Prostate Cancer Foundation of Australia

Griffith UNIVERSITY

ECONOMIC MODELLING OF HEALTHCARE SERVICES FOR PROSTATE CANCER

APRIL 2016

MONOGRAPHS IN PROSTATE CANCER

OUR VISION, MISSION AND VALUES

Prostate Cancer Foundation of Australia (PCFA) is a broad based community organisation and the peak national body for prostate cancer in Australia.

We are dedicated to reducing the impact of prostate cancer on Australian men, their partners and families, recognising the diversity of the Australian community.

We do this by:

- Promoting and funding world leading, innovative research into prostate cancer
- Implementing awareness and advocacy campaigns and education programs for the Australian Community, health professionals and Government
- Supporting men and their families affected by prostate cancer through evidence-based information and resources, support groups and Prostate Cancer Specialist Nurses.

PCFA relies on the generosity of individuals, the community and partnerships to carry out our essential work.

ABOUT CAHE

The Centre for Applied Health Economics (CAHE) is a research centre located within the School of Medicine, Griffith University. Led by Professor Paul Scuffham, the Centre currently employs a team of health economists. In addition, associated with the Centre are Post-doctoral Fellows, PhD students, and an Associate Professor in Biostatistics.

Research and Key skill areas:

— High-quality health research relating to improved quality of life for Australian and international populations

— Contract research for government and industry to have a direct impact on health policy in Australia and internationally

— Education and training of higher degree research students and the workshops in Health Economics

— Methods of economic evaluation relating to health care interventions (pharmaceuticals, medical devices, health care programs)

— Health care financing including preferences and priority setting in health care

— Evaluation of health services and health policy

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ECONOMIC MODELLING OF HEALTHCARE SERVICES FOR PROSTATE CANCER

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LIST OF ACRONYMS & ABBREVIATIONS

ABS	Australian Bureau of Statistics
ADT	Androgen Deprivation Therapy
AU$	Australian Dollars
adv	Advanced
AIHW	Australian Institute of Health and Welfare
AR-DRG	Australian Refined Diagnosis-Related Group
AS	Active Surveillance
CI	Confidence Interval
CRPC	Castrate-Resistant Prostate Cancer
CRUK	Cancer Research UK
DRE	Digital Rectal Examination
EBRT	External Beam Radiation Therapy
ESPRC	European Randomized Study of Screening for Prostate Cancer
EV	Expected Value
GB/gb	Guided Biopsy
GI	Gleason Score
GP	General Practitioner
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
inc	Incremental
inf	Inferior To Current Practice
int	Intermediate
IQR	Interquartile Range
LYS	Life Years Saved
MR	Magnetic Resonance
MRGB	Magnetic Resonance-Guided Biopsy
MRI	Magnetic Resonance Imaging
mpMRI	Multiparametric Magnetic Resonance Imaging
MBS	Medicare Benefits Schedule
MSAC	Medical Services Advisory Committee
n/a	Not Applicable
NICE	National Institute for Health and Care Excellence
PBS	Pharmaceutical Benefits Scheme
PCa	Prostate Cancer
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
popn	Population
Prob	Probability
PSA	Prostate-Specific Antigen
QALYs	Quality-Adjusted Life Years
rad	Radiation
rel	Relative
SD	Standard Deviation
SEER	Surveillance, Epidemiology and End Results Program
sup	Superior to Current Practice
TRUS	Transrectal Ultrasound
tx	Treatment
UK	United Kingdon
US	United States of America
VCR	Victorian Cancer Registry
WTP	Willingness-to-Pay
yr	Year

EXECUTIVE SUMMARY

Health services and treatments for prostate cancer are rapidly changing as researchers and clinicians look for better ways to control this disease. Over 20,000 men are diagnosed with prostate cancer each year and there is an estimated 200,000 men currently living with this disease in Australia. Consequently, prostate cancer is common and exerts a substantial burden to men and families affected by it. It also presents an immense challenge to the health system for planning of future services and we need to better understand the healthcare resources used in prostate cancer diagnosis and treatment and their impact.

This report documents the development and construction of a generic economic model for the healthcare services involved in prostate cancer treatment. It also presents findings of descriptive analyses on the disease burden and three cost-effectiveness analyses. Specifically, the objectives of this project were to:

1. Build a generic economic model structure;
2. Populate the model with data estimates;
3. Validate the generic model internally and externally;
4. Undertake descriptive analyses of costs and patient outcomes; and
5. Undertake three cost-effectiveness analyses comparing strategies of interest with the status quo and integrating the generic model structure.

A large comprehensive model was constructed in the computer package *TreeAge Pro 2015 V2.* The model is a Markov health state transition model with 17 health states and centres around four key health states: 1) very low- or low-risk, 2) intermediate-risk, 3) high-risk to locally-advanced cancer, and 4) metastatic prostate cancer. There are health states for active treatments such as radiation, surgery, androgen deprivation therapy and for other management strategies such as active surveillance, watchful waiting, castrate-resistant prostate cancer and palliation. The lifetime model ensures that treatment of relapse or progression is dependent on patient characteristics and previous treatments. It also includes the probabilities, health utilities (similar to quality of life) and costs of treatment complications. Two clinicians validated the model structure and the model predictions have been externally validated using Australian and international epidemiological trends in prostate cancer mortality, costs and health utilities.

Key findings from analysing the generic model include:

- On average, each case of prostate cancer has an estimated lifetime cost to the health system of $26,646, with the majority of costs incurred in the few years after being diagnosed.
- The lifetime cost of prostate cancer is less expensive for low-risk disease $19,681 and increases linearly by disease severity up to a case of metastatic disease costing $45,477.
- For privately insured men, the estimated out-of-pocket costs to men over the long term were on average $9,150 but this is highly dependent on physician fees. Out-of-pocket costs will be substantially lower for men treated in the public system.
- The total estimated cost of prostate cancer treatment to the Australian health system in 2016 was $383.6 million rising to $543.9 million in 2025, an increase of 42%.
- For men diagnosed at age 65 years, age-adjusted survival was 87% at five years and 70% at 10 years.
- With consideration of quality of life impacts and side effects of treatment, the average quality-adjusted life years were 7.8 per case of prostate cancer (discounted).

The three cost-effectiveness analyses performed addressed the following research questions:

1. What is the cost-effectiveness of multiparametric magnetic resonance imaging (mpMRI) with or without magnetic resonance (MR)-guided biopsy in the diagnosis of prostate cancer compared with the status quo?
2. What is the cost-effectiveness of increased uptake of active surveillance in eligible men with prostate cancer compared with the status quo?
3. What parameters would constitute cost-effective prostate-specific antigen (PSA) based screening of asymptomatic men for early detection of prostate cancer?

The results of these analyses, including thorough sensitivity analyses to address uncertainty of parameters and structures, are summarised in Table 1. They show that PSA screening and mpMRI are generally not cost effective and these results are driven by the lack of benefit for patients rather than high costs. PSA screening, if limited to two infrequent screens in young men (50 years), would be cost-effective. Increased uptake of active surveillance is both cost-saving and beneficial to patients in terms of quality-adjusted life years gained; however, these health gains are relatively small over the longer term.

TABLE 1: SUMMARY OF COST-EFFECTIVENESS ANALYSIS FINDINGS

Intervention & comparator	Cost-effective	Probability of being cost-effective
1. mpMRI with/without MR-guided biopsy versus TRUS-guided biopsy	No	7.7%
mpMRI with/without MR- or TRUS- or TPUS-guided biopsy versus TRUS-guided biopsy	No	22.2%
2. Active surveillance: increased uptake versus current practice	Yes	63.9%
Active surveillance: increased uptake and partial uptake by men with intermediate risk cancers versus current practice	Yes	75.6%
Active surveillance: mpMRI selection to surveillance versus current practice	No	0.6%
3. PSA screening, starting age 60 years, maximum of 2 screens 4 years apart versus current practice	No	20.0%
PSA screening, starting age 50 years, maximum of 2 screens 4 years apart versus current practice	Yes	83.8%

mpMRI = multiparametric magnetic resonance imaging; MR-guided = magnetic resonance; PSA = prostate-specific antigen; TRUS = transrectal ultrasound

In summary, this large and detailed model of prostate cancer treatment from diagnosis to end-stage disease is operational and was adapted for three economic evaluations. The model uses contemporary sources and agrees well with observational data of prostate cancer in the UK and US giving confidence that the model is reliable. The main strength of this model is that it was designed and informed by high-quality clinical and economic evidence together with practising clinicians. This should ensure its relevance and currency in clinical practice. Health economics has a critical role in policy decisions for determining whether new treatments and services are cost-effective. This generic model is a flexible resource for assessing the cost-effectiveness of new and existing interventions in the management of prostate cancer.

1.0 PROJECT AIM & OBJECTIVES

The overall aim of this project was to provide health economic estimates of prostate cancer burden and the cost-effectiveness of a selection of existing and proposed new treatments or services for enhanced cancer control.

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The key project objectives were to:

1. Build a generic economic model structure;
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5. Undertake three cost-effectiveness analyses comparing strategies of interest with current practice and integrating the generic model structure.

The following sections of the report provide the methods and results of these tasks.

2.0 CONSTRUCTION OF GENERIC ECONOMIC MODEL FOR PROSTATE CANCER

2.1 MODEL DEVELOPMENT

Two literature reviews were undertaken at the outset of the project to: 1) identify Australian research on prostate cancer during the last 10 years; and 2) identify cost-effectiveness studies published on prostate cancer interventions during the last 15 years (see Appendix 1 for search details). These determined the current work that could inform the structure of our model and enabled an understanding of the Australian research into prostate cancer more broadly. Both searches provided guidance on the patterns of care provided to Australian men with prostate cancer, along with their patient outcomes. The economic studies undertaken were from any country and informed the structure of our model and the types of technologies tested. Clinical practice guidelines were reviewed to further understand the management options by risk stratification recommended from an international perspective [1-4].

2.2 MODEL STRUCTURE

A Markov health state transition cohort model was built in *TreeAge Pro 2015 V2.* The model describes the patterns of care for diseases over long periods where patients can move between different specified health states. Both the health system costs and patient outcomes were assigned to the different health states in the model. Patients move through the model and face different probabilities of treatment pathways and outcomes. In this case, the model is based around the risk or stages of prostate cancer according to the US National Comprehensive Cancer Network Guidelines (2015) [4].

There are 17 health states in the model starting at the point when a man has a confirmed diagnosis of prostate cancer. From here the first four health states are defined by clinical and test markers (i.e. tumour size (T), Gleason (Gl) scores and prostate-specific antigen (PSA)) as follows:

1. Very low and low risk (T1-T2a, Gl ≤6, PSA <10ng/ml);
2. Intermediate risk (T2b-T2c, Gl 7, PSA 10-20ng/ml);
3. High risk to locally advanced (T3-T4, Gl 8-10, PSA >20ng/ml);
4. Advanced disease (node positive, metastatic).

The model explicitly describes the health states that reflect typical treatments within the first two years after diagnosis when the majority of health care and resource use occurs. As shown in Figure 1, individuals will either receive curative treatments appropriate to the cancer stage or other management options that involve surveillance or palliative care. For very low and low-risk individuals, a proportion of men will undergo active surveillance or watchful waiting while the remaining will receive surgery or radiation (either external beam radiation therapy (EBRT) or brachytherapy). For intermediate and high-risk individuals, some men will undergo watchful waiting but most will receive active treatment. Major treatments in the first three health states include surgery and/or radiation if indicated, radiation alone or following androgen deprivation therapy. Treatment for advanced disease consists of androgen deprivation therapy or if the patient experiences disease progression, therapies for castrate-resistant prostate cancer such as hormone manipulation and first-line chemotherapy. At any health state, over time men may also die from causes other than prostate cancer.

There are eight health states that describe subsequent health states after the first year of diagnosis, including:

1. Post surgery (low risk);
2. Post surgery (intermediate to high risk);
3. Post radiation as first-line (low risk);
4. Post radiation as first-line (intermediate to high risk);
5. Post androgen deprivation therapy + radiation;
6. Post surgery + radiation;
7. Post first-line chemotherapy; and
8. Post second-line chemotherapy.

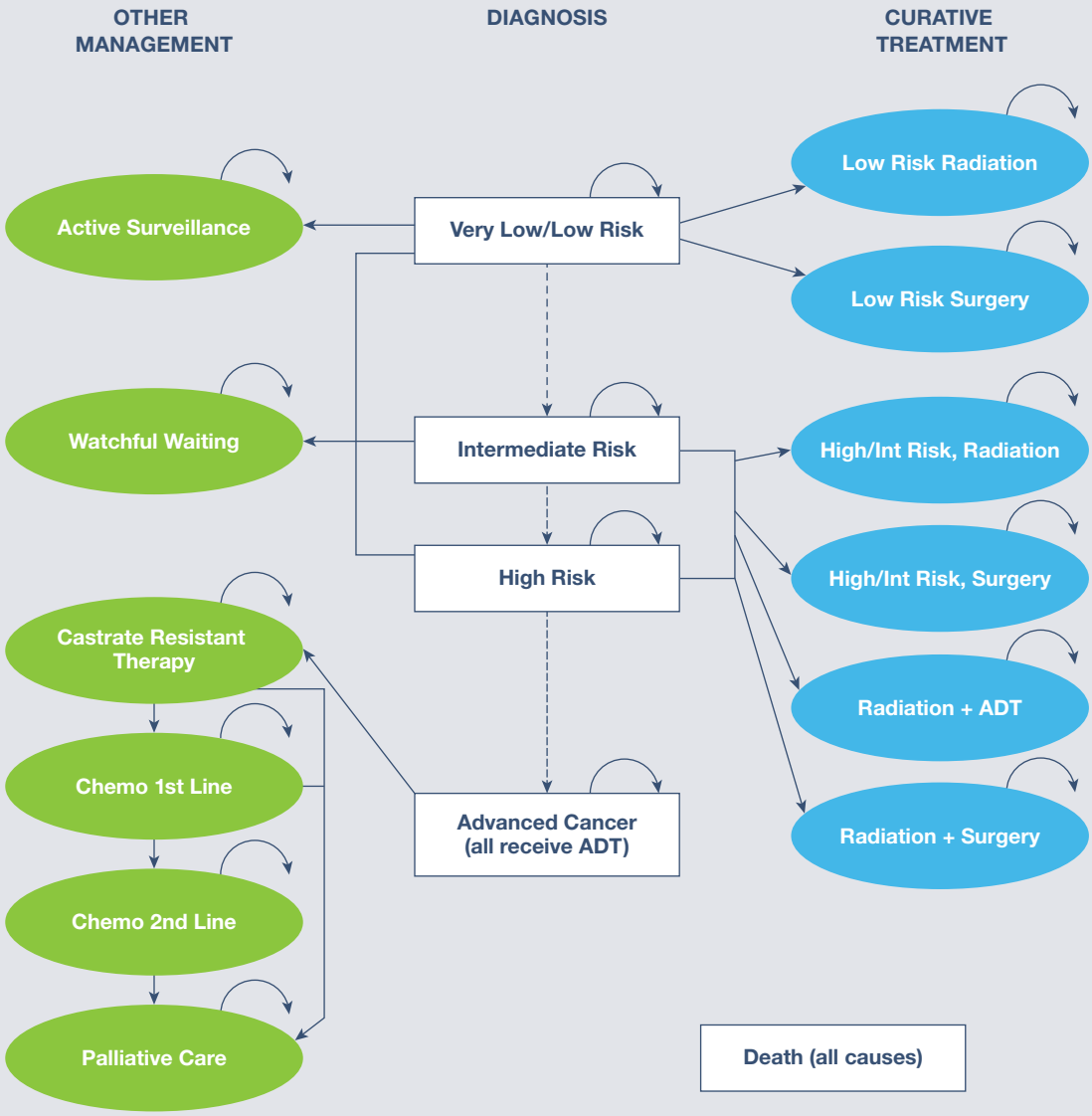
These health states describe the care options after the first year of diagnosis and treatment while preserving the history of their first year treatment. The various treatments have different probability values associated with progression or stable disease. The remaining health states are:

1. Castrate-resistant prostate cancer
2. Active surveillance
3. Watchful waiting
4. Palliative care
5. Death

Except for ‘death’ in which no further transitions occur, patients in the above health states will remain in these unless their cancer progresses and they move into the relevant options of active treatment, advanced disease or they die.

2.0 CONSTRUCTION OF GENERIC ECONOMIC MODEL FOR PROSTATE CANCER *(continued)*

Figure 1: Simplified schematic of generic economic model



Note: All boxes/ovals are health states in the model. The four central boxes under diagnosis are health states and include first-line treatment or management. Blue ovals are post-treatment health states where patients remain until death or disease progression occurs to increased risk states and subsequent management. The dashed lines indicate disease progression but this occurs (indirectly) following the treatment/management options. High risk disease includes 'locally advanced' disease also. Men can enter the death state at any time from any health state.

ADT = androgen deprivation therapy; Int = intermediate

2.3 MODEL INPUTS

KEY MODEL SPECIFICATIONS

A number of key decisions were made on the basic structure of the model. These are detailed in Table 2.

TABLE 2: KEY STRUCTURAL ASSUMPTIONS

Input	Value(s)	Rationale
Cohort age	67% of men are aged 55-75 years with a mean of 65 years. A normal distribution is applied.	Median age of men diagnosed with prostate cancer in Australia is 65 years, tested over various age cohorts.
Model duration	Lifetime, maximum is when men reach age 90 unless they die earlier	Lifetime to reflect long natural history of disease, and obtain long term outcomes/costs for ongoing therapies, model was tested over various durations
Discounting	5% costs and quality-adjusted life years, annually, life years remains undiscounted to reflect life expectancy	Standard practice for Australian cost-effectiveness. Undiscounted results are also presented.
Cycles	Annual	Practical for lifetime model duration and many inputs are annual.

The key outputs of the model include:

1. Health system costs;
2. Life years (survival); and
3. Quality-adjusted life years (QALYs).

The main categories of inputs in the model are broken down into probabilities, costs and utilities (similar to quality of life scores). These inputs are described in detail below.

PROBABILITIES

Probability values were obtained from a systematic search of literature and included various study types; meta-analyses, randomised controlled trials, observational studies, as well as studies identified through Australian and international registries. Where appropriate, systematic reviews and meta-analyses were preferred for studies reporting recurrence rates after different treatments [5-7], and high-quality studies reporting disease progression [8-11]. Table 3 summarises the final model transition probabilities with their values and sources. Where values were obtained for rates, such as mortality rates, these were converted into annual probabilities using the rate to probability formula; $1 - \exp^{-\text{rate} \times \text{time}}$.

COSTS

The perspective used to determine the costs was that from the health system and physician fees were used as a proxy for costs of magnetic resonance imaging (MRI) which are increasingly used but not reimbursed by Medicare. Hospital costing reports and national Medicare reports (via the Medicare Benefits Schedule and Pharmaceutical Benefits Scheme) were used to value these resources. Other key studies and clinical guidelines identified in the literature review were used to identify resource types used for a particular treatment (Table 4). Costs were adjusted for inflation where necessary into 2015 values.

Separately, costs were considered for those borne by patients and families for healthcare services. These included out-of-pocket expenses for all aspects of healthcare services, therapies and medicines received from the time of diagnosis onwards. Additional costs for travel, parking and accommodation expenses are omitted but these can also be particularly substantial for persons living in rural and remote areas [12].

Appendix 2 provides the values and sources used for the analysis of patient costs.

TABLE 3: TRANSITION PROBABILITIES IN THE MODEL

Model probabilities	Value	95% CI / range	Distribution [a]	Source
Initial diagnosis				
Probability of being diagnosed with very low to low-risk disease	29%	27%, 31%	Dirichlet (785;1201;647;91)	Evans (2013); Victorian Cancer Registry [13]
Probability of being diagnosed with intermediate-risk disease	44%	42%, 46%	Dirichlet (785;1201;647;91)	Evans (2013); Victorian Cancer Registry [13]
Probability of being diagnosed with high-risk to locally-advanced disease	24%	26%, 22%	Dirichlet (785;1201;647;91)	Evans (2013); Victorian Cancer Registry [13]
Probability of being diagnosed with advanced-disease (N1 or M1)	3%	2.5%, 3.5%	Dirichlet (785;1201;647;91)	Evans (2013); Victorian Cancer Registry [13]
Treatment modality				
Probability of no treatment (active surveillance or observation) in low-risk	41%	37%, 45%	Beta (299,437)	Evans (2013); Victorian Cancer Registry [13]
Probability of surgery in low-risk (of those treated)	68%	63%, 73%	Beta (291,134)	Evans (2013); Victorian Cancer Registry [13]
Probability of radiation in low-risk (of those treated)	1-68%	–	–	–
Probability of EBRT in low-risk (remainder are brachytherapy)	31%	23%, 39%	Beta (41,91)	Evans (2013); Victorian Cancer Registry [13]
Probability of no treatment (observation) in intermediate-risk	16%	13%, 19%	Beta (198,1003)	Evans (2013); Victorian Cancer Registry [13]
Probability of surgery in intermediate-risk (of those treated)	59%	56%, 62%	Dirichlet (579;76;253;76)	Evans (2013); Victorian Cancer Registry [13]
Probability of surgery and radiation in intermediate-risk (of those treated)	8%	6%, 10%	Dirichlet (579;76;253;76)	Evans (2013); Victorian Cancer Registry [13]
Probability of radiation in intermediate-risk (of those treated)	26%	23%, 29%	Dirichlet (579;76;253;76)	Evans (2013); Victorian Cancer Registry [13]
Probability of EBRT in intermediate-risk (remainder are brachytherapy)	62%	54%, 68%	Beta (139,84)	Evans (2013); Victorian Cancer Registry [13]
Probability of ADT and radiation in intermediate-risk (of those treated)	8%	6%, 10%	Dirichlet (579;76;253;76)	Evans (2013); Victorian Cancer Registry [13]
Probability of no treatment in high-risk & locally-advanced	14%	11%, 17%	Beta (80,495)	Evans (2013); Victorian Cancer Registry [13]
Probability of surgery in high-risk (of those treated)	38%	33%, 43%	Dirichlet (179;51;76;166)	Evans (2013); Victorian Cancer Registry [13]
Probability of surgery and radiation in high-risk (of those treated)	11%	8%, 14%	Dirichlet (179;51;76;166)	Evans (2013); Victorian Cancer Registry [13]
Probability of radiation in high-risk (of those treated)	16%	13%, 19%	Dirichlet (179;51;76;166)	Evans (2013); Victorian Cancer Registry [13]
Probability of ADT and radiation in high-risk (of those treated)	35%	30%, 40%	Dirichlet (179;51;76;166)	Evans (2013); Victorian Cancer Registry [13]
Treatment complications				
Probability of erectile dysfunction due to radiation	33%	25%, 41%	Beta (40,83)	Smith (2009); after adjusting for baseline erectile dysfunction [14]
Probability of erectile dysfunction due to surgery	50%	46%, 54%	Beta (489, 492)	Smith (2009); after adjusting for baseline erectile dysfunction [14]
Probability of erectile dysfunction due to ADT	34%	22%, 46%	Beta (21,40)	Smith (2009); after adjusting for baseline erectile dysfunction [14]
Probability of incontinence due to radiation	2.4%	0.4%, 4.4%	Beta (22,469)	Smith (2009); after adjusting for baseline incontinence [14]
Probability of incontinence due to surgery	10%	8%,12%	Beta (100,881)	Smith (2009); after adjusting for baseline incontinence [14]

Model probabilities	Value	95% CI / range	Distribution [a]	Source
Recurrence and progression[b]				
Probability of recurrence after 1st line surgery in low-risk	1%	0.5%, 2%	Beta (220,1981)	Mullins (2012); cohort (1992-2011), 10% recurred in 15 years [10]
Probability of recurrence after radiation treatment as 1st line in low-risk	2%	0.5%, 3.5%	Beta (3555,14221)	Grimm (2012) and Cooperberg (2013); 20% recurrence in 10 years [8, 9]
Probability of recurrence after surgery in intermediate to high-risk	2.4%	0.5%, 4.5%	Beta (355,785)	Mullins (2012); cohort (1992-2011), 31% recurred in 15 years [10]
Probability of recurrence after 1st line radiation in intermediate and high-risk	4%	2%, 6%	Beta (2211,4107)	Grimm (2012) and Cooperberg (2013); 35% recurrence in 10 years [8, 9]
Probability of recurrence after ADT and radiation	4%	2%, 6%	Beta (639,1122)	A meta-analysis of six studies by Zhou (2013); around 36% had recurrence over 10 years [7]
Probability of recurrence after surgery plus radiation	6%	4%, 8%	Beta (222,600)	A meta-analysis by Thompson (2013) of the three randomised trials SWOG 8794, EORTC22911, and ARO 96-02; around 27% had recurrence in 5 years [6]
Probability of recurrence as advanced disease following surgery in intermediate to high-risk patients	1%	0.5%, 1.5%	Beta (131,993)	Mullins (2012); around 10% of intermediate-risk and 25% of high-risk patients developed metastatic disease over 15 years [10]
Probability of recurrence as advanced disease following radiation in intermediate and high-risk patients	2%	1%, 3%	Beta (311,1290)	Zelefsky (2008); around 30% high-risk and 10% of intermediate-risk patients developed metastases after radiation [11]
Probability of progression to CRPC in advanced disease	23%	20%, 26%	Beta (663,741)	From Ross (2008); 300/553 (54%) patients progressed in 36 months [15]
Probability of symptomatic metastases with CRPC	95%	92%, 98%	Beta (247,13)	Small (2004); around 95% of patients had metastatic disease confirmed by imaging [16]
Probability of progression on surveillance program	9%	7%, 11%	Beta (70,731)	From the meta-analysis by Simpkin (2015) of 26 registries; the annual probability of progression was 8.8% [5]
Probability to develop symptoms on observation	3%	2%, 4%	Beta (99,162)	Bill-Axelson (2014); around 38% of the patients on observation developed metastatic disease over 18 years [17]
Probability of progression after 1st line chemotherapy	24%	20%, 30%	Beta (127,208)	TAX 327 Study by Tannock (2004); 38% progressed over 21 months [18]
Probability of progression after 2nd line chemotherapy	75%	70%, 80%	Beta (598,199)	de Bono (2011); 75% of the patient on abiraterone progressed in 12 [19]

Model probabilities	Value	95% CI / range	Distribution [a]	Source
Mortality[b]				
Probability of age related mortality	Table	–	Age dependent mortality	ABS life tables
Relative mortality rate from localised disease (including locally-advanced)	101%	100%, 102%	Normal (1.01,0.005)	SEER data from the US, 100% survival in 5 years, 99% in 10 years relative to men without prostate cancer
Probability of death from advanced disease	22%	19%, 25%	Beta (1245,1043)	Prostate Cancer Trialists' Collaborative Group meta-analysis; 71% died in 5 years [20]
Probability of death after 1st line chemotherapy	28.9%	24%, 34%	Beta (166,169)	In TAX 327 Study by Tannock (2004); 50% of Docetaxel+prednisone patients died in 2 years [18]
Probability of death after 2nd line chemotherapy	42%	37%, 47%	Beta (333-464)	de Bono (2011); 42% of the patients on abiraterone died in 12 months [19]

ABS = Australian Bureau of Statistics; ADT = androgen deprivation therapy; CI = confidence interval; CRPC = castrate-resistant prostate cancer; EBRT = external beam radiation therapy; SEER = Surveillance, Epidemiology and End Results Program

[a] Distributions are assigned to the variables to account for variation. Different distributions reflect the nature of certain variables and beta distributions were assigned to probabilities and utilities, gamma distributions to costs and Dirichlet distributions to a set of treatment probabilities for one branch. The Dirichlet distribution allows for univariate sensitivity analyses while preserving the proportional probabilities of the remaining values in that set so that the total probability does not exceed 1.0 for the set.

[b] Rates were converted into annual probabilities using the rate to probability formula; 1 – exp –rate x time

TABLE 4: HEALTHCARE COSTS IN THE MODEL

Item	Value	95% CI / range	Distribution	Source and calculation
Prostate-specific antigen test	$43/test	Fixed	–	MBS items 66660 and 73928 www.mbsonline.gov.au
Urology consultation and digital rectal examination	$86/visit	Fixed	–	MBS Item 104
Ultrasound guided biopsy	$700/procedure	Fixed	–	MBS items 37219, 55600,72825, antibiotic prophylaxis and complications
Testosterone level	$30.5/test	Fixed	–	MBS item 66695
Anti-androgen	$52/2weeks	Fixed	–	Biclutamide 50mg tab. PBS monthly price for 28 tablets
Medical androgen deprivation therapy	$4,436/year	Fixed	–	Leuprorelin acetate 22.5mg injection every three months or goserelin 10.8mg every three months. PBS monthly price for both is $1109/3months.
Active surveillance in Year 1	$1,044/year	Fixed	–	2 urology visits, four PSA tests, one biopsy
Active surveillance after Year 1	$608/year	Fixed	–	2 urology visits, two PSA tests, biopsy every two years
Observation (watchful waiting)	$193.5/year	Fixed	–	1 to 2 urology visits and PSA tests
Follow-up after treatment for localised disease	$155/year	Fixed	–	2 urology visits, four PSA tests, one biopsy
Follow-up with androgen deprivation therapy	$465/year	Fixed	–	2 urology visits, two PSA tests, biopsy every two years
Recurrence workup	$1,176/workup	Fixed	–	1 to 2 urology visits and PSA tests
Bone scans	$700/image	$500, $1000	Gamma (12,0.02)	MBS item 61421
Second line chemotherapy	$4,500/month	$3,500, $5,500	Gamma (20,0.004)	Abiraterone 1g daily (4 tablets of 250mg), cost per month = $3,600. Cabazitaxel 25mg/m2 (for BSA 1.8m2), cost per month = $5,916. Enzalutamide capsules, cost per month $3,700 Average monthly cost = $4,500.
Treating incontinence	$546/year	Fixed		Continence Aids Payment Scheme in Australia
Radical prostatectomy	$14,840	$12,800, $16,800	Gamma (55,0.004)	MSAC Application 1089.1 [21]
External beam radiation therapy	$13,680	$11,680, $15,680	Gamma (40,0.003)	MSAC Application 1158. Assuming the same number of fractions for adjuvant treatment [22]
Low-dose rate brachytherapy	$13,143	$11,143, $15,143	Gamma (43,0.003)	MSAC Application 1089.1 [21]
Palliative care	$33,000/year	$28,000, $38,000	Gamma (44,0.001)	Yabroff (2008); the cost for the last 12 months of prostate cancer treatment in USA was $33,000; (approximate) [23]
Supportive care for androgen deprivation therapy	$7,000/year	$6,000, $8,000	Gamma (49,0.007)	Includes zoledronic acid at 4mg every 3 to 4 weeks ($450; PBS DPMQ) + calcium and vitamin D ($30/month) +dual-energy x-ray absorptiometry scan at $102 (MBS item 12306). Total per year = $7000
First-line chemotherapy	$350/cycle	$300, $400	Gamma (49,0.1)	Cost of docetaxel 75mg/m2 + prednisone 5mg, for BSA of 1.8m2 every 3 weeks; the cycle cost = $200 (PBS) + $65 administration cost (MBS item 13915) + $5 premedication cost (dexamethasone tablets) + $20 blood test + $50 complication cost (febrile neutropenia in 3% of patients at $ 1,700 per episode)

BSA = body surface area; CI = confidence interval; DPMQ = dispensed price for maximum quantity; MBS = Medicare Benefits Schedule; MSAC = Medical Services Advisory Committee; PSA = prostate-specific antigen;
PBS = Pharmaceutical Benefits Scheme

2.0 CONSTRUCTION OF GENERIC ECONOMIC MODEL FOR PROSTATE CANCER *(continued)*

UTILITIES

Health utilities are similar to health-related quality of life scores but specifically used in economic evaluations. The scores range from 0 to 1 with 0 representing death and 1 representing best possible health status. The utility scores or weights are applied to survival to obtain the outcome 'quality-adjusted life years' or QALYs. In the model, health utilities are applied to most health states and also disutilities are used for treatment complications. Table 5 provides details on the health utilities used in the model.

The literature review identified several key studies that reported utility weights for relevant health states for patients with prostate cancer. The pivotal study by Stewart et al. 2005 [24] provided utilities (using the standard gamble approach) from 162 men aged 60 years and over (52% of patients were diagnosed with prostate cancer). A systematic review and meta-analysis in 2007 [25] summarised the published evidence on health utilities for outcomes for prostate cancer.

TABLE 5: HEALTH UTILITIES IN THE MODEL

Health state	Value	95% CI / range	Distribution	Source
Low-risk disease	0.84	0.80, 0.88	Beta (281,54)	Stewart (2005) and Stewart (2012) [26, 27]
Intermediate-risk disease	0.81	0.75, 0.87	Beta (138,32)	Stewart (2005) and Stewart (2012) [26, 27]
High-risk to locally-advanced disease	0.71	0.65, 0.77	Beta (162,66)	Stewart (2005) and Stewart (2012) [26, 27]
Advanced disease	0.67	0.61, 0.73	Beta (164,81)	Stewart (2005) and Stewart (2012) [26, 27]
Castration resistant prostate cancer	0.40	0.30, 0.50	Beta (38,57)	Hatoum (2013) and Bayoumi (2000) [28, 29]
Chemotherapy treatment	0.40	0.30, 0.50	Beta (38,57)	Hatoum (2013) and Bayoumi (2000) [28, 29]
Palliative care	0.40	0.30, 0.50	Beta (38,57)	Hatoum (2013) and Bayoumi (2000) [28, 29]
Observation (Watchful waiting)	0.80	0.77, 0.83	Beta (141,35)	Australian norms for age >75 years, 0.85 in Clemens (2014) [30]
Active surveillance	0.85	0.83, 0.87	Beta (1083,191)	Australian norms for age 55-65 years, 0.85 in Clemens (2014) [30]
Disutility from erectile dysfunction	0.05	0.03, 0.07	Gamma (25,500)	From Cooperberg (2013), disutility was 0.1 in two years [8]
Disutility from incontinence	0.10	0.05, 0.15	Gamma (4,40)	From Cooperberg (2013), disutility was 0.2 in two years [8]

CI = confidence interval

2.4 MODEL VALIDATION

The model was modified several times to improve the integrity of the key options but ensuring its efficiency. In-depth checking of all pathways occurred with two practising urologists. This provided face validation of the current structure, confirmed current Australian practice and resolved questions around best practice in Australia. Australian physicians adhere to the US practice guidelines by the National Comprehensive Cancer Network. Our model is currently based on these 2015 updated international guidelines [4].

The model was externally validated to ensure it produced outputs that are observed in other sources. This was achieved first for mortality data and visual assessment of survival curves by all men with prostate cancer and by severity of disease. Table 6 provides details on the survival proportion each year as men age in the general Australian population versus the men in the model with prostate cancer (all risk stages). These figures are illustrated in survival curves in Figure 2. The findings show that for men diagnosed with prostate cancer at age 65 years, the model predicts 5-year survival, relative to all men of the same age, at 96.6%, 10-year survival at 90.1% and 20-year survival at 78.3%.

TABLE 6: SURVIVAL PERCENTAGE OF MEN IN GENERAL POPULATION VERSUS MODEL POPULATION, BY AGE

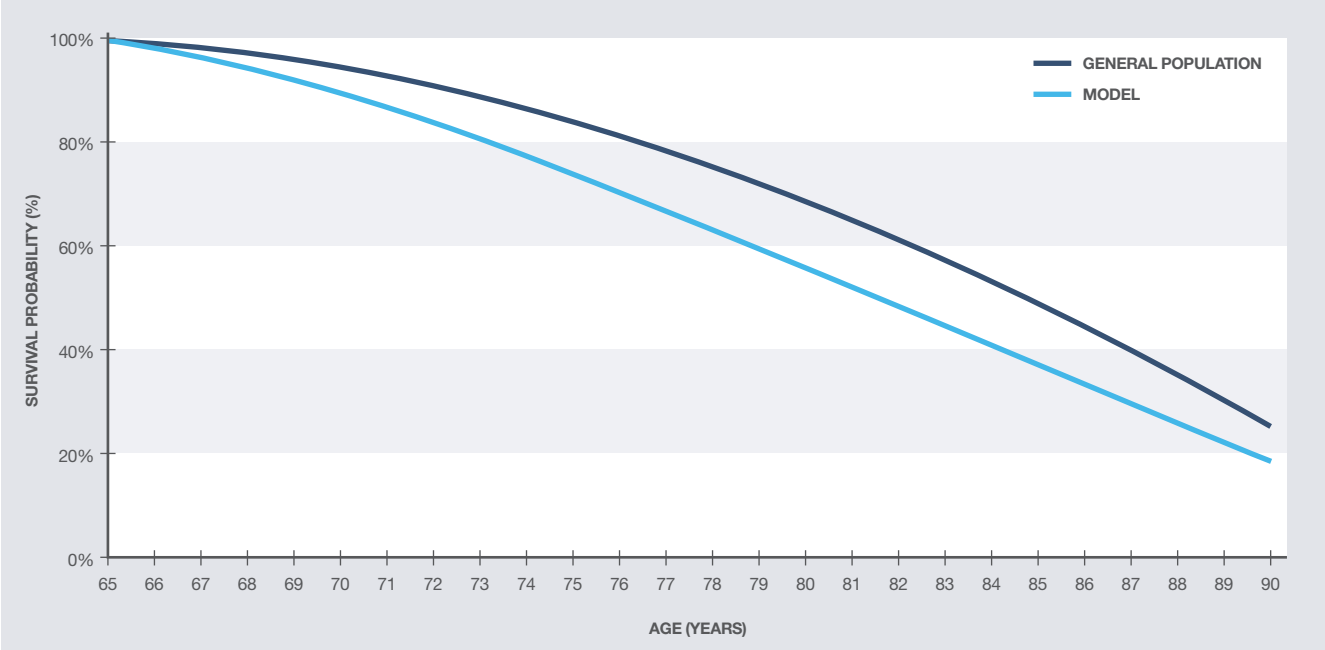
Male age	Survival in Australian men (ABS)[a] (men in general population)	Survival predicted by model (men with prostate cancer)	Relative survival, %
65	1	1	
66	0.989098	0.984612	99.5%
67	0.977192	0.968734	99.1%
68	0.964178	0.949564	98.5%
69	0.949978	0.927566	97.6%
70	**0.934498**	**0.903029**	**96.6%**
71	0.917683	0.876257	95.5%
72	0.899430	0.847548	94.2%
73	0.879681	0.817204	92.9%
74	0.858335	0.785456	91.5%
75	**0.835253**	**0.752470**	**90.1%**
76	0.810287	0.718371	88.7%
77	0.783255	0.682776	87.2%
78	0.754021	0.646384	85.7%
79	0.722446	0.609451	84.4%
80	**0.688439**	**0.572026**	**83.1%**
81	0.651990	0.534111	81.9%
82	0.613120	0.495736	80.9%
83	0.572013	0.456993	79.9%
84	0.528908	0.418045	79.0%
85	**0.484183**	**0.379140**	**78.3%**
86	0.438350	0.340597	77.7%
87	0.392072	0.302837	77.2%
88	0.346147	0.266329	76.9%
89	0.301433	0.231555	76.8%
90	0.255000	0.198955	78.0%

ABS = Australian Bureau of Statistics, 3302.0.55.001 - Life Tables, States, Territories and Australia, 2011-2012

[a] Rates were converted into annual probabilities using the rate to probability formula; 1 – exp $^{-\text{rate x time}}$

2.0 CONSTRUCTION OF GENERIC ECONOMIC MODEL FOR PROSTATE CANCER *(continued)*

Figure 2: Survival curves for men in general population vs men with prostate cancer



ABS = Australian Bureau of Statistics, 3302.0.55.001 - Life Tables, States, Territories and Australia, 2011-2012

A comparison of the modelled survival estimates and external sources of survival data in men with prostate cancer is provided in Table 7. The relative survival rate is thought to be a better indicator of the impact of prostate cancer because it recognises that men will die of other diseases in the general population. When the relative survival rate is over 100%, it indicates that men are dying of other diseases more frequently than prostate cancer.

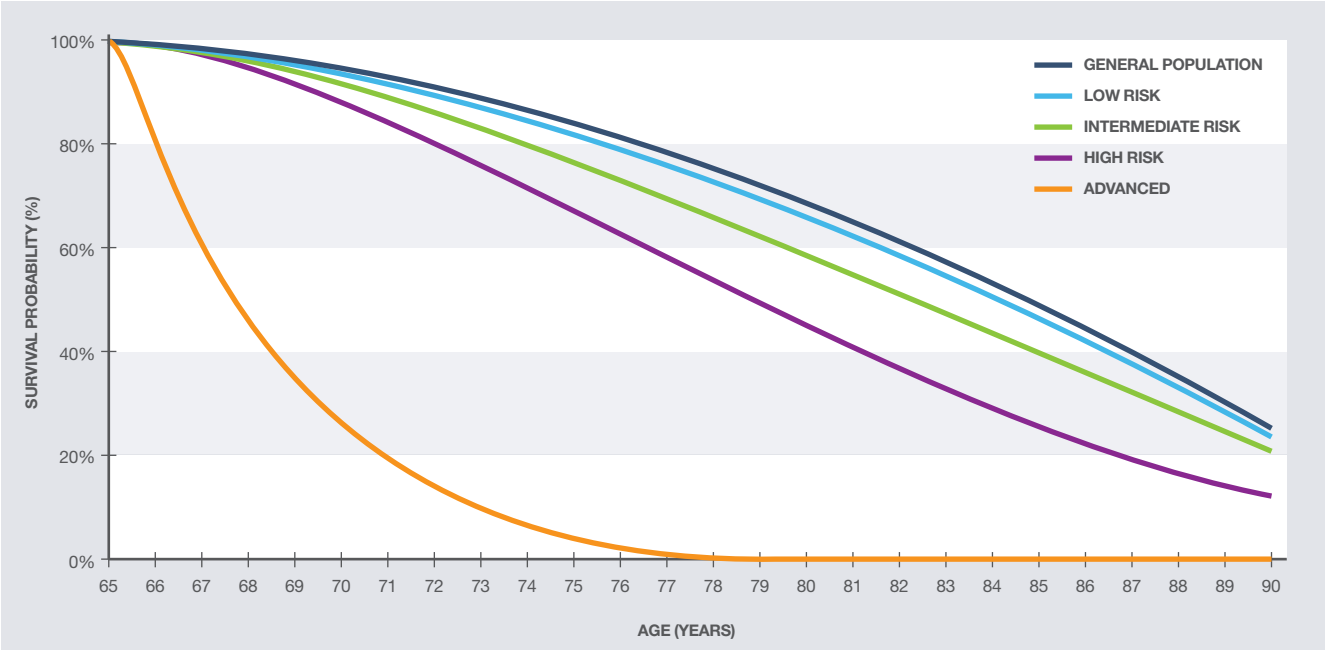
TABLE 7: COMPARISON OF SURVIVAL ESTIMATES FROM THE MODEL AND EXTERNAL SOURCES, ALL STAGES

Survival	Model 2015-2025	AIHW [31] 2007-2011	SEER (US) 2007-2011 [32]	SEER (US) [33] 1973-2000	CRUK (UK) 2006-2010	Canada 2006-2008
1-year relative	99.3%	98.3%	–	–	94%	–
5-year relative	95.5%	93.2%	100%	101.2%	99%	96%
10-year relative	87.9%	–	99%	99.0%	94%	–
Stage of cancer, 5-year relative survival					**2002-2006**	
Low risk	99.7%	n/a	Local = 100%	Stage I = 106.1%	Stage I = 112%	Local = 100%
Intermediate risk	98.5%	n/a	–	Stage II = 105.1%	Stage II = 99%	–
High risk	95.9%	n/a	Regional = 100%	Stage III & IV = 92.3%	Stage III = 93%	Regional = 100%
Advanced	35%	n/a	Advanced = 28%	Advanced = 31.3%	Stage IV = 30%	Advanced = 31%

Data sources: AIHW 2014 [31], SEER US [32], SEER US [33], Cancer Research UK [34], Canada Cancer Society[35]
AIHW = Australian Institute of Health and Welfare; CRUK = Cancer Research UK; n/a = not applicable; SEER = Surveillance, Epidemiology, and End Results Program;
When the relative survival rate is over 100%, it means men are dying of other diseases more frequently than prostate cancer.

The modelled survival estimates are similar or slightly higher than those from external sources. This seems appropriate as the model reflects estimated survival going forward in time and should reflect improvements gained from recently approved treatments in advanced disease but would not be revealed in the external sources of past survival. However, the modelled estimates are not so different that the incremental differences are not implausible. Stage-specific survival curves predicted by the model are presented in Figure 3.

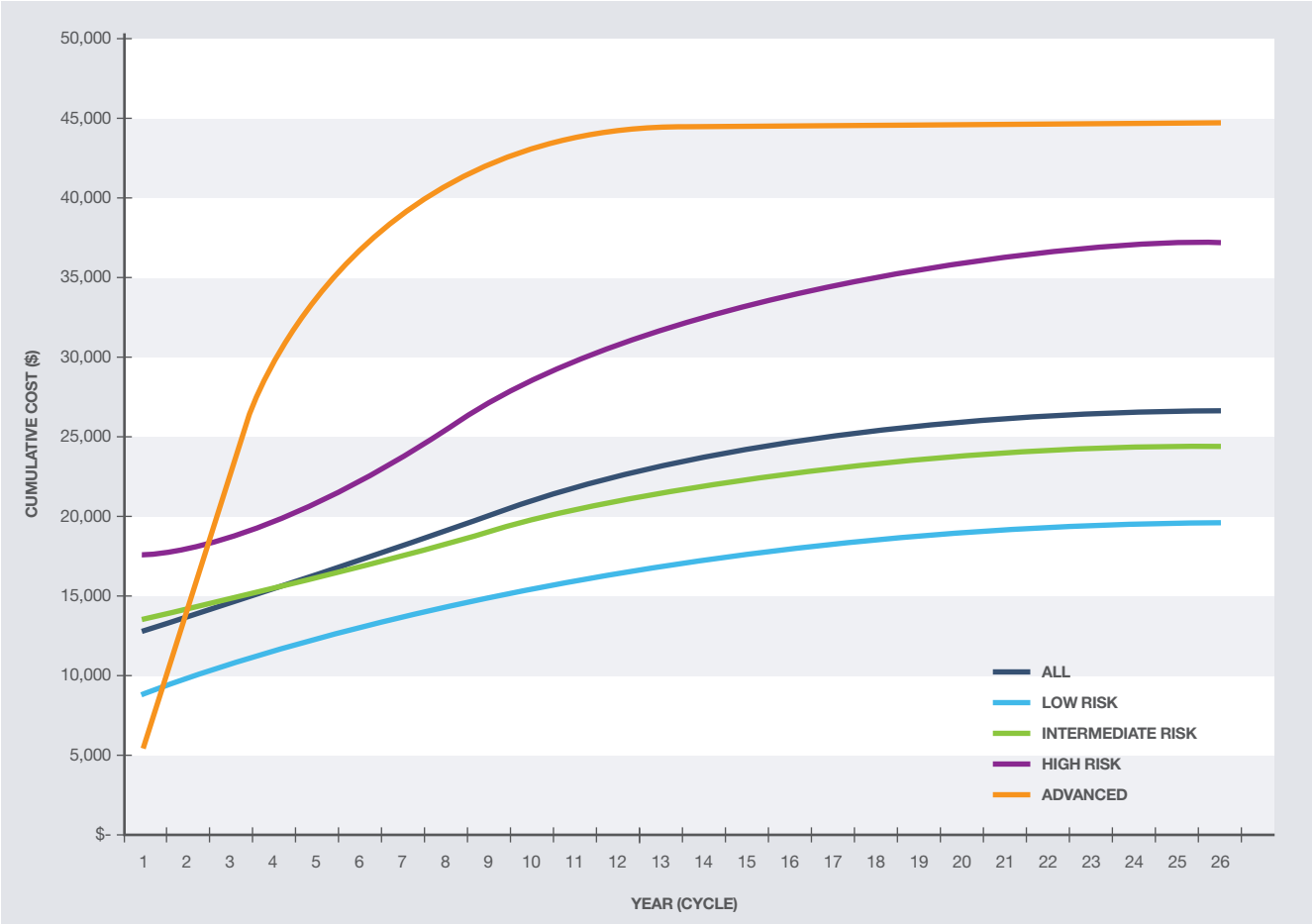
Figure 3: Stage-specific survival curves predicted from model for men aged 65 years



2.0 CONSTRUCTION OF GENERIC ECONOMIC MODEL FOR PROSTATE CANCER *(continued)*

Figure 4 illustrates the costs predicted by the model for prostate cancer overall and by cancer risk. This shows that costs mostly accumulate in the early years of the disease and differ depending on stage of disease with costs highest for advanced cancer and lowest for low-risk disease.

Figure 4: Cumulative prostate cancer cost from a health system perspective (AU$ 2015)



Costs were considered for two time horizons; 1) the first 12 months from diagnosis and 2) lifetime costs of prostate cancer. The model predicted that the average cost for the first year of treatment was AU$13,264 for all stages. In another Australian study, the per-patient direct health care cost was 2015 AU$20,118 relating to 2005 resources [36]. The cost for the first year of treatment from two Canadian studies [37, 38] that were 2004 CAD 8,636 (2015 AU$13,772) up to 2004 CAD 17,067 (2015 AU$23,939). Two studies from the US [23, 39] reported higher costs in the first year of treatment between USD 9,000-10,612 (2015 AU$ 17,412 to $20,531). The model predicted that the cumulative lifetime cost of cancer treatment for all stages was AU$26,646.

Figure 4 illustrates the cumulative cost for each disease stage over the model duration, and this confirms the concentration of costs in the early years but also the higher-cost treatments for more advanced disease, in agreement with other findings [37, 40].

The health utilities used in the model were validated with those obtained from the Victorian Cancer Registry (patient-level data, unpublished) where health utilities were collected on the SF-6D utility tool (see Table 8). The values used in the model were derived from the standard gamble method and so some differences may be expected due different populations and utility survey tools.

TABLE 8: COMPARISON OF THE UTILITIES IN OUR MODEL WITH VICTORIAN CANCER REGISTRY DATA

	Model		Victorian Cancer Registry data		
Health state	**Value**	**95% CI**	**n**	**Value**	**95% CI**
Low-risk disease	0.84	0.80, 0.88	1743	0.81	0.81, 0.82
Intermediate-risk disease	0.81	0.75, 0.87	3071	0.80	0.80, 0.81
High-risk to locally-advanced disease	0.71	0.65, 0.77	1595	0.77	0.77, 0.78
Advanced disease	0.67	0.61, 0.73	203	0.72	0.70, 0.74
Castration resistant prostate cancer	0.40	0.30, 0.50	26	0.61	0.56, 0.67
Chemotherapy treatment	0.40	0.30, 0.50	57	0.63	0.59, 0.67
Palliative care	0.40	0.30, 0.50	84	0.68	0.64, 0.71
Observation (watchful waiting)	0.80	0.77, 0.83	246	0.75	0.74, 0.77
Active surveillance	0.85	0.83, 0.87	1219	0.81	0.80, 0.82
Disutility from erectile dysfunction	0.05	0.03, 0.07 [a]	–	–	
Disutility from incontinence	0.10	0.05, 0.15 [a]	–	–	

CI = confidence interval; VCR = Victorian Cancer Registry data
Bold = *VCR values are substantially different*
[a] *Estimated range*

The estimates for the utilities derived from the SF-6D tool (using selected items from the SF-36 survey) were very similar to six values in our model and were mostly within the 95% confidence interval (CI) ranges specified in the model. Most importantly, the values for the first four key health states of disease risk are consistent between the two sets of values. However, the mean utility estimates for the health states chemotherapy, castrate-resistant prostate cancer and palliative care were higher in the Victorian registry data than those used in the model by approximately 0.20. The reason for this variation is unknown. In order to remain consistent with estimates from the literature, the model used estimates derived from the Hatoum et al. (2013) and Bayoumi et al. (2000) studies [28, 29].

2.5 ANALYSES

The model was analysed by an expected value analysis. The probabilities, costs, survival and health utilities were aggregated across all branches and mean values derived. Due to the model predicting outcomes into the future, across the remaining lifetime, 'discounting' was applied. This accounts for time preferences and brings values back to the present. Discounting is standard practice for long-term economic modelling (beyond one year) but it means that programs where benefits that occur in the future may be penalised. Therefore, undiscounted results are important also for screening and prevention programs.

One-way sensitivity analyses were performed to determine the key variables of the economic model and their influence on the stability of the results in the base case. This was achieved by re-analysing the model with one variable varied each time, usually over the 95% confidence limit or other plausible range. In multivariate analyses, probabilistic sensitivity analyses were undertaken and this involved random sampling of all model inputs simultaneously from their assigned distributions. This technique addresses parameter uncertainty and the stability of the base case results. Distributions were assigned to reflect uncertainty with the values in the model. Beta distributions were assigned to probabilities and utilities, gamma distributions to costs and *Dirichlet* distributions were assigned to a set of treatment options. A total of either 1000 or 5000 Monte Carlo simulations were performed and the means and standard deviations extracted.

3.0 DESCRIPTIVE ANALYSES

3.1 KEY OUTCOMES

Key outcomes of the model are provided in Table 9 for mean costs, mean QALYs and mean life years (or survival), and by different age cohorts and disease stage. The model predicted mean QALYs of 7.8 (standard deviation (SD) 1.7). Clinically-localised disease (including locally-advanced cancer) represented 97% of the all new cases and had an average treatment cost of $26,109 (SD $4,730) over a lifetime. This contrasts with advanced disease representing 3% of new cases with an average cost of $45,477 (SD $3,697) over remaining life. The highest cumulative cost for advanced disease was $45,477 followed by high-risk $37,349, intermediate-risk $24,442, and low-risk disease $19,681.

TABLE 9: KEY OUTCOMES OF THE ECONOMIC MODEL OVER REMAINING LIFE [a]

	Mean cost (SD)	Mean QALYs (SD)	Mean life years (SD)
Base case (discounted)	**$26,646 ($4,414)**	**7.8 (1.7)**	**n/a**
Base case, undiscounted	$34,794 ($7,898)	12.6 (4.1)	16.4 (0.1)
Cohorts with different mean age [b]:			
50 years mean	$32,400 ($1,717)	10.0 (0.2)	24.9 (0.3)
55 years mean	$30,824 ($1,764)	9.5 (0.2)	22.1 (0.2)
60 years mean	$28,989 ($1,647)	8.8 (0.2)	19.3 (0.1)
70 years mean	$24,278 ($1,384)	6.9 (0.1)	13.4 (0.1)
75 years mean	$20,785 ($1,273)	5.7 (0.1)	10.4 (0.04)
80 years mean	$18,153 ($1,122)	4.3 (0.1)	7.5 (0.02)
Stage of disease			
Localised cancer	$26,109 ($4,730)	8.0 (1.8)	16.8 (0.1)
Very low / low risk	$19,681 ($4,639)	9.0 (2.2)	18.1 (0.1)
Intermediate risk	$24,442 ($4,477)	8.3 (1.8)	17.0 (0.1)
High risk to locally advanced	$37,349 ($5,212)	6.6 (1.2)	14.7 (0.4)
Advanced cancer	$45,477 ($3,697)	1.7 (0.1)	4.0 (0.1)

n/a = not applicable; SD = standard deviation; QALYs = quality-adjusted life years

[a] All figures are from probabilistic sensitivity analysis outcomes from 1000 Monte Carlo simulations.

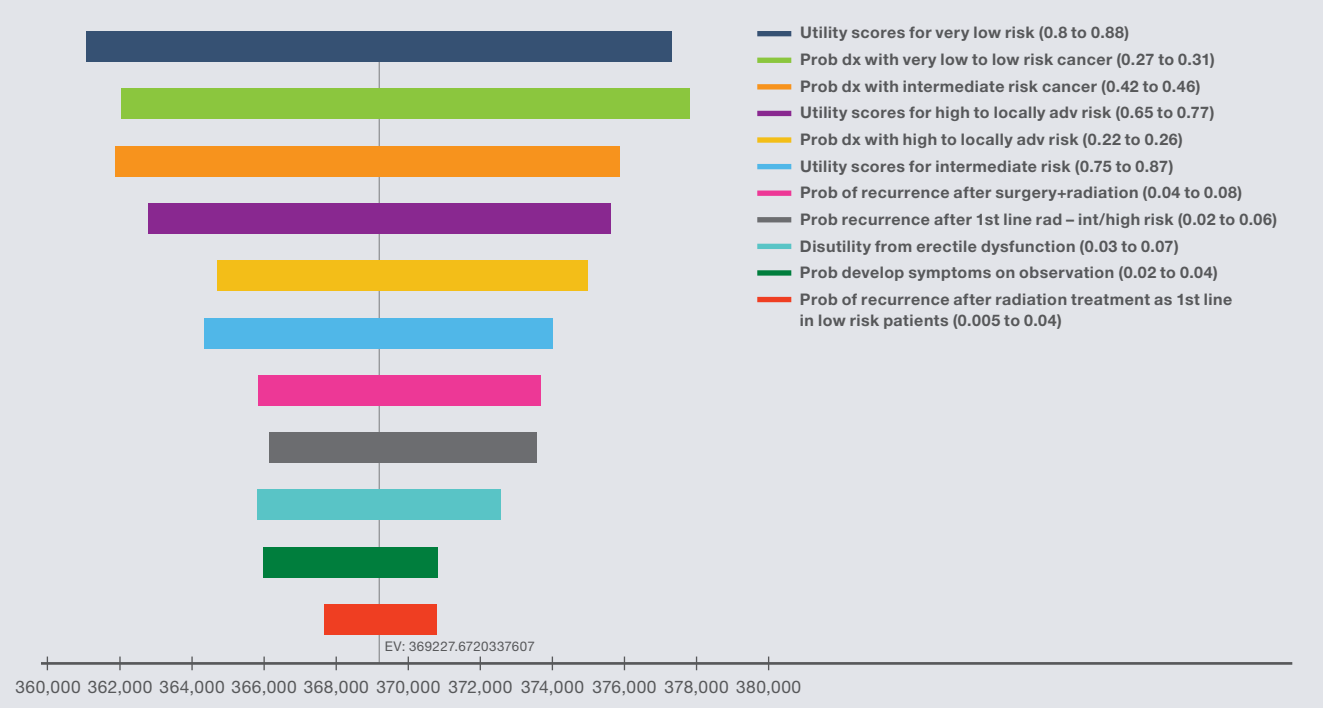
[b] The base case uses a mean of age 65 years.

The results in Table 9 indicate that the health system cost for each case of prostate cancer, is on average $26,646 per case. The cost per case is more expensive as disease becomes more advanced and this is directly a function of more therapies and more expensive therapies associated with progressed disease. Costs are somewhat higher for men who are younger; however, these should be viewed with caution as with any lifetime model, costs are heavily dependent on longer survival and the ongoing monitoring costs accruing with age. Currently the model has no option for exiting follow-up care and men will be followed-up for their remaining life. It is uncertain if this would be the case in all men. At all ages (mostly over 40 years), men can be diagnosed with either localised or advanced cancer. As Figure 4 shows, costs mostly accumulate in the early years of the disease and depend on stage of disease.

Sensitivity analyses allow interrogation of the model inputs and their relative contribution to the results. One-way sensitivity analyses were undertaken on all variables where uncertainty was possible for that value. The model was re-run with one variable value varied and the results observed. The values tested are the ranges in Tables 3 to 5 and they are mainly the high and low 95% confidence limits.

The key drivers of the model were: the health utility scores and probabilities of very low- to low-risk disease, intermediate-risk disease and high- to locally-advanced disease (Figure 5). These were followed by the probabilities of recurrence after surgery and radiation, first-line radiation for intermediate- or high-risk patients and after first-line androgen deprivation therapy. When these values varied over their respective high and low estimates, they made the greatest impact on the results (Figure 5).

Figure 5: Tornado diagram of the most influential variables in the model



ADT = androgen deprivation therapy; adv = advanced; dx = diagnosis; EV = expected value; int = intermediate; Prob = Probability; rad = radiation

In Figure 5, the vertical line represents the expected net monetary value of $369,228. This is calculated by the $50,000 willingness-to-pay for one QALY gain multiplied by the mean QALYs (7.92) minus mean costs ($26,769). The mean costs and QALYs are not from the Monte Carlo simulations but a simple expected values calculation. The bars to either side of the vertical line are the variation in the net monetary value from the high and low values tested. As indicated, at most these vary between $361,000 and $378,000.

3.0 DESCRIPTIVE ANALYSES
(continued)

3.2 EXTRAPOLATION OF COSTS AUSTRALIA-WIDE

To estimate the health system costs of prostate cancer over the next 10 years in Australia, data were extrapolated using the following approach:

1. The estimated prevalence of prostate cancer for 2016 was extracted from a study by Yu et al. (2015) where the number of prevalent cases in Australia were estimated at between 185,700 to 201,700 in 2017 [41]. The low value of 185,700 was used from 2016 onwards. An average age of prevalent men of 65 years was assumed and mortality was accounted for as predicted by our model. An average cost of $478 per year was applied for the ongoing costs of follow-up, also taken from our modelled costs, being the average of the last 20 years of the model.
2. Incidence of prostate cancer was obtained from the Australian Institute of Health and Welfare (AIHW) Australian Cancer Incidence and Mortality Book for prostate cancer [42]. This was used to predict the trend of new cases of prostate cancer over the next 10 years and assumes that current *ad hoc* PSA screening and population growth continues at current levels. Expected incidence was obtained by 5-year age group level.
3. Victorian Cancer Registry data were analysed to obtain the proportion of men within each disease risk category (i.e. very low/low-risk, intermediate-risk, high-risk + locally-advanced and metastatic disease) by the 5-year age group (n=8,065).
4. The expected cases of prostate cancer within each disease risk and age group was estimated as the product of the AIHW and Victorian registry data.
5. The annual costs of the first 10 years of treatment were derived from the model, separately for each disease risk and multiplied by expected numbers of new cases. Average cost for all prostate cancer was applied to the prevalent cases.

Using the expected mortality rates predicted by the generic model, all estimates were adjusted for mortality from prostate cancer and other causes. The results are provided in Table 10 and Figure 6. As expected, the estimates presented here beginning in 2016 are higher than those last reported by the AIHW; $346.6 million in 2008/09 or 7.7% of all cancer expenditure [43].

TABLE 10: ESTIMATED NUMBERS OF MEN AND AUSTRALIA-WIDE COSTS OF MEN WITH PROSTATE CANCER ($ MILLION)

Stage	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
Estimated numbers of men with prostate cancer										
Prevalent men[a]	185,700	182,361	175,925	165,973	152,547	136,117	117,534	97,908	78,452	60,289
Low risk	5,437	10,935	16,427	21,842	27,107	32,148	36,897	41,295	45,299	48,882
Intermediate risk	9,630	19,364	29,087	38,646	47,868	56,576	64,613	71,857	78,241	83,751
High risk[b]	6,150	12,374	18,596	24,685	30,475	35,801	40,524	44,566	47,916	50,628
Advanced	1,089	1,962	2,523	2,820	2,967	3,054	3,125	3,193	3,260	3,328
Total	**208,006**	**226,996**	**242,558**	**253,966**	**260,963**	**263,695**	**262,692**	**258,820**	**253,168**	**246,878**
Estimated healthcare costs of men with prostate cancer ($ million)										
Prevalent cases[a]	88.8	87.2	84.1	79.3	72.9	65.1	56.2	46.8	37.5	28.8
Low risk	48.5	48.5	53.0	59.0	64.6	70.0	78.3	83.2	87.7	91.8
Intermediate risk	131.5	131.5	139.8	147.9	156.8	166.2	181.5	190.5	198.8	206.1
High risk[b]	108.3	108.3	112.7	119.8	128.7	138.3	154.8	163.8	171.7	178.4
Advanced	6.5	6.5	14.7	19.0	20.9	21.7	22.3	22.8	23.3	23.8
Total ($millions)	**383.6**	**407.3**	**429.8**	**450.4**	**469.1**	**502.1**	**516.5**	**528.3**	**537.6**	**543.9**

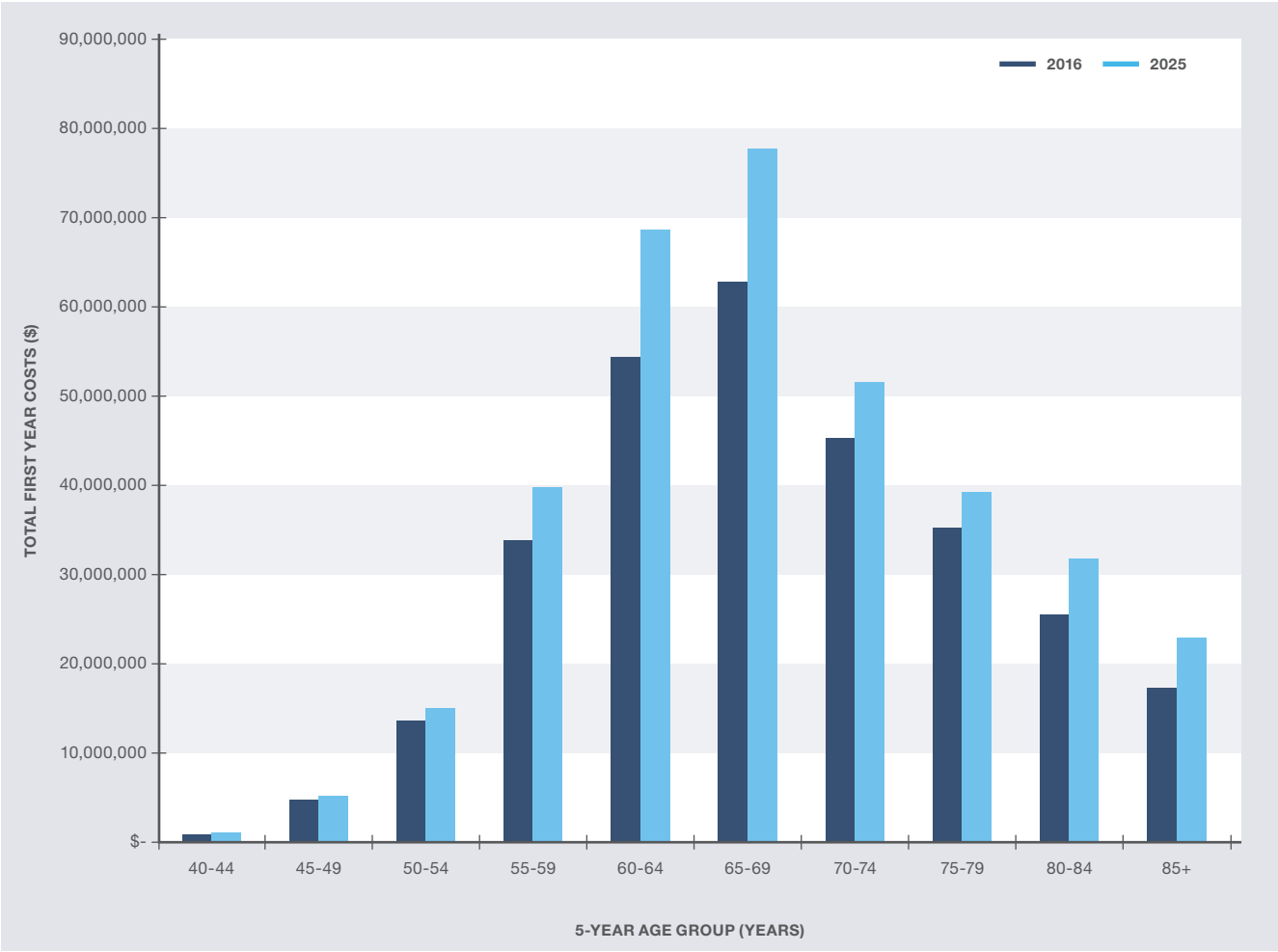
[a] *All risk stages*

[b] *Includes locally-advanced cancer*

Using our generic model and other sources, the total estimated healthcare costs of prostate cancer treatment in 2016 was $383.6 million rising to $543.9 million in 2025, an expected increase of 42% in the next 10 years.

Costs in the first year of prostate cancer are substantial where the majority of the key treatments occur, compared with following years. Figure 6 presents the calculated costs, for each risk stage and by each 5-year age group based on the expected cases for 2016 and 2025.

Figure 6: Total first year costs of prostate cancer treatment by 5-year age group (2016 and 2025)



Men aged in the two most common age groups for diagnosis of prostate cancer 60-64 years and 65-69 years are expected to have the most growth in healthcare costs over the next 10 years.

4.0 OVERVIEW OF ECONOMIC EVALUATIONS

In the following sections, three economic evaluations are reported. The topics of these analyses include cost-effectiveness and cost-utility analyses of the following:

1. Multiparametric magnetic resonance imaging (mpMRI) for diagnosis of prostate cancer;
2. Active surveillance strategies for low-risk prostate cancer; and
3. PSA screening for early detection of prostate cancer.

The three economic evaluations are reported over four sub-sections including a background and rationale, methods, results and discussion. In addition, the separate sections end with 'The Bottom Line' summary of the findings. Some commonalities across the studies are mentioned here with the intervention specifics further detailed in the following sections.

The generic model was used in all analyses and altered to specifically address the research questions. These alterations are fully detailed and consequently, three unique models were developed, which are named the mpMRI model, the active surveillance model and the PSA screening model. Accompanying these structural changes are additional data inputs. These were sourced from literature searches and the best available evidence at hand. Additional costs were obtained from hospital costing reports, the Medicare Benefits Schedule and Pharmaceutical Benefits Schedule. When costs were derived from international sources and in a preceding time period, the costs were corrected to 2015 Australian dollars. Future benefits and costs were discounted at 5% per year to reflect time preference. Half-cycle corrections were also applied.

In all analyses, the main outcomes reported were healthcare costs, QALYs and life years. Other outcomes were added where relevant. The main measure from cost-effectiveness analyses is the incremental cost-effectiveness ratio (ICER) and the formula is:

$$\text{ICER} = \frac{\textit{Cost (Intervention)} - \textit{Cost (Current Scenario)}}{\textit{Effect (Intervention)} - \textit{Effect (Current Scenario)}}$$

The ICER is the difference in costs between the intervention of interest and the current scenario divided by the difference in effects (i.e. QALYs and life years). Because new interventions usually cost more and give additional patient benefits, the ICER can be interpreted as the additional costs of the new intervention in relation to the additional benefits. In Australia, when the ICER is up to $50,000 per QALY or life year saved, in general the new intervention is considered cost-effective. If costs of the intervention are less than those for the current scenario, and effects are higher, the intervention is said to be superior. Conversely, if costs are higher and effects lower, the intervention is inferior to the current scenario.

One-way and probabilistic sensitivity analyses were performed as explained in Section 2.5. The Monte Carlo simulation findings were presented in cost-effectiveness acceptability curves and incremental cost-effectiveness scatter plots and the interpretation of these diagrams is provided.

4.1 COST-EFFECTIVENESS ANALYSIS OF MULTIPARAMETRIC MRI

BACKGROUND & RATIONALE

The presence of prostate cancer is normally assessed with a PSA test and/or DRE. If cancer is suspected, a transrectal ultrasound (TRUS)-guided biopsy followed by histopathological grading (Gleason score) is performed to confirm a diagnosis. However, TRUS/ Gleason score approach does not always distinguish well between serious, clinically significant prostate tumours and clinically insignificant tumours. Consequently, the combined low sensitivity of PSA and DRE tests for prostate cancer has led to the over detection and subsequent over treatment of clinically insignificant prostate cancers. Problematically, there is also under treatment of the clinically significant prostate cancers. Recent evidence suggests that mpMRI could increase the accuracy of detecting clinically significant prostate cancer, and in the process, reduce the need to perform biopsies [44] of indolent tumours. Potentially, a more targeted less-invasive approach for patients is mpMRI which is thought to improve the efficiency of the current diagnostic pathway [45]. In general, when mpMRI is offered and it is positive for prostate cancer, a confirmatory biopsy is still necessary. Alternative types of biopsies are used by clinicians in Australia including TRUS-, transperineal ultrasound (TPUS)- and MR-guided biopsy.

Clinicians have identified three potential roles for mpMRI in prostate cancer management including:

1. To guide patient selection for initial biopsy (biopsy naïve patients);
2. To guide patient selection for repeat biopsy; and
3. To guide patient selection in active surveillance of very low- to low-risk prostate cancers [46].

The current clinical guidelines in Australia recommend the consideration of mpMRI for men in the repeat biopsy stage, that is, men remaining at risk of prostate cancer despite a prior negative TRUS-guided biopsy [1]. This is due to the concern that men given the 'all clear' from first TRUS biopsy remain at risk of harbouring clinically significant disease. A systematic review showed MRI-guided biopsies detect 16% more clinically significant prostate cancers compared with TRUS-guided biopsy [47].

Where mpMRI is available in centres throughout Australia, men with suspected prostate cancer can receive mpMRI in the private system at an out-of-pocket cost of ~$500-$600. There is no reimbursement of this fee through Medicare. However, there is a current submission to the Medical Services Advisory Committee (MSAC) from the Urological Society of Australia and New Zealand for government reimbursement of mpMRI with or without a subsequent MR-guided biopsy, for patients who are biopsy naïve but suspected of prostate cancer through abnormal PSA/ DRE [48].

Multiparametric MRI is a reasonably new technology that has existed for less than five years although many consider it standard practice in Australia and elsewhere around the world. However, there is still uncertainty around issues such as the best MRI-guided biopsy approach to use after lesion detection on mpMRI (MRI-in bore, MRI-TRUS fusion); whether to use mpMRI with or without MRI-guided biopsy as a substitute or a complement to the standard TRUS-guided biopsy; and the possible cost-effectiveness of introducing an expensive technology like MRI for the detection of prostate cancer. The aim of this study was to perform a cost-effectiveness analysis comparing two MR-based strategies versus a TRUS-based strategy in Australia for men suspected for prostate cancer but who have not had a prior biopsy (that is, they are biopsy naïve). This population of men matches that proposed by the current MSAC application.

METHODS

Our generic economic model was modified to evaluate the diagnostic accuracy, quality of life, patient survival and economic costs associated with three strategies. Specifically, the model compared:

Strategy 1: no mpMRI and TRUS-guided biopsy;

Strategy 2: mpMRI with or without MR-guided biopsy; and

Strategy 3: mpMRI with or without either TRUS-, TPUS- or MR-guided biopsy.

In the mpMRI strategies, patients with a suspected prostate cancer will receive a biopsy but only one repeat biopsy is required for a negative mpMRI result, where PSA and/or DRE still indicate cancer may be present. Strategy 3 is intended to reflect current practice where either of the three types of biopsies are performed depending on clinician preferences.

The TRUS-guided biopsy with 21-24 sextant cores is currently recommended for definitive diagnosis of prostate cancer [1]. Both the transrectal and transperineal approaches are accepted choices and are equivalent in both efficacy and safety [49]. There are several published studies on the cost-effectiveness of mpMRI versus TRUS-guided biopsy but they differ slightly in their targeted populations including biopsy naïve, prior biopsy or a mixed population of both. They also differ in their model structures which cover the diagnostic phase only with no longer-term downstream effects [44, 50-52] as possible with our generic model.

Building on the generic model, the mpMRI model structure has three additional health states that are depicted in Figure 7 for Strategy 1. The three additional health states are:

1. **Biopsy naïve:** In Strategy 1, all men with elevated PSA and/or suspicious DRE are given a TRUS-guided biopsy. This would reveal the presence or absence of cancer. In those suspected to have cancer, branches representing low-, intermediate-and high-risk cancer are added. Each cancer risk branch has sub-branches representing the subsequent diagnostic accuracy of the TRUS-guided biopsy.
2. **PCa negative, Missed PCa:** In those men who actually do have cancer but the biopsy is found to be negative (false negatives), these men remain with elevated PSA and undergo one only repeat biopsy (all receive TRUS). The model assumes that if the cancer is not accurately detected after the second biopsy, the man would continue to be monitored (moving to the 'PCA negative: PSA monitor' arm) but no further biopsies occur.
3. **PCa negative, PSA monitor:** Men who truly do not have cancer (true negatives) also receive a confirmatory repeat biopsy and thereafter continue to be monitored with PSA and/or DRE tests only. The risk of cancer can occur in a small proportion of men during this follow-up period while receiving regular PSA tests. This risk is spread over two decades.

When prostate cancer is detected, the men enter the existing health states of the generic model and receive all treatments and follow-up relevant to their stage of cancer.

4.0 OVERVIEW OF ECONOMIC EVALUATIONS *(continued)*

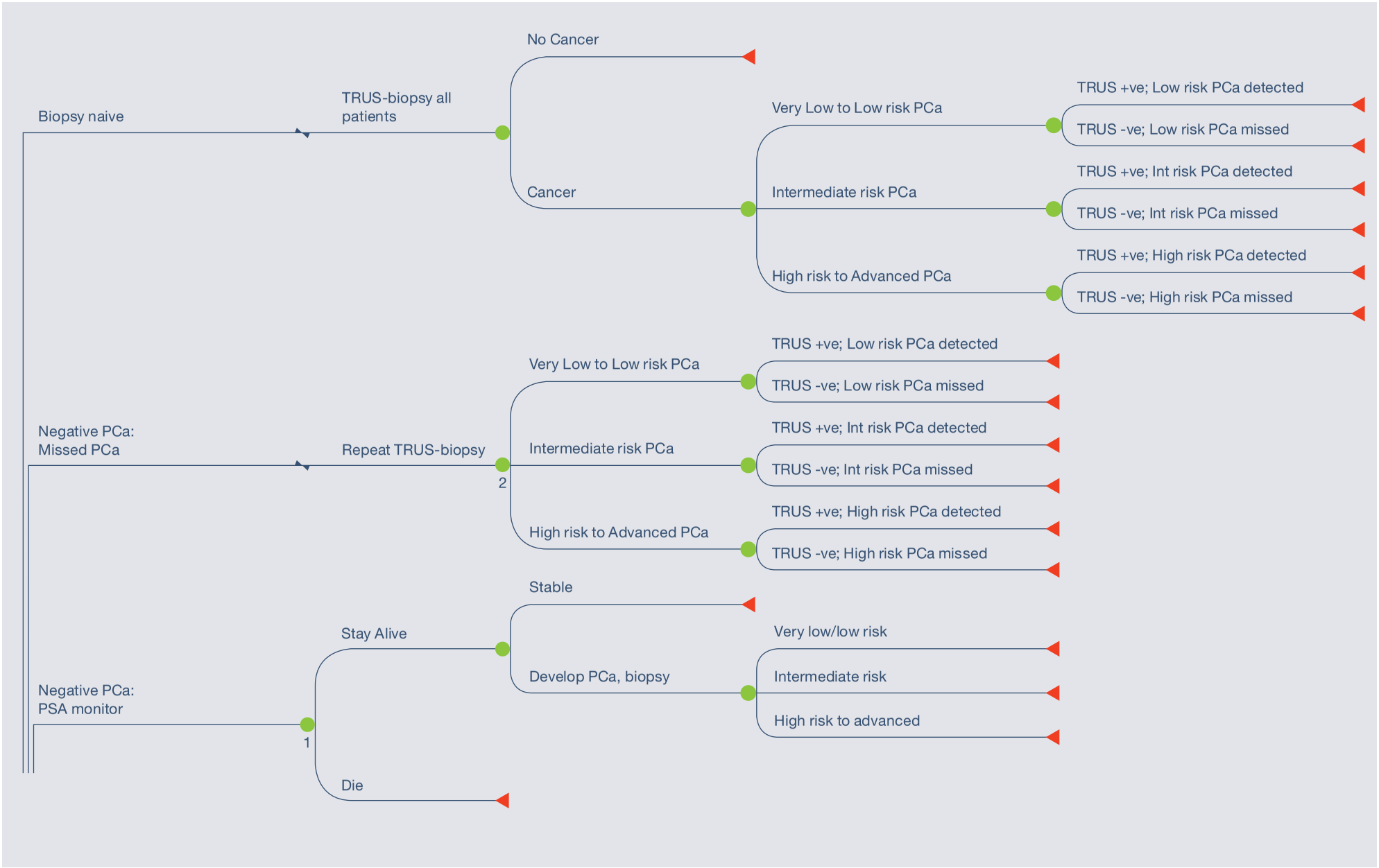
The model structure also has three additional health states for the MR strategies, which are shown in Figure 8. The only difference between these two strategies are the types of biopsies performed and their relative diagnostic performance. The three additional health states are:

1. **Biopsy naïve:** In Strategies 2 and 3, all men with elevated PSA and/or suspicious DRE are given an mpMRI scan. This provides a positive or negative result for the presence or absence of cancer. In those believed to have cancer, the men would proceed to a MR-guided biopsy (Strategy 2) or either a TRUS, TPUS or MR-guided biopsy (a weighted figure for 33.3% of each type was assumed) (Strategy 3). Men with a positive result for cancer are stratified by risk of cancer and the subsequent diagnostic accuracy of the MR-guided biopsy (Strategy 2), or weighted accuracy figures for TRUS, TPUS or MR-guided biopsy. If men have a false negative result for cancer, they will go to the *'PCa negative: Missed PCa'* health state or, if they are truly negative, to the *'PCA negative: PSA monitor'* health state.
2. **PCa negative:** Missed PCa: This is identical to Strategy 1 described earlier.
3. **PCa negative:** PSA monitor: This is identical to Strategy 1 described earlier.

As previously, when prostate cancer is detected, the men enter the generic model health states and receive all treatments and follow up as per standard care.

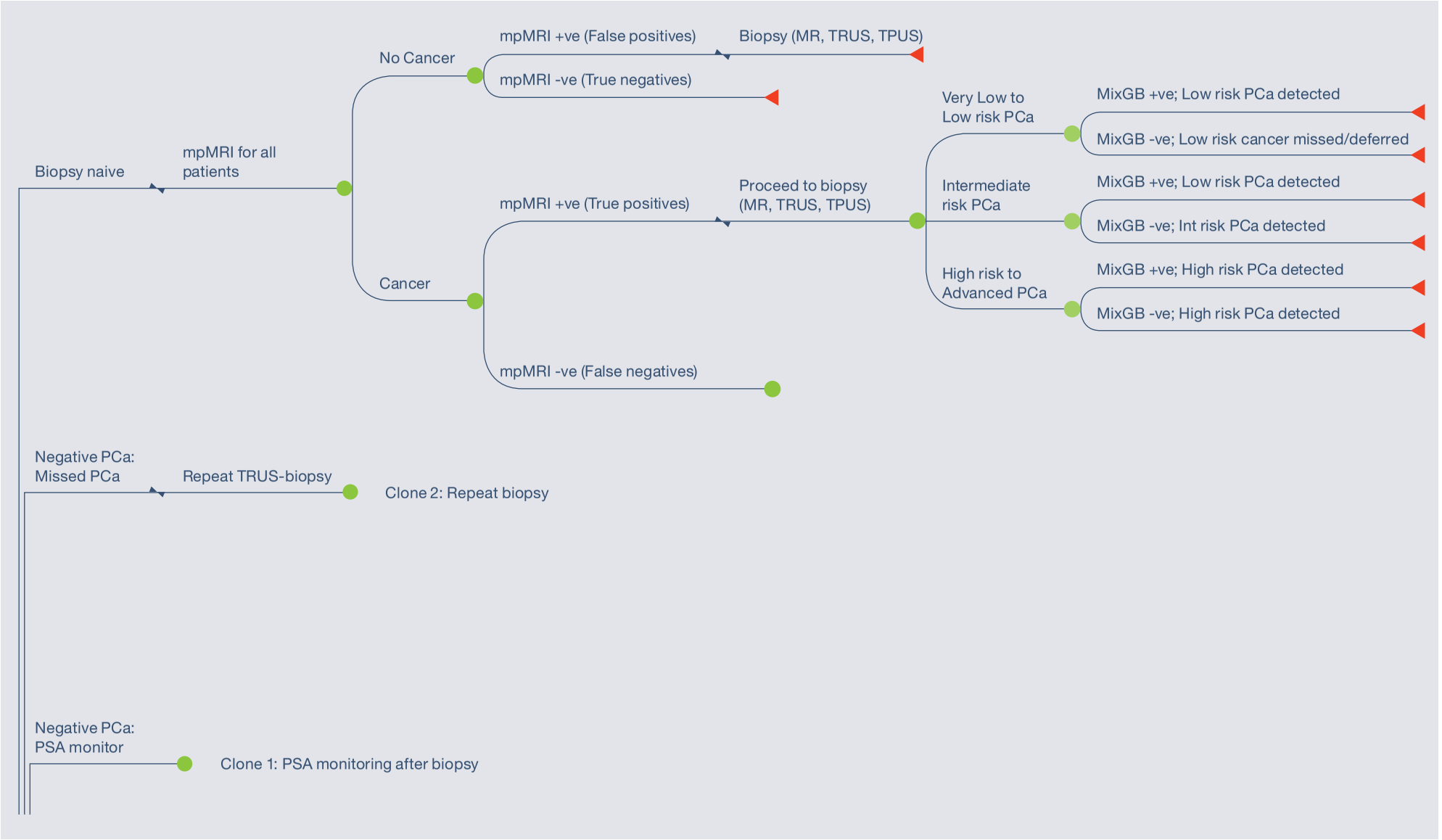
The transitional probabilities, diagnostic accuracy of screening tests, costs and utilities/disutilities were obtained from a literature review (Table 11). An Australian study by Thompson et al. (2014) [53] was used to populate most of the key estimates of mpMRI diagnostic accuracy in our model and were similar to those reported in a recent systematic review [45]. The Thompson (2014) study was a single-centre, prospective diagnostic study analysing 150 consecutive men (88% were biopsy-naïve) recruited through two urologists in Sydney, Australia (April 2012 to April 2013). The type of MR-guided biopsy used was either MRI/TRUS fusion or cognitive MR, both transperineal. The index test was transperineal ultrasound biopsy. This study was selected because it was Australian, reflected current local practice and it was reasonably consistent with the population of biopsy naïve men. Although Pokorny et al. (2014) also included biopsy naïve men [54], the negative predictive value (~97%) may be over-stated because of the inclusion of men with Gleason 7 cancers. Schoots et al. (2014) systematic review was used to complete the sensitivity and specificity values not available in Thompson and the TRUS was used as the index test (n=1657 cancers). A limitation of these pooled estimates was the high heterogeneity across studies (Table 11).

Figure 7: TRUS-guided biopsy: additional model branches to the generic model



Int = intermediate; PCa = prostate cancer; PSA = prostate-specific antigen; TRUS = transrectal ultrasound; +ve = positive; -ve = negative

Figure 8: Strategies 2 and 3 mpMRI options with additional model branches to the generic model



Note: Strategy 2 differs than Strategy 3 only for the type of biopsy performed; MR-guided biopsy for Strategy 2 and MR-, TRUS- or TPUS-guided biopsy. Clones relate to identical structures to Figure 7.

FN = false negative; FP = false positive; Int = intermediate; mpMRI = multiparametric magnetic resonance imaging; MR = magnetic resonance; MRGB = magnetic resonance guided biopsy; MRI = magnetic resonance imaging; TN = true negative; TP = true positive; PCa = prostate cancer; PSA = prostate-specific antigen; +ve = positive; -ve = negative

4.0 OVERVIEW OF ECONOMIC EVALUATIONS *(continued)*

For the mpMRI model, the cancer prevalence, the proportion of insignificant tumours (very low or low risk) and significant tumours (intermediate risk and above) were obtained from Thompson *et al*. (2014). The probability of men being diagnosed with prostate cancer after negative tests and biopsies was assumed to be similar to the rate captured over 2.8 years, from Gann *et al*. (2010) [55]. A rate-to-probability formula was applied and resulted in a probability of 9.7% per year. Similarly, deaths from men being monitored on a PSA testing regimen were based on observational data captured over 13 years from the European Randomized Study of Screening for Prostate Cancer (0.38% per year) [56].

Prostate biopsies can be associated with adverse events in some men, namely, bleeding, pain, infections, sepsis, vasovagal episodes, erectile dysfunction as well as anxiety [51, 57]. No studies were found that reported health utilities for any type of biopsy. It is unclear whether an MR-guided biopsy would be any different to TPUS- or TRUS-guided biopsy in terms of the temporary impact on quality of life. In a cost-utility analysis by Zhang et al. (2012) a disutility of 0.05 was used but originally came from a study on sentinel lymph node biopsy for breast cancer [58, 59]. The MR approach uses fewer needles (2 to 4 cores) than the TRUS-guided biopsy (12-32 cores). Because fewer cores are taken during the MR-guided approach, there may be a smaller chance of complications (infections, pain, etc.) following the biopsy and better temporary quality of life outcomes. However, in the MR-guided approach, men are locally-anaesthetized and may suffer embarrassment or anxiety. Therefore, a disutility of 0.035 for all biopsy types was applied in the model. Due to the significant uncertainty of this estimate, these disutilities were varied in sensitivity analyses.

TABLE 11: KEY INPUTS USED IN THE MARKOV MODEL FOR THE mpMRI ANALYSIS

Model probabilities & source	Value	95% CI	Source
Baseline characteristics			
Proportion biopsy naive	88%	–	Thompson (2014) [53];
Starting age	60 yrs	–	Assumption. Median baseline age = 62.4 years in Thompson (2014) [53]
Model duration	30 yrs	–	Assumption. Life-time model, tested over 10 and 20 years
Disease characteristics			
Cancer prevalence	61%	53%, 69%	Thompson (2014) [53]; 92/150
Probability of developing PCa after a negative biopsy during PSA follow-up (annual)	9.7%	–	Gann (2010) [55]; 465 out of 1871 patients over 2.8 years after previous biopsy
% Very low /low risk PCa	45%	35%, 55%	Thompson (2014) [53]; 41/92
% Int/high risk PCa	55%	45%, 65%	Thompson (2014) [53]; 51/92 with 36/92 int risk and 15/92 high risk (i.e. 39%, 16%)
Diagnostic accuracy			
Sensitivity: mpMRI scan	76%	66%, 84%	Meta-analysis by de Rooij (2014), ref std =biopsy (p.345) [60]
Specificity: mpMRI scan	86%	79%, 91%	Meta-analysis by de Rooij (2014), ref std =biopsy (p.345) [60]
Sensitivity: MRGB for very low/low-risk PCa	47%	17%, 79%	Schoots (2014) [45]; n=1657[a]
Sensitivity: MRGB for int/high-risk PCa	94%	84%, 98%	Thompson (2014) [53]; 48/51, similar to Schoots (93%)
Sensitivity: TRUS-gb for very low/low-risk PCa	87%	74%, 94%	Schoots (2014) [45]; n=1657[a]

4.0 OVERVIEW OF ECONOMIC EVALUATIONS *(continued)*

TABLE 11: KEY INPUTS USED IN THE MARKOV MODEL FOR THE mpMRI ANALYSIS

Model probabilities & source	Value	95% CI	Source
Sensitivity: TRUS-gb for int/high-risk PCa	85%	73%, 93%	Schoots (2014) [45]; n=1657a
Sensitivity: mixed biopsy for very low/low-risk PCa	73.8%	As above	Accuracy of TRUS and TPUS is no different (shen) therefore 33% sensitivity for MRGB + 67% for TRUS - low risk PCa
Sensitivity: mixed biopsy for int/high-risk PCa	88.0%	As above	Accuracy of TRUS and TPUS is no different (shen) therefore 33% sensitivity for MRGB + 67% for TRUS - int/high risk PCa
Probability of mortality			
Under PSA monitoring – annual probability	0.38%	–	ERSPC trial [56]; 355/7408 over 13 years
Costs			
mpMRI scan	$570	$399, $741	MSAC Application consultation protocol [48]
MRI-guided biopsy (weighted average)	$1,552	$1,086, $2,018	Assumption. Weighted average of MRI-in bore ($2,349) and TRUS fusion ($755) with 50-50 split
TRUS-guided biopsy	$700	$490, $910	Includes costs of core biopsy, prophylaxis and complications (see Table 4)
TRUS-guided biopsy	$600		Assumption
Disutility			
Any biopsy	0.035	0.020, 0.050	Assumption – based on Zhang et al. 2012 [58, 59]

AR-DRG = Australian refined diagnosis-related group; CI = confidence interval; ERSPC = European Randomized Study of Screening for Prostate Cancer; gb = guided biopsy; mpMRI = multiparametric magnetic resonance imaging; MR = magnetic resonance; MRGB = magnetic resonance guided biopsy; MRI = magnetic resonance imaging; MSAC = Medical Services Advisory Committee; NICE = National Institute for Health and Care Excellence; PCa = prostate cancer; PSA = prostate-specific antigen; TRUS = transrectal ultrasound; int = intermediate; VCR = Victorian Cancer Registry data

[a] Meta-analysis results were used from the initial biopsy cohort (6 prospective studies which included Australian study by Pokorny [54]

The key outcomes of the analysis were health system costs, QALYs, life years and:

- the number of clinically significant prostate cancers detected;
- the number of clinically insignificant prostate cancers detected; and
- the number of avoided biopsies.

Given the findings of the generic model, and the structure and cost inputs used with the MR strategy, the expected concurrent changes of the outcomes in the model are as follows:

- Costs of mpMRI scans are slightly less than a TRUS-guided biopsy but many men in the MR strategy will also get MR-guided biopsy – therefore overall diagnosis costs are likely to be higher;
- Fewer biopsies will occur as men with negative mpMRI avoid or delay having a biopsy, men will also avoid decrements in health utilities (better quality of life);
- MR strategies will detect fewer low-risk cancers – associated with fewer men accruing relatively lower treatment costs and higher utilities; and
- MR strategies will find more significant cancers – associated with more men accruing higher costs, lower utilities and shorter life.

RESULTS

The results of the modelled analysis are presented in Table 12.

TABLE 12: KEY RESULTS OF mpMRI WITH/WITHOUT MR-GUIDED BIOPSY VERSUS TRUS-GUIDED BIOPSY

	Strategy 1	Strategy 2	Strategy 3	Difference		Incremental cost per effect ratios	
Means	**No mpMRI +TRUS**	**mpMRI ± MRGB**	**mpMRI ± TRUS/ TPUS or MRGB**	**Difference Strategy 2 vs 1**	**Difference Strategy 3 vs 1**	**Strategy 2 vs 1**	**Strategy 3 vs 1**
Costs	$24,203	$24,943	$24,337	$740 higher	$134 higher	–	–
QALYs	7.82	7.70	7.77	-0.12 (negligible)	-0.05 (negligible)	Marginally inferior	Marginally inferior
Life years	21.90	21.90	21.97	0	-0.30 (negligible)	Marginally inferior	$1,914 per life year gained
No. Biopsies (per 1000 men)	1,440	1,140	1,100	300 avoided	340 avoided	$2467 per biopsy avoided	$394 per biopsy avoided
No. Significant cancers (per 1000 men)	530	590	550	60 more	20 more	$12,333 per significant cancer detected	$6,700 per significant cancer detected
No. Insignificant cancers (per 1000 men)	430	380	420	50 fewer	10 fewer	Inferior	Inferior

LYS = life years saved; MRGB = magnetic resonance guided biopsy; mpMRI = multiparametric magnetic resonance imaging; MR = magnetic resonance; QALYs = quality-adjusted life years; TRUS = transrectal ultrasound

The results show that the MR strategies increase costs and have slightly lower QALYs compared with the no MRI and TRUS option. That is, both MR strategies are marginally inferior to the no MRI and TRUS option. Mean costs are $740 higher; however, no additional benefits gained in terms of QALYs, life years are produced, and the numbers of biopsies avoided are relatively small. For every 1000 men tested, the MR strategies accurately detected up to 60 more significant prostate cancers and up to 50 fewer insignificant cancers.

The MR strategies were successful in more accurately diagnosing prostate cancer; however, it is a costly technology. More accurate diagnosis of significant cancers means that the relative QALYs compared to current practice is lower; however, health utility gains occurred from avoided biopsies were not enough to produce a net positive gain in QALYs for the MR strategy. It should be emphasised that the goal of the MR strategy is not to downshift cancers as in earlier detection, but rather to more accurately diagnose significant cancers.

One-way sensitivity analyses were performed on the variables in Table 11, those most relevant to the two strategies. The results are shown in Table 13 and Figure 9.

4.0 OVERVIEW OF ECONOMIC EVALUATIONS *(continued)*

TABLE 13: RESULTS OF ONE-WAY SENSITIVITY ANALYSES OF mpMRI MODEL

		mpMRI± MRGB vs TRUS			mpMRI ± MRGB/TRUS/TPUS vs TRUS		
	Value tested	Incr costs	Incr QALYs	ICER	Incr costs	Incr QALYs	ICER
Base model	–	$740	-0.12	-$6167	$134	-0.05	-$2680
Start age 55 years	55	$728	-0.13	-$5600	$125	-0.06	-$2083
Start age 65 years	65	$756	-0.07	-$8400	$151	-0.03	-$3775
Model duration – 10 years	10	$536	-0.07	-$7657	$21	-0.04	-$525
Model duration – 20 years	20	$677	-0.11	-$6155	$92	-0.05	-$1840
Probability of cancer – low	53%	$628	-0.09	-$6978	$90	-0.03	-$3000
Probability of cancer – high	69%	$844	-0.14	-$6029	$175	-0.06	-$2917
mpMRI sensitivity – low	66%	$539	-0.12	-$4492	$9	-0.06	-$150
mpMRI sensitivity – high	84%	$901	-0.12	-$7508	$234	-0.05	-$4680
mpMRI specificity – low	79%	$782	-0.12	-$6517	$160	-0.05	-$3200
mpMRI specificity – high	91%	$710	-0.12	-$5917	$116	-0.05	-$2320
Sensitivity TRUS biospy low risk – low	74%	$602	-0.12	-$5017	$69	-0.07	-$1021
Sensitivity TRUS biospy low risk – high	94%	$819	-0.11	-$7445	$172	-0.04	-$4300
Sensitivity TRUS biospy int risk – low	73%	$826	-0.16	-$5163	$132	-0.08	-$1650
Sensitivity TRUS biospy int risk – high	93%	$713	-0.07	-$10186	$150	-0.02	-$7500
Sensitivity MRGB – low risk -low	17%	$983	-0.18	-$5461	$214	-0.07	-$3057
Sensitivity MRGB – low risk -high	79%	$481	-0.05	-$9620	$49	-0.03	-$1633
Sensitivity MRGB – int risk - low	84%	$614	-0.11	-$5582	$92	-0.05	-$1840
Sensitivity MRGB – int risk - high	98%	$790	-0.12	-$6583	$151	-0.05	-$3020
Cost MRI – low	$399	$597	-0.12	-$4975	-$9	-0.05	$180
Cost MRI – high	$741	$884	-0.12	-$7367	$278	-0.05	-$5560
Cost TRUS-guided biospy – low	$490	$962	-0.12	-$8017	$319	-0.05	-$6380
Cost TRUS-guided biospy – high	$910	$519	-0.12	-$4325	-$50	-0.05	$1000
Cost MRGB – low	$1,086	$497	-0.12	-$4142	$53	-0.05	-$1060
Cost MRGB – high	$2,018	$982	-0.12	-$8183	$215	-0.05	-$4300
Disutility MRGB – low	0.02	$740	-0.04	-$18500	$134	-0.04	-$3350
Disutility MRGB – high	0.05	$740	-0.13	-$5692	$134	-0.06	-$2233
Disutility TRUS-guided biospy – low	0.02	$740	-0.06	-$12333	$134	-0.06	-$2233
Disutility TRUS-guided biospy – high	0.05	$740	-0.11	-$6727	$134	-0.04	-$3350

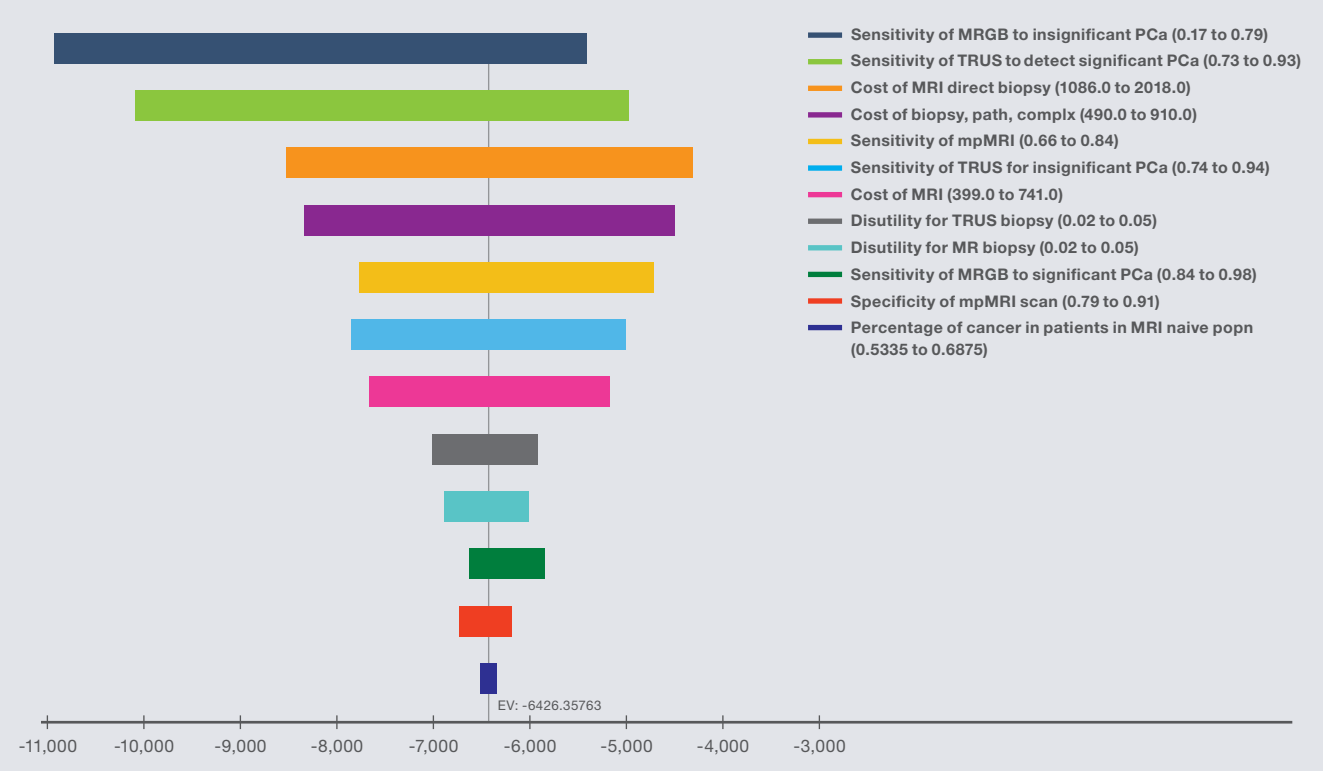
ICER = incremental cost-effectiveness ratio; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; MRGB = magnetic resonance guided biopsy; QALYs = quality-adjusted life years; TRUS = transrectal ultrasound

Bolded = more favourable cost-effectiveness scenarios for mpMRI

Values were tested across 95% confidence intervals or other plausible ranges due to their uncertainty. Overall, the modelling conclusions were stable to variation in most model inputs with one exception. In virtually all results, the costs were higher for the MRI strategies and the QALYs were (negligibly) lower and therefore the TRUS strategy remained superior. However, the MR strategy had lower costs (by $9 per person) when the MRI scan unit cost was lowered to $490.

The ranking of the most influential values in the model are provided in the tornado diagrams in Figures 9 and 10. The critical values were the sensitivity of TRUS and MRGB to detect significant and insignificant cancers and the costs of biopsies. It should be noted that the range of values tested for the diagnostic accuracy of MRGB included sensitivity and specificity values reported in a meta-analysis (pooled estimates) involving mixed and prior-biopsy populations [45].

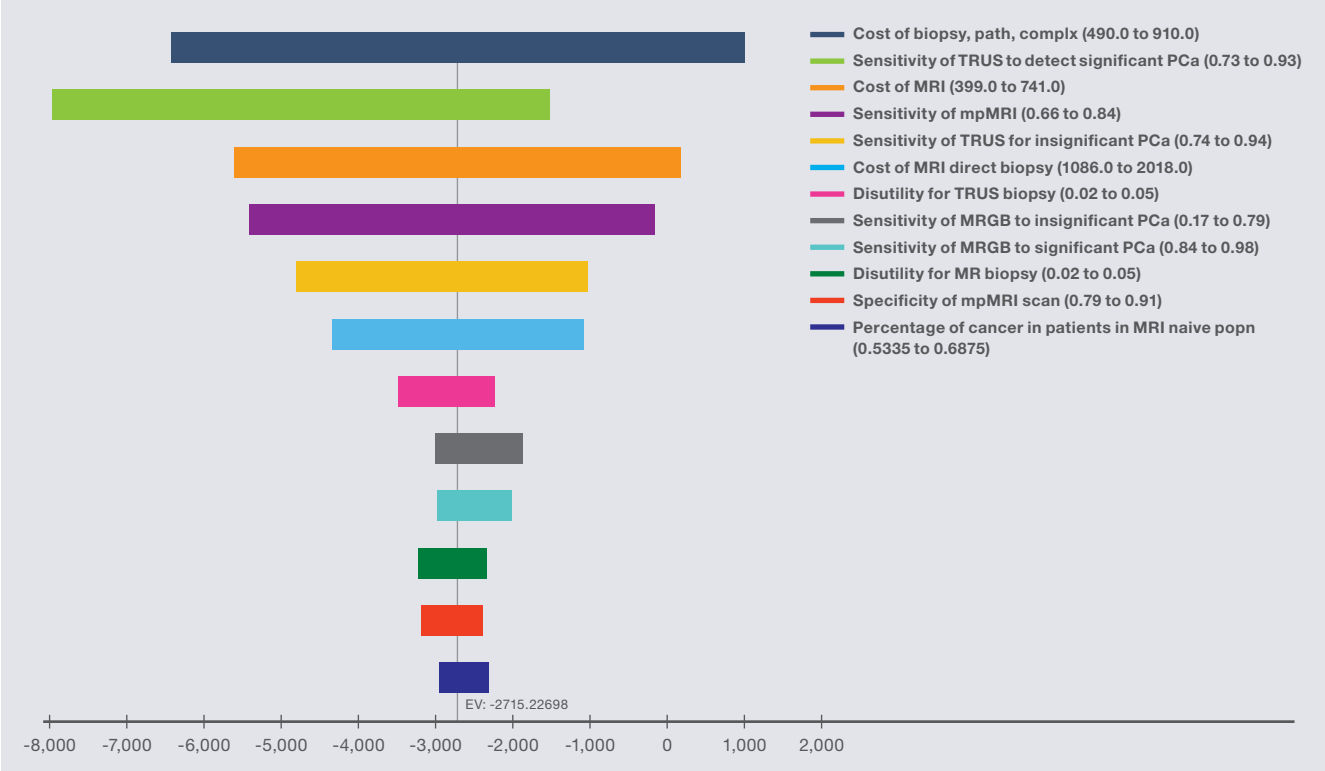
Figure 9: Tornado diagram of the most influential variables –mpMRI± MRGB versus TRUS



EV = expected value; MRGB = magnetic resonance guided biopsy; MRI = magnetic resonance imaging; mpMRI = multiparametric magnetic resonance imaging; PCa = prostate cancer; TRUS = transrectal ultrasound

4.0 OVERVIEW OF ECONOMIC EVALUATIONS *(continued)*

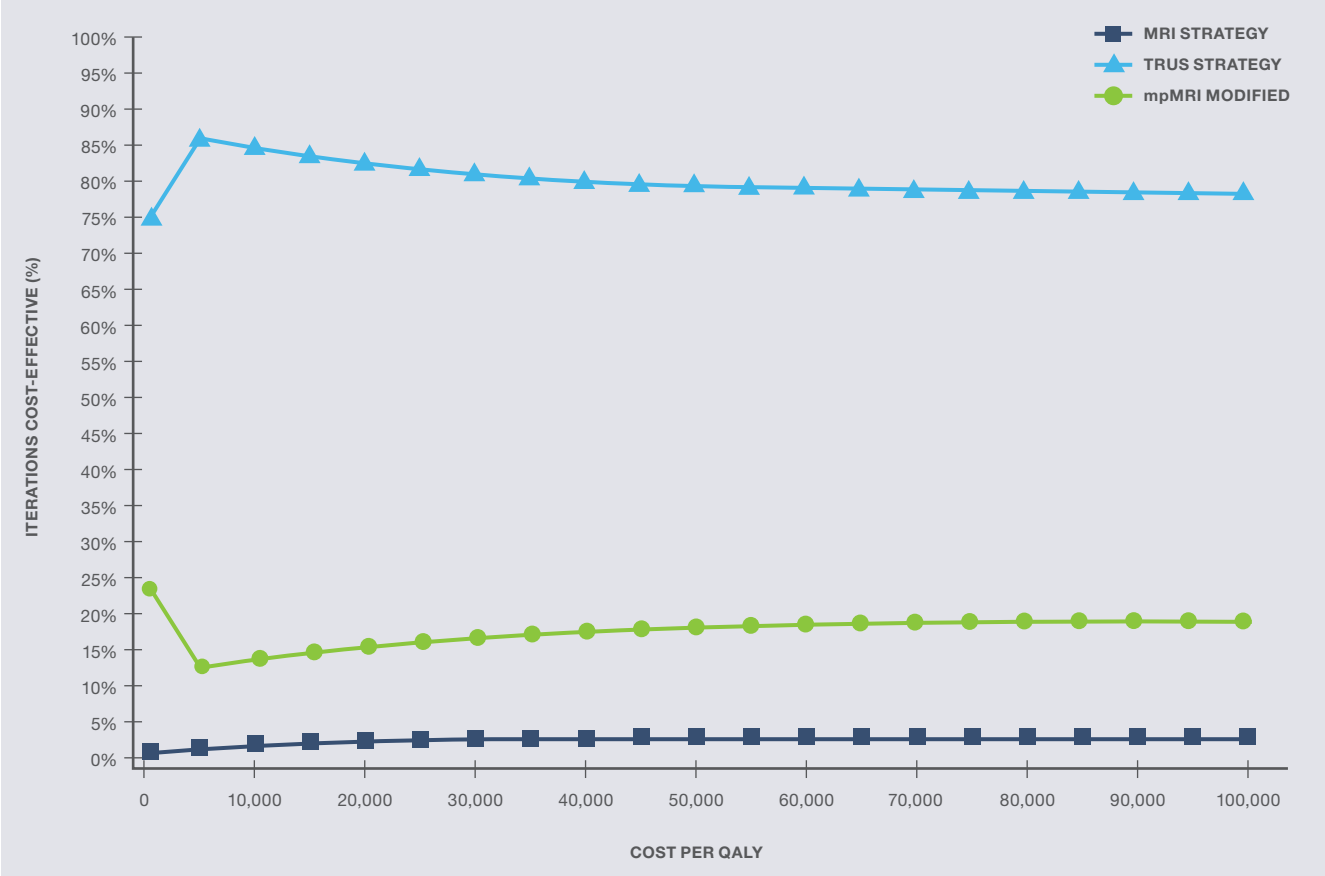
Figure 10: Tornado diagram of the most influential variables –mpMRI± MRGB/TRUS/TPUS versus TRUS



EV = expected value; MRGB = magnetic resonance guided biopsy; MRI = magnetic resonance imaging; mpMRI = multiparametric magnetic resonance imaging; PCa = prostate cancer; TRUS = transrectal ultrasound

Results of the probabilistic sensitivity analyses are provided in Figure 11 where it is demonstrated that at any level of willingness-to-pay threshold for cost per QALY gain, the likelihood of the mpMRI strategies being cost-effective never approaches that for the TRUS strategy.

Figure 11: Cost-effectiveness acceptability curves for the three strategies

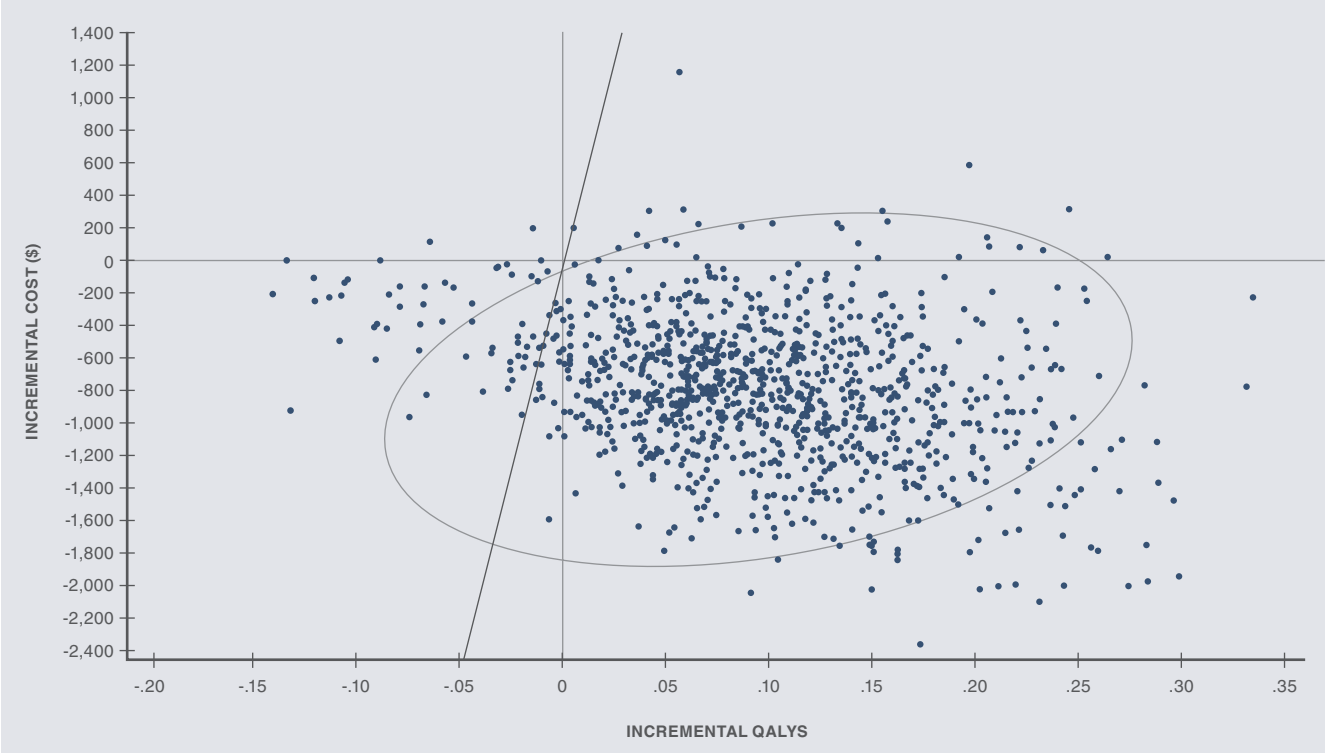


MRI = magnetic resonance imaging; TRUS = transrectal ultrasound; QALY = quality adjusted life years

4.0 OVERVIEW OF ECONOMIC EVALUATIONS
(continued)

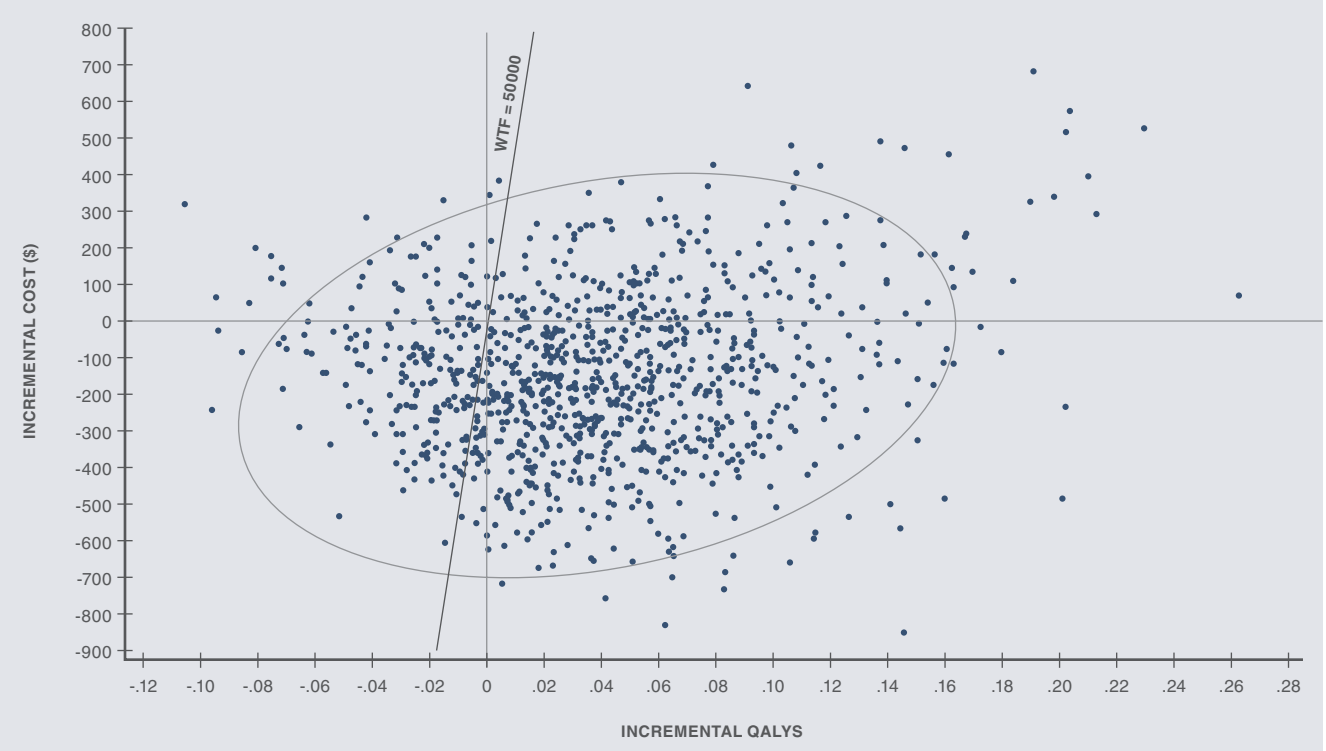
Figures 12 and 13 illustrate the probability of the two mpMRI strategies being cost-effective (versus the TRUS strategy) based on the outputs of 5000 Monte Carlo simulations.

Figure 12: Incremental cost-effectiveness scatter plot for TRUS vs mpMRI ± MRGB



Interpretation: the proportion of dots to the right of the diagonal line representing the willingness-to-pay of $50,000 per QALY is 92.3%. The chance that the TRUS strategy is cost-effective is 92.3%. MpMRI was inferior to TRUS in 7.7% of simulations.mpMRI = multiparametric magnetic resonance imaging; QALYs = quality-adjusted life years; WTP = willingness-to-pay

Figure 13: Incremental cost-effectiveness scatter plot for TRUS vs mpMRI ± MRGB/TRUS/TPUS



Interpretation: the proportion of dots to the right of the diagonal line representing the willingness-to-pay of $50,000 per QALY is 92.3%. The chance that the TRUS strategy is cost-effective is 92.3%. MpMRI was inferior to TRUS in 7.7% of simulations.mpMRI = multiparametric magnetic resonance imaging; QALYs = quality-adjusted life years; WTP = willingness-to-pay

Compared with the TRUS strategy, the probability of an mpMRI ± MRGB strategy being cost-effective was 7.7%, and the mpMRI ± MRGB or TPUS or TRUS strategy was 22.2%, based on an Australian acceptability threshold of $50,000 per QALY gain and the assumptions and values used in the model.

4.0 OVERVIEW OF ECONOMIC EVALUATIONS *(continued)*

DISCUSSION

This sub-study has provided information on the long-term expected costs and outcomes of a strategy that improves the diagnosis of prostate cancer in men with suspected prostate cancer. As expected, there were clear patient benefits in terms of fewer biopsies (with avoided decrements in quality of life), accurate diagnoses of cancer stage, and appropriate subsequent treatment. However, the costs are significant for both mpMRI scans and MR-guided biopsy compared with TRUS-guided biopsy. Further, what prevents this technology from being cost-effective is the detection of more significant cancers that are associated with more men accruing higher costs, lower utilities and shorter life expectancy. The detection of fewer low-risk cancers does not result in sufficient offset of avoided over treatment costs according to the current mix of treatments in Australian practice.

A recent study by de Rooij *et al.* (2014) of the only other cost-effectiveness study of mpMRI with/without MR-guided biopsy versus current practice with TRUS-guided biopsy, in biopsy naïve men, also modelled the costs and effects using a Markov model [44]. The de Rooij study found that mpMRI was cost-effective when the sensitivity of MR-guided biopsy exceeded 20%. They found that costs were comparable between groups and that QALYs were slightly higher (0.10) in the MR strategy but the authors stated these were highly uncertain [44]. There are several shortcomings of the de Rooij *et al.* (2014) study. These included: it ignored the costs and health utilities associated with biopsy complications, it ignored repeated biopsies, the specificity and sensitivity of MR-guided biopsy were assumed and not evidence-based, and it used very low probabilities of treatment of cancers with radical prostatectomy [44]. This is likely to account for the similar costs found in the two groups. In contrast, our study is more specific with the detailed generic model health states for treatment and also stratifies the MR-guided biopsy sensitivity and specificity by cancer risk (low and intermediate/high). Further, our model was 30 years in duration whereas the de Rooij study was 10 years long.

Our model relied heavily on the Thompson *et al*. (2014) diagnostic study for the effectiveness of MR-guided biopsy. This is a relatively small study and MR-guided biopsy sensitivity and specificity data confidence intervals were wide. A large randomised controlled trial for definitive figures would enhance the reliability of the cost-effectiveness results here. A more favourable cost-effective result is likely to occur if over treatment is reduced and treatment of low-risk disease is less invasive. Consequently, any rise in the uptake of active surveillance in eligible men would improve its cost-effectiveness.

A source of uncertainty with the findings of our model is the decision about the number of biopsies after an initial negative biopsy is received but PSA levels are still elevated. Whether there is one biopsy only or several for all men with elevated PSA levels in Australia is unknown and this will affect the biopsies avoided and costs in our model. Further research on this variable would assist in more accurately reflecting real world practice. Also, the associated health utilities for men undergoing biopsies are unclear until further research can unearth better evidence on this and whether there are any differences in the relative quality of life impacts of both TRUS- and MR-guided biopsies.

THE BOTTOM LINE

- A strategy of mpMRI and if indicated, subsequent MR-guided biopsy (or TRUS or TPUS biopsies), for the detection of prostate cancer has clear patient benefits in terms of fewer biopsies, avoided decrements in quality of life and more accurate diagnosis of cancer, and appropriate subsequent treatment.
- The mpMRI strategies were not considered cost-effective compared with the current TRUS strategy with the likelihood of cost-effectiveness being between 7.7% and 22.2%.
- The MR strategy does not comprise early detection. Preventing this technology from being cost-effective is the detection of more significant cancers that are associated with more men accruing higher costs, lower utilities and shorter life expectancy relative to the current practice of TRUS-guided biopsy.

4.2 COST-EFFECTIVENESS ANALYSIS OF ACTIVE SURVEILLANCE STRATEGIES

BACKGROUND & RATIONALE

Active surveillance is a proactive management plan for men diagnosed with low-risk prostate cancer where close monitoring is undertaken, including regular biopsies, and curative treatment begins only when the tumour appears to progress. The approach has developed from concerns about the overtreatment of prostate cancer among men with slow growing or indolent tumours that would otherwise not cause major harm. In men diagnosed with very low- or low-risk cancer, active surveillance is increasingly more acceptable among clinicians and patients [61]. The current balance of evidence supports active surveillance as a safe and superior alternative in terms of quality of life compared with first-line treatment with radical prostatectomy. There also appears to be no clear survival advantage of current treatments for low-risk prostate cancer over active surveillance [62]. The potential advantage of active surveillance is avoided detriments to quality of life for men from averted surgery, EBRT or brachytherapy and avoidance of common treatment-related complications that follow. However, while on active surveillance, some distress and anxiety does exist among men when faced with a 'do nothing' option for a diagnosis of cancer [63].

There remain some concerns and unanswered questions around this relatively new option. To date, there is no consensus around the criteria for selecting men into an active surveillance program, the exact protocol of the program as well as duration and the triggers or clinical indicators for switching to active therapy. In addition, existing programs suggest there are barriers to uptake due to personal preferences and anxiety around the initial decision. Concerns are also raised on the initial diagnosis made by PSA, DRE and TRUS-guided biopsy which are known to misclassify the risk of disease in some cases. It has been reasonably proposed that some men exhibiting tumour progression while on an active surveillance program may have been misclassified at initial biopsy [61]. PSA testing is inadequate to distinguish cancers that will be clinically insignificant or significant over time and currently this can only be determined in retrospect [61].

From an economic standpoint, healthcare resource use is expected to be reduced because active surveillance offers either, a delay in treatment for a proportion of men with low-risk disease who switch to curative treatment and experience related side effects or, complete avoidance of treatment and related side effects with tumours that do not progress. Where outcomes are assessed in full economic evaluations such as cost-effectiveness analysis, quality of life improvements are expected from active surveillance while survival outcomes are expected to be the same.

In Victoria, the proportion of men receiving no treatment for very low- to low-risk prostate cancer is 41% [13] which includes management with either active surveillance or watchful waiting. Compared to men receiving active surveillance, watchful waiting is appropriate for older men with shorter life expectancy and other comorbidities. Watchful waiting involves fewer PSA tests and no biopsies. In low-risk prostate cancer, the rate of annual progression to upgraded disease risk is 8.8% (95% CI: 6.7% to 11%) from a meta-analysis of 26 cohorts on active surveillance programs (n=7,627) with median follow-up of 3.5 years [5]. In Australia, the cessation rate from active surveillance was 19% in men from one series of 154 men after mean of 2.4 years (range 0.2-7.9 years) [61].

METHODS

The objective of this study was to look at the cost-effectiveness of three active surveillance scenarios to compare with current practice in Australia, that is, existing levels of active surveillance. The specific research questions of this study are:

1. Compared with current practice, what are the cost and effectiveness outcomes under increased uptake of active surveillance for men with very low- or low-risk disease?
2. Compared with current practice, what is the cost-effectiveness of increased uptake in low risk and widening the eligibility criteria for entry into active surveillance by including men with early intermediate risk prostate cancer?
3. Compared with current practice, what is the cost-effectiveness of mpMRI scan with or without MR-guided biopsy in the first year of active surveillance to guide treatment decisions?

Descriptions of the four comparative groups (i.e. current practice and three active surveillance scenarios) are provided below:

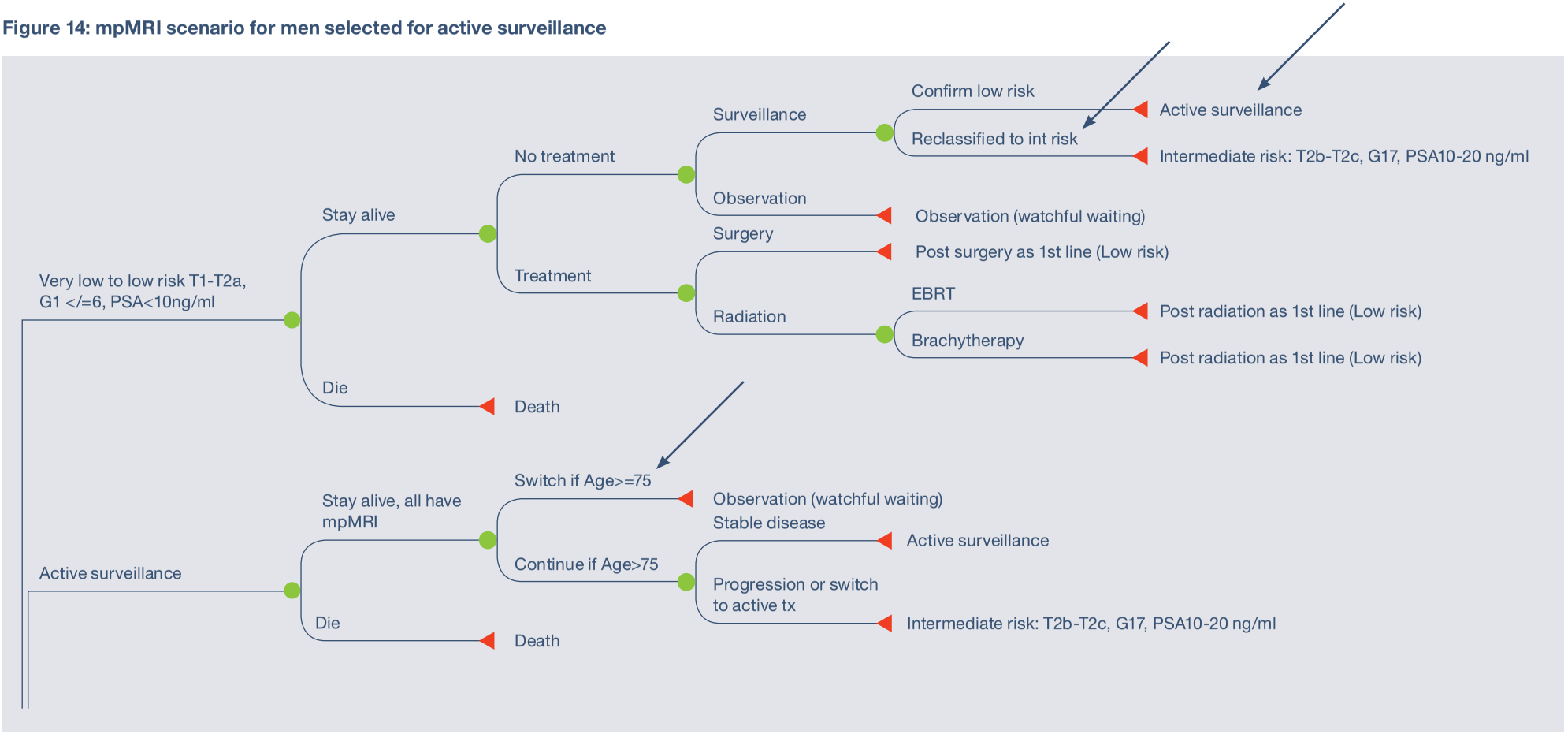
1. Current practice: Based on TRUS biopsy and clinical judgement, a man is diagnosed with very low- or low-risk prostate cancer and may enter into active surveillance. In the first year, this consists of 6-monthly DRE, 4 PSA tests and 1 TRUS-guided biopsy. Thereafter, the DREs remain 6-monthly, 2 PSA tests are taken annually and 1 TRUS-guided biopsy every 2 years. While on surveillance, some cancers will progress. The rate of progression to intermediate risk cancers were drawn from a study by Klotz *et al*. (2015) with the longest reported follow-up in an active surveillance cohort [64].

4.0 OVERVIEW OF ECONOMIC EVALUATIONS
(continued)

2. Increased uptake scenario: This scenario is essentially the same as current practice with the only difference being an increased proportion of men entering active surveillance, instead of active therapies of prostatectomy or radiation. Surveillance is deemed to be underutilised and this is simply a 'what if' scenario where those eligible to enter surveillance (excluding those appropriate for watchful waiting) do so assuming no barriers exist. Currently, 41% of men diagnosed in Australia with very low- or low-risk prostate cancer receive no treatment – either watchful waiting or surveillance. The increased surveillance will raise this probability to 80%, with 60% and 100% tested in sensitivity analyses.
3. Intermediate risk scenario: This scenario is to understand whether a select group of men with *early* intermediate-risk disease would be suitable for active surveillance. Although it may be some time before research can definitively inform clinicians of the safety and efficacy of active surveillance in this group, men at intermediate risk are the largest group within clinically-localised disease and potentially this is where surveillance could have the most benefit. It is difficult to tell the percentage of patients with more favourable intermediate risk as there is some subjectivity in the assessment. In general, patients with only one risk parameter are favourable [65]. Risk parameters include PSA between 10-20ng/ml, Gleason score 3+4; or T1-T2. It may be reasonable to consider patients with intermediate-risk disease currently treated with EBRT alone as those having favourable risk. In this scenario, we assumed that 16% of men with intermediate-risk disease received active surveillance instead of first-line radiation therapy. In all other respects, this scenario is the same as for current practice.
4. mpMRI scenario: mpMRI is thought to have an increasing role at various time points during prostate cancer management. One of these is with the active surveillance population by confirming the initial selection of men into this pathway. This scenario assumes that after men enter a surveillance program, an mpMRI is undertaken at least 6 weeks after the core biopsy and within the first year. A minimal gap of 6 weeks between TRUS-guided and MR-guided biopsies is necessary because of the trauma caused by the TRUS-guided biopsy can mimic cancer cells. If the mpMRI indicates intermediate-risk disease, an MR-guided biopsy is performed. Based on these results, the patient may either stay on active surveillance or be reclassified as having intermediate-risk disease and follow the appropriate treatment options.

The generic model was adapted to answer the research questions within this analysis. The four scenarios were created by adding three new strategy arms alongside the current practice arm. For the 'increased uptake' strategy, the current practice arm was cloned with the probability of receiving no treatment altered. For the 'intermediate risk uptake' strategy, a surveillance option replaced the EBRT only option and men instead were sent into the 'active surveillance' health state. For the 'mpMRI' scenario, structural changes were made to the 'active surveillance' health state (Figure 14). Minor changes were made to the generic model structure for the 'intermediate risk uptake' scenario as mentioned above (Figure 15).

Figure 14: mpMRI scenario for men selected for active surveillance

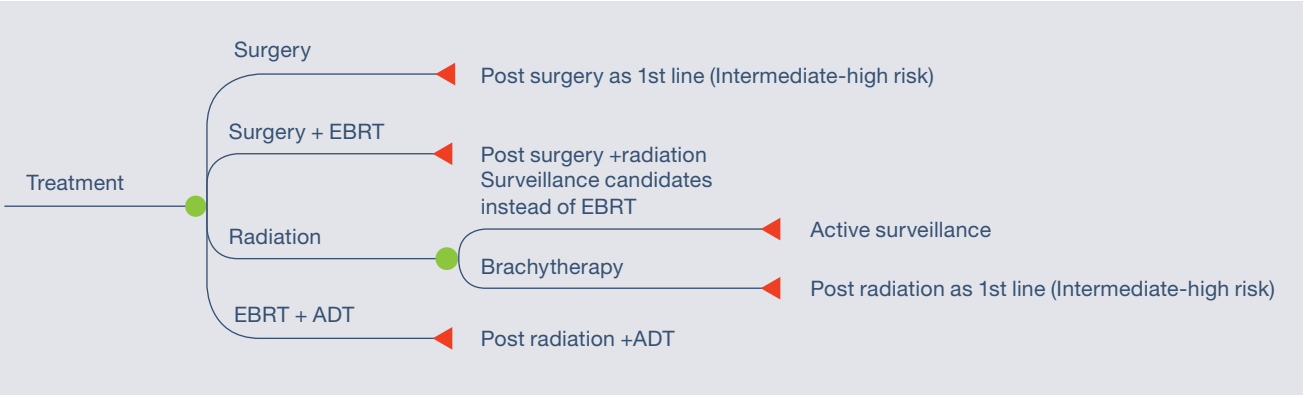


Note: blue arrows indicate changes from generic model

EBRT = external beam radiation therapy; Int = intermediate; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; PSA = prostate-specific antigen

4.0 OVERVIEW OF ECONOMIC EVALUATIONS *(continued)*

Figure 15: Early intermediate risk uptake of active surveillance



Note: blue arrows indicate changes from generic model
ADT = androgen deprivation therapy; EBRT = external beam radiation therapy

The model inputs were derived from literature searches and the most relevant studies. The additional inputs and sources are listed below in Tables 14 and 15.

In addition to these model inputs, two changes were made to the generic model in light of these specific research questions. The first involved adding an exit age for men on surveillance. A man on an active surveillance program would not remain indefinitely on this program with advancing age. This is consistent with the model's entry criteria where men aged 75 or over would instead be on watchful waiting. Similarly, in the model the maximum age a man can remain on active surveillance is 74 years and then he would switch to watchful waiting. Essentially, the main difference is that he would stop receiving TRUS-guided biopsies bi-annually.

The second change involved adding a new time-dependent table of probabilities for men who switch to active therapy while on active surveillance. This data comes from a long-term follow-up study by Klotz et al. (2015) on a prospective cohort of 993 patients followed for a median duration of 6.4 years (range 0.2 to 19.8 years). The data are presented in Table 14. The reasons for switching were indicators of worsening disease (e.g. short PSA doubling time, grade progression, stage progression, biopsy volume increase, ureteral obstruction) as well as patient preferences.

TABLE 14: PROBABILITIES OF MEN ON ACTIVE SURVEILLANCE SWITCHING TO ACTIVE THERAPY

Year	% remaining in program	% leaving program for therapy	Transition probabilities used in model
5	75.7%	24.3%	Years 1-5: 4.86%
10	63.5%	36.5%	Years 6-10: 2.44%
15	55.0%	45.0%	Years 11-15: 1.7%
20	55.0%	45.0%	Years 16-20: 0%

Source: Klotz et al. (2015) [64]

TABLE 15: KEY MODEL INPUTS FOR THE ACTIVE SURVEILLANCE SCENARIOS

Description	Value	Range	Source/rationale
Current scenario			
Probability of no treatment (active surveillance or observation) in low risk	40.6%	37%-45%	Evans (2013) [13]; based on 299/736
In those receiving no treatment, the probability of undergoing active surveillance	100% if <75 years	–	Assumption regarding threshold age 75 years, men 75 years and over undergo watchful waiting
Threshold age for active surveillance	75 years	72 - 78 years	Assumption; Life expectancy and comorbidities would limit active surveillance participation
Cost of ultrasound guided biopsy	$700	$490, $910	(MBS items 37219, 55600, 72825 + ciprofloxacin ($20) + complication cost (0.02 x $5276))
Cost of active surveillance in Year 1	$1,044/year	$731, $1357	2 urology visits, 4 PSAs, 1 biopsy, ±30%
Cost of active surveillance after Year 1	$608/year	$426, $790	2 urology visits, 2 PSAs, biopsy every 2 years, ±30%
Increased uptake scenario			
Probability of men with low-risk cancer receiving no treatment	80%	60%-100%	Assumption; The proportions of men receiving active surveillance or watchful waiting depend on the age threshold (above).
Intermediate risk scenario			
Probability receiving no treatment	80%	60%-100%	Assumption for % all eligible
Probability of intermediate risk entering surveillance program (from those being treated)	16.0%	13.9%-17.5%	Evans (2013) [13]; Of all men treated, 25.7% receive radiation (EBRT or brachytherapy) x 62.3% of these get EBRT only = 16.0%
mpMRI scenario			
Cost of mpMRI scan	$570	$399, $741	MSAC Protocol; ±30%
Cost of MR-guided biopsy (in-bore)	$2349	$1552	MSAC Protocol; $1552 is the weighted average of in-bore and fusion techniques (see Table 11)
Probability reclassified to intermediate risk	20.3%	14.2-26.4%	Vargas (2012) [66]

EBRT = external beam radiation therapy; MSAC = Medical Services Advisory Committee; mpMRI = multiparametric magnetic resonance imaging; MR = magnetic resonance; MBS = Medical Benefits Schedule

Costing of the mpMRI scan and MR-guided biopsy has significant uncertainty as they are not funded by government at this time. Therefore, variations in costing were tested.

4.0 OVERVIEW OF ECONOMIC EVALUATIONS *(continued)*

RESULTS

The results of the lifetime model for a cohort of men with a mean age of 65 years are presented in Table 16 for mean costs, QALYs and life years.

TABLE 16: KEY RESULTS OF ACTIVE SURVEILLANCE STRATEGIES

Means	Current practice	Increased uptake	Intermediate risk uptake	With mpMRI
Costs	$28,031	$27,316	$27,125	$28,818
QALYs	7.89	7.92	8.01	7.88
Life years	16.36	16.35	16.48	16.35
Incremental cost per QALY	Referent	Superior	Superior	Inferior
Incremental cost per LYS	Referent	Superior	Superior	Inferior

mpMRI = multiparametric magnetic resonance imaging, LYS = life years saved, QALYs = quality-adjusted life years

Compared with current practice, the results show that cost savings will occur in the increased uptake and intermediate risk uptake scenarios but the mpMRI strategy will be slightly more costly. QALYs are higher for the increased uptake and intermediate risk uptake scenarios and negligibly different in the mpMRI strategy. Therefore, the increased uptake and intermediate risk uptake scenarios are cost-effective and they both represent a win-win situation with cost savings and better patient outcomes.

In one-way sensitivity analyses, the variables of relevance to the active surveillance strategies are tested to see their influence on the results (see Table 17).

TABLE 17: RESULTS OF ONE-WAY SENSITIVITY ANALYSES OF THE ACTIVE SURVEILLANCE SCENARIOS

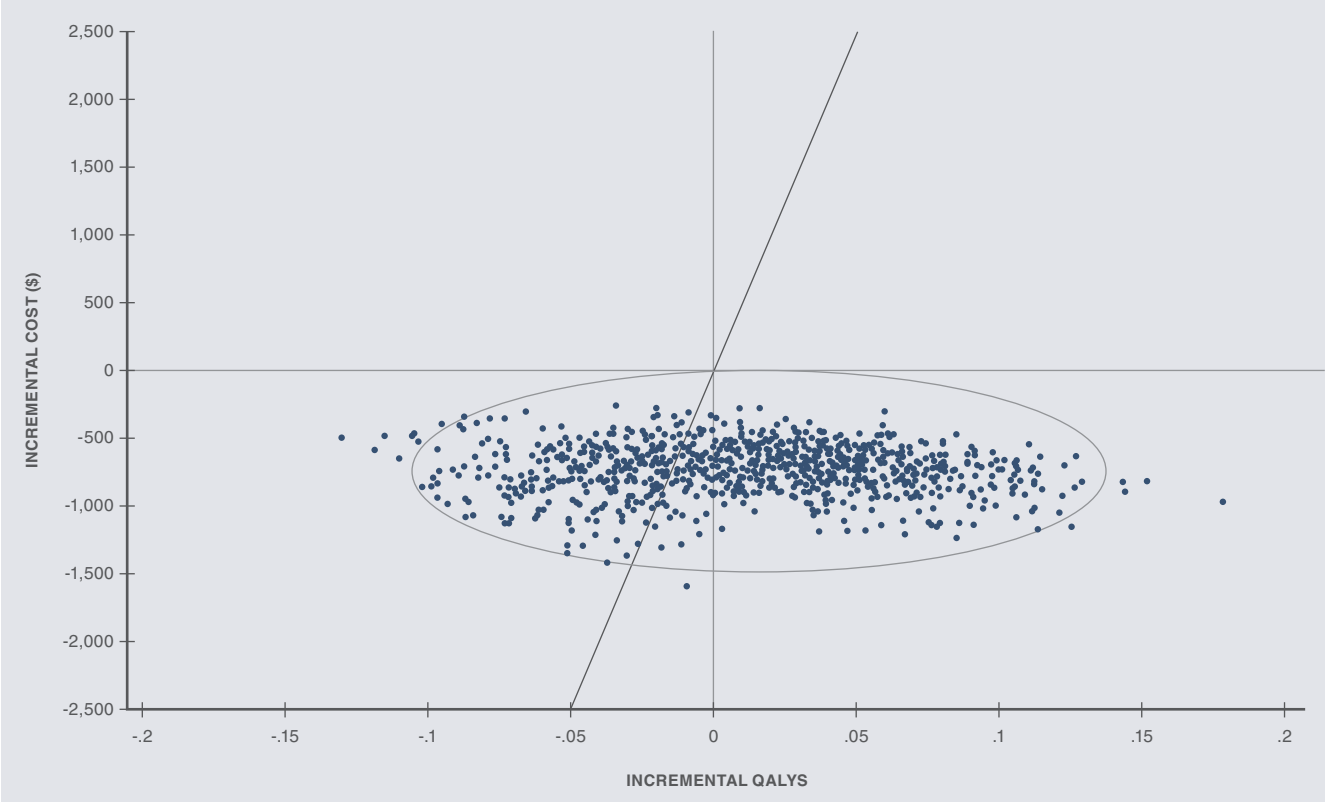
		Increased uptake scenario			Intermediate risk scenario			mpMRI scenario		
	Value tested	Inc QALYs	Inc costs	ICER	Inc QALYs	Inc costs	ICER	Inc QALYs	Inc costs	ICER
Base model	**–**	**0.03**	**-$715**	**sup**	**0.12**	**-$906**	**sup**	**-0.01**	**$787**	**inf**
Duration 5 years	5	-0.01	-$1,237	$123K	0.01	-$1,205	sup	-0.01	$615	inf
Duration 10 years	10	0.02	-$1,012	sup	0.07	-$860	sup	-0.01	$775	inf
AS age threshold – low	72 yrs	0.00	-$686	sup	0.08	-$958	sup	-0.01	$685	inf
AS age threshold – high	78 yrs	0.03	-$747	sup	0.14	-$940	sup	-0.02	$881	inf
Cost AS Year 1 – low	$731	0.03	-$751	sup	0.12	-$870	sup	-0.01	$797	inf
Cost AS Year 1 – high	$1357	0.03	-$681	sup	0.12	-$1,115	sup	-0.01	$782	inf
Cost AS after Year 1 – low	$426	0.03	-$841	sup	0.12	-$695	sup	-0.01	$812	inf
Cost AS after Year 1 – high	$790	0.03	-$591	sup	0.12	-$1,039	sup	-0.01	$767	inf
Cost MRI – lower	$399	0.03	-$809	sup	0.12	-$773	sup	-0.01	$806	inf
Cost MRI – high	$741	0.03	-$624	sup	0.12	-$906	sup	-0.01	$772	inf
Cost TRUS – low	$490	0.03	-$716	sup	0.12	-$906	sup	-0.01	$645	inf
Cost TRUS – high	$910	0.03	-$715	sup	0.12	-$906	sup	-0.01	$933	inf
Cost MRGB – lower	$1,552	0.03	-$716	sup	0.12	-$906	sup	-0.01	$789	inf
Prob no tx – current, low	37%	0.03	-$782	sup	0.12	-$972	sup	-0.01	$723	inf
Prob no tx – current, high	45%	0.02	-$636	sup	0.11	-$826	sup	-0.02	$869	inf
Prob no tx – inc, low	60%	0.01	-$352	sup	0.10	-$542	sup	-0.01	$789	inf
Prob no tx – inc, high	100%	0.04	-$1,080	sup	0.13	-$1360	sup	-0.01	$789	inf
Prob reclassify – low	14.2%	0.03	-$716	sup	0.12	-$906	sup	-0.01	$741	inf
Prob reclassify – high	26.4%	0.03	-$716	sup	0.12	-$906	sup	-0.02	$839	inf
Prob AS if int risk – low	13.9%	0.03	-$716	sup	0.10	-$880	sup	-0.01	$789	inf
Prob AS if int risk – high	17.5%	0.03	-$716	sup	0.13	-$922	sup	-0.01	$790	inf

AS = active surveillance; ICER = incremental cost-effectiveness ratio; inc = incremental; inf = inferior to current practice; int = intermediate; mpMRI = multiparametric magnetic resonance imaging; Prob = probability; MRGB = magnetic resonance guided biopsy; MRI = magnetic resonance imaging; sup = superior to current practice; TRUS = transurectal ultrasound guided biopsy; tx = treatment; QALYs = quality-adjusted life years; yrs = years

4.0 OVERVIEW OF ECONOMIC EVALUATIONS
(continued)

In probabilistic sensitivity analyses, with 1000 Monte Carlo simulations, the incremental scatterplots are presented in Figures 16 to 18. These figures demonstrate that the likelihood of being cost-effective for the increased uptake scenario was 63.9%, for the intermediate risk uptake scenario was 75.6%, and 0.6% for the mpMRI scenario.

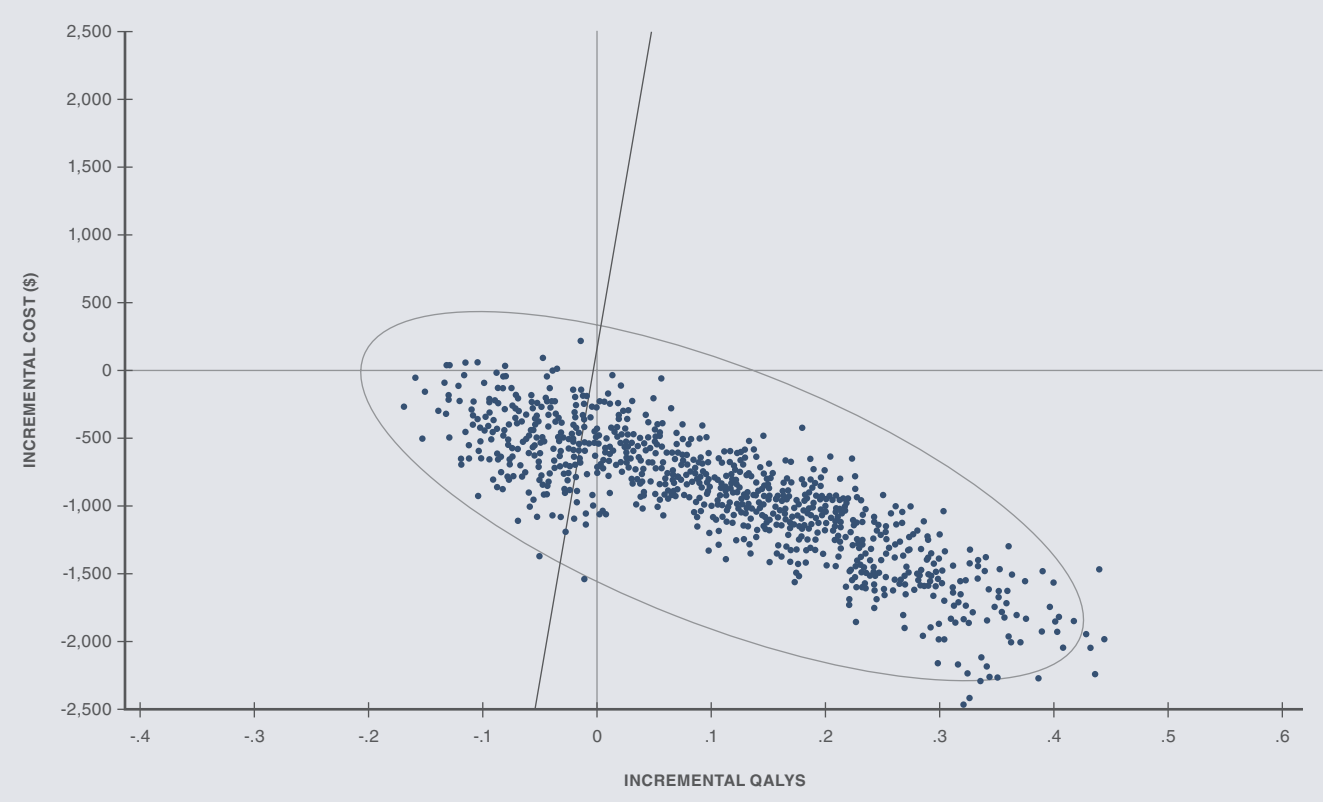
Figure 16: Incremental cost-effectiveness scatter plot for increased uptake



Interpretation: The proportion of dots to the right of the diagonal line representing the willingness-to-pay of $50,000 per QALY is 63.9%. The oval is the 95% confidence ellipse. The chance that the increased uptake scenario is cost-effective is 63.9%.

QALY = quality-adjusted life year

Figure 17: Incremental cost-effective scatter plot for intermediate risk uptake

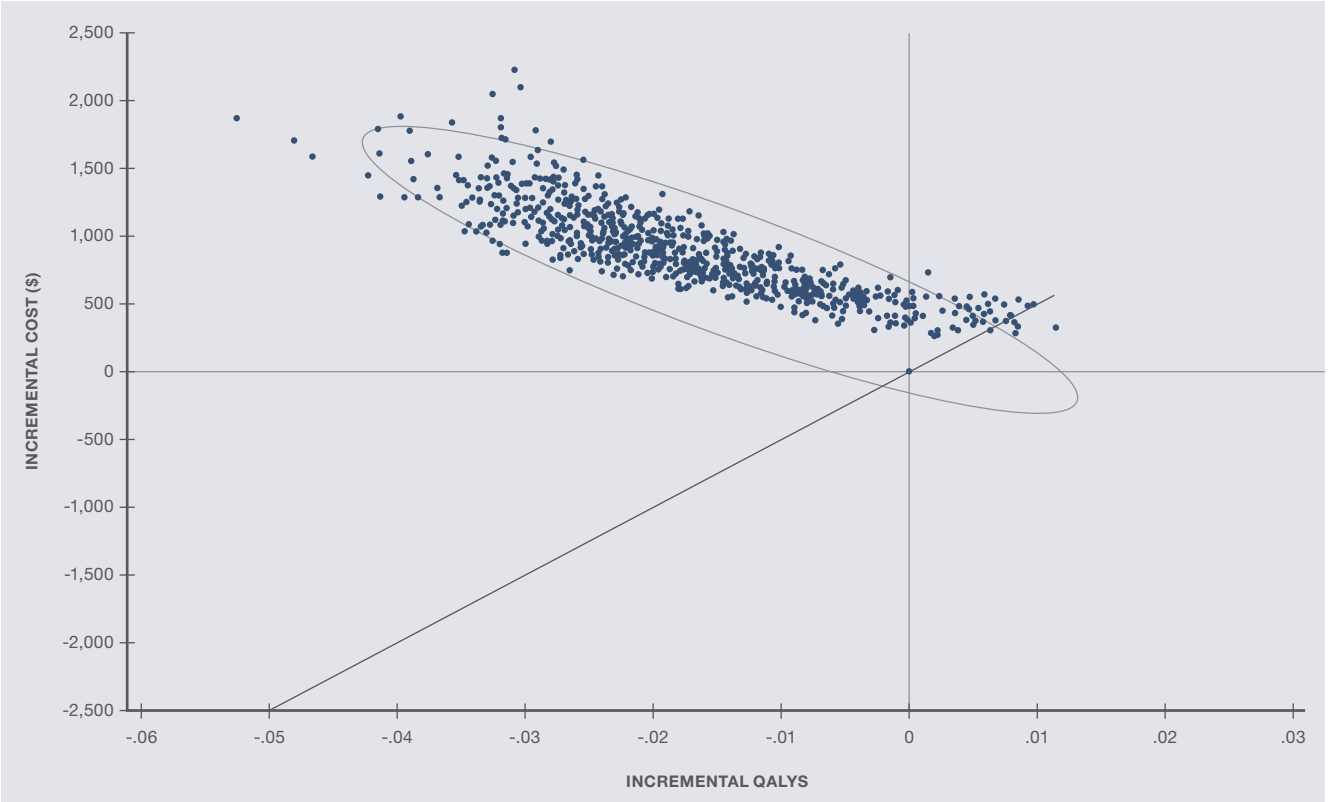


Interpretation: The proportion of dots to the right of the diagonal line representing the willingness-to-pay of $50,000 per QALY is 75.6%. The oval is the 95% confidence ellipse. The chance that the intermediate uptake scenario is cost-effective is 75.6%.

QALY = quality-adjusted life year

4.0 OVERVIEW OF ECONOMIC EVALUATIONS
(continued)

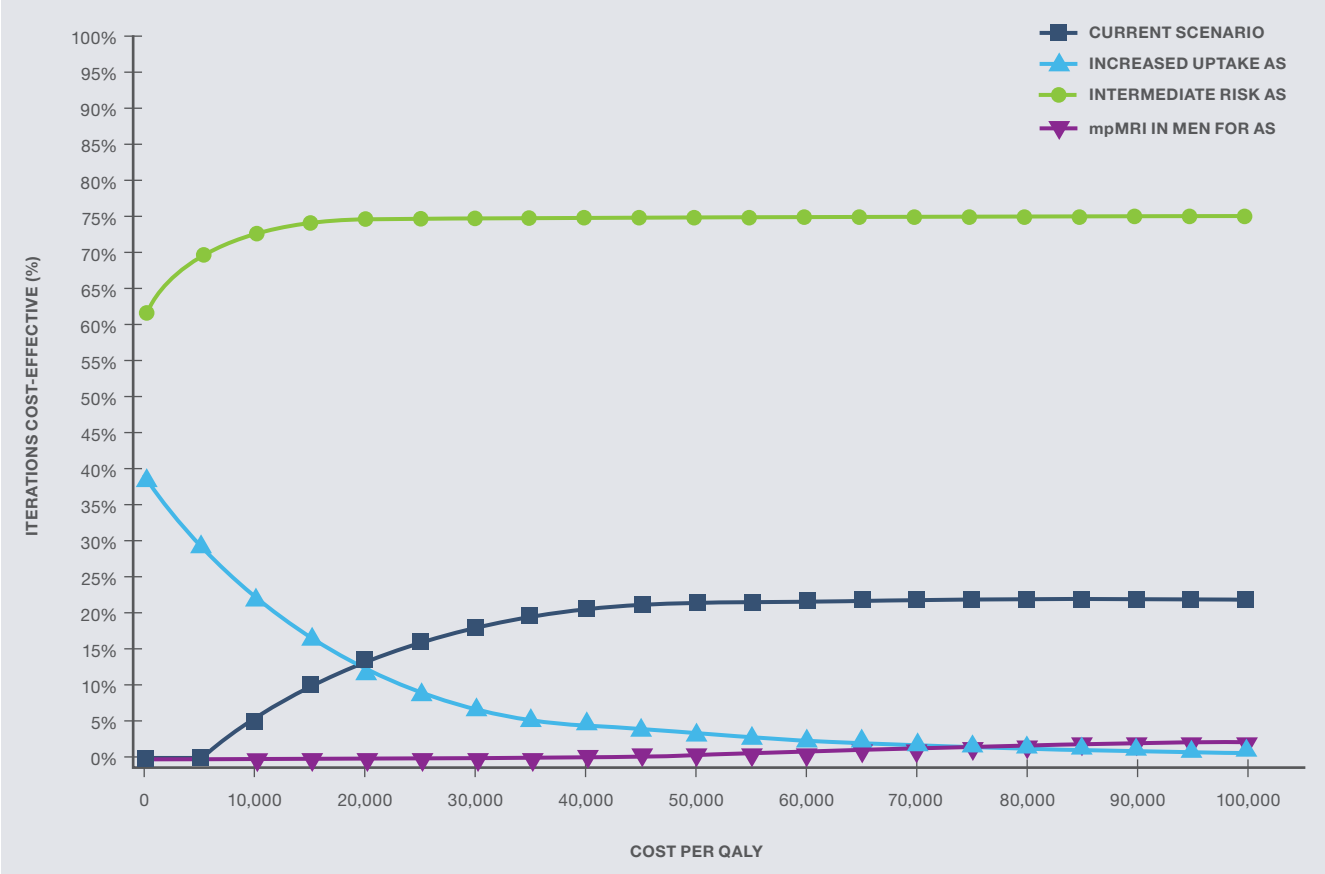
Figure 18: Incremental cost-effectiveness scatter plot for mpMRI strategy



Interpretation: The proportion of dots to the right of the diagonal line representing the willingness-to-pay of $50,000 per QALY is 0.6%. The oval is the 95% confidence ellipse. 16% of dots are at the origin. The chance that the mpMRI scenario is cost-effective is 0.6%. mpMRI = multiparametric magnetic resonance imaging; QALY = quality-adjusted life year

Figure 19 further illustrates that the relative proportion of cost-effectiveness for the four scenarios is dominated by the intermediate risk scenario at all cost per QALY thresholds.

Figure 19: Cost-effectiveness acceptability curves for all strategies



Interpretation: Relative to each other, the intermediate risk scenario and increased uptake scenario are preferred at lower willingness-to-pay levels of cost per QALY.

AS = active surveillance; QALY = quality-adjusted life year

4.0 OVERVIEW OF ECONOMIC EVALUATIONS
(continued)

DISCUSSION

The findings of this analysis show that favourable economic and patient outcomes may be possible if greater uptake of active surveillance occurs in Australia in men with very low- or low-risk prostate cancer. In addition, if a small proportion of men with favourable intermediate-risk prostate cancer also underwent active surveillance, significantly more gains in QALYs and cost savings may occur. Increasing active surveillance produced a 'win-win' result where there were gains to health-related quality of life together with resource savings to the health system.

Sensitivity analyses indicate that the mean cost savings could range from $352 to $1237 depending on other input values in the model. This represents a potentially large cost savings to the health system if applied to all new cases of men with low-risk prostate cancer each year (i.e. estimated 6,624 cases x $715 = $4.7 million). However, QALY gains were minor but were consistently better than the status quo ranging from 0.01 to 0.14 in sensitivity analyses. Larger QALY gains are possible for the 'intermediate risk' uptake scenario since the more serious treatment effects and adverse events could be avoided.

A limitation to this analysis is that it is purely exploratory and no actual intervention is assessed that guarantees this switch in current uptake levels, either directed at clinicians or their patients. If this had occurred, healthcare costs of delivering the intervention would be necessary. Currently, an National Health and Medical Research Council funded project for a randomised controlled trial of an online decision-support intervention is underway, specifically designed to increase uptake of active surveillance in Australia. A health economic analysis of this intervention will be forthcoming. The current analysis suggests that as long as the trialled intervention does not exceed $715 per patient, then favourable cost-effectiveness will be preserved.

This is the first study to look at the cost-effectiveness of increased versus current active surveillance uptake. Other cost-effectiveness studies generally compare radical prostatectomy versus active surveillance [67-70] whereas here, we undertake a more realistic comparator of including the current mix of treatments offered to men including active surveillance, radical prostatectomy, EBRT or brachytherapy and assessing what the changes in impacts are with increased uptake of surveillance. In addition, our model is long term and we have incorporated health utilities into the key outcomes as preferred in economic evaluations.

THE BOTTOM LINE

— Doubling the current uptake of active surveillance by Australian men with low-risk prostate or low-risk and favourable intermediate-risk cancer potentially increases QALYs and saves healthcare costs.

— The likelihood of cost-effectiveness for increasing uptake of low-risk prostate was 63.9%, and for increasing uptake of low-risk and a proportion of men intermediate-risk cancer was 75.6%.

— The likelihood of cost-effectiveness of using mpMRI for selecting men into active surveillance, in comparison to the other increasing uptake scenarios, was 0.6%.

4.3 COST-EFFECTIVENESS ANALYSIS OF PSA SCREENING

BACKGROUND & RATIONALE

Widespread PSA screening for early detection of prostate cancer in asymptomatic men is currently not recommended at a population level in Australia and elsewhere around the world. Concerns about over diagnosis of low-risk prostate cancer by as much as 40-50% of screen-detected cases, subsequent overtreatment and adverse events are believed to outweigh the benefits of early diagnosis of curable disease [1]. Two pivotal randomised clinical trials of long-term follow up of screened and unscreened populations provide critical information for this controversial topic [56, 71].

Unhelpfully though, these two trials have produced inconsistent results. The US Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial found a 13% increase in prostate cancer mortality (not statistically significant) in the screening group after 13 years [71]. Conversely, the European Randomized Study of Screening for Prostate Cancer (ERSPC) found a statistically significant 20% fall in prostate cancer mortality after 13 years [56]. All-cause mortality did not differ between the intervention and control groups. A comparison of the main features of the two trials and their results are listed in Table 18.

TABLE 18: COMPARISON OF THE ERSPC AND PLCO PROSTATE CANCER SCREENING TRIALS (13 YEARS FOLLOW-UP)

	ERSPC trial	PLCO trial
Key publication of latest results	Andriole (2012) [71]	$27,316
Setting	7 countries in Europe	10 centres in US
Population of men	55-69 years	55-74 years
Intervention	PSA test 4 yearly DRE optional	Annual PSA test for 6 years Annual DRE for 4 years
Total N intervention/control	72891/89352	38340/38345
Prostate cancers detected N intervention/control	7408/6107	4250/3815
Prostate cancers detected – rate ratio	1.57 (95%CI: 1.51, 1.62)	1.12 (95%CI: 1.07, 1.17)
Prostate cancer deaths N intervention/control	355/545	158/145
Prostate cancers detected – rate ratio	0.73 (95%CI: 0.61, 0.88) [a]	1.09 (95%CI: 0.87, 1.36)
All deaths – rate ratio	1.00 (95%CI: 0.98, 1.02)	1.19 (95%CI: 0.83, 1.72) [b]

CI = confidence interval; DRE = digital rectal examination; ERSPC = European Randomized Study of Screening for Prostate Cancer; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening; PSA = prostate-specific antigen

[a] Adjusted for attenders

[b] 55-74 age group

4.0 OVERVIEW OF ECONOMIC EVALUATIONS *(continued)*

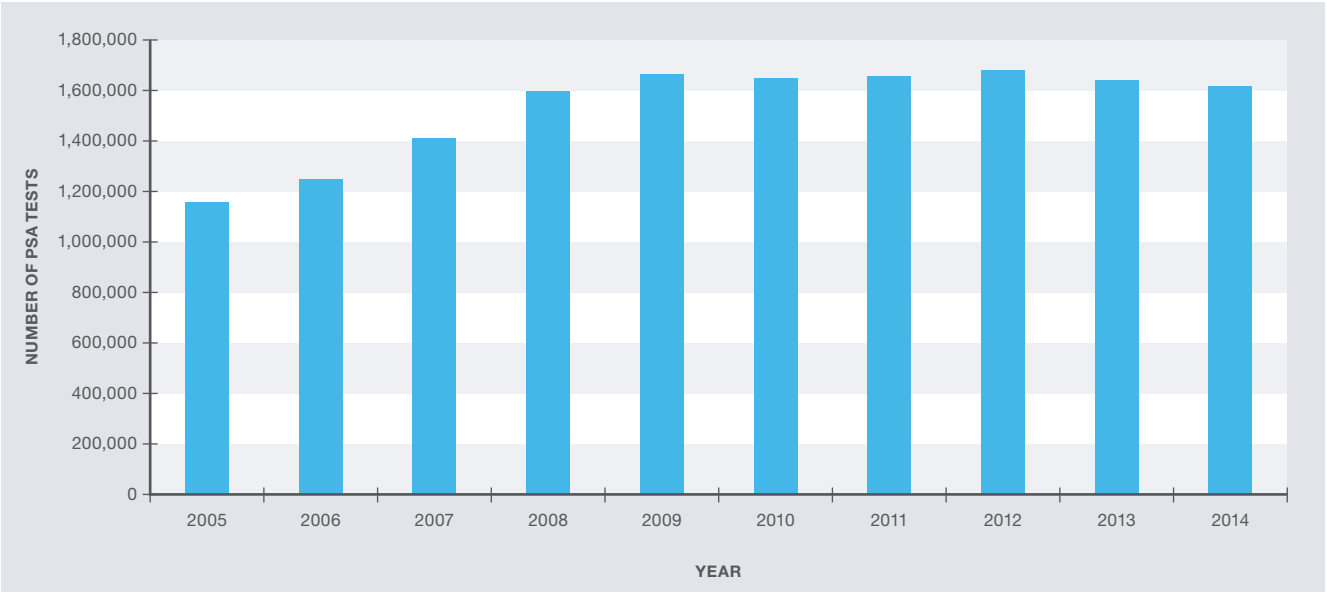
Both studies are well-respected [72], have huge samples, sophisticated randomisation protocols (each with equal intervention and control groups), long 13-year follow-ups and rigorous methods for blinding of death record reviews, high compliance of status and testing rates. The long follow up is likely to be too short and does not capture all expected deaths from prostate cancer due to the long natural history of this disease.

Cancer Council Australia and Prostate Cancer Foundation of Australia have recently published clinical practice guidelines for PSA testing and early management of test-detected prostate cancer (2016) [1]. These guidelines were developed by an expert advisory panel from a range of specialist health, primary care disciplines and consumer representatives. In these guidelines, it confirms that there is insufficient evidence to support population-wide screening but there remains a role for PSA testing in clinical practice where men might request a test or clinicians offer a test. PSA testing is known to be an imprecise test with sub-optimal levels of diagnostic accuracy. However, over 3,300 men each year die of prostate cancer in Australia and in the absence of a better alternative test, it remains the first-line investigation for detecting prostate cancer alongside DRE. Confirmation of cancer is undertaken through biopsy and histopathology assessment.

Ultimately, the goal of screening is to prevent early deaths from prostate cancer, which occurs through early detection; detecting cancers at an early stage before they have spread and before the man faces a poorer prognosis. This is essentially the idea behind breast, cervical and colorectal cancer screening programs currently in place in Australia. The major problems of PSA screening is the diagnostic inaccuracy of staging the tumour, the slow growth of many prostate cancers (which if left alone may not cause any harm) and the surgical or radiation treatment options which are costly and produce very common and detrimental side effects (i.e. incontinence, erectile dysfunction and bowel problems) [14].

Each year it is estimated that 20% of Australian men aged 45 to 74 years have a PSA test [1]. Medicare item reports indicate that 1.6 million PSA tests were undertaken in 2014 at a cost to the Australian Government of $30.2 million. However, as shown in Figure 20, the volume of testing has remained stable since 2008. With these testing levels, it is clear that PSA screening is occurring opportunistically or informally in Australia already, much the same as it is for skin cancer screening in primary care settings.

Figure 20: Number of PSA tests ordered in Australia (2005-2014)



Source: Medicare item statistics for PSA items 66659, 66660, 66656, 66655
PSA = prostate-specific antigen

Several cost-effectiveness studies have investigated the value of population-level PSA testing [73-76]. In general, these modelling studies demonstrate that the benefits of widespread PSA testing do not outweigh the potential harms of treatments and their side effects. Intuitively, for a PSA testing program to be viable at a population level, there needs to be substantial down-shifting of tumours from high-grade to low-grade that produce meaningful gains in survival and ideally less-invasive treatments with fewer side effects than current options. These features deal with both the survival and quality of life gains of PSA testing while resource costs also need to be acceptable to decision makers.

Using our generic model and extending the structure, the purpose of this study was to assess the cost-effectiveness of PSA testing and investigate the main parameters of the model and the mix of variables that would make it cost-effective.

METHODS

The research question of this study is: What mix of parameters would make PSA testing to detect early-stage prostate cancer in asymptomatic men cost-effective?

This study relied on the generic model for the pathways of treatment and follow-up from the time of diagnosis. Two groups were compared; asymptomatic men who receive screening versus the current scenario of no testing, or more accurately, the current scenario in Australia presently with ad hoc testing. The model structure was altered to include branches for men who may or may not develop prostate cancer. These additions to the model structure are illustrated in Figure 21.

Figure 21: Additional branches to generic model for the PSA screening analysis

adv = advanced; PCa = prostate cancer; PSA = prostate-specific antigen

The types of variables normally important in evaluating prostate screening programs include the frequency and duration of testing, the age of men screened, diagnostic accuracy, subsequent treatments, side effects and costs for all components involved. In this study, the 13-year ERSPC findings reported by Schröder (2014) provided most of the key inputs [56]. In agreement with the expert advisory committee of the recent guidelines, the ERSPC trial was chosen as a more robust research study because of the following: (i) ERSPC trial had lower contamination of screening in the control group (30% vs. 52% had screening in PLCO), (ii) PLCO trial had an overall older age distribution, (iii) 45% of the PLCO trial's overall sample had a PSA test before trial randomisation, and (iv) ERSPC results for prostate cancer deaths were internally consistent across the centres in the study, despite their centre-level heterogeneity [1].

4.0 OVERVIEW OF ECONOMIC EVALUATIONS
(continued)

The two comparison groups in the model are:

1. PSA screening group: Asymptomatic men will receive a PSA screen at age 60 which involves a general practitioner (GP) visit, the PSA test and pathology assessment. A second screen is offered 4 years after the first screen. For the model duration, men will either be cancer-free (and remain without cancer) or have cancer after urology consultation and confirmatory biopsy. The grade of the cancer is determined from the trial and men will face all the usual treatment and follow-up care as detailed in the generic model stratified by cancer risk. The data on screen-detected cancers are based on findings from Schröder (2014) [56] and include all interval or missed cancers over the 13-year observational period of the trial. Therefore, sensitivity and specificity parameters have not been explicitly included in the model because they are directly incorporated in the detected prostate cancers from the ERSPC trial.
2. No screening group: The structure of the model and possible prostate cancer diagnosis or not is identical to the PSA screening group but the proportion of detected cancers are different, as reported in the ERSPC trial data (for the 'no screening' group).

Table 19 presents the key variables for the additional branches of the PSA testing analysis. The model assumes a maximum of two screens per man, 4 years apart in keeping with the ERSPC trial. The screening age at baseline was 60 years and this was tested at various ages. The model duration was lifetime up to a maximum of 90 years of age.

TABLE 19: ADDITIONAL MODEL VALUES FOR THE PSA TESTING ANALYSIS

Model probabilities	Value	95% CI	Source
Frequency of screening	4 yearly	–	Assumption; Schröder (2014), Martin (2013) [56, 73]
Number of screens	2	1, 3	Based on Schröder (2014) mean 2.1, range 1.0-3.5 screens per man [56]. Model assumes first screen in Year 1 and 2nd screen in Year 5.
Screening age in years	60	50, 55, 65 yrs	Assumption; Schröder (2014) median 61.1 years (IQR 57.9-66.1) [56]
Cost of screening	$80.05	–	Cost of GP $37.05 + (cost of PSA test + pathology $43.00)
Cost of core biopsy (TRUS)	$700	$490, $910	(MBS items 37219, 55600, 72825 + ciprofloxacin ($20) + complication cost (0.02 x $5276))
Cost of urologist consult	$86	–	MBS item 104 specialist consult
Incidence of cancers [a]			
Screening group			
Proportion of low-risk cancers	4.87%	4.36%, 5.38%	Schröder (2014); 4441/6838 [56]
Proportion of int-risk cancers	1.81%	1.50%, 2.13%	Schröder (2014); 1625/6838 [56]
Proportion of high-risk cancers	0.58%	0.40%. 0.76%	Schröder (2014); 518/6838 [56]
Proportion of advanced cancers	0.29%	0.16%, 0.41%	Schröder (2014); 254/6838 [56]
No screening group			
Proportion of low-risk cancers	3.49%	3.01%, 3.97%	Schröder (2014); 2543/5507 [56]
Proportion of int-risk cancers	2.36%	1.96%, 2.76%	Schröder (2014); 1711/5507 [56]
Proportion of high-risk cancers	0.93%	0.67%, 1.18%	Schröder (2014); 667/5507 [56]
Proportion of advanced cancers	0.82%	0.58%, 1.05%	Schröder (2014); 586/5507 [56]
Relative risk of overall deaths for screened versus unscreened groups	1.00	0.98, 1.02	Schröder (2014) [56]; This result was used to calibrate the model to ensure relative overall survival did not differ between the two groups. The background mortality rate (as a function of age) was increased in the screening group by 27%.
Health utilities			
Utility without cancer	0.85	0.90	Clemens (2014) [30]; background utility 55-64 year olds
Disutility of core biopsy (TRUS)	0.035	0.02, 0.05	Assumption; (see Table 11)
Disutility of being in PSA program	0.05	0.00, 0.07	Assumption; to account for anxiety

MBS = Medicare Benefits Schedule; CI = confidence interval; TRUS = transrectal ultrasound; PSA = prostate-specific antigen; IQR = interquartile range; GP = general practitioner;; int = intermediate

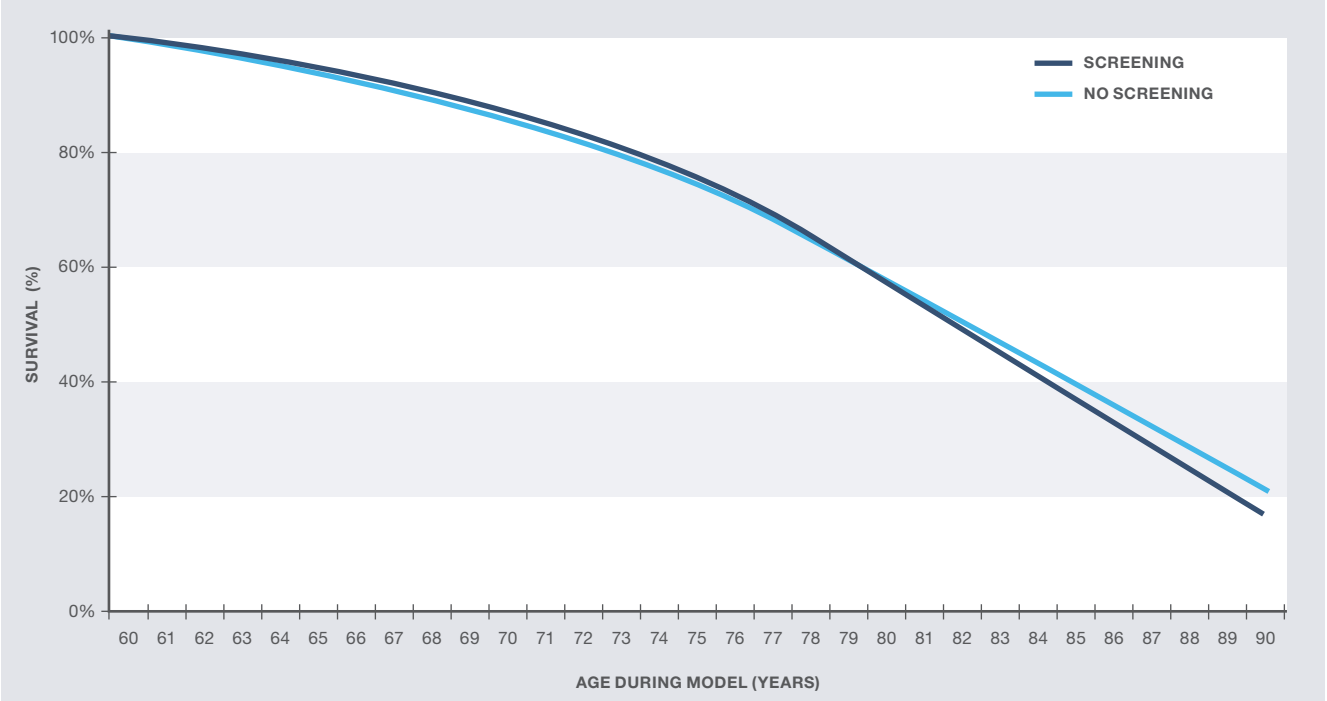
[a] Values from Schröder (2014) were over 13 years therefore a rate to probability formula was used to convert to annual probabilities. The denominator in these figures exclude 570 men in screening group and 600 in the unscreened group where risk status was missing.

4.0 OVERVIEW OF ECONOMIC EVALUATIONS *(continued)*

Some additional changes to health utilities also occurred. For men who were asymptomatic and remained cancer-free, a normal background utility value was used (0.85) [30]. This was tested at 0.90 in a sensitivity analysis. A disutility was incurred that was associated with a core biopsy and this value was consistent with the mpMRI model (see Table 11). Finally a small disutility was attached to being in a PSA program among those men who were cancer-free as this might be attributable to anxiety or diagnostic inaccuracy. This applied only for five years to cover the two screens the men would receive.

In the ERSPC trial, prostate cancer mortality was statistically significantly lower in the screening group than in the control group (rate ratio 0.83 (95% CI: 0.73 to 0.94) using deaths per person-years. However, all-cause mortality was similar between groups with a rate ratio of 1.00 (95% CI: 0.98 to 1.02). This implies that deaths from other causes were higher in the screening group than in the control group. To avoid underestimating deaths, we calibrated the model and increased the background mortality rate in the screening group by 27% to reflect the equal overall mortality rates across the two groups in the ERSPC trial. A comparison of the final survival curves used is presented in Figure 22.

Figure 22: Comparison of survival curves estimated in the model



ABS = Australian Bureau of Statistics, 3302.0.55.001 - Life Tables, States, Territories and Australia, 2011-2012

A scenario analysis was also undertaken to assess PSA screening every two years in men aged 50-69 years, in accordance with the recommended protocol in the current guidelines [1].

RESULTS

The results of the model outcomes are provided in Table 20.

TABLE 20: KEY OUTCOMES FOR THE PSA SCREENING MODEL

Means [a]	PSA screening	No screening	Incremental difference
Costs	$15,184	$17,975	-$2,798
QALYs	9.97	10.03	-0.06
Life years	21.24	21.27	-0.03
Incremental Cost per QALY	$46,633	Referent	–
Incremental Cost per LYS	$93,267	Referent	–

LYS = life years saved; QALYs = quality-adjusted life years; PSA = prostate-specific antigen

[a] Results are based on 5000 Monte Carlo simulations

The results of the model show that when QALYs are the outcome of choice, PSA screening is less expensive by $2,798 per person and produces slightly lower QALYs than no screening. The costs are lower in the PSA screening arm because proportionally more men experience stage migration to low-risk disease, which is associated with treatments that are less expensive than those for higher-risk disease. Similarly, improved quality of life outcomes due to early-stage disease also occurred but these improvements were eroded by decrements in quality of life from more biopsies and being in a PSA testing program.

While cost savings to the healthcare system were found for PSA testing over the long run, there were no notable patient gains in survival or QALYs. Due to the PSA screening option demonstrating no additional benefit for patients in terms of QALYs, representing both quality of life and survival in one metric, PSA screening cannot be viewed as cost effective.

One-way sensitivity analyses were undertaken on all key variables described in Table 21. The main drivers of the model results were the probabilities of advanced cancers detected in the screening and no screening groups, the starting age of the men entering screening and the disutility of being in a screening program.

4.0 OVERVIEW OF ECONOMIC EVALUATIONS *(continued)*

TABLE 21: RESULTS OF ONE-WAY SENSITIVITY ANALYSES ON KEY VARIABLES IN THE PSA MODEL

	Value tested	Inc costs	Inc QALYs	ICER
Base model	–	-$2,798	-0.06	$46,633
Starting age	50	-$3,146	0.10	Superior [a]
Starting age	55	-$2,993	0.02	Superior [a]
Protocol in guidelines [1]				
PSA testing every 2 years from 50-69 years	-$2,953	0.10	Superior [a]	
More frequent testing	PSA testing annually from 50-69 years	-$2,438	-0.06	$40,633
Cost of TRUS-guided biopsy – low	$490	-$2,804	-0.06	$46,733
Cost of TRUS-guided biopsy – high	$910	-$2,754	-0.06	$45,900
Probability of cancer in screen group				
Low-risk cancer – low	4.36%	-$3,057	-0.05	$61,140
Low-risk cancer – high	5.38%	-$2,526	-0.08	$31,575
Intermediate-risk cancer – low	1.50%	-$3,225	-0.04	$80,625
Intermediate-risk cancer – high	2.13%	-$2,354	-0.09	$26,156
High-risk cancer – low	0.40%	-$3,231	-0.03	$107,700
High-risk cancer – high	0.76%	-$2,339	-0.10	$23,390
Advanced cancer – low	0.16%	-$3,187	0.00	Superior [a]
Advanced cancer – high	0.41%	-$2,375	-0.13	$18,269
Low-risk cancer – low	3.01%	-$2,589	-0.06	$43,150
Low-risk cancer – high	3.97%	-$2,952	-0.06	$49,200
Intermediate-risk cancer – low	1.96%	-$2,270	-0.08	$28,375
Intermediate-risk cancer – high	2.76%	-$3,258	-0.04	$81,450
High-risk cancer – low	0.67%	-$2,171	-0.10	$21,710
High-risk cancer – high	1.18%	-$3,369	-0.02	$168,450
Advanced cancer – low	0.58%	-$2,053	-0.17	$12,076
Advanced cancer – high	1.05%	-$3,488	0.06	Superior [a]
Health utilities				
Disutility of TRUS-guided biopsy – low	0.02	-$2,802	-0.06	$44,573
Disutility of TRUS-guided biopsy – high	0.05	-$2,802	-0.06	$44,609
Disutility of being in PSA program – low	0.00	-$2,780	0.13	Superior [a]
Disutility of being in PSA program – high	0.07	-$2,780	-0.54	$5,148
Utility when cancer-free	0.90	-$2,780	-0.06	$46,333

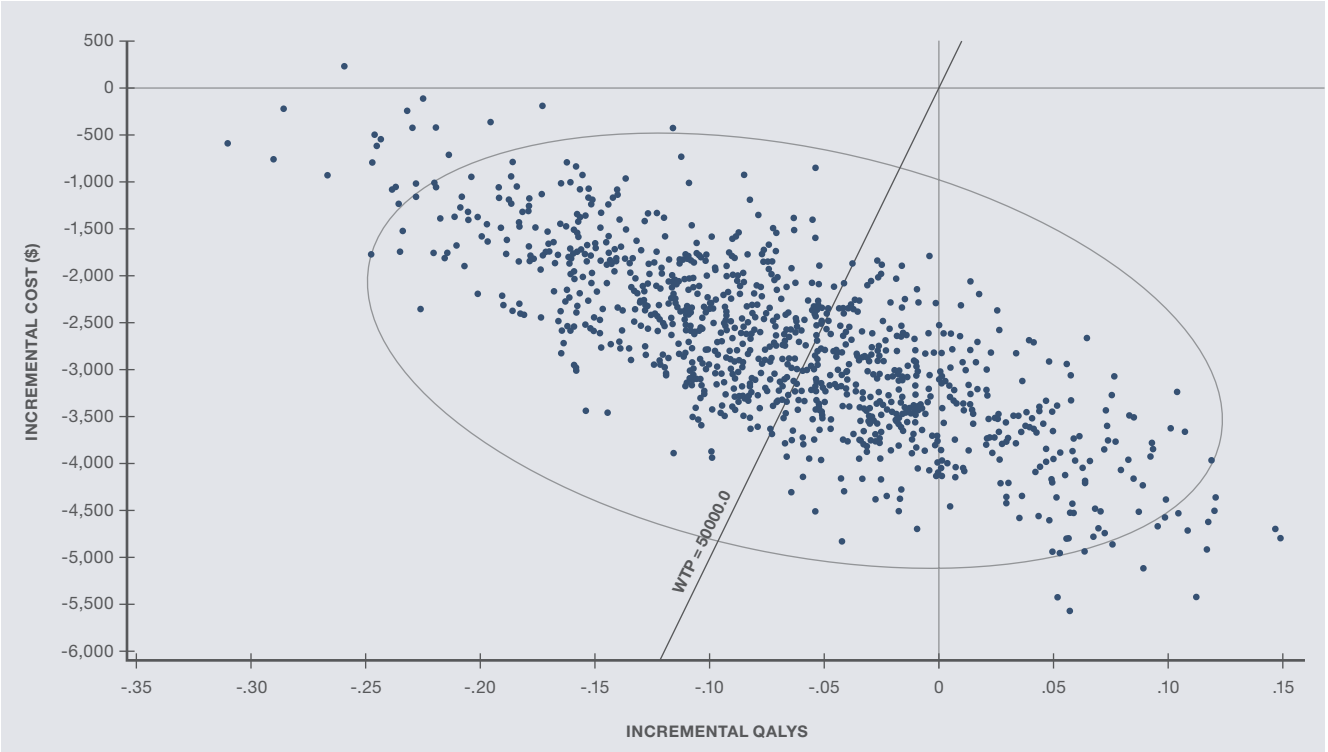
ICER = incremental cost-effectiveness ratio; inc = incremental; PSA = prostate-specific antigen; QALYs = quality-adjusted life years; TRUS = transrectal ultrasound

[a] This indicates that the PSA screenng strategy is superior because it is cost-saving and produces more QALYs (albeit negligibly more) than no screening.

The sensitivity analyses show that most changes in variables do not materially affect the main results. However, when the probability of detecting advanced cancers in the screening group decreases from 0.29% to 0.16% (the lower 95% confidence limit) or conversely increases in the non-screening group (from 0.58% to 1.05%), PSA screening is cost-effective. PSA screening is also cost-effective when the starting age of the screening program is either 50 or 55 years and in the scenario of testing every two years in ages 50-69 years. Finally, if the model assumed no disutility for being in a PSA screening program, PSA would be cost-effective. In all of these situations where PSA was cost-effective, the effectiveness in terms of QALYs is very small ranging from -0.17 to 0.13 QALY gain or one to seven weeks of additional good quality life over at least 30 years duration.

In probability sensitivity analyses, 5000 simulations of the model were performed and values randomly selected from the parameter distributions. At an acceptability threshold of $50,000 per QALY, the likelihood that PSA screening was cost-effective was 20.0% when the starting age was 60 years (Figure 23) and 83.8% at 50 years (Figure 24). For the protocol in the guidelines of PSA testing every two years from age 50 to 69 years, the probability of being cost-effective was 83.1%.

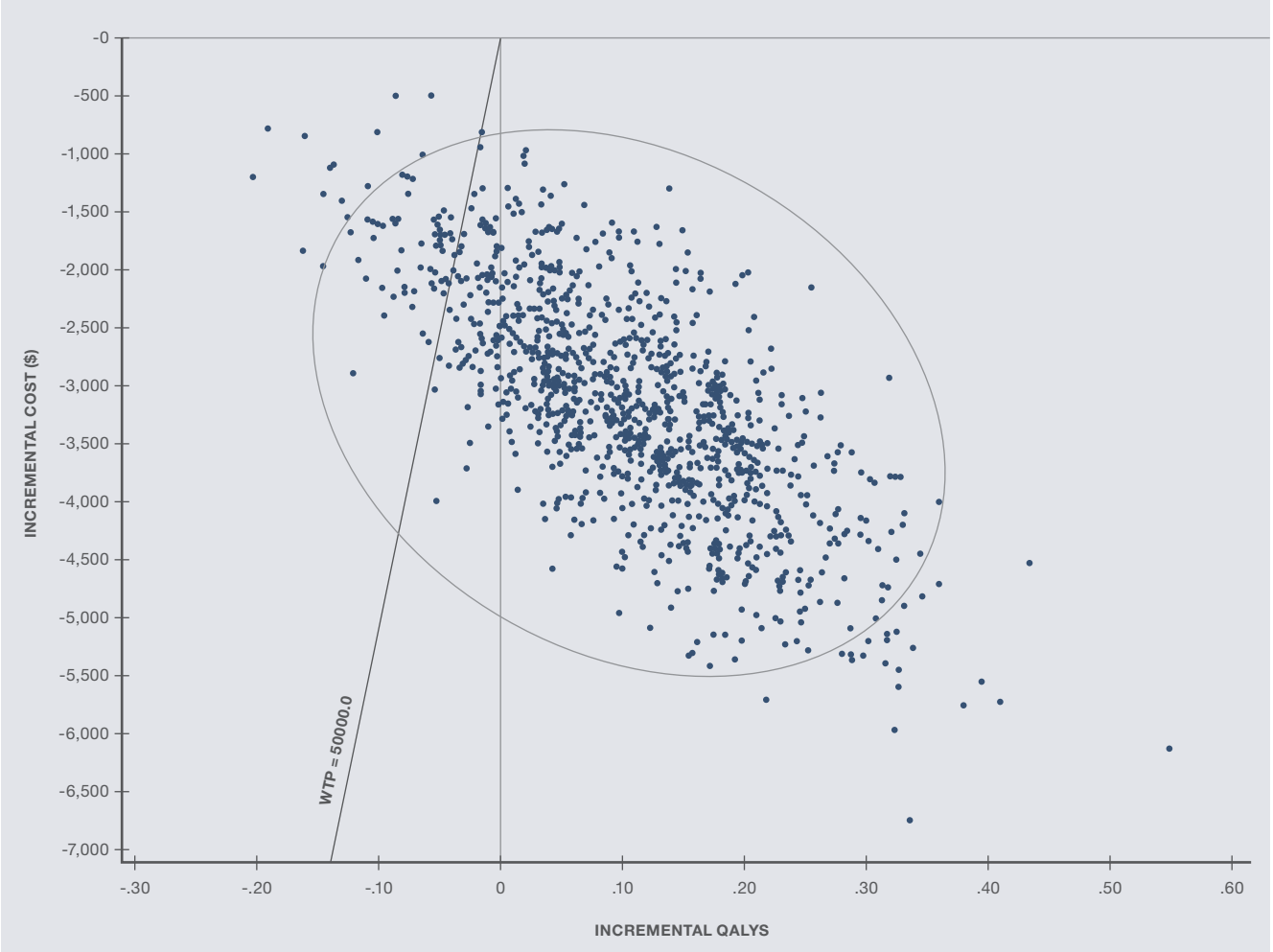
Figure 23: Incremental cost-effectiveness scatter plot for PSA screening (60 year olds)



Interpretation: the proportion of dots to the right of the diagonal line representing the willingness-to-pay of $50,000 per QALY is 20.0%.
The oval is the 95% confidence ellipse. The chance that the PSA screening scenario is cost-effective is 20%.
PSA = prostate-specific antigen; QALY = quality-adjusted life year; WTP = willingness-to-pay

4.0 OVERVIEW OF ECONOMIC EVALUATIONS
(continued)

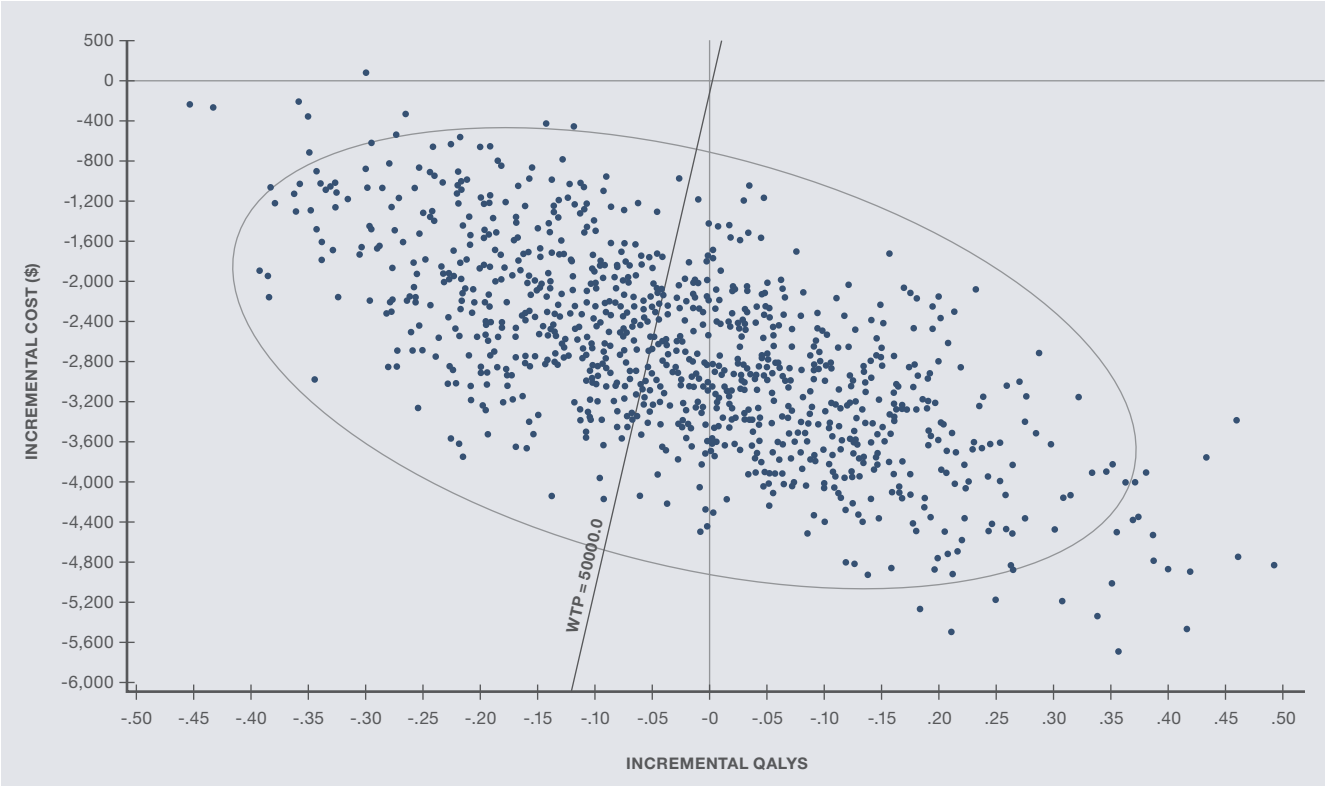
Figure 24: Incremental cost-effectiveness scatter plot for PSA screening (50 year olds)



Interpretation: the proportion of dots to the right of the diagonal line representing the willingness-to-pay of $50,000 per QALY is 83.8%.
The oval is the 95% confidence ellipse. The chance that the PSA screening scenario is cost-effective is 83.8%.
PSA = prostate-specific antigen; QALY = quality-adjusted life year; WTP = willingness-to-pay

In terms of life years saved, ignoring quality of life impacts, the probability that PSA screening was cost-effective was 43.6% (Figure 25).

Figure 25: Incremental cost-effectiveness scatter plot for PSA screening (LYS)



Interpretation: the proportion of dots to the right of the diagonal line representing the willingness-to-pay of $50,000 per LYS is 43.6%.
The oval is the 95% confidence ellipse. The chance that the PSA screening scenario is cost-effective is 43.6%.
LYS = life years saved; PSA = prostate-specific antigen; WTP = willingness-to-pay

4.0 OVERVIEW OF ECONOMIC EVALUATIONS
(continued)

In all the above figures, virtually all dots fell below zero on the vertical axis meaning that PSA testing is potentially cost-saving over the 30 year model duration.

DISCUSSION

In response to the research question of the optimal mix of parameters to make a PSA program cost-effective, our results show that offering one screen to men at age 50 years and a second screen four years later would produce a cost-effective PSA screening protocol. Similarly for two-yearly screens from ages 50 to 69 years. However, it should be emphasized that the QALY gains are small and favourable cost-effectiveness depends on the extent and accuracy of advanced cancers detected. This analysis uses data based on the ERSPC trial.

From an economic standpoint only, cost savings arise from PSA screening. In all sensitivity analyses, costs savings occurred. Therefore, PSA screening is attractive purely from a health system budget viewpoint.

The model assumes full compliance to the PSA screening program but in the ERSPC trial, 64% of men overall were screened at least once. Whether the costs of PSA screening to all Australian men aged 50 is feasible would require a budget impact analysis; however, this analysis shows that initial costs could produce a return on investment in the longer term. What is more of a concern are the patient benefits, which are small at best and uncertain. This analysis indicates benefits would only occur in younger men on average and this assumes the yield of cancers does not change by age. In the ERSPC trial, the median age was 61.1 years old and interquartile range of 57.9 to 66.1 years old.

PSA test-based screening will be more attractive if the harms from treatment of low-risk cancers are minimised. This is likely when active surveillance is increased and the harms and costs of overtreatment are reduced. Our model used US Surveillance, Epidemiology and End Results Program data and other studies to estimate prostate cancer deaths by stage. Prostate cancer mortality rates are highest in Australia and New Zealand but it is unclear if the rates differ by stage compared to other countries. If in Australia, rates of advanced or high-risk disease are worse than what the model currently estimates, PSA screening will be even more attractive at lowering cancer deaths through migration to low-risk disease. This uncertainty is not easily resolved as staging of cancers reported to registries in Australia are not mandatory and not readily available.

THE BOTTOM LINE

- A PSA screening program for asymptomatic men at age 60 years is not cost-effective at current treatment options in Australia, based on findings from the European Randomized Study of Screening for Prostate Cancer.
- The scenario of offering one PSA test to screen for prostate cancer in asymptomatic men at age 50 years, and a second screen four years later, would produce a cost-effective PSA screening program. Similarly, two-yearly screens from ages 50-69 is also a cost-effective option. However, in both these strategies, very small QALYs are gained with no improvements to life expectancy.
- Subject to caveats, the likelihood of cost-effectiveness of a PSA testing program for asymptomatic men at age 50, with a maximum of two PSA tests, is 83.8%.

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APPENDIX 1: SEARCH STRATEGIES FOR MODEL DEVELOPMENT

GOALS

1. To obtain Australian research projects on prostate cancer patterns of care; and
2. To obtain studies of cost-effectiveness analyses on treatments for prostate cancer.

TIMEFRAME

— Goal 1: 2005 onwards (last 10 years) to ensure contemporary research

— Goal 2: 2000 onwards to capture earlier economy studies

SEARCH STRATEGY

To ensure that all relevant studies were identified, comprehensive searches of the published literature were conducted. The following approach was used:

1. A search of published literature databases using OVID SP for Medline and PubMed databases
2. A search of HTA databases using International Network of Agencies of Health Technology Assessment, Database of Abstracts of Reviews and Effects and Centre of Reviews and Dissemination CRD
3. A search of trials and systematic reviews using The Cochrane Library, International Clinical Trials Registry Platform and clinicaltrials.gov

The search was conducted on 20-22 January 2015.

INCLUSION CRITERIA

1. Studies were selected if they related to prostate cancer in Australia (i.e., patterns of care, diagnostic and therapeutic tests), from 2005 onwards.
2. Studies were selected if cost-effectiveness analysis, cost-benefit analysis, cost-utility analysis or economic evaluation mentioned in title or abstract, from 2000 onwards and not limited to country.

EXCLUSION CRITERIA

Wrong time period

— Pre 2005 PCa Australia

— Pre 2000 CEA

Wrong study

— Not related to patient management (Diagnose, AS, WW, Survivorship, palliative) or

— Not related to intervention/outcome (surgery (RP), radiotherapy (EBRT or brachytherapy), hormone therapy (ADT) and chemotherapy) or

— Wrong population (not PCa) or

— Not Australian (for Goal 1.)

KEYWORDS

— Prostate cancer, Australia

MESH TERMS

— [Prostatic neoplasms], [Australia]

SEARCH RESULTS — OVID SP

PROSTATE CANCER AUSTRALIA

No.	Query	Results
#1	Prostate cancer.mp OR Prostatic Neoplasms[MeSH]	109,671
#2	Prostate AND (cancer* OR carcinoma* OR malignanc* OR tumo#r* OR neoplas*).mp	106,807
#3	1 OR 2	122,546
#4	3 and Australia.cp	1,438
#5	Australia*.mp OR Australia [MeSH]	137,811
#6	3 AND 5	662
#7	4 OR 6	1,905
#8	Limit 7 to (yr =“2005-Current” AND “all adult (19 plus years)”)	685

HTA DATABASES: INAHTA, DARE AND CRD

- DARE and CRD: 622 articles found (search terms: prostate cancer 2005-2015)

TRIALS AND SYSTEMATIVE REVIEWS

- Cochrane Library: 30 articles found (search terms: prostate cancer)
- International Trials Registry: 169 imported (search terms: prostate cancer and Australia) *NCT trials excluded (60)*
- Clinical trials.gov: 87 studies (search terms: prostate cancer Australia) included

SUMMARY

- Total articles found: 1607
- Duplicates removed: 22
  Therefore left with: 1571
  (60 from Clinical Trials Registry were on NCT clinicaltrials.gov)

- Excluded: not relevant to research question
- Wrong study: 546
- Wrong time period: 159
- Studies left after exclusions: 864

STUDIES INCLUDED:

1. **PCA Australia: 168**
   - Chemotherapy: 6
   - Detection/Diagnosis: 24
   - Hormone Therapy (ADT): 13
   - Management (AS or WW or palliative): 5
   - Multiple therapies (usually RT plus ADT): 6
   - Pyschological: 25
   - QoL: 3
   - Radiotherapy (EBRT or brachytherapy): 22
   - Surgery (RP or orchidectomy or robotic laproscopy): 13
   - Working folder: 52
2. **CEA PCa: 67 studies**
   - Bisphosphonates: 5
   - Chemotherapy: 7
   - Detection/diagnosis: 13
   - Hormone therapy (ADT): 12
   - Management: 4
   - Radiotherapy: 14
   - Steroid Therapy: 1
   - Surgery: 7
   - Working folder: 6

ADDITIONAL LITERATURE SEARCH (TARGET META-ANALYSIS AND SYSTEMATIC REVIEWS, SNOWBALLING)

- An additional literature search was conducted by Haitham which located 60 studies (incl duplicates).
- An additional literature search (Ovid) was conducted by Robbie which located 114 extra studies.

Search strategy: Prostatic Neoplasms [MeSH] AND Quality-Adjusted Life Years [MeSH] After duplicates and studies before 2000 were removed, 72 studies remained for use.

UTILITIES: CEA REGISTRY

Searched utilities for prostate cancer (accessed on 9 March 2015): 224 results saved/100 accessed

CLINICAL GUIDELINES

Updated to endnote on 6 March 2014.

APPENDIX 2: RESULTS OF OUT-OF-POCKET EXPENSES ANALYSIS

The values used in the model to represent out-of-pocket expenses are detailed in Table A1. There is little research to support these values and collection of this data from patients can be problematic. Recall bias is an issue and the alternative of cost diaries to capture every service paid for is generally too burdensome for men going through treatments and repeated doctors and clinic visits. Nevertheless, the sources used are reasonable to estimate these important costs for men.

It should be noted that these costs relate to men who are privately insured and treated in a private hospital. Publicly treated men would not pay anything for services in hospital including surgery, biopsies, radiation therapies, chemotherapy and imaging services. All patients would pay for out-of-hospital services such as GP and urologist consultations, x-rays and scans (in community radiology clinics) and also co-payments for medications and incontinence aids. Often PSA and other pathology tests are bulk-billed and here we assume no out-of-pocket expense. A limitation of this analysis is that palliative care costs have not been included due to a lack of data on this.

TABLE A1: ESTIMATED OUT-OF-POCKET COSTS TO PRIVATELY INSURED MEN WITH PROSTATE CANCER

Item	Value	Distribution	Source and calculation
Prostate-specific antigen test	$0/test	–	MBS items 66660 and 73928; assumed pathologist bulk bills
Urology consultation and digital rectal examination	$51/visit	–	MBS Item 104
Ultrasound guided biopsy	$926/ procedure	Gamma (44,0.048)	Financial Impact of Prostate Cancer in Australia 2013, page 67, Table 4.22, based on actual expenses by one survey participant, added 10% to expenses due to 2009 prices. MBS items cytoscopy 36812, needle biopsy 37219, ultrasound 55603, urologist 105, pre-consult anaethetist 17610, 31-35 minutes 20910, urologist 105.
Testosterone level	$0/test	–	MBS item 66695; assumed pathologist bulk bills
Anti-androgen	$37.70	–	Biclutamide 50mg tab. PBS monthly price for 28 tablets
Medical androgen deprivation therapy	$452.4/year	–	Leuprorelin acetate 22.5mg injection every three months or goserelin 10.8mg every three months. PBS monthly price for both is $37.70.
Active surveillance in Year 1	$1597/year	–	2 urology visits, 4 PSA tests, 1 biopsy
Active surveillance after Year 1	$565/year	–	2 urology visits, 2 PSA tests, biopsy every 2 years
Observation (watchful waiting)	$76/year	–	1 to 2 urology visits and PSA tests
Follow-up after treatment for localised disease	$61/year	–	Urology visit and PSA 4 times in Year 1, then 2 times in Years 2-3, then once a year. Averaged over the model years = $61/year.
Follow-up with androgen deprivation therapy	$153/year	–	Urology visit, PSA and testosterone every 3 to 6 months. Assumed every 4 months in the model. Assumed pathologist bulk bills.
Recurrence workup	$1252/ workup	–	Urology visit, biopsy and bone scans
Bone scans	$275/image	Gamma (44,0.162)	2013 Financial Impact of Prostate Cancer in Australia, page 67, Table 4.22, based on actual expenses by one survey participant, added 10% to expenses due to 2009 prices.
Second-line chemotherapy	$37.70/month	–	Abiraterone 1g daily (4 tablets of 250mg), cost/mth = $37.70. Cabazitaxel 25mg/m2 (for BSA 1.8m2), cost/mth = $37.70. Enzalutamide capsules, cost per month $37.70 Average monthly cost = $37.70.

TABLE A1: ESTIMATED OUT-OF-POCKET COSTS TO PRIVATELY INSURED MEN WITH PROSTATE CANCER

Item	Value	Distribution	Source and calculation
Treating incontinence	$406/year	Gamma (44,0.109)	2013 Financial Impact of Prostate Cancer in Australia, page 67, Table 4.22, based on actual expenses by one survey participant, added 10% to expenses due to 2009 prices
Radical prostatectomy	$6,567	Gamma (44,0.007)	2013 Financial Impact of Prostate Cancer in Australia, page 38, Table 4.5, based on analysis of Medicare data
External beam radiation therapy	$1,658	Gamma (44,0.027)	As above
Low-dose rate brachytherapy	$7,251	Gamma (44,0.006)	As above
Palliative care	$0	–	Excluded this from the analysis
Supportive care for androgen deprivation therapy	$914/year	Gamma (44,0.049)	Includes zoledronic acid at 4mg every 3 to 4 weeks ($37.70 for 4 months; PBS DPMQ) + calcium and vitamin D ($30/month) + DEXA scan at $102 (MBS item 12306).
First-line chemotherapy	$312/cycle	Gamma (44,0.14v	Cost of docetaxel 75mg/m2 + prednisone 5mg, for BSA of 1.8m2 every 3 weeks; the cycle cost $37.70 (PBS) + $65 administration cost (MBS item 13915) + $5 premedication cost (dexamethasone tablets) + $20 Blood test + $50 complication cost (febrile neutropenia in 3% of patients at $ 1,700 per episode).

BSA = body surface area; DEXA = dual energy X-ray absorptiometry; MBS = Medicare Benefits Schedule; DPMQ = dispensed price for maximum quantity; PBS = Pharmaceutical Benefits Scheme; PSA = prostate-specific antigen

TABLE A2: OUT-OF-POCKET EXPENSES FOR HEALTHCARE ESTIMATED OVER REMAINING LIFE [a]

	Mean cost (SD)
Base case (discounted)	**$9,150 ($611)**
Base case, undiscounted	$10,679 ($669)
Cohorts with different mean age b:	
50 years mean	$11,586 ($734)
55 years mean	$10,928 ($696)
60 years mean	$10,140 ($665)
70 years mean	$7,896 ($547)
75 years mean	$5,588 ($468)
80 years mean	$5,158 ($455)
Stage of disease	
Localised cancer	$9,249 ($626)
Very low / low risk	$10,201 ($711)
Intermediate risk	$8,673 ($652)
High risk to locally advanced	$9,166 ($570)
Advanced cancer	$6,274 ($481)

SD = standard deviation

[a] All figures are from probabilistic sensitivity analysis outcomes from 1000 Monte Carlo simulations.

[b] The base case uses a mean of age 65 years.

APPENDIX 2: RESULTS OF OUT-OF-POCKET EXPENSES ANALYSIS

(continued)

The results show that there was little difference in out-of-pocket costs for those with the three risk levels within localised disease. Furthermore, there was little difference among men 50, 55, 60 or 65 years (base case)of age and this starts to drop as men are older.

Figure A1: Cumulative out-of-pocket costs for men with prostate cancer by disease stage