Hybritech Tandem PSA assay (Unaffected by multiple freeze thaws) Calibration not described	Hybritech Tandem free PSA assay (Unaffected by multiple freeze thaws) Calibration not described	4.0-10 ng/mL Subgroup analysis of age	Indications for biopsy unclear assumed men with PSA ≥4.0ng/mL referred for biopsy Pathologists blinded to %fPSA and laboratory scientists blinded to diagnosis The same serum sample was used to determine both tPSA and fPSA
Catalona 1999 (USA)	Retrospective	Participants in prostate cancer research protocols with non-suspicious DRE and referred for biopsy Excluded men with biopsy antedating blood collection by 6 weeks, prior prostatic surgery or concurrent hormonal treatment for prostate disease N = 368 Aged 50 – 90 years Median age = 64 years	tPSA >2.51ng/mL or suspicious DRE	≥6 core TRUS biopsy	Serum samples were processed and refrigerated within 3 hours of collection Stored at -70°C until analysis	Hybritech Tandem-R PSA assay Calibration not described	Hybritech Tandem-R free PSA assay Calibration not described	**2.51** – 4.0 ng/mL	All men with prostate cancer underwent prostatectomy

		89% Caucasian							
Egawa 2002 (Japan)	Prospective	Men attending urology department mostly for urinary tract problems and referred for biopsy between January 1999 and July 2000 N = 171 Median age = 68 years	tPSA >2ng/mL or DRE appeared questionable	Median 8 core systematic TRUS biopsy (range 6-12 cores)	Serum samples stored at 4°C for 2-3 hours, centrifuged and frozen at -70°C for <3 months Samples thawed immediately before analysis	Dainapack AxSYM PSA assay Calibration not described	AxSYM PSA assay Calibration not described	2.1 – 4.0 ng/mL	19.4% repeat biopsies Interval between tPSA test and biopsy usually <1 month
ERSPC – Goteborg cohort Lodding 1998 (Sweden)	Prospective	Men who have undergone **initial** screening and referred for biopsy between January 1995 and December 1996 N = 611 Aged 50 – 66 years Median age = 61 years *Subgroup* Biopsy between January 1995 and December 1996 , PSA 3.0 - 4.0ng/mL and normal DRE N = 217	tPSA ≥3ng/mL (3.4 ng/mL WHO calibration)	6 core TRUS biopsy	Serum samples processed and stored at -20°C <3 hours of collection tPSA and fPSA measured <2 weeks of collection and <3 hours after thawing	Delfia ProStatus PSA free/total dual assay Calibration not described	Delfia ProStatus PSA free/total dual assay Calibration not described	3.0 – 4.0 ng/mL	
Kobayashi 2005 (Japan)	Prospective	Men attending prostate cancer screening between January 2000 and March 2004 with tPSA 2-4ng/mL and referred for biopsy Excluded men with abnormal DRE, a history of prostate surgery or who had received any	tPSA **>2ng**/mL or abnormal DRE	6 – 10 core biopsy	Serum samples frozen at -70°C immediately after collection and analysed within 3 days	Hybritech Tandem-R PSA assay Calibration not described	Not specified Calibration not described	**2.0** – 4.0 ng/mL	

		medications that might influence serum PSA N = 139 Aged 41 – 79 years Median age = 69 years							
Kravchick 2005 (Israel)	Prospective	Men and referred for biopsy between November 2002 and May 2004 with PSA levels 2.0 to 4.0 ng/mL N = 171 Aged 50 – 70 years Mean age = 63.3 years	tPSA ≥2ng/mL	8 core biopsy if prostate volume <40cm^3 9 core biopsy if prostate volume ≥40 cm^3 10 core biopsy if prostate volume ≥80 cm^3	Blood collection, processing and storage condition not described	DPC Immulite 2000 assay Calibration not described	Not specified Assume Immulite 2000 Calibration not described	2.0 – 4.0 ng/mL	
Luboldt 2001 (Germany)	Prospective	Men recruited to prostate cancer early detection trial in November 1997 who underwent screening and were referred for biopsy who had tPSA levels between 4.0 and 10.0 ng/mL Excluded men with a cancer history and men with abnormal DRE N = 633 Aged 45 – 75 years Median age = 66 years	tPSA >4ng/mL and/or suspicious DRE	6 core systematic biopsy	Serum processed within 3 hours and tPSA analysed within 24-36 hours Samples stored at -80°C until fPSA analysis Temperature at which sera kept prior to freezing not described	Hybritech Tandem-R assay Calibration not described	Hybritech Tandem free PSA assay Calibration not described	4.0 – 10 ng/mL Subgroup analysis of age	Laboratory personnel blind to diagnosis and physician blinded to fPSA levels
Okihara 2001 (USA)	Prospective	Men participating in a prostate cancer early detection program between November 1998 and January 2000 who agreed to undergo biopsy	tPSA ≥ 2.5ng/mL	11 core multisite directed biopsy	Serum samples immediately processed and stored at -70°C until analysis	Tosoh assay (screening) Hybritech Tandem-R assay (f/tPSA)	Hybritech Tandem-R assay Calibration not described	2.5 – 4.0 ng/mL	

		Excluded men who had received any medications or food supplement except saw palmetto, that may influence serum PSA or who had a history of TURP, suprapubic or retropubic prostatectomy N = 151 Aged 43 – 74 years Median age = 62 years				Calibration not described			
ERSPC – Rotterdam side study Raaijmakers 2004 (Netherlands)	Prospective	Men who have undergone **round 2 screening** between April 2001 and December 2002 with tPSA 2.0-3.9ng/mL who accepted an offer of prostate biopsy N = 7344 Aged 59 – 74 years	tPSA ≥ 2ng/mL	6 core laterally-directed biopsy	Serum samples processed and refrigerated within 3 hours of collection Samples not analysed on the same day stored at -70°C until analysis	Hybritech total PSA assay Calibration not described	Hybritech free PSA assay Calibration not described	2.0 – 3.9 ng/mL	83.4% of men with PSA 2.0 – 3.9 ng/mL underwent biopsy
Reissigl 1996 (Austria)	Retrospective	Men attending prostate cancer screening and referred for biopsy N = 266 Aged 45 – 75 years Mean age = 63 years	tPSA >age-specific reference ranges (Oesterling 1993)	8 core systematic TRUS biopsy	Serum samples stored at -80°C until analysis Time between collection and storage not described	Abbott microparticle enzyme immunoassay (screening) Delfia PSA dual label f/tPSA kit (f/tPSA) Calibration not described	Delfia PSA dual label free/total PSA kit Calibration not described	> Age-specific reference ranges	Age-specific reference ranges used 40-49 years 0 - 2.50 ng/mL 50-59 years 0 - 3.50 ng/mL 60-69 years 0 - 4.50 ng/mL 70-79 years 0 - 6.50 ng/mL

	Prospective	Men attending prostate cancer screening from March 1995 to May 1996 and referred for biopsy N = 106 Aged 45 – 75 years	tPSA >age-specific reference ranges (Oesterling 1993)	8 core systematic TRUS biopsy	Blood collection, processing and storage condition not described	Delfia PSA dual label free/total PSA kit Calibration not described	Delfia PSA dual label free/total PSA kit Calibration not described	> Age-specific reference ranges - <10 ng/mL	fPSA measured immediately after obtaining results of tPSA
Reissigl 1997 (Austria)	Prospective	Men attending prostate cancer screening from August 1995 to May 1996 and referred for biopsy N = 308	Assume tPSA >age-specific reference ranges (Oesterling 1993)	TRUS biopsy (number of cores not described)	Blood collection, processing and storage condition not described	Delfia PSA dual label f/tPSA kit Calibration not described	Delfia PSA dual label free/total PSA kit Calibration not described	> Age-specific reference ranges - <10 ng/mL	Indications for biopsy unclear assumed tPSA >age-specific reference ranges
Roehl 2002 (USA)	Prospective	Men attending prostate cancer screening from May 1995 until March 2001 with tPSA 2.6 - 4.0ng/mL on initial or repeat screening referred for initial biopsy Excluded men with suspicious DRE N = 965 9% African American Aged 42 – 88 years Median age = 64 years	tPSA >2.5 ng/mL	6 core TRUS biopsy	Blood collection, processing and storage condition not described	Until May 2000: Hybritech Tandem-E PSA assay From May 2000: Beckman Coulter Access analyser using Hybritech antibodies Calibration not described	Until May 2000: Hybritech Tandem-R free PSA assay From May 2000: Beckman Coulter Access analyser using Hybritech antibodies Calibration not described	2.6 – 4.0 ng/mL	Pathologists blinded to free PSA values Include some men included in Catalona 1997
Safarinejad 2006 (Iran)	Prospective	Men attending prostate cancer screening between 1996 and 2004 and referred for biopsy Excluded men with a history of prostate	tPSA ≥2.1ng/mL or f/t PSA% ≤15% or suspicious DRE	8 core (systematic 6 core + 2 cores from transitional zone) TRUS biopsy	Blood collection, processing and storage condition not described	Delfia PSA dual label free/total PSA assay Calibration not described	Delfia PSA dual label free/total PSA assay Calibration not described	2.1 – 4.0 ng/mL	Data for men with tPSA ≥ 2.1ng/mL and ≥ 4.1 ng/mL not extracted as an error in data for reported for tPSA >10.0

	cancer, prostatitis, prostatectomy or other conditions that interfered with voiding	Hypoechoic lesions biopsied separately
	N = 167 Aged 40 – 82 years	Men with PIN underwent repeat biopsy

DRE = digital rectal examination; ERSPC = the European Randomised Study of Screening for Prostate Cancer; fPSA = free prostate specific antigen; PIN = prostatic intraepithelial neoplasia; PSA = prostate specific antigen; tPSA = total prostate specific antigen; TRUS = transrectal ultrasonography of the prostate; TURP = transurethral resection of the prostate; WHO = World Health Organisation

2.4 Quality Appraisal

Table 2: Assessment of risk of bias of included diagnostic studies (n = 13 articles, 14 studies)

Quality Category	N (%)
I. Selection of participants	
Low risk of bias	7 (50.0)
High risk of bias	-
Unclear risk of bias	7 (50.0)
II. Index test 1	
Low risk of bias	-
High risk of bias	-
Unclear risk of bias	14 (100.0)
III. Index test 2	
Low risk of bias	8 (57.1)
High risk of bias	-
Unclear risk of bias	6 (42.9)
IV. Reference standard	
Low risk of bias	-
High risk of bias	14 (100.0)
Unclear risk of bias	-
V. Flow and timing	
Low risk of bias	14 (100.0)
High risk of bias	-
Unclear risk of bias	-

Table 3: Assessment of risk of bias in individual included diagnostic studies (n = 13 articles, 14 studies)

	Patient selection	Index test 1	Index test 2	Reference standard [a]	Flow and timing [b]	Overall risk of bias
Catalona 1998	Low	Unclear	Low	High	Low	**At risk**
Catalona 1999	Unclear	Unclear	Unclear	High	Low	**At risk**
Egawa 2002	Low	Unclear	Unclear	High	Low	**At risk**
Kobayashi 2005	Low	Unclear	Low	High	Low	**At risk**
Kravchick 2005	Unclear	Unclear	Low	High	Low	**At risk**
Lodding 1998	Low	Unclear	Low	High	Low	**At risk**
Luboldt 2001	Low	Unclear	Low	High	Low	**At risk**
Okihara 2001	Low	Unclear	Low	High	Low	**At risk**
Raaijmakers 2004	Unclear	Unclear	Low	High	Low	**At risk**
Reissigl 1996 (Retrospective)	Unclear	Unclear	Unclear	High	Low	**At risk**
Reissigl 1996 (Prospective)	Unclear	Unclear	Unclear	High	Low	**At risk**
Reissigl 1997	Unclear	Unclear	Unclear	High	Low	**At risk**
Roehl 2002	Unclear	Unclear	Unclear	High	Low	**At risk**
Safarinejad 2006	Low	Unclear	Low	High	Low	**At risk**

[a.] An adequate biopsy was pre-specified as 12 or more cores; [b.] An appropriate interval was pre-specified as up to 1 year, for biopsy referral cohorts where the interval was not stated the interval was assumed to be less than one year

Key to overall rating

Low risk of bias: A study rated at “low” risk of bias for all domains

At risk of bias: A study rated “high” or “unclear” risk of bias for one or more domains

I tPSA RANGE 2.0/2.1 – 3.9/4.0 ng/mL

Table 4: Results of studies comparing performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **2.0/2.1 – 3.9/4.0 ng/mL**

Study	No. biopsied	CDR (%)	f/t PSA% + tPSA						tPSA				f/t PSA% + tPSA vs tPSA			
			f/t PSA% threshold (%)	f/t PSA% sensitivity* (%)	f/t PSA% specificity* (%)	TP	FP	FP/ TP	tPSA threshold (ng/mL)	TP	FP	FP/ TP	Unnecessary biopsies avoided ΔFP	Cancers missed ΔTP	ΔFP/ ΔTP	p value AUCs
Not restricted to normal or non-suspicious DRE																
Egawa 2002	171	NR														NS
ERSPC side study Raaijmakers 2004	734	17.2	< 25	88	18	111	498	4.49	≥ 2.0	126	608	4.83	110	15	7.33	
			< 20	72	44	91	342	3.76					266	35	7.60	
			< 15	41	75	52	154	2.96					454	74	6.14	
			< 10	10	96	13	25	1.92					583	113	5.16	
Kravchick 2005	171	22.8	21.6	80	57	31	57	1.84	≥ 2.0	39	132	3.39	75	8	9.38	NR
			19.3	51	82	20	24	1.20					108	19	5.68	
Safarinejad 2006	167	18.0	≤ 18	93	38	28	85	3.04	≥ 2.1	30	137	4.57	52	2	26.00	
			≤ 15	77	59	23	56	2.44					81	7	11.57	
Normal or non-suspicious DRE only																
Kobayashi 2005	139	22.3	< 29.2	95	15	29	92	3.17	**> 2.0**	31	108	3.48	16	2	8.00	0.331
			< 25.5	90	26	28	79	2.82					29	3	9.67	

** Relative to tPSA TPs and FPs in tPSA range specified;*

ΔFP = difference in false positives; ΔTP = difference in true positives; AUC = area under the receiver operator curves; CDR = cancer detection rate; DRE = digital rectal examination; ERSPC = European Randonmized Study of Screening for Prostate Cancer; FP = false positives; fPSA = free prostate specific antigen; f/t PSA% = percentage free-to-total prostate specific antigen; NR = not reported; NS = not significant; TP = true positives; tPSA = total prostate specific antigen

II tPSA > AGE-SPECIFIC REFERENCE THRESHOLDS

Table 5: Results of studies comparing performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection for tPSA > age–specific reference thresholds

Study	No. biopsied	CDR (%)	f/t PSA% + tPSA						tPSA				f/t PSA% + tPSA vs tPSA			
			f/t PSA% threshold (%)	f/t PSA% sensitivity* (%)	f/t PSA% specificity* (%)	TP	FP	FP/ TP	tPSA threshold (ng/mL)	TP	FP	FP/ TP	Unnecessary biopsies avoided ΔFP	Cancers missed ΔTP	ΔFP/ ΔTP	p value AUCs
Not restricted to normal or non-suspicious DRE																
Reissigl 1996 retrospective	266	24.1	≤ 18	94	37	60	127	2.12	Age-specific	64	202	3.16	75	4	18.8	NR
Reissigl 1996 prospective	106	34.9	22	97	30	36	48	1.33	Age-specific	37	69	1.87	21	1	21.0	NR
			20	90	36	33	44	1.33					25	4	6.25	
			18	75	44	28	39	1.39					30	9	3.33	
Reissigl 1997 prospective	308	18.8	< 20	100	45.5	58	136	2.35	Age-specific	58	250	4.31	114	0		NR

**relative to tPSA TPs and FPs in tPSA range specified;*

ΔFP = difference in false positives; ΔTP = difference in true positives; AUC = area under the receiver operator curves; CDR = cancer detection rate; DRE = digital rectal examination; FP = false positives; fPSA = free prostate specific antigen; f/t PSA% = percentage free-to-total prostate specific antigen; NR = not reported; TP = true positives; tPSA = total prostate specific antigen

III tPSA RANGE 2.51/2.6 – 4.0 ng/mL

Table 6: Results of studies comparing performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **2.51/2.6 – 4.0 ng/mL**

Study	No. biopsied	CDR (%)	f/t PSA% + tPSA						tPSA				f/t PSA% + tPSA vs tPSA			
			f/t PSA% threshold (%)	f/t PSA% sensitivity* (%)	f/t PSA% specificity* (%)	TP	FP	FP/ TP	tPSA threshold (ng/mL)	TP	FP	FP/ TP	Unnecessary biopsies avoided ΔFP	Cancers missed ΔTP	ΔFP/ ΔTP	p value AUCs
Not restricted to normal or non-suspicious DRE																
Okihara 2001	151	24.5	31	95	11	35	102	2.91	≥ 2.5	37	114	3.08	12	2	6.00	NR
			31	92	11	34	102	3.00					12	3	4.00	
			30	89	11	33	102	3.09					12	4	3.00	
			23	76	30	28	80	2.86					34	9	3.78	
			14	51	80	19	23	1.21					91	18	5.06	
Normal or non-suspicious DRE only																
Catalona 1999	368	14.7	≤ 15	54	67	29	104	3.59	> 2.51	54	314	5.82	210	25	8.40	NR
			≤ 14	50	72	27	88	3.26					226	27	8.37	
			≤ 13	41	79	22	66	3.00					248	32	7.75	
			≤ 12	33	83	18	53	2.94					261	36	7.25	
			≤ 11	30	90	16	31	1.94					283	38	7.45	
			≤ 10	30	94	16	19	1.19					295	38	7.76	
Roehl 2002	965	25.0	≤ 30	93	9	224	659	2.94	≥ 2.6	241	724	3.00	65	17	3.82	NR
			≤ 25	85	19	205	586	2.86					138	36	3.83	

**relative to TPs and FPs in tPSA range specified;*

ΔFP = difference in false positives; ΔTP = difference in true positives; AUC = area under the receiver operator curves; CDR = cancer detection rate; DRE = digital rectal examination; FP = false positives; fPSA = free prostate specific antigen; f/t PSA% = percentage free-to-total prostate specific antigen; NR = not reported; TP = true positives; tPSA = total prostate specific antigen

IV tPSA RANGE 3.0 – 4.0 ng/mL

Table 7: Results of studies comparing performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **3.0 - 4.0 ng/mL**

Study	No. biopsied	CDR (%)	f/t PSA% + tPSA						tPSA				f/t PSA% + tPSA vs tPSA			
			f/t PSA% threshold (%)	f/t PSA% sensitivity * (%)	f/t PSA% specificity* (%)	TP	FP	FP/ TP	tPSA threshold (ng/mL)	TP	FP	FP/ TP	Unnecessary biopsies avoided ΔFP	Cancers missed ΔTP	ΔFP/ ΔTP	p value AUCs
Normal or non-suspicious DRE																
ERSPC – Goteborg *Initial screening* Lodding 1998	217	12.4	26	93	13	25	165	6.60	≥ 3.0 (3.4 on WHO calibration)	27	190	7.04	25	2	12.50	NR

**relative to tPSA TPs and FPs in tPSA range specified;*

ΔFP = difference in false positives; ΔTP = difference in true positives; AUC = area under the receiver operator curves; CDR = cancer detection rate; DRE = digital rectal examination; ERSPC = European Randomized Study of Screening for Prostate Cancer; FP = false positives; fPSA = free prostate specific antigen; f/t PSA% = percentage free-to-total prostate specific antigen; NR = not reported; TP = true positives; tPSA = total prostate specific antigen; WHO = World Health Organisation

V tPSA RANGE 4.0/4.1 – 10.0 ng/mL

Table 8: Results of studies comparing performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **4.0/4.1 – 10.0 ng/mL**

Study	No. biopsied	CDR (%)	f/t PSA% + tPSA						tPSA				f/t PSA% + tPSA vs tPSA			
			f/t PSA% threshold (%)	f/t PSA% sensitivity* (%)	f/t PSA% specificity * (%)	TP	FP	FP/ TP	tPSA threshold (ng/mL)	TP	FP	FP/ TP	Unnecessary biopsies avoided ΔFP	Cancers missed ΔTP	ΔFP/ ΔTP	p value AUCs
Normal or non-suspicious DRE only																
Catalona 1998																
Subgroups aged 50-59 years	205	53.7	25	98	11	108	85	0.79	≥ 4.0	110	95	0.86	10	2	5.00	NR
60-69 years	408	48.8	25	94	19	187	170	0.91	≥ 4.0	199	209	1.05	39	12	3.25	
70-75 years	160	43.8	25	90	34	63	59	0.94	≥ 4.0	70	90	1.29	31	7	4.43	
Luboldt 2001																
Subgroups aged 45-69 years	457	14.2	22	94	10	61	353	5.79	> 4.0	65	392	6.03	39	4	9.75	NR
			20	94	13	61	341	5.59					51	4	12.75	
			18	91	19	59	318	5.39					74	6	12.33	
			16	85	29	55	278	5.06					114	10	11.40	
			14	83	42	54	227	4.20					165	11	15.00	
			12	77	56	50	172	3.44					220	15	14.67	
			10	62	72	40	110	2.75					282	25	11.28	
Subgroup aged over 69 years	177	14.7	22	96	21	25	119	4.76	> 4.0	26	151	5.81	32	1	32.00	
			20	96	26	25	112	4.48					39	1	39.00	
			18	96	36	25	97	3.88					54	1	54.00	
			16	96	50	25	75	3.00					76	1	76.00	

	14	88	59	23	62	2.70		89	3	29.67
	12	73	72	19	42	2.21		109	7	15.57
	10	54	82	14	27	1.93		124	12	10.33

**relative to tPSA TPs and FPs in tPSA range specified;*

∆FP = difference in false positives; ∆TP = difference in true positives; AUC = area under the receiver operator curves; CDR = cancer detection rate; DRE = digital rectal examination; FP = false positives; fPSA = free prostate specific antigen; f/t PSA% = percentage free-to-total prostate specific antigen; NR = not reported; TP = true positives; tPSA = total prostate specific antigen

2.6 Body of Evidence - All included studies

I. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **2.0/2.1 – 3.9/4.0 ng/mL**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence *	Risk of bias **	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (ΔFP)	Cancers missed^ (ΔTP)	ΔFP/ ΔTP	p value AUCs
Not restricted to normal or non-suspicious DRE													
Egawa 2002 Japan	Prospective	171	NR	Median = 8 Range= 6 -12	III-2	At risk	NR	NR	NR	NR	NR	NR	NS
Raaijmakers 2004 Netherlands ERSPC	Prospective (includes screening population)	734	17.2	6	III-2	At risk	≥ 2.0	< 25	11.9	110	15	7.33	NR
								< 20	27.8	266	35	7.60	
								< 15	58.8	454	74	6.14	
								< 10	89.9	583	113	5.16	
Kravchick 2005 Israel	Prospective	171	22.8	Prostate volume: <40 cm^3 = 8 ≥40 cm^3 = 9 ≥80 cm^3 = 10	III-2	At risk	≥ 2.0	21.6	20.5	75	8	9.38	NR
								19.3	48.7	108	19	5.68	
Safarinejad 2006 Iran	Prospective (includes screening population)	167	18.0	8	III-2	At risk	≥ 2.1	≤ 18	6.7	52	2	26.0	NR
								≤ 15	23.3	81	7	11.57	
Normal or non-suspicious DRE only													
Kobayashi 2005 Japan	Prospective (includes screening population)	139	22.3	6 - 10	III-2	At risk	≥ 2.0	< 29.2	6.5	16	2	8.00	0.331
								<25.5	9.7	29	3	9.67	

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA alone for specified tPSA range;*

ΔFP = difference in false positives; ΔTP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; ERSPC = European Randomized Study of Screening for Prostate Cancer; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; NS = not significantly different; TP = true positive; tPSA = total prostate specific antigen;

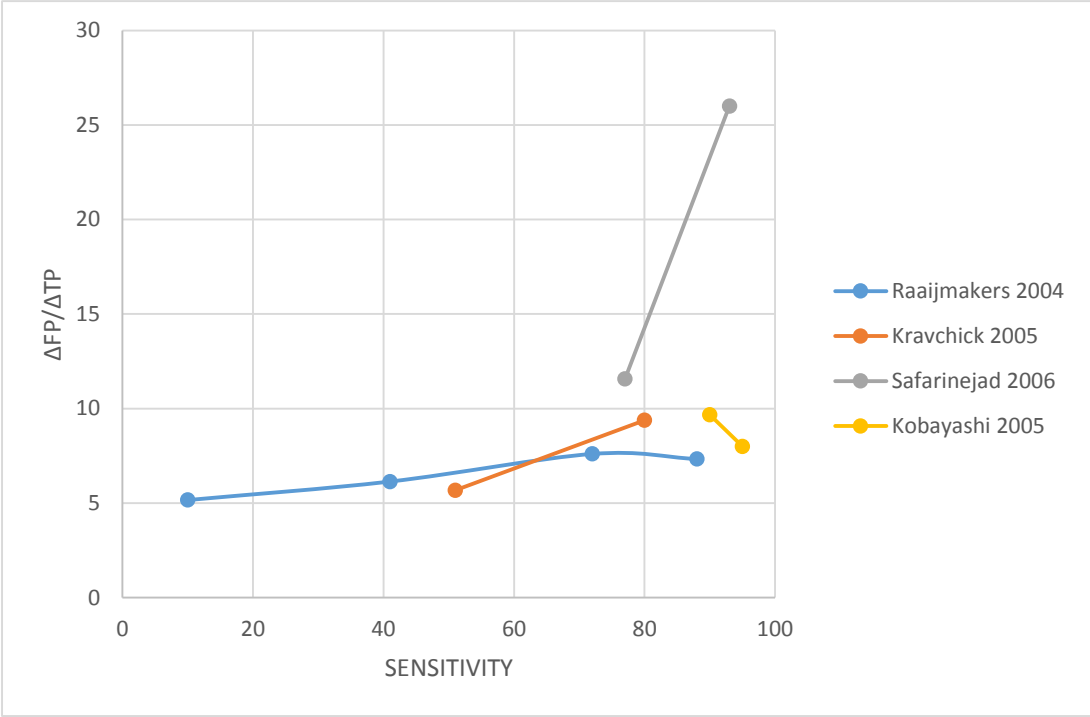


Figure 2. Diagnostic outcomes of studies that investigated the use of f/t PSA% to increase specificity in detecting prostate cancers compared with tPSA alone: tPSA range 2.0/2.1 – 3.9/4.0 ng/mL

II. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **> age–specific reference thresholds**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence*	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (ΔFP)	Cancers missed^ (ΔTP)	ΔFP/ ΔTP	p value AUCs
Not restricted to normal or non-suspicious DRE													
Reissigl 1996 Austria	Retrospective (includes screening population)	266	24.1	8	III-2	At risk	Age-Specific	≤18	6.25	75	4	18.8	NR
Reissigl 1996 Austria	Prospective (includes screening population)	106	34.9	8	III-2	At risk	Age-Specific	22	2.7	21	1	21.0	NR
								20	10.8	25	4	6.25	
								18	24.3	30	9	3.33	
Reissigl 1997 Austria	Prospective (includes screening population)	308	18.8	NR	III-2	At risk	Age-Specific	<20	0	114	0	NR	NR

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA alone for specified tPSA range;*

ΔFP = difference in false positives; ΔTP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen

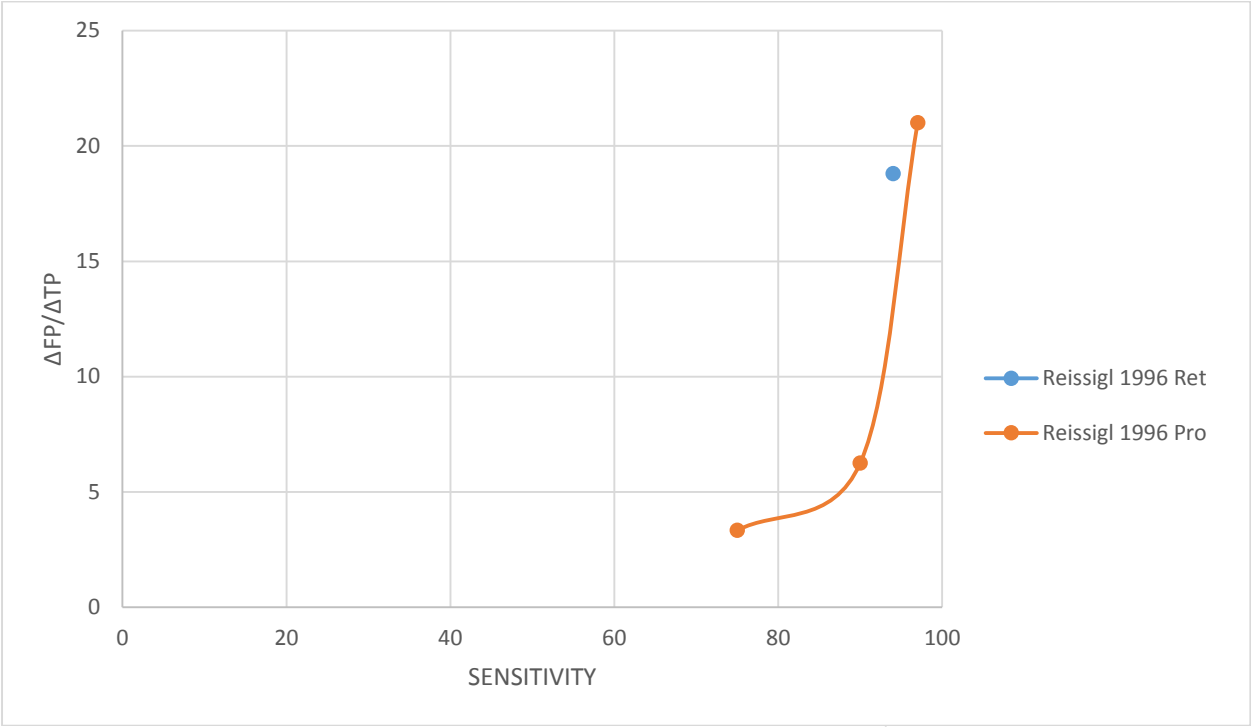


Figure 3. Diagnostic outcomes of studies that investigated the use of f/t PSA% to increase specificity in detecting prostate cancers compared with tPSA alone: tPSA range > age-specific threshold

III. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **2.51/2.6 – 4.0 ng/mL**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence*	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (ΔFP)	Cancers missed^ (ΔTP)	ΔFP/ ΔTP	p value AUCs
Not restricted to normal or non-suspicious DRE													
Okihara 2001 Japan	Prospective	151	24.5	11	III-2	At risk	≥2.5	31	5.4	12	2	6.00	NR
								31	8.1	12	3	4.00	
								30	10.8	12	4	3.00	
								23	24.3	34	9	3.78	
								14	48.6	91	18	5.06	
Normal or non-suspicious DRE only													
Catalona 1999 USA	Retrospective	368	14.7	≥6	III-2	At risk	>2.51	≤ 15	46.3	210	25	8.40	NR
								≤ 14	50	226	27	8.37	
								≤ 13	59.3	248	32	7.75	
								≤ 12	66.7	261	36	7.25	
								≤ 11	70.4	283	38	7.45	
								≤ 10	70.4	295	38	7.76	
Roehl 2002 USA	Prospective (includes screening population)	965	25.0	6	III-2	At risk	>2.6	≤ 30	7.1	65	17	3.82	NR
								≤ 25	14.9	138	36	3.83	

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA alone for specified tPSA range;*

ΔFP = difference in false positives; ΔTP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen;

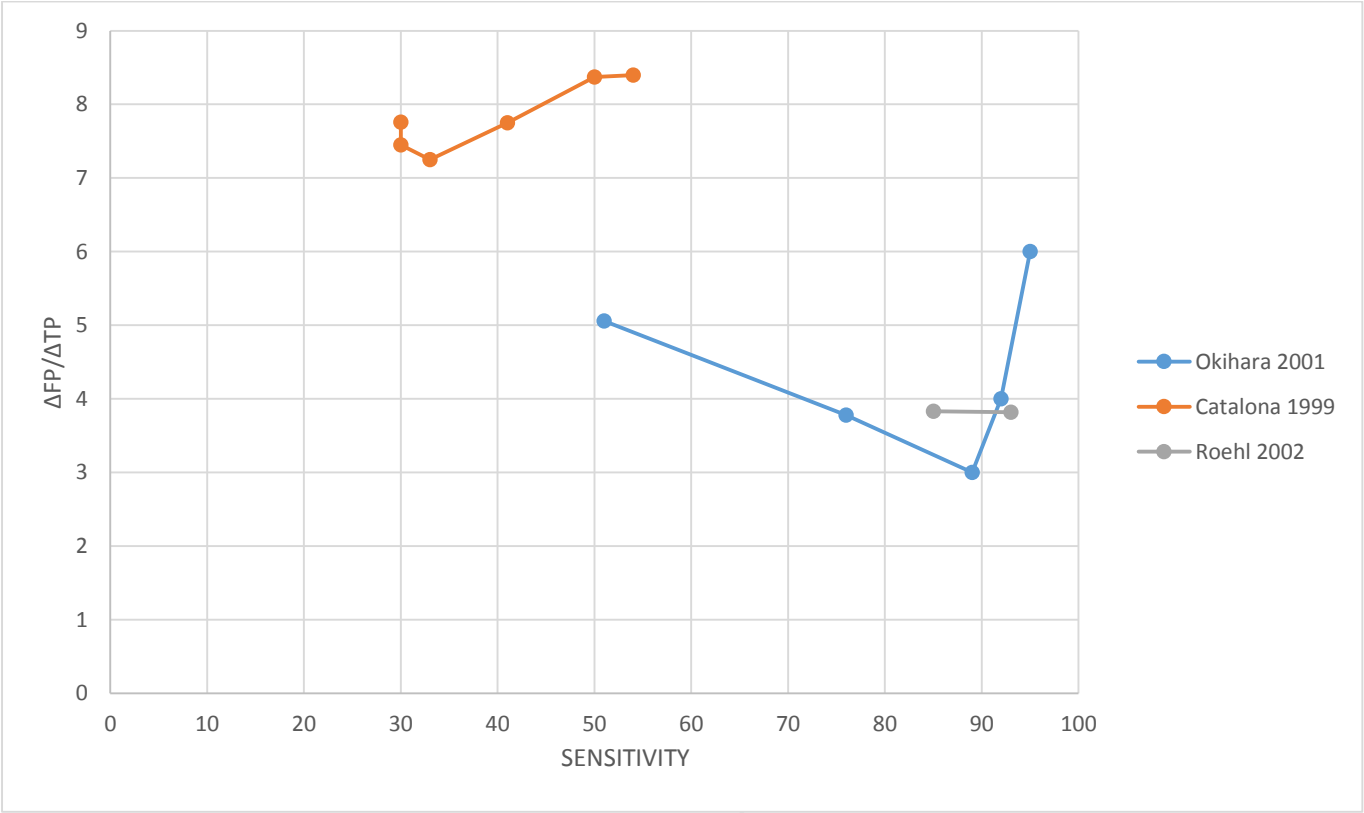


Figure 4. Diagnostic outcomes of studies that investigated the use of f/t PSA% to increase specificity in detecting prostate cancers compared with tPSA alone: tPSA range 2.51/2.6 – 4.0 ng/mL

IV. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **3.0 – 4.0 ng/mL**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence*	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (ΔFP)	Cancers missed^ (ΔTP)	ΔFP/ ΔTP	p value AUCs
Normal or non-suspicious DRE only													
Lodding 1998 Sweden ERSPC - Goteborg	Prospective (includes screening population)	217	12.4	6	III-2	At risk	≥ 3.0 (3.4 on WHO calibration)	26	7.4	25	2	12.50	NR

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA alone for specified tPSA range;*

ΔFP = difference in false positives; ΔTP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; ERSPC = European Randomized Study of Screening for Prostate Cancer; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen; WHO = World Health Organisation

V. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **4.0/4.1 – 10 ng/mL**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence*	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (ΔFP)	Cancers missed^ (ΔTP)	ΔFP/ ΔTP	p value AUCs
Normal or non-suspicious DRE only													
Catalona 1998 USA ***Subgroups*** *aged 50-59 years*	Prospective (includes screening population)	205	53.7	6	III-2	At risk	≥ 4.0	25	1.8	10	2	5.00	NR
aged 60-69 years		408	48.8	6	III-2	At risk	≥ 4.0	25	6.0	39	12	3.25	
aged 70-75 years		160	43.8	6	III-2	At risk	≥ 4.0	25	10	31	7	4.43	
Luboldt 2001 Germany ***Subgroups*** *aged 45-69 years*	Prospective (includes screening population)	457	14.2	6	III-2	At risk	> 4.0	22	6.2	39	4	9.75	NR
								20	6.2	51	4	12.75	
								18	9.2	74	6	12.33	
								16	15.4	114	10	11.40	
								14	16.9	165	11	15.00	
								12	23.1	220	15	14.67	
								10	38.5	282	25	11.28	
aged over 69 years		177	14.7	6	III-2	At risk	> 4.0	22	3.8	32	1	32.00	
								20	3.8	39	1	39.00	
								18	3.8	54	1	54.00	
								16	3.8	76	1	76.00	

14	11.5	89	3	29.67
12	26.9	109	7	15.57
10	46.2	124	12	10.33

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA only for specified tPSA range;*
∆FP = difference in false positives; ∆TP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen

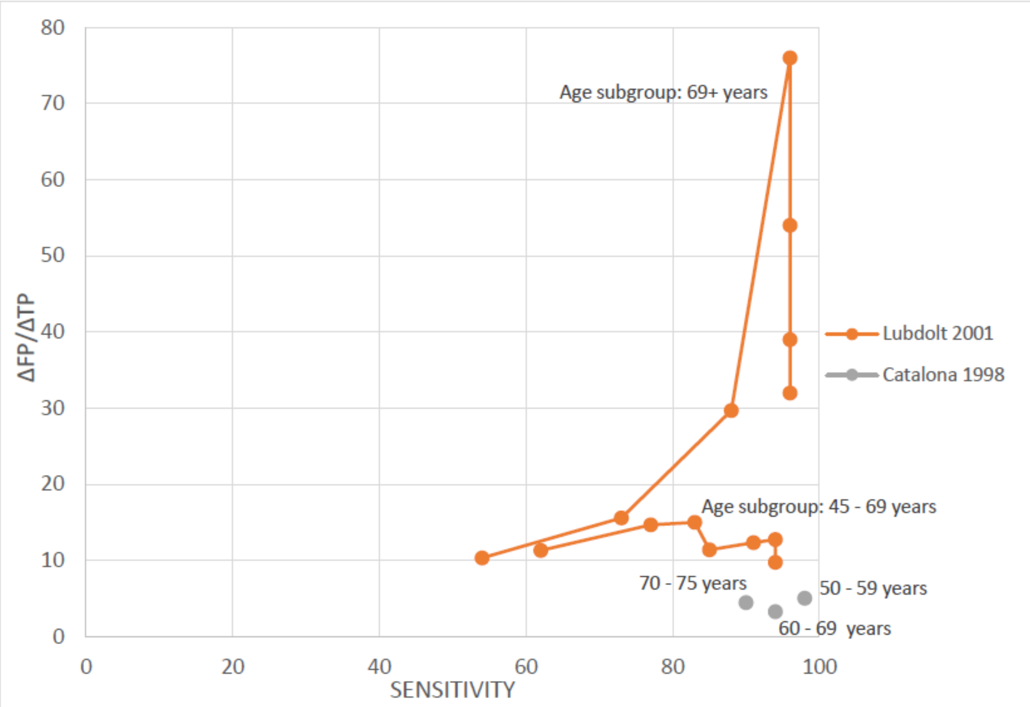


Figure 5: Diagnostic outcomes of studies that investigated the use of f/t PSA% to increase specificity in detecting prosdtate cancers compared with tPSA alone: tPSA range 4.0 – 10.0ng/mL

2.7 BODY OF EVIDENCE - Studies with biopsy core number >6

I. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **2.0/2.1 – 3.9/4.0 ng/mL -** Studies with **biopsy core number >6**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence*	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (∆FP)	Cancers missed^ (∆TP)	∆FP/ ∆TP	p value AUCs
Not restricted to normal or non-suspicious DRE													
Kravchick 2005 Israel	Prospective	171	22.8	Prostate volume: <40 cm^3 = 8 ≥40 cm^3 = 9 ≥80 cm^3 = 10	III-2	At risk	≥ 2.0	21.6	20.5	75	8	9.38	NR
								19.3	48.7	108	19	5.68	
Safarinejad 2006 Iran	Prospective	167	18.0	8	III-2	At risk	≥ 2.1	≤ 18	6.7	52	2	26.0	NR
								≤ 15	23.3	81	7	11.57	
								<25.5	9.7	29	3	9.67	

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA for specified tPSA range;*

∆FP = difference in false positives; ∆TP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen;

II. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **> age–specific reference thresholds -** Studies with **biopsy core number >6**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence*	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (ΔFP)	Cancers missed^ (ΔTP)	ΔFP/ ΔTP	p value AUCs
Not restricted to normal or non-suspicious DRE													
Reissigl 1996 Austria	Retrospective	266	24.1	8	III-2	At risk	Age-Specific	≤18	6.25	75	4	18.8	NR
Reissigl 1996 Austria	Prospective	106	34.9	8	III-2	At risk	Age-Specific	22	2.7	21	1	21.0	NR
								20	10.8	25	4	6.25	
								18	24.3	30	9	3.33	

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA only for specified tPSA range;*

ΔFP = difference in false positives; ΔTP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen;

III. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **2.51/2.6 – 4.0 ng/mL-** Studies with **biopsy core number >6**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence *	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (ΔFP)	Cancers missed^ (ΔTP)	ΔFP/ ΔTP	p value AUCs
Not restricted to normal or non-suspicious DRE													
Okihara 2001 Japan	Prospective	151	24.5	11	III-2	At risk	≥2.5	31	5.4	12	2	6.00	NR
								31	8.1	12	3	4.00	
								30	10.8	12	4	3.00	
								23	24.3	34	9	3.78	
								14	48.6	91	18	5.06	
								≤ 25	14.9	138	36	3.83	

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA only for specified tPSA range;*

ΔFP = difference in false positives; ΔTP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen;

2.8 BODY OF EVIDENCE - Prospective studies

I. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **2.0/2.1 – 3.9/4.0 ng/mL- Prospective studies**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence *	Risk of bias **	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (ΔFP)	Cancers missed^ (ΔTP)	ΔFP/ ΔTP	p value AUCs
Not restricted to normal or non-suspicious DRE													
Egawa 2002 Japan	Prospective	171	NR	Median = 8 Range = 6 -12	III-2	At risk	NR	NR	NR	NR	NR	NR	NS
Raaijmakers 2004 Netherlands ERSPC	Prospective	734	17.2	6	III-2	At risk	≥ 2.0	< 25	11.9	110	15	7.33	NR
								< 20	27.8	266	35	7.60	
								< 15	58.8	454	74	6.14	
								< 10	89.9	583	113	5.16	
Kravchick 2005 Israel	Prospective	171	22.8	Prostate volume: <40 cm^3 = 8 ≥40 cm^3 = 9 ≥80 cm^3 = 10	III-2	At risk	≥ 2.0	21.6	20.5	75	8	9.38	NR
								19.3	48.7	108	19	5.68	
Safarinejad 2006 Iran	Prospective	167	18.0	8	III-2	At risk	≥ 2.1	≤ 18	6.7	52	2	26.0	NR
								≤ 15	23.3	81	7	11.57	
Normal or non-suspicious DRE only													
Kobayashi 2005 Japan	Prospective	139	22.3	6 - 10	III-2	At risk	≥ 2.0	< 29.2	6.5	16	2	8.00	0.331
								<25.5	9.7	29	3	9.67	

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA only for specified tPSA range;*

∆FP = difference in false positives; ∆TP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; ERSPC = European Randomized Study of Screening for Prostate Cancer; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; NS = not significantly different; SD = significantly different; TP = true positive; tPSA = total prostate specific antigen;

II. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **> age–specific reference thresholds - Prospective studies**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence *	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (∆FP)	Cancers missed^ (∆TP)	∆FP/ ∆TP	p value AUCs
Not restricted to normal or non-suspicious DRE													
Reissigl 1996 Austria	Prospective	106	34.9	8	III-2	At risk	Age-Specific	22	2.7	21	1	21.0	NR
								20	10.8	25	4	6.25	
								18	24.3	30	9	3.33	
Reissigl 1997 Austria	Prospective	308	18.8	NR	III-2	At risk	Age-Specific	<20	0	114	0	NR	NR

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA only for specified tPSA range;*

∆FP = difference in false positives; ∆TP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen;

III. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **2.51/2.6 – 4.0 ng/mL - Prospective studies**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence*	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (ΔFP)	Cancers missed^ (ΔTP)	ΔFP/ ΔTP	p value AUCs
Not restricted to normal or non-suspicious DRE													
Okihara 2001 Japan	Prospective	151	24.5	11	III-2	At risk	≥2.5	31	5.4	12	2	6.00	NR
								31	8.1	12	3	4.00	
								30	10.8	12	4	3.00	
								23	24.3	34	9	3.78	
								14	48.6	91	18	5.06	
Normal or non-suspicious DRE only													
Roehl 2002 USA	Prospective	965	25.0	6	III-2	At risk	>2.6	≤ 30	7.1	65	17	3.82	NR
								≤ 25	14.9	138	36	3.83	

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA only for specified tPSA range;*

ΔFP = difference in false positives; ΔTP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen;

IV. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **3.0 – 4.0 ng/mL - Prospective studies**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence *	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (∆FP)	Cancers missed^ (∆TP)	∆FP/ ∆TP	p value AUCs
Normal or non-suspicious DRE only													
Lodding 1998 Sweden ERSPC - Goteborg	Prospective	217	12.4	6	III-2	At risk	≥ 3.0 (3.4 on WHO calibration)	26	7.4	25	2	12.50	NR

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected for specified tPSA range;*

∆FP = difference in false positives; ∆TP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; ERSPC = European Randomized Study of Screening for Prostate Cancer; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen; WHO = World Health Organisation

V. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **4.0/4.1 – 10 ng/mL - Prospective studies**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence*	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (ΔFP)	Cancers missed^ (ΔTP)	ΔFP/ ΔTP	p value AUCs
Normal or non-suspicious DRE only													
Catalona 1998 USA ***Subgroups*** *aged 50-59 years*	Prospective (includes screening population)	205	53.7	6	III-2	At risk	≥ 4.0	25	1.8	10	2	5.00	NR
aged 60-69 years		408	48.8	6	III-2	At risk	≥ 4.0	25	6.0	39	12	3.25	
aged 70-75 years		160	43.8	6	III-2	At risk	≥ 4.0	25	10	31	7	4.43	
Luboldt 2001 Germany ***Subgroups*** *aged 45-69 years*	Prospective (includes screening population)	457	14.2	6	III-2	At risk	> 4.0	22	6.2	39	4	9.75	NR
								20	6.2	51	4	12.75	
								18	9.2	74	6	12.33	
								16	15.4	114	10	11.40	
								14	16.9	165	11	15.00	
								12	23.1	220	15	14.67	
								10	38.5	282	25	11.28	
aged over 69 years		177	14.7	6	III-2	At risk	> 4.0	22	3.8	32	1	32.00	
								20	3.8	39	1	39.00	
								18	3.8	54	1	54.00	

			16	3.8	76	1	76.00
			14	11.5	89	3	29.67
			12	26.9	109	7	15.57
			10	46.2	124	12	10.33

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA only for specified tPSA range;*

∆FP = difference in false positives; ∆TP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen

2.9 BODY OF EVIDENCE - Studies that include screening populations

I. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **2.0/2.1 – 3.9/4.0 ng/mL – Includes screening populations**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence*	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (∆FP)	Cancers missed^ (∆TP)	∆FP/ ∆TP	p value AUCs
Not restricted to normal or non-suspicious DRE													
Raaijmakers 2004 Netherlands ERSPC	Prospective	734	17.2	6	III-2	At risk	≥ 2.0	< 25	11.9	110	15	7.33	NR
								< 20	27.8	266	35	7.60	
								< 15	58.8	454	74	6.14	
								< 10	89.9	583	113	5.16	
Safarinejad 2006 Iran	Prospective	167	18.0	8	III-2	At risk	≥ 2.1	≤ 18	6.7	52	2	26.0	NR
								≤ 15	23.3	81	7	11.57	
Normal or non-suspicious DRE only													
Kobayashi 2005 Japan	Prospective	139	22.3	6 - 10	III-2	At risk	≥ 2.0	< 29.2	6.5	16	2	8.00	0.331
								<25.5	9.7	29	3	9.67	

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA only for specified tPSA range;*

∆FP = difference in false positives; ∆TP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; ERSPC = European Randomized Study of Screening for Prostate Cancer; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen

II. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **> age–specific reference thresholds - Includes screening populations**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence *	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (ΔFP)	Cancers missed^ (ΔTP)	ΔFP/ ΔTP	p value AUCs
Not restricted to normal or non-suspicious DRE													
Reissigl 1996 Austria	Retrospective	266	24.1	8	III-2	At risk	Age-Specific	≤18	6.25	75	4	18.8	NR
Reissigl 1996 Austria	Prospective	106	34.9	8	III-2	At risk	Age-Specific	22	2.7	21	1	21.0	NR
								20	10.8	25	4	6.25	
								18	24.3	30	9	3.33	
Reissigl 1997 Austria	Prospective	308	18.8	NR	III-2	At risk	Age-Specific	<20	0	114	0	NR	NR

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA only for specified tPSA range;*

ΔFP = difference in false positives; ΔTP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen;

III. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **2.51/2.6 – 4.0 ng/mL - Includes screening populations**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence *	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (ΔFP)	Cancers missed^ (ΔTP)	ΔFP/ ΔTP	p value AUCs
Normal or non-suspicious DRE only													
Roehl 2002 USA	Prospective	965	25.0	6	III-2	At risk	>2.6	≤ 30	7.1	65	17	3.82	NR
								≤ 25	14.9	138	36	3.83	

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA only for specified tPSA range;*

ΔFP = difference in false positives; ΔTP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen;

IV. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **3.0 – 4.0 ng/mL - Includes screening populations**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence *	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (ΔFP)	Cancers missed^ (ΔTP)	ΔFP/ ΔTP	p value AUCs
Normal or non-suspicious DRE only													
Lodding 1998 Sweden ERSPC - Goteborg	Prospective	217	12.4	6	III-2	At risk	≥ 3.0 (3.4 on WHO calibration)	26	7.4	25	2	12.50	NR

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA only for specified tPSA range;*

ΔFP = difference in false positives; ΔTP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; ERSPC = European Randomized Study of Screening for Prostate Cancer; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen; WHO = World Health Organisation

V. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **4.0/4.1 – 10 ng/mL - Includes screening populations**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence*	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (ΔFP)	Cancers missed^ (ΔTP)	ΔFP/ ΔTP	p value AUCs
Normal or non-suspicious DRE only													
Catalona 1998 USA ***Subgroups*** *aged 50-59 years*	Prospective (includes screening population)	205	53.7	6	III-2	At risk	≥ 4.0	25	1.8	10	2	5.00	NR
aged 60-69 years		408	48.8	6	III-2	At risk	≥ 4.0	25	6.0	39	12	3.25	
aged 70-75 years		160	43.8	6	III-2	At risk	≥ 4.0	25	10	31	7	4.43	
Luboldt 2001 Germany ***Subgroups*** *aged 45-69 years*	Prospective (includes screening population)	457	14.2	6	III-2	At risk	> 4.0	22	6.2	39	4	9.75	NR
								20	6.2	51	4	12.75	
								18	9.2	74	6	12.33	
								16	15.4	114	10	11.40	
								14	16.9	165	11	15.00	
								12	23.1	220	15	14.67	
								10	38.5	282	25	11.28	
aged over 69 years		177	14.7	6	III-2	At risk	> 4.0	22	3.8	32	1	32.00	
								20	3.8	39	1	39.00	
								18	3.8	54	1	54.00	

	16	3.8	76	1	76.00
	14	11.5	89	3	29.67
	12	26.9	109	7	15.57
	10	46.2	124	12	10.33

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA only for specified tPSA range;*

∆FP = difference in false positives; ∆TP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen

2.10 BODY OF EVIDENCE Studies of European populations

I. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **2.0/2.1 – 3.9/4.0 ng/mL - European populations**

Name of study	Study type/ Population	N	Cancer detection rate	Biopsy core number	Level of evidence *	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (ΔFP)	Cancers missed^ (ΔTP)	ΔFP/ ΔTP	p value AUCs
Not restricted to normal or non-suspicious DRE													
Raaijmakers 2004 Netherlands ERSPC	Prospective (includes screening)	734	17.2	6	III-2	At risk	≥ 2.0	< 25	11.9	110	15	7.33	NR
								< 20	27.8	266	35	7.60	
								< 15	58.8	454	74	6.14	
								< 10	89.9	583	113	5.16	

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA only for specified tPSA range;*

ΔFP = difference in false positives; ΔTP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; ERSPC = European Randomized Study of Screening for Prostate Cancer; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen;

II. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **> age–specific reference thresholds - European populations**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence*	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (ΔFP)	Cancers missed^ (ΔTP)	ΔFP/ ΔTP	p value AUCs
Not restricted to normal or non-suspicious DRE													
Reissigl 1996 Austria	Retrospective (includes screening)	266	24.1	8	III-2	At risk	Age-Specific	≤18	6.25	75	4	18.8	NR
Reissigl 1996 Austria	Prospective (includes screening)	106	34.9	8	III-2	At risk	Age-Specific	22	2.7	21	1	21.0	NR
								20	10.8	25	4	6.25	
								18	24.3	30	9	3.33	
Reissigl 1997 Austria	Prospective (includes screening)	308	18.8	NR	III-2	At risk	Age-Specific	<20	0	114	0	NR	NR

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA only for specified tPSA range;*

ΔFP = difference in false positives; ΔTP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen;

III. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **3.0 – 4.0 ng/mL**
European populations

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence*	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (∆FP)	Cancers missed^ (∆TP)	∆FP/ ∆TP	p value AUCs
Normal or non-suspicious DRE only													
Lodding 1998 Sweden ERSPC - Goteborg	Prospective (includes screening)	217	12.4	6	III-2	At risk	≥ 3.0 (3.4 on WHO calibration)	26	7.4	25	2	12.50	NR

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA for specified tPSA range;*

∆FP = difference in false positives; ∆TP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; ERSPC = European Randomized Study of Screening for Prostate Cancer; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen; WHO = World Health Organisation

IV. Performance characteristics of f/t PSA% + tPSA with those of tPSA alone with respect to prostate cancer detection in tPSA range **4.0/4.1 – 10 ng/mL - European populations**

Name of study	Study type	N	Cancer detection rate	Biopsy core number	Level of evidence*	Risk of bias**	tPSA threshold	f/t PSA% threshold	% cancers missed^	Unnecessary biopsies prevented^ (ΔFP)	Cancers missed^ (ΔTP)	ΔFP/ ΔTP	p value AUCs
Normal or non-suspicious DRE only													
Luboldt 2001 Germany	Prospective (includes screening population)	457	14.2	6	III-2	At risk	> 4.0	22	6.2	39	4	9.75	NR
								20	6.2	51	4	12.75	
								18	9.2	74	6	12.33	
Subgroups *aged 45-69 years*								16	15.4	114	10	11.40	
								14	16.9	165	11	15.00	
								12	23.1	220	15	14.67	
								10	38.5	282	25	11.28	
aged over 69 years		177	14.7	6	III-2	At risk	> 4.0	22	3.8	32	1	32.00	
								20	3.8	39	1	39.00	
								18	3.8	54	1	54.00	
								16	3.8	76	1	76.00	
								14	11.5	89	3	29.67	
								12	26.9	109	7	15.57	
								10	46.2	124	12	10.33	

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for risk of bias appraisals; ^ relative to number detected by tPSA only for specified tPSA range;*

ΔFP = difference in false positives; ΔTP = difference in true positives; AUC = area under the receiver operator curve; DRE = digital rectal examination; FP = false positive; f/t PSA% = percentage free-to-total prostate specific antigen; NR= not reported; TP = true positive; tPSA = total prostate specific antigen

Clinical significance of size of effect is addressed in the assessment of clinical impact in the NHMRC evidence statement form.

Assessment of the relevance of the evidence in terms of whether the outcomes were directly relevant to the patient or surrogate outcomes was not assessed as it was not considered relevant to diagnostic performance studies.

References: Included studies

1. Catalona WJ, Partin AW, Slawin KM, Brawer MK, Flanigan RC, Patel A, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. JAMA 1998 May 20;279(19):1542-7.

2. Catalona WJ, Partin AW, Finlay JA, Chan DW, Rittenhouse HG, Wolfert RL, et al. Use of percentage of free prostate-specific antigen to identify men at high risk of prostate cancer when PSA levels are 2.51 to 4 ng/mL and digital rectal examination is not suspicious for prostate cancer: an alternative model. Urology 1999 Aug;54(2):220-4.

3. Egawa S, Suyama K, Matsumoto K, Kuwao S, Baba S. Prospective evaluation of prostate cancer detection by prostate specific antigen related parameters: comparison in serum and plasma samples. J Urol 2002 Jan;167(1):97-102.

4. Kobayashi T, Kawahara T, Nishizawa K, Ogura K, Mitsumori K, Ide Y. Volume-adjusted prostate-specific antigen (PSA) variables in detecting impalpable prostate cancer in men with PSA levels of 2-4 ng/mL: transabdominal measurement makes a significant contribution. BJU International 2005 Jun;95(9):1245-8.

5. Kravchick S, Peled R, Dorfman D, Agulansky L, Ben-Dor D, Cytron S. Predictive criteria for prostate cancer detection in men with serum PSA concentration of 2.0 to 4.0 ng/mL. Urology 2005 Sep;66(3):542-6.

6. Lodding P, Aus G, Bergdahl S, Frosing R, Lilja H, Pihl CG, et al. Characteristics of screening detected prostate cancer in men 50 to 66 years old with 3 to 4 ng./ml. Prostate specific antigen. J Urol 1998 Mar;159(3):899-903.

7. Luboldt HJ, Swoboda A, Borgermann C, Fornara P, Rubben H, Early Detection Project Group of the German Society of Urology. Clinical usefulness of free PSA in early detection of prostate cancer. Onkologie 2001 Feb;24(1):33-7.

8. Okihara K, Fritsche HA, Ayala A, Johnston DA, Allard WJ, Babaian RJ. Can complexed prostate specific antigen and prostatic volume enhance prostate cancer detection in men with total prostate specific antigen between 2.5 And 4.0 Ng./Ml. J Urol 2001;165:1930-6.

9. Raaijmakers R, Blijenberg BG, Finlay JA, Rittenhouse HG, Wildhagen MF, Roobol MJ, et al. Prostate cancer detection in the prostate specific antigen range of 2.0 to 3.9 ng/ml: value of percent free prostate specific antigen on tumor detection and tumor aggressiveness. J Urol 2004 Jun;171:2245-9.

10. Reissigl A, Klocker H, Pointner J, Fink K, Horninger W, Ennemoser O, et al. Usefulness of the ratio free/total prostate-specific antigen in addition to total PSA levels in prostate cancer screening. Urology 1996 Dec;48(6A):62-6.

11. Reissigl A, Horninger W, Fink K, Klocker H, Bartsch G. Prostate carcinoma screening in the county of Tyrol, Austria: experience and results. Cancer 1997 Nov 1;80(9):1818-29.

12. Roehl KA, Antenor JA, Catalona WJ. Robustness of free prostate specific antigen measurements to reduce unnecessary biopsies in the 2.6 to 4.0 ng./ml. range. J Urol 2002 Sep;168(3):922-5.

13. Safarinejad MR. Population-based screening for prostate cancer by measuring free and total serum prostate-specific antigen in Iran. Annals of Oncology 2006 Jul;17(7):1166-71.

APPENDICES

Appendix A: Search strategies used

For Medline database:

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	(free adj2 (total PSA or total prostate specific antigen or PSA or prostate specific antigen)).mp.
5	(f adj2 (tPSA or total PSA or total prostate specific antigen)).mp.
6	(ratio adj2 free to total adj2 (PSA or prostate specific antigen)).mp.
7	(derivative$ adj2 (PSA or prostate specific antigen)).mp.
8	(%fPSA or fPSA or FTPSA or f?tPSA or f tPSA or f t PSA).mp.
9	4 or 5 or 6 or 7 or 8
10	3 and 9
11	salvage.mp.
12	bisphosphonates.mp. or diphosphonates/
13	cryotherapy.mp.
14	brachytherapy.mp.
15	focal therapy.mp.
16	androgen deprivation.mp.
17	biochemical recurrence.mp.
18	biochemical relapse.mp.
19	biochemical disease.mp.
20	biochemical failure.mp.
21	active surveillance.mp.
22	(castrate resistant or castrate resistance).mp.
23	(hormone resistant or hormone resistance).mp.
24	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25	10 not 24
26	limit 25 to (english language and humans and yr="1990-current")

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database

#	Searches
1	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neopla* OR metast* OR adeno*)
2	'prostate cancer'/exp
3	1 OR 2
4	[embase]/lim AND [1990-2014]/py AND [english]/lim AND [humans]/lim
5	salvage:ab OR chemotherapy:ab OR bisphosphonate*:ab OR brachytherapy:ab OR cryotherapy:ab OR recurrence:ab OR relapse:ab OR castration:ab
6	%fpsa OR fpsa OR ftpsa OR 'f/tpsa' OR 'f/t psa' OR 'f tpsa' OR 'f t psa'
7	free NEAR/2 ('total psa' OR 'total prostate specific antigen' OR psa OR 'prostate specific antigen')
8	f NEAR/2 (tpsa OR 'total psa' OR 'total prostate specific antigen')
9	('free/total' OR 'free to total') NEAR/2 (psa OR 'prostate specific antigen')
10	derivative* NEAR/2 (psa OR 'prostate specific antigen')
11	6 OR 7 OR 8 OR 9 OR 10
12	3 AND 4 AND 11
13	12 NOT 5

ATSI search terms used

#	Searches
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

For Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment database

#	Searches
1	(prostat$ adj3 (cancer$ OR carcinoma$ OR malignan$ OR tumo?r$ OR neoplas$ OR metastas$ OR adeno$)).tw

APPENDIX B:

Level of Evidence rating criteria – Diagnostic accuracy studies

Level	Study design
I	Meta-analysis or a systematic review of level II studies
II	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation
III-1	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation
III-2	A comparison with reference standard that does not meet the criteria required for level II and III-1 evidence
III-3	Diagnostic case-control study
IV	Study of diagnostic yield (no reference standard)

According to the standards of the National Health and Medical Research Council

Appendix C:

Potentially relevant guidelines identified and reason why not adopted

Year	Organisation	Title	Reason why not adopted
2008	National Academy of Clinical Biochemistry	National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for Use of Tumor Markers in Testicular, Prostate, Colorectal, Breast, and Ovarian Cancers	Not based on a systematic review
2012	Royal College of Pathologists of Australasia	Prostate specific antigen testing: Age-related interpretation in early prostate cancer detection	Consensus based

Excluded studies

Study	Reason for Exclusion
Agnihotri 2014	Inappropriate population
Agyei-Frempong 2008	Inappropriate population
Akdas 1997	Inappropriate population
Alivizatos 1996	Inappropriate population
Amirrasouli 2010	No extractable data
Auprich 2011	Inappropriate population
Auvinen 1996	Inappropriate population
Auvinen 2004	No extractable data
Babaian 1998	Inappropriate population
Bajramovic 2012	Inappropriate or unclear indications for biopsy
Baltaci 2003	Inappropriate population
Bangma 1995	More mature data published
Bangma 1997a	More mature data published
Bangma 1997b (the)	Inappropriate population
Bartoletti 1997	Inappropriate population
Barutcuoglu 2009	Inappropriate population
Basso 2000	Inappropriate population
Becker 2000a	Inappropriate study design
Becker 2000b	Inappropriate population
Becker 2003	Inappropriate population
Benecchi 2011	Inappropriate or unclear indications for biopsy
Benecchi 2006	Inappropriate population
Bjork 1996	Inappropriate study design
Blijenberg 2001	Inappropriate study design
Boegemann 2013	Inappropriate or unclear indications for biopsy
Boegemann 2009	Inappropriate population
Bratslavsky 2008	No extractable data

Brawer 1998	Inappropriate population
Brawer 2000	Use of unspecified or inappropriate tPSA or fPSA assays
Bruno 2007	Use of unspecified or inappropriate tPSA or fPSA assays
Canto 2004	No extractable data
Carlson 1998	Use of unspecified or inappropriate tPSA or fPSA assays
Carter 1997	Inappropriate population
Castaldo 1997	Inappropriate population
Catalona 1995	Inappropriate population
Catalona 1997	More mature data published
Catalona 2000a	Inappropriate population
Catalona 2000b	Inappropriate population
Catalona 2003	Inappropriate population
Catalona 2004	Inappropriate or unclear indications for biopsy
Catalona 2011	Inappropriate or unclear indications for biopsy
Chakraborty 2012	Use of unspecified or inappropriate tPSA or fPSA assays
Chen 1996	Use of unspecified or inappropriate tPSA or fPSA assays
Chi-Fai 2012a	Use of unspecified or inappropriate tPSA or fPSA assays
Chi-Fai 2012b	Inappropriate population
Ciatto 2001	Inappropriate population
Ciatto 2004	Inappropriate or unclear indications for biopsy
Ciatto 2006	Inappropriate population
Ciatto 2008	Inappropriate population
Collins 1999	No extractable data
Correale 1996	Inappropriate population
Dadkhah 2010	Use of unspecified or inappropriate tPSA or fPSA assays
Dalva 1999	Inappropriate population
De la Taille 2011	Use of unspecified or inappropriate tPSA or fPSA assays
De la Taille 1998	No extractable data
De Luca 2013	Inappropriate or unclear indications for biopsy
Demura 1996	Use of unspecified or inappropriate tPSA or fPSA assays
Dincel 1999	Inappropriate population
Djavan 1998	Inappropriate population
Djavan 2002	No extractable data
Djavan 1999a	Inappropriate or unclear indications for biopsy
Djavan 1999b	No relevant outcomes
Djavan 1999c	Relevant data published previously
Dowell 1996	Unable to collect
Eekers 2008	Inappropriate or unclear indications for biopsy
Egawa 1997	Inappropriate study design
Egawa 2002	Inappropriate population

Elabbady 2006	No extractable data
Elgamal 1996	Use of unspecified or inappropriate tPSA or fPSA assays
Ellison 2002	Inappropriate population
El-Shafei 2012	Inappropriate population
Emara 2013	Inappropriate or unclear indications for biopsy
Erol 2014	No extractable data
Eskicorapei 2006	Inappropriate or unclear indications for biopsy
Espana 1998	Inappropriate population
Etzioni 2004	Inappropriate population
Ezenwa 2012	Inappropriate population
Faria 2010	Inappropriate population
Faria 2012	Relevant data published previously
Ferreira 2005	Use of unspecified or inappropriate tPSA or fPSA assays
Ferro 2013a	Inappropriate or unclear indications for biopsy
Ferro 2013b	Use of unspecified or inappropriate tPSA or fPSA assays
Ferro 2012	Inappropriate or unclear indications for biopsy
Filella 1995	Inappropriate population
Filella 1997a	Inappropriate study design
Filella 1997b	Inappropriate study design
Filella 1999	Inappropriate study design
Filella 2000	No extractable data
Filella 2001	Inappropriate population
Filella 2004a	More mature data published
Filella 2004b	Inappropriate population
Filella 2007	Inappropriate study design
Filella 2014	Published after March 2014
Fillee 2011	No relevant outcomes
Finne 2000	Inappropriate population
Finne 2002	Inappropriate population
Finne 2004	No extractable data
Finne 2008	No extractable data
Fischer 2005	Inappropriate study design
Foj 2014	Published after March 2014
Fowler 2000	Use of unspecified or inappropriate tPSA or fPSA assays
Froehner 2009	Inappropriate or unclear indications for biopsy
Froehner 2006	Inappropriate population
Froschermaier 1996	Inappropriate study design
Fuchsova 2014	Published after March 2014
Furuya 200	Inappropriate study design
Ganguly 2013	Inappropriate or unclear indications for biopsy

Gann 2002	Inappropriate study design
Ghalia 1996	Inappropriate study design
Gilson 1997	Inappropriate study population
Gion 1998	Inappropriate population
Gion 2000	No extractable data
Gjengsto 2005	Inappropriate or unclear indications for biopsy
Gregorio 2007	Inappropriate study population
Guazzoni 2011	Inappropriate or unclear indications for biopsy
Gulkesen 2010	Inappropriate or unclear indications for biopsy
Haese 2013	Inappropriate or unclear indications for biopsy
Haese 2002	Inappropriate or unclear indications for biopsy
Haese 2001	Unable to collect
Haese 1997	Inappropriate or unclear indications for biopsy
Han 2000	Systematic review – not all included studies meet inclusion criteria
Hara 2006	Inappropriate or unclear indications for biopsy
Haroun 2011	No extractable data
Herrmann 2004	No extractable data
Higashihara 1996a	Inadequate biopsy performed
Higashihara 1996b	Inadequate biopsy performed
Hofer 2000	Inappropriate population
Hoffman 2000	Systematic review – not all included studies meet inclusion criteria
Horninger 2004	No extractable data
Horninger 2002	Inappropriate or unclear indications for biopsy
Horninger 1998	Inappropriate or unclear indications for biopsy
Huang 2014	Published after March 2014
Hugosson 2003	Inappropriate population
Im 2004	Inappropriate population
Iqbal 2005	Inappropriate study population
Ishidoya 2008	No relevant outcomes
Ismail 2002	Use of unspecified or inappropriate tPSA or fPSA assays
Ito 2013	Inappropriate or unclear indications for biopsy
Ito 2003	Inappropriate or unclear indications for biopsy
Jain 2002	Narrative review
Jansen 2010	No extractable data
Jeong 2008	Use of unspecified or inappropriate tPSA or fPSA assays
Jitendra 2003	Unable to collect
Jung 2001	No extractable data
Jung 2000	Inappropriate study population
Jung 2001	Inappropriate study population
Jung 1996	Inappropriate study design

Jung 1999	Inappropriate study design
Jung 1998	Inappropriate or unclear indications for biopsy
Junker 1997	Inappropriate study design
Kang 2006	Use of unspecified or inappropriate tPSA or fPSA assays
Kapoor 2006	Unable to collect
Khan 2003	Inappropriate population
Khan 2004	No extractable data
Kikuchi 2000	Use of unspecified or inappropriate tPSA or fPSA assays
Kitagawa 2014	Inappropriate or unclear indications for biopsy
Klingler 1998	Inappropriate population
Kobayashi 2005	Inappropriate population
Kobayashi 2004	No relevant outcomes
Kobori 2008	Inappropriate or unclear indications for biopsy
Kocer 2013	Inappropriate or unclear indications for biopsy
Kochansko-Dziurowicz 1999	No extractable data
Kochansko-Dziurowicz 1998	Inappropriate population
Koliakos 2000	Use of unspecified or inappropriate tPSA or fPSA assays
Kral 2011	No relevant outcomes
Kurita 1998	Use of unspecified or inappropriate tPSA or fPSA assays
Kuriyama 1998a	Inappropriate population
Kuriyama 1998b	Inappropriate or unclear indications for biopsy
Kuriyama 1999	Use of unspecified or inappropriate tPSA or fPSA assays
Kwiatkowski 2004	No extractable data
Kwiatkowski 1998	Inappropriate population
Lazzeri 2014	No relevant outcomes
Lazzeri 2013a	Inappropriate or unclear indications for biopsy
Lazzeri 2013b	Inappropriate or unclear indications for biopsy
Lazzeri 2013c	Inappropriate or unclear indications for biopsy
Lazzeri 2012	Inappropriate population
Lazzeri 2011	Inappropriate or unclear indications for biopsy
Lee 2011	Inappropriate population
Lee 2006	Systematic review – not all included studies meet inclusion criteria
Lein 2005	Inappropriate or unclear indications for biopsy
Lein 2003	Inappropriate or unclear indications for biopsy
Lein 2001a	Inappropriate or unclear indications for biopsy
Lein 2001b	Inappropriate study design
Lein 2000	Inappropriate population
Leung 1997	Inappropriate population
Li 2005	No extractable data
Li 1999	Inappropriate study design

Liang 2011	Inappropriate population
Liao 2001	Inappropriate population
Lieberman 1999	Inappropriate population
Lista 2012	Inappropriate or unclear indications for biopsy
Ljesevic 2014	Published after March 2014
Lopez-Saez 2007	No extractable data
Lopez-Saez 2004	No extractable data
Lucarelli 2012	Inappropriate study design
Luderer 1995	Use of unspecified or inappropriate tPSA or fPSA assays
Lughezzani 2012	Inappropriate or unclear indications for biopsy
Lynn 2000	Inappropriate population
Maattanen 2007	No extractable data
Maeda 1998	Inappropriate or unclear indications for biopsy
Maeda 1999	Inappropriate population
Magklara 1999	Inappropriate study design
Makinen 2001	No relevant outcomes
Mankoo 2013	Narrative review
Marley 1996	Inappropriate or unclear indications for biopsy
Martin 2006	No extractable data
Martin 2004	Inappropriate population
Martinez-Pineiro 2004	Inappropriate population
Masters 1998	Inappropriate population
Matsuyama 2000	Use of unspecified or inappropriate tPSA or fPSA assays
McArdle 2004	No extractable data
McNicholas 2013a	Inappropriate or unclear indications for biopsy
McNicholas 2013b	Inappropriate or unclear indications for biopsy
Mearini 2014	Unable to collect
Mettlin 1999	Inappropriate or unclear indications for biopsy
Michielsen 2004	Use of unspecified or inappropriate tPSA or fPSA assays
Miele 2001	Inappropriate population
Mikolajczyk 2004	Inappropriate or unclear indications for biopsy
Milicevic 2014	No relevant outcomes
Milkovic 2010	No extractable data
Milkovic 2007	Inappropriate or unclear indications for biopsy
Miller 2001	Inappropriate or unclear indications for biopsy
Minardi 2001	Inappropriate population
Miotto 2004	Use of unspecified or inappropriate tPSA or fPSA assays
Mitchell 2001	Inappropriate or unclear indications for biopsy
Miyake 2001	Inappropriate population
Miyakubo 2009	Inappropriate or unclear indications for biopsy

Moon 2000	Use of unspecified or inappropriate tPSA or fPSA assays
Moon 1999	Use of unspecified or inappropriate tPSA or fPSA assays
Morote 1997a	Inappropriate population
Morote 1997b	Inappropriate population
Morote 1999	Inappropriate population
Morote 2002	Inappropriate population
Mungan 2007	No extractable data
Murphy 1996	Inappropriate population
Na 2013	No extractable data
Na 2012	Use of unspecified or inappropriate tPSA or fPSA assays
Nakano 2005	Inappropriate or unclear indications for biopsy
Naya 2005	Inappropriate or unclear indications for biopsy
Naya 2002	Inappropriate or unclear indications for biopsy
Ng 2014	Inappropriate population
Ochiai 2013	Use of unspecified or inappropriate tPSA or fPSA assays
Ohori 1998	Use of unspecified or inappropriate tPSA or fPSA assays
Okegawa 2000a	No extractable data
Okegawa 2000b	No extractable data
Okegawa 2000c	Inappropriate population
Okihara 2002	No extractable data
Okihara 2004	Inappropriate population
Okihara 2011	Use of unspecified or inappropriate tPSA or fPSA assays
Oliver 2004	No extractable data
Onur 2003	Inappropriate population
Oremek 2003	Inappropriate study design
Ozdal 2004	Inappropriate or unclear indications for biopsy
Ozen 2001	Inappropriate population
Ozveri 2001	Inappropriate population
Parsons 2004	Inappropriate or unclear indications for biopsy
Partin 2003	Inappropriate or unclear indications for biopsy
Partin 1996a	Inappropriate or unclear indications for biopsy
Partin 1996b	Narrative review
Patel 2000	Inappropriate population
Pelekanos 2008	No extractable data
Pelzer 2005	Inappropriate or unclear indications for biopsy
Pepe 2007	Inappropriate or unclear indications for biopsy
Perdona 2013	Inappropriate or unclear indications for biopsy
Perdona 2012a	Inappropriate or unclear indications for biopsy
Perdona 2012b	No extractable data
Pfister 2005	No extractable data

Ploussard 2010	Inappropriate population
Pourmand 2013	Inappropriate or unclear indications for biopsy
Prestigiacomo 1997	Use of unspecified or inappropriate tPSA or fPSA assays
Prestigiacomo 1996	Inappropriate study design
Prestigiacomo 1995	Inappropriate study design
Rafi 2003	Inappropriate or unclear indications for biopsy
Randazzo 2014	Published after March 2014
Recker 1998a	Inappropriate study design
Recker 1998b	Inappropriate study design
Reissigl 1997a	Relevant data published previously
Reissigl 1997a	Relevant data published previously
Reiter 1999	Inappropriate study design
Reiter 1997	Inappropriate population
Reiter 1996	Inappropriate population
Roddam 2005	Systematic review – not all included studies meet inclusion criteria
Roehrborn 1996	Inappropriate population
Rowe 2005	No relevant outcomes
Rowe 2006	Inappropriate population
Saavedra 2013	Inappropriate or unclear indications for biopsy
Saika 2002	Inappropriate or unclear indications for biopsy
Sakai 2004	Inappropriate study design
Sanda 2013	No extractable data
Santotoribio 2014	Published after March 2014
Sasaki 2014	Published after March 2014
Sasaki 2013a	Use of unspecified or inappropriate tPSA or fPSA assays
Sasaki 2013b	Inappropriate study design
Sasaki 2012	Inappropriate study design
Sasaki 2000	Inappropriate population
Scattoni 2013a	No extractable data
Scattoni 2013b	Inappropriate or unclear indications for biopsy
Scorilas 2003	Inappropriate or unclear indications for biopsy
Segawa 2003	No extractable data
Semjonow 2011	Inappropriate or unclear indications for biopsy
Serdar 2002	No extractable data
Shao 2000	Inappropriate study design
Skrepetis 2001	Inappropriate or unclear indications for biopsy
Smrkolj 2013	Inappropriate or unclear indications for biopsy
Sokoll 2003	Inappropriate or unclear indications for biopsy
Sokoll 2008	Inappropriate or unclear indications for biopsy
Sokoll 2010	Inappropriate population

Southwick 2001	Narrative review
Sozen 2005	Inappropriate population
Stamey 2000	Inappropriate or unclear indications for biopsy
Stangelberger 2007	Narrative review
Stattin 2001	Inappropriate population
Stephan 2013a	Inappropriate or unclear indications for biopsy
Stephan 2013b	Inappropriate or unclear indications for biopsy
Stephan 2013c	Inappropriate population
Stephan 2013d	Inappropriate or unclear indications for biopsy
Stephan 2012	Inappropriate or unclear indications for biopsy
Stephan 2011	Inappropriate or unclear indications for biopsy
Stephan 2005	Inappropriate population
Steuber 2007	Inappropriate population
Strittmatter 2011	Inappropriate or unclear indications for biopsy
Szalay 2011	Inappropriate study design
Tamimi 2010	No extractable data
Tanguay 2002	Inappropriate or unclear indications for biopsy
Tello 2001	Inappropriate or unclear indications for biopsy
Thakur 2003	Inappropriate or unclear indications for biopsy
Thiel 1996	Use of unspecified or inappropriate tPSA or fPSA assays
Topolcan 2012	Inappropriate or unclear indications for biopsy
Tornblom 1999	Inappropriate or unclear indications for biopsy
Toubert 1996	Use of unspecified or inappropriate tPSA or fPSA assays
Trinkler 1998	Inappropriate population
Trygg 1997	Inappropriate population
Uzzo 2003	No relevant outcomes
Van Cangh 1996a	Inappropriate population
Van Cangh 1996b	Inappropriate or unclear indications for biopsy
Vashi 1997	Inappropriate or unclear indications for biopsy
Veltri 1999	Inappropriate or unclear indications for biopsy
Veneziano 2005	Inappropriate population
Vessella 2000	Inappropriate population
Vickers 2009	No extractable data
Vilanova 2011	No extractable data
Vincendeau 2011	Inappropriate or unclear indications for biopsy
Vogl 1997	Inappropriate or unclear indications for biopsy
Vukotic 2005	Inappropriate or unclear indications for biopsy
Wald 2000	Inappropriate population
Walz 2008	Inappropriate or unclear indications for biopsy
Wang 2006	Systematic review – not all included studies meet inclusion criteria

Wang 2004	Inappropriate population
Wang 1999	No relevant outcomes
Wechsel 1997	Inappropriate study design
Wesseling 2003	Inappropriate population
Wians 2002	Inappropriate or unclear indications for biopsy
Winkler 2004	Inappropriate or unclear indications for biopsy
Wolff 1997	Inappropriate or unclear indications for biopsy
Wolff 1996	Inappropriate or unclear indications for biopsy
Wu 2000	Inappropriate or unclear indications for biopsy
Wu 1998	Inappropriate population
Wymenga 2000	Inappropriate population
Yamamoto 2008	Inappropriate or unclear indications for biopsy
Yang 2005	Use of unspecified or inappropriate tPSA or fPSA assays
Yeniyol 2001	Inappropriate or unclear indications for biopsy
Yokomizo 2009	Inappropriate population
Yoshida 1999	Inappropriate or unclear indications for biopsy
Zambon 2012	Inappropriate or unclear indications for biopsy
Zhang 2000a	Inappropriate or unclear indications for biopsy
Zhang 2000b	Relevant data previously published
Zhang 1999	No extractable data
Zhao 2007	Inappropriate or unclear indications for biopsy
Zheng 2008	Use of unspecified or inappropriate tPSA or fPSA assays

References: Excluded Studies

1. Agnihotri S, Mittal RD, Ahmad S, Mandhani A. Free to total serum prostate specific antigen ratio in symptomatic men does not help in differentiating benign from malignant disease of the prostate. Indian J Urol 2014;30(1):28-32.

2. Agyei-Frempong MT, Frempong NYF, Aboah K, Boateng KA. Correlation of serum free/total prostate specific antigen ratio with histological features for differential diagnosis of prostate cancer. J Med Sci (Pakistan) 2008;8(6):540-6.

3. Akdas A, Cevik I, Tarcan T, Turkeri L, Dalaman G, Emerk K. The role of free prostate-specific antigen in the diagnosis of prostate cancer. Br J Urol 1997 Jun;79(6):920-3.

4. Alivizatos G, Deliveliotis C, Mitropoulos D, Raptides G, Louras G, Karayiannis A, et al. Does free to total ratio of prostate-specific antigen alter decision-making on prostatic biopsy? Urology 1996 Dec;48(6A):71-5.

5. Amirrasouli H, Kazerouni F, Sanadizade M, Sanadizade J, Kamalian N, Jalali M, et al. Accurate cut-off point for free to total prostate-specific antigen ratio used to improve differentiation of prostate cancer from benign prostate hyperplasia in Iranian population. Urology Journal 2010;7(2):99-104.

6. Auprich M, Augustin H, Budaus L, Kluth L, Mannweiler S, Shariat SF, et al. A comparative performance analysis of total prostate-specific antigen, percentage free prostate-specific antigen, prostate-specific antigen velocity and urinary prostate cancer gene 3 in the first, second and third repeat prostate biopsy. BJU Int 2012 Jun;109(11):1627-35.

7. Auvinen A, Tammela T, Stenman UH, Uusi-Erkkila I, Leinonen J, Schroder FH, et al. Screening for prostate cancer using serum prostate-specific antigen: a randomised, population-based pilot study in Finland. British Journal of Cancer 1996 Aug;74(4):568-72.

8. Auvinen A, Maattanen L, Finne P, Stenman U-H, Aro J, Juusela H, et al. Test sensitivity of prostate-specific antigen in the Finnish randomised prostate cancer screening trial. Int J Cancer 2004;111(6):940-3.

9. Babaian RJ, Fritsche HA, Zhang Z, Zhang KH, Madyastha KR, Barnhill SD. Evaluation of prostAsure index in the detection of prostate cancer: a preliminary report. Urology 1998 Jan;51(1):132-6.

10. Bajramovic S, Junuzovic D. Optimal marker for reduction of unnecessary prostate biopsies. Urology 2012;80(3):S279.

11. Baltaci S, Aksoy H, Turkolmez K, Elhan AH, Ozden E, Gogus O. Use of percent free prostate-specific antigen density to improve the specificity for detecting prostate cancer in patients with normal rectal examinations and intermediate prostate-specific antigen levels. Urol Int 2003;70(1):36-41.

12. Bangma CH, Kranse R, Blijenberg BG, Schroder FH. The value of screening tests in the detection of prostate cancer. Part I: Results of a retrospective evaluation of 1726 men. Urology 1995 Dec;46(6):773-8.

13. Bangma CH, Kranse R, Blijenberg BG, Schroder FH. Free and total prostate-specific antigen in a screened population. Br J Urol 1997 May;79(5):756-62. (a)

14. Bangma CH, Rietbergen JB, Kranse R, Blijenberg BG, Petterson K, Schroder FH. The free-to-total prostate specific antigen ratio improves the specificity of prostate specific antigen in screening for prostate cancer in the general population. J Urol 1997 Jun;157(6):2191-6. (b)

15. Bartoletti R, D'Agata A, Travaglini F, Cappelli G, Agostini S, Barbagli G, et al. Free to total prostatic specific antigen ratio as a new diagnostic tool in prostatic carcinoma. Anticancer Res 1997 Mar;17(2B):1297-301.

16. Barutcuoglu B, Bozdemir AE, Ertan Y, Kabaroglu C, Tamsel S, Hekimgil M, et al. Performance of total prostate specific antigen and free prostate specific antigen ratio for screening prostate cancer in a Turkish population. Turk J Cancer 2009;39(1):18-25.

17. Basso D, Fogar P, Piva MG, Navaglia F, Mazza S, Prayer-Galetti T, et al. Total PSA, free PSA/total PSA ratio, and molecular PSA detection in prostate cancer: which is clinically effective and when? Urology 2000 May;55(5):710-5.

18. Becker C, Piironen T, Pettersson K, Bjork T, Wojno KJ, Oesterling JE, et al. Discrimination of men with prostate cancer from those with benign disease by measurements of human glandular kallikrein 2 (HK2) in serum. J Urol 2000 Jan;163(1):311-6.

19. Becker C, Piironen T, Pettersson K, Hugosson J, Lilja H. Clinical value of human glandular kallikrein 2 and free and total prostate-specific antigen in serum from a population of men with prostate-specific antigen levels 3.0 ng/mL or greater. Urology 2000 May;55(5):694-9.

20. Becker C, Piironen T, Pettersson K, Hugosson J, Lilja H. Testing in serum for human glandular kallikrein 2, and free and total prostate specific antigen in biannual screening for prostate cancer. J Urol 2003 Oct;170:1169-74.

21. Benecchi L. Optimum PSA reflex-range. Archivio Italiano di Urologia, Andrologia 2006 Jun;78(2):44-8.

22. Benecchi L, Potenzoni M, Pastizzaro CD, Uliano N, Pieri AM. Value of longitudinal percent free PSA in prostate cancer diagnosis. J Urol 2011;185(4S):e809.

23. Bjork T, Piironen T, Pettersson K, Lovgren T, Stenman UH, Oesterling JE, et al. Comparison of analysis of the different prostate-specific antigen forms in serum for detection of clinically localized prostate cancer. Urology 1996 Dec;48(6):882-8.

24. Blijenberg BG, Yurdakul G, Van Zelst BD, Bangma CH, Wildhagen MF, Schroder FH. Discordant performance of assays for free and total prostate-specific antigen in relation to the early detection of prostate cancer. BJU Int 2001 Oct;88(6):545-50.

25. Boegemann M, Vincendeau S, Stephan C, Houlgatte A, Krabbe L-M, Semjonow A, et al. Use of [-2]proPSA and prostate health index (phi) to improve the diagnostic accuracy of prostate cancer compared to t-PSA and %f-PSA in young men (65 years old). J Clin Oncol 2013;31(15).

26. Borgermann C, Swoboda A, Luboldt HJ, vom DF, Rubben H. The f/t-PSA ratio in diagnosis of in-patients and out-patients: a unitary cutoff value is not useful! World Journal of Urology 2009 Oct;27(5):581-5.

27. Bratslavsky G, Fisher HA, Kaufman RP, Jr., Voskoboynik D, Nazeer T, Mian BM. PSA-related markers in the detection of prostate cancer and high-grade disease in the contemporary era with extended biopsy. Urol Oncol 2008 Mar;26(2):166-70.

28. Brawer MK, Meyer GE, Letran JL, Bankson DD, Morris DL, Yeung KK, et al. Measurement of complexed PSA improves specificity for early detection of prostate cancer. Urology 1998 Sep;52(3):372-8.

29. Brawer MK, Cheli CD, Neaman IE, Goldblatt J, Smith C, Schwartz MK, et al. Complexed prostate specific antigen provides significant enhancement of specificity compared with total prostate specific antigen for detecting prostate cancer. J Urol 2000 May;163(5):1476-80.

30. Bruno JJ, Armenakas NA, Fracchia JA. Influence of prostate volume and percent free prostate specific antigen on prostate cancer detection in men with a total prostate specific antigen of 2.6 to 10.0 ng/ml. J Urol 2007 May;177(5):1741-4.

31. Canto EI, Singh H, Shariat SF, Kadmon D, Miles BJ, Wheeler TM, et al. Effects of systematic 12-core biopsy on the performance of percent free prostate specific antigen for prostate cancer detection. J Urol 2004 Sep;172(3):900-4.

32. Carlson GD, Calvanese CB, Partin AW. An algorithm combining age, total prostate-specific antigen (PSA), and percent free PSA to predict prostate cancer: results on 4298 cases. Urology 1998 Sep;52(3):455-61.

33. Carter HB, Partin AW, Luderer AA, Metter EJ, Landis P, Chan DW, et al. Percentage of free prostate-specific antigen in sera predicts aggressiveness of prostate cancer a decade before diagnosis. Urology 1997 Mar;49(3):379-84.

34. Castaldo G, Cecere G, di F, V, Prezioso D, d'Armiento M, Salvatore F. Prostate-specific antigen (protein and mRNA) analysis in the differential diagnosis and staging of prostate cancer. Clin Chim Acta 1997 Sep 8;265(1):65-76.

35. Catalona WJ, Smith DS, Wolfert RL, Wang TJ, Rittenhouse HG, Ratliff TL, et al. Evaluation of percentage of free serum prostate-specific antigen to improve specificity of prostate cancer screening. JAMA 1995 Oct 18;274(15):1214-20.

36. Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination. Enhancement of specificity with free PSA measurements. JAMA 1997 May 14;277(18):1452-5.

37. Catalona WJ, Southwick PC, Slawin KM, Partin AW, Brawer MK, Flanigan RC, et al. Comparison of percent free PSA, PSA density, and age-specific PSA cutoffs for prostate cancer detection and staging. Urology 2000 Aug 1;56(2):255-60.

38. Catalona WJ, Partin AW, Slawin KM, Naughton CK, Brawer MK, Flanigan RC, et al. Percentage of free PSA in black versus white men for detection and staging of prostate cancer: a prospective multicenter clinical trial. Urology 2000 Mar;55(3):372-6.

39. Catalona WJ, Bartsch G, Rittenhouse HG, Evans CL, Linton HJ, Amirkhan A, et al. Serum pro prostate specific antigen improves cancer detection compared to free and complexed prostate specific antigen in men with prostate specific antigen 2 to 4 ng/ml. J Urol 2003 Dec;170(6:Pt 1):t-5.

40. Catalona WJ, Bartsch G, Rittenhouse HG, Evans CL, Linton HJ, Horninger W, et al. Serum pro-prostate specific antigen preferentially detects aggressive prostate cancers in men with 2 to 4 ng/ml prostate specific antigen. J Urol 2004 Jun;171:2239-44.

41. Catalona WJ, Partin AW, Sanda MG, Wei JT, Klee GG, Bangma CH, et al. A multicenter study of [-2]pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/ml prostate specific antigen range.[Erratum appears in J Urol. 2011 Jul;186(1):354]. J Urol 2011 May;185(5):1650-5.

42. Chakraborty L, Ahmed AN, Paul BK, Haque A, Ara A, Nabi S, et al. Comparative study of total prostate specific antigen and free to total prostate specific antigen ratio in the diagnosis of prostate cancer. Mymensingh Medical Journal: MMJ 2012 Jan;21(1):98-102.

43. Chen YT, Luderer AA, Thiel RP, Carlson G, Cuny CL, Soriano TF. Using proportions of free to total prostate-specific antigen, age, and total prostate-specific antigen to predict the probability of prostate cancer. Urology 1996 Apr;47(4):518-24.

44. Chi-Fai N, Peter KFC, Ny L, Hc L, Kim WML, Eddie S, et al. Comparison of free-to-total PSA ratio, p2psa-to-free PSA ratio and Prostate Health Index (Phi) in the prediction of prostate biopsy outcome in patients who have serum psa level between 4 to 10 Ng/ Ml receiving first transrectal ultrasound guided biopsy. Int J Urol 2012;19:253. (a)

45. Chi-Fai N, Peter KFC, Ny L, Hc L, Kim WML, Eddie S, et al. To assess the role of total PSA, free-tototal PSA and prostate health index (PHI) in the differentiation of high and low grade prostate cancer in patients with serum PSA level between 4 to 10 ng/ml. Int J Urol 2012;19:278. (b)

46. Ciatto S, Bonardi R, Lombardi C, Cappelli G, Castagnoli A, D'Agata A, et al. Predicting prostate biopsy outcome by findings at digital rectal examination, transrectal ultrasonography, PSA, PSA density and

free-to-total PSA ratio in a population-based screening setting. International Journal of Biological Markers 2001 Jul;16(3):179-82.

47. Ciatto S, Rubeca T, Confortini M, Pontenani G, Lombardi C, Zendron P, et al. Free to total PSA ratio is not a reliable predictor of prostate biopsy outcome. Tumori 2004 May;90(3):324-7.

48. Ciatto S, Rubeca T, Franceschini R, Trevisiol C, Confortini M, Pontenani G, et al. On the clinical usefulness of the free-to-total prostate-specific antigen ratio. International Journal of Biological Markers 2006 Jan;21(1):1-5.

49. Ciatto S, Rubeca T, Martinelli F, Pontenani G, Lombardi C, Di LS. PSA doubling time as a predictor of the outcome of random prostate biopsies prompted by isolated PSA elevation in subjects referred to an outpatient biopsy facility in a routine clinical scenario. International Journal of Biological Markers 2008 Jul;23(3):187-91.

50. Collins GN, Alexandrou K, Wynn-Davies A, Mobley S, O'reilly PH. Free prostate-specific antigen 'in the field': a useful adjunct to standard clinical practice. BJU Int 1999 Jun;83(9):1000-2.

51. Correale M, Pagliarulo A, Donatuti G, Sturda F, Capobianco AM, Stigliani V, et al. Preliminary clinical evaluation of free/total PSA ratio by the IMMULITE system. International Journal of Biological Markers 1996 Jan;11(1):24-8.

52. Dadkhah F, Safarinejad MR, Amini E, Lashay AR, Baghayee A. Utility of prostate specific antigen density and free to total prostate specific antigen ratio for detecting prostate cancer in Iranian men: A prospective study of 187 cases. Curr Urol 2010;4(1):1-5.

53. Dalva I, Akan H, Yildiz O, Telli C, Bingol N. The clinical value of the ratio of free prostate specific antigen to total prostate specific antigen. International Urology & Nephrology 1999;31(5):675-80.

54. De La Taille A, Houlgatte A, Houdelette P, Goluboff ET, Berlizot P, Ricordel I. Influence of free-to-total prostate specific antigen variability on the early diagnosis of prostate cancer: a comparative study of three immunoassays. Br J Urol 1998 Sep;82(3):389-92.

55. De La Taille A, Irani J, Graefen M, Chun F, de RT, Kil P, et al. Clinical evaluation of the PCA3 assay in guiding initial biopsy decisions. J Urol 2011 Jun;185(6):2119-25.

56. De LS, Parziale A, Caccia P, Cavallini A, Faraone N, Giargia E, et al. Comparison of prostate health index, urinary pca3 assay and % free PSA in predicting prostate cancer at first biopsy. Anticancer Res 2013;33(5):2277-8.

57. Demura T, Shinohara N, Tanaka M, Enami N, Chiba H, Togashi M, et al. The proportion of free to total prostate specific antigen: a method of detecting prostate carcinoma. Cancer 1996 Mar 15;77(6):1137-43.

58. Dincel C, Caskurlu T, Tasci AI, Cek M, Sevin G, Fazlioglu A. Prospective evaluation of prostate specific antigen (PSA), PSA density, free-to-total PSA ratio and a new formula (prostate malignancy index) for detecting prostate cancer and preventing negative biopsies in patients with normal rectal examinations and intermediate PSA levels. International Urology & Nephrology 1999;31(4):497-509.

59. Djavan B, Zlotta AR, Byttebier G, Shariat S, Omar M, Schulman CC, et al. Prostate specific antigen density of the transition zone for early detection of prostate cancer. J Urol 1998;160(2):411-8.

60. Djavan B, Zlotta A, Kratzik C, Remzi M, Seitz C, Schulman CC, et al. PSA, PSA density, PSA density of transition zone, free/total PSA ratio, and PSA velocity for early detection of prostate cancer in men with serum PSA 2.5 to 4.0 ng/mL. Urology 1999 Sep;54(3):517-22. (a)

61. Djavan B, Zlotta AR, Remzi M, Ghawidel K, Bursa B, Hruby S, et al. Total and transition zone prostate volume and age: how do they affect the utility of PSA-based diagnostic parameters for early prostate cancer detection? Urology 1999 Nov;54(5):846-52. (b)

62. Djavan B, Remzi M, Zlotta AR, Seitz C, Wolfram R, Hruby S, et al. Combination and multivariate analysis of PSA-based parameters for prostate cancer prediction. Techniques in Urology 1999 Jun;5(2):71-6. (c)

63. Djavan B, Remzi M, Zlotta AR, Ravery V, Hammerer P, Reissigl A, et al. Complexed prostate-specific antigen, complexed prostate-specific antigen density of total and transition zone, complexed/total prostate-specific antigen ratio, free-to-total prostate-specific antigen ratio, density of total and transition zone prostate-specific antigen: results of the prospective multicenter European trial. Urology 2002 Oct;60(4A):4-9.

64. Dowell B, Friese J, Dunlop C, Booker M, Weigand R, Barnes W, et al. Free/Total PSA Ratios in an early detection study. KLIN LABOR 1996;42(6):521-3.

65. Eekers DB, Laschet A, de GM, Roelofs E, Kester A, Delaere K, et al. Why determine only the total prostate-specific antigen, if the free-to-total ratio contains the information? Annals of Clinical Biochemistry 2008 May;45(Pt:3):270-4.

66. Egawa S, Soh S, Ohori M, Uchida T, Gohji K, Fujii A, et al. The ratio of free to total serum prostate specific antigen and its use in differential diagnosis of prostate carcinoma in Japan. Cancer 1997 Jan 1;79(1):90-8.

67. Egawa S, Suyama K, Takashima R, Kuwao S, Baba S. Probability of prostate cancer at various levels of per cent free prostate specific antigen in Japanese men with total PSA of 4.1-10.0 ng/ml. Prostate Cancer & Prostatic Diseases 2002;5(2):115-8.

68. El-Shafei A, Zaytoun O, Vargo E, Li J, Berglund R, Gong M, et al. PSA slope as a predictor of prostate cancer & high grade cancer on repeat biopsy. J Urol 2012;187(4):e774.

69. Elabbady AA, Khedr MM. Free/total PSA ratio can help in the prediction of high gleason score prostate cancer in men with total serum prostate specific antigen (PSA) of 3-10 ng/ml. International Urology & Nephrology 2006;38(3-4):553-7.

70. Elgamal AA, Cornillie FJ, Van Poppel HP, Van de Voorde WM, McCabe R, Baert LV. Free-to-total prostate specific antigen ratio as a single test for detection of significant stage T1c prostate cancer. J Urol 1996;156(3):1042-7.

71. Ellison L, Cheli CD, Bright S, Veltri RW, Partin AW. Cost-benefit analysis of total, free/total, and complexed prostate-specific antigen for prostate cancer screening. Urology 2002 Oct;60(4A):42-6.

72. Emara A, Maiti R, Bott S, Khan S, Nedas T, Hindley R. Validation of PSA free to total ratio and PSA density against template biopsies of prostate. J Urol 2013;189(4):e909.

73. Erol B, Gulpinar MT, Bozdogan G, Ozkanli S, Onem K, Mungan G, et al. The cutoff level of free/total prostate specific antigen (f/t PSA) ratios in the diagnosis of prostate cancer: A validation study on a Turkish patient population in different age categories. Kaohsiung J Med Sci 2014.

74. Eskicorapci SY, Ozkara HA, Onder E, Akdogan B, Erkan I, Ciliv G, et al. Serum ribonuclease activity in the diagnosis of prostate cancer in men with serum prostate-specific antigen levels between 2.5 and 20 ng/mL. Clinical Biochemistry 2006 Apr;39(4):363-6.

75. Espana F, Royo M, Martinez M, Enguidanos MJ, Vera CD, Estelles A, et al. Free and complexed prostate specific antigen in the differentiation of benign prostatic hyperplasia and prostate cancer: studies in serum and plasma samples. J Urol 1998 Dec;160:2081-8.

76. Etzioni R, Falcon S, Gann PH, Kooperberg CL, Penson DF, Stampfer MJ. Prostate-specific antigen and free prostate-specific antigen in the early detection of prostate cancer: do combination tests improve detection? Cancer Epidemiology, Biomarkers & Prevention 2004 Oct;13(10):1640-5.

77. Ezenwa EV, Tijani KH, Jeje EA, Soriyan OO, Ogunjimi MA, Ojewola RW, et al. The value of percentage free prostate specific antigen (PSA) in the detection of prostate cancer among patients with intermediate levels of total PSA (4.0-10.0 ng/mL) in Nigeria. Arab J Urol 2012;10(4):394-401.

78. Faria EF, Carvalhal GF, Vieira RAC, Silva TB, Mauad EC, Carvalho AL. Program for prostate cancer screening using a mobile unit: Results from Brazil. Urology 2010;76(5):1052-7.

79. Faria EF, Carvalhal GF, dos Reis RB, Tobias-Machado M, Vieira RA, Reis LO, et al. Use of low free to total PSA ratio in prostate cancer screening: detection rates, clinical and pathological findings in Brazilian men with serum PSA levels <4.0 ng/mL. BJU Int 2012 Dec;110(11b):E653-E657.

80. Ferreira MD, Koff WJ. Assessment of serum level of prostate-specific antigen adjusted for the transition zone volume in early detection of prostate cancer. International Braz J Urol 146 20;31(2):137-45.

81. Ferro M, Bruzzese D, Perdona S, Mazzarella C, Marino A, Sorrentino A, et al. Predicting prostate biopsy outcome: prostate health index (phi) and prostate cancer antigen 3 (PCA3) are useful biomarkers. Clin Chim Acta 2012 Aug 16;413(15-16):1274-8.

82. Ferro M, Bruzzese D, Perdona S, Marino A, Mazzarella C, Perruolo G, et al. Prostate Health Index (Phi) and Prostate Cancer Antigen 3 (PCA3) Significantly Improve Prostate Cancer Detection at Initial Biopsy in a Total PSA Range of 2-10 ng/ml. PLoS ONE 2013;8(7). (a)

83. Ferro M, Marino A, Gargiulo L, Cosimato V, Mazzarella C, Perruolo G, et al. Increasing prostate cancer detection by a model including prostate health index (PHI) and prostate cancer antigen 3 (PCA3). Anticancer Res 2013;33(5):2275-6. (b)

84. Filella X, Alcover J, Molina R, Gimenez N, Rodriguez A, Jo J, et al. Clinical usefulness of free PSA fraction as an indicator of prostate cancer. Int J Cancer 1995 Dec 11;63(6):780-4.

85. Filella X, Alcover J, Molina R, Rodriguez A, Carretero P, Ballesta AM. Clinical evaluation of free PSA/total PSA (prostate-specific antigen) ratio in the diagnosis of prostate cancer. European Journal of Cancer 1997 Jul;33(8):1226-9.

86. Filella X, Alcover J, Molina R, Rodriguez A, Carretero P, Ballesta AM. Free and total PSA in the diagnosis of prostate cancer. Tumour Biology 1997;18(6):332-40.

87. Filella X, Alcover J, Quinto L, Molina R, Bosch-Capblanch X, Carretero P, et al. Evaluation of a multivariate prostate-specific antigen and percentage of free prostate-specific antigen logistic regression model in the diagnosis of prostate cancer. Tumour Biology 1999 Nov;20(6):312-8.

88. Filella X, Alcover J, Molina R, Corral JM, Carretero P, Ballesta AM. Measurement of complexed PSA in the differential diagnosis between prostate cancer and benign prostate hyperplasia. Prostate 2000 Feb 15;42(3):181-5.

89. Filella X, Alcover J, Manuel CJ, Molina R, Beardo P, Ballesta AM. Free to complexed PSA ratio in differentiating benign prostate hyperplasia from prostate cancer. Anticancer Res 2001;21(5):3717-20.

90. Filella X, Truan D, Alcover J, Gutierrez R, Molina R, Coca F, et al. Complexed prostate-specific antigen for the detection of prostate cancer. Anticancer Res 2004 Nov;24(6):4181-5. (a)

91. Filella X, Truan D, Alcover J, Quinto L, Molina R, Luque P, et al. Comparison of several combinations of free, complexed, and total PSA in the diagnosis of prostate cancer in patients with urologic symptoms. Urology 2004;63(6):1100-3. (b)

92. Filella X, Alcover J, Molina R, Luque P, Corral JM, Auge JM, et al. Usefulness of proprostate-specific antigen in the diagnosis of prostate cancer. Anticancer Res 2007 Jan;27(1B):607-10.

93. Filella X, Foj L, Auge JM, Molina R. Evaluation of the P2PSA and prostate health index to improve prostate cancer detection. Tumor Biol 2014;35:S13.

94. Fillee C, Philippe M, Tombal B. Clinical evaluation of prostate health indexin a general population in order to detect prostate cancer. Clin Chem Lab Med 2011;49:S237.

95. Finne P, Zhang WM, Auvinen A, Leinonen J, Maattanen L, Rannikko S, et al. Use of the complex between prostate specific antigen and alpha 1-protease inhibitor for screening prostate cancer. J Urol 2000 Dec;164(6):1956-60.

96. Finne P, Auvinen A, Aro J, Juusela H, Maattanen L, Rannikko S, et al. Estimation of prostate cancer risk on the basis of total and free prostate-specific antigen, prostate volume and digital rectal examination. European Urology 2002;41(6):619-26.

97. Finne P, Finne R, Bangma C, Hugosson J, Hakama M, Auvinen A, et al. Algorithms based on prostate-specific antigen (PSA), free PSA, digital rectal examination and prostate volume reduce false-positive PSA results in prostate cancer screening. Int J Cancer 2004 Aug 20;111(2):310-5.

98. Finne P, Auvinen A, Maattanen L, Tammela TL, Ruutu M, Juusela H, et al. Diagnostic value of free prostate-specific antigen among men with a prostate-specific antigen level of <3.0 microg per liter. European Urology 2008 Aug;54(2):362-70.

99. Fischer K, Loertzer H, Fornara P. The use of complexed PSA for the early detection of prostate cancer. Anticancer Res 2005 May;25(3A):1591-6.

100. Foj L, Mila M, Mengual L, Luque P, Alcaraz A, Jimenez W, et al. Real-time PCR PCA3 assay is a useful test measured in urine to improve prostate cancer detection. Clin Chim Acta 2014;435:53-8.

101. Fowler JE, Jr., Sanders J, Bigler SA, Rigdon J, Kilambi NK, Land SA. Percent free prostate specific antigen and cancer detection in black and white men with total prostate specific antigen 2.5 to 9.9 ng./ml. J Urol 2000 May;163(5):1467-70.

102. Froehner M, Hakenberg OW, Koch R, Schmidt U, Meye A, Wirth MP. Comparison of the clinical value of complexed PSA and total PSA in the discrimination between benign prostatic hyperplasia and prostate cancer. Urol Int 2006;76(1):27-30.

103. Froehner M, Buck LM, Koch R, Hakenberg OW, Wirth MP. Derivatives of prostate-specific antigen as predictors of incidental prostate cancer. BJU Int 2009 Jul;104(1):25-8.

104. Froschermaier SE, Pilarsky CP, Wirth MP. Clinical significance of the determination of noncomplexed prostate-specific antigen as a marker for prostate carcinoma. Urology 1996 Apr;47(4):525-8.

105. Fuchsova R, Topolcan O, Windrichova J, Hora M, Kucera R, Dolejsova O. Serum levels of markers in early detection of prostate cancer. Tumor Biol 2014;35:S30.

106. Furuya Y, Akakura K, Ito H. Value of free-to-total prostate-specific antigen ratio for detection and staging of prostate cancer. Int J Clin Oncol 2000;5(1):8-11.

107. Ganguly R, Narula A. Can free PSA/total PSA ratio predict the outcome of prostate biopsy? J Pathol 2013;231:S43.

108. Gann PH, Ma J, Catalona WJ, Stampfer MJ. Strategies combining total and percent free prostate specific antigen for detecting prostate cancer: a prospective evaluation. J Urol 2002 Jun;167(6):2427-34.

109. Ghalia AHA, Khalifa A, El-Gharib AM. Comparison between serum total PSA, free PSA levels and free/total PSA index in detecting prostatic carcinoma. CANCER MOL BIOL 1996;3(6):937-44.

110. Gilson G, Lamy S, Humbel RL. First clinical results with Enzymun-Test for free PSA. Anticancer Res 1997 Jul;17(4B):2861-4.

111. Gion M, Mione R, Barioli P, Barichello M, Zattoni F, Prayer-Galetti T, et al. Percent free prostate-specific antigen in assessing the probability of prostate cancer under optimal analytical conditions. Clinical Chemistry 1998 Dec;44(12):2462-70.

112. Gion M, Mione R, Barioli P, Barichello M, Zattoni F, Prayer-Galetti T, et al. Clinical evaluation of percent free prostate-specific antigen using the AxSYM system in the best analytical scenario. European Urology 2000 Apr;37(4):460-9.

113. Gjengsto P, Paus E, Halvorsen OJ, Eide J, Akslen LA, Wentzel-Larsen T, et al. Predictors of prostate cancer evaluated by receiver operating characteristics partial area index: a prospective institutional study. J Urol 2005 Feb;173(2):425-8.

114. Gregorio EP, Grando JP, Saqueti EE, Almeida SH, Moreira HA, Rodrigues MA. Comparison between PSA density, free PSA percentage and PSA density in the transition zone in the detection of prostate cancer in patients with serum PSA between 4 and 10 ng/mL. International Braz J Urol 2007 Mar;33(2):151-60.

115. Guazzoni G, Nava L, Lazzeri M, Scattoni V, Lughezzani G, Maccagnano C, et al. Prostate-specific antigen (PSA) isoform p2PSA significantly improves the prediction of prostate cancer at initial extended prostate biopsies in patients with total PSA between 2.0 and 10 ng/ml: results of a prospective study in a clinical setting. European Urology 2011 Aug;60(2):214-22.

116. Gulkesen KH, Koksal IT, Bilge U, Saka O. Comparison of methods for prediction of prostate cancer in Turkish men with PSA levels of 0-10 ng/mL. Journal of B 2010 Jul;15(3):537-42.

117. Haese A, Graefen M, Noldus J, Hammerer P, Huland E, Huland H. Prostatic volume and ratio of free-to-total prostate specific antigen in patients with prostatic cancer or benign prostatic hyperplasia. J Urol 1997 Dec;158(6):2188-92.

118. Haese A, Partin AW. New serum tests for the diagnosis of prostate cancer. Drugs Today 2001;37(9):607-16.

119. Haese A, Dworschack RT, Partin AW. Percent free prostate specific antigen in the total prostate specific antigen 2 to 4 ng./ml. range does not substantially increase the number of biopsies needed to detect clinically significant prostate cancer compared to the 4 to 10 ng./ml. range. J Urol 2002 Aug;168(2):504-8.

120. Haese A, Lazzeri M, De La Taille A, Palou J, McNicholas T, Scattoni V, et al. Serum isoform [(plus or minus)2]propsa derivates (%P2PSA and PHI) significantly improves the prediction of prostate cancer at initial biopsy in a TPSA range 2-10 NG/ML. A multicentric european study. J Urol 2013;189(4):e913-e914.

121. Han M, Potter SR, Partin AW. The role of free prostate-specific antigen in prostate cancer detection. [Review] [40 refs]. Current Urology Reports 2000 May;1(1):78-82.

122. Hara N, Kitamura Y, Saito T, Komatsubara S. Total and free prostate-specific antigen indexes in prostate cancer screening: value and limitation for Japanese populations. Asian J Androl 2006 Jul;8(4):429-34.

123. Haroun AA, Hadidy AS, Awwad ZM, Nimri CF, Mahafza WS, Tarawneh ES. Utility of free prostate specific antigen serum level and its related parameters in the diagnosis of prostate cancer. Saudi Journal of Kidney Diseases & Transplantation 2011 Mar;22(2):291-7.

124. Herrmann W, Stockle M, Sand-Hill M, Hubner U, Herrmann M, Obeid R, et al. The measurement of complexed prostate-specific antigen has a better performance than total prostate-specific antigen. Clin Chem Lab Med 2004;42(9):1051-7.

125. Higashihara E, Nutahara K, Kojima M, Okegawa T, Miura I, Miyata A, et al. Significance of serum free prostate specific antigen in the screening of prostate cancer. J Urol 1996;156(6):1964-8. (a)

126. Higashihara E, Nutahara K, Kojima M, Okegawa T, Miura I, Miyata A, et al. Significance of free prostate-specific antigen and gamma-seminoprotein in the screening of prostate cancer. Prostate - Supplement 1996;7:40-7. (b)

127. Hofer C, Sauerstein P, Wolter C, Scholz M, Hartung R, Breul J. Value of free prostate-specific antigen (Hybritech Tandem-R) in symptomatic patients consulting the urologist. Urol Int 2000;64(1):18-23.

128. Hoffman RM, Clanon DL, Littenberg B, Frank JJ, Peirce JC. Using the free-to-total prostate-specific antigen ratio to detect prostate cancer in men with nonspecific elevations of prostate-specific antigen levels. Journal of General Internal Medicine 2000 Oct;15(10):739-48.

129. Horninger W, Reissigl A, Klocker H, Rogatsch H, Fink K, Strasser H, et al. Improvement of specificity in PSA-based screening by using PSA-transition zone density and percent free PSA in addition to total PSA levels. Prostate 1998;37(3):133-7.

130. Horninger W, Cheli CD, Babaian RJ, Fritsche HA, Lepor H, Taneja SS, et al. Complexed prostate-specific antigen for early detection of prostate cancer in men with serum prostate-specific antigen levels of 2 to 4 nanograms per milliliter. Urology 2002 Oct;60(4:Suppl 1):Suppl-5.

131. Horninger W, Berger A, Pelzer A, Klocker H, Oberaigner W, Schonitzer D, et al. Screening for prostate cancer: updated experience from the Tyrol study. Current Urology Reports 2004 Jun;5(3):220-5.

132. Huang M, Lin Y, Xu A, Uhlman M, Deng X, Lin X, et al. Percent free prostate-specific antigen does not improve the effectiveness of prostate cancer detection in Chinese men with a prostate-specific antigen of 2.5-20.0 ng/ml: A multicenter study. Med Oncol 2014;31(4).

133. Hugosson J, Aus G, Bergdahl S, Fernlund P, Frosing R, Lodding P, et al. Population-based screening for prostate cancer by measuring free and total serum prostate-specific antigen in Sweden. BJU Int 2003 Dec;92(Suppl 2):39-43.

134. Im YJ, Kim JW, Hong SJ, Chung BH. Proper cut-off value of free to total PSA ratio for detection of prostate cancer in Korean men. Yonsei Medical Journal 2004 Oct 31;45(5):873-8.

135. Iqbal N, Chaughtai N. Evaluation of the diagnostic use of free prostate specific antigen/total prostate specific antigen ratio in detecting prostate cancer. JPMA - Journal of the Pakistan Medical Association 2005 Aug;55(8):318-20.

136. Ishidoya S, Ito A, Orikasa K, Kawamura S, Tochigi T, Kuwahara M, et al. The outcome of prostate cancer screening in a normal Japanese population with PSA of 2-4 ng/ml and the free/total PSA under 12%. Japanese Journal of Clinical Oncology 2008 Dec;38(12):844-8.

137. Ismail AH, Pollak M, Behlouli H, Tanguay S, Begin LR, Aprikian AG. Insulin-like growth factor-1 and insulin-like growth factor binding protein-3 for prostate cancer detection in patients undergoing prostate biopsy. J Urol 2002 Dec;168(6):2426-30.

138. Ito K, Yamamoto T, Ohi M, Kurokawa K, Suzuki K, Yamanaka H. Free/total PSA ratio is a powerful predictor of future prostate cancer morbidity in men with initial PSA levels of 4.1 to 10.0 ng/mL. Urology 2003 Apr;61(4):760-4.

139. Ito K, Miyakubo M, Sekine Y, Koike H, Matsui H, Shibata Y, et al. Diagnostic significance of [-2]pro-PSA and prostate dimension-adjusted PSA-related indices in men with total PSA in the 2.0-10.0 ng/mL range. World Journal of Urology 2013 Apr;31(2):305-11.

140. Jain S, Bhojwani AG, Mellon JK. Improving the utility of prostate specific antigen (PSA) in the diagnosis of prostate cancer: The use of PSA derivatives and novel markers. Postgrad Med J 2002;78(925):646-50.

141. Jansen FH, van Schaik RH, Kurstjens J, Horninger W, Klocker H, Bektic J, et al. Prostate-specific antigen (PSA) isoform p2PSA in combination with total PSA and free PSA improves diagnostic accuracy in prostate cancer detection. European Urology 2010 Jun;57(6):921-7.

142. Jeong IG, Lee KH, Korean Urological Oncologic Society Prostate Cancer Study Group. Percent free prostate specific antigen does not enhance the specificity of total prostate specific antigen for the

detection of prostate cancer in Korean men 50 to 65 years old: a prospective multicenter study. J Urol 2008 Jan;179(1):111-6.

143. Jitendra N, Sandhu MS, Khuller GK, Sharma SK. Role of the ratio of free to total prostate specific antigen (PSA) in the diagnosis of prostate cancer. JMS J Med Soc 2003;17(1):3-7.

144. Jung K, Stephan C, Lein M, Henke W, Schnorr D, Brux B, et al. Analytical performance and clinical validity of two free prostate-specific antigen assays compared. Clinical Chemistry 1996 Jul;42(7):1026-33.

145. Jung K, Meyer A, Lein M, Rudolph B, Schnorr D, Loening SA. Ratio of free-to-total prostate specific antigen in serum cannot distinguish patients with prostate cancer from those with chronic inflammation of the prostate. J Urol 1998 May;159(5):1595-8.

146. Jung K, Brux B, Lein M, Knabich A, Sinha P, Rudolph B, et al. Determination of alpha1-antichymotrypsin-PSA complex in serum does not improve the differentiation between benign prostatic hyperplasia and prostate cancer compared with total PSA and percent free PSA. Urology 1999 Aug;53(6):1160-7.

147. Jung K, Elgeti U, Lein M, Brux B, Sinha P, Rudolph B, et al. Ratio of free or complexed prostate-specific antigen (PSA) to total PSA: which ratio improves differentiation between benign prostatic hyperplasia and prostate cancer? Clinical Chemistry 2000 Jan;46(1):55-62.

148. Jung K, Stephan C, Elgeti U, Lein M, Brux B, Kristiansen G, et al. Molecular forms of prostate-specific antigen in serum with concentrations of total prostate-specific antigen <4 (mu)g/L: Are they useful tools for early detection and screening of prostate cancer? Int J Cancer 2001;93(5):759-65.

149. Jung K, Stephan C, Lein M, Brux B, Sinha P, Schnorr D, et al. Receiver-operating characteristic as a tool for evaluating the diagnostic performance of prostate-specific antigen and its molecular forms--What has to be considered? Prostate 2001 Mar 1;46(4):307-10.

150. Junker R, Brandt B, Zechel C, Assmann G. Comparison of prostate-specific antigen (PSA) measured by four combinations of free PSA and total PSA assays. Clinical Chemistry 1997 Sep;43(9):1588-94.

151. Kang SH, Bae JH, Park HS, Yoon DK, Moon DG, Kim JJ, et al. Prostate-specific antigen adjusted for the transition zone volume as a second screening test: a prospective study of 248 cases. Int J Urol 2006 Jul;13(7):910-4.

152. Kapoor N, Jain R, Surange S, Bhardwaj VK, Srivastava A. Prostate specific antigen ratio: for diagnosis and assessment of aggressiveness of malignancy of prostate.[Erratum appears in Indian J Pathol Microbiol. 2006 Jul;49(3):476]. Indian Journal of Pathology & Microbiology 2006 Apr;49(2):178-81.

153. Khan MA, Partin AW, Rittenhouse HG, Mikolajczyk SD, Sokoll LJ, Chan DW, et al. Evaluation of proprostate specific antigen for early detection of prostate cancer in men with a total prostate specific antigen range of 4.0 to 10.0 ng/ml. J Urol 2003 Sep;170(3):723-6.

154. Khan MA, Sokoll LJ, Chan DW, Mangold LA, Mohr P, Mikolajczyk SD, et al. Clinical utility of proPSA and "benign" PSA when percent free PSA is less than 15%. Urology 2004 Dec;64(6):1160-4.

155. Kikuchi E, Nakashima J, Ishibashi M, Ohigashi T, Asakura H, Tachibana M, et al. Prostate specific antigen adjusted for transition zone volume: the most powerful method for detecting prostate carcinoma. Cancer 2000 Aug 15;89(4):842-9.

156. Kitagawa Y, Ueno S, Izumi K, Kadono Y, Konaka H, Mizokami A, et al. Cumulative probability of prostate cancer detection in biopsy according to free/total PSA ratio in men with total PSA levels of 2.1-10.0 ng/ml at population screening. J Cancer Res Clin Oncol 2014 Jan;140(1):53-9.

157. Klingler HC, Woo H, Rosario D, Cutinha PE, Anderson J, Ward AM, et al. The value of prostate specific antigen (PSA) density and free: total PSA ratio in selecting patients with a normal digital rectal examination and intermediate total PSA levels for further investigation. Br J Urol 1998 Sep;82(3):393-7.

158. Kobayashi T, Nishizawa K, Ogura K, Mitsumori K, Ide Y. Detection of prostate cancer in men with prostate-specific antigen levels of 2.0 to 4.0 ng/mL equivalent to that in men with 4.1 to 10.0 ng/mL in a Japanese population. Urology 2004 Apr;63(4):727-31.

159. Kobayashi T, Kamoto T, Nishizawa K, Mitsumori K, Ogura K, Ide Y. Prostate-specific antigen (PSA) complexed to alpha1-antichymotrypsin improves prostate cancer detection using total PSA in Japanese patients with total PSA levels of 2.0-4.0 ng/mL. BJU Int 2005 Apr;95(6):761-5.

160. Kobori Y, Kitagawa Y, Mizokami A, Komatsu K, Namiki M. Free-to-total prostate-specific antigen (PSA) ratio contributes to an increased rate of prostate cancer detection in a Japanese population screened using a PSA level of 2.1-10.0 ng/ml as a criterion. Int J Clin Oncol 2008;13(3):229-32.

161. Kocer D, Karakukcu C, Karaman H, Tasdemir A, Ali EM. PSA-based parameters and their diagnostic performances in patients with prostate cancer and benign prostatic hyperplasia. Turk J Biochem 2013;38(1):37-42.

162. Kochanska-Dziurowicz AA, Mielniczuk MR, Stojko A, Kaletka J. The clinical utility of measuring free-to-total prostate-specific antigen (PSA) ratio and PSA density in differentiating between benign prostatic hyperplasia and prostate cancer. Br J Urol 1998 Jun;81(6):834-8.

163. Kochanska-Dziurowicz AA, Mielniczuk M, Kaletka J, Teneta L. Evaluation of prostate specific antigen (t-PSA and f-PSA) in blood serum in screening research on prostate cancer. Med Sci Monit 1999;5(5):870-3.

164. Koliakos G, Chatzivasiliou D, Dimopoulos T, Trachana V, Paschalidou K, Galiamoutsas V, et al. The significance of PSA/IGF-1 ratio in differentiating benign prostate hyperplasia from prostate cancer. Disease Markers 2000;16(3-4):143-6.

165. Kral M, Hradil D, Grepl M, Hrabec M, Petrek M, Kolar Z, et al. Prostate Health Index (PHI) in patients with prostate cancer and with BPH. Eur Urol Suppl 2011;10(9):647.

166. Kurita Y, Terada H, Masuda H, Suzuki K, Fujita K. Prostate specific antigen (PSA) value adjusted for transition zone volume and free PSA (gamma-seminoprotein)/PSA ratio in the diagnosis of prostate cancer in patients with intermediate PSA levels. Br J Urol 1998 Aug;82(2):224-30.

167. Kuriyama M, Ueno K, Uno H, Kawada Y, Akimoto S, Noda M, et al. Clinical evaluation of serum prostate-specific antigen-alpha1-antichymotrypsin complex values in diagnosis of prostate cancer: a cooperative study. Int J Urol 1998 Jan;5(1):48-54. (a)

168. Kuriyama M, Kawada Y, Arai Y, Maeda H, Egawa S, Koshiba K, et al. Significance of free to total PSA ratio in men with slightly elevated serum PSA levels: a cooperative study. Japanese Journal of Clinical Oncology 1998 Nov;28(11):661-5. (b)

169. Kuriyama M, Uno H, Watanabe H, Yamanaka H, Saito Y, Shida K. Determination of reference values for total PSA, F/T and PSAD according to prostatic volume in japanese prostate cancer patients with slightly elevated serum PSA levels. Japanese Journal of Clinical Oncology 1999 Dec;29(12):617-22.

170. Kwiatkowski M, Huber A, Moschopulos M, Lehmann K, Wernli M, Hafeli A, et al. Prostate cancer screening: results of a prospective trial in Canton Aargau, Switzerland. Swiss Medical Weekly 2004 Oct 2;134(39-40):580-5.

171. Kwiatkowski MK, Recker F, Piironen T, Pettersson K, Otto T, Wernli M, et al. In prostatism patients the ratio of human glandular kallikrein to free PSA improves the discrimination between prostate cancer and benign hyperplasia within the diagnostic "gray zone" of total PSA 4 to 10 ng/mL. Urology 1998 Sep;52(3):360-5.

172. Lazzeri M. Prostate cancer: The Prostate Health Index (PHI) may guide diagnostic and treatment. Tumor Biol 2011;32:S40.

173. Lazzeri M, Briganti A, Scattoni V, Lughezzani G, Larcher A, Gadda GM, et al. Serum index test %[-2]proPSA and Prostate Health Index are more accurate than prostate specific antigen and %fPSA in predicting a positive repeat prostate biopsy. J Urol 2012 Oct;188(4):1137-43.

174. Lazzeri M, Lughezzani G, Lista G, Larcher A, Cestari A, Buffi N, et al. Clinical performance of serum isoform [-2]proPSA (p2PSA) and its derivatives, namely %p2PSA and PHI (Prostate Health Index) in men with family history of prostate cancer. Results from a multicentric European study (PROMEtheuS project). Eur Urol Suppl 2013;12(1):e848-e849. (a)

175. Lazzeri M, Haese A, Abrate A, De La Taille A, Redorta JP, McNicholas T, et al. Clinical performance of serum prostate-specific antigen isoform [-2]proPSA (p2PSA) and its derivatives, %p2PSA and the prostate health index (PHI), in men with a family history of prostate cancer: results from a multicentre European study, the PROMEtheuS project. BJU Int 2013 Aug;112(3):313-21. (b)

176. Lazzeri M, Haese A, De La Taille A, Palou RJ, McNicholas T, Lughezzani G, et al. Serum isoform [-2]proPSA derivatives significantly improve prediction of prostate cancer at initial biopsy in a total PSA range of 2-10 ng/ml: a multicentric European study. European Urology 2013 Jun;63(6):986-94. (c)

177. Lazzeri M, Abrate A, Lughezzani G, Gadda GM, Freschi M, Mistretta F, et al. Relationship of chronic histologic prostatic inflammation in biopsy specimens with serum isoform [-2]proPSA (p2PSA), %p2PSA, and prostate health index in men with a total prostate-specific antigen of 4-10 ng/ml and normal digital rectal examination. Urology 2014 Mar;83(3):606-12.

178. Lee BH, Moussa AS, Li J, Fareed K, Jones JS. Percentage of free prostate-specific antigen: implications in modern extended scheme prostate biopsy. Urology 2011 Apr;77(4):899-903.

179. Lee R, Localio AR, Armstrong K, Malkowicz SB, Schwartz JS, Free PSA Study Group. A meta-analysis of the performance characteristics of the free prostate-specific antigen test. Urology 2006 Apr;67(4):762-8.

180. Lein M, Jung K, Elgeti U, Brux B, Sinha P, Schnorr D, et al. Ratio of alpha 1-antichymotrypsin--prostate specific antigen to total prostate specific antigen in prostate cancer diagnosis. Anticancer Res 2000 Nov;20(6D):4997-5001.

181. Lein M, Jung K, Hammerer P, Graefen M, Semjonow A, Stieber P, et al. A multicenter clinical trial on the use of alpha1-antichymotrypsin-prostate-specific antigen in prostate cancer diagnosis. Prostate 2001 May 1;47(2):77-84. (a)

182. Lein M, Jung K, Elgeti U, Petras T, Stephan C, Brux B, et al. Comparison of the clinical validity of free prostate-specific antigen, alpha-1 antichymotrypsin-bound prostate-specific antigen and complexed prostate-specific antigen in prostate cancer diagnosis. European Urology 2001 Jan;39(1):57-64. (b)

183. Lein M, Kwiatkowski M, Semjonow A, Luboldt HJ, Hammerer P, Stephan C, et al. A multicenter clinical trial on the use of complexed prostate specific antigen in low prostate specific antigen concentrations. J Urol 2003 Oct;170(4:Pt 1):t-9.

184. Lein M, Semjonow A, Graefen M, Kwiatkowski M, Abramjuk C, Stephan C, et al. A multicenter clinical trial on the use of (-5, -7) pro prostate specific antigen. J Urol 2005 Dec;174(6):2150-3.

185. Leung HY, Lai LC, Day J, Thomson J, Neal DE, Hamdy FC. Serum free prostate-specific antigen in the diagnosis of prostate cancer. Br J Urol 1997 Aug;80(2):256-9.

186. Li W, Ren Y, Mee V, Wong PY. Prostate-specific antigen ratio correlates with aggressiveness of histology grades of prostate cancer. Clinical Biochemistry 1999 Feb;32(1):31-7.

187. Li X-M, Zhang L, Li J, Li Y, Wang H-L, Ji G-Y, et al. Measurement of serum zinc improves prostate cancer detection efficiency in patients with PSA levels between 4 ng/mL and 10 ng/mL. Asian J Androl 2005;7(3):323-8.

188. Liang Y, Ankerst DP, Ketchum NS, Ercole B, Shah G, Shaughnessy JD, Jr., et al. Prospective evaluation of operating characteristics of prostate cancer detection biomarkers. J Urol 2011 Jan;185(1):104-10.

189. Liao CH, Liu SP, Pu YS, Huang CY, Yu HJ, Chen J. Effect of percent free prostate-specific antigen measurement on improving the specificity of serum prostate-specific antigen testing in Taiwanese patients. Journal of the Formosan Medical Association 2001 Feb;100(2):113-9.

190. Lieberman S. Can percent free prostate-specific antigen reduce the need for prostate biopsy? Effective Clinical Practice 1999 Nov;2(6):266-71.

191. Lista G, Lughezzani G, Lazzeri M, Scattoni V, Nava L, Centemero A, et al. Isoform [-2]proPSA (p2PSA) and its derivates, %p2PSA and PHI values differ between BPH, ASAP, HG-PIN and PCa in a set of contemporary men undergoing prostate biopsy. Eur Urol Suppl 2012;11(1):e910-e910a.

192. Ljesevic S, Joksimovic D, Stojadinovic D, Nedeljkovic T. The role of F/T(%) ratio for differential diagnosis between benign prostatic hyperplasia and prostatic carcinoma in patient at the clinical center of Kragujevac in Serbia. Tumor Biol 2014;35:S47.

193. Lopez-Saez J-B, Otero M, Senra-Varela A, Ojea A, Saez Martin JL, Duran MB, et al. Prospective observational study to assess value of prostate cancer diagnostic methods. J Diagn Med Sonogr 2004;20(6):383-93.

194. Lopez-Saez J-B, Otero M, Villar MD, Penuelas AL, Navarro PR, Moreira PG, et al. Diagnostic methods in the detectiion of prostate cancer: Prospective observational study. Curr Med Imaging Rev 2007;3(1):27-35.

195. Lucarelli G, Fanelli M, Larocca AMV, Germinario CA, Rutigliano M, Vavallo A, et al. Serum sarcosine increases the accuracy of prostate cancer detection in patients with total serum PSA less than 4.0 ng/ml. Prostate 2012;72(15):1611-21.

196. Luderer AA, Chen YT, Soriano TF, Kramp WJ, Carlson G, Cuny C, et al. Measurement of the proportion of free to total prostate-specific antigen improves diagnostic performance of prostate-specific antigen in the diagnostic gray zone of total prostate-specific antigen. Urology 1995 Aug;46(2):187-94.

197. Lughezzani G, Lazzeri M, Scattoni V, Larcher A, Gadda G, Nava L, et al. Clinical cut-offs of isoform [-2]proPSA (p2PSA) derivatives, namely %p2PSA and PHI (Prostate Health Index) for guiding biopsy decision in Caucasian population. Eur Urol Suppl 2012;11(1):e909-e909a.

198. Lynn NNK, Collins GN, Alexandrou K, Brown SCW, Brooman PJC, O'reilly PH. Comparative analysis of the role of prostate specific antigen parameters in clinical practice. Prostate J 2000;2(4):205-10.

199. Maattanen L, Hakama M, Tammela TL, Ruutu M, Ala-Opas M, Juusela H, et al. Specificity of serum prostate-specific antigen determination in the Finnish prostate cancer screening trial. British Journal of Cancer 2007 Jan 15;96(1):56-60.

200. Maeda H, Arai Y, Okubo K, Aoki Y, Okada T, Maekawa S. Value of the free to total prostate specific antigen ratio and prostate specific antigen density for detecting prostate cancer in Japanese patients. Int J Urol 1998 Jul;5(4):343-8.

201. Maeda H, Arai Y, Aoki Y, Okubo K, Okada T, Maekawa S. Complexed prostate-specific antigen and its volume indexes in the detection of prostate cancer. Urology 1999 Aug;54(2):225-8.

202. Magklara A, Scorilas A, Catalona WJ, Diamandis EP. The combination of human glandular kallikrein and free prostate-specific antigen (PSA) enhances discrimination between prostate cancer and benign prostatic hyperplasia in patients with moderately increased total PSA. Clinical Chemistry 1999 Nov;45(11):1960-6.

203. Makinen T, Tammela TL, Hakama M, Stenman UH, Rannikko S, Aro J, et al. Prostate cancer screening within a prostate specific antigen range of 3 to 3.9 ng./ml.: a comparison of digital rectal examination and free prostate specific antigen as supplemental screening tests. J Urol 2001 Oct;166(4):1339-42.

204. Mankoo K. ProPSA and the Prostate H ealth index in the role of prostate cancer diagnosis. Where are they now? A review of the current literature. BJU Int 2013;112(Suppl 1):3.

205. Marley GM, Miller MC, Kattan MW, Zhao G, Patton KP, Vessella RL, et al. Free and complexed prostate-specific antigen serum ratios to predict probability of primary prostate cancer and benign prostatic hyperplasia. Urology 1996 Dec;48(6A):16-22.

206. Martin BJ, Finlay JA, Sterling K, Ward M, Lifsey D, Mercante D, et al. Early detection of prostate cancer in African-American men through use of multiple biomarkers: human kallikrein 2 (hK2), prostate-specific antigen (PSA), and free PSA (fPSA). Prostate Cancer & Prostatic Diseases 2004;7(2):132-7.

207. Martin BJ, Cheli CD, Sterling K, Ward M, Pollard S, Lifsey D, et al. Prostate specific antigen isoforms and human glandular kallikrein 2--which offers the best screening performance in a predominantly black population? J Urol 2006 Jan;175(1):104-7.

208. Martinez-Pineiro L, Garcia Mediero JM, Gonzalez GP, Tabernero A, Lozano D, Lopez-Tello JJ, et al. Probability of prostate cancer as a function of the percentage of free prostate-specific antigen in patients with a non-suspicious rectal examination and total prostate-specific antigen of 4-10 ng/ml. World Journal of Urology 2004 Jun;22(2):124-31.

209. Masters JG, Keegan PE, Hildreth AJ, Greene DR. Free/total serum prostate-specific antigen ratio: how helpful is it in detecting prostate cancer? Br J Urol 1998 Mar;81(3):419-23.

210. Matsuyama H, Baba Y, Yamakawa G, Yamamoto N, Naito K. Diagnostic value of prostate-specific antigen-related parameters in discriminating prostate cancer. Int J Urol 2000 Nov;7(11):409-14.

211. McArdle PA, Pollock MA, Wallace AM, McMillan DC, Crooks JE, Underwood MA. Comparison of total, complexed and free prostate-specific antigens and their ratios in the detection of prostate cancer in a non-screened population. Annals of Clinical Biochemistry 2004 May;41:201-6.

212. McNicholas T, Lazzeri M, Haese A, De La Taille A, Palou J, Lughezzani G, et al. Serum isoform [-2]proPSA (p2PSA) and its derivatives, namely %p2PSA and PHI (prostate health index) in men younger than 60 years of age for prediction of prostate cancer. Results from a multicentric european study (prometheus project). J Urol 2013;189(4):e790. (a)

213. McNicholas T, Lazzeri M, Haese A, De La Taille A, Palou J, Lughezzani G, et al. PHI (Prostate Health Index) and %p2PSA for prediction of prostate cancer in men younger than 60 years of age. A nested-case control study from PROpsa Multicentric European Study (PROMEtheuS project). Eur Urol Suppl 2013;12(1):e137-e138. (b)

214. Mearini L, Ferri C, Lazzeri M, Bini V, Nunzi E, Fiorini D, et al. Evaluation of Prostate-Specific Antigen Isoform p2PSA and Its Derivates, %p2PSA, Prostate Health Index and Prostate Dimension-Adjusted Related Index in the Detection of Prostate Cancer at First Biopsy: An Exploratory, Prospective Study. Urol Int 2014.

215. Mettlin C, Chesley AE, Murphy GP, Bartsch G, Toi A, Bahnson R, et al. Association of free PSA percent, total PSA, age, and gland volume in the detection of prostate cancer. Prostate 1999 May 15;39(3):153-8.

216. Michielsen DPJ, Braeckman JG, De Reijke TM, Vijverberg PLM, De La Rosette JJMC. Prediction of free PSA, PSA density and PSA density transition zone in the outcome of sextant prostate biopsies in patients with total PSA between 3 and 15 ng/ml. UroOncology 2004;4(2):71-6.

217. Miele ME. Percent free PSA as an additional measure in a prostate cancer screen. Clinical Laboratory Science 2001;14(2):102-7.

218. Mikolajczyk SD, Catalona WJ, Evans CL, Linton HJ, Millar LS, Marker KM, et al. Proenzyme forms of prostate-specific antigen in serum improve the detection of prostate cancer. Clinical Chemistry 2004 Jun;50(6):1017-25.

219. Milicevic N, Mrcela M, Lukic I, Mandic S, Horvat V, Galic J. Comparison between clinical significance of serum proinflammatory protein interleukin-6 and classic tumor markers total PSA, free PSA and free/total PSA prior to prostate biopsy. Collegium Antropologicum 2014 Mar;38(1):147-50.

220. Milkovic B, Hadzi-Djokic J, Dzamic Z, Pejcic T. The significance of TPSA, free to total PSA ratio and PSA density in prostate carcinoma diagnostics. Acta Chirurgica Iugoslavica 2007;54(4):105-7.

221. Milkovic B, Dzamic Z, Pejcic T, Kajmakovic B. (F/T)/PSAD ratio determination according to the prostate volume with the patients in Serbia. Eur Urol Suppl 2010;9(6):601.

222. Miller MC, O'Dowd GJ, Partin AW, Veltri RW. Contemporary use of complexed PSA and calculated percent free PSA for early detection of prostate cancer: impact of changing disease demographics. Urology 2001 Jun;57(6):1105-11.

223. Minardi D, Galosi AB, Recchioni A, Giammarco L, Polito M, Muzzonigro G. Diagnostic accuracy of percent free prostate-specific antigen in prostatic pathology and its usefulness in monitoring prostatic cancer patients. Urol Int 2001;67(4):272-82.

224. Miotto A, Jr., Srougi M, Brito GA, Leite KM, Nesrallah AJ, Ortiz V. Value of various PSA parameters for diagnosing prostate cancer in men with normal digital rectal examination. International Braz J Urol 2004 Mar;30(2):109-13.

225. Mitchell ID, Croal BL, Dickie A, Cohen NP, Ross I. A prospective study to evaluate the role of complexed prostate specific antigen and free/total prostate specific antigen ratio for the diagnosis of prostate cancer. J Urol 2001 May;165(5):1549-53.

226. Miyake H, Hara S, Nomi M, Arakawa S, Kamidono S, Hara I. Value of prostate specific antigen (alpha)1-antichymotrypsin complex for the detection of prostate cancer in patients with a PSA level of 4.1-10.0 ng/mL: Comparison with PSA-related parameters. Int J Urol 2001;8(11):589-93.

227. Miyakubo M, Ito K, Yamamoto T, Takechi H, Ohi M, Suzuki K. Proprostate-specific antigen: its usefulness in the era of multiple-core prostate biopsy. Int J Urol 2009 Jun;16(6):561-5.

228. Moon DG, Cheon J, Kim JJ, Yoon DK, Koh SK. Prostate-specific antigen adjusted for the transition zone volume versus free-to-total prostate-specific antigen ratio in predicting prostate cancer. Int J Urol 1999 Sep;6(9):455-62.

229. Moon DG, Yu JW, Lee JG, Kim JJ, Koh SK, Cheon J. The influence of prostate volume on the prostate-specific antigen (PSA) level adjusted for the transition zone volume and free-to-total PSA ratio: a prospective study. BJU Int 2000 Oct;86(6):670-4.

230. Morote J, Raventos CX, Lorente JA, Lopez-Pacios MA, Encabo G, de T, I, et al. Comparison of percent free prostate specific antigen and prostate specific antigen density as methods to enhance prostate specific antigen specificity in early prostate cancer detection in men with normal rectal examination and prostate specific antigen between 4.1 and 10 ng./ml. J Urol 1997 Aug;158(2):502-4. (a)

231. Morote J, Raventos CX, Lorente JA, Lopez-Pacios MA, Encabo G, de T, I, et al. Measurement of free PSA in the diagnosis and staging of prostate cancer. Int J Cancer 1997 May 29;71(5):756-9. (b)

232. Morote J, Encabo G, Lopez M, de Torres IM. Individual variations of total and percent free serum prostatic specific antigen: could they change the indication of prostatic biopsy? Oncol Rep 1999 Jul;6(4):887-90.

233. Morote J, Trilla E, Esquena S, Serrallach F, Abascal JM, Munoz A, et al. The percentage of free prostatic-specific antigen is also useful in men with normal digital rectal examination and serum prostatic-specific antigen between 10.1 and 20 ng/ml. European Urology 2002 Oct;42(4):333-7.

234. Mungan AG, Erol B, Akduman B, Bozdogan G, Kiran S, Yesilli C, et al. Values for free/total prostate-specific antigen ratio as a function of age: necessity of reference validation in a Turkish

population.[Erratum appears in Clin Chem Lab Med. 2007;45(11):1570]. Clinical Chemistry & Laboratory Medicine 2007;45(7):912-6.

235. Murphy GP, Barren RJ, Erickson SJ, Bowes VA, Wolfert RL, Bartsch G, et al. Evaluation and comparison of two new prostate carcinoma markers. Free-prostate specific antigen and prostate specific membrane antigen.[Erratum appears in Cancer 1996 Oct 1;78(7):1524]. Cancer 1996 Aug 15;78(4):809-18.

236. Na R, Jiang H, Kim ST, Wu Y, Tong S, Zhang L, et al. Outcomes and trends of prostate biopsy for prostate cancer in Chinese men from 2003 to 2011. PLoS ONE [Electronic Resource] 2012;7(11):e49914.

237. Na R, Wu Y, Xu J, Jiang H, Ding Q. Age-specific prostate specific antigen cutoffs for guiding biopsy decision in Chinese population. PLoS ONE [Electronic Resource] 2013;8(6):e67585.

238. Nakano Y, Okamura K, Takamura S, Okamoto N, Narishima M, Yoshino Y, et al. Measurement of prostate specific antigen complexed to alpha1-antichymotrypsin to avoid unnecessary biopsy in patients with serum prostate specific antigen levels 4-20 ng/mL. Int J Urol 2005 Aug;12(8):721-7.

239. Naya Y, Stamey TA, Cheli CD, Partin AW, Sokoll LJ, Chan DW, et al. Can volume measurement of the prostate enhance the performance of complexed prostate-specific antigen? Urology 2002 Oct;60(4A):36-41.

240. Naya Y, Fritsche HA, Bhadkamkar VA, Mikolajczyk SD, Rittenhouse HG, Babaian RJ. Evaluation of precursor prostate-specific antigen isoform ratios in the detection of prostate cancer. Urol Oncol 2005 Jan;23(1):16-21.

241. Ng CF, Chiu PKF, Lam NY, Lam HC, Lee KWM, Hou SSM. The Prostate Health Index in predicting initial prostate biopsy outcomes in Asian men with prostate-specific antigen levels of 4-10 ng/mL. Int Urol Nephrol 2014;46(4):711-7.

242. Ochiai A, Okihara K, Kamoi K, Oikawa T, Shimazui T, Murayama S, et al. Clinical utility of the prostate cancer gene 3 (PCA3) urine assay in Japanese men undergoing prostate biopsy. BJU Int 2013 May;111(6):928-33.

243. Ohori M, Egawa S, Koshiba K. The utility of free to total PSA ratio for detecting prostate cancer in Japanese men with total PSA between 2.1 and 10 ng/ml. Urol Oncol 1998;4(3):80-5.

244. Okegawa T, Noda H, Nutahara K, Higashihara E. Comparison of two investigative assays for the complexed prostate-specific antigen in total prostate-specific antigen between 4.1 and 10.0 ng/mL. Urology 2000 May;55(5):700-4. (a)

245. Okegawa T, Kinjo M, Watanabe K, Noda H, Kato M, Miyata A, et al. The significance of the free-to-complexed prostate-specific antigen (PSA) ratio in prostate cancer detection in patients with a PSA level of 4.1-10.0 ng/mL. BJU Int 2000 Apr;85(6):708-14. (b)

246. Okegawa T, Noda H, Nutahara K, Higashihara E. Comparisons of the various combinations of free, complexed, and total prostate-specific antigen for the detection of prostate cancer. European Urology 2000 Oct;38(4):380-7. (c)

247. Okihara K, Cheli CD, Partin AW, Fritche HA, Chan DW, Sokoll LJ, et al. Comparative analysis of complexed prostate specific antigen, free prostate specific antigen and their ratio in detecting prostate cancer. J Urol 2002 Apr;167(5):2017-23.

248. Okihara K, Ukimura O, Nakamura T, Mizutani Y, Kawauchi A, Naya Y, et al. Can complexed prostate specific antigen enhance prostate cancer detection in Japanese men? European Urology 2004 Jul;46(1):57-64.

249. Okihara K, Ochiai A, Kamoi K, Miki T. Utility of PCA3 urine assay in Japanese men undergoing prostate biopsy. J Clin Oncol 2011;29(7).

250. Oliver SE, Holly J, Peters TJ, Donovan J, Persad R, Gillatt D, et al. Measurement of insulin-like growth factor axis does not enhance specificity of PSA-based prostate cancer screening. Urology 2004 Aug;64(2):317-22.

251. Onur R, Ilhan N, Orhan I, Ilhan N. Increased discrimination between benign prostatic hyperplasia and prostate cancer with equimolar total prostate specific antigen measurement. World Journal of Urology 2003 May;21(1):43-7.

252. Oremek GM, Sapoutzis N, Eden F, Jonas D. Complexed PSA in routine diagnosis. Anticancer Res 2003 Mar;23(2A):975-7.

253. Ozdal OL, Aprikian AG, Begin LR, Behlouli H, Tanguay S. Comparative evaluation of various prostate specific antigen ratios for the early detection of prostate cancer. BJU Int 2004;93(7):970-4.

254. Ozen H, Aygun C, Ergen A, Sozen S, Aki FT, Uygur MC. Combined use of prostate-specific antigen derivatives decreases the number of unnecessary biopsies to detect prostate cancer. American Journal of Clinical Oncology 2001 Dec;24(6):610-3.

255. Ozveri H, Cam K, Tarcan T, Turkeri L, Akdas A. Significance of free to total PSA ratio in men with normal digital rectal examination, normal transrectal ultrasonography, and intermediate total serum PSA levels. J B U ON 2001;6(1):79-82.

256. Parsons JK, Brawer MK, Cheli CD, Partin AW, Djavan R. Complexed prostate specific antigen (PSA) reduces unnecessary prostate biopsies in the 2.6-4.0 ng/mL range of total PSA. BJU Int 2004 Jul;94(1):47-50.

257. Partin AW, Carter HB. The use of prostate-specific antigen and free/total prostate-specific antigen in the diagnosis of localized prostate cancer. Urol Clin North Am 1996;23(4):531-40.

258. Partin AW, Catalona WJ, Southwick PC, Subong EN, Gasior GH, Chan DW. Analysis of percent free prostate-specific antigen (PSA) for prostate cancer detection: influence of total PSA, prostate volume, and age. Urology 1996 Dec;48(6A):55-61.

259. Partin AW, Brawer MK, Bartsch G, Horninger W, Taneja SS, Lepor H, et al. Complexed prostate specific antigen improves specificity for prostate cancer detection: results of a prospective multicenter clinical trial. J Urol 2003 Nov;170(5):1787-91.

260. Patel D, White PA, Milford WA. A comparison of six commercial assays for total and free prostate specific antigen (PSA): the predictive value of the ratio of free to total PSA. BJU Int 2000 Apr;85(6):686-9.

261. Pelekanos C, Beardi J, Jonas D, Oremek GM. Isoforms of PSA (prostate-specific antigen) in the diagnosis of prostate cancer. Clin Exp Med Lett 2008;49(1):23-5.

262. Pelzer AE, Volgger H, Bektic J, Berger AP, Rehder P, Bartsch G, et al. The effect of percentage free prostate-specific antigen (PSA) level on the prostate cancer detection rate in a screening population with low PSA levels. BJU Int 2005 Nov;96(7):995-8.

263. Pepe P, Panella P, Savoca F, Cacciola A, D'Arrigo L, Dibenedetto G, et al. Prevalence and clinical significance of prostate cancer among 12,682 men with normal digital rectal examination, low PSA levels (< or =4 ng/ml) and percent free PSA cutoff values of 15 and 20%. Urol Int 2007;78(4):308-12.

264. Perdona S, Quarto G, Sorrentino D, De DR, Cariati F, Sorrentino A, et al. Phi and PCA3 significantly improve diagnostic accuracy in patients undergoing prostate biopsy. Anticancer Res 2012;32(5):1920. (a)

265. Perdona S, Quarto G, De DR, Sorrentino D, Ferro M, Altieri V, et al. Work-up in patients without a specific risk of prostate cancer (PSA (less-than or equal to)10 ng/ml): A multiparametric mri scoring system. Anticancer Res 2012;32(5):1892. (b)

266. Perdona S, Bruzzese D, Ferro M, Autorino R, Marino A, Mazzarella C, et al. Prostate health index (phi) and prostate cancer antigen 3 (PCA3) significantly improve diagnostic accuracy in patients undergoing prostate biopsy. Prostate 2013 Feb 15;73(3):227-35.

267. Pfister C, Basuyau JP, Normandy Urological Association. Current usefulness of free/total PSA ratio in the diagnosis of prostate cancer at an early stage. World Journal of Urology 2005 Sep;23(4):236-42.

268. Ploussard G, Haese A, Van PH, Marberger M, Stenzl A, Mulders PFA, et al. The prostate cancer gene 3 (PCA3) urine test in men with previous negative biopsies: Does free-to-total prostate-specific antigen ratio influence the performance of the PCA3 score in predicting positive biopsies? BJU Int 2010;106(8):1143-7.

269. Pourmand G. Preventing unnecessary invasive cancer-diagnostic tests. Eur Urol Suppl 2013;12(6):163.

270. Prestigiacomo AF, Stamey TA. Clinical usefulness of free and complexed PSA. Scandinavian Journal of Clinical and Laboratory Investigation Supplement 1995;221:32-4.

271. Prestigiacomo AF, Lilja H, Pettersson K, Wolfert RL, Stamey TA. A comparison of the free fraction of serum prostate specific antigen in men with benign and cancerous prostates: the best case scenario. J Urol 1996 Aug;156:350-4.

272. Prestigiacomo AF, Stamey TA. Can free and total prostate specific antigen and prostatic volume distinguish between men with negative and positive systematic ultrasound guided prostate biopsies? J Urol 1997 Jan;157(1):189-94.

273. Rafi T, Sattar A, Asif N, Dawood MM, Aamir M, Rehman Z. The Comparison of Percent Free PSA with total PSA in the diagnosis of Prostate Cancer. J Pak Med Assoc 2003;53(6):233-6.

274. Randazzo M, Beatrice J, Huber A, Grobholz R, Manka L, Recker F, et al. Future risk for intermediate or high risk prostate cancer in men with baseline PSA of 1-3ng/mL and low free-to-total PSA-ratio in a prospective population-based screening trial (ERSPC AARAU). J Urol 2014;191(4S):e815.

275. Recker F, Kwiatkowski MK, Piironen T, Pettersson K, Lummen G, Wernli M, et al. The importance of human glandular kallikrein and its correlation with different prostate specific antigen serum forms in the detection of prostate carcinoma. Cancer 1998 Dec 15;83(12):2540-7.

276. Recker F, Kwiatkowski MK, Piironen T, Pettersson K, Goepel M, Tscholl R. Free-to-total prostate-specific antigen (PSA) ratio improves the specificity for detecting prostate cancer in patients with prostatism and intermediate PSA levels. Br J Urol 1998 Apr;81(4):532-8.

277. Reissigl A, Klocker H, Pointner J, Ennemoser O, Falk M, Bartsch G. Improvement of prostate cancer screening by determination of the ratio free/total PSA in addition to PSA levels. Prostate 1997 Mar 1;30(4):243-7. (a)

278. Reissigl A, Bartsch G. Prostate-specific antigen as a screening test. The Austrian experience. Urol Clin North Am 1997 May;24(2):315-21. (b)

279. Reiter W, Stieber P, Schmeller N, Nagel D, Pahl H, Mattes M, et al. Free PSA: A useful marker in the differential diagnosis of benign hyperplasia and cancer of the prostate? TUMOR DIAGN THER 1996;17(3):88-92.

280. Reiter W, Stieber P, Schmeller N, Nagel D, Jansen HM, Schambeck C, et al. The ratio of free to total prostate specific antigen: an advantageous addition in the differential diagnosis of benign hyperplasia and cancer of the prostate? Anticancer Res 1997 Jul;17(4B):2987-91.

281. Reiter W. The clinical value of the Enzymun-Test for total and free PSA--a multicentre evaluation. Anticancer Res 1999 Nov;19(6C):5559-62.

282. Roddam AW, Duffy MJ, Hamdy FC, Ward AM, Patnick J, Price CP, et al. Use of prostate-specific antigen (PSA) isoforms for the detection of prostate cancer in men with a PSA level of 2-10 ng/ml: systematic review and meta-analysis. [Review] [96 refs]. European Urology 2005 Sep;48(3):386-99.

283. Roehrborn CG, Gregory A, McConnell JD, Sagalowsky AI, Wians FH, Jr. Comparison of three assays for total serum prostate-specific antigen and percentage of free prostate-specific antigen in predicting prostate histology. Urology 1996 Dec;48(6A):23-32.

284. Rowe EW, Laniado ME, Walker MM, Patel A. Prostate cancer detection in men with a 'normal' total prostate-specific antigen (PSA) level using percentage free PSA: a prospective screening study. BJU Int 2005 Jun;95(9):1249-52.

285. Rowe EW, Laniado ME, Walker MM, Anup P. Incidental acute prostatic inflammation is associated with a lower percentage of free prostate-specific antigen than other benign conditions of the prostate: a prospective screening study. BJU Int 2006 May;97(5):1039-42.

286. Saavedra II, Konstantinidis C, Celma A, Agreda F, Placer J, Planas J, et al. PSA kinetics does not predict prostate cancer in men subjected to prostate biopsy. J Urol 2013;189(4):e789.

287. Saika T, Tsushima T, Nasu Y, Kusaka N, Miyaji Y, Takamoto H, et al. Prostate specific antigen complexed to alpha-1-antichymotrypsin in patients with intermediate prostate specific antigen levels. Cancer 2002 Mar 15;94(6):1685-91.

288. Sakai I, Harada K, Hara I, Eto H, Miyake H. Limited usefulness of the free-to-total prostate-specific antigen ratio for the diagnosis and staging of prostate cancer in Japanese men. Int J Clin Oncol 2004 Feb;9(1):64-7.

289. Sanda M, Wei J, Broyles D, Shin S, Partin A, Klee G, et al. Prostate health index (Phi) for reducing overdetection of indolent prostate cancer and unnecessary biopsy while improving detection of aggressive cancers. J Urol 2013;189(4):e843.

290. Santotoribio JD, Garcia-De La Torre A, Canavate-Solano C, Arce-Matute F, Perez-Ramos S. LDH and %FPSA for diagnosis of prostate cancer. Tumor Biol 2014;35:S47.

291. Sasaki M, Ishidoya S, Ito A, Saito H, Yamada S, Mitsuzuka K, et al. Low percentage of free prostate-specific antigen is a strong predictor of later detection of prostate cancer among men with serum levels of total PSA 4.0ng/mL or under. Urology 2013;82(3 Suppl 1):S69. (a)

292. Sasaki M. Pathological outcomes for patients with PSA 2.0-4.0 ng/mL and free/total PSA under 12% at prostate cancer screening in Japan. J Urol 2013;189(4):e795. (b)

293. Sasaki M, Ishidoya S, Ito A, Saito H, Shibuya D, Arai Y. Diagnostic value of free prostate-specific antigen among men with prostate-specific antigen 2.0 to 4.0ng/ml at screening cohort in Japan. J Urol 2012;187(4):e773-e774.

294. Sasaki M, Ishidoya S, Ito A, Numahata K, Shibuya D, Arai Y. Early detection of clinically significant prostate cancer: Low free prostate-specific antigen levels as a criterion for prostate biopsy in patients with low total prostate-specific antigen levels. J Urol 2014;191(4):e715.

295. Sasaki R, Habuchi T, Sato K, Akao T, Kakinuma H, Zhang LQ, et al. The clinical utility of measuring total PSA, PSA density, gamma-seminoprotein and gamma-seminoprotein/total PSA in prostate cancer prediction. Jpn J Clin Oncol 2000 Aug;30(8):337-42.

296. Scattoni V, Lazzeri M, Lughezzani G, De LS, Passera R, Bollito E, et al. Comparison between PCA3 and phi specificty and sensitivity in predicting the presence of cancer at initial or repeat biopsy. Anticancer Res 2013;33(5):2293. (a)

297. Scattoni V, Lazzeri M, Lughezzani G, De LS, Passera R, Bollito E, et al. Head-to-head comparison of prostate health index and urinary PCA3 for predicting cancer at initial or repeat biopsy. J Urol 2013 Aug;190(2):496-501. (b)

298. Scorilas A, Plebani M, Mazza S, Basso D, Soosaipillai AR, Katsaros N, et al. Serum human glandular kallikrein (hK2) and insulin-like growth factor 1 (IGF-1) improve the discrimination between prostate cancer and benign prostatic hyperplasia in combination with total and %free PSA. Prostate 2003 Feb 15;54(3):220-9.

299. Segawa N, Gohji K, Iwamoto Y, Ueda H, Katsuoka Y. Prostate cancer detection by prostate-specific antigen-related parameters. Hinyokika Kiyo - Acta Urologica Japonica 2003 Jul;49(7):405-10.

300. Semjonow A, Bogemann M, Eminaga O, Hinkelammert R, Abbas M, Eltze E, et al. [-2] proPSA improves prediction of repeat prostate biopsy results. Urologe Ausg A 2011;50:73.

301. Serdar MA, Oguz O, Olgun A, Seckin B, Ilgan S, Hasimi A, et al. Diagnostic approach to prostate cancer using total prostate specific antigen-based parameters together. Annals of Clinical & Laboratory Science 2002;32(1):22-30.

302. Shao Y, Zhang Z-B. Evaluation of free-to-total prostate specific antigen ratio in the diagnosis of prostate cancer. Chin J Cancer Res 2000;12(2):114.

303. Skrepetis K, Doumas K, Kiminas E, Davilas E, Lykourinas M. Clinical usefulness of free to total PSA in the detection of prostate cancer in men with total PSA of 2 to 4 ng/ml and normal prostate digital rectal examination. J B U ON 2001;6(1):83-5.

304. Smrkolj T, Osredkar J. Performance of early prostate cancer antigen-2 (EPCA2), propsa, free PSA (FPSA) and prostate health index (PHI) in detection of prostatic carcinoma. Biochim Clin 2013;37:S196.

305. Sokoll LJ, Chan DW, Mikolajczyk SD, Rittenhouse HG, Evans CL, Linton HJ, et al. Proenzyme psa for the early detection of prostate cancer in the 2.5-4.0 ng/ml total psa range: preliminary analysis. Urology 2003 Feb;61(2):274-6.

306. Sokoll LJ, Wang Y, Feng Z, Kagan J, Partin AW, Sanda MG, et al. [-2]proenzyme prostate specific antigen for prostate cancer detection: a national cancer institute early detection research network validation study. J Urol 2008;180(2):539-43.

307. Sokoll LJ, Sanda MG, Feng Z, Kagan J, Mizrahi IA, Broyles DL, et al. A prospective, multicenter, National Cancer Institute Early Detection Research Network study of [-2]proPSA: improving prostate cancer detection and correlating with cancer aggressiveness. Cancer Epidemiology, Biomarkers & Prevention 2010 May;19(5):1193-200.

308. Southwick PC. The role of free PSA in the detection of prostate cancer. Lab Med 2001;32(5):259-63.

309. Sozen S, Eskicorapci S, Kupeli B, Irkilata L, Altinel M, Ozer G, et al. Complexed prostate specific antigen density is better than the other PSA derivatives for detection of prostate cancer in men with total PSA between 2.5 and 20 ng/ml: results of a prospective multicenter study. European Urology 2005 Mar;47(3):302-7.

310. Stamey TA, Yemoto CE. Examination of the 3 molecular forms of serum prostate specific antigen for distinguishing negative from positive biopsy: relationship to transition zone volume. J Urol 2000 Jan;163(1):119-26.

311. Stangelberger A, Margreiter M, Seitz C, Djavan B. Prostate cancer screening markers. J Men's Health Gender 2007;4(3):233-44.

312. Stattin P, Stenman UH, Riboli E, Hallmans G, Kaaks R. Ratios of IGF-I, IGF binding protein-3, and prostate-specific antigen in prostate cancer detection. Journal of Clinical Endocrinology & Metabolism 2001 Dec;86(12):5745-8.

313. Stephan C, Stroebel G, Heinau M, Lenz A, Roemer A, Lein M, et al. The ratio of prostate-specific antigen (PSA) to prostate volume (PSA density) as a parameter to improve the detection of prostate carcinoma in PSA values in the range of < 4 ng/mL. Cancer 2005 Sep 1;104(5):993-1003.

314. Stephan C, Vincendeau S, Houlgatte A, Semjonow A. Prostate health index (PHI) using [-2]Propsa improves detection of prostate cancer preferentially identifying aggressive cancers. Clin Chem Lab Med 2011;49:S269.

315. Stephan C, Jung K, Semjonow A. Prospective head-to-head evaluation of [-2]proPSA, PCA3 and TMPRSS2:ERG in patients referred for prostate biopsy. Tumor Biol 2012;33:S49.

316. Stephan C, Vincendeau S, Houlgatte A, Miller K, Semjonow A. [-2]proPSA and prostate health index (phi) improve detection of prostate cancer at initial and repeated biopsies in young men ((less-than or equal to) 60 year old) preferentially detecting clinically significant cancer. Eur Urol Suppl 2013;12(1):e853. (a)

317. Stephan C, Semjonow A, Boegemann M, Miller K, Friedersdorff F. Parallel measurement of urinary PCA3 and TMPRSS2:ERG with serum [-2]proPSA based Phi for prostate cancer detection. Urologe Ausg A 2013;52(1):119. (b)

318. Stephan C, Jung K, Semjonow A, Schulze-Forster K, Cammann H, Hu X, et al. Comparative assessment of urinary prostate cancer antigen 3 and TMPRSS2:ERG gene fusion with the serum [-2]proprostate-specific antigen-based prostate health index for detection of prostate cancer. Clinical Chemistry 2013 Jan;59(1):280-8. (c)

319. Stephan C, Vincendeau S, Houlgatte A, Cammann H, Jung K, Semjonow A. Multicenter evaluation of [-2]proprostate-specific antigen and the prostate health index for detecting prostate cancer. Clinical Chemistry 2013 Jan;59(1):306-14. (d)

320. Steuber T, Vickers A, Haese A, Kattan MW, Eastham JA, Scardino PT, et al. Free PSA isoforms and intact and cleaved forms of urokinase plasminogen activator receptor in serum improve selection of patients for prostate cancer biopsy. Int J Cancer 2007 Apr 1;120(7):1499-504.

321. Strittmatter F, Stieber P, Nagel D, Fullhase C, Walther S, Stief CG, et al. Detection of prostate cancer with complexed PSA and complexed/total PSA ratio - is there any advantage? European Journal of Medical Research 2011 Oct 10;16(10):445-50.

322. Szalay I, Bordas N, Pajor L, Farkas G, Salgo L. A new way in the early detection of prostate cancer: The [-2]pro prostate specific antigen. Clin Chem Lab Med 2011;49:S276.

323. Tamimi W, Dafterdar R, Mansi M, Alsaad K, Alarifi SA. Complexed and total PSA in patients with benign prostatic hyperplasia and prostate cancer. British Journal of Biomedical Science 2010;67(4):184-8.

324. Tanguay S, Begin LR, Elhilali MM, Behlouli H, Karakiewicz PI, Aprikian AG. Comparative evaluation of total PSA, free/total PSA, and complexed PSA in prostate cancer detection. Urology 2002 Feb;59(2):261-5.

325. Tello FL, Prats CH, Gonzalez MD. Free and complexed prostate-specific antigen (PSA) in the early detection of prostate cancer. Clinical Chemistry & Laboratory Medicine 2001 Feb;39(2):116-20.

326. Thakur V, Singh PP, Talwar M, Mukherjee U. Utility of free/total prostate specific antigen (f/t PSA) ratio in diagnosis of prostate carcinoma. Disease Markers 2003;19(6):287-92.

327. Thiel RP, Oesterling JE, Wojno KJ, Partin AW, Chan DW, Carter HB, et al. Multicenter comparison of the diagnostic performance of free prostate-specific antigen. Urology 1996 Dec;48(6A):45-50.

328. Topolcan O, Fuchsova R, Klecka J, Hora M, Vrzalova J. Tumor markers serum levels for early diagnosis of prostate cancer. Tumor Biol 2012;33:S47-S48.

329. Tornblom M, Norming U, Adolfsson J, Becker C, Abrahamsson PA, Lilja H, et al. Diagnostic value of percent free prostate-specific antigen: retrospective analysis of a population-based screening study with emphasis on men with PSA levels less than 3.0 ng/mL. Urology 1999 May;53(5):945-50.

330. Toubert ME, Guillet J, Chiron M, Meria P, Role C, Schlageter MH, et al. Percentage of free serum prostate-specific antigen: a new tool in the early diagnosis of prostatic cancer. European Journal of Cancer 1996 Nov;32A(12):2088-93.

331. Trinkler FB, Schmid DM, Hauri D, Pei P, Maly FE, Sulser T. Free/total prostate-specific antigen ratio can prevent unnecessary prostate biopsies. Urology 1998 Sep;52(3):479-86.

332. Trygg G, Pousette A, Ekengren J, Hahn RG. Free and total prostate-specific antigen serum concentrations do not help to detect prostate cancer in patients with urinary outlet obstruction. Br J Urol 1997;80(4):618-22.

333. Uzzo RG, Pinover WH, Horwitz EM, Parlanti A, Mazzoni S, Raysor S, et al. Free prostate-specific antigen improves prostate cancer detection in a high-risk population of men with a normal total PSA and digital rectal examination. Urology 2003 Apr;61(4):754-9.

334. Van Cangh PJ, De NP, De VL, Sauvage P, Tombal B, Lorge F, et al. Free to total prostate-specific antigen (PSA) ratio improves the discrimination between prostate cancer and benign prostatic hyperplasia (BPH) in the diagnostic gray zone of 1.8 to 10 ng/mL total PSA. Urology 1996 Dec;48(6A):67-70. (a)

335. Van Cangh PJ, De NP, Sauvage P, Tombal B, Elsen M, Lorge F, et al. Free to total prostate-specific antigen (PSA) ratio is superior to total-PSA in differentiating benign prostate hypertrophy from prostate cancer. Prostate - Supplement 1996;7:30-4. (b)

336. Vashi AR, Wojno KJ, Henricks W, England BA, Vessella RL, Lange PH, et al. Determination of the "reflex range" and appropriate cutpoints for percent free prostate-specific antigen in 413 men referred for prostatic evaluation using the AxSYM system. Urology 1997 Jan;49(1):19-27.

337. Veltri RW, Miller MC. Free/total PSA ratio improves differentiation of benign and malignant disease of the prostate: critical analysis of two different test populations. Urology 1999 Apr;53(4):736-45.

338. Veneziano S, Pavlica P, Compagnone G, Martorana G. Usefulness of the (F/T)/PSA density ratio to detect prostate cancer. Urol Int 2005;74(1):13-8.

339. Vessella RL, Lange PH, Partin AW, Chan DW, Sokoll LJ, Sasse EA, et al. Probability of prostate cancer detection based on results of a multicenter study using the AxSYM free PSA and total PSA assays. Urology 2000 Jun;55(6):909-14.

340. Vickers AJ, Wolters T, Savage CJ, Cronin AM, O'Brien MF, Pettersson K, et al. Prostate-specific antigen velocity for early detection of prostate cancer: result from a large, representative, population-based cohort. European Urology 2009 Nov;56(5):753-60.

341. Vilanova JC, Barcelo-Vidal C, Comet J, Boada M, Barcelo J, Ferrer J, et al. Usefulness of prebiopsy multifunctional and morphologic MRI combined with free-to-total prostate-specific antigen ratio in the detection of prostate cancer. AJR Am J Roentgenol 2011 Jun;196(6):W715-W722.

342. Vincendeau S, Stephan C, Houlgatte A, Semjonow A. The beckman coulter prostate health index (PHI) Increases the specificity of detection of prostate cancer and reduces the number of negative biopsies. Clin Chem Lab Med 2011;49:S270.

343. Vogl M, Muller MM, Holtl W. Clinical usefulness of percentage of free serum prostate specific antigen. Clin Chim Acta 1997 Feb 3;258(1):79-90.

344. Vukotic V, Cerovic S, Kozomara M, Lazic M. The predictive value of PSA in diagnosis of prostate cancer in non screened population. Acta Chirurgica Iugoslavica 2005;52(4):81-7.

345. Wald NJ, Watt HC, George L, Knekt P, Helzlsouer KJ, Tuomilehto J. Adding free to total prostate-specific antigen levels in trials of prostate cancer screening. British Journal of Cancer 2000 Feb;82(3):731-6.

346. Walz J, Haese A, Scattoni V, Steuber T, Chun FK, Briganti A, et al. Percent free prostate-specific antigen (PSA) is an accurate predictor of prostate cancer risk in men with serum PSA 2.5 ng/mL and lower. Cancer 2008 Nov 15;113(10):2695-703.

347. Wang TJ, Linton HJ, Payne J, Rittenhouse HG, Chan DW, Partin AW, et al. Generation of PSA-ACT-specific monoclonal antibodies and their application in a sandwich immunoassay. Hybridoma 1999 Dec;18(6):535-41.

348. Wang Y, Sun G, Pan JG, Guo ZJ, Li T. Performance of tPSA and f/tPSA for prostate cancer in Chinese. A systematic review and meta-analysis. [Review] [16 refs]. Prostate Cancer & Prostatic Diseases 2006;9(4):374-8.

349. Wang Z, Zhang P, Chong T, Zhao L. The clinical significance of percent free PSA in differentiating prostate cancer and benign prostate hyperplasia. Acad J Xi'An Jiaotong Univ 2004;16(1):75-7.

350. Wechsel PH, Petri E, Bichler KH, Schreiber M. Free PSA in the detection of prostatic carcinoma. Anticancer Res 1997 Jul;17(4B):3015-8.

351. Wesseling S, Stephan C, Semjonow A, Lein M, Brux B, Sinha P, et al. Determination of non-alpha1-antichymotrypsin-complexed prostate-specific antigen as an indirect measurement of free prostate-specific antigen: analytical performance and diagnostic accuracy. Clinical Chemistry 2003 Jun;49(6):887-94.

352. Wians FH, Jr., Cheli CD, Balko JA, Bruzek DJ, Chan DW, Sokoll LJ. Evaluation of the clinical performance of equimolar- and skewed-response total prostate-specific antigen assays versus complexed and free PSA assays and their ratios in discriminating between benign prostatic hyperplasia and prostate cancer. Clin Chim Acta 2002 Dec;326(1-2):81-95.

353. Winkler MH, Kulinskaya E, Gillatt DA. Prediction of prostate cancer in extended-field biopsies of the prostate. BJU Int 2004 Mar;93(4):516-21.

354. Wolff JM, Borchers H, Effert PJ, Habib FK, Jakse G. Free-to-total prostate-specific antigen serum concentrations in patients with prostate cancer and benign prostatic hyperplasia. Br J Urol 1996 Sep;78(3):409-13.

355. Wolff JM, Boeckmann W, Effert PJ, Habib FK, Jakse G. Increased discrimination between benign prostatic hyperplasia and prostate cancer through measurement of percentage free PSA. Anticancer Res 1997 Jul;17(4B):2993-4.

356. Wu CT, Chuang CK, Chou CC, Chu SH, Chen HW, Chen CS, et al. The role of free to total prostate-specific antigen ratio for prostate cancer in screening patients with total serum levels between 4 and 20 ng/ml. Chang Gung Medical Journal 2000 Mar;23(3):142-8.

357. Wu JT, Liu GH, Zhang P, Stephenson RA. Monitoring percent free PSA in serial specimens: improvement of test specificity, early detection, and identification of occult tumors. Journal of Clinical Laboratory Analysis 1998;12(1):26-31.

358. Wymenga LF, Duisterwinkel FJ, Groenier K, Visser-van BP, Marrink J, Mensink HJ. Clinical implications of free-to-total immunoreactive prostate-specific antigen ratios. Scandinavian Journal of Urology & Nephrology 2000 Jun;34(3):181-7.

359. Yamamoto S, Maruyama T, Kondoh N, Nojima M, Takiuchi H, Hirota S, et al. Diagnostic efficacy of free to total ratio of prostate-specific antigen and prostate-specific antigen velocity, singly and in combination, in detecting prostate cancer in patients with total serum prostate-specific antigen between 4 and 10 ng/ml. International Urology & Nephrology 2008;40(1):85-9.

360. Yang CR, Su CK, Chiu KY, Ho HC, Ou YC, Cheng CL, et al. Free / total prostate specific antigen ratio for prostate cancer detection: a prospective blind study. Anticancer Res 2005 May;25(3c):2439-43.

361. Yeniyol CO, Bozkaya G, Cavusoglu A, Arslan M, Karaca B, Ayder AR. The relation of prostate biopsy results and ratio of free to total PSA in patients with a total PSA between 4-20 ng/mL. International Urology & Nephrology 2001;33(3):503-6.

362. Yokomizo Y, Miyoshi Y, Nakaigawa N, Makiyama K, Ogawa T, Yao M, et al. Free PSA/total PSA ratio increases the detection rate of prostate cancer in twelve-core biopsy. Urol Int 2009;82(3):280-5.

363. Yoshida K, Honda M, Sumi S, Arai K, Suzuki S, Kitahara S. Levels of free prostate-specific antigen (PSA) can be selectively measured by heat treatment of serum: free/total-PSA ratios improve detection of prostate carcinoma. Clin Chim Acta 1999 Feb;280(1-2):195-203.

364. Zambon CF, Prayer-Galetti T, Basso D, Padoan A, Rossi E, Secco S, et al. Effectiveness of the combined evaluation of KLK3 genetics and free-to-total prostate specific antigen ratio for prostate cancer diagnosis. J Urol 2012 Oct;188(4):1124-30.

365. Zhang WM, Finne P, Leinonen J, Vesalainen S, Nordling S, Stenman UH. Measurement of the complex between prostate-specific antigen and alpha1-protease inhibitor in serum. Clinical Chemistry 1999 Jun;45:814-21.

366. Zhang WM, Finne P, Leinonen J, Salo J, Stenman UH. Determination of prostate-specific antigen complexed to alpha(2)-macroglobulin in serum increases the specificity of free to total PSA for prostate cancer. Urology 2000 Aug 1;56(2):267-72. (a)

367. Zhang WM, Finne P, Leinonen J, Stenman UH. Characterization and determination of the complex between prostate-specific antigen and alpha 1-protease inhibitor in benign and malignant prostatic diseases. Scandinavian Journal of Clinical and Laboratory Investigation Supplement 2000;233:51-8. (b)

368. Zhao Z, Liu J, Li S, Shen W. Serum insulin-like growth factor I/free prostate specific antigen (IGF-I/fPSA) ratio enhances prostate cancer detection in men with total PSA 4.0-10.0 ng/ml. Journal of Surgical Oncology 2007 Jul 1;96(1):54-61.

369. Zheng XY, Xie LP, Wang YY, Ding W, Yang K, Shen HF, et al. The use of prostate specific antigen (PSA) density in detecting prostate cancer in Chinese men with PSA levels of 4-10 ng/mL. Journal of Cancer Research & Clinical Oncology 2008 Nov;134(11):1207-10.

Systematic review report for question 6.4

Clinical Question 6: In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what tests for prostate cancer should be offered in addition to a PSA test?

Candidate tests include:

Free-to total PSA %

PSA velocity

Prostate health index

Repeated total PSA

PICO Question 6.4: For asymptomatic men with initial total PSA above 3.0 ng/mL, does repeating the total PSA test and using an initial and repeat total PSA above 3.0 ng/mL as the indication for biopsy, improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL as the indication for biopsy?

Population	Index Test 1	Index Test 2	Reference standard	Outcomes
Men without prostate cancer diagnosis or symptoms that might indicate prostate cancer	Total PSA >3.0 ng/mL on initial and repeat test performed within 3 months	Total PSA >3.0 ng/mL only	Prostate biopsy	Diagnostic performance

1. Methods

1.1. Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption guidelines had to be evidence based and meet the pre-specified criteria of scores of greater or equal to 70% for the domains rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

1.2. Literature Search

Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched from 1990 using text terms and, where available, database-specific subject headings. Each database was searched for articles dealing with prostate cancer. In Medline and Embase databases the prostate cancer search was combined with a search for repeat prostate-specific antigen (PSA). To identify studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples. A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 which were added to the relevant database after February 2014. Alerts were checked until July 2014. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched regularly up until April 2014 for relevant reviews published after the initial search. All related citations of an article with

particular relevance (Rosario 2008) were examined via Web of Science database. Reference lists of all relevant articles were checked for potential additional articles.

1.3. Inclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Diagnostic performance	Predictive accuracy
Study design	Fully paired diagnostic study, or paired randomised cohort study	Diagnostic case-control or studies of diagnostic yield
Population	Men without prostate cancer diagnosis or symptoms that might indicate prostate cancer, who had an initial total PSA >2.0 ng/mL but <5.5 ng/mL, unless participants were at higher risk of prostate cancer, aged over 60 or there were subgroup analyses for age, risk or PSA level^^, and who had undergone prostate biopsy or TURP and at least 80% of those undergoing biopsy had undergone an initial rather than a repeat prostate biopsy	- Included men with prostate cancer or some other urologic disease e.g. bladder cancer or men undergoing a particular treatment e.g. finasteride. - Restricted to men who only had an abnormal DRE and/or abnormal TRUS. - Included men whose cancer status was not based on biopsy or TURP pathology.
Index test 1	An elevated **initial** total PSA result followed within 3 months by an elevated **repeat** total PSA result as an indication for biopsy	- Bloods were drawn for a repeat PSA test after biopsy. - Used total PSA thresholds which were greater than 4.0 ng/mL^^ and not age-specific reference upper limits. - Did not use a commercial total PSA test (e.g. Hybritech, Immulite, Abbott, Roche, Bayer).
Index test 2	An elevated **initial** total PSA result as an indict ion for biopsy	
Reference standard	Prostate biopsy which included 6 or more cores, or TURP	
Indications for biopsy	Indications for biopsy include a total PSA level above thresholds of 4.0 ng/mL or less, or age-specific reference upper limits	Indications for biopsy not precisely defined and no subgroup analysis for men with PSA >4.0 ng/mL^
Outcomes	Diagnostic performance relative** to using total PSA alone: - Relative specificity (% unnecessary biopsies avoided), - Relative sensitivity (% cancers detected missed), - Unnecessary biopsies avoided per cancer missed.	
Language	English	
Publication period	After 31st December 1989 and before1st March 2014	

TURP = transurethral resection of the prostate

**Verification bias is a major issue when assessing the diagnostic performance of tests for prostate cancer as men normally do not undergo biopsy unless they are test positive. As a result most studies examining the performance of tests in diagnosing prostate cancer are only able to report numbers of true positives and false positives. Where there is a comparison of two index tests in the same patient and where one index test is identifying a subgroup of those positive with the other index test so as to reduce the number of false positives, as when the total PSA tests is repeated for men with PSA levels above the PSA threshold, this data can be used to calculate the decrease in true positives and relative sensitivity, the decrease in false positives and relative

specificity and the number of unnecessary biopsies avoided (decrease in false positives) for each cancer missed (decrease in true positives); findings that will not be subject to verification bias.

^If indications for biopsy not reported assumed that all men with PSA >4.0 ng/mL were offered biopsy due to the elevated total PSA result alone

^^This question focuses on repeating the total PSA test as a means to improve specificity for men with a total PSA level above 3.0 ng/mL. Because of the analytical and biological variability of total PSA, including the chronological rise in PSA in men in their sixties, this review focused on studies that used total PSA thresholds between 2.0 and 4.0 ng/mL or age-specific thresholds. Restricting the evidence to studies that used a total PSA threshold of 3.0 ng/mL would have limited the evidence and would not have taken into account analytical variation in the total PSA test over the last two decades.
Men with only slightly elevated levels are less likely to have prostate cancer and could benefit from attempts to improve specificity without compromising sensitivity, whereas men with higher PSA levels are more likely to have prostate cancer and for such men attempts to reduce unnecessary biopsies could compromise the effectiveness of the recommended PSA testing strategy. As a result, studies using a single total PSA threshold were restricted to those whose participants had a total PSA ≤ 5.5 ng/mL unless there were analyses for older men (who are more likely not to have prostate cancer despite a total PSA > 5.5 ng/mL).

Conference proceedings identified by the literature searches were included if they met the inclusion criteria.

2. Results

2.1. Guidelines

Three guidelines were identified that contained potentially relevant recommendations. These recommendations were not adopted as they either were not based on a systematic review or did not meet the pre-specified AGREE II criteria for adoption. These guidelines and the reason why they were not adopted are listed in Appendix C.

In Australia, the Royal College of Pathologists of Australasia has consensus based recommendations regarding the role of repeating PSA to improve specificity:

"The response to an initial test should be:

a. If the total PSA level is at or above 10 µg/L, the patient should either have the PSA confirmed in 4 weeks and be referred if the result is confirmed or be immediately referred for specialist management.

b. If the total PSA level is abnormal (above 97.5% age-related, method-specific reference limit) but below 10 µg/L, the PSA should be confirmed in 4 weeks including an estimation of the Free to Total PSA ratio (F/T PSA ratio). If confirmed and/or the result of the F/T PSA ratio is <10%, the patient should be immediately referred for specialist management.

(http://www.rcpa.edu.au/Library/College-Policies/Position-Statements/Prostate-Specific-Antigen-Testing-Age-related-inte, accessed 20th October 2014).

2.2. Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the systematic review. The Medline search identified 1,935 citations, the Embase search an additional 919 citations, the search of the Cochrane Database of Systematic Reviews 59 citations, the Database of Abstracts of Reviews of Effects 282 citations and the Health Technology Assessment database 216 citations, resulting in a total of 3,411 citations. The Web of Science search identified 26 citations. Titles and abstracts were examined and 19 articles were retrieved for a more detailed evaluation. An additional 2 potential citations were identified from the reference list of retrieved articles.

Two trials reported in 2 articles met the inclusion criteria and were included in the review. There were no studies of Aboriginal and/or Torres Strait Islander men that met the inclusion criteria.

The retrieved articles that were not included and the reason for their exclusion are documented in Appendix C. In summary, the main reasons for exclusion were articles were indications for biopsy were unclear or inappropriate or no relevant outcomes were reported.

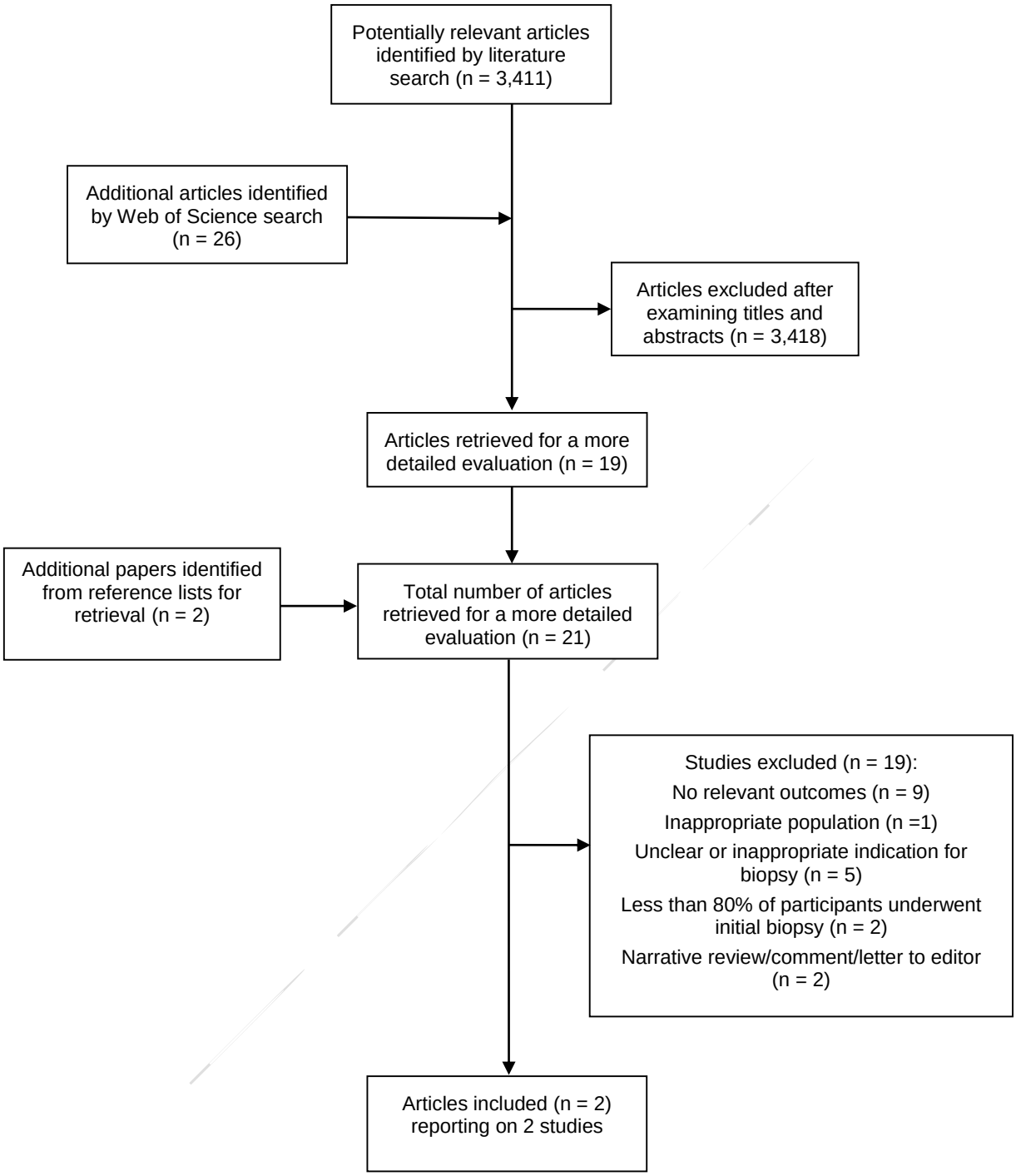


Figure 1. Process of inclusion and exclusion of studies

2.3. Study Characteristics

Characteristics of included studies are described in Table 1.

Table 1: Characteristics of studies comparing performance of initial and repeat PSA with those of initial PSA alone with respect to prostate cancer detection

Study	Participants	Design	Indication for biopsy	PSA assay	Blood collection and processing	Interval between PSA tests	Biopsy	Comments
Boddy 2005 (UK)	Men aged 45-79 years (mean age 66) with PSA above their age-specific cut-off (median 7.5, range 3.6 -1400 ng/mL) referred from their GPs or from urology team of outpatient department for biopsy between February 2003 and February 2004; Exclusion criteria: >80 years old; previous prostate biopsy, history of treatment with 5-α-reductase inhibitor; evidence of nitrites or moderate/large leucocytes on urine dipstick, catheterisation; **N = 160**	Prospective	Initial PSA above age-specific cut-off 40-49 years: >2.5 ng/mL 50-59 years: >3.5 ng/mL 60-69 years: >4.0 ng/mL 70-79 years: >6.5 ng/mL	Centaur Calibration: NR	NR	NR	8-10 cores, targeting the lateral and apical areas of the peripheral zone	Initial and repeat PSA measurements done in the same laboratory; Mean coefficient of variation 5.3%; Patients with suspected urinary tract infection as the cause for elevated PSA not subjected to biopsy "until it is clear that it has failed to normalise with the passage of time"
Rosario 2008 (UK)	Men aged 58-67 years (median age 62.2) with initial PSA levels between 3.0-19.9 ng/mL underwent repeat PSA testing prior to biopsy between 1 January 2002 and 31 October 2006. **N = 4,102**	Prospective, multi-center	Initial PSA ≥3.0 ng/mL	NR Calibration: NR	Blood taken for repeat PSA on attending for biopsy prior to any manipulation;	Median 50 days (IQR 33-69)	10-core lateral biopsy template	Serum for repeat PSA treated and analysed similarly to the initial specimen; All laboratories participate in the UK National External Quality Assessment Service programme for PSA testing;

GPs = general practitioners; IQR = interquartile range; NR = not reported; PSA = prostate-specific antigen; WHO = World Health Organisation;

2.4. Study Quality/ Risk of Bias

Assessment of risk of bias of included diagnostic studies is described in Tables 2 and 3.

Table 2: Assessment of risk of bias of included diagnostic studies (n = 2)

Quality Category	N (%)
I. Selection of participants	
Low risk of bias	-
High risk of bias	1 (50.0)
Unclear risk of bias	1 (50.0)
II. Index test 1	
Low risk of bias	-
High risk of bias	-
Unclear risk of bias	2 (100.0)
III. Index test 2	
Low risk of bias	-
High risk of bias	-
Unclear risk of bias	2 (100.0)
IV. Reference standard	
Low risk of bias	-
High risk of bias	2 (100.0)
Unclear risk of bias	-
V. Flow and timing	
Low risk of bias	1 (50.0)
High risk of bias	-
Unclear risk of bias	1 (50.0)

Table 3: Risk of bias of included diagnostic studies (n = 2)

	Patient selection	Index test 1	Index test 2	Reference standard [a]	Flow and timing [b]	Overall Risk of bias
Boddy 2005	High	Unclear	Unclear	High	Unclear	**At risk**
Rosario 2008	Unclear	Unclear	Unclear	High	Low	**At risk**

[a] *Adequate reference standard pre-specified as biopsy ≥12 cores*
[b] *Appropriate interval between index test(s) and reference standard pre-specified as less than 1 year – for biopsy referral cohorts where interval was not stated, assumed to be less than 1 year*

Key to overall rating

Low risk of bias: Received "low" for all domains

At risk of bias: Received "high" or "unclear" for one or more domains

2.5. Study Results

I DETECTION OF PROSTATE CANCER

Table 4: Results of studies comparing diagnostic performance of initial and repeat PSA with those of initial PSA alone

Biopsy indication	Screen positives biopsied (N)	TP (N)	FP (N)	Unnecessary biopsies prevented ΔFP (N)*	Cancers missed ΔTP (N)*	ΔFP/ΔTP	% unnecessary biopsies avoided*	% cancers missed*	PPV (%)
Boddy 2005 N = 160	Age-specific PSA cut-off								
Elevated initial PSA	160	83	77	Reference	Reference	Reference	Reference	Reference	51.9
Elevated initial PSA and repeat PSA	139	78	61	16	5	3.20	20.8	6.0	56.1
Rosario 2008 N = 4,102	PSA cut-off >3.0ng/mL								
Initial PSA >3.0	4,102	1,318	2,784	Reference	Reference	Reference	Reference	Reference	32.1
Initial PSA >3.0 and repeat PSA >2.0	3,915	1,294	2,621	163	24	6.79	5.9	1.8	33.1
Initial PSA >3.0 and repeat PSA >2.5	3,757	1,274	2,483	301	44	6.84	10.8	3.3	33.9
Initial PSA >3.0 and repeat PSA >3.0	3,419	1,204	2,215	569	114	4.99	20.4	8.6	35.2
Initial PSA >3.0 and repeat PSA >3.5	2,852	1,061	1,791	993	257	3.86	35.7	19.5	37.2
Initial PSA >3.0 and repeat PSA >4.0	2,313	916	1,397	1,397	402	3.45	50.2	30.5	39.6
Initial PSA >3.0 and ≤30% reduction in repeat PSA	3,635	1,240	2,395	389	78	4.99	14.0	5.9	34.1
Initial PSA >3.0 and ≤20% reduction in repeat PSA	3,318	1,169	2,149	635	149	4.26	22.8	11.3	35.2
Initial PSA >3.0 and ≤10% reduction in repeat PSA	2,697	992	1,705	1,079	326	3.31	38.8	24.7	36.8
Subgroup analyses									
Initial tPSA 3.00 – 3.99 ng/mL ***Aged ≤ 60 years***	691	~159	~532	Reference	Reference	Reference	Reference	Reference	~23.0

Initial tPSA 3.00 – 3.99 ng/mL and ≤20% reduction in repeat PSA ***Aged ≤ 60 years***	511	~139	~372	~160	~20	~8.0	~30.1	~12.6	~27.2
Initial tPSA 3.00 – 3.99 ng/mL ***Aged > 60 years***	1,008	~242	~766	Reference	Reference	Reference	Reference	Reference	~24.0
Initial tPSA 3.00 – 3.99 ng/mL and ≤20% reduction in repeat PSA ***Aged > 60 years***	847	~221	~626	~140	~21	~6.7	~18.3	~8.7	~26.1

* Relative to initial tPSA alone in tPSA range specified

~ Calculated by systematic review team from estimated risk of cancer on biopsy

ΔFP = difference in false positives; ΔTP = difference in true positives; FP = false positives; PPV = positive predictive value (true positives/screen positive biopsied); PSA = prostate-specific antigen; TP = true positives; tPSA = total PSA

II DETECTION OF GLEASON SCORE >6 PROSTATE CANCER

Table 5: Results of studies comparing performance of repeat and initial PSA with those of initial PSA alone with respect to detection of GS >6 prostate cancer

Biopsy indication	Screen-positives biopsied (N)	TP (N)	Cancers missed ΔTP (N)*	% cancer missed*	PPV (%)
Rosario 2008 N = 4,102	PSA cut-off >3.0ng/mL				
Initial PSA >3.0	4,102	366	Reference	Reference	8.9
Initial PSA >3.0 and repeat PSA >2.0	3,915	364	2	0.5	9.3
Initial PSA >3.0 and repeat PSA >2.5	3,757	363	3	0.8	9.7
Initial PSA >3.0 and repeat PSA >3.0	3,419	351	15	4.1	10.3
Initial PSA >3.0 and repeat PSA >3.5	2,852	331	35	9.6	11.6
Initial PSA >3.0 and repeat PSA >4.0	2,313	305	61	16.7	13.2
Initial PSA >3.0 and ≤30% reduction in repeat PSA	3,635	356	10	2.7	9.8
Initial PSA >3.0 and ≤20% reduction in repeat PSA	3,318	342	24	6.6	10.3
Initial PSA >3.0 and ≤10% reduction in repeat PSA	2,697	305	61	16.7	11.3

* Relative to initial tPSA alone in tPSA range specified

ΔFP = difference in false positives; ΔTP = difference in true positives; FP = false positives; TP = true positives; PPV = positive predictive value (true positives/screen positive biopsied); PSA = prostate-specific antigen; tPSA = total PSA

2.6. Body of Evidence

Study	Study type	N	Level of evidence*	Risk of bias**	Biopsy indication	% Cancers missed^	% unnecessary biopsies prevented^	ΔFP/ ΔTP	PPV (%)
Age-specific PSA cut-off									
Boddy 2005	Prospective	160	III-2	At risk	Initial PSA > age-specific cut-off	-	-	-	51.9
					Initial and repeat PSA > age-specific cut-off	6.0	20.8	3.20	56.1
PSA cut-off >3.0ng/mL									
Rosario 2008	Prospective	4,102	III-2	At risk	Initial PSA >3.0	-	-	-	32.1
					Initial PSA >3.0 and repeat PSA >2.0	1.8	5.9	6.79	33.1
					Initial PSA >3.0 and repeat PSA >2.5	3.3	10.8	6.84	33.9
					Initial PSA >3.0 and repeat PSA >3.0	8.6	20.4	4.99	35.2
					Initial PSA >3.0 and repeat PSA >3.5	19.5	35.7	3.86	37.2
					Initial PSA >3.0 and repeat PSA >4.0	30.5	50.2	3.45	39.6
					Initial PSA >3.0 and ≤30% reduction in repeat PSA	5.9	14.0	4.99	34.1
					Initial PSA >3.0 and ≤20% reduction in repeat PSA	11.3	22.8	4.26	35.2
					Initial PSA >3.0 and ≤10% reduction in repeat PSA	24.7	38.8	3.31	36.8
					Subgroup analyses				
					Initial PSA 3.00 – 3.99 and ≤20% reduction in repeat PSA				
					Aged ≤ 60 years	~12.6	~30.1	~8.0	~27.2
					> 60 years	~8.7	~18.3	~6.7	~26.1
					Diagnosis of GS>6 cancer:				
					Initial PSA >3.0	-	-	-	8.9
					Initial PSA >3.0 and repeat PSA >2.0	0.5	-	-	9.3
					Initial PSA >3.0 and repeat PSA >2.5	0.8	-	-	9.7
					Initial PSA >3.0 and repeat PSA >3.0	4.1	-	-	10.3
					Initial PSA >3.0 and repeat PSA >3.5	9.6	-	-	11.6
					Initial PSA >3.0 and repeat PSA >4.0	16.7	-	-	13.2
					Initial PSA >3.0 and ≤30% reduction in repeat PSA	2.7	-	-	9.8
					Initial PSA >3.0 and ≤20% reduction in repeat PSA	6.6	-	-	10.3
					Initial PSA >3.0 and ≤10% reduction in repeat PSA	16.7	-	-	11.3

** refer to appendix B for detailed explanations of rating scores; ** see tables 2 and 3 for quality appraisals; ^ Relative to initial tPSA alone;*

~ Calculated by systematic review team from estimated risk of cancer on biopsy

Highlighted data = data for total PSA threshold of 3.0 ng/mL and age-specific total PSA thresholds

ΔFP = difference in false positives; ΔTP = difference in true positives; FP = false positives; PPV = positive predictive value (true positives/screen positive biopsied); PSA = prostate-specific antigen; TP = true positives; tPSA = total PSA

Clinical significance of size of effect is addressed in the assessment of clinical impact in the NHMRC evidence statement form.

Assessment of the relevance of the evidence in terms of whether the outcomes were directly relevant to the patient or surrogate outcomes was not assessed as it was not considered relevant to diagnostic performance studies.

2.7. References: Included studies

1. Boddy JL, Pike DJ, Al-Hayek S, Shaida N, Malone PR. An elevated PSA, which normalizes, does not exclude the presence of prostate cancer. *Prostate Cancer & Prostatic Diseases* 2005; 8(4):349-352.

2. Rosario DJ, Lane JA, Metcalfe C, Catto JW, Dedman D, Donovan JL et al. Contribution of a single repeat PSA test to prostate cancer risk assessment: experience from the ProtecT study. *European Urology* 2008; 53(4):777-784.

APPENDICES

Appendix A: Search strategies used

For Medline database:

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	((repeat$ or review$ or replicat$ or re-measur$ or subsequent$ or following or follow-up or followup or second or initial$ or multiple or serial$ or variab$ or variat$ or fluctuat$) adj3 (PSA or tPSA or prostate specific antigen)).mp.
5	3 and 4
6	limit 5 to (english language and humans and yr="1990 -Current")

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database:

#	Searches
1	prostat* near/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR metast* OR adeno*))
2	'prostate cancer'/exp
3	1 or 2
4	(repeat* OR review* OR replicat* OR remeasure* OR subsequent* OR following OR 'follow up' OR followup OR second OR initial* OR multiple OR serial* OR variab* OR variat* OR fluctuat*) NEAR/3 (psa OR tpsa OR 'prostate specific antigen)
5	4 AND [humans]/lim AND [english]/lim AND [embase]/lim NOT [medline]/lim AND [1990-3000]/py

ATSI search terms used

#	Searches
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

For Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases:

#	**Searches**
1	(prostat$ adj3 (cancer$ OR carcinoma$ OR malignan$ OR tumo?r$ OR neoplas$ OR metastas$ OR adeno$)).tw

Appendix B:

Level of Evidence rating criteria – Diagnostic accuracy studies

Level	Study design
I	Meta-analysis or a systematic review of level II studies
II	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation
III-1	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation
III-2	A comparison with reference standard that does not meet the criteria required for level II and III-1 evidence
III-3	Diagnostic case-control study
IV	Study of diagnostic yield (no reference standard)

According to the standards of the National Health and Medical Research Council

Appendix C:

Potentially relevant guidelines identified and reason why not adopted

Year	Organization	Title	Reason why not adopted
2010	National Health Service	Prostate Cancer Risk Management Programme: PSA testing in asymptomatic men	Consensus based
2012	NZ Ministry of Health	Diagnosis and Management of Prostate Cancer in New Zealand Men: Recommendations from the Prostate Cancer Taskforce	Did not meet pre-specified AGREE II criteria for adoption
2012	Royal College of Pathologists of Australasia	Prostate specific antigen testing: Age-related interpretation in early prostate cancer detection	Consensus based

Excluded Studies

Study	Reason for exclusion
1. Carter 1993	No relevant outcomes
2. Carter 1997	Narrative review/comment/letter to editor (no original data)
3. Christensson 2010	No relevant outcomes
4. Connolly 2009	No relevant outcomes
5. Eastham 2003	No relevant outcomes
6. Ellis 2001	No relevant outcomes
7. Haller 2012	No relevant outcomes
8. Helfand 2012	Unclear or inappropriate indications for biopsy
9. Kacker 2012	Inappropriate population
10. Kobayashi 2005	Less than 80% of participants underwent initial biopsy
11. Komatsu 1996	No relevant outcomes
12. Loeb 2008	Narrative review/comment/letter to editor (no original data)
13. Lynn 2000	Unclear or inappropriate indications for biopsy
14. Morote 1999	Unclear or inappropriate indications for biopsy
15. Morote 1999	Unclear or inappropriate indications for biopsy
16. Roehrborn 1996	No relevant outcomes
17. Saavedra 2013	Less than 80% of participants underwent initial biopsy
18. Singh 2003	Unclear or inappropriate indications for biopsy
19. Soletormos 2005	No relevant outcomes

References: Excluded Studies

1. Carter HB, Pearson JD, Metter EJ, Brant LJ, Chan DW, Andres R et al. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. *JAMA* 1992; 267(16):2215-2220.

2. Carter HB. PSA variability versus velocity. *Urology* 1997; 49(2):305.

3. Christensson A, Bruun L, Bjork T, Cronin AM, Vickers AJ, Savage CJ et al. Intra-individual short-term variability of prostate-specific antigen and other kallikrein markers in a serial collection of blood from men under evaluation for prostate cancer. *BJU International* 2011; 107(11):1769-1774.

4. Connolly D, Black A, Murray LJ, Nambirajan T, Keane PF, Gavin A. Repeating an abnormal prostate-specific antigen (PSA) level: how relevant is a decrease in PSA? *Prostate Cancer & Prostatic Diseases* 2009; 12(1):47-51.

5. Eastham JA, Riedel E, Scardino PT, Shike M, Fleisher M, Schatzkin A et al. Variation of serum prostate-specific antigen levels: an evaluation of year-to-year fluctuations. *JAMA* 2003; 289(20):2695-2700.

6. Ellis WJ, Etzioni R, Vessella RL, Hu C, Goodman GE. Serial prostate specific antigen, free-to-total prostate specific antigen ratio and complexed prostate specific antigen for the diagnosis of prostate cancer. *J Urol* 1998; 166(1):93-98.

7. Haller H, El-Shafei A, Moussa A, Fareed K, Ramanathan R, Berglund R et al. Value of serial psa measurements for prostate cancer prediction on screening using a maximum likelihood estimation-prostate specific antigen (MLE-PSA) model. *J Urol* 2012; 187(4):e587.

8. Helfand BT, Hu Q, Loeb S, Kim DY, Cooper PR, Hofer MD et al. Do men fluctuate above and below their age-specific median PSA values as they age? *J Urol* 2012; 187(4):e774.

9. Kacker R, Elsobky S, Loughlin K. Psa stratifies risk of prostate cancer after high grade prostatic intraepithelial neoplasia. *J Urol* 2012; 187(4):e586.

10. Kobayashi M, Kurokawa S, Tokue A. Intraindividual variation in total and percent free prostate-specific antigen levels in prostate cancer suspects. *Urologia Internationalis* 2005; 74(3):198-202.

11. Komatsu K, Wehner N, Prestigiacomo AF, Chen Z, Stamey TA. Physiologic (intraindividual) variation of serum prostate-specific antigen in 814 men from a screening population. *Urology* 1996; 47(3):343-346.

12. Loeb S, Catalona WJ. What to do with an abnormal PSA test. [Review] [45 refs]. *Oncologist* 2008; 13(3):299-305.

13. Lynn NN, Collins GN, O'Reilly PH. The short-term prostate-specific antigen velocity before biopsy can be used to predict prostatic histology. *BJU Int* 2000; 85(7):847-850.

14. Morote J, Raventos CX, Lorente JA, Enbabo G, Lopez M, de T, I. Intraindividual variations of total and percent free serum prostatic-specific antigen levels in patients with normal digital rectal examination. *European Urology* 1999; 36(2):111-115. (a)

15. Morote J, Encabo G, Lopez M, De Torres IM. Individual variations of total and percent free serum prostatic specific antigen: could they change the indication of prostatic biopsy? *Oncol Rep* 1999; 6(4):887-890. (b)

16. Roehrborn CG, Pickens GJ, Carmody T, III. Variability of repeated serum prostate-specific antigen (PSA) measurements within less than 90 days in a well-defined patient population. *Urology* 1996; 47(1):59-66.

17. Saavedra II, Konstantinidis C, Celma A, Agreda F, Placer J, Planas J et al. PSA kinetics does not predict prostate cancer in men subjected to prostate biopsy. *J Urol* 2013; 189(4):e789.

18. Singh R, Cahill D, Popert R, O'Brien TS. Repeating the measurement of prostate-specific antigen in symptomatic men can avoid unnecessary prostatic biopsy. *BJU International* 2003; 92(9):932-935.

19. Soletormos G, Semjonow A, Sibley PE, Lamerz R, Petersen PH, Albrecht W et al. Biological variation of total prostate-specific antigen: a survey of published estimates and consequences for clinical practice. *Clin Chem* 2005; 51(8):1342-1351.

Systematic review report for question 7

Clinical Question 7: *"What constitutes an adequate prostate biopsy?"*

PICO Question 7: "*For men undergoing an initial prostate biopsy how many biopsy cores, which pattern of biopsy sampling sites and which approach constitute an adequate prostate biopsy?"*

Population	Intervention	Comparator	Outcomes
Men with a suspicion of prostate cancer undergoing an initial prostate biopsy	A specified biopsy protocol (numbers of biopsy cores, patterns and/or approaches)	An alternative biopsy protocol (numbers of biopsy cores, patterns and/or approaches)	Detection of prostate cancer, or Detection of Gleason Score >6 cancer, or Adverse events

1. Methods

1.1. Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption guidelines had to evidence based and meet the pre-specified criteria of scores of greater or equal to 70% for the domains *rigour of development*, *clarity of presentation* and *editorial independence* in the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

Twelve potentially relevant guidelines were identified. One of these[1] was of particular relevance, and the corresponding systematic review[2] by Eicher et al., 2006 was comprehensive and assessed to be of high quality (please see Tables 9 and 10). In view of the vast literature available it was decided to use the systematic review by Eichler et al., 2006 as a starting point and to limit inclusion to studies published thereafter, to systematic biopsies and to the initial biopsy setting. Eichler et al., 2006 conducted searches of the literature published from 1980 to May 2004. To ensure all relevant literature was captured, searches to update this review were conducted starting from 31st December 2003 - five months before the date of literature cut-off of the Eichler systematic review. Retrieved studies that met the inclusion criteria but were already included in the Eichler systematic review were excluded.

[1] National Health Service – Prostate Cancer Risk Management Programme: PCRMP Guide No 1 - Undertaking a transrectal ultrasound guided biopsy of the prostate. Published Dec 2006 | ISBN 978 1 84463 041 7.

[2] Eichler K, Hempel S, Wilby J, Myers L, Bachmann LM, Kleijnen J. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. [Review] [42 refs]. *J Urol* 2006; 175(5):1605-1612.

1.2. Literature Search

To update the Eichler review Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched from 2004 or from the date at which the database started (which ever occurred later) to 1st March 2014 using text terms and, where available, database-specific subject headings. Each database was searched for

articles dealing with prostate cancer. In Medline and Embase databases prostate biopsy search terms were added to the prostate cancer search. To identify studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples. A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 which were either published after the initial search was completed and/or added to the relevant database after the search was completed. Alerts were checked until July 2014. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched regularly up until April 2014 for relevant reviews published after the initial search. Reference lists of all relevant articles were checked for potential additional articles.

1.3. Inclusion Criteria

Selection criteria	**Inclusion criteria**
Study type	Intervention
Study design	Randomized controlled trials or sequential sampling studies[1], or systematic reviews/meta-analyses thereof
Population	Men with a suspicion of prostate cancer undergoing an initial prostate biopsy (Eichler systematic review) Men with a suspicion of prostate cancer undergoing an initial prostate biopsy (Eichler systematic review update)
Intervention	A specific prostate biopsy protocol (a specific number of biopsy cores, sampling pattern and approach) (Eichler systematic review) A specific systematic prostate biopsy protocol (a specific number of biopsy cores, sampling pattern and approach) (Eichler systematic review update)
Comparator	A different prostate biopsy protocol (different numbers of biopsy cores, a different sampling pattern and/or a different approach) (Eichler systematic review update) A different systematic prostate biopsy protocol (different numbers of biopsy cores, a different sampling pattern and/or a different approach) (Eichler systematic review update)
Outcomes	Detection of prostate cancer (Cancer Detection Rate), or Detection of Gleason Score >6 cancer, or Adverse events
Language	English
Publication period	After 31st December 2003 and before1st March 2014

Conference proceedings identified by the literature searches were included if they met the inclusion criteria.

[1] Studies in which results for each of the compared sampling strategies were obtained from each of the participating men, the less extensive set of biopsy cores being a subset of the more extensive set.

2. Results

2.1. Guidelines

Ten guidelines were identified that contained potentially relevant recommendations. These recommendations were not adopted as they either were not based on a systematic review, did not meet the pre-specified AGREE II criteria for adoption or were published more that 5 years ago and thus considered unlikely to be up-to date. These guidelines and the reasons why they were not adopted are listed in Appendix C. The NICE 2006 guidelines, Undertaking a Transrectal Ultrasound Guided Biopsy of the Prostate, met the pre-specified AGREE II criteria for adoption. Published in 2006 they were considered out of date, however as described in section 1.1, the systematic reviews for the NICE 2006 guidelines were included in the current systematic review to cover the primary studies published up until 2004.

Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the systematic review. The Medline search identified 6,346 citations, the Embase search an additional 5,764 citations, the search of the Cochrane Database of Systematic Reviews 59 citations, the Database of Abstracts of Reviews of Effects 282 citations and the Health Technology Assessment database 216 citations, resulting in a total of 12,667 citations. Titles and abstracts were examined and 410 articles were retrieved for a more detailed evaluation. An additional 28 potential citations were identified from the reference list of retrieved articles.

Twenty three articles were included reporting 22 primary studies and one systematic review. There were no studies of Aboriginal and/or Torres Strait Islander men that met the inclusion criteria.

The retrieved articles that were not included and the reasons for their exclusion are documented in Appendix C. In summary, most articles were excluded because they had included men with prostate cancer or men who had previously undergone a prostate biopsy, had used an inappropriate study design, did not compare different biopsy schemes, did not report any relevant outcomes, were narrative reviews/comments, were duplicate publications of studies already included, were already included in the published systematic review, or provided insufficient information to determine whether the inclusion criteria were met.

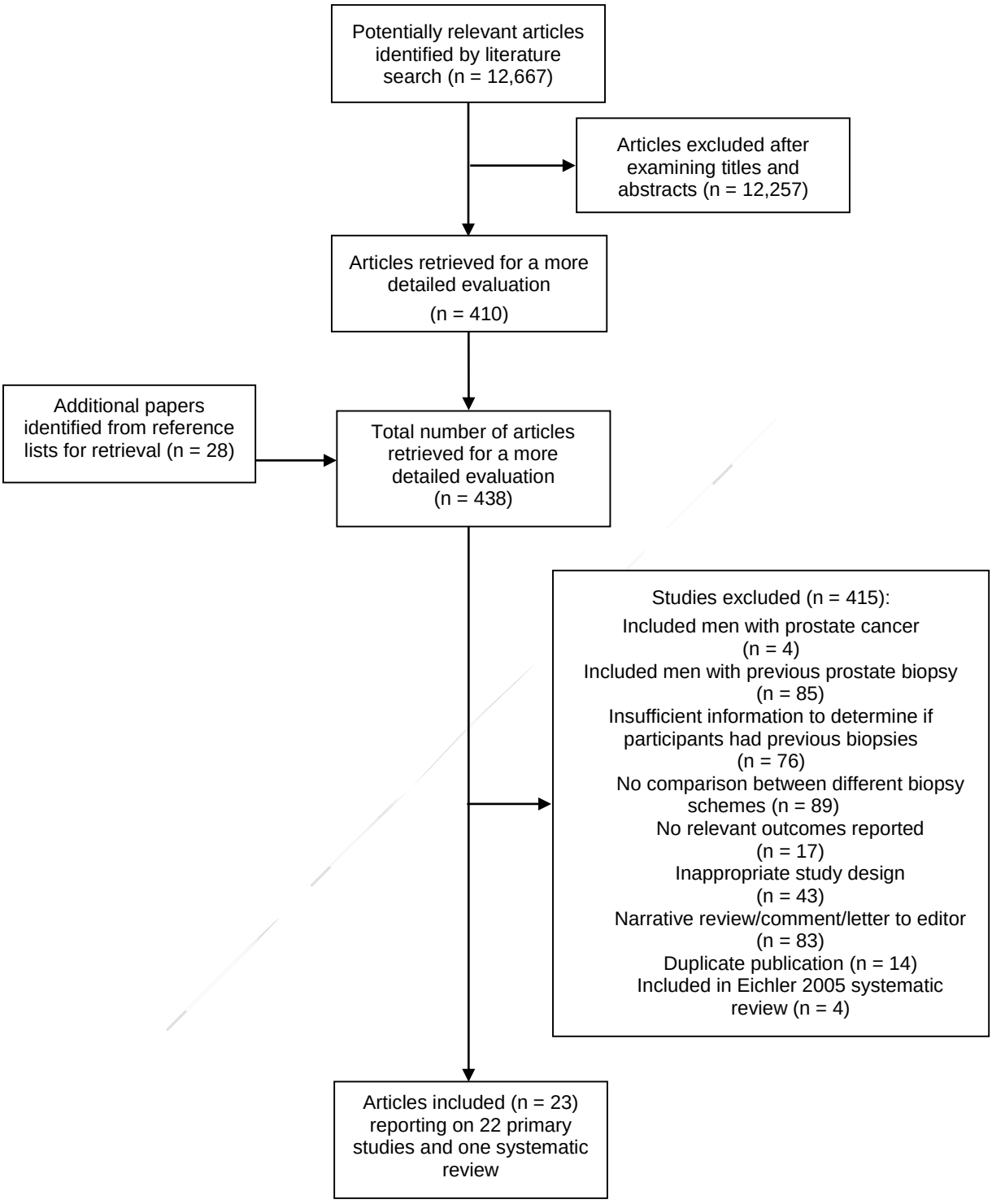


Figure 1. Results of literature searches and exclusion of studies

2.3 Study Characteristics

Characteristics of included studies are described in Tables 1-8.

Table 1: Intervention studies examining different biopsy schemes in men undergoing prostate biopsy: study characteristics

Study	Participants	Design	Intervention (N studies, population[c])	Comparison	Outcomes	Comments
Eichler 2006 (UK) (USA N = 27, Canada N = 7, Europe N = 35, Japan N = 11 studies)	Men of all age groups scheduled for a prostate biopsy in the diagnostic investigation for possible prostate cancer due to increased PSA and/or positive DRE; PSA threshold for biopsy indication 4 ng/ml for 72% of studies, 2-4 ng/ml for 9 studies, 1.25 ng/ml for one study; **exclusion criteria:** men with proven prostate cancer; **included 10 studies with initial, 11 with repeat, 13 with mixed biopsy population and 53 with no respective information available;** **Mean age (range)** (57.7-70.9) years (17 studies NR) **Mean PSA (range)** (4.8-52.2) ng/mL (22 studies NR) **Mean prostate volume (range)** (30.5-70) mL (52 studies NR) **N = 87 studies** **N = 20,698 men**	SR of RCTs (N = 7) and SS studies (N = 80)	Data extracted from selected comparisons (79 studies: comparisons with 2 or more studies; outcome adverse events - only RCTs): 8 cores MPZ+TZ(+MLiPZ) (16 studies[a,b], mixed) 8 cores MPZ+LPZ (7[a,b], mixed) 10 cores MPZ (2, repeat) 10 cores MPZ+LPZ (13[a], mixed) 10/11 cores MPZ+TZ(+MLiPZ) (4, mixed) 10/11 MPZ+LPZ+TZ(+MLiPZ) cores (3[a], repeat) 12 cores MPZ+TZ(+MLiPZ) (3, repeat) 12 cores MPZ+LPZ (16[a,b], mixed) 12/13 MPZ+LPZ+TZ(+MLiPZ) cores (8[b], repeat) 14 cores MPZ+LPZ+TZ(+MLiPZ) (2[a], mixed) ≥18cores MPZ+LPZ+TZ+MLiPZ (4[b], repeat) 14 cores MPZ+LPZ+TZ(+MLiPZ) (1, unclear)	6 cores MPZ (78% of studies) 10 cores MPZ+LPZ	*Detection of prostate cancer* *Adverse events*	Comprehensive literature searches without language restriction from 1980 to May 2004; TR approach in 77% of studies, TP in 7, TR+TP in 6 studies (7 studies NR); mostly biplanar multi-plane of 3D ultrasound probes (53 studies NR), scan frequencies 5-10 MHz (34 studies NR), 18-G needle in 52 studies, 1 study 14-G needle for TP biopsies; needle length 10-23mm (79 studies NR) **Anaesthesia methods of RCTs:** None in 8, local in 18, spinal/peridural in 4 (TP approach), IV sedation in 4, general anaesthesia in 2 studies; (NR in 59% of studies) **Antibiotic scheme of RCTs:** 36 studies reported prophylaxis (often with substance, dosage information), NR in 51 studies (39 transrectal approach) **Examiner details:** biopsies performed by urologists in 26 studies, by radiologists in 3 studies (56 studies NR); 1-7 examiners per study, case load NR, amount of training mentioned in 5 studies **Quality of included studies:** Insufficient information to conclude that the patient spectrum was representative in 48% of studies; clearly described selection criteria in 32%; pathologist blinded to test sequence in 1 study; suitable methods for random sequence generation in 3 of 7 RCTs, mention of allocation concealment in 2 RCTs

DRE = digital rectal examination; LPZ = lateral peripheral zone; MLiPZ = midline peripheral zone; MPZ = mid-lobar peripheral zone; NR = not reported; PSA = prostate specific antigen; RCT = randomized controlled trial; SR = systematic review; SS = sequential sampling (comparison of different schemes within same man); TP = transperineal approach; TR = transrectal approach; TZ = transition zone

[a] Included one or more studies with lesion-directed biopsies for men with suspicious findings on imaging; [b] Included one or more studies with transperineal biopsy approach; [c] Included population undergoing intial biopsy, or repeat biopsy, or mixed population of both initial and repeat biopsy

Table 2: Sequential sampling studies examining extended vs. 6/8-core biopsy schemes in men undergoing an initial prostate biopsy: study characteristics

Study	Participants	Design	Intervention	Comparison	Outcomes	Comments
10 vs. 6 cores (MPZ**+LPZ** vs. MPZ)						
Dai 2008 (China)	Patients undergoing biopsy at urology department of cancer hospital due to abnormal DRE and/or PSA >4 ng/mL **Exclusion criteria:** NR **Age median (range)** 69 (44-91) years **PSA median (range)** 13.5 (0.8-6006.2) ng/mL **Prostate volume median (range)** 37.1 (16.5-131.5) mL **Men with abnormal DRE** 58.0% **Men with abnormal TRUS** 69.2% **N = 221**	SS	**10 cores** 6 MPZ + **4 LPZ (base, midgland)**	**6 cores** 6 MPZ	*Detection of prostate cancer* **Histological processing:** Specimens labelled according to site, submitted in individual formalin-filled containers; cores embedded in blocks individually with ≥5 sections obtained from each block; atypical cases further evaluated with immunohistochemical markers Follow-up 100%	Left lateral decubitus position with knees and hips flexed at 90 degrees Falcon 2101 EXL TRUS with 8808 5-10 Mhz probe, UA 1257 biopsy adaptor, 18-G needle on spring-loaded automatic biopsy gun used to obtain 22 mm long cores **Power calculation:** NR
10 vs. 8 cores (PZ+ALH**+TZ** vs. PZ+ALH)						
Miyake 2005 (Japan)	Men undergoing biopsy due to abnormal DRE or PSA 2.0-100 ng/mL **Exclusion criteria**: NR **Mean age (SD)** 69.8 (5.6) years **Mean PSA (SD)** 6.92 (10.63) ng/mL **Mean prostate volume (SD)** 28.9 (33.5) mL **Men with abnormal DRE** 17.0%	SS	**10 cores** 6 PZ + 2 ALH + **2 TZ**	**8 cores** 6 PZ + 2 ALH	*Detection of prostate cancer* *Detection of GS>6 cancer (incl. subgroup analysis prostatectomy)* **Pathological processing, reporting:** Prostate specimens fixed and wholemount step sections cut transversely at 5 mm intervals from apex to tips of seminal vesicles;	TRUS-guidance with model 1846 console with multiplane transducer; spring-loaded Biopty biopsy gun, 18-G Tru-cut needle; **Power calculation:** NR

	Men with abnormal TRUS 31.9% **N = 788**				Pathological examinations according to UICC TNM classification system by a single pathologist Follow-up 100%	

ALH = anterior lateral horn; DRE = digital rectal examination; GS = Gleason score; LPZ = lateral peripheral zone; MPZ = mid-lobar peripheral zone; NR = not reported; PSA = prostate specific antigen; SD = standard deviation; SS = sequential sampling study (comparison of different schemes within same man); TRUS = transrectal ultrasound; TZ = transition zone

Table 3: Randomized controlled trials examining volume-dependant vs. 6/8-core biopsy schemes in men undergoing an initial prostate biopsy: study characteristics

Study	Participants	Design	Intervention	Comparison	Outcomes	Comments
Volume-dependant number of cores vs. 6 cores (LPZ**+MPZ+flpz** vs. LPZ)						
Mariappan 2004 (Malaysia)	Men <80 years with PSA 4-20 ng/mL (despite antibiotics and repeat PSA persistently raised) and without malignant features on DRE recruited from urology clinic and three prostate-awareness campaigns; **Exclusion criteria**: previous prostate biopsy or TURP, recent cystoscopy, acute urinary retention, tender or nodular prostate, requiring lesion-directed biopsy, diabetes mellitus, renal failure, immunocompromise **Mean age (SD)** 68.7 (9.412) years **Mean PSA** 9.41 ng/mL **Prostate volume median** "in the 20-60 mL groups" **N = 132**	RCT	Increased number of cores according to prostate volume: PV ≤20 mL: **6** PV 20-40 mL: **8** PV 40-60 mL: **10** PV 60-80 mL: **12** PV ≥80 mL: **14** 6 LPZ + **2 midgland MPZ** **+** **2 basal MPZ** **+** **2 apical MPZ** **+** **2 basal far LPZ** N = 63	**6 cores** 6 LPZ N = 69	*Detection of prostate cancer* *Adverse events* **Histological processing, reporting**: NR Pain assessed during and within 30 minutes of completing biopsy; Rectal bleeding, haematuria, haemospermia documented by patients who were reviewed at 1 and 2 weeks after biopsy (patients advised to return to clinic in case of fever) Follow-up: Cancer detection – 100% Pain ≈ 81.8% (>5% difference between groups)	7 Mhz biplanar probe, 18-G needle, spring-loaded biopsy gun, 15 mm core length **Antibiotic scheme:** Third-generation cephalosporins or quinolones **Anaesthesic scheme:** Paracetamol after biopsy **Power calculation:** calculations for a power of 80% and a clinically significant difference (95% CI) with a positive biopsy rate of 10% for sextant and 30% for the increased-core regime indicated that 132 patients were required
Volume-, age-dependant number of cores vs. 8 cores (**LPZ** vs. LPZ)						
Lecuona 2011 (South Africa)	Men with PSA >2.5 ng/mL undergoing biopsy in university hospital, stratified according to PSA level prior to randomization; **Exclusion criteria:** previous prostate surgery, previous diagnosis of prostate cancer,	RCT	**6-18** (mean 10.2) **LPZ cores** according to Vienna nomogram (Remzi et al 2005) (prostate volume, age)	**8 LPZ cores**	*Detection of prostate cancer* *Adverse events* **Histological processing, reporting:** NR	TRUS guidance with 6-Mhz probe **Antibiotic scheme:** 1g ciprofloxacin 1 hour before biopsy, two 500mg doses at 12 hour intervals after biopsy **Anaesthetic scheme:**

	history of urinary retention, previous histological evidence of prostatitis, confirmed urinary tract infection **Mean age** (range) Nomogr. Group: 65.1 (45-82) years 8-core group: 63.4 (40-81) years **Mean PSA (range)** Nomogr. Group: 9.4 (2.2-46) ng/mL 8-core group: 9.2 (2.6-48) ng/mL **Mean prostate volume (range)** Nomogr. Group: 47.4 (11-220) mL 8-core group: 51.5 (10-194) mL **Men with abnormal DRE** Nomogr. group: 16.5% 8-core group: 23.8% **N = 303**		N = 152	N = 151	No details reported regarding assessment of complications Follow-up 100% for cancer detection, 59.7% for complications (2.9% difference between groups)	Periprostatic infiltration of 2% lignocaine **Power calculation:** A two-tailed p-value <0.05 was accepted as significant with a power of 80%

DRE = digital rectal examination; fLPZ = far lateral peripheral zone; LPZ = lateral peripheral zone; MPZ = mid-lobar peripheral zone; NR = not reported; PSA = prostate specific antigen; PV = prostate volume; RCT = randomized controlled trial; SD = standard deviation; TRUS = transrectal ultrasound; TURP = transurethral resection of the prostate; TZ = transition zone;

Table 4: Sequential sampling study examining extended vs. 10-core biopsy schemes in men undergoing an initial prostate biopsy: study characteristics

Study	Participants	Design	Intervention	Comparison	Outcomes	Comments
12 vs. 10 cores (MPZ+LPZ**+AAPZ** vs. MPZ+LPZ)						
Orikasa 2008 (Japan)	Biopsies performed at university hospital on patients with abnormal DRE and/or PSA >4.01 ng/mL or 2.0-4.0 ng/mL, or free/total PSA <0.12 **Exclusion criteria**: NR **Age median (SD)** 68.0 (8.31) years **PSA median (SD)** 5.9 (49.0) ng/mL **Prostate volume median (SD)** 32.9 (19.2) mL **Men with abnormal DRE** 33.7%	SS	**12 cores** 6 MPZ + 4 LPZ (base, midgland) + **2 AAPZ**	**10 cores** 6 MPZ + 4 LPZ (base, midgland)	*Detection of prostate cancer* **Histological reporting:** All diagnoses by single pathologist Follow-up 100%	TRUS-guidance with ALOKA Pro Sound 5000, 5Mhz probe, 18-G needle, spring-loaded biopsy gun; **Power calculation**: NR

	N = 549					

AAPZ = anterior apical peripheral zone; DRE = digital rectal examination; GS = Gleason score; LPZ = lateral peripheral zone; MLiPZ = midline peripheral zone; MPZ = mid-lobar peripheral zone; NR = not reported; PSA = prostate specific antigen; SD = standard deviation; SS = sequential sampling study (comparison of different schemes within same man); TRUS = transrectal ultrasound; TZ = transition zone;

Table 5: Randomized controlled trial examining extended vs. 6-12-core biopsy schemes in men undergoing an initial prostate biopsy: study characteristics

Study	Participants	Design	Intervention	Comparison	Outcomes	Comments
24 vs. 6-12 (MPZ**+LPZ+TZ+mlipz** vs. MPZ(+LPZ)						
Sur 2004 (USA)	Patients with elevated PSA (incl. % free PSA) and/or abnormal DRE **Exclusion criteria:** NR **Age median** 24-core group: 61.3 years 6-12-core group: 62.8 years **PSA median** 24-core group: 5.4ng/mL 6-12-core group: 5.5ng/mL **Prostate volume median** 24-core group: 35.5cm^3 6-12-core group: 30.0cm^3 **N = 197**	RCT	**24 cores** **8** MPZ **+** **8** LPZ **+** **4 TZ** **+** **4 MLiPZ** IV sedation with fentanyl, midazolam according to individual patient requirements/tolerance 10 minutes prior to biopsy (biopsy lasted 5-10 minutes) N = NR	**6-12 cores** (number determined by urologist; mean 10.1 cores) 6 MPZ (+ ≤6 LPZ) 10 cm^3 of 2% lidocaine gel 15 minutes prior to biopsy N = NR	*Detection of prostate cancer* *Detection of GS>6 cancer* *Adverse events* **Histological processing, reporting:** NR Complications assessed by questionnaire filled out by patients on the day of biopsy, 1 day, 1 week and 2 weeks after Follow-up 92.4% for cancer detection, 83.2% for complications, NR for pain	Patients in 6-12-core group statistically significantly older (p=0.022) and had smaller prostates (p=0.015) TRUS guidance with 7 Mhz bipolar probe, automatic biopsy gun, 18-G needle; Clinic setting, lateral decubitus position; **Antibiotic protocol**: Fluoroquinolone per os from day before biopsy for 3 days Two fleet enemas immediately before procedure 12 different urologists

GS = Gleason score; LPZ = lateral peripheral zone; MLiPZ = midline peripheral zone; MPZ = mid-lobar peripheral zone; NR = not reported; PSA = prostate specific antigen; RCT = randomized controlled trial; TRUS = transrectal ultrasound; TZ = transition zone;

Table 6: Intervention studies examining extended vs. 12/14-core biopsy schemes in men undergoing an initial prostate biopsy: study characteristics

Study	Participants	Design	Intervention	Comparison	Outcomes	Comments
15 vs. 12 cores (MPZ+LPZ**+ALH+mlipz** vs. MPZ+LPZ)						
Rochester 2009 (UK)	Patients attending a diagnostic prostate clinic with normal DRE and PSA ≤20 ng/mL, but persistently over the age-specific threshold (40-49 years >2.5 ng/mL, 50-59 years >3.5 ng/mL, 60-69 years >4.5 ng/mL, 70-79 years >6.5 ng/mL) **Mean age (SD)** 15-core group: 66.2 (7.2) years 12-core group: 67.8 (9.4) years **Mean PSA (range)** 15-core group: 6.5 (1.4-18.5) ng/mL 12-core group: 6.7 (2.3-24.5) ng/mL **Mean prostate volume** 15-core group: 37 (10-165) mL 12-core group: 37 (10-101) mL **N = 250 (RCT)** **N = NR (SS)**	RCT, SS	**15 cores** 6 MPZ + 6 LPZ + **2 ALH** **+** **1 MLiPZ** N = NR	**12 cores** 6 MPZ + 6 LPZ N = NR	*Detection of prostate cancer* *Detection of GS>6 cancer* **Histological processing, reporting:** Each set of cores labelled accordingly in separate pots and analysed separately by a uro-pathologist Follow-up 97.6%	Biopsies performed by one urologist; B-K Medical 7.5 Mhz probe, 18-G Angiotech Uro II needle **Antibiotic protocol:** 500 mg ciprofloxacin pre-biopsy and continuing twice daily for 5 days **Anaesthetic protocol:** Peri-prostatic block with 20 mL 0.5% bupivacaine injected into prostate apex in the midline, and at base bilaterally, adjacent to neurovascular bundles **Power calculation:** NR
18 vs. 12 cores (MPZ+LPZ**+MLPZ** vs. MPZ+LPZ)						
Park 2010 (South Korea)	Patients with PSA ≥3 ng/ml underwent biopsy at single tertiary academic center **Age median** 68.0 years **PSA median** 7.1 ng/mL **PSA density median** 0.184 ng/mL/cm^3 **Prostate volume median** 42.0 cm^3 **Men with abnormal DRE**	RCT, SS	**18 cores** 6 MPZ + 6 LPZ + **6 MLPZ** N = 115	**12 cores** 6 MPZ + 6 LPZ N = 118 (RCT)	*Detection of prostate cancer* *Detection of GS>6 cancer* *Adverse events* **Histological processing:** Specimens labelled by biopsy site and submitted in separate formalin-filled containers No details reported regarding assessment of complications	Transrectal approach, biopsy gun provided 17mm long tissue cores, 18-G needle **Antibiotic protocol:** Levofloxacin antibiotics for 3 days from the day of biopsy **Anaesthetic protocol:** Local anaesthesia with 5mL 1% lidocaine injection to both neuromuscular bundles Cleansing enema before biopsies

	18-core group: 37.3% 12-core group: 38.3% **Men with positive family history** 18-core group: 0.85% 12-core group: 0.00% **N = 233 (RCT)** **N = 115 (SS)**				Follow-up 100%	**Power calculation:** NR
18 vs. 12 cores (LPZ**+far LPZ** vs. LPZ)						
Rodriguez-Covarrubias 2011 (Mexico)	Men undergoing a TRUS guided prostate biopsy due to abnormal DRE and/or PSA 4 to 20 ng/mL; **exclusion criteria:** previous diagnosis of prostate cancer, clinical stage T3/T4, previous 5α-reductase inhibitor/androgen deprivation therapy **Age median (range)** 64.8 (41-80) years **PSA median (range)** 8.65 (0.86-19.80) ng/mL **Prostate volume median (range)** 53.56 (13.60-219.00) mL **Men with abnormal DRE** 14.7**%** **N = 150 (RCT)** **N = 75 (SS of 18-core group)**	RCT, SS	**18 cores** 12 LPZ + **6 far LPZ** N = 75	**12 cores** 12 LPZ N = 75	*Detection of prostate cancer* *Detection of GS>6 cancer* *Adverse events* **Histological processing:** each tissue placed in its own container that identified the corresponding site complications assessed by questionnaire completed by participants 7 days after procedure Follow-up 100%	Transrectal approach, automatic biopsy gun, 18-G needle **Antibiotic protocol:** Piperacilllin/Tazobactam 4/0.5g SD IV 15 minutes prior to biopsy **Anaesthetic protocol:** Mild IV sedation Cleansing enema 12 and 3 hours prior to biopsy; anticoagulant use interrupted before the procedure **Power calculation**: Total number of patients estimated to be 150 to achieve 80% power, assuming a 30% detection rate in the 12 core biopsy group and a 10% difference in detection rate between groups
20 vs. 12 cores (**MPZ+LPZ** vs. MPZ+LPZ)						

Irani 2013 (France)	Men with PSA 3 - 20 ng/mL and no nodule on DRE (T1c or possible T2a stage), **Exclusion criteria:** previous 5a-reductase inhibitor use or androgen deprivation therapy **Mean age** 63.1 years (men analyzed) **Mean PSA** 7.0 ng/mL (men analyzed) **Mean prostate volume** 47.6 cc (men analyzed) **N = 339 (men randomized)** **(N = 335 men analyzed)**	RCT (multicenter)	**20 cores** 10 MPZ + 10 LPZ N = 169	**12 cores** 6 MPZ + 6 LPZ N = 170	*Detection of prostate cancer* *Adverse events* **Histological processing:** NR adverse events assessed by questionnaire completed by patients before, 5 days after and 21 days after procedure Follow-up: 98.8% for cancer detection 90.3% for complications NR for pain	TRUS guidance with 7.5 Mhz biplane probe, spring-loaded biopsy gun, 18-G needle **Antibiotic protocol:** Systematic antibiotic prophylaxis **Anaesthetic protocol:** Local anaesthesia **Power calculation:** Total number of patients to include was 338 to achieve an 80% power with an alpha risk of 5% assuming a 40% CDR in the 12-core group and a 55% CDR in the 20-core group
26 vs. 12 cores (TR**+TP** vs. TR)						
Numao 2012 (Japan) [Same study as Takeshita 2013]	Men underwent biopsy at urology departments of university hospital or cancer institute hospital due to PSA 2.5-20 ng/mL and/or abnormal DRE; **exclusion criteria:** diabetes mellitus, rectal disease, apparently palpable mass, age ≥75 years, PSA ≥20 ng/mL, poor state of health **Age median (IQR)** 66 (61-71) years **PSA median (IQR)** 6.1 (4.7-8.5) ng/mL **Prostate volume median (IQR)** 35 (27-47) mL **Men with abnormal DRE** 16% **N = 715**	SS	**26 cores** 6 MPZ + 6 LPZ + **4 anterior** **+** **2 anterolateral** **+** **4 posterior** **+** **2 posterolateral** **+** **2 TZ** **transperineal** + transrectal	**12 cores** 6 MPZ + 6 LPZ transrectal	*Detection of prostate cancer* *Detection of GS>6 cancer* **Histological processing, reporting:** cores individually labelled, evaluated by a single pathologist according to 2005 International Society of Urologic Pathology Consensus on Gleason Grading Follow-up 100% for cancer detection	TRUS guidance, 18-G needle, automatic Magnum biopsy gun; TP: fan-technique **Power calculation:** NR
26 vs. 14 cores (TP**+TR** vs. TP)						
Takeshita 2013	Men with PSA between 2.5-20 ng/mL or abnormal DRE undergoing	SS	**26 cores**	**14 cores**	*Detection of prostate cancer*	TRUS guidance, 18-G needle, automatic Magnum biopsy gun; TP: fan-technique

(Japan) [Same study as Numao 2012]]	biopsy at urology departments of university hospital or cancer institute hospital **exclusion criteria:** diabetes mellitus, rectal disease, apparently palpable T3/4 tumor, age ≥75 years **Age median (IQR)** 65 (60-71) years **PSA median (IQR)** 6.1 (4.6-8.5) ng/mL **Prostate volume median (IQR)** 35 (27-47) cc **Men with abnormal DRE** 16% **N = 744**		4 anterior + 2 anterolateral + 4 posterior + 2 posterolateral + 2 TZ + **6 MPZ** **+** **6 LPZ** **transrectal** + transperineal	4 anterior + 2 anterolateral + 4 posterior + 2 posterolateral + 2 TZ transperineal	*Detection of GS>6 cancer* **Histological processing, reporting:** cores individually labelled, histological grading according to 2005 International Society of Urologic Pathology Consensus on Gleason Grading Follow-up 100% for cancer detection	**Power calculation:** NR
24-72 vs. 12 cores (posterior+posterolateral**+anterolateral+AAPZ+TZ** vs. posterior+posterolateral)						
Bittner 2013 (USA)	Consecutive men with confirmed elevated age-adjusted PSA for who were self-referred for transperineal template-guided mapping biopsy or receiving anticoagulation **Exclusion criteria**: NR **Age median** 64.6 years **PSA median** 5.2 ng/mL **Prostate volume median** 46.8 cm^3 **Men with abnormal DRE** 0% **N = 191**	SS	**24-72 cores** (1-3 cores per 24 regions) 6-**18** posterior + 6-**18** posterolateral + **6-18 anterolateral** **+** **2-6 AAPZ** **+** **4-12 TZ**	**12 cores** (“theoretically”) 6 posterior + 6 posterolateral	*Detection of prostate cancer* **Histological reporting:** Single pathologist with expertise in urologic pathology Follow-up 100%	**Transperineal** approach (template-guided, stabilising needle) TRUS-guidance with 5.0-7.5 transducer; 18-G, 25 cm long Max-Core needle; operating room setting, dorsal lithotomy position; **Power calculation:** NR

AAPZ = anterior apical peripheral zone; ALH = anterior lateral horn; DRE = digital rectal examination; GS = Gleason score; IQR = interquartile range; LPZ = lateral peripheral zone; MLiPZ = midline peripheral zone; MLPZ = mediolateral peripheral zone; MPZ = mid-lobar peripheral zone; NR = not reported; PSA = prostate specific antigen; RCT = randomized controlled trial; SD = standard deviation; SS = sequential sampling study (comparison of different schemes within same man); TP = transperineal approach; TR = transrectal approach; TRUS = transrectal ultrasound; TZ = transition zone;

Table 7: Sequential sampling studies examining multiple comparisons of biopsy schemes in men undergoing an initial prostate biopsy: study characteristics

Study	Participants	Design	Intervention	Comparison	Outcomes	Comments
Multiple comparisons of schemes						
Moussa 2010 (US/Egypt)	Men with increased PSA and/or abnormal DRE **Exclusion criteria**: NR **Mean age (SD)** 62.3 (7.7) years **Mean PSA (SD)** 5 (5.3) ng/mL **Mean total prostate volume (SD)** 43.3 (22.7) cm^3 **Men with abnormal DRE** 27.1% **Men with positive family history** 20% **N = 181**	SS	**10 vs. 8 cores** **12 vs. 8 cores** **14 vs. 8 cores** **12 vs. 10 cores** **14 vs. 10 cores** **14 vs. 12 cores** 6 MPZ + 2 apical LPZ + **2 midgland LPZ** **+** **2 basal LPZ** **+** **2 extreme AAPZ**		*Detection of prostate cancer* **Histological processing, reporting:** Cores collected in order and placed on wet Telfa dressings, marked by ink for identification; all examined by one pathologist (grades reported and assigned according to Gleason grading system Follow-up 100%	TRUS-guidance, office-based procedure; **Power calculation:** NR
Ficarra 2005 (Italy)	Consecutive patients with PSA 4-20 ng/mL and/or positive DRE **Exclusion criteria:** NR **Mean age (range)** 65.8 (42-85) years **Mean PSA (SD)** 7.6 (6.8) ng/mL **Mean prostate volume (SD)** 41.6 (36.7) cm^3 **Men with positive DRE** 32.7% **N = 480**	SS	**10 vs. 8 cores** **12 vs. 8 cores** **14 vs. 8 cores** **12 vs. 10 cores** **14 vs. 10 cores** **14 vs. 12 cores** 6 MPZ + 2 apical LPZ + **2 midgland LPZ** **+** **2 ALH** **+** **2 anterior TZ**		*Detection of prostate cancer* **Histological processing, reporting:** Cores stretched and placed in cassettes between 2 nylon meshes, cores numbered and identified by site and lobe; cores distributed in couples on labelled tissue cassettes; Separate diagnosis according to Gleason system by two expert uro-pathologists Follow-up 100%	Transperineal approach with single median access 1.5 cm above the anal sphincter; TRUS-guidance with 7.75 Mhz linear probe; 17-G coaxial needle (13cm long); lithotomy position; **Power calculation:** NR

Uno 2008 (Japan)	Men undergoing biopsy at General Hospital or University Graduate School of Medicine due to PSA >4.0 ng/mL and/or abnormal DRE, or PSA 2.5-4.0ng/mL for men <60 years, or PSA velocity >0.75 ng/mL/year **Exclusion criteria**: clinical prostatitis within 1 month of biopsy, active UTI, unable to tolerate procedure **Mean age (range)** 69.9 (45-88) years **Mean PSA (range)** 23.8 (0.477-2,000) ng/mL **Mean prostate volume (range)** 40.4 (7.9-353) mL **N = 313**	SS	**14 vs. 8 cores** **14 vs. 12 cores** 6 MPZ + **6 far LPZ +/ 2 TZ**	*Detection of prostate cancer* **Histological reporting:** One pathologist Follow-up 100%	TRUS guidance, automatic spring-loaded 18-G needle on Magnum Biopsy gun; lithotomy position; **Power calculation:** NR
Ploussard 2012 (France)	Patients underwent 21-core biopsy on the basis of abnormal DRE, PSA >4 ng/mL (if >60 years old >3 ng/mL), %fPSA <10% **Exclusion criteria:** NR **Mean age (SD)** 64.2 (7.8) years **Mean PSA (SD)** 12.5 (72) ng/mL **Mean fPSA (SD)** 16.3 (8.5) % **Mean PSA density (SD)** 0.296 (1.6) ng/mL per gram **Mean prostate volume (SD)** 46.4 (25.3) mL **Men with clinical stage >T1c** 11.6**%** **N = 2753**	SS	**15 vs. 12 cores** **18 vs. 12 cores** **21 vs. 12 cores** **21 vs. 15 cores** **21 vs. 18 cores** 6 MPZ + 6 LPZ + **3 MLiPZ +/ 6 TZ**	*Detection of prostate cancer* *Detection of GS>6 cancer* **Histological processing**, **reporting:** Each core numbered according to biopsy protocol, mapped for location, placed in its own container and analyzed separately by two senior uro-pathologists Follow-up 100%	Transrectal approach; spring-loaded gun able to collect 17mm long tissue cores, 18-G needle; Three experienced urologists performing biopsies **Power calculation:** NR

Patel 2007 (USA)	Consecutive patients with PSA >2.5 ng/mL undergoing biopsy in office-based setting **Mean age (range)** 63 (38-89) years **Mean PSA (range)** 7.3 (2.6-72.6) ng/mL **N = 139**	SS	24 vs. 8 cores 24 vs. 16 cores **8 MPZ (midgland, base) + 16 LPZ**	*Detection of prostate cancer* *Detection of GS>6 cancer* **Histological processing:** Cores "properly" labelled Follow-up 100%	Transrectal approach, spring-loaded biopsy gun; left lateral decubitus position **Power calculation:** NR
Janane 2012 (Morocco) [Abstract only]	Men with PSA <10 ng/mL undergoing biopsy at Military Hospital for Instruction **Exclusion criteria:** NR **N = 79**	**SS**	**18 vs. 12 cores** **24 vs. 12 cores** **24 vs. 18 cores** 6 MPZ cores + 6 posterolateral PZ + **6 TZ** **+** **6 MLiPZ**	*Detection of prostate cancer* **Histological processing:** Each core listed and analysed separately	TRUS-guided

AAPZ = anterior apical peripheral zone; ALH = anterior lateral horn; DRE = digital rectal examination; GS = Gleason score; LPZ = lateral peripheral zone; MLiPZ = midline peripheral zone; MLPZ = mediolateral peripheral zone; MPZ = mid-lobar peripheral zone; NR = not reported; PSA = prostate specific antigen; RCT = randomized controlled trial; SD = standard deviation; SS = sequential sampling study (comparison of different schemes within same man); TP = transperineal approach; TR = transrectal approach; TRUS = transrectal ultrasound; TZ = transition zone; UTI = urinary tract infection;

Table 8: Randomized controlled trials examining biopsies with transperineal vs. transrectal approach in men undergoing an initial prostate biopsy: study characteristics

Study	Participants	Design	Intervention	Comparison	Outcomes	Comments
Alireza 2012 (Iran) [Abstract only]	Indications included PSA >4 ng/mL **N = 390**	RCT	**12 cores** **Transperineal** N = 195	**12 cores** **Transrectal** N = 195	*Detection of prostate cancer* **Histological processing, reporting:** NR Follow-up 100%	TRUS guidance **Power calculation:** NR
Hara 2008 (Japan)	Men with PSA between 4.0 and 20.0 ng/mL underwent biopsy after evaluation with DRE and TRUS **Exclusion criteria:** previous history of prostate cancer, clinical evidence of prostatitis **Mean age (SD)** TP: 71.0 (7.29) years TR: 71.7 (7.55) years **Mean PSA (SD)** TP: 8.34 (3.44) ng/mL TR: 8.48 (3.90) ng/mL **Mean prostate volume (SD)** TP: 33.2 (15.2) cc TR: 36.0 (17.1) cc **Men with abnormal DRE (n)** TP: 14 TR: 22 **Men with abnormal TRUS (n)** TP: 23 TR: 12 **N = 246**	RCT	**12 cores** 2 MPZ + 2 LPZ + 2 far LPZ + 2 apical PZ + 4 TZ (anterior, posterior) **Transperineal** Spinal anaesthesia with 0.5% bupivacaine 5-7.5 Mhz linear probe N = 126	**12 cores** 2 MPZ + 2 basal PZ + 2 far LPZ + 2 apical PZ + 4 TZ (midgland, base) **Transrectal** Caudal block with 1% lidocaine 5.0 Mhz convex probe N = 120	*Detection of prostate cancer* *Adverse events* **Histological processing, reporting:** NR Patients asked about complications occurring after the procedure 1-2 weeks after Follow-up: 100% (cancer detection) 99.6% (complications)	TRUS guidance (SSD-2000), 18-G Tru-Cut needle with 22mm cutting length, lithotomy position **Antibiotic protocol:** 200 mg levofloxacin PO on the day of biopsy **Anaesthetic protocol:** TP patients: perineum disinfected with 10% povidone iodine immediately before procedure; Foley catheter left in situ over night; Discontinued anticoagulants for ≥7 days, enema on the morning of biopsy; **Power calculation:** NR
Takenaka 2008 (Japan) [May overlap with Hara 2008]	Men with PSA >4 ng/mL and/or abnormal findings on DRE or TRUS; **Exclusion criteria:** NR **Mean age (SD)** TP: 71.1 (7.53) years TR: 72.1 (7.42) years **Mean PSA (SD)** TP: 17.1 (30.1) ng/mL	RCT	**12 cores** 6 PZ + 4 TZ + 2 apical PZ	**12 cores** 6 PZ + 4 TZ + 2 apical PZ	*Detection of prostate cancer* *Adverse events* **Histological processing, reporting:** NR	**Preoperative preparation:** 300 mg levofloxacin for 1 day, enema on morning of biopsy; TRUS guidance, lithotomy position, 18-G Monopty needle **Power calculation:** NR

TR: 19.6 (43.2) ng/mL **Mean prostate volume (SD)** TP: 34.5 (18.9) mL TR: 37.2 (19.7) mL **Men with abnormal DRE (%)** TP: 16 TR: 28 **Men with abnormal TRUS (%)** TP: 28 TR: 22 **N = 200**			Follow-up 100% for cancer detection, NR for complications
	Transperineal	**Transrectal**	
	Saddle blockade with 0.5% bupivacaine	Caudal blockade with 1% lidocaine	
	7.5 Mhz linear probe	5 Mhz radial probe with needle guidance attachment	
	N = 100	N = 100	

DRE = digital rectal examination; LPZ = lateral peripheral zone; MPZ = mid-lobar peripheral zone; NR = not reported; PSA = prostate specific antigen; RCT = randomized controlled trial; SD = standard deviation; TP = transperineal approach; TR = transrectal approach; TRUS = transrectal ultrasound; TZ = transition zone

2.4 Study Quality

Methodological quality of included systematic review/meta-analysis is described in Tables 9 and 10.

Methodological quality of included randomised controlled trials is described in Tables 11 and 12.

Methodological quality of included sequential sampling studies is described in Tables 13 and 14.

Table 9: Methodological quality of included **systematic review/meta-analysis** (n = 1)

Quality Category	N (%)
Ia. Was an adequate search strategy used?	
2 - Very thorough	1 (100)
1 - Adequate	-
0 - No, not described	-
Ib. Were the inclusion criteria appropriate and applied in an unbiased way?	
2 - Yes (e.g. pre-specified inclusion criteria applied independently by two people	1 (100)
1 - Adequate – pre-specific inclusion criteria applied by one person	-
0 - No – inclusion decided in an arbitrary fashion, not described	-
II. Were the studies assessed for quality?	
2 - Yes (e.g. appropriate assessment, independently by two people)	1 (100)
1 - Adequate (e.g. problems with quality issues, assessed by one person only)	-
0 - No (e.g. inappropriate, no quality assessment undertaken, not described)	-
III. Were the characteristics and results of individual studies appropriate described?	
2 - Yes (e.g. summary descriptive tables, estimates of treatment effects)	1 (100)
1 - Adequate (e.g. more information desirable)	-
0 - No	-
IV. Were the methods used for pooling the data appropriate?	
2 - Yes	1 (100)
0 - No	-
V. If there was heterogeneity, were sources of heterogeneity explored?	
2 - Yes	1 (100)
1 - Some attempt was made	-
0 - No	-
N/A – no heterogeneity	-

Table 10: Methodological quality of included **systematic review/meta-analysis** (n = 1)

	Search strategy	Inclusion criteria	Quality assessments	Study characteristics	Methods for pooling data	Heterogeneity	**Quality**	**Risk of bias**
Eichler 2006	2	2	2	2	2	2	**High**	**Low**

Key to overall quality rating
High quality: a systematic review/meta-analysis that received 2 for each criterion
Medium quality: received 2 and/or 1 for all criteria
Low quality: received 0 for any of the criteria

Questions 4 and 5 are relevant only to meta-analyses

Table 11: Methodological quality of included **randomized controlled trials examining adverse events** (n = 8)

Quality Category	N (%)
I. Was the study double-blinded?	
2 - Reasonably certain double-blind (e.g. identical placebo)	0 (0.0)
1 - Single-blind, objective outcomes	0 (0.0)
0 - Not blinded, not reported	8 (100)
II. Concealment of treatment allocation schedule	
2 - Adequately concealed (e.g. central randomisation)	0 (0.0)
1 - Inadequately concealed (e.g. sealed envelopes)	1 (12.5)
0 - No concealment, not reported	7 (87.5)
III. Inclusion of all randomized participants in analysis of majority of outcomes (i.e. ITT)	
2 - No exclusions, or survival analysis used	5 (62.5)
1 - Exclusions not likely to cause bias	0 (0.0)
0 - Too many exclusions, not reported	3 (37.5)
IV. Generation of allocation sequences	
1 - Adequate (e.g. computer random number generator)	2 (25.0)
0 - Inadequate, not reported	6 (75.0)

ITT = intention-to-treat analysis

Table 12: Methodological quality of included **randomized controlled trials examining adverse events** (n = 8)

	Blinding	Allocation concealment	Inclusion of all participants (ITT)	Generation of allocation sequence*	**Overall rating**	**Risk of bias**
Hara 2008	0	0	2	0	**Low**	**High**
Irani 2013	0	0	2	1	**Low**	**High**
Lecuona 2011	0	0	2	1	**Low**	**High**
Mariappan 2004	0	0	0	0	**Low**	**High**
Park 2010	0	0	2	0	**Low**	**High**
Rodriguez-Covarrubias 2011	0	1	2	0	**Low**	**High**
Sur 2004	0	0	0	0	**Low**	**High**
Takenaka 2008	0	0	0	0	**Low**	**High**

*Ratings for outcome adverse events * not considered when calculating the overall evidence quality rating;*
ITT = intention-to-treat

Key to overall quality rating
High quality: a study that received 2 for three main criteria (double-blinding, concealment of treatment allocation schedule, Inclusion of all randomised participants in analysis (i.e. ITT))
Medium quality: received 2 and/or 1 for all three main criteria
Low quality: received 0 for any of the three criteria

Table 13: Risk of bias of included **sequential sampling studies and randomized controlled trials comparing cancer detection rates** (n = 22)

Quality Category	N (%)*
I. Selection of participants (no case-control design, consecutive sample, exclusions appropriate)	
Low risk of bias	3 (13.6)
High risk of bias	7 (31.8)
Unclear risk of bias	12 (54.5)
II. Index tests (blinding, independent assessment of both tests)	
Low risk of bias	0 (0.0)
High risk of bias	6 (27.3)
Unclear risk of bias	16 (72.7)
III. Flow and timing (inclusion of all patients in analysis)	
Low risk of bias	19 (86.4)
High risk of bias	1 (4.5)
Unclear risk of bias	2 (9.1)

*Selected items from QUADAS-2 based on systematic review Eichler 2006 * where a study has comparisons in both the same men (sequential sampling) and men assigned to different protocols, quality rating based on results for sequential sampling*

Table 14: Risk of bias of included **sequential sampling studies and RCT examining cancer detection rate** (n = 22)

	Selection of participants	Index tests	Flow and timing*	**Overall risk of bias**	**Quality rating**
Alireza 2012	High	Unclear	Low	**High**	**Low**
Bittner 2013	Unclear	High	Low	**High**	**Low**
Dai 2008	Unclear	High	Low	**High**	**Low**
Ficarra 2005	Low	High	Low	**Moderate**	**Medium**
Hara 2008	High	Unclear	Low	**High**	**Low**
Irani 2013	High	Unclear	Low	**High**	**Low**
Janane 2012	Unclear	Unclear	Unclear	**High**	**Low**
Lecuona 2011	High	Unclear	Low	**High**	**Low**
Mariappan 2004	High	Unclear	Low	**High**	**Low**
Miyake 2005	Unclear	Unclear	Low	**High**	**Low**
Moussa 2010	Unclear	Unclear	Low	**High**	**Low**
Numao 2012	Low	Unclear	Low	**Moderate**	**Medium**
Orikasa 2008	Unclear	Unclear	Low	**High**	**Low**
Park 2010	Unclear[a]	High[a]	Low[a]	**High**[a]	**Low**[a]
	High[b]	High[b]	Low[b]	**High**[b]	**Low**[b]
Patel 2007	Unclear	Unclear	Low	**High**	**Low**
Ploussard 2012	Unclear	Unclear	Low	**High**	**Low**
Rochester 2009	Unclear[c]	Unclear[c]	Low[c]	**High**[c]	**Low**[c]
	High[d]	Unclear[d]	Low[d]	**High**[d]	**Low**[d]

Roderiguez-Covarrubias 2011	Unclear[a]	High[a]	Low[a]	**High**[a]	**Low**[a]
	High[b]	High[b]	Low[b]	**High**[b]	**Low**[b]
Sur 2004	High	Unclear	High	**High**	**Low**
Takenaka 2008	High	Unclear	Low	**High**	**Low**
Takeshita 2013	Low	Unclear	Low	**Moderate**	**Medium**
Uno 2008	Unclear	Unclear	Low	**High**	**Low**

*RCT = randomised controlled trial; * Pre-specified criterion for low risk of bias was equal to or greater than 95% patients included in the analysis*

[a] Comparison for men who underwent both 12- and 18-core biopsy (sequential sampling)

[b] Comparison for men randomized to either 12- or 18-core biopsy

[c] Comparison for men who underwent both 12- and 15-core biopsy (sequential sampling)

[d] Comparison for men randomized to either 12- or 15-core biopsy

[e] Comparison for men who underwent both 12- and 18-core biopsy (sequential sampling)

[f] Comparison for men randomized to either 12- or 18-core biopsy

Key to overall risk of bias rating

Low risk of bias: a study that received "low" for all three criteria

Moderate risk of bias: received "low" for selection of participants and flow and timing criteria, and "high" or "unclear" for index tests criterion

High risk of bias: received "high" or "unclear" for selection of participants and/or flow and timing (and index tests) criteria

This is a modification of the QUADAS rating

Low risk of bias: A study rated at low risk of bias for all domains

At risk of bias: A study rated at high or unclear risk of bias for one or more domains

Using these QUADAS ratings, all studies would have been rated "at risk of bias". To distinguish those at greater risk of bais, the QUADAS rating was modified to include a moderate and high risk of bias rather than "at risk of bias".

2.5 Study Results

I DETECTION OF PROSTATE CANCER

1. Extended vs. standard scheme

- Comparison scheme 6 cores mixed/repeat biopsy population (Table 15)
- Comparison scheme 6 cores initial biopsy population (Table 16)
- Comparison scheme 8 cores initial biopsy population (Table 17)
- Comparison scheme 6/8 cores – nomograms initial biopsy population (Table 18)
- Comparison scheme 10 cores initial biopsy population (Table 19)
- Comparison scheme 6-12 cores initial biopsy population (Table 20)
- Comparison scheme 12/14 cores initial biopsy population (Table 21)
- Comparison scheme ≥15 cores initial biopsy population (Table 22)

2. Transperineal vs. transrectal approach initial biopsy population (Table 23)

II DETECTION OF GLEASON SCORE ≥6 CANCER

1. Extended vs. standard scheme

- Comparison scheme 8 cores initial biopsy population (Table 24)
- Comparison scheme 6-12 cores initial biopsy population (Table 25)
- Comparison scheme 12/14 cores initial biopsy population (Table 26)
- Comparison scheme 16 cores initial biopsy population (Table 27)

III ADVERSE EVENTS

1. Extended vs. standard scheme

- Comparison scheme 6 cores mixed/unclear biopsy population (Table 28)
- Comparison scheme 10 cores unclear biopsy population (Table 29)
- Comparison scheme 6 cores initial biopsy population (Table 30)
- Comparison scheme 6/8 cores – nomograms initial biopsy population (Table 31)
- Comparison scheme 6-12 cores initial biopsy population (Table 32)
- Comparison scheme 12 cores initial biopsy population (Table 33)

2. Transperineal vs. transrectal approach initial biopsy population (Table 34)

I DETECTION OF PROSTATE CANCER

Table 15. Results of sequential sampling studies examining effects of extended vs. 6-core biopsy schemes on prostate cancer detection (mixed/repeat biopsy population)

Study	Outcome Definition	Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value
8 vs. 6 cores (MPZ**+LPZ** vs. MPZ)								
Eichler 2006 (7 SS, mixed population)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	2,437#	NR	NR	RPR = 1.19	1.14 – 1.24	NR
8 vs. 6 cores (MPZ**+TZ(+MLiPZ)** vs. MPZ)								
Eichler 2006 (16 SS, mixed population)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	5,013#	NR	NR	RPR = 1.04***	1.02 – 1.06	NR
10 vs. 6 cores (**MPZ** vs. MPZ)								
Eichler 2006 (2 SS, repeat population)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	254	NR	NR	RPR = 1.09	1.03 – 1.16	NR
10 vs. 6 cores (MPZ**+LPZ** vs. MPZ)								
Eichler 2006 (13 SS, mixed population)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	3,155#	NR	NR	RPR = 1.25***	1.19 – 1.33	NR
10/11 vs. 6 cores (MPZ**+TZ(+MLiPZ)** vs. MPZ)								
Eichler 2006 (4 SS, mixed population)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	955#	NR	NR	RPR = 1.13***	1.04 – 1.24	NR
10/11 vs. 6 cores (MPZ**+LPZ+TZ(+MLiPZ)** vs. MPZ)								
Eichler 2006 (3 SS, repeat population)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	963#	NR	NR	RPR = 1.38***	1.08 – 1.76	NR

12 vs. 6 cores (MPZ**+LPZ** vs. MPZ)								
Eichler 2006 (13 SS, mixed population)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	2178[#]	NR	NR	RPR = 1.31	1.25 – 1.37	NR
12 vs. 6 cores (MPZ**+TZ** vs. MPZ)								
Eichler 2006 (3 SS, repeat population)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	512[#]	NR	NR	RPR = 1.23	1.11 – 1.36	NR
12/13 vs. 6 cores (MPZ**+LPZ+TZ(+MLiPZ)** vs. MPZ)								
Eichler 2006 (8 SS, repeat population)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	2,111[#]	NR	NR	RPR = 1.21***	1.13 – 1.30	NR
14 vs. 6 cores (MPZ**+LPZ+TZ** vs. MPZ)								
Eichler 2006 (2 SS, mixed population)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	342[#]	NR	NR	RPR = 1.33	1.15 – 1.54	NR
18-22 vs. 6 cores (MPZ**+LPZ+TZ** vs. MPZ)								
Eichler 2006 (3 SS, repeat population[a])	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	657[#]	NR	NR	RPR = 1.48	1.32 – 1.66	NR

LPZ = lateral peripheral zone; MLiPZ = midline peripheral zone; MPZ = mid-lobar peripheral zone; NR = not reported; RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy/men diagnosed out of men undergoing comparison biopsy); SS = sequential sampling study (comparison of different schemes within same man); TZ = transition zone

** Calculated by reviewers; ** Includes negative values – set to 0 as not applicable for sequential sampling study design; *** Significant heterogeneity; [#] Combined number of participants from included studies;*

[a] Three studies included the comparisons of TR 21 cores vs. TR 6 cores, TR+TP 22 cores vs. TR 6 cores, and TR + TP 8-20 cores (age- and volume-adjusted) vs. TR+TP 6 cores

Table 16. Results of sequential sampling studies examining effects of extended vs. 6-core biopsy schemes on prostate cancer detection (initial biopsy population)

Study	Outcome Definition	Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	P value
8 vs. 6 cores (MPZ**+TZ(+MLiPZ)** vs. MPZ)								
Eichler 2006 (2 SS)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	435[#]	NR	NR	RPR = 1.01	0.99 –1.03	NR
12 vs. 6 cores (MPZ**+TZ** vs. MPZ)								
Dai 2008	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	221	40.7 (90)	38.0* (84)	RD = 2.7%* RPR = 1.07*	1.2 – 5.3* [c] 1.01 – 1.13*	0.031[c]
	Subgroup PSA 0-10 ng/mL	% (n)	99	6.1 (6)	3.0 (3)	RD = 3.0%* RPR = 2.00*	0.0** – 7.4* [c] 0.90 – 4.45* [c]	<0.001[a]
	Subgroup PSA 10.1-20 ng/mL	% (n)	36	22.2 (8)	16.7 (6)	RD = 5.6%* RPR = 1.33*	0.0** – 15.8* [c] 0.89 - 1.99* [c]	NR
	Subgroup PSA 20.1-50 ng/mL	% (n)	23	69.6 (16)	65.2 (15)	RD = 4.3%* RPR = 1.07*	0.0** – 17.0* [c] 0.94 – 1.21* [c]	NR
	Subgroup PSA 50.1-100 ng/mL	% (n)	29	89.7 (26)	89.7 (26)	RD = 0* RPR = 1.00*	0.0** – 3.4* [c] 1.00 – 1.00* [c]	NR
	Subgroup PSA >100 ng/mL	% (n)	34	100 (34)	100 (34)	RD = 0* RPR = 1.00*	0.0** – 2.9* [c] 1.00 – 1.00* [c]	NR

MLiPZ = midline peripheral zone; MPZ = mid-lobar peripheral zone; RCT = randomized controlled trial; RD = risk difference (men diagnosed out of men undergoing intervention biopsy – men diagnosed out of men undergoing comparison biopsy); RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy/men diagnosed out of men undergoing comparison biopsy); SS = sequential sampling study (comparison of different schemes within same man); TZ = transition zone

** Calculated by reviewers; ** Includes negative values – set to 0 as not applicable for sequential sampling study design;*

[a] *Chi-square test;*

[b] *Fisher's exact test*

[c] *McNemar's test*

Table 17. Results of sequential sampling studies examining effects of extended vs. 8-core biopsy schemes on prostate cancer detection (initial biopsy population)

Study	Outcome Definition	Outcome Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value
10 vs. 8 cores (MPZ+apical**+midgland LPZ** vs. MPZ+apical LPZ)								
Moussa 2010	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	181	42.0 (76*)	42.0 (76*)	RD = 0.0* RPR = 1.00*	0.0** – 0.6* [c] 1.00 – 1.00* [c]	1.000
10 vs. 8 cores (MPZ+apical**+midgland LPZ** vs. MPZ+apical LPZ)								
Ficarra 2005	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	480	40.8 (196)	38.8 (186)	RD = 2.1%* RPR = 1.05*	0.0** – 3.6* [c] 1.02 – 1.09* [c]	NR
	Subgroup: prostate volume ≤30 ml	% (n)	159	58.5 (93)	57.2 (91)	RD = 1.3%* RPR = 1.02*	0.0** – 3.6* [c] 1.00 – 1.05* [c]	NR
	Subgroup: prostate volume 30.1-50 ml	% (n)	197	39.1 (77)	37.1 (73)	RD = 2.0%* RPR = 1.05*	0.0** – 4.5* [c] 1.00 – 1.11* [c]	NR
	Subgroup: prostate volume >50 ml	% (n)	124	21.0 (26)	17.7 (22)	RD = 3.2%* RPR = 1.18*	0.0** – 7.1* [c] 1.00 – 1.39* [c]	NR
10 vs. 8 cores (PZ+ALH**+TZ** vs. PZ+ALH)								
Miyake 2005	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	788	26.5 (209)	25.1* (198*)	RD = 1.4%* RPR = 1.06*	0.4 – 2.3* [c] 1.02 – 1.09* [c]	NR
	Subgroup: prostate volume <30 ml	% (n)	315	37.8* (119)	35.9* (113)	RD = 1.9%* RPR =1.05*	0.1 – 3.7* [c] 1.01 – 1.10* [c]	NR
	Subgroup: prostate volume 30-49.9 ml	% (n)	351	19.4* (68)	18.2* (64)	RD = 1.1* RPR = 1.06*	0.0** – 2.5* [c] 1.00 - 1.13* [c]	NR
	Subgroup: prostate volume ≥50 ml	% (n)	122	18.0* (22)	17.2* (21)	RD = 0.8%* RPR = 1.05*	0.0** – 3.2* [c] 0.96 – 1.15* [c]	NR
	Subgroup: PSA <4 ng/ml	% (n)	193	11.4* (22)	10.8* (21)	RD = 0.5%* RPR = 1.05	0.0** – 2.0* [c] 0.96 – 1.15* [c]	NR

	Subgroup: PSA 4-9.9 ng/ml	% (n)	413	25.0* (103)	24.5* (101)	RD = 0.5%* RPR = 1.02*	0.0** – 1.4* [c] 0.99 – 1.05* [c]	NR
	Subgroup: PSA ≥10 ng/ml	% (n)	182	46.2* (84)	41.8* (76)	RD = 4.4%* RPR = 1.11*	0.1 – 7.9* [c] 1.03 – 1.18* [c]	NR
12 vs. 8 cores (MPZ+apical**+midgland LPZ+ALH** vs. MPZ+apical LPZ)								
Ficarra 2005	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	480	42.1 (202)	38.8 (186)	RD = 3.3%* RPR = 1.09*	1.5 – 5.1* [c] 1.04 – 1.13* [c]	NR
	Subgroup: prostate volume ≤30 ml	% (n)	159	59.1 (94)	57.2 (91)	RD = 1.9%* RPR = 1.03*	0.0** – 4.6* [c] 1.00 – 1.07* [c]	NR
	Subgroup: prostate volume 30.1-50 ml	% (n)	197	40.6 (80)	37.1 (73)	RD = 3.6%* RPR = 1.10*	0.4 – 6.6* [c] 1.02 – 1.17* [c]	NR
	Subgroup: prostate volume >50 ml	% (n)	124	22.6 (28)	17.7 (22)	RD = 4.8%* RPR = 1.27*	0.3 – 9.4* [c] 1.05 – 1.54* [c]	NR
12 vs. 8 cores (**MPZ+LPZ** vs. MPZ+LPZ)								
Moussa 2010	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	181	44.2 (80*)	42.0 (76*)	RD = 2.2%* RPR = 1.05*	0.0** – 4.9* [c] 1.00 – 1.11* [c]	NR
14 vs. 8 cores (**MPZ+LPZ+extreme AAPZ** vs. MPZ+LPZ)								
Moussa 2010	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	181	47.5 (86*)	42. 0 (76*)	RD = 5.5%* RPR = 1.13*	1.6 – 9.4* [c] 1.05 – 1.22* [c]	NR
14 vs. 8 cores (far LPZ+TZ+**MPZ** vs. far LPZ+TZ)								
Uno 2008	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	313	40.6 (127)	32.3* (111*)	RD = 5.1%* RPR = 1.14*	2.3 – 7.9* [c] 1.08 – 1.22* [c]	NR
	Subgroup: PSA ≤4 ng/ml	% (n)	29	17.2 (5)	17.2 (5*)	RD = 0.0* RPR = 1.00	0.0** – 0.3* [c] 1.00 – 1.00* [c]	NR
	Subgroup: PSA 4.01-10 ng/ml	% (n)	181	30.4 (55)	24.9* (45*)	RD = 5.5%* RPR = 1.22*	1.6 – 9.4* [c] 1.08 – 1.38* [c]	NR

	Subgroup: PSA 10.01-20 ng/ml	% (n)	57	50.9 (29)	49.1* (28*)	RD = 1.8%* RPR = 1.04*	0.0** – 6.9* [c] 0.97 – 1.11* [c]	NR
	Subgroup: PSA >20 ng/ml	% (n)	46	82.6 (38)	71.8* (33*)	RD = 10.9%* RPR = 1.15*	0.0** – 22.0* [c] 1.02 – 1.30* [c]	NR
14 vs. 8 cores (MPZ+TZ**+far LPZ** vs. MPZ+TZ)								
Uno 2008	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	313	40.6 (127)	30.9* (103*)	RD = 7.7%* RPR = 1.23*	4.4 – 10.9* [c] 1.13 – 1.34* [c]	NR
	Subgroup: PSA ≤4 ng/ml	% (n)	29	17.2 (5)	13.8* (4*)	RD = 3.4%* RPR = 1.25*	0.0** – 13.5* [c] 0.80 – 1.94* [c]	NR
	Subgroup: PSA 4.01-10 ng/ml	% (n)	181	30.4 (55)	20.4* (37*)	RD = 9.9%* RPR = 1.49*	5.0 – 14.9* [c] 1.24 – 1.79* [c]	NR
	Subgroup: PSA 10.01-20 ng/ml	% (n)	57	50.9 (29)	45.6* (26*)	RD = 5.3%* RPR = 1.12*	0.0** – 12.8* [c] 0.99 – 1.26* [c]	NR
	Subgroup: PSA >20 ng/ml	% (n)	46	82.6 (38)	78.3* (36*)	RD = 4.3%* RPR = 1.06*	0.0** – 12.4* [c] 0.98 – 1.14* [c]	
14 vs. 8 cores (MPZ+apical+midgland LPZ**+ALH+anterior TZ** vs. MPZ+apical LPZ)								
Ficarra 2005	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	480	43.8 (210)	38.8 (186)	RD = 5.0%* RPR = 1.13*	2.8 – 7.1* [c] 1.08 – 1.19* [c]	NR
	Subgroup: prostate volume ≤30 ml	% (n)	159	60.4 (96)	57.2 (91)	RD = 3.1%* RPR = 1.05*	0.0** – 6.5* [c] 1.01 – 1.11* [c]	0.06 [c]
	Subgroup: prostate volume 30.1-50 ml	% (n)	197	42.6 (84)	37.1 (73)	RD = 5.6%* RPR = 1.15*	1.9 – 9.3* [c] 1.06 – 1.25* [c]	0.001 [c]
	Subgroup: prostate volume >50 ml	% (n)	124	24.2 (30)	17.7 (22)	RD = 6.5%* RPR = 1.36*	1.3 – 11.6* [c] 1.10 – 1.69* [c]	NR
24 vs. 8 cores (MPZ**+LPZ** vs. MPZ)								

Patel 2007	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	139	44.6 (62)	28.8* (40*)	RD = 15.8% RPR = 1.55*	9.0 – 22.6* [c] 1.29 – 1.86* [c]	NR

AAPZ = anterior apical peripheral zone; ALH = anterior lateral horn; LPZ = lateral peripheral zone; MLiPZ = midline peripheral zone; MLPZ = mediolateral peripheral zone; MPZ = mid-lobar peripheral zone; NR = not reported; PSA = prostate specific antigen; RD = risk difference (men diagnosed out of men undergoing intervention biopsy – men diagnosed out of men undergoing comparison biopsy); RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy/men diagnosed out of men undergoing comparison biopsy); TZ = transition zone

** calculated by reviewers; ** includes negative values – set to 0 as not applicable for sequential sampling study design*

[a] *Chi-square test*

[b] *Fisher's exact test*

[c] *McNemar's test*

[d] *Regression analysis*

[e] *Rank sum test*

Table 18. Results of randomized controlled trials examining effects of volume-dependant vs. 6/8-core biopsy schemes on prostate cancer detection (initial biopsy population)

Study	Outcome Definition	Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value
Volume-dependant number of cores vs. 6 cores (8-14 LPZ**+MPZ+fLPZ** vs. LPZ)								
Mariappan 2004	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	132	30.2* (19) N = 63	18.8* (13) N = 69 [f]	RD = 11.3%* RPR = 1.60*	-3.3 – 25.9* [b] 0.86 – 2.97* [b] 1.03 – 10.23	0.130* [b] 0.023 [b]
	Subgroup: prostate volume >20 ml	% (n)	123	30.2* (19) N = 63	16.7* (10) N = 60	RD = 13.5%* RPR = 1.81*	-1.3 – 28.2* [b] 0.92 – 3.57* [b] 1.55 – 18.35[b]	0.078* [b] 0.036 [b]
	Subgroup: prostate volume 20-40 ml	% (n)	42	36.4* (8) N = 22	20.0 (4) N = 20	RD = 16.4%* RPR = 1.82*	-10.3 – 43.0* [b] 0.65 – 5.12* [b]	0.241* [b] /0.34 [b]
	Subgroup: prostate volume >40 ml	% (n)	81	26.8* (11) N = 41	15.0 (6) N = 40	RD = 11.8%* RPR = 1.79*	-5.7 – 29.3* [b] 0.73 – 4.37* [b]	0.19[b]
Volume-, age-dependant number of cores vs. 8 cores (6-18 **LPZ** vs. LPZ)								
Lecuona 2011	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	303	35.5 (54) N = 152	38.4 (58) N = 151	RD = -2.9%* RPR = 0.92*	-13.8 – 8.0* [b] 0.69 – 1.24* [b]	0.603* [b] /0.6351[b]
	Subgroup: prostate volume >50 ml	% (n)	112	22.0 (11) N = 50	25.8 (16) N = 62	RD = -3.8%* RPR = 0.85*	-19.6 – 12.0* [b] 0.44 – 1.67* [b]	0.640* [b] /0.6642[b]
	Subgroup: PSA <10 ng/ml	% (n)	226	28.1 (32) N = 114	33.0 (37) N = 112	RD = -5.0%* RPR = 0.85*	-17.0 – 7.0* [b] 0.57 – 1.26* [b]	0.418* [b] /0.4710[b]

fIPZ = far lateral periphearal zone; LPZ = lateral peripheral zone; MPZ = mid-lobar peripheral zone; NR = not reported; PSA = prostate specific antigen; RD = risk difference (men diagnosed out of men undergoing intervention biopsy – men diagnosed out of men undergoing comparison biopsy); RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy/men diagnosed out of men undergoing comparison biopsy)

** Calculated by reviewers*

[a] Chi-square test

[b] Fisher's exact test

[c] McNemar's test

[d] Regression analysis

[e] Rank sum test

[f] Nine of these men had prostate volumes <20 ml and had sextant biopsies

Table 19. Results of sequential sampling studies examining effects of extended vs. 10-core biopsy schemes on prostate cancer detection (initial biopsy population)

Study	Outcome Definition	Outcome Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value
12 vs. 10 cores (MPZ+LPZ**+extreme AAPZ** vs. MPZ+LPZ)								
Moussa 2010	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	181	44.2 (80*)	42.0 (76*)	RD = 2.2%* RPR = 1.05*	0.0** – 4.9* [c] 1.00 – 1.10* [c]	0.167
12 vs. 10 cores (MPZ+LPZ**+AAPZ** vs. MPZ+LPZ)								
Orikasa 2008	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	549	45.9 (252)	43.5 (239)	RD = 2.4%* RPR = 1.05*	0.1 – 3.8* [c] 1.02 – 1.09* [c]	NR
12 vs. 10 cores (MPZ+apical+midgland LPZ**+ALH** vs. MPZ+apical+midgland LPZ)								
Ficarra 2005	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	480	42.1 (202)	40.8 (196)	RD = 1.3%* RPR = 1.03*	0.0** – 2.4* [c] 1.01 – 1.06* [c]	NR
	Subgroup: prostate volume ≤30 ml	% (n)	159	59.1 (94)	58.5 (93)	RD = 0.6%* RPR = 1.01*	0.0** – 2.5* [c] 0.99 – 1.03* [c]	NR
	Subgroup: prostate volume 30.1-50 ml	% (n)	197	40.6 (80)	39.1 (77)	RD = 1.5%* RPR = 1.04*	0.0** – 3.7* [c] 0.99 – 1.08* [c]	NR
	Subgroup: prostate volume >50 ml	% (n)	124	22.6 (28)	21.0 (26)	RD = 1.6%* RPR = 1.08*	0. 0** – 4.6* [c] 0.97 – 1.19* [c]	NR
14 vs. 10 cores (MPZ+apical+midgland LPZ**+ALH+TZ** vs. MPZ+apical+midgland LPZ)								
Ficarra 2005	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	480	43.8 (210)	40.8 (196)	RD = 2.9%* RPR = 1.07*	1.2 – 4.6* [c] 1.03 – 1.11* [c]	NR
	Subgroup: prostate volume ≤30 ml	% (n)	159	60.4 (96)	58.5 (93)	RD = 1.9%* RPR = 1.03*	0.0** – 4.6* [c] 1.00 – 1.07* [c]	0.25 [c]
	Subgroup: prostate volume 30.1-50 ml	% (n)	197	42.6 (84)	39.1 (77)	RD = 3.6%* RPR = 1.09*	0.5 – 6.6* [c] 1.02 – 1.16* [c]	0.01 [c]

	Subgroup: prostate volume >50 ml	% (n)	124	24.2 (30)	21.0 (26)	RD = 3.2%* RPR = 1.15*	0.0** – 7.1* [c] 1.00 – 1.33* [c]	NR
14 vs. 10 cores (**MPZ+LPZ+extreme AAPZ** vs. MPZ+LPZ)								
Moussa 2010	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	181	47.5 (86*)	42.0 (76*)	RD = 5.5%* RPR = 1.13*	1.6 – 9.4* [c] 1.05 – 1.22* [c]	NR

AAPZ = anterior apical peripheral zone; ALH = anterior lateral horn; LPZ = lateral peripheral zone; MLiPZ = midline peripheral zone; MLPZ = mediolateral peripheral zone; MPZ = mid-lobar peripheral zone; NR = not reported; RD = risk difference (men diagnosed out of men undergoing intervention biopsy – men diagnosed out of men undergoing comparison biopsy); RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy/men diagnosed out of men undergoing comparison biopsy); TZ = transition zone

** Calculated by reviewers;*

*** Includes negative values – set to 0 as not applicable for sequential sampling study design*

[a] *Chi-square test*

[b] *Fisher's exact test*

[c] *McNemar's test*

[d] *Regression analysis*

[e] *Rank sum test*

Table 20. Results of randomized controlled trial examining effects of extended vs. 6-12 core biopsy schemes on prostate cancer detection (initial biopsy population)

Study	Outcome Definition	Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value
24 vs. 6-12 cores (MPZ**+LPZ+TZ+MLiPZ** vs. MPZ(+LPZ))								
Sur 2004	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	182	41.5 (39) N = 94	38.6 (34) N = 88	RD = 2.9%* RPR = 1.07*	-11.4 – 17.1* [b] 0.75 – 1.53* [b]	0.692[a]
	Subgroup: prostate volume ≥40 g	% (n)	64	33.3 (13) N = 39	40.0 (10) N = 25	RD = -6.7%* RPR = 0.83*	-30.9 – 17.6* [b] 0.433 – 1.60* [b]	0.588 [a]
	Subgroup: prostate volume <40 g	% (n)	118	47.3 (26) N = 55	38.1 (24) N = 63	RD = 9.1%* RPR = 1.24*	-8.7 – 27.0* [b] 0.81 – 1.89* [b]	0.314 [a]
	Subgroup: PSA ≥10 ng/ml	% (n)	26	85.7 (12) N = 14	66.7 (8) N = 12	RD = 19.0%* RPR = 1.29*	-13.3 – 51.4* [b] 0.82 – 2.02* [b]	0.250 [a]
	Subgroup: PSA <10 ng/ml	% (n)	156	33.8 (27) N = 80	34.2* (26) N = 76	RD = -0.5%* RPR = 0.99*	-15.3 – 14.4* [b] 0.64 – 1.53* [b]	0.952[a]

LPZ = lateral peripheral zone; MLiPZ = midline peripheral zone; MPZ = mid-lobar peripheral zone; NR = not reported; PSA = prostate specific antigen; RD = risk difference (men diagnosed out of men undergoing intervention biopsy – men diagnosed out of men undergoing comparison biopsy); RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy/men diagnosed out of men undergoing comparison biopsy); TZ = transition zone;
** Calculated by reviewers*
[a] *Chi-square test*
[b] *Fisher's exact test*
[c] *McNemar's test*
[d] *Regression analysis*
[e] *Rank sum test*

Table 21. Results of studies examining effects of extended vs. 12/14 core biopsy schemes on prostate cancer detection (initial biopsy population)

Study	Outcome Definition	Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value
14 vs. 12 cores (MPZ+LPZ**+extreme AAPZ** vs. MPZ+LPZ)								
Moussa 2010 (SS)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	181	47.5 (86)	44.2 (80*)	RD = 3.3%* RPR = 1.08*	0.1 – 6.5* [c] 1.01 – 1.14* [c]	0.046

14 vs. 12 cores (MPZ+apical+midgland LPZ+ALH**+anterior TZ** vs. MPZ+apical+midgland LPZ+ALH)								
Ficarra 2005 (SS)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	480	43.8 (210)	42.1 (202)	RD = 1.7%* RPR = 1.04*	0.3 – 3.0* [c] 1.01 – 1.07* [c]	NR
	Subgroup: prostate volume ≤30 ml	% (n)	159	60.4 (96)	59.1 (94)	RD = 1.3%* RPR = 1.02*	0.0** – 3.6* [c] 0.99 – 1.05* [c]	0.50 [c]
	Subgroup: prostate volume 30.1-50 ml	% (n)	197	42.6 (84)	40.6 (80)	RD = 2.0%* RPR = 1.05*	0.0** – 4.5* [c] 1.00 – 1.10* [c]	0.12 [c]
	Subgroup: prostate volume >50 ml	% (n)	124	24.2 (30)	22.6 (28)	RD = 1.6%* RPR = 1.07*	0.0** – 4.6* [c] 0.97 – 1.18* [c]	NR
14 vs. 12 cores (MPZ+fLPZ**+TZ** vs. MPZ+fLPZ)								
Uno 2008 (SS)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	313	40.6 (127)	40.3* (126*)	RD = 0.3%* RPR = 1.01*	0.0** – 1.2* [c] 0.99 – 1.02* [c]	NR
	Subgroup: PSA ≤4 ng/ml	% (n)	29	17.2 (5)	17.2* (5*)	RD = 0.0* RPR = 1.00*	0.0** – 0.3* [c] 1.00 – 1.00* [c]	NR
	Subgroup: PSA 4.01-10 ng/ml	% (n)	181	30.4 (55)	29.8* (54*)	RD = 0.6%* RPR = 1.02*	0.0** – 2.2* [c] 0.98 – 1.06* [c]	NR
	Subgroup: PSA 10.01-20 ng/ml	% (n)	57	50.9 (29)	50.9* (29*)	RD = 0.0* RPR = 1.00*	0.0** – 1.8* [c] 1.00 – 1.00* [c]	NR
	Subgroup: PSA >20 ng/ml	% (n)	46	82.6 (38)	82.6* (38*)	RD = 0.0* RPR = 1.00*	0.0** – 2.2* [c] 1.00 – 1.00* [c]	NR
15 vs. 12 cores (MPZ+LPZ**+MLiPZ** vs. MPZ+LPZ)								
Ploussard 2012 (SS)	*Cancer Detection Rate* Cancer detected/men undergoing biopsy	% (n)	2753	41.6 (1145*)	40.4 (1111)	RD = 1.2%* RPR = 1.03*	0.8 – 1.7* [c] 1.02 – 1.04* [c]	NR

15 vs. 12 cores (MPZ+LPZ**+ALH+MLiPZ** vs. MPZ+LPZ)								
Rochester 2009 (RCT)	*Cancer Detection Rate* Cancer detected/men undergoing biopsy	% (n)	244	41.0 (50) N = 122	51.6 (63) N = 122	RD = -10.7%* RPR = 0.79*	-23.1 – 1.8* [b] 0.60 – 1.04* [b]	0.095* [b]
Rochester 2009 (SS, 15-core group)	*Cancer Detection Rate* Cancer detected/men undergoing biopsy	% (n)	122	41.0 (50)	39.3 (48)	RD = 1.6%* RPR = 1.04*	0.0** – 4.7* [c] 0.98 – 1.10* [c]	0.0125[c]
18 vs. 12 cores (LPZ**+fLPZ** vs. LPZ)								
Rodriguez-Covarrubias 2011 (RCT)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	150	48.0 (36) N = 75	30.7 (23) N = 75	RD = 17.3%* RPR = 1.57*	1.9 – 32.7* [b] 1.03 – 2.37* [b]	0.030* [b] /0.02[a]
	Subgroup: prostate volume ≤65ml	% (n)	108	52.8 (28) N = 53	30.9 (17) N = 55	RD = 21.9%* RPR = 1.71*	3.8 – 40.1* [b] 1.07 – 2.73* [b]	0.02[a]
	Subgroup: prostate volume >65ml	% (n)	42*	NR	NR	NR	NR	NS[a]
	Subgroup: PSA ≤10ng/ml	% (n)	103	38.4 (20) N = 52	19.6 (10) N = 51	RD = 18.9%* RPR = 1.96*	1.7 – 36.0* [b] 1.02 – 3.77* [b]	0.035* [b] /0.03[a]
	Subgroup: PSA >10ng/ml	% (n)	47*	NR	NR	NR	NR	NS[a]
Rodriguez-Covarrubias 2011 (SS, 18-core group)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	75	48.0 (36)	45.3 (34)	RD = 2.7% RPR = 1.06*	NR	NR
18 vs. 12 cores (MPZ+ LPZ**+TZ** vs. MPZ+ LPZ)								
Ploussard 2012 (SS)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	2753	42.4 (1167*)	40.4 (1111)	RD = 2.0%* RPR = 1.05	1.5 – 2.6* [c] 1.09 – 1.06* [c]	<0.001
18 vs. 12 cores (MPZ+posterolateral PZ**+TZ** vs. MPZ+posterolateral PZ)								

Janane 2012 (SS)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	79	17.3 (14*)	14.3 (11*)	RD = 3.8% RPR = 1.27	0.0** – 9.3* [c] 0.97 – 1.67* [c]	NR
18 vs. 12 cores (MPZ+LPZ**+MLPZ** vs. MPZ+LPZ)								
Park 2010 (RCT)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	233	42.6 (49) N = 115	33.9 (40) N = 118	RD = 8.7%* RPR = 1.26* OR = 1.448	-3.7 – 21.1* [b] 0.90 – 1.75* [b] 0.851 – 2.462[a]	0.171* [b] 0.173[a]
	Subgroup: prostate volume <45cm^3	% (n)	127	44.1 (26) N = 59	44.1 (30) N = 68	RD = 0.0* RPR = 1.00*	-17.4 – 17.3* [b] 0.67 – 1.48* [b]	0.996[a]
	Subgroup: prostate volume ≥45cm^3	% (n)	106	41.1 (23) N = 56	20.0 (10) N = 50	RD = 21.1%* RPR = 2.05*	4.1 – 38.1* [b] 1.09 – 3.88* [b]	0.018[a]
	Subgroup: PSA <7ng/ml	% (n)	115	26.8 (15) N = 56	23.7 (14) N = 59	RD = 3.1%* RPR = 1.13*	-12.8 – 18.9* [b] 0.60 – 2.12* [b]	0.706* [b] /0.709 [a]
	Subgroup: PSA ≥7ng/ml	% (n)	118	57.6 (34) N = 59	44.1 (26) N = 59	RD = 13.6%* RPR = 1.31*	-4.3 – 31.4* [b] 0.91 – 1.88* [b]	0.141* [b] /0.143 [a]
Park 2010 (SS)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	115	42.6 (49) N = 115	34.8 (40) N = 115	RD = 7.8%* RPR = 1.23*	2.0 – 13.6* [c] 1.07 – 1.40 * [c]	NR
20 vs. 12 cores (**MPZ+LPZ** vs. MPZ+LPZ)								
Irani 2013 (SS)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	335	48.8 (81) N = 166	42.0 (71) N = 169	RD = 6.8%* RPR = 1.16* OR = 0.76	NR NR 0.49 – 1.17	NR NR >0.2 [b]
21 vs. 12 cores (MPZ+LPZ**+TZ+MLiPZ** vs. MPZ+LPZ)								
Ploussard 2012 (SS)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	2753	43.3 (1191)	40.4 (1111)	RD = 2.9%* RPR = 1.07*	2.2 – 3.6* [c] 1.06 – 1.09* [c]	<0.001[c]
	Subgroup: prostate volume <50 ml	% (n)	NR	48.0	45.0	RPR = 1.07*	NR	<0.001 [c]
	Subgroup: prostate volume >50ml	% (n)	977*	31.9 (312*)	29.3 (286*)	RD = 2.7%* RPR = 1.09*	1.6 – 3.8* [c] 1.05 – 1.12* [c]	<0.001 [c]

	Subgroup: prostate volume >70 ml	% (n)	NR	24.4	21.6	RPR = 1.13*	NR	<0.001 [c]
	Subgroup: PSA >10 ng/ml	% (n)	630*	61.6 (387*)	59.0 (371*)	RD = 2.5%* RPR = 1.04*	1.2 – 3.9* [c] 1.02 – 1.06* [c]	<0.001 [c]
	Subgroup: PSA <10 ng/ml	% (n)	NR	37.9	34.9	RPR = 1.09*	NR	<0.001 [c]
	Subgroup: PSA <4ng/ml	% (n)	297*	24.7 (73)	20.9 (62)	RD = 3.7%* RPR = 1.18*	1.2 – 6.2* [c] 1.07 – 1.30* [c]	<0.001 [c]
24 vs. 12 cores (MPZ+LPZ**+TZ+MLiPZ** vs. MPZ+posterolateral PZ)								
Janane 2012 (SS)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	79	22.8 (18*)	14.3 (11*)	RD = 8.9%* RPR = 1.64*	1.3 – 16.4* [c] 1.13 – 2.37* [c]	NR
26 vs. 12 cores (TR**+TP** vs. TR)								
Numao 2012 (SS)	*Cancer Detection Rate* Cancers detected/men undergoing biopsy	% (n)	715	35.9 (257)	28.5 (204)	RD = 7.4%* RPR = 1.26*	5.4 – 9.5* [C] 1.19 – 1.34* [C]	<0.001 [c]
	Subgroup: prostate volume ≥48 ml	%	NR	~20	~13	RPR ≈ 1.54*	NR	NR
	Subgroup: prostate volume 36-47 ml	%	NR	~22	~17	RPR ≈ 1.29*	NR	NR
	Subgroup: prostate volume 27-35 ml	%	NR	~43	~33	RPR ≈ 1.30*	NR	NR
	Subgroup: prostate volume ≤26 ml	%	NR	~63	~55	RPR ≈ 1.15*	NR	NR
26 vs. 14 (TP**+TR** vs. TP)								
Takeshita 2013 (SS)	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	744	36.2 (269)	31.0 (231)	RD = 5.1%* RPR = 1.16*	3.4 – 6.8* [C] 1.11 – 1.22* [C]	<0.001 [c]
	Subgroup: prostate volume ≤29 cc	%	NR	~54	~50	RPR ≈ 1.08*	NR	NR
	Subgroup: prostate volume 30-49 cc	%	NR	~29	~24	RPR ≈ 1.21*	NR	NR

	Subgroup: prostate volume ≥50 cc	%	NR	~15	~11	RPR ≈ 1.36*	NR	NR
	Subgroup: PSA ≤3.9 ng/ml	%	NR	~24	~22	RPR ≈ 1.09*	NR	NR
	Subgroup: PSA 4-9.9 ng/ml	%	NR	~35	~30	RPR ≈ 1.17*	NR	NR
	Subgroup: PSA 10-20 ng/ml	%	NR	~51	~45	RPR ≈ 1.13*	NR	NR
24-72 vs. 12 cores (posterior+posterolateral**+anterolateral+AAPZ** vs. posterior+posterolateral)								
Bittner 2013 (SS)	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	191	73.3 (140)	56.0 (107)	RD = 17.3%* RPR = 1.31*	11.3 – 23.2* C 1.19 – 1.43* [C]	NR

AAPZ = anterior apical peripheral zone; ALH = anterior lateral horn; flpz = far lateral peripheral zone; LPZ = lateral peripheral zone; MLiPZ = midline peripheral zone; MLPZ = mediolateral peripheral zone; MPZ = mid-lobar peripheral zone; NR = not reported; PSA = prostate specific antigen; OR = odds ratio; RCT = randomized controlled trial design; RD = risk difference (men diagnosed out of men undergoing intervention biopsy – men diagnosed out of men undergoing comparison biopsy); RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy / men diagnosed out of men undergoing comparison biopsy); SS = sequential sampling design; TP = transperineal; TR = transrectal; TZ = transition zone;

** Calculated by reviewers; ** Includes negative values – set to 0 as not applicable for sequential sampling study design;*

[a] *Chi-square test*

[b] *Fisher's exact test*

[c] *McNemar's test*

[d] *Regression analysis*

[e] *Rank sum test.*

Table 22. Results of sequential sampling studies examining effects of extended vs. ≥15 core biopsy schemes on prostate cancer detection (initial biopsy population)

Study	Outcome Definition	Outcome Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value
21 vs. 15 cores (MPZ+LPZ+MLiPZ**+TZ** vs. MPZ+LPZ+MLiPZ)								
Ploussard 2012	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	2753	43.3 (1191)	41.6 (1145*)	RD = 1.6%* RPR = 1.04*	1.2 – 2.2* [C] 1.03 – 1.05* [C]	NR
24 vs. 16 cores (LPZ**+MPZ** vs. LPZ)								
Patel 2007	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	139	44.6* (62)	38.1* (53*)	RD = 6.5%* RPR = 1.17*	1.7 – 11.3* [C] 1.06 – 1.30* [C]	NR
21 vs. 18 cores (MPZ+LPZ+TZ**+MLiPZ** vs. MPZ+LPZ+TZ)								
Ploussard 2012	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	2753	43.3 (1191)	42.4 (1167*)	RD = 0.9%* RPR = 1.02*	0.4 – 1.3* [C] 1.01 – 1.03* [C]	NR
24 vs. 18 cores (MPZ+posterolateral PZ+TZ**+MLiPZ** vs. MPZ+posterolateral PZ+TZ)								
Janane 2012	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	79	22.8 (18*)	17.3 (14*)	RD=5.5%* RPR = 1.29*	0.0** – 11.1* [C] 1.00 – 1.65* [C]	NR

LPZ = lateral peripheral zone; MPZ = mid-lobar peripheral zone; MLiPZ = midline peripheral zone; MLPZ = mediolateral peripheral zone; NR = not reported; PSA = prostate specific antigen; RD = risk difference (men diagnosed out of men undergoing intervention biopsy – men diagnosed out of men undergoing comparison biopsy); RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy / men diagnosed out of men undergoing comparison biopsy); TZ = transition zone;
* Calculated by reviewers; ** Includes negative values – set to 0 as not applicable for sequential sampling study design;
[a] Chi-square test
[b] Fisher's exact test
[c] McNemar's test
[d] Regression analysis
[e] Rank sum test

Table 23. Results of randomized controlled trials examining effects of transperineal vs. transrectal biopsy approach on prostate cancer detection (initial biopsy population)

Study	Outcome Definition	Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value
Alireza 2012	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	390	36.4 (71) N = 195	31.3* (61) N = 195	RD = 5.1%* RPR = 1.16*	-4.3 – 14.5* [b] 0.88 – 1.54* [b]	0.285* [b]
	Subgroup: PSA 4.1-10.0 ng/ml	%	NR	31.4	17.8	RD = 13.7% PR = 1.76*	NR	<0.05
Hara 2008	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	246	42.1 (53) N = 126	48.3 (58) N = 120	RD = - 6.3% RPR = 0.87*	-18.7 – 6.1* [b] 0.66 – 1.15* [b]	0.323[a]
	Subgroup: prostate volume <30 cc	% (n)	114	55.0 (33) N = 60	59.3 (32) N = 54	RD = - 4.3%* RPR = 0.93*	-22.4 – 13.9* [b] 0.68 – 1.28* [b]	0.647* [b] 0.788[a]
	Subgroup: prostate volume 30-50 cc	% (n)	96	32.7 (16) N = 49	44.7 (21) N = 47	RD = -12.0% RPR = 0.73*	-31.4 – 7.3* [b] 0.44 – 1.22* [b]	0.226* [b] 0.317[a]
	Subgroup: prostate volume >50 cc	% (n)	36	23.5 (4) N = 17	26.3 (5) N = 19	RD = - 2.8%* RPR = 0.89*	-31.0 – 0.25* [b] 0.29 – 2.80* [b]	0.847* [b] >0.999[a]
	Subgroup: PSA 4.0-10.0 ng/ml	% (n)	183	36.2 (34) N = 94	42.7 (38) N = 89	RD = -6.5%* RPR = 0.85*	-20.7 – 7.6* [b] 0.59 – 1.21* [b]	0.366[a]
	Subgroup: PSA 10.1-20.0 ng/ml	% (n)	63	59.4 (19) N = 32	64.5 (20) N = 31	RD = -5.1%* RPR = 0.92*	-29.1 – 18.8* [b] 0.62 – 1.36* [b]	0.674[a]
Takenaka 2008	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	200	47.0 (47) N = 100	53.0 (53) N = 100	RD = -6.0%* RPR = 0.89*	-19.8 – 7.8* [b] 0.67 – 1.17* [b]	0.396* [b] 0.480[a]
	Subgroup: PSA 0-4.0 ng/ml	% (n)	4	100 (2) N = 2	0.0 (0) N = 2	RD = 100%* RPR = N/A	100 – 100* [b]	0.046* [b] 0.333[a]
	Subgroup: PSA 4.1-10.0 ng/ml	% (n)	118	36.1 (22) N = 61	35.1 (20) N = 57	RD = 9.8%* RPR = 1.03*	-16.3 – 18.3* [b] 0.63 – 1.67* [b]	0.912* [b] >0.999[a]

Subgroup: PSA 10.1-20.0 ng/ml	% (n) N =	44	47.6 (10) N = 21	69.6 (16) N = 23	RD = -21.9%* RPR = 0.68*	-50.4 – 6.5* [b] 0.41 – 1.16* [b]	0.139* [b] 0.220[a]
Subgroup: PSA ≥20.0 ng/ml	% (n) N =	34	81.3 (13) N = 16	94.4 (17) N = 18	RD = -13.2%* RPR = 0.86*	-35.1 – 8.7* [b] 0.66 – 1.12* [b]	0.233* [b] 0.323[a]

*NR = not reported; PSA = prostate specific antigen; RD = risk difference (men diagnosed out of men undergoing intervention biopsy – men diagnosed out of men undergoing comparison biopsy); RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy / men diagnosed out of men undergoing comparison biopsy); * calculated by reviewers[a] chi-square test; [b] Fisher's exact test.*

II DETECTION OF GLEASON SCORE >6 CANCER

Table 24. Results of sequential sampling studies examining effects of extended vs. 8-core biopsy schemes on detection of GS>6 cancer (initial biopsy population)

Study	Outcome Definition	Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value
10 vs. 8 cores (PZ**+TZ** vs. PZ)								
Miyake 2005	*Detection rate of GS>7 cancer* cancers detected/men undergoing biopsy	% (n)	788	4.7* (37)	4.6* (36)	RD = 0.1* RPR = 1.03*	0.0** – 0.5* [C] 0.97 – 1.08* [C]	NR
	Subgroup: men who underwent prostatectomy	% (n)	98	14.3* (14)	13.3* (13)	RD = 1.0%* RPR = 1.08*	0.0** – 4.3* [C] 0.93 – 1.25* [C]	NR
	Detection rate of GS=7 cancer cancers detected/men undergoing biopsy	% (n)	788	8.8* (69)	8.4* (66)	RD = 0.4%* RPR = 1.05*	0.0** – 0.9* [C] 0.99 – 1.10* [C]	NR
	Subgroup: men who underwent prostatectomy	% (n)	98	31.6* (31)	29.6* (29)	RD = 2.0%* RPR = 1.07*	0.0** – 5.9* [C] 0.97 – 1.17* [C]	NR
24 vs. 8 cores (MPZ**+LPZ** vs. MPZ)								
Patel 2007	*Detection rate of GS>7 cancer* cancers detected/men undergoing biopsy	% (n)	139	3.6* (5)	2.1* (3*)	RD = 1.4%* RPR = 1.67*	0.0** – 4.1* [C] 0.81 – 3.41* [C]	NR
	Detection rate of GS=7 cancer cancers detected/men undergoing biopsy	% (n)	139	12.9* (18)	8.6* (12*)	RD = 4.3%* RPR = 1.50*	0.2 – 8.4* [C] 1.08 – 2.08* [C]	NR
	Detection rate of GS=6 cancer cancers detected/men undergoing biopsy	% (n)	139	28.1* (39)	18.0* (25*)	RD = 10.1%* RPR = 1.56*	4.3 – 15.8* [C] 1.23 – 1.97* [C]	NR

GS = Gleason Score; LPZ = lateral peripheral zone; MPZ = mid-lobar peripheral zone; MLiPZ = midline peripheral zone; NR = not reported; RD = risk difference (men diagnosed out of men undergoing intervention biopsy – men diagnosed out of men undergoing comparison biopsy); RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy / men diagnosed out of men undergoing comparison biopsy); TZ = transition zone;

** Calculated by reviewers; ** Includes negative values – set to 0 as not applicable for sequential sampling study design*

[a] *Chi-square test*

[b] *Fisher's exact test*

[c] *McNemar's test*

[d] *Regression analysis*

[e] *Rank sum test*

Table 25. Results of randomized controlled trial examining effects of extended vs. 6-12 core biopsy schemes on detection of GS>6 cancer (initial biopsy population)

Study	Outcome Definition	Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value
24 vs. 6-12 cores (MPZ+**LPZ+TZ+MLiPZ** vs. MPZ(+LPZ))								
Sur 2004	*Detection rate of GS>7 cancer* cancers detected/men undergoing biopsy	% (n)	182	5.3 (5) N = 94	2.3 (2) N = 88	RD = 3.0%* RPR = 2.34*	-2.5 – 8.5* [b] 0.17 – 11.75* [b]	0.286* [b]
	Detection rate of GS=7 cancer cancers detected/men undergoing biopsy	% (n)	182	14.9 (14) N = 94	13.6 (12) N = 88	RD = 1.3%* RPR = 1.09*	-8.9 – 11.4* [b] 0.53 – 2.23* [b]	0.809* [b]

*GS = Gleason Score; LPZ = lateral peripheral zone; MLiPZ = midline peripheral zone; MPZ = mid-lobar peripheral zone; RD = risk difference (men diagnosed out of men undergoing intervention biopsy – men diagnosed out of men undergoing comparison biopsy); RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy / men diagnosed out of men undergoing comparison biopsy); * calculated by reviewers; [a] chi-square test; [b] Fisher's exact test; [c] McNemar's test; [d] regression analysis; [e] rank sum test.*

Table 26. Results of studies examining effects of extended vs. 12/14-core biopsy schemes on detection of GS>6 cancer (initial biopsy population)

Study	Outcome Definition	Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value
15 vs. 12 cores (MPZ+LPZ**+ALH+MLiPZ** vs. MPZ+LPZ)								
Rochester 2009 (RCT)	*Detection rate of GS>6 cancer* cancer detected/men undergoing biopsy	% (n)	244	25.4 (31) N = 122	31.1 (38) N = 122	RD = - 5.7%* RPR = 0.82*	-17.0 – 5.5* [b] 0.55 – 1.22* [b]	0.320* [b]
Rochester 2009 (SS, 15-core group)	*Detection rate of GS>6 cancer* cancer detected/men undergoing biopsy	% (n)	122	25.4 (31)	25.4 (31)	RD = 0.0* RPR = 1.00*	0.0** – 0.8* [C] 1.00 – 1.00* [C]	NR
18 vs. 12 cores (LPZ**+far LPZ** vs. LPZ)								
Rodriguez-Covarrubias 2011	*Detection rate of GS>7 cancer* cancers detected/men undergoing biopsy	% (n)	150	6.7 (5) N = 75	6.7 (5) N = 75	RD = 0.0* RPR = 1.00*	-0.8 – 8.0* [b] 0.30 – 3.31* [b]	1.000* [b] /NS[a]

(RCT)	Subgroup: prostate volume ≤65ml	% (n)	108	7.4 (4) N = 53	9.1 (5) N = 55	RD = -1.5%* RPR = 0.83*	-12.0 – 8.9* [b] 0.24 – 2.93* [b]	0.772* [b]
	Subgroup: PSA ≤10ng/mL	% (n)	103	1.9 (1) N = 52	5.9 (3) N = 51	RD = -4.0%* RPR = 0.33*	-11.4 – 3.5* [b] 0.04 – 3.04* [b]	0.298* [b]
	Detection rate of GS=7 cancer cancers detected/men undergoing biopsy	% (n)	150	13.3 (10) N = 75	6.7 (5) N = 75	RD = 6.7%* RPR = 2.00	-2.9 – 16.2* [b] 0.72 – 5.57* [b]	0.174* [b]
	Subgroup: prostate volume ≤65ml	% (n)	108	17.0 (9) N = 53	9.0 (5) N = 55	RD = 7.9%* RPR = 1.87*	-4.8 – 20.5* [b] 0.67 – 5.21* [b]	0.222* [b]
	Subgroup: PSA ≤10ng/mL	% (n)	103	9.6 (5) N = 52	2.0 (1) N = 51	RD = 7.7%* RPR = 4.90*	-1.2 – 16.5* [b] 0.59 – 40.53* [b]	0.097* [b]
18 vs. 12 cores (MPZ+LPZ**+MLPZ** vs. MPZ+LPZ)								
Park 2010 (RCT)	*Detection rate of GS>7 cancer* *cancers detected/men undergoing biopsy*	% (n)	233	12.2 (14) N = 115	3.4 (4) N = 118	RD = 8.8%* RPR = 3.59*	2.0 – 15.6* [b] 1.22 – 10.59* [b]	0.012* [b]
	Detection rate of GS=7 cancer cancers detected/men undergoing biopsy	% (n)	233	10.4 (12) N = 115	12.7 (15) N = 118	RD = -2.3%* RPR = 0.82*	-10.5 – 5.9* [b] 0.40 – 1.68* [b]	0.587* [b]
	Detection rate of GS=6 cancer cancers detected/men undergoing biopsy	% (n)	233	20.0 (23) N = 115	17.8 (21) N = 118	RD = 2.2%* RPR = 1.12*	-7.9 – 12.3* [b] 0.66 – 1.91* [b]	0.668* [b]
21 vs. 12 cores (MPZ+LPZ**+TZ+MLiPZ** vs. MPZ + LPZ)								
Ploussard 2012 (SS)	*Detection rate of GS>6 cancer* cancers detected/men undergoing biopsy	% (n)	2753	19.2* (529*)	18.7 (516*)	RD = 0.5%* RPR = 1.03*	0.2 – 0.8* [C] 1.01 – 1.04* [C]	NR
26 vs. 12 cores (TR**+TP** vs. TR)								
Numao 2012 (SS)	*Detection rate of GS>7 cancer* cancers detected/men undergoing biopsy	% (n)	715	8.5 (61) N = 715	8.0 (57) N = 715	RD = 0.6%* RPR = 1.07*	0.0** – 1.2* [C] 1.00 – 1.14* [C]	NR

	Detection rate of GS=7 cancer cancers detected/men undergoing biopsy	% (n)	715	15.8 (113) N = 715	13.3 (95) N = 715	RD = 2.5%* RPR = 1.19*	1.2 – 3.8* [C] 1.10 – 1.29* [C]	NR

26 vs. 14 cores (TP**+TR** vs. TP)								
Takeshita 2013 (SS)	*Detection rate of GS>7 cancer* cancers detected/men undergoing biopsy	% (n)	744	8.5 (63) N = 744	7.8 (58) N = 744	RD = 6.7%* RPR = 1.09*	0.0** – 1.4* [C] 1.01 – 1.17* [C]	NR
	Detection rate of GS=7 cancer cancers detected/men undergoing biopsy	% (n)	744	15.7 (117) N = 744	13.7 (102) N = 744	RD = 2.0%* RPR = 1.15*	0.9 – 3.1* [C] 1.07 – 1.23* [C]	NR

*GS = Gleason Score; LPZ = lateral peripheral zone; MLiPZ = midline peripheral zone; MPZ = mid-lobar peripheral zone; NR = not reported; PSA = prostate specific antigen; RCT = randomized controlled trial design; RD = risk difference (men diagnosed out of men undergoing intervention biopsy – men diagnosed out of men undergoing comparison biopsy); RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy / men diagnosed out of men undergoing comparison biopsy); SS = sequesntial sampling design; TR = transrectal approach; TP = transperineal approach; * calculated by reviewers; ** includes negative values – set to 0 as not applicable for sequential sampling study design; [a] chi-square test; [b] Fisher's exact test; [c] McNemar's test; [d] regression analysis; [e] rank sum test.*

Table 27. Results of sequential sampling study examining effects of <u>extended vs. 16 core biopsy schemes</u> on detection of GS>6 cancer (initial biopsy population)

Study	Outcome Definition	Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value
24 vs. 16 cores (LPZ**+MPZ** vs. LPZ)								
Patel 2007	*Detection rate of GS>7 cancer* cancers detected/men undergoing biopsy	% (n)	139	3.6* (5)	3.6* (5*)	RD = 0.0* RPR = 1.00*	0.0** – 0.7* [C] 1.00 – 1.00* [C]	NR
	Detection rate of GS=7 cancer cancers detected/men undergoing biopsy	% (n)	139	12.9* (18)	12.2* (17*)	RD = 0.7%* RPR = 1.06*	0.0** – 2.8* [C] 0.95 – 1.18* [C]	NR
	Detection rate of GS=6 cancer cancers detected/men undergoing biopsy	% (n)	139	28.1* (39)	22.3* (31*)	RD = 5.8%* RPR = 1.26*	1.2 – 10.3* [C] 1.07 – 1.48* [C]	NR

*GS = Gleason Score; LPZ = lateral peripheral zone; MPZ = mid-lobar peripheral zone; NR = not reported; RD = risk difference (men diagnosed out of men undergoing intervention biopsy – men diagnosed out of men undergoing comparison biopsy); SD = standard deviation; SS = sequential sampling study (comparison of different schemes within same man); RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy / men diagnosed out of men undergoing comparison biopsy); * calculated by reviewers; ** includes negative values – set to 0 as not applicable for sequential sampling study design; [a] chi-square test; [b] Fisher's exact test; [c] McNemar's test; [d] regression analysis; [e] rank sum test.*

III ADVERSE EVENTS

Table 28. Results of randomized controlled trials examining effects of extended vs. 6-core biopsy schemes on adverse events (mixed/unclear biopsy population)

Study	Outcome Definition	Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value	Follow up/ Timing
10 vs. 6 cores (MPZ**+LPZ** vs. LPZ)									
Eichler 2006 (1 RCT, unclear population)	*Complication rate*	%	200				NR	NR	1 month
	Minor *Infection*			2.2	2.4	RD = -0.2%			
	Haematuria			72.0	57.6	RD = 14.4%			
	Haemospermia			75.0	65.3	RD = 9.7%			
	Rectal bleeding			29.3	18.3	RD = 11.0%			
	Pain			33.0	31.8	RD = 1.2%			
	Chills			3.3	1.2	RD = 2.1%			
	patients experiencing complications			N = NR	N = NR				
12 vs. 6 cores (MPZ**+LPZ** vs. LPZ)									
Eichler 2006 (1 RCT, mixed population)	*Complication rate*	%	244				NR	NS	NR
	Minor *Infection*			4	6	RD = -2%			
	Haematuria			55	50	RD = 5%			
	Haemospermia			82	73	RD = 9%			
	Rectal bleeding			23	17	RD = 6%			
	patients experiencing complications			N = NR	N = NR				

*NR = not reported; NS = not significant; PSA = prostate specific antigen; RCT = randomized controlled trial; RD = risk difference (men experiencing adverse events out of men undergoing intervention biopsy – men experiencing experiencing adverse events out of men undergoing comparison); SD = standard deviation; * calculated by reviewers; [a] chi-square test; [b] Fisher's exact test; [c] McNemar's test; [d] regression analysis; [e] rank sum test;*

Table 29. Results of randomized controlled trial examining effects of extended vs. 10-core biopsy schemes on adverse events (unclear biopsy population)

Study	Outcome Definition	Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value	Follow up/ Timing
14 vs. 10 cores (MPZ+TZ(+MLiPZ) vs. MPZ+TZ(+MLiPZ))									
Eichler 2006 (1 RCT, unclear population)	*Pain* patients with discomfort	%	222	64.8 N = NR	27.9 N = NR	RD = 36.9%	NR	NR	NR

MLiPZ = midline peripheral zone; MPZ = mid-lobar peripheral zone; NR = not reported; PSA = prostate specific antigen; RCT = randomized controlled trial; RD = risk difference (men experiencing adverse events out of men undergoing intervention biopsy – men experiencing experiencing adverse events out of men undergoing comparison); TZ = transition zone;

Table 30. Results of randomized controlled trials examining effects of extended vs. 6-core biopsy schemes on adverse events (initial biopsy population)

Study	Outcome Definition	Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value	Follow up/ Timing
12 vs. 6 cores (MPZ**+LPZ** vs. LPZ)									
Eichler 2006 (1 RCT, initial population)	*Complication rate*	%	214				NR	NR	≤3 months
	Minor *Infection*			0	0	RD = 0%			
	Haematuria			43	45	RD = -2%			
	Haemospermia			74	79	RD = -5%			
	Voiding difficulties			0	0	RD = 0%			
	patients experiencing complications			N = NR	N = NR				

LPZ = lateral peripheral zone; MLPZ = mediolateral peripheral zone; MPZ = mid-lobar peripheral zone; NR = not reported; RCT = randomized controlled trial; RD = risk difference (men experiencing adverse events out of men undergoing intervention biopsy – men experiencing experiencing adverse events out of men undergoing comparison);

Table 31. Results of randomized controlled trials examining effects of volume-dependant vs. 6/8-core biopsy schemes on adverse events (initial biopsy population)

Study	Outcome Definition	Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value	Follow up/ Timing
Volume-dependant number of cores vs. 6 cores (8-14 LPZ**+MPZ+far LPZ** vs. LPZ)									
Mariappan 2004	*Pain - Visual Analogue Scale* Score (1-10)	Mean	NR	~2.0 N = NR	~2.1 N = NR	NR	NR	NS	during+within 30 minutes of biopsy
	"Do you think you needed anaesthesia during this procedure?	NR	NR	NR	NR	NR	NR	NS	within 30 minutes of biopsy
	"If you had this procedure again, would you agree to undergo it without anaesthesia?"	NR	NR	NR	NR	NR	NR	NS	1 week
	Rectal bleeding men experiencing bleeding beyond the day of biopsy	n (%)	132	48 (76.2*)	42 (60.9*)	RD = 15.3%*	-0.3 – 30.9* [b]	0.059* [b] /0.08 [d]	≦2 weeks
	Haematuria men experiencing haematuria	n (%)	132	20 (31.7*)	21 (30.4*)	RD = 1.3%*	-14.5 – 17.1* [b]	0.871* [b] /0.38 [d]	≦2 weeks
	Haemospermia men experiencing haematuria	n (%)	132	30 (47.6*)	27 (39.1*)[f]	RD = 8.5%* [f]	8.4 – 25.4 * [b]	0.325* [b] /0.59 [d]	≦2 weeks
	Fever patients returning to the clinic due to fever	n (%)	132	1 (1.6*) N = 63	1 (1.4*) N = 69	RD = 0.1%*	-4.0 – 4.3 * [b]	0.948* [b]	NR
Volume-, age-dependant number of cores vs. 8 cores (6-18 **LPZ** vs. LPZ)									
Lecuona 2011	*Complications* (any)	n (%)	181	45 (48.4)	43 (48.9)	RD = 0.5%	-15.0 – 14.1* [b]	0.949* [b]	NR
	Fever (requiring systemic antibiotics)			4 (4.3)	5 (5.7)	RD = 1.4%*	-7.7 – 5.0* [b]	0.669* [b]	
	Urinary retention (secondary to gross haematuria requiring catheterization and irrigation) patients experiencing complications			1 (1.1) N = 93	0 (0.00) N = 88	RD = 1.1%	-1.0 – 3.2* [b]	0.329* [b] /NS[b]	

	Subgroup: prostate volume >50 ml *Complications* (any) patients experiencing complications	n (%)	64	16 (59.3) N = 27	14 (37.8) N = 37	RD =21.4%*	-2.8 – 45.7* [b]	0.090* [b] /0.1286[b]	NR

*LPZ = lateral peripheral zone; MPZ = mid-lobar peripheral zone; NR = not reported; NS = not significant; RD = risk difference (men experiencing adverse events out of men undergoing intervention biopsy – men experiencing experiencing adverse events out of men undergoing comparison); * calculated by reviewers; [a] chi-square test; [b] Fisher's exact test; [c] McNemar's test; [d] regression analysis; [e] rank sum test; [f] numbers calculated by reviewers were used here as the original article appeared to have reporting error;*

Table 32. Results of randomized controlled trial examining effects of extended vs. 6-12-core biopsy schemes on adverse events (initial biopsy population)

Study	Outcome Definition	Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value	Follow up/ Timing
24 vs. 6-12 cores (MPZ+LPZ**+TZ+MLiPZ** vs. MPZ(+LPZ))									
Sur 2004	*International Prostate Symptom Score + 4 questions about haematuria, haematochezia, haemospermia, pain* Score (11-66; higher scores indicate worse symptoms)	median	164	~17.8	~19.2			NR	pre-biopsy
		median	164	~24.8	~23.0			NS [e]	1 day
		median	164	~22.8	~22.7			NS [e]	1 week
		median	164	~21.0 N = NR	~20.5 N = NR			NS [e]	2 weeks
	Pain experienced during biopsy Score (0-6; higher scores indicate worse pain)	mean	NR	0.9 N = NR	2.6 N = NR			<0.001 [e]	1 day
	Complication rate	n (%)	NR						NR
	Urinary retention			4 (4.3)	0	RD = 4.3%*	0.2 – 8.3* [b]	0.050* [b]	
	Atrial fibrillation			1 (1.1)	0		-1.0 – 3.1* [b]	0.332* [b]	
	Significant rectal bleeding				0	RD = 1.1%*	0.0* [b]	1.000* [b]	
	Significant haematuria			N = 94	0	0.0* [b]	0.0* [b]	1.000* [b]	
	patients experiencing complications				N = 88	0.0* [b]			

*LPZ = lateral peripheral zone; MPZ = mid-lobar peripheral zone; MLiPZ = midline peripheral zone; NR = not reported; NS = not significant; PSA = prostate specific antigen; RD = risk difference (men experiencing adverse events out of men undergoing intervention biopsy – men experiencing experiencing adverse events out of men undergoing comparison); TZ = transition zone; * calculated by reviewers; [a] chi-square test; [b] Fisher's exact test; [c] McNemar's test; [d] regression analysis; [e] rank sum test; [f] numbers calculated by reviewers were used here as the original article appeared to have reporting error;*

Table 33. Results of randomized controlled trials examining effects of extended vs. 12-core biopsy schemes on adverse events (initial biopsy population)

Study	Outcome Definition	Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value	Follow up/ Timing
18 vs. 12 (LPZ**+fLPZ** vs. LPZ)									
Rodriguez-Covarrubias 2011	*Complication rate*	n (%)	150						7 days
	any complication			28 (37.3)	27 (36.0)	RD = 1.3%*	-14.1 – 16.8* [b]	0.866* [b]	
	Clavien grade 1			26 (34.7)	25 (33.3)	RD = 1.3%*	-13.8 – 16.5* [b]	0.863* [b]	
	Clavien grade 2			1 (1.3)	1 (1.3)	RD = 0.00*	-0.037 – 0.037* [b]	1.000* [b]	
	Clavien grade 3a			1 (1.3)	1 (1.3)	RD = 0.00*	-0.037 – 0.037* [b]	1.000* [b]	
	patients experiencing complications			N = 75	N = 75				
	Haematuria	NR	NR	NR	NR	NR	NR	0.52[a]	7 days
	Haematochezia			NR	NR	NR	NR	0.38 [a]	
	Haemospermia			NR	NR	NR	NR	0.19 [a]	
	Pain (Visual Analogue Scale)			NR	NR	NR	NR	0.82 [a]	
	days of experiencing complications								
18 vs. 12 cores (MPZ+LPZ**+MLPZ** vs. MPZ+LPZ)									
Park 2010	*Complication rate*	n (%)	233	9 (7.8)	4 (3.4)	RD = 4.4* [b]	-1.5 – 10.3* [b]	0.140* [b] /0.144 [a]	NR
				N = 115	N = 118				
20 vs. 12 cores (**MPZ+LPZ** vs. MPZ+LPZ)									
Irani 2013	*Pain – Visual Analogue Scale* Score (0-10; higher scores indicate more pain)	Mean	306	2.8 N = 148	2.4 N = 158	NR	NR	>0.18[fh]	evening of biopsy
	International Prostate Symptom Score - overall	Median (Mean)	306	6.0	5.0	NR	NR	NS	before biopsy
	Score (0-35; higher scores indicate worse symptoms)			6.5 (7.6)	5.0 (6.9)	NR	NR	0.16 [f]	5 days
				5.0 (6.8)	4.5 (6.5)	NR	NR	0.46 [f]	15 days
				N = 148	N = 158				

International Prostate Symptom Score - QOL item	Median (Mean)	306	2.0	2.0	NR	NR	NS	before biopsy
Score (0-6; higher scores indicate feeling worse)			3.0 (2.9)	3.0 (2.8)	NR	NR	0.46 [f]	5 days
			3.0 (2.9)	2.0 (2.7)	NR	NR	0.22 [f]	15 days
			N = 148	N = 158				
Fever	n (%)	306	3 (2.0)	5 (3.2)	RD = -1.1%*	NR	>0.7 [b]	5 days
			0	0	RD = 0.0%*	NR	NR	15 days
Dysuria			26 (17.6)	15 (9.5)	RD = 8.1%*	NR	0.043 [b]	5 days
			13 (8.8)	16 (10.1)	RD = -1.3%*	NR	>0.6 [b]	15 days
Haematuria			69 (46.6)	68 (43.0)	RD = 3.6%*	NR	>0.5 [b]	5 days
			25 (16.9)	16 (10.1)	RD = 6.8%*	NR	>0.1 [b]	15 days
Haemospermia			2 (1.4)	4 (2.5)	RD = -1.2%*	NR	>0.6 [b]	5 days
			71 (48.0)	64 (40.5)	RD = 7.5%*	NR	>0.2 [b]	15 days
Rectal bleeding			28 (19.0)	28 (17.7)	RD = 1.2%*	NR	>0.7 [b]	5 days
			5 (3.4)	5 (3.2)	RD = 0.2%*	NR	>0.9 [b]	15 days
patients experiencing complications								
			N = 148	N = 158				
Complication rate	n (%)	306						NR
Clavien-Dindo grade 1			7 (4.7)	7 (4.4)	RD = 0.3%*	NR	NR	
Clavien-Dindo grade 2			1 (0.7)	1 (0.6)	RD <0.1%*	NR	NR	
Clavien-Dindo grade 3(a)			2 (1.4)	2 (1.3)	RD = 0.1%*	NR	NR	
Clavien-Dindo grade 4			0 (0.0)	1 (0.6)	RD = -0.6%*	NR	NR	
Clavien-Dindo grade 5			0 (0.0)	0 (0.0)	RD = 0.0%*	NR	NR	
patients experiencing complications								
			N = 148	N = 158				

fIPZ = far lateral peripheral zone; GS = Gleason Score; MPZ = mid-lobar peripheral zone; LPZ = lateral peripheral zone; TZ = transition zone; MLiPZ = midline peripheral zone; NR = not reported; NS = not significant; QOL = quality of life (as assessed by International Prostate Symptom Score); RD = risk difference (men experiencing adverse events out of men undergoing intervention biopsy – men experiencing experiencing adverse events out of men undergoing comparison);

** Calculated by reviewers*

[a] Chi-square test

[b] Fisher's exact test

[c] McNemar's test

[d] Regression analysis

[e] Rank sum test

[f] Mann-Whitney test

Table 34. Results of randomized controlled trial examining effects of biopsies with transperineal vs. transrectal approach on adverse events (initial biopsy populations)

Study	Outcome Definition	Measure	N actual	Intervention	Comparison	Size of effect	Size of effect Confidence interval	p value	Follow up/ Timing
Hara	*Complication rate*	n (%)	245						1-2 weeks
2008	Major Sepsis/mortality			0 (0)	0 (0)	RD = 0.0*	0.0 – 0.0* [b]	1.000[a]	
	Fever >38.5ºC			0 (0)	2 (1.7)	RD = -1.7%*	-4.0 – 0.6* [b]	0.146* [b] /0.136[a]	
	Rectal bleeding			0 (0)	0 (0)	RD = 0.0*	0.0 – 0.0* [b]	1.000[a]	
	Urinary retention			2 (1.6)	3 (2.5)	RD = -0.9%	-4.5 – 2.6* [b]	0.612[a]	
	Minor Haematuria >1 day			13 (10.3)	11 (9.2)	RD = 1.2%*	--6.3 – 8.6* [b]	0.761[a]	
	Haemospermia			2 (1.6)	0 (0)	RD = 1.6%	-0.6 – 3.8* [b]	0.166[a]	
	Vasovagal event			1 (0.8)	2 (1.7)	RD = -0.9%*	-3.6 – 1.9* [b]	0.533[a]	
	Post-dural puncture headache			5 (4.0)	0 (0)	RD = 4.0%*	0.6 – 7.4* [b]	0.028[a]	
	patients experiencing complications			N = 125	N = 120				
Takenaka	*Complication rate*	n	NR						4 weeks
2008	Macrohaematuria			11	12 (1)	NR	NR	>0.999[a]	
	Fever >38.5ºC			1 (1)	2 (2)	NR	NR	>0.999[b]	
	Urinary retention			2	3 (1)	NR	NR	>0.999[b]	
	Haemospermia			2	0	NR	NR	0.498[b]	
	Rectal bleeding			0	1	NR	NR	>0.999[b]	
	Vasovagal episode			1	2	NR	NR	>0.999[b]	
	Post-dural puncture headache			2	0	NR	NR	0.498[b]	
	patients experiencing complications (major complications)			N = NR	N = NR				

NR = not reported; PSA = prostate specific antigen; RCT = randomized controlled trial; RD = risk difference (men experiencing adverse events out of men undergoing intervention biopsy – men experiencing experiencing adverse events out of men undergoing comparison biopsy)

** calculated by reviewers; [a] chi-square test; [b] Fisher's exact test; [c] McNemar's test; [d] regression analysis; [e] rank sum test*

2.6 Patient-level regression analysis 2014

I AUTHORSHIP

This analysis was done by Mr Sam Egger, Biostatistician Cancer Council NSW, under the oversight of Professor Dianne O'Connell and with advice from members of the guideline development group (Professor Villis Marshall and Associate Professor Paul McKenzie) and Professor Bruce Armstrong.

II RATIONALE FOR ANALYSIS

A number of studies have attempted to quantify the effect of increasing the number of prostate biopsy core samples on prostate cancer diagnostic yield. This has been difficult to do in individual studies, however, because it is often not clear how much of any increase in prostate cancer yield is due to the additional core numbers and how much is due to the choice of prostate regions selected as the sources of the additional cores (i.e. a problem of collinearity). We sought to overcome this problem by combining the data from all studies that were randomised controlled trials or had a sequential sampling design[2] and that compared different prostate biopsy protocols, included only men with a suspicion of prostate cancer undergoing an initial prostate biopsy, and reported at least the cancer detection rate for each protocol studied. In what follows, we refer to a prostate biopsy as the complete set of biopsy cores taken from one man and to a biopsy component as a set of biopsy cores taken from a single region or a specified set of regions of a man's prostate for which a cancer detection rate can be calculated. Biopsy components can overlap and can also be the complete set of biopsy cores taken.

III STUDIES

Only studies that were not included in the systematic review of Eichler et al. (2006) have been included in this analysis. This was mainly due to the fact that Eichler et al. had used broader inclusion criteria (i.e. included studies of repeat, mixed and unclear biopsy populations, and studies that included lesion-directed biopsies) and had not reported cancer detection rates of individual biopsy components of included studies.

Nineteen studies provided enough information to be included in the analysis of all cancers (first authors Bittner, Dai, Ficarra, Irani, Janane, Lecuona, Mariappan, Miyake, Moussa, Orikasa, Park, Patel, Ploussard, Rochester, Rodriguez, Sur, Takeshita, Takenaka and Uno; Table 35). Three studies were excluded: Alireza (provided no information on the prostate region sampled); Numao (it was unknown which patients were also in the larger Takeshita study and substituting Numao for Takeshita did not change the results appreciably); and Hara (core locations in this RCT were unique to it, thus its location effects were indistinguishable from its study effect). A 14-core biopsy component reported by Takeshita was also excluded because it was taken from an already sampled region of the prostate.

Six studies provided enough information to be included in an analysis of the detection of Gleason Score >6 (GS>6) cancers (Park, Patel, Ploussard, Rochester, Rodriguez and Sur). Although Miyake also provided diagnostic yield results for GS>6 cancers, this study was excluded from the GS>6 analysis because it included biopsy cores taken from regions of the prostate that were unique in the studies reporting on detection of GS>6 cancers (i.e. location effects were indistinguishable from study effect).

[2] Studies in which results for each of the compared sampling strategies were obtained from each of the participating men, the less extensive set of biopsy cores being a subset of the more extensive set.

IV METHODS

Data extraction

Patient-level data were reconstructed from the published results of each study. The reconstructed data records included study name, a constructed patient identifier and, for each biopsy component, the direction of the biopsy (transrectal or transperineal), the region(s) of the prostate sampled and the number of cores. There were four studies that each had one or more biopsy components where the number of cores taken varied according to patient characteristics (Bittner, Lecuona, Mariappan and Sur) and there was no published distribution of numbers of patients by number of cores. For these biopsy components, median or mean core numbers were used (Table 35).

Statistical Methods

The analysis used logistic regression with generalised estimating equation adjustment to account for multiple (sometimes one but mostly two or more) biopsy components analysed from each man (using the patient identifier as the panel variable). The dependent variable in each regression model was cancer detection for each biopsy component (classified as cancer detected or cancer not detected). Independent variables included study and the direction, region(s) of, and number of cores in each biopsy component. Number of cores was modelled as a linear continuous independent variable (against the logit scale) as this functional form provided a better model fit (quantified by the Quasi Information Criterion[1]) than treating number of cores as a categorical or continuous variable after a logarithmic transformation. Exchangeable and independent working correlation structures were used for adjusted and unadjusted models respectively as these provided the most plausible correlation structures. Robust variance estimators were used in all regression models. PSA level was not included as a predictor of cancer detection because we were not able to reconstruct individual patient PSA levels from the published data where only mean or median PSA level for all patients were reported.

V RESULTS

Across the included studies, 23,822 biopsy components from 8,221 men were assessed for all cancers and 9,851 biopsy components from 3,701 men were assessed for GS>6 cancers (Table 35). Table 36 indicates that for a given number of cores, biopsy components from the LPZ region were not significantly more or less likely to detect cancer than biopsy components from the MPZ region, but the somewhat low number of biopsy components from LPZ alone (n=661) produced a relatively wide 95% confidence interval for this comparison (OR=1.12 95%CI 0.91, 1.39). Biopsy components from the MPZ+LPZ (OR=1.12 95%CI 1.03, 1.22), MPZ+LPZ+AAPZ (OR=1.17 95%CI 1.03, 1.33), and MPZ+LPZ+MLiPZ+ALH (OR=1.20 95%CI 1.00, 1.45) regions were all significantly associated with higher cancer diagnostic yields than MPZ alone. Cancer was least likely to be detected in the TZ region (OR=0.47 95%CI 0.36, 0.61). For any given biopsy region or set of regions, men who had 24 cores taken had nearly double the odds of having cancer detected than men who had 6 cores taken (OR=1.98 95%CI 1.52, 2.58). There was little evidence to suggest that the transrectal approach was more or less likely to detect cancer than the transperineal approach (OR=1.27 95%CI 0.73, 2.22) after accounting for differences in regions from which cores were taken and numbers of cores. However, this comparison was based on transperineal biopsies from 1,515 patients (3,626 transperineal biopsy components) only. Results for the detection of GS>6 cancers were similar to those for all cancer (Table 37), and this was also true when this comparison was restricted to the six studies in which results for detection of GS>6 cancers were reported.

The modelled curves in Figure 2 suggest that the magnitude of increases in prostate cancer diagnostic yield resulting from increases in the number of cores sampled is dependent on the underlying cancer rates. For a hypothetical group of men whose 6-core diagnostic yield for all cancers is 10%, increasing the number of cores to 24 (with the additional cores sampled from the same prostate region) would be expected to increase the yield to 18.0%, an increment of 8.0%. If the 6-core diagnostic yield for all cancers is 40%, increasing the number of cores sampled to 24 would be expected to increase the yield to 56.9%, an increment of 16.9%. Similar diagnostic yields were predicted for GS>6 cancers.

Table 35: Diagnostic yields by study group, location of cores and number of cores

Study^	Location of cores (pattern)	Number of cores	Biopsy direction (approach)	Patients assessed	All cancers		Gleason Score >6	
					Cancers detected	Diagnostic yield	Cancers detected	Diagnostic yield
Bittner (Group 1)	MPZ LPZ	12	TP	191	107	56%		
Bittner (Group 2)	MPZ LPZ AAPZ TZ	24 to 72 (54) #	TP	191	140	73%		
Dai	MPZ	6	TR	221	84	38%		
	MPZ LPZ	10	TR	221	90	41%		
Ficarra	MPZ	6	TP	480	169	35%		
	MPZ LPZ	8	TP	480	186	39%		
	MPZ LPZ	10	TP	480	196	41%		
	MPZ LPZ ALH	12	TP	480	202	42%		
	MPZ LPZ ALH TZ	14	TP	480	210	44%		
Irani (Group 1)	MPZ LPZ	12	TR	170	71	42%		
Irani (Group 2)	MPZ LPZ	20	TR	169	81	48%		
Janane	MPZ	6	TR	79	8	10%		
	MPZ LPZ	12	TR	79	11	14%		
	MPZ LPZ TZ	18	TR	79	14	18%		
	MPZ LPZ MLiPZ TZ	24	TR	79	18	23%		
Lecuona (Group 1)	LPZ	8	TR	151	58	38%		
Lecuona (Group 2)	LPZ	6 to 18 (10) #	TR	152	54	36%		
Mariappan (Group 1)*	LPZ	6	TR	69	13	19%		
Mariappan (Group 2)*	MPZ LPZ	8 to 14 (10) #	TR	63	19	30%		
Miyake	MPZ LPZ ALH	8	TR	788	198	25%		
	MPZ LPZ ALH TZ	10	TR	788	209	27%		
Moussa	MPZ	6	TR	181	58	32%		
	MPZ LPZ	8	TR	181	76	42%		
	MPZ LPZ	10	TR	181	76	42%		
	MPZ LPZ	12	TR	181	80	44%		
	MPZ LPZ AAPZ	14	TR	181	86	48%		
Orikasa	MPZ LPZ	10	TR	549	239	44%		
	MPZ LPZ AAPZ	12	TR	549	252	46%		

Park (Group 1)	MPZ LPZ	12	TR	118	40	34%	19	16%
Park (Group 2)	MPZ LPZ	12	TR	115	40	35%		
Park (Group 2)	MPZ LPZ MLPZ	18	TR	115	49	43%	26	23%
Patel	MPZ	8	TR	139	40	29%	15	11%
	LPZ	16	TR	139	53	38%	22	16%
	MPZ LPZ	24	TR	139	62	45%	23	17%
Ploussard	MPZ	6	TR	2,753	896	33%	473	17%
	MPZ LPZ	12	TR	2,753	1,111	40%	516	19%
	MPZ LPZ TZ	18	TR	2,753	1,167	42%		
	MPZ LPZ MLiPZ TZ	21	TR	2,753	1,191	43%	529	19%
Rochester (Group 1)	MPZ LPZ	6	TR	122	51	42%	32	26%
Rochester (Group 1)	MPZ LPZ MLiPZ ALH	12	TR	122	63	52%	38	31%
Rochester (Group 2)	MPZ	6	TR	122	36	30%	26	21%
Rochester (Group 2)	MPZ LPZ	12	TR	122	48	39%	31	25%
Rochester (Group 2)	MPZ LPZ MLiPZ ALH	15	TR	122	50	41%	31	25%
Rodriguez (Group 1)	LPZ	12	TR	75	23	31%	10	13%
Rodriguez (Group 2)	LPZ	12	TR	75	34	45%		
Rodriguez (Group 2)	LPZ fLPZ	18	TR	75	36	48%	15	20%
Sur (Group 1)	MPZ LPZ	6 to 12 (10) #	TR	88	34	39%	14	16%
Sur (Group 2)	MPZ LPZ MLiPZ TZ	24	TR	94	39	41%	19	20%
Takenaka (Group 1)	MPZ LPZ TZ	12	TR	100	53	53%		
Takenaka (Group 2)	MPZ LPZ TZ	12	TP	100	47	47%		
Takeshita	MPZ LPZ TZ	14	TP	744	231	31%		
Uno	MPZ	6	TR	313	99	32%		
	TZ	2	TR	313	49	16%		
	fLPZ	6	TR	313	106	34%		
	MPZ TZ	8	TR	313	103	33%		
	fLPZ TZ	8	TR	313	111	35%		
	MPZ fLPZ	12	TR	313	126	40%		
	MPZ fLPZ TZ	14	TR	313	127	41%		

^ Biopsy components were studied in a single group of men unless multiple groups are specified;
 # Number of cores sampled varied according to patient characteristics; Mean number of cores in brackets for analyses of Lecuona, Mariappan and Sur and median number of cores in brackets for Bittner;
** Results included in the analysis are those for prostate volume >20 ml;*

AAPZ = anterior apical peripheral zone; ALH = anterior lateral horn; fLPZ = far lateral peripheral zone; LPZ = lateral peripheral zone; MLiPZ = midline peripheral zone; MLPZ = mediolateral peripheral zone; MPZ = mid-lobar peripheral zone; TP = transperineal approach; TR = transrectal approach; TZ = transition zone;

Table 36: Associations between prostate cancer detection and biopsy-section characteristics

Biopsy-section characteristics	Cancers/ biopsy components (%)	Unadjusted OR (95%CI)	Adjusted^ OR (95%CI)
Total:	**9,120/23,822 (38.3)**		
Number of cores: range (reference point for OR*)			
2 to 8 (6)	2,341/7,331 (31.9)	1.00	1.00
10 to 12 (11)	3,225/8,065 (40.0)	1.18 (1.16, 1.21)	1.21 (1.12, 1.30)
14 to 16 (14)	757/1,979 (38.3)	1.31 (1.26, 1.35)	1.36 (1.21, 1.52)
18 to 20 (18)	1,347/3,191 (42.2)	1.50 (1.42, 1.57)	1.58 (1.32, 1.88)
21 to 54 (24)	1,450/3,256 (44.5)	1.83 (1.70, 1.98)	1.98 (1.52, 2.58)
overall p-value		<0.001	<0.001
Location of cores			
MPZ	1,390/4,288 (32.4)	1.00	1.00
LPZ	235/661 (35.6)	1.15 (0.97, 1.36)	1.12 (0.91, 1.39)
TZ	49/313 (15.7)	0.39 (0.29, 0.52)	0.47 (0.36, 0.61)
fLPZ	106/313 (33.9)	1.07 (0.85, 1.35)	1.11 (0.91, 1.34)
MPZ LPZ	2,618/6,402 (40.9)	1.44 (1.37, 1.51)	1.12 (1.03, 1.22)
MPZ TZ	103/313 (32.9)	1.02 (0.81, 1.28)	0.98 (0.92, 1.05)
fLPZ TZ	111/313 (35.5)	1.15 (0.91, 1.44)	1.10 (0.91, 1.33)
MPZ fLPZ	126/313 (40.3)	1.40 (1.13, 1.75)	1.16 (0.99, 1.36)
LPZ fLPZ	36/75 (48.0)	1.92 (1.22, 3.04)	1.04 (0.82, 1.32)
MPZ LPZ TZ	1,512/3,776 (40.0)	1.39 (1.31, 1.48)	0.97 (0.82, 1.15)
MPZ LPZ ALH	400/1,268 (31.5)	0.96 (0.85, 1.09)	1.09 (0.95, 1.24)
MPZ LPZ AAPZ	338/730 (46.3)	1.80 (1.54, 2.10)	1.17 (1.03, 1.33)
MPZ fLPZ TZ	127/313 (40.6)	1.42 (1.14, 1.77)	1.09 (0.91, 1.31)
MPZ LPZ MLPZ	49/115 (42.6)	1.55 (1.06, 2.25)	1.24 (0.96, 1.62)
MPZ LPZ MLiPZ TZ	1,248/2,926 (42.7)	1.55 (1.46, 1.65)	0.90 (0.72, 1.12)
MPZ LPZ ALH TZ	419/1,268 (33.0)	1.03 (0.91, 1.16)	1.08 (0.92, 1.27)
MPZ LPZ MLiPZ ALH	113/244 (46.3)	1.80 (1.39, 2.32)	1.20 (1.00, 1.45)
MPZ LPZ AAPZ TZ	140/191 (73.3)	5.72 (4.13, 7.94)	0.49 (0.23, 1.02)
overall p-value		<0.001	<0.001
Direction of biopsy			
TP	1,488/3,626 (41.0)	1.00	1.00
TR	7,632/20,196 (37.8)	0.87 (0.76, 1.00)	1.27 (0.73, 2.22)
overall p-value		0.047	0.396

** Reference points equal the mean number of cores within each category for all for all biopsy components in the all cancers analysis; ORs for reference points obtained from the β coefficient for the continuous linear predictor "number of cores";*
^ Adjusted for study, direction of biopsy, number of cores and region(s) sampled;

AAPZ = anterior apical peripheral zone; ALH = anterior lateral horn; fLPZ = far lateral peripheral zone; LPZ = lateral peripheral zone; MLiPZ = midline peripheral zone; MLPZ = mediolateral peripheral zone; MPZ = mid-lobar peripheral zone; OR = odds ratio; TP = transperineal approach; TR = transrectal approach; TZ = transition zone;

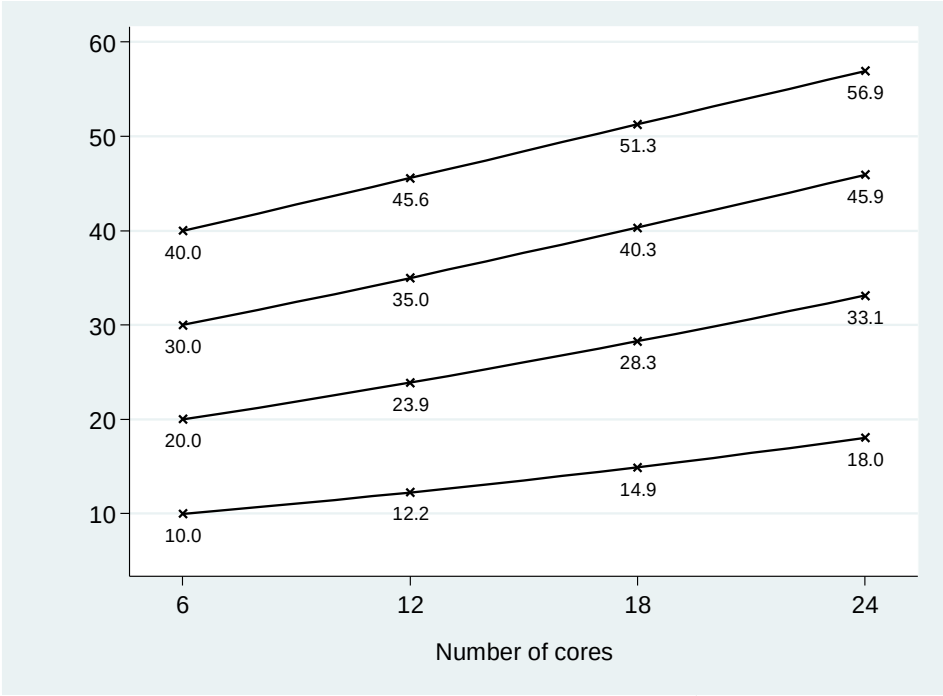
Table 37: Associations between prostate cancer detection and biopsy component characteristics for the 6 studies that were included in the Gleason Score >6 analysis

		Gleason Score >6		All cancers
		Unadjusted	Adjusted^	Adjusted^
Biopsy-section characteristics	**Cancers/ biopsy components**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
Total:	**1839/9851 (18.7)**			
Number of cores: range (reference point for OR*)				
6 to 8 (6)	546/3136 (17.4)	1.00	1.00	1.00
10 to 12 (11)	628/3278 (19.2)	1.03 (1.02, 1.05)	1.22 (1.04, 1.42)	1.19 (1.05, 1.34)
14 to 16 (14)	53/261 (20.3)	1.06 (1.03, 1.09)	1.37 (1.07, 1.76)	1.31 (1.07, 1.61)
18 to 20 (18)	41/190 (21.6)	1.09 (1.04, 1.13)	1.60 (1.11, 2.33)	1.50 (1.11, 2.03)
21 to 24 (24)	571/2986 (19.1)	1.13 (1.06, 1.21)	2.03 (1.16, 3.55)	1.84 (1.17, 2.90)
overall p-value		<0.001	0.013	0.008
Location of cores				
MPZ	514/3014 (17.1)	1.00	1.00	1.00
LPZ	32/214 (15.0)	0.86 (0.59, 1.25)	1.14 (0.99, 1.31)	1.16 (0.95, 1.41)
MPZ LPZ	635/3342 (19.0)	1.14 (1.09, 1.19)	0.88 (0.73, 1.07)	1.15 (0.98, 1.35)
LPZ fLPZ	15/75 (20.0)	1.22 (0.69, 2.16)	1.47 (0.60, 3.56)	1.97 (0.98, 3.94)
MPZ LPZ MLPZ	26/115 (22.6)	1.42 (0.91, 2.22)	1.06 (0.50, 2.26)	1.35 (0.73, 2.50)
MPZ LPZ MLiPZ TZ	548/2847 (19.2)	1.16 (1.11, 1.21)	0.64 (0.40, 1.02)	0.95 (0.65, 1.40)
MPZ LPZ MLiPZ ALH	69/244 (28.3)	1.92 (1.45, 2.54)	0.85 (0.62, 1.18)	1.26 (0.94, 1.67)
overall p-value		<0.001	<0.001	<0.001
Direction of biopsy				
TP	0/0	.	.	.
TR	1839/9851 (18.7)	.	.	.
overall p-value		.	.	.

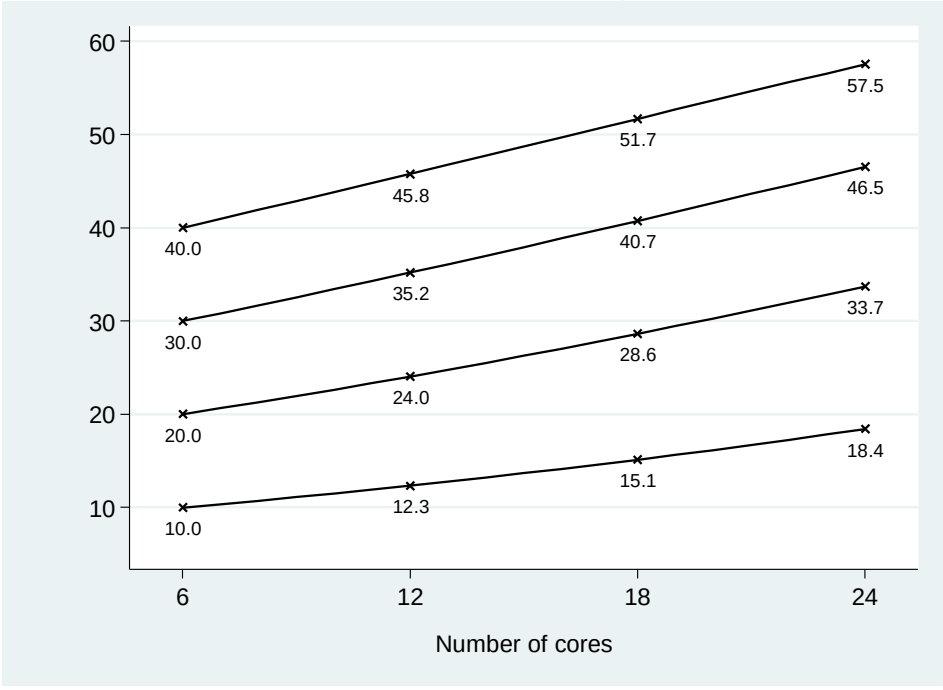
** Reference points equal the mean number of cores within each category for all biopsy components in the all cancers analysis; ORs for reference points obtained from the β coefficient for the continuous linear predictor "number of cores";*
^ Adjusted for study, number of cores and region of cores;

AAPZ = anterior apical peripheral zone; ALH = anterior lateral horn; fLPZ = far lateral peripheral zone; LPZ = lateral peripheral zone; MLiPZ = midline peripheral zone; MLPZ = mediolateral peripheral zone; MPZ = mid-lobar peripheral zone; OR = odds ratio; TP = transperineal approach; TR = transrectal approach; TZ = transition zone;

a. Gleason Score ≥6 cancers



b. Gleason Score >6 cancers



Diagnostic yields predicted from models adjusted for study, number of cores, region of cores and direction of biopsy

Figure 2: Predicted prostate cancer diagnostic yields by number of cores sampled when 6-core diagnostic yields are 10, 20, 30 or 40%

VI REFERENCES

Methods

1. Cui, James. "QIC program and model selection in GEE analyses." *Stata journal* 7, no. 2 (2007): 209-220.

Included studies

2. Alireza N, Pegah N. A prospective randomized comparison of diagnostic efficacy between transperineal and transrectal 12-core prostate biopsy. Int J Urol 2012; 19:361.

3. Bittner N, Merrick GS, Bennett A, Butler WM, Andreini HJ, Taubenslag W et al. Diagnostic performance of initial transperineal template-guided mapping biopsy of the prostate gland. Am J Clin Oncol Cancer Clin Trials 2013.

4. Dai B, Ye DW, Kong YY, Shen YJ, Wang BH. Individualized prostate biopsy strategy for Chinese patients with different prostate-specific antigen levels. Asian J Androl 2008; 10(2):325-331.

5. Eichler K, Hempel S, Wilby J, Myers L, Bachmann LM, Kleijnen J. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. J Urol 2006; 175(5):1605-1612.

6. Ficarra V, Novella G, Novara G, Galfano A, Pea M, Martignoni G et al. The potential impact of prostate volume in the planning of optimal number of cores in the systematic transperineal prostate biopsy. Eur Urol 2005; 48(6):932-937.

7. Hara R, Jo Y, Fujii T, Kondo N, Yokoyoma T, Miyaji Y et al. Optimal approach for prostate cancer detection as initial biopsy: prospective randomized study comparing transperineal versus transrectal systematic 12-core biopsy. Urology 2008; 71(2):191-195.

8. Irani J, Blanchet P, Salomon L, Coloby P, Hubert J, Malavaud B et al. Is an extended 20-core prostate biopsy protocol more efficient than the standard 12-core? A randomized multicenter trial. J Urol 2013; 190(1):77-83.

9. Janane A, Ould Ismail T, Hajji F, Ghadouane M, Ameur A, Abbar M. Saturation biopsy performed safely could enhance the detection of prostate cancer in a sub group of patients with PSA levels <10ng/ml: Results in first set of biopsies. Urology 2012; 80(3):S284.

10. Lecuona A, Heyns CF. A prospective, randomized trial comparing the Vienna nomogram to an eight-core prostate biopsy protocol. BJU Int 2011; 108(2):204-208.

11. Mariappan P, Chong WL, Sundram M, Mohamed SR. Increasing prostate biopsy cores based on volume vs the sextant biopsy: a prospective randomized controlled clinical study on cancer detection rates and morbidity. BJU Int 2004; 94(3):307-310.

12. Miyake H, Kurahashi T, Muramaki M, Yamanak K, Hara I. Significance of routine transition zone biopsies in Japanese men undergoing transrectal ultrasound-guided prostate biopsies. Int J Urol 2005; 12(11):964-968.

13. Moussa AS, Meshref A, Schoenfield L, Masoud A, Abdel-Rahman S, Li J et al. Importance of additional "extreme" anterior apical needle biopsies in the initial detection of prostate cancer. Urology 2010; 75(5):1034-1039.

14. Numao N, Kawakami S, Sakura M, Yoshida S, Koga F, Saito K et al. Characteristics and clinical significance of prostate cancers missed by initial transrectal 12-core biopsy. BJU Int 2012; 109(5):665-671.

15. Orikasa K, Ito A, Ishidoya S, Saito S, Endo M, Arai Y. Anterior apical biopsy: is it useful for prostate cancer detection? Int J Urol 2008; 15(10):900-904.

16. Park HK, Lee KY, Kim KH, Jung H, Yoon SJ, Kim TB. Intermediate versus low or high prostate-specific antigen density level: comparison of cancer detection rate between 12- and 18-core prostate biopsy. Scandinavian Journal of Urology & Nephrology 2010; 44(6):391-398.

17. Patel AR, Jones JS, Zhou M, Schoenfield L, Magi-Galluzzi C. Parasagittal biopsies are more important as part of an initial biopsy strategy than as part of a repeat biopsy strategy: observations from a unique population. Prostate Cancer & Prostatic Diseases 2007; 10(4):352-355.

18. Ploussard G, Nicolaiew N, Marchand C, Terry S, Vacherot F, Vordos D et al. Prospective evaluation of an extended 21-core biopsy scheme as initial prostate cancer diagnostic strategy. Eur Urol 2014; 65(1):154-161.

19. Rochester MA, Griffin S, Chappell B, McLoughlin J. A prospective randomised trial of extended core prostate biopsy protocols utilizing 12 versus 15 cores. Urologia Internationalis 2009; 83(2):155-159.

20. Rodriguez-Covarrubias F, Gonzalez-Ramirez A, Aguilar-Davidov B, Castillejos-Molina R, Sotomayor M, Feria-Bernal G. Extended sampling at first biopsy improves cancer detection rate: results of a prospective, randomized trial comparing 12 versus 18-core prostate biopsy. J Urol 2011; 185(6):2132-2136.

21. Sur RL, Borboroglu PG, Roberts JL, Amling CL. A prospective randomized comparison of extensive prostate biopsy to standard biopsy with assessment of diagnostic yield, biopsy pain and morbidity. Prostate Cancer & Prostatic Diseases 2004; 7(2):126-131.

22. Takenaka A, Hara R, Ishimura T, Fujii T, Jo Y, Nagai A et al. A prospective randomized comparison of diagnostic efficacy between transperineal and transrectal 12-core prostate biopsy. Prostate Cancer & Prostatic Diseases 2008; 11(2):134-138.

23. Takeshita H, Numao N, Kijima T, Yokoyama M, Ishioka J, Matsuoka Y et al. Diagnostic performance of initial transperineal 14-core prostate biopsy to detect significant cancer. Int Urol Nephrol 2013;45(3):645-52.

24. Uno H, Nakano M, Ehara H, Deguchi T. Indications for extended 14-core transrectal ultrasound-guided prostate biopsy. Urology 2008; 71(1):23-27.

2.7 Body of Evidence

I DETECTION OF PROSTATE CANCER

i. Meta-analyses

Name of study	Study type	N	Level of evidence*	Quality of evidence**	Risk of bias	Size of effect (95% CI)	p value	Relevance of evidence*
Extended vs. 2 to 8 core (mean = 6) scheme (initial biopsy)								
Patient-level regression analysis 2014 ***10 to 12 core (mean = 11)***	MA	N/A	I	N/A	N/A	OR^ = 1.21 (1.12 - 1.30)	NR	1
14 to 16 core (mean = 14)	MA	N/A	I	N/A	N/A	OR^ = 1.36 (1.21 - 1.52)	NR	1
18 to 20 core (mean = 18)	MA	N/A	I	N/A	N/A	OR^ = 1.58 (1.32 - 1.88)	NR	1
21 to 54 core (mean = 24)	MA	N/A	I	N/A	N/A	OR^ = 1.98 (1.52 - 2.58)	NR	1
							Overall p value <0.001	
Extended vs. 6 core scheme (mixed population of initial and repeat biopsies)								
Eichler 2006 (7 studies) ***8*** *MPZ+LPZ vs. MPZ*	MA (SS)	2,437	I	High	Low	RPR = 1.19 (1.14 – 1.24)	NR	1
Eichler 2006 (16 studies) ***8*** *MPZ+TZ(+MLiPZ) vs. MPZ*	MA (SS)	5,013	I	High	Low	RPR = 1.04 (1.02 – 1.06)	NR	1
Eichler 2006 (13 studies) ***10*** *MPZ+LPZ vs. MPZ*	MA (SS)	3,155	I	High	Low	RPR = 1.25 (1.19 – 1.33)	NR	1
Eichler 2006	MA (SS)	955	I	High	Low	RPR = 1.13 (1.04 – 1.24)	NR	1

(4 studies) ***10/11*** *MPZ+TZ vs. MPZ*						significant heterogeneity		
Eichler 2006 (13 studies) ***12*** *MPZ+LPZ vs. MPZ*	MA (SS)	2,178	I	High	Low	RPR = 1.31 (1.25 –1.37)	NR	1
Eichler 2006 (2 studies) ***14*** *MPZ+LPZ+TZ vs. MPZ*	MA (SS)	342	I	High	Low	RPR = 1.33 (1.15 – 1.54)	NR	1
Extended vs. 6 core scheme (initial biopsy population)								
Eichler 2006 (2 studies) ***8*** *MPZ+TZ(+MLiPZ) vs. MPZ*	MA (SS)	435	I	High	Low	RPR = 1.01 (0.99 – 1.03)	NR	1
Location of cores - other vs MPZ (initial biopsy population)								
Patient-level regression analysis 2014								
LPZ	MA	N/A	I	N/A	N/A	OR^ = 1.15 (0.97- 1.36)	NR	1
TZ	MA	N/A	I	N/A	N/A	OR^ = 0.39 (0.29 - 0.52)	NR	1
fLPZ	MA	N/A	I	N/A	N/A	OR^ = 1.07 (0.85 - 1.35)	NR	1
MPZ LPZ	MA	N/A	I	N/A	N/A	OR^ = 1.44 (1.37 - 1.51)	NR	1
MPZ TZ	MA	N/A	I	N/A	N/A	OR^ = 1.02 (0.81 - 1.28)	NR	1
fLPZ TZ	MA	N/A	I	N/A	N/A	OR^ = 1.15 (0.91 - 1.44)	NR	1
MPZ fLPZ	MA	N/A	I	N/A	N/A	OR^ = 1.40 (1.13 - 1.75)	NR	1
LPZ fLPZ	MA	N/A	I	N/A	N/A	OR^ = 1.92 (1.22 - 3.04)	NR	1
MPZ LPZ TZ	MA	N/A	I	N/A	N/A	OR^ = 1.39 (1.31 - 1.48)	NR	1
MPZ LPZ ALH	MA	N/A	I	N/A	N/A	OR^ = 0.96 (0.85 - 1.09)	NR	1

MPZ LPZ AAPZ	MA	N/A	I	N/A	N/A	OR^ = 1.80 (1.54 - 2.10)	NR	1
MPZ fLPZ TZ	MA	N/A	I	N/A	N/A	OR^ = 1.42 (1.14 - 1.77)	NR	1
MPZ LPZ MLPZ	MA	N/A	I	N/A	N/A	OR^ = 1.55 (1.06 - 2.25)	NR	1
MPZ LPZ MLiPZ TZ	MA	N/A	I	N/A	N/A	OR^ = 1.55 (1.46 - 1.65)	NR	1
MPZ LPZ ALH TZ	MA	N/A	I	N/A	N/A	OR^ = 1.03 (0.91 - 1.16)	NR	1
MPZ LPZ MLiPZ ALH	MA	N/A	I	N/A	N/A	OR^ = 1.80 (1.39 - 2.32)	NR	1
MPZ LPZ AAPZ TZ	MA	N/A	I	N/A	N/A	OR^ = 5.72 (4.13 - 7.94)	NR	1
							overall p-value <0.001	
Transrectal vs transperineal approach (initial biopsy population)								
Patient-level regression analysis 2014	MA	N/A	I	N/A	N/A	OR^ = 1.27 (0.73 – 2.22)	0.396	1

AAPZ = anterior apical peripheral zone; ALH = anterior lateral horn; CI = confidence interval; fLPZ = far lateral peripheral zone; LPZ = lateral peripheral zone; MA = meta-analysis; MLiPZ = midline peripheral zone; MLPZ = mediolateral peripheral zone; MPZ = mid-lobar peripheral zone; N/A = not applicable; NNT = number needed to treat (test); NR = not reported; PSA = prostate specific antigen; OR = odds ratio from patient level regression analysis; RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy / men diagnosed out of men undergoing comparison biopsy); SS = sequential sampling design; TR = transrectal approach; TP = transperineal approach; TZ = transition zone;

^ Adjusted for study, direction of biopsy, number of cores and region(s) sampled;

** Refer to appendix B for detailed explanations of rating scores*

*** See table 9-14 for detailed quality appraisals*

The QUADAS rating, "at risk of bias" was modified to include a moderate and high risk of bias so as to distinguish the studies at greater risk of bias.

Sequential sampling studies were not included in NHMRC evidence hierarchy. This study design was considered superior to RCT design and thus was considered at least level II evidence.

ii. Primary studies published post 2004 – unshaded studies included in 2014 patient–level regression analyses

Name of study	Study type	N	Level of evidence*	Quality of evidence**	Risk of bias	Results summary			p value	Relevance of evidence*
						RPR (95% CI)	RD (95% CI)	NNT		
Extended vs. 6 core scheme (initial biopsy population)										
Dai 2008 - overall	SS	221	II	Low	High	1.07 (1.01 – 1.13)	2.7% (1.2 – 5.3)	13	0.031	1
PSA <10		99				2.00 (0.90 – 4.45)	3.0% (0.0 – 7.4)	15	<0.001	
PSA 10-20		36				1.33 (0.89 – 1.99)	5.6% (0.0 – 15.8)	14	NR	
PSA 20-50		23				1.07 (0.94 – 1.21)	4.3% (0.0 – 17.0)	10	NR	
PSA 50-100		29				1.00 (1.00 – 1.00)	0.0% (0.0 – 3.4)	11	NR	
PSA >100		34				1.00 (1.00 – 1.00)	0.0% (0.0 – 2.9)	10	NR	
10 *MPZ+TZ vs. MPZ*										
Extended vs. 8 core scheme (initial biopsy population)										
Moussa 2010	SS	181	II	Low	High	1.00 (1.00 – 1.00)	0.0% (0.0 – 0.6)	N/A	1.000	1
10 *MPZ+apical+midgland LPZ vs. MPZ+apical LPZ*										
Ficarra 2005 - overall	SS	480	II	medium	moderate	1.05 (1.02 – 1.09)	2.1% (0.6 – 3.6)	48	NR	1
vol <30		159				1.02 (1.00 – 1.05)	1.2% (0.0 – 3.6)	80	NR	
vol 30-50		197				1.05 (1.00 – 1.11)	2.0% (0.0 – 4.5)	50	NR	
vol >50		124				1.18 (1.00 – 1.39)	3.2% (0.0 – 7.1)	31	NR	
10 *MPZ+apical+midgland LPZ vs. MPZ+apical LPZ*										
Miyake 2005 - overall	SS	788	II	Low	High	1.06 (1.02 – 1.09)	1.4% (0.4 – 2.3)	72	NR	1
vol <30		315				1.05 (1.01 – 1.10)	1.9% (0.1 – 3.7)	53	NR	
vol 30-50		351				1.06 (1.00 – 1.13)	1.1% (0.0 – 2.5)	88	NR	
vol >50		122				1.05 (0.96 – 1.15)	0.8% (0.0 – 3.2)	122	NR	
PSA <4		193				1.05 (0.96 – 1.15)	0.5% (0.0 – 2.0)	193	NR	
PSA 4-10		413				1.02 (0.99 – 1.05)	0.5% (0.0 – 1.4)	207	NR	
PSA >10		182				1.11 (1.03 – 1.18)	4.4% (0.1 – 7.9)	23	NR	
10 *PZ+ALH+TZ vs. PZ+ALH*										
Ficarra 2005 - overall	SS	480	II	Medium	Moderate	1.09 (1.04 – 1.13)	3.3% (1.5 – 5.1)	30	NR	1
vol <30		159				1.03 (1.00 – 1.07)	1.9% (0.0 – 4.6)	53	NR	
vol 30-50		197				1.10 (1.02 – 1.17)	3.6% (0.4 – 6.6)	29	NR	
vol >50		124				1.27 (1.05 – 1.54)	4.8% (0.3 – 9.4)	21	NR	

***12** MPZ+apical+midgland LPZ+ALH vs. MPZ+apical LPZ*										
Moussa 2010	SS	181	II	Low	High	1.05 (1.00 – 1.11)	2.2% (0.0 – 4.9)	46	NR	1
***12** MPZ+LPZ vs. MPZ+LPZ*										
Moussa 2010	SS	181	II	Low	High	1.13 (1.05 – 1.22)	5.5% (1.6 – 9.4)	19	NR	1
***14** MPZ+LPZ+extreme AAPZ vs. MPZ+LPZ*										
Uno 2008 - overall	SS	313	II	Low	High	1.14 (1.07 – 1.22)	5.1% (2.3 – 7.9)	20	NR	1
PSA <4		29				1.00 (1.00 – 1.00)	0.0% (0.0 – 0.3)	N/A	NR	
PSA 4-10		181				1.22 (1.08 – 1.38)	5.5% (1.6 – 9.4)	19	NR	
PSA 10-20		57				1.04 (0.97 – 1.11)	1.8% (0.0 – 6.9)	57	NR	
PSA >20		46				1.15 (1.02 – 1.30)	10.9% (0.0 – 22.0)	10	NR	
***14** fLPZ+TZ+MPZ vs. fLPZ+TZ*										
Uno 2008 - overall	SS	313	II	Low	High	1.23 (1.13 – 1.34)	7.7% (4.4 – 10.9)	14	NR	1
PSA <4		29				1.25 (0.81 – 1.94)	3.4% (0.0 – 13.5)	29	NR	
PSA 4-10		181				1.49 (1.24 – 1.79)	9.9% (5.0 – 14.9)	11	NR	
PSA 10-20		57				1.12 (0.99 – 1.26)	5.3% (0.0 – 12.8)	19	NR	
PSA >20		46				1.06 (0.98 – 1.14)	4.3% (0.0 – 12.4)	23	NR	
***14** MPZ+TZ+fLPZ vs. MPZ+TZ*										
Ficarra 2005 - overall	SS	480	II	Medium	Moderate	1.13 (1.08 – 1.19)	5.0% (2.8 – 7.1)	20	NR	1
vol <30		159				1.05 (1.01 – 1.11)	3.1% (0.0 – 6.5)	32	NR	
vol 30-50		197				1.15 (1.06 – 1.25)	5.6% (1.9 – 9.3)	18	NR	
vol >50		124				1.36 (1.10 – 1.69)	6.5% (1.3 – 11.6)	16	NR	
***14** MPZ+apical+midgland LPZ+ALH+anterior TZ vs. MPZ+apical LPZ*										
Patel 2007	SS	139	II	Low	High	1.55 (1.29 – 1.86)	15.8% (9.0 – 22.6)	7	NR	1
***24** MPZ+LPZ vs. MPZ*										
Volume-dependant vs. 6/8 core scheme (initial biopsy population)										
Mariappan 2004 - overall	RCT	132	II	Low	High	1.60 (0.86 – 2.97)	11.3% (-3.3 – 25.9)	9	0.130	1
vol >20		23				1.81 (0.92 – 3.57)	13.5% (-1.3 – 28.2)	8	0.078	
vol 20-40		42				1.82 (0.65 – 5.12)		7	0.241	

vol >40 *vol-dependant **8-14** LPZ+MPZ+fLPZ vs. LPZ*		81				1.79 (0.73 – 4.37)	16.4% (-10.3 – 43.0) 11.8 (-5.7 – 29.3)	9	0.191	
Lecuona 2011 vol >50 PSA <10 *vol-, age-dependant **6-18** LPZ vs. LPZ*	RCT	303 112 226	II	Low	High	0.92 (0.69 – 1.24) 0.85 (0.44 – 1.69) 0.85 (0.57 – 1.26)	-2.9% (-13.8 – 8.0) -3.8% (-19.6 – 12.0) -5.0% (-17.0 – 7.0)	35 27 21	0.603 0.640 0.418	1
Extended vs. 10 core scheme (initial biopsy population)										
Moussa 2010 ***12** MPZ+LPZ+extreme AAPZ vs. MPZ+LPZ*	SS	181	II	Low	High	1.05 (1.00 – 1.11)	2.2% (0.0 – 4.9)	46	0.167	1
Orikasa 2008 ***12** MPZ+LPZ+AAPZ vs. MPZ+LPZ*	SS	549	II	Low	High	1.05 (1.02 – 1.09)	2.4% (0.1 – 3.8)	43	NR	1
Ficarra 2005 - overall vol <30 vol 30-50 vol >50 ***12** MPZ+apical+midgland LPZ+ALH vs. MPZ+apical+midgland LPZ*	SS	480 159 197 124	II	Medium	Moderate	1.03 (1.01 – 1.06) 1.01 (0.99 – 1.03) 1.04 (0.99 – 1.08) 1.08 (0.97 – 1.19)	1.3% (0.0 – 2.4) 0.6% (0.0 – 2.5) 1.5% (0.0 – 3.7) 1.6% (0.0 – 4.6)	80 159 66 62	NR NR NR NR	1
Ficarra 2005 - overall vol <30 vol 30-50 vol >50 ***12** MPZ+apical+midgland LPZ+ALH+TZ vs. MPZ+apical+midgland LPZ*	SS	480 159 197 124	II	Medium	Moderate	1.07 (1.03 – 1.11) 1.03 (1.00 – 1.07) 1.09 (1.02 – 1.16) 1.15 (1.00 – 1.33)	2.9% (1.2 – 4.6) 1.9% (0.0 – 4.6) 3.6% (0.5 – 6.6) 3.2% (0.0 – 7.1)	35 53 29 31	NR NR NR NR	1

Moussa 2010 ***14*** *MPZ+LPZ+extreme AAPZ vs. MPZ+LPZ*	SS	181	II	Low	High	1.13 (1.05 – 1.22)	5.5 (1.6 – 9.4)	19	NR	1
Extended vs. 6-12 core scheme (initial biopsy population)										
Sur 2004 - overall	RCT	197	II	Low	High	1.07 (0.75 – 1.53)	2.9% (-11.4 – 17.1)	36	0.695	1
vol ≥40		64				0.83 (0.43 – 1.60)	-6.7% (-30.9 – 17.6)	15	0.588	
vol <40		118				1.24 (0.81 – 1.89)	9.2% (-8.7 – 27.0)	11	0.314	
PSA ≥10		26				1.29 (0.82 – 2.02)	19.0% (-13.3–51.4)	6	0.251	
PSA <10		158				0.99 (0.64 – 1.53)	-0.5% (-15.3 – 14.4)	218	0.952	
24 *MPZ+LPZ+TZ+MLiPZ vs. MPZ(+LPZ)*										
Extended vs. 12/14 core scheme (initial biopsy population)										
Moussa 2010 ***14*** *MPZ+LPZ+extreme AAPZ vs. MPZ+LPZ*	SS	181	II	Low	High	1.08 (1.01 – 1.14)	3.3 (0.1 – 6.5)	31	0.046	1
Ficarra 2005 - overall	SS	480	II	Medium	Moderate	1.04 (1.01 – 1.07)	1.7% (0.3 – 3.0)	60	NR	1
vol <30		159				1.02 (0.99 – 1.05)	1.3% (0.0 – 3.6)	80	NR	
vol 30-50		197				1.05 (1.00 – 1.10)	2.0% (0.0 – 4.5)	50	NR	
vol >50		124				1.07 (0.97 – 1.18)	1.6% (0.0 – 4.6)	62	NR	
14 *MPZ+apical+midgland LPZ+ALH+anterior TZ vs. MPZ+apical+midgland LPZ+ALH*										
Uno 2008 - overall	SS	313	II	Low	High	1.01 (0.99 – 1.02)	0.3% (0.0 – 1.2)	313	NR	1
PSA <4		29				1.00 (1.00 – 1.00)	0.0% (0.0 – 0.3)	N/A	NR	
PSA 4-10		181				1.02 (0.98 – 1.06)	0.6% (0.0 – 2.2)	181	NR	
PSA 10-20		57				1.00 (1.00 – 1.00)	0.0% (0.0 – 1.8)	N/A	NR	
PSA >20		46				1.00 (1.00 – 1.00)	0.0% (0.0 – 2.2)	N/A	NR	
14 *MPZ+fLPZ+TZ vs. MPZ+fLPZ*										

Ploussard 2012 ***15*** *MPZ+LPZ+MLiPZ vs. MPZ+LPZ*	SS	2753	II	Low	High	1.03 (1.02 – 1.04)	1.2 (0.8 – 1.7)	81	NR	1
Rochester 2009 ***15*** *MPZ+LPZ+ALH +MLiPZ vs. MPZ+LPZ*	RCT SS	250 NR	II	Low	High	0.79 (0.60 – 1.04) 1.04 (0.98 – 1.10)	-10.7% (-23.1 – 1.8) 1.6% (0.0 – 4.7)	10 61	0.095 0.125	1
Rodriguez-Covarrubias 2011 ***18*** *LPZ+fLPZ vs. LPZ*	RCT, SS	150	II	Low	High					1
overall (RCT)		108				1.57 (1.03 – 2.37) 1.71 (1.07 – 2.73)	17.3% (1.9 – 32.7) 21.9% (3.8 – 40.1)	6 5	0.030 0.021	
vol ≤65		42				NR	NR	N/A	NS	
vol >65		103				1.96 (1.02 – 3.77)	18.9% (1.7 – 36.0)	6	0.035	
PSA ≤10		47				NR	NR	N/A	NS	
PSA >10		75				1.06	2.7%	NR	NR	
overall (SS)										

Irani 2013 ***20*** *MPZ+LPZ vs. MPZ+LPZ*	RCT	339	II	Low	High	RPR = 1.16	6.8%	15	0.21	1
Ploussard 2012 ***18*** *MPZ+LPZ+TZ vs. MPZ+LPZ*	SS	2753	II	Low	High	1.05 (1.04 – 1.06)	2.0 (1.5 – 2.6)	50	<0.001	1
Janane 2012 ***18*** *MPZ+posterolateral PZ+TZ vs. MPZ+posterolateral PZ*	SS	79	II	Low	High	1.27 (0.97 – 1.67)	3.8% (0.0 – 9.3)	27	NR	1
Park 2010 - overall (RCT)	RCT	233	II	Low	High	1.26 (0.90 – 1.75)	8.7% (-3.7 – 21.1)	12	0.171	1
vol <45		127				1.00 (0.67 – 1.48)	0.0% (-17.4 – 17.3)	N/A	0.996	
vol ≥45		106				2.05 (1.09 – 3.88)	21.1% (4.1 – 38.1)	5	0.019	
PSA <7		115				1.13 (0.60 – 2.12)	3.1% (-12.8 – 18.9)	33	0.706	
PSA ≥7		118				1.31 (0.91 – 1.88)	13.6% (-4.3 – 31.4)	8	0.141	
overall (SS) ***18*** *MPZ+LPZ+MLPZ vs. MPZ+LPZ*	SS	115		Low	High	1.23 (1.07 – 1.40)	7.8% (2.0 – 13.6)	13	NR	
Ploussard 2012 - overall	SS	2753	II	Low	High	1.07 (1.06 – 1.09)	2.9% (2.2 – 3.6)	35	<0.001	1
vol <50		NR				1.07	3.0%	33	<0.001	
vol 50-70		997				1.09 (1.06 – 1.13)	2.7% (1.6 – 3.8)	37	<0.001	
vol >70		NR				1.13	2.8%	36	<0.001	
PSA >10		630				1.04 (1.02 – 1.06)	2.5% (1.2 – 3.9)	40	<0.001	
PSA 4-10		NR				1.09	3.0%	33	<0.001	
PSA <4 ***21*** *MPZ+LPZ+TZ+MLiPZ vs. MPZ+LPZ*		297				1.18 (1.07 – 1.30)	3.7% (1.2 – 6.2)	27	<0.001	
Janane 2012 ***24*** *MPZ+posterolateral PZ+TZ+MLiPZ vs. MPZ+posterolateral PZ*	SS	79	II	Low	High	1.64 (1.13 – 2.37)	8.9% (1.3 – 16.4)	12	NR	1
Numao 2012 - overall	SS	715	II	Medium	Moderate	1.26 (1.18 – 1.34)	7.4% (5.4 – 9.5)	14	<0.001	1
vol >48		NR				~1.54*	~7%	NR	NR	

vol 36-47		NR				~1.29*	~5%	NR	NR	
vol 27-35		NR				~1.30*	~10%	NR	NR	
vol <26		NR				~1.15*	~8%	NR	NR	
26 *TR+TP vs. TR*										
Takeshita 2013 - overall	SS	744	II	Medium	Moderate	1.16 (1.11 – 1.22)	5.1% (3.4 – 6.8)	20	<0.001	1
vol <29		NR				~1.08	~4%	NR	NR	
vol 30-50		NR				~1.21	~5%	NR	NR	
vol >50		NR				~1.36	~4%	NR	NR	
PSA <4		NR				~1.09	~2%	NR	NR	
PSA 4-10		NR				~1.17	~5%	NR	NR	
PSA 10-20		NR				~1.13	~6%	NR	NR	
26 *TP+TR vs. TP*										
Bittner 2013 ***24-72*** *posterior+postero-lateral+anterolateral+AAPZ vs. posterior+posterolateral*	SS	191	II	Low	High	1.31 (1.19 – 1.43)	17.3% (11.3 – 23.2)	6	NR	1
Extended vs. ≥15 core scheme (initial biopsy population)										
Ploussard 2012 ***21*** *MPZ+LPZ+MLiPZ+TZ vs.* ***15*** *MPZ+LPZ+MLiPZ*	SS	2,753	II	Low	High	1.04 (1.03 – 1.05)	1.7% (1.2 – 2.2)	60	NR	1
Patel 2007 ***24*** *LPZ+MPZ vs.****16*** *LPZ*	SS	139	II	Low	High	1.17 (1.06 – 1.30)	6.5% (1.7 – 11.3)	16	NR	1
Ploussard 2012 ***21*** *MPZ+LPZ+TZ+MLiPZ vs.* ***18*** *MPZ+LPZ+TZ*	SS	2753	II	Low	High	1.02 (1.01 – 1.03)	0.9% (0.4 – 1.3)	115	NR	1
Janane 2012 ***24*** *MPZ+posterolateral PZ+TZ+MLiPZ vs.* ***18*** *MPZ+posterolateral PZ+TZ*	SS		II	Low	High	1.29 (1.00 – 1.65)	5.1% (0.0 – 11.1)	20	NR	1

Transperineal vs. transrectal approach (initial biopsy population)										
Alireza 2012 - overall	RCT	390	II	Low	High	1.16 (0.88 – 1.54)	5.1% (-4.3 – 14.5)	20	0.285	1
PSA 4-10		NR				1.76	13.7%	NR	<0.05	
12 vs. 12										
Hara 2008 - overall	RCT	246	II	Low	High	0.87 (0.66 – 1.15)	-6.3% (-18.7 – 6.1)	16	0.323	1
vol <30		114				0.93 (0.68 – 1.28)	-4.3% (-22.4 – 13.9)	24	0.788	
vol 30-50		96				0.73 (0.44 – 1.22)	-12.0% (-31.4 – 7.3)	9	0.317	
vol >50		36				0.89 (0.29 – 2.80)	-2.8% (-31.0 – 0.25)	36	>0.999	
PSA 4-10		183				0.85 (0.59 – 1.21)	-6.5% (-20.7 – 7.6)	16	0.366	
PSA 10-20		63				0.92 (0.62 – 1.36)	-5.1% (-29.1 – 18.8)	20	0.674	
12 vs. 12										
Takenaka 2008 - overall	RCT	200	II	Low	High	0.89 (0.67 – 1.17)	-6% (-19.8 – 7.8)	17	0.480	1
PSA <4		4				N/A	100% (100 – 100)	1	0.333	
PSA 4-10		118				1.03 (0.63 – 1.67)	9.8% (-16.3 – 18.3)	103	>0.999	
PSA 10-20		44				0.68 (0.41 – 1.16)	-21.9% (-50.4 – 6.5)	5	0.220	
PSA >20		34				0.86 (0.66 – 1.12)	-13.2% (-35.1 – 8.7)	8	0.323	
12 vs. 12										

AAPZ = anterior apical peripheral zone; ALH = anterior lateral horn; CI = confidence interval; fLPZ = far lateral peripheral zone; LPZ = lateral peripheral zone; MLiPZ = midline peripheral zone; MLPZ = mediolateral peripheral zone; MPZ = mid-lobar peripheral zone; N/A = not applicable; NNT = number needed to treat (test); NR = not reported; NS = not statistically significantly different; PSA = prostate specific antigen; OR = odds ratio from patient level regression analysis; RCT = randomized controlled trial; RD = risk difference (men diagnosed out of men undergoing intervention biopsy – men diagnosed out of men undergoing comparison biopsy); RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy / men diagnosed out of men undergoing comparison biopsy); SS = sequential sampling design; TR = transrectal approach; TP = transperineal approach; TZ = transition zone;

** Refer to appendix B for detailed explanations of rating scores*

*** See table 9-14 for detailed quality appraisals*

The QUADAS rating, "at risk of bias" was modified to include a moderate and high risk of bias so as to distinguish the studies at greater risk of bias.

Sequential sampling studies were not included in NHMRC evidence hierarchy. This study design was considered superior to RCT design and thus was considered at least level II evidence.

II DETECTION OF GLEASON SCORE>6 CANCER

i. Meta-analyses

Name of study	Study type	N	Level of evidence*	Quality of evidence**	Risk of bias	OR^ (95% CI)	p value	Relevance of evidence*
Extended vs. 6 to 8 core (mean = 6) scheme (initial biopsy)								
Patient-level regression analysis 2014 ***10 to 12 core (mean = 11)***	MA	N/A	I	N/A	N/A	1.22 (1.04 - 1.42)	NR	1
14 to 16 core (mean = 14)	MA	N/A	I	N/A	N/A	1.37 (1.07 - 1.76)	NR	1
18 to 20 core (mean = 18)	MA	N/A	I	N/A	N/A	1.60 (1.11 - 2.33)	NR	1
21 to 54 core (mean = 24)	MA	N/A	I	N/A	N/A	2.03 (1.16 - 3.55)	NR	1
							overall p-value 0.013	
Location of cores vs MPZ (initial biopsy population)								
Patient-level regression analysis 2014 LPZ	MA	N/A	I	N/A	N/A	1.14 (0.99 - 1.31)	NR	1
MPZ LPZ	MA	N/A	I	N/A	N/A	0.88 (0.73 - 1.07)	NR	1
LPZ fLPZ	MA	N/A	I	N/A	N/A	1.47 (0.60 - 3.56)	NR	1
MPZ LPZ MLPZ	MA	N/A	I	N/A	N/A	1.06 (0.50 - 2.26)	NR	1
MPZ LPZ MLiPZ TZ	MA	N/A	I	N/A	N/A	0.64 (0.40 - 1.02)	NR	1

MPZ LPZ MLiPZ ALH	MA	N/A	I	N/A	N/A	0.85 (0.62 - 1.18)	NR	1
							overall p-value <0.001	

ALH = anterior lateral horn; CI = confidence interval; fLPZ = far lateral peripheral zone; GS = Gleason Score; LPZ = lateral peripheral zone; MA = meta-analysis; MLPZ = mediolateral peripheral zone; MLiPZ = midline peripheral zone; MPZ = mid-lobar peripheral zone; N/A = not applicable; NNT = number needed to treat (test); NR = not reported; OR = odds ratio from patient level regression analysis; PSA = prostate specific antigen; TZ = transition zone;

** Refer to appendix B for detailed explanations of rating scores*

*** See Tables 9-14 for quality appraisals*

^ Adjusted for study, direction of biopsy, number of cores and region(s) sampled
The QUADAS rating, "at risk of bias" was modified to include a moderate and high risk of bias so as to distinguish the studies at greater risk of bias.

Clinical significance of size of effect is addressed in the assessment of clinical impact in the evidence statement table of content template.

Sequential sampling studies were not included in NHMRC evidence hierarchy. This study design was considered superior to RCT design and thus was considered at least level II evidence.

ii. Primary studies published post 2004 – unshaded studies included in 2014 patient–level regression analyses

Name of study	Study type	N	Level of evidence*	Quality of evidence**	Risk of bias	Results summary			p value	Relevance of evidence*
						RPR (95% CI)	RD (95% CI)	NNT		
Extended vs. 8 core scheme (initial biopsy population)										
Miyake 2005	SS		II	Low	High					1
GS>7 - overall		788				1.03 (0.97 – 1.08)	0.1% (0.0 – 0.5)	788	NR	
prostatectomy subgroup		98				1.08 (0.93 – 1.25)	1.0% (0.0 – 4.3)	98	NR	
GS=7 - overall		788				1.05 (0.99 – 1.10)	0.4% (0.0 – 0.9)	263	NR	
prostatectomy subgroup		98				1.07 (0.97 – 1.17)	2.0% (0.0 – 5.9)	49	NR	
10 *PZ+TZ vs. PZ*										
Patel 2007	SS		II	Low	High					1
GS>7		139				1.67 (0.81 – 3.4)	1.4% (0.0 – 4.1)	70	NR	
GS=7		139				1.50 (1.08 – 2.08)	4.3% (0.2 – 8.4)	24	NR	
24 *MPZ+LPZ vs. MPZ*										
Extended vs. 6-12 core scheme (initial biopsy population)										
Sur 2004	RCT		II	Low	High					1
GS>7		197				2.34 (0.47 – 11.8)	3.0% (-2.5 – 8.5)	33	0.286	
GS=7		182				1.09 (0.53 – 2.23)	1.3% (-8.9 – 11.4)	80	0.809	
24 *MPZ+LPZ+TZ+MLiPZ vs. MPZ(+LPZ)*										
Extended vs. 12/14 core scheme (initial biopsy population)										
Rochester 2009	RCT		II	Low	High					1
GS≥7 (RCT)		244				0.82 (0.55 – 1.22)	-5.7% (-17.0 – 5.5)	18	0.320	
GS≥7 (SS)		122				1.00 (1.00 – 1.00)	0.0% (0.0 – 0.8)	N/A	NR	
15 *MPZ+LPZ+MLiPZ+ALH vs. MPZ+LPZ*										

Rodriguez-Covarrubias 2011	RCT	150	II	Low	High					1
GS>7 - overall		108				1.00 (0.30 – 3.31)	0.0% (-0.8 – 8.0)	N/A	1.000	
vol ≤65		103				0.83 (0.24 – 2.93)	-1.5% (-12.0 – 8.9)	65	0.772	
PSA ≤10		150				0.33 (0.04 – 3.04)	-4.0% (-11.4 – 3.5)	26	0.298	
GS=7 - overall		108				2.00 (0.72 – 5.57)	6.7% (-2.9 – 16.2)	15	0.174	
vol ≤65		103				1.87 (0.67 – 5.21)	7.9% (-4.8 – 20.5)	13	0.222	
PSA ≤10						4.90 (0.59–40.53)	7.7% (-1.2 – 16.5)	14	0.097	
18 *MPZ+LPZ+fLPZ vs. MPZ+LPZ*										
Park 2010	RCT	233	II	Low	High					1
GS>7						3.59 (1.22–10.59)	8.8% (2.0 – 15.6)	12	0.012	
GS=7						0.82 (0.40 – 1.68)	-2.3% (-10.5 – 5.9)	44	0.587	
18 *MPZ+LPZ+MLPZ vs. MPZ+LPZ*										
Ploussard 2010	SS	2,753	II	Low	High					1
GS>6						1.03 (1.01 – 1.04)	0.5% (0.2 – 0.8)	212	NR	
21 *MPZ+LPZ+MLiPZ+TZ vs. MPZ+LPZ*										
Numao 2012	SS	715	II	Medium	Moderate					1
GS>7						1.07 (1.00 – 1.14)	0.6% (0.0 – 1.2)	179	NR	
GS=7						1.19 (1.10 – 1.29)	2.5% (1.2 – 3.8)	40	NR	
26 *TR+TP vs. TR*										
Takeshita 2013	SS	744	II	Medium	Moderate					1
GS>7						1.09 (1.01 – 1.17)	6.7% (0.0 – 1.4)	149	NR	
GS=7						1.15 (1.07 – 1.23)	2.0% (0.9 – 3.1)	50	NR	
26 *TP+TR vs. TP*										
Extended vs. 16 core scheme (initial biopsy population)										
Patel 2007	SS	139	II	Low	high					1

GS>7	1.00 (1.00 – 1.00)	0.0% (0.0 – 0.7)	N/A	NR
GS=7	1.06 (0.95 – 1.18)	0.7% (0.0 – 2.8)	139	NR
24 *LPZ+MPZ vs. LPZ*				

ALH = anterior lateral horn; CI = confidence interval; fLPZ = far lateral peripheral zone; GS = Gleason Score; LPZ = lateral peripheral zone; MLPZ = mediolateral peripheral zone; MLiPZ = midline peripheral zone; MPZ = mid-lobar peripheral zone; N/A = not applicable; NNT = number needed to treat (test); NR = not reported; NS = not statistically significantly different; PSA = prostate specific antigen; RCT = randomized controlled trial; RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy / men diagnosed out of men undergoing comparison biopsy); RD = risk difference (men diagnosed out of men undergoing intervention biopsy – men diagnosed out of men undergoing comparison biopsy); SS = sequential sampling design; TP = transperineal approach; TR = transrectal approach; TZ = transition zone;

** Refer to appendix B for detailed explanations of rating scores*

*** See Tables 9-14 for quality appraisals*
The QUADAS rating, "at risk of bias" was modified to include a moderate and high risk of bias so as to distinguish the studies at greater risk of bias.

Clinical significance of size of effect is addressed in the assessment of clinical impact in the evidence statement table of content template.

Sequential sampling studies were not included in NHMRC evidence hierarchy. This study design was considered superior to RCT design and thus was considered at least level II evidence.

III ADVERSE EVENTS

Name of study	Study type	N	Level of evidence*	Quality of evidence**	Risk of bias	Results summary	RD (95% CI)	NNT	p value	Relevance of evidence*
Extended vs. 6 core scheme (mixed population of initial and repeat biopsies)										
Eichler 2006 (1 study) ***10*** *MPZ+LPZ vs. LPZ*	SR/RCT	200	II	Low	High	infection haematuria haemospermia rectal bleeding pain chills *% patients experiencing complications*	-0.2% 14.4% 9.7% 11.0% 1.2% 2.1%	500 7 11 10 84 49	NR NR NR NR NR NR	1
Eichler 2006 (1 study) ***12*** *MPZ+LPZ vs. LPZ*	SR/RCT	244	II	Medium	Moderate	infection haematuria haemospermia rectal bleeding *% patients experiencing complications*	-2% 5% 9% 6%	50 20 12 17	NR NR NR NR	1
Extended vs. 10 core scheme (unclear biopsy population)										
Eichler 2006 (1 study) ***14*** *MPZ+TZ(+MLiPZ) vs. MPZ+TZ(+MLiPZ)*	SR/RCT	222	II	Medium	Moderate	pain *% patients with discomfort*	36.9%	3	NR	1
Extended vs. 6 core scheme (initial biopsy population)										
Eichler 2006 (1 study) ***12*** *MPZ+LPZ vs. LPZ*	SR/RCT	214	II	Low	High	infection haematuria haemospermia voiding difficulties	0% -2% -5% 0%	N/A 50 20 N/A	NR NR NR NR	1

						% patients experiencing complications				
Volume-dependant vs. 6/8 core scheme (initial population)										
Mariappan 2004 *vol-dependant **8-14** LPZ+MPZ+fLPZ vs. LPZ*	RCT	132	II	Low	High	rectal bleeding haematuria haemospermia fever	15.3% (-0.3 – 30.9) 1.3% (-14.5 – 17.1) 4.6% (-8.4 – 25.4) 0.1% (-4.0 – 4.3)	7 77 12 725	0.059 0.871 0.325 0.948	1
Lecuona 2011 - overall *vol-, age-dependant **6-18** MPZ+ vs. MPZ*	RCT	303	II	Low	High	complication rate Subgroup: vol >50 fever urinary retention	-0.5% (-15.0 – 14.1) 21.4% (-2.8 – 45.6) -1.4% (-7.7 – 5.0) 1.1% (-1.0 – 3.2)	210 73 93 5	0.949 0.090 0.669 0.329	1
Extended vs. 6-12 core scheme (initial biopsy population)										
Sur 2004 ***24*** *MPZ+LPZ+TZ+MLiPZ vs. MPZ(+LPZ)*	RCT	197	II	Low	High	urinary retention atrial fibrillation rectal bleeding haematura	4.3% (0.2 – 8.3) 1.1% (-1.0 – 3.1) 0.0% (0.0 – 0.0) 0.0% (0.0 – 0.0)	234 94 N/A N/A	0.050 0.332 N/A N/A	1
Extended vs. 12 core scheme (initial biopsy population)										
Rodriguez-Covarrubias 2011 ***18** LPZ+fLPZ vs. LPZ*	RCT	150	II	Low	High	complication rate grade 1 grade 2 grade 3a	1.3% (-14.1 – 16.8) 1.3% (-13.8 – 16.5) 0.0% (-3.7 – 3.7) 0.0% (-3.7 – 3.7)	75 75 N/A N/A	0.866 0.863 1.000 1.000	1
Park 2010 ***18** MPZ+LPZ+MLPZ vs. MPZ+LPZ*	RCT	233	II	Low	High	complication rate	4.4% (-1.4 – 10.3)	23	0.140	1
Irani 2013 ***20** MPZ+LPZ vs. MPZ+LPZ*	RCT	339	II	Low	High	pain - VAS (med) IPSS (med) – baseline IPSS (med) – 5 days IPSS (med) – 15 days	20: 2.8; 12: 2.4 20: 6.0; 12: 5.0 20: 6.5; 12: 5.0 20: 5.0; 12: 4.5	NR NR NR NR	>0.18 NS 0.16 0.46	1 1 1 1

						QOL item (med) – basel.	20: 2.0; 12: 2.0	NR	NS	1
						QOL item (med) – 5 d	20: 3.0; 12: 3.0	NR	0.46	1
						QOL item (med) – 15 d	20: 3.0; 12: 2.0	NR	0.22	1
						fever - 5 d	-1.1%	88	>0.7	1
						fever - 15 d	0.0%	N/A	NR	1
						dysuria - 5 d	8.1%	13	0.043	1
						dysuria - 15 d	-1.3%	75	>0.6	1
						haematuria - 5 d	3.6%	28	>0.5	1
						haematuria - 15 d	6.8%	15	>0.1	1
						haemospermia – 5 d	-1.2%	85	>0.6	1
						haemospermia – 15 d	7.5%	14	>0.2	1
						rectal bleeding – 5 d	1.2%	84	>0.7	1
						rectal bleeding – 15 d	0.2%	468	>0.9	1
						complication rate				1
						grade 1	0.3%	335	NR	1
						grade 2	<0.1%	2339	NR	1
						grade 3a	0.1%	1170	NR	1
						grade 4	-0.6%	158	NR	1
						grade 5	0.0%	N/A	NR	1
Transperineal vs. transrectal approach (initial biopsy population)										
Hara 2008 *12 vs. 12*	RCT	246	II	Low	High	sepsis/mortality	0.0% (0.0 – 0.0)		N/A	N/A	1
						fever	-1.7% (-4.0 – 0.6)		60	0.146	
						rectal bleeding	0.0% (0.0 – 0.0)		N/A	N/A	
						urinary retention	-0.9% (-4.5 – 2.6)		110	0.612	
						haematuria >1 day	1.2% (-6.3 – 8.6)		87	0.761	
						haemospermia	1.6% (-0.6 – 3.8)		63	0.166	
						vasovagal event	-0.9% (-3.6 – 1.9)		115	0.533	
						headache	4.0% (0.6 – 7.4)		26	0.028	
Takenaka 2008 *12 vs. 12*	RCT	200	II	Low	High	macrohaematuria	11	12 (1)	N/A	>0.999	1
						fever	1 (1)	2 (2)	N/A	>0.999	
						urinary retention	2	3 (1)	N/A	>0.999	
						haemospermia	2	0	N/A	0.498	
						rectal bleeding	0	1	N/A	>0.999	
						vasovagal episode	1	2	N/A	>0.999	

	headache	2	0	N/A	0.498
	patients experiencing (major) complications	N = NR	N = NR		

CI = confidence interval; N/A = not applicable; NR = not reported; NS = not statistically significantly different; NNT = number needed to treat (test); PSA = prostate specific antigen; RCT = randomized controlled trial; RD = risk difference (men experiencing adverse events out of men undergoing intervention biopsy – men experiencing adverse events out of men undergoing comparison biopsy); RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy / men diagnosed out of men undergoing comparison biopsy); SS = sequential sampling design; SR = systematic review; TP = transperineal approach; TR = transrectal approach;

** Refer to appendix B for detailed explanations of rating scores; ** See Tables 9-14 for quality appraisals;*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the evidence statement table of content template 2

Appendices

Appendix A: Search strategies used

For Medline database:

#	Searches
1	exp Prostatic Neoplasms/
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
3	1 or 2
4	exp Biopsy/
5	(biops$ and core$).tw.
6	((needle or extend$ or saturation or target$ or systematic$ or core) adj1 biops$).tw.
7	((sextant or peripheral) adj3 biops$).tw.
8	((transrectal or transperineal) adj4 biops$).tw.
9	((transrectal or transperineal) adj1 ultraso$) or TRUS or TPUS).tw.
10	4 or 5 or 6 or 7 or 8 or 9
11	3 and 10
12	(lesion-directed or directed or suspicious).tw.
13	Elasticity Imaging Technique/ or (elastograph$ or sonoelastograph$).tw.
14	Ultrasonography/ or (ultrasound or ultrasonograph$ or sonograph$).tw.
15	Ultrasonography, Doppler/ or Ultrasonography, Doppler, Pulsed/ or Ultrasonography, Doppler, Duplex/ or Ultrasonography, Doppler, Color/ or doppler.tw.
16	(PDU$ or CE-PDUS or CEUS or CECD$ or CPS or TRUS or TPUS or TRES).tw.
17	exp Contrast Media/ or (contrast-enhanced or cadence-contrast or (contrast adj2 agent$) or (harmonic and imaging)).tw.
18	(3D or 3-D or three-dimension$ or 3-dimension$).tw.
19	Magnetic Resonance Imaging/ or Diffusion Magnetic Resonance Imaging/
20	((magnetic resonance and biops$) or (mr$ adj6 biops$)).tw.
21	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	11 and 21
23	limit 11 to (humans and english language and yr=”2004-current”)
24	limit 22 to (humans and english language and yr=”1990-current”)
25	23 or 24

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database:

#	Searches
#1	'prostate cancer'/exp
#2	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR metast* OR adeno*)
#3	#1 OR #2
#4	'biopsy'/exp
#5	biops* AND core*
#6	(sextant OR peripheral) NEAR/3 biops*
#7	(needle OR extend* OR saturation OR target* OR systematic* OR core) NEXT/1 biops*
#8	(transperineal OR transrectal) NEAR/4 biops*
#9	(transrectal OR transperineal) NEXT/1 ultraso*
#10	'TRUS'/exp OR TRUS OR TPUS
#11	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12	#3 AND #11
#13	'prostate biopsy'/exp
#14	#12 OR #13
#15	'lesion directed' OR directed OR suspicious
#16	'ultrasound'/exp OR sonograph* OR ultrasonsograph* OR ultrasound
#17	'doppler echography'/exp OR 'doppler flowmetry'/exp OR 'color ultrasound flowmetry'/exp OR doppler
#18	'contrast enhanced' OR 'contrast medium'/exp OR contrast NEAR/2 agent* OR (harmonic AND imaging)
#19	PDU* OR 'CE PDUS' OR CEUS OR CECD* OR CPS OR TRUS OR TPUS OR TRES
#20	3D OR '3 D' OR 'three dimension*' OR ‘3 dimension*’
#21	'elastography'/exp OR elastograph* OR sonoelastograph* OR tissue NEAR/2 elasticity
#22	'nuclear magnetic resonance imaging'/exp
#23	MR* NEAR/6 biops*
#24	magnetic NEXT/1 resonance AND biops*
#25	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
#26	#14 AND #25
#27	**#14 AND** [humans]/lim AND [english]/lim AND [2004-3000]/py NOT [medline]/lim
#28	**#26 AND** [humans]/lim AND [english]/lim AND [1990-3000]/py NOT [medline]/lim
#29	**#27 OR #28**

ATSI search terms used

#	Searches
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti

3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

For Cochrane Database of Systematic Reviews – The Cochrane Library:

Title, abstracts, keywords: “prostate”

For Database of Abstracts of Reviews of Effects and Health Technology Assessment database (via OvidSP):

#	**Searches**
1	exp Prostatic Neoplasms/
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
3	1 or 2

Appendix B:

Level of Evidence rating criteria – Intervention studies

Level	Study design
I	Meta-analysis or a systematic review of level II studies
II	Randomised controlled trial or a phase III/IV clinical trial
III-1	Pseudo-randomised controlled trial or a meta-analysis/systematic review of level III-1 studies
III-2	Comparative study with concurrent controls: - Phase II clinical trial - Non-randomised, experimental trial9 - Controlled pre test/post test study - Adjusted indirect comparisons - Interrupted time series with a control group - Cohort study - Case-control study or a meta-analysis/systematic review of level III-2 studies
III-3	A comparative study without concurrent controls: - Phase I clinical trial - Historical control study - Two or more single arm study10 - Unadjusted indirect comparisons - Interrupted time series without a parallel control group or a meta-analysis/systematic review of level III-3 studies
IV	Case series with either post-test or pre-test/post-test outcomes or a meta-analysis/systematic review of level IV studies

According to the standards of the National Health and Medical Research Council; Sequential sampling studies were not included in NHMRC evidence hierarchy. This study design was considered supiror to RCT design and thus were considered at least level II evidence;

Relevance of the evidence

Rating	Relevance
1	Evidence of an effect on patient-relevant clinical outcomes including benefits and harms, quality of life and survival.
2	Evidence of an effect on a surrogate outcome* that has been shown to be predictive of patient-relevant outcomes for the same intervention.
3	Evidence of an effect on proven surrogate outcomes but for a different intervention.
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population.
5	Evidence confined to unproven surrogate outcomes.

**'surrogate outcome' refers to reasonable indicators of whether there has been some effect (e.g. blood pressure measurements or levels of serum cholesterol)*

Points for considering patient-relevant outcomes:
i) The goal of decision making in health care is to choose the intervention(s) (which may include doing nothing) that is (are) most likely to deliver the outcomes that patients find desirable.
ii) Surrogate outcomes (such as blood pressure measurements or levels of serum cholesterol) may be reasonable indicators of whether there has been some effect. However, they should not be the basis for clinical decisions unless they reliably predict an effect on the way the patient feels, otherwise they will not be of interest to the patient or their carers.
iii) All possible outcomes that are of most interest to patients (particularly harms) should be identified and evaluated.

adapted from table 1.10 of: National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra: NHMRC; 2000. http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp69.pdf

Appendix C:

Potentially relevant guidelines identified and reason why not adopted

Year	Organisation	Title	Reason why not adopted
2009	American Urological Association	Prostate-Specific Antigen Best Practice Statement	Did not meet pre-specified AGREE II criteria for inclusion
2009	Canadian Urological Asscoiation	Guidelines on Prostate Biopsy Methodology	Did not meet pre-specified AGREE II criteria for inclusion
2011	Canadian Urological Asscoiation	Prostae Cancer Screening: Canadian Guidelines	Did not meet pre-specified AGREE II criteria for inclusion
2013	European Association of Urology	Guidelines on Prostate Cancer: Part 1 Screening, diagnosis and local treatment with curative intent	Did not meet pre-specified AGREE II criteria for inclusion
2011	European Association of Urology Nurses	Transrectal Ultrasound Guided Biopsy of the Prostate	Did not meet pre-specified AGREE II criteria for inclusion
2010	European Society for Medical Oncology	A Clinical Practice Guideline for Patients with Prostate Cancer	Did not meet pre-specified AGREE II criteria for inclusion
2006	Japanese Urological Association	Evidence-based Clinical Practice Guidelines for Prostate Cancer	Did not meet pre-specified AGREE II criteria for inclusion Considered out-of-date
2012	NCCN	Prostate Cancer Early Detection	Consensus-based
2010	NICE	Transperineal template biopsy and mapping of the prostate	Did not meet pre-specified AGREE II criteria for inclusion
2006	NICE	Undertaking a Transrectal Ultrasound Guided Biopsy of the Prostate	Considered out-of-date

Excluded studies

Study		Reason for Exclusion
1.	Abd Alazeez 2011	Insufficient information to determine if participants had previous biopsies
2.	Abd 2010	Inappropriate study design
3.	Abouassaly 2008	Included men with previous prostate biopsy
4.	Aboumarzouk 2011	Included men with previous prostate biopsy
5.	Abul 2007	No comparison between different biopsy schemes
6.	Acimovic 2005	Inappropriate study design
7.	Aganovic 2012	No comparison between different biopsy schemes
8.	Ahmad S 2011	No comparison between different biopsy schemes
9.	Ahmad S 2013	Included men with previous prostate biopsy
10.	Ahmed 2012 a	Narrative review/comment/letter to editor (no original data)
11.	Ahmed 2012 b	Insufficient information to determine if participants had previous biopsies
12.	Aigner 2009	Insufficient information to determine if participants had previous biopsies
13.	Aigner 2010 a	Included men with previous prostate biopsy
14.	Aigner 2010 b	Narrative review/comment/letter to editor (no original data)
15.	Aigner 2012	Included men with previous prostate biopsy
16.	Akatsuka 2012	Insufficient information to determine if participants had previous biopsies
17.	Akyol 2008	Narrative review/comment/letter to editor (no original data)
18.	Al-Ghamdi 2008	Insufficient information to determine if participants had previous biopsies
19.	Al-Ghazo 2005	No comparison between different biopsy schemes
20.	Al-Hussain 2011	Included men with previous prostate biopsy
21.	Amsellem-Ouazana 2005	Included men with previous prostate biopsy
22.	Andriole 2009	Narrative review/comment/letter to editor (no original data)
23.	Banek 2012	Included men with previous prostate biopsy
24.	Bartoletti 2013	Narrative review/comment/letter to editor (no original data)
25.	Berglund 2008	Included men with previous prostate biopsy
26.	Berglund 2012	Narrative review/comment/letter to editor (no original data)
27.	Bertaccini 2007	No relevant outcomes reported
28.	Biljetina 2013	Included men with previous prostate biopsy
29.	Bjurlin 2013	No relevant outcomes reported
30.	Blaut 2013	Included men with previous prostate biopsy
31.	Boccon-Gibod 2006	Inappropriate study design
32.	Bogers 1999	No comparison between different biopsy schemes
33.	Bonekamp 2011	Narrative review/comment/letter to editor (no original data)
34.	Bostwick 2006	Narrative review/comment/letter to editor (no original data)
35.	Bott 2004	Narrative review/comment/letter to editor (no original data)

36.	Bott 2006	Included men with previous prostate biopsy
37.	Bowden 2008	Narrative review/comment/letter to editor (no original data)
38.	Bree 1997	Narrative review/comment/letter to editor (no original data)
39.	Brnic 2005	No comparison between different biopsy schemes
40.	Brock 2012	No comparison between different biopsy schemes
41.	Brossner 2005	Inappropriate study design
42.	Busby 2004	Included men with previous prostate biopsy
43.	Campos-Fernandes 2008	Inappropriate study design (same protocol for initial and repeat biopsy compared)
44.	Canto 2004	Included men with previous prostate biopsy
45.	Caras 2014	Narrative review/comment/letter to editor (no original data)
46.	Carlsson 2013	Narrative review/comment/letter to editor (no original data)
47.	Carmona 2012	No relevant outcomes reported
48.	Chappel 2005	Narrative review/comment/letter to editor (no original data)
49.	Chartier-Kastler 2012	No relevant outcomes reported
50.	Chen 2012	No comparison between different biopsy schemes (included lesion-directed cores for some patients)
51.	Cheng 2001	No comparison between different biopsy schemes
52.	Chiang 2009 a	Inappropriate study design
53.	Chiang 2009 b	Inappropriate study design
54.	Ching 2012	Included men with previous prostate biopsy
55.	Choi 2011	Duplicate publication
56.	Choo 2007	Included men with prostate cancer
57.	Chrouser 2004	Narrative review/comment/letter to editor (no original data)
58.	Chun 2007	Inappropriate study design
59.	Chun 2010	Narrative review/comment/letter to editor (no original data)
60.	Clements 2002	Narrative review/comment/letter to editor (no original data)
61.	Cochlin 2002	No comparison between different biopsy schemes
62.	Coffin 2011	Insufficient information to determine if participants had previous biopsies (abstract only)
63.	Coffin 2012	No relevant outcomes reported (poster: only positive cores were reported)
64.	Colleselli 2007	No comparison between different biopsy schemes
65.	Cool 2012	Insufficient information to determine if participants had previous biopsies
66.	Cornelis 2013	Included men with previous prostate biopsy
67.	Cornud 1997	Insufficient information to determine if participants had previous biopsies
68.	Davis 2010	Inappropriate study design
69.	Dawam 2007	Narrative review/comment/letter to editor (no original data)
70.	De la Taille 2008 a	Narrative review/comment/letter to editor (no original data)
71.	De la Taille 2008 b	Duplicate publication
72.	De Laet 2009	Insufficient information to determine if participants had previous biopsies

73.	De Sio 2005	Narrative review/comment/letter to editor (no original data)
74.	Delongchamps 2009 a	Inappropriate study design (ex vivo study)
75.	Delongchamps 2009 b	Narrative review/comment/letter to editor (no original data)
76.	Delongchamps 2013	No comparison between different biopsy schemes
77.	Demura 2005	No comparison between different biopsy schemes
78.	Descazeaud 2006	Insufficient information to determine if participants had previous biopsies
79.	Devonec 1990	No comparison between different biopsy schemes
80.	Dickinson 2011	No comparison between different biopsy schemes
81.	Dickinson 2013 a	Narrative review/comment/letter to editor
82.	Dickinson 2013 b	Narrative review/comment/letter to editor
83.	Djavan 2000	No comparison between different biopsy schemes
84.	Djavan 2001	No comparison between different biopsy schemes
85.	Djavan 2006	Inappropriate study design
86.	Djavan 2007	Narrative review/comment/letter to editor (no original data)
87.	Djavan 2012	Narrative review/comment/letter to editor (no original data)
88.	Donaldson 2013	Insufficient information to determine if participants had previous biopsies
89.	Dukic 2011	Inappropriate study design
90.	Durkan 2000	Narrative review/comment/letter to editor (no original data)
91.	Elabbady 2006	Insufficient information to determine if participants had previous biopsies
92.	Eldred-Evans 2013	Insufficient information to determine if participants had previous biopsies
93.	Emiliozzi 2004	Already included in the Eichler systematic review 2005
94.	Engehausen 2012	Included men with previous prostate biopsy
95.	Eskicorapci 2004	Already included in the Eichler systematic review 2005
96.	Falzarano 2010	Included men with previous prostate biopsy
97.	Ferda 2013	No comparison between different biopsy schemes
98.	Ferrari 2009	No comparison between different biopsy schemes
99.	Fiard 2013	Included men with previous prostate biopsy
100.	Fine 2012	Narrative review/comment/letter to editor (no original data)
101.	Fleshner 1999	No comparison between different biopsy schemes
102.	Frauscher 2002	Insufficient information to determine if participants had previous biopsies
103.	Furuno 2004	No comparison between different biopsy schemes
104.	Galfano 2007	Included men with previous prostate biopsy
105.	Ganzer 2012	No comparison between different biopsy schemes
106.	Ghai 2012	Narrative review/comment/letter to editor (no original data)
107.	Ghani 2004	Inappropriate study design
108.	Glasler 2012	Narrative review/comment/letter to editor (no original data)
109.	Gomella 2012	Narrative review/comment/letter to editor (no original data)
110.	Gosselaar 2008	No comparison between different biopsy schemes

		(included lesion-directed cores, screening Rotterdam)
111.	Graefen 2013	narrative review/comment/letter to editor (no original data)
112.	Grepl 2009	No comparison between different biopsy schemes
113.	Grummet 2013 a	Included men with previous biopsies
114.	Grummet 2013 b	No relevant outcomes (survey of practices)
115.	Guichard 2007	Duplicate publication/more recent data available
116.	Guo 2012	Insufficient information to determine if participants had previous biopsies
117.	Gupta 2013	narrative review/comment/letter to editor (no original data)
118.	Guzzo 2005	Inappropriate study design
119.	Haarer 2009	Inappropriate study design
120.	Habchi 2014	No comparison between different biopsy schemes
121.	Hadaschik 2011	No comparison between different biopsy schemes
122.	Hadaschik 2012	Duplicate publication
123.	Haffner 2011	No comparison between different biopsy schemes
124.	Halpern 2002 a	Included men with previous prostate biopsy
125.	Halpern 2002 b	Included men with previous prostate biopsy
126.	Halpern 2002 c	No comparison between different biopsy schemes
127.	Halpern 2005	Included men with previous prostate biopsy
128.	Halpern 2012	Included men with previous prostate biopsy
129.	Hamann 2011	Insufficient information to determine if participants had previous biopsies
130.	Hamann 2013	Included men with previous prostate biopsy
131.	Hambrock 2011	Included men with previous prostate biopsy
132.	Harvey 2012	Narrative review/comment/letter to editor (no original data)
133.	Hedgire 2012	Narrative review/comment/letter to editor
134.	Heijmink 2006	Insufficient information to determine if participants had previous biopsies
135.	Heijmink 2007	Insufficient information to determine if participants had previous biopsies
136.	Hernando Arteche 2011	Inappropriate study design
137.	Ho 2011	No comparison between different biopsy schemes
138.	Hoeks 2013	No comparison between different biopsy schemes
139.	Hong 2009	Insufficient information to determine if participants had previous biopsies
140.	Hwang 2009	Insufficient information to determine if participants had previous biopsies
141.	Inahara 2004	Insufficient information to determine if participants had previous biopsies
142.	Inoue 2012	Insufficient information to determine if participants had previous biopsies
143.	Introini 2006	Insufficient information to determine if participants had previous biopsies
144.	Ishimura 2004	No comparison between different biopsy schemes (included lesion-directed biopsies)

145.	Ismail 2013	Narrative review/comment/letter to editor (no original data)
146.	Javed 2012	Included men with previous prostate biopsy
147.	Jiang 2010	Included men with previous prostate biopsy
148.	Jiang 2013	Systematic review: not all studies meet the inclusion criteria (inappropriate study design)
149.	Jinga 2011	Insufficient information to determine if participants had previous biopsies
150.	Johnstone 2007	Narrative review/comment/letter to editor (no original data)
151.	Jones 2006	Inappropriate study design
152.	Jones 2007	Narrative review/comment/letter to editor (no original data)
153.	Kahl 2009	Inappropriate study design
154.	Kamoi 2008	No comparison between different biopsy schemes
155.	Kamoi 2011	Insufficient information to determine if participants had previous biopsies
156.	Kamoi 2012	No relevant outcomes reported
157.	Kamrava 2013	Insufficient information to determine if participants had previous biopsies
158.	Kan 2013	No relevant outcomes reported
159.	Kapoor 2011	Insufficient information to determine if participants had previous biopsies
160.	Karakose 2013	Insufficient information to determine if participants had previous biopsies
161.	Karaman 2005	No comparison between different biopsy schemes
162.	Kasivisvanathan 2012	Duplicate publication
163.	Kasivisvanathan 2013	No comparison between different biopsy schemes
164.	Kathpalia 2011	No relevant outcomes reported
165.	Kattan 2010	Narrative review/comment/letter to editor (no original data)
166.	Kawakami 2004	Included men with previous prostate biopsy
167.	Kawakami 2006	Duplicate publication (more mature data available, see Numao 2011)
168.	Kawakami 2007	Duplicate publication (more mature data available, see Numao 2011)
169.	Kayhan 2009	Narrative review/comment/letter to editor
170.	Kelly 2013	No comparison between different biopsy schemes
171.	Kibel 2007	Narrative review/comment/letter to editor (no original data)
172.	Kim 2004	Insufficient information to determine if participants had previous biopsies
173.	Kimura 2005	Insufficient information to determine if participants had previous biopsies
174.	Kimura 2012	Insufficient information to determine if participants had previous biopsies
175.	King 2011 a	Included men with previous prostate biopsy
176.	King 2004 b	Insufficient information to determine if participants had previous biopsies
177.	Kirby 2012	Included men with previous prostate biopsy

178.	Kirkham 2006	No comparison between different biopsy schemes
179.	Kobayashi 2004	Included men with previous prostate biopsy
180.	Kobus. 2012	Included men with previous prostate biopsy
181.	Kokeny 2000	Insufficient information to determine if participants had previous biopsies
182.	Komai 2013	Insufficient information to determine if participants had previous biopsies
183.	Konig 2005	No comparison between different biopsy schemes
184.	Kravchick 2003	Insufficient information to determine if participants had previous biopsies
185.	Kravchick 2004	Insufficient information to determine if participants had previous biopsies
186.	Kruecker 2011	No relevant outcomes reported
187.	Kuligowska 2001	Insufficient information to determine if participants had previous biopsies
188.	Kumar R 2008	No comparison between different biopsy schemes
189.	Kumar V 2007	No comparison between different biopsy schemes
190.	Kuru 2011	Insufficient information to determine if participants had previous biopsies
191.	Kuru 2013 a	No comparison between different biopsy schemes
192.	Kuru 2013 b	No comparison between different biopsy schemes
193.	Kwee 2008	Narrative review/comment/letter to editor
194.	Labanaris 2010 a	No comparison between different biopsy schemes
195.	Labanaris 2010 b	No comparison between different biopsy schemes
196.	Lan 2007	Included men with previous prostate biopsy
197.	Lane 2008	Included men with previous prostate biopsy
198.	Langer 1999	Narrative review/comment/letter to editor (no original data)
199.	Lattouf 2007	Included men with previous prostate biopsy
200.	Laurila 2010	No comparison between different biopsy schemes
201.	Lavoipierre 1998	No comparison between different biopsy schemes
202.	Leibowitz 1996	No comparison between different biopsy schemes
203.	Leitao 2011	Insufficient information to determine if participants had previous biopsies
204.	Leite 2008	Included men with previous prostate biopsy
205.	Lenherr 2012	Insufficient information to determine if participants had previous biopsies
206.	Lenherr 2013	Insufficient information to determine if participants had previous biopsies
207.	Leslie 2012	Included men with previous prostate biopsy
208.	Li H 2007	Insufficient information to determine if participants had previous biopsies
209.	Li Y 2013	No comparison between different biopsy schemes
210.	Linden 2007	Insufficient information to determine if participants had previous biopsies

211.	Loch 2004	Insufficient information to determine if participants had previous biopsies
212.	Lu 2011	Insufficient information to determine if participants had previous biopsies
213.	Luciani 2006	Insufficient information to determine if participants had previous biopsies
214.	Lughezzani 2010	Narrative review/comment/letter to editor (no original data)
215.	Luscombe 2004	Narrative review/comment/letter to editor (no original data)
216.	Mabjeesh 2012	Included men with previous prostate biopsy
217.	Maccagnano 2012	Included men with previous prostate biopsy
218.	Macchia 2004	Narrative review/comment/letter to editor (no original data)
219.	Madej 2011	Inappropriate study design
220.	Maksem 2007	Narrative review/comment/letter to editor (no original data)
221.	Marihart 2006	Narrative review/comment/letter to editor (no original data)
222.	Marks 2013	Narrative review/comment/letter to editor (no original data)
223.	Masood 2007	Narrative review/comment/letter to editor (no original data)
224.	Master 2005	Inappropriate study design
225.	Matsumoto 2005	Included men with previous prostate biopsy
226.	Matsuoka 2012	No relevant outcomes reported
227.	Melchior 1996	Narrative review/comment/letter to editor (no original data)
228.	Meng 2006	Inappropriate study design
229.	Minagawa 2010	No comparison between different biopsy schemes
230.	Mitterberger 2007 a	Included men with previous prostate biopsy
231.	Mitterberger 2007 b	No comparison between different biopsy schemes
232.	Mitterberger 2009	Included men with previous prostate biopsy
233.	Mitterberger 2010 a	No comparison between different biopsy schemes
234.	Mitterberger 2010 b	Included men with previous prostate biopsy
235.	Miyagawa 2009	No comparison between different biopsy schemes
236.	Miyagawa 2011	Included men with previous prostate biopsy
237.	Miyake 2004 a	No comparison between different biopsy schemes
238.	Miyake 2004 b	Inappropriate study design
239.	Miyake 2007	Insufficient information to determine if participants had previous biopsies
240.	Moore 2012	Duplicate publication
241.	Moore 2013	Included men with previous prostate biopsy
242.	Morelli 2011	No comparison between different biopsy schemes
243.	Mouraviev 2012	Included men with previous prostate biopsy
244.	Mowatt 2013	No comparison between different biopsy schemes
245.	Nagel 2013	Included men with previous prostate biopsy
246.	Narayanan 2008	Narrative review/comment/letter to editor (no original data)
247.	Natarajan 2011	Included men with previous prostate biopsy
248.	Naya 2004	Included men with previous prostate biopsy

249.	Neill 2008	No comparison between different biopsy schemes (included lesion-directed cores for some patients)
250.	Nelson 2007	Insufficient information to determine if participants had previous biopsies
251.	Nogueira 2010	Included men with previous prostate biopsy
252.	Noh 2013	No comparison between different biopsy schemes
253.	Norberg 1996	Insufficient information to determine if participants had previous biopsies
254.	Norberg 1997	Insufficient information to determine if participants had previous biopsies
255.	Numao 2007	Duplicate publication (more recent data available)
256.	Numao 2013 a	Insufficient information to determine if participants had previous biopsies
257.	Numao 2013 b	No comparison between different biopsy schemes
258.	O'Connell 2004	Already included in the Eichler systematic review 2005
259.	Ochiai 2008	Included men with previous prostate biopsy
260.	Ohira 2011	Inappropriate study design
261.	Olson 1994	Insufficient information to determine if participants had previous biopsies
262.	Onik 2009	Included men with previous prostate biopsy
263.	Onur 2004	No comparison between different biopsy schemes
264.	Onur 2014	Narrative review/comment/letter to editor (no original data)
265.	Ou 2009	No comparison between different biopsy schemes
266.	Ouzzane 2011	Included men with previous prostate biopsy
267.	Overduin 2013	Included men with previous prostate biopsy (Systematic Review)
268.	Ozdedeli 2013	Insufficient information to determine if participants had previous biopsies
269.	Pallwein 2007 a	Narrative review/comment/letter to editor (no original data)
270.	Pallwein 2007 b	Insufficient information to determine if participants had previous biopsies
271.	Papatheodorou 2005	Narrative review/comment/letter to editor (no original data)
272.	Park 2011	No comparison between different biopsy schemes
273.	Patel 2007	Narrative review/comment/letter to editor (no original data)
274.	Patel 2009	Narrative review/comment/letter to editor (no original data)
275.	Patel 2011	Included men with previous prostate biopsy
276.	Paul 2004	Already included in the Eichler systematic review 2005
277.	Peltier 2013	Inappropriate study design
278.	Pelzer 2005 a	Included men with previous prostate biopsy
279.	Pelzer 2005 b	No comparison between different biopsy schemes
280.	Pelzer 2005 c	Inappropriate study design
281.	Peng 2013	No comparison between different biopsy schemes
282.	Pepe 2003	No comparison between different biopsy schemes

283.	Pepe 2007	Inappropriate study design
284.	Pepe 2008	Included men with previous prostate biopsy
285.	Perez-Guillermo 2005	Narrative review/comment/letter to editor (no original data)
286.	Philip 2004	Insufficient information to determine if participants had previous biopsies
287.	Philip 2009	Included men with previous prostate biopsy
288.	Pinto 2011	Included men with previous prostate biopsy
289.	Pitt 2008	Narrative review/comment/letter to editor (no original data)
290.	Ploussard 2009	Duplicate publication/more recent data available
291.	Ploussard 2012	Duplicate publication of Ploussard 2014 (included)
292.	Pondman 2008	No comparison between different biopsy schemes
293.	Popert 2013	Narrative review/comment/letter to editor (no original data)
294.	Presti 2003	No comparison between different biopsy schemes
295.	Presti 2007	Narrative review/comment/letter to editor (no original data)
296.	Presti 2009	Included men with previous prostate biopsy
297.	Puech 2013	Included men with previous prostate biopsy
298.	Quinlan 2009	Included men with previous prostate biopsy
299.	Quintana 2013	Inappropriate study design
300.	Ragde 1997	Included men with previous prostate biopsy
301.	Rais-Bahrami 2013	Included men with previous prostate biopsy
302.	Raja 2006	Narrative review/comment/letter to editor (no original data)
303.	Ramachandran 2005	Narrative review/comment/letter to editor (no original data)
304.	Ravery 2008	Inappropriate study design
305.	Remzi 2004	No comparison between different biopsy schemes
306.	Remzi 2005	Inappropriate study design
307.	Richard 2012	Included men with previous prostate biopsy
308.	Rietbergen 1997	Inappropriate study design
309.	Roberts 2013	Inappropriate study design
310.	Robertson 2012	Insufficient information to determine if participants had previous biopsies
311.	Robinson 2010	No relevant outcomes reported
312.	Roy 2003	No comparison between different biopsy schemes
313.	Rud 2012	Included men with previous prostate biopsy
314.	Rusu 2012	Insufficient information to determine if participants had previous biopsies
315.	Sabir 2013	Included men with previous prostate biopsy
316.	Sadeghi-Nejad 2006	Narrative review/comment/letter to editor (no original data)
317.	Sajadi 2007	Included men with previous prostate biopsy
318.	San Francisco 2004	Included men with prostate cancer only
319.	Sano 2010	Insufficient information to determine if participants had previous biopsies
320.	Sartor 2010	Narrative review/comment/letter to editor (no original data)
321.	Sauvain 2003	Inappropriate study design

322.	Scattoni 2002	Included men with previous prostate biopsy
323.	Scattoni 2006	Narrative review/comment/letter to editor (no original data)
324.	Scattoni 2007	Narrative review/comment/letter to editor (no original data)
325.	Scattoni 2008	Inappropriate study design
326.	Scattoni 2010 a	narrative review/comment/letter to editor (no original data)
327.	Scattoni 2010 b	No relevant outcomes reported (225 possible combinations of 24 cores, and only mean CDR reported)
328.	Schulte 2008	Included men with previous prostate biopsy
329.	Schwab 2013	No relevant outcomes reported
330.	Sciarra 2011 a	Narrative review/comment/letter to editor
331.	Sciarra 2011 b	Narrative review/comment/letter to editor
332.	Seltzer 1996	Insufficient information to determine if participants had previous biopsies
333.	Sfakianos 2011	No comparison between different biopsy schemes
334.	Sharma 2007	Narrative review/comment/letter to editor (no original data)
335.	Shen 2008	Narrative review/comment/letter to editor (no original data)
336.	Shen 2012	Included men with previous prostate biopsy (systematic review)
337.	Shigemura 2007	Inappropriate study design
338.	Shigemura 2013	Inappropriate study design
339.	Shim 2007 a	No comparison between different biopsy schemes
340.	Shim 2007 b	No comparison between different biopsy schemes
341.	Shim 2007 c	No comparison between different biopsy schemes (included lesion-directed cores for some patients)
342.	Siddiqui 2013 a	Duplicate publication (more current data available)
343.	Siddiqui 2013 b	Included men with previous prostate biopsy
344.	Singh AK 2007	Included men with previous prostate biopsy
345.	Singh H 2004 a	Included only men with positive biopsy
346.	Singh H 2004 b	Included only men with positive biopsy
347.	Siu 2005	Inappropriate study design
348.	Slonim 1993	Insufficient information to determine if participants had previous biopsies
349.	Smeenge 2011	Narrative review/comment/letter to editor (no original data)
350.	Song 2005	Insufficient information to determine if participants had previous biopsies
351.	Sonn 2013	Included men with previous prostate biopsy
352.	Spajic 2006	No comparison between different biopsy schemes
353.	Spajic 2007	Insufficient information to determine if participants had previous biopsies
354.	Sparchez 2010	Narrative review/comment/letter to editor (no original data)
355.	Sperando 2003	No comparison between different biopsy schemes
356.	Stamatiou 2007	No comparison between different biopsy schemes (included lesion-directed cores for some patients)
357.	Suardi 2013	Included men with prostate cancer only

358.	Taira 2010	No comparison between different biopsy schemes
359.	Takahashi 2002	Insufficient information to determine if participants had previous biopsies
360.	Takenaka 2006	Included men with previous prostate biopsy
361.	Takeshita 2012	Duplicate publication
362.	Tarcan 1997	Insufficient information to determine if participants had previous biopsies
363.	Taverna 2009	Duplicate publication
364.	Taverna 2011	No comparison between different biopsy schemes
365.	Taverna 2013	Insufficient information to determine if participants had previous biopsies
366.	Teng 2012	No comparison between different biopsy schemes
367.	Terris 2009	Included men with previous prostate biopsy
368.	Testa 2010	Included men with previous prostate biopsy
369.	Thiesler 2007	Insufficient information to determine if participants had previous biopsies
370.	Tobiume 2008	Inappropriate study design
371.	Toi 2007	Included men with previous prostate biopsy
372.	Tsai 2007	Narrative review/comment/letter to editor (no original data)
373.	Tsivian 2011	Narrative review/comment/letter to editor (no original data)
374.	Turkbey 2011	No comparison between different biopsy schemes
375.	Turkeri 1996	Insufficient information to determine if participants had previous biopsies
376.	Ukimura 2013 a	Insufficient information to determine if participants had previous biopsies
377.	Ukimura 2013 b	Narrative review/comment/letter to editor (no original data)
378.	Uno 2011	Inappropriate study design
379.	Van der Kwast 2008	Narrative review/comment/letter to editor (no original data)
380.	Van Leeuwen 2009	No comparison between different biopsy schemes included only men with negative biopsies (screening Rotterdam)
381.	Vasdev 2011	Narrative review/comment/letter to editor (no original data)
382.	Vassilios 2011	Included men with previous prostate biopsy
383.	Villa 2012	Included men with prostate cancer only
384.	Villa 2013	Inappropriate study design
385.	Villers 2012	Narrative review/comment/letter to editor (no original data)
386.	Vora 2011	No relevant outcomes reported
387.	Vourganti 2013	No comparison between different biopsy schemes
388.	Vyas 2012	Included men with previous prostate biopsy
389.	Wareing 2004	No relevant outcomes reported
390.	Watanabe 2005	No comparison between different biopsy schemes
391.	Watanabe 2012	Inappropriate study design
392.	Watanabe 2013	Insufficient information to determine if participants had previous biopsies

393.	Wei 2010	Narrative review/comment/letter to editor (no original data)
394.	Werahera 2012	Included men with previous prostate biopsy
395.	Williamson 2013	Narrative review/comment/letter to editor (no original data)
396.	Winter 2013	Insufficient information to determine if participants had previous biopsies
397.	Wright 2006	Included men with previous prostate biopsy
398.	Wysock 2013	No comparison between different biopsy schemes
399.	Xie 2011	Insufficient information to determine if participants had previous biopsies
400.	Xu S 2007	No relevant outcomes reported
401.	Xu S 2008	No relevant outcomes reported
402.	Yacoub 2012	Narrative review/comment/letter to editor (no original data)
403.	Yakar 2008	Narrative review/comment/letter to editor (no original data)
404.	Yamamoto 2004	Inappropriate study design
405.	Yan 2009	No comparison between different biopsy schemes ("nomogram", but no control)
406.	Yang 2008	Insufficient information to determine if participants had previous biopsies
407.	Yerram 2012	Insufficient information to determine if participants had previous biopsies
408.	Yoon 2012	Insufficient information to determine if participants had previous biopsies
409.	Yuasa 2008	Included men with previous prostate biopsy
410.	Yunkai 2010	No comparison between different biopsy schemes included lesion-directed cores for some patients
411.	Zackrisson 2004	Inappropriate study design
412.	Zaytoun 2011	Included men with previous prostate biopsy
413.	Zhang 2012	Insufficient information to determine if participants had previous biopsies
414.	Zhao 2012	No comparison between different biopsy schemes
415.	Zhao 2013	Insufficient information to determine if participants had previous biopsies

References: Excluded Studies

1. Abd Alazeez M, Moore C, Ahmed HU, Arya M, Freeman A, Kirkham A et al. Can pre-biopsy multiparametric MRI be used to detect significant prostate cancer? *Urology* 2011; 78(3):S42.

2. Abd TT, Goodman M, Hall J, Ritenour CW, Petros JA, Marshall FF et al. Comparison of 12-core versus 8-core prostate biopsy: multivariate analysis of large series of US veterans. *Urology* 2011; 77(3):541-547.

3. Abouassaly R, Lane BR, Jones JS. Staging saturation biopsy in patients with prostate cancer on active surveillance protocol. *Urology* 2008; 71(4):573-577.

4. Aboumarzouk OM, Ogston S, Huang Z, Evans A, Melzer A, Stolzenberg JU et al. Diagnostic accuracy of transrectal elastosonography (TRES) imaging for the diagnosis of prostate cancer: a systematic review and meta-analysis. *BJU Int* 2012; 110(10):1414-1423.

5. Abul FT, Arun N, Abu-Assi MA, Asbeutah AM. Transrectal ultrasound guided biopsy for detecting prostate cancer: can random biopsies be reduced using the 4-dimensional technique? *International Urology & Nephrology* 2007; 39(2):517-524.

6. Acimovic M, Tulic C, Dzamic Z, Radosavljevic R, Filimonovic J, Jovanovic M et al. Standardization of transrectal ultrasound-guided biopsy. *Acta Chirurgica Iugoslavica* 2005; 52(4):41-44.

7. Aganovic D, Prcic A, Kulovac B, Hadziosmanovic O. Influence of the prostate volume, prostate specific antigen density and number of biopsy samples on prostate cancer detection. *Medicinski Arhiv* 2012; 66(1):41-44.

8. Ahmad S, Dadgar AR. Sensitivity and specificty of transrectal ultrasonography (TRUS) in diagnosing prostate cancer. *Pak J Med Health Sci* 2011; 5(4):741-744.

9. Ahmad S, Cao R, Varghese T, Bidaut L, Nabi G. Transrectal quantitative shear wave elastography in the detection and characterisation of prostate cancer. *Surg Endosc* 2013;1-8.

10. Ahmed HU, Emberton M, Kepner G, Kepner J. A biomedical engineering approach to mitigate the errors of prostate biopsy. *Nat Rev Urol* 2012; 9(4):227-231. (a)

11. Ahmed S, Aboumarzouk O, Lang S, Nabi G. Quantative shear wave elastosonogrpahy in the detection of prostate cancers. *J Urol* 2012; 187(4):e820-e821. (b)

12. Aigner F, Pallwein L, Mitterberger M, Pinggera GM, Mikuz G, Horninger W et al. Contrast-enhanced ultrasonography using cadence-contrast pulse sequencing technology for targeted biopsy of the prostate. *BJU Int* 2009; 103(4):458-463.

13. Aigner F, Pallwein L, Junker D, Schafer G, Mikuz G, Pedross F et al. Value of real-time elastography targeted biopsy for prostate cancer detection in men with prostate specific antigen 1.25 ng/ml or greater and 4.00 ng/ml or less. *J Urol* 2010; 184(3):913-917. (a)

14. Aigner F, Mitterberger M, Rehder P, Pallwein L, Junker D, Horninger W et al. Status of transrectal ultrasound imaging of the prostate. *J Endourol* 2010; 24(5):685-691. (b)

15. Aigner F, Schafer G, Steiner E, Jaschke W, Horninger W, Herrmann TR et al. Value of enhanced transrectal ultrasound targeted biopsy for prostate cancer diagnosis: a retrospective data analysis. *World Journal of Urology* 2012; 30(3):341-346.

16. Akatsuka J, Kimura G, Suzumura K, Nomura S, Minowa T, Iigaya S et al. Clinical usefulness of the ultrasound contrast agent perflubutane in the diagnosis of prostatic cancer: A prospective clinical trial. *Urology* 2012; 80(3):S12.

17. Akyol I, Adayener C. Transient impotence after transrectal ultrasound-guided prostate biopsy. *Journal of Clinical Ultrasound* 2008; 36(1):33-34.

18. Al-Ghamdi AM, Lockwood G, Toi A, Kulkarni GS, Evans A, Finelli A et al. Extended pattern prostate biopsy does not minimize the volume-grade bias in prostate cancer detection. *J Urol* 2008; 179(4):1332-1334.

19. Al-Ghazo MA, Ghalayini IF, Matalka II. Ultrasound-guided transrectal extended prostate biopsy: a prospective study. *Asian J Androl* 2005; 7(2):165-169.

20. Al-Hussain TO, Epstein JI. Initial high-grade prostatic intraepithelial neoplasia with carcinoma on subsequent prostate needle biopsy: findings at radical prostatectomy. *American Journal of Surgical Pathology* 2011; 35(8):1165-1167.

21. Amsellem-Ouazana D, Younes P, Conquy S, Peyromaure M, Flam T, Debre B et al. Negative prostatic biopsies in patients with a high risk of prostate cancer. Is the combination of endorectal MRI and magnetic resonance spectroscopy imaging (MRSI) a useful tool? A preliminary study. *Eur Urol* 2005; 47(5):582-586.

22. Andriole GL. Pathology: the lottery of conventional prostate biopsy. *Nat Rev Urol* 2009; 6(4):188-189.

23. Banek S, Kramer U, Alloussi S, Kaufmann S, Schwentner C, Stenzl A et al. Fusion of non-contrast-3tesla-MRI and trus-imaging: Implementation of a new biopsy technique to detect prostate cancer. *J Urol* 2012; 187(4):e591.

24. Bartoletti R, Cai T. Prostate biopsies should be performed according to a standard of care. *Eur Urol* 2013; 63(3):528-529.

25. Berglund RK, Masterson TA, Vora KC, Eggener SE, Eastham JA, Guillonneau BD. Pathological upgrading and up staging with immediate repeat biopsy in patients eligible for active surveillance. *J Urol* 2008; 180(5):1964-1967.

26. Berglund RK, Jones JS. Optimal Prostate Biopsy Regimen. *Curr Urol Rep* 2012;1-5.

27. Bertaccini A, Fandella A, Prayer-Galetti T, Scattoni V, Galosi AB, Ficarra V et al. Systematic development of clinical practice guidelines for prostate biopsies: a 3-year Italian project. *Anticancer Res* 2007; 27(1B):659-666.

28. Biljetina Z, Zhang J, Yilmaz A, Trpkov K. Long term follow-up (F/U) in patients with initial PIN and benign prostate biopsies. *Lab Invest* 2013; 93:198A.

29. Bjurlin MA, Carter HB, Schellhammer P, Cookson MS, Gomella LG, Troyer D et al. Optimization of initial prostate biopsy in clinical practice: sampling, labeling and specimen processing. *J Urol* 2013; 189(6):2039-2046.

30. Blaut S, Rodel S, Kittner T, Steinbach F. Characteristics of prostate cancer diagnosed by MR-guided prostate biopsy. *J Urol* 2013; 189(4):e603.

31. Boccon-Gibod LM, de Longchamps NB, Toublanc M, Boccon-Gibod LA, Ravery V. Prostate saturation biopsy in the reevaluation of microfocal prostate cancer. *J Urol* 963; 176(3):961-963.

32. Bogers HA, Sedelaar JP, Beerlage HP, de la Rosette JJ, Debruyne FM, Wijkstra H et al. Contrast-enhanced three-dimensional power Doppler angiography of the human prostate: correlation with biopsy outcome. *Urology* 1999; 54(1):97-104.

33. Bonekamp D, Jacobs MA, El-Khouli R, Stoianovici D, Macura KJ. Advancements in MR imaging of the prostate: from diagnosis to interventions. *Radiographics* 2011; 31(3):677-703.

34. Bostwick DG, Meiers I. Prostate biopsy and optimization of cancer yield. *Eur Urol* 2006; 49(3):415-417.

35. Bott SR, Henderson A, McLarty E, Langley SE. A brachytherapy template approach to standardize saturation prostatic biopsy. *BJU Int* 2004; 93(4):629-630.

36. Bott SR, Henderson A, Halls JE, Montgomery BS, Laing R, Langley SE. Extensive transperineal template biopsies of prostate: modified technique and results. *Urology* 2006; 68(5):1037-1041.

37. Bowden FJ, Roberts J, Collignon PJ. Prostate cancer screening and bacteraemia. *Medical Journal of Australia* 2008; 188(1):60.

38. Bree RL. The role of color Doppler and staging biopsies in prostate cancer detection. *Urology* 1997; 49(3A:Suppl):Suppl-4.

39. Brnic Z, Gasparov S, Lozo PV, Anic P, Patrlj L, Ramljak V. Is quadrant biopsy sufficient in men likely to have advanced prostate cancer? Comparison with extended biopsy. *Pathology Oncology Research* 2005; 11(1):40-44.

40. Brock M, Von Bodman C, Palisaar RJ, Loppenberg B, Sommerer F, Deix T et al. The impact of real-time elastography guiding a systematic prostate biopsy to improve cancer detection rate: A prospective study of 353 patients. *J Urol* 2012; 187(6):2039-2043.

41. Brossner C, Madersbacher S, de MP, Ponholzer A, Al-Ali B, Rauchenwald M. Follow-up of men obtaining a six-core versus a ten-core benign prostate biopsy 7 years previously. *World Journal of Urology* 2005; 23(6):419-421.

42. Busby JE, Evans CP. Determining variables for repeat prostate biopsy. *Prostate Cancer & Prostatic Diseases* 2004; 7(2):93-98.

43. Campos-Fernandes JL, Bastien L, Nicolaiew N, Robert G, Terry S, Vacherot F et al. Prostate cancer detection rate in patients with repeated extended 21-sample needle biopsy. *Eur Urol* 2009; 55(3):600-606.

44. Canto EI, Singh H, Shariat SF, Kadmon D, Miles BJ, Wheeler TM et al. Effects of systematic 12-core biopsy on the performance of percent free prostate specific antigen for prostate cancer detection. *J Urol* 2004; 172(3):900-904.

45. Caras RJ, Sterbis JR. Prostate Cancer Nomograms: A Review of Their Use in Cancer Detection and Treatment. *Curr Urol Rep* 2014; 15(3):1-6.

46. Carlsson S, Vickers A, Hugosson J. Four-hundredfold overestimation of biopsy mortality. *BJU Int* 2013; 111(3):E16-E17.

47. Carmona LM, Negro CLA, Fiorito C, Popert R, Nurse D, Muir GH. Limited template appears equivalent to saturation approach in transperineal prostate biopsies. *Eur Urol Suppl* 2012; 11(1):e155-e155a.

48. Chappell B, McLoughlin J. Technical considerations when obtaining and interpreting prostatic biopsies from men with suspicion of early prostate cancer: part 2. [Review] [58 refs]. *BJU Int* 2005; 95(8):1141-1145.

49. Chartier-Kastler E, Coffin G, Chevreau G, Renard-Penna R, Comperat E, Vitrani M et al. Comparison between systematic and mri targeted prostate biopsy for patient with no history of prostate cancer attending a first round of trans-rectal ultrasound biopsy procedure. *Urology* 2012; 80(3):S279-S280.

50. Chen MK, Luo Y, Zhang H, Lu MH, Pang J, Gao X. Investigation of optimal prostate biopsy schemes for Chinese patients with different clinical characteristics. *Urologia Internationalis* 2012; 89(4):425-432.

51. Cheng S, Rifkin MD. Color Doppler imaging of the prostate: Important adjunct to endorectal ultrasound of the prostate in the diagnosis of prostate cancer. *Ultrasound Q* 2001; 17(3):185-189.

52. Chiang IN, Chang SJ, Pu YS, Huang KH, Yu HJ, Huang CY. Diagnostic value of finger-guided prostate nodule biopsy combined with systemic random biopsy. *Journal of the Formosan Medical Association* 2009; 108(9):713-718. (a)

53. Chiang IN, Chang SJ, Pu YS, Huang KH, Yu HJ, Huang CY. Comparison of 6- and 12-core prostate biopsy in Taiwanese men: impact of total prostate-specific antigen, prostate-specific antigen density and prostate volume on prostate cancer detection. *Urologia Internationalis* 2009; 82(3):270-275. (b)

54. Ching CB, Zaytoun O, Moussa AS, Li J, Avallone A, Jones JS. Type of transrectal ultrasonography probe influences prostate cancer detection rates on repeat prostate biopsy. *BJU Int* 2012; 110(2:Pt 2):t-9.

55. Choi HY, Park JW, Park SY, Lee HM, Jeon SS, Seo SI et al. Prospective evaluation of 3T magnetic resonance imaging performed prior to an initial transrectal ultrasound-guided biopsy in the detection of prostate cancer. *Int J Urol* 2011; 18(5):398-399.

56. Choo R, Danjoux C, Morton G, Szumacher E, Sugar L, Gardner S et al. How much does Gleason grade of follow-up biopsy differ from that of initial biopsy in untreated, Gleason score 4-7, clinically localized prostate cancer? *Prostate* 2007; 67(15):1614-1620.

57. Chrouser KL, Lieber MM. Extended and saturation needle biopsy for the diagnosis of prostate cancer. *Curr Urol Rep* 2004; 5(3):226-230.

58. Chun FK, Briganti A, Graefen M, Montorsi F, Porter C, Scattoni V et al. Development and external validation of an extended 10-core biopsy nomogram. *Eur Urol* 2007; 52(2):436-444.

59. Chun FK, Epstein JI, Ficarra V, Freedland SJ, Montironi R, Montorsi F et al. Optimizing performance and interpretation of prostate biopsy: a critical analysis of the literature. [Review]. *Eur Urol* 2010; 58(6):851-864.

60. Clements R. The role of transrectal ultrasound in diagnosing prostate cancer. *Curr Urol Rep* 2002; 3(3):194-200.

61. Cochlin DL, Ganatra RH, Griffiths DF. Elastography in the detection of prostatic cancer. *Clin Radiol* 2002; 57(11):1014-1020.

62. Coffin G, Torterotot C, Baumann M, Vitrani MA, Morel G, Chevreau G et al. Trus prostate biopsies pierced area can impact cancer rate detection. *J Endourol* 2011; 25(9):A35.

63. Coffin G, Chevreau G, Renard-Penna R, Comperat E, Vitrani MA, Torterotot C et al. Comparison between systematic and MRI targeted prostate biopsy for patients with no history of prostate cancer attending a first round of trans-rectal ultrasound biopsy procedure. *Eur Urol Suppl* 2012; 11(1):e794-e794a.

64. Colleselli D, Bektic J, Schaefer G, Frauscher F, Mitterberger M, Brunner A et al. The influence of prostate volume on prostate cancer detection using a combined approach of contrast-enhanced ultrasonography-targeted and systematic grey-scale biopsy. *BJU Int* 2007; 100(6):1264-1267.

65. Cool DW, Romagnoli C, Izawa JI, Chin J, Gardi L, Ward AD et al. Enhanced tumour sampling and gleason grading through fusion of mri to 3d transrectal ultrasound (TRUS) biopsy. *J Urol* 2012; 187(4):e819-e820.

66. Cornelis F, Rigou G, Le BY, Coutouly X, Hubrecht R, Yacoub M et al. Real-time contrast-enhanced transrectal US-guided prostate biopsy: diagnostic accuracy in men with previously negative biopsy results and positive MR imaging findings. *Radiology* 2013; 269(1):159-166.

67. Cornud F, Belin X, Piron D, Chretien Y, Flam T, Casanova JM et al. Color Doppler-guided prostate biopsies in 591 patients with an elevated serum PSA level: impact on Gleason score for nonpalpable lesions. *Urology* 1997; 49(5):709-715.

68. Davis JW, Kim J, Ward JF, Wang X, Nakanishi H, Babaian RJ et al. Radical prostatectomy findings in patients predicted to have low-volume/low-grade prostate cancer diagnosed by extended-core biopsies: an analysis of volume and zonal distribution of tumour foci. *BJU Int* 2010; 105(10):1386-1391.

69. Dawam D, Bhatt T, Kourieffs C, Naseem M, Masood S, Sheriff M et al. Psagraph: a simple graphical and useful tool for follow-up and decision on biopsy and treatment of patients with prostatic diseases. *BJU Int* 2007; 99(5):1169.

70. de la Taille A, Jones JS, Klein EA. Open to debate. The motion: at least 18 cores are necessary to make a prostatic biopsy useful. [Review] [17 refs]. *Eur Urol* 2008; 53(3):659-662.

71. de la Taille A, Jones JS, Klein EA. The Motion: At Least 18 Cores are Necessary to Make a Prostatic Biopsy Useful. *Eur Urol* 2008; 53(3):659-662.

72. De Laet K, de la Taille A, Ploussard G, Hoznek A, Vordos D, Yiou R et al. Predicting tumour location in radical prostatectomy specimens: same-patient comparisons of 21-sample versus sextant biopsy. *BJU Int* 2009; 104(5):616-620.

73. De Sio M, D'Armiento M, Di LG, Damiano R, Perdona S, De PS et al. The need to reduce patient discomfort during transrectal ultrasonography-guided prostate biopsy: what do we know. *BJU Int* 2005; 96(7):977-983.

74. Delongchamps NB, de la Roza G, Chandan V, Jones R, Threatte G, Jumbelic M et al. Diagnostic accuracy of extended biopsies for the staging of microfocal prostate cancers in autopsy specimen. *Prostate Cancer & Prostatic Diseases* 2009; 12(2):137-142. (a)

75. Delongchamps NB, Haas GP. Saturation biopsies for prostate cancer: current uses and future prospects. *Nat Rev Urol* 2009; 6(12):645-652. (b)

76. Delongchamps NB, Peyromaure M, Schull A, Beuvon F, Bouazza N, Flam T et al. Prebiopsy magnetic resonance imaging and prostate cancer detection: comparison of random and targeted biopsies. *J Urol* 2013; 189(2):493-499.

77. Demura T, Hioka T, Furuno T, Kaneta T, Gotoda H, Muraoka S et al. Differences in tumor core distribution between palpable and nonpalpable prostate tumors in patients diagnosed using extensive transperineal ultrasound-guided template prostate biopsy. *Cancer* 2005; 103(9):1826-1832.

78. Descazeaud A, Rubin M, Chemama S, Larre S, Salomon L, Allory Y et al. Saturation biopsy protocol enhances prediction of pT3 and surgical margin status on prostatectomy specimen. *World Journal of Urology* 2006; 24(6):676-680.

79. Devonec M, Fendler JP, Monsallier M, Mouriquand P, Maquet JH, Mestas JL et al. The significance of the prostatic hypoechoic area: results in 226 ultrasonically guided prostatic biopsies. *J Urol* 1990; 143(2):316-319.

80. Dickinson L, Walkden M, Moore C, Ahmed H, Freeman A, Allen C et al. Can pre-biopsy multi-parametric MRI reduce the number of TRUS cores required to diagnose prostate cancer in an 'at-risk' population of men? *Urology* 2011; 78(3):S44.

81. Dickinson L, Ahmed HU, Allen C, Barentsz JO, Carey B, Futterer JJ et al. Clinical applications of multiparametric MRI within the prostate cancer diagnostic pathway. *Urol Oncol Semin Orig Invest* 2013; 31(3):285-287. (a)

82. Dickinson L, Ahmed HU, Allen C, Barentsz JO, Carey B, Futterer JJ et al. Scoring systems used for the interpretation and reporting of multiparametric MRI for prostate cancer detection, localization, and characterization: could standardization lead to improved utilization of imaging within the diagnostic pathway?. *J Magn Reson Imaging* 2013; 37(1):48-58. (b)

83. Djavan B, Zlotta A, Remzi M, Ghawidel K, Basharkhah A, Schulman CC et al. Optimal predictors of prostate cancer on repeat prostate biopsy: a prospective study of 1,051 men. *J Urol* 2000; 163(4):1144-1148.

84. Djavan B, Waldert M, Zlotta A, Dobronski P, Seitz C, Remzi M et al. Safety and morbidity of first and repeat transrectal ultrasound guided prostate needle biopsies: results of a prospective European prostate cancer detection study. *J Urol* 2001; 166(3):856-860.

85. Djavan B. Prostate biopsies and the Vienna nomograms. *Eur Urol Suppl* 2006; 5(6):500-510.

86. Djavan B, Margreiter M. Biopsy standards for detection of prostate cancer. *World Journal of Urology* 2007; 25(1):11-17.

87. Djavan B, Rocco B. Optimising prostate biopsy. *BMJ (Online)* 2012; 344(7840).

88. Donaldson I, Freeman A, Allen C, Moore C, Emberton M. Results of mri targeted, visually registered, trans-rectal ultrasound guided prostate biopsy. *J Urol* 2013; 189(4):e907.

89. Dukic M, Popov M, Vojinov S, Grbic D, Dimtric Z, Zivojinov S et al. Technique modalities of transrectal biopsy of prostate apex. *Eur Urol Suppl* 2011; 10(9):584.

90. Durkan GC, Greene DR. Diagnostic dilemmas in detection of prostate cancer in patients undergoing transrectal ultrasound-guided needle biopsy of the prostate. *Prostate Cancer Prostatic Dis* 2000; 3(1):13-20.

91. Elabbady AA, Khedr MM. Extended 12-core prostate biopsy increases both the detection of prostate cancer and the accuracy of Gleason score. *Eur Urol* 2006; 49(1):49-53.

92. Eldred-Evans D, Sturch P, Duong K, Kinsella J, McGovern M, Robinson A et al. Multi-parametric MRI - Ultrasound fusion targeted biopsies using varian brachytherapy software: A practical solution to deliver targeted biopsies. *Int J Surg* 2013; 11(8):593.

93. Emiliozzi P, Scarpone P, DePaula F, Pizzo M, Federico G, Pansadoro A et al. The incidence of prostate cancer in men with prostate specific antigen greater than 4.0 ng/ml: a randomized study of 6 versus 12 core transperineal prostate biopsy. *J Urol* 2004; 171(1):197-199.

94. Engehausen DG, Engelhard K, Schwab SA, Uder M, Wach S, Wullich B et al. Magnetic resonance image-guided biopsies with a high detection rate of prostate cancer. *Sci World J* 2012; 2012.

95. Eskicorapci SY, Baydar DE, Akbal C, Sofikerim M, Gunay M, Ekici S et al. An extended 10-core transrectal ultrasonography guided prostate biopsy protocol improves the detection of prostate cancer. *Eur Urol* 448; 45(4):444-448.

96. Falzarano SM, Zhou M, Hernandez AV, Moussa AS, Jones JS, Magi-Galluzzi C. Can saturation biopsy predict prostate cancer localization in radical prostatectomy specimens: a correlative study and implications for focal therapy. *Urology* 2010; 76(3):682-687.

97. Ferda J, Kastner J, Hora M, Hes O, Finek J, Topolcan O et al. A role of multifactorial evaluation of prostatic 3T MRI in patients with elevated prostatic-specific antigen levels: prospective comparison with ultrasound-guided transrectal biopsy. *Anticancer Res* 2013; 33(6):2791-2795.

98. Ferrari FS, Scorzelli A, Megliola A, Drudi FM, Trovarelli S, Ponchietti R. Real-time elastography in the diagnosis of prostate tumor. *J Ultrasound* 2009; 12(1):22-31.

99. Fiard G, Hohn N, Descotes JL, Rambeaud JJ, Troccaz J, Long JA. Targeted MRI-guided prostate biopsies for the detection of prostate cancer: Initial clinical experience with real-time 3-dimensional transrectal ultrasound guidance and magnetic resonance/transrectal ultrasound image fusion. *Urology* 2013; 81(6):1372-1378.

100. Fine SW, Reuter VE. Anatomy of the prostate revisited: implications for prostate biopsy and zonal origins of prostate cancer. *Histopathology* 2012; 60(1):142-152.

101. Fleshner NE, O'Sullivan M, Premdass C, Fair WR. Clinical significance of small (less than 0.2 cm3) hypoechoic lesions in men with normal digital rectal examinations and prostate-specific antigen levels less than 10 ng/mL. *Urology* 1999; 53(2):356-358.

102. Frauscher F, Klauser A, Volgger H, Halpern EJ, Pallwein L, Steiner H et al. Comparison of contrast enhanced color Doppler targeted biopsy with conventional systematic biopsy: impact on prostate cancer detection. *J Urol* 2002; 167(4):1648-1652.

103. Furuno T, Demura T, Kaneta T, Gotoda H, Muraoka S, Sato T et al. Difference of cancer core distribution between first and repeat biopsy: In patients diagnosed by extensive transperineal ultrasound guided template prostate biopsy. *Prostate* 2004; 58(1):76-81.

104. Galfano A, Novara G, Iafrate M, Cosentino M, Cavalleri S, Artibani W et al. Prostate Biopsy: The Transperineal Approach. *EAU EBU Update Ser* 2007; 5(6):241-249.

105. Ganzer R, Brandtner A, Wieland WF, Fritsche HM. Prospective blinded comparison of real-time sonoelastography targeted versus randomised biopsy of the prostate in the primary and re-biopsy setting. *World Journal of Urology* 2012; 30(2):219-223.

106. Ghai S, Toi A. Role of transrectal ultrasonography in prostate cancer. *Radiologic Clinics of North America* 2012; 50(6):1061-1073.

107. Ghani KR, Dundas D, Patel U. Bleeding after transrectal ultrasonography-guided prostate biopsy: a study of 7-day morbidity after a six-, eight- and 12-core biopsy protocol. *BJU Int* 2004; 94(7):1014-1020.

108. Glaser AP, Novakovic K, Helfand BT. The impact of prostate biopsy on urinary symptoms, erectile function, and anxiety. [Review]. *Curr Urol Rep* 2012; 13(6):447-454.

109. Gomella LG. The quest for the perfect prostate biopsy continues. *J Urol* 2012; 187(6):1954-1955.

110. Gosselaar C, Roobol MJ, Roemeling S, Wolters T, van Leenders GJ, Schroder FH. The value of an additional hypoechoic lesion-directed biopsy core for detecting prostate cancer. *BJU Int* 2008; 101(6):685-690.

111. Graefen M, Schlomm T. From diagnostic tool to disease monitoring: The growing role of prostate biopsies. *Eur Urol* 2013; 63(2):231-233.

112. Grepl M, Student V, Furst T, Furstova J. Prostate cancer detection yield in repeated biopsy is independent of the diagnosis of earlier biopsies. *Biomedical Papers of the Medical Faculty of Palacky University in Olomouc, Czech Republic* 2009; 153(4):297-302.

113. Grummet J, Reeves F, Frydenberg M. Transperineal prostate biopsy: A comparison of two techniques. *BJU Int* 2013; 111:99. (a)

114. Grummet J, Davis P. Current practices of prostate biopsy in Australia and New Zealand - the survey. *BJU Int* 2013; 111:96. (b)

115. Guichard G, Larre S, Gallina A, Lazar A, Faucon H, Chemama S et al. Extended 21-sample needle biopsy protocol for diagnosis of prostate cancer in 1000 consecutive patients. *Eur Urol* 2007; 52(2):430-435.

116. Guo YF, Li FH, Xie SW, Xia JG, Fang H, Li HL. Value of contrast-enhanced sonographic micro flow imaging for prostate cancer detection with t-PSA level of 4-10 ng/mL. *Eur J Radiol* 2012; 81(11):3067-3071.

117. Gupta RT, Kauffman CR, Polascik TJ, Taneja SS, Rosenkrantz AB. The state of prostate MRI in 2013. *Oncology (Williston Park)* 2013; 27(4):262-270.

118. Guzzo TJ, Vira M, Hwang WT, D'Amico A, Tomaszewski J, Whittington R et al. Impact of multiple biopsy cores on predicting final tumor volume in prostate cancer detected by a single microscopic focus of cancer on biopsy. *Urology* 2005; 66(2):361-365.

119. Haarer CF, Gopalan A, Tickoo SK, Scardino PT, Eastham JA, Reuter VE et al. Prostatic transition zone directed needle biopsies uncommonly sample clinically relevant transition zone tumors. *J Urol* 2009; 182(4):1337-1341.

120. Habchi H, Bratan F, Paye A, Pagnoux G, Sanzalone T, Mege-Lechevallier F et al. Value of prostate multiparametric magnetic resonance imaging for predicting biopsy results in first or repeat biopsy. *Clin Radiol* 2014; 69(3):e120-e128.

121. Hadaschik B, Kuru T, Roethke M, Teber D, Pahernik S, Schlemmer H et al. MRI-navigated stereotactic prostate biopsy. *Urology* 2012; 80(3):S180-S181.

122. Hadaschik BA, Kuru TH, Tulea C, Rieker P, Popeneciu IV, Simpfendorfer T et al. A novel stereotactic prostate biopsy system integrating pre-interventional magnetic resonance imaging and live ultrasound fusion. *J Urol* 2011; 186(6):2214-2220.

123. Haffner J, Lemaitre L, Puech P, Haber GP, Leroy X, Jones JS et al. Role of magnetic resonance imaging before initial biopsy: comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection. *BJU Int* 2011; 108(8:Pt 2):t-8.

124. Halpern EJ, Frauscher F, Rosenberg M, Gomella LG. Directed biopsy during contrast-enhanced sonography of the prostate. *AJR* 2002; American(4):915-919. (a)

125. Halpern EJ, Frauscher F, Strup SE, Nazarian LN, O'Kane P, Gomella LG. Prostate: high-frequency Doppler US imaging for cancer detection. *Radiology* 2002; 225(1):71-77. (b)

126. Halpern EJ, Frauscher F, Forsberg F, Strup SE, Nazarian LN, O'Kane P et al. High-frequency Doppler US of the prostate: effect of patient position. *Radiology* 2002; 222(3):634-639. (c)

127. Halpern EJ, Ramey JR, Strup SE, Frauscher F, McCue P, Gomella LG. Detection of prostate carcinoma with contrast-enhanced sonography using intermittent harmonic imaging. *Cancer* 2005; 104(11):2373-2383.

128. Halpern EJ, Gomella LG, Forsberg F, McCue PA, Trabulsi EJ. Contrast enhanced transrectal ultrasound for the detection of prostate cancer: a randomized, double-blind trial of dutasteride pretreatment. *J Urol* 2012; 188(5):1739-1745.

129. Hamann C, Schenk E, Hamann M, Naumann C, Junemann K. Histoscanning-guided prostate biopsy in comparison to a systemic 14-fold transrectal prostate biopsy. *Urology* 2011; 78(3):S299.

130. Hamann MF, Hamann C, Schenk E, Al-Najar A, Naumann CM, Junemann KP. Computer-aided (HistoScanning) biopsies versus conventional transrectal ultrasound-guided prostate biopsies: do targeted biopsy schemes improve the cancer detection rate? *Urology* 2013; 81(2):370-375.

131. Hambrock T, Hoeks C, Hulsbergen-van de Kaa C, Scheenen T, Futterer J, Bouwense S et al. Prospective assessment of prostate cancer aggressiveness using 3-T diffusion-weighted magnetic resonance imaging-

guided biopsies versus a systematic 10-core transrectal ultrasound prostate biopsy cohort. *Eur Urol* 2012; 61(1):177-184.

132. Harvey CJ, Pilcher J, Richenberg J, Patel U, Frauscher F. Applications of transrectal ultrasound in prostate cancer. *British Journal of Radiology* 2012; 85:Spec-17.

133. Hedgire S, Oei T, McDermott S, Cao K, Patel Z, Harisinghani M. Multiparametric magnetic resonance imaging of prostate cancer. *Indian J Radiol Imaging* 2012; 22(3):160-169.

134. Heijmink SW, van MH, Kiemeney LA, Witjes JA, Frauscher F, Barentsz JO. A comparison of the diagnostic performance of systematic versus ultrasound-guided biopsies of prostate cancer. *Eur Radiol* 2006; 16(4):927-938.

135. Heijmink SW, Barentsz JO. Contrast-enhanced versus systematic transrectal ultrasound-guided prostate cancer detection: an overview of techniques and a systematic review. *Eur J Radiol* 2007; 63(3):310-316.

136. Hernando Arteche A, San Jose Manso L, Galante Romo I, Casado Varela J, Leon Rueda M, Useros Rodriguez E et al. Prognostic significance of the number of biopsies in the diagnosis of prostate cancer. *Urology* 2011; 78(3):S301.

137. Ho C, Khor T, Singam P, Goh E, Tan G, Bahadzor B et al. Power doppler ultrasonography-directed prostate biopsy in men with elevated serum prostate specific antigen levels. *Urology* 2011; 78(3):S301.

138. Hoeks CA, Vos EK, Bomers JGR, Barentsz JO, Hulsbergen-van de Kaa CA, Scheenen TW. Diffusion-weighted magnetic resonance imaging in the prostate transition zone: Histopathological validation using magnetic resonance-guided biopsy specimens. *Invest Radiol* 2013.

139. Hong SK, Han BK, Lee ST, Kim SS, Min KE, Jeong SJ et al. Prediction of Gleason score upgrading in low-risk prostate cancers diagnosed via multi (> or = 12)-core prostate biopsy. *World Journal of Urology* 2009; 27(2):271-276.

140. Hwang SI, Lee HJ, Cho JY, Kim SH, Lee SE, Byun SS et al. Should transition zone biopsies be added to 12-core systematic biopsies of the prostate? *Journal of Clinical Ultrasound* 2009; 37(5):281-284.

141. Inahara M, Suzuki H, Nakamachi H, Kamiya N, Shimbo M, Komiya A et al. Clinical evaluation of transrectal power doppler imaging in the detection of prostate cancer. *International Urology & Nephrology* 2004; 36(2):175-180.

142. Inoue S, Honda M, Iwamoto H, Satoh M, Morizane S, Yao A et al. The evaluation of effectiveness in the lesion suspicious biopsies detected by ultrasonography and MRI. *Urology* 2012; 80(3):S134.

143. Introini C, Naselli A, Vigliercio G, Spina B, Truini M, Puppo P. Can biopsy be a reliable predictor of spatial distribution of prostate cancer? Comparison of a novel biopsy regimen with radical prostatectomy findings. *Urology* 2006; 68(6):1301-1304.

144. Ishimura T, Sakai I, Hara I, Eto H, Miyake H. Clinical outcome of transrectal ultrasound-guided prostate biopsy, targeting eight cores, for detecting prostate cancer in Japanese men. *International Journal of Clinical Oncology* 2004; 9(1):47-50.

145. Ismail MT, Gomella LG. Transrectal prostate biopsy. *Urol Clin North Am* 2013; 40(4):457-472.

146. Javed S, John B, Chadwick E, Montgomery B, Bott S, Langley S. Should transperineal template guided prostate biopsies be used as gold standard for diagnosis of prostate cancer? *Eur Urol Suppl* 2012; 11(1):e819-e819a.

147. Jiang J, Colli J, El-Galley R. A simple method for estimating the optimum number of prostate biopsy cores needed to maintain high cancer detection rates while minimizing unnecessary biopsy sampling. *J Endourol* 2010; 24(1):143-147.

148. Jiang X, Zhu S, Feng G, Zhang Z, Li C, Li H et al. Is an initial saturation prostate biopsy scheme better than an extended scheme for detection of prostate cancer? A systematic review and meta-analysis. *Eur Urol* 2013; 63(6):1031-1039.

149. Jinga V, Budau M, Braticevici B, Radavoi D, Calin C, Badescu D et al. Prostate cancer detection using cadence contrast pulse sequencing technology for targeted biopsies. *Urology* 2011; 78(3):S48.

150. Johnstone PA, Rossi PJ, Jani AB, Master V. 'Insignificant' prostate cancer on biopsy: pathologic results from subsequent radical prostatectomy. *Prostate Cancer & Prostatic Diseases* 2007; 10(3):237-241.

151. Jones JS, Patel A, Schoenfield L, Rabets JC, Zippe CD, Magi-Galluzzi C. Saturation technique does not improve cancer detection as an initial prostate biopsy strategy. *J Urol* 2006; 175(2):485-488.

152. Jones JS. Saturation biopsy for detecting and characterizing prostate cancer. *BJU Int* 2007; 99(6):1340-1344.

153. Kahl P, Wolf S, Adam A, Heukamp LC, Ellinger J, Vorreuther R et al. Saturation biopsy improves preoperative Gleason scoring of prostate cancer. *Pathology, Research & Practice* 2009; 205(4):259-264.

154. Kamoi K, Okihara K, Ochiai A, Ukimura O, Mizutani Y, Kawauchi A et al. The utility of transrectal real-time elastography in the diagnosis of prostate cancer. *Ultrasound in Medicine & Biology* 2008; 34(7):1025-1032.

155. Kamoi K, Okihara K, Takaha N, Nakamura T, Hongo F, Naito Y et al. The role of magnetic resonance imaging in targeting prostate cancer in patients with elevated prostate-specific antigen levels. *J Clin Oncol* 2011; 29(15).

156. Kamoi K, Okihara K, Iwata T, Kawauchi A, Miki T. Magnetic resonance imaging/ultrasound fusion guided prostate biopsy for patients with small lesions suspicious for cancer revealed by multiparametric magnetic resonance imaging. *Urology* 2012; 80(3):S13.

157. Kamrava M, Chang E, Dorey F, Kupelian P, Marks L. Do targeted ultrasound/MRI fusion biopsies significantly change maximum prostate gleason score compared with systematic biopsies? *Int J Radiat Oncol Biol Phys* 2013; 87(2):S23-S24.

158. Kan RWM, Ho LY, Kan CF, Chan SWH. The accuracy of prostate biopsy and magnetic resonance imaging in predicting the laterality of prostate cancer: How wrong can it go? *BJU Int* 2013; 111(Supp S2).

159. Kapoor A, Kapoor A, Mahajan G, Sidhu BS. Real-time elastography in the detection of prostate cancer in patients with raised PSA level. *Ultrasound Med Biol* 2011; 37(9):1374-1381.

160. Karakose A, Yuksel MB, Gorgel SN, Pirincci N, Atesci YZ, Gumus B. Can cancer detection rate increase when transrectal biopsies taken from the laterally? *Eur Urol Suppl* 2013; 12(4):e1291.

161. Karaman CZ, Unsal A, Akdilli A, Taskin F, Erol H. The value of contrast enhanced power Doppler ultrasonography in differentiating hypoehoic lesions in the peripheral zone of prostate. *Eur J Radiol* 2005; 54(1):148-155.

162. Kasivisvanathan V, Dufour R, Moore C, Ahmed H, Freeman A, Charman S et al. Magnetic resonance image-guided prostate biopsy versus transperineal template prostate biopsy in the diagnosis of clinically significant prostate cancer. *J Urol* 2012; 187(4):e826-e827.

163. Kasivisvanathan V, Dufour R, Moore CM, Ahmed HU, Abd-Alazeez M, Charman SC et al. Transperineal magnetic resonance image targeted prostate biopsy versus transperineal template prostate biopsy in the detection of clinically significant prostate cancer. *J Urol* 2013; 189(3):860-866.

164. Kathpalia R, Singh D, Goel A. Contrast-enhanced color Doppler-targeted prostate biopsy: An innovative method to improve an accuracy of a transrectal biopsy in patients with suspected cancer prostate. *Indian J Urol* 2011; 27(2):299-300.

165. Kattan MW, Jones JS. The ultimate prostate cancer biopsy decision support tool. *Eur Urol* 2010; 57(1):9-10.

166. Kawakami S, Kihara K, Fujii Y, Masuda H, Kobayashi T, Kageyama Y. Transrectal ultrasound-guided transperineal 14-core systematic biopsy detects apico-anterior cancer foci of T1c prostate cancer. *Int J Urol* 2004; 11(8):613-618.

167. Kawakami S, Hyochi N, Yonese J, Yano M, Fujii Y, Kageyama Y et al. Three-dimensional combination of transrectal and transperineal biopsies for efficient detection of stage T1c prostate cancer. *International Journal of Clinical Oncology* 2006; 11(2):127-132.

168. Kawakami S, Yamamoto S, Numao N, Ishikawa Y, Kihara K, Fukui I. Direct comparison between transrectal and transperineal extended prostate biopsy for the detection of cancer. *Int J Urol* 2007; 14(8):719-724.

169. Kayhan A, Fan X, Oto A. Dynamic contrast-enhanced magnetic resonance imaging in prostate cancer. *Topics in Magnetic Resonance Imaging* 2009; 20(2):105-112.

170. Kelly D, Jackson J, Mark J, Halpern E, Forsberg F, McCue P et al. Contrast enhanced ultrasound for the detection of prostate cancer: Do targeted biopsies result in more accurate clinical staging? *J Urol* 2013; 189(4):e829.

171. Kibel AS. Optimizing prostate biopsy techniques. *J Urol* 2007; 177(6):1976-1977.

172. Kim JW, Lee HY, Hong SJ, Chung BH. Can a 12 core prostate biopsy increase the detection rate of prostate cancer versus 6 core?: a prospective randomized study in Korea. *Yonsei Medical Journal* 2004; 45(4):671-675.

173. Kimura G, Nishimura T, Kimata R, Saito Y, Yoshida K. Random systematic sextant biopsy versus power doppler ultrasound-guided target biopsy in the diagnosis of prostate cancer: positive rate and clinicopathological features. *Journal of Nippon Medical School = Nihon Ika Daigahu Zasshi* 2005; 72(5):262-269.

174. Kimura G, Akatsuka J, Suzumura K, Nomura S, Saito Y, Kondo Y. What can we do to maximize the detection rates of prostate cancer? *Urology* 2012; 80(3):S13-S14.

175. King AC, Livermore A, Laurila TAJ, Huang W, Jarrard DF. Impact of immediate TRUS rebiopsy in a patient cohort considering active surveillance for favorable risk prostate cancer. *Urol Oncol Semin Orig Invest* 2011.

176. King CR, McNeal JE, Gill H, Presti JC, Jr. Extended prostate biopsy scheme improves reliability of Gleason grading: implications for radiotherapy patients. *International Journal of Radiation Oncology, Biology, Physics* 2004; 59(2):386-391.

177. Kirby R, Fitzpatrick JM. Optimising repeat prostate biopsy decisions and procedures. [Review]. *BJU Int* 2012; 109(12):1750-1754.

178. Kirkham AP, Emberton M, Allen C. How good is MRI at detecting and characterising cancer within the prostate?. *Eur Urol* 2006; 50(6):1163-1174.

179. Kobayashi T, Nishizawa K, Watanabe J, Ogura K, Mitsumori K, Ide Y. Effects of sextant transrectal prostate biopsy plus additional far lateral cores in improving cancer detection rates in men with large prostate glands. *Int J Urol* 2004; 11(6):392-396.

180. Kobus T, Vos PC, Hambrock T, De RM, Hulsbergen-Van de Kaa CA, Barentsz JO et al. Prostate cancer aggressiveness: in vivo assessment of MR spectroscopy and diffusion-weighted imaging at 3 T. *Radiology* 2012; 265(2):457-467.

181. Kokeny GP, Cerri GG, de Oliveira Cerri LM, de BN. Correlations among prostatic biopsy results, transrectal ultrasound findings and PSA levels in diagnosing prostate adenocarcinoma. *European Journal of Ultrasound* 2000; 12(2):103-113.

182. Komai Y, Numao N, Yoshida S, Matsuoka Y, Nakanishi Y, Ishii C et al. High diagnostic ability of multiparametric magnetic resonance imaging to detect anterior prostate cancer missed by transrectal 12-core biopsy. *J Urol* 2013; 190(3):867-873.

183. Konig K, Scheipers U, Pesavento A, Lorenz A, Ermert H, Senge T. Initial experiences with real-time elastography guided biopsies of the prostate. *J Urol* 2005; 174(1):115-117.

184. Kravchick S, Cytron S, Peled R, Altshuler A, Ben-Dor D. Using gray-scale and two different techniques of color Doppler sonography to detect prostate cancer. *Urology* 2003; 61(5):977-981.

185. Kravchick S, Cytron S, Peled R, London D, Sibi Y, Ben-Dor D. Optimal combinations for detection of prostate cancer: systematic sextant and laterally directed biopsies versus systematic sextant and color Doppler-targeted biopsies. *Urology* 2004; 63(2):301-305.

186. Kruecker J. Prostate biopsy with image fusion: System validation and clinical results. *Int J Comput Assisted Radiol Surg* 2011; 6:S13-S14.

187. Kuligowska E, Barish MA, Fenlon HM, Blake M. Predictors of prostate carcinoma: accuracy of gray-scale and color Doppler US and serum markers. *Radiology* 2001; 220(3):757-764.

188. Kumar R, Nayyar R, Kumar V, Gupta NP, Hemal AK, Jagannathan NR et al. Potential of magnetic resonance spectroscopic imaging in predicting absence of prostate cancer in men with serum prostate-specific antigen between 4 and 10 ng/ml: a follow-up study. *Urology* 2008; 72(4):859-863.

189. Kumar V, Jagannathan NR, Kumar R, Thulkar S, Gupta SD, Hemal AK et al. Transrectal ultrasound-guided biopsy of prostate voxels identified as suspicious of malignancy on three-dimensional (1)H MR spectroscopic imaging in patients with abnormal digital rectal examination or raised prostate specific antigen level of 4-10 ng/ml. *NMR in Biomedicine* 2007; 20(1):11-20.

190. Kuru TH, Hadaschik BA, Hohenfellner M. A novel stereotactic prostate biopsy system integrating preinterventional MRI with live us fusion. *J Endourol* 2011; 25(9):A17-A18.

191. Kuru TH, Roethke M, Simpfendoerfer T, Boxler S, Seidenader J, Schlemmer HP et al. Critical evaluation of MRI-targeted TRUS-guided transperineal fusion biopsy for detection of prostate cancer. *J Clin Oncol* 2013; 31(15). (a)

192. Kuru TH, Roethke MC, Seidenader J, Simpfendorfer T, Boxler S, Alammar K et al. Critical evaluation of magnetic resonance imaging targeted, transrectal ultrasound guided transperineal fusion biopsy for detection of prostate cancer. *J Urol* 2013; 190(4):1380-1386. (b)

193. Kwee SA, DeGrado T. Prostate biopsy guided by 18F-fluorocholine PET in men with persistently elevated PSA levels. *European Journal of Nuclear Medicine & Molecular Imaging* 2008; 35(8):1567-1569.

194. Labanaris AP, Zugor V, Smiszek R, Nutzel R, Kuhn R, Engelhard K. Guided e-MRI prostate biopsy can solve the discordance between Gleason score biopsy and radical prostatectomy pathology. *Magnetic Resonance Imaging* 2010; 28(7):943-946.

195. Labanaris AP, Engelhard K, Zugor V, Nutzel R, Kuhn R. Prostate cancer detection using an extended prostate biopsy schema in combination with additional targeted cores from suspicious images in conventional and functional endorectal magnetic resonance imaging of the prostate. *Prostate Cancer & Prostatic Diseases* 2010; 13(1):65-70.

196. Lan SK, Tsai YS, Lin YH, Tzai TS. Diagnostic performance of a random versus lesion-directed biopsy of the prostate from transrectal ultrasound: results of a 5-year consecutive clinical study in 1 institution in South Taiwan. *Journal of Ultrasound in Medicine* 2007; 26(1):11-17.

197. Lane BR, Zippe CD, Abouassaly R, Schoenfield L, Magi-Galluzzi C, Jones JS. Saturation technique does not decrease cancer detection during followup after initial prostate biopsy. *J Urol* 2008; 179(5):1746-1750.

198. Langer JE. The current role of transrectal ultrasonography in the evaluation of prostate carcinoma. *Seminars in Roentgenology* 1999; 34(4):284-294.

199. Lattouf JB, Grubb RL, III, Lee SJ, Bjurlin MA, Albert P, Singh AK et al. Magnetic resonance imaging-directed transrectal ultrasonography-guided biopsies in patients at risk of prostate cancer. *BJU Int* 2007; 99(5):1041-1046.

200. Laurila M, van der Kwast T, Bubendorf L, di LS, Pihl CG, Ciatto S et al. Detection rates of cancer, high grade PIN and atypical lesions suspicious for cancer in the European Randomized Study of Screening for Prostate Cancer. *European Journal of Cancer* 2010; 46(17):3068-3072.

201. Lavoipierre AM, Snow RM, Frydenberg M, Gunter D, Reisner G, Royce PL et al. Prostatic cancer: role of color Doppler imaging in transrectal sonography. *AJR* 1998; American(1):205-210.

202. Leibowitz CB, Staub PG. Transrectal ultrasound-guided biopsy of the prostate: what you see is not what you get. *Australasian Radiology* 1996; 40(3):240-243.

203. Leitao T, Rodrigues T, Soares C, Silva R, Garcia R, Martinho D et al. A prospective randomized trial of prostate biopsy protocols comparing the vienna nomogram and a standard 10-core biopsy scheme. *Urology* 2011; 78(3):S302.

204. Leite KR, Camara-Lopes LH, Cury J, Dall'Oglio MF, Sanudo A, Srougi M. Prostate cancer detection at rebiopsy after an initial benign diagnosis: results using sextant extended prostate biopsy. *Clinics (Sao Paulo, Brazil)* 2008; 63(3):339-342.

205. Lenherr O, Liske P, Lahme S, Fayyazi A. The detection rates of Real-Time-Elastography (RTE) and multiple core biopsies in the diagnosis of prostate cancer. A comparison after 283 patients. *Eur Urol Suppl* 2012; 11(1):e820-e820a.

206. Lenherr O, Fayyazi A, Lahme S, Liske P. Real-time-elastography (RTE): Its detection rate compared to multiple core biopsy and an evaluation of psa and prostate volume as predictors. *J Urol* 2013; 189(4):e904.

207. Leslie S, Goh A, Lewandowsk PM, Huang EYH, De Castro Abreu AL, Berger AK et al. Contemporary image-guided targeted prostate biopsy better characterizes cancer volume, gleason grade and its 3d location compared to systematic biopsy. *J Urol* 2012; 187(4):e827.

208. Li H, Yan W, Zhou Y, Ji Z, Chen J. Transperineal ultrasound-guided saturation biopsies using 11-region template of prostate: report of 303 cases. *Urology* 2007; 70(6):1157-1161.

209. Li Y, Tang J, Fei X, Gao Y. Diagnostic performance of contrast enhanced ultrasound in patients with prostate cancer: a meta-analysis. *Academic Radiology* 2013; 20(2):156-164.

210. Linden RA, Trabulsi EJ, Forsberg F, Gittens PR, Gomella LG, Halpern EJ. Contrast enhanced ultrasound flash replenishment method for directed prostate biopsies. *J Urol* 2007; 178(6):2354-2358.

211. Loch T, Eppelmann U, Lehmann J, Wullich B, Loch A, Stockle M. Transrectal ultrasound guided biopsy of the prostate: random sextant versus biopsies of sono-morphologically suspicious lesions. *World Journal of Urology* 2004; 22(5):357-360.

212. Lu Z, Wang Y, Chen Q, Wang C. The relationship of prostate volume, prostate biopsy cores and prostate cancer (PCA) detection rate. *J Endourol* 2011; 25:A190.

213. Luciani LG, De GG, Valotto C, Zanin M, Bierti S, Zattoni F. Role of transperineal six-core prostate biopsy in patients with prostate-specific antigen level greater than 10 ng/mL and abnormal digital rectal examination findings. *Urology* 2006; 67(3):555-558.

214. Lughezzani G, Sun M, Budaus L, Thuret R, Shariat SF, Perrotte P et al. Effect of the number of biopsy cores on prostate cancer detection and staging. *Future Oncology* 2010; 6(3):381-390.

215. Luscombe CJ, Cooke PW. Pain during prostate biopsy. *Lancet* 2004; 363(9424):1840-1841.

216. Mabjeesh NJ, Lidawi G, Chen J, German L, Matzkin H. High detection rate of significant prostate tumours in anterior zones using transperineal ultrasound-guided template saturation biopsy. *BJU Int* 2012; 110(7):993-997.

217. Maccagnano C, Gallina A, Roscigno M, Raber M, Capitanio U, Sacca A et al. Prostate saturation biopsy following a first negative biopsy: state of the art. *Urologia Internationalis* 2012; 89(2):126-135.

218. Macchia RJ. Biopsy of the prostate--an ongoing evolution. *J Urol* 2004; 171(4):1487-1488.

219. Madej A, Wilkosz J, Rozanski W, Lipinski M. Complication rates after prostate biopsy according to numbers of cores. *Eur Urol Suppl* 2011; 10(9):614.

220. Maksem JA, Berner A, Bedrossian C. Fine needle aspiration biopsy of the prostate gland. *Diagnostic Cytopathology* 2007; 35(12):778-785.

221. Marihart S, Porsova M, Djavan B. Technical innovations in prostate biopsy. *J Men's Health Gender* 2006; 3(4):363-367.

222. Marks L, Young S, Natarajan S. MRI-ultrasound fusion for guidance of targeted prostate biopsy. *Current Opinion in Urology* 2013; 23(1):43-50.

223. Masood J, Hafeez A, Calleary J, Barua JM. Aspirin use and transrectal ultrasonography-guided prostate biopsy: a national survey. *BJU Int* 2007; 99(5):965-966.

224. Master VA, Chi T, Simko JP, Weinberg V, Carroll PR. The independent impact of extended pattern biopsy on prostate cancer stage migration. *J Urol* 2005; 174(5):1789-1793.

225. Matsumoto K, Satoh T, Egawa S, Shimura S, Kuwao S, Baba S. Efficacy and morbidity of transrectal ultrasound-guided 12-core biopsy for detection of prostate cancer in Japanese men. *Int J Urol* 2005; 12(4):353-360.

226. Matsuoka Y, Numao N, Saito K, Tanaka H, Kijima T, Kobayashi S et al. Combination of 14-core biopsy and magnetic resonance imaging can identify appropriate candidates for hemiablative focal therapy of prostate cancer. *J Urol* 2012; 187(4):e151.

227. Melchior SW, Brawer MK. Role of transrectal ultrasound and prostate biopsy. *Journal of Clinical Ultrasound* 1996; 24(8):463-471.

228. Meng MV, Elkin EP, Duchane J, Carroll PR. Impact of increased number of biopsies on the nature of prostate cancer identified. *J Urol* 2006; 176(1):63-68.

229. Minagawa T, Murata Y, Uehara T, Imamura T, Ishizuka O. Impact of high-consistency area evaluated under hand-operated transrectal compression using a sonographic probe on prostate cancer detection: clinicopathological analysis. *Int J Urol* 2010; 17(10):876-880.

230. Mitterberger M, Pinggera GM, Horninger W, Bartsch G, Strasser H, Schafer G et al. Comparison of contrast enhanced color Doppler targeted biopsy to conventional systematic biopsy: impact on Gleason score. *J Urol* 2007; 178(2):464-468. (a)

231. Mitterberger M, Horninger W, Pelzer A, Strasser H, Bartsch G, Moser P et al. A prospective randomized trial comparing contrast-enhanced targeted versus systematic ultrasound guided biopsies: impact on prostate cancer detection. *Prostate* 2007; 67(14):1537-1542. (b)

232. Mitterberger M, Horninger W, Aigner F, Pinggera GM, Rehder P, Steiner E et al. Contrast-enhanced colour Doppler-targeted vs a 10-core systematic repeat biopsy strategy in patients with previous high-grade prostatic intraepithelial neoplasia. *BJU Int* 2009; 105(12):1660-1662.

233. Mitterberger M, Aigner F, Pinggera GM, Steiner E, Rehder P, Ulmer H et al. Contrast-enhanced colour Doppler-targeted prostate biopsy: correlation of a subjective blood-flow rating scale with the histopathological outcome of the biopsy. *BJU Int* 2010; 106(9):1315-1318. (a)

234. Mitterberger MJ, Aigner F, Horninger W, Ulmer H, Cavuto S, Halpern EJ et al. Comparative efficiency of contrast-enhanced colour Doppler ultrasound targeted versus systematic biopsy for prostate cancer detection. *Eur Radiol* 2010; 20(12):2791-2796. (b)

235. Miyagawa T, Tsutsumi M, Matsumura T, Kawazoe N, Ishikawa S, Shimokama T et al. Real-time elastography for the diagnosis of prostate cancer: evaluation of elastographic moving images. *Japanese Journal of Clinical Oncology* 2009; 39(6):394-398.

236. Miyagawa T, Ishikawa S, Ichioka D, Emura M, Kojima T, Tsutsumi M et al. Real-time virtual sonography for prostate-targeted biopsy based on MRI data: Evaluation of accuracy with resected specimens. *Urology* 2011; 78(3):S305-S306.

237. Miyake H, Sakai I, Ishimura T, Hara I, Eto H. Significance of cancer detection in the anterior lateral horn on systematic prostate biopsy: the effect on pathological findings of radical prostatectomy specimens. *BJU Int* 2004; 93(1):57-59. (a)

238. Miyake H, Sakai I, Harada K, Hara I, Eto H. Increased detection of clinically significant prostate cancer by additional sampling from the anterior lateral horns of the peripheral zone in combination with the standard sextant biopsy. *Int J Urol* 2004; 11(6):402-406. (b)

239. Miyake H, Harada K, Inoue TA, Takenaka A, Hara I, Fujisawa M. Additional sampling of dorsal apex on systematic prostate biopsy: impact on early detection of prostate cancer. *Urology* 2007; 69(4):738-742.

240. Moore C, Robertson N, Arsanious N, Middleton T, Taneja S, Villers A et al. A systematic review: Are MR targeted biopsies as efficient as standard trus biopsies in the detection of clinically significant prostate cancer? *Urology* 2012; 80(3):S136-S137.

241. Moore CM, Robertson NL, Arsanious N, Middleton T, Villers A, Klotz L et al. Image-guided prostate biopsy using magnetic resonance imaging-derived targets: A systematic review. *Eur Urol* 2013; 63(1):125-140.

242. Morelli G, Pagni R, Mariani C, Minervini R, Morelli A, Gori F et al. Results of vardenafil mediated power Doppler ultrasound, contrast enhanced ultrasound and systematic random biopsies to detect prostate cancer. *J Urol* 2011; 185(6):2126-2131.

243. Mouraviev V, Pugnale M, Kalyanaraman B, Verma S, Nistor V, Zhai Q et al. The feasibility of a novel MRI-TRUS navigation system for targeted fusion biopsy of early stage prostate cancer: The preliminary experience. *J Endourol* 2012; 26:A42.

244. Mowatt G, Scotland G, Boachie C, Cruickshank M, Ford JA, Fraser C et al. The diagnostic accuracy and cost-effectiveness of magnetic resonance spectroscopy and enhanced magnetic resonance imaging techniques in aiding the localisation of prostate abnormalities for biopsy: a systematic review and economic evaluation. [Review]. *Health Technology Assessment (Winchester, England)* 2013; 17(20)

245. Nagel KN, Schouten MG, Hambrock T, Litjens GJ, Hoeks CM, ten HB et al. Differentiation of prostatitis and prostate cancer by using diffusion-weighted MR imaging and MR-guided biopsy at 3 T. *Radiology* 2013; 267(1):164-172.

246. Narayanan R, Werahera PN, Barqawi A, Crawford ED, Shinohara K, Simoneau AR et al. Adaptation of a 3D prostate cancer atlas for transrectal ultrasound guided target-specific biopsy. *Physics in Medicine & Biology* 2008; 53(20):N397-N406.

247. Natarajan S, Marks LS, Margolis DJ, Huang J, Macairan ML, Lieu P et al. Clinical application of a 3D ultrasound-guided prostate biopsy system. *Urol Oncol* 2011; 29(3):334-342.

248. Naya Y, Ochiai A, Troncoso P, Babaian RJ. A comparison of extended biopsy and sextant biopsy schemes for predicting the pathological stage of prostate cancer. *J Urol* 2004; 171(6:Pt 1):t-8.

249. Neill MG, Toi A, Lockwood GA, Evans A, Tammsalu L, Fleshner NE. Systematic lateral prostate biopsy--are the benefits worth the costs? *J Urol* 2008; 179(4):1321-1326.

250. Nelson ED, Slotoroff CB, Gomella LG, Halpern EJ. Targeted biopsy of the prostate: the impact of color Doppler imaging and elastography on prostate cancer detection and Gleason score. *Urology* 2007; 70(6):1136-1140.

251. Nogueira L, Wang L, Fine SW, Pinochet R, Kurta JM, Katz D et al. Focal treatment or observation of prostate cancer: pretreatment accuracy of transrectal ultrasound biopsy and T2-weighted MRI. *Urology* 2010; 75(2):472-477.

252. Noh TI, Shin YS, Shim JS, Yoon JH, Kim JH, Bae JH et al. Are hypoechoic lesions on transrectal ultrasonography a marker for clinically significant prostate cancer? *Korean J Urol* 2013; 54(10):666-670.

253. Norberg M, Holmberg L, Busch C, Haggman M, Egevad L, Magnusson A. Multiple transrectal ultrasound-guided biopsies for the detection of prostate cancer and determination of tumor volume, grade, and seminal vesicle invasion. *Eur Radiol* 1996; 6(1):56-61.

254. Norberg M, Egevad L, Holmberg L, Sparen P, Norlen BJ, Busch C. The sextant protocol for ultrasound-guided core biopsies of the prostate underestimates the presence of cancer. *Urology* 1997; 50(4):562-566.

255. Numao N, Kawakami S, Yokoyama M, Yonese J, Arisawa C, Ishikawa Y et al. Improved accuracy in predicting the presence of Gleason pattern 4/5 prostate cancer by three-dimensional 26-core systematic biopsy. *Eur Urol* 2007; 52(6):1663-1668.

256. Numao N, Ito M, Fukushima H, Takeshita H, Yoshida S, Matsuoka Y et al. Magnetic resonance imaging guided prostate biopsy versus systematic 14-core prostate biopsy including anterior samplings in detecting significant cancer and assessing cancer aggressiveness. *J Urol* 2013; 189(4):e603-e604. (a)

257. Numao N, Yoshida S, Komai Y, Ishii C, Kagawa M, Kijima T et al. Usefulness of pre-biopsy multiparametric magnetic resonance imaging and clinical variables to reduce initial prostate biopsy in men with suspected clinically localized prostate cancer. *J Urol* 2013; 190(2):502-508. (b)

258. O'Connell MJ, Smith CS, Fitzpatrick PE, Keane CO, Fitzpatrick JM, Behan M et al. Transrectal ultrasound-guided biopsy of the prostate gland: value of 12 versus 6 cores. *Abdominal Imaging* 2004; 29(1):132-136.

259. Ochiai A, Troncoso P, Babaian RJ. Comparison of cancers detected at only a sextant or alternative location. *BJU Int* 2008; 101(7):837-840.

260. Ohira S, Hara R, Obatake A, Fujita M, Shouhei T, Hukumotou K et al. Efficacy of transperineal versus transrectal 12-core initial prostate biopsy with PSA levels between 4.0 and 20.0 ng/ml. *Urology* 2011; 78(3):S47.

261. Olson MC, Posniak HV, Fisher SG, Flisak ME, Salomon CG, Flanigan RC et al. Directed and random biopsies of the prostate: indications based on combined results of transrectal sonography and prostate-specific antigen density determinations. *AJR* 1994; American(6):1407-1411.

262. Onik G, Miessau M, Bostwick DG. Three-dimensional prostate mapping biopsy has a potentially significant impact on prostate cancer management. *J Clin Oncol* 2009; 27(26):4321-4326.

263. Onur Rahm, Littrup PJ, Pontes JE, Bianco Jr. Comtemporary impact of transrectal ultrasound lesions for prostate cancer detection. *The Journal of Urology* 2004; 172(2):512-514.

264. Onur MR, Turgut AT, Dogra V. Ultrasound-guided biopsy of the prostate: New updates. *Ultrasound Cln* 2014; 9(1):81-94.

265. Ou Y, Shen D, Zeng J, Sun L, Moul J, Davatzikos C. Sampling the spatial patterns of cancer: optimized biopsy procedures for estimating prostate cancer volume and Gleason Score. *Medical Image Analysis* 2009; 13(4):609-620.

266. Ouzzane A, Puech P, Lemaitre L, Leroy X, Nevoux P, Betrouni N et al. Combined multiparametric MRI and targeted biopsies improve anterior prostate cancer detection, staging, and grading. *Urology* 2011; 78(6):1356-1362.

267. Overduin CG, Futterer JJ, Barentsz JO. MRI-guided biopsy for prostate cancer detection: A systematic review of current clinical results. *Curr Urol Rep* 2013; 14(3):209-213.

268. Ozdedeli KO, Demir ZD, Akdere HA, Kuyumcuoglu UK, Cek MC. Comparison of ten core biopsy protocol with Vienna nomogram in the detection of prostate cancer. *Eur Urol Suppl* 2013; 12(4):e1283.

269. Pallwein L, Mitterberger M, Gradl J, Aigner F, Horninger W, Strasser H et al. Value of contrast-enhanced ultrasound and elastography in imaging of prostate cancer. [Review] [49 refs]. *Current Opinion in Urology* 2007; 17(1):39-47. (a)

270. Pallwein L, Mitterberger M, Struve P, Horninger W, Aigner F, Bartsch G et al. Comparison of sonoelastography guided biopsy with systematic biopsy: impact on prostate cancer detection. *Eur Radiol* 2007; 17(9):2278-2285. (b)

271. Papatheodorou A, Ellinas P, Tandeles S, Takis F, Poulias H, Nikolaou I et al. Transrectal ultrasonography and ultrasound-guided biopsies of the prostate gland: How, when, and where. *Curr Probl Diagn Radiol* 2005; 34(2):76-83.

272. Park BK, Park JW, Park SY, Kim CK, Lee HM, Jeon SS et al. Prospective evaluation of 3-T MRI performed before initial transrectal ultrasound-guided prostate biopsy in patients with high prostate-specific antigen and no previous biopsy. *AJR* 2011; American(5):W876-W881.

273. Patel A. Finding a balanced strategy in prostate cancer diagnosis for case detection by prostate needle biopsy at first presentation: "all for more cores and more cores for all" or individualised sampling regimens? Which way forward? *Eur Urol* 2007; 52(2):313-315.

274. Patel AR, Jones JS. Optimal biopsy strategies for the diagnosis and staging of prostate cancer. *Current Opinion in Urology* 2009; 19(3):232-237.

275. Patel V, Merrick GS, Allen ZA, Andreini H, Taubenslag W, Singh S et al. The incidence of transition zone prostate cancer diagnosed by transperineal template-guided mapping biopsy: implications for treatment planning. *Urology* 2011; 77(5):1148-1152.

276. Paul R, Scholer S, van RH, Kubler H, Alschibaja M, Busch R et al. Morbidity of prostatic biopsy for different biopsy strategies: is there a relation to core number and sampling region? *Eur Urol* 2004; 45(4):450-455.

277. Peltier A, Aoun F, El-Khoury F, Hawaux E, Limani K, Narahari K et al. 3D versus 2D systematic transrectal ultrasound-guided prostate biopsy: Higher cancer detection rate in clinical practice. *Prostate Cancer* 2013.

278. Pelzer A, Bektic J, Berger AP, Pallwein L, Halpern EJ, Horninger W et al. Prostate cancer detection in men with prostate specific antigen 4 to 10 ng/ml using a combined approach of contrast enhanced color Doppler targeted and systematic biopsy. *J Urol* 2005; 173(6):1926-1929. (a)

279. Pelzer AE, Bektic J, Berger AP, Halpern EJ, Koppelstatter F, Klauser A et al. Are transition zone biopsies still necessary to improve prostate cancer detection? Results from the tyrol screening project. *Eur Urol* 2005; 48(6):916-921. (b)

280. Pelzer AE, Tewari A, Bektic J, Berger AP, Frauscher F, Bartsch G et al. Detection rates and biologic significance of prostate cancer with PSA less than 4.0 ng/mL: observation and clinical implications from Tyrol screening project. *Urology* 2005; 66(5):1029-1033. (c)

281. Peng Y, Jiang Y, Yang C, Brown JB, Antic T, Sethi I et al. Quantitative analysis of multiparametric prostate MR images: differentiation between prostate cancer and normal tissue and correlation with Gleason score--a computer-aided diagnosis development study. *Radiology* 2013; 267(3):787-796.

282. Pepe P, Patane D, Panella P, Aragona F. Does the adjunct of ecographic contrast medium Levovist improve the detection rate of prostate cancer? *Prostate Cancer & Prostatic Diseases* 2003; 6(2):159-162.

283. Pepe P, Aragona F. Saturation prostate needle biopsy and prostate cancer detection at initial and repeat evaluation. *Urology* 2007; 70(6):1131-1135.

284. Pepe P, Fraggetta F, Galia A, Grasso G, Piccolo S, Aragona F. Is quantitative histologic examination useful to predict nonorgan-confined prostate cancer when saturation biopsy is performed? *Urology* 2008; 72(6):1198-1202.

285. Perez-Guillermo M, Acosta-Ortega J, Garcia-Solano J. The continuing role of fine-needle aspiration of the prostate gland into the 21st century: a tribute to Torsten Lowhagen. *Diagnostic Cytopathology* 2005; 32(5):315-320.

286. Philip J, Ragavan N, Desouza J, Foster CS, Javle P. Effect of peripheral biopsies in maximising early prostate cancer detection in 8-, 10- or 12-core biopsy regimens. *BJU Int* 2004; 93(9):1218-1220.

287. Philip J, Manikandan R, Javle P, Foster CS. Prostate cancer diagnosis: should patients with prostate specific antigen >10ng/mL have stratified prostate biopsy protocols? *Cancer Detection & Prevention* 2009; 32(4):314-318.

288. Pinto PA, Chung PH, Rastinehad AR, Baccala AA, Jr., Kruecker J, Benjamin CJ et al. Magnetic resonance imaging/ultrasound fusion guided prostate biopsy improves cancer detection following transrectal ultrasound biopsy and correlates with multiparametric magnetic resonance imaging. *J Urol* 2011; 186(4):1281-1285.

289. Pitt WR. Comments on: Saturation biopsy for detecting and characterizing prostate cancer; and A review of targeted screening for prostate cancer: introducing the IMPACT study. *BJU Int* 2008; 101(3):392.

290. Ploussard G, Plennevaux G, Allory Y, Salomon L, Azoulay S, Vordos D et al. High-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation on initial 21-core extended biopsy scheme: incidence and implications for patient care and surveillance. *World Journal of Urology* 2009; 27(5):587-592.

291. Ploussard G, Marchand C, Nicolaiew N, Terry S, Vacherot F, Vordos D et al. Prospective Evaluation of an Extended 21-Core Biopsy Scheme as Initial Prostate Cancer Diagnostic Strategy. *Eur Urol* 2012.

292. Pondman KM, Futterer JJ, ten HB, Schultze Kool LJ, Witjes JA, Hambrock T et al. MR-guided biopsy of the prostate: an overview of techniques and a systematic review. *Eur Urol* 2008; 54(3):517-527.

293. Popert R. Transperineal magnetic resonance imaging--ultrasound fusion targeted biopsies (MRI-US FTB) of the prostate: the future of prostate diagnostics. *BJU International* 2013; 112(5):537-538.

294. Presti JC, Jr., O'Dowd GJ, Miller MC, Mattu R, Veltri RW. Extended peripheral zone biopsy schemes increase cancer detection rates and minimize variance in prostate specific antigen and age related cancer rates: results of a community multi-practice study. *J Urol* 2003; 169(1):125-129.

295. Presti JC, Jr. Prostate biopsy strategies. *Nature Clinical Practice Urology* 2007; 4(9):505-511.

296. Presti JC, Jr. Repeat prostate biopsy--when, where, and how. *Urol Oncol* 2009; 27(3):312-314.

297. Puech P, Rouviere O, Renard-Penna R, Villers A, Devos P, Colombel M et al. Prostate cancer diagnosis : Multiparametric mr-targeted biopsy with cognitive and transrectal us-mr fusion guidance versus systematic biopsy-prospective multicenter study. *Radiology* 2013; 268(2):461-469.

298. Quinlan MR, Casey RG, Flynn R, Grainger R, McDermott TE, Thornhill JA. A review of repeat prostate biopsies and the influence of technique on cancer detection: our experience. *Irish Journal of Medical Science* 2009; 178(3):287-290.

299. Quintana LM, Ward A, Genega E, Ye H. Utility of saturation prostate biopsy in detection of aggressive prostate cancer. *Lab Invest* 2013; 93:242A.

300. Ragde H, Kenny GM, Murphy GP, Landin K. Transrectal ultrasound microbubble contrast angiography of the prostate. *Prostate* 1997; 32(4):279-283.

301. Rais-Bahrami S, Siddiqui MM, Stamatakis L, Vourganti S, Hoang AN, Walton-Diaz A et al. Correlating multiparametric prostate MRI (MP-MRI) suspicion for prostate cancer with MRI/ultrasound (MR/US) fusion guided biopsy results and gleason grade. *J Urol* 2013; 189(4):e897.

302. Raja J, Ramachandran N, Munneke G, Patel U. Current status of transrectal ultrasound-guided prostate biopsy in the diagnosis of prostate cancer. *Clin Radiol* 2006; 61(2):142-153.

303. Ramachandran N, MacKinnon A, Allen C, Dundas D, Patel U. Biopsy of the prostate guided by transrectal ultrasound: Relation between warfarin use and incidence of bleeding complications [1]. *Clin Radiol* 2005; 60(10):1130.

304. Ravery V, Dominique S, Panhard X, Toublanc M, Boccon-Gibod L, Boccon-Gibod L. The 20-core prostate biopsy protocol--a new gold standard? *J Urol* 2008; 179(2):504-507.

305. Remzi M, Dobrovits M, Reissigl A, Ravery V, Waldert M, Wiunig C et al. Can Power Doppler enhanced transrectal ultrasound guided biopsy improve prostate cancer detection on first and repeat prostate biopsy? *Eur Urol* 2004; 46(4):451-456.

306. Remzi M, Fong YK, Dobrovits M, Anagnostou T, Seitz C, Waldert M et al. The Vienna nomogram: validation of a novel biopsy strategy defining the optimal number of cores based on patient age and total prostate volume. *J Urol* 2005; 174(4:Pt 1):t-60.

307. RiChard JL, Motamedinia P, De Castro GJ, McKiernan JM, Benson MC. Routine transition zone biopsy during active surveillance for prostate cancer rarely provides unique evidence of disease progression. *J Urol* 2012; 187(4):e144.

308. Rietbergen JB, Kruger AE, Kranse R, Schroder FH. Complications of transrectal ultrasound-guided systematic sextant biopsies of the prostate: evaluation of complication rates and risk factors within a population-based screening program. *Urology* 1997; 49(6):875-880.

309. Roberts MJ, Parambi A, Barrett L, Hadway P, Gardiner RA, Hajkowicz KM et al. Multifocal abscesses due to multiresistant Escherichia coli after transrectal ultrasound-guided prostate biopsy. *Medical Journal of Australia* 2013; 198(5):282-284.

310. Robertson N, Moore C, Villers A, Klotz L, Emberton M. The ability of mri guided biopsy to detect clinically significant prostate cancer: A systematic review. *J Urol* 2012; 187(4):e491-e492.

311. Robinson K, Creed J, Reguly B, Powell C, Wittock R, Klein D et al. Accurate prediction of repeat prostate biopsy outcomes by a mitochondrial DNA deletion assay. *Prostate Cancer Prostatic Dis* 2010; 13(2):126-131.

312. Roy C, Buy X, Lang H, Saussine C, Jacqmin D. Contrast enhanced color Doppler endorectal sonography of prostate: efficiency for detecting peripheral zone tumors and role for biopsy procedure. *J Urol* 2003; 170(1):69-72.

313. Rud E, Baco E, Eggesbo HB. MRI and ultrasound-guided prostate biopsy using soft image fusion. *Anticancer Res* 2012; 32(8):3383-3389.

314. Rusu F, Rusu E, Radulian G, Enache G, Rusu A, Pahontu EM et al. Improved prostate cancer detection using different biopsy strategies for patients with metabolic syndrome. *Obes Rev* 2011; 12:202.

315. Sabir S, Choi H, Ward J, Ahrar K, McRae SE. Transgluteal MR-guided prostate biopsy: Results of a freehand technique in a closed 1.5t MRI. *J Vasc Intervent Radiol* 2013; 24(4):S176-S177.

316. Sadeghi-Nejad H, Simmons M, Dakwar G, Dogra V. Controversies in transrectal ultrasonography and prostate biopsy. *Ultrasound Q* 2006; 22(3):169-175.

317. Sajadi KP, Kim T, Terris MK, Brown JA, Lewis RW. High yield of saturation prostate biopsy for patients with previous negative biopsies and small prostates. *Urology* 2007; 70(4):691-695.

318. San Francisco IF, Regan MM, DeWolf WC, Olumi AF. Outcome of patients after radical retropubic prostatectomy: A comparison of prostate cancer diagnosed using extended needle biopsy technique vs. non-extended needle biopsy technique. *UroOncology* 2004; 4(2):85-90.

319. Sano F, Terao H, Kawahara T, Miyoshi Y, Sasaki T, Noguchi K et al. Contrast-enhanced ultrasonography of the prostate: various imaging findings that indicate prostate cancer. *BJU Int* 2011; 107(9):1404-1410.

320. Sartor O. Prostate cancer. Saturation biopsy does not accurately localize tumors. *Nat Rev Urol* 2010; 7(9):479-480.

321. Sauvain JL, Palascak P, Bourscheid D, Chabi C, Atassi A, Bremon JM et al. Value of power doppler and 3D vascular sonography as a method for diagnosis and staging of prostate cancer. *Eur Urol* 2003; 44(1):21-30.

322. Scattoni V, Zlotta AR, Nava L, Roscigno M, Montorsi F, Rigatti P. Prostatic transrectal ultrasound (TRUS) guided biopsy schemes and TRUS prostatic lesion-guided biopsies. *European Urology, Supplement* 2002; 1(6):28-34.

323. Scattoni V. Systematic prostate biopsies are more and more often becoming saturation biopsies. *Eur Urol* 2006; 50(2):202-204.

324. Scattoni V, Zlotta A, Montironi R, Schulman C, Rigatti P, Montorsi F. Extended and saturation prostatic biopsy in the diagnosis and characterisation of prostate cancer: a critical analysis of the literature. *Eur Urol* 2007; 52(5):1309-1322.

325. Scattoni V, Roscigno M, Raber M, Deho F, Maga T, Zanoni M et al. Initial extended transrectal prostate biopsy--are more prostate cancers detected with 18 cores than with 12 cores? *J Urol* 2008; 179(4):1327-1331.

326. Scattoni V, Maccagnano C, Zanni G, Angiolilli D, Raber M, Roscigno M et al. Is extended and saturation biopsy necessary?. *Int J Urol* 2010; 17(5):432-447. (a)

327. Scattoni V, Raber M, Abdollah F, Roscigno M, Deho F, Angiolilli D et al. Biopsy schemes with the fewest cores for detecting 95% of the prostate cancers detected by a 24-core biopsy. *Eur Urol* 2010; 57(1):1-8. (b)

328. Schulte RT, Wood DP, Daignault S, Shah RB, Wei JT. Utility of extended pattern prostate biopsies for tumor localization: pathologic correlations after radical prostatectomy. *Cancer* 2008; 113(7):1559-1565.

329. Schwab SA, Kuefner MA, Adamietz B, Engelhard K, Keck B, Kunath F et al. MRI-guided core biopsy of the prostate in the supine position - Introduction of a simplified technique using large-bore magnet systems. *Eur Radiol* 2013; 23(5):1415-1419.

330. Sciarra A, Barentsz J, Bjartell A, Eastham J, Hricak H, Panebianco V et al. Advances in magnetic resonance imaging: how they are changing the management of prostate cancer. [Review]. *Eur Urol* 2011; 59(6):962-977. (a)

331. Sciarra A, Panebianco V, Salciccia S, Cattarino S, Lisi D, Gentilucci A et al. Modern role of magnetic resonance and spectroscopy in the imaging of prostate cancer. [Review]. *Urol Oncol* 2011; 29(1):12-20. (b)

332. Seltzer MA, Shinohara K, Bhargava V, Carroll PR, Presti J. Comparison of systematic sextant and lesion directed biopsies in prostate cancer detection. *Urol Oncol* 1996; 2(5):136-138.

333. Sfakianos JP, Thorner DA, Dovirak O, Weiss JP, Karanikolas NT. Optimizing prostate cancer detection during biopsy by standardizing the amount of tissue examined per core. *BJU Int* 2011; 108(10):1578-1581.

334. Sharma SP. Anterior apical biopsy helps prostate-cancer detection. *Lancet Oncology* 2007; 8(1):11.

335. Shen F, Shinohara K, Kumar D, Khemka A, Simoneau AR, Werahera PN et al. Three-dimensional sonography with needle tracking: role in diagnosis and treatment of prostate cancer. *Journal of Ultrasound in Medicine* 2008; 27(6):895-905.

336. Shen PF, Zhu YC, Wei WR, Li YZ, Yang J, Li YT et al. The results of transperineal versus transrectal prostate biopsy: a systematic review and meta-analysis. *Asian J Androl* 2012; 14(2):310-315.

337. Shigemura K, Arakawa S, Yamanaka K, Kataoka N, Yuien K, Fujisawa M. Significance of lateral biopsy specimens during transrectal ultrasound-guided prostate biopsies in Japanese men. *Int J Urol* 2007; 14(10):935-938.

338. Shigemura K, Yamashita M, Fujisawa M. Do additional cores from MRI-cancer suspicious lesion to systematic 12-core transrectal prostate biopsy give better cancer detection? *J Urol* 2013; 189(4):e904.

339. Shim HB, Park HK, Lee SE, Ku JH. Optimal site and number of biopsy cores according to prostate volume prostate cancer detection in Korea. *Urology* 2007; 69(5):902-906. (a)

340. Shim HB, Lee SE, Park HK, Ku JH. Significance of suspicious lesions at transrectal ultrasonography in men with serum prostate-specific antigen levels of < 20 ng/ml. *Tumori* 2007; 93(2):178-181. (b)

341. Shim HB, Lee SE, Park HK, Ku JH. Prostate biopsy in subjects with abnormal transrectal ultrasonography but normal digital examination findings and prostate-specific antigen levels. *International Urology & Nephrology* 2007; 39(4):1115-1120. (c)

342. Siddiqui MM, Rais-Bahrami S, Stamatakis L, Vourganti S, Hoang A, Nix J et al. Gleason score upgrading on mri/ultrasound fusion guided prostate biopsy versus systematic 12-core trus biopsy. *J Urol* 2013; 189(4):e910. (a)

343. Siddiqui MM, Rais-Bahrami S, Truong H, Stamatakis L, Vourganti S, Nix J et al. Magnetic resonance imaging/ultrasound-fusion biopsy significantly upgrades prostate cancer versus systematic 12-core transrectal ultrasound biopsy. *Eur Urol* 2013; 64(5):713-719. (b)

344. Singh AK, Kruecker J, Xu S, Glossop N, Guion P, Ullman K et al. Initial clinical experience with real-time transrectal ultrasonography-magnetic resonance imaging fusion-guided prostate biopsy. *BJU Int* 2008; 101(7):841-845.

345. Singh H, Canto EI, Shariat SF, Kadmon D, Miles BJ, Wheeler TM et al. Improved detection of clinically significant, curable prostate cancer with systematic 12-core biopsy. *J Urol* 2004; 171(3):1089-1092. (a)

346. Singh H, Canto EI, Shariat SF, Kadmon D, Miles BJ, Wheeler TM et al. Six additional systematic lateral cores enhance sextant biopsy prediction of pathological features at radical prostatectomy. *J Urol* 2004; 171(1):204-209. (b)

347. Siu W, Dunn RL, Shah RB, Wei JT. Use of extended pattern technique for initial prostate biopsy. *J Urol* 2005; 174(2):505-509.

348. Slonim SM, Cuttino JT, Jr., Johnson CJ, Yankaskas BC, Smith JJ, III, Silverman ML et al. Diagnosis of prostatic carcinoma: value of random transrectal sonographically guided biopsies. *AJR* 1993; American(5):1003-1006.

349. Smeenge M, Mischi M, Laguna Pes MP, de la Rosette JJ, Wijkstra H. Novel contrast-enhanced ultrasound imaging in prostate cancer. *World Journal of Urology* 2011; 29(5):581-587.

350. Song JM, Kim CB, Chung HC, Kane RL. Prostate-specific antigen, digital rectal examination and transrectal ultrasonography: a meta-analysis for this diagnostic triad of prostate cancer in symptomatic korean men. *Yonsei Medical Journal* 2005; 46(3):414-424.

351. Sonn G, Natarajan S, Margolis D, Chang E, Macairan M, Lieu P et al. Targeted biopsy with MRI-ultrasound fusion. *J Urol* 2013; 189(4):e519.

352. Spajic B, Brigic I, Stimac G, Justinic D, Kruslin B, Kraus O. Complications of transrectal ultrasound guided prostate needle biopsy: Our experience and review of the literature. *Acta Clin Croat* 2006; 45(2):87-90.

353. Spajic B, Eupic H, Tomas D, Stimac G, Kruslin B, Kraus O. The incidence of hyperechoic prostate cancer in transrectal ultrasound-guided biopsy specimens. *Urology* 2007; 70(4):734-737.

354. Sparchez Z, Radu P, Zaharia T, Kacso G, Grigorescu I, Badea R. Contrast enhanced ultrasound guidance: a new tool to improve accuracy in percutaneous biopsies. *Medical Ultrasonography* 2010; 12(2):133-138.

355. Sperandeo G, Sperandeo M, Morcaldi M, Caturelli E, Dimitri L, Camagna A. Transrectal ultrasonography for the early diagnosis of adenocarcinoma of the prostate: a new maneuver designed to improve the differentiation of malignant and benign lesions. *J Urol* 2003; 169(2):607-610.

356. Stamatiou K, Alevizos A, Karanasiou V, Mariolis A, Mihas C, Papathanasiou M et al. Impact of additional sampling in the TRUS-guided biopsy for the diagnosis of prostate cancer. *Urologia Internationalis* 2007; 78(4):313-317.

357. Suardi N, Capitanio U, Gallina A, Abdollah F, Passoni N, Gandaglia G et al. The number of biopsy cores taken is a major predictor of unfavorable prostate cancer at final pathology in patients candidate for active surveillance: Clinical implications. *J Urol* 2013; 189(4):e916.

358. Taira AV, Merrick GS, Galbreath RW, Andreini H, Taubenslag W, Curtis R et al. Performance of transperineal template-guided mapping biopsy in detecting prostate cancer in the initial and repeat biopsy setting. *Prostate Cancer & Prostatic Diseases* 2010; 13(1):71-77.

359. Takahashi S, Yamada Y, Homma Y, Horie S, Hosaka Y, Kitamura T. Power Doppler ultrasonography-directed prostate biopsy in men with elevated serum PSA levels: an evaluation of the clinical utility and limitations. *Urology* 2002; 60(2):248-252.

360. Takenaka A, Hara R, Hyodo Y, Ishimura T, Sakai Y, Fujioka H et al. Transperineal extended biopsy improves the clinically significant prostate cancer detection rate: a comparative study of 6 and 12 biopsy cores. *Int J Urol* 2006; 13(1):10-14.

361. Takeshita H, Numao N, Kawakami S, Tatokoro M, Sakura M, Yokoyama M et al. Characteristics of prostate cancers missed by initial transperineal extended biopsy. *J Urol* 2012; 187(4):e892-e893.

362. Tarcan T, Ozveri H, Biren T, Turkeri L, Akdas A. Evaluation of prostate specific antigen density and transrectal ultrasonography-guided biopsies in 100 consecutive patients with a negative digital rectal examination and intermediate serum prostate specific antigen levels. *Int J Urol* 1997; 4(4):362-367.

363. Taverna G, Seveso M, Grizzi F, Benetti A, Piccinelli A, Giusti G et al. Color doppler and microbubble contrast agent do not improve the cancer detection rate in trans-rectal prostate bioptic sampling. *J Urol* 2009; 181(4):644.

364. Taverna G, Morandi G, Seveso M, Giusti G, Benetti A, Colombo P et al. Colour Doppler and microbubble contrast agent ultrasonography do not improve cancer detection rate in transrectal systematic prostate biopsy sampling. *BJU Int* 2011; 108(11):1723-1727.

365. Taverna G, Magnoni P, Giusti G, Seveso M, Benetti A, Hurle R et al. Impact of real-time elastography versus systematic prostate biopsy method on cancer detection rate in men with a serum prostate-specific antigen between 2.5 and 10 ng/mL. *ISRN Oncol* 2013; 1(1).

366. Teng J, Chen M, Gao Y, Yao Y, Chen L, Xu D. Transrectal sonoelastography in the detection of prostate cancers: a meta-analysis. [Review]. *BJU Int* 2012; 110(11:Pt B):t-20.

367. Terris MK. Strategies for repeat prostate biopsies. *Curr Urol Rep* 2009; 10(3):172-178.

368. Testa C, Schiavina R, Lodi R, Salizzoni E, Tonon C, D'Errico A et al. Accuracy of MRI/MRSI-based transrectal ultrasound biopsy in peripheral and transition zones of the prostate gland in patients with prior negative biopsy. *NMR in Biomedicine* 2010; 23(9):1017-1026.

369. Thiesler T, Trinkler F, Horcic M, Willi N, Cathomas G, Hailemariam S. Patients with low prostate-specific antigen levels (< or =4 ng/ml) would benefit from a twelve-core biopsy protocol for prostate cancer detection. *Urologia Internationalis* 2007; 78(4):318-322.

370. Tobiume M, Yamada Y, Nakamura K, Honda N. Retrospective study comparing six- and twelve-core prostate biopsy in detection of prostate cancer. *International Braz J Urol* 2008; 34(1):9-14.

371. Toi A, Neill MG, Lockwood GA, Sweet JM, Tammsalu LA, Fleshner NE. The continuing importance of transrectal ultrasound identification of prostatic lesions. *J Urol* 2007; 177(2):516-520.

372. Tsai YS, Chen CH, Lin YH, Tzai TS. Transrectal ultrasound for prostate cancer: Perspectives from National Cheng Kung University Hospital. *J Med Ultrasound* 2007; 15(3):183-190.

373. Tsivian M, Polascik TJ. The role of transrectal saturation biopsy in tumour localization: pathological correlation after retropubic radical prostatectomy and implication for focal ablative therapy. *BJU Int* 2011; 108(3):371.

374. Turkbey B, Xu S, Kruecker J, Locklin J, Pang Y, Shah V et al. Documenting the location of systematic transrectal ultrasound-guided prostate biopsies: correlation with multi-parametric MRI. *Cancer Imaging* 2011; 11:31-36.

375. Turkeri L, Tarcan T, Biren T, Kullu S, Akdas A. Correlation of transrectal ultrasonography and core biopsies with pathology results in radical prostatectomy specimens. *Int J Urol* 1996; 3(6):459-461.

376. Ukimura O, Marien A, Palmer S, De Castro Abreu AL, Leslie S, Shoji S et al. Magnetic resonance imaging targeted prostate biopsy with 3-dimensional ultrasound tracking system in comparative analysis to systematic

random biopsy on 131 consecutive patients with prebiopsy magnetic resonance imaging. *J Urol* 2013; 189(4):e896. (a)

377. Ukimura O, Coleman JA, de la Taille A, Emberton M, Epstein JI, Freedland SJ et al. Contemporary role of systematic prostate biopsies: Indications, techniques, and implications for patient care. *Eur Urol* 2013; 63(2):214-230. (b)

378. Uno H, Saito A, Toyoda S, Takada T, Tamaki M, Komeda H et al. Indications for transperineal ultrasound-guided prostate biopsy: Analysis comparing transperineal versus transrectal 14-core biopsy. *Urology* 2011; 78(3):S7-S8.

379. van der Kwast TH, Wolters T, Evans A, Roobol M. Single Prostatic Cancer Foci on Prostate Biopsy. *Eur Urol Suppl* 2008; 7(8):549-556.

380. van LP, van den Bergh R, Wolters T, Schroder F, Roobol M. Screening: should more biopsies be taken in larger prostates? *BJU Int* 2009; 104(7):919-924.

381. Vasdev N, Dominguez-Escrig JL, Paez E, Thorpe AC, Greene D. Are saturation biopsies of the prostate essential? *Curr Urol* 2011; 5(1):1-5.

382. Vassilios S, Dounis A, Evagelou I, Metsinis M, Skouteris M, Papaioannou D et al. Transperineal template-guided mapping biopsy for detection of prostate cancer as an initial approach. *Eur J Intern Med* 2011; 22:S88.

383. Villa L, Capitanio U, Scattoni V, Suardi N, Gallina A, Abdollah F et al. Misclassification of micro-focus prostate cancer decreases with the extent of biopsy sampling. Importance of accurate detection. *Eur Urol Suppl* 2012; 11(1):e150.

384. Villa L, Nazareno S, Capitanio U, Damiano R, Bianchi M, Nini A et al. Association between the number of cores taken at initial prostate biopsy and insignificant prostate cancer at radical prostatectomy in patients suitable for active surveillance. Need for accurate biopsy sampling. *J Urol* 2013; 189(4):e790-e791.

385. Villers A, Marliere F, Ouzzane A, Puech P, Lemaitre L. MRI in addition to or as a substitute for prostate biopsy: The clinician's point of view. *Daign Intervent Imaging* 2012; 93(4):262-267.

386. Vora A, Williams H, Khadoury S, Kreuker J, Buckner C, Turkbey B et al. Apical undersampling of the prostate on twelve core transrectal ultrasound (TRUS) biopsy detected by mri-guided electromagnetic mapped fusion biopsy. *J Endourol* 2011; 25:A268.

387. Vourganti S, Logan J, Rais-Bahrami S, Siddiqui MM, Stamatakis L, Walton-Diaz A et al. Verification of traditional extended sextant 12 core trus prostate biopsy locations. *J Urol* 2013; 189(4):e911.

388. Vyas L, Popert R, Kinsella J, Yamamoto H, Acher P, Smith J et al. Transperineal sector prostate biopsy technique and morbidity. *BJU Int* 2012; 109:41.

389. Wareing M. Transrectal ultrasound and prostate biopsy clinic. [Review] [30 refs]. *Nursing Standard* 2004; 18(24):33-37.

390. Watanabe M, Hayashi T, Tsushima T, Irie S, Kaneshige T, Kumon H. Extensive biopsy using a combined transperineal and transrectal approach to improve prostate cancer detection. *Int J Urol* 2005; 12(11):959-963.

391. Watanabe Y, Terai A, Araki T, Nagayama M, Okumura A, Amoh Y et al. Detection and localization of prostate cancer with the targeted biopsy strategy based on ADC map: a prospective large-scale cohort study. *J Magn Reson Imaging* 2012; 35(6):1414-1421.

392. Watanabe Y, Nagayama M, Araki T, Terai A, Okumura A, Amoh Y et al. Targeted biopsy based on ADC map in the detection and localization of prostate cancer: A feasibility study. *J Magn Reson Imaging* 2013; 37(5):1168-1177.

393. Wei JT. Limitations of a contemporary prostate biopsy: the blind march forward. *Urol Oncol* 2010; 28(5):546-549.

394. Williamson DA, Barrett LK, Rogers BA, Freeman JT, Hadway P, Paterson DL. Infectious complications following transrectal ultrasound-guided prostate biopsy: new challenges in the era of multidrug-resistant Escherichia coli. [Review]. *Clinical Infectious Diseases* 2013; 57(2):267-274.

395. Werahera PN, Sullivan K, La Rosa FG, Kim FJ, Lucia MS, O'Donnell C et al. Optimization of prostate cancer diagnosis by increasing the number of core biopsies based on gland volume. *International Journal of Clinical & Experimental Pathology* 2012; 5(9):892-899.

396. Winter M, Bergersen P, Woo HH, Chalasani V. Complications after prostate biopsy: A meta-analysis of transrectal prostate biopsy versus transperineal prostate biopsy. *BJU Int* 2013; 111:97.

397. Wright JL, Ellis WJ. Improved prostate cancer detection with anterior apical prostate biopsies. *Urol Oncol* 2006; 24(6):492-495.

398. Wysock JS, Rosenkrantz AB, Huang WC, Stifelman M, Lepor H, Taneja SS. A prospective comparative study of targeted prostate biopsy directed to mri-suspicious regions versus artemis(trademark) computerized 12 core template biopsy. *J Urol* 2013; 189(4):e909-e910.

399. Xie SW, Li HL, Du J, Xia JG, Guo YF, Xin M et al. Contrast-enhanced ultrasonography with contrast-tuned imaging technology for the detection of prostate cancer: comparison with conventional ultrasonography. *BJU Int* 2012; 109(11):1620-1626.

400. Xu S, Kruecker J, Guion P, Glossop N, Neeman Z, Choyke P et al. Closed-loop control in fused MR-TRUS image-guided prostate biopsy. *Medical Image Computing & Computer-Assisted Intervention: MICCAI* 2007; 10(Pt:1):1-35.

401. Xu S, Kruecker J, Turkbey B, Glossop N, Singh AK, Choyke P et al. Real-time MRI-TRUS fusion for guidance of targeted prostate biopsies. *Computer Aided Surgery* 2008; 13(5):255-264.

402. Yacoub JH, Verma S, Moulton JS, Eggener S, Aytekin O. Imaging-guided prostate biopsy: conventional and emerging techniques. *Radiographics* 2012; 32(3):819-837.

403. Yakar D, Hambrock T, Hoeks C, Barentsz JO, Futterer JJ. Magnetic resonance-guided biopsy of the prostate: feasibility, technique, and clinical applications. *Topics in Magnetic Resonance Imaging* 2008; 19(6):291-295.

404. Yamamoto S, Ito T, Aizawa T, Noda K, Umezu K, Ohtsuru N et al. Does transrectal ultrasound guided eight-core prostate biopsy improve cancer detection rates in patients with prostate-specific antigen levels of 4.1-10 ng/mL? *Int J Urol* 2004; 11(6):386-391.

405. Yan W, Li H, Zhou Y, Huang Z, Rong S, Xia M et al. Prostate carcinoma spatial distribution patterns in Chinese men investigated with systematic transperineal ultrasound guided 11-region biopsy. *Urol Oncol* 2009; 27(5):520-524.

406. Yang JC, Tang J, Li J, Luo Y, Li Y, Shi H. Contrast-enhanced gray-scale transrectal ultrasound-guided prostate biopsy in men with elevated serum prostate-specific antigen levels. *Academic Radiology* 2008; 15(10):1291-1297.

407. Yerram NK, Volkin D, Turkbey B, Nix J, Hoang AN, Vourganti S et al. Low suspicion lesions on multiparametric magnetic resonance imaging predict for the absence of high-risk prostate cancer. *BJU Int* 2012; 110(11:Pt B):t-8.

408. Yoon BI, Shin TS, Cho HJ, Hong SH, Lee JY, Hwang TK et al. Is it effective to perform two more prostate biopsies according to prostate-specific antigen level and prostate volume in detecting prostate cancer? Prospective study of 10-core and 12-core prostate biopsy. *Urology Journal* 2012; 9(2):491-497.

409. Yuasa T, Tsuchiya N, Kumazawa T, Inoue T, Narita S, Saito M et al. Characterization of prostate cancer detected at repeat biopsy. *BMC Urol* 2008; 8:14.

410. Yunkai Z, Yaqing C, Ren W, Yongchang Z. Are transition zone biopsies necessary in transrectal ultrasound-guided transperineal prostate biopsy protocol? Results of a Chinese population-based study. *Clinical Imaging* 2010; 34(1):43-46.

411. Zackrisson B, Aus G, Bergdahl S, Lilja H, Lodding P, Pihl CG et al. The risk of finding focal cancer (less than 3 mm) remains high on re-biopsy of patients with persistently increased prostate specific antigen but the clinical significance is questionable. *J Urol* 2004; 171(4):1500-1503.

412. Zaytoun OM, Jones JS. Prostate cancer detection after a negative prostate biopsy: lessons learnt in the Cleveland Clinic experience. [Review]. *Int J Urol* 2011; 18(8):557-568.

413. Zhang Y, Tang J, Li YM, Fei X, He EH, Li QY et al. The contribution of strain patterns in characterization of prostate peripheral zone lesions at transrectal ultrasonography. *Acta Radiologica* 2012; 53(1):119-126.

414. Zhao HX, Zhu Q, Wang ZC. Detection of prostate cancer with three-dimensional transrectal ultrasound: correlation with biopsy results. *British Journal of Radiology* 2012; 85(1014):714-719.

415. Zhao HX, Xia CX, Yin HX, Guo N, Zhu Q. The value and limitations of contrast-enhanced transrectal ultrasonography for the detection of prostate cancer. *Eur J Radiol* 2013.

Systematic review report for question 8.1

Clinical Question 8: *If prostate cancer is not found in an adequate biopsy what if any additional steps should be taken and what recommendations should be made regarding the strategy for subsequent PSA testing?*

PICO Question 8.1: *In men who have been referred with suspected prostate cancer, what are the prognostic factors that determine the need for further investigation following a prior negative biopsy?*

Identification of existing relevant guidelines

1. Methods

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by literature searches for each PICO question and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption or adaptation guidelines had to be evidence based and meet the pre-specified criteria of scaled scores of greater or equal to 70% for the domains rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

2. Results

2.1 Search for relevant guidelines

Searches for guidelines identified one guideline that contained potentially relevant recommendations, an updated version of the UK National Institute for Health and Care Excellence evidence-based Clinical Guidelines for Prostate Cancer Diagnosis and Treatment (NICE Guidelines; National Collaborating Centre for Cancer 2014a[1]). The 2014 version of the NICE guidelines contained a number of new questions. Of these, the following questions were identified as relevant to the clinical question above;

- In men who have been referred with suspected prostate cancer, what are the prognostic factors that determine the need for further investigation following a prior negative biopsy?
- In men with suspected prostate cancer whose initial TRUS biopsy is negative what should be the next investigation(s)?

2.2 Assessment with AGREE II instrument

The 2014 NICE guidelines were independently assessed by 4 appraisers using the AGREE II instrument. The scaled score for the rigour domain was 84.4%, the scaled score for the clarity of presentation domain was 76.0% and the scaled score for editorial independence was 85.4% and as such these guidelines met the inclusion criteria for adoption or adaptation. As a result, the authors decided to update the NICE systematic reviews for these questions to 1st March 2014, and adopt or adapt the NICE recommendations for these questions on the basis of results of the updated systematic reviews.

The following systematic review updates to 1st March 2014 the existing systematic review[2] of literature undertaken by the National Collaborating Centre for Cancer (NICE systematic review) for the question:

In men who have been referred with suspected prostate cancer, what are the prognostic factors that determine the need for further investigation following a prior negative biopsy?

1. National Collaborating Centre for Cancer. Prostate cancer: diagnosis and treatment. National Collaborating Centre for Cancer; 2014.
2. National Collaborating Centre for Cancer. Draft Evidence Review for Update of Clinical Guidelines 58 Prostate cancer: diagnosis and treatment accessed 29/01/14 - . final version accessed 18/11/14 http://www.nice.org.uk/guidance/cg175/evidence/cg175-prostate-cancer-appendix-m2

Updated NICE systematic review – methods and results

NICE question: *In men who have been referred with suspected prostate cancer, what are the prognostic factors that determine the need for further investigation following a prior negative biopsy(s)?*

NICE PICO

Population	Prognostic factors	Outcomes
Men whose initial biopsy proved negative for prostate cancer	PSA velocity PSA level PSA density Free-to-total PSA Clinical stage Family history Ethnicity Pathological features on biopsy (ASAP, PIN) Biomarkers Age	Diagnostic accuracy

ASAP - Atypical small acinar proliferation, PIN – prostatic intra-epithelial neoplasm

1. METHODS

1.1 Literature search for updated NICE systematic review

The NICE systematic review search cut-off date was May 2013. To ensure all the relevant literature available was captured, searches for the updated systematic review were conducted from 1/1/2012. Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effect and Health Technology Assessments databases were searched using text terms and, where available, database specific subject headings. Each database was searched for articles dealing with prostate cancer. The Medline database was searched using the strategy documented in the NICE systematic review. The Embase search strategy used was based on the Medline strategy. To identify studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples.

A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 which were either published after the initial search was completed and/or added to the relevant database after the search was completed. Alerts were checked until July 2014. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched regularly up until April 2014 for relevant reviews published after the initial search.

1.2 Inclusion Criteria

The inclusion criteria for the updated NICE systematic review were derived from the PICO table and methods for this question, and an examination of the data extracted and reasons for excluding studies for this question as reported in the NICE systematic review.

Selection criteria	**Inclusion criteria**	
Study type	Prognostic studies	Diagnostic accuracy
Study design	Cohort studies	
Population	Men whose initial biopsy was at least 8 cores and negative for prostate cancer and undergoing repeat biopsy with a minimum of 10 cores	
Prognostic factor/Index test	PSA velocity at initial biopsy PSA level at initial biopsy PSA density at initial biopsy free-to-total PSA % at initial biopsy clinical stage family history ethnicity pathological features on Biopsy (ASAP, PIN) biomarkers, for example PHI, PCA-3 at initial biopsy age	
Comparator	No or lower level of prognostic factor	-
Outcomes/Reference standard	Diagnosis of prostate cancer	A minimum of 10 prostate biopsy cores
Language	English	
Publication period	After 31st December 2011 and prior to 1st March 2014	

ASAP - Atypical small acinar proliferation, PIN – prostatic intra-epithelial neoplasm, PHI – prostate health index, PCA-3 – prostate cancer antigen-3

2. RESULTS

2.1. Results of the literature search for updated NICE systematic review

Figure 1 outlines the process of identifying relevant articles for the systematic review. The Medline search identified 264 citations, the Embase search 600 citations, the search of the Cochrane Database of Systematic Reviews 59 citations, the Database of Abstracts of Reviews of Effects search 282 citations and the search of the Health Technology Assessment database identified an additional 216 citations, resulting in a total of 1421 citations. Titles and abstracts were examined and 24 articles were retrieved for a more detailed evaluation.

Three articles met the inclusion criteria and were included in the updated systematic review. There were no studies of ATSI men that met the inclusion criteria.

The retrieved articles that were not included and the reason for their exclusion are documented in Appendix C. In summary, most articles were excluded because they did not report any relevant outcomes or used inappropriate study designs.

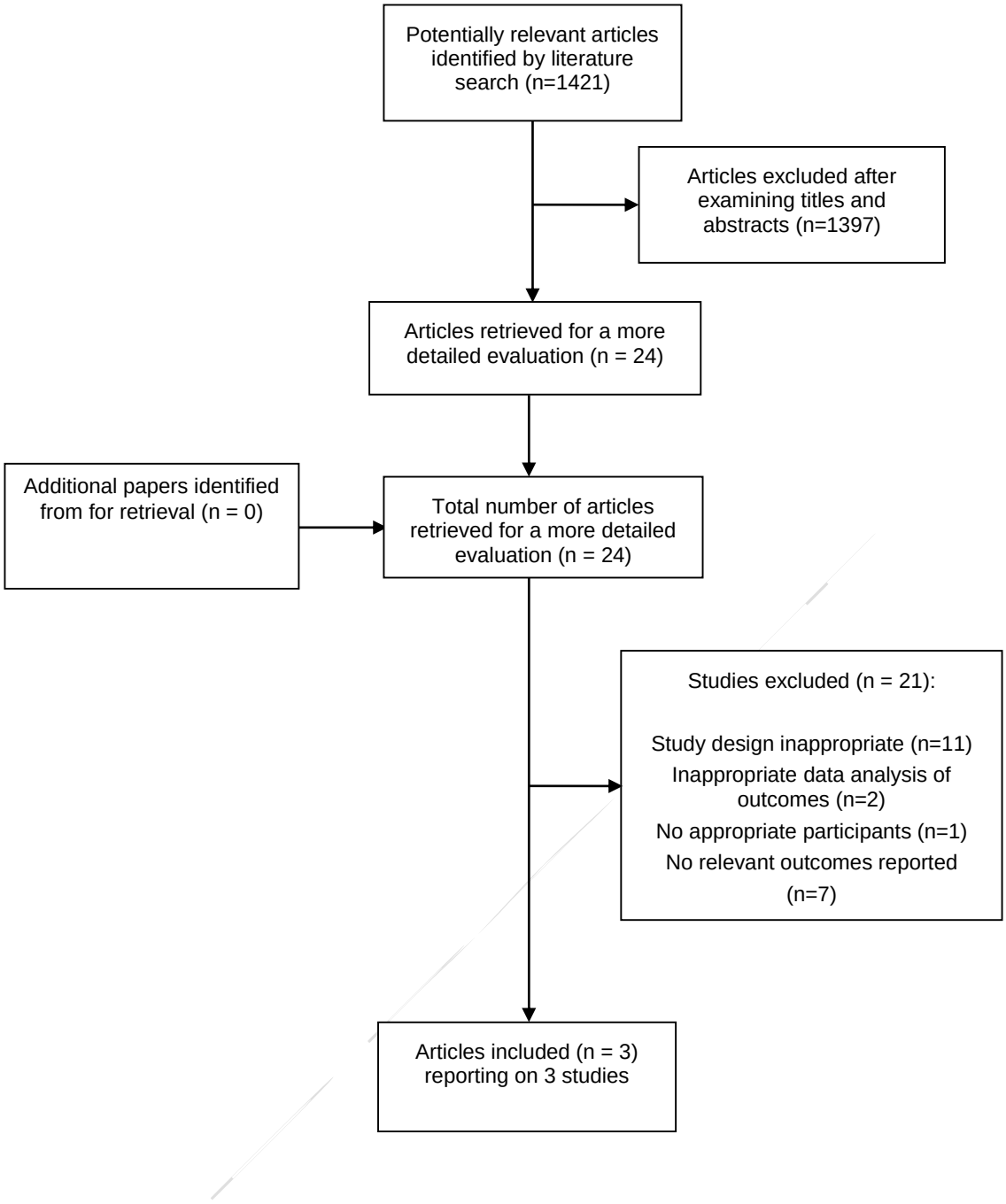


Figure 1. Results of literature searches and exclusion of studies

2.2 Study Characteristics

Table 1. Summary of characteristics of studies included in updated NICE systematic review: studies included in NICE systematic review and 3 additional studies (shaded)

Study	Type of study	Country	Time period	No. under-going repeat biopsy	Exclusion criteria	Initial biopsy scheme	Repeat biopsy scheme	Time between biopsies (median)	Indications for repeat biopsy
Gittelman et al. (2013)	Prospective cohort	USA		466	<8 cores at last biopsy, previous biopsy was done <42 days before post–DRE urine collection, aged < 50, prior history of PCa, use of medication known to affect PSA levels in last 90 days, urinary tract infection	(≥8 cores)	TRUS-guided (≥12 cores)	> 42 days	Not described
ElShafei et al. (2013)	Retrospective cohort	USA	2000-2011	682	Men that had received initial biopsy at another institution or did not undergo second biopsy	TRUS-guided extended (8-14 cores)	TRUS-guided (mean = 15.7 cores)	1.92 years (mean)	Previous suspicious pathological findings (ASAP with or without HGPIN or HGPIN exclusively), abnormal DRE, and/or persistently elevated or rising serum PSA. The attending urologist's practice pattern was the major factor determining the decision to repeat biopsy
Stewart et al. (2013)	Retrospective cohort	UK & Belgium	2005-	483	ASAP or AGSC in the initial biopsy, incomplete methylation profile	(5-21 cores)	(5-21 cores)	7.3 months	Not described
Auprich et al. (2011)	Prospective cohort	Austria	2008-2009	127	Aged > 70 years;	(8-10 cores)	(12 or 24 cores)	> 12 months	Suspicious DRE &/or persistently elevated age-specific PSA (2.5-6.5 ng/ml); ASAP; HGPIN
Merrimen et al. (2009 & 2010)	Retrospective cohort	Canada	1999-2007	225	History of prior treatment; ASAP; < 10 cores in either initial or re-biopsy	(≥ 10 cores)	Extended	1.4 – 2.4 years*	
Xu et al. (2011)	Retrospective cohort	China	1999-2010	129	Stable PSA < 4.0 ng/ml	TRUS-guided	Sextant TRUS- guided		PSA continuously elevated (≥ 10 ng/mL) or persistently increasing (velocity ≥ 0.75 ng/mL/y)

Grepl et al. (2009)	Prospective cohort	Czech Republic	2006-2008	191	Adenosis; atrophy; PSA > 50 ng/ml	TRUS-guided		12 months	Abnormal DRE &/or PSA > 2.5 ng/ml
Campos-Fernandes et al. (2009) & Ploussard et al. (2013)	Prospective cohort	France	2001-2007	231		Extended (21 cores)	Extended (21 cores)	10 months*	Persistently elevated PSA (> 4 ng/ml); PSA increase during follow-up; PIN; ASAP
Chun et al. (2007)	Prospective cohort	Germany		721			(≥ 10 cores)		Suspicious DRE, persistently ab- normal PSA or free-to-total PSA, HGPIN or ASAP
Engehausen et al. (2012)	Prospective cohort	Germany	2003-2007	96	Contraindications to MRI (e.g. cardiac pacemakers)	TRUS-guided	Endorectal MRI-guided (2-6 cores)		Continuing clinical suspicion of PCa
Kravchick et al. (2009)	Prospective cohort	Israel		600	Normal DRE and PSA ≤ 4 ng/ml	TRUS-guided lateral aspects (8-16 cores)	TRUS-guided medial aspects (8-16 cores)		
Mabjeesh et al. (2012)	Prospective cohort	Israel		92	< 2 previous negative biopsies	TRUS-guided transrectal (10-12 cores)	Transperineal saturation		Persistent PSA elevation despite ≥2 pervious biopsies
Abdollah et al. (2011)	Retrospective cohort	Italy	2005-2008	472		Transrectal (70%) or Transperineal (30%) (24 cores)	TRUS-guided saturation (24 cores)		Persistent PSA ≥ 10 ng/ml; PSA <10 ng/ml & free-to-total PSA ≤ 0.2; abnormal DRE; HGPIN; ASAP
Benecchi et al. (2008)	Prospective cohort	Italy	2001-2007	419	PSA interference (e.g. 5-alpha- reductase therapy)		TRUS-guided (12-24 cores)		Abnormal DRE &/or abnormal PSA
Bollito et al. (2012)	Prospective cohort	Italy	2008-2010	515	Positive DRE or ASAP	Peripheral zone (10-14 cores)	Peripheral & transition zone		
Lazzeri et al. (2012)	Prospective cohort	Italy	2010-2011	222	Medical therapy known to affect PSA; previous invasive treat- ment for BPH; UTI; acute proc-tatitis; blood protein alterations		TRUS-guided (14-18 cores)		Persistent suspicion of PCa (increasing &/or persistent elevation of PSA, DRE, ASAP or HGPIN)
Pepe et al. (2010)	Prospective cohort	Italy	2003-2008	262		Extended (12 cores)		15.2 months	Abnormal DRE; PSA > 10 ng/ml; PSA 4.1-10.0 & free-to-total PSA ≤0.25 or 2.6-4.0 ng/ml & free-to-total PSA ≤ 0.20; HGPIN; ASAP

Pepe et al. (2012a & b)	Prospective cohort	Italy	2009-2011	74/118	PSA > 10 ng/mL	Extended	Transperineal saturation		Persistently high or increasing PSA (PSA > 10 ng/ml; PSA 4.1-10 ng/ml with free-to-total PSA ≤ 25%; PSA 2.6-4.0 ng/ml with free-to-total PSA ≤20%
Scattoni et al. (2011)	Prospective cohort	Italy	2005-2008	340		TRUS-guided (≥ 12 cores)	TRUS-guided sextant saturation (24 cores)		PSA > 4 ng/ml &/or abnormal DRE &/or HGPIN or ASAP
Sciarra et al. (2012)	Cohort results from RCT	Italy	2008-2011	168	Positive for HGPIN or DRE; prior hormonal, surgical or radiation therapy; MRSI not possible	TRUS-guided laterally-directed (10 core)	TRUS-guided laterally Directed (10 core)	≤ 90 days	Persistently elevated PSA > 4 ng/ml
Shimbo et al. (2009)	Prospective cohort	Japan	2004-2005	77	Patients treated with transurethral resection due to an enlarged prostate with concomitant lower urinary tract symptoms	Transperineal TRUS-guided (10 cores)	Transperineal TRUS-guided (14 cores)		Persistent increase or continuing and fluctuating level of serum PSA between 4 & 20 ng/ml
Kim et al. (2012)	Retrospective cohort	Korea	2006-2012	42	PSA < 4 ng/ml; abnormal DRE; hypoechoic lesions; prior 5- alpha-reductase inhibitors; prostatitis				Elevated PSA (≥ 4 ng/ml)
Eskicorapci et al. (2007)	Prospective cohort	Turkey	2001-2005	211		Sextant or 10-core	TRUS-guided (14 cores)		PSA > 4 ng/ml; increasing PSA */or abnormal DRE &/or HGPIN
Rochester et al. (2009)	Retrospective cohort	UK	-	110			TRUS-guided extended (≥ 10 cores)		
Goode et al. (2013)	Retrospective cohort	US		167	Prior history of PCa	TRUS-guided transrectal (12 core)	TRUS-guided transrectal (12 core)		Elevated PSA, abnormal DRE, or abnormal PIN or ASAP
Kumar et al. (2009)	Retrospective cohort	US	1999-2004	31	Atypia; HGPIN; < 3 PSA meas- urements between biopsies	(≥ 12 cores)		27.4 months*	Rising PSA
Lee et al. (2011)	Retrospective cohort	US	1999-2010	617	Lack of data; known diagnosis of PCa				Physician preference; family history, DRE, PSA, HGPIN, ASAP
Moussa et al. (2010)	Prospective cohort	US	1999-2008	408		Extended (10-12 cores) (91%)	Saturation transrectal (≥ 20 cores)		Included: persistently elevated PSA;abnormal DRE; HGPIN or ASAP

Naya et al. (2004) & Mian et al. (2002)	Prospective cohort	US	1997-2003	136	Patients undergoing sextant or directed biopsies	Extended multi- site directed	Any (extended, sextant or di-rected)	3 months < 1 year (78%) > 1 year (22%)	Persistently elevated PSA, rising PSA, low free-to-total PSA, abnormal DRE or TRUS, HGPIN, or AGSC
San Fran-cisco et al. (2003)	Retrospective cohort	US	1996-1997	64	Cancer, atypia or prostatic biopsy with < 10 cores	TRUS-guided extended (≥ 10 cores)		29-30 months	Two successive increases in PSA level or any change in findings of DRE.
Singh et al. (2004)	Prospective cohort	US	1999-2002	99	No suspicion of cancer (normal DRE & PSA ≤ 2.5 ng/ml)	12 core	12 core		Free-to-total PSA ≤ 15 ng/ml &/or PSA velocity ≥ 0.75 ng/ml/y
Thompson et al. (2008)	Prospective cohort	US		687	Age < 55 years; abnormal DRE; PSA ≤ 3 ng/mL				Suspicious DRE; PSA ≥ 4 ng/ml
Wu et al. (2012)	Retrospective cohort	US		103	Missing data on PCA3, PSA, PSA density, DRE or TRUS		TRUS-guided sextant ≥12 cores		Suspicious DRE; persistently elevated PSA; previous suspicious histology; patient preference
Marks et al. (2007)	Prospective cohort	US & Canada	2004-2006	226	PSA < 2.5 ng/ml				
Ploussard et al. (2010)	Retrospective cohort	European	2006-2007	301	PSA < 2.5 or > 10 ng/ml; medical therapy known to affect PSA; UTI; invasive treatment for BPH	≥10 peripheral cores	≥10 peripheral cores		
Barbera et al. (2012)	Prospective cohort	Italy	2010-2012	177	Positive DRE	Extended (12-18 cores)	Saturation (median 28 cores)		PSA >10 ng/ml; PSA 4.1-10.0/2.6-4.0 with ftPSA < 25%/20%
Porpiglia et al. (2013)	Prospective cohort	Italy		100		≥ 12 samples	18 samples		Abnormal PSA, ASAP or PIN
Bhojani et al. (2013)	Retrospective cohort	US	1998-2011	1226	Patients not undergoing holmium laser enucleation of the prostate				Elevated PSA
Fiori et al. (2013)	Prospective cohort	Italy		50		12 samples	18 samples		Abnormal PSA, pathological (ASAP or HGPIN) or strong clinical suspicion
Busetto et al. (2013)	Prospective cohort	Italy		43	Prior hormonal, surgical or radiation therapy; < 10 core biopsy; positive DRE	≥ 10 core	Random 10-core TRUS-guided		PSA ≥ 4 ng/ml & < 10 ng/ml

AGSC = atypical glands suspicious for carcinoma; ASAP = atypical small acinar proliferation; BPH = benign prostatic hyperplasia; DRE = digital rectal examination; ftPSA = free to total prostate specific antigen; HGPIN = high grade prostatic intraepithelial neoplasia; MRI = magnetic resonance imaging; PCa = prostate cancer; PSA = prostate specific antigen; TRUS = transrectal ultrasound; UTI = urinary tract infection

**Mean reported where median not available.*

2.3 Study Results

Summary of results of studies included in updated NICE systematic : studies included in NICE systematic review and 3 additional studies (shaded blue) in Tables 2-3

Table 2. Results of uni- and multi-variate models from studies comparing prognostic factors and re-biopsy detection rates

Prognostic factor	Study	Univariate analyses			Multivariate analyses			Variables include in multivariate model									
		OR	95% CI	p-value	OR	95% CI	p-value	Age	PSA	ftPSA	PSAd	PSAv	HG-PIN	ASAP	DRE	Volume	Other
Age at first biopsy (continuous)	Gittelman 2013	-	-	**0.02**	1.007	(0.98-1.04)	0.65	✓	✓	-	-	-	-	-	✓	-	Family history, race, PCA3 score, No. of previous -ve Bx
	ElShafei, 2013	-	-	**0.046**	1.47[4]	(1.1-1.97)	SD	✓	-	-	-	✓	✓	✓	✓	✓	No. of cores, family history, race
	Stewart, 2013	-	-	-	1.01	-	0.50	✓	✓	-	-	-	✓	-	✓	-	DNA methylation
	Naya 2004	-	-	0.06		-	NS	✓	✓	✓	✓	✓	✓		✓		cPSA; no. cores HGPIN+; AGSC
	Mian 2002[1]	-	-	-		(0.94 – 1.12)	0.60	✓	✓	✓			✓		✓	✓	TRUS; AGSC
	San Francisco 2003	-	-	0.15		-	-	-	-	-	-	-	-	-	-	-	-
	Merrimen 2010	-	-	-		-	0.54	✓	✓	-	-	-	-	-	-	-	Pathologist
	Merrimen 2009[2]	-	-	-		-	**0.05**	✓	✓	-	-	-	-	-	-	-	Sampling extent; pathologist
	Xu 2011	-	-	0.57		-	-	-	-	-	-	-	-	-	-	-	-
	Singh 2004	-	-	**0.01**		-	-	-	-	-	-	-	-	-	-	-	-
	Shimbo 2009	-	-	**0.02**		-	-	-	-	-	-	-	-	-	-	-	-
	Scattoni 2011	1.04	(1.00-1.07)	**0.05**		-	-	-	-	-	-	-	-	-	-	-	-
	Rochester 2009	-	-	0.41		-	NS	✓	✓	✓		✓			✓	✓	
	Moussa 2010	-	-	-		-	0.27	✓	✓			✓	✓	✓	✓	✓	No. –ive cores; BMI; family history; months since prior Bx; months since initial Bx
	Mabjeesh 2012	-	-	**0.005**	1.08	(0.97-1.20)	0.16	✓	✓			✓			✓	✓	Free PSA; histology; no. prior Bx
	Lee 2011	-	-	-	1.1	(0.9-1.3)	NS	✓	✓	✓			✓	✓	✓		Ethnicity; family history; > 20 cores
	Lazzeri 2012	-	-	0.55	1.01	(0.97 – 1.06)	0.52	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Kim 2012	-	-	**0.01**		-	-	-	-	-	-	-	-	-	-	-	-
	Engehausen 2012	-	-	0.69		-	-	-	-	-	-	-	-	-	-	-	-
	Chun 2007	1.01	-	0.50		-	**0.01**	✓	✓	✓					✓	✓	NR; no. prior Bx
	Campos-	-	-	0.15		-	-	-	-	-	-	-	-	-	-	-	-

	Fernandez 2009																
	Benecchi 2008	-	-	-	-	-	NS	✓	✓	✓	✓	✓	✓		✓		
	Auprich 2011	-	-	0.38	-	-	-	-	-	-	-	-	-	-	-		-
	Abdollah 2011	1.01	(0.97-1.05)	0.7	1.02	(0.98 – 1.07)	0.3	✓	✓				✓	✓	✓	✓	No. prior Bx
	Kravchick 2009	-	-	-	1.01	-	0.21	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Eskicorapci 2007	-	-	0.21	-	-	-	-	-	-	-	-	-	-	-	-	-
	Bollito 2012	1.47	(0.98-2.21)	0.06	-	-	-	-	-	-	-	-	-	-	-	-	-
	Bhojani 2013	1.08	-	**<0.001**	1.09	-	**<0.001**	✓	✓	-	-	-	-	-	-	✓	Weight of prostate
> 60 vs ≤ 60	Campos-Fernandez 2009	-	-	0.655	-	-	0.844	-	-	-	-	-	-	-	-	-	-
≤ 62 vs > 62	Singh 2004	3.24	(1.14-9.22)	**0.02**	-	-	-	-	-	-	-	-	-	-	-	-	-
PSA level at first biopsy																	
PSA level	ElShafei 2013	-	-	0.77	-	-	-	-	-	-	-	-	-	-	-	-	-
	Naya 2004	-	-	0.28		-	NS	✓	✓	✓	✓	✓	✓		✓		cPSA; no. cores HGPIN+; AGSC
	Mian 2002[1]	-	-	-		(0.94 – 1.15)	0.49	✓	✓	✓			✓		✓	✓	TRUS; AGSC
	San Francisco 2003	-	-	0.44		-	-	-	-	-	-	-	-	-	-	-	-
	Xu 2011	-	-	**0.02**		(1.00 – 1.04)	**0.04**		✓	✓	✓				✓	✓	Volume-to-Bx ratio
	Wu 2012	-	-	-	0.93	(0.86 – 1.01)	NS		✓		✓				✓		TRUS; PCA3
	Singh 2004	-	-	0.15		-	-	-	-	-	-	-	-	-	-	-	-
	Shimbo 2009	-	-	0.72		-	-	-	-	-	-	-	-	-	-	-	-
	Scattoni 2011	1.02	(0.99-1.05)	0.2	-	-	-	-	-	-	-	-	-	-	-	-	-
	Rochester 2009	-	-	0.74	-	-	NS	✓	✓	✓		✓			✓	✓	
	Ploussard 2010	-	-	-	-	-	0.26		✓	✓					✓	✓	PCA3; no. prior Bx
	Moussa 2010	-	-	-	-	-	**0.003**	✓	✓			✓	✓	✓	✓	✓	No. -ive cores; BMI; family history; months since prior Bx; months since initial Bx
	Mabjeesh 2012	-	-	0.06	0.96	(0.89 – 1.03)	0.25	✓	✓			✓			✓	✓	Free PSA; histology; no. prior Bx
	Lee 2011	-	-	-	1.0	(1.0 – 1.1)	NS	✓	✓	✓			✓	✓	✓		Ethnicity; family history; >20 cores
	Lazzeri 2012	-	-	0.66	1.02	(0.88 – 1.18)	0.81		✓	✓	✓				✓	✓	Free PSA
	Kim 2012	-	-	0.71		-	-	-	-	-	-	-	-	-	-	-	-
	Grepl 2009	-	-	**0.002**		-	-	-	-	-	-	-	-	-	-	-	-
	Engehausen 2012	-	-	**0.004**		-	-	-	-	-	-	-	-	-	-	-	-

	Chun 2007	1.04	-	**0.001**		-	**0.03**	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Campos-Fernandez 2009	-	-	**<0.001**		-	-	-	-	-	-	-	-	-	-	-	-
	Benecchi 2008	-	-	-	-	-	NS	✓	✓	✓	✓	✓	✓		✓		
	Auprich 2011	-	-	0.21	-	-	-	-	-	-	-	-	-	-	-	-	-
	Abdollah 2011	0.98	(0.93 – 1.03)	0.3	1.04	(0.97 – 1.10)	0.2	✓	✓	-	-	-	-	-	-	✓	No. prior Bx
	Eskicorapci 2007	-	-	**0.05**	-	-		✓	✓	-	-	-	-	-	-	-	
	Bhojani 2013	1.01	-	0.1	1.02	-	0.14	✓	✓							✓	Weight of prostate
LogPSA	Merrimen 2010	-	-			-	0.25	✓	✓								Pathologist
	Merrimen 2009[2]	-	-			-	0.54	✓	✓								Sampling extent; pathologist
PSA: 4-10 vs <4	Bollito 2012	1.55	(0.52-4.63)	0.44		(0.53 – 14.54)	0.22		✓	✓							PCA3 (39)
						(0.41 – 12.23)	0.35		✓	✓							PCA3 (50)
PSA: >10 vs < 4	Bollito 2012	2.47	(0.80-7.67)	0.12		(1.03 – 32.59)	**0.05**		✓	✓							PCA3 (39)
						(0.82 – 27.76)	0.08		✓	✓							PCA3 (50)
PSA: >10 vs ≤10	Campos-Fernandes 2009	1.57	-	0.027	-	-	0.705	✓	✓	✓	✓	✓	-	-	-	✓	T-stage
PSA: ≥10 vs <10	Stewart 2013	-	-	-	1.59	-	0.18	✓	✓	-	-	-	✓	-	✓	-	DNA methylation
PSA: >6 vs ≤6	Campos-Fernandes 2009	2.08	-	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	-
Free-to-total PSA at first biopsy																	
ftPSA (continuous)	ElShafei 2013	-	-	0.14	-	-	-	-	-	-	-	-	-	-	-	-	-
	Naya 2004	-	-	0.25	-	-	NS	✓	✓	✓	✓	✓	✓		✓		cPSA; no. cores HGPIN+; AGSC
	Mian 2002[1]	-	-	-	1.05	(0.94 – 1.17)	0.43	✓	✓	✓			✓		✓	✓	TRUS; AGSC
	Xu 2011	-	-	**< 0.001**		(0.78 – 0.96)	**0.01**		✓	✓	✓				✓	✓	Volume-to-Bx ratio
	Shimbo 2009	-	-	0.33		-	-	-	-	-	-	-	-	-	-	-	-
	Scattoni 2011	0.97	(0.93-1.00)	**0.05**	-	-	-	-	-	-	-	-	-	-	-	-	-
	Rochester 2009	-	-	0.13	-	-	NS	✓	✓	✓		✓			✓	✓	
	Ploussard 2010	-	-	0.07	-	-	0.10		✓	✓					✓	✓	PCA3; no. prior Bx
	Mabjeesh 2012	-	-	0.50	-	-	-	-	-	-	-	-	-	-	-	-	-
	Lee 2011	-	-	-	1.4	(1.1 – 1.7)	**<0.05**										Ethnicity; family history; > 20 cores;
	Lazzeri 2012	-	-	**0.01**	1.00	(0.995-1.006)	0.87										Free PSA
	Grepl 2009	-	-	**0.002**		-	-	-	-	-	-	-	-	-	-	-	-
	Engehausen 2012	-	-	**0.005**		-	-	-	-	-	-	-	-	-	-	-	-

	Chun 2007	0.91	-	**<0.001**		-	**<0.001**	✓	✓	✓					✓	✓	NR; no. prior Bx
	Benecchi 2008	-	-	**-**	-	-	**<0.05**	✓	✓	✓	✓	✓	✓		✓		
	Auprich 2011	-	-	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	-
	Eskicorapci 2007	-	-	0.11	-	-	-	-	-	-	-	-	-	-	-	-	-
	Campos-Fernandez 2009	-	-	0.014	-	-	-	-	-	-	-	-	-	-	-	-	-
ftPSA ≤ 0.1 vs > 0.2	Ploussard 2010	-	-	**0.03**	-	-	-	-	-	-	-	-	-	-	-	-	-
ftPSA > 0.15 vs ≤ 0.15	Campos-Fernandez 2009	0.47	-	**0.003**	-	-	0.063	-	-	-	-	-	-	-	-	-	-
ftPSA > 0.2 vs < 0.1	Bollito 2012	0.42	(0.19-0.91)	**0.03**	0.46	(0.19 – 0.11)	0.08		✓	✓							PCA3 (39)
					0.50	(0.21 – 1.20)	0.12		✓	✓							PCA3 (50)
ftPSA 0.1-0.2 vs > 0.2	Ploussard 2010	-	-	NS	-	-	-	-	-	-	-	-	-	-	-	-	-
ftPSA 0.1-0.2 vs < 0.1	Bollito 2012	0.54	(0.28 – 1.07)	0.08	0.70	(0.32 – 1.53)	0.38		✓	✓							PCA3 (39)
					0.71	(0.32 – 1.54)	0.38		✓	✓							PCA3 (50)
ftPSA 0.1-0.2 vs ≤ 0.1	Ploussard 2010	-	-	NS	-	-	-	-	-	-	-	-	-	-	-	-	-
ftPSA ≤ 0.1 vs > 0.1	Ploussard 2010	-	-	-	1.80	(0.85 – 3.82)	0.13			✓							PCA3
PSA density at first biopsy (ng/ml/ml)																	
PSAd	ElShafei 2013	-	-	0.06	-	-	**-**	-	-	-	-	-	-	-	-	-	-
	Naya 2004	-	-	**0.03**	-	-	**0.002**	✓	✓	✓	✓	✓	✓		✓		cPSA; no. cores HGPIN+; AGSC
	Xu 2011	-	-	**0.003**	-	-	-	-	-	-	-	-	-	-	-		-
	Shimbo 2009	-	-	0.26		-	-	-	-	-	-	-	-	-	-	-	-
	Lazzeri 2012	-	-	0.09	1.005	(0.998-1.012)	0.16		✓	✓	✓				✓	✓	Free PSA
	Kim 2012	-	-	**0.04**		-	-	-	-	-	-	-	-	-	-	-	-
	Campos-Fernandez 2009	-	-	**<0.001**		-	-	-	-	-	-	-	-	-	-	-	-
	Benecchi 2008	-	-	**-**	-	-	**<0.05**	✓	✓	✓	✓	✓	✓		✓		
	Eskicorapci 2007	-	-	**0.001**	-	-	-	-	-	-	-	-	-	-	-	-	-
PSAd: > 0.15	Wu 2012	-	-	**-**	2.3	(1.4 – 4.0)	**<0.05**		✓		✓				✓		TRUS; PCA3
	Campos-Fernandez 2009	2.60	-	**<0.001**	2.34		**0.012**	✓	✓	✓	✓	✓				✓	T-stage
PSAd: > 0.20		2.66	-	**<0.001**		-	-	-	-	-	-	-	-	-	-	-	-
PSA velocity at first biopsy (ng/ml/year)																	
≥0.75 vs <0.75	Naya 2004	-	-	0.48			NS	✓	✓	✓	✓	✓	✓		✓		cPSA; no. cores HGPIN+; AGSC
>0.75 vs ≤0.75	Campos-	-	-	0.797			0.701	✓	✓	✓	✓	✓	-	-	-	✓	T-stage

	Fernandez 2009																
≤0.93 vs >0.93	Singh 2004	3.39	(0.62-18.49)	0.14		-	-	-	-	-	-	-	-	-	-	-	-
PSAv (continuous)	Xu 2011	-	-	0.12	-	-	-	-	-	-	-	-	-	-	-	-	-
	Singh 2004	-	-	0.32		-	-	-	-	-	-	-	-	-	-	-	-
	Shimbo 2009	-	-	0.33		-	-	-	-	-	-	-	-	-	-	-	-
	Rochester 2009	-	-	**0.02**	1.34	(1.03-1.74)	**<0.05**	✓	✓	✓		✓			✓	✓	
	Mabjeesh 2012	-	-	**<0.001**	1.58	(1.06 – 2.35)	**0.03**	✓	✓			✓			✓	✓	Free PSA; histology; no. prior Bx
	Benecchi 2008	-	-	-	-	-	**<0.05**	✓	✓	✓	✓	✓	✓		✓		
	Auprich 2011	-	-	**0.03**	-	-	-	-	-	-	-	-	-	-	-		-
	Kumar 2009	-	-	**0.007**	-	-	-	-	-	-	-	-	-	-	-		-
	Campos-Fernandez 2009	-	-	0.813	-	-	-	-	-	-	-	-	-	-	-	-	-
Abnormal DRE at first biopsy (vs normal DRE)																	
	Stewart 2013	-	-	-	1.36	-	0.30	✓	✓	-	-	-	✓	-	✓	-	DNA methylation
	Naya 2004	-	-	0.99	-	-	NS	✓	✓	✓	✓	✓	✓		✓		cPSA; no. cores HGPIN+; AGSC
	Mian 2002[1]	-	-	-	0.63	(0.16 – 2.46)	0.51	✓	✓	✓			✓		✓	✓	TRUS; AGSC
	San Francisco 2003	-	-	0.12		-	-	-	-	-	-	-	-	-	-	-	-
	Xu 2011	-	-	**0.002**		(1.62 – 13.07)	**0.004**		✓	✓	✓				✓	✓	Volume-to-Bx ratio
	Wu 2012	-	-			(0.60 – 75.50)	NS		✓		✓				✓		TRUS; PCA3
	Singh 2004	1.32	(0.13-4.63)	0.82		-	-	-	-	-	-	-	-	-	-	-	-
	Scattoni 2011	1.45	(0.69-3.06)	0.3	-	-	-	-	-	-	-	-	-	-	-	-	-
	Rochester 2009	-	-	0.44			NS		✓	✓	✓		✓		✓	✓	
	Ploussard 2010	-	-	-			**<0.001**								✓	✓	PCA3; no. prior Bx
	Moussa 2010	-	-	-			0.26	✓	✓			✓	✓	✓	✓	✓	No. –ive cores; BMI; family history; months since prior Bx; months since initial Bx
	Mabjeesh 2012	-	-	**0.04**	2.58	(0.45 – 14.90)	0.29	✓	✓			✓			✓	✓	Free PSA; histology; no. prior Bx
	Lee 2011	-	-	-	0.4	(0.1 – 1.5)	NS	✓	✓	✓			✓	✓	✓		Ethnicity; family history; > 20 cores;
	Lazzeri 2012	-	-	0.06	1.82	(0.76 – 4.37)	0.18		✓	✓	✓				✓	✓	Free PSA
	Chun 2007	2.80	-	**<0.001**			**0.002**	✓	✓	✓					✓	✓	NR; no. prior Bx
	Campos-Fernandez 2009	-	-	0.39	-	-	-	-	-	-	-	-	-	-	-	-	
	Benecchi 2008	-	-	-			**<0.05**	✓	✓	✓	✓	✓	✓		✓	✓	

	Auprich 2011	-	-	0.49				-	-	-	-	-	-	-	-	-	
	Abdollah 2011	2.65	(1.24-5.67)	**0.01**	2.63	(1.14 – 6.08)	**0.02**	✓	✓				✓	✓	✓	✓	No. prior Bx
PIN at first biopsy																	
HGPIN	ELShafei 2013	-	-	0.001	1.87	(1.23 – 2.85)	**SD**	✓	-	-	-	✓	✓	✓	✓	✓	No. of cores, family history, race
	Stewart 2013	-	-	-	1.25	-	0.5	✓	✓	-	-	-	✓	-	✓	-	DNA methylation
	Naya 2004	-	-	0.57			NS	✓	✓	✓	✓	✓	✓		✓		cPSA; no. cores HGPIN+; AGSC
	Mian 2002[1]	-	-	-	0.13	(0.02 – 1.06)	0.06	✓	✓	✓			✓		✓	✓	TRUS; AGSC
	Merrimen 2009[2]	-	-	**0.02**	1.38	-	**0.03**	✓	✓	-	-	-	-	-	-	-	Sampling extent; pathologist
	Singh 2004	5.07	(1.54 – 16.74)	**0.01**	-	-	-	-	-	-	-	-	-	-	-	-	
	Scattoni 2011	1.24	(0.72 – 2.13)	0.4	-	-	-	-	-	-	-	-	-	-	-	-	
	Rochester 2009	-	-	0.78			NS	✓	✓	✓	-	✓	-	-	✓	✓	
	Moussa 2010	-	-	-			**<0.001**	✓	✓			✓	✓	✓	✓	✓	No. –ive cores; BMI; family history; months since prior Bx;
	Mabjeesh 2012	-	-	0.28	-	-	-	-	-	-	-	-	-	-	-	-	
	Lee 2011	-	-	-	3.2	(1.8 – 5.6)	**<0.05**	✓	✓	✓			✓	✓	✓		Ethnicity; family history; > 20 cores;
	Benecchi 2008	-	-	-			**<0.05**	✓			✓			✓		✓	
	Abdollah 2011	1.27	(0.42-3.83)	0.6	1.26	(0.38 – 4.23)	0.7	✓	✓			✓			✓	✓	No. prior Bx
PIN	San Francisco 2003	-	-	**0.01**	-	-	-	-	-	-	-	-	-	-	-	-	
	Campos-Fernandez 2009	-	-	0.75	-	-	-	-	-	-	-	-	-	-	-	-	
ASAP at first biopsy																	
ASAP	ELShafei 2013	-	-	**0.005**	1.92	(1.07 – 3.46)	**SD**	✓	-	-	-	✓	✓	✓	✓	✓	No. of cores, family history, race
	Scattoni 2011	3.12	(1.50-6.47)	**0.002**	-	-	-	-	-	-	-	-	-	-	-	-	
	Moussa 2010	-	-	-			**0.01**	✓	✓			✓	✓	✓	✓	✓	No. –ive cores; BMI; family history; months since prior Bx; months since initial Bx
	Mabjeesh 2012	-	-	0.28	-	-	-	-	-	-	-	-	-	-	-	-	
	Lee 2011	-	-	-	3.0	(1.3 – 6.7)	**<0.05**	✓	✓	✓			✓	✓	✓		Ethnicity; family history; > 20 cores;
	Campos-Fernandez 2009	-	-	0.13	3.65	(1.09 – 12.29)	**0.04**	✓			✓			✓		✓	
	Abdollah 2011	2.79	(1.50-5.18)	**0.001**	3.36	(1.68 – 6.71)	**<0.001**	✓	✓				✓	✓	✓	✓	No. prior Bx
AGSC at first biopsy																	

AGSC	Naya 2004	-	-	**<0.001**			**<0.001**	✓	✓	✓	✓	✓	✓		✓		cPSA; no. cores HGPIN+; AGSC
	Mian 2002[1]	-	-	-	20.71	(4.45 – 96.36)	**<0.001**	✓	✓	✓			✓		✓	✓	TRUS; AGSC
PCA3 score																	
PCA3 (continuous)	Wu 2012	-	-	-	1.02	(1.003 – 1.03)	**<0.05**		✓		✓				✓		TRUS; PCA3
	Ploussard 2010	-	-	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	
	Auprich 2011	-	-	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	
	Bollito 2012	-	-	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	
PCA3 < 15 vs ≥ 15	Bollito 2012	4.82	(2.57 – 9.07)	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	
PCA3 < 20 vs ≥ 20	Bollito 2012	7.19	(3.84 – 13.48)	**<0.001**													
PCA3 > 25 vs <25	Ploussard 2010	-	-	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	
PCA3 > 30 vs <30	Ploussard 2010	-	-	-	3.01	(1.74 – 5.23)	**<0.001**			✓							PCA3
	Ploussard 2010	-	-	-			**0.03**		✓	✓					✓	✓	PCA3; no. prior Bx
PCA3 > 35 vs <35	Ploussard 2010	-	-	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	
	Goode 2013	-	-	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	
	Bollito 2012	6.89	(4.31 - 11.03)	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	
PCA3 < 39 vs ≥ 39	Bollito 2012	7.89	(4.94 - 12.62)	**<0.001**	9.44	(5.15 – 17.31)	**<0.001**		✓	✓							PCA3
PCA3 < 50 vs ≥ 50	Bollito 2012	7.43	(4.77 - 11.58)	**<0.001**	9.29	(5.11 – 16.89)	**<0.001**		✓	✓							PCA3
PCA3 < 70 vs ≥ 70	Bollito 2012	6.94	(4.39 - 10.96)	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	
DNA Methylation (APC, GSTP1, RASSF1)																	
DNA Methylation	Stewart 2013	-	-	-	3.17	(1.81 – 5.53)	**<0.0001**	✓	✓	-	-	-	✓	-	✓	-	DNA Methylation
Family history of PCa																	
Family history	ElShafei 2013	-	-	0.15	1.33	(0.81 – 2.18)	**NS**	✓	-	-	-	✓	✓	✓	✓	✓	No. of cores, family history, race
	Gittelman 2013	-	-	0.51	0.92	(0.50 – 1.72)	**0.80**	✓	✓	-	-	-	-	-	✓	-	Family history, race, PCA3 score, No. of previous -ve Bx
	Moussa 2010	-	-	-			**0.001**	✓	✓	-	-	✓	✓	✓	✓	✓	No. –ive cores; BMI; family history; months since prior Bx; months since initial Bx
	Lee 2011	-	-	-	3.1	(1.2 – 8.0)	**<0.05**	✓	✓	✓	-	-	✓	✓	✓	-	Ethnicity; family history; > 20 cores;
Ethnicity																	
Black vs non-black	Gittelman 2013	-	-	-	0.58	(0.23 – 1.45)	0.24	✓	✓	-	-	-	-	-	✓	-	Family history, race, PCA3 score, No. of previous -ve Bx
	ElShafei 2013			0.92	1.21	(0.63 – 2.31)	NS	✓	-	-	-	✓	✓	✓	✓	✓	No. of cores, family history, race

Caucasian vs not Caucasian	Lee 2011	-	-	-	0.8	(0.4 – 1.6)	NS	✓	✓	✓	-	-	✓	✓	✓	-	Ethnicity; family history; > 20 cores;
Clinical stage																	

AGSC = atypical glands suspicious for carcinoma; ASAP = atypical small acinar proliferation; BMI = Body Mass Index; Bx = biopsy; cPSA = complexed PSA;CI = Confidence Interval; DRE = digital rectal examination; ftPSA = free-to- total PSA; HGPIN = high grade prostatic intraepithelial neoplasia; NR = not reported; NS = not significant;OR =Odds Ratio; PPV = positive predictive value; PSA = Prostate Specific Antigen; PSAd = PSA density; PSAv = PSA velocity

[1]Secondary to Naya 2004; [2]secondary to Merrimen 2010 [3]secondary to Pepe 2012a. [4]OR is for 75th centile of age relative to the 25th centile of age, and this is true for other continuous variables in Elshafei et al (2013 analyses)

Table 3. Diagnostic accuracy outcomes from studies comparing prognostic factors and re-biopsy (reference standard)

Prognostic factor	Study	Number undergoing re-biopsy	Number included by cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
Age								
Age > 62.4	Singh 2004	149	99	*28.6*	*66.4*	*10.7*	*86.8*	-
PSA level (ng/ml)								
PSA > 1.0	Thompson 2008	687	-	87.5	28.7	19.3	92.2	-
PSA > 1.5	Thompson 2008	687	-	80.4	39.1	20.5	91.1	-
PSA > 2.0	Thompson 2008	687	-	73.2	49.2	21.9	90.4	-
PSA > 2.5	Thompson 2008	687	-	66.1	57.6	23.3	89.7	-
PSA > 3.0	Thompson 2008	687	-	58.0	63.1	23.5	88.5	-
PSA > 3.2	Lazzeri 2012	222	-	12.7	92.0	42.8	69.1	-
PSA > 4.0	Thompson 2008	687	-	48.2	76.5	28.6	88.4	-
	Goode 2013	167	-	79	27	-	-	-
PSA > 5.3	Auprich 2011	127	-	95.0	14.5	37.2	85.7	-
PSA > 5.9	Auprich 2011	127	-	85.0	18.1	35.2	68.2	-
PSA > 6.0	Thompson 2008	687	-	16.1	93.0	31.0	85.1	-
PSA > 6.7	Auprich 2011	127	-	75.0	30.1	36.3	69.4	-
PSA > 7.5	Lazzeri 2012	222	-	56.3	54.3	36.7	72.5	-
PSA > 8.0	Thompson 2008	687	-	6.3	97.4	31.8	84.2	-
PSA > 10.0	Thompson 2008	687	-	2.7	98.4	25.0	83.9	-
PSA ≥ 10	Wu 2012	103	39	40	61	40	62	-
PSA > 12.8	Mabjeesh 2012	92	76	58.3	62.7	35.9	80.8	-
PSA > 17.2	Lazzeri 2012	222	-	93.0	8.6	32.4	72.3	-
Free-to-total PSA								
ftPSA > 0.09	Lazzeri 2012	222	-	23.9	91.4	56.7	71.8	-
ftPSA > 0.1	Lee 2011	617	-	-	90.0	-	-	-
ftPSA ≥ 0.15	Engehausen 2012	96	33	*28.6*	*37.5*	*24.2*	*42.9*	-
ftPSA > 0.15	Pepe 2012a	74	43	66.7	51.0	42.8	73.5	56.6
	Lazzeri 2012	222	-	54.9	56.3	37.1	72.6	-
	Auprich 2011	127	-	75.0	65.1	52.5	81.8	-

ftPSA > 0.18	Auprich 2011	127	-	85.0	41.0	43.0	82.9	-
ftPSA > 0.20	Pepe 2012a	74	58	85.1	28.6	39.6	87.5	46.6
ftPSA > 0.23	Auprich 2011	127	-	95.0	22.9	39.6	90.5	-
ftPSA > 0.24	Lazzeri 2012	222	-	91.6	13.9	33.4	77.9	-
ftPSA > 0.25	Pepe 2012a	74	66	96.3	14.3	32.9	88.9	44.8
PSA density								
PSAd > 0.15	Wu 2012	103	50	66	60	51	74	-
PSA velocity (ng/ml/year)								
NR	Kumar 2009	31	-	87.5	63.6	-	-	-
PSAv > 0.28	Auprich 2011	127	-	95.0	4.8	34.7	66.7	-
PSAv > 0.75	Auprich 2011	127	-	85.0	27.7	38.8	79.3	-
PSAv > 0.93	Singh 2004	57	29	*25.0*	*46.9*	*7.1*	*79.3*	-
PSAv > 1.19	Auprich 2011	127	-	75.0	42.2	40.7	76.1	-
PSAv > 2.13	Mabjeesh 2012	92	76	79.0	79.7	55.6	92.2	-
PIN								
PIN	San Francisco 2003	64	13	*83.3*	*72.4*	*23.8*	*97.7*	-
HGPIN	Naya 2004	175	57	*28.1*	*66.4*	*15.8*	*80.5*	-
	Singh 2004	99	14	*33.3*	*85.9*	*33.3*	*85.9*	-
	Merrimen 2010	225	120	*58.8*	*43.1*	*14.3*	*86.7*	-
	Rochester 2009	87	30	*37.0*	*66.1*	*33.3*	*69.6*	-
	Mabjeesh 2012	92	4	*8.3*	*97.1*	*50.0*	*75.0*	-
ASAP								
ASAP	Scattoni 2011	340	33	*23.6*	*91.6*	*51.5*	*76.0*	-
	Mabjeesh 2012	92	4	*8.3*	*97.1*	*50.0*	*75.0*	-
AGSC								
AGSC	Naya 2004	136	22	*21.9*	*96.5*	*58.3*	*84.7*	-
Abnormal DRE								
Abnormal DRE	San Francisco 2003	64	-	*0.0*	*56.3*	*0.0*	*64.3*	-
	Xu 2011	129	44	*55.9*	*73.7*	*43.2*	*82.4*	-
	Wu 2012	103	13	22	88	53	64	-
	Singh 2004	99	4	*5.0*	*95.9*	*20.0*	*80.0*	-
	Rochester 2009	87	18	*25.9*	*81.4*	*38.9*	*70.6*	-
	Mabjeesh 2012	92	12	*25.0*	*91.2*	*50.0*	*77.5*	-

	Grepl 2009	169	28	*33.3*	*88.0*	*42.9*	*83.0*	-
	Auprich 2011	127	14	*13.6*	*90.4*	*42.9*	*66.4*	-
PCA3 score								
PCA3 > 10	Marks 2007	226	-	87	28	-	-	-
PCA3 > 12	Auprich 2011	127	-	95.0	12.0	36.5	83.3	-
PCA3 ≥ 15	Bollito 2012	509	-	88.2	34.6	36.9	87.1	-
PCA3 > 19	Auprich 2011	127	-	85.0	25.3	38.0	77.8	-
PCA3 > 20	Pepe 2012a	74	58	70.4	43.5	42.2	71.5	51.4
	Pepe 2012b	118	91	90.6	27.9	31.9	88.9	-
	Barbera 2013	177	140	91.7	25.6	31.5	89.5	43.5
PCA3 ≥ 20	Bollito 2012	509	-	88.2	44.3	40.7	89.6	-
PCA3 > 25	Wu 2012	103	47	67	64	52	78	-
	Ploussard 2010: Group I (ftPSA ≤ 0.1)	46	-	68.8	56.7	45.8	77.3	-
	Ploussard 2010: Group II (ftPSA 0.1-0.2)	138	-	72.7	62.9	38.1	88.0	-
	Ploussard 2010: Group III(ftPSA > 0.2)	117	-	77.3	53.7	27.9	91.1	-
PCA3 > 30	Ploussard 2010: Group I (ftPSA ≤ 0.1)	46	-	50.0	66.7	44.4	71.4	-
	Ploussard 2010: Group II (ftPSA 0.1-0.2)	138	-	60.6	67.6	37.0	84.5	-
	Ploussard 2010: Group III (ftPSA > 0.2)	117	-	68.2	64.2	30.6	89.7	-
PCA3 > 35	Pepe 2012b	74	46	71.9	41.8	31.5	80.0	
	Pepe 2012a	118	73	92.6	21.6	43.1	88.9	55.5
	Wu 2012	103	32	38	77	50	66	-
	Sciarra 2012: Group I	84	-	68.0	74.5	53.1	84.6	72.6
	Sciarra 2012: Group II	84	-	79.3	72.7	60.5	86.9	75.0
	Ploussard 2010: Group I (ftPSA ≤ 0.1)	46	-	43.8	66.7	41.2	69.0	-
	Ploussard 2010: Group II (ftPSA 0.1-0.2)	138	-	51.5	79.1	43.6	83.8	-
	Ploussard 2010: Group III (ftPSA > 0.2	117	82	59.1	67.4	29.6	87.7	-
	Marks 2007	226	-	58	72	-	-	-
	Goode 2013	167	25	42	70	-	-	-
	Bollito 2012: Group I (PSA < 4)	509		75.0	52.3	23.0	91.6	-
	Bollito 2012: Group II (PSA 4-10)	509	356	81.4	65.4	40.9	92.3	-
	Bollito 2012: Group III (PSA > 10)	509	128	70.7	72.4	54.7	84.0	-
	Barbera 2013	177	100	73.0	41.8	35.0	80.6	50.2

	Porpiglia 2013	100	-	16.7	55.7	13.6	60.9	44.0
PCA3 ≥ 35	Bollito 2012	509	-	75.2	69.8	52.0	86.7	-
	Busetto 2013	43	-	76.9	66.6	80.0	62.5	
PCA3 > 39	Auprich 2011	127	-	75.0	57.8	48.5	81.4	-
PCA3 ≥ 39	Bollito 2012	509	-	74.1	74.4	55.7	86.9	74.4
PCA3 > 50	Marks 2007	226	60	47	81	-	-	-
PCA3 ≥ 50	Bollito 2012	509	-	65.8	81.1	60.2	84.5	76.5
PCA3 ≥ 70	Bollito 2012	509	-	65.8	65.8	45.5	81.6	-
Not reported	Fiori 2013	50	-	66.7	97.1	90.9	87.2	88.0
DNA Methylation								
APC	Stewart 2013	483	-	46	78	31	87	72
GSTP1	Stewart 2013	483	-	41	87	41	87	79
RASSF1	Stewart 2013	483	-	80	31	20	88	40
GSTP1+APC	Stewart 2013	483	-	68	60	27	90	62
GSTP1+RASSF1	Stewart 2013	483	-	56	64	26	87	63
APC+RASSF1	Stewart 2013	483	-	62	61	26	88	61
APC+RASSF1 +GSTP1	Stewart 2013	483	-	68	64	29	90	65

AGSC = atypical glands suspicious for carcinoma; ASAP = atypical small acinar proliferation; DRE = digital rectal examination; ftPSA = free-to-total PSA; HGPIN = high grade prostatic intraepithelial neoplasia; NR = not reported; PSA = Prostate specific antigen; PSAd = PSA density; PSAv = PSA velocity;

Figures in italics are calculated

2.4 Study Quality

Table 4: Methodological quality of additional cohort studies (n = 3)

Quality Category	N (%)
Selection of the exposed and non-exposed cohorts	
Low risk of bias	3 (100)
Moderate risk of bias	-
High risk of bias	-
Measurement of exposure	
Low risk of bias	1 (33.3)
Moderate risk of bias	1 (33.3)
High risk of bias	1 (33.3)
Measurement of outcome	
Low risk of bias	1 (33.3)
Moderate risk of bias	-
High risk of bias	2 (66.7)
Was outcome of interest absent at the time to which the exposure refers?	3 (100)
Low risk of bias	-
Moderate risk of bias	-
High risk of bias	
Was follow-up long enough for outcome to occur?	
Low risk of bias	3 (100)
High risk of bias	-
Participation rate	
Low risk of bias	3 (100)
Moderate risk of bias	-
High risk of bias	-
Completeness of follow-up	
Low risk of bias	1 (33.3)
Moderate risk of bias	-
High risk of bias	2 (66.7)
Accuracy of dates of outcome or censoring	
Low risk of bias	2 (66.7)
Moderate risk of bias	1 (33.3)
Difference in follow-up between exposed and non-exposed	
Low risk of bias	1 (33.3)
Moderate risk of bias	1 (33.3)
High risk of bias	1 (33.3)
Difference in missing data for exposure between those with or without the outcome	
Low risk of bias	1 (33.3)
Moderate risk of bias	-
High risk of bias	2 (66.7)
Comparability of exposed and non-exposed cohorts with respect to potentially important confounding variables	3 (100)
Low risk of bias	-
Moderate risk of bias	-
Covariates are appropriately included in statistical analysis models	
Low risk of bias	3 (100)
High risk of bias	-

Table 5: Methodological quality of included additional cohort studies (n = 3)

	ElShafei 2013	Gittelman 2013	Stewart 2013
Selection of the exposed and non-exposed cohorts	1	1	1
Measurement of exposure	2	3	1
Measurement of outcome	3	3	1
Was outcome of interest absent at the time to which the exposure refers?	1	1	1
Was follow-up long enough for outcome to occur?	1	1	1
Participation rate	1	1	1
Completeness of follow-up	3	3	1
Accuracy of dates of outcome or censoring	2	1	1
Difference in follow-up between exposed and non-exposed	3	2	1
Difference in missing data for exposure between those with or without the outcome	3	1	3
Comparability of exposed and non-exposed cohorts with respect to potentially*	1	1	1
Covariates are appropriately included in statistical analysis models^	1	1	1
Overall Risk of bias	High	High	High
Overall quality rating	Low	Low	Low

* Multivariate analysis only. Pre-specified confounders were age, tPSA, ftPSA, PSA density, PSA velocity, HG-PIN, ASAP, DRE and prostate volume

^Multivariate analysis only

Key to overall rating
High risk of bias – high risk of bias in any domain
Moderate risk of bias – moderate or low risk of bias in all domains
Low risk of bias – all domains low risk of bias

Table 6: Methodological quality of included additional diagnostic performance study (n = 1)

Quality Category	N (%)
I. Selection of participants	
Low risk of bias	-
High risk of bias	1 (100)
Unclear risk of bias	-
II. Index test 1	
Low risk of bias	-
High risk of bias	-
Unclear risk of bias	1 (100)
III. Index test 2	
Low risk of bias	-
High risk of bias	-
Unclear risk of bias	-
Not applicable	1 (100)
IV. Reference standard	
Low risk of bias	-
High risk of bias	1 (100)
Unclear risk of bias	-
Not applicable	
V. Flow and timing	
Low risk of bias	-
High risk of bias	1 (100)
Unclear risk of bias	-
Not applicable	-

Table 7: Methodological quality of included additional diagnostic performance study (n = 1)

	Patient selection	Index test 1	Index test 2	Reference standard	Flow and timing	**Overall Risk of bias**
Stewart 2013	high	unclear	Not applicable	high	high	**At risk**

Key to overall rating

If study "**low"** for all domains then overall low risk of bias

If study "**high" or "unclear"** for one or more domains then "at risk of bias"

Clinical significance of size of effect is addressed in the assessment of clinical impact in the NHMRC evidence statement form.

The relevance of the evidence provided by the studies examining factors that might predict prostate cancer on repeat biopsy was rated 1 (see Appendix B for ratings)

Assessment of the relevance of the evidence in terms of whether the outcomes of diagnostic performance studies were directly relevant to the patient or whether they were surrogate outcomes was not assessed as it was not considered relevant to diagnostic performance studies.

References: Additional studies included as a result of updated literature search

1. ElShafei A, Li Y-H, Hatem A, Moussa AS, Ethan V, Krishnan N, et al. The utility of PSA velocity in prediction of prostate cancer and high grade cancer after an initially negative prostate biopsy. *Prostate* 2013; 73:1796-1802.

2. Gittelman MC, Hertzman B, Bailen J, Williams T, Koziol I, Henderson RJ et al. PCA3 molecular urine test as a predictor of repeat prostate biopsy outcome in men with previous negative biopsies: a prospective multicenter clinical study. *Journal of Urology* 2013; 190:64-9.

3. Stewart GD, Van Neste L, Delvenne P, Delrée P, Delga A, McNeill SA et al. Clinical utility of an epigenetic assay to detect occult prostate cancer in histopathologically negative biopsies: results of the MATLOC study. *Journal of Urology* 2013; 189:1110-6.

APPENDICES

Appendix A: Search strategies used

For Medline database:

#	Searches
1	exp prostatic neoplasms/
2	exp prostatic intraepithelial neoplasia/
3	PIN.tw.
4	(prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.
5	1 or 2 or 3 or 4
6	negative.tw.
7	false negative reactions/
8	6 or 7
9	(rebiops$ or re-biops$).tw.
10	((repeat$ or review$ or follow-up or followup) adj3 biops$).tw.
11	((saturat$ or extend$ or template) adj3 biops$).tw.
12	exp biopsy/ or biops$.tw.
13	5 and 8 and 12
14	9 or 10 or 11
15	5 and 14
16	13 or 15
17	limit 16 to (english language and humans and yr="2013-current")

From NICE. Evidence Review for Update of Clinical Guidelines 58 Prostate cancer: diagnosis and treatment accessed 29/01/14 - . final version accessed 18/11/14 http://www.nice.org.uk/guidance/cg175/evidence/cg175-prostate-cancer-appendix-m2

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database:

#	Searches
1	'prostate tumor'/exp
2	'prostatic intraepithelial neoplasia'/exp
3	pin
4	prostat* NEAR/3 (cancer* OR carcinoma* OR adeno* OR malignan* OR tum?r* OR neoplas* OR intraepithelial*)
5	1 OR 2 OR 3 OR 4
6	negative
7	'laboratory diagnosis'/exp
8	6 OR 7
9	rebiops* OR 're-biopsy' OR 're-biopsied' OR 're-biopsies'
10	(repeat* OR review* OR 'follow-up' OR followup) NEAR/3 biops*
11	(saturat* OR extend* OR template) NEAR/3 biops*
12	'biopsy'/exp OR biops*
13	5 AND 8 AND 12
14	9 OR 10 OR 11
15	5 AND 14
16	13 OR 15
17	[embase]/lim AND [2013-2014]/py AND [english]/lim AND [humans]/lim
18	16 AND 17

Adaptation of Medline search from NICE. Evidence Review for Update of Clinical Guidelines 58 Prostate cancer: diagnosis and treatment accessed 29/01/14 - . final version accessed 18/11/14 http://www.nice.org.uk/guidance/cg175/evidence/cg175-prostate-cancer-appendix-m2

ATSI search terms used

#	Searches
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

For Cochrane Database of Systematic Reviews – The Cochrane Library:

Title, abstracts, keywords: "prostate"

For Database of Abstracts of Reviews of Effects and Health Technology Assessment database (via OvidSP):

#	Searches
1	exp Prostatic Neoplasms/
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
3	1 or 2

Appendix B:

Level of Evidence rating criteria – Prognostic studies

Level	Study design
I	A systematic review of level II studies
II	A prospective cohort study
III-1	All or none
III-2	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial
III-3	A retrospective cohort study
IV	Case series, or cohort study of persons at different stages of disease

According to the standards of the National Health and Medical Research Council

Relevance of the Evidence

Rating	Relevance
1	Evidence of an effect on patient-relevant clinical outcomes including benefits and harms, quality of life and survival.
2	Evidence of an effect on a surrogate outcome* that has been shown to be predictive of patient-relevant outcomes for the same intervention.
3	Evidence of an effect on proven surrogate outcomes but for a different intervention.
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population.
5	Evidence confined to unproven surrogate outcomes.

**'surrogate outcome' refers to reasonable indicators of whether there has been some effect (e.g. blood pressure measurements or levels of serum cholesterol)*

Points to considering patient-relevant outcomes:
i) The goal of decision making in health care is to choose the intervention(s) (which may include doing nothing) that is (are) most likely to deliver the outcomes that patients find desirable
ii) Surrogate outcomes (such as blood pressure measurements or levels of serum cholesterol) may be reasonable indicators of whether there has been some effect. However, they should not be the basis for clinical decisions unless they reliably predict an effect on the way the patient feels; otherwise they will not be of interest to the patient or their carers
iii) All possible outcomes that are of most interest to patients (particularly harms) should be identified and evaluated

Adapted from table 1.10: National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra: NHMRC; 2000. http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp69.pdf

Appendix C: Excluded studies identified by updated literature search

Study	Reason for Exclusion
Boegemann 2013	No relevant outcomes reported
Bulbul 2013	Study design inappropriate
Butoescu 2014	Study design inappropriate
Capoluongo 2014	Study design inappropriate
De Luca 2013	No relevant outcomes reported
Kingman 2013	No relevant outcomes reported
Lughezzani 2013	Inappropriate data analysis of outcomes
Maddox 2013	No relevant outcomes reported
Maiti 2013	Study design inappropriate
Moreira 2013	No relevant outcomes reported
Murray 2013	Study design inappropriate
Ngo 2013	Study design inappropriate
Park 2014	Inappropriate data analysis of outcomes
Roobol 2013	Study design inappropriate
Saavedra 2013	Study design inappropriate
Soydan 2013	No appropriate participants
Scattoni 2013	No relevant outcomes reported
Schröder 2014	Study design inappropriate
Van Neste 2013	Study design inappropriate
Venigalla 2013	No relevant outcomes reported. Study design inappropriate
Zhang 2013	Study design inappropriate

References: Excluded studies identified by updated literature search

1. Boegemann M, Vincendeau S, Stephan C, Houlgatte A, Krabbe LM, Semjonow A et al. Use of [-2] proPSA and prostate health index (phi) to improve the diagnostic accuracy of prostate cancer compared to t-PSA and %f-PSA in young men (≤ 65 years old). *Journal of Clinical Oncology* 2013; 31(15 Suppl.) Abstract 5074.

2. Bulbul M, Shahait M. Prostate specific antigen follow up kinetics in relation to pathological findings in patients with negative first prostate needle biopsy. *Urology* 2013; 82:S277.

3. Butoescu V, Ambroise J, Stainier A, Dekairelle AF, Gala JL, Tombal B. Does genotyping of risk-associated single nucleotide polymorphisms improve patient selection for prostate biopsy when combined with a prostate cancer risk calculator? *Prostate* 2014; 74:365-371.

4. Capoluongo E, Zambon CF, Basso D, Boccia S, Rocchetti S, Leoncini E et al. PCA3 score of 20 could improve prostate cancer detection: Results obtained on 734 Italian individuals. *Clin Chim Acta* 2014; 429:46-50.

5. De Luca S, Caccia P, Cavallini A, Faraone N, Giargia E, Pasquale M et al. Histological chronic prostatitis at the first biopsy is not associated with a lower risk of prostate cancer (PCA) at repeated extended biopsy. *Anticancer Research* 2013; 33:2269.

6. Kingman AT, Milburn P, Swanson G. High grade PIN and the risk of prostate cancer. *Journal of Urology* 2013; 189:e508.

7. Lughezzani G, Lazzeri M, Haese A, McNicholas T, de la Taille A, Buffi NM et al. Multicenter European External Validation of a Prostate Health Index-based Nomogram for Predicting Prostate Cancer at Extended Biopsy. *European Urology* 2013; 66(5):906-912.

8. Maddox M, Renzulli J, Golijanin D, Elsamra S, Somerville M, Cohen S. Prostate specific antigen density velocity on dutasteride helps predict negative prostate biopsy: analysis of the reduce trial. *Journal of Urology* 2013; 189:e796-e797.

9. Maiti R, Silverman J, Bott S, Nedas T, Emara A, Hindley R: Are free/total prostate-specific antigen and prostate-specific antigen density useful prior to transperineal template prostate biopsy? *Urology* 2013; 82:S68.

10. Moreira D, Nickel JC, Gerber L, Muller R, Andriole G, Castro-Santamaria R et al. Baseline prostate atrophy is associated with reduced risk of prostate cancer in men undergoing repeat prostate biopsy: results from the reduce study. *Journal of Urology* 2013;189:e796.

11. Murray NP, Reyes E, Tapia P, Badinez L, Orellana N, Fuentealba C, et al. A performance analysis of the presence of malignant circulating prostate cells as a predictive factor for the detection of prostate cancer in the first, second and third prostate biopsy. *Archivos Españoles de Urología* 2013 May; 66(4):335-41.

12. Ngo CC, Chan TY, Yu C, Chu SK, Man CW. Case control study on predictors of prostate cancer on repeat prostate biopsy. *BJU International* 2013; 111:9.

13. Park K, Dalton JT, Narayanan R, Barbieri CE, Hancock ML, Bostwick DG et al. TMPRSS2:ERG gene fusion predicts subsequent detection of prostate cancer in patients with high-grade prostatic intraepithelial neoplasia. *Journal of Clinical Oncology* 2014; 32:206-211.

14. Roobol MJ, Zhu X, Schroder FH, van Leenders GJ, van Schaik RH, Bangma CH et al. A Calculator for Prostate Cancer Risk 4 Years After an Initially Negative Screen: Findings from ERSPC Rotterdam. *European Urology* 2013; 63:627-633.

15. Saavedra II, Konstantinidis C, Celma A, Ágreda F, Placer J, Planas J et al. PSA kinetics does not predict prostate cancer in men subjected to prostate biopsy. *Journal of Urology* 2013; 189(S4):e789.

16. Soydan H, Yesildal C, Okcelik S, Yilmaz O, Ates F, Karademir F. Early Rebiopsy is Not Necessary for Patients Prior Detected Atypical Small Acinar Proliferation (ASAP) at 12 Core TRUS Guided Prostate Biopsy and Candidate for Active Surveillance. *Urology* 2013; 82:S275-S276.

17. Scattoni V, Lazzeri M, Lughezzani G, De Luca S, Passera Rea: Comparison between PCA3 and phi specificity and sensitivity in predicting the presence of cancer at initial or repeat biopsy. *Anticancer Research* 2013; 33:2293.

18. Schroder FH, Venderbos LD, van den Bergh RC, Hessels D, van Leenders GJ, van Leeuwen PJ et al. Prostate cancer antigen 3: diagnostic outcomes in men presenting with urinary prostate cancer antigen 3 scores ≥100. *Urology* 2014; 83:613-616.

19. Van Neste L, Van Criekinge W, Thas O, Bigley J, Stewart GD, Harrison DJ: Prediction of risk for prostate cancer in histopathologically negative biopsies by multigene epigenetic assay. *Journal of Clinical Oncology* 2013; 31(6 Suppl.) Abstract 95.

20. Venigalla S, Zhao C, Miyamoto H: Histopathologic features of atypical glands on prostate biopsy: nucleolar size is a predictor of subsequent detection of prostatic adenocarcinoma. *Prostate* 2013; 73:376-381.

21. Zhang M, Amberson JB, Epstein JI: Two sequential diagnoses of atypical foci suspicious for carcinoma on prostate biopsy: a follow-up study of 179 cases. *Urology* 2013; 82:861-864.

Systematic review report for question 8.2

Clinical Question 8: *If prostate cancer is not found in an adequate biopsy what if any additional steps should be taken and what recommendations should be made regarding the strategy for subsequent PSA testing?*

PICO Question 8.2: *In men with suspected prostate cancer whose initial TRUS biopsy is negative, what should be the next investigation(s)?*

Identification of existing relevant guidelines

Methods

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by literature searches for each PICO question and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption or adaptation guidelines had to be evidence based and meet the pre-specified criteria of scaled scores of greater or equal to 70% for the domains rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

Results

Search for relevant guidelines

Searches for guidelines identified one guideline that contained potentially relevant recommendations, an updated version of the UK National Institute for Health and Care Excellence evidence-based Clinical Guidelines for Prostate Cancer Diagnosis and Treatment (NICE Guidelines; National Collaborating Centre for Cancer 2014a[1]). The 2014 version of the NICE guidelines contained a number of new questions. Of these, the following questions were identified as relevant to the clinical question above;

- In men who have been referred with suspected prostate cancer, what are the prognostic factors that determine the need for further investigation following a prior negative biopsy?
- In men with suspected prostate cancer whose initial TRUS biopsy is negative what should be the next investigation(s)?

Assessment with AGREE II instrument

The NICE guidelines were independently assessed by 4 appraisers using the AGREE II instrument. The scaled score for the rigour domain was 84.4%, the scaled score for the clarity of presentation domain was 76.0% and the scaled score for editorial independence was 85.4% and as such these guidelines met the inclusion criteria for adoption or adaptation. As a result the authors decided to update the NICE systematic reviews for these questions to 1st March 2014 and on the basis of results of the updated systematic reviews adopt or adapt the NICE recommendations for these questions.

The following systematic review updates to 1st March 2014 the existing systematic review[2] of literature undertaken by the National Collaborating Centre for Cancer (NICE systematic review) for the question: **In men with suspected prostate cancer whose initial TRUS biopsy is negative what should be the next investigation(s)?**

1. National Collaborating Centre for Cancer. Prostate cancer: diagnosis and treatment. National Collaborating Centre for Cancer; 2014.
2. National Collaborating Centre for Cancer. Draft Evidence Review for Update of Clinical Guidelines 58 Prostate cancer: diagnosis and treatment accessed 29/01/14 - . final version accessed 18/11/14 http://www.nice.org.uk/guidance/cg175/evidence/cg175-prostate-cancer-appendix-m2

Updated NICE systematic review – methods and results

NICE question: *In men with suspected prostate cancer whose initial TRUS biopsy is negative what should be the next investigation(s)?*

NICE PICO

Population	Tests	Outcomes
Men whose initial biopsy proved negative for prostate cancer	- Repeat TRUS biopsy - Multiparametric MRI (or MRS) + repeat TRUS biopsy - Extended/saturation TRUS biopsy - 3D ultrasound and biopsy - Template biopsy - Review of initial biopsy - Contrast enhanced US and biopsy - Elastography and biopsy	- Diagnostic yield - Diagnostic process-related morbidity - Diagnostic process-related mortality - Health-related quality of life

1. METHODS

1.1 Literature search for updated NICE systematic review

The NICE systematic review search cut-off date was May 2013. To ensure all the relevant literature available was captured, searches for the updated systematic review were conducted from 1/1/2012. Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effect and Health Technology Assessments databases were searched using text terms and, where available, database specific subject headings. Each database was searched for articles dealing with prostate cancer. The Medline database was searched using the strategy documented in the NICE systematic review. The Embase search strategy used was based on the Medline strategy. To identify

studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples.

A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 which were either published after the initial search was completed and/or added to the relevant database after the search was completed. Alerts were checked until July 2014. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched regularly up until April 2014 for relevant reviews published after the initial search.

1.2 **Inclusion Criteria**

Selection criteria	**Inclusion criteria**
Study type	Intervention
Study design	Randomized controlled trials or sequential sampling studies[1], or systematic reviews/meta-analyses thereof
Population	Men whose initial biopsy was at least 8 cores and negative for prostate cancer and for whom there remains a suspicion of prostate cancer
Intervention	Review of initial biopsy, or Repeat TRUS 10-12 core biopsy, or Extended or saturated TRUS biopsy, or Template biopsy, or Multi-parametric magnetic resonance imaging (MRI) including magnetic resonance spectroscopy (MRS) or T2 MRI, and repeat biopsy, or 3 dimensional ultrasound and repeat biopsy, or Contrast enhanced US and repeat biopsy, or Elastography and repeat biopsy
Comparator	Review of initial biopsy, or Repeat TRUS 10-12 core biopsy, or Extended or saturated TRUS biopsy, or Template biopsy, or Multi-parametric magnetic resonance imaging (MRI) including magnetic resonance spectroscopy (MRS) or T2 MRI, and repeat biopsy, or 3 dimensional ultrasound and repeat biopsy, or Contrast enhanced US and repeat biopsy, or Elastography and repeat biopsy
Outcomes	Detection of prostate cancer (Cancer Detection Rate), or Diagnostic process-related morbidity Diagnostic process-related mortality Health-related quality of life
Language	English
Publication period	After 1st January 2012 and prior to 1st March 2014.

[1] Studies in which results for each of the compared sampling strategies were obtained from each of the participating men, the less extensive set of biopsy cores being a subset of the more extensive set.

The inclusion criteria for the updated NICE systematic review were derived from the PICO table and methods for this question, and an examination of the data extracted and reasons for excluding studies for this question as reported in the NICE systematic review.

2. RESULTS

2.1 Results of literature search for the updated NICE systematic review

Figure 1 outlines the process of identifying relevant articles for the systematic review. The Medline search identified 52 citations, the Embase search 181 citations, the search of the Cochrane Database of Systematic Reviews 59 citations, the Database of Abstracts of Reviews of Effects 282 citations and the Health Technology Assessment database 216 citations, resulting in a total of 790 citations. Titles and abstracts were examined and 53 articles were retrieved for a more detailed evaluation.

Eight articles met the inclusion criteria and were included in the updated systematic review. There were no studies of ATSI men that met the inclusion criteria.

Our aim was to update the relevant tables of the primary studies in the NICE systematic review. However in doing so we encountered difficulties interpreting the results presented. To provide clarity and comparable estimates of the potential benefits of targeted biopsies, changes in cancer yields as a result of adding the different types of targeted biopsies to standard biopsies were extracted not only from the 8 studies identified by the updated literature searches, but also from the 4 primary studies on targeted mpMRI biopsies included in the NICE systematic review (Arsov 2012, Lee 2012, Portalez 2012, Vourganti 2012). As a result 12 studies were included in this update of the NICE systematic review.

The 12 included articles reported 12 studies examining the addition of targeted biopsies to standard (random or systematic) biopsies, and 9 of them examined mpMRI targeted biopsies.

The retrieved articles that were not included and the reason for their exclusion are documented in Appendix C. In summary, most articles were excluded because they did not report any relevant outcomes or used inappropriate study designs.

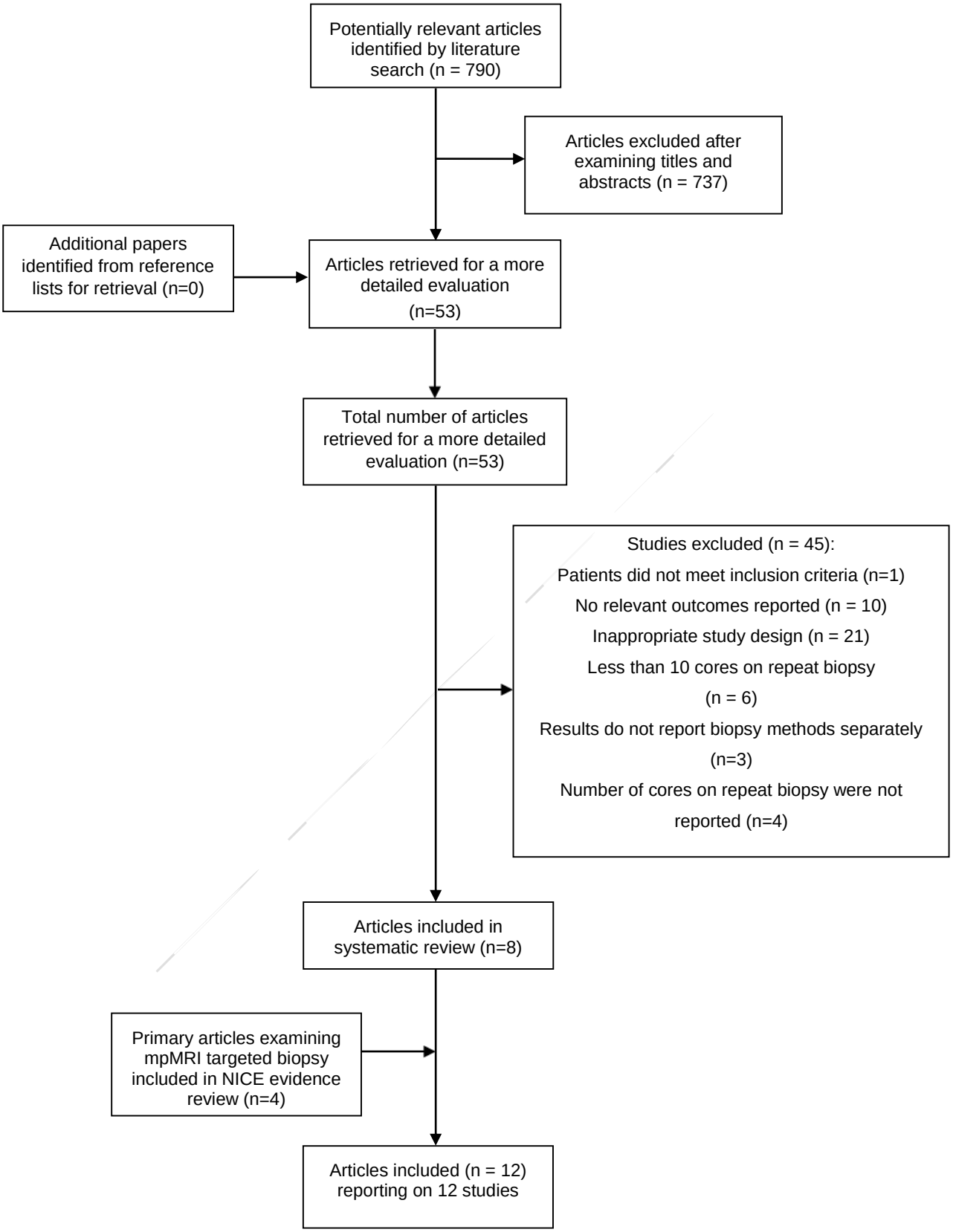


Figure 1. Results of literature searches and exclusion of studies

2.2 Study Characteristics

Table 1: Study characteristics adapted from NICE systemic review (primary studies included NICE systematic review examining mpMRI targeted biopsies and new additional studies identified by updated searches shaded blue)

Ref.	No. of patients	Mean age (range)	No. of previous biopsies (range)	Initial biopsy technique	Mean (range/SD) PSA level, ng/mL	Indication for repeat biopsy	Repeat Bx approach		Comments
							Targeted	Systematic	
Salomon 2014	449	NR	Mean = 1.8 (1-9)	NR	10.4	NR	RTE (4 cores)	TRUS guided Bx (10 cores)	
Abd-Alazeez 2014	54	Median = 64 (39-75)	Mean = 1.5 (1-3)	TRUS guided BX (10-12 cores)	Median = 10 (2-23)	Increasing or persistently high PSA levels	mpMRI (T2W, DW and DCE) and cognitive registration Bx (2-9 targets per patient)	Systematic template mapping Bx (≥20 cores)	
Costa 2013	38	64 (48-77)	≥2 (2-5)	Extended (mean 15 cores)	14.4 (1.8-33.1)	PSA >4 ng/mL PSAV >0.75ng/mL/year Prior Bx inconclusive	mpMRI (T2W and DCE) TRUS guided Bx	TRUS guided Bx	The numbers of cores obtained in systematic or targeted biopsies varied with urologist judgement.
Tang 2013	39	64.1	Median = 1	TRUS	11.0	NR	mpMRI (T2W and DWI) and MRI/US fusion Bx	Transperineal systematic Bx	
Sonn 2013	105	Median = 65	Median = 2	TRUS (median 13 cores)	Median = 7.5 (5.0-11.2)	Persistently high PSA levels	mpMRI and MR-US fusion Bx (1-9 cores per target, 1-3 targets per patient)	Systematic Bx (12 cores)	
Pepe 2013	78	Median = 63 (49-72)	NR	TRUS extended (median 18 cores)	11 (3.7-45)	Abnormal DRE and PSA >10 ng/mL. PSA between 4.1 – 10ng/mL with ftPSA <25%. PSA between 2.6 – 4 ng/mL with ftPSA <20%. Persistently high PSA levels.	mpMRI (T2W, DWI, DCE and spectroscopy) and TRUS guided Bx (3-4 cores per patient)	Saturated transperineal Bx (median 28 cores, range 26-32)	

Cornelis 2013	178	62 (47-78)	Mean = 1.8 (1-5)	TRUS	Median = 10.76 (2.5-50)	PSA > 2ng/mL. PCa target at mpMRI Increasing or persistently high PSA levels.	mpMRI (T2W and DCE) targeted and CEUS guided Bx (2-5 cores per patient) mpMRI (T2W and DCE) and CEUS targeted Bx (2-5 cores per patient)	Random Bx (12 cores) outside of the targeted region	
Yerram 2012	206	61.7 (37-80)	Mean = 2.2 (1-9)	TRUS	14.0 (0.3 -103)	NR	MRI/US fusion Bx	TRUS guided Bx (12 cores)	
Portalez 2012	129	64.7 (47-79)	Mean = 1.3 (1-4)	TRUS	9.6 (2.7-40.0)	NR	mpMRI (T2W, DWI and DCE) US fusion BX	Sextant random systematic cores	
Arsov 2012	58	Median = 67.0 years (42 -78)	(1-6)	TRUS-GB (≥10 cores)	9.30 (4.6-108.0)	PSA >4ng/mL	fMRI: T2W, T1W, DWI and perfusion imaging	TRUS guided Bx (mean 10.6 cores)	No relevant outcomes Quality appraisal considered unnecessary
Vourganti 2012	195	Median = 62 (37-80)	Median = 2 (1-9)	NR	9.13 (0.3-103)	NR	mpMRI: T2W, DWI, DCE and Spectroscopy US fusion Bx (2-14 cores, median 5 cores per patient)	TRUS guided BX (12 cores)	
Lee 2012	87	Median =87 (48-74)	Mean = 2 (1-4)	TRUS (12 cores)	Patients +ve PCa: 7.90 Patients –ve PCa: 9.48	PSA > 4ng/mL PSAV >0.75ng/ml/years Increasing or persistently high PSA levels	mpMRI: T2W + DWI (6-14 cores per patient)	TRUS guided BX (12 cores)	

Bx: Biopsy; DCE: Dynamic contrast enhanced; DWI: Diffusion weighted imaging; CEUS: Contrast enhanced ultrasound guided; fMRI: Multi-parametric functional magnetic resonance imaging; ftPSA: free to total PSA; NR: Not reported; PBx: Prostate biopsy; PCa: Prostate cancer; PSA: Prostate specific antigen; PSAV: Prostate specific antigen velocity; RTE: Real-time elastography; mpMRI: Multi-parametric magnetic resonance imaging; T2W: T2-weighted; TRUS: Transrectal ultrasound; US: ultrasound; Guided: probe or ultrasound is used to guide biopsy needles to the prostate; Targeted: an MRI image or the fusion of MRI and ultrasound images are used to direct a needle to biopsy suspicious region(s) of the prostate.

2.3 Study Quality

Methodological quality of included diagnostic studies is described in Tables 2 and 3.

Table 2. Risk of bias of included sequential sampling studies (n = 11, primary studies included NICE systematic review examining mpMRI targeted biopsies and new additional studies identified by updated searches shaded blue)

	Patient selection	Index test 1	Flow and timing*	Overall Risk of bias
Sonn 2014	High	Unclear	Low	**High risk of bias**
Cornelis 2013	High	High	Low	**High risk of bias**
Abd-Alazeez 2014	High	Unclear	Low	**High risk of bias**
Costa 2013	Unclear	Low	Low	**High risk of bias**
Yerram 2012	Unclear	Unclear	Low	**High risk of bias**
Pepe 2013	Unclear	Unclear	Low	**High risk of bias**
Tang 2013	Unclear	Unclear	Unclear	**High risk of bias**
Salomon 2013	Unclear	Unclear	Low	**High risk of bias**
Lee 2012	Unclear	Low	Unclear	**High risk of bias**
Portalez 2012	Unclear	High	Unclear	**High risk of bias**
Vourganti 2012	High	Low	Unclear	**High risk of bias**

* *Pre-specified criterion for low risk of bias was equal to or greater than 95% patients included in the analysis*

Key to overall risk of bias rating

Low risk of bias: a study that received "low" for all three criteria
Moderate risk of bias: received "low" for selection of participants and flow and timing criteria, and "high" or "unclear" for index tests criterion
High risk of bias: received "high" or "unclear" for selection of participants and/or flow and timing (and index tests) criteria

This is a modification of the QUADAS rating

Low risk of bias: A study rated at low risk of bias for all domains

At risk of bias: A study rated at high or unclear risk of bias for one or more domains

Using these QUADAS ratings, all studies would have been rated "at risk of bias". To distinguish those at greater risk of bias, the QUADAS rating was modified to include a moderate and high risk of bias rather than "at risk of bias".

Table 3. Risk of bias of included sequential sampling studies (n = 11)

Quality Category	N (%) *
I. Selection of participants	
Low risk of bias	-
High risk of bias	3 (27.3)
Unclear risk of bias	8 (72.7)
II. Index test 1	
Low risk of bias	3 (27.3)
High risk of bias	2 (18.2)
Unclear risk of bias	6 (54.5)
III. Index test 2	
Low risk of bias	-
High risk of bias	-
Unclear risk of bias	-
Not applicable	11(100)
IV. Reference standard	
Low risk of bias	-
High risk of bias	-
Unclear risk of bias	-
Not applicable	11 (100)
V. Flow and timing	
Low risk of bias	8 (72.7)
High risk of bias	-
Unclear risk of bias	3 (27.3)
Not applicable	-

Selected items from QUADAS-2 based on systematic review Eichler 2006 (Eichler K, Hempel S, Wilby J, Myers L, Bachmann LM, Kleijnen J. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. J Urol 2006; 175(5):1605-1612).

2.4 Study Results

Table 4. Results of intervention studies examining *targeted and systematic biopsies vs. systematic biopsies only* in **all men** undergoing biopsy

Study	Outcome Definition	Measure	N actual	Intervention *Targeted and Systematic*	Comparison *Systematic*	Size of effect	Size of effect Confidence interval	p value
RTE targeted + TRUS guided Bx vs. TRUS guided Bx								
Salomon 2014	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	449	39.2 (176)	31.4 (141)	RD = 7.8% RPR = 1.2	NR	NR
mpMRI (T2W, DW and DCE) targeted + systematic template mapping Bx vs. systematic template mapping Bx								
Abd-Alazeez 2014	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	54	63.0 (34)	63.0 (34)	RD = 0% RPR = 1.0	NA	NA
mpMRI (T2W and DCE) targeted + TRUS guided Bx vs. TRUS guided Bx								
Costa 2013	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	38	34.2 (13)	7.9 (3)	RD = 26.3% RPR = 4.3	NR	NR
mpMR: (T2W and DWI) targeted + Transperineal systematic Bx vs. Transperineal systematic Bx								
Tang 2013	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	39	41.0 (16)	28.2 (11)	RD = 12.8% RPR = 1.5	NR	NR
mpMRI targeted+ Systematic Bx vs. Systematic Bx								
Sonn 2014	*Cancer Detection Rate* cancers detected/men receiving both targeted and standard biopsy	% (n)	94	33.0 (31)	26.6 (25)	RD = 6.4% RPR = 1.2	NR	NR
mpMRI (T2W, DWI, DCE and spectroscopy) targeted + Saturated TP Bx vs. Saturated TP Bx								
Pepe 2013	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	78	41.0 (32)	35.9 (28)	RD = 5.1% RPR = 1.1	NR	NR
mpMRI (T2W and DCE) targeted and CEUS guided Bx + TRUS Bx vs.TRUS Bx								

Cornelis 2013	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	178	46.6 (83)	36.5 (65)	RD = 10.1% RPR =1.3	NR	NR
MRI targeted + TRUS guided Bx vs. TRUS guided Bx								
Yerram 2012	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	206	36.9 (76)	26.7 (55)	RD = 10.2% RPR = 1.4	NR	NR
mpMRI (T2W + DWI +DCE) targeted + sextant systematic cores vs. sextant random systematic cores								
Portalez 2012	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	129	48.1 (62)	20.9 (27)	RD = 27.2% RPR = 2.3	NR	NR
mpMRI (T2W + DWI +DCE + spectroscopy) targeted + TRUS guided BX vs. TRUS guided BX								
Vourganti 2012	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	195	37.4 (73)	23.1 (45)	RD = 14.3% RPR = 1.6	NR	NR
mpMRI (T2W + DWI) targeted + TRUS guided Bx vs. TRUS guided BX								
Lee 2012	*Cancer Detection Rate* cancers detected/men undergoing biopsy	% (n)	87	52.9 (46)	10.3 (9)	RD = 42.6% RPR = 5.1	NR	NR

Bx: biopsy; CEUS: Contrast enhanced ultrasound DCE: Dynamic contrast-enhanced; DWI: Diffusion-weighted imaging; mpMRI: multiparametric magnetic resonance imaging; NA: not available; NR: not reported; RD = risk difference (men diagnosed out of men undergoing intervention – men diagnosed out of men undergoing comparison biopsy); RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy /men diagnosed out of men undergoing comparison biopsy); RTE: Real-time elastography; T2W: T2-weighted; TP: Transperineal; TRUS: Transrectal; US: ultrasound; Guided: probe or ultrasound is used to guide biopsy needles to the prostate; Targeted: an MRI image or the fusion of MRI and ultrasound images are used to direct a needle to biopsy suspicious region(s) of the prostate.

Table 5. Results of intervention studies examining *targeted and systematic biopsies vs. systematic biopsies only* in **men with positive findings on imaging**

Study	Outcome Definition	Measure	N actual	Intervention *Targeted and Systematic*	Comparison *Systematic*	Size of effect	Size of effect Confidence interval	p value
RTE targeted + TRUS guided Bx vs. TRUS guided Bx								
Salomon 2014	*Cancer Detection Rate* cancers detected/men positive on RTE	% (n)	NR	(119)	(84)	RPR = 1.4	NR	NR
mpMRI (T2W, DW and DCE) targeted + systematic template mapping Bx vs. systematic template mapping Bx								
Abd-Alazeez 2014	*Cancer Detection Rate* cancers detected/men receiving MRI targeted biopsies[1]	% (n)	15	53.3 (8)	53.3 (8)	RD = 0% RPR = 1.0	NA	NA
mpMRI (T2W and DCE) targeted + TRUS guided Bx vs. TRUS guided Bx								
Costa 2013	*Cancer Detection Rate* cancers detected/men positive on MRI	% (n)	22	54.5 (12)	9.1 (2)	RD = 45.4% RPR = 6.0	NR	NR
mpMRI targeted + Systematic Bx vs. Systematic Bx								
Sonn 2014	*Cancer Detection Rate* cancers detected/men receiving MRI targeted biopsies	% (n)	94	33.0 (31)	26.6 (25)	RD = 6.4% RPR = 1.2	NR	NR
mpMRI (T2W, DWI, DCE and spectroscopy) targeted + Saturated TP Bx vs. Saturated TPBx								
Pepe 2013	*Cancer Detection Rate* cancers detected/men positive on MRI	% (n)	46	56.5 (26)	47.8 (22)	RD = 8.7% RPR = 1.2	NR	NR
mpMRI(T2W and DCE) targeted and CEUS guided Bx + TRUS Bx vs. TRUS Bx								
Cornelis 2013	*Cancer Detection Rate* cancers detected/men with positive findings on MRI	% (n)	178	46.6 (83)	36.5 (65)	RD = 10.1% RPR = 1.3	NR	NR
mpMRI (T2W and DCE) and CEUS targeted Bx + TRUS Bx vs. TRUS Bx								
Cornelis 2013	*Cancer Detection Rate* cancers detected/men with positive MRI+CE-US findings	% (n)	158	47.5 (75)	36.1 (57)	RD = 11.4% RPR = 1.3	NR	NR
mpMRI (T2W + DWI +DCE + spectroscopy) targeted + TRUS BX vs. TRUS BX								

Vourganti 2012	*Cancer Detection Rate* cancers detected/men with positive MRI findings	% (n)	195	37.4 (73)	23.1(45)	RD=14.3% RPR = 1.6	NR	NR
mpMRI (T2W + DWI) targeted + TRUS guided Bx vs. TRUS guided BX								
Lee 2012	*Cancer Detection Rate* cancers detected/men with positive MRI findings	% (n)	82	53.7 (44)	8.5 (7)	RD = 45.2% RPR = 6.3	NR	NR

Bx: biopsy; CEUS: Contrast enhanced ultrasound; DCE: Dynamic contrast-enhanced; DWI: Diffusion-weighted imaging; mpMRI: Multiparametric Magnetic resonance imaging; NA: not available; NR: not reported; RD = risk difference (men diagnosed out of men undergoing intervention – men diagnosed out of men undergoing comparison biopsy); RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy/men diagnosed out of men undergoing comparison biopsy); RTE: Real-time elastography; T2W: T2-weighted; TP: Transperineal; TRUS: Transrectal ultrasound; US: ultrasound; Guided: probe or ultrasound is used to guide biopsy needles to the prostate; Targeted: an MRI image or the fusion of MRI and ultrasound images are used to direct a needle to biopsy suspicious region(s) of the prostate.

1. = 45 men were positive on MRI, but only 15 received additional biopsies on areas suspicious for cancer on MRI.

2.5 Body of Evidence

I. Detection of prostate cancer for all patients undergoing biopsies

Name of study	Study type	N	Level of evidence*	Quality of evidence**	Risk of bias**	Results summary			p value	95% CI	Relevance of evidence*
						RPR	RD	NNT			
RTE targeted + TRUS guided Bx vs. TRUS guided Bx											
Salomon 2012 Targeted: 4 cores Systematic**:** 10 cores	SS	449	II	Low	high	1.2	7.8%	13	NR	NR	1
mpMRI (T2W, DW, and DCE) targeted + systematic template mapping Bx vs. systematic template mapping Bx											
Abd-Alazeez 2014 Targeted: 2-9 cores Systematic: ≥ 20 cores	SS	54	II	Low	High	1.0	0%	-	NA	NA	1
mpMRI (T2W and DCE) targeted + TRUS guided Bx vs. TRUS guided Bx											
Costa 2013 Number of cores: NR	SS	38	II	Low	High	4.3	26.3%	4	NR	NR	1
mpMRI (T2W and DWI) targeted + Transperineal systematic Bx vs. Transperineal systematic Bx											
Tang 2013 Number of cores: NR	SS	39	II	Low	High	1.5	12.8%	8	NR	NR	1
mpMRI targeted + systematic Bx vs. systematic Bx											
Sonn 2014 Targeted: 1-9 cores/target, 1-3 targets/patient Systematic: 12 cores	SS	94	II	Low	High	1.2	6.4%	16	NR	NR	1
mpMRI (T2W, DWI, DCE and spectroscopy) targeted + Saturated TP Bx vs. Saturated TP Bx											

Pepe 2013 Targeted: 3-4 cores Systematic: 26-32 cores	SS	78	II	Low	High	1.1	5.1%	20	NR	NR	1
mpMRI targeted and CEUS guided +TRUS Bx vs. TRUS Bx											
Cornelis 2013 Targeted: 2-5 cores Systematic: 12 cores	SS	178	II	Low	High	1.3	10.1%	10	NR	NR	1
MRI targeted + TRUS guided Bx vs. TRUS guided Bx											
Yerram 2012 Number of cores: NR	SS	206	II	Low	High	1.4	10.2%	10	NR	NR	1
mpMRI (T2W + DWI +DCE) targeted + sextant random systematic cores											
Portalez 2012 Number of cores: NR	SS	129	II	Low	High	2.3	27.2%	4	NR	NR	1
mpMRI (T2W + DWI + DCE + spectroscopy) targeted + TRUS guided Bx vs. TRUS guided Bx											
Vourganti 2012 Targeted: 2-14 cores Systematic: 12 cores	SS	195	II	Low	High	1.6	14.3%	7	NR	NR	1
mpMRI (T2W + DWI) targeted + TRUS guided Bx vs. TRUS guided Bx											
Lee 2012 Targeted: 6-14 cores Systematic: 12 cores	SS	87	II	Low	High	5.1	42.6%	2	NR	NR	1

Bx: biopsy; CEUS: Contrast enhanced ultrasound guided; DCE: Dynamic contrast-enhanced; DWI: Diffusion-weighted imaging; MpMRI: Multiparametric magnetic resonance imaging; NA: not available; NNT: Numbers needed to treat; NR: not reported; RD = risk difference (men diagnosed out of men undergoing intervention – men diagnosed out of men undergoing comparison biopsy); RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy /men diagnosed out of men undergoing comparison biopsy); RTE: Real-time elastography; SS: Sequential sampling; T2W: T2-weighted; TP: Transperineal; TRUS: Transrectal ultrasound; US: Ultrasound; Guided: probe or ultrasound is used to guide biopsy needles to the prostate; Targeted: an MRI image or the fusion of MRI and ultrasound images are used to direct a needle to biopsy suspicious region(s) of the prostate.

**Refer to appendix B for detailed explanations of rating scores; ** See Table 4 for quality appraisals*

II. Cancer detection rate for patients with positive findings on imaging

Name of study	Study type	N	Level of evidence*	Quality of evidence**	Risk of bias	Results summary			p value	95% CI	Relevance of evidence*
						RPR	RD	NNT			
RTE targeted + TRUS guided Bx vs. TRUS guided Bx											
Salomon 2012 Targeted: 4 cores Systematic**:** 10 cores	SS	NR	II	low	high	1.4	NA	NA	NR	NR	1
mpMRI (T2W, DW, and DCE) targeted + systematic template mapping Bx vs. systematic template mapping Bx											
Abd-Alazeez 2014 Targeted: 2-9 cores Systematic: ≥ 20 cores	SS	15	II	Low	High	1.0	0%	-	NA	NA	1
mpMRI (T2W and DCE) targeted + TRUS guided Bx vs. TRUS guided Bx											
Costa 2013 Number of cores: NR	SS	22	II	Low	High	6.0	45.4%	2	NR	NR	1
mpMRI targeted + systematic Bx vs. systematic Bx											
Sonn 2014 Targeted: 1-9 cores/target, 1-3 targets/ patient Systematic: 12 cores	SS	94	II	Low	High	1.2	6.4%	16	NR	NR	1
mpMRI (T2W, DWI, DCE and spectroscopy) targeted + Saturated TP Bx vs. Saturated TP Bx											
Pepe 2013 Targeted: 3-4 cores Systematic: 26-32 cores	SS	46	II	Low	High	1.2	8.7%	11	NR	NR	1
mpMRI targeted and CEUS guided + TRUS Bx vs. TRUS Bx											
Cornelis 2013 Targeted: 2-5 cores	SS	178	II	Low	High	1.3	10.1%	10	NR	NR	1

Systematic: 12 cores											
mpMRI and CEUS targeted + TRUS Bx vsTRUS Bx											
Cornelis 2013 Targeted: 2-5 cores Systematic: 12 cores	SS	158	II	Low	High	1.3	11.4%	9	NR	NR	1
mpMRI (T2W + DWI + DCE + spectroscopy) targeted + TRUS guided Bx vs. TRUS guided Bx											
Vourganti 2012 Targeted: 2-14 cores Systematic: 12 cores	SS	195	II	Low	High	1.6	14.3%	7	NR	NR	1
mpMRI (T2W + DWI) targeted + TRUS guided Bx vs. TRUS guided Bx											
Lee 2012 Targeted: 6-14 cores Systematic: 12 cores	SS	82	II	Low	High	6.3	45.2%	2	NR	NR	1

Bx: biopsy; CEUS: Contrast enhanced ultrasound guided; DCE: Dynamic contrast-enhanced; DWI: Diffusion-weighted; MpMRI: Multiparametric Magnetic resonance imaging; N/A: not available; NNT: Numbers needed to treat; NR: not reported; RD = risk difference (men diagnosed out of men undergoing intervention – men diagnosed out of men undergoing comparison biopsy); RPR = relative positivity rate (men diagnosed out of men undergoing intervention biopsy /men diagnosed out of men undergoing comparison biopsy); RTE: Real-time elastography; SS: Sequential sampling; T2W: T2-weighted; TP: Transperineal; TRUS: Transrectal; US: Ultrasound; Guided: probe or ultrasound is used to guide biopsy needles to the prostate; Targeted: an MRI image or the fusion of MRI and ultrasound images are used to direct a needle to biopsy suspicious region(s) of the prostate.

**Refer to appendix B for detailed explanations of rating scores; ** See Table 2-3 for quality appraisals*

Sequential sampling studies were not included in NHMRC evidence hierarchy. This study design was considered superior to RCT design and thus was considered at least level II evidence.

Clinical significance of size of effect is addressed in the assessment of clinical impact in the NHMRC evidence statement form.

References: Included Studies

1. Abd-Alazeez M, Ahmed HU, Arya M, Charman SC, Anastasiadis E, Freeman A et al The accuracy of multiparametric MRI in men with negative biopsy and elevated PSA level--can it rule out clinically significant prostate cancer? *Urol Oncol* 2014;32:45-22.

2. Arsov C, Quentin M, Rabenalt R, Antoch G, Albers P, Blondin D. Repeat Transrectal Ultrasound Biopsies with Additional Targeted Cores According to Results of Functional Prostate MRI Detects High-risk Prostate Cancer in Patients with Previous Negative Biopsy and Increased PSA GÇô A Pilot Study*. Anticancer Research* 2012; 32(3):1087-1092.

3. Cornelis F, Rigou G, Le BY, Coutouly X, Hubrecht R, Yacoub M et al. Real-time contrast-enhanced transrectal US-guided prostate biopsy: diagnostic accuracy in men with previously negative biopsy results and positive MR imaging findings. *Radiology* 2013;269:159-166.

4. Costa DN, Bloch BN, Yao DF, Sanda MG, Ngo L, Genega EM et al. Diagnosis of relevant prostate cancer using supplementary cores from magnetic resonance imaging-prompted areas following multiple failed biopsies. *Magn Reson Imaging* 2013;31:947-952.

5. Lee S, Chung M, Kim J, Oh Y, Rha K, Chung B. Magnetic Resonance Imaging targeted biopsy in men with previously negative prostate biopsy results. *Journal of Endourology* 2012; 26(7):787-791

6. Pepe P, Garufi A, Priolo G, Candiano G, Pietropaolo F, Pennisi M et al. Prostate cancer detection at repeat biopsy: can pelvic phased-array multiparametric MRI replace saturation biopsy? *Anticancer Res* 2013;33:1195-1199.

7. Portalez D, Mozer P, Cornud F, Renard-Penna R, Misrai V, Thoulouzan M et al. Validation of the European Society of Urogenital Radiology Scoring System for Prostate Cancer Diagnosis on Multiparametric Magnetic Resonance Imaging in a Cohort of Repeat Biopsy Patients. *European Urology* 2012; 62(6):986-996.

8. Salomon G, Drews N, Autier P, Beckmann A, Heinzer H, Hansen J et al. Incremental detection rate of prostate cancer by real-time elastography targeted biopsies in combination with a conventional 10-core biopsy in 1024 consecutive patients. *BJU Int* 2014;113:548-553.

9. Sonn GA, Chang E, Natarajan S, Margolis DJ, Macairan M, Lieu P et al. Value of Targeted Prostate Biopsy Using Magnetic Resonance-Ultrasound Fusion in Men with Prior Negative Biopsy and Elevated Prostate-specific Antigen. *Eur Urol* 2013.

10. Tang SYW, Lawrence EM, Koo B, Nelson AW, Wadhwa K, Barrett T, et al. Performance of MRI-TRUS fusion in transperineal template prostate re-biopsy. *European Urology Supplements* 2013;12:e142-e143.

11. Vourganti S, Rastinehad A, Yerram N, Nix J, Volkin D, Hoang A et al. Multiparametric Magnetic Resonance Imaging and Ultrasound Fusion Biopsy Detect Prostate Cancer in Patients with Prior Negative Transrectal Ultrasound Biopsies. *The Journal of Urology* 2012; 188(6):2152-2157.

12. Yerram N, Volkin D, Nix J, Vourganti S, Hoang A, Ahmed F et al. Multiparametric magnetic resonance imaging and ultrasound fusion biopsy detects prostate cancer in patients with prior negative TRUS biopsies. *The Journal of Urology* 2012;187:e828.

3. APPENDICES

Appendix A: Search strategies used

For Medline database:

#	Searches
1	exp prostatic neoplasms/
2	exp prostatic intraepithelial neoplasia/
3	PIN.tw.
4	(prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.
5	1 or 2 or 3 or 4
6	((transrectal or trans-rectal) adj ultraso$).tw.
7	((transrectal or trans-rectal) adj3 biops$).tw.
8	(TRUS or TRUSB).tw.
9	6 or 7 or 8
10	negative.tw.
11	false negative reactions/
12	10 or 11
13	9 and 12
14	5 and 13
15	((repeat$ or review$) adj3 biops$).tw.
16	rebiops$.tw.
17	((saturat$ or extend$ or template) adj3 biops$).tw.
18	exp biopsy/ or biops$.tw.
19	elasticity imaging techniques/
20	(elastograph$ or elastogram$).tw.
21	sonoelastogra$.tw.
22	(vibroacoustogram$ or vibro-acoustogra$).tw.
23	(elasticity adj2 imag$).tw.
24	(arfi adj imag$).tw.
25	(acoustic adj2 imag$).tw.
26	*Imaging, Three Dimensional/
27	(3DUS or 3D-US or 3d ultraso$).tw.
28	((tridimension$ or three dimension$) adj (imag$ or ultraso$)).tw.
29	(contrast enhance$ adj2 (imag$ or ultraso$)).tw.

30	(CETRUS or CE-TRUS).tw.
31	(DCE adj (imag$ or ultraso$ or MR$)).tw.
32	((multi-parametric$ or multiparametric$) adj2 (MR$ or imag$)).tw.
33	(MP-MR$ or MPMR$).tw.
34	T2 weighted MR$.tw.
35	T2W$.tw.
36	(diffusion adj2 (imag$ or MR$)).tw.
37	DWI$.tw.
38	magnetic spectroscop$.tw.
39	MRS*.tw.
40	MR spectroscop$.tw.
41	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42	18 and 41
43	15 or 16 or 17 or 42
44	14 and 43
45	limit 44 to (english language and humans and yr="2012-current")

From NICE. Evidence Review for Update of Clinical Guidelines 58 Prostate cancer: diagnosis and treatment accessed 29/01/14 - . final version accessed 18/11/14 http://www.nice.org.uk/guidance/cg175/evidence/cg175-prostate-cancer-appendix-m2

ATSI search terms used

#	**Searches**
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database:

#	Searches
1	'prostate tumor'/exp
2	'prostatic intraepithelial neoplasia'/exp
3	pin
4	prostat* NEAR/3 (cancer* OR carcinoma* OR adeno* OR malignan* OR tum?r* OR neoplas* OR intraepithelial*)
5	1 OR 2 OR 3 OR 4
6	(transrectal OR 'trans-rectal') NEAR/1 ultraso*
7	(transrectal OR 'trans-rectal') NEAR/3 biops*
8	trus OR trusb
9	6 OR 7 OR 8
10	negative
11	'laboratory diagnosis'/exp
12	10 OR 11
13	9 AND 12
14	5 AND 13
15	(repeat* OR review*) NEAR/3 biops*
16	rebiops*
17	(saturat* OR extend* OR template) NEAR/3 biops*
18	'biopsy'/exp OR biops*
19	'elastography':de
20	elastograph* OR elastogram*
21	sonoelastogra*
22	vibroacoustogram* OR vibro NEXT/1 acoustogra*
23	elasticity NEAR/2 imag*
24	arfi NEAR/1 imag*
25	acoustic NEAR/2 imag*
26	'three dimensional imaging':de
27	3dus OR '3d us' OR 3d NEAR/1 ultraso*
28	(tridimension OR 'three dimension' OR 'three dimensions' OR 'three dimensional') NEAR/1 (imag* OR ultraso*)

29	('contrast enhance' OR 'contrast enhanced' OR 'contrast enhances' OR 'contrast enhancement' OR 'contrast enhancing') NEAR/2 (imag* OR ultraso*)
30	cetrus OR 'ce-trus'
31	dce NEAR/1 (imag* OR ultraso* OR mr*)
32	('multi-parametric$' OR multiparametric*) NEAR/2 (mr* OR imag*)
33	'mp-mr$' OR mpmr*
34	't2 weighted mr$'
35	t2w
36	diffusion NEAR/2 (imag* OR mr*)
37	dwi
38	magnetic NEAR/1 spectroscop*
39	mrs*
40	mr NEAR/1 spectroscop*
41	19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40
42	18 AND 41
43	15 OR 16 OR 17 OR 42
44	14 AND 43
45	[embase]/lim AND [2012-2014]/py AND [english]/lim AND [humans]/lim
46	44 AND 45

Adaptation of Medline search from NICE. Evidence Review for Update of Clinical Guidelines 58 Prostate cancer: diagnosis and treatment accessed 29/01/14 - . final version accessed 18/11/14 http://www.nice.org.uk/guidance/cg175/evidence/cg175-prostate-cancer-appendix-m2

ATSI search terms used

#	**Searches**
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

Appendix B:

Level of Evidence rating criteria – Intervention studies

Level	Study design
I	Meta-analysis or a systematic review of level II studies
II	Randomised controlled trial or a phase III/IV clinical trial
III-1	Pseudo-randomised controlled trial or a meta-analysis/systematic review of level III-1 studies
III-2	Comparative study with concurrent controls: - Phase II clinical trial - Non-randomised, experimental trial9 - Controlled pre test/post test study - Adjusted indirect comparisons - Interrupted time series with a control group - Cohort study - Case-control study or a meta-analysis/systematic review of level III-2 studies
III-3	A comparative study without concurrent controls: - Phase I clinical trial - Historical control study - Two or more single arm study10 - Unadjusted indirect comparisons - Interrupted time series without a parallel control group or a meta-analysis/systematic review of level III-3 studies
IV	Case series with either post-test or pre-test/post-test outcomes or a meta-analysis/systematic review of level IV studies

According to the standards of the National Health and Medical Research Council; Sequential sampling studies were not included in NHMRC evidence hierarchy. This study design was considered supiror to RCT design and thus were considered at least level II evidence;

Relevance of the evidence

Rating	Relevance
1	Evidence of an effect on patient-relevant clinical outcomes including benefits and harms, quality of life and survival.
2	Evidence of an effect on a surrogate outcome* that has been shown to be predictive of patient-relevant outcomes for the same intervention.
3	Evidence of an effect on proven surrogate outcomes but for a different intervention.
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population.
5	Evidence confined to unproven surrogate outcomes.

**'surrogate outcome' refers to reasonable indicators of whether there has been some effect (e.g. blood pressure measurements or levels of serum cholesterol)*

Appendix C: Excluded studies

Study	Reason for Exclusion
Bardgett 2013	Less than 10 cores on repeat biopsy
Bittner 2013	Inappropriate study design (Case series)
Bowen 2013	Inappropriate study design (Case series)
Busetto 2013	Results do not report biopsy methods separately
Cantiani 2013	Inappropriate study design (Cohort study without sequential sampling)
Di Silverio 2012	No relevant outcomes reported
Dönmez 2012	Inappropriate study design (Case series)
Durmus 2013	Less than 10 cores on repeat biopsy
Ekwueme 2013	Inappropriate study design (Case series)
Engelhard 2011	Less than 10 cores on repeat biopsy
Esperto 2012	Inappropriate study design (Cohort study without sequential sampling)
Ganie 2013	Less than 10 cores on repeat biopsy
Gershman 2013	Inappropriate study design (Case series)
Giannini 2013	No relevant outcomes (Targeted MRI biopsy did not report standard biopsy method)
Golabek 2013	Number of cores on repeat biopsy was not reported
Hsi 2012	Inappropriate study design (Case series)
Hu 2012	Patients did not meet inclusion criteria
Javed 2012	Inappropriate study design (Case series)
Junker 2013	Results do not report biopsy methods separately
Kasivisvanathan 2013	No relevant outcomes reported
Klatte 2013	Inappropriate study design (Case series)
Kuru 2013	Inappropriate study design (Cohort study without sequential sampling)
Kuru 2013	Inappropriate study design (Case series)
Li 2013	No relevant outcomes reported (Reports findings from initial biopsy only)
Lombardo 2013	Inappropriate study design (Cohort study without sequential sampling)
Lombardo 2013	Inappropriate study design (Cohort study without sequential sampling)
Lombardo 2013	Inappropriate study design (Cohort study without sequential sampling)
Lombardo 2013	Inappropriate study design (Cohort study without sequential sampling)
Manka 2013	No relevant outcomes reported
Mockel 2012	Less than 10 cores on repeat biopsy

Pandit 2013	Inappropriate study design (Case series)
Parsy 2012	Inappropriate study design (Cohort study without sequential sampling)
Perdona 2013	Results do not report biopsy methods separately.
Porpiglia 2013	No relevant outcomes reported
Quentin 2013	No relevant outcomes reported (Result do not separate between initial and repeat biopsy data)
Saeh-Parsy 2012	Inappropriate study design (Cohort study without sequential sampling)
Schade 2013	Number of cores on repeat biopsy was not reported
Schoth 2013	Less than 10 cores on repeat biopsy
Simpson 2012	No relevant outcomes reported (Result do not separate between initial and repeat biopsy data)
Sturch 2013	No relevant outcomes reported
Thompson 2012	Inappropriate study design (Review article)
Ubee 2013	Number of cores on repeat biopsy was not reported
Wadhwa 2012	Number of cores on repeat biopsy was not reported
Yates 2013	No relevant outcomes reported (Result do not separate between initial and repeat biopsy data)
Young 2013	Inappropriate study design (Targeted MRI biopsy did not report standard biopsy method)

References: Excluded Studies

1. Bardgett H, Addla S, Dabbagh V. Can prostatic MRI be used to target transrectal ultrasound guided prostate biopsy-initial experience form a UK cancer centre. *Journal of Medical Imaging and Radiation Oncology* 2013; 57:13, Abstract 16.

2. Bittner N, Merrick GS, Butler WM, Bennett A, Galbreath RW: Incidence and pathological features of prostate cancer detected on transperineal template guided mapping biopsy after negative transrectal ultrasound guided biopsy. *Journal of Urology* 2013; 190:509-514.

3. Bowen M, Murtagh K, Mellon JK, Khan MA. The emerging role of transperineal template prostate biopsy in patients with a persistently raised PSA despite one negative TRUS-guided prostate biopsy. *International Journal of Surgery* 2013; 11:727.

4. Busetto GM, De BE, Sciarra A, Panebianco V, Giovannone R, Rosato S et al. Prostate cancer gene 3 and multiparametric magnetic resonance can reduce unnecessary biopsies: decision curve analysis to evaluate predictive models. *Urology* 2013; 82:1355-1360.

5. Cantiani A, Kuru TH, Lombardo R, Wadhwa K, Saeb-Parsy K, Nelson A et al. Repeat prostate biopsy after initial benign standard biopsies - comparison of 3 advanced techniques; MRI/TRUS fusion transperineal, transperineal sector, extensive transrectal prostate biopsies (MD Anderson protocol). *Journal of Urology* 2013; 189:e511.

6. Di SF, Salciccia S, Busetto GM, Panebianco V, Lisi D, Alfarone A et al. Is prostate biopsy still necessary? *European Urology Supplements* 2012; 11:e261-e261a.

7. Dönmez MI, Yazici MS, Akdoğan B, Bozac AC, Lűleci H, Őzen H. Transrectal ultrasound guided saturation biopsy of the prostate using stereotactic transperineal technique. *European Urology Supplements* 2012; 11:141, Abstract S37.

8. Durmus T, Reichelt U, Huppertz A, Beyersdorff D, Franiel T. MRI-guided biopsy of the prostate: Correlation between the cancer detection rate and the number of previous negative TRUS biopsies. *Diagnostic and Interventional Radiology* 2013; 19:411-417.

9. Ekwueme K, Simpson H, Zakhour H, Parr NJ. Transperineal template-guided saturation biopsy using a modified technique: outcome of 270 cases requiring repeat prostate biopsy. *BJU International* 2013; 111:E365-E373.

10. Engelhard K, Hollenbach HP, Winker A, Engehausen D. Patho-histological correlation of MRI findings with results of biopsy and prostatectomy at MRI-guided prostate biopsy. *European Society of Radiology* 2011.

11. Esperto F, Saeb-Parsy K, Moss B, Tang S, Mikhai M, Omar I et al. Comparison of cancer detection rates between transperineal template versus MD Anderson protocol transrectal prostate biopsies. *Anticancer Research* 2012; 32:1888.

12. Ganie F, Wani M, Shaheen F, Wani ML, Ganie S, Mir MF et al. Endorectal coil MRI and MR-spectroscopic imaging in patients with elevated serum prostate specific antigen with negative TRUS transrectal ultrasound guided biopsy. *Urology Annals* 2013; 5:172-178.

13. Gershman B, Zietman AL, Feldman AS, McDougal WS. Transperineal template-guided prostate biopsy for patients with persistently elevated PSA and multiple prior negative biopsies. *Urologic Oncology* 2013; 31:1093-1097.

14. Giannini V, Mazzetti S, Vignati A, Bracco C, Stasi M, Russo F et al. Multiparametric CAD system for MR prostate cancer detection. *Anticancer Research* 2013; 33:2334, Abstract #127.

15. Golabek T, Lipczynski W, Czech A, Kusionowicz J, Zembrzuski M, Dudek P et al. C89 Value of MRI-ultrasound fusion for guidance of targeted prostate biopsy. *European Urology Supplements* 2013; 12:e1197, abstract C89.

16. Hsi RA, Moeller RJ, Mitchell M, Bildsten S, Kozlowski P, Porter CR. Clinical outcomes after transperineal template-guided prostate biopsy. *Journal of Clinical Oncology* 2012; 30(5 Suppl.) Abstract 156.

17. Hu Y, Ahmed HU, Carter T, Arumainayagam N, Lecornet E, Barzell W et al. A biopsy simulation study to assess the accuracy of several transrectal ultrasonography (TRUS)-biopsy strategies compared with template prostate mapping biopsies in patients who have undergone radical prostatectomy. *BJU International* 2012; 110:812-820.

18. Javed S, John B, Chadwick E, Montgomery B, Bott S, Langley S. Should transperineal template guided prostate biopsies be used as gold standard for diagnosis of prostate cancer? *European Urology Supplements* 2012; 11:e819-e819a.

19. Junker D, Schafer G, Edlinger M, Kremser C, Bektic J, Horninger W, et al. Evaluation of the PI-RADS scoring system for classifying mpMRI findings in men with suspicion of prostate cancer. *BioMed Research International* 2013; 252939 (published online).

20. Kasivisvanathan V, Moore CM, Eggener S, Emberton M, Futterer J, Gill I, et al. Standards in reporting of MRI-targeted prostate biopsies (START): Recommendations from an international working party. *European Urology Supplements* 2013; 12:e138-e139.

21. Klatte T, Swietek N, Schatzl G, Waldert M: Transperineal template-guided biopsy for diagnosis of prostate cancer in patients with at least two prior negative biopsies. *Wiener Klinische Wochenschrift* 2013; 125:669-673.

22. Kuru T, Roethke M, Seidenader J, Simpfendorfer T, Boxler S, Popeneciu V et al. Critical Evaluation of MRI-Targeted TRUS-Guided Transperineal Fusion Biopsy for Detection of Prostate Cancer. *Urology* 2013; 82:(3 Supplement 1), S25.

23. Kuru T, Roethke M, Simpfendoerfer T, Boxler S, Seidenader J, Schlemmer H et al. Detecting clinically significant prostate cancer by MRI-targeted TRUS-guided transperineal fusion biopsy. European Urology Supplements 2013; 12:e222.

24. Li Y, Elshafei A, Hatem A, Fareed K, Gong M, Jones JS. Potential value of transrectal saturation biopsy as an initial biopsy strategy: decreased likelihood of finding cancer on repeat biopsy. *Journal of Urology* 2013; 189:e905-e906.

25. Lombardo R, Cantiani A, Esperto F, Kastner C. MRI/TRUS Fusion Against MD Anderson Protocol Against Transperineal Sector Prostate Biopsies: A Comparative Study. *Anticancer research 33*: 2245-2342 (2013).

26. Lombardo RL, Cantiani AC, Kuru THK, Saeb-Parsy KSB, Nelson AN, Koo BK et al. Repeat prostate biopsy after initial benign standard biopsies - comparison of 3 advanced techniques; MRI/TRUS fusion transperineal, transperineal sector, extensive transrectal prostate biopsies (MD Anderson protocol). *BJU International* 2013; 111(Supplement 3):9-16, Abstract #A3.

27. Lombardo R, Andrea A, Cantiani A, Kastner C. MRI transperineal prostate biopsies- are there any benefits in MRI/TRUS fusion targeting over cognitive detection? *Anticancer Research* 2013, 33:2286, Abstract #61.

28. Lombardo R, Cantiani A, Esperto F, Kastner C. MRI TRUS/fusion biopsies: is MRI accurate in predicting high grade prostate cancer? *Anticancer Research* 2013; 33:2283, Abstract #56.

29. Manka L, Grindei M, Steinwender T, Dellmann A, Slojewski M, Kwiatkowski M, Hammerer P, Prado L. Prospective Evaluation of Real Time Tissue Imaging by Elastography in Patients with Previous Negative Biopsy and Rising PSA. *Urology* 2013; 82(3 Suppl. 1) S68.

30. Mockel C, Porcellini B, Haldemann R, Koch E, Hailemariam S, Fehr JL. Experiences with the MRI-guided biopsy of the prostate gland as second biopsy (rebiopsy). *European Urology Supplements* 2012; 11:e796-e796a.

31. Pandit A, Thomas H, O'Brien C, Featherstone J, Fenn N, Bose P. Repeat transrectal prostate biopsies incorporating targeted anterior zone sampling - is template biopsy really necessary? *European Urology Supplements* 2013; 12:e3.

32. Parsy K, Wadhwa K, Moss B, Esperto F, Tang S, Omar I et al. Comparison of cancer detection rates between transperineal template versus md anderson protocol transrectal prostate biopsies in initial biopsy negative men. *Journal of Endourology* 2012; 26:A42.

33. Perdona S, Di LG, Autorino R, Buonerba C, De SM, Setola SV et al. Combined magnetic resonance spectroscopy and dynamic contrast-enhanced imaging for prostate cancer detection. *Urologic Oncology* 2013; 31:761-765.

34. Porpiglia F, Fiori C, Manfredi M, Mele F, Bertolo R, Grande S et al. Repeated prostate biopsy: Evaluation of a new diagnostic pathway using mp-MRI, PCA3 and pro-PSA in the selection of patients. *European Urology Supplements* 2013; 12:e710-e711.

35. Quentin M, Schimm+Âller L, Arsov C, Rabenalt R, Antoch G, Albers P et al. 3-T in-bore MR-guided prostate biopsy based on a scoring system for target lesions characterization. *Acta Radiologica* 2013; 54:1224-1229.

36. Saeb-Parsy K, Moss B, Mikhail M, Papoutsoglou N, Doble A, Kastner C. Diagnostic accuracy of zonal transperineal template or MD Anderson prostate biopsies as second stage approach - more certainty for patients. *European Urology Supplements* 2012; 11:e814-e814a.

37. Schade GR, Kunju LP, Wei JT, Weizer AZ, Montgomery JS, Miller DC et al. Transperineal mapping template prostate biopsy after previous transrectal ultrasound prostate biopsy detects worse disease burden. *The Journal of Urology* 2013; 189:e908.

38. Schoth F, Weibrecht M, Bruhn R, Apitzsch JC, Kuhl C. MR-guided prostate biopsies following several negative TRUS-guided biopsies. *Cardiovascular and Interventional Radiology* 2013; 36:S261.

39. Simpson HM, Ekwuame K, Hughes D, Parr NJ, Zakhour H. Pre-biopsy MRI can accurately determine prostate cancer location when compared to saturation biopsy results, allowing focused biopsy regimes. *European Urology Supplements* 2012; 11:e885-e885a.

40. Sturch P, Morris E, Tsui M, Kinsella J, Chandra A, Cahill D et al. Transperineal Sector Prostate Biopsies: The Outcome of Negative Biopsies. *Urology* 2013; 82(3 Supplement 1);S70, Abstract MP-05.13.

41. Thompson J, Lawrentschuk N, Frydenberg M, Thompson L, Stricker P, USANZ: The role of magnetic resonance imaging in the diagnosis and management of prostate cancer. *BJU International* 2013; 112:6-20.

42. Ubee S, Hann L, Patel R, Jaganathan R. Operator bias and cancer pickup rate with diffusion weighted MRI guided prostate biopsy. *BJU International* 2013; 111(Supplement S1):101, Abstract #177.

43. Wadhwa K, Tang S, Richard A, Saeb-Parsy K, Warren A, Lawrence E et al. Does MRI-TRUS fusion guided planning improve outcomes of transperineal prostate biopsies? - An early experience. *Endourology* 2012; 26:A41, Abstract MP03-10.

44. Yates DR, Gregory GC, Roupret M, Malki MM, Haynes MD, Hamdy FC et al. Transurethral resection biopsy as part of a saturation biopsy protocol: a cohort study and review of the literature. *Urologic Oncology* 2013; 31:542-548.

45. Young M, Levey R, Rosoff J, Smith J, Ghareeb G, Lane B et al. Is MRI with diffusion weighted imaging effective in detecting prostate cancer in men with previous negative biopsies? *Journal of Urology* 2013; 189:e903-e904.

Systematic review report for question 9 (Intervention studies)

Clinical question 9: *"What should be the criteria for choosing active surveillance in preference to definitive treatment to offer as primary management to men who have a positive prostate biopsy?"*

PICO Question 9: *"For men with biopsy-diagnosed prostate cancer, for which patients (based on diagnostic, clinical and other criteria) does active surveillance achieve equivalent or better outcomes in terms of length and quality of life than definitive treatment?"*

Population	Intervention	Comparator	Outcomes
Men with biopsy (histologically) confirmed prostate cancer	Active surveillance	Immediate definitive treatment	- Overall mortality, or - Prostate cancer-specific mortality, or - Quality of life, or - Adverse events

1. METHODS

1.1 Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption guidelines had to be evidence based and meet the pre-specified criteria of scores of greater or equal to 70% for the domains; Rigour of Development, Clarity of Presentation, and Editorial Independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

1.2 Literature Search

Medline (01/01/1990 - 01/03/2014), Embase (01/01/1990 - 01/03/2014), Cochrane Database of Systematic Reviews (01/01/2005 - 01/03/2014), Database of Abstracts of Reviews of Effects and Health Technology Assessment databases up until 01/03/2014 were searched using text terms and, where available, database specific subject headings. Each database was searched for articles dealing with prostate cancer. In Medline and Embase databases the prostate cancer search was coupled with a search for active surveillance (AS), and database specific filters for identifying randomised controlled trials (RCTs); or systematic reviews (SR) and meta-analyses of case-control or cohort studies; or immediate verses deferred curative treatment studies. To identify studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 which were added to the relevant database after February 2014. Alerts were checked until July 2014. A complete list of the terms used for all search strategies are included as Appendix A. Reference lists of all relevant articles were checked for potential additional articles.

1.3 Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	Nomograms (or predictive model) that have not been validated in a separate cohort
Study design	Randomised, or pseudo-randomised controlled trial, or cohort study, or nested case-control study, or meta-analysis/systematic review thereof	
Population	Men with histologically confirmed prostate cancer	Studies that restricted participants based on biomarker status
Intervention	Active surveillance	
Comparator	Immediate definitive treatment	
Outcomes	Overall mortality, or Prostate cancer-specific mortality, or Quality of life, or Adverse events	
Language	English	
Publication period	After 31st December 1989 and before1st March 2014	

Conference proceedings identified by the search literature searches were included if they met the inclusion criteria.

1.5 Definitions

Active Surveillance

AS entails close follow-up of patients diagnosed with early stage, low-risk prostate cancer. The objective is to avoid unnecessary treatment of men with indolent cancer, and only treat patients who show signs of disease progression. Monitoring of these patients usually involves prostate specific antigen (PSA) testing, digital rectal examination (DRE), transperineal prostate biopsies, and multi parametric prostate magnetic resonance imaging (MRI). Therapy is recommended at a time when cure is deemed possible and when disease progression is detected. Active surveillance aims to avoid unnecessary treatment in order to avoid untoward quality of life or side effects that may occur as a result. AS may be also called 'active monitoring'.

2. RESULTS

2.1 Guidelines

Seventeen potentially relevant guidelines were identified. Three sets of guidelines (AHRQ, KCE, and NCCN) contained recommendations regarding active surveillance however they were not included as they failed to meet our pre-specified criteria for inclusion score of ≥70% for each of the 3 domains assessed (Rigour of Development, Clarity of Presentation, and Editorial Independence) in the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/). An additional relevant guideline was also found. This guideline was titled the National Institute for Health and Care Excellence's (NICE) Clinical Guideline for Prostate Cancer: Diagnosis and Treatment (UK National Collaborating Centre for Cancer 2014a[1]). This NICE

guideline addressed the clinical question: *Which men with localised prostate cancer should be offered active surveillance?* This NICE guideline used a different approach and assessed prognostic factors for men undergoing active surveillance rather than comparing the effects of different interventions in different groups of men. This guideline (and our literature update) is described in a separate report. The remaining guidelines were not based on systematic reviews .

2.2 Results of Literature Search

Figure 1 outlines the process of identifying relevant articles from the systematic review. In total, four individual search strategies were undertaken for Medline and Embase databases. The first search attempted to identify randomised controlled trials that met the inclusion criteria. The second search attempted to identify systematic reviews or meta-analyses of case-control and cohort studies that met the inclusion criteria. The third search attempted to identify case-control and cohort studies that met the inclusion criteria. As all these three searched outlined above failed to identify literature that met the inclusion criteria, a fourth search was performed to identify case-control studies of immediate verse deferred curative treatment.

The Medline search identified 1,426 citations (Search #1=190, Search #2=206, Search #3=707, and Search #4=323), the Embase search 1,695 citations (Search #1=94, Search #2=25, Search #3=668, and Search #4=908), and the search of the Cochrane Database of Systematic Reviews 59 citations, the Database of Abstracts of Reviews of Effects search 282 citations and the search of the Health Technology Assessment database identified an additional 216 citations, resulting in a total of 3,678 citations. Titles and abstracts were examined and 87 articles were retrieved for a more detailed evaluation. One (1) additional potential citation was identified from the reference list of retrieved articles.

Three (3) studies reported in 3 articles met the inclusion criteria and were included in the review. There were no studies of ATSI men that met the inclusion criteria. The retrieved articles that were not included and the reason for their exclusion are documented in Appendix C. In summary, most articles were excluded because they used inappropriate study designs (e.g. many Klotz *et al.* studies) or did not report relevant outcomes.

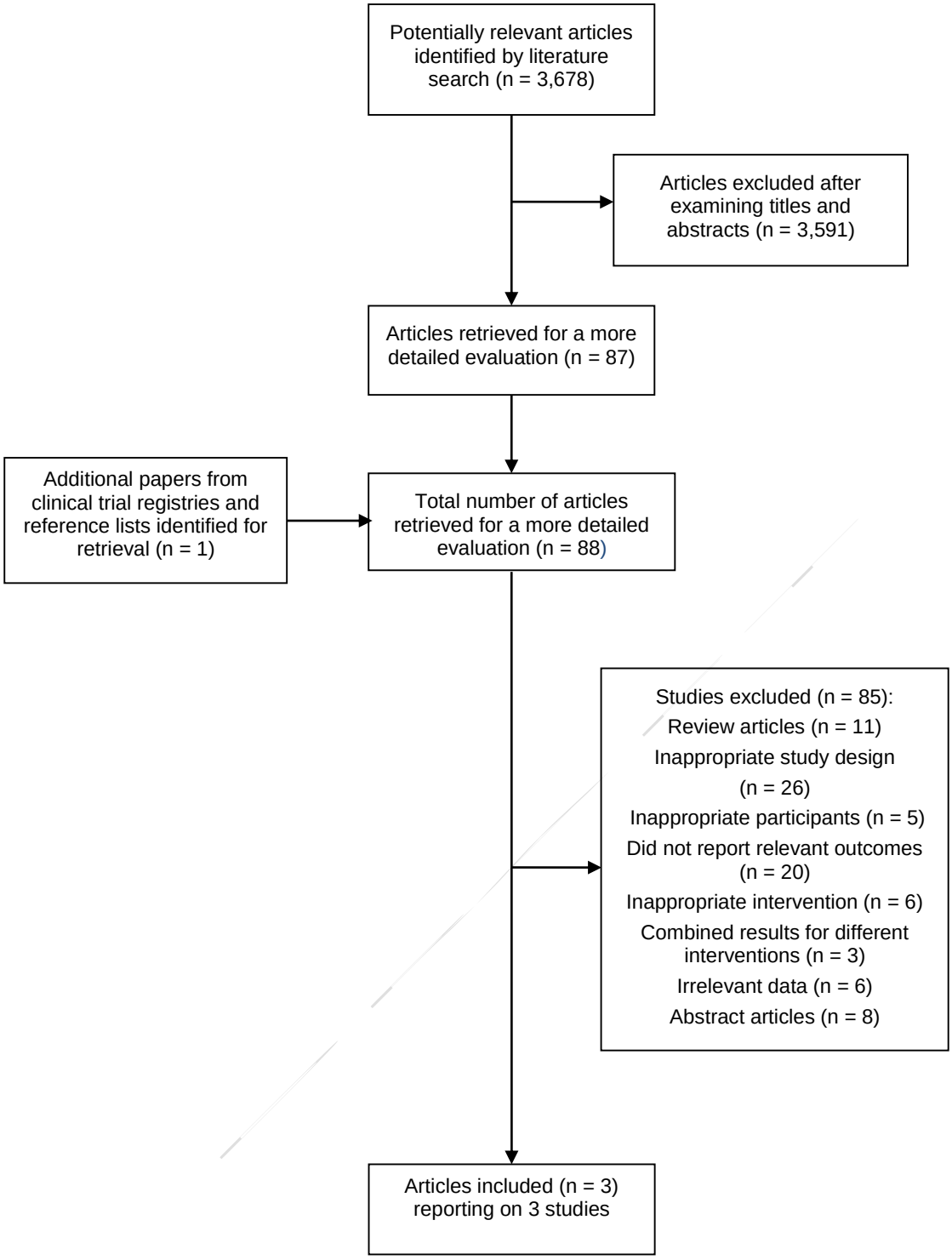


Figure 1. Process of inclusion and exclusion of studies

2.3 Study Characteristics

Table 1: Characteristics of intervention studies examining active surveillance and immediate treatment or delayed and immediate radical prostatectomy for improving outcomes in prostate cancer patients

Study	Participants	Design	Intervention	Immediate Treatment	Outcomes	Comments
Active Surveillance vs. Immediate Treatment (RP/EBRT/ADT)						
Kakehi 2008 (Japan)	Men aged 50-80 years with an initial PSA level ≤20 ng/mL, offered active surveillance with T1cN0M0 cancer (UICC TNM 4th edition, 1987), 1 or 2 positive cores per 6-12 systematic biopsy cores, Gleason score ≤6 and ≤50% cancer involvement in any of the positive biopsy cores (confirmed by central pathologist) recruited from 7 Cancer Centre hospitals and 6 University hospitals between January 2002 and December 2003 **Exclusion criteria:** Past history of cerebral infarction, unstable angina, diabetes uncontrollable with insulin, severe hypertension, myocardial infarction within 6 months **Age (years):** ≤59: 3.7% 60-69: 42.5% 70-74: 38.1% 75≥: 15.7% **PSA (ng/mL):** Mean: 7.3 <10: 80.6% ≥10: 19.4% **Gleason score:** 5: 11.2% 6: 88.8% **N = 134**	Cohort study multi-centre (prospective)	**Active Surveillance** (accepted active surveillance) <u>Monitoring protocol:</u> PSA monitored every 2 months for 6 months then every 3 months thereafter; re-measurements of unnatural increases of PSA allowed within 3 months; Local progression examined with DRE and TRUS at least twice per year and because of rising PSA; Chest X-ray, CT scan or MRI for abdominal/pelvic cavity and bone scintigraphy performed at least once every 2 years to rule out metastases; <u>Triggers for intervention:</u> Aggressive treatment recommended if PSADT ≤2 years after 6 months, thereafter treatment recommended if PSADT ≤2 years within 1 year; Re-biopsy recommended after 1 year on AS; men who did not fit initial selection criteria recommended to start treatment **N = 118**	**Immediate Treatment** (rejected active surveillance) **Radical Prostatectomy** (81.3%) **External Beam Radiotherapy** (12.5%) **Androgen Deprivation Therapy** (6.3%) **N = 16**	**Primary:** *None relevant* **Secondary:** *Adverse events* (no relevant data reported) *Health- and Disease-related quality of life* (assessed at baseline and 1 year later. No relevant data reported) *Overall mortality* *Prostate-cancer specific mortality* Follow-up until 31st October 2006 (2.8-4.8 years)	All patients encouraged to start AS for at least 6 months; patients who declined immediately started treatment; Study designed to evaluate the validity of selection criteria for AS. Point estimate of primary endpoint (% of patients on AS showing PSADT >2 years at initial 6-month assessment) expected to be >80% for validation; Planned sample size of 100 patients opting for AS based on the precision of estimate to give the width of 95% confidence intervals for the primary endpoint within 10%;

Delayed Radical Prostatectomy vs. Immediate Radical Prostatectomy						
Holmström 2010 (Sweden)	Men aged 41-70 years with PSA level <20 ng/mL and Gleason score ≤6 who had been diagnosed with clinical stage T1-2 N0/X M0/X prostate cancer **Mean age (years):** Deferred RP: 61.9 Immediate RP: 61.1 **PSA (ng/mL):** Deferred RP: 6.7 (mean) Immediate RP: 7.8 (mean) 0-4: 11.9% 4-10: 63.6% 10-20: 24.6% **Tumour stage:** T1a: 1.8% T1b: 1.2% T1c: 59.6% T2: 37.3% **Gleason score:** 2-4: 11.0% 5: 22.6%; 6: 66.6% N = 7,492 (entire cohort) **N = 2,566** (eligible men who underwent RP)	Cohort study (retro-spective)	**Deferred Radical Prostatectomy** Median 19.2 months after diagnosis <u>Triggers for intervention:</u> Initiated by PSA progression in 50%, by other signs of progression in 9%, by other causes in 39%; **N = 222**	**Immediate Radical Prostatectomy** Median 3.5 months after date of diagnosis **N = 2,344**	**Primary:** *All-cause mortality* *Prostate cancer-specific mortality* (prostate cancer coded as "underlying cause of death") Data on observations made ≥6 months after diagnosis gathered from the Swedish Cancer Register (capture rate ≥96.3% for all tumors), the Swedish Cause of Death Register and the National Prostate Cancer Register of Sweden up to 31st December 2008 Death certificates reviewed for men who died between 1st January 2008 and 31st December 2008 to determine cause of death; Median follow up = 8.2 years	Treatment decisions made in routine clinical practice **- no pre-defined criteria for selection of treatment, no protocol for surveillance and no pre-set trigger for initiation of deferred treatment**; Cohort included men who underwent primary or deferred radiotherapy, primary or deferred hormone therapy or continued surveillance until end of follow-up (watchful waiting or active surveillance); **No patient characteristics or outcome data reported**;

Sun 2012 (Canada)	Men aged ≥66 years on SEER-Medicare insurance program-linked database as diagnosed with prostate cancer between 1995 – 2005 as their first malignant disease, who had undergone RP, had clinical stage T1-2N0M0 disease and Gleason score <7. **Median age**: 68 years **Race: 7.4% African American** **Gleason score:** 2-4: 3.9% 5-6: 96.1% **Charlson index:** 0: 56.5% 1: 27.1% 2: 10.1% ≥3: 6.4% **N = 17,153**	Cohort Study (retro-spective)	**Delayed Radical Prostatectomy** Radical prostatectomy performed >3 months after diagnosis. Median time to treatment 5.0 months (mean 11.5 months) **Reasons for delay not described** 24.5% received ADT **N = 2,576**	**Immediate Radical Prostatectomy** Radical prostatectomy performed ≤3 months after diagnosis Median time to treatment 2.0 months (mean 1.6 months) 10.4% received ADT **N = 14,577**	**Primary:** *Urinary incontinence (ICD codes for diagnosis or treatment)* *Erectile dysfunction (ICD codes for diagnosis or treatment)* *Prostate cancer-specific mortality (ICD-9 185.9 or ICD-10 C619).* Follow up 2-12 years	Active surveillance may be one of a number of reasons for delayed radical prostatectomy SEER- Medicare insurance program-linked database does not contain details on reasons for delay

ADT = androgen deprivation therapy; AS = active surveillance; DRE = digital rectal examination; EBRT = external beam radiotherapy; ICD-9 = International Classification of Diseases Ninth revision; ICD-10 = International Classification of Diseases Tenth revision; MRI = magnetic resonance imaging; PSA = prostate specific antigen; PSADT = prostate specific antigen doubling time; RP = radical prostatectomy; SEER = Surveillance, Epidemiology, and End Results*; TRUS = transrectal ultrasound-guided; UICC = Union for International Cancer Control*

.

2.4 Study Quality

Methodological quality of included cohort studies is described in Table 2.

Table 2: Methodological quality of included cohort studies (n = 3)

Quality Category	N (%)
IA. Subject Selection – 'New technology' group	
2 = Representative of eligible patients	1 (33.3)
1 = Selected group	1 (33.3)
0 = Highly selected or not described	1 (33.3)
IB. Subject Selection – Comparison group	
2 = Representative of eligible patients	1 (33.3)
1 = Selected group	1 (33.3)
0 = Highly selected or not described	1 (33.3)
II. Comparability of groups on demographic characteristics	
2 = Comparable	-
1 = Not comparable but adjusted analysis used	1 (33.3)
0 = Not comparable and not adjusted for differences	2 (66.7)
IIIA. Were outcomes measures blinded to intervention used?	
2 = Yes	1 (33.3)
1 = No, but objective measure used	1 (33.3)
0 = No or not described	1 (33.3)
IIIB. Were the same method of measurement used across comparison groups?	
2 = Yes	2 (66.7)
0 = No or not described	1 (33.3)
IV. Completeness of follow-up	
2 = Yes (>95% or intention-to-treat analysis)	2 (66.7)
1 = Reasonable follow-up of all groups (>80%)	-
0 = No or not described	1 (33.3)

This assessment tool is based on the Newcastle-Ottowa Scale (Wells GA et al., Quality Assessment Scales for Observational Studies. Ottowa Health Research Institute 2004).

Table 3: Methodological quality of included cohort studies (n = 3)

	Subject selection (New tech)	Subject selection (Comp group)	Groups demo	Measurement of outcome (blinded)#	Measurement of outcome (Same method)#	Follow up	Overall rating	Risk of bias
Holmström 2010	0	0	1	1	2	2	Low	High
Kakehi 2008	1	1	0	0	0	0	Low	High
Sun 2012	2	2	0	0	2	2	Low	High

- primary outcomes assessed, tech = technology, comp = comparison, demo = demographics.

Key to overall quality rating
High quality: a review that received 2 for all quality criteria.
Medium quality: Received 2 and 1 for all quality criteria.
Low quality: Received 0 for all quality criteria or 1 and 0 all quality criteria or received 0 for any of the quality criteria

2.5 Study Results

Effect of intervention on relevant outcomes are described in Tables 4-8

I Overall Mortality/All-cause Mortality

Table 4: Results of studies comparing effects of active surveillance with immediate treatment on overall mortality

Study	Outcome Definition	Measure	N actual	Active Surveillance	Immediate Treatment	Size of effect	Size of effect CI	p value	Follow up
Active Surveillance vs. Immediate Treatment									
Kakehi 2008	**Overall mortality**	% (n)	134	1.7 (2) N = 118	6.3 (1) N = 16	NR	NR	NR	4.5 years

CI = confidence interval; NR = not reported

Table 5: Results of studies comparing effects of delayed radical prostatectomy with immediate radical prostatectomy on all-cause mortality

Study	Outcome Definition	Measure	N actual	Delayed Radical Prostatectomy	Immediate Radical Prostatectomy	Size of effect	Size of effect CI	p value	Follow up
Delayed Radical Prostatectomy vs. Immediate Radical Prostatectomy									
Holmström 2010	**All-cause mortality** *cumulative incidence*	% (n)	2,566	6.3* (14) N = 222	6.9* (161) N = 2,344	ARD = -0.6%*	NR	>0.05[a]	8.2 years median

ARD = absolute risk difference, negative values indicate a benefit of delayed radical prostatectomy over immediate radical prostatectomy; CI = confidence interval; NR = not reported;

** calculated by reviewers*

a = competing risk analysis (observation time - from date of diagnosis, time at risk - from date of radical prostatectomy)

II Prostate Cancer-Specific Mortality

Table 6: Results of studies comparing effects of active surveillance with immediate treatment on prostate cancer-specific mortality

Study	Outcome Definition	Measure	N actual	Active Surveillance	Immediate Treatment	Size of effect	Size of effect CI	p value	Follow up
Active Surveillance vs. Immediate Treatment									
Kakehi 2008	**Prostate cancer-specific mortality**	% (n)	134	0 (0) N = 118	0 (0) N = 16	NR	NR	NR	2.8-4.8 years

CI = confidence interval; NR = not reported

Table 7: Results of studies comparing effects of delayed radical prostatectomy with immediate radical prostatectomy on prostate cancer-specific mortality

Study	Outcome Definition	Measure	N actual	Delayed Radical Prostatectomy	Immediate Radical Prostatectomy	Size of effect	Size of effect CI	p value	Follow up
Delayed Radical Prostatectomy vs. Immediate Radical Prostatectomy									
Holmström 2010	**Prostate cancer-specific mortality**	% (n)	2,566	0.9* (2) N = 222	0.7 (16) N = 2,344	ARD = 0.2%*	NR	>0.05[a]	8.2 years median
Sun 2012	**Prostate cancer-specific mortality** *Cumulative incidence 10-year rate*	% (n)	17,153	13.1 (337*) N = 2,576	13.7 (1,997*) N = 14,577	NR	NR	0.70	2-12 years

ARD = absolute risk difference, negative values indicate a benefit of delayed radical prostatectomy over immediate radical prostatectomy; CI = confidence interval; NR = not reported;

** calculated by reviewers*

a = competing risk analysis (observation time - from date of diagnosis, time at risk - from date of radical prostatectomy)

III Quality of Life

Table 8: Results of studies comparing effects of delayed radical prostatectomy with immediate radical prostatectomy on quality of life

Study	Outcome Definition	Measure	N actual	Delayed Radical Prostatectomy	Immediate Radical Prostatectomy	Size of effect (OR)	Size of effect (CI)	p value	Follow up
Delayed Radical Prostatectomy vs. Immediate Radical Prostatectomy									
Sun 2012	**Incontinence**[a]								
	(≥18 months after surgery)								
	Treatment (ICD-9 codes)		17,153	NR	NR	1.16	1.01 – 1.18	<0.05	2-12 years
	Diagnosis (ICD-9 codes)		17,153	NR	NR	1.01	0.92 – 1.11	NS	
	Erectile Dysfunction[a]								
	(≥18 months after surgery)								
	Treatment (ICD-9 codes)		17,153	NR	NR	1.33	1.13 – 1.57	<0.05	2-12 years
	Diagnosis (ICD-9 codes)		17,153	NR	NR	1.24	1.13 – 1.35	<0.001	

CI = confidence interval; ICD = International Classification of Diseases, Ninth revision; NR = not recorded; NS = not significantly different; OR = odds ratio.

a = Adjusted for age, race, comorbidity, Gleason sum, postoperative radiation, androgen deprivation therapy, baseline urinary incontinence, baseline erectile dysfunction, socioeconomic status, marital status, registries, population density, year of surgery, and pathological stage.

2.6 Body of Evidence

Effects of interventions on relevant outcomes are described in Tables 9-13.

I Overall Mortality/All-cause Mortality

Table 9: Body of evidence examining the effects of active surveillance with immediate treatment on overall mortality

Name of study	Study type	N	Level of evidence *	Quality of evidence**	Risk of bias	Results summary	Size of Effect	p value	95% CI	Relevance of evidence
Active Surveillance vs. Immediate Treatment										
Kakehi 2008 **Participants:** **Age (years)** ≤69:46.2% ≥70:53.8% **Mean PSA** 7.3 ng/mL **Gleason score** 5: 11.2% 6: 88.8% Follow up 2.8 - 4.8 years	Prospective Cohort (multi-centre)	134 (IT = 16)	III-2	Low	High	**Overall mortality (%):** AS: 1.7 (N = 2) IT: 6.3 (N = 1)	ARD=-4.6%	NR	NR	1

ARD = absolute risk difference, negative values indicate a benefit of active surveillance over immediate treatment; AS = active surveillance; CI = confidence interval; IT = immediate treatment; NR = not reported; PSA = prostate specific antigen.

** Refer to Appendix B for detailed explanations of rating scores; ** See table 2 for quality appraisals*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the evidence statement table of content template.

Table 10: Body of evidence examining the effects of delayed radical prostatectomy with immediate radical prostatectomy on all-cause mortality

Name of study	Study type	N	Level of evidence *	Quality of evidence**	Risk of bias	Results summary	Size of Effect	p value	95% CI	Relevance of evidence
Delayed Radical Prostatectomy vs. Immediate Radical Prostatectomy										
Holmström 2010 **Participants:** **Mean age (years):** dRP: 61.9 iRP: 61.1 **Mean PSA (ng/mL)** dRP: 6.7 iRP: 7.8 **Gleason score** ≤5: 33.4% 6: 66.6% **Tumour stage** T1: 62.6% T2: 37.3% Follow up 8.2 years median	Retrospective Cohort	2,566	III-2	Low	High	**All-cause mortality (%):** dRP: 6.3 iRP: 6.9	ARD= -0.6%	NS	NR	1

ARD = absolute risk difference, negative values indicate a benefit of delayed radical prostatectomy over immediate radical prostatectomy; CI = confidence interval; dRP = delayed radical prostatectomy; iRP = immediate radical prostatectomy; NR= not reported; NS = not significantly different; PSA = prostate specific antigen

** Refer to Appendix B for detailed explanations of rating scores; ** See table 2 for quality appraisals*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the evidence statement table of content template.

II Prostate Cancer-Specific Mortality

Table 11: Body of evidence examining the effects of active surveillance with immediate treatment on prostate cancer-specific mortality

Name of study	Study type	N	Level of evidence *	Quality of evidence**	Risk of bias	Results summary	Size of effect	p value	95% CI	Relevance of evidence
Active Surveillance vs. Definitive Treatment										
Kakehi 2008 **Participants:** **Age (years):** ≤69: 46.2% ≥70: 53.8% **Mean PSA:** 7.3 ng/mL **Gleason score** 5: 11.2% 6: 88.8% Follow up 2.8 - 4.8 years	Prospective Cohort (multi-centre)	134 (DT:16)	III-2	Low	High	**Prostate cancer-specific mortality (%):** AS:0 IT:0	ARD=0	NR	NR	1

ARD = absolute risk difference; AS = active surveillance; CI = confidence interval; IT = immediate treatment; NR = not reported; PSA = prostate specific antigen.

** Refer to Appendix B for detailed explanations of rating scores; ** See table 2 for quality appraisals*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the evidence statement table of content template.

Table 12: Body of evidence examining the effects of delayed radical prostatectomy with immediate radical prostatectomy on prostate cancer-specific mortality

Name of study	Study type	N	Level of evidence *	Quality of evidence**	Risk of bias	Results summary	Size of effect	p value	95% CI	Relevance of evidence
Delayed Radical Prostatectomy vs. Immediate Radical Prostatectomy										
Holmström 2010 **Participants:** **Mean age (years)** dRP: 61.9 iRP: 61.1 **Mean PSA (ng/mL)** dRP: 6.7 iRP: 7.8 **Gleason score** ≤5: 33.4% 6: 66.6% **Tumour stage** T1:62.6% T2: 37.3% Follow up 8.2 years median	Retrospective Cohort	2,566	III-2	Low	High	**Prostate cancer-specific mortality (%):** dRP: 0.9 iRP: 0.7	ARD=0.2%	NR	NS	1
Sun 2012 **Participants:** **Median age** 68 years **Gleason score** 2-4: 3.9% 5-6: 96.1% **Charlson index** 0: 56.5% ≥1: 43.5% Follow up 2-12 years	Retrospective Cohort	17,153	III-2	Low	High	**Prostate cancer-specific mortality (%):** dRP: 13.1 iRP: 13.7	ARD=-0.6%	0.70	NR	1

ARD = absolute risk difference, negative values indicate a benefit of delayed radical prostatectomy over immediate radical prostatectomy; CI = confidence interval; dRP = delayed radical prostatectomy; iRP = immediate radical prostatectomy; NR= not reported; NS = not significantly different; PSA = prostate specific antigen.
** Refer to Appendix B for detailed explanations of rating scores; ** See table 2 for quality appraisals*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the evidence statement table of content template.

III Quality of Life

Table 13: Body of evidence examining the effects of delayed radical prostatectomy with immediate radical prostatectomy on quality of life

Name of study	Study type	N	Level of evidence *	Quality of evidence**	Risk of bias	Results summary	Size of Effect (OR)	P value	95% CI	Relevance of evidence
Delayed Radical Prostatectomy vs. Immediate Radical Prostatectomy										
Sun 2012	Retrospective Cohort	17,153	III-2	Low	High	**Incontinence (%):**				
						iRP: 20.8 dRP (3-5 months): 19.7	0.90	NS	0.79-1.02	1
Participants:		17,153				iRP: 20.8 dRP (5-9 months): 24.2	1.12	NS	0.90-1.38	1
Median age		17,153				iRP: 20.8 dRP (≥9 months): 31.8	1.73	<0.001	1.40-2.14	1
68 years										
Gleason score		17,153				**Erectile dysfunction (%):**				
2-4: 3.9%		17,153				iRP: 5.7 dRP (3-5 months): 6.3	1.10	NS	0.89-1.36	1
5-6: 96.1%		17,153				iRP: 5.7 dRP (5-9 months): 9.2	1.63	<0.05	1.18-2.24	1
Charlson index						iRP: 5.7 dRP (≥9 months): 11.8	1.85	<0.001	1.36-2.52	1
0: 56.5%										
≥1: 43.5%										
Follow up 2 - 12 years										

CI = confidence interval; dRP = delayed radical prostatectomy performed greater than 3 months following diagnosis (range of time to treatment in brackets); iRP = immediate radical prostatectomy within 3 months of diagnosis; NS = not statistically significantly different; OR = odds ratio.

** Refer to Appendix B for detailed explanations of rating scores; ** See table 2 for quality appraisals*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the NHMRC evidence statement form.

2.7 References: Included studies

1. Holmström B, Holmberg E, Egevad L, Adolfsson J, Johansson JE, Hugosson J et al. Outcome of primary versus deferred radical prostatectomy in the National Prostate Cancer Register of Sweden Follow-Up Study. *Journal of Urology* 2010; 184:1322-7.

2. Kakehi Y, Kamoto T, Shiraishi T, Ogawa O, Suzukamo Y, Fukuhara S et al. Prospective evaluation of selection criteria for active surveillance in Japanese patients with stage T1cN0M0 prostate cancer. *Japanese Journal of Clinical Oncology* 2008; 38:122-8.

3. Sun M, Abdollah F, Hansen J, Trinh QD, Bianchi M, Tian Z et al. Is a treatment delay in radical prostatectomy safe in individuals with low-risk prostate cancer? *Journal of Sexual Medicine* 2012; 9:2961-9.

3. APPENDICES

Appendix A: Search strategies used:

Search #1 – Randomised Controlled Trials for Active Surveillance

For Medline database:

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	randomized controlled trial.pt.
5	controlled clinical trial.pt.
6	placebo.ab.
7	randomi?ed.ab.
8	randomly.ab.
9	trial.ab.
10	groups.ab.
11	4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp animals/ not humans.sh.
13	11 not 12
14	(active adj2 surveillance).mp
15	(expectant$ adj2 (management or treat$)).mp
16	delay$ intervention.mp
17	(active adj1 monitoring).tw
18	'active monitoring'.tw
19	'conservative monitoring'.tw
20	'delayed treatment$'.tw
21	'watchful observation'.tw
22	'watchful surveillance'.tw
23	'watchful monitoring'.tw
24	'expectant monitoring'.tw
25	'expectant surveillance'.tw
26	'delayed therap$'.tw
27	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28	3 AND 13 AND 27

Used the Cochrane sensitivity maximizing filters for identifying randomised controlled trials (http://handbook.cochrane.org, accessed 20/02/2013/ Centre for Reviews and Dissemination systematic review/ meta-analyses strategy 2.(Lee et al, (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. ***BMC Medical Research Methodology*** *12:51)*

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
3	prostate cancer.mp. or exp Prostatic Neoplasms/
4	1 AND (2 OR 3)

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database:

#	Searches
1	'prostate cancer'/exp OR 'prostate cancer'
2	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR metast* OR adeno*)
3	#1 OR #2
4	active NEAR/2 surveillance
5	expectant* NEAR/2 (management OR treat*)
6	delay* NEAR/3 intervention
7	#4 OR #5 OR #6
8	rct
9	'randomized controlled trial'/exp OR 'randomized controlled trial'
10	'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomised controlled trial'/exp OR 'randomised controlled trial' OR 'randomized controlled trials'/exp OR 'randomized controlled trials' OR 'randomised controlled trials'
11	'random allocation'/exp OR 'random allocation'
12	'randomly allocated'
13	'randomization'/exp OR 'randomization'
14	allocated NEAR/2 random
15	'double blind procedure'/exp OR 'double blind procedure'
16	'single blind procedure'/exp OR 'single blind procedure'
17	single NEXT/1 blind*
18	double NEXT/1 blind*
19	(treble OR triple) NEXT/1 blind*
20	placebo*
21	'placebo'/exp OR 'placebo'
22	'prospective study'/exp OR 'prospective study'
23	'crossover procedure'/exp OR 'crossover procedure'
24	'clinical trial'/exp OR 'clinical trial'
25	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
26	'case study'/exp OR 'case study'
27	case AND report
28	'abstract report'/exp OR 'abstract report'

29	'letter'/exp OR 'letter'
30	#26 OR #27 OR #28 OR #29
31	#25 NOT #30
32	[1990-3000]/py
33	[english]/lim
34	[humans]/lim
35	#32 and #33 and #34
36	[medline]/lim
37	#35 NOT #36
38	#3 AND #7 AND #31 AND #37

Search #2 - Systematic Review/Meta-Analysis of Case-Control & Cohort studies for Active Surveillance

For Medline database:

#	Searches
1	Active NEAR/2 surveillance
2	expectant* NEAR/2 (management OR treat*)
3	delay* NEAR/3 intervention
4	1 OR 2 OR 3
5	'prostate cancer'/exp OR 'prostate cancer'
6	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR metast* OR adeno*)
7	5 OR 6
8	meta-analysis/
9	review literature/
10	meta-analy$.tw
11	metaanal$.tw
12	(systematic$ adj4 (review$ or overview$)).mp
13	meta-analysis.pt
14	review.pt
15	review.ti
16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17	case report/
18	letter.pt
19	historical article.pt
20	17 or 18 or 19
21	16 not 20
22	[1990-3000]/py
23	[english]/lim
24	[medline]/lim
25	[humans]/lim
26	22 AND 23 AND 25
27	26 NOT 24
28	4 AND 7 AND 21 AND 27

For Embase database:

#	Searches
1	'prostate cancer'/exp OR 'prostate cancer'
2	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR metast* OR adeno*)
3	#1 OR #2
4	active NEAR/2 surveillance
5	expectant* NEAR/2 (management OR treat*)
6	delay* NEAR/3 intervention
7	#4 OR #5 OR #6
8	'meta analysis'/exp OR 'meta analysis'
9	'review'/exp OR review AND ('literature'/exp OR literature)
10	'systematic review'/exp OR 'systematic review'
11	systematic AND overview
12	'review'/exp OR review
13	#8 OR # 9 OR #10 OR #11 OR #12
14	case AND report
15	'letter'/exp OR letter
16	historical AND ('article'/exp OR article)
17	#14 OR #15 OR #16
18	#13 NOT #17
19	[1990-3000]/py
20	[english]/lim
21	[humans]/lim
22	[medline]/lim
23	(#19 AND #20 AND #21) NOT #22
24	#3 AND #7 AND #18 AND #23

Search #3 - Case-Control and Cohort studies for Active Surveillance

For Medline database:

#	Searches
1	(active adj2 surveillance).mp.
2	(expectant$ adj2 (management or treat$)).mp.
3	delay$ intervention.mp.
4	1 OR 2 OR 3
5	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
6	prostate cancer.mp. or exp Prostatic Neoplasms/
7	5 OR 6
8	4 and 7
9	limit 8 to yr="1990 -Current"
10	limit 9 to (english language and humans)
11	commentary/
12	case report/
13	letter.pt.
14	historical article.pt.
15	salvage.mp.
16	chemotherapy.mp.
17	editorial.pt.
18	11 or 12 or 13 or 14 or 15 or 16 or 17
19	10 not 18

For Embase database:

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	#1 or #2
4	active NEAR/2 surveillance
5	expectant* NEAR/2 (management OR treat*)
6	delay* NEAR/3 intervention
7	#4 OR #5 OR #6
8	‘commentary’
9	'case report'/exp OR 'case report'
10	'letter'/exp OR letter
11	'historical article'
12	Salvage
13	'chemotherapy'/exp OR chemotherapy
14	'editorial'/exp OR editorial

15	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
16	[1990-3000]/py
17	[english]/lim
18	[medline]/lim
19	[humans]/lim
20	(#16 AND #17 AND #19) NOT #18
21	#3 AND #7 AND #20
22	#21 NOT #15

*Used the SIGN filter for identifying randomised controlled trials (*www.sign.ac.uk/methodology/filters.html#systematic *accessed 20/02/2013)*

For Embase database: ATSI search terms used

#	**Searches**
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

For Cochrane Database of Systematic Reviews 2005 to March 2014, Database of Abstracts of Reviews of Effects 1st quarter 2014 and Health Technology Assessment database 1st quarter 2014.

#	**Searches**
1	(prostat$ adj3 (cancer$ OR carcinoma$ OR malignan$ OR tumo?r$ OR neoplas$ OR metastas$ OR adeno$)).tw
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 OR 2

Search #4 – Case-Control Studies of Immediate verses Deferred Curative Treatment

For Medline database:

#	Searches
1	(active adj2 surveillance).mp.
2	(expectant$ adj2 (management or treat$)).mp.
3	delay$ intervention.mp.
4	1 or 2 or 3
5	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
6	prostate cancer.mp. or exp Prostatic Neoplasms/
7	5 or 6
8	4 and 7
9	limit 8 to yr="1990 -Current"
10	limit 9 to (english language and humans)
11	commentary/
12	case report/
13	letter.pt.
14	historical article.pt.
15	salvage.mp
16	chemotherapy.mp.
17	editorial.pt.
18	11 or 12 or 13 or 14 or 15 or 16 or 17
19	10 not 18
20	(delay$ or immediate or defer$ or observation$).ti.
21	1 or 2 or 20
22	7 and 21
23	limit 22 to yr="1990 -Current"
24	limit 23 to (english language and humans)
25	24 not 18
26	25 not 19

For Embase database:

#	**Searches**
1	active NEAR/2 surveillance
2	expectant* NEAR/2 (management OR treatment*)
3	delay* OR immediate OR defer* OR observation*:ti
4	1 OR 2 OR 3
5	'prostate cancer'/exp
6	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR metast* OR adeno*)
7	5 OR 6
8	[humans]/lim AND [english]/lim AND [1990-3000]/py NOT [medline]/lim
9	'commentary'
10	'case report'/exp OR 'case report'
11	'letter' OR 'letter'/exp OR letter
12	'historical article'
13	salvage
14	'chemotherapy'/exp OR 'chemotherapy'
15	'editorial'/exp OR 'editorial'
16	8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15
17	4 AND 7 AND 8
18	17 NOT 16

Appendix B:

Level of Evidence rating criteria – Intervention studies

Level	Study design
I	Meta-analysis or a systematic review of level II studies
II	Randomised controlled trial or a phase III/IV clinical trial
III-1	Pseudo-randomised controlled trial or a meta-analysis/systematic review of level III-1 studies
III-2	Comparative study with concurrent controls: - Phase II clinical trial - Non-randomised, experimental trial9 - Controlled pre-test/post-test study - Adjusted indirect comparisons - Interrupted time series with a control group - Cohort study - Case-control study or a meta-analysis/systematic review of level III-2 studies
III-3	A comparative study without concurrent controls: - Phase I clinical trial - Historical control study - Two or more single arm study10 - Unadjusted indirect comparisons - Interrupted time series without a parallel control group or a meta-analysis/systematic review of level III-3 studies
IV	Case series with either post-test or pre-test/post-test outcomes or a meta-analysis/systematic review of level IV studies

According to the standards of the National Health and Medical Research Council

Relevance of the evidence

Rating	Relevance
1	Evidence of an effect on patient-relevant clinical outcomes including benefits and harms, quality of life and survival.
2	Evidence of an effect on a surrogate outcome* that has been shown to be predictive of patient-relevant outcomes for the same intervention.
3	Evidence of an effect on proven surrogate outcomes but for a different intervention.
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population.
5	Evidence confined to unproven surrogate outcomes.

**'surrogate outcome' refers to reasonable indicators of whether there has been some effect (e.g. blood pressure measurements or levels of serum cholesterol)*

Points to considering patient-relevant outcomes:
i) The goal of decision making in health care is to choose the intervention(s) (which may include doing nothing) that is (are) most likely to deliver the outcomes that patients find desirable
ii) Surrogate outcomes (such as blood pressure measurements or levels of serum cholesterol) may be reasonable indicators of whether there has been some effect. However, they should not be the basis for clinical decisions unless they reliably predict an effect on the way the patient feels; otherwise they will not be of interest to the patient or their carers
iii) All possible outcomes that are of most interest to patients (particularly harms) should be identified and evaluated

Adapted from table 1.10: National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra: NHMRC; 2000. http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp69.pdf

Appendix C:

Potentially relevant guidelines identified

YEAR	ORGANISATION	TITLE	REASONS FOR NOT ADOPTING
2010	American Cancer Society	American Cancer Society Guideline for the Early Detection of Prostate Cancer	Not a systematic review
2011	Agency for Healthcare Research and Quality	An Evidence Review of Active Surveillance in Men with Localized Prostate Cancer	Did not meet 70% scores for domains of Rigour, Clarity and Editorial Independence on AGREE instrument
2007	American Urology Association	Guideline for the Management of Clinically Localized Prostate Cancer: 2007 Update	Not a systematic review
2009	American Urology Association	Prostate-Specific Antigen Best Practice Statement: 2009 Update	Not a systematic review
2011	Canadian Urology Association	Prostate Cancer Screening: Canadian Guidelines 2011	Not a systematic review
2012	European Association of Urology	Guidelines on Prostate Cancer (Feb 2012)	Not a comprehensive systematic review
2013	European Association of Urology	Guidelines on Prostate Cancer (Mar 2013)	Not a comprehensive systematic review
2009	Institute for Clinical and Economic Review	Management Options for Low-Risk Prostate Cancer: A Report on Comparative Effectiveness and Value	Not a systematic review
2006	Japanese Urological Association	Evidence-based Clinical Practice Guidelines for Prostate Cancer	Not a systematic review
2012	KCE/Belgium Health Care Knowledge Centre	A National Clinical Practice Guideline on the management of localised prostate cancer	Did not meet 70% scores for domains of Rigour, Clarity and Editorial Independence on AGREE instrument
2013	National Comprehensive Cancer Network	NCCN Clinical Practice Guidelines in Oncology: Prostate cancer (version 2.2013)	Did not meet 70% scores for domains of Rigour, Clarity and Editorial Independence on AGREE instrument
2013	National Comprehensive Cancer Network	NCCN Clinical Practice Guidelines in Oncology: Prostate cancer (version 4.2013)	Did not meet 70% scores for domains of Rigour, Clarity and Editorial Independence on AGREE instrument
2008	National Institute for Health and Clinical Excellence	Prostate cancer: diagnosis and treatment	Contains relevant recommendations to this clinical question that have since been updated (2014)
2014	National Institute for Health and Clinical Excellence	Prostate cancer: diagnosis and treatment	Relevant sections to this clinical question
2011	National Institute of Health	Role of Active Surveillance in the Management of Men with Localized Prostate Cancer	Not a systematic review
2012	Prostate Cancer Taskforce NZ	Diagnosis and Management of Prostate Cancer in New Zealand Men	Not a systematic review
2012	Memorial Sloan-Kettering Cancer Center	Screening Guidelines: Prostate Cancer	Not a systematic review

Excluded Studies

Search #1 – Randomised Controlled Trials

Study	Reason for Exclusion
Bastian 2009	Review with inappropriate study design
Bul 2012	Inappropriate study design. Not randomised.
Dahabreh 2012	Inappropriate study design. No appropriate data in paper.
Godtman 2013	Inappropriate study design. Single-arm AS cohort study.
Heidenreich 2011	EAU guidelines. No appropriate data in paper.
Khatami 2006	Inappropriate study design. Not biopsy determined PCa.
Khatami 2009	Biomarker analysis. No appropriate data in paper.
Klotz 2004	Inappropriate study design. No appropriate data in paper.
Klotz 2008	No appropriate data in paper.
Klotz 2010	Inappropriate study design. No appropriate data in paper.
Lane 2010	No appropriate data in paper.
Mhaskar 2012	No appropriate data in paper.
Mullins 2013	Inappropriate study design. No appropriate data in paper.
Roach 2012	Inappropriate study design. Intervention is WW, not AS.
Roemeling 2006	Inappropriate study design. Intervention (WW not AS) not randomised.
Roemeling 2007a (EU)	Inappropriate study design. Intervention not randomised.
Roemeling 2007b (C)	Inappropriate study design
van den Bergh 2010	Inappropriate study design
Wever 2013	Inappropriate study design
Wilt 1994	Inappropriate study design. A RCT with WW as the intervention
Wilt 1995	Inappropriate study design. A RCT with WW as the intervention.
Wilt 1997	No appropriate data in paper.
Wong 2012	Inappropriate study design. No appropriate data in paper.

Search #2 – Systematic reviews

Study	Reason for Exclusion
Abern 2013	Did not report relevant outcomes
Bangma 2012	Inappropriate study design
Bastian 2009	Review article that did not report relevant outcomes and had inappropriate study design
Dahabreh 2012	Review with inappropriate study design
Dall'Era 2010	Did not report relevant outcomes
Dall'Era 2012	Review with inappropriate study design
Furlan 2011	No relevant information
Heinderich 2011	No relevant information
Lees 2012	Did not report relevant outcomes
van den Bergh 2010	Did not report relevant outcomes
van den Bergh 2013	Review article that did not report relevant outcomes and inappropriate study design, and inappropriate intervention
Weissbach 2009	Review with inappropriate study design

Search #3 – Case-Cohort studies

Study	Reason for Exclusion
Abern 2013	Did not report relevant outcomes
Ahallal 2013	Abstract article from conference proceedings
Albertsen 2010	Review article with Inappropriate study designs
Barry 2001	Inappropriate intervention
Bellardita 2012	Abstract article from conference proceedings
Bergman 2012	Review article with Inappropriate study designs
Burnet 2007	Inappropriate participants
Chopra 2012	Abstract article from conference proceedings
Cooperberg 2009	Combined results for different interventions.
Fleshner 2012	Inappropriate intervention
Hayes 2011	Inappropriate study design
Hegarty 2011	Review article that did not report relevant outcomes
Ip 2011	Inappropriate intervention
Khurana 2012	Abstract article from conference proceedings
Miocinovic 2011	Did not report relevant outcomes
Mishra 2013	Inappropriate intervention
Mohler 1997	Did not report relevant outcomes
Punnen 2013	Abstract article from conference proceedings
Roach 2012	Review articles with inappropriate intervention
Roemeling 2006	Inappropriate intervention
Selvadurai 2013	Inappropriate study design
Sieh 2013	Abstract article from conference proceedings
Singh 2010	Review articles with inappropriate study designs
Stattin 2008	Combined results for different interventions
Stattin 2010	Combined results for different interventions.
Thomas 2013	Abstract article from conference proceedings
Thong 2010	Inappropriate study design
van den Bergh 2010	Did not report relevant outcomes
van Vugt 2012	Did not report relevant outcomes
Victorson 2013	Abstract article from conference proceedings
Warlick 2006	Did not report relevant outcomes
Xia 2012	Inappropriate study design

Search #4 – Immediate vs deferred treatment

Study	Reason for Exclusion
Abdollah 2011	Inappropriate study design
Abdollah 2012	Inappropriate study design
Abern 2013	Did not report relevant outcomes
Andrews 2004	Inappropriate study design
Dall'Era 2010	Did not report relevant outcomes
Graefen 2005	Did not report relevant outcomes
Khan 2004	Did not report relevant outcomes
Korets 2011	Did not report relevant outcomes/Inappropriate participants
Kwan 2006	Did not report relevant outcomes
Lee 2006	Did not report relevant outcomes
Nguyen 2005	Inappropriate intervention
O'Brien 2011	Did not report relevant outcomes
Phillips 2007	Did not report relevant outcomes
Shappley 2009	Inappropriate study design
Sun 2012	Did not report relevant outcomes
Torring 2013	Inappropriate study design
van den Bergh 2010	Did not report relevant outcomes
Vickers 2006	Inappropriate study design/Did not report relevant outcomes

References: Excluded Studies (Search #1 – RCT)

1. Bastian PJ, Carter BH, Bjartell A, Seitz M, Stanislaus P, Montorsi F et al. Insignificant prostate cancer and active surveillance: from definition to clinical implications. *European Urology* 2009; 55:1321-30.

2. Bul M, van den Bergh RC, Zhu X, Rannikko A, Vasarainen H, Bangma CH et al. Outcomes of initially expectantly managed patients with low or intermediate risk screen-detected localized prostate cancer. *BJU International* 2012; 110:1672-7.

3. Dahabreh IJ, Chung M, Balk EM, Yu WW, Mathew P, Lau J, Ip S. Active surveillance in men with localized prostate cancer: a systematic review. *Annals of Internal Medicine.* 2012; 156(8):582-90.

4. Godtman RA, Holmberg E, Khatami A, Stranne J, Hugosson J. Outcome following active surveillance of men with screen-detected prostate cancer. Results from the Goteborg randomised population-based prostate cancer screening trial. *European Urology* 2013; 63:101-7.

5. Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. *European Urology* 2011; 59:61-71.

6. Khatami A, Aus G, Damber JE, Lilja H, Lodding P, Hugosson J. PSA doubling time predicts the outcome after active surveillance in screening-detected prostate cancer: results from the European randomized study of screening for prostate cancer, Sweden section. *International Journal of Cancer* 2006; 120(1):170-4.

7. Khatami A, Hugosson J, Wang W, Damber JE: Ki-67 in screen-detected, low-grade, low-stage prostate cancer, relation to prostate-specific antigen doubling time, Gleason score and prostate-specific antigen relapse after radical prostatectomy. *Scandinavian Journal of Urology & Nephrology* 2009; 43:12-8.

8. Klotz L. Active surveillance with selective delayed intervention: Using natural history to guide treatment in good risk Prostate cancer. *Journal of Urology* 2004; 172:S48–S51.

9. Klotz L. Active surveillance for prostate cancer: trials and tribulations*. World Journal of Urology* 2008; 26:437-42.

10. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical Results of Long-Term Follow-Up of a Large, Active Surveillance Cohort with Localized Prostate Cancer. *Journal of Clinical Oncology* 2010; 28(1):126-31.

11. Lane JA, Hamdy FC, Martin RM, Turner EL, Neal DE, Donovan JL. Latest results from the UK trials evaluating prostate cancer screening and treatment: the CAP and ProtecT studies. *European Journal of Cancer.* 2010; 46(17):3095-101.

12. Mhaskar AR, Quinn G, Vadaparampil S,Djulbegovic B, Gwede CK, Kumar A. Timing of first-line cancer treatments - early versus late - a systematic review of phase III randomized trials. *Cancer Treatment Reviews* 2010; 36(8):621-8.

13. Mullins JK, Bonekamp D, Landis P, Begum H, Partin AW, Epstein JI et al. Multiparametric magnetic resonance imaging findings in men with low-risk prostate cancer followed using active surveillance. *BJU International* 2013; 111:1037-45.

14. Roach M III, Thomas K. Overview of randomized controlled treatment trials for clinically localized prostate cancer: implications for active surveillance and the United States preventative task force report on screening? *Journal of the National Cancer Institute Monographs* 2012; 45:221-9.

15. Roemeling S, Roobol MJ, Postma R, Gosselaar C, van der Kwast TH, Bangma CH et al. Management and survival of screen-detected prostate cancer patients who might have been suitable for active surveillance. *European Urology* 2006; 50:475-82.

16. Roemeling S, Roobol MJ, de Vries SH, Wolters T, Gosselaar C, van Leenders GJ et al. Active surveillance for prostate cancers detected in three subsequent rounds of a screening trial: characteristics, PSA doubling times, and outcome. *European Urology* 2007; 1251(51):1244-50.

17. Roemeling S, Roobol MJ, Kattan MW, van der Kwast TH, Steyerberg EW, Schroder FH. Nomogram use for the prediction of indolent prostate cancer: impact on screen-detected populations. *Cancer* 2007; 110:2218-21.

18. van den Bergh RC, Steyerberg EW, Khatami A, Aus G, Pihl CG, Wolters T et al. Swedish and Dutch sections of the European Randomized Study of Screening for Prostate Cancer. Is delayed radical prostatectomy in men with low-risk screen-detected prostate cancer associated with a higher risk of unfavorable outcomes? *Cancer* 2010; 116:1281-90.

19. Wever EM, Heijnsdijk EA, Draisma G, Bangma CH, Roobol MJ, Schroder FH et al. Treatment of local-regional prostate cancer detected by PSA screening: benefits and harms according to prognostic factors. *British Journal of Cancer* 2013; 108:1971-7.

20. Wilt TJ, Brawer MK. The Prostate Cancer Intervention Versus Observation Trial: a randomized trial comparing radical prostatectomy versus expectant management for the treatment of clinically localized prostate cancer. *Journal of Urology* 1994; 152:1910-4.

21. Wilt TJ, Brawer MK. The Prostate cancer Intervention versus Observation Trial (PIVOT): A randomized trial comparing radical prostatectomy versus expectant management for the treatment of clinically localized prostate cancer. *Cancer* 1995; 75:1963-8.

22. Wilt TJ, Brawer MK. The Prostate Cancer Intervention versus Observation Trial (PIVOT). *Oncology* 1997; 11(8):1133-43.

23. Wong LM, Neal DE, Johnston RB, Shah N, Sharma N, Warren AY et al. International multicentre study examining selection criteria for active surveillance in men undergoing radical prostatectomy. *British Journal of Cancer* 2012; 107:1467-73.

References: Excluded Studies (Search #2 – Systematic Reviews/Meta-Analysis)

1. Abern MR, Aronson WJ, Terris MK, Kane CJ, Presti JC, Jr., Amling CL et al. Delayed radical prostatectomy for intermediate-risk prostate cancer is associated with biochemical recurrence: possible implications for active surveillance from the SEARCH database. *Prostate* 2013; 73:409-17.

2. Bangma CH, Bul M, Roobol M. The Prostate cancer Research International: Active Surveillance study. *Current Opinion in Urology* 2012; 22:216-21.

3. Bastian PJ, Carter BH, Bjartell A, Seitz M, Stanislaus P, Montorsi F et al. Insignificant prostate cancer and active surveillance: from definition to clinical implications. *European Urology* 2009; 55:1321-30.

4. Dahabreh IJ, Chung M, Balk EM, Yu WW, Mathew P, Lau J et al. Active surveillance in men with localized prostate cancer: a systematic review. *Annals of Internal Medicine* 2012; 156:582-90.

5. Dall'Era MA, Cowan JE, Simko J, Shinohara K, Davies B, Konety BR et al. Surgical management after active surveillance for low-risk prostate cancer: pathological outcomes compared with men undergoing immediate treatment. *BJU International* 2011; 107:1232-7.

6. Dall'Era MA, Albertsen PC, Bangma C, Carroll PR, Carter HB, Cooperberg MR et al. Active surveillance for prostate cancer: a systematic review of the literature. *European Urology* 2012; 62:976-83.

7. Ip S, Dahabreh IJ, Chung M, Yu WW, Balk EM, Iovin RC et al. An evidence review of active surveillance in men with localized prostate cancer. *Evidence Report/Technology Assessment* 2011; 204:1-341.

8. Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. *European Urology* 2011; 59:61-71.

9. Lees K, Durve M, Parker C. Active surveillance in prostate cancer: patient selection and triggers for intervention. *Current Opinion in Urology* 2012; 22:210-5.

10. van den Bergh RC, Steyerberg EW, Khatami A, Aus G, Pihl CG, Wolters T et al, Swedish and Dutch sections of the European Randomized Study of Screening for Prostate Cancer. Is delayed radical prostatectomy in men with low-risk screen-detected prostate cancer associated with a higher risk of unfavorable outcomes? *Cancer* 2010; 116:1281-90.

11. van den Bergh RCN, Albertsen PC, Bangma CH, Freedland SJ, Graefen M, Vickers A et al. Timing of curative treatment for prostate cancer: A systematic review. *European Urology* 2013; 64:204-15.

12. Weissbach L, Altwein J. Active surveillance or active treatment in localized prostate cancer? *Deutsches Arzteblatt International* 2009;106:371-6

References: Excluded Studies (Search #3 – Case-Control Studies)

1. Abern MR, Aronson WJ, Terris MK, Kane CJ, Presti JC, Jr., Amling CL et al. Delayed radical prostatectomy for intermediate-risk prostate cancer is associated with biochemical recurrence: possible implications for active surveillance from the SEARCH database. *Prostate* 2013; 73:409-17.

2. Ahallal Y, Barret E, Sanchez-Salas R, Durand M, Mascle L, Giedelman C et al. The psychological impact of the different treatment modalities in men with localized prostate cancer. *Journal of Urology* 2013; 189:e412-e413.

3. Albertsen PC. Treatment of localized prostate cancer: when is active surveillance appropriate? *Nature Reviews Clinical Oncology* 2010; 7:394-400.

4. Barry MJ, Albertsen PC, Bagshaw MA, Blute ML, Cox R, Middleton RG et al. Outcomes for men with clinically nonmetastatic prostate carcinoma managed with radical prostactectomy, external beam radiotherapy, or expectant management: a retrospective analysis. *Cancer* 2001; 91:2302-14.

5. Bellardita L, Avuzzi B, Rancati T, Villani D, Catania S, Magnani T et al. Quality of life in prostate cancer patients: Radiotherapy compared to Active Surveillance. *Radiotherapy and Oncology* 2012; 103:S262.

6. Bergman J, Litwin MS. Quality of life in men undergoing active surveillance for localized prostate cancer. *Journal of the National Cancer Institute Monographs* 2012; 45:242-9.

7. Burnet KL, Parker C, Dearnaley D, Brewin CR, Watson M. Does active surveillance for men with localized prostate cancer carry psychological morbidity? *BJU International* 2007; 100:540-3.

8. Chopra S, Thanigasalam R, Beattie K, Egger S, Smith D, Symons J et al. Quality of life outcomes amongst men undergoing contemporary techniques for the treatment of localised prostate cancer: A prospective study. *Journal of Urology* 2012; 187:e596-e597.

9. Cooperberg MR, Broering JM, Carroll PR. Risk assessment for prostate cancer metastasis and mortality at the time of diagnosis. *Journal of the National Cancer Institute* 2009; 101:878-87.

10. Fleshner NE, Lucia MS, Egerdie B, Aaron L, Eure G, Nandy I et al. Dutasteride in localised prostate cancer management: the REDEEM randomised, double-blind, placebo-controlled trial. *Lancet* 2012; 379:1103-11.

11. Hayes JH, Ollendorf DA, Pearson SD, Barry MJ, Kantoff PW, Stewart ST et al. Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis. *JAMA* 2010; 304:2373-80.

12. Hegarty J, Bailey DE, Jr. Active surveillance as a treatment option for prostate cancer. *Seminars in Oncology Nursing* 2011; 27:260-6.

13. Ip S, Dahabreh IJ, Chung M, Yu WW, Balk EM, Iovin RC et al. An evidence review of active surveillance in men with localized prostate cancer. *Evidence Report/Technology Assessment* 2011; 204:1-341.

14. Khurana KK, Klink JC, Jianbo L, Krebs TL, Prots DJ, Isariyawongse BK et al. Urinary continence (UC) and sexual function (SF) among men with localized prostate cancer treated with active surveillance (AS), radical prostatectomy (RP), and brachytherapy (PI): Interim results of a prospective, longitudinal health-related quality-of-life (HRQOL) study. *Journal of Urology* 2012; 187:e155.

15. Miocinovic R, Jones JS, Pujara AC, Klein EA, Stephenson AJ. Acceptance and durability of surveillance as a management choice in men with screen-detected, low-risk prostate cancer: improved outcomes with stringent enrolment criteria. *Urology* 2011; 77:980-4.

16. Mishra MV, Shen X, Den RB, Champ CE, Trabulsi EJ, Lallas CD et al. Patterns of care for elderly men diagnosed with favorable-risk prostate cancer from 2004 to 2008: A population-based analysis. *American Journal of Clinical Oncology* 2013; 36(6):606-11.

17. Mohler JL, Williams BT, Freeman JA. Expectant management as an option for men with stage T1c prostate cancer: a preliminary study. *World Journal of Urology* 1997; 15:364-8.

18. Punnen S, Cowan J, Carroll P, Cooperberg M. Long term health related quality of life outcomes after primary treatment for localized prostate cancer: Results from the capsure registry. *Journal of Urology* 2013; 189:e411-e412.

19. Roach M, III, Thomas K. Overview of randomized controlled treatment trials for clinically localized prostate cancer: implications for active surveillance and the United States preventative task force report on screening? *Journal of the National Cancer Institute Monographs* 2012; 45:221-9.

20. Roemeling S, Roobol MJ, Postma R, Gosselaar C, van der Kwast TH, Bangma CH et al.Management and survival of screen-detected prostate cancer patients who might have been suitable for active surveillance. *European Urology* 2006; 50:475-82.

21. Selvadurai ED, Singhera M, Thomas K, Mohammeda K, Woode-Amissah R, Horwich A et al. Medium-term Outcomes of Active Surveillance for Localised Prostate Cancer. *European Urology* 2013; 64:981-7.

22. Sieh W, Lichtensztajn DY, Nelson DO, Cockburn M, West DW, Brooks JD et al. Treatment and mortality in men with localized prostate cancer: A population-based study in California. *Open Prostate Cancer Journal* 2013; 6:1-9.

23. Singh J, Trabulsi EJ, Gomella LG. Is there an optimal management for localized prostate cancer? *Clinical Interventions In Aging* 2010; 5:187-97.

24. Stattin P, Holmberg E, Bratt O, Adolfsson J, Johansson JE, Hugosson J, National Prostate CR. Surveillance and deferred treatment for localized prostate cancer. Population based study in the National Prostate Cancer Register of Sweden. *Journal of Urology* 2008; 180:2423-9.

25. Stattin P, Holmberg E, Johansson JE, Holmberg L, Adolfsson J, Hugosson J, National Prostate Cancer Register (NPCR) of Sweden. Outcomes in localized prostate cancer: National Prostate Cancer Register of Sweden follow-up study. *Journal of the National Cancer Institute* 2010; 102:950-8.

26. Thomas A, Kim B, Jung H, Porter K, Zheng C, Gelfond J et al. Quality of life outcomes in men undergoing treatment of localized prostate cancer: Initial results from the kaiser permanente southern California region. *Journal of Urology* 2013; 189:e146.

27. Thong MS, Mols F, Kil PJ, Korfage IJ, van de Poll-Franse LV. Prostate cancer survivors who would be eligible for active surveillance but were either treated with radiotherapy or managed expectantly: comparisons on long-term quality of life and symptom burden. *BJU International* 2010; 105:652-8.

28. van den Bergh RC, Steyerberg EW, Khatami A, Aus G, Pihl CG, Wolters T et al. Swedish and Dutch sections of the European Randomized Study of Screening for Prostate Cancer: Is delayed radical prostatectomy in men with low-risk screen-detected prostate cancer associated with a higher risk of unfavorable outcomes? *Cancer* 2010; 116:1281-90.

29. van Vugt HA, Roobol MJ, van der Poel HG, van Muilekom EH, Busstra M, Kil P, Oomens EH et al. Selecting men diagnosed with prostate cancer for active surveillance using a risk calculator: a prospective impact study. *BJU International* 2012; 110:180-7.

30. Victorson D, Helfand B, Stein D, Kundu S, Nadler R, Casey J et al. Do pre-treatment differences exist between men who choose active surveillance or radical prostatectomy in self-reported QoL, anxiety or urological symptoms? *Journal of Urology* 2013; 189:e554-e555.

31. Warlick C, Trock BJ, Landis P, Epstein JI, Carter HB. Delayed versus immediate surgical intervention and prostate cancer outcome. *Journal of the National Cancer Institute* 2006; 98:355-7.

32. Xia J, Trock BJ, Cooperberg MR, Gulati R, Zeliadt SB, Gore JL et al. Prostate cancer mortality following active surveillance versus immediate radical prostatectomy. *Clinical Cancer Research* 2012; 18:5471-8.

Search #4 – Case-Control Studies of Immediate vs Deferred Curative Treatment

1. Abdollah F, Sun M, Schmitges J, Tian Z, Jeldres C, Briganti A et al. Cancer-specific and other-cause mortality after radical prostatectomy versus observation in patients with prostate cancer: competing-risks analysis of a large North American population-based cohort. *European Urology* 2011; 60:920-30.

2. Abdollah F, Sun M, Schmitges J, Thuret R, Tian Z, Shariat SF et al. Competing-risks mortality after radiotherapy vs. observation for localized prostate cancer: a population-based study. *International Journal of Radiation Oncology, Biology, Physics* 2012; 84:95-103.

3. Abern MR, Aronson WJ, Terris MK, Kane CJ, Presti JC, Amling CL et al. Delayed radical prostatectomy for intermediate-risk prostate cancer is associated with biochemical recurrence: possible implications for active surveillance from the SEARCH database. *Prostate* 2013; 73:409-17.

4. Andrews SF, Horwitz EM, Feigenberg SJ, Eisenberg DF, Hanlon AL, Uzzo RG et al. Does a delay in external beam radiation therapy after tissue diagnosis affect outcome for men with prostate carcinoma? *Cancer* 2005; 104:299-304.

5. Dall'Era MA, Cowan JE, Simko J, Shinohara K, Davies B, Konety BR et al. Surgical management after active surveillance for low-risk prostate cancer: pathological outcomes compared with men undergoing immediate treatment. BJU International 2010; 107:1232-7.

6. Graefen M, Walz J, Chun KH, Schlomm T, Haese A, Huland H. Reasonable delay of surgical treatment in men with localized prostate cancer--impact on prognosis? *European Urology* 2005; 47:756-60.

7. Khan MA, Mangold LA, Epstein JI, Boitnott JK, Walsh PC, Partin AW. Impact of surgical delay on long-term cancer control for clinically localized prostate cancer. *Journal of Urology* 2004; 172:1835-9.

8. Korets R, Seager CM, Pitman MS, Hruby GW, Benson MC, McKiernan JM. Effect of delaying surgery on radical prostatectomy outcomes: a contemporary analysis. *BJU International* 2012; 110:211-6.

9. Kwan W, Pickles T, Duncan G, Liu M, Paltiel C. Relationship between delay in radiotherapy and biochemical control in prostate cancer. *International Journal of Radiation Oncology, Biology, Physics* 2006; 66:663-8.

10. Lee DK, Allareddy V, Michael A, O'Donnell MA, Williams RD, Konety BR. Does the interval between prostate biopsy and radical prostatectomy affect the immediate postoperative outcome? *BJU International* 2006; 97:48-50.

11. Nam RK, Jewett MA, Krahn MD, Robinette MA, Tsihlias J, Toi A et al. Delay in surgical therapy for clinically localized prostate cancer and biochemical recurrence after radical prostatectomy. *Canadian Journal of Urology* 2003; 10:1891-8.

12. Nguyen PL, Whittington R, Koo S, Schultz D, Cote KB, Loffredo M et al. The impact of a delay in initiating radiation therapy on prostate-specific antigen outcome for patients with clinically localized prostate carcinoma. *Cancer* 2005; 103:2053-9.

13. O'Brien D, Loeb S, Carvalhal GF, McGuire BB, Kan D, Hofer MD et al. Delay of Surgery in Men with Low Risk Prostate Cancer. *Journal of Urology* 2011; 185:2143-7.

14. Phillips JJ, Hall MC, Lee WR, Clark PE. Does a delay in initiating definitive therapy affect biochemical recurrence rates in men with clinically localized prostate cancer? *Urologic Oncology* 2007; 25:196-200.

15. Shappley WV, III, Kenfield SA, Kasperzyk JL, Qiu W, Stampfer MJ, Sanda MG et al. Prospective study of determinants and outcomes of deferred treatment or watchful waiting among men with prostate cancer in a nationwide cohort. *Journal of Clinical Oncology* 2009; 27:4980-5.

16. Torring ML, Frydenberg M, Hansen RP, Olesen F, Vedsted P. Evidence of increasing mortality with longer diagnostic intervals for five common cancers: A cohort study in primary care. *European Journal of Cancer* 2013; 49:2187-98.

17. van den Bergh RC, Steyerberg EW, Khatami A, Aus G, Pihl CG, Wolters T et al. Swedish and Dutch sections of the European Randomized Study of Screening for Prostate Cancer: Is delayed radical prostatectomy in men with low-risk screen-detected prostate cancer associated with a higher risk of unfavorable outcomes? *Cancer* 2010; 116:1281-90.

18. Vickers AJ, Bianco FJ, Jr., Boorjian S, Scardino PT, Eastham JA. Does a delay between diagnosis and radical prostatectomy increase the risk of disease recurrence? *Cancer* 2006; 106:576-80.

Systematic review report for question 9 (NICE Guideline)

Clinical question 9: *What should be the criteria for choosing active surveillance in preference to definitive treatment to offer as primary management to men who have a positive prostate biopsy?*

PICO Question 9: *"For men with biopsy-diagnosed prostate cancer, for which patients (based on diagnostic, clinical and other criteria) does active surveillance achieve equivalent or better outcomes in terms of length and quality of life than definitive treatment?"*

1. METHODS

1.1 Outline

The systematic review that addressed the clinical question and PICO outlined above found that high quality randomised controlled trials comparing active surveillance protocols to immediate treatment were lacking in the literature. Given the lack of high quality relevant published evidence addressing the PICO question above, it was decided to complement this systematic review with a systematic review undertaken by the National Institute for Health and Care Excellence's (NICE) Clinical Guideline for Prostate Cancer: Diagnosis and Treatment (UK National Collaborating Centre for Cancer 2014a[1]). This NICE guideline addressed the question: *Which men with localised prostate cancer should be offered active surveillance?* This NICE guideline used a different approach and assessed prognostic factors for men undergoing active surveillance rather than comparing the effects of different interventions in different groups of men.

[1]National Collaborating Centre for Cancer. Prostate cancer: diagnosis and treatment. National Collaborating Centre for Cancer; 2014.

1.2 Search for Relevant Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by literature searches for each PICO question and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

1.3 Assessment with AGREE II instrument

To be considered for adoption or adaptation guidelines had to be evidence based and meet the pre-specified criteria of scaled scores of ≥70% for the following domains: Rigour of Development, Clarity of Presentation, and Editorial Independence in the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

2. RESULTS

2.1 Search for Relevant Guidelines

In January 2014 the search for guidelines undertaken as part of the systematic review process identified the publication by the UK National Collaborating Centre for Cancer, which was an updated version of the UK National Institute for Health and Care Excellence evidence-based Clinical Guidelines for Prostate Cancer Diagnosis and Treatment[1]. The 2014 version of the NICE guideline contained a number of new questions. Of these, the following question was identified as relevant to the clinical question above:

NICE question: *Which men with localised prostate cancer should be offered active surveillance?*

NICE PICO

Population	Prognostic Factors	Outcomes
Men with biopsy-confirmed localised prostate cancer (T1 or T2, Gleason ≤ 7, PSA ≤ 20)	- Multiparametric MRI - MRI - PSA velocity - PSA level - PSA density - Free-to-total PSA - Clinical stage - Family history - Ethnicity - Pathological features on biopsy (Gleason score, perineural invasion, volume) - Biomarkers - Age	- Overall survival - Progression-free survival - Rate of conversion from active surveillance to other treatment - Conversion-free survival

2.2 Assessment with AGREE II instrument

The 2014 NICE guideline[2] were independently assessed by 4 appraisers using the AGREE II instrument. The scaled score for the Rigour Domain was 84.4%, the scaled score for the Clarity of Presentation domain was 76.0% and the scaled score for Editorial Independence was 85.4%. As such these guidelines met the inclusion criteria for adoption or adaptation.

[2]National Collaborating Centre for Cancer. Draft Evidence Review for Update of Clinical Guidelines 58 Prostate cancer: diagnosis and treatment accessed 29/01/14. Final version accessed 18/11/2014. http://www.nice.org.uk/guidance/cg175/evidence/cg175-prostate-cancer-appendix-m2

3. Literature Updated for NICE Guideline

3.1 Outline

The authors decided to update the NICE systematic review for the NICE question: *Which men with localised prostate cancer should be offered active surveillance?* up to 1st March 2014. This updated NICE systematic review in conjunction with the systematic review for the original PICO: *For men with biopsy-diagnosed prostate cancer, for which patients (based on diagnostic, clinical and other criteria) does active surveillance achieve equivalent or better outcomes in terms of length and quality of life than definitive treatment?* was then used to draft recommendations as to which men should be offered active surveillance.

3.2 Methods

The NICE systematic review search cut-off date was May 2013. To ensure all the relevant literature available was captured, searches for the updated systematic review were conducted from 1/1/2012. Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effect and Health Technology Assessments databases were searched using text terms and, where available, database specific subject headings. Each database was searched for articles dealing with prostate cancer. The Medline database was searched using a combination of the prognostic and active surveillance strategies as documented in the NICE

systematic review. The Embase search strategy used was based on the Medline strategy. To identify studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples.

A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 which were either published after the initial search was completed and/or added to the relevant database after the search was completed. Alerts were checked until July 2014.

3.3 Inclusion Criteria

The inclusion criteria for the NICE guideline update literature search was derived from the NICE PICO table for this clinical question, and is outlined in the NICE 2014 – Prostate Cancer Diagnosis and Treatment Evidence Review (pages 394-395).

Selection criteria	**Inclusion criteria**
Study type	Prognostic
Study design	Cohort
Population	Men with biopsy-confirmed localised prostate cancer (T1 or T2, Gleason ≤7, PSA ≤20 ng/mL) and following an active surveillance protocol
Prognostic factor	Multi-parametric magnetic resonance imaging (MRI) MRI PSA velocity PSA level PSA density Free-to-total PSA percentage Clinical stage Family history Ethnicity Pathological features on biopsy (Gleason score, perineural invasion, volume) Biomarkers Age
Comparator	No or lower level of prognostic factor
Outcomes	overall survival progression-free survival rate of conversion from active surveillance to other treatment conversion-free survival With a median follow-up of 5 years or more
Language	English
Publication period	After 30th June 2012 and prior to 1st March 2014

Conference proceedings identified by the search literature searches were included if they met the inclusion criteria.

3.4 Results of NICE Guideline update literature search

Figure 1 outlines the process of identifying relevant articles for the updated NICE systematic review. The Medline search identified 168 citations, the Embase search 595 citations, the search of the Cochrane Database of Systematic Reviews 59 citations, the Database of Abstracts of Reviews of Effects search 282 citations and

the search of the Health Technology Assessment database identified an additional 216 citations, resulting in a total of, 1320 citations. Titles and abstracts were examined and 50 articles were retrieved for a more detailed evaluation.

No studies met the inclusion criteria. As a result the NICE systematic review did not require updating and was used as published to contribute to the evidence base for the question: *Which men with localised prostate cancer should be offered active surveillance?* No studies of ATSI men met the inclusion criteria. The reason for excluding the retrieved articles is documented in Appendix C. In summary, most articles were excluded because they did not report relevant outcomes, or reported a median/mean follow-up of less than 5 years.

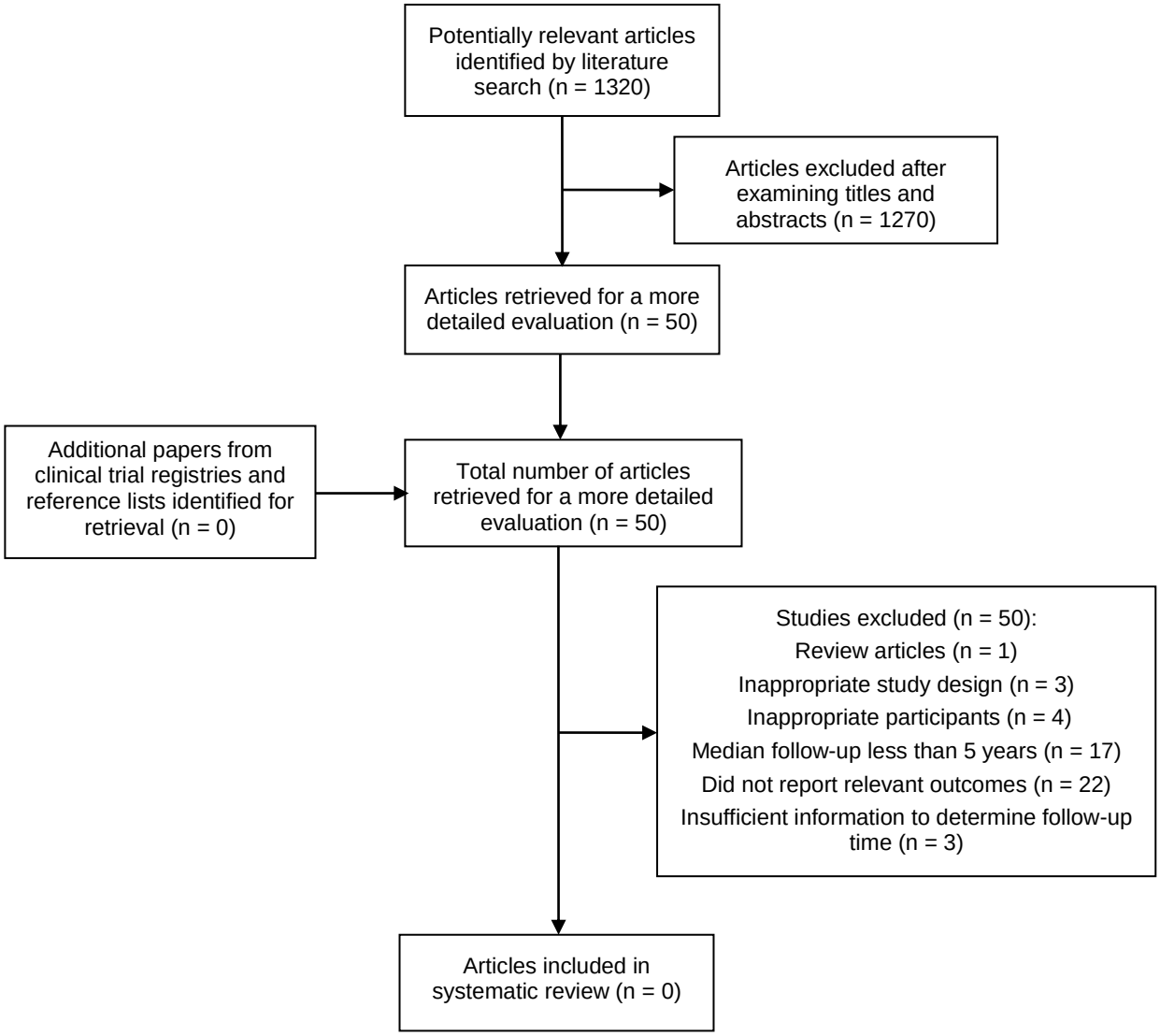


Figure 1. Process of inclusion and exclusion of studies

APPENDICES

Appendix A: Search strategies used

For Medline database:

#	Searches
1	prostatic neoplasms/
2	(prostat$ adj5 (cancer$ or carcin$ or tumor$ or tumour$ or neoplasm$)).tw.
3	((carcinoma or neoplasia or neoplasm$ or adenocarcinoma or cancer$ or tumor$ or tumour$ or malignan$) adj3 prostat$).tw.
4	1 or 2 or 3
5	prognostic methods.mp.
6	predictive factors.mp.
7	(prognos$ adj10 (relapse$ or recurrence$ or survival$ or death$ or mortality or progress$ or disease free or psa failure$ or biochemical failure$)).ti,ab.
8	(predict$ adj10 (relapse$ or recurrence$ or survival$ or death$ or mortality or progress$ or disease free or psa failure$ or biochemical failure$)).ti,ab.
9	(neural network$ adj10 (relapse$ or recurrence$ or survival$ or death$ or mortality or progress$ or disease free or psa failure$ or biochemical failure$)).ti,ab.
10	survival rate/
11	exp prognosis/ and (relapse$ or recurrence$ or survival$ or death$ or mortality or progress$ or disease free or psa failure$ or biochemical failure$).ti,ab.
12	disease free survival/
13	mortality/
14	recurrence/
15	neural networks computer/ and (relapse$ or recurrence$ or survival$ or death$ or mortality or progress$ or dis-ease free or psa failure$ or biochemical failure$).ti,ab.
16	exp models statistical/ and (relapse$ or recurrence$ or survival$ or death$ or mortality or progress$ or disease free or psa failure$ or biochemical failure$).ti,ab.
17	algorithms/ and (relapse$ or recurrence$ or survival$ or death$ or mortality or progress$ or disease free or psa failure$ or biochemical failure$).ti,ab.
18	(algorithm$ adj10 (relapse$ or recurrence$ or survival$ or death$ or mortality or progress$ or disease free or psa failure$ or biochemical failure$)).ti,ab.
19	exp survival analysis/
20	nomogram$.mp.
21	((marker$ or biomarker$) adj10 (prognos$ or predict$)).mp.
22	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23	letter.pt.
24	comment.pt.
25	(animal or cell line$ or vitro or invitro or rat or rats or mouse or mice).ti,ab.
26	23 or 24 or 25
27	(4 and 22) not 26
28	limit 27 to yr="2012-Current"
29	exp prostatic neoplasms/
30	Prostatic Intraepithelial Neoplasia/
31	(prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.
32	PIN.tw.
33	29 or 30 or 31 or 32
34	(active adj1 surveillance).tw.
35	(active adj1 monitoring).tw.
36	watchful wait$.tw.
37	(watch$ adj2 wait$).tw.
38	watchful observation.tw.

39	watchful surveillance.tw.
40	watchful monitoring.tw.
41	active surveillance.tw.
42	active monitoring.tw.
43	expectant manag$.tw.
44	expectant monitoring.tw.
45	expectant surveillance.tw.
46	deferred treatment$.tw.
47	deferred therap$.tw.
48	delayed treatment$.tw.
49	delayed therap$.tw.
50	conservative monitoring.tw.
51	Watchful waiting/
52	34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53	33 and 52
54	limit 53 to yr="2012-Current"
55	28 and 54

Based on searches undertaken for NICE evidence review: National Collaborating Centre for Cancer. Draft Evidence Review for Update of Clinical Guidelines 58 Prostate cancer: diagnosis and treatment accessed 29/01/14 - . final version accessed 18/11/14 http://www.nice.org.uk/guidance/cg175/evidence/cg175-prostate-cancer-appendix-m2

ATSI search terms used

#	**Searches**
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database:

#	Searches
1	'prostatic neoplasms'/exp OR 'prostatic neoplasms'
2	'prostatic intraepithelial neoplasia'
3	(prostat* NEAR/3 (cancer* OR carcinoma* OR adeno* OR malignan* OR tum?r* OR neoplas* OR intraepithelial*)):ti
4	pin:ti
5	#1 OR #2 OR #3 OR #4
6	(active NEAR/1 surveillance):ti
7	(active NEAR/1 monitoring):ti
8	(watchful NEXT/1 wait*):ti
9	(watch* NEAR/2 wait*):ti
10	'watchful observation':ti
11	'watchful surveillance':ti
12	'watchful monitoring':ti
13	'active surveillance':ti
14	'active monitoring':ti
15	(expectant NEXT/1 manag*):ti
16	'expectant monitoring':ti
17	'expectant surveillance':ti
18	(deferred NEXT/1 treatment*):ti
19	(deferred NEXT/1 therap*):ti
20	(delayed NEXT/1 treatment*):ti
21	(delayed NEXT/1 therap*):ti
22	'conservative monitoring':ti
23	'watchful waiting'
24	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
25	#5 AND #24
26	[2012-3000]/py
27	#25 AND #26
28	'prostatic neoplasms'
29	(prostat* NEAR/5 (cancer* OR carcin* OR tumor* OR tumour* OR neoplasm*)):ti
30	(prostat* NEAR/3 (carcinoma OR neoplasia OR neoplasm* OR adenocarcinoma OR cancer* OR tumor* OR tumour*OR malignan*)):ti
31	#28 OR #29 OR #30
32	'prognostic methods'
33	'predictive factors'
34	(prognos* NEAR/10 (relapse* OR recurrence* OR survival* OR death* OR mortality OR progress* OR 'disease free'OR 'psa failure' OR 'biochemical failure')):ab,ti
35	(predict* NEAR/10 (relapse* OR recurrence* OR survival* OR death* OR mortality OR progress* OR 'disease free' OR 'psa failure' OR 'biochemical failure')):ab,ti
36	('neural network' NEAR/10 (relapse* OR recurrence* OR survival* OR death* OR mortality OR progress* OR 'disease free' OR 'PSA failure' OR 'biochemical failure')):ab,ti
37	'survival rate'
38	prognosis:ab,ti AND (relapse*:ab,ti OR recurrence*:ab,ti OR survival*:ab,ti OR death*:ab,ti OR mortality:ab,ti OR progress*:ab,ti OR 'disease free':ab,ti OR 'PSA failure':ab,ti OR 'biochemical failure':ab,ti)
39	'disease free survival'
40	'mortality'
41	'recurrence'

42	'neural networks computer':ab,ti AND (relapse*:ab,ti OR recurrence*:ab,ti OR survival*:ab,ti OR death*:ab,ti OR mortality:ab,ti OR progress*:ab,ti OR 'disease free':ab,ti OR 'psa failure':ab,ti OR 'biochemical failure':ab,ti)
43	'models statistical':ab,ti AND (relapse*:ab,ti OR recurrence*:ab,ti OR survival*:ab,ti OR death*:ab,ti OR mortality:ab,ti OR progress*:ab,ti OR 'disease free':ab,ti OR 'psa failure':ab,ti OR 'biochemical failure':ab,ti)
44	'algorithms':ab,ti AND (relapse*:ab,ti OR recurrence*:ab,ti OR survival*:ab,ti OR death*:ab,ti OR mortality:ab,ti OR progress*:ab,ti OR 'disease free':ab,ti OR 'psa failure':ab,ti OR 'biochemical failure':ab,ti)
45	(algorithm* NEAR/10 (relapse* OR recurrence* OR survival* OR death* OR mortality OR progress* OR 'disease free' OR 'PSA failure' OR 'biochemical failure')):ab,ti
46	'survival analysis'
47	nomogram*
48	(marker* OR biomarker*) NEAR/10 (prognos* OR predict*)
49	#32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48
50	letter:it
51	comment:it
52	animal:ab,ti OR (cell:ab,ti AND line*:ab,ti) OR vitro:ab,ti OR invitro:ab,ti OR rat:ab,ti OR rats:ab,ti OR mouse:ab,ti ORmice:ab,ti
53	#50 OR #51 OR #52
54	#31 OR #49
55	#54 NOT #53
56	#26 AND #55
57	#27 AND #56

ATSI search terms used:

#	**Searches**
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	(#1 AND #2) OR #3

For Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment database

#	**Searches**
1	(prostat$ adj3 (cancer$ OR carcinoma$ OR malignan$ OR tumo?r$ OR neoplas$ OR metastas$ OR adeno$)).tw

Appendix B:

Level of Evidence rating criteria – Prognostic studies

Level	Study design
I	A systematic review of level II studies
II	A prospective cohort study
III-1	All or none
III-2	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial
III-3	A retrospective cohort study
IV	Case series, or cohort study of persons at different stages of disease

According to the standards of the National Health and Medical Research Council

Appendix C: Excluded studies

Study	Reason for Exclusion
Abdollah 2013	Inappropriate study design
Akhter 2013	Inappropriate study design
Bonekamp 2013	Median follow-up less than 5 years
Bul 2012	Did not report relevant outcomes
Cary 2013	Median follow-up less than 5 years
Cooperberg 2013	Insufficient information to determine follow-up period.
Drouin 2012	Did not report relevant outcomes
Eichholz 2014	Did not report relevant outcomes
El 2013	Did not report relevant outcomes
Fu 2013	Median follow-up less than 5 years
Guzzo 2012	Did not report relevant outcomes
Han 2012	Median follow-up less than 5 years
Hirama 2014	Median follow-up less than 5 years
Iremashvili 2012	Inappropriate participants
Iremashvili 2013 (Biopsy features)	Median follow-up less than 5 years
Iremashvili 2013 (Improving risk)	Median follow-up less than 5 years
Iremashvili 2013 (A nomogram)	Median follow-up less than 5 years
Iremashvili 2013 (Comprehensive)	Median follow-up less than 5 years
Khan 2014	Did not report relevant outcomes
Klein 2013	Inappropriate study design
Lee 2013 (Tumor lesion)	Did not report relevant outcomes
Lee 2013 (Low-risk) JJCO	Did not report relevant outcomes
Lee 2013 (Low risk) EUS	Did not report relevant outcomes
Lucarelli 2012	Did not report relevant outcomes
Margel 2013	Inappropriate participants
McGuire 2012	Did not report relevant outcomes
Mullins 2013	Did not report relevant outcomes
Nicolai 2013	Median follow-up less than 5 years
Park 2013	Did not report relevant outcomes
Ploussard 2013	Median follow-up less than 5 years
Porpiglia 2013 (Is mpMRI)	Did not report relevant outcomes
Porpiglia 2013 (Active surveill)	Did not report relevant outcomes
Reese 2013 (Critical)	Did not report relevant outcomes. Inappropriate participants.
Reese 2013 (Expanded)	Did not report relevant outcomes
Sanguedolce 2013	Median follow-up less than 5 years
Situmorang 2012	Inappropriate participants
Somford 2013	Did not report relevant outcomes
Stamatakis 2013	Insufficient information to determine follow-up period.
Sternberg 2014	Median follow-up less than 5 years
Thomsen 2012	Median follow-up less than 5 years
Truong 2013	Inappropriate participants
Turkbey 2013	Did not report relevant outcomes
Vargas 2012	Did not report relevant outcomes
Vasarainen 2013	Median follow-up less than 5 years

Vellekoop 2013	Did not report relevant outcomes
Wang 2014	Median follow-up less than 5 years
Welty 2014	Median follow-up less than 5 years
Westphalen 2013	Insufficient information to determine follow-up period.
Wever 2013	Did not report relevant outcomes
Wong 2012	Review article. Did not report relevant outcomes.

References: Excluded Studies

1. Abdollah F, Di TE, Castiglione F, Passoni NM, Capitanio U, Gallina A et al. Spatial distribution of positive cores decreases misclassification rates of patients with low risk prostate cancer candidate for active surveillance. *Journal of Urology* 2013; 189:e102.

2. Akhter W, Benton S, Chinegwundoh F. Are PSA, free to total PSA ratio, & p2PSA levels helpful to monitor pathological grades of prostate cancer patients on active surveillance? *Journal of Endourology* 2013; 27:A289.

3. Bonekamp D, Bonekamp S, Mullins JK, Epstein JI, Carter HB, Macura KJ. Multiparametric magnetic resonance imaging characterization of prostate lesions in the active surveillance population: incremental value of magnetic resonance imaging for prediction of disease reclassification. *Journal of Computer Assisted Tomography* 2013; 37:948-956.

4. Bul M, Zhu X, Rannikko A, Staerman F, Valdagni R, Pickles T et al. Radical prostatectomy for low-risk prostate cancer following initial active surveillance: Results from a prospective observational study. *European Urology* 2012; 62:195-200.

5. Cary KC, Cowan JE, Sanford M, Shinohara K, Perez N, Chan JM et al. Predictors of Pathologic Progression on Biopsy Among Men on Active Surveillance for Localized Prostate Cancer: The Value of the Pattern of Surveillance Biopsies. *European Urology* 2014; 66(2):337-342.

6. Cooperberg M, Simko J, Falzarano S, Maddala T, Chan J, Cowan J et al. Development and validation of the biopsy-based genomic prostate score (GPS) as a predictor of high grade or extracapsular prostate cancer to improve patient selection for active surveillance. *Journal of Urology* 2013; 189:e873.

7. Drouin SJ, Comperat E, Cussenot O, Bitker MO, Haertig A, Roupret M. Clinical characteristics and pathologic findings in patients eligible for active surveillance who underwent radical prostatectomy. *Urologic Oncology* 2012; 30:402-407.

8. Eichholz A, McCarthy F, Dennis N, Thomas K, Howlett T, Iqbal J et al. Evaluation of the prostate health index (phi) as a novel biomarker in active surveillance of prostate cancer. *Journal of Clinical Oncology* 2014; 32(Feb Suppl.):81.

9. El HA, Ploussard G, de la Taille A, Allory Y, Vordos D, Hoznek A et al. Patient selection and pathological outcomes using currently available active surveillance criteria. *BJU International* 2013; 112:471-477.

10. Fu Q, Moul JW, Banez L, Sun L, Mouraviev V, Xie D et al. Preoperative predictors of pathologic stage T2a and pathologic Gleason score <6 in men with clinical low-risk prostate cancer treated with radical prostatectomy: reference for active surveillance. *Medical Oncology* 2013; 30:326.

11. Guzzo TJ, Resnick MJ, Canter DJ, Bivalacqua TJ, Rosen MA, Bergey MR et al. Endorectal T2-weighted MRI does not differentiate between favorable and adverse pathologic features in men with prostate cancer who would qualify for active surveillance. *Urologic Oncology: Seminars and Original Investigations* 2012; 30:301-305.

12. Han JS, Toll AD, Amin A, Carter HB, Landis P, Lee S et al. Low prostate-specific antigen and no gleason score upgrade despite more extensive cancer during active surveillance predicts insignificant prostate cancer at radical prostatectomy. *Urology* 2012; 80:883-888.

13. Hirama H, Sugimoto M, Ito K, Shiraishi T, Kakehi Y. The impact of baseline [-2]proPSA-related indices on the prediction of pathological reclassification at 1 year during active surveillance for low-risk prostate cancer: the Japanese multicenter study cohort. *Journal of Cancer Research and Clinical Oncology* 2014; 140:257-263.

14. Iremashvili V, Pelaez L, Manoharan M, Jorda M, Rosenberg DL, Soloway MS. Pathologic prostate cancer characteristics in patients eligible for active surveillance: A head-to-head comparison of contemporary protocols. *European Urology* 2012; 62:462-468.

15. Iremashvili V, Manoharan M, Rosenberg DL, Soloway MS. Biopsy features associated with prostate cancer progression in active surveillance patients: comparison of three statistical models. *BJU International* 2013; 111:574-579.

16. Iremashvili V, Burdick-Will J, Soloway MS. Improving risk stratification in patients with prostate cancer managed by active surveillance: a nomogram predicting the risk of biopsy progression. *BJU International* 2013; 112:39-44.

17. Iremashvili V, Joshua B-W, Mure A, Soloway MS. A nomogram predicting the risk of progression in patients managed by active surveillance. *Journal of Urology* 2013; 189:e275-e276.

18. Iremashvili V, Manoharan M, Lokeshwar SD, Rosenberg DL, Pan D, Soloway MS. Comprehensive analysis of post-diagnostic prostate-specific antigen kinetics as predictor of a prostate cancer progression in active surveillance patients. *BJU International* 2013; 111:396-403.

19. Khan FM, Fernandez G, Scott R, Lance RS, Cordon-Cardo C, Klotz L et al. A quantitative image analysis model of prostate biopsies for predicting clinical risk in men enrolled in an active surveillance program. *Journal of Clinical Oncology* 2014; 32(Feb Suppl.):111.

20. Klein EA: A genomic approach to active surveillance: A step toward precision medicine. *Asian Journal of Andrology* 2013; 15:340-341.

21. Lee DH, Koo KC, Lee SH, Rha KH, Choi YD, Hong SJ, et al. Tumor lesion diameter on diffusion weighted magnetic resonance imaging could help predict insignificant prostate cancer in patients eligible for active surveillance: Preliminary analysis. *Journal of Urology* 2013; 190:1213-1217.

22. Lee DH, Koo KC, Lee SH, Rha KH, Choi YD, Hong SJ et al. Low-risk prostate cancer patients without visible tumor (T1c) on multiparametric MRI could qualify for active surveillance candidate even if they did not meet inclusion criteria of active surveillance protocol. *Japanese Journal of Clinical Oncology* 2013; 43:553-558.

23. Lee DH, Kim KH, Lee SH, Rha KH, Choi YD, Hong SJ et al. Low risk prostate cancer patients without visible tumor (T1c) on diffusion-weighted MRI could qualify for active surveillance candidate regardless of inclusion criteria of active surveillance protocol. *European Urology Supplement* 2013; 12:e269.

24. Lucarelli G, Fanelli M, Larocca AM, Germinario CA, Rutigliano M, Vavallo A et al. Serum sarcosine increases the accuracy of prostate cancer detection in patients with total serum PSA less than 4.0 ng/ml. *Prostate* 2012; 72:1611-1621.

25. Margel D, Nandy I, Wilson TH, Castro R, Fleshner N. Predictors of pathological progression among men with localized prostate cancer undergoing active surveillance: A sub-analysis of the REDEEM study. *Journal of Urology* 2013; 190:2039-2045.

26. McGuire BB, Helfand BT, Kundu S, Hu Q, Banks JA, Cooper P et al. Association of prostate cancer risk alleles with unfavourable pathological characteristics in potential candidates for active surveillance. *BJU International* 2012; 110:338-343.

27. Mullins JK, Bonekamp D, Landis P, Begum H, Partin AW, Epstein JI et al. Multiparametric magnetic resonance imaging findings in men with low-risk prostate cancer followed using active surveillance. *BJU International* 2013; 111:1037-1045.

28. Nicolai N, Alvisi MF, Rancati T, Salvioni R, Stagni S, Marenghi C et al. Different predictors of upgrading and upsizing at 1-year repeat biopsy inmen with low-risk prostate cancer undergoing active surveillance in prospective trials. *European Urology Supplement* 2013; 12:153-154.

29. Park BH, Choo SH, Jang HJ, Suh YS, Jeong U.S., Song W et al. Role of multiparametric 3.0 Tesla magnetic resonance imaging in prostate cancer patients eligible for active surveillance. *European Urology Supplement* 2013; 12:e266-e267.

30. Ploussard G, de la Taille A, Terry S, Allory Y, Ouzaid I, Vacherot F et al. Detailed biopsy pathologic features as predictive factors for initial reclassification in prostate cancer patients eligible for active surveillance. *Urologic Oncology* 2013; 31:1060-1066.

31. Porpiglia F, Fiori C, Mele F, Manfredi M, Grande S, Poggio M, et al. Is multiparametric MRI reliable in selecting patients with prostate cancer for active surveillance? *Anticancer Research* 2013; 33:2323-2324.

32. Porpiglia F, Fiori C, Mele F, Manfredi M, Grande S, Poggio M et al. Active surveillance for prostate cancer: Diagnostic accuracy of multiparametric MRI in selection of patients. *Journal of Urology* 2013; 189:e905.

33. Reese A, Landis P, Han M, Epstein J, Carter B. Critical assessment of criteria used to identify men eligible for active surveillance of low-risk prostate cancer. *Journal of Urology* 2013; 189:e226.

34. Reese AC, Landis P, Han M, Epstein JI, Carter HB. Expanded criteria to identify men eligible for active surveillance of low risk prostate cancer at Johns Hopkins: A preliminary analysis. *Journal of Urology* 2013; 190:2033-2038.

35. Sanguedolce F, Padhani AR, Anyamene N, Beatty J, Hellawell G. Impact of multiparametric prostate MRI on the selection of active surveillance patients. *European Urology Supplement* 2013; 12:e268-e269.

36. Situmorang GR, Umbas R, Mochtar CA, Santoso RB. Prostate cancer in younger and older patients: Do we treat them differently? *Asian Pacific Journal of Cancer Prevention* 2012; 13:4577-4580.

37. Somford DM, Hoeks CM, Hulsbergen-Van De Kaa CA, Hambrock T, Futterer JJ, Witjes JA et al. Evaluation of diffusion-weighted MR imaging at inclusion in an active surveillance protocol for low-risk prostate cancer. *Investigative Radiology* 2013; 48:152-157.

38. Stamatakis L, Siddiqui MM, Nix JW, Logan J, Rais-Bahrami S, Walton-Diaz A et al. Accuracy of multiparametric magnetic resonance imaging in confirming eligibility for active surveillance for men with prostate cancer. *Cancer* 2013; 119:3359-3366.

39. Sternberg IA, Yu C, Keren Paz GE, Kim PH, Bernstein M, Lakin P, et al. Predicting progression in patients followed with active surveillance for low-risk prostate cancer. *Journal of Clinical Oncology* 2014; 32(Feb Suppl.):38.

40. Thomsen F, Roder M, Hvarness H, Iversen P, Brasso K. Active surveillance for patients with low-risk prostate cancer: How does PSA doubling time affect the risk of histo-pathological progression at re-biopsy? *Urology* 2012; 80:S26.

41. Truong M, Slezak JA, Lin CP, Iremashvili V, Sado M, Razmaria AA et al. Development and multi-institutional validation of an upgrading risk tool for Gleason 6 prostate cancer. *Cancer* 2013; 119:3992-4002.

42. Turkbey B, Mani H, Aras O, Ho J, Hoang A, Rastinehad AR et al. Prostate cancer: Can multiparametric MR imaging help identify patients who are candidates for active surveillance? *Radiology* 2013; 268:144-152.

43. Vargas HA, Akin O, Afaq A, Goldman D, Zheng J, Moskowitz CS et al. Magnetic resonance imaging for predicting prostate biopsy findings in patients considered for active surveillance of clinically low risk prostate cancer. *Journal of Urology* 2012; 188:1732-1738.

44. Vasarainen H, Lahdensuo K, Savolainen R, Ruutu M, Taari K, Rannikko A. Diffusion-weighted magnetic resonance imaging in prostate cancer patients on active surveillance one year after diagnosis and before repeat biopsy. *Scandinavian Journal of Urology* 2013; 47:456-461.

45. Vellekoop A, Loeb S, Folkvaljon Y, Stattin P. Population based study of predictors of adverse pathology among candidates for active surveillance with Gleason 6 prostate cancer. *Journal of Urology* 2014; 191:350-357.

46. Wang S-Y, Cowan JE, Cary KC, Chan JM, Carroll PR, Cooperberg MR. Limited ability of existing nomograms to predict outcomes in men undergoing active surveillance for prostate cancer. *BJU International* 2014; published online ahead of print.

47. Welty CJ, Cowan JE, Nguyen H, Shinohara K, Perez N, Greene KL et al. Factors associated with biopsy progression on active surveillance. *Journal of Clinical Oncology* 2014; 32(Feb Suppl.):19.

48. Westphalen AC, Liang C, Noworolski SM, Viigneron DB, Flavell R, Kurhanewicz J. Predicting disease progression with multiparametric magnetic resonance imaging of prostate cancer managed with active surveillance. *Abdominal Imaging* 2013; 38:629.

49. Wever EM, Heijnsdijk EA, Draisma G, Bangma CH, Roobol MJ, Schroder FH et al. Treatment of local-regional prostate cancer detected by PSA screening: benefits and harms according to prognostic factors. *British Journal of Cancer* 2013; 108:1971-1977.

50. Wong LM, Neal DE, Johnston RB, Shah N, Sharma N, Hovens CM et al. International multicentre study examining selection criteria for active surveillance in men undergoing radical prostatectomy. *British Journal of Cancer* 2012; 107:1467-1473.

Systematic review report for question 10

Clinical question 10: *"What is the best monitoring protocol for active surveillance and what should be the criteria for intervention?"*

PICO Question 10: *'For men with biopsy-diagnosed prostate cancer following an active surveillance protocol, which combination of monitoring tests, testing frequency and clinical or other criteria for intervention achieve the best outcomes in terms of length and quality of life?*'

Population	Intervention	Comparator	Outcomes
Men with biopsy (histologically) confirmed prostate cancer	Active surveillance protocol (monitoring, triggers for intervention)	An alternative active surveillance protocol and immediate definitive treatment, or immediate definitive treatment	- Overall mortality, or - Prostate cancer-specific mortality, or - Quality of life, or - Adverse events

1. METHODS

1.1 Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption guidelines had to be evidence based and meet the pre-specified criteria of scores of greater or equal to 70% for the domains rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

1.2 Literature Search

Medline (01/01/1990 - 01/03/2014), Embase (01/01/1990 - 01/03/2014), Cochrane Database of Systematic Reviews (01/01/2005 - 01/03/2014), Database of Abstracts of Reviews of Effects and Health Technology Assessment databases up until 01/03/2014 were searched using text terms and, where available, database specific subject headings. Each database was searched for articles dealing with prostate cancer. In Medline and Embase databases the prostate cancer search was coupled with a search for active surveillance (AS), and database specific filters to identify the highest level of evidence that met the inclusion criteria[1]. To identify studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples. A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 which were added to the relevant database after February 2014. Alerts were checked until July 2014. Reference lists of all relevant articles were checked for potential additional articles.

[1] NHMRC Evidence Hierarchy, www.nhmrc.gov.au

1.3 Inclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	Nomograms (or predictive model) that have not been validated in a separate cohort
Study design	Randomised, or pseudo-randomised controlled trials, or cohort study, or nested case-control study, or meta-analysis/systematic reviews thereof	
Population	Men with histologically confirmed prostate cancer	Studies that restricted participants based on biomarker status
Intervention	Active Surveillance	Studies that do not report monitoring protocols, or triggers for intervention
Comparator	An alternative active surveillance protocol and immediate definitive treatment, or immediate definitive treatment	
Outcomes	- Overall mortality, or - Prostate cancer-specific mortality, or - Quality of life, or - Adverse events	
Language	English	
Publication period	After 31st December 1989 and before1st March 2014	

Conference proceedings identified by the search literature searches were included if they met the inclusion criteria.

1.5 Definitions

Active Surveillance

AS entails close follow-up of patients diagnosed with early stage, low-risk prostate cancer. The objective is to avoid unnecessary treatment of men with indolent cancer, and only treat patients who show signs of disease progression. Monitoring of these patients usually involves prostate specific antigen (PSA) testing, digital rectal examination (DRE), transperineal prostate biopsies, and multi parametric prostate magnetic resonance imaging (MRI). Therapy is recommended at a time when cure is deemed possible and when disease progression is detected. Active surveillance aims to avoid unnecessary treatment in order to avoid untoward quality of life or side effects that may occur as a result. AS may be also called ‘active monitoring’.

2. RESULTS

2.1 Guidelines

Seventeen potentially relevant guidelines were identified. Three sets of guidelines (AHRQ, KCE, and NCCN) contained recommendations regarding active surveillance however they were not adopted as they failed to meet our pre-specified criteria for inclusion score of ≥70% for each of the 3 domains assessed (Rigour of Development, Clarity of Presentation, and Editorial Independence) in the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/). An additional relevant guideline was also found. This guideline was titled the National Institute for Health and Care Excellence's (NICE) Clinical Guideline for Prostate Cancer: Diagnosis and Treatment (UK National Collaborating Centre for Cancer 2014a[1]). This NICE guideline addressed the clinical question: *Which men with localised prostate cancer should be offered active surveillance?* This NICE guideline used a different approach and assessed prognostic factors for men undergoing active surveillance rather than comparing the effects of different interventions in different groups of men. This guideline (and our literature update thereof) is described in a separate report. The remaining guidelines were not based on systematic reviews.

2.2 Results of Literature Search

Figure 1 outlines the process of identifying relevant articles from the systematic review. In total, four individual search strategies were undertaken for Medline and Embase databases. The first search attempted to identify randomised controlled trials that met the inclusion criteria. The second search attempted to identify systematic reviews or meta-analyses of case-control and cohort studies that met the inclusion criteria. The third search attempted to identify case-control and cohort studies that met the inclusion criteria. As all these three searched failed to identify literature that met the inclusion criteria, a fourth search was performed to identify case-control studies of immediate verse deferred curative treatment.

The Medline search identified 1,426 citations (Search#1=190, Search#2=206, Search#3=707, and Search#4=323), the Embase search 1,695 citations (Search#1=94, Search#2=25, Search#3=668, and Search#4=908), and the search of the Cochrane Database of Systematic Reviews 59 citations, the Database of Abstracts of Reviews of Effects search 282 citations and the search of the Health Technology Assessment database identified an additional 216 citations, resulting in a total of 3,678 citations. Titles and abstracts were examined and 87 articles were retrieved for a more detailed evaluation. One (1) additional potential citation was identified from the reference list of retrieved articles.

Three (3) studies reported in 3 articles met the inclusion criteria and were included in the review. There were no studies of ATSI men that met the inclusion criteria.

The retrieved articles that were not included and the reason for their exclusion are documented in Appendix C. In summary, most articles were excluded because they used inappropriate study designs (e.g. many Klotz *et al.* studies) or did not report relevant outcomes.

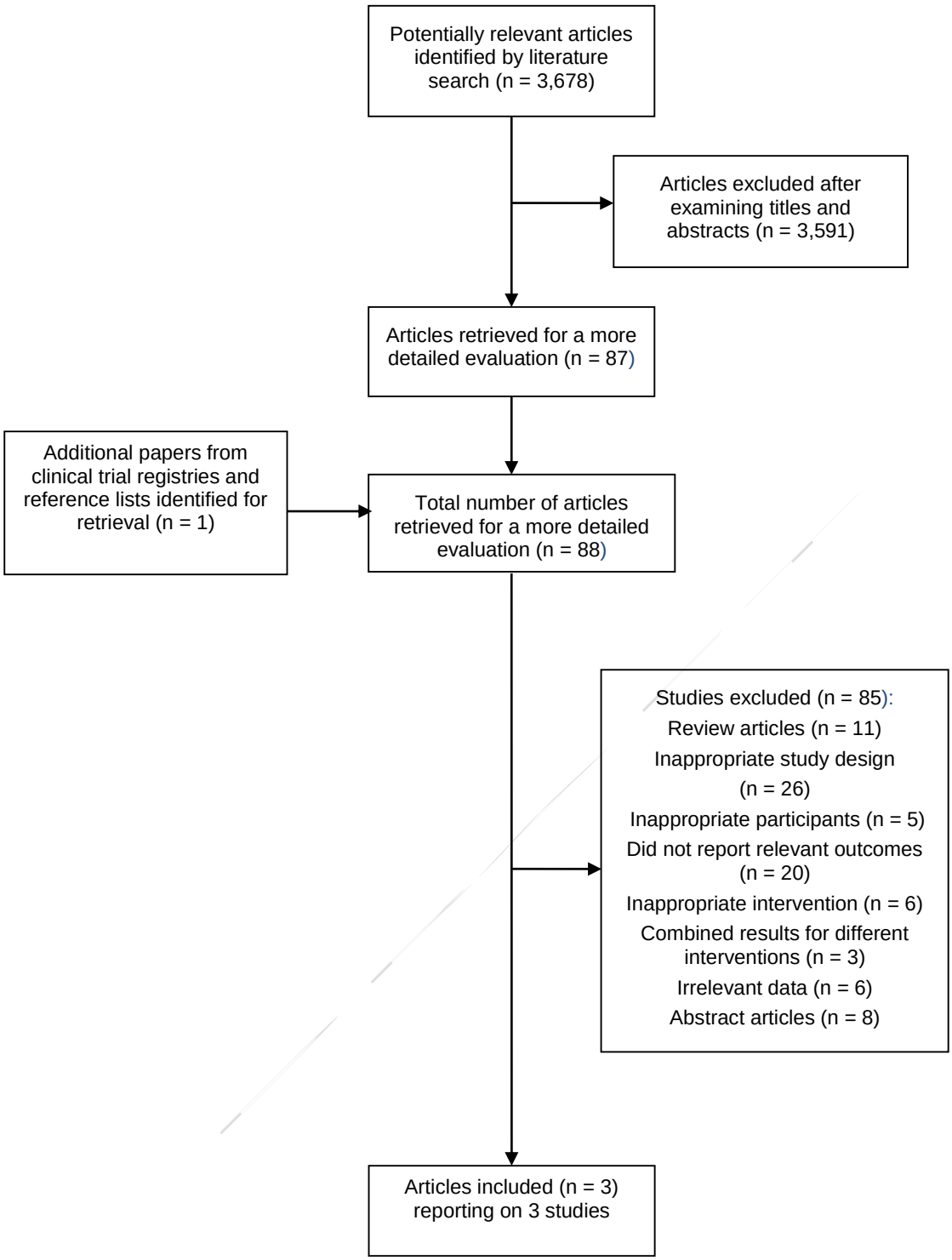


Figure 1. Process of inclusion and exclusion of studies

2.3 Study Characteristics

Table 1: Characteristics of intervention studies examining active surveillance and immediate treatment or delayed and immediate radical prostatectomy for improving outcomes in prostate cancer patients

Study	Participants	Design	Intervention	Immediate Treatment	Outcomes	Comments
Active Surveillance vs. Immediate Treatment (RP/EBRT/ADT)						
Kakehi 2008 (Japan)	Men aged 50-80 years with an initial PSA level ≤20 ng/mL, offered active surveillance with T1cN0M0 cancer (UICC TNM 4th edition, 1987), 1 or 2 positive cores per 6-12 systematic biopsy cores, Gleason score ≤6 and ≤50% cancer involvement in any of the positive biopsy cores (confirmed by central pathologist) recruited from 7 Cancer Centre hospitals and 6 University hospitals between January 2002 and December 2003 **Exclusion criteria:** Past history of cerebral infarction, unstable angina, diabetes uncontrollable with insulin, severe hypertension, myocardial infarction within 6 months **Age (years):** ≤59: 3.7% 60-69: 42.5% 70-74: 38.1% 75≥: 15.7% **PSA (ng/mL):** Mean 7.3. <10: 80.6% ≥10: 19.4% **Gleason score:** 5: 11.2% 6: 88.8% **N = 134**	Cohort study multi-centre (prospective)	**Active Surveillance** (accepted active surveillance) <u>Monitoring protocol:</u> PSA monitored every 2 months for 6 months then every 3 months thereafter; re-measurements of unnatural increases of PSA allowed within 3 months; Local progression examined with DRE and TRUS at least twice per year and because of rising PSA; Chest X-ray, CT scan or MRI for abdominal/pelvic cavity and bone scintigraphy performed at least once every 2 years to rule out metastases; <u>Triggers for intervention:</u> Aggressive treatment recommended if PSADT ≤2 years after 6 months, thereafter treatment recommended if PSADT ≤2 years within 1 year; Re-biopsy recommended after 1 year on AS; men who did not fit initial selection criteria recommended to start treatment **N = 118**	**Immediate Treatment** (rejected active surveillance) **Radical Prostatectomy** (81.3%) **External Beam Radiotherapy** (12.5%) **Androgen Deprivation Therapy** (6.3%) **N = 16**	**Primary:** *None relevant* **Secondary:** *Adverse events* (no relevant data reported) *Health- and Disease-related quality of life* (assessed at baseline and 1 year later. No relevant data reported) *Overall mortality* *Prostate-cancer specific mortality* Follow-up until 31st October 2006 (2.8-4.8 years)	All patients encouraged to start AS for at least 6 months; patients who declined immediately started treatment; Study designed to evaluate the validity of selection criteria for AS. Point estimate of primary endpoint (% of patients on AS showing PSADT >2 years at initial 6-month assessment) expected to be >80% for validation; Planned sample size of 100 patients opting for AS based on the precision of estimate to give the width of 95% confidence intervals for the primary endpoint within 10%;

Delayed Radical Prostatectomy vs. Immediate Radical Prostatectomy						
Holmström 2010 (Sweden)	Men aged 41-70 years with PSA level <20 ng/mL and Gleason score ≤6 who had been diagnosed with clinical stage T1-2 N0/X M0/X prostate cancer **Mean age (years):** Deferred RP: 61.9 Primary RP: 61.1 **PSA (ng/mL):** Deferred RP: 6.7 (mean) Primary RP: 7.8 (mean) 0-4: 11.9% 4-10: 63.6% 10-20: 24.6% **Tumour stage:** T1a: 1.8% T1b: 1.2% T1c: 59.6% T2: 37.3% **Gleason score:** 2-4: 11.0% 5: 22.6%; 6: 66.6% N = 7492 (entire cohort) **N = 2566** (eligible men who underwent RP)	Cohort study (retro-spective)	**Deferred Radical Prostatectomy** Median 19.2 months after diagnosis <u>Triggers for intervention:</u> Initiated by PSA progression in 50%, by other signs of progression in 9%, by other causes in 39%; **N = 222**	**Immediate Radical Prostatectomy** Median 3.5 months after date of diagnosis **N = 2344**	**Primary:** *All-cause mortality* *Prostate cancer-specific mortality* (prostate cancer coded as "underlying cause of death") Data on observations made ≥6 months after diagnosis gathered from the Swedish Cancer Register (capture rate ≥96.3% for all tumors), the Swedish Cause of Death Register and the National Prostate Cancer Register of Sweden up to 31st December 2008 Death certificates reviewed for men who died between 1st January 2008 and 31st December 2008 to determine cause of death; Median follow up = 8.2 years	Treatment decisions made in routine clinical practice **- no pre-defined criteria for selection of treatment, no protocol for surveillance and no pre-set trigger for initiation of deferred treatment**; Cohort included men who underwent primary or deferred radiotherapy, primary or deferred hormone therapy or continued surveillance until end of follow-up (watchful waiting or active surveillance); **No patient characteristics or outcome data reported**;

Sun 2012 (Canada)	Men aged ≥66 years on SEER-Medicare insurance program-linked database as diagnosed with prostate cancer between 1995 – 2005 as their first malignant disease, who had undergone RP, had clinical stage T1-2N0M0 disease and Gleason score <7. **Median age**: 68 years **Race: 7.4% African American** **Gleason score:** 2-4=3.9%; 5-6=96.1% **Charlson index:** 0=56.5%; 1=27.1%; 2=10.1%; ≥3=6.4% **N=17153**	Cohort Study (retro-spective)	**Delayed Radical Prostatectomy** Radical prostatectomy performed >3 months after diagnosis. Median time to treatment 5.0 months (mean 11.5 months) **Reasons for delay not described** 24.5% received ADT **N=2576**	**Immediate Radical Prostatectomy** Radical prostatectomy performed ≤3 months after diagnosis Median time to treatment 2.0 months (mean 1.6 months) 10.4% received ADT **N=14577**	**Primary:** *Urinary incontinence (ICD codes for diagnosis or treatment)* *Erectile dysfunction (ICD codes for diagnosis or treatment)* *Prostate cancer mortality (ICD-9 185.9 or ICD-10 C619).* Follow up 2-12 years	Active surveillance may be one of a number of reasons for delayed radical prostatectomy SEER- Medicare insurance program-linked database does not contain details on reasons for delay

ADT = androgen deprivation therapy; AS = active surveillance; DRE = digital rectal examination; EBRT = external beam radiotherapy; ICD-9 = International Classification of Diseases Ninth revision; ICD-10 = International Classification of Diseases Tenth revision; MRI = Magnetic resonance imaging; *PSA = prostate specific antigen; PSADT = prostate specific antigen doubling time; RP = radical prostatectomy; SEER* = Surveillance, Epidemiology, and End Results*; TRUS = transrectal ultrasound-guided; UICC = Union for International Cancer Control.*

2.4 Study Quality

Methodological quality of included cohort studies is described in Table 2.

Table 2: Methodological quality of included cohort studies (n = 3)

Quality Category	N (%)
IA. Subject Selection – 'New technology' group	
2 = Representative of eligible patients	1 (33.3)
1 = Selected group	1 (33.3)
0 = Highly selected or not described	1 (33.3)
IB. Subject Selection – Comparison group	
2 = Representative of eligible patients	1 (33.3)
1 = Selected group	1 (33.3)
0 = Highly selected or not described	1 (33.3)
II. Comparability of groups on demographic characteristics	
2 = Comparable	-
1 = Not comparable but adjusted analysis used	1 (33.3)
0 = Not comparable and not adjusted for differences	2 (66.7)
IIIA. Measurement of outcomes - blinded	
2 = Yes	1 (33.3)
1 = No, but objective measure used	1 (33.3)
0 = No or not described	1 (33.3)
IIIB. Measurement of outcomes - same method	
2 = Yes	2 (66.7)
0 = No or not described	1 (33.3)
IV. Completeness of follow-up	
2 = Yes (>95% or intention-to-treat analysis)	2 (66.7)
1 = Reasonable follow-up of all groups (>80%)	-
0 = No or not described	1 (33.3)

Table 3: Methodological quality of included cohort studies (n = 3)

	Subject selection (New tech)	Subject selection (Comp group)	Groups demo	Measurement of outcome (Blinded)#	Measurement of outcome (Same method)#	Follow up	Overall rating	Risk of bias
Holmström 2010	0	0	1	1	1	2	Low	High
Kakehi 2008	1	1	0	0	0	0	Low	High
Sun 2012	2	2	0	0	2	2	Low	High

- primary outcomes assessed, tech = technology, comp = comparison, demo = demographics.

Key to overall quality rating

High quality: a review that received 2 for all quality criteria.

Medium quality: Received 2 and 1 for all quality criteria.

Low quality: Received 0 for all quality criteria or 1 and 0 all quality criteria or received 0 for any of the quality criteria

2.5 Study Results

Effect of intervention on relevant outcomes are described in Tables 4-8

I Overall Mortality/All-cause Mortality

Table 4: Results of studies comparing effects of active surveillance with immediate treatment on overall mortality

Study	Outcome Definition	Measure	N actual	Active Surveillance	Immediate Treatment	Size of effect	Size of effect CI	p value	Follow up
Active Surveillance vs. Immediate Treatment									
Kakehi 2008	**Overall mortality**	% (n)	134	1.7 (2) N = 118	6.3 (1) N = 16	NR	NR	NR	4.5 years

CI = confidence interval; NR = not reported

Table 5: Results of studies comparing effects of delayed radical prostatectomy with immediate radical prostatectomy on all-cause mortality

Study	Outcome Definition	Measure	N actual	Delayed Radical Prostatectomy	Immediate Radical Prostatectomy	Size of effect	Size of effect CI	p value	Follow up
Delayed Radical Prostatectomy vs. Immediate Radical Prostatectomy									
Holmström 2010	**All-cause mortality** *cumulative incidence*	% (n)	2566	6.3* (14) N = 222	6.9* (161) N = 2344	ARD = -0.6%*	NR	>0.05[a]	8.2 years median

ARD = absolute risk difference, negative values indicate a benefit of delayed radical prostatectomy over immediate radical prostatectomy; CI = confidence interval; NR = not reported.

** calculated by reviewers*
a = competing risk analysis (observation time - from date of diagnosis, time at risk - from date of radical prostatectomy)

II Prostate Cancer Mortality

Table 6: Results of studies comparing effects of active surveillance with immediate treatment on prostate cancer mortality

Study	Outcome Definition	Measure	N actual	Active Surveillance	Immediate Treatment	Size of effect	Size of effect CI	p value	Follow up
Active Surveillance vs. Immediate Treatment									
Kakehi 2008	**Prostate cancer mortality**	% (n)	134	0 (0) N = 118	0 (0) N = 16	NR	NR	NR	2.8-4.8 years

CI = confidence interval; NR = not reported

Table 7: Results of studies comparing effects of delayed radical prostatectomy with immediate radical prostatectomy on prostate cancer mortality

Study	Outcome Definition	Measure	N actual	Delayed Radical Prostatectomy	Immediate Radical Prostatectomy	Size of effect	Size of effect CI	p value	Follow up
Delayed Radical Prostatectomy vs. Immediate Radical Prostatectomy									
Holmström 2010	**Prostate cancer mortality**	% (n)	2566	0.9* (2) N = 222	0.7 (16) N = 2,344	ARD = 0.2%*	NR	>0.05[a]	8.2 years median
Sun 2012	**Prostate cancer mortality** *Cumulative incidence 10-year rate*	% (n)	17153	13.1 (337*) N = 2576	13.7 (1997*) N = 14577	NR	NR	0.70	2-12 years

*ARD = absolute risk difference, negative values indicate a benefit of delayed radical prostatectomy over immediate radical prostatectomy; CI = confidence interval; NR = not reported; * calculated by reviewers.*

a = competing risk analysis (observation time - from date of diagnosis, time at risk - from date of radical prostatectomy)

III Quality of Life

Table 8: Results of studies comparing effects of delayed radical prostatectomy with immediate radical prostatectomy on quality of life

Study	Outcome		N actual	Delayed Radical Prostatectomy	Immediate Radical Prostatectomy	Size of effect (OR)	Size of effect (CI)	p value	Follow up
	Definition	**Measure**							
Delayed Radical Prostatectomy vs. Immediate Radical Prostatectomy									
Sun 2012	**Incontinence**[a]								
	(≥18 months after surgery)								
	Treatment (ICD-9 codes)		17153	NR	NR	1.16	1.01 – 1.18	<0.05	2-12 years
	Diagnosis (ICD-9 codes)			NR	NR	1.01	0.92 – 1.11	NS	
	Erectile Dysfunction[a]								
	(≥18 months after surgery)								
	Treatment (ICD-9 codes)		17153	NR	NR	1.33	1.13 – 1.57	<0.05	2-12 years
	Diagnosis(ICD-9 codes)			NR	NR	1.24	1.13 – 1.35	<0.001	

CI = confidence interval; ICD = International Classification of Diseases, Ninth revision; NR = not recorded; NS = not significantly different; OR = odds ratio.

a = Adjusted for age, race, comorbidity, Gleason sum, postoperative radiation, androgen deprivation therapy, baseline urinary incontinence, baseline erectile dysfunction, socioeconomic status, marital status, registries, population density, year of surgery, and pathological stage.

2.6 Body of Evidence

Effects of interventions on relevant outcomes are described in Tables 9-13.

I Overall Mortality/All-cause Mortality

Table 9: Body of evidence examining the effects of active surveillance with immediate treatment on overall mortality

Name of study	Study type	N	Level of evidence *	Quality of evidence**	Risk of bias	Results summary	Size of Effect	p value	95% CI	Relevance of evidence
Active Surveillance vs. Immediate Treatment										
Kakehi 2008 **Monitoring:** PSA monitored every 2 months for 6 months then every 3 months thereafter; re-measurements of unnatural increases of PSA allowed within 3 months. Local progression examined with DRE and TRUS at least twice per year and because of rising PSA. Chest X-ray, CT scan or MRI for abdominal/pelvic cavity and bone scintigraphy performed at least once every 2 years to rule out metastases; **Intervention criteria:** Aggressive treatment recommended if PSADT ≤2 yrs after 6 months, thereafter treatment recommended if PSADT ≤2 yrs within 1 year. Re-biopsy recommended after 1 year on AS; men who did not fit initial selection criteria recommended to start treatment Follow-up = 4.5 years	Prospective Cohort (multi-centre)	134 (DT = 16)	III-2	Low	High	**Overall mortality (%):** AS: 1.7 (N = 2) IT: 6.3 (N = 1)	ARD=-4.6%	NR	NR	1

ARD = absolute risk difference, negative values indicate a benefit of active surveillance over definitive treatment; AS = active surveillance; CI = confidence interval; CT = computer tomography; DRE = digital rectal examination; IT = immediate treatment; MRI = magnetic resonance imaging; NR = not reported; PSA = prostate specific antigen; PSADT = prostate-specific antigen doubling time; TRUS = transrectal ultrasound.
** Refer to Appendix B for detailed explanations of rating scores; ** See table 2 for quality appraisals*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the evidence statement table of content template

Table 10: Body of evidence examining the effects of delayed radical prostatectomy with immediate radical prostatectomy on all-cause mortality

Name of study	Study type	N	Level of evidence *	Quality of evidence**	Risk of bias	Results summary	Size of Effect	p value	95% CI	Relevance of evidence
Delayed Radical Prostatectomy vs. Immediate Radical Prostatectomy										
Holmström 2010 **Monitoring:** No predefined protocol for surveillance because treatment decisions were made in routine clinical practice. **Intervention criteria:** Initiated by PSA progression in 50%, by other signs of progression in 9%, by other causes in 39%. Follow-up = 8.2 years	Retrospective Cohort	2566	III-2	Low	High	**All-cause mortality (%):** dRP: 6.3 iRP: 6.9	ARD= -0.6%	NS	NR	1

ARD = absolute risk difference, negative values indicate a benefit of delayed radical prostatectomy over immediate radical prostatectomy; CI = confidence interval; dRP = delayed radical prostatectomy; iRP = immediate radical prostatectomy; NR= not reported; NS = not significantly different; PSA = prostate specific antigen.

** Refer to Appendix B for detailed explanations of rating scores; ** See table 2 for quality appraisals*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the evidence statement table of content template

II Prostate Cancer Mortality

Table 11: Body of evidence examining the effects of active surveillance with immediate treatment on prostate cancer-specific mortality

Name of study	Study type	N	Level of evidence *	Quality of evidence**	Risk of bias	Results summary	Size of effect	p value	95% CI	Relevance of evidence
Active Surveillance vs. Immediate Treatment										
Kakehi 2008 **Monitoring:** PSA monitored every 2 months for 6 months then every 3 months thereafter; re-measurements of unnatural increases of PSA allowed within 3 months. Local progression examined with DRE and TRUS at least twice per year and because of rising PSA. Chest X-ray, CT scan or MRI for abdominal/pelvic cavity and bone scintigraphy performed at least once every 2 years to rule out metastases; **Intervention criteria:** Aggressive treatment recommended if PSADT ≤2 yrs after 6 months, thereafter treatment recommended if PSADT ≤2 yrs within 1 year. Re-biopsy recommended after 1 year on AS; men who did not fit initial selection criteria recommended to start treatment Follow-up = 4.5 years	Prospective Cohort (multi-centre)	134 (DT:16)	III-2	Low	High	**Prostate cancer-specific mortality (%):** AS:0 IT:0	ARD=0	NR	NR	1

ARD = absolute risk difference; AS = active surveillance; CI = confidence interval; CT = computer tomography; DRE = digital rectal examination; IT = immediate treatment; MRI = magnetic resonance imaging; NR = not reported; PSA = prostate specific antigen; PSADT = prostate-specific antigen doubling time; TRUS = transrectal ultrasound.

** Refer to Appendix B for detailed explanations of rating scores; ** See table 2 for quality appraisals*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the evidence statement table of content template

Table 12: Body of evidence examining the effects of delayed radical prostatectomy with immediate radical prostatectomy on prostate cancer-specific mortality

Name of study	Study type	N	Level of evidence *	Quality of evidence**	Risk of bias	Results summary	Size of effect	p value	95% CI	Relevance of evidence
Delayed Radical Prostatectomy vs. Immediate Radical Prostatectomy										
Holmström 2010 **Monitoring:** No predefined protocol for surveillance because treatment decisions were made in routine clinical practice. **Intervention criteria:** Initiated by PSA progression in 50%, by other signs of progression in 9%, by other causes in 39%. Follow-up = 8.2 years	Retrospective cohort	2566	III-2	Low	High	**Prostate cancer-specific mortality (%):** dRP: 0.9 iRP: 0.7	ARD=0.2%	NR	NS	1
Sun 2012 **Monitoring:** Not reported **Intervention criteria:** Not reported. Follow-up = 10 years	Retrospective cohort	17153	III-2	Low	High	**Prostate cancer-specific mortality (%):** dRP: 13.1 iRP: 13.7	ARD=-0.6%	0.70	NR	1

ARD = absolute risk difference, negative values indicate a benefit of delayed radical prostatectomy over immediate radical prostatectomy; CI = confidence interval; dRP = delayed radical prostatectomy; iRP = immediate radical prostatectomy; NR= not reported; NS = not significantly different; PSA = prostate specific antigen.

** Refer to Appendix B for detailed explanations of rating scores; ** See table 2 for quality appraisals*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the evidence statement table of content template

III Quality of Life

Table 13: Body of evidence examining the effects of delayed radical prostatectomy with immediate radical prostatectomy on quality of life

Name of study	Study type	N	Level of evidence *	Quality of evidence**	Risk of bias	Results summary	Size of Effect (OR)	P value	95% CI	Relevance of evidence
Delayed Radical Prostatectomy vs. Immediate Radical Prostatectomy										
Sun 2012	Retrospe		III-2	Low	High	**Incontinence (%):**				
	ctive	17153				iRP: 20.8 dRP (3-5 months): 19.7	0.90	NS	0.79-1.02	1
Monitoring:	cohort	17153				iRP: 20.8 dRP (5-9 months): 24.2	1.12	NS	0.90-1.38	1
Not reported		17153				iRP: 20.8 dRP (≥9 months): 31.8	1.73	<0.001	1.40-2.14	1
						Erectile dysfunction (%):				
Intervention criteria:		17153				iRP: 5.7 dRP (3-5 months): 6.3	1.10	NS	0.89-1.36	1
Not reported.		17153				iRP: 5.7 dRP (5-9 months): 9.2	1.63	<0.05	1.18-2.24	1
		17153				iRP: 5.7 dRP (≥9 months): 11.8	1.85	<0.001	1.36-2.52	1
Follow-up = 10 years										

CI = confidence interval; dRP = delayed radical prostatectomy performed greater than 3 months following diagnosis (range of time to treatment in brackets); iRP = immediate radical prostatectomy within 3 months of diagnosis; NS = not statistically significantly different; OR = odds ratio.

** Refer to Appendix B for detailed explanations of rating scores; ** See table 2 for quality appraisals*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the NHMRC evidence statement form.

2.7 References: Included studies

1. Holmström B, Holmberg E, Egevad L, Adolfsson J, Johansson JE, Hugosson J et al. Outcome of primary versus deferred radical prostatectomy in the National Prostate Cancer Register of Sweden Follow-Up Study. *Journal of Urology* 2010; 184:1322-7.

2. Kakehi Y, Kamoto T, Shiraishi T, Ogawa O, Suzukamo Y, Fukuhara S et al. Prospective evaluation of selection criteria for active surveillance in Japanese patients with stage T1cN0M0 prostate cancer. *Japanese Journal of Clinical Oncology* 2008; 38:122-8.

3. Sun M, Abdollah F, Hansen J, Trinh QD, Bianchi M, Tian Z et al. Is a treatment delay in radical prostatectomy safe in individuals with low-risk prostate cancer? *Journal of Sexual Medicine* 2012; 9:2961-9.

3. APPENDICES

Appendix A: Search strategies used:

Search #1 – Randomised Controlled Trials for Active Surveillance

For Medline database:

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	randomized controlled trial.pt.
5	controlled clinical trial.pt.
6	placebo.ab.
7	randomi?ed.ab.
8	randomly.ab.
9	trial.ab.
10	groups.ab.
11	4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp animals/ not humans.sh.
13	11 not 12
14	(active adj2 surveillance).mp
15	(expectant$ adj2 (management or treat$)).mp
16	delay$ intervention.mp
17	(active adj1 monitoring).tw
18	'active monitoring'.tw
19	'conservative monitoring'.tw
20	'delayed treatment$'.tw
21	'watchful observation'.tw
22	'watchful surveillance'.tw
23	'watchful monitoring'.tw
24	'expectant monitoring'.tw
25	'expectant surveillance'.tw
26	'delayed therap$'.tw
27	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28	3 AND 13 AND 27

Used the Cochrane sensitivity maximizing filters for identifying randomised controlled trials (http://handbook.cochrane.org, accessed 20/02/2013/ Centre for Reviews and Dissemination systematic review/ meta-analyses strategy 2.(Lee et al, (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. ***BMC Medical Research Methodology*** *12:51)*

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
3	prostate cancer.mp. or exp Prostatic Neoplasms/
4	1 AND (2 OR 3)

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database

#	Searches
1	'prostate cancer'/exp OR 'prostate cancer'
2	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR metast* OR adeno*)
3	#1 OR #2
4	active NEAR/2 surveillance
5	expectant* NEAR/2 (management OR treat*)
6	delay* NEAR/3 intervention
7	#4 OR #5 OR #6
8	rct
9	'randomized controlled trial'/exp OR 'randomized controlled trial'
10	'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomised controlled trial'/exp OR 'randomised controlled trial' OR 'randomized controlled trials'/exp OR 'randomized controlled trials' OR 'randomised controlled trials'
11	'random allocation'/exp OR 'random allocation'
12	'randomly allocated'
13	'randomization'/exp OR 'randomization'
14	allocated NEAR/2 random
15	'double blind procedure'/exp OR 'double blind procedure'
16	'single blind procedure'/exp OR 'single blind procedure'
17	single NEXT/1 blind*
18	double NEXT/1 blind*
19	(treble OR triple) NEXT/1 blind*
20	placebo*
21	'placebo'/exp OR 'placebo'
22	'prospective study'/exp OR 'prospective study'
23	'crossover procedure'/exp OR 'crossover procedure'
24	'clinical trial'/exp OR 'clinical trial'
25	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
26	'case study'/exp OR 'case study'
27	case AND report
28	'abstract report'/exp OR 'abstract report'
29	'letter'/exp OR 'letter'
30	#26 OR #27 OR #28 OR #29

31	#25 NOT #30
32	[1990-3000]/py
33	[english]/lim
34	[humans]/lim
35	#32 and #33 and #34
36	[medline]/lim
37	#35 NOT #36
38	#3 AND #7 AND #31 AND #37

Search #2 - Systematic Review/Meta-Analysis of Case-Control & Cohort studies for Active Surveillance

For Medline database:

#	Searches
1	active NEAR/2 surveillance
2	expectant* NEAR/2 (management OR treat*)
3	delay* NEAR/3 intervention
4	1 OR 2 OR 3
5	'prostate cancer'/exp OR 'prostate cancer'
6	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR metast* OR adeno*)
7	5 OR 6
8	meta-analysis/
9	review literature/
10	meta-analy$.tw
11	metaanal$.tw
12	(systematic$ adj4 (review$ or overview$)).mp
13	meta-analysis.pt
14	review.pt
15	review.ti
16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17	case report/
18	letter.pt
19	historical article.pt
20	17 or 18 or 19
21	16 not 20
22	[1990-3000]/py
23	[english]/lim
24	[medline]/lim
25	[humans]/lim
26	22 AND 23 AND 25
27	26 NOT 24
28	4 AND 7 AND 21 AND 27

For Embase database:

#	Searches
1	'prostate cancer'/exp OR 'prostate cancer'
2	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR metast* OR adeno*)
3	#1 OR #2
4	active NEAR/2 surveillance
5	expectant* NEAR/2 (management OR treat*)
6	delay* NEAR/3 intervention
7	#4 OR #5 OR #6
8	'meta analysis'/exp OR 'meta analysis'
9	'review'/exp OR review AND ('literature'/exp OR literature)
10	'systematic review'/exp OR 'systematic review'
11	systematic AND overview
12	'review'/exp OR review
13	#8 OR # 9 OR #10 OR #11 OR #12
14	case AND report
15	'letter'/exp OR letter
16	historical AND ('article'/exp OR article)
17	#14 OR #15 OR #16
18	#13 NOT #17
19	[1990-3000]/py
20	[english]/lim
21	[humans]/lim
22	[medline]/lim
23	(#19 AND #20 AND #21) NOT #22
24	#3 AND #7 AND #18 AND #23

Search#3 - Case-Control and Cohort studies for Active Surveillance

For Medline database:

#	Searches
1	(active adj2 surveillance).mp.
2	(expectant$ adj2 (management or treat$)).mp.
3	delay$ intervention.mp.
4	1 or 2 or 3
5	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
6	prostate cancer.mp. or exp Prostatic Neoplasms/
7	5 or 6
8	4 and 7
9	limit 8 to yr="1990 -Current"
10	limit 9 to (english language and humans)
11	commentary/
12	case report/
13	letter.pt.
14	historical article.pt.
15	salvage.mp.
16	chemotherapy.mp.
17	editorial.pt.
18	11 or 12 or 13 or 14 or 15 or 16 or 17
19	10 not 18

For Embase database:

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	#1 or #2
4	active NEAR/2 surveillance
5	expectant* NEAR/2 (management OR treat*)
6	delay* NEAR/3 intervention
7	#4 OR #5 OR #6
8	‘commentary’
9	'case report'/exp OR 'case report'
10	'letter'/exp OR letter
11	'historical article'
12	Salvage
13	'chemotherapy'/exp OR chemotherapy
14	'editorial'/exp OR editorial
15	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
16	[1990-3000]/py
17	[english]/lim
18	[medline]/lim

19	[humans]/lim
20	(#16 AND #17 AND #19) NOT #18
21	#3 AND #7 AND #20
22	#21 NOT #15

Used the SIGN filter for identifying randomised controlled trials (www.sign.ac.uk/methodology/filters.html#systematic accessed 20/02/2013)

For Embase database: ATSI search terms used

#	Searches
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3
5	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
6	prostate cancer.mp. or exp Prostatic Neoplasms/
7	#5 AND #6
8	#4 AND #7

For Cochrane Database of Systematic Reviews 2005 to March 2014, Database of Abstracts of Reviews of Effects 1st quarter 2014 and Health Technology Assessment database 1st quarter 2014.

#	Searches
1	(prostat$ adj3 (cancer$ OR carcinoma$ OR malignan$ OR tumo?r$ OR neoplas$ OR metastas$ OR adeno$)).tw
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 OR 2

Search #4 – Case-Control Studies of Immediate verses Deferred Curative Treatment

For Medline database:

#	Searches
1	(active adj2 surveillance).mp.
2	(expectant$ adj2 (management or treat$)).mp.
3	delay$ intervention.mp.
4	1 or 2 or 3
5	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
6	prostate cancer.mp. or exp Prostatic Neoplasms/
7	5 or 6
8	4 and 7
9	limit 8 to yr="1990 -Current"
10	limit 9 to (english language and humans)
11	commentary/
12	case report/

13	letter.pt.
14	historical article.pt.
15	salvage.mp
16	chemotherapy.mp.
17	editorial.pt.
18	11 or 12 or 13 or 14 or 15 or 16 or 17
19	10 not 18
20	(delay$ or immediate or defer$ or observation$).ti.
21	1 or 2 or 20
22	7 and 21
23	limit 22 to yr="1990 -Current"
24	limit 23 to (english language and humans)
25	24 not 18
26	25 not 19

For Embase database:

#	Searches
1	active NEAR/2 surveillance
2	expectant* NEAR/2 (management OR treatment*)
3	delay* OR immediate OR defer* OR observation*:ti
4	1 OR 2 OR 3
5	'prostate cancer'/exp
6	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR metast* OR adeno*)
7	5 OR 6
8	[humans]/lim AND [english]/lim AND [1990-3000]/py NOT [medline]/lim
9	'commentary'
10	'case report'/exp OR 'case report'
11	'letter' OR 'letter'/exp OR letter
12	'historical article'
13	salvage
14	'chemotherapy'/exp OR 'chemotherapy'
15	'editorial'/exp OR 'editorial'
16	8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15
17	4 AND 7 AND 8
18	17 NOT 16

APPENDIX B:

Level of Evidence rating criteria – Intervention studies

Level	Study design
I	Meta-analysis or a systematic review of level II studies
II	Randomised controlled trial or a phase III/IV clinical trial
III-1	Pseudo-randomised controlled trial or a meta-analysis/systematic review of level III-1 studies
III-2	Comparative study with concurrent controls: - Phase II clinical trial - Non-randomised, experimental trial9 - Controlled pre-test/post-test study - Adjusted indirect comparisons - Interrupted time series with a control group - Cohort study - Case-control study or a meta-analysis/systematic review of level III-2 studies
III-3	A comparative study without concurrent controls: - Phase I clinical trial - Historical control study - Two or more single arm study10 - Unadjusted indirect comparisons - Interrupted time series without a parallel control group or a meta-analysis/systematic review of level III-3 studies
IV	Case series with either post-test or pre-test/post-test outcomes or a meta-analysis/systematic review of level IV studies

According to the standards of the National Health and Medical Research Council

Relevance of the evidence

Rating	Relevance
1	Evidence of an effect on patient-relevant clinical outcomes including benefits and harms, quality of life and survival.
2	Evidence of an effect on a surrogate outcome* that has been shown to be predictive of patient-relevant outcomes for the same intervention.
3	Evidence of an effect on proven surrogate outcomes but for a different intervention.
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population.
5	Evidence confined to unproven surrogate outcomes.

**'surrogate outcome' refers to reasonable indicators of whether there has been some effect (e.g. blood pressure measurements or levels of serum cholesterol)*

Points to considering patient-relevant outcomes:
i) The goal of decision making in health care is to choose the intervention(s) (which may include doing nothing) that is (are) most likely to deliver the outcomes that patients find desirable
ii) Surrogate outcomes (such as blood pressure measurements or levels of serum cholesterol) may be reasonable indicators of whether there has been some effect. However, they should not be the basis for clinical decisions unless they reliably predict an effect on the way the patient feels; otherwise they will not be of interest to the patient or their carers
iii) All possible outcomes that are of most interest to patients (particularly harms) should be identified and evaluated

adapted from table 1.10: National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence.

Appendix C:

Potential relevant guidelines identified but not adopted

YEAR	ORGANISATION	TITLE	REASONS FOR NOT ADOPTING
2010	American Cancer Society	American Cancer Society Guideline for the Early Detection of Prostate Cancer	Not a systematic review
2011	Agency for Healthcare Research and Quality	An Evidence Review of Active Surveillance in Men with Localized Prostate Cancer	Did not meet 70% scores for domains of Rigour, Clarity and Editorial Independence on AGREE instrument
2007	American Urology Association	Guideline for the Management of Clinically Localized Prostate Cancer: 2007 Update	Not a systematic review
2009	American Urology Association	Prostate-Specific Antigen Best Practice Statement: 2009 Update	Not a systematic review
2011	Canadian Urology Association	Prostate Cancer Screening: Canadian Guidelines 2011	Not a systematic review
2012	European Association of Urology	Guidelines on Prostate Cancer (Feb 2012)	Not a comprehensive systematic review
2013	European Association of Urology	Guidelines on Prostate Cancer (Mar 2013)	Not a comprehensive systematic review
2009	Institute for Clinical and Economic Review	Management Options for Low-Risk Prostate Cancer: A Report on Comparative Effectiveness and Value	Not a systematic review
2006	Japanese Urological Association	Evidence-based Clinical Practice Guidelines for Prostate Cancer	Not a systematic review
2012	KCE/Belgium Health Care Knowledge Centre	A National Clinical Practice Guideline on the management of localised prostate cancer	Did not meet 70% scores for domains of Rigour, Clarity and Editorial Independence on AGREE instrument
2013	National Comprehensive Cancer Network	NCCN Clinical Practice Guidelines in Oncology: Prostate cancer (version 2.2013)	Did not meet 70% scores for domains of Rigour, Clarity and Editorial Independence on AGREE instrument
2013	National Comprehensive Cancer Network	NCCN Clinical Practice Guidelines in Oncology: Prostate cancer (version 4.2013)	Did not meet 70% scores for domains of Rigour, Clarity and Editorial Independence on AGREE instrument
2008	National Institute for Health and Clinical Excellence	Prostate cancer: diagnosis and treatment	Contains relevant recommendations to this clinical question that have since been updated
2014	National Institute for Health and Clinical Excellence	Prostate cancer: diagnosis and treatment	Relevant sections to this clinical question
2011	National Institute of Health	Role of Active Surveillance in the Management of Men with Localized Prostate Cancer	Not a systematic review
2012	Prostate Cancer Taskforce NZ	Diagnosis and Management of Prostate Cancer in New Zealand Men	Not a systematic review
2012	Memorial Sloan-Kettering Cancer Center	Screening Guidelines: Prostate Cancer	Not a systematic review

Excluded Studies

Search #1 – Randomised Controlled Trials

Study	Reason for Exclusion
Bastian 2009	Review with inappropriate study design
Bul 2012	Inappropriate study design. Not randomised.
Dahabreh 2012	Inappropriate study design. No appropriate data in paper.
Godtman 2013	Inappropriate study design. Single-arm AS cohort study.
Heidenreich 2011	EAU guidelines. No appropriate data in paper.
Khatami 2006	Inappropriate study design. Not biopsy determined PCa.
Khatami 2009	Biomarker analysis. No appropriate data in paper.
Klotz 2004	Inappropriate study design. No appropriate data in paper.
Klotz 2008	No appropriate data in paper.
Klotz 2010	Inappropriate study design. No appropriate data in paper.
Lane 2010	No appropriate data in paper.
Mhaskar 2012	No appropriate data in paper.
Mullins 2013	Inappropriate study design. No appropriate data in paper.
Roach 2012	Inappropriate study design. Intervention is WW, not AS.
Roemeling 2006	Inappropriate study design. Intervention (WW not AS) not randomised.
Roemeling 2007a (EU)	Inappropriate study design. Intervention not randomised.
Roemeling 2007b (C)	Inappropriate study design
van den Bergh 2010	Inappropriate study design
Wever 2013	Inappropriate study design
Wilt 1994	Inappropriate study design. A RCT with WW as the intervention
Wilt 1995	Inappropriate study design. A RCT with WW as the intervention.
Wilt 1997	No appropriate data in paper.
Wong 2012	Inappropriate study design. No appropriate data in paper.

Search #2 (Systematic reviews)

Study	Reason for Exclusion
Abern 2013	Did not report relevant outcomes
Bangma 2012	Inappropriate study design
Bastian 2009	Review article that did not report relevant outcomes and had inappropriate study design
Dahabreh 2012	Review with inappropriate study design
Dall'Era 2010	Did not report relevant outcomes
Dall'Era 2012	Review with inappropriate study design
Furlan 2011	No relevant information
Heinderich 2011	No relevant information
Lees 2012	Did not report relevant outcomes
van den Bergh 2010	Did not report relevant outcomes
van den Bergh 2013	Review article that did not report relevant outcomes and inappropriate study design, and inappropriate intervention
Weissbach 2009	Review with inappropriate study design

Search #3 (Case-Cohort studies)

Study	Reason for Exclusion
Abern 2013	Did not report relevant outcomes
Ahallal 2013	Abstract article from conference proceedings
Albertsen 2010	Review article with Inappropriate study designs
Barry 2001	Inappropriate intervention
Bellardita 2012	Abstract article from conference proceedings
Bergman 2012	Review article with Inappropriate study designs
Burnet 2007	Inappropriate participants
Chopra 2012	Abstract article from conference proceedings
Cooperberg 2009	Combined results for different interventions.
Fleshner 2012	Inappropriate intervention
Hayes 2011	Inappropriate study design
Hegarty 2011	Review article that did not report relevant outcomes
Ip 2011	Inappropriate intervention
Khurana 2012	Abstract article from conference proceedings
Miocinovic 2011	Did not report relevant outcomes
Mishra 2013	Inappropriate intervention
Mohler 1997	Did not report relevant outcomes
Punnen 2013	Abstract article from conference proceedings
Roach 2012	Review articles with inappropriate intervention
Roemeling 2006	Inappropriate intervention
Selvadurai 2013	Inappropriate study design
Sieh 2013	Abstract article from conference proceedings
Singh 2010	Review articles with inappropriate study designs
Stattin 2008	Combined results for different interventions
Stattin 2010	Combined results for different interventions.
Thomas 2013	Abstract article from conference proceedings
Thong 2010	Inappropriate study design
van den Bergh 2010	Did not report relevant outcomes
van Vugt 2012	Did not report relevant outcomes
Victorson 2013	Abstract article from conference proceedings
Warlick 2006	Did not report relevant outcomes
Xia 2012	Inappropriate study design

Search #4 (Immediate vs deferred treatment)

Study	Reason for Exclusion
Abdollah 2011	Inappropriate study design
Abdollah 2012	Inappropriate study design
Abern 2013	Did not report relevant outcomes
Andrews 2004	Inappropriate study design
Dall'Era 2010	Did not report relevant outcomes
Graefen 2005	Did not report relevant outcomes
Khan 2004	Did not report relevant outcomes
Korets 2011	Did not report relevant outcomes/Inappropriate participants
Kwan 2006	Did not report relevant outcomes
Lee 2006	Did not report relevant outcomes
Nguyen 2005	Inappropriate intervention
O'Brien 2011	Did not report relevant outcomes
Phillips 2007	Did not report relevant outcomes
Shappley 2009	Inappropriate study design
Sun 2012	Did not report relevant outcomes
Torring 2013	Inappropriate study design
van den Bergh 2010	Did not report relevant outcomes
Vickers 2006	Inappropriate study design/Did not report relevant outcomes

References: Excluded Studies (Search #1 – RCT)

1. Bastian PJ, Carter BH, Bjartell A, Seitz M, Stanislaus P, Montorsi F et al. Insignificant prostate cancer and active surveillance: from definition to clinical implications. *European Urology* 2009; 55:1321-30.

2. Bul M, van den Bergh RC, Zhu X, Rannikko A, Vasarainen H, Bangma CH et al. Outcomes of initially expectantly managed patients with low or intermediate risk screen-detected localized prostate cancer. *BJU International* 2012; 110:1672-7.

3. Dahabreh IJ, Chung M, Balk EM, Yu WW, Mathew P, Lau J et al. Active surveillance in men with localized prostate cancer: a systematic review. *Annals of Internal Medicine* 2012; 156(8):582-90.

4. Godtman RA, Holmberg E, Khatami A, Stranne J, Hugosson J. Outcome following active surveillance of men with screen-detected prostate cancer. Results from the Goteborg randomised population-based prostate cancer screening trial. *European Urology* 2013; 63:101-7.

5. Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. *European Urology* 2011; 59:61-71.

6. Khatami A, Aus G, Damber JE, Lilja H, Lodding P, Hugosson J. PSA doubling time predicts the outcome after active surveillance in screening-detected prostate cancer: results from the European randomized study of screening for prostate cancer, Sweden section. *International Journal of Cancer* 2006; 120(1):170-4.

7. Khatami A, Hugosson J, Wang W, Damber JE: Ki-67 in screen-detected, low-grade, low-stage prostate cancer, relation to prostate-specific antigen doubling time, Gleason score and prostate-specific antigen relapse after radical prostatectomy. *Scandinavian Journal of Urology & Nephrology* 2009; 43:12-8.

8. Klotz L. Active surveillance with selective delayed intervention: Using natural history to guide treatment in good risk Prostate cancer. *Journal of Urology* 2004; 172:S48–S51.

9. Klotz L. Active surveillance for prostate cancer: trials and tribulations. *World Journal of Urology* 2008; 26:437-42.

10. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical Results of Long-Term Follow-Up of a Large, Active Surveillance Cohort with Localized Prostate Cancer. *Journal of Clinical Oncology* 2010; 28(1):126-31.

11. Lane JA, Hamdy FC, Martin RM, Turner EL, Neal DE, Donovan JL. Latest results from the UK trials evaluating prostate cancer screening and treatment: the CAP and ProtecT studies. *European Journal of Cancer.* 2010; 46(17):3095-101.

12. Mhaskar AR, Quinn G, Vadaparampil S,Djulbegovic B, Gwede CK, Kumar A. Timing of first-line cancer treatments - early versus late - a systematic review of phase III randomized trials. *Cancer Treatment Reviews* 2010; 36(8):621-8.

13. Mullins JK, Bonekamp D, Landis P, Begum H, Partin AW, Epstein JI et al. Multiparametric magnetic resonance imaging findings in men with low-risk prostate cancer followed using active surveillance. *BJU International* 2013; 111:1037-45.

14. Roach M, III, Thomas K. Overview of randomized controlled treatment trials for clinically localized prostate cancer: implications for active surveillance and the United States preventative task force report on screening? *Journal of the National Cancer Institute Monographs* 2012; 45:221-9.

15. Roemeling S, Roobol MJ, Postma R, Gosselaar C, van der Kwast TH, Bangma CH et al. Management and survival of screen-detected prostate cancer patients who might have been suitable for active surveillance. *European Urology* 2006; 50:475-82.

16. Roemeling S, Roobol MJ, de Vries SH, Wolters T, Gosselaar C, van Leenders GJ et al. Active surveillance for prostate cancers detected in three subsequent rounds of a screening trial: characteristics, PSA doubling times, and outcome. *European Urology* 2007; 1251(51):1244-50.

17. Roemeling S, Roobol MJ, Kattan MW, van der Kwast TH, Steyerberg EW, Schroder FH. Nomogram use for the prediction of indolent prostate cancer: impact on screen-detected populations. *Cancer* 2007; 110:2218-21.

18. van den Bergh RC, Steyerberg EW, Khatami A, Aus G, Pihl CG, Wolters T et al. Swedish and Dutch sections of the European Randomized Study of Screening for Prostate Cancer. Is delayed radical prostatectomy in men with low-risk screen-detected prostate cancer associated with a higher risk of unfavorable outcomes? *Cancer* 2010; 116:1281-90.

19. Wever EM, Heijnsdijk EA, Draisma G, Bangma CH, Roobol MJ, Schroder FH et al. Treatment of local-regional prostate cancer detected by PSA screening: benefits and harms according to prognostic factors. *British Journal of Cancer* 2013; 108:1971-7.

20. Wilt TJ, Brawer MK. The Prostate Cancer Intervention Versus Observation Trial: a randomized trial comparing radical prostatectomy versus expectant management for the treatment of clinically localized prostate cancer. *Journal of Urology* 1994; 152:1910-4.

21. Wilt TJ, Brawer MK. The Prostate cancer Intervention versus Observation Trial (PIVOT): A randomized trial comparing radical prostatectomy versus expectant management for the treatment of clinically localized prostate cancer. *Cancer* 1995; 75:1963-8.

22. Wilt TJ, Brawer MK. The Prostate Cancer Intervention versus Observation Trial (PIVOT). *Oncology* 1997; 11(8):1133-43.

23. Wong LM, Neal DE, Johnston RB, Shah N, Sharma N, Warren AY et al. International multicentre study examining selection criteria for active surveillance in men undergoing radical prostatectomy. *British Journal of Cancer* 2012; 107:1467-73.

References: Excluded Studies (Search #2 – Systematic Reviews/Meta Analysis)

1. Abern MR, Aronson WJ, Terris MK, Kane CJ, Presti JC, Jr., Amling CL et al. Delayed radical prostatectomy for intermediate-risk prostate cancer is associated with biochemical recurrence: possible implications for active surveillance from the SEARCH database. *Prostate* 2013; 73:409-17.

2. Bangma CH, Bul M, Roobol M. The Prostate cancer Research International: Active Surveillance study. *Current Opinion in Urology* 2012; 22:216-21.

3. Bastian PJ, Carter BH, Bjartell A, Seitz M, Stanislaus P, Montorsi F et al. Insignificant prostate cancer and active surveillance: from definition to clinical implications. *European Urology* 2009; 55:1321-30.

4. Dahabreh IJ, Chung M, Balk EM, Yu WW, Mathew P, Lau J et al. Active surveillance in men with localized prostate cancer: a systematic review. *Annals of Internal Medicine* 2012; 156:582-90.

5. Dall'Era MA, Cowan JE, Simko J, Shinohara K, Davies B, Konety BR et al. Surgical management after active surveillance for low-risk prostate cancer: pathological outcomes compared with men undergoing immediate treatment. *BJU International* 2011; 107:1232-7.

6. Dall'Era MA, Albertsen PC, Bangma C, Carroll PR, Carter HB, Cooperberg MR et al. Active surveillance for prostate cancer: a systematic review of the literature. *European Urology* 2012; 62:976-83.

7. Ip S, Dahabreh IJ, Chung M, Yu WW, Balk EM, Iovin RC et al. An evidence review of active surveillance in men with localized prostate cancer. *Evidence Report/Technology Assessment* 2011; 204:1-341.

8. Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. *European Urology* 2011; 59:61-71.

9. Lees K, Durve M, Parker C. Active surveillance in prostate cancer: patient selection and triggers for intervention. *Current Opinion in Urology* 2012; 22:210-5.

10. van den Bergh RC, Steyerberg EW, Khatami A, Aus G, Pihl CG, Wolters T et al, Swedish and Dutch sections of the European Randomized Study of Screening for Prostate Cancer. Is delayed radical prostatectomy in men with low-risk screen-detected prostate cancer associated with a higher risk of unfavorable outcomes? *Cancer* 2010; 116:1281-90.

11. van den Bergh RCN, Albertsen PC, Bangma CH, Freedland SJ, Graefen M, Vickers A et al. Timing of curative treatment for prostate cancer: A systematic review. *European Urology* 2013; 64:204-15.

12. Weissbach L, Altwein J. Active surveillance or active treatment in localized prostate cancer? *Deutsches Arzteblatt International* 2009; 106:371-6

References: Excluded Studies (Search #3 – Case-Control Studies)

1. Abern MR, Aronson WJ, Terris MK, Kane CJ, Presti JC, Jr., Amling CL et al. Delayed radical prostatectomy for intermediate-risk prostate cancer is associated with biochemical recurrence: possible implications for active surveillance from the SEARCH database. *Prostate* 2013; 73:409-17.

2. Ahallal Y, Barret E, Sanchez-Salas R, Durand M, Mascle L, Giedelman C et al. The psychological impact of the different treatment modalities in men with localized prostate cancer. *Journal of Urology* 2013; 189:e412-e413.

3. Albertsen PC. Treatment of localized prostate cancer: when is active surveillance appropriate? *Nature Reviews Clinical Oncology* 2010; 7:394-400.

4. Barry MJ, Albertsen PC, Bagshaw MA, Blute ML, Cox R, Middleton RG et al. Outcomes for men with clinically nonmetastatic prostate carcinoma managed with radical prostactectomy, external beam radiotherapy, or expectant management: a retrospective analysis. *Cancer* 2001; 91:2302-14.

5. Bellardita L, Avuzzi B, Rancati T, Villani D, Catania S, Magnani T et al. Quality of life in prostate cancer patients: Radiotherapy compared to Active Surveillance. *Radiotherapy and Oncology* 2012; 103:S262.

6. Bergman J, Litwin MS. Quality of life in men undergoing active surveillance for localized prostate cancer. *Journal of the National Cancer Institute Monographs* 2012; 45:242-9.

7. Burnet KL, Parker C, Dearnaley D, Brewin CR, Watson M. Does active surveillance for men with localized prostate cancer carry psychological morbidity? *BJU International* 2007; 100:540-3.

8. Chopra S, Thanigasalam R, Beattie K, Egger S, Smith D, Symons J et al. Quality of life outcomes amongst men undergoing contemporary techniques for the treatment of localised prostate cancer: A prospective study. *Journal of Urology* 2012; 187:e596-e597.

9. Cooperberg MR, Broering JM, Carroll PR. Risk assessment for prostate cancer metastasis and mortality at the time of diagnosis. *Journal of the National Cancer Institute* 2009; 101:878-87.

10. Fleshner NE, Lucia MS, Egerdie B, Aaron L, Eure G, Nandy I et al. Dutasteride in localised prostate cancer management: the REDEEM randomised, double-blind, placebo-controlled trial. *Lancet* 2012; 379:1103-11.

11. Hayes JH, Ollendorf DA, Pearson SD, Barry MJ, Kantoff PW, Stewart ST et al. Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis. *JAMA* 2010; 304:2373-80.

12. Hegarty J, Bailey DE, Jr. Active surveillance as a treatment option for prostate cancer. *Seminars in Oncology Nursing* 2011; 27:260-6.

13. Ip S, Dahabreh IJ, Chung M, Yu WW, Balk EM, Iovin RC et al. An evidence review of active surveillance in men with localized prostate cancer. *Evidence Report/Technology Assessment* 2011; 204:1-341.

14. Khurana KK, Klink JC, Jianbo L, Krebs TL, Prots DJ, Isariyawongse BK et al. Urinary continence (UC) and sexual function (SF) among men with localized prostate cancer treated with active surveillance (AS), radical prostatectomy (RP), and brachytherapy (PI): Interim results of a prospective, longitudinal health-related quality-of-life (HRQOL) study. *Journal of Urology* 2012; 187:e155.

15. Miocinovic R, Jones JS, Pujara AC, Klein EA, Stephenson AJ. Acceptance and durability of surveillance as a management choice in men with screen-detected, low-risk prostate cancer: improved outcomes with stringent enrolment criteria*. Urology* 2011; 77:980-4.

16. Mishra MV, Shen X, Den RB, Champ CE, Trabulsi EJ, Lallas CD et al. Patterns of care for elderly men diagnosed with favorable-risk prostate cancer from 2004 to 2008: A population-based analysis. *American Journal of Clinical Oncology* 2013; 36(6):606-11.

17. Mohler JL, Williams BT, Freeman JA. Expectant management as an option for men with stage T1c prostate cancer: a preliminary study. *World Journal of Urology* 1997; 15:364-8.

18. Punnen S, Cowan J, Carroll P, Cooperberg M. Long term health related quality of life outcomes after primary treatment for localized prostate cancer: Results from the capsure registry. *Journal of Urology* 2013; 189:e411-e412.

19. Roach M III, Thomas K. Overview of randomized controlled treatment trials for clinically localized prostate cancer: implications for active surveillance and the United States preventative task force report on screening? *Journal of the National Cancer Institute Monographs* 2012; 45:221-9.

20. Roemeling S, Roobol MJ, Postma R, Gosselaar C, van der Kwast TH, Bangma CH et al.Management and survival of screen-detected prostate cancer patients who might have been suitable for active surveillance. *European Urology* 2006; 50:475-82.

21. Selvadurai ED, Singhera M, Thomas K, Mohammeda K, Woode-Amissah R, Horwich A et al. Medium-term Outcomes of Active Surveillance for Localised Prostate Cancer. *European Urology* 2013; 64:981-7.

22. Sieh W, Lichtensztajn DY, Nelson DO, Cockburn M, West DW, Brooks JD et al. Treatment and mortality in men with localized prostate cancer: A population-based study in California. *Open Prostate Cancer Journal* 2013; 6:1-9.

23. Singh J, Trabulsi EJ, Gomella LG. Is there an optimal management for localized prostate cancer? *Clinical Interventions In Aging* 2010; 5:187-97.

24. Stattin P, Holmberg E, Bratt O, Adolfsson J, Johansson JE, Hugosson J, National Prostate CR. Surveillance and deferred treatment for localized prostate cancer. Population based study in the National Prostate Cancer Register of Sweden. *Journal of Urology* 2008; 180:2423-9.

25. Stattin P, Holmberg E, Johansson JE, Holmberg L, Adolfsson J, Hugosson J, National Prostate Cancer Register (NPCR) of Sweden. Outcomes in localized prostate cancer: National Prostate Cancer Register of Sweden follow-up study. *Journal of the National Cancer Institute* 2010; 102:950-8.

26. Thomas A, Kim B, Jung H, Porter K, Zheng C, Gelfond J et al. Quality of life outcomes in men undergoing treatment of localized prostate cancer: Initial results from the kaiser permanente southern California region. *Journal of Urology* 2013; 189:e146.

27. Thong MS, Mols F, Kil PJ, Korfage IJ, van de Poll-Franse LV. Prostate cancer survivors who would be eligible for active surveillance but were either treated with radiotherapy or managed expectantly: comparisons on long-term quality of life and symptom burden. *BJU International* 2010; 105:652-8.

28. van den Bergh RC, Steyerberg EW, Khatami A, Aus G, Pihl CG, Wolters T et al. Swedish and Dutch sections of the European Randomized Study of Screening for Prostate Cancer: Is delayed radical prostatectomy in men with low-risk screen-detected prostate cancer associated with a higher risk of unfavorable outcomes? *Cancer* 2010; 116:1281-90.

29. van Vugt HA, Roobol MJ, van der Poel HG, van Muilekom EH, Busstra M, Kil P, Oomens EH et al. Selecting men diagnosed with prostate cancer for active surveillance using a risk calculator: a prospective impact study. *BJU International* 2012; 110:180-7.

30. Victorson D, Helfand B, Stein D, Kundu S, Nadler R, Casey J et al. Do pre-treatment differences exist between men who choose active surveillance or radical prostatectomy in self-reported QoL, anxiety or urological symptoms? *Journal of Urology* 2013; 189:e554-e555.

31. Warlick C, Trock BJ, Landis P, Epstein JI, Carter HB. Delayed versus immediate surgical intervention and prostate cancer outcome. *Journal of the National Cancer Institute* 2006; 98:355-7.

32. Xia J, Trock BJ, Cooperberg MR, Gulati R, Zeliadt SB, Gore JL et al. Prostate cancer mortality following active surveillance versus immediate radical prostatectomy. *Clinical Cancer Research* 2012; 18:5471-8.

Search #4 – Case-Control Studies of Immediate vs Deferred Curative Treatment

1. Abdollah F, Sun M, Schmitges J, Tian Z, Jeldres C, Briganti A et al. Cancer-specific and other-cause mortality after radical prostatectomy versus observation in patients with prostate cancer: competing-risks analysis of a large North American population-based cohort. *European Urology* 2011; 60:920-30.

2. Abdollah F, Sun M, Schmitges J, Thuret R, Tian Z, Shariat SF et al. Competing-risks mortality after radiotherapy vs. observation for localized prostate cancer: a population-based study. *International Journal of Radiation Oncology, Biology, Physics* 2012; 84:95-103.

3. Abern MR, Aronson WJ, Terris MK, Kane CJ, Presti JC, Amling CL et al. Delayed radical prostatectomy for intermediate-risk prostate cancer is associated with biochemical recurrence: possible implications for active surveillance from the SEARCH database. *Prostate* 2013; 73:409-17.

4. Andrews SF, Horwitz EM, Feigenberg SJ, Eisenberg DF, Hanlon AL, Uzzo RG et al. Does a delay in external beam radiation therapy after tissue diagnosis affect outcome for men with prostate carcinoma? *Cancer* 2005; 104:299-304.

5. Dall'Era MA, Cowan JE, Simko J, Shinohara K, Davies B, Konety BR et al. Surgical management after active surveillance for low-risk prostate cancer: pathological outcomes compared with men undergoing immediate treatment. BJU International 2010; 107:1232-7.

6. Graefen M, Walz J, Chun KH, Schlomm T, Haese A, Huland H. Reasonable delay of surgical treatment in men with localized prostate cancer--impact on prognosis? *European Urology* 2005; 47:756-60.

7. Khan MA, Mangold LA, Epstein JI, Boitnott JK, Walsh PC, Partin AW. Impact of surgical delay on long-term cancer control for clinically localized prostate cancer. *Journal of Urology* 2004; 172:1835-9.

8. Korets R, Seager CM, Pitman MS, Hruby GW, Benson MC, McKiernan JM. Effect of delaying surgery on radical prostatectomy outcomes: a contemporary analysis. *BJU International* 2012; 110:211-6.

9. Kwan W, Pickles T, Duncan G, Liu M, Paltiel C. Relationship between delay in radiotherapy and biochemical control in prostate cancer. *International Journal of Radiation Oncology, Biology, Physics* 2006; 66:663-8.

10. Lee DK, Allareddy V, Michael A, O'Donnell MA, Williams RD, Konety BR. Does the interval between prostate biopsy and radical prostatectomy affect the immediate postoperative outcome? *BJU International* 2006; 97:48-50.

11. Nam RK, Jewett MA, Krahn MD, Robinette MA, Tsihlias J, Toi A et al. Delay in surgical therapy for clinically localized prostate cancer and biochemical recurrence after radical prostatectomy. *Canadian Journal of Urology* 2003; 10:1891-8.

12. Nguyen PL, Whittington R, Koo S, Schultz D, Cote KB, Loffredo M et al. The impact of a delay in initiating radiation therapy on prostate-specific antigen outcome for patients with clinically localized prostate carcinoma. *Cancer* 2005; 103:2053-9.

13. O'Brien D, Loeb S, Carvalhal GF, McGuire BB, Kan D, Hofer MD et al. Delay of Surgery in Men with Low Risk Prostate Cancer. *Journal of Urology* 2011; 185:2143-7.

14. Phillips JJ, Hall MC, Lee WR, Clark PE. Does a delay in initiating definitive therapy affect biochemical recurrence rates in men with clinically localized prostate cancer? *Urologic Oncology* 2007; 25:196-200.

15. Shappley WV, III, Kenfield SA, Kasperzyk JL, Qiu W, Stampfer MJ, Sanda MG et al. Prospective study of determinants and outcomes of deferred treatment or watchful waiting among men with prostate cancer in a nationwide cohort. *Journal of Clinical Oncology* 2009; 27:4980-5.

16. Torring ML, Frydenberg M, Hansen RP, Olesen F, Vedsted P. Evidence of increasing mortality with longer diagnostic intervals for five common cancers: A cohort study in primary care. *European Journal of Cancer* 2013; 49:2187-98.

17. van den Bergh RC, Steyerberg EW, Khatami A, Aus G, Pihl CG, Wolters T et al. Swedish and Dutch sections of the European Randomized Study of Screening for Prostate Cancer: Is delayed radical prostatectomy in men with low-risk screen-detected prostate cancer associated with a higher risk of unfavorable outcomes? *Cancer* 2010; 116:1281-90.

18. Vickers AJ, Bianco FJ, Jr., Boorjian S, Scardino PT, Eastham JA. Does a delay between diagnosis and radical prostatectomy increase the risk of disease recurrence? *Cancer* 2006; 106:576-80.

Systematic review report for question 11

Clinical Question 11: *"What should be the criteria for choosing watchful waiting in preference to definitive treatment to offer as primary management to men who have a positive prostate biopsy?"*

PICO Question 11: "*For men with biopsy-diagnosed prostate cancer, for which patients (based on diagnostic, clinical and other criteria) does watchful waiting achieve equivalent or better outcomes in terms of length and quality of life than definitive treatment?"*

Population	Intervention	Comparator	Outcomes
Men with biopsy (histologically) confirmed prostate cancer	Watchful waiting	Immediate definitive treatment	Overall mortality, or Prostate cancer-specific mortality, or Metastatic disease, or Quality of life, or Adverse events

1. METHODS

1.1 Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption guidelines had to be evidence based and meet the pre-specified criteria of scores of ≥70% for the domains: Rigour of Development, Clarity of Presentation, and Editorial Independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

1.2 Literature Search

Medline (01/01/1990-01/03/2014), Embase (01/01/1990-01/03/2014), Cochrane Database of Systematic Reviews (01/01/2005-01/03/2014), Database of Abstracts of Reviews of Effects (until 01/03/2014) and Health Technology Assessment databases (until 01/03/2014) were searched using text terms and, where available, database specific subject headings. Each database was searched for articles dealing with prostate cancer. In Medline and Embase databases the prostate cancer search was coupled with a search for watchful waiting, and database specific filters for identifying randomised controlled trials (RCTs). To identify studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples. A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 added to the relevant database after February 2014. Alerts were checked until July 2014. Reference lists of all relevant articles were checked for potential additional articles.

1.3 Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	Nomograms (or predictive model) that have not been validated in a separate cohort
Study design	Randomised controlled trial, or meta-analysis/systematic review thereof	
Population	Men with histologically confirmed prostate cancer	Studies that restricted participants based on biomarker status
Intervention	Watchful waiting	
Comparator	Immediate definitive treatment	
Outcomes	Overall mortality, or Prostate cancer-specific mortality, or Quality of life, or Metastatic disease, or Adverse events	
Language	English	
Publication period	After 31st December 1989 and before1st March 2014	

Conference proceedings identified by the literature searches were included if they met the inclusion criteria.

1.5 Definitions

Watchful Waiting

Watchful waiting does not aim to cure prostate cancer, but to relieve its symptoms. Watchful waiting involves the conscious decision to avoid treatment unless symptoms or signs of progressive disease develop. The reason for delaying therapy is to avoid side effects which accompany all treatments and, by doing so, maximise patients' quality of life. Reasons for undertaking watchful waiting include: the cancer has advanced and is not curable with local treatments, the patient's life expectancy is limited and prostate cancer is unlikely to cause significant problems in that patient's lifetime, and a patient's choice; some patients may elect to undertake a program of watchful waiting rather than proceed with any of the localised disease management options. When treatment is implemented following a period of watchful waiting, it almost always involves androgen deprivation therapy (ADT) with transurethral resection of the prostate (TURP) used to relieve any bladder outflow obstruction.

It is important to differentiate 'watchful waiting' from 'active surveillance'. With the latter the patient is monitored closely with the intention to proceed to a treatment with curative intent if there is evidence of tumour progression or if and when the patient wishes to undertake treatment.

2. RESULTS

2.1 Guidelines

One guideline by the Belgian Health Care Knowledge Centre (KCE - A national clinical practice guideline on the management of localised prostate cancer 2012) contained recommendations regarding watchful waiting. After assessment using the AGREE II instrument, this guideline failed our pre-specified criteria scores outlined above. The identified guideline is documented in Appendix C.

2.2 Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the systematic review. The Medline search identified 298 citations, the Embase search 80 citations, the search of the Cochrane Database of Systematic Reviews 59 citations, the Database of Abstracts of Reviews of Effects search 282 citations and the search of the Health Technology Assessment database identified an additional 216 citations, resulting in a total of 935 citations. Titles and abstracts were examined and 36 articles were retrieved for a more detailed evaluation. An additional 2 potential citations were identified from the clinical trial registries and reference lists of retrieved article, leading to a total of 38 articles requiring a more detailed evaluation

Two RCTs reported in four articles met the inclusion criteria and were included in the review. There were no studies of ATSI men that met the inclusion criteria.

The retrieved articles that were not included and the reason for their exclusion are documented in Appendix C. In summary, most articles were excluded because they reported immature outcome data from RCTs, were review articles, or used inappropriate study designs.

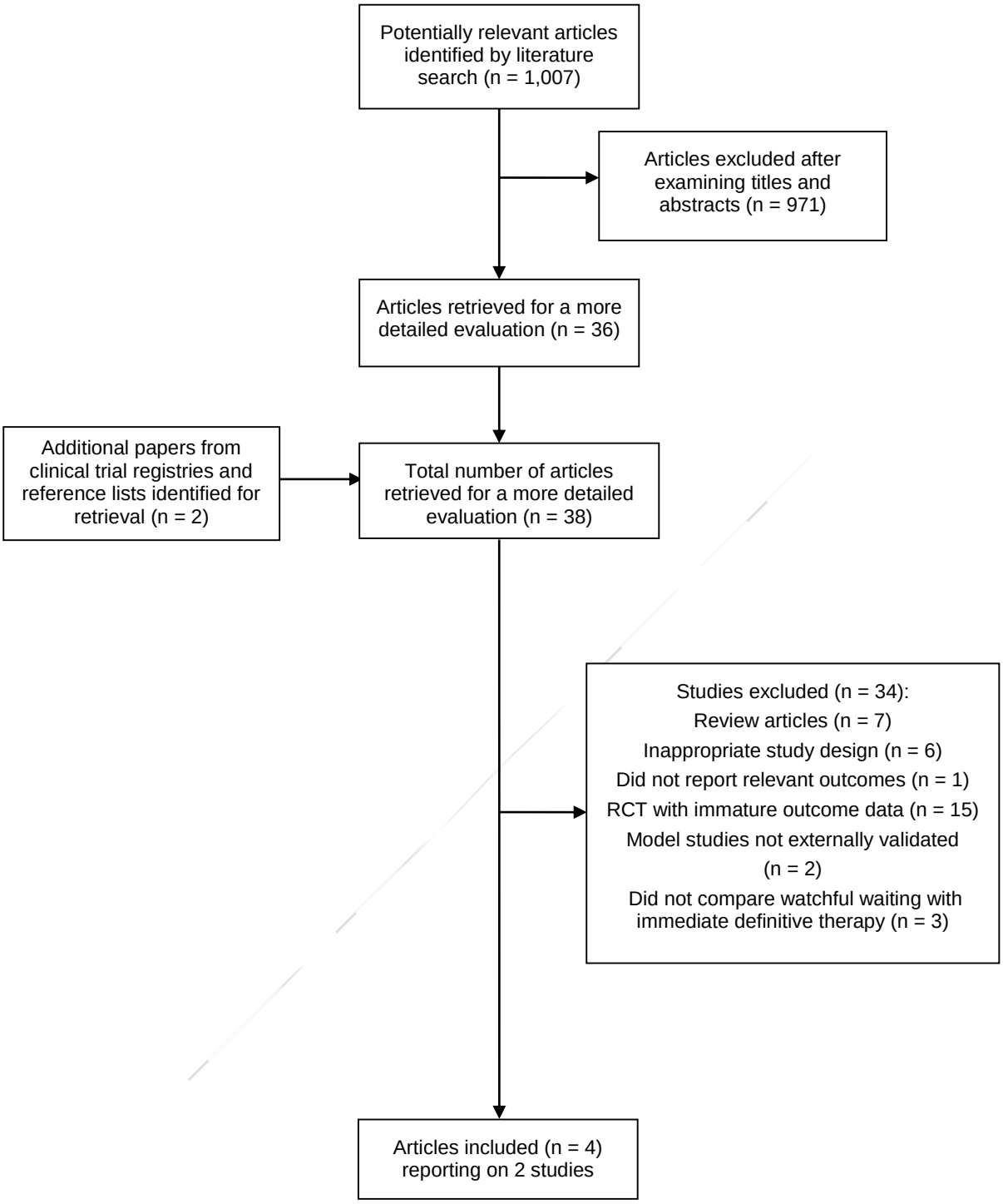


Figure 1. Process of inclusion and exclusion of studies.

2.3 Study Characteristics

Characteristics of included studies are described in Table 1.

Table 1: Characteristics of intervention studies examining watchful waiting and definitive treatment for improving outcomes in prostate cancer patients

Study	Participants	Design	Watchful Waiting	Definitive Treatment	Relevant Outcomes	Comments
Watchful Waiting vs. Radical Prostatectomy						
Wilt 2012 (USA) PIVOT	Men aged ≤75 years with clinically localised prostate cancer (T1-2NxM0 as per AJCC 5th edition; negative bone scan) of any grade diagnosed by biopsy within the previous 12 months, recruited from November 1994 – January 2002 with an estimated life expectancy ≥10 years and a PSA ≤50 ng/mL, who were medically and surgically fit for radical prostatectomy, were not currently receiving ADT and had not previously received any therapy for prostate cancer (except TURP for obstructive symptoms) **Mean age** 67 years **Race** White: 61.8% African American: 31.7% **Charlson Comorbidity Index[a]** 0: 56.1%; ≥1: 43.5%. **Performance status** Fully active: 85.1% **PSA (ng/mL):** Median: 7.8 ≤10.0: 65.5%; >10.0: 34.3%. **Gleason score** <7: 70.5%; ≥7: 25.1%. **Risk category (D'Amico)** Low: 40.5% Intermediate: 34.1% High: 21.5% **Clinical stage** T1a/b: 4.0%; T1c: 50.3%; T2a: 24.8%; T2b: 12.5%; T2c: 7.8%. **N = 731**	RCT (multi-centre - 52 sites)	**Watchful Waiting** Therapeutic decisions at physician's discretion while adhering to the principle of using palliative therapies with low morbidity rates for symptomatic or local progression (TURP), metastatic disease progression, ADT, RT or chemotherapy RP, definitive radiation therapy, early ADT or treatment for asymptomatic progression, including an increase in PSA, proscribed 20.4% of participants in WW arm received definitive therapy,10.1% underwent RP **N = 367**	**Radical Prostatectomy** Performed within 6 weeks of randomisation; technique at surgeon's discretion (e.g. retropubic, transperineal, use of lymph node dissection, nerve sparing surgery) Additional early aggressive intervention for disease persistence or recurrence Physician discretion allowed maximum flexibility consistent with current clinical practice 77.2% of participants underwent RP, 14.6% of participants in RP arm did not receive any definitive therapy **N = 364**	**Primary:** *All-cause mortality. Cumulative incidence of mortality (at 4, 8, 12 years, and end of study)* **Secondary:** *Prostate cancer mortality (death definitely or probably due to prostate cancer or prostate cancer treatment). Bone metastases. Adverse events within 30 days of surgery* *Urinary incontinence* *Bowel dysfunction* *Erectile dysfunction* Median follow up = 10.0 years (range 9-15 years)	Follow up visits 6 weeks after randomisation, every 3 months for year 1, then every 6 months, with urologic symptoms and quality of life questionnaires and a PSA test at every visit, and bone scans at least every 5 years Estimated that 740 participants would provide 91% power to detect a 25% relative reduction in all-cause mortality with 15 years of follow up and a median survival of 10 years **Subgroup analyses:** Age, race, Charlson Comorbidity Index, performance status, PSA level, Gleason score, risk category

Bill-Axelson 2011 **Johansson 2011** **Steineck 2002** (Sweden, Finland & Iceland) SPCG-4	Men newly diagnosed (<4months) with histologically or cytologically confirmed localised prostate cancer recruited from 14 different centres October 1989 – December 1999. Clinical stage T1 or T2 (UICC 3rd ed. 1978). T1c included after 1994. Tumour of high or intermediate differentiation grade (WHO classification) No other known cancers. PSA <50 ng/mL and age <75 years. Negative bone scan and life expectancy >10 years and fit to undergo prostatectomy. **Mean age** 64.6 years **PSA (ng/mL):** Mean: 12.9 <4:15.3%; 4-6.9: 17.3%; 7-10: 19.4%; 10.1-20: 28.1%; >20: 18.6% **Gleason Score:** 2-4: 13.1%; 5-6: 47.6%; 7: 22.9%; ≥8: 5.0%. **Clinical Stage:** T1b: 11.9%; T1c: 11.7%; T2: 76.1% 55.5% prostate cancer detected as a result of symptoms or TURP. 5.2% prostate cancer detected as a result of opportunistic PSA testing. **N = 695** ***Subgroups***	RCT (multi-centre)	**Watchful Waiting** No immediate treatment. TURP if signs of obstructive voiding disorders ADT if metastases detected or, from 2003, if any sign of tumour progression including rising PSA levels 50 men (14.4%) received curative treatment **N = 348**	**Radical Prostatectomy** Performed if local nodes were negative for prostate cancer, radical excision given preference over nerve sparing ADT if signs of local recurrence developed (palpable nodule or histologically confirmed recurrence) or metastases detected or, from 2003, if any sign of tumour progression including rising PSA levels 294 (84.7%) men underwent immediate radical prostatectomy 44 (12.7%) men received no curative therapy **N = 347**	**Primary:** *Prostate cancer-specific mortality* **Secondary:** *Overall mortality* *Quality of life* *Distant metastases* Median follow up = 12.8 years Patients followed until 31/12/2009. No loss to follow up	Intention-to-treat analysis All patients followed up with a clinical examination and determination of haemoglobin, creatinine, PSA, AP levels twice a year for the first two years and then annually. A bone scan and chest radiograph were obtained annually until 2003 and then biennially. After 1996 chest x-rays were performed. Sample size of 700 calculated to detect an absolute difference in disease-specific survival rate of 6% with 5% risk of Type I error and 20% risk of Type II error, if disease-specific survival rate was 95% in one group. **Subgroup analyses:** Age, PSA level, Gleason score
Steineck 2002 **N = 376**	Swedish participants alive 1997-1998 enrolled prior to 29/02/1996	**N = 187**	**N = 189**	*Quality of life* Mean follow up = 4.1 years	Current quality of life measured using a questionnaire 86.7% response rate
Johansson 2011 **N = 400**	Swedish and Finnish participants alive 2006-2008	**N = 192**	**N = 208**	*Quality of life* Median follow up = 12.2 years	Current quality of life measured using same questionnaire as above 87.3% response rate

ADT = androgen deprivation therapy; AJCC = American Joint Committee on Cancer; AP = alkaline phosphatase; DRE = digital rectal examination; PSA = prostate-specific antigen; RCT = randomised controlled trial; RP = radical prostatectomy; RT = radiotherapy; TURP = transurethral resection of the prostate; UICC = International Union Against Cancer; WHO = World Health Organisation; WW = watchful waiting;

a = CharIson Comorbidity Index based on a point weighting derived from current or past history of myocardial infarction, chronic congestive heart failure, peripheral vascular disease, cerebrovascular disease or stroke, diabetes (with end-organ damage), dementia, chronic pulmonary disease, liver disease, renal disease, cancers, acquired immune deficiency syndrome (0 = no comorbidities).

2.4 Study Quality

Methodological quality of included RCTs is described in Tables 2-5.

Table 2: Methodological quality for the outcomes **overall mortality** and **prostate cancer mortality** in the included RCTs (n = 2)

Quality Category	N (%)
I. Was the study double-blinded?	
2 = Reasonably certain double-blind (e.g. identical placebo)	-
1 = Single-blind, objective outcomes	2 (100)
0 = Not blinded, not reported	-
II. Concealment of treatment allocation schedule	
2 = Adequately concealed (e.g. central randomisation)	2 (100)
1 = Inadequately concealed (e.g. sealed envelopes)	-
0 = No concealment, not reported	-
III. Inclusion of all randomised participants in analysis of majority of outcomes (i.e. ITT)	
2 = No exclusions, survival analysis used	2 (100)
1 = Exclusions not likely to cause bias	-
0 = Too many exclusions, not reported	-
IV. Generation of allocation sequences	
1 = Adequate (e.g. computer random number generator)	-
0 = Inadequate, not reported	2 (100)

ITT = intention-to-treat

Table 3: Methodological quality for the outcomes **quality of life** and **adverse events** in the included RCTs (n = 2)

Quality Category	N (%)
1. Was the study double-blinded?	
2 = Reasonably certain double-blind (e.g. identical placebo)	-
1 = Single-blind, objective outcomes	-
0 = Not blinded, not reported	2 (100)
2. Concealment of treatment allocation schedule	
2 = Adequately concealed (e.g. central randomisation)	2 (100)
1 = Inadequately concealed (e.g. sealed envelopes)	-
0 = No concealment, not reported	-
3. Inclusion of all randomised participants in analysis of majority of outcomes (i.e. ITT)	
2 = No exclusions, survival analysis used	-
1 = Exclusions not likely to cause bias	1 (50)
0 = Too many exclusions, not reported	1 (50)
4. Generation of allocation sequences	
1 = Adequate (e.g. computer random number generator)	-
0 = Inadequate, not reported	2 (100)

ITT = intention-to-treat

Table 4: Methodological quality for the outcomes **overall mortality** and **prostate cancer mortality** in the included RCTs (n = 2)

	Blinding	Allocation concealment	Inclusion of all participants (ITT)	Generation of allocation sequence*	Overall rating	Risk of bias
SPCG-4 Bill-Axelson 2011	1	2	2	0	Medium	Moderate
PIVOT Wilt 2012	1	2	2	0	Medium	Moderate

ITT = intention-to-treat

Table 5: Methodological quality for the outcomes **quality of life** and **adverse events** in the included RCTs (n = 2)

	Blinding	Allocation concealment	Inclusion of all participants (ITT)	Generation of allocation sequence*	Overall rating	Risk of bias
SPCG-4						
Johansson 2011	0	2	1	0	Low	High
Steineck 2002	0	2	1	0	Low	High
PIVOT						
Wilt 2012	0	2	0	0	Low	High

ITT = intention-to-treat

Key to overall quality rating:

High quality: a study that received 2 for the 3 main criteria (double-blinding, concealment of treatment allocation schedule, inclusion of all randomised participants in analysis (i.e. ITT)).

Medium quality: received 2 and/or 1 for all three main criteria.

Low quality: received 0 for all three criteria or 0 and 1 for all three criteria or received 0 for any of the 3 main criteria.

*Answer for question 4 is considered as additional information and not considered when calculating the overall quality score. Quality assessment questions 1 to 3 for randomised controlled trials are evidence-based categories (Schulz *et al.*, 1995; Jadad *et al.*, 1996). Generation of allocation sequences has been shown not to influence outcomes.

2.5 Study results

Effects of intervention on relevant outcomes are described in Tables 6-8.

I All-cause mortality and overall survival

Table 6: Results of studies examining the effects of watchful waiting compared with definitive treatments on all-cause mortality/overall survival.

Study	Outcome			N actual	Watchful Waiting	Definitive Treatment	Size of effect	Size of effect (95% CI)	p value (test)	Follow up/ Timing
Watchful Waiting vs. Radical Prostatectomy										
Wilt 2012	**All-cause mortality** *Cumulative incidence of ascertained deaths/men randomised to management protocol – at end of study*			731	49.9	47.0	HR=0.88 ARD=2.9%	0.71-1.08 -4.3 to 10.1	0.22[a]	10 years median
	Cumulative incidence of deaths at 4 years (%)			731	14.2	9.6	ARD=4.6%	-0.2 to 9.3	NS[a]	4 years
	Cumulative incidence of deaths at 8 years (%)			731	29.7	26.7	ARD=3.1%	-3.5 to 9.5	NS[a]	8 years
	Cumulative incidence of deaths at 12 years (%)			731	43.9	40.9	ARD=2.9%	-4.2 to 10.0	NS[a]	12 years
	Subgroup analyses (cumulative incidence %)									
	Age	<65 years		253	38.2	35.3	HR=0.89	0.59-1.34	0.58[b]	10 years median
		≥65 years		478	56.4	52.9	HR=0.84	0.63-1.08	0.17[b]	
	Race	White		452	54.1	50.4	HR=0.84	0.65-1.08	0.18[b]	10 years median
		Black		232	43.8	41.4	HR=0.93	0.62-1.38	0.70[b]	
		Other		47	42.3	38.1	HR=0.85	0.34-2.11	0.72[b]	
	CCI[c]	No comorbidities		444	39.1	36.6	HR=0.90	0.66-1.21	0.48[b]	10 years median
		≥1 comorbidities		287	66.0	63.6	HR=0.84	0.63-1.13	0.25[b]	
	Performance score[d]	Fully active (0)		622	47.1	44.6	HR=0.89	0.71-1.13	0.34[b]	10 years median
		Not fully active (1-4)		109	64.9	61.5	HR=0.82	0.51-1.31	0.40[b]	
	PSA at Baseline	≤10 ng/mL		479	43.6	46.2	HR=1.03	0.79-1.35	0.82[b]	10 years median
		>10ng/mL		251	61.6	48.4	HR=0.67	0.48-0.94	0.02[b]	
	Risk category[e]	Central	Low[g]	233*	38.5	40.5	ARD=-2.0	-14.4 to 10.4	0.72[b]	10 years median
			Intermediate[g]	295*	52.5	47.4	ARD=5.1	-6.6 to 16.0	0.29[b]	

			Intermediate or high[g]	458	NR	NR	HR=0.81	0.63 – 1.0	0.10[b]	
			High[g]	163*	58.8	55.1	ARD=3.7	-11.3 to 18.5	0.25[b]	
		Local	Low[g]	296	36.5	41.9	HR = 1.15	0.80 – 1.66	0.45[b]	
			Intermediate[g]	249	58.3	45.7	HR = 0.69	0.49 – 0.98	0.037[b]	
			Intermediate or high[g]	406	NR	NR	HR = 0.71	0.54 – 0.92	0.01[b]	
			High	157	61.3	54.6	HR = 0.74	0.49 – 1.13	0.16[b]	
	Gleason score[f]	Central	<7	364*	44.9	41.1	ARD=3.8	-6.3 to 13.8	0.63[b]	10 years median
			≥7	322*	54.4	52.9	ARD=1.9	-9.0 to 12.6	0.14[b]	
		Local	<7	515	47.9	44.5	HR = 0.86	0.67 – 1.12	0.26[b]	
			≥7	184	54.7	51.0	HR = 0.84	0.56 – 1.25	0.38[b]	
Bill-Axelson 2011	**All-Cause Mortality** *Cumulative incidence of death at 15 years: % (95%CI)*			695	52.7	46.1	HR=0.75 NNT=15	0.61-0.92	0.007[h]	15 years
	Subgroup Analyses (cumulative incidence %)									
	Age	<65 years		323	47.4	33.9	HR=0.52 NNT=8	0.37-0.73	<0.001[h]	12.8 years median
		≥65 years		372	57.4	56.7	HR=0.98	0.75-1.28	0.89[h]	
	Low risk cancer[i]			263	44.6	31.4	HR=0.62 NNT=8	0.43-0.92	0.02[h]	12.8 years median
	PSA <10 vs ≥10 ng/mL at diagnosis			No modification of treatment effect: p for interaction = 0.72						12.8 years median
	Gleason score <7 vs ≥7 at diagnosis			No modification of treatment effect: p for interaction = 0.36						

*ARD = absolute risk difference, a negative ARD indicates advantage of WW over immediate definitive treatment; CI = confidence interval; NNT = numbers needed to treat; HR = hazard ratio >1.0 indicates advantage of WW over immediate definitive treatment; NR = not reported; NS = not statistically significantly different; PSA = prostate-specific antigen; * = calculated by reviewers*

a = Proportional-hazards model

b = Cox proportional-hazards model to test for treatment effects and interaction between group assignment and subgroup category, with no correction for multiple comparisons

c = Charlson Comorbidity Index based on a point weighting derived for current or past history of myocardial infarction, chronic congestive heart failure, peripheral vascular disease, cerebrovascular disease or stroke, diabetes (with end-organ damage), dementia, chronic pulmonary disease, liver disease, renal disease, cancers, acquired immune deficiency syndrome, (0 = no comorbidities)

d = Performance score of 0 = fully active, 1-4 = not fully active with a range of movement ability from light work (1) to completely disabled (4)

e = According to tumour stage determined before study entry, and PSA and biopsy findings (Gleason score) determined centrally or locally after randomisation

f = According to tumour stage determined centrally or locally after randomisation

g = Low includes PSA level ≤10 ng/mL, Gleason score ≤6 and tumour stage T1/T2a; Intermediate includes PSA level 10-20ng/mL or Gleason score = 7 or tumour stage T2b; High includes PSA level >20 ng/mL or Gleason score 8-10 or Tumour stage T2c (staging according to American Joint Committee on Cancer 5th edition 1997)

h = Grays test

i = Low risk cancer is classified as a PSA level <10ng/mL and Gleason score of <7 or a WHO grade of 1 in the preoperative specimen

II Prostate cancer-specific mortality

Table 7: Results of studies examining the effects of watchful waiting compared with definitive treatments on prostate cancer-specific mortality.

Study	Outcome			N actual	Watchful Waiting	Definitive Treatment	Size of effect	Size of effect (95% CI)	p value (test)	Follow up/ Timing
Watchful Waiting vs. Radical Prostatectomy										
Wilt 2012	**Prostate Cancer Mortality** *Cumulative incidence of deaths ascertained as definitely due to prostate cancer/men randomised to management protocol*			731	4.9	4.4	NR	NR	NS[a]	10 years median
	Prostate Cancer Mortality *Cumulative incidence of deaths ascertained as probably or definitely due to prostate cancer/men randomised to management protocol (at end of study)*			731	8.4	5.8	HR=0.63 ARD=2.6%	0.36-1.09 -1.1 to 6.5	0.09[b]	10 years median
	Cumulative incidence of deaths at 4 years (%)			731	1.6	1.7	ARD=0.0%	-2.1 to 2.1	NS[a]	4 years
	Cumulative incidence of deaths at 8 years (%)			731	4.9	3.0	ARD=1.9%	-1.0 to 4.9	NS[a]	8 years
	Cumulative incidence of deaths at 12 years (%)			731	7.4	4.4	ARD=3.9%	-0.5 to 6.5	NS[a]	12 years
	Subgroup Analyses (cumulative incidence %)									
	Age	<65 years		253	9.2	4.9	HR=0.52	0.20-1.39	0.19[b]	10 years median
		≥65 years		478	8.1	6.2	HR=0.68	0.34-1.33	0.25[b]	
	Race	White		452	10.0	6.5	HR=0.57	0.30-1.10	0.09[b]	10 years median
		Black		232	5.8	4.5	HR=0.80	0.25-2.54	0.71[b]	
		Other		47	7.7	4.8	HR=0.56	0.05-6.17	0.63[b]	
	CCI	No comorbidities		444	8.6	6.3	HR=0.69	0.34-1.37	0.29[b]	10 years median
		≥ 1 comorbidities		287	8.2	5.0	HR=0.54	0.21-1.38	0.19[b]	
	Performance Status[c]	Fully active (0)		622	8.1	5.8	HR=0.67	0.37-1.23	0.19[b]	10 years median
		Not fully active (1-4)		109	10.5	5.8	HR=0.41	0.10-1.71	0.21[b]	
	PSA at baseline	≤10 ng/mL		479	6.2	5.9	HR=0.92	0.44-1.91	0.82[b]	10 years median
		>10 ng/mL		251	12.8	5.6	HR=0.36	0.15-0.89	0.02[b]	
	Risk category [d]	Central	Low [f]	233*	4.1	0.9	ARD=3.2%	-1.5 to 8.4	0.13[b]	10 years

			Intermediate [f]	293*	5.8	7.1	ARD=-1.3%	-7.2 to 4.7	0.84[b]	median
			High [f]	163*	20.0	11.5	ARD=8.5%	-3.0 to 19.6	0.05[b]	
		Local	Low [f]	296	2.7	4.1	HR=1.48	0.42 – 5.24	0.54 [b]	
			Intermediate [f]	249	10.8	6.2	HR = 0.50	0.21 – 1.21	0.12 [b]	
			High [f]	157	17.5	9.1	HR = 0.40	0.16 – 1.00	0.04 [b]	
	Gleason score [e]	Central	<7	363*	4.6	1.2	ARD = 3.4%	-0.3 to 7.4	0.07[b]	10 years median
			≥7	322*	14.2	10.9	ARD = 3.3%	-4.0 to 10.8	0.11[b]	
		Local	<7	515	5.8	4.3	HR = 0.68	0.31 – 1.49	0.34[b]	
			≥7	184	17.4	10.2	HR = 0.51	0.23 – 1.14	0.10[b]	
Bill-Axelson 2011	**Prostate Cancer Mortality** *Cumulative incidence of death*			695	20.7	14.6	0.62	0.44-0.87	0.001[g]	15 years
	Subgroup Analyses									
	Age	<65 years	% (n)	323	25.8	16.4	0.49	0.31-0.79	0.008[g]	12.8 years median
		≥ 65 years	% (n)	372	16.0	13.0	0.83	0.50-1.39	0.41[g]	
	Low risk cancer [h]		% (n)	263	11.0	6.8	0.53	0.24-1.14	0.14[g]	15 years
	PSA <10 vs ≥10 ng/mL at diagnosis			No modification of treatment effect: p for interaction = 0.30						15 years
	Gleason score <7 vs ≥7 at diagnosis			No modification of treatment effect: p for interaction = 0.52						

ARD = absolute risk difference, a negative ARD indicates advantage of watchful waiting over immediate definitive treatment; CCI = Charlson Comorbidity Index, based on a point weighting derived for current or past history of myocardial infarction, chronic congestive heart failure, peripheral vascular disease, cerebrovascular disease or stroke, diabetes (with end-organ damage), dementia, chronic pulmonary disease, liver disease, renal disease, cancers, acquired immune deficiency syndrome; (0 = no comorbid conditions); *CI = confidence interval; HR = hazard ratio >1.0 indicates advantage of watchful waiting over immediate definitive treatment; NNT = numbers needed to treat; NR = not reported; NS = not statistically significantly different; PSA = prostate-specific antigen*

* calculated by reviewers

a = Proportional-hazards model

b = Cox proportional-hazards model to test for treatment effects and interaction between group assignment and subgroup category, with no correction for multiple comparisons

c = Performance score of 0 = fully active, performance score of 1-4 = not fully active with a range of movement ability from light work (1) to completely disabled (4)

d = According to tumour stage determined before study entry, and PSA and biopsy findings (Gleason score) determined centrally or locally after randomisation

e = According to tumour stage determined centrally or locally after randomisation

f = Low includes PSA level ≤10 ng/mL, Gleason score ≤6 and tumour stage T1/T2a; Intermediate includes PSA level 10-20 ng/mL or Gleason score = 7 or tumour stage T2b; High includes PSA level >20 ng/mL or Gleason score 8-10 or Tumour stage T2c (staging according to American Joint Committee on Cancer 5th edition 1997)

g = Gray's test

h = Low risk cancer is classified as a PSA level <10 ng/mL and Gleason score of <7 or a WHO grade of 1 in the preoperative specimens

III Quality of Life and Adverse Events

Table 8: Results of studies examining the effects of watchful waiting compared with definitive treatments on quality of life and adverse events.

Study	Outcome		N actual	Watchful Waiting	Definitive Treatment	Size of effect	Size of effect (95% CI)	p value (test)	Follow up /Timing
Watchful Waiting vs. Radical Prostatectomy									
Wilt 2012	**Urinary incontinence** *Significant problems with dribbling or dysfunction*	% (n)	571	6.3 (18) N = 284	17.1 (49) N = 287	ARD=-11.0	NR	<0.001[a]	2 years
	Erectile dysfunction *Inability to have erection sufficient for vaginal penetration*	% (n)	566	44.1 (124) N = 281	81.1 (231) N = 285	ARD=-37	NR	<0.001	2 years
	Bowel dysfunction *Dysfunction as "moderate" or "big" problem*	% (n)	568	11.3 (32) N = 282	12.2 (35) N = 286	ARD=-0.9	NR	0.74	2 years
	Bone Metastasis								
Cumulative Incidence of bone metastasis (%)	*Overall*		731	10.6	4.7	HR = 0.40	0.22 – 0.70	<0.001	10 years median
	4 years		731	3.3	1.4	RR = 0.42	0.15 – 1.18	NS	4 years
	8 years		731	7.1	1.9	RR = 0.27	0.12 – 0.62	SD	8 years
	12 years		731	9.5	3.9	RR = 0.40	0.22 – 0.74	SD	12 years
	Age	<65 years	253	9.9	5.7	RR = 0.58	0.24 – 1.40	0.19	10 years median
		≥65 years	478	11.0	4.1	RR = 0.38	0.19 - 0.76	0.002	
	Race	White	452	12.7	5.2	RR = 0.41	0.21 – 0.78	0.002	
		Black	232	6.6	2.7	RR = 0.41	0.11 – 1.50	0.15	
		Other	47	11.5	9.5	RR = 0.83	0.15 – 4.49	0.83	
	CCI	No comorbidities	444	12.3	6.3	RR = 0.51	0.27 – 0.94	0.02	
		≥ 1 comorbidities	287	8.2	2.1	RR = 0.26	0.08 – 0.91	0.02	
	Performance Status	Fully active (0)	622	10.3	4.8	RR = 0.47	0.26 – 0.84	0.005	
		Not fully active (1-4)	109	12.3	3.9	RR = 0.31	0.07 – 1.44	0.07	

Cumulative Incidence of bone metastasis (%)	PSA at baseline		≤10 ng/mL	479	8.7	5.0	RR = 0.58	0.29 – 1.15	0.09	10 years median
			>10 ng/mL	251	14.4	4.0	RR = 0.28	0.11 – 0.72	0.001	
	Risk Category	Central	Low	233*	4.9	0.9	RR = 0.18	0.02 – 1.50	0.08	
			Intermediate	295*	11.5	6.5	RR = 0.56	0.26 – 1.19	0.08	
			High	163*	17.7	6.4	RR = 0.36	0.14 – 0.95	0.01	
		Local	Low	296	6.1	4.1	RR = 0.67	0.24 – 1.83	0.39	
			Intermediate	249	15.8	4.7	RR = 0.29	0.12 – 0.71	0.002	
			High	157	13.8	5.2	RR = 0.38	0.13 – 1.14	0.03	
	Gleason Score	Central	<7	364*	4.1	1.2	RR = 0.29	0.06 – 1.35	0.10	
			≥7	322*	19.6	8.1	RR = 0.41	0.23 – 0.75	0.0001	
		Local	<7	515	8.1	3.5	RR = 0.44	0.21 – 0.94	0.02	
			≥7	184	20.9	7.1	RR = 0.34	0.15 – 0.78	0.003	
Steineck 2002 Johannson 2011	**Sexual function**									
	Seldom or never sufficient for intercourse		% (n)	319	45 (71) N = 158	80 (129) N = 161	RR = 1.8	1.5 – 2.2	NR	4.1 years mean
	Never sufficient for intercourse		% (n)	326	80 (122) N = 153	84 (146) N = 173	RR = 1.08[b]	0.98 – 1.18	NS	12.2 years median
	Distress from erectile dysfunction *% moderate or great distress*		% (n)	307	43 (65) N = 152	58 (90) N = 155	RR = 1.4	1.0 – 1.7	SD	4.1 years mean
			% (n)	322	36 (56) N = 154	48 (80) N = 168	RR = 1.3[b]	1.00 – 1.70	SD	12.2 years median
	Distress from decreased sexual ability *% moderate to great distress*		% (n)	317	35 (53) N = 150	37 (61) N = 167	RR = 1.01[b]	0.76 – 1.34	NS	12.2 years median
	Urinary function									
	Weak urinary stream *% on more than one of 5 occasions*		% (n)	317	44 (68) N = 153	28 (46) N = 164	RR=0.6	0.5 – 0.9	SD	4.1 years mean
	Weak urinary stream *% on more than half of occasions*		% (n)	334	40 (64) N = 160	29 (50) N = 174	RR=0.71[b]	0.53 – 0.96	SD	12.2 years median

Distress from obstructed voiding *% moderate or great distress*	% (n)	321	22 (34) N = 157	21 (34) N = 164	RR=1.0	0.60 – 1.5	NS	4.1 years mean
	% (n)	337	32 (52) N = 161	27 (48) N = 176	RR=0.82[b]	0.60 – 1.14	NS	12.2 years median
Patient assessed urine leakage *% moderate or severe leakage*	% (n)	315	2 (3) N = 152	18 (30) N = 163	RR=9.3	2.9 – 29.9	SD	4.1 years mean
	% (n)	341	11 (18) N = 164	23 (41) N = 177	RR=2.14[b]	1.28 – 3.58	SD	12.2 years median
Distress from urinary leakage *% moderate or great distress*	% (n)	322	9 (15) N = 158	29 (47) N = 164	RR=3.0	1.8 – 5.2	SD	4.1 years mean
Distress from daytime urinary leakage *% moderate or great distress*	% (n)	336	15 (25) N = 162	28 (48) N = 174	RR=1.80[b]	1.17 – 2.78	SD	12.2 years median
Distress from night time urinary leakage *% moderate or great distress*	% (n)	341	9 (14) N = 164	18 (31) N = 177	RR=2.08[b]	1.15 – 3.78	SD	12.2 years median
Regular dependence on some form of protective aid	% (n)	319	10 (16) N = 154	43 (71) N = 165	RR=4.1	2.5 – 6.8	SD	4.1 years mean
	% (n)	338	25 (41) N = 163	54 (94) N = 175	RR=2.15[b]	1.60 – 2.90	SD	12.2 years median
Overall distress from all urinary symptoms *% moderate or great distress*	% (n)	320	18 (28) N = 157	27 (44) N = 163	RR=1.5	1.0 – 2.3	SD	4.1 years mean
Subjective estimation of the degree of leakage *% moderate or severe leakage*	% (n)	315	2 (3) N = 152	18 (30) N = 163	RR=9.9	2.9 – 29.9	SD	4.1 years mean
	% (n)	341	11 (18) N = 164	23 (41) N = 177	RR=2.14 [b]	1.28 – 3.58	SD	12.2 years median
Psychological Symptoms								
Anxiety *% moderate or high* *(highest 5 of 7 categories)*	% (n)	321	31 (48) N = 157	23 (37) N = 164	RR=0.7	0.5-1.1	NS	4.1 years mean
	% (n)	339	43 (69) N = 161	43 (77) N = 178	RR=0.97[b]	0.76-1.24	NS	12.2 years median
Depression *% moderate or high*	% (n)	321	38 (60) N = 157	35 (57) N = 164	RR=0.9	0.7-1.2	NS	4.1 years mean

	(highest 5 of 7 categories)	% (n)	339	52 (82) N = 159	47 (85) N = 180	RR=0.92[b]	0.74-1.14	NS	12.2 years median
	Psychological wellbeing *% low or moderate (lowest 5 of 7)*	% (n)	322	36 (57) N = 158	35 (57) N = 164	RR=1.0	0.7-1.3	NS	4.1 years mean
	Psychological wellbeing *% high (highest 2 of 7 categories)*	% (n)	340	44 (71) N = 161	41 (73) N = 179	RR=0.89[b]	0.70-1.13	NS	12.2 years median
	General Function								
	Physical well-being - % low or moderate *(lowest 5 of 7 possible categories)*	% (n)	321	50 (78) N = 157	41 (68) N = 164	RR=0.8	0.7-1.1	NS	4.1 years mean
	Patient assessed quality of life *% low or moderate (lowest 5 of 7)*	% (n)	310	45 (68) N = 151	40 (64) N = 159	RR=0.9	0.7-1.2	NS	4.1 years mean
	Patient assessed quality of life *% high (highest 2 of 7 possible categories)*	% (n)	339	34 (55) N = 160	35 (62) N = 179	RR=0.98[b]	0.73-1.15	NS	12.2 years median
Bill-Axelson 2011	**Distant Metastases**								
	Cumulative Incidence of distant metastases at 15 yrs		695	33.4	21.7	RR=0.59	0.45 – 0.79	<0.001	15 years
	Low-risk cancer		263	21.4	9.9	RR = 0.43	0.23 – 0.79	0.008	12.8 years median
	Age: < 65 yr		323	39.8	21.5	RR = 0.47	0.32 – 0.70	0.001	
	Age: ≥ 65 yr		372	27.5	22.1	RR = 0.77	0.51 – 1.51	0.14	
Wilt 2012	**Perioperative complications**								
	Wound infection	% (n)	280	-	4.3 (12)	-	-	-	30 days after Radical Prostatectomy
	Bowel injury requiring surgical repair	% (n)	280	-	1.1 (3)	-	-	-	
	Additional surgical repair required	% (n)	280	-	2.5 (7)	-	-	-	
	Bleeding required transfusion	% (n)	280	-	2.1 (6)	-	-	-	
	Urinary tract infection	% (n)	280	-	2.5 (7)	-	-	-	
	Urinary catheter present > 30 days after surgery	% (n)	280	-	2.1 (6)	-	-	-	
	Death	% (n)	280	-	0.4 (1)	-	-	-	

*ADT = androgen deprivation therapy; ARD = absolute risk difference, a negative ARD indicates advantage of watchful waiting over immediate definitive treatment; CI = confidence interval; NR = not reported; NS = not statistically significant, p value of ≥0.05 or 95% CI that includes 1.0; OR = odds ratio; RR = relative risk > 1.0 indicates advantage of watchful waiting over immediate definitive treatment; TURP = transurethral resection of the prostate; * =* calculated by reviewers
a = analysis of variance test used
b - age-adjusted

2.6 Body of Evidence

Effects of intervention on relevant outcomes are described in Tables 9-11.

I All-cause mortality

Table 9: Body of evidence examining the effects of watchful waiting compared with definitive treatments on all-cause mortality

Name of study	Study type	Level of evidence*	Quality of evidence **	Risk of bias	N	Results summary %	Size of effect	p value	95% CI	Relevance of evidence
Watchful waiting vs. Radical Prostatectomy										
Wilt 2012 (multi-centre) **Participants:** Mean age = 67 years T1: 54.3% T2: 45.1% Median PSA = 7.8 ng/mL Gleason score <7: 70.56% Median follow up 10 years Life expectancy ≥10 years	RCT	II	Medium	Moderate	731	**All-cause mortality:** WW: 49.9 RP: 47.0	HR=0.88	NS	0.71 – 1.08	1
						Subgroup analyses:				
						Age (years):				
					253	<65: WW:38.2 RP:35.3	HR=0.89	NS	0.59 – 1.34	1
					478	≥65: WW:56.4 RP:52.9	HR=0.84	NS	0.63 – 1.08	1
						Race:				
					452	White: WW:54.1 RP:50.4	HR=0.84	NS	0.65 – 1.08	1
						Charlson Comorbidity Index [a]:				
					444	0: WW:39.1 RP:36.6	HR=0.90	NS	0.66 – 1.21	1
					287	≥1: WW:66.0 RP:63.6	HR=0.84	NS	0.63 – 1.13	1
						Performance score [b]:				
					622	0: WW:47.1 RP:44.6	HR=0.89	NS	0.71 – 1.13	1

					109	1-4: WW:64.9 RP:61.5	HR=0.82	NS	0.51 – 1.31	1
						PSA level (ng/mL):				
					479	≤10: WW:43.6 RP:46.2	HR=1.03	NS	0.79 – 1.35	1
					251	>10: WW:61.6 RP:48.4	HR=0.67	**0.02**	0.48 – 0.94	1
						Tumour Risk (central) [c]:				
					233[#]	Low: WW:38.5 RP:40.5	ARD=-2.0%	NS	-14.4 to 10.4	1
					295[#]	Int: WW:52.5 RP:47.4	ARD=5.1%	NS	-6.6 to 16.0	1
					163[#]	High: WW:58.8 RP:55.1	ARD=3.7%	NS	-11.3 to 18.5	1
						Tumour Risk (local) [c]:				
					296	Low: WW:36.5 RP:41.9	ARD=-2.0%	NS	0.80 – 1.66	1
					249	Int: WW: 58.3 RP:45.7	ARD=12.6	SD	0.49 – 0.98	1
					157	High: WW: 61.3 RP: 54.6	ARD=6.7%	NS	0.49 – 1.13	1
						Gleason score (central) [d]:				
					364[#]	<7: WW:44.9 RP: 41.1	ARD=3.8%	NS	-6.3 to 13.8	1
					322[#]	≥7: WW:54.7 RP: 52.9	ARD=1.9%	NS	-9.0 to 12.6	1
						Gleason score (local) [d]:				
					515	<7: WW:47.9 RP:44.5	ARD=3.4%	NS	0.67 – 1.12	1
					184	≥7: WW: 54.7 RP:51.0	ARD=3.6%	NS	0.56 – 1.25	1
Bill-Axelson 2011	RCT (multi-centre)	II	Medium	Moderate		**All-cause mortality:**				
					695	WW: 52.7 RP: 46.1	HR=0.75	**0.007**	0.61 – 0.92	1
Participants:										
Mean age = 64.6 years						**<u>Subgroup analyses:</u>**				
T1: 23.6%						**Age (years):**				
T2: 76.1%					323	<65: WW:47.4 RP: 33.9	HR=0.52	**<0.001**	0.37 – 0.73	1
Median PSA = 12.9 ng/mL					372	≥65: WW:57.4 RP: 56.7	HR=0.98	NS	0.75 – 1.28	1
Gleason score <7: 60.7%										
Follow up 12.8 years						**Low risk cancer[e]:**				
					263	WW:44.6 RP:31.4	HR=0.62	**0.02**	0.43 – 0.92	1

ARD = absolute risk difference, a negative ARD indicates advantage of watchful waiting over immediate definitive treatment; HR = hazard ratio < 1.0 indicates an advantage to the immediate treatment group; PSA = prostate specific antigen; RCT = randomised controlled trial; RP = radical prostatectomy; WW = watchful waiting

[#] Calculated by systematic review team from published data
a = Charlson Comorbidity Index based on a point weighting derived for current or past history of myocardial infarction, chronic congestive heart failure, peripheral vascular disease, cerebrovascular disease or stroke, diabetes (with end-organ damage), dementia, chronic pulmonary disease, liver disease, renal disease, cancers, acquired immune deficiency syndrome (0 = no comorbidities)
b = Performance score of 0=fully active, performance score of 1-4 =not fully active with a range of movement ability from light work (1) to completely disabled (4)
c = according to tumour stage determined before study entry, and PSA and biopsy findings (Gleason score) determined centrally or locally after randomisation
d = according to tumour stage determined centrally or locally after randomisation
e = Low risk cancer classified as PSA level <10ng/ml and Gleason score of <7 or a WHO grade of 1 in the perioperative specimens.

**Refer to appendix B for detailed explanations of rating scores; ** See Table 4 for quality appraisals*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the evidence statement table of content template.

II Prostate cancer-specific mortality

Table 10: Body of evidence examining the effects of watchful waiting compared with definitive treatments on prostate cancer-specific mortality

Name of study	Study type	Level of evidence *	Quality of evidence**	Risk of bias	N	Results summary %	Size of effect	p value	95% CI	Relevance of evidence
Watchful Waiting vs. Radical Prostatectomy										
Wilt 2012 **Participants:** Mean age = 67 years T1: 54.3% T2: 45.1% Median PSA = 7.8 ng/mL Gleason score <7: 70.56% Median follow up 10 years Life expectancy ≥10 years	RCT (multi-centre)	II	Medium	Moderate		**Prostate cancer specific mortality:**				
					731	WW: 8.4 RP: 5.8	HR=0.63	NS	0.36 – 1.09	1
						Subgroup analyses:				
						Age (years):				
					253	<65: WW:9.2 RP:4.9	HR=0.52	NS	0.20 – 1.39	1
					478	≥65: WW:8.1 RP:6.2	HR=0.68	NS	0.34 – 1.33	1
						Race:				
					452	White: WW:10.0 RP:6.5	HR=0.57	NS	0.30 – 1.10	1
						Charlson Comorbidity Index [a]:				
					444	0: WW:8.6 RP:6.3	HR=0.69	NS	0.34 – 1.37	1
					287	≥1: WW:8.2 RP:5.0	HR=0.54	NS	0.21 – 1.38	1
						Performance Score [b]:				
					622	0: WW:8.1 RP:5.8	HR=0.67	NS	0.37 – 1.23	1
					109	1-4: WW:10.5 RP:5.8	HR=0.41	NS	0.10 – 1.71	1
						PSA level (ng/mL):				
					479	≤10: WW:6.2 RP:5.9	HR=0.92	NS	0.44 – 1.91	1
					251	>10: WW:12.8 RP:5.6	HR=0.36	**0.02**	0.15 – 0.89	1
						Tumour Risk (central) [c]:				
					233#	Low: WW:4.1 RP:0.9	ARD=3.2%	NS	-1.5 - 8.4	1
					293#	Int: WW:5.8 RP:7.1	ARD=-1.3%	NS	-7.2 - 4.7	1
					163#	High: WW:20.0 RP:11.5	ARD=8.5%	NS	-3.0 -19.6	1
						Tumour Risk (local) [c]:				
					296	Low: WW: 2.7 RP: 4.1	ARD=-1.4%	NS	0.42 – 5.24	1

					249	Int: WW: 10.8 RP:6.2	ARD=4.6%	NS	0.21 – 1.12	1
					157	High: WW:17.5 RP:9.1	ARD=8.4%	SD	0.16 – 1.00	1
						Gleason score (central) [d]:				
					363[#]	<7: WW:4.6 RP: 1.2	ARD=3.4%	NS	-0.3 - 7.4	1
					322[#]	≥7: WW:14.2 RP: 10.9	ARD=3.3%	NS	-4.0 - 10.8	1
						Gleason score (local) [d]:				
					515	<7: WW:5.7 RP:4.3	ARD=0.34%	NS	0.31-1.49	1
					184	≥7: WW: 17.4 RP:10.2	ARD=0.10%	NS	0.23-1.14	1
Bill-Axelson 2011	RCT (multi-centre)	II	Medium	Moderate		**Prostate cancer mortality[e] :**				
					695	WW: 20.7 RP: 14.6	HR=0.62	**0.001**	0.44 – 0.87	1
Participants:										
Mean age = 64.6 years						**<u>Subgroup analyses:</u>**				
T1: 23.6%						**Age (years):**				
T2: 76.1%					323	<65: WW:25.8 RP: 16.4	HR=0.49	**0.008**	0.31 – 0.79	1
Median PSA = 12.9 ng/mL					372	≥65: WW:16.0 RP: 13.0	HR=0.83	NS	0.50 – 1.39	1
Gleason score <7: 60.7%						**Low risk cancer[f] :**				
Follow up 12.8 years					263	WW:11.0 RP: 6.8	HR=0.53	NS	0.24 – 1.14	1

ARD = absolute risk difference, a negative ARD indicates advantage of watchful waiting over immediate definitive treatment; HR = hazard ratio < 1.0 indicates an advantage to the immediate treatment group; NS = not statistically significant, p value of ≥0.05 or 95% CI that includes 1.0; PSA = prostate-specific antigen; RCT = randomised controlled trial; RP = radical prostatectomy; WHO = World Health Organisation; WW = watchful waiting

[#] = Calculated by systematic review team from published data
a = Charlson Comorbidity Index based on a point weighting derived for current or past history of myocardial infarction, chronic congestive heart failure, peripheral vascular disease, cerebrovascular disease or stroke, diabetes (with end-organ damage), dementia, chronic pulmonary disease, liver disease, renal disease, cancers, acquired immune deficiency syndrome (0 = no comorbidities)
b = performance score of 1-4 = not fully active with a range of movement ability from light work (1) to completely disabled (4)
c = according to tumour stage determined before study entry, and PSA and biopsy findings (Gleason score) determined centrally or locally after randomisation
d = Gleason score determined centrally or locally after randomisation
e = Prostate cancer mortality - accumulative incidence of deaths ascertained as probably or definitely due to prostate cancer/men randomised to management protocol
f = Low risk cancer classified as PSA level <10 ng/mL and Gleason score of <7 or a WHO grade of 1 in the perioperative specimens

**Refer to appendix B for detailed explanations of rating scores; ** See Table 4 for quality appraisals*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the evidence statement table of content template.

III Quality of Life and Adverse events

Table 11: Body of evidence examining the effects of watchful waiting compared with definitive treatments on quality of life and adverse events

Name of study	Study type	Level of evidence *	Quality of evidence **	Risk of bias	N	Results summary %	Size of effect	p value	95% CI	Relevance of evidence
Urinary Symptoms										
Wilt 2012 **Participants:** Mean age = 67 years T1: 54.3% T2: 45.1% Median PSA = 7.8 ng/mL Gleason score <7: 70.56% Median follow up 10 years Life expectancy ≥10 years	RCT (multi-centre)	II	Low	High	571	**Urinary incontinence:** (2 years) WW: 6.3 RP: 17.1	ARD=-11.0%	**<0.001**	NR	1
Steineck 2002 **Johannson 2011** **Participants:** Mean age = 64.6 years T1: 23.6% T2: 76.1% Median PSA = 12.9 ng/mL Gleason score <7: 60.7% Follow up 4.1 & 12.2 yrs	RCT (multi-centre)	II	Low	High	322	**Urinary leakage distress:** *Moderate or great distress* (4.1 years[b]) WW: 9 RP: 29	RR=3.0	SD	1.8 – 5.2	1
					336	**Distress from daytime urinary leakage:** *Moderate or great distress* (12.2 years[c]) WW: 15 RP: 28	RR=1.80[a]	SD	1.17 – 2.78	1
					341	**Distress from night time Urinary leakage:** *Moderate or great distress* (12.2 years[c]) WW: 9 RP: 18	RR=2.08[a]	SD	1.15 – 3.78	1
					320	**Overall distress from all urinary symptoms:** *Moderate or great distress* (4.1 years[b]) WW:18 RP: 27	RR=1.5	SD	1.0 – 2.3	1
					319	**Regular dependence on some form of aids against urinary leakage:** (4.1 years[b]) WW:10 RP:43	RR=4.1	SD	2.5 – 6.8	1
					338	(12.2 years[c]) WW:25 RP:54	RR=2.15[a]	SD	1.60 – 2.90	1

Sexual function symptoms										
Wilt 2012 **Participants:** Mean age = 67 years T1: 54.3% T2: 45.1% Median PSA = 7.8 ng/mL Gleason score <7: 70.56% Median follow up 10 years	RCT (multi-centre)	II	Low	High	566	**Erectile dysfunction:** (2 years) WW: 44.1 RP: 81.1	ARD=-37%	**<0.001**	NR	1
Steineck 2002, Johannson 2011 **Participants:** Mean age = 64.6 years T1: 23.6% T2: 76.1% Median PSA = 12.9 ng/mL Gleason score <7: 60.7% Follow up 4.1 & 12.2 yrs	RCT (multi-centre)	II	Low	High	319	**Erectile function:** *Seldom/never sufficient for intercourse* (4.1 years[b]) WW:45 RP:80	RR=1.8	SD	1.5 – 2.2	1
					326	*Never sufficient for intercourse:* (4.1 years[b]) WW:80 RP:84	RR=1.08[a]	NS	0.98 – 1.18	1
						Distress from erectile dysfunction: *Moderate or great distress*				
					307	(4.1 years[b]) WW:43 RP:58	RR=1.4	SD	1.0 – 1.7	1
					322	(12.2 years[c]) WW:36 RP:48	RR=1.3[a]	SD	1.00 – 1.70	1
Bowel symptoms										
Wilt 2012 **Participants:** Mean age = 67 years T1: 54.3% T2: 45.1% Median PSA = 7.8 ng/mL Gleason score <7: 70.56% Median follow up 10 years	RCT (multi-centre)	II	Low	High	568	**Bowel dysfunction:** *moderate/big problem* (2 years) WW: 11.3 RP:12.2	ARD=-0.9%	NS	NR	1
Psychological symptoms										

Steineck 2002, Johannson 2011 **Participants:** Mean age = 64.6 years T1: 23.6% T2: 76.1% Median PSA = 12.9 ng/mL Gleason score <7: 60.7% Follow up 4.1 & 12.2 years	RCT (multi-centre)	II	Low	High		**Anxiety:** *moderate or high (highest 5 of 7)*				
					321	(4.1 years[b]) WW: 31 RP: 23	RR=0.7	NS	0.5 – 1.1	1
					339	(12.2 years[c]) WW: 43 RP: 43	RR=0.97[a]	NS	0.76 – 1.24	1
						Depression: *moderate or high (highest 5 of 7)*				
					321	(4.1 years[b]) WW:38 RP:35	RR=0.9	NS	0.7 – 1.2	1
					339	(12.2 years[c]) WW:52 RP:47	RR=0.92[a]	NS	0.74 – 1.14	1
						Psychological wellbeing: *low or moderate (lowest 5 of 7)*				
					322	(4.1 years[b]) WW:36 RP:35	RR=1.0	NS	0.7 – 1.3	1
						High (highest 2 of 7 possible categories)				
					340	(12.2 years[c]) WW:44 RP: 41	RR=0.89[a]	NS	0.70 – 1.13	1
						Distress from erectile dysfunction: *% moderate or great distress*				
					307	(4.1 years[b]) WW:43 RP:58	RR=1.4	**SD**	1.0 – 1.7	1
					322	(12.2 years[c]) WW:36 RP:48	RR=1.3[a]	**SD**	1.0 – 1.7	1
						Distress from decreased sexual ability: *% moderate to great distress*				
					317	(12.2 years[c]) WW:35 RP: 37	RR=1.01[a]	NS	0.76 – 1.34	1
						Distress from obstructed voiding: *% moderate or great distress*				
					321	(4.1 years[b]) WW:22 RP:31	RR=1.0	NS	0.60 – 1.5	1
					337	(12.2 years[c]) WW:32 RP:27	RR=0.82[e]	NS	0.60 – 1.14	1
General symptoms										
Steineck 2002, Johannson 2011 **Participants:** Mean age = 64.6 years T1: 23.6% T2: 76.1% Median PSA = 12.9 ng/mL Gleason score <7: 60.7% Follow up 4.1 & 12.2 years	RCT (multi-centre)	II	Low	High		**Physical well-being:** *low or moderate (lowest 5 of 7)*				
					321	(4.1 years[b]) WW: 50 RP: 41	RR=0.8	NS	0.7 – 1.1	1
						Patient assessed QoL: *low or moderate (lowest 5 of 7)*				
					310	(4.1 years[b]) WW:45 RP: 40	RR=0.9	NS	0.7 – 1.2	1
						High (highest 2 of 7 categories)				
					339	(12.2 years[c]) WW:34 RP:35	RR=0.98[a]	NS	0.73 – 1.15	1

Adverse Events										
Wilt 2012 **Participants:** Mean age = 67 years T1: 54.3% T2: 45.1% Median PSA = 7.8 ng/mL Gleason score <7: 70.56% Median follow up 10 years	RCT (multi-centre)	II	Low	High	280 280 280 280 280 280 280	**Wound infection:** WW: - RP: 4.3 **Bowel injury requiring repair:** WW: - RP: 1.1 **Additional surgical repair:** WW: - RP: 2.5 **Blood transfusion:** WW: - RP: 2.1 **Urinary tract infection:** WW: - RP:2.5 **Urinary catheter >30 days:** WW: - RP: 2.1 **Death:** WW: - RP: 0.4	- - - - - - -	- - - - - - -	- - - - - - -	1 1 1 1 1 1 1

Metastases										
Bill-Axelson 2011 **Participants:** Mean age = 64.6 years T1: 23.6% T2: 76.1% Median PSA = 12.9 ng/mL Gleason score <7: 60.7% Median follow up 12.8 yrs	RCT (multi-centre)	II	Medium	Moderate		**Distant metastases:**				
					695	WW: 33.4 RP: 21.7	RR=0.59	<0.001	0.45 - 0.79	1
						<u>Subgroup analyses</u>:				
						Low-risk cancer:				
					263	WW: 21.4 RP: 9.9	RR = 0.43	0.008	0.23 - 0.79	1
						Age (years):				
					323	<65: WW: 39.8 RP: 21.5	RR = 0.47	0.001	0.32 - 0.70	1
					372	≥65: WW: 27.5 RP: 22.1	RR = 0.77	0.14	0.51 - 1.51	1
Wilt 2012 **Participants:** Mean age = 67 years T1: 54.3% T2: 45.1% Median PSA = 7.8 ng/mL Gleason score <7: 70.56% Median follow up 10 years	RCT (multi-centre)	II	Medium	Moderate		**Bone metastases:**				
					731	WW: 10.6 RP: 4.7	HR = 0.40	<0.001	0.22 - 0.70	1
						<u>Subgroup analyses:</u>				
						Age (years):				
					253	<65: WW:9.9 RP:5.7	RR = 0.58	0.19	0.24 - 1.40	1
					478	≥65: WW:11.0 RP:4.1	RR = 0.38	0.002	0.19 - 0.76	1
						Race:				
					452	White: WW: 12.7 RP:5.2	RR = 0.41	0.002	0.21 – 0.78	1
						Charlson Comorbidity Index:				
					444	0: WW: 12.3 RP: 6.3	RR = 0.51	0.02	0.27 – 0.94	1
					287	≥1: WW: 8.2 RP: 2.1	RR = 0.26	0.02	0.08 – 0.91	1
						Performance Status:				
					622	0: WW: 10.3 RP: 4.8	RR = 0.47	0.005	0.26 – 0.84	1
					109	1-4: WW: 12.3 RP: 3.9	RR = 0.31	0.07	0.07 – 1.44	1
						PSA level (ng/mL):				
					479	≤10: WW:8.7 RP:5.0	RR = 0.58	0.09	0.29 - 1.15	1
					251	>10: WW:14.4 RP:4.0	RR = 0.28	0.001	0.11 - 0.72	1
						Tumour Risk (central):				
					233[#]	Low: WW:4.9 RP:0.9	RR = 0.18	0.08	0.02 - 1.50	1

295[#]	Int: WW:11.5 RP:6.5	RR = 0.56	0.08	0.26 - 1.19	1
163[#]	High: WW:17.7 RP:6.4	RR = 0.36	0.01	0.14 - 0.95	1
	Tumour Risk (local):				
296	Low: WW:6.1 RP:4.1	RR = 0.67	0.39	0.24 – 1.83	1
249	Int: WW: 15.8 RP:4.7	RR = 0.29	0.002	0.12 – 0.71	1
157	High: WW:13.8 RP5.2:	RR = 0.38	0.03	0.13 – 1.14	1
	Gleason Score (central):				
364[#]	<7: WW:4.1 RP:1.2	RR = 0.29	0.10	0.06 - 1.35	1
322[#]	≥7: WW:19.6 RP:8.1	RR = 0.41	0.0001	0.23 - 0.75	1
	Gleason Score (local):				
515	<7: WW:8.1 RP:3.5	RR = 0.44	0.02	0.21 – 0.94	1
184	≥7: WW: 20.9 RP:7.1	RR = 0.34	0.003	0.15 – 0.78	1

ARD = absolute risk difference, a negative ARD indicates advantage of watchful waiting over immediate definitive treatment; HR = hazard ratio < 1.0 indicates an advantage to the immediate treatment group; NS = not significant, p value of ≥0.05 or 95% CI that includes 1.0; NR = not reported; PSA = prostate specific antigen; QoL = quality of life; RCT = randomised controlled trial; RP = radical prostatectomy; RR = relative risk, < 1.0 indicates an advantage to the delayed treatment group; TURP = transurethral resection of the prostate; WW = watchful waiting

[#] = calculated by systematic review team from published data
a = age-adjusted
b = median years follow up
c = mean years follow up

**Refer to appendix B for detailed explanations of rating scores; ** See Table 5 for quality appraisals*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the NHMRC evidence statement form

References: Included studies

1. Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *New England Journal of Medicine* 2011; 364:1708-17.

2. Johansson E, Steineck G, Holmberg L, Johansson JE, Nyberg T, Ruutu M et al. Long-term quality-of-life outcomes after radical prostatectomy or watchful waiting: the Scandinavian Prostate Cancer Group-4 randomised trial. *Lancet Oncology* 2011; 12(9):891-9.

3. Steineck G, Helgesen F, Adolfsson J, Dickman PW, Johansson JE, Norlen BJ et al. Quality of life after radical prostatectomy or watchful waiting. *New England Journal of Medicine* 2002; 347:790-6.

4. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S et al. Prostate Cancer Intervention versus Observation Trial (PIVOT) Study Group. Radical prostatectomy versus observation for localized prostate cancer. *New England Journal of Medicine* 2012; 367:203-13.

APPENDICES

Appendix A: Search strategies used

For Medline database:

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	randomized controlled trial.pt.
5	controlled clinical trial.pt.
6	placebo.ab.
7	randomi?ed.ab.
8	randomly.ab.
9	trial.ab.
10	groups.ab.
11	4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp animals/ not humans.sh.
13	11 not 12
14	(watch$ adj2 wait$).mp.
15	defer$ treat$.mp.
16	(symptom adj2 treat$).mp.
17	defer$ therap$.mp.
18	(wait adj2 see).mp.
19	(conservative adj2 (manage$ or treat$ or therap$)).mp.
20	(active adj1 monitoring).tw
21	'active monitoring'.tw
22	'conservative monitoring'.tw
23	'delayed treatment$'.tw
24	'watchful observation'.tw
25	'watchful surveillance'.tw
26	'watchful monitoring'.tw
27	'expectant monitoring'.tw
28	'expectant surveillance'.tw
29	'delayed therap$'.tw
30	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31	3 AND 13 AND 30

Used the Cochrane sensitivity maximizing filters for identifying randomized controlled trials (http://handbook.cochrane.org, accessed 20/02/2013/ Centre for Reviews and Dissemination systematic review/ meta-analyses strategy 2.(Lee et al, (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. ***BMC Medical Research Methodology*** *12:51)*

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database:

#	Searches
1	'prostate cancer'/exp OR 'prostate cancer'
2	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR metast* OR adeno*)
3	#1 OR #2
4	watch* NEAR/2 wait*
5	defer* NEXT/1 treat*
6	symptom NEAR/2 treat*
7	defer* NEXT/1 therap*
8	wait* NEAR/2 see*
9	active NEAR/1 monitoring OR 'active monitoring'
10	watchful NEXT/1 (observation OR surveillance OR monitoring)
11	expectant NEXT/1 (monitoring OR surveillance)
12	delayed NEXT/1 (treatment*, OR therapy*)
13	'conservative monitoring'
14	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
15	rct
16	'randomized controlled trial'/exp OR 'randomized controlled trial'
17	'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomised controlled trial'/exp OR 'randomised controlled trial' OR 'randomized controlled trials'/exp OR 'randomized controlled trials' OR 'randomised controlled trials'
18	'random allocation'/exp OR 'random allocation'
19	'randomly allocated'
20	'randomization'/exp OR 'randomization'
21	allocated NEAR/2 random
22	'double blind procedure'/exp OR 'double blind procedure'
23	'single blind procedure'/exp OR 'single blind procedure'
24	single NEXT/1 blind*
25	double NEXT/1 blind*
26	(treble OR triple) NEXT/1 blind*
27	placebo*
28	'placebo'/exp OR 'placebo'
29	'prospective study'/exp OR 'prospective study'
30	'crossover procedure'/exp OR 'crossover procedure'
31	'clinical trial'/exp OR 'clinical trial'
32	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31

33	'case study'/exp OR 'case study'
34	case AND report
35	'abstract report'/exp OR 'abstract report'
36	'letter'/exp OR 'letter'
37	33 OR 34 OR 35 OR 36
38	32 NOT 37
39	[1990-3000]/py
40	[english]/lim
41	[humans]/lim
42	#39 and #40 and #41
43	[medline]/lim
44	#42 NOT #43

*Used the SIGN filter for identifying randomized controlled trials (*www.sign.ac.uk/methodology/filters.html#systematic *accessed 20/02/2013)*

ATSI search terms used

#	Searches
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

For Cochrane Database of Systematic Reviews 2005 to 1st quarter 2014, Database of Abstracts of Reviews of Effects and Health Technology Assessment database via OVID platform

#	Searches
1	(prostat$ adj3 (cancer$ OR carcinoma$ OR malignan$ OR tumo?r$ OR neoplas$ OR metastas$ OR adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 OR 2

Appendix B:

Level of Evidence rating criteria – Intervention studies

Level	Study design
I	Meta-analysis or a systematic review of level II studies
II	Randomised controlled trial or a phase III/IV clinical trial
III-1	Pseudo-randomised controlled trial or a meta-analysis/systematic review of level III-1 studies
III-2	Comparative study with concurrent controls: - Phase II clinical trial - Non-randomised, experimental trial9 - Controlled pre-test/post-test study - Adjusted indirect comparisons - Interrupted time series with a control group - Cohort study - Case-control study or a meta-analysis/systematic review of level III-2 studies
III-3	A comparative study without concurrent controls: - Phase I clinical trial - Historical control study - Two or more single arm study10 - Unadjusted indirect comparisons - Interrupted time series without a parallel control group or a meta-analysis/systematic review of level III-3 studies
IV	Case series with either post-test or pre-test/post-test outcomes or a meta-analysis/systematic review of level IV studies

According to the standards of the National Health and Medical Research Council

Relevance of the evidence

Rating	Relevance
1	Evidence of an effect on patient-relevant clinical outcomes including benefits and harms, quality of life and survival.
2	Evidence of an effect on a surrogate outcome* that has been shown to be predictive of patient-relevant outcomes for the same intervention.
3	Evidence of an effect on proven surrogate outcomes but for a different intervention.
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population.
5	Evidence confined to unproven surrogate outcomes.

**'surrogate outcome' refers to reasonable indicators of whether there has been some effect (e.g. blood pressure measurements or levels of serum cholesterol)*

Points to considering patient-relevant outcomes:
i) The goal of decision making in health care is to choose the intervention(s) (which may include doing nothing) that is (are) most likely to deliver the outcomes that patients find desirable
ii) Surrogate outcomes (such as blood pressure measurements or levels of serum cholesterol) may be reasonable indicators of whether there has been some effect. However, they should not be the basis for clinical decisions unless they reliably predict an effect on the way the patient feels; otherwise they will not be of interest to the patient or their carers
iii) All possible outcomes that are of most interest to patients (particularly harms) should be identified and evaluated

Adapted from table 1.10: National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra: NHMRC; 2000. http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp69.pdf

Appendix C:
Potentially relevant guidelines identified

YEAR	ORGANISATION	TITLE	REASONS FOR NOT ADOPTING
2012	KCE/Belgium Health Care Knowledge Centre	A National Clinical Practice Guideline on the management of localised prostate cancer	Did not meet 70% scores for domains of Rigour, Clarity and Editorial Independence on AGREE instrument

Excluded Studies

Study	Reason for Exclusion
Alibhai 2004	Review article
Bill-Axelson 2005	RCT with immature outcome data
Bill-Axelson 2008	RCT with immature outcome data
Bill-Axelson 2013	No relevant outcomes
Bul 2012	Inappropriate study design
Chou 2011	Review article
Dahabreh 2012	Review article
Fransson 2001	RCT with immature outcome data
Fransson 2009	Inappropriate study design
Graversen 1990	RCT with immature outcome data
Hegarty 2007	No relevant outcomes
Holmberg 2002	RCT with immature outcome data
Holmberg 2012	Review article
Iversen 1995	Inappropriate study design
Iversen 2006	RCT with immature outcome data
Iversen 2010	Inappropriate study design
Jereczek-Fossa 2009	Review article
Johansson 2009	RCT with immature outcome data
Kwiatkowski 2004	Inappropriate study design
Lyth 2012	Modelling was not externally validated in another cohort of patients
McLeod 2006	RCT with immature outcome data
Mhaskar 2012	Review article
Sculpher 2004	Inappropriate study design
See 2001	RCT with immature outcome data
See 2002	RCT with immature outcome data
Studer 2006	Does not compare watchful waiting with immediate definitive therapy
Studer 2008	Does not compare watchful waiting with immediate definitive therapy
Studer 2013	Does not compare watchful waiting with immediate definitive therapy
Vickers 2012	Modelling was not externally validated in another cohort of patients
Wilt 1994	RCT with immature outcome data
Wilt 1997	RCT with immature outcome data
Wilt 2009	RCT with immature outcome data
Wilt 2012	RCT with immature outcome data
Wirth 2004	RCT with immature outcome data

References: Excluded Studies

1. Alibhai SM and Klotz LH. A systematic review of randomized trials in localized prostate cancer. *Canadian Journal of Urology* 2004; 11(1):2110-7.

2. Bill-Axelson A, Holmberg L, Ruutu M, Haggman M, Andersson SO, Bratell S et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *New England Journal of Medicine* 2005; 352(19):1977-84.

3. Bill-Axelson A, Holmberg L, Filen F, Ruutu M, Garmo H, Busch C et al. Johansson JE, Scandinavian Prostate Cancer Group. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. *Journal of the National Cancer Institute* 2008; 100:1144-54.

4. Bill-Axelson A, Garmo H, Holmberg L, Johansson JE, Adami HO, Steineck G et al. Long-term Distress After Radical Prostatectomy Versus Watchful Waiting in Prostate Cancer: A Longitudinal Study from the Scandinavian Prostate Cancer Group-4 Randomized Clinical Trial. *European Urology* 2013; 64(6):920-8.

5. Bul M, van den Bergh RC, Zhu X, Rannikko A, Vasarainen H, Bangma CH et al. Outcomes of initially expectantly managed patients with low or intermediate risk screen-detected localized prostate cancer. *BJU International* 2012; 110(11):1672-7.

6. Chou R, Croswell JM, Dana T, Bougatsos C, Blazina I, Fu R et al. Screening for prostate cancer: a review of the evidence for the U.S. Preventive Services Task Force. *Annals of Internal Medicine* 2011; 155:762-71.

7. Dahabreh IJ, Chung M, Balk EM, Yu WW, Mathew P, Lau J et al. Active surveillance in men with localized prostate cancer: a systematic review. *Annals of Internal Medicine* 2012; 156(8):582-90

8. Fransson P, Damber JE, Tomic R, Modig H, Nyberg G, Widmark A. Quality of life and symptoms in a randomized trial of radiotherapy versus deferred treatment of localized prostate carcinoma. *Cancer* 2001; 92:3111-9.

9. Fransson P, Damber JE, Widmark A. Health-related quality of life 10 years after external beam radiotherapy or watchful waiting in patients with localized prostate cancer. *Scandinavian Journal of Urology and Nephrology* 2009; 43:119-26.

10. Graversen PH, Nielsen KT, Gasser TC, Corle DK, Madsen PO. Radical prostatectomy versus expectant primary treatment in stages I and II prostatic cancer. A fifteen-year follow-up. *Urology* 1990; 36(6):493-8.

11. Hegarty J, Beirne P, Comber H, Wallace M. Watchful waiting versus prostatectomy for prostate cancer**.** *Cochrane Database of Systematic Review* 2008; 4.

12. Holmberg L, Bill-Axelson A, Helgesen F, Salo JO, Folmerz P, Haggman M et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. *New England Journal of Medicine* 2002; 347:781-9.

13. Holmberg L, Bill-Axelson A, Steineck G, Garmo H, Palmgren J, Johansson E et al. Results from the Scandinavian Prostate Cancer Group Trial Number 4: a randomized controlled trial of radical

prostatectomy versus watchful waiting. *Journal of the National Cancer Institute Monographs* 2012; 2012(45):230-3.

14. Iversen P, Madsen PO, Corle DK. Radical prostatectomy versus expectant treatment for early carcinoma of the prostate. Twenty-three year follow-up of a prospective randomized study. *Scandinavian Journal of Urology and Nephrology Supplement* 1995; 172:65-72.

15. Iversen P, Johansson JE, Lodding P, Kylmälä T, Lundmo P, Klarskov P et al. Bicalutamide 150 mg in addition to standard care for patients with early non-metastatic prostate cancer: updated results from the Scandinavian Prostate Cancer Period Group-6 Study after a median follow-up period of 7.1 years. *Scandinavian Journal of Urology and Nephrology* 2006; 40(6):441-52.

16. Iversen P, McLeod DG, See WA, Morris T, Armstrong J, Wirth MP. Antiandrogen monotherapy in patients with localized or locally advanced prostate cancer: final results from the bicalutamide Early Prostate Cancer programme at a median follow-up of 9.7 years. *BJU International* 2010; 105(8):1074-81.

17. Jereczek-Fossa BA, Curigliano G, Orecchia R. Systemic therapies for non-metastatic prostate cancer: review of the literature. *Onkologie* 2009; 32(6):359-63.

18. Johansson E, Bill-Axelson A, Holmberg L, Onelov E, Johansson JE, Steineck G et al. Time, symptom burden, androgen deprivation, and self-assessed quality of life after radical prostatectomy or watchful waiting: the Randomized Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) clinical trial. *European Urology* 2009; 55:422-30.

19. Kwiatkowski M, Huber A, Moschopulos M, Lehmann K, Wernli M, Hafeli A et al. Prostate cancer screening: results of a prospective trial in Canton Aargau, Switzerland. *Swiss Medical Weekly* 2004; 134(39-40):580-5.

20. Lyth J, Andersson SO, Andren O, Johansson JE, Carlsson P, Shahsavar N. A decision support model for cost-effectiveness of radical prostatectomy in localized prostate cancer. *Scandinavian Journal of Urology & Nephrology* 2012; 46(1):19-25.

21. McLeod DG, Iversen P, See WA, Morris T, Armstrong J, Wirth MP. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. *BJU International* 2006; 97(2):247-54.

22. Mhaskar AR, Quinn G, Vadaparampil S, Djulbegovic B, Gwede CK, Kumar A. Timing of first-line cancer treatments - early versus late - a systematic review of phase III randomized trials. *Cancer Treatment Reviews* 2012; 36(8) 621-8.

23. Sculpher M, Bryan S, Fry P, de Winter P, Payne H, Emberton M. Patients' preferences for the management of non-metastatic prostate cancer: discrete choice experiment. *BMJ* 2004; 328(7436):382.

24. See WA, McLeod D, Iversen P, Wirth M. The bicalutamide early prostate cancer program: Demography. *Urology Oncology* 2001; 6:43-7.

25. See WA, Wirth MP, McLeod DG, Iversen P, Klimberg I, Gleason D et al. Bicalutamide as immediate therapy either alone or as adjuvant to standard care of patients with localized or locally advanced prostate cancer: first analysis of the early prostate cancer program. *Journal of Urology* 2002; 168(2):429-35

26. Studer UE, Whelan P, Albrecht W, Casselman J, De Reijke T, Hauri D et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European organisation for research and treatment of cancer (EORTC) trial 30891. *Journal of Clinical Oncology* 2006; 24:1868-76.

27. Studer UE, Collette L, Whelan P, Albrecht W, Casselman J, de Reijke T et al. Using PSA to Guide Timing of Androgen Deprivation in Patients with T0-4 N0-2 M0 Prostate Cancer not Suitable for Local Curative Treatment (EORTC 30891). *European Urology* 2008; 53:941–9.

28. Studer UE, Whelan P, Wimpissinger F, Casselman J, de Reijke TM, Knönagel H et al. Differences in Time to Disease Progression Do Not Predict for Cancer-specific Survival in Patients Receiving Immediate or Deferred Androgen-deprivation Therapy for Prostate Cancer: Final Results of EORTC Randomized Trial 30891 with 12 Years of Follow-up. *European Urology* 2013; 66(5):829-38.

29. Vickers A, Bennette C, Steineck G, Adami HO, Johansson JE, Bill-Axelson A et al. Individualized estimation of the benefit of radical prostatectomy from the Scandinavian Prostate Cancer Group randomized trial. *European Urology* 2012; 62(2):204-9.

30. Wilt TJ, Brawer MK. The Prostate Cancer Intervention Versus Observation Trial (PIVOT). *Oncology* 1997; 11(8):1133-9.

31. Wilt TJ, Brawer MK. The Prostate Cancer Intervention Versus Observation Trial: a randomized trial comparing radical prostatectomy versus expectant management for the treatment of clinically localized prostate cancer. *Journal of Urology* 1994; 152(5 Pt 2):1910-4.

32. Wilt TJ, Brawer MK, Barry MJ, Jones KM, Kwon Y, Gingrich JR et al. The Prostate cancer Intervention Versus Observation Trial:VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT): design and baseline results of a randomized controlled trial comparing radical prostatectomy to watchful waiting for men with clinically localized prostate cancer. *Contemporary Clinical Trials* 2009; 30:81-7.

33. Wilt TJ. The Prostate Cancer Intervention Versus Observation Trial: VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT): design and baseline results of a randomized controlled trial comparing radical prostatectomy with watchful waiting for men with clinically localized prostate cancer. *Journal of the National Cancer Institute Monographs* 2012; 184-90.

34. Wirth MP, See WA, McLeod DG, Iversen P, Morris T, Carroll K. Bicalutamide 150 mg in addition to standard care in patients with localized or locally advanced prostate cancer: results from the second analysis of the early prostate cancer program at median follow up of 5.4 years. *Journal of Urology* 2004; 172(5 Pt 1):1865-70.

Systematic review report for question 12

Clinical Question 12: "*What is the best monitoring protocol for watchful waiting and what should be the criteria for intervention?*

PICO Question 12: *"For men with biopsy-diagnosed prostate cancer following a watchful waiting protocol, which combination of monitoring tests, testing frequency and clinical or other criteria for intervention achieve the best outcomes in terms of length and quality of life?"*

Population	Intervention	Comparator	Outcomes
Men with biopsy (histologically) confirmed prostate cancer	Watchful waiting	An alternative watchful waiting protocol and immediate definitive treatment, or immediate definitive treatment	Overall mortality, or Prostate cancer-specific mortality, or Metastatic disease, or Quality of life, or Adverse events

1. METHODS

1.1 Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption guidelines had to be evidence based and meet the pre-specified criteria of scores of ≥70% for the domains: Rigour of Development, Clarity of Presentation, and Editorial Independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

1.2 Literature Search

Medline (01/01/1990-01/03/2014), Embase (01/01/1990-01/03/2014), Cochrane Database of Systematic Reviews (01/01/2005-01/03/2014), Database of Abstracts of Reviews of Effects (until 01/03/2014) and Health Technology Assessment databases (until 01/03/2014) were searched using text terms and, where available, database specific subject headings. Each database was searched for articles dealing with prostate cancer. In Medline and Embase databases the prostate cancer search was coupled with a search for watchful waiting, and database specific filters for identifying randomised controlled trials (RCTs). To identify studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples. A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 added to the relevant database after February 2014. Alerts were checked until July 2014. Reference lists of all relevant articles were checked for potential additional articles.

1.3 Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	Nomograms (or predictive model) that have not been validated in a separate cohort
Study design	Randomised controlled trial, or meta-analysis/systematic review thereof	
Population	Men with histologically confirmed prostate cancer	Studies that restricted participants based on biomarker status
Intervention	Watchful Waiting	Studies that do not report monitoring protocols, or triggers for intervention
Comparator	An alternative watchful waiting protocol and immediate definitive treatment, or immediate definitive treatment	
Outcomes	Overall mortality, or Prostate cancer-specific mortality, or Quality of life, or Metastatic disease, or Adverse events	
Language	English	
Publication period	After 31st December 1989 and before1st March 2014	

Conference proceedings identified by the literature searches were included if they met the inclusion criteria.

1.4 Definitions

Watchful Waiting

Watchful waiting does not aim to cure prostate cancer, but to relieve its symptoms. Watchful waiting involves the conscious decision to avoid treatment unless symptoms or signs of progressive disease develop. The reason for delaying therapy is to avoid side effects which accompany all treatments and, by doing so, maximise patients' quality of life. Reasons for undertaking watchful waiting include: the cancer has advanced and is not curable with local treatments, the patient's life expectancy is limited and prostate cancer is unlikely to cause significant problems in that patient's lifetime, and some patients may elect to undertake a program of watchful waiting rather than proceed with any of the localised disease management options. When treatment is implemented following a period of watchful waiting, it almost always involves androgen deprivation therapy (ADT) with transurethral resection of the prostate (TURP) used to relieve any bladder outflow obstruction.

It is important to differentiate 'watchful waiting' from 'active surveillance'. With the latter the patient is monitored closely with the intention to proceed to a treatment with curative intent if

there is evidence of tumour progression or if and when the patient wishes to undertake treatment.

2. RESULTS

2.1 Guidelines

One guideline by the Belgian Health Care Knowledge Centre (KCE - A national clinical practice guideline on the management of localised prostate cancer 2012) contained recommendations regarding watchful waiting. After assessment using the AGREE II instrument, this guideline failed our pre-specified criteria scores outlined above. The identified guideline is documented in Appendix C.

2.2 Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the systematic review. The Medline search identified 298 citations, the Embase search 80 citations, the search of the Cochrane Database of Systematic Reviews 59 citations, the Database of Abstracts of Reviews of Effects search 282 citations and the search of the Health Technology Assessment database identified an additional 216 citations, resulting in a total of 935 citations. Titles and abstracts were examined and 36 articles were retrieved for a more detailed evaluation. An additional 2 potential citations were identified from the clinical trial registries and reference lists of retrieved article, leading to a total of 38 articles requiring a more detailed evaluation.

Three RCTs reported in seven articles met the inclusion criteria and were included in the review. There were no studies of ATSI men that met the inclusion criteria.

The retrieved articles that were not included and the reason for their exclusion are documented in Appendix C. In summary, most articles were excluded because they reported immature outcome data from RCTs, were review articles, or used inappropriate study designs.

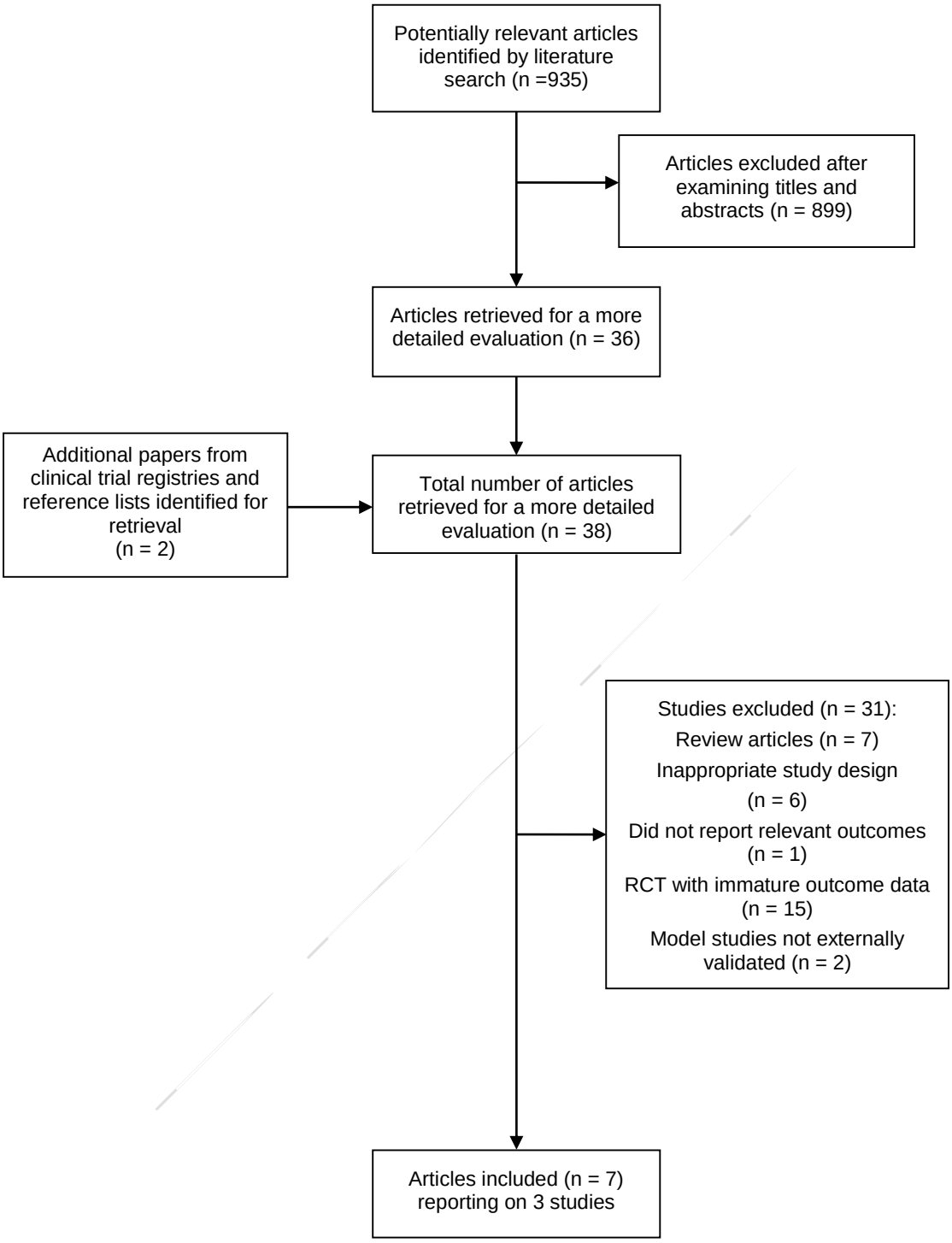


Figure 1. Process of inclusion and exclusion of studies.

2.3 Study Characteristics

Characteristics of included studies are described in Table 1.

Table 1: Characteristics of intervention studies examining watchful waiting and definitive treatment for improving outcomes in prostate cancer patients

Study	Participants	Design	Watchful Waiting	Definitive Treatment	Relevant Outcomes	Comments
Watchful Waiting vs. Radical Prostatectomy						
Wilt 2012 (USA) PIVOT	Men aged ≤75 years with clinically localised prostate cancer (T1-2NxM0 - AJCC 5th edition; -ve bone scan) of any grade diagnosed by biopsy within the previous 12 months, with an estimated life expectancy ≥10 years and a PSA ≤50 ng/mL, who were medically and surgically fit for radical prostatectomy, were not currently receiving ADT and had not previously received any therapy for prostate cancer (except TURP for obstructive symptoms) **Mean age** 67 years **Race** White: 61.8% African American: 31.7% **Charlson Comorbidity Index[a]** 0: 56.1%; ≥1: 43.5%. **Performance status** Fully active: 85.1% **PSA (ng/mL):** Median: 7.8 ≤10.0: 65.5%; >10.0: 34.3%. **Gleason score** <7: 70.5%; ≥7: 25.1%. **Risk category (D'Amico)** Low: 40.5% Intermediate: 34.1% High: 21.5% **Clinical stage** T1a/b: 4.0%; T1c: 50.3%; T2a: 24.8%; T2b: 12.5%; T2c: 7.8%. **N = 731**	RCT (multi-centre - 52 sites)	**Watchful Waiting** Therapeutic decisions at physician's discretion while adhering to the principle of using palliative therapies with low morbidity rates for symptomatic or local progression (TURP), metastatic disease progression, ADT, RT or chemotherapy RP, definitive radiation therapy, early ADT or treatment for asymptomatic progression, including an increase in PSA proscribed 20.4% of participants in WW arm received definitive therapy,10.1% underwent RP **N = 367**	**Radical Prostatectomy** Performed within 6 weeks of randomisation; technique at surgeon's discretion (e.g. retropubic, transperineal, use of lymph node dissection, nerve sparing surgery) Additional early aggressive intervention for disease persistence or recurrence Physician discretion allowed maximum flexibility consistent with current clinical practice 76.9% of participants underwent RP, 14.6% of participants in RP arm did not receive any definitive therapy **N = 364**	**Primary:** *All-cause mortality. Cumulative incidence of mortality (at 4, 8, 12 years, and end of study)* **Secondary:** *Prostate cancer mortality (death definitely or probably due to prostate cancer or prostate cancer treatment). Adverse events within 30 days of surgery* *Urinary incontinence* *Bowel dysfunction* *Erectile dysfunction* Median follow up = 10.0 years (range 9-15 years)	Follow up visits 6 weeks after randomisation, every 3 months for year 1, then every 6 months, with urologic symptoms and quality of life questionnaires and a PSA test at every visit, and bone scans at least every 5 years Estimated that 740 participants would provide 91% power to detect a 25% relative reduction in all-cause mortality with 15 years of follow up and a median survival of 10 years **Subgroup analyses:** Age, race, Charlson Comorbidity Index, performance status, PSA level, Gleason score, risk category

Bill-Axelson 2011 **Johansson 2011** **Steineck 2002** (Sweden, Finland & Iceland) SPCG-4	Men newly diagnosed (<4months) with histologically or cytologically confirmed localised prostate cancer recruited from 14 different centres October 1989 – December 1999. Clinical stage T1 or T2 (UICC 3rd ed. 1978). T1c included after 1994. Tumour of high or intermediate differentiation grade (WHO classification) No other known cancers. PSA <50 ng/mL and age <75 years. Negative bone scan and life expectancy >10 years and fit to undergo prostatectomy. **Mean age** 64.6 years **PSA (ng/mL):** Mean: 12.9 <4:15.3%; 4-6.9: 17.3%; 7-10: 19.4%; 10.1-20: 28.1%; >20: 18.6% **Gleason Score:** 2-4: 13.1%; 5-6: 47.6%; 7: 22.9%; ≥8: 5.0%. **Clinical Stage:** T1b: 11.9%; T1c: 11.7%; T2: 76.1% 55.5% prostate cancer detected as a result of symptoms or TURP. 5.2% prostate cancer detected as a result of opportunistic PSA testing. **N = 695**	RCT (multi-centre)	**Watchful Waiting** No immediate treatment. TURP if signs of obstructive voiding disorders ADT if metastases detected or, from 2003, if any sign of tumour progression including rising PSA levels 50 men (14.4%) received curative treatment **N = 348**	**Radical Prostatectomy** Performed if local nodes were negative for prostate cancer, radical excision given preference over nerve sparing ADT if signs of local recurrence developed (palpable nodule or histologically confirmed recurrence) or metastases detected or, from 2003, if any sign of tumour progression including rising PSA levels 289 (83.3%) men underwent immediate radical prostatectomy 44 (12.7%) men received no curative therapy **N = 347**	**Primary:** *Prostate cancer-specific mortality* **Secondary:** *Overall mortality* *Quality of life* Median follow up = 12.8 years Patients followed until 31/12/2009. No loss to follow up	Intention-to-treat analysis All patients followed up with a clinical examination and determination of haemoglobin, creatinine, PSA, AP levels twice a year for the first two years and then annually. A bone scan and chest radiograph were obtained annually until 2003 and then biennially. After 1996 chest x-rays were performed. Sample size of 700 calculated to detect an absolute difference in disease-specific survival rate of 6% with 5% risk of Type I error and 20% risk of Type II error, if disease-specific survival rate was 95% in one group. **Subgroup analyses:** Age, PSA level, Gleason score
	Subgroups					
Steineck 2002	Swedish participants alive 1997-1998 enrolled prior to 29/02/1996 **N = 376**		**N = 187**	**N = 189**	*Quality of life* Mean follow up = 4.1 years	Current quality of life measured using a questionnaire 86.7% response rate
Johansson 2011	Swedish and Finnish participants alive 2006-2008 **N = 400**		**N = 192**	**N = 208**	*Quality of life* Median follow up = 12.2 years	Current quality of life measured using same questionnaire as above 87.3% response rate

Deferred ADT vs. Immediate ADT						
Studer 2006 **Studer 2008** **Studer 2013** (Switzerland, UK, Austria, Belgium, Netherlands, Spain) EORTC 30891	Men aged 52-81 years with histologically or cytologically confirmed localised prostate cancer (T0-4 N0-2 M0 as per UICC 3rd edition 1978 – negative pelvic CT, bone scan, chest X-ray) diagnosed within previous 105 days, with a life expectancy of ≥6 months, who were not suitable for local curative treatment, but asymptomatic and who had not previously undergone local or systemic treatment (TURP for voiding difficulties allowed) and had not had a second malignancy within previous 10 years **Median age** 73.0 years **Men with associated chronic diseases** 76.8% **WHO Performance status** Fully active: 68.5% **PSA (ng/mL)** Median: 16.3 ≤8: 25.5%; 8.1-20: 31.8%; 20.1-50: 23.9%; >50: 18.8%. **WHO histopathological grade** G1: 27.7%; G2: 48.9%; G3: 22.2%. **Clinical stage** T0/1: 17.4%; T2: 35.5%; T3/4: 46.8% N0: 77.8%; N1/2: 5.7% **N = 985**	RCT (multi-centre)	**Deferred ADT** Upon systemic disease progression or life-threatening complications such as symptomatic metastases, increase in prostate cancer-related pain, deterioration in performance status or ureteric obstruction ADT not initiated on PSA or AP rise or on appearance of asymptomatic new hot spots in bone scan or soft tissue metastases Further ADT treatment upon symptomatic progression at the discretion of physician 54% of participants received deferred ADT (median 2.8 years after study entry), 14.4% of these men had changed treatment not in accordance with the protocol 44% never underwent ADT and 2% of participants in deferred ADT arm received immediate therapy **N = 493**	**Immediate ADT** Subcapsular orchiectomy or LHRH agonist therapy (Buserelin 6.3mg SC bimonthly) within 1 month of randomisation Initial antiandrogen therapy (Cyproterone acetate 50mg three times daily for 2 weeks) 96.5% of participants in immediate ADT arm were treated immediately **N = 492**	**Primary:** *All-cause mortality/overall survival* **Secondary:** *Prostate cancer mortality.* *Symptoms and Adverse Events.* Median follow up = 12.8 years (8 years for symptoms and adverse events) Follow up 100% (94.8% for pain)	2.5% ineligible men included Follow-up biannually for first 2 years, then annually with DRE, PSA, AP; chest X-ray, liver ultrasound, pelvic CT, bone scan, bone X-ray in case of suspected progression Sample size of 900 recommended to provide 80% power to rule out a ≥7% decrease from an assumed 65% 5-year survival with a one-sided 5% significance level. Primary objective to demonstrate equivalent overall survival between groups **Subgroup analyses:** PSA level, PSA doubling time

ADT = androgen deprivation therapy; AJCC = American Joint Committee on Cancer; AP = alkaline phosphatase; CT = computed tomography; DRE = digital rectal examination; LHRH = luteinizing-hormone-releasing hormone; PSA = prostate-specific antigen; RCT = randomised controlled trial; RP = radical prostatectomy; RT = radiotherapy; TURP = transurethral resection of the prostate; UICC = International Union against Cancer; WHO = World Health Organisation; WW = watchful waiting;

a = CharIson Comorbidity Index based on a point weighting derived from current or past history of myocardial infarction, chronic congestive heart failure, peripheral vascular disease, cerebrovascular disease or stroke, diabetes (with end-organ damage), dementia, chronic pulmonary disease, liver disease, renal disease, cancers, acquired immune deficiency syndrome (0 = no comorbidities).

2.4 Study Quality

Methodological quality of included RCTs is described in Tables 2-5.

Table 2: Methodological quality for the outcomes **overall mortality** and **prostate cancer-specific mortality** in the included RCTs (n = 3)

Quality Category	N (%)
I. Was the study double-blinded?	
2 = Reasonably certain double-blind (e.g. identical placebo)	-
1 = Single-blind, objective outcomes	3 (100)
0 = Not blinded, not reported	-
II. Concealment of treatment allocation schedule	
2 = Adequately concealed (e.g. central randomisation)	3 (100)
1 = Inadequately concealed (e.g. sealed envelopes)	-
0 = No concealment, not reported	-
III. Inclusion of all randomised participants in analysis of majority of outcomes (i.e. ITT)	
2 = No exclusions, survival analysis used	3 (100)
1 = Exclusions not likely to cause bias	-
0 = Too many exclusions, not reported	-
IV. Generation of allocation sequences	
1 = Adequate (e.g. computer random number generator)	1 (33.3)
0 = Inadequate, not reported	2 (66.7)

ITT = intention-to-treat

Table 3: Methodological quality for the outcomes **quality of life** and **adverse events** in the included RCTs (n = 3)

Quality Category	N (%)
I. Was the study double-blinded?	
2 = Reasonably certain double-blind (e.g. identical placebo)	-
1 = Single-blind, objective outcomes	-
0 = Not blinded, not reported	3 (100)
II. Concealment of treatment allocation schedule	
2 = Adequately concealed (e.g. central randomisation)	3 (100)
1 = Inadequately concealed (e.g. sealed envelopes)	-
0 = No concealment, not reported	-
III. Inclusion of all randomised participants in analysis of majority of outcomes (i.e. ITT)	
2 = No exclusions, survival analysis used	1 (33.3)
1 = Exclusions not likely to cause bias	1 (33.3)
0 = Too many exclusions, not reported	1 (33.3)
IV. Generation of allocation sequences	
1 = Adequate (e.g. computer random number generator)	1 (33.3)
0 = Inadequate, not reported	2 (66.7)

ITT = intention-to-treat

Table 4: Methodological quality for the outcomes **overall mortality** and **prostate cancer mortality** in the included RCTs (n = 3)

	Blinding	Allocation concealment	Inclusion of all participants (ITT)	Generation of allocation sequence*	**Overall rating**	**Risk of bias**
SPCG-4						
Bill-Axelson 2011	1	2	2	0	**Medium**	**Moderate**
EORTC 30891						
Studer 2006	1	2	2	1	**Medium**	**Moderate**
Studer 2008	1	2	2	1	**Medium**	**Moderate**
Studer 2013	1	2	2	1	**Medium**	**Moderate**
PIVOT						
Wilt 2012	1	2	2	0	**Medium**	**Moderate**

ITT = intention-to-treat

Key to overall quality rating
High quality: a study that received 2 for the 3 main criteria (double-blinding, concealment of treatment allocation schedule, inclusion of all randomised participants in analysis (i.e. ITT)).
Medium quality: received 2 and/or 1 for all three main criteria.
Low quality: received 0 for all three criteria or 0 and 1 for all three criteria or received 0 for any of the 3 main criteria.

*Answer for question 4 is considered as additional information and not considered when calculating the overall quality score. Quality assessment questions 1 to 3 for randomised controlled trials are evidence-based categories (Schulz *et al.*, 1995; Jadad *et al.*, 1996). Generation of allocation sequences has been shown not to influence outcomes.

Table 5: Methodological quality for the outcomes **quality of life** and **adverse events** in the included RCTs (n = 3)

	Blinding	Allocation concealment	Inclusion of all participants (ITT)	Generation of allocation sequence*	**Overall rating**	**Risk of bias**
SPCG-4						
Johansson 2011	0	2	1	0	**Low**	**High**
Steineck 2002	0	2	1	0	**Low**	**High**
EORTC 30891						
Studer 2006	0	2	2	1	**Low**	**High**
Studer 2008	0	2	2	1	**Low**	**High**
Studer 2013	0	2	2	1	**Low**	**High**
PIVOT						
Wilt 2012	0	2	0	0	**Low**	**High**

ITT = intention-to-treat

Key to overall quality rating
High quality: a study that received 2 for the 3 main criteria (double-blinding, concealment of treatment allocation schedule, inclusion of all randomised participants in analysis (i.e. ITT)).
Medium quality: received 2 and/or 1 for all three main criteria.
Low quality: received 0 for all three criteria or 0 and 1 for all three criteria or received 0 for any of the 3 main criteria.

*Answer for question 4 is considered as additional information and not considered when calculating the overall quality score. Quality assessment questions 1 to 3 for randomised controlled trials are evidence-based categories (Schulz *et al.*, 1995; Jadad *et al.*, 1996). Generation of allocation sequences has been shown not to influence outcomes.

2.5 Study results

Effects of intervention on relevant outcomes are described in Tables 6-8.

I All-cause mortality and overall survival

Table 6: Results of studies examining the effects of watchful waiting compared with definitive treatments on all-cause mortality/overall survival.

Study	Outcome			N actual	Watchful Waiting	Definitive Treatment	Size of effect	Size of effect (CI)	p value (test)	Follow up/ Timing
Watchful Waiting vs. Radical Prostatectomy										
Wilt 2012	**All-cause mortality** *Cumulative incidence of ascertained deaths/men randomised to management protocol – at end of study*		% (n)	731	49.9 (183) N = 367	47.0 (171) N = 364	HR=0.88 ARD=2.9%	0.71-1.08 -4.3 to 10.1	0.22[a]	10 years median
	4 years		% (n)	731	14.2 (52*) N = 367	9.6 (35*) N = 364	ARD=4.6%	-0.2 to 9.3	NS[a]	4 years
	8 years		% (n)	731	29.7 (109*) N = 367	26.7 (97*) N = 364	ARD=3.1%	-3.5 to 9.5	NS[a]	8 years
	12 years		% (n)	731	43.9 (161*) N = 367	40.9 (149*) N = 364	ARD=2.9%	-4.2 to 10.0	NS[a]	12 years
	Subgroup analyses									
	Age	<65 years	% (n)	253	38.2 (50) N = 131	35.3 (43) N = 122	HR=0.89	0.59-1.34	0.58[b]	10 years median
		≥65 years	% (n)	478	56.4 (133) N = 236	52.9 (128) N = 242	HR=0.84	0.63-1.08	0.17[b]	
	Race	White	% (n)	452	54.1 (119) N = 220	50.4 (117) N = 232	HR=0.84	0.65-1.08	0.18[b]	10 years median
		African American	% (n)	232	43.8 (53) N = 121	41.4 (46) N = 111	HR=0.93	0.62-1.38	0.70[b]	
		Other	% (n)	47	42.3 (11) N = 26	38.1 (8) N = 21	HR=0.85	0.34-2.11	0.72[b]	
	CCI[c]	No comorbidities	% (n)	444	39.1 (86) N = 220	36.6 (82) N = 224	HR=0.90	0.66-1.21	0.48[b]	10 years median
		≥1 comorbidities	% (n)	287	66.0 (97) N = 147	63.6 (89) N = 140	HR=0.84	0.63-1.13	0.25[b]	
	Performance score[d]	Fully active (0)	% (n)	622	47.1 (146) N = 310	44.6 (139) N = 312	HR=0.89	0.71-1.13	0.34[b]	10 years median
		Not fully active (1-4)	% (n)	109	64.9 (37) N = 57	61.5 (32) N = 52	HR=0.82	0.51-1.31	0.40[b]	
	PSA at Baseline	≤10 ng/mL	% (n)	479	43.6 (105) N = 241	46.2 (110) N = 238	HR=1.03	0.79-1.35	0.82[b]	10 years median

		>10ng/mL	% (n)	251	61.6 (77) N = 125	48.4 (61) N = 126	HR=0.67	0.48-0.94	0.02[b]	
	Risk category[e]	Low[g]	% (n)	233*	38.5 (47) N = 122*	40.5 (45) N = 111*	ARD=-2.0	-14.4 to 10.4	0.72[b]	10 years median
		Intermediate[g]	% (n)	295*	52.5 (73) N = 139*	47.4 (74) N = 156*	ARD=5.1	-6.6 to 16.0	0.29[b]	
		Intermediate or high[g]	% (n)	458	54.9 (123) N = 224	50.0 (117) N =234	HR=0.81 ARD=4.9	0.63-1.0	0.10[b]	
		High[g]	% (n)	163*	58.8 (50) N = 85*	55.1 (43) N = 78*	ARD=3.7	-11.3 to 18.5	0.25[b]	
	Gleason score[f]	<7	% (n)	364*	44.9 (88) N = 196*	41.1 (69) N = 168*	ARD=3.8	-6.3 to 13.8	0.63[b]	10 years median
		≥7	% (n)	322*	54.7 (81) N = 148*	52.9 (92) N = 174*	ARD=1.9	-9.0 to 12.6	0.14[b]	
Bill-Axelson 2011	**All-Cause Mortality** *Cumulative incidence of death at 15 years: %(95%CI)*		% (n)	695	52.7 (201) N = 348	46.1 (166) N = 347	HR=0.75 NNT=15	0.61-0.92	0.007[h]	15 years
	Subgroup Analyses									
	Age	<65 years	% (n)	323	47.4 (91) N = 157	33.9 (55) N = 166	HR=0.52 NNT=8	0.37-0.73	<0.001[h]	12.8 years median
		≥65 years	% (n)	372	57.4 (110) N = 190	56.7 (101) N = 182	HR=0.98	0.75-1.28	0.89[h]	
	Low risk cancer[i]		% (n)	263	44.6 (68) N = 139	31.4 (42) N = 124	HR=0.62 NNT=8	0.43-0.92	0.02[h]	12.8 years
	PSA <10 vs ≥10 ng/mL at diagnosis		No modification of treatment effect: p for interaction = 0.72							12.8 years median
	Gleason score <7 vs ≥7 at diagnosis		No modification of treatment effect: p for interaction = 0.36							
Deferred ADT vs. Immediate ADT										
Studer 2013	**Overall Survival**		% (n)	985	19.7 (97) N = 493	24.2 (119) N = 492	HR=1.21	1.05-1.39	0.72[j] 0.0085[b]	12.8 years median
	All-Cause Mortality *Cumulative incidence of recorded deaths/men randomised to management protocol at final analysis*		% (n)	985	80.3 (396) N = 493	75.8 (373) N = 492	ARD=4.5%	NR	NR	12.8 years median
	10 years		% (n)	985	73 (365*) N = 493	64 (315*) N = 492	ARD=9%	NR	NR	10 years
	7.8 years median		% (n)	939	57.7 (272) N = 471	51.1 (239) N = 468	ARD=6.6%	NR	NR	7.8 years median

ADT = androgen deprivation therapy; ARD = absolute risk difference, a negative ARD indicates advantage of WW over immediate definitive treatment; CI = confidence interval; HR = hazard ratio >1.0 indicates advantage of WW over immediate definitive treatment; NNT = numbers needed to treat; NR = not reported; NS = not statistically significantly different; PSA = prostate-specific antigen
** = calculated by reviewers*
a = Proportional-hazards model

b = Cox proportional-hazards model to test for treatment effects and interaction between group assignment and subgroup category, with no correction for multiple comparisons
c = Charlson Comorbidity Index based on a point weighting derived for current or past history of myocardial infarction, chronic congestive heart failure, peripheral vascular disease, cerebrovascular disease or stroke, diabetes (with end-organ damage), dementia, chronic pulmonary disease, liver disease, renal disease, cancers, acquired immune deficiency syndrome, (0 = no comorbidities)
d = Performance score of 0 = fully active, 1-4 = not fully active with a range of movement ability from light work (1) to completely disabled (4)
e = According to tumour stage determined before study entry, and PSA and biopsy findings (Gleason score) determined centrally after randomisation
f = According to tumour stage determined centrally after randomisation
g = Low includes PSA level ≤10 ng/mL, Gleason score ≤6 and tumour stage T1/T2a; Intermediate includes PSA level 10-20ng/mL or Gleason score = 7 or tumour stage T2b; High includes PSA level >20 ng/mL or Gleason score 8-10 or Tumour stage T2c (staging according to American Joint Committee on Cancer 5th edition 1997)
h = Grays test
i = Low risk cancer is classified as a PSA level <10ng/mL, Gleason score of <7 or a WHO grade of 1 in the preoperative specimens
j = Kaplan-Meier survival analysis was used to demonstrate non-inferiority of watchful waiting protocol

II Prostate cancer-specific mortality

Table 7: Results of studies examining the effects of watchful waiting compared with definitive treatments on prostate cancer-specific mortality.

Study	Outcome			N actual	Watchful Waiting	Definitive Treatment	Size of effect	Size of effect (CI)	p value (test)	Follow up/ Timing
Watchful Waiting vs. Radical Prostatectomy										
Wilt 2012	**Prostate Cancer Mortality** *Cumulative incidence of deaths ascertained as definitely due to prostate cancer/men randomised to management protocol*		% (n)	731	4.9 (18) N = 367	4.4 (16) N = 364	NR	NR	NS[a]	10 years median
	Prostate Cancer Mortality *Cumulative incidence of deaths ascertained as probably or definitely due to prostate cancer/men randomised to management protocol (at end of study)*		%(n)	731	8.4 (31) N = 367	5.8 (21) N = 364	HR=0.63 ARD=2.6%	0.36-1.09 -1.1 to 6.5	0.09[b]	10 years median
	4 years		% (n)	731	1.6 (52*) N = 367	1.7 (6*) N = 364	ARD=0.0%	-2.1 to 2.1	NS[a]	4 years
	8 years		% (n)	731	4.9 (109*) N = 367	3.0 (97*) N = 364	ARD=1.9%	-1.0 to 4.9	NS[a]	8 years
	12 years		% (n)	731	7.4 (161*) N = 367	4.4 (149*) N = 364	ARD=3.9%	-0.5 to 6.5	NS[a]	12 years
	Subgroup Analyses									
	Age	<65 years	% (n)	253	9.2 (12) N = 131	4.9 (6) N = 122	HR=0.52	0.20-1.39	0.19[b]	10 years median
		≥65 years	% (n)	478	8.1 (19) N = 236	6.2 (15) N = 242	HR=0.68	0.34-1.33	0.25[b]	
	Race	White	% (n)	452	10.0 (22) N = 220	6.5 (15) N = 232	HR=0.57	0.30-1.10	0.09[b]	10 years median
		African American	% (n)	232	5.8 (7) N = 121	4.5 (5) N = 111	HR=0.80	0.25-2.54	0.71[b]	
		Other	% (n)	47	7.7 (2) N = 26	4.8 (1) N = 21	HR=0.56	0.05-6.17	0.63[b]	
	CCI	No comorbidities	% (n)	444	8.6 (19) N = 220	6.3 (14) N = 224	HR=0.69	0.34-1.37	0.29[b]	10 years median
		≥ 1 comorbidities	% (n)	287	8.2 (12) N = 147	5.0 (7) N = 140	HR=0.54	0.21-1.38	0.19[b]	
	Performance Status[c]	Fully active (0)	% (n)	622	8.1 (25) N = 310	5.8 (18) N = 312	HR=0.67	0.37-1.23	0.19[b]	10 years median

		Not fully active (1-4)	% (n)	109	10.5 (6) N = 57	5.8 (3) N = 52	HR=0.41	0.10-1.71	0.21[b]	
	PSA at baseline	≤10 ng/ml	% (n)	479	6.2 (15) N = 241	5.9 (14) N = 238	HR=0.92	0.44-1.91	0.82[b]	10 years median
		>10 ng/ml	% (n)	251	12.8 (16) N = 125	5.6 (7) N = 126	HR=0.36	0.15-0.89	0.02[b]	
	Risk category[d]	Low[f]	% (n)	233*	4.1 (5) N = 122*	0.9 (1) N = 111*	ARD=3.2%	-1.5 to 8.4	0.13[b]	10 years median
		Intermediate[f]	% (n)	293*	5.8 (8) N = 138*	7.1 (11) N = 155*	ARD=-1.3%	-7.2 to 4.7	0.84[b]	
		High[f]	% (n)	163*	20.0 (17) N = 85*	11.5 (9) N = 78*	ARD=8.5%	-3.0 to 19.6	0.05[b]	
	Gleason score[e]	<7	% (n)	363*	4.6 (9) N = 196*	1.2 (2) N = 167*	ARD=3.4%	-0.3 to 7.4	0.07[b]	10 years median
		≥7	% (n)	322*	14.2 (21) N = 148*	10.9 (19) N = 174*	ARD=3.3%	-4.0 to 10.8	0.11[b]	
Bill-Axelson 2011	**Prostate Cancer Mortality** *Cumulative incidence of death*		% (n)	695	20.7 (81) N = 348	14.6 (55) N = 347	0.62	0.44-0.87	0.001[g]	15 years
	Subgroup Analyses									
	Age	<65 years	% (n)	323	25.8 (49) N = 157	16.4 (28) N = 166	0.49	0.31-0.79	0.008[g]	12.8 years median
		≥ 65 years	% (n)	372	16.0 (32) N = 190	13.0 (27) N = 182	0.83	0.50-1.39	0.41[g]	
	Low risk cancer[h]		% (n)	263	11.0 (15*) N = 139	6.8 (8*) N = 124	0.53	0.24-1.14	0.14[g]	15 years
	PSA <10 vs ≥10 ng/mL at diagnosis				No modification of treatment effect: p for interaction = 0.30					15 years
	Gleason score <7 vs ≥7 at diagnosis				No modification of treatment effect: p for interaction = 0.52					
Deferred ADT vs. Immediate ADT										
Studer 2006 Studer 2008	**Prostate Cancer Mortality** *Cumulative incidence of deaths ascertained as due to prostate cancer/men randomised to management protocol*		% (n)	985	27.6* (136) N = 493	27.0* (133) N = 492	HR=1.05	0.83-1.33	0.70[i]	12.8 years median
	7.8 years		% (n)	939	20.2 (95) N = 471	18.6 (87) N = 468	NR	NR	NR	7.8 years median
Studer 2013	10 years		% (n)	985	25 N = 493	23 N = 492	NR	NR	NS[i]	10 years

Prostate Cancer Mortality *Incidence of recorded deaths during study period*		% (n)	985	10.1* (50*) N = 493	5.9* (29*) N = 492	ARD=4.9*	NR	0.0153[i]	3-5 years
Subgroup Analyses									
PSA at baseline[d]	≤8 ng/mL	% (n)	239	12.1 (15) N = 124	7.8 (9) N = 115	NR	NR	NR	7.8 years median
	8.1-20.0 ng/mL	% (n)	299	16.6* (25) N = 151	14.9* (22) N = 148	HR=1.18	0.67-2.10	0.28[i]	7.8 years median
	20.1-50 ng/mL	% (n)	224	23.1* (25) N = 108	20.0* (22) N = 116	HR=1.40	0.79-2.50	0.12[i]	7.8 years median
	>50ng/mL	% (n)	177	34.1* (30) N = 88	38.2* (34) N = 89	NR	NR	NR	7.8 years median
	>50 ng/mL (7 years cumulative)	% (n)	177	31.6(28*) N = 88	29.4 (26*) N = 89	HR=1.44	0.86-2.41	0.0878[i]	7 years

ADT = androgen deprivation therapy; ARD = absolute risk difference, a negative ARD indicates advantage of watchful waiting over immediate definitive treatment; CCI =Charlson Comorbidity Index, based *on a point weighting derived for current or past history of myocardial infarction, chronic congestive heart failure, peripheral vascular disease, cerebrovascular disease or stroke, diabetes (with end-organ damage), dementia, chronic pulmonary disease, liver disease, renal disease, cancers, acquired immune deficiency syndrome; (0 = no comorbid conditions)*; CI = confidence interval; HR = hazard ratio >1.0 indicates advantage of watchful waiting over immediate definitive treatment; NNT = numbers needed to treat; NR = not reported; NS = not statistically significantly different; PSA = prostate-specific antigen

* calculated by reviewers
a = Proportional-hazards model
b = Cox proportional-hazards model to test for treatment effects and interaction between group assignment and subgroup category, with no correction for multiple comparisons
c = Performance score of 0 = fully active, performance score of 1-4 = not fully active with a range of movement ability from light work (1) to completely disabled (4)
d = According to tumour stage determined before study entry, and PSA and biopsy findings (Gleason score) determined centrally after randomisation
e = According to tumour stage determined centrally after randomisation
f = Low includes PSA level ≤10 ng/mL, Gleason score ≤6 and tumour stage T1/T2a; Intermediate includes PSA level 10-20 ng/mL or Gleason score = 7 or tumour stage T2b; High includes PSA level >20 ng/mL or Gleason score 8-10 or Tumour stage T2c (staging according to American Joint Committee on Cancer 5th edition 1997)
g = Gray's test
h = Low risk cancer is classified as a PSA level <10 ng/mL, Gleason score of <7 or a WHO grade of 1 in the preoperative specimens
i = Estimated by Fine and Gray models for competing events (non-prostate cancer related deaths).

III Quality of Life and Adverse Events

Table 8: Results of studies examining the effects of watchful waiting compared with definitive treatments on quality of life and adverse events.

Study	Outcome		N actual	Watchful Waiting	Definitive Treatment	Size of effect	Size of effect (CI)	p value (test)	Follow up /Timing
Watchful Waiting vs. Radical Prostatectomy									
Wilt 2012	**Urinary incontinence** *Significant problems with dribbling or dysfunction*	% (n)	571	6.3 (18) N = 284	17.1 (49) N = 287	ARD=-11.0	NR	<0.001[a]	2 years
	Erectile dysfunction *Inability to have erection sufficient for vaginal penetration*	% (n)	566	44.1 (124) N = 281	81.1 (231) N = 285	ARD=-37	NR	<0.001	2 years
	Bowel dysfunction *Dysfunction as "moderate" or "big" problem*	% (n)	568	11.3 (32) N = 282	12.2 (35) N = 286	ARD=-0.9	NR	0.74	2 years
Steineck 2002 Johannson 2011	**Sexual function**								
	Seldom or never sufficient for intercourse	% (n)	319	45 (71) N = 158	80 (129) N = 161	RR=1.8	1.5-2.2	NR	4.1 years mean
	Never sufficient for intercourse	% (n)	326	80 (122) N = 153	84 (146) N = 173	RR=1.08[e]	0.98-1.18	NS	12.2 years median
	Distress from erectile dysfunction *% moderate or great distress*	% (n)	307	43 (65) N = 152	58 (90) N = 155	RR=1.4	1.0-1.7	SD	4.1 years mean
		% (n)	322	36 (56) N = 154	48 (80) N = 168	RR=1.3[e]	1.00-1.70	SD	12.2 years median
	Distress from decreased sexual ability *% moderate to great distress*	% (n)	317	35 (53) N = 150	37 (61) N = 167	RR=1.01[e]	0.76-1.34	NS	12.2 years median
	Urinary function								
	Weak urinary stream *% on more than one of 5 occasions*	% (n)	317	44 (68) N = 153	28 (46) N = 164	RR=0.6	0.5-0.9	SD	4.1 years mean
	Weak urinary stream *% on more than half of occasions*	% (n)	334	40 (64) N = 160	29 (50) N = 174	RR=0.71[e]	0.53-0.96	SD	12.2 years median

Distress from obstructed voiding *% moderate or great distress*	% (n)	321	22 (34) N = 157	21 (34) N = 164	RR=1.0	0.60-1.5	NS	4.1 years mean
	% (n)	337	32 (52) N = 161	27 (48) N = 176	RR=0.82[e]	0.60-1.14	NS	12.2 years median
Patient assessed urine leakage *% moderate or severe leakage*	% (n)	315	2 (3) N = 152	18 (30) N = 163	RR=9.3	2.9-29.9	SD	4.1 years mean
	% (n)	341	11 (18) N = 164	23 (41) N = 177	RR=2.14[e]	1.28-3.58	SD	12.2 years median
Distress from urinary leakage *% moderate or great distress*	% (n)	322	9 (15) N = 158	29 (47) N = 164	RR=3.0	1.8-5.2	SD	4.1 years mean
Distress from daytime urinary leakage *% moderate or great distress*	% (n)	336	15 (25) N = 162	28 (48) N = 174	RR=1.80[e]	1.17-2.78	SD	12.2 years median
Distress from night time urinary leakage *% moderate or great distress*	% (n)	341	9 (14) N = 164	18 (31) N = 177	RR=2.08[e]	1.15-3.78	SD	12.2 years median
Regular dependence on some form of protective aid	% (n)	319	10 (16) N = 154	43 (71) N = 165	RR=4.1	2.5-6.8	SD	4.1 years mean
	% (n)	338	25 (41) N = 163	54 (94) N = 175	RR=2.15[e]	1.60-2.90	SD	12.2 years median
Overall distress from all urinary symptoms *% moderate or great distress*	% (n)	320	18 (28) N = 157	27 (44) N = 163	RR=1.5	1.0-2.3	SD	4.1 years mean
Subjective estimation of the degree of leakage *% moderate or severe leakage*	% (n)	315	2 (3) N = 152	18 (30) N = 163	RR=9.9	2.9-29.9	SD	4.1 years mean
	% (n)	341	11 (18) N = 164	23 (41) N = 177	RR=2.14[e]	1.28-3.58	SD	12.2 years median
Psychological Symptoms								
Anxiety *% moderate or high (highest 5 of 7 categories)*	% (n)	321	31 (48) N = 157	23 (37) N = 164	RR=0.7	0.5-1.1	NS	4.1 years mean
	% (n)	339	43 (69) N = 161	43 (77) N = 178	RR=0.97[e]	0.76-1.24	NS	12.2 years median

	Depression *% moderate or high* *(highest 5 of 7 categories)*	% (n)	321	38 (60) N = 157	35 (57) N = 164	RR=0.9	0.7-1.2	NS	4.1 years mean
		% (n)	339	52 (82) N = 159	47 (85) N = 180	RR=0.92[e]	0.74-1.14	NS	12.2 years median
	Psychological wellbeing *% low or moderate (lowest 5 of 7)*	% (n)	322	36 (57) N = 158	35 (57) N = 164	RR=1.0	0.7-1.3	NS	4.1 years mean
	Psychological wellbeing *% high (highest 2 of 7 categories)*	% (n)	340	44 (71) N = 161	41 (73) N = 179	RR=0.89[e]	0.70-1.13	NS	12.2 years median
	General Function								
	Physical well-being - % low or moderate *(lowest 5 of 7 possible categories)*	% (n)	321	50 (78) N = 157	41 (68) N = 164	RR=0.8	0.7-1.1	NS	4.1 years mean
	Patient assessed quality of life *% low or moderate (lowest 5 of 7)*	% (n)	310	45 (68) N = 151	40 (64) N = 159	RR=0.9	0.7-1.2	NS	4.1 years mean
	Patient assessed quality of life *% high (highest 2 of 7 possible categories)*	% (n)	339	34 (55) N = 160	35 (62) N = 179	RR=0.98[e]	0.73-1.15	NS	12.2 years median
Deferred ADT vs. Immediate ADT									
Studer 2006 Studer 2013	**Symptoms and Adverse Events** *Cumulative incidence of men experiencing events/men randomised to management protocol*								
	Headaches	% (n)	985	2.2 (11) N = 493	9.1 (45) N = 492	ARD=-6.9%*	NR	<0.0001[b]	8 years
	Ureteric obstruction *(requiring TURP)*	% (n)	985	22.9 (113) N = 493	11.2 (55) N = 492	ARD=11.7%*	NR	<0.0001[b]	8 years
	Hot flushes	% (n)	985	17.9* (88*) N = 493	56.3* (277*) N = 492	ARD=-38.5%*	NR	<0.0001[b]	8 years
	Gynaecomastia	% (n)	985	7.5* (37*) N = 493	21.3* (105*) N = 492	ARD=-21.2%*	NR	<0.0001[c]	8 years
	Skin complaints	% (n)	985	2.0 (10) N = 493	10.0 (49) N = 492	ARD=-7.9%*	NR	<0.0001[b]	8 years

	Pain	% (n)	985	36.7 (181) N = 493	28.7 (141) N = 492	ARD=8.0%*	NR	0.0002[d]	8 years
Wilt 2012	**Perioperative complications**								30 days after Radical Prostatectomy
	Wound infection	% (n)	280	-	4.3 (12)	-	-	-	
	Bowel injury requiring surgical repair	% (n)	280	-	1.1 (3)	-	-	-	
	Additional surgical repair required	% (n)	280	-	2.5 (7)	-	-	-	
	Bleeding required transfusion	% (n)	280	-	2.1 (6)	-	-	-	
	Urinary catheter present > 30 days after surgery	% (n)	280	-	2.1 (6)	-	-	-	
	Death	% (n)	280	-	0.4 (1)	-	-	-	

ADT = androgen deprivation therapy; ARD = absolute risk difference, a negative ARD indicates advantage of watchful waiting over immediate definitive treatment; CI = confidence interval; NR = not reported; NS = not statistically significantly different; OR = odds ratio; RR = relative risk > 1.0 indicates advantage of watchful waiting over immediate definitive treatment; SD = significantly different P< 0.05; TURP = transurethral resection of the prostate

* = calculated by reviewers
a = analysis of variance test used
b = Gray's test to assess for differences in cumulative incidence
c = trend test
d = repeated measures logistic regression model (year by year)
e = age-adjusted.

2.6 Body of Evidence

Effects of intervention on relevant outcomes are described in Tables 9-12.

I All-cause mortality

Table 9: Body of evidence examining the effects of watchful waiting compared with definitive treatments on all-cause mortality

Name of study	Study type	Level of evidence *	Quality of evidence**	Risk of bias	N	Results summary %	Size of effect	p value	95% CI	Relevance of evidence
Watchful waiting vs. Radical Prostatectomy										
Wilt 2012 **Monitoring**: Observation and testing every 6 months for 8-15 years or until death. Bone scans every 5, 10 and 15 years. **Triggers:** Palliative care or chemotherapy was initiated at symptomatic or metastatic progression Median follow up = 10 years	RCT (multi-centre)	II	Medium	Moderate	731	**All-cause mortality:** WW: 49.9 RP: 47.0	HR=0.88	NS	0.71 – 1.08	1
						<u>Subgroup analyses:</u>				
						Age (years):				
					253	<65: WW:38.2 RP:35.3	HR=0.89	NS	0.59 – 1.34	1
					478	≥65: WW:56.4 RP:52.9	HR=0.84	NS	0.63 – 1.08	1
						Race:				
					452	White: WW:54.1 RP:50.4	HR=0.84	NS	0.65 – 1.08	1
						Charlson Index[a] :				
					444	0: WW:39.1 RP:36.6	HR=0.90	NS	0.66 – 1.21	1
					287	≥1: WW:66.0 RP:63.6	HR=0.84	NS	0.63 – 1.13	1
						Performance score[b]:				
					622	0: WW:47.1 RP:44.6	HR=0.89	NS	0.71 – 1.13	1
					109	1-4: WW:64.9 RP:61.5	HR=0.82	NS	0.51 – 1.31	1
						PSA level (ng/mL):				
					479	≤10: WW:43.6 RP:46.2	HR=1.03	NS	0.79 – 1.35	1
					251	>10: WW:61.6 RP:48.4	HR=0.67	**0.02**	0.48 – 0.94	1
						Tumour Risk[c]:				
					233#	Low: WW:38.5 RP:40.5	ARD=-2.0%	NS	-14.4 to 10.4	1
					295#	Int: WW:52.5 RP:47.4	ARD=5.1%	NS	-6.6 to 16.0	1
					163#	High: WW:58.8 RP:55.1	ARD=3.7%	NS	-11.3 to 18.5	1
						Gleason score[d]:				
					364#	<7: WW:44.9 RP: 41.1	ARD=3.8%	NS	-6.3 to 13.8	1
					322#	≥7: WW:54.7 RP: 52.9	ARD=1.9%	NS	-9.0 to 12.6	1
Bill-Axelson 2011 **Monitoring:**	RCT (multi-centre)	II	Medium	Moderate	695	**All-cause mortality:** WW: 52.7 RP: 46.1	HR=0.75	**0.007**	0.61 – 0.92	1
						<u>Subgroup analyses:</u>				

Clinical examination, DRE, PSA and AP testing every 6 months for 2 years, then annually for ≥10 years. Bone scans annually until 2003 then every 2nd year. Chest radiographs annually until 1997 then annually for only the first two years after randomisation.		**Age (years):**				
	323	<65: WW:47.4 RP: 33.9	HR=0.52	**<0.001**	0.37 – 0.73	1
	372	≥65: WW:57.4 RP: 56.7	HR=0.98	NS	0.75 – 1.28	1
		Low risk cancer[e]:				
	263	WW:44.6 RP:31.4	HR=0.62	**0.02**	0.43 – 0.92	1
Triggers: ADT initiated at metastatic or tumour progression or elevated PSA (>2003). Orchidectomy considered with symptom-producing recurrence and/or uraemia. Obstructive voiding treated with TURP						
Median follow up = 12.8 years						

AP = alkaline phosphatase; ARD = absolute risk difference, a negative ARD indicates advantage of watchful waiting over immediate definitive treatment; DRE = digital rectal examination; HR = hazard ratio < 1.0 indicates an advantage to the immediate treatment group; PSA = prostate specific antigen; RCT = randomised controlled trial; RP = radical prostatectomy; TURP = transurethral resection of the prostate; WW = watchful waiting

 # = calculated by systematic review team from published data
a = Charlson Comorbidity Index based on a point weighting derived for current or past history of myocardial infarction, chronic congestive heart failure, peripheral vascular disease, cerebrovascular disease or stroke, diabetes (with end-organ damage), dementia, chronic pulmonary disease, liver disease, renal disease, cancers, acquired immune deficiency syndrome (0 = no comorbidities)
b = Performance score of 0=fully active, performance score of 1-4 =not fully active with a range of movement ability from light work (1) to completely disabled (4)
c = according to tumour stage determined before study entry, and PSA and biopsy findings (Gleason score) determined centrally after randomisation
d = according to tumour stage determined centrally after randomisation
e = Low risk cancer classified as PSA level <10ng/ml, Gleason score of <7 or a WHO grade of 1 in the perioperative specimens.

**Refer to appendix B for detailed explanations of rating scores; ** See Table 4 for quality appraisals*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the evidence statement table of content template.

II Overall survival

Table 10: Body of evidence examining the effects of deferred ADT compared with immediate ADT on overall survival

Name of study	Study type	Level of evidence *	Quality of evidence**	Risk of bias	N	Results summary %	Size of effect	p value	95% CI	Relevance of evidence
Deferred ADT vs. Immediate ADT										
Studer 2013 **Monitoring:** Observation, rectal palpation, PSA and AP measurements every 6 months for 2 years and then annually till death. Chest x-ray, liver ultrasound, pelvic CT, bone scan, or bone x-rays were performed in the event of suspected progression. **Triggers:** Symptomatic metastases. Increase in pain score or deterioration of WHO performance status by two levels. Ureteric obstruction. Treatment not initiated by rising PSA or AP or asymptomatic new hot spots in bone scans or soft tissue metastases. Median follow up = 12.8 years	RCT	II	Medium	Moderate	985	**Overall survival:** dADT:19.7 iADT: 24.2	HR=1.21	**0.0085**	1.05 – 1.39	1

ADT = androgen deprivation therapy; AP = alkaline phosphatase; CT = computed tomography; dADT = deferred androgen deprivation therapy; HR = hazard ratio; iADT = immediate androgen deprivation therapy; RCT = randomised controlled trial; WHO = World Health Organisation;

**Refer to appendix B for detailed explanations of rating scores; ** See Table 4 for quality appraisals*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the evidence statement table of content template.

III Prostate cancer-specific mortality

Table 11: Body of evidence examining the effects of watchful waiting compared with definitive treatments on prostate cancer-specific mortality

Name of study	Study type	Level of evidence *	Quality of evidence **	Risk of bias	N	Results summary %	Size of effect	p value	95% CI	Relevance of evidence
Watchful Waiting vs. Radical Prostatectomy										
Wilt 2012 **Monitoring:** Observation and testing every 6 months for 8-15 years or until death. Bone scans every 5, 10 and 15 years. **Triggers:** Palliative care or chemotherapy was initiated at symptomatic or metastatic progression. Median follow up = 10 years	RCT (multi-centre)	II	Medium	Moderate		**Prostate cancer-specific mortality:**				
					731	WW: 8.4 RP: 5.8	HR=0.63	NS	0.36 – 1.09	1
						<u>Subgroup analyses:</u>				
						Age (years):				
					253	<65: WW:9.2 RP:4.9	HR=0.52	NS	0.20 – 1.39	1
					478	≥65: WW:8.1 RP:6.2	HR=0.68	NS	0.34 – 1.33	1
						Race:				
					452	White:WW:10.0 RP:6.5	HR=0.57	NS	0.30 – 1.10	1
						Charlson Index[a]:				
					444	0: WW:8.6 RP:6.3	HR=0.69	NS	0.34 – 1.37	1
					287	≥1: WW:8.2 RP:5.0	HR=0.54	NS	0.21 – 1.38	1
						Performance Score[b]:				
					622	0: WW:8.1 RP:5.8	HR=0.67	NS	0.37 – 1.23	1
					109	1-4: WW:10.5 RP:5.8	HR=0.41	NS	0.10 – 1.71	1
						PSA level (ng/mL):				
					479	≤10: WW:6.2 RP:5.9	HR=0.92	NS	0.44 – 1.91	1
					251	>10: WW:12.8 RP:5.6	HR=0.36	**0.02**	0.15 – 0.89	1
						Tumour Risk[c] :				
					233[#]	Low: WW:4.1 RP:0.9	ARD=3.2%	NS	-1.5 to 8.4	1
					293[#]	Int: WW:5.8 RP:7.1	ARD=-1.3%	NS	-7.2 to 4.7	1
					163[#]	High: WW:20.0 RP:11.5	ARD=8.5%	NS	-3.0 to 19.6	1
						Gleason score[d]:				
					363[#]	<7: WW:4.6 RP: 1.2	ARD=3.4%	NS	-0.3 to 7.4	1
					322[#]	≥7: WW:14.2 RP: 10.9	ARD=3.3%	NS	-4.0 to 10.8	1

Bill-Axelson 2011 **Monitoring:** Clinical examination, DRE, PSA and AP testing every 6 months for 2 years, then annually for ≥10 years. Bone scans annually until 2003 then every 2nd year. Chest radiographs annually until 1997 then annually for only the first two years after randomisation. **Triggers**: ADT initiated at metastatic or tumour progression or elevated PSA (>2003). Orchidectomy considered with symptom-producing recurrence and/or uraemia. Obstructive voiding treated with TURP Median follow up = 12.8 years	RCT (multi-centre)	II	Medium	Moderate	695	**Prostate cancer mortality[e] :** WW: 20.7 RP: 14.6	HR=0.62	**0.001**	0.44 – 0.87	1
						Subgroup analyses:				
						Age (years):				
					323	<65: WW:25.8 RP: 16.4	HR=0.49	**0.008**	0.31 – 0.79	1
					372	≥65: WW:16.0 RP: 13.0	HR=0.83	NS	0.50 – 1.39	1
						Low risk cancer[f] :				
					263	WW:11.0 RP: 6.8	HR=0.53	NS	0.24 – 1.14	1
Deferred ADT vs. Immediate ADT										
Studer 2013 **Monitoring:** Observation, rectal palpation, PSA and AP measurements every 6 months for 2 years and then annually till death. Chest x-ray, liver ultrasound, pelvic CT, bone scan, or bone x-rays were performed in the event of suspected progression. **Triggers:** Symptomatic metastases. Increase in pain score or deterioration of WHO performance status by two levels. Ureteric obstruction. Treatment not initiated by rising PSA or AP or asymptomatic new hot spots in bone scans or soft tissue metastases. Median follow up =12.8 years	RCT	II	Medium	Moderate	985	**Prostate cancer mortality[g] :** dADT: 27.6* iADT: 27.0*	HR=1.05	NS	0.83 – 1.33	1
						Subgroup analyses:				
						PSA level[g] (ng/mL):				
					239	≤ 8: dADT:12.1 iADT: 7.8	NR	-	-	1
					299	8.1-20.0: dADT:16.6 iADT:14.9*	HR=1.18	NS	0.67 – 2.10	1
					224	20.1-50.0: dADT:23.1 iADT:20.0*	HR=1.40	NS	0.79 – 2.50	1
					177[#]	>50: dADT:31.6 iADT:29.4	HR=1.44	NS	0.86 – 2.41	1

ADT = androgen deprivation therapy; AP = alkaline phosphatase; ARD = absolute risk difference, a negative ARD indicates advantage of watchful waiting over immediate definitive treatment; CT = computed tomography; dADT = deferred androgen deprivation therapy; DRE = digital rectal examination; HR = hazard ratio < 1.0 indicates an advantage to the immediate treatment group; iADT = immediate androgen deprivation therapy; PSA = prostate-specific antigen; RCT = randomised controlled trial; RP = radical prostatectomy; TURP = transurethral resection of the prostate; WHO = World Health Organisation; WW = watchful waiting;

= Calculated by systematic review team from published data

a = Charlson Comorbidity Index based on a point weighting derived for current or past history of myocardial infarction, chronic congestive heart failure, peripheral vascular disease, cerebrovascular disease or stroke, diabetes (with end-organ damage), dementia, chronic pulmonary disease, liver disease, renal disease, cancers, acquired immune deficiency syndrome (0 = no comorbidities)
b = performance score of 1-4 = not fully active with a range of movement ability from light work (1) to completely disabled (4)
c = according to tumour stage determined before study entry, and PSA and biopsy findings (Gleason score) determined centrally after randomisation
d = Gleason score determined centrally after randomisation
e = Prostate cancer mortality - accumulative incidence of deaths ascertained as probably or definitely due to prostate cancer/men randomised to management protocol
f = Low risk cancer classified as PSA level <10 ng/mL, Gleason score of <7 or a WHO grade of 1 in the perioperative specimens
g = Prostate cancer mortality- cumulative incidence of deaths ascertained as due to prostate cancer/men randomised to management protocol at final analysis
h = PSA measurements standardized by adjusting them proportionally from the institution – specific upper normal limit of 4 ng/mL

**Refer to appendix B for detailed explanations of rating scores; ** See Table 4 for quality appraisals*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the evidence statement table of content template

IV Quality of life and adverse events

Table 12: Body of evidence examining the effects of watchful waiting compared with definitive treatments on quality of life and adverse events

Name of study	Study type	Level of evidence *	Quality of evidence**	Risk of bias	N	Results summary %	Size of effect	p value	95% CI	Relevance of evidence
Urinary Symptoms										
Wilt 2012 **Monitoring:** Observation and testing every 6 months for 8-15 years or until death. Bone scans every 5, 10 and 15 years. **Triggers:** Palliative care or chemotherapy was initiated at symptomatic or metastatic progression. Median follow up = 10 years	RCT	II	Low	High	571	**Urinary incontinence:** WW: 6.3 RP: 17.1	ARD=-11.0%	**<0.001**	NR	1
Steineck 2002 **Monitoring:** Clinical examination, DRE, PSA and AP testing every 6 months for 2 years, then annually for ≥10 years. Bone scans annually until 2003 then every 2nd year. Chest radiographs annually until 1997 then annually for only the first two years after randomisation. **Triggers**: ADT initiated at metastatic or tumour progression or elevated PSA (>2003). Orchiectomy considered with symptom-producing recurrence and/or uraemia. Obstructive voiding treated with TURP. Median follow up = 12.8 years	RCT	II	Low	High	322	**Urinary leakage distress:** *Moderate or great distress* WW: 9 RP: 29	RR=3.0	NR	1.8 – 5.2	1
					320	**Overall distress from all urinary symptoms:** *Moderate or great distress* WW:18 RP: 27	RR=1.5	NR	1.0 – 2.3	1

Name of study	Study type	Level of evidence *	Quality of evidence**	Risk of bias	N	Results summary %	Size of effect	p value	95% CI	Relevance of evidence
Sexual function symptoms										
Wilt 2012 **Monitoring:** Observation and testing every 6 months for 8-15 years or until death. Bone scans every 5, 10 and 15 years. **Triggers:** Palliative care or chemotherapy was initiated at symptomatic or metastatic progression. Median follow up = 10 years	RCT	II	Low	High	566	**Erectile dysfunction:** WW: 44.1 RP: 81.1	ARD=-37%	**<0.001**	NR	1
Steineck 2002 **Johannson 2011** **Monitoring:** Clinical examination, DRE, PSA and AP testing every 6 months for 2 years, then annually for ≥10 years. Bone scans annually until 2003 then biennale. Chest radiographs annually until 1997 then annually for only the first two years after randomisation. **Triggers**: ADT initiated at metastatic or tumour progression or elevated PSA (>2003). Orchidectomy considered with symptom-producing recurrence and/or uraemia. Obstructive voiding treated with TURP. Median follow up = 12.8 years	RCT	II	Low	High	319 326	**Erectile function:** *Seldom or never sufficient for intercourse* WW:45 RP:80 *Never sufficient for intercourse:* WW:80 RP:84	RR=1.8 RR=1.08[a]	NS NS	1.5-2.2 0.98-1.18	1 1

Name of study	Study type	Level of evidence *	Quality of evidence**	Risk of bias	N	Results summary %	Size of effect	p value	95% CI	Relevance of evidence
Psychological symptoms										
Steineck 2002, Johannson 2011 **Monitoring:** Clinical examination, DRE, PSA and AP testing every 6 months for 2 years, then annually for ≥10 years. Bone scans annually until 2003 then every 2nd year. Chest radiographs annually until 1997 then annually for only the first two years after randomisation. **Triggers**: ADT initiated at metastatic or tumour progression or elevated PSA (>2003). Orchidectomy considered with symptom-producing recurrence and/or uraemia. Obstructive voiding treated with TURP. Median follow up = 12.8 years	RCT	II	Low	High		**Anxiety:** *Moderate or high (highest 5 of 7)*				
					321	(4.1 years[b]) WW: 31 RP: 23	RR=0.7	NS	0.5 – 1.1	1
					339	(12.2 years[c]) WW: 43 RP: 43	RR=0.97[a]	NS	0.76 – 1.24	1
						Depression: *Moderate or high (highest 5 of 7)*				
					321	(4.1 years[b]) WW:38 RP:35	RR=0.9	NS	0.7 – 1.2	1
					339	(12.2 years[c]) WW:52 RP:47	RR=0.92[a]	NS	0.74 – 1.14	1
						Psychological wellbeing: *Low or moderate (lowest 5 of 7)*				
					322	(4.1 years[b]) WW:36 RP:35	RR=1.0	NS	0.7 – 1.3	1
						High (highest 2 of 7 possible categories)				
					340	(12.2 years[c]) WW:44 RP: 41	RR=0.89[a]	NS	0.70 – 1.13	1
						Distress from erectile dysfunction: *% moderate or great distress*				
					307	*(4.1 years[b]) WW:43 RP:58*	RR=1.4	**SD**	1.0 – 1.7	1
					322	*(12.2 years[c]) WW:36 RP:48*	RR = 1.3[a]	**SD**	1.0 – 1.7	1
						Distress from decreased sexual ability *% moderate to great distress*				
					317	(12.2 years[c]) WW:35 RP: 37	RR=1.01[a]	NS	0.76 – 1.34	1
						Distress from obstructed voiding: *% moderate or great distress*				
					321	(4.1 years[b]) WW:22 RP:31	RR=1.0	NS	0.60 – 1.5	1
					337	(12.2 years[c]) WW:32 RP:27	RR=0.82[e]	NS	0.60 – 1.14	1

Name of study	Study type	Level of evidence *	Quality of evidence**	Risk of bias	N	Results summary %	Size of effect	p value	95% CI	Relevance of evidence
Bowel symptoms										
Wilt 2012 **Monitoring:** Observation and testing every 6 months for 8-15 years or until death. Bone scans every 5, 10 and 15 years. **Triggers:** Palliative care or chemotherapy was initiated at symptomatic or metastatic progression. Median follow up = 10 years	RCT	II	Low	High	568	**Bowel dysfunction:** *Moderate/big problem* WW: 11.3 RP:12.2	ARD=-0.9%	NS	NR	1
General symptoms										
Steineck 2002, Johannson 2011 **Monitoring:** Clinical examination, DRE, PSA and AP testing every 6 months for 2 years, then annually for ≥10 years. Bone scans annually until 2003 then every 2nd year. Chest radiographs annually until 1997 then annually for only the first two years after randomisation. **Triggers**: ADT initiated at metastatic or tumour progression or elevated PSA (>2003). Orchidectomy considered with symptom-producing recurrence and/or uraemia. Obstructive voiding treated with TURP. Median follow up = 12.8 years	RCT	II	Low	High	321	**Physical well-being:** *Low or moderate (lowest 5 of 7)* (4.1 years[b]) WW: 50 RP: 41	RR=0.8	NS	0.7 – 1.1	1
					310	**Patient assessed QoL:** *Low or moderate (lowest 5 of 7)* (4.1 years[b]) WW:45 RP: 40	RR=0.9	NS	0.7 – 1.2	1
					339	*High (highest 2 of 7 categories)* (12.2 years[c]) WW:34 RP:35	RR=0.98[a]	NS	0.73 – 1.15	1

Name of study	Study type	Level of evidence *	Quality of evidence**	Risk of bias	N	Results summary %	Size of effect	p value	95% CI	Relevance of evidence
Adverse Events										
Wilt 2012 **Monitoring:** Observation and testing every 6 months for 8-15 years or until death. Bone scans every 5, 10 and 15 years. **Triggers:** Palliative care or chemotherapy was initiated at symptomatic or metastatic progression. Median follow up = 10 years	RCT	II	Low	High	280	**Wound infection:** WW: - RP: 4.3	-	-	-	1
					280	**Bowel injury requiring repair:** WW: - RP: 1.1	-	-	-	1
					280	**Additional surgical repair:** WW: - RP: 2.5	-	-	-	1
					280	**Blood transfusion:** WW: - RP: 2.1	-	-	-	1
					280	**Urinary catheter >30 days:** WW: - RP: 2.1	-	-	-	1
					280	**Death:** WW: - RP: 0.4	-	-	-	1
Studer 2006 **Monitoring:** Observation, rectal palpation, PSA and AP measurements every 6 months for 2 years and then annually till death. Chest x-ray, liver ultrasound, pelvic CT, bone scan, or bone x-rays were performed in the event of suspected progression. **Triggers:** Symptomatic metastases. Increase in pain score or deterioration of WHO performance status by two levels. Ureteric obstruction. Treatment not initiated by rising PSA or AP or asymptomatic new hot spots in bone scans or soft tissue metastases. Median follow up = 8 years	RCT	II	Low	High	985	**Headache:** dADT: 2.2 iADT: 9.1	ARD=-6.9%	**<0.0001**	NR	1
					985	**Ureteric obstruction:** dADT:22.9 iADT:11.2	ARD=11.7%	**<0.0001**	NR	1
					985	**Hot flushes:** dADT: 17.9# iADT:56.3#	ARD=-38.5%	**<0.0001**	NR	1
					985	**Gynaecomastia:** dADT: 7.5# iADT: 21.3#	ARD=-21.2%	**<0.0001**	NR	1
					985	**Skin complaints:** dADT: 2.0 iADT: 10.0	ARD=-7.9%	**<0.0001**	NR	1
					985	**Pain:** dADT: 36.7# iADT: 28.7#	ARD=8.0#%	**<0.0002**	NR	1

ADT = androgen deprivation therapy; AP = alkaline phosphatase; ARD = absolute risk difference, a negative ARD indicates advantage of watchful waiting over immediate definitive treatment; CI = confidence interval; CT = computed tomography; dADT = deferred androgen deprivation therapy; iADT = immediate androgen deprivation therapy; NR = not reported; NS = not statistically significantly different; OR = odds ratio; PSA = prostate specific antigen; RP = radical prostatectomy; SD = significantly different P< 0.05; QoL = quality of life; RR = relative risk > 1.0 indicates advantage of watchful waiting over immediate definitive treatment; TURP = transurethral resection of the prostate WHO = World Health Organisation; WW = watchful waiting

# = Calculated by systematic review team from published data
a = age-adjusted
b = median years follow up
c = mean years follow up

**Refer to appendix B for detailed explanations of rating scores; ** See Table 5 for quality appraisals*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the NHMRC evidence statement form.

References: Included studies

1. Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *New England Journal of Medicine* 2011; 364:1708-17.

2. Johansson E, Steineck G, Holmberg L, Johansson JE, Nyberg T, Ruutu M et al. Long-term quality-of-life outcomes after radical prostatectomy or watchful waiting: the Scandinavian Prostate Cancer Group-4 randomised trial. *Lancet Oncology* 2011; 12(9):891-9.

3. Steineck G, Helgesen F, Adolfsson J, Dickman PW, Johansson JE, Norlen BJ et al. Quality of life after radical prostatectomy or watchful waiting. *New England Journal of Medicine* 2002; 347:790-6.

4. Studer UE, Whelan P, Albrecht W, Casselman J, De Reijke T, Hauri D et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European organisation for research and treatment of cancer (EORTC) trial 30891. *Journal of Clinical Oncology* 2006; 24:1868-76.

5. Studer UE, Collette L, Whelan P, Albrecht W, Casselman J, de Reijke T et al. Using PSA to Guide Timing of Androgen Deprivation in Patients with T0–4 N0–2 M0 Prostate Cancer not Suitable for Local Curative Treatment (EORTC 30891). *European Urology* 2008; 53:941–9.

6. Studer UE, Whelan P, Wimpissinger F, Casselman J, de Reijke TM, Knönagel H et al. Differences in Time to Disease Progression Do Not Predict for Cancer-specific Survival in Patients Receiving Immediate or Deferred Androgen-deprivation Therapy for Prostate Cancer: Final Results of EORTC Randomized Trial 30891 with 12 Years of Follow-up. *European Urology* 2013 (published online ahead of print).

7. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S et al. Prostate Cancer Intervention versus Observation Trial (PIVOT) Study Group. Radical prostatectomy versus observation for localized prostate cancer. *New England Journal of Medicine* 2012; 367:203-13.

APPENDICES

Appendix A: Search strategies used

For Medline database:

#	Searches
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	randomized controlled trial.pt.
5	controlled clinical trial.pt.
6	placebo.ab.
7	randomi?ed.ab.
8	randomly.ab.
9	trial.ab.
10	groups.ab.
11	4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp animals/ not humans.sh.
13	11 not 12
14	(watch$ adj2 wait$).mp.
15	defer$ treat$.mp.
16	(symptom adj2 treat$).mp.
17	defer$ therap$.mp.
18	(wait adj2 see).mp.
19	(conservative adj2 (manage$ or treat$ or therap$)).mp.
20	(active adj1 monitoring).tw
21	'active monitoring'.tw
22	'conservative monitoring'.tw
23	'delayed treatment$'.tw
24	'watchful observation'.tw
25	'watchful surveillance'.tw
26	'watchful monitoring'.tw
27	'expectant monitoring'.tw
28	'expectant surveillance'.tw
29	'delayed therap$'.tw
30	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31	3 AND 13 AND 30

Used the Cochrane sensitivity maximizing filters for identifying randomized controlled trials (http://handbook.cochrane.org, accessed 20/02/2013/ Centre for Reviews and Dissemination systematic review/ meta-analyses strategy 2.(Lee et al, (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. ***BMC Medical Research Methodology*** *12:51)*

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database:

#	**Searches**
1	'prostate cancer'/exp OR 'prostate cancer'
2	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR metast* OR adeno*)
3	#1 OR #2
4	watch* NEAR/2 wait*
5	defer* NEXT/1 treat*
6	Symptom NEAR/2 treat*
7	defer* NEXT/1 therap*
8	wait* NEAR/2 see*
9	active NEAR/1 monitoring OR 'active monitoring'
10	watchful NEXT/1 (observation OR surveillance OR monitoring)
11	expectant NEXT/1 (monitoring OR surveillance)
12	delayed NEXT/1 (treatment*, OR therapy*)
13	'conservative monitoring'
14	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
15	rct
16	'randomized controlled trial'/exp OR 'randomized controlled trial'
17	'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomised controlled trial'/exp OR 'randomised controlled trial' OR 'randomized controlled trials'/exp OR 'randomized controlled trials' OR 'randomised controlled trials'
18	'random allocation'/exp OR 'random allocation'
19	'randomly allocated'
20	'randomization'/exp OR 'randomization'
21	allocated NEAR/2 random
22	'double blind procedure'/exp OR 'double blind procedure'
23	'single blind procedure'/exp OR 'single blind procedure'
24	single NEXT/1 blind*
25	double NEXT/1 blind*
26	(treble OR triple) NEXT/1 blind*
27	placebo*
28	'placebo'/exp OR 'placebo'
29	'prospective study'/exp OR 'prospective study'
30	'crossover procedure'/exp OR 'crossover procedure'
31	'clinical trial'/exp OR 'clinical trial'
32	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31

33	'case study'/exp OR 'case study'
34	case AND report
35	'abstract report'/exp OR 'abstract report'
36	'letter'/exp OR 'letter'
37	33 OR 34 OR 35 OR 36
38	32 NOT 37
39	[1990-3000]/py
40	[english]/lim
41	[humans]/lim
42	#39 and #40 and #41
43	[medline]/lim
44	#42 NOT #43

*Used the SIGN filter for identifying randomized controlled trials (*www.sign.ac.uk/methodology/filters.html#systematic *accessed 20/02/2013)*

ATSI search terms used

#	**Searches**
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

For Cochrane Database of Systematic Reviews 2005 to 1st quarter 2014, Database of Abstracts of Reviews of Effects and Health Technology Assessment database via OVID platform

#	**Searches**
1	(prostat$ adj3 (cancer$ OR carcinoma$ OR malignan$ OR tumo?r$ OR neoplas$ OR metastas$ OR adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 OR 2

Appendix B:

Level of Evidence rating criteria – Intervention studies

Level	Study design
I	Meta-analysis or a systematic review of level II studies
II	Randomised controlled trial or a phase III/IV clinical trial
III-1	Pseudo-randomised controlled trial or a meta-analysis/systematic review of level III-1 studies
III-2	Comparative study with concurrent controls: - Phase II clinical trial - Non-randomised, experimental trial9 - Controlled pre test/post test study - Adjusted indirect comparisons - Interrupted time series with a control group - Cohort study - Case-control study or a meta-analysis/systematic review of level III-2 studies
III-3	A comparative study without concurrent controls: - Phase I clinical trial - Historical control study - Two or more single arm study10 - Unadjusted indirect comparisons - Interrupted time series without a parallel control group or a meta-analysis/systematic review of level III-3 studies
IV	Case series with either post-test or pre-test/post-test outcomes or a meta-analysis/systematic review of level IV studies

According to the standards of the National Health and Medical Research Council

Relevance of the evidence

Rating	Relevance
1	Evidence of an effect on patient-relevant clinical outcomes including benefits and harms, quality of life and survival.
2	Evidence of an effect on a surrogate outcome* that has been shown to be predictive of patient-relevant outcomes for the same intervention.
3	Evidence of an effect on proven surrogate outcomes but for a different intervention.
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population.
5	Evidence confined to unproven surrogate outcomes.

**'surrogate outcome' refers to reasonable indicators of whether there has been some effect (e.g. blood pressure measurements or levels of serum cholesterol)*

Points to considering patient-relevant outcomes:
i) The goal of decision making in health care is to choose the intervention(s) (which may include doing nothing) that is (are) most likely to deliver the outcomes that patients find desirable
ii) Surrogate outcomes (such as blood pressure measurements or levels of serum cholesterol) may be reasonable indicators of whether there has been some effect. However, they should not be the basis for clinical decisions unless they reliably predict an effect on the way the patient feels; otherwise they will not be of interest to the patient or their carers
iii) All possible outcomes that are of most interest to patients (particularly harms) should be identified and evaluated

Adapted from table 1.10: National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra: NHMRC; 2000. http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp69.pdf

Appendix C:

Potential relevant guidelines identified

YEAR	ORGANISATION	TITLE	REASONS FOR NOT ADOPTING
2012	KCE/Belgium Health Care Knowledge Centre	A National Clinical Practice Guideline on the management of localised prostate cancer	Did not meet 70% scores for domains of Rigour, Clarity and Editorial Independence on AGREE instrument

Excluded Studies

Study	Reason for Exclusion
Alibhai 2004	Review article
Bill-Axelson 2005	RCT with immature outcome data
Bill-Axelson 2008	RCT with immature outcome data
Bill-Axelson 2013	No relevant outcomes
Bul 2012	Inappropriate study design
Chou 2011	Review article
Dahabreh 2012	Review article
Fransson 2001	RCT with immature outcome data
Fransson 2009	Inappropriate study design
Graversen 1990	RCT with immature outcome data
Hegarty 2007	No relevant outcomes
Holmberg 2002	RCT with immature outcome data
Holmberg 2012	Review article
Iversen 1995	Inappropriate study design
Iversen 2006	RCT with immature outcome data
Iversen 2010	Inappropriate study design
Jereczek-Fossa 2009	Review article
Johansson 2009	RCT with immature outcome data
Kwiatkowski 2004	Inappropriate study design
Lyth 2012	Modelling was not externally validated in another cohort of patients
McLeod 2006	RCT with immature outcome data
Mhaskar 2012	Review article
Sculpher 2004	Inappropriate study design
See 2001	RCT with immature outcome data
See 2002	RCT with immature outcome data
Vickers 2012	Modelling was not externally validated in another cohort of patients
Wilt 1994	RCT with immature outcome data
Wilt 1997	RCT with immature outcome data
Wilt 2009	RCT with immature outcome data
Wilt 2012	RCT with immature outcome data
Wirth 2004	RCT with immature outcome data

References: Excluded Studies

1. Alibhai SM and Klotz LH. A systematic review of randomized trials in localized prostate cancer. *Canadian Journal of Urology* 2004; 11(1):2110-7.

2. Bill-Axelson A, Holmberg L, Ruutu M, Haggman M, Andersson SO, Bratell S et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *New England Journal of Medicine* 2005; 352(19):1977-84.

3. Bill-Axelson A, Holmberg L, Filen F, Ruutu M, Garmo H, Busch C et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. *Journal of the National Cancer Institute* 2008; 100:1144-54.

4. Bill-Axelson A, Garmo H, Holmberg L, Johansson JE, Adami HO, Steineck G et al. Long-term Distress After Radical Prostatectomy Versus Watchful Waiting in Prostate Cancer: A Longitudinal Study from the Scandinavian Prostate Cancer Group-4 Randomized Clinical Trial. *European Urology* 2013; 64(6):920-8.

5. Bul M, van den Bergh RC, Zhu X, Rannikko A, Vasarainen H, Bangma CH et al. Outcomes of initially expectantly managed patients with low or intermediate risk screen-detected localized prostate cancer. *BJU International* 2012; 110(11):1672-7.

6. Chou R, Croswell JM, Dana T, Bougatsos C, Blazina I, Fu R et al. Screening for prostate cancer: a review of the evidence for the U.S. Preventive Services Task Force. *Annals of Internal Medicine* 2011; 155:762-71.

7. Dahabreh IJ, Chung M, Balk EM, Yu WW, Mathew P, Lau J et al. Active surveillance in men with localized prostate cancer: a systematic review. *Annals of Internal Medicine* 2012; 156(8):582-90

8. Fransson P, Damber JE, Tomic R, Modig H, Nyberg G, Widmark A. Quality of life and symptoms in a randomized trial of radiotherapy versus deferred treatment of localized prostate carcinoma. *Cancer* 2001; 92:3111-9.

9. Fransson P, Damber JE, Widmark A. Health-related quality of life 10 years after external beam radiotherapy or watchful waiting in patients with localized prostate cancer. *Scandinavian Journal of Urology and Nephrology* 2009; 43:119-26.

10. Graversen PH, Nielsen KT, Gasser TC, Corle DK, Madsen PO. Radical prostatectomy versus expectant primary treatment in stages I and II prostatic cancer. A fifteen-year follow-up. *Urology* 1990; 36(6):493-8.

11. Hegarty J, Beirne P, Comber H, Wallace M. Watchful waiting versus prostatectomy for prostate cancer**.** *Cochrane Database of Systematic Review* 2008; 4.

12. Holmberg L, Bill-Axelson A, Helgesen F, Salo JO, Folmerz P, Haggman M et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. *New England Journal of Medicine* 2002; 347:781-9.

13. Holmberg L, Bill-Axelson A, Steineck G, Garmo H, Palmgren J, Johansson E et al. Results from the Scandinavian Prostate Cancer Group Trial Number 4: a randomized controlled trial of radical prostatectomy versus watchful waiting. *Journal of the National Cancer Institute Monographs* 2012; 45:230-3.

14. Iversen P, Madsen PO, Corle DK. Radical prostatectomy versus expectant treatment for early carcinoma of the prostate. Twenty-three year follow-up of a prospective randomized study. *Scandinavian Journal of Urology and Nephrology Supplement* 1995; 172:65-72.

15. Iversen P, Johansson JE, Lodding P, Kylmälä T, Lundmo P, Klarskov P et al. Bicalutamide 150 mg in addition to standard care for patients with early non-metastatic prostate cancer: updated results from the Scandinavian Prostate Cancer Period Group-6 Study after a median follow-up period of 7.1 years. *Scandinavian Journal of Urology and Nephrology* 2006; 40(6):441-52.

16. Iversen P, McLeod DG, See WA, Morris T, Armstrong J, Wirth MP. Antiandrogen monotherapy in patients with localized or locally advanced prostate cancer: final results from the bicalutamide Early Prostate Cancer programme at a median follow-up of 9.7 years. *BJU International* 2010; 105(8):1074-81.

17. Jereczek-Fossa BA, Curigliano G, Orecchia R. Systemic therapies for non-metastatic prostate cancer: review of the literature. *Onkologie* 2009; 32(6):359-63.

18. Johansson E, Bill-Axelson A, Holmberg L, Onelov E, Johansson JE, Steineck G. Time, symptom burden, androgen deprivation, and self-assessed quality of life after radical prostatectomy or watchful waiting: the Randomized Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) clinical trial. *European Urology* 2009; 55:422-30.

19. Kwiatkowski M, Huber A, Moschopulos M, Lehmann K, Wernli M, Hafeli A et al. Prostate cancer screening: results of a prospective trial in Canton Aargau, Switzerland. *Swiss Medical Weekly* 2004; 134(39-40):580-5.

20. Lyth J, Andersson SO, Andren O, Johansson JE, Carlsson P, Shahsavar N. A decision support model for cost-effectiveness of radical prostatectomy in localized prostate cancer. *Scandinavian Journal of Urology and Nephrology* 2012; 46(1):19-25.

21. McLeod DG, Iversen P, See WA, Morris T, Armstrong J, Wirth MP et al. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. *BJU International* 2006; 97(2):247-54.

22. Mhaskar AR, Quinn G, Vadaparampil S, Djulbegovic B, Gwede CK, Kumar A. Timing of first-line cancer treatments - early versus late - a systematic review of phase III randomized trials. *Cancer Treatment Reviews* 2012; 36(8):621-8.

23. Sculpher M, Bryan S, Fry P, de Winter P, Payne H, Emberton M. Patients' preferences for the management of non-metastatic prostate cancer: discrete choice experiment. *BMJ* 2004; 328(7436):382-4.

24. See WA, McLeod D, Iversen P, Wirth M. The bicalutamide early prostate cancer program: Demography. *Urology Oncology* 2001; 6:43-7.

25. See WA, Wirth MP, McLeod DG, Iversen P, Klimberg I, Gleason D et al. Bicalutamide as immediate therapy either alone or as adjuvant to standard care of patients with localized or locally advanced prostate cancer: first analysis of the early prostate cancer program. *Journal of Urology* 2002; 168(2):429-35

26. Vickers A, Bennette C, Steineck G, Adami HO, Johansson JE, Bill-Axelson A et al. Individualized estimation of the benefit of radical prostatectomy from the Scandinavian Prostate Cancer Group randomized trial. *European Urology* 2012; 62(2):204-9.

27. Wilt TJ, Brawer MK. The Prostate Cancer Intervention Versus Observation Trial (PIVOT). *Oncology* 1997; 11(8):1133-9.

28. Wilt TJ, Brawer MK. The Prostate Cancer Intervention Versus Observation Trial: a randomized trial comparing radical prostatectomy versus expectant management for the treatment of clinically localized prostate cancer. *Journal of Urology* 1994; 152(5 Pt 2):1910-4.

29. Wilt TJ, Brawer MK, Barry MJ, Jones KM, Kwon Y, Gingrich JR et al. The Prostate cancer Intervention Versus Observation Trial:VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT): design and baseline results of a randomized controlled trial comparing radical prostatectomy to watchful waiting for men with clinically localized prostate cancer. *Contemporary Clinical Trials* 2009; 30:81-7.

30. Wilt TJ. The Prostate Cancer Intervention Versus Observation Trial: VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT): design and baseline results of a randomized controlled trial comparing radical prostatectomy with watchful waiting for men with clinically localized prostate cancer. *Journal of the National Cancer Institute Monographs* 2012; 45:184-90.

31. Wirth MP, See WA, McLeod DG, Iversen P, Morris T, Carroll K. Bicalutamide 150 mg in addition to standard care in patients with localized or locally advanced prostate cancer: results from the second analysis of the early prostate cancer program at median follow up of 5.4 years. *Journal of Urology* 2004; 172(5 Pt 1):1865-70.

Quality assessment tools

Each main study design was assessed using quality assessment tools. The following were used:

1. Systematic reviews

2. Randomised controlled trials

3. Quasi-experimental (Pseudo-randomised trials, on-randomised trials)

4. Cohort

5. Diagnostic accuracy study – QUADAS-2

6. Risk factor – Nested case control study

7. Risk factor – Cohort study

Quality appraisal form: Systematic reviews and meta-analysis

Was an adequate search strategy used?

- Very thorough – included appropriate search terms and databases
- Adequate – search terms and/or choice of databases could have been improved upon
- No or not described

Were the inclusion criteria appropriate and applied in an unbiased way?

- Yes – pre-specified inclusion criteria applied independently by two people
- Adequate – inclusion criteria were pre-specified and applied by one person
- No – inclusion was decided in an arbitrary fashion or not described

Were the studies assessed for quality (relating to the minimisation of biases)?

- Yes – appropriate quality issues were assessed independently by two people
- Adequate – some problems with quality issues or assessed by one person only
- No – quality assessment either not undertaken, inappropriate or not described

Were the characteristics and results of individual studies appropriately summarised?

- Yes – summary descriptive tables of subjects, interventions, outcomes etc are provided and estimates of treatment effect displayed
- Adequate – more information would be desirable
- No

The following questions are only relevant for systematic reviews that pooled data
Were the methods used for pooling the data appropriate?

- Yes
- No

If there was heterogeneity, were sources of heterogeneity explored?

- Yes
- Some attempt was made
- No
- No heterogeneity

Overall quality assessment:
Based on the answers you have given, the recommended evidence quality rating

Quality appraisal help sheet: Systematic reviews and meta-analysis

1. Studies included in the systematic review or meta-analysis

a) Was an adequate search strategy used?

2= Very thorough – included appropriate search terms and databases
1= Adequate – search terms and/or choice of databases could have been improved upon
0= No or not described

b) Were the inclusion criteria appropriate and applied in an unbiased way?

2= Yes – pre-specified inclusion criteria applied independently by two people
1= Adequate – inclusion criteria were pre-specified and applied by one person
0= No – inclusion was decided in an arbitrary fashion or not described

2. Were the studies assessed for quality (relating to the minimisation of biases)?

2= Yes – appropriate quality issues were assessed independently by two people
1= Adequate – some problems with quality issues or assessed by one person only
0= No – inappropriate, no quality assessment undertaken or not described

3. Were the characteristics and results of individual studies appropriately

2= Yes - summary descriptive tables of subjects, intervention, outcomes etc. are provided and estimates of treatment effect displayed
1= Adequate – more information would be desirable
0= No

The following questions are only relevant for systematic reviews that pooled data

4. Were the methods used for pooling the data appropriate?

2= Yes
0= No

5. If there was heterogeneity, were sources of heterogeneity explored?

2= Yes
1= Some attempt was made
0= No
N/A No heterogeneity

Key to overall quality rating

High quality: A review that received 2 for all relevant questions (Question 1-3)

Medium quality: A review that received 1 and 2 for all relevant questions (Question 1-3)

Low quality: A review that received 0 for any of the relevant questions (Question 1-3)

Answers to question 4 and 5 serve as additional quality information for systematic reviews that pooled data. They are not factored into the calculation of the overall quality score.

Quality assessment form: Randomised controlled trial

Was the trial double-blinded?

I am reasonably certain that the trial was double-blinded (eg identical placebo, active placebo, double-dummy, no revealing side-effects).

Trial was double-blinded but may have limitations (eg method of blinding inappropriate, tablet vs injection with no double-dummy, different treatment schedules, side-effects may unblind)
or
single-blinded (eg outcomes assessed blind, objective outcomes, no revealing side-effects).

Outcomes not blinded, substantial side-effects, or not reported.

Was the treatment allocation schedule concealed?

Adequately concealed (e.g. central randomisation, numbered or coded bottles, drugs prepared by pharmacy).

Inadequately concealed (e.g. numbered/sealed envelopes, alternation, medical record number, date of birth).

No concealment or unclear (e.g. no approach described, open randomisation lists, person doing recruitment tossing a coin).

Were all randomised participants included in the analysis?

No exclusions or survival analysis used with all subjects included (>95% follow-up for all groups).

Exclusions not likely to cause bias (>80% follow-up for all groups, <5% difference in follow-up between groups)

Too many exclusions, differential loss in comparison groups, or not reported.

How was the allocation schedule generated?

Adequate (e.g. random number table, computer random generator, coin tossing, card shuffling)

Inadequate or not reported

Overall quality assessment:

Based on the answers you have given, the recommended evidence quality rating

Quality assessment help sheet: Randomised Controlled Trials

Was the trial double-blinded?

2 = I am reasonably certain that the trial was double-blinded (e.g. identical placebo, active placebo, double-dummy, no revealing side-effects).
1 = Trial was double-blinded but may have limitations (e.g. method of blinding inappropriate, ta injection with no double-dummy, different treatment schedules, side-effects may unblind)
or
single-blinded (e.g. outcomes assessed blind, objective outcomes, no revealing side-effects).
0 = Outcomes not blinded, substantial side-effects, or not reported.

2. Concealment of treatment allocation schedule

2 = Adequately concealed (e.g. central randomisation, numbered or coded bottles, drugs prepared by pharmacy).
1 = Inadequately concealed (e.g. numbered envelopes, sealed envelopes, alternation, medical record number, date of birth).
0 = No concealment or unclear (e.g. no approach described, open randomisation lists, person doing recruitment to toss a coin).

3. Inclusion of all randomised participants in analysis (i.e. intention-to-treat analysis)

2 = No exclusions or survival analysis used with all subjects included (note: follow-up may not be complete but balanced between the comparison groups).
1 = Exclusions not likely to cause bias (some incomplete follow-up but balanced between comparison groups + survival analysis not used).
0 = Too many exclusions, differential loss in comparison groups, or not reported.

4. Generation of allocation sequences

1 = Adequate (e.g. random number table, computer random number generator, coin tossing, card shuffling).
0 = Inadequate or not reported.

Key to overall quality rating

High quality: A review that received 2 for three main criteria (double-blinding, concealment of treatment allocation schedule, Inclusion of all randomised participants in analysis (i.e. ITT))

Medium quality: Received 2 and 1 for all three main criteria

Low quality: Received 0 for all three criteria or 0 and 1 for all three criteria or received 0 for any of the three criteria

Answer for question 4 is considered as additional information and not considered when calculating the overall quality score. Quality assessment questions 1 to 3 for randomised control trials are evidence-based categories (Schulz et al (1995); Jadad et al (1996). Generation of allocation sequences has been shown not to influence outcomes.

Quality assessment form: Quasi-experimental study

Subject selection procedures

- Representative of eligible patients
- Selected group
- Highly selected or not described

Comparability of groups on demographic characteristics and clinical features

- Comparable
- Not comparable but adjusted analysis used
- Not comparable and not adjusted for differences

Measurement of outcomes

Outcome measures blind to technology used

- Yes
- No, but objective measures used
- No or not described

Completeness of follow-up

Was follow-up complete and were all patients included in the analysis?

- Yes (follow-up >95%) or survival analysis using all patients
- Reasonable follow-up of all groups (>80% overall and <5% difference between groups)
- No or not described

Overall quality assessment:

Based on the answers you have given, the recommended evidence quality rating is

Quality assessment help sheet: Quasi-experimental studies (Pseudo-randomised)

1. Subject Selection

2= Representative of eligible patients
1= Selected group
0= Highly selected or not described

2. Measurement of outcomes

Outcome measures blind to technology used?
2= Yes
1= No, but objective measures used
Measurement of outcomes not likely to be influenced by knowing which group subjects belonged to (e.g. objective outcomes such as mortality)
0= No or not described
Issues of blinding not described, subjective measurements used (e.g. QOL, pain, hospital length of stay), blinding not possible (e.g. different treatment schedules)

2. Comparability of groups on demographic characteristics and clinical features

2= Comparable
1= Not comparable but adjusted analysis used
0= Not comparable and not adjusted for differences

4. Completeness of follow-up

Follow-up complete and all patients included in the analysis?
2= Yes (follow-up > 95% included or intention to treat) or survival analysis using all patients
1= Reasonable follow-up of all groups (>80% subjects included)
0= No or not described

Key to overall quality rating

High quality: A review that received 2 for all quality criteria

Medium quality: Received 2 and 1 for all quality criteria

Low quality: Received 0 for all quality criteria or 1 and 0 all quality criteria or received 0 for any of the quality criteria

Quality assessment form: Cohort study

Subject selection

a) New technology group

Representative of eligible patients.
Consecutive or random sample (e.g. states all patients recruited in given time frame).
AND
In the case of patient selection of technology, all offered option - those who accepted formed the new technology group
OR
In the case of surgeon selection of technology, all patients with a particular surgeon, at a particular hospital or in a given time frame received the technology

Selected group
Debatable whether group is representative (e.g. consecutive sample but extensive exclusion criteria)

Highly selected or not described
Selection at surgeon's discretion (regardless of whether sample consecutive), unclear how group was selected, or not described

b) Comparison group

Representative of eligible patients
Consecutive or random sample (e.g. states all patients recruited in given time frame).
AND
In the case of patient selection of technology, all offered option - those who declined formed the new technology group.
OR
In the case of surgeon selection of technology, all patients with a particular surgeon, at a particular hospital or in a given time frame did not receive the technology.

Selected group
Matched with new technology group for baseline characteristics either prospectively or using historical controls, or debatable whether group is representative (e.g. consecutive sample but extensive exclusion criteria).

Highly selected or not described
Selected at surgeon's discretion or patients not eligible for technology (e.g. technology contraindicated) (regardless of whether sample consecutive), unclear how group was selected, or not described.

Comparability of groups on demographic characteristics and clinical features

Comparable

Groups closely matched - comparable on age, extent of disease (e.g. number of bone metastases sites), stage of illness, performance status.

Not comparable but adjusted analysis used

Groups not comparable but adjusted analysis used, groups match on the majority of variables but not all.

Not comparable and not adjusted for differences

Not reported or not comparable.

Measurement of outcomes

a) Outcome measures blind to technology used

Yes

States outcomes were blinded to whether subject was in technology or control group.

No, but objective measures used

Measurement of outcomes not likely to be influenced by knowing which group subjects belonged to (e.g. objective outcomes such as mortality).

No or not described

Issues of blinding not described, subjective measurements used (e.g. QOL, pain, hospital length of stay), blinding not possible (e.g. different treatment schedules).

b) Same method of measurement used across comparison groups

Yes

Concurrent controls, all subjects treated during the same time period.

No or not described

Controls measured at different times, locations, personnel, to technology group (e.g. historical controls, controls at different hospital to technology group).

Completeness of follow-up

Was follow-up complete and were all patients included in the analysis?

Yes (follow-up >95%) or survival analysis using all patients

>95% of subjects included or intention to treat.

Reasonable follow-up of all groups (>80%)

>80 % subjects included.

No or not described

Considerable drop outs, differential drop out in intervention and control groups, or no information provided.

Quality assessment help form: Cohort studies

1. Subject Selection

(a) "New technology" group

2= Representative of eligible patients

Consecutive or random sample (e.g. states all patients recruited in given time frame)
and
In the case of patient selection of technology, all offered option - those who accepted formed the new technology group.
or
In the case of surgeon selection of technology, all patients with a particular surgeon, at a particular hospital or in a given time frame received the technology.

1= Selected group

Debatable whether group is representative (e.g. consecutive sample but extensive exclusion criteria)

0= Highly selected or not described

Selection at surgeon's discretion (regardless of whether sample consecutive), unclear how group was selected, or not described.

(b) Comparison group

2= Representative of eligible patients

Consecutive or random sample (e.g. states all patients recruited in given time frame), from same population as new technology group, and would be eligible for new technology. and
In the case of patient selection of technology, all offered option - those who declined formed control group.
or
In the case of surgeon selection of technology, all patients with a particular surgeon, at a particular hospital or in a given time frame did not receive the technology.

1= Selected group

Matched with new technology group for baseline characteristics either prospectively or using historical controls, or debatable whether group is representative (e.g. consecutive sample but extensive exclusion criteria)

0= Highly selected or not described

Selected at surgeon's discretion or patients not eligible for technology (e.g. technology contraindicated) (regardless of whether sample consecutive), unclear how group was selected, or not described.

2. Comparability of groups on demographic characteristics and clinical features

2= Comparable

Groups closely matched - comparable on age, extent of disease (e.g. number of bone metastases sites), stage of illness, performance status.

1= Not comparable but adjusted analysis used

Groups not comparable but adjusted analysis used, groups match on the majority of variables but not all.

0= Not comparable and not adjusted for differences

Not reported or not comparable

3. Measurement of outcomes

(a) Outcome measures blind to technology used?

2= Yes

States outcomes were blinded to whether subject was in technology or control group.

1= No, but objective measures used

Measurement of outcomes not likely to be influenced by knowing which group subjects belonged to (e.g. objective outcomes such as mortality)

0= No or not described

Issues of blinding not described, subjective measurements used (e.g. quality of life, pain, hospital length of stay), blinding not possible (e.g. different treatment schedules)

(b) Same method of measurement used across comparison groups?

2= Yes

Concurrent controls, all subjects treated during the same time period.

0= No or not described

Controls measured at different times, locations, personnel, to technology group (e.g. historical controls, controls at different hospital to technology group).

4. Completeness of follow-up

Follow-up complete and all patients included in the analysis?

2= Yes (follow-up > 95%) or survival analysis using all patients >95% of subjects included or intention to treat.

1= Reasonable follow-up of all groups (>80%)

>80 % subjects included.

0= No or not described

Considerable drop outs, differential drop out in intervention and control groups, or no information provided.

Key to overall quality rating

High quality: A review that received 2 for all quality criteria

Medium quality: Received 2 and 1 for all quality criteria

Low quality: Received 0 for all quality criteria or 1 and 0 all quality criteria or received 0 for any of the quality criteria

Quality assessment help sheet: Diagnostic accuracy study
Quadas-2 appraisal tool

The QUADAS-2 appraisal tool is designed to assess the quality of primary diagnostic accuracy studies. It consists of four key domains covering patient selection, index test, reference standard, and flow of patients through the study and timing of the index test(s) and reference standard ("flow and timing"). Each section asks to complete information fields and questions to support the risk of bias judgment of each key domain.

1. Patient selection

(see also 1.2.1 DOMAIN 1: PATIENT SELECTION in Quadas-2 background document):

Intended use of test:

Prior tests and any referral filters:

Describe prior tests and any referral filters

Presentation:

Describe condition that defined entry into study

Setting:

Describe setting e.g. tertiary, hospital, specialist clinic or primary care

Was a diagnostic case-control design avoided?[i]
Yes/No/Unclear

Either consecutive or random sample?[i]
Yes/No/Unclear

Did study avoid inappropriate exclusions?
Yes/No/Unclear

Please enter reasons in text field below:

If comparing more than one index test was the design fully paired (both tests performed on same patient) or paired randomised?

Yes/No/Unclear/Not applicable (only 1 index test)

If a paired randomised design was used, was allocation to groups concealed and was the generation of allocation sequence adequate?

Yes/No/Unclear/Not applicable (did not use paired randomised design)

Could the selection of participants have introduced bias?

RISK: Low/High/Unclear

2. Index test 1
(see also 1.2.2 DOMAIN 2: INDEX TEST in Quadas-2 background document):

Describe index test and how it was conducted and interpreted:

Were the index test results interpreted without knowledge of the results of the reference standard? i
Yes/No/Unclear/Not applicable (no reference standard)

If a threshold was used, was it pre-specified?
Yes/No/Unclear/Not applicable (no threshold used)

If 2 tests are being compared have they been assessed independently/ blind to each other? i
Yes/No/Unclear/Not applicable (only I index test)

Could the conduct or interpretation of the index test have introduced bias?

RISK: Low/High/Unclear

3. Index test 2 – if comparing 2 index tests

Describe index test and how it was conducted and interpreted:

Were the index test results interpreted without knowledge of the results of the reference standard? i
Yes/No/Unclear/Not applicable (no reference standard used/ only 1 index test)

If a threshold was used, was it pre-specified?
Yes/No/Unclear/Not applicable – (no threshold used/ only 1 index test)

Could the conduct or interpretation of the index test have introduced bias?

RISK: Low/High/Unclear

4. Reference Standard
(see also 1.2.3 DOMAIN 3: REFERENCE STANDARD in Quadas-2 background document):

Reference standard
Describe the reference standard and how it was conducted and interpreted:

Is the reference standard likely to correctly classify the target condition? [i*]
Yes/No/Unclear/Not applicable (no reference standard used)

*Note: If the ref standard is not 100% accurate the reviewer/working group will need to pre-specify, which % if any would be acceptable e.g. 99%, 98%?

Were the reference standard results interpreted without knowledge of the results of the index test/s?
Yes/No/Unclear/Not applicable (no reference standard used)

Was the reference test standard independent of the index test (i.e. the index test did not form part of the reference standard**)?**
Yes/No/Unclear/Not applicable (no reference standard used)

Could the reference standard, its conduct, or its interpretation have introduced bias?

RISK: Low/High/Unclear/Not applicable

5. Flow and Timing

Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table

Describe the time interval and any interventions between index test(s) and reference standard

If a predictive test i.e. the reference standard is a later event that the test aims to predict, were any subsequent interventions between test and later event blind to test result?
Yes/No/Unclear/Not applicable (not a predictive test)

Was there an appropriate interval between index test(s) and reference standard (If appropriate appraisers/working party will need to predefine what is an appropriate interval)?

Yes/No/Unclear/Not applicable (no reference test)

Did all participants or a random sample of participants receive a reference standard test?[i]
Yes/No (If "No" appraisers/working party will need to predefine maximum acceptable proportion not verified)/Unclear/Not applicable (no reference test)

Did all patients receive the same reference standard irrespective of index test result?[i]
Yes/No/Unclear/Not applicable- no reference test

Were all test results including unclear results reported?
Yes/No/Unclear

Were all patients included in the analysis?
Yes/No/Unclear

Could the patient flow have introduced bias?

RISK: Low/High/Unclear

[i] This is relevant to assess the level of evidence.

Overall rating

High risk of bias – high risk of bias in any domain

Moderate risk of bias – moderate or low risk of bias in all domains, no high risk domains

Low risk of bias – all domains low risk of bias, no moderate or high risk domains

Quality assessment: nested case-control study, risk factors
(wiki tool)

Bias in selection of participants into cohort study

Sources of cases and controls

Drawn from the same population (low risk)

Drawn from different populations but unlikely to introduce bias (moderate risk)

Drawn from different populations and likely to introduce bias OR insufficient information to tell (high risk)

Selection of cases and controls

Cases and controls are randomly selected from all available cases and controls, controls matched to cases by risk set (either at selection or during analysis) (low risk)

Only one of the two criteria is met (moderate risk)

Neither criteria are met OR insufficient information to tell (high risk)

Bias due to error in outcome measurement

Definition of cases (outcome)

Outcome precisely specified and with pathological or other objective confirmation (low risk)

Outcome precisely specified but without known pathological or other objective confirmation OR outcome precisely specified, self-reported and cases blind to hypotheses related to outcome (moderate risk)

Outcome imprecisely specified OR outcome self-reported and cases not blind to hypotheses related to outcome OR insufficient information to tell (high risk)

Definition of controls

Objective evidence of no past history of outcome of interest (low risk)

Self-report of no past history of outcome of interest OR insufficient information to tell (moderate risk)

Was outcome of interest likely to have been absent at the time to which the exposure refers?

Yes (low risk)

No but outcome unlikely to affect exposure measurement (moderate risk)

No and outcome likely to affect exposure measurement OR insufficient information to tell (high risk)

Was follow-up long enough for outcome to occur as a consequence of the measured exposure? (Requires prior specification of a sufficient follow-up period)

Yes (low risk)

No OR insufficient information to tell (high risk)

Bias due to error in exposure measurement

Measurement of exposure

Objective measurements from pre-existing records or baseline physical or biological assessment, each blind to case or control status (low risk).

Objective measurements from pre-existing records or baseline physical or biological assessment, not blind to case or control status OR structured interview blind to case or control status (medium risk).

Structured interview not blind to case or control status OR self-administered questionnaire OR insufficient information to tell (high risk)

Was the same method used to measure exposure in cases and controls?

Yes (low risk)

No OR insufficient information to tell (high risk)

Bias due to non-participation

Participation rate in cohort

Participation rate in exposed cohort ≤10 percentage points different from non-exposed cohort OR exposed and non-exposed are from the same cohort (low risk)

Participation rate in exposed cohort >10 percentage points but <20 percentage points different from non-exposed cohort (moderate risk)

Participation rate in exposed cohort ≥20 percentage points different from non-exposed cohort OR insufficient information to tell (high risk)

Participation (response) rate for cases

≥70% participation rate (≥80% response rate) (low risk)

≥50 to <70% participation rate (≥60 to <80% response rate) (moderate risk)

<50% participation rate (<60% response rate) OR insufficient information to tell (high risk)

Not applicable – new data not being collected from participants

Participation (response) rate for controls

≥ 60% participation rate (≥70% response rate) (low risk)

≥40 to <60% participation rate (≥50 to <70% response rate) (moderate risk)

< 40% participation rate (<50% response rate) OR insufficient information to tell (high risk)

Not applicable – new data not being collected from participants

Difference in participation rate (response rate) between cases and controls

Participation or response rate in cases ≤10 percentage points different from controls (low risk)

Participation or response rate in cases >10 to ≤15 percentage points different from controls (moderate risk)

Participation or response rate in cases >15 percentage points different from controls OR insufficient information to tell (high risk)

Not applicable – new data not being collected from participants

Bias due to missing data

Completeness of follow-up of cohort

Active or passive follow-up of participants with methods for ascertainment of outcome and death clearly described AND with methods for ascertainment of emigration from population-at-risk clearly described or censoring at date of last follow-up OR there is a plausible estimate of >90% follow-up (low risk)

Active or passive follow-up with methods for ascertainment of outcome, death and emigration from population-at-risk not clearly described OR there is a plausible estimate of 70 – 90% follow-up (moderate risk)

Active or passive follow-up with methods for ascertainment of one or more of outcome, death or emigration not described OR there was probably <70% follow-up OR insufficient information to tell (high risk)

Accuracy of dates of outcome or censoring

Dates of outcome or censoring ascertained to within one year (low risk)

One or more of dates of outcome or censoring not ascertained to within one year OR insufficient information to tell (moderate risk)

Difference in follow-up between exposed and non-exposed members of cohort

Follow-up methods are the same and likely to achieve the same completeness of follow-up in exposed and unexposed participants (low risk)

Completeness of follow-up in exposed and unexposed participants is unlikely to be the same but difference between the two is, or is likely to be, small (<10%) (moderate risk)

Completeness of follow-up in exposed and unexposed participants is very unlikely to be the same and difference between the two is, or is likely to be, large (≥10%) OR insufficient information to tell (high risk)

Difference in missing data for exposure between cases and controls

Difference in missing data for exposure < 10 percentage points (low risk)

Difference in missing data for exposure ≥10 to <20 percentage points (moderate risk)

Difference in missing data for exposure ≥20 percentage points OR insufficient information to tell (high risk)

Bias due to confounding

Comparability of cases and controls with respect to potentially important confounding variables (Requires prior specification of potentially important confounders)

Age and other potentially important confounders measured and controlled by design or in analysis (low risk)

Age and some but not all other potentially important confounders controlled by design or in analysis (moderate risk)

No potentially important confounders or only age controlled by design or in analysis OR insufficient information to tell (high risk)

Analysis bias

Analysis appropriate to design

When controls are frequency-matched to cases, matching variables are controlled in the analysis OR when controls are individually matched to cases, a conditional analysis is used or matching variables are controlled in the analysis (low risk)

None of the above OR insufficient information to tell (high risk)

Covariates are appropriately included in statistical analysis models

Variables measuring the same underlying concept or lying in the same causal pathway ARE NOT included together as covariates in statistical analysis models (low risk)

Variables measuring the same underlying concept or lying in the same causal pathway ARE included together as covariates in statistical analysis models OR insufficient information to tell (high risk)

Overall quality assessment:
Based on the answers you have given, the recommended evidence quality rating

NESTED CASE-CONTROL STUDIES QUALITY ASSESSMENT HELP FORM (RISK FACTORS)

(Adapted from the Newcastle-Ottawa tool for QA of clinical cohort studies and case-control studies for use in the Prostate Cancer Foundation of Australia and Cancer Council Australia auspiced - *Development of Clinical Practice Guidelines for PSA Testing and Early Management of Test-Detected Prostate Cancer*)

Bias in selection of participants into nested case-control study

Sources of cases and controls

1. Drawn from the same population* (low risk)
2. Drawn from different populations but unlikely to introduce bias (moderate risk)
3. Drawn from different populations and likely to introduce bias OR insufficient information to tell (high risk)

* This will usually be the case when a case-control study is nested in a single cohort containing exposed and unexposed people and cases accrue during follow-up of the whole cohort.

Selection of cases and controls

1. Cases and controls are randomly selected from all available cases and controls; controls matched to cases by risk set* (either at selection or during analysis) (low risk)
2. Only one of the two criteria in 1 is met (moderate risk)
3. Neither criterion in 1 is met OR insufficient information to tell (high risk)

*Risk set defined by sex, age group, date of entry into cohort and date of case-defining event

Bias due to error in outcome measurement

Definition of cases (outcome)

1. Outcome precisely specified and with pathological or other objective confirmation (low risk)
2. Outcome precisely specified but without known pathological or other objective confirmation OR outcome precisely specified, self-reported and cases blind to hypotheses related to outcome (moderate risk)
3. Outcome imprecisely specified OR outcome self-reported and cases not blind to hypotheses related to outcome OR insufficient information to tell (high risk)

Definition of controls

1. Objective evidence of no past history of outcome of interest (low risk)
2. Self-report of no past history of outcome of interest OR insufficient information to tell (moderate risk)

Was outcome of interest likely to have been absent at the time to which the exposure refers?

1. Yes (low risk)
2. No but outcome unlikely to affect exposure measurement (moderate risk)
3. No and outcome likely to affect exposure measurement OR insufficient information to tell (high risk)

Was follow-up long enough for outcome to occur as a consequence of the measured exposure? (Requires prior specification of a sufficient follow-up period)

1. Yes (low risk)
2. No OR insufficient information to tell (high risk)

Bias due to error in exposure measurement

Measurement of exposure

1. Objective measurements from pre-existing records or baseline[1] physical or biological assessment or structured interview, each blind to case or control status (low risk)
2. Objective measurements from pre-existing records or baseline[1] physical or biological assessment not blind to case or control status OR structured interview blind to case or control status (moderate risk)
3. Structured interview not blind to case or control status OR self-administered questionnaire OR insufficient information to tell (high risk)

Was the same method used to measure exposure in cases and controls?

1. Yes (low risk)
2. No OR insufficient information to tell (high risk)

Bias due to non-participation

Participation rate in cohort

1. Participation rate in exposed cohort is ≤10 percentage points different from non-exposed cohort OR exposed and non-exposed are from the same cohort (low risk)
2. Participation rate in exposed cohort is >10 percentage points but <20 percentage points different from non-exposed cohort (moderate risk)
3. Participation rate in exposed cohort ≥20 percentage points different from non-exposed cohort OR insufficient information to tell (high risk)

Participation (response) rate for cases

1. ≥70% participation rate (≥80% response rate) (low risk)
2. ≥50 to <70% participation rate (≥60 to <80% response rate) (moderate risk)
3. <50% participation rate (<60% response rate) OR insufficient information to tell (high risk)
4. Not applicable – new data not being collected from participants

Participation (response) rate for controls

1. ≥60% participation rate (≥70% response rate) (low risk)
2. ≥40 to <60% participation rate (≥50 to <70% response rate) (moderate risk)
3. <40% participation rate (<50% response rate) OR insufficient information to tell (high risk)
4. Not applicable – new data not being collected from participants

[1] Existing at or before baseline, where baseline is the time at which a participant is recorded to have entered the cohort or, if obtained after baseline, a time before onset of symptoms of the outcome or any likely effect of the developing outcome on the exposure

Difference in participation rate (response rate) between cases and controls

1. Participation or response rate in cases ≤10 percentage points different from controls (low risk)

2. Participation or response rate in cases is >10 to ≤15 percentage points different from controls (moderate risk)
3. Participation or response rate in cases is >15 percentage points different from controls OR insufficient information to tell (high risk)
4. Not applicable - new data not being collected from participants

Bias due to missing data

Completeness of follow-up of cohort

1. Active or passive follow-up of participants with methods for ascertainment of outcome and death clearly described AND with methods for ascertainment of emigration from population-at-risk clearly described or censoring at date of last follow-up OR there is a plausible estimate of >90% follow-up (low risk)
2. Active or passive follow-up with methods for ascertainment of outcome, death and emigration from population-at-risk not clearly described OR there is a plausible estimate of 70 – 90% follow-up (moderate risk)
3. Active or passive follow-up with methods for ascertainment of one or more of outcome, death or emigration not described OR there was probably <70% follow-up OR insufficient information to tell (high risk)

Accuracy of dates of outcome or censoring

1. Dates of outcome or censoring ascertained to within one year (low risk)
2. One or more of dates of outcome or censoring not ascertained to within one year OR insufficient information to tell (moderate risk)

Difference in follow-up between exposed and non-exposed members of cohort

1. Follow-up methods are the same and likely to achieve the same completeness of follow-up in exposed and unexposed participants (low risk)
2. Completeness of follow-up in exposed and unexposed participants is unlikely to be the same but difference between the two is, or would be likely to be, small (<10%) (moderate risk)
3. Completeness of follow-up in exposed and unexposed participants is very unlikely to be the same and difference between the two is, or is likely to be, large (≥10%) OR insufficient information to tell (high risk)

Difference in missing data for exposure between cases and controls

1. Difference in missing data for exposure <10 percentage points (low risk)
2. Difference in missing data for exposure ≥10 to <20 percentage points (moderate risk)
3. Difference in missing data for exposure ≥20 percentage points OR insufficient information to tell (high risk)

Bias due to confounding

Comparability of cases and controls with respect to potentially important confounding variables (Requires prior specification of potentially important confounders)

1. Age and other potentially important confounders measured and controlled by design or in analysis (low risk)
2. Age and some but not all other potentially important confounders controlled by design or in analysis (moderate risk)
3. No potentially important confounders or only age controlled by design or in analysis OR insufficient information to tell (high risk)

Analysis bias

Analysis appropriate to design

1. When controls are frequency matched to cases, matching variables are controlled in the analysis OR when controls are individually matched to cases, a conditional analysis is used or matching variables are controlled in the analysis (low risk)
2. None of the above OR insufficient information to tell (high risk)

Covariates are appropriately included in statistical analysis models

1. Variables measuring the same underlying concept or lying in the same causal pathway ARE NOT included together as covariates in statistical analysis models (low risk)
2. Variables measuring the same underlying concept or lying in the same causal pathway ARE included together as covariates in statistical analysis models OR insufficient information to tell (high risk)

Overall rating

High risk of bias – high risk of bias in any domain

Moderate risk of bias – moderate or low risk of bias in all domains, no high risk domains

Low risk of bias – all domains low risk of bias, no moderate or high risk domains

Quality appraisal form: cohort study, risk factors

Bias in selection of participants into study

Selection of the exposed and non-exposed cohorts

- Drawn from the same population (low risk)
- Drawn from different populations but unlikely to introduce bias (moderate risk)
- Drawn from different populations and likely to introduce bias OR insufficient information to tell (high risk)

Bias due to error in exposure measurement

Measurement of exposure

- Objective measurements from pre-existing records or baseline physical or biological assessment blind to outcome status (low risk)
- Objective measurements from pre-existing records or baseline physical or biological assessment not blind to outcome status, OR structured interview (moderate risk)
- Self-administered questionnaire OR insufficient information to tell (high risk)

Bias due to error in outcome measurement

Measurement of outcome

- Outcome measurement unlikely to be influenced by exposure (low risk)
- Objective outcome measurement possibly influenced by exposure (moderate risk)
- Objective outcome measurement probably influenced by exposure OR self-reported outcome OR insufficient information to tell (high risk)

Was outcome of interest absent at the time to which the exposure refers?

- Yes (low risk)
- No but outcome unlikely to affect exposure measurement (moderate risk)
- No and outcome likely to affect exposure measurement OR insufficient information to tell (high risk)

Was follow-up long enough for outcome to occur as a consequence of measured exposure? (Requires prior specification of a sufficient follow-up period)

- Yes (low risk)
- No OR insufficient information to tell (high risk)

Bias due to non-participation

Participation rate in cohort

Participation rate in exposed cohort ≤10 percentage points different from non-exposed cohort OR exposed and non-exposed are from the same cohort (low risk)

Participation rate in exposed cohort >10 percentage points but <20 percentage points different from non-exposed cohort (moderate risk)

Participation rate in exposed cohort ≥20 percentage points different from non-exposed cohort OR insufficient information to tell (high risk)

Bias due to missing data

Completeness of follow-up of cohort

Active or passive follow-up of participants with methods for ascertainment of outcome and death clearly described AND with methods for ascertainment of emigration from population-at-risk clearly described or censoring at date of last follow-up OR there is a plausible estimate of >90% follow-up (low risk)

Active or passive follow-up with methods for ascertainment of outcome, death and emigration from population-at-risk not clearly described OR there is a plausible estimate of 70 – 90% follow-up (moderate risk)

Active or passive follow-up with methods for ascertainment of one or more of outcome, death or emigration not described OR there was probably < 70% follow-up OR insufficient information to tell (high risk)

Accuracy of dates of outcome or censoring

Dates of outcome or censoring ascertained to within one year (low risk)

One or more of dates of outcome or censoring not ascertained to within one year OR insufficient information to tell (moderate risk)

Difference in follow-up between exposed and non-exposed members of cohort

Follow-up methods are the same and likely to achieve the same completeness of follow-up in exposed and non-exposed participants (low risk)

Completeness of follow-up in exposed and non-exposed participants is unlikely to be the same but difference between the two is, or is likely to be, small (<10%) (moderate risk)

Completeness of follow-up in exposed and non-exposed participants is very unlikely to be the same and difference between the two is, or is likely to be, large (≥10%) OR insufficient information to tell (high risk)

Difference in missing data for exposure between those with or without the outcome

Difference in missing data for exposure < 10 percentage points (low risk)

Difference in missing data for exposure ≥10 to <20 percentage points (moderate risk)

Difference in missing data for exposure ≥20 percentage points OR insufficient information to tell (high risk)

Bias due to confounding

Comparability of exposed and non-exposed cohorts with respect to potentially important confounding variables (Requires prior specification of potentially important confounders)

Age and other potentially important confounders measured and controlled by design or in analysis (low risk)

Age and some but not all other potentially important confounders controlled by design or in analysis (moderate risk)

No potentially important confounders or only age controlled by design or in analysis OR insufficient information to tell (high risk)

Analysis bias

Covariates are appropriately included in statistical analysis models

Variables measuring the same underlying concept or lying in the same causal pathway ARE NOT included together as covariates in statistical analysis models (low risk)

Variables measuring the same underlying concept or lying in the same causal pathway ARE included together as covariates in statistical analysis models OR insufficient information to tell (high risk)

Overall quality assessment:

Based on the answers you have given, the recommended evidence quality rating

COHORT STUDIES QUALITY ASSESSMENT HELP FORM (RISK FACTORS)

(Adapted from the Newcastle-Ottawa tool for QA of clinical cohort studies for use in the Prostate Cancer Foundation of Australia and Cancer Council Australia auspiced - *Development of Clinical Practice Guidelines for PSA Testing and Early Management of Test-Detected Prostate Cancer*)

Bias in selection of participants into study

Selection of the exposed and non-exposed cohorts

1. Drawn from the same population (low risk)
2. Drawn from different populations but unlikely to introduce bias (moderate risk)
3. Drawn from different populations and likely to introduce bias OR insufficient information to tell (high risk)

Bias due to error in exposure measurement

Measurement of exposure

1. Objective measurements from pre-existing records or baseline[1] physical or biological assessment blind to outcome status (low risk)
2. Objective measurements from pre-existing records or baseline[1] physical or biological assessment not blind to outcome status, OR structured interview (moderate risk)
3. Self-administered questionnaire OR insufficient information to tell (high risk)

Bias due to error in outcome measurement

Measurement of outcome

1. Outcome measurement unlikely to be influenced by exposure (low risk)
2. Objective outcome measurement possibly influenced by exposure (moderate risk)
3. Objective outcome measurement probably influenced by exposure OR self-reported outcome OR insufficient information to tell (high risk)

Was outcome of interest absent at the time to which the exposure refers?

1. Yes (low risk)
2. No but outcome unlikely to affect exposure measurement (moderate risk
3. No and outcome likely to affect exposure measurement OR insufficient information to tell (high risk)

Was follow-up long enough for outcome to occur as a consequence of measured exposure? (Requires prior specification of a sufficient follow-up period)

1. Yes (low risk)
2. No OR insufficient information to tell (high risk)

[1] Existing at or before baseline, where baseline is the time at which a participant is recorded to have entered the cohort or, if obtained after baseline, before onset of symptoms of the outcome or any likely effect of the developing outcome on the exposure

Bias due to non-participation

Participation rate

1. Participation rate in exposed cohort is ≤10 percentage points different from non-exposed cohort OR exposed and non-exposed are from the same cohort (low risk)
2. Participation rate in exposed cohort is >10 percentage points but <20 percentage points different from non-exposed cohort (moderate risk)
3. Participation rate in exposed cohort ≥20 percentage points different from non-exposed cohort OR insufficient information to tell (high risk)

Bias due to missing data

Completeness of follow-up

1. Active or passive follow-up of participants with methods for ascertainment of outcome and death clearly described AND with methods for ascertainment of emigration from population-at-risk clearly described or censoring at date of last follow-up OR there is a plausible estimate of >90% follow-up (low risk)
2. Active or passive follow-up with methods for ascertainment of outcome, death and emigration from population-at-risk not clearly described OR there is a plausible estimate of 70 – 90% follow-up (moderate risk)
3. Active or passive follow-up with methods for ascertainment of one or more of outcome, death or emigration not described OR there was probably <70% follow-up OR insufficient information to tell (high risk)

Accuracy of dates of outcome or censoring

1. Dates of outcome or censoring ascertained to within one year (low risk)
2. One or more of dates of outcome or censoring not ascertained to within one year OR insufficient information to tell (moderate risk)

Difference in follow-up between exposed and non-exposed

1. Follow-up methods are the same and likely to achieve the same completeness of follow-up in exposed and unexposed participants (low risk)
2. Completeness of follow-up in exposed and unexposed participants is unlikely to be the same but difference between the two is, or would be likely to be, small (<10%) (moderate risk)
3. Completeness of follow-up in exposed and unexposed participants is very unlikely to be the same and difference between the two is, or is likely to be, large (≥10%) OR insufficient information to tell (high risk)

Difference in missing data for exposure between those with or without the outcome

1. Difference in missing data for exposure <10 percentage points (low risk)
2. Difference in missing data for exposure ≥10 to <20 percentage points (moderate risk)
3. Difference in missing data for exposure ≥20 percentage points (high risk) OR insufficient information to tell (high risk)

Bias due to confounding

Comparability of exposed and non-exposed cohorts with respect to potentially important confounding variables (Requires prior specification of potentially important confounders)

1. Age and other potentially important confounders measured and controlled by design or in analysis (low risk)
2. Age and some but not all other potentially important confounders controlled by design or in analysis (moderate risk)
3. No potentially important confounders or only age controlled by design or in analysis OR insufficient information to tell (high risk)

Analysis bias

Covariates are appropriately included in statistical analysis models

1. Variables measuring the same underlying concept or lying in the same causal pathway ARE NOT included together as covariates in statistical analysis models (low risk)
2. Variables measuring the same underlying concept or lying in the same causal pathway ARE included together as covariates in statistical analysis models OR insufficient information to tell (high risk)

Overall rating

High risk of bias – high risk of bias in any domain

Moderate risk of bias – moderate or low risk of bias in all domains, no high risk domains

Low risk of bias – all domains low risk of bias, no moderate or high risk domains

List of abbreviations

APC	Adenomatous polyposis coli
ASAP	Atypical small acinar proliferation
ASGC	Australian Standard Geographic Classification (Australian Bureau of Statistics)
BCRA1	Breast cancer type 1 susceptibility gene
BCRA2	Breast cancer type 2 susceptibility gene
CI	Confidence interval
DALYs	Disability-adjusted life years
DRE	Digital rectal examination
ERSPC	European Randomized Study of Screening for Prostate Cancer
FP	False positive
G84E HOXB13	The G84E mutation of the *HOXB13*gene
GS	Gleason score
GSTP1	Glutathione S-transferase pi 1
HR	Hazard ratio
LPZ	Lateral peripheral zone
MBS	Medicare Benefits Schedule
MPZ	Mid-peripheral zone
MRI	Magnetic resonance imaging
ng/mL	Nanograms per millilitre
NHMRC	National Health and Medical Research Council
NND	Number needed to diagnosis
PCA3	Prostate cancer gene 3
PICO	Population, intervention, comparator, outcome (research question format)
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening
PSA	Prostate-specific antigen
RASSF1	Ras association (RalGDS/AF-6) domain family member 1
RCT	Randomised-controlled trial
RR	Relative risk
TP	True positive
WHO	World Health Organization