A Cost Utility Analysis of Prostate Cancer Screening in Australia

Dr. Andrew Keller[1,2], Prof. Christian Gericke[1,2], Assoc. Prof. Jennifer A Whitty[1], Dr. John Yaxley[3], Dr. Boon Kua[3], Dr Geoff Coughlin[3] and Dr. TroyGianduzzo[1,3].

Corresponding Author: Dr. Andrew Keller

Andrewthomaskeller@gmail.com

+61438618610

1. University of Queensland, Brisbane, QLD, Australia.
2. Wesley Research Institute, The Wesley Private Hospital, Brisbane, QLD Australia
3. The Wesley Private Hospital, Brisbane, QLD, Australia

Abstract

Background and Objectives

The Göteborg randomised population-based prostate cancer screening trial demonstrated that Prostate Specific Antigen (PSA) based screening reduces prostate cancer deaths compared with an age matched control group. Utilising the prostate cancer detection rates from this study we have investigated the clinical and cost-effectiveness of a similar PSA-based screening strategy for an Australian population of men aged 50-69 years.

Methods

A decision model that incorporated Markov processes was developed from a health system perspective. The base case scenario compared a population-based screening programme with current opportunistic screening practices. Costs, utility values, treatment patterns and background mortality rates were derived from Australian data. All costs were adjusted to reflect July 2015 Australian dollars. An alternative scenario compared systematic with opportunistic screening but with optimisation of active surveillance (AS) uptake in both groups. A discount rate of 5% for costs and benefits was utilised. Univariate and probabilistic sensitivity analyses were performed to assess the effect of variable uncertainty on model outcomes.

Results

Our model very closely replicated the number of deaths from bothprostate cancer and background mortality in the Göteborg study. The incremental cost per quality-adjusted life-year (QALY) for PSA screeningwas $AU147,528. However, for years of life gained (LYGs) PSA based screening ($AU45,890/LYG) appeared more favourable. Our alternative scenario with optimised AS improved cost-utility to $AU45,881/QALY, with screening becoming cost-effective at a 92% AS uptake rate. Both modelled scenarios were most sensitive to the utility of patients before and after intervention, and the discount rate used.

Conclusion

PSA-based screening is not cost-effective compared to Australia's assumed willingness to pay threshold of $AU50,000/QALY. It appears more cost-effective if LYGs are used as the relevant outcome, and is more cost effective than the established Australian breast cancer screening programme on this basis. Optimised utilisation of AS increases the cost-effectiveness of prostate cancer screeningdramatically.

Key Points for Decision Makers:

- PSA-based prostate cancer screening is not cost effective in an Australianpopulation with current treatment patterns.
- Increased utilisation of active surveillance (AS) enhances the cost-effectiveness of prostatecancer screening, with screening becoming cost-effective at high AS uptake rates.
- At current Australian treatment patterns PC screening is more cost-effective than the current Australian breast cancer screening programme.

1. Introduction:

Prostate cancer (PC) is currently the most commonly diagnosed cancer in Australia, after non-melanomatous skin cancer, with Australia and New Zealand having amongst the highest incidences in the world.[1, 2]

PC deaths in Australia totalled 3294 in 2011, the last year for which data is available, making it the fourth most common cause of death in Australian males, and the second most common cause of cancer related death after lung cancer.[3] PC mortality consequently outnumbers both breast (2,680) and sex specific bowel cancer deaths (2,219 deaths in men) both of which have established population based screening programmes.[3]

Despite the documented burden of disease that PC presents, the Royal Australian College of General Practioners' (RACGP) guidelines currently recommend against discussing the subject of prostate cancer screening unless the subject is raised by the patient themselves.[4]

The RACGP cite the recent PSA based population screening studies of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) and the 2009 results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) as evidence of no mortality benefit for prostate specific antigen (PSA) based prostate cancer screening. [4] However, both PLCO and ERSPC studies suffered from methodological failures.[5] The PLCO suffered from a short screening period of only 6 years, a high proportion of randomised patients (44%) having had a serum PSA performed in the last 3 years, and 52% of the control group receiving a PSA test over the 6 year screening period. [6] Compared to the Göteborg trial, the ERSPC suffered from heterogeneous, and on average higher, PSA thresholds (2.5-10ng/mL) and heterogeneous, and on average longer, screening intervals (2-7 years) and shorter follow-up.[7,8]

The more recently published results of the Göteborg Randomised Population-based prostate-cancerscreening trial have demonstrated the greatest survival benefit and lowest number needed to treat (NNT) of any of the PSA screening trials.[8] Of the randomised controlled trials exploring PSA based population screening the Göteborg has the longest follow-up and the most robust trial protocol with a standardised serum PSA threshold (2.5ng/mL) and test interval of two years for the duration of the trial. [8]

The cost-effectiveness of prostate cancer screening has also been explored in numerous cost-effectiveness analyses (CEAs) which have produced widely varying results. No CEA to date, however, has used the findings of the Göteborg cohort, with most modelling the results of the 9 year follow-up data from the ERSPC, which had a significantly higher NNT.[9-11]

Active surveillance (AS), an approach of monitoring rather than immediately treating low risk PC, has been demonstrated to decrease the harm of overtreatment, whilst preserving the benefits of screening.[12] Decision analyses investigating the cost-effectiveness of AS protocols compared to primary intervention for low risk prostate cancer found that AS dominated primary intervention at all modelled time horizons.[13, 14]

1. Aim

We aimed to investigate the predicted cost utility of a theoretical Australian PSA-based population screening programme. In our model, prostate cancer diagnoses were risk stratified, and any subsequent treatment based upon current Australian treatment patterns. The accumulated costs, utilities and cancer specific mortality rates between hypothetical screening and non-screening cohorts were recorded and compared. We aimed to compare two systematic screening strategies to current opportunistic screening practices: (i) a screening strategy where any cancer diagnoses would be treated in accordance with current Australian treatment patterns and (ii) an active surveillance-optimised strategy where anylow risk PC diagnoses were followed with an active surveillance protocol instead of receiving primary intervention until clinical disease progression.

2. Methodology

2.1 Study Population

The model evaluated the outcomes of a uniformly distributed Australian male cohorts aged between 50-69 years. A uniform distribution was selected to better reflect the recruitment method of the Göteborg study, as opposed to all men entering the model at a set age, as is commonly employed in other decision models.[9-11]

2.2 Screening Strategies

The model assessed the cost-utility of two screening strategies for prostate cancer: strategy 1) Asystematic population screening strategy, with invitation for screening with a serum PSA test every 2 years, with any supra-threshold PSA tests offered a Trans-Rectal Ultrasound guided biopsy (TRUS); strategy 2) Opportunistic prostate cancer screening, representing current standard practice.

Two separate scenarios were created utilising the same two screening strategies. The first scenario, or base case, compared both screening programmes with any subsequent prostate cancer diagnoses being treated in accordance with current Australian clinical practices, with treatment strategies determined by both cancer risk stratification and patient preference. The second scenario, or the AS-optimised model, differed inthat subsequent low risk prostate cancer diagnoses were all treated initially with AS instead of the majority of cases receiving primary intervention. Those on active surveillance that had PSA progression (PSA ≥10ng/mL) or PC upgrading (Gleason score >6) on subsequent TRUS biopsy would proceed to definitive intervention based upon their new risk stratification.

2.3 Markov Model Structure and Health States

To investigate the cost-utility of a PSA based screening programme in a simulated Australian population we built a decision model utilising Markov processes in TreeAge Pro 2014 software suite. (TreeAge Software Inc., Williamstown, MA, USA)

All men entered the model in a cancer-free/pre-diagnosis health state. Literature based probabilities sawmen either remain 1) disease free, 2) die of background (non-PC) causes or diagnosed with 3) low-risk, 4) intermediate-risk, 5) high-risk or 6) advanced (metastatic) PC.

Following diagnosis of non-metastatic PC the patient would either undergo AS (surveillance with curative intent, limited to those with low risk diagnoses), surgery, radiation or watchful waiting (WW; surveillance with palliative intent, limited to those with a life expectancy less than 10 years or contraindications to curative therapy). Curative treatment options were limited to the most commonly available Australian treatment options of Radical Retro-pubic Prostatectomy (RRP) and External Beam Radiation Therapy (EBRT). Following diagnosis and treatment men would stay in risk stratified post-treatment health states until natural deathor development of metastatic disease. (Figure 1)

In line with the Göteborg study, PSA screening would cease once a patient reached age 69 years, but they would continue to cycle through the model.[8] A one year cycle length was selected to best represent the slow natural history of PC. A 20 year time horizon was selected owing to the paucity of quality literature on both the natural history of PC and EBRT failure rates after this length of time.

2.4.1 Model Inputs

Electronic literature searches utilising PubMed, Ovid MEDLINE and The Cochrane Library were performed to select model inputs for transition probabilities, utilities and costs. Australian studies were preferentially selected when available and where follow-up was appropriate for the model timeline. Where Australian studies were unable to wholly cover the timeline of the model, they were synthesized with estimates from international literature with longer follow-up. Where Australian studies were wholly lacking, mostly in the case oftransition probabilities, hand selection of the international literature was performed. Synthesized estimates were given preference over estimates from individual series. Where systematic reviews were non-existent, individualpapers were analysed, with those papers with protocols best representing current Australian practice, the largest numbers of recruited patients and the longest follow-up, where appropriate, being selected.

2.4.2 Probabilities

Probabilities of diagnoses of low, intermediate, high risk and advanced disease were drawn from the cumulative incidences for each diagnosis in both screening and control populations in the Göteborg study. [8] Yearly incidence rates were then calculated for each disease state diagnosis after adjusting for age and mortality related drop-out rates. Prostate cancer risk stratification in the Göteborg trial was based upon D'Amico's 1998 classification for prostate cancer: Low risk - Gleason score on biopsy ≤6, PSA ≤10, clinical stage ≤T1a, Intermediate risk – Gleason score ≤7, PSA ≤20, clinical stage ≤T2b, High risk – Gleason score >7, PSA >20, clinical stage >T2b).[15]

Current treatment practices for each PC risk classification were drawn from Australian data.[16, 17]Treatments were limited to RRP, EBRT, WW and AS as these are the most universally available Australian treatment options. AS was only an option for patients diagnosed with low risk disease, consistent with current European Association of Urology guidelines and similar to those of the Prostate Cancer Foundation of Australia, which allows very low volume Gleason 3+4 and PSA values of <20 ng/mL.[18, 19] (Table 1) In the basecase (Scenario 1) the AS uptake rate was as per current Australian treatment patterns (15% of low-risk diagnoses), in Scenario 2, all low risk diagnoses were treated with AS until clinical disease progression (serum PSA ≥10, or Gleason score >6 on subsequent biopsy).

Probability of progression to definitive therapy after entering the AS disease state was derived from a synthesis based estimate of AS series, and was dependant on time spent in the disease state.[20] Progression rates in the short-term (5 year) were similar to rates from an Australian AS cohort.[17]

A treatment threshold of equal or greater to 76 years old was selected as described in Campbell-Walsh Urology. At this age all patients currently in the AS health state would transition to the WW health state.[21]

Probabilities of disease recurrence for each risk stratification following definitive treatment were derived from analysis of 6,652 D'Amico risk stratified men receiving PC therapy at a high volume centre.[22]

Probability of disease progression to metastasis for those in watchful waiting disease states was drawn from the Prostate Intervention Versus Observation Trial (PIVOT), being more contemporaneous (published 2012 vs 2002), with longer median follow-up (10 years vs 6.2) and having more participants in the observation arm (367 vs 349 men) than the next largest study published by Holmberg et al.[23,24]

Risk of progression to the advanced disease state following post-treatment recurrence was drawn from an international study which followed 2,426 men with biochemical recurrence after RRP with a median follow-up of 6.6 years.[25]

Adjustment for the possibility of initial clinical under-staging of low risk disease was performed, utilizing the results of the largest published prostatectomy specimen series of 626 patients meeting the strict Prostate Cancer Research International: Active Surveillance (PRIAS) criteria.[26]

Probabilities of background mortality were drawn from Australian Bureau of Statistics age related mortality rates, and adjustments made for age related prostate cancer specific death rates.[27, 28] Although there is evidence androgen deprivation therapy (ADT) might increase the rate of cardiovascular events, an increase in cardiovascular mortality has not been conclusively demonstrated conclusively with significant discordance in results between published trials.[29-31] Additionally, in our model ADT was only initiated when metastases were present, reflecting more conservative practice and resulting in lower total ADT exposure. As such, we did not adjust the transition probability to non-cancer related death for those in the metastatic disease state. We also did not adjust for peri-operative mortality in the RRP group, however, Björklund et al's paper demonstrated that the 90 day per-operative mortality in >22,000 men receiving RRP was lower than the age-matched cohort (<0.2%).[32]

2.4.3 Utility Values

Health states were each assigned a utility value representing the health-related quality of life of anaverage patient inhabiting that disease state. All health state utility values were derived from Australian data where possible. (Table 2)

PC screening has been criticised as increasing anxiety and reducing health related quality of life (HRQoL) during and after diagnosis.[4] However, in the Dutch and Finnish centres of the ERSPC it was shown that screening does not induce short termHRQoL effect.[33, 34] Even those patients who had false positive results tended to regard screening as a positive experience.[35] Likewise participating in an active surveillance protocol does not appear to impact HRQoL or increase anxiety when compared to controls, with participants' HRQoL similar to age adjusted controls.[34, 36, 37] Utility scores were consequently unaffected by screening or AS in our model.

We elected to use a single Australian study for our post-treatment utility scores. Smith et al. followed thesame large cohort (1500) of 50-69 year old men for 3 years before and after definitive treatment, comparing their utility directly against an age and pre-morbidity matched control cohort over the same three year period, using the same health instrument. This study utilised the University of California, prostate cancer index, a validated instrument which includes all 12 components of the commonly used 12-item short form (SF-12) questionnaire. They demonstrated a relative utility value of 0.95 when compared to age-matched controls at 3 yearsfollowing treatment.[36]

Despite widely ranging protocols for administration of androgen deprivation therapy our model conservatively initiated its usage only when patients transitioned to the metastatic health state. Of the treatment options androgen deprivation therapy is widely regarding as having the greatest effect on HRQoL, however, this may reflect the poor baseline of patients selected for androgen deprivation therapy.[36, 38] The metastatic health state utility value was drawn from a combination of Australian and international studies. [36, 39] Smith et al's Australian HRQoL study demonstrated a utility of 0.9 at initiation of androgen deprivation therapy, however follow-up was inadequate to assess the utility of terminal prostate cancer.[36] The utility of PC at its terminal stage was drawn from Farkilla et al, which assessed HRQoL using multiple health instruments (15D, EQ-5D, VAS, EORTC QLQ-C30) from which our utility value of terminal PC of 0.6 was synthesized.[39] The utilityof the advanced disease state thus fell from0.9 to 0.6 over a five year period to represent deteriorating wellbeing

with increasing burden of disease. This terminal illness health state utility is quite conservative compared to other cost utility analyses.[10, 38]

All utility values for disease-states listed above used above were not absolute values, but were multipliers for the age related baseline utility in a contemporary Australian male population.[40]

2.4.4 Costs

Costs were accumulated by both being in a specific disease state (state costs) as well discrete events (transition costs), such as having surgery.

A health system perspective was used to assign costs for screening, AS and treatment, as the model aims to approximate the costs of a government-run screening programme. Out of pocket and time costs forprogramme participants were therefore not included. Transition and state costings were derived from a combination of Australian studies, Medicare Benefits Schedule (MBS), Pharmaceutical Benefits Scheme (PBS) and Australian Refined – Diagnosis Related Groups (AR-DRGs). (Table 3) All costs were inflated to 10 July 2015 dollars using annual inflation rates from the Reserve Bank of Australia.

The cost of annual screening was calculated from the overall number of PSA blood tests and TRUS biopsies performed in the Göteborg study. A fractional annual test frequency per patient was calculated after adjusting for model dropout for either natural death or reaching the age limit of screening. The Australian costs of a serum PSA test and a TRUS biopsy, allowing for a 2% rate of post-TRUS sepsis were then used to arrive at thefinal cost of screening per man aged 50-69 in the screening cohort.[21]

2.5 Model Outcomes

The primary model output was Quality Adjusted Life Years (QALYs) for each screening strategyover 20 years. Costs effectiveness was measured as an Incremental Cost Effectiveness Ratio (ICER) and expressed in $/QALY. Life Years Gained (LYG) was used as an alternative model output to allow comparison with other cost-analyses that did not use the QALY metric.

All future costs, QALYs and LYGs were discounted 5% and compared to a societal willingness to pay (WTP) of $50,000/QALY in line with Pharmaceutical Benefits Advisory Committee guidelines and a half-cyclecorrection was applied to all Markov processes. [41] Undiscounted QALYs and LYGs are also presented due to ongoing controversy regarding the discounting of future health outcomes, particularly for screening and prevention programmes.[42, 43] Cancer-specific mortalities, and interventions saved per 10,000 men was also used to compare treatment strategies.

2.6.1 Univariant Sensitivity Analysis

We conducted univariate sensitivity analyses of all probabilities, cost and utility values to determine the effect of uncertainty of each variable upon the models output. All cost and utility values were varied 20% above and below the base case value. Transition probabilities were varied within their 95% confidence intervals. Simulations were also run with a lifelong timeline and a cohort start age of 50 to assess possible impact on model outcomes.

Univariate sensitivity analysis outside of the confidence intervals was performed for the probability of entering the active surveillance health state following a diagnosis of low risk PC. This was done to determine what rate of primary active surveillance was required in order to achieve an increase in QALYs at a sub-threshold WTP value.

2.6.2 Probabilistic Sensitivity Analysis

Multivariate probabilistic sensitivity analysis was performed for all variables in the both scenarios to assess overall model uncertainty. A second order Monte Carlo analysis was performed with all variables drawn simultaneously. Beta and gamma distributions were estimated for utility and costings values respectively from normal distributions with standard deviations of 20% above and below the base case values. A combination of Dirichlet and beta distributions were drawn for probability values based on their standard error values, as per Table 1. 10,000 samples were drawn for each probabilistic sensitivity analysis.

2.6.3 External validation

In order to validate our models we ran our base case model with a 15 year time horizon and 9958 men in each arm, to simulate the follow-up and cohort numbers of the Göteborg. Our model very closely replicated the number of deaths from both prostate cancer and background mortality in the Göteborg study with 40 screening and 72 non-screening prostate cancer specific deaths, and 1791 screening and 1788 non-screening deaths from background mortality. This compares with 44 screening and 78 non-screening prostate cancer specific deaths, and 1937 screening and 1904 non-screening deaths from background mortality in the Göteborg study.

3 Results

3.1.1 Scenario 1 - Base case

With conservative modelling our theoretical population screening programme base case yielded an additional 0.00554 QALYs per patient at 20 years for an incremental cost of $817 per patient when compared to the control group, opportunistic prostate cancer detection. This yielded an Incremental Cost Effectiveness Ratio (ICER) for screening of $147,528/QALY.

With QALYs undiscounted an additional 0.01102 QALYs per patient were gained with the screening programme yielding an ICER of $74,165/QALY.

With LYGs as the model output, screening yielded an additional 0.01781 LYGs per patient compared to current screening practices. This yielded an ICER of $45,890/LYG. (Table 4)

3.1.2 Scenario 2 - Optimised Active Surveillance

In our active surveillance optimised scenario the screening programme generated higher incremental QALYs than Scenario 1 (base case), with an additional 0.01222 QALYs per patient when compared to the opportunistic screening group. The cost of screening was also lower than Scenario 1, with an additional cost of $560 per patient in the opportunistic screening group. This yielded an ICER for the AS-optimised screening scenario of $45,882/QALY compared to opportunistic screening. (Table 4)

With QALYs undiscounted an additional 0.0229 QALYS per patient were gained with the screening programme yielding an ICER of $24,483/QALY.

Whilst the AS-optimised screening Scenario 2 dominated Scenario 1(base case) in which usual treatment approaches were implemented, this increase in QALYs and reduction in cost compared to Scenario 1 came at the expense of one additional prostate cancer specific death per 10,000 men in both screened and unscreened cohorts. The number of interventions performed in both the screening (208 fewer RRP, 355 fewer EBRT) and non-screening groups per 10,000 men (105 fewer RRP, 149 fewer EBRT) was significantly reduced.

3.2.1 Univariate Sensitivity Analyses

Univariate sensitivity analyses of both modelled scenarios were dominated by utility following definitive therapy, particularly for Model 1. Varying the post-definitive therapy utility co-efficient from 0.95 to 0.90 led to net disutility for the entire screening cohort in Model 1, and resulted in the point estimate for Model 2 exceeding the WTP threshold. (Table 5)

After post-treatment utility the next most influential variables were, in order: age-related utility, discountrate and the utility of advanced disease. Cost variability within 20% of the base case value had little effect onoverall model output with almost all transition probabilities being more influential. Reducing the age of model entry to 50 years old, rather than utilising a uniformly distribution between ages 50-69, had the effect of reducingthe value of the point estimates without affecting the outcomes of the modelled scenarios. Similarly, utilising a lifelong timeline, as opposed to a 20 year time horizon resulted in lower point estimates without affecting scenario outcome. Whilst varying model inputs universally affected the value of the point estimates, it rarely affected the outcome; Scenario 1 remained cost in-effective and Scenario 2 remained cost-effective in most simulations. Results of the 4 variables with the most influence on ICER in the univariate sensitivity analysis are presented in Tornado diagrams (Figure 2 and 3) and the ICERs of the most influential variables are presented in Table 4.

When we varied the probability of entering the AS health state after a diagnosis of low-risk PC outside of its confidence intervals in Model 1 the screening arm became cost effective at an AS uptake rate of 91.9% assuming an acceptable threshold for cost-effectiveness of $AU50,000/QALY. (Figure 4)

3.2.2 Probabilistic Sensitivity Analyses

Probabilistic sensitivity analysis was performed for base model (Scenario 1) in order to ascertain the proportion of simulations in which it proved cost-effective. Assuming a willingness-to-pay threshold of $AU50,000/QALY the base case model was cost effective in 38% of simulations, delivered improved QALYs at supra-threshold WTP in 38%, and decreased QALYs in 24.5% of simulations. (Figure 5)

For Scenario 2, Optimised Active Surveillance, the probabilistic sensitivity analysis demonstrated cost-effectiveness in 53% of all simulations, provided an increase in QALYs at a supra-threshold WTP in 27% of simulations and decreased QALYs in 19% of simulations. (Figure 6)

A cost-effectiveness acceptability curve was plotted for scenario 2 to demonstrate the effect of increasing WTP on the number of cost-effective iterations, at a WTP of $100,000/QALY screening was cost effective in 66% of all iterations. (Figure 7)

4.1 Discussion

Our model is the first to explore the effectiveness and the cost of instituting a PSA-based populationscreening programme based on the results of the Göteborg Randomised Population-based prostate-cancer screening trial. Other CEAs to date have based their assumptions upon the results of the PLCO or ERSPC trials, however, the protocols of both trials were flawed.[5]

In our base case scenario, screening was not found to be cost effective as although it increased QALYs, it did so at an incremental cost of $147,528/QALY, which was well above our nominal willingness to pay(WTP) of $50,000/QALY.

When the results are viewed with a LYG metric the results appear more favourable, with a cost of $45,890/LYG. It must be stressed that the seemingly large difference between the cost/QALY and cost/LYG is not due simply to patient disutility following treatment. Rather, as evidenced by the univariate sensitivity analysis, two of most influential model variables were the pre-morbid utility score and the discount rate of future outcomes/costs, consequently multiple lives needed to be extended in order to generate a single additional QALY. The cost-effectiveness of our model compares favourably with other CEAs, which have demonstrated highly variable results.[9]

Pataky et al., in an ERSPC-based Canadian micro-simulation study, found screening strategies cost between $27,000 - $54,000/LYG compared to non-screening strategies.[9] They also found that all strategies resulted in decreased QALYs for the screened population, however, this result was very sensitive to the utility values used.[9]

An American CEA based upon the NNT of the ERSPC (48 men) found at 9 years follow-up that screening was not cost-effective based upon their societal WTP of $100,000/LYG.[11] However, they found that screening became cost effective when the NNT was less than 21, which compares favourably with the Göteborg's NNT of 12.[8, 11]

Only one CEA is published that aims to model an Australian prostate cancer screening programme, and it is based upon the 9 year follow-up data from the ERSPC.[10] This model failed to demonstrate cost-utility for a population screening model in Australia, with a cost of $291,817/QALY at 10 years follow-up, however, this analysis disregards the role of active surveillance completely.[10] Furthermore, every man in this model diagnosed with PC assumed a 0.05 disutility and all lifetime treatment costs immediately. This model also arguably overestimates costs by assuming the cost accrual of 100% screening compliance while assuming the compliance-unadjusted mortality reduction of the ERSPC which had only 82% of screened men having at least one PSA test, and 86% of men undergoing TRUS when recommended.[7]

Whilst our model suggests population-based screening at current AS uptake rates is not cost-effective when compared to Australia's WTP, it does appear to compare favourably with established Australian screening programmes. BreastScreen Australia have not performed a comprehensive cost-utility analysis to directly compare cost/QALY against.[44] They have, however, performed a CEA, with the Markov model output unit being cost per LYG. Similar to our model, BreastScreen Australia also focused on a population of 50-69 year olds, used a biennial screening test and a 5% discount rate for future costs and benefits. After adjusting for inflation, the estimated cost per LYG over a 20 year time horizon was $47,776/LYG.[44] Using the same LYG metric, a 5% discount rate at a 20 year time horizon PSA based screening was more cost-effective at $45,890/LYG.

Similarly, no true cost-utility analyses of the established Australian colon cancer screening programme have been performed, however, a CEA examining cost/LYG has been undertaken.[45] The projected cost of $53,989/LYG, after adjustment to today's dollars, was higher than for our prostate cancer model, however, the time horizon the authors in this study selected was only 10 years. [46]

A long-standing criticism of PC screening is the over-diagnosis and consequent overtreatment of clinically indolent cancers. [7] The increasing uptake of active surveillance internationally might facilitate separation between low-grade PC diagnosis and its treatment.[47, 48] There is an increasing body ofevidence demonstrating that active surveillance can decrease the harm of overtreatment whilst maintaining the mortality benefits of screening.[12, 49] Indeed, while the base case for our model was found not to be cost-effectivebased upon current Australian treatment preferences, the cost/QALY wasshown to decrease dramatically with increased active surveillance utilisation. Other CEAs investigating the role of active surveillance in primary prostate cancer treatment have demonstrated that AS both increased QALYs and decreased treatment costs when compared to primary intervention.[13, 14] Koerber found that active surveillance dominated primary intervention for low risk PC, with AS yielding both lower costs and higher QALYs across modelled time horizons of 5, 15 and 30 years follow-up.[14] Orlendorf et al found that while AS yielded higherlifetime treatment costs than primary intervention this was offset by increased QALYs, with AS being the more cost-effective treatment.[20] Our study extends these promising findings to suggest the AS-optimised model maybe cost-effective in the Australian setting.

The AS uptake rate required for cost effectiveness in our model was 92%, which whilst high, may not be unattainable. Data from the Victorian Prostate Cancer Registry (VPCR) demonstrates increasing AS utilisation in recent years, with 36% of all new low risk diagnoses initially selecting AS.[50] In Sweden, AS is nowthe most commonly selected primary treatment for low risk PC, with 72% of all new diagnoses initially managed with AS.[51]

Concerns about clinical under-grading and under-staging of prostate cancer exist and are perhaps contributingto under-utilisation of AS as a treatment option for low risk prostate cancer.[26, 52] However, the clinical effect of an initial under-grading of prostate cancer in AS patients is yet to be established and it is not reason enough to deny patients the option of AS. The un-marrying of PC diagnosis and its immediate treatment and theincreased utilisation of AS as a treatment option are crucial to the cost-effectiveness of PSA based prostatecancer screening and essential in reducing screening-related harm.[53, 54]

This difficulty in establishing a disconnection between PC diagnosis and treatment might be alleviated by the increasing utilisation of multi-parametric Magnetic Resonance Imaging (mpMRI).[55]. MpMRI hasshown utility as a second line diagnostic tool in lieu of TRUS biopsy.[55] It allows preferential detection ofthose intermediate and high risk prostate cancers more likely to benefit from intervention, thereby avoiding detection

of cancers unlikely to be clinically significant.[55] A cost-effectiveness analysis in the Netherlands has demonstrated similar costs for both mpMRI and TRUS pathways, but with a superior HRQoL in the mpMRI cohort due to reduced interventions for low risk disease.[56] In addition mpMRI has been demonstrated to aid correct risk stratification of patients prior to enrolment in an active surveillance protocol.[57]

4.2 Limitations

Our study has several limitations. Firstly probabilities are drawn from a prostate cancer screening study performed on a cohort of Swedish men. We did not adjust for Australia's higher incidence of PC as this may merely be an artefact of detection bias.[58]

While we did account for immediate costs of complications for RRP, such as readmission within 30 days for haematoma or infection, we did not account for cost of pads, incontinence surgeries or other treatment long-term complication costs. However, analysis of post-procedure costs in the sensitivity analysis reveals this ishighly unlikely to have had significant effect on the model's outcome.

Costs were not adjusted for societal costs of time off work for treatment, and likewise we did not adjust for loss of ability to work from terminal disease. However, it is argued by many health economists that these time costs exaggerate the true cost of a disease on the economy.[59] Our study was not intended to capture asocietal perspective; therefore, it may have underestimated the total societal costs associated with screening, treatment, or premature death.

A further limitation is utilisation of a time horizon of 20 years instead of lifelong time horizon. As demonstrated in our sensitivityanalysis, a longer time horizon led to increased cost effectiveness in both models, particularly Scenario 1, although its ICER remained well above the WTP threshold, and as such did not change the decision outcome. (Table 4)

Another limitation is the use of non-time dependant probabilities for disease recurrence post-treatment, andfor development of metastases following disease recurrence. However, sensitivity analysis reveals the model to be relatively insensitive to these variables, and consequently it is unlikely thisaffected model outcomes.

The most significant limitation of our study compared to an actuarial population screening program is that the cohort of men that entered the model were aged between 50-69 in a uniform distribution to better parallel the recruitment method of the Göteborg study. A programme where all participants first underwent screening at age

50 should allow earlier detection of prostate cancers and potentially increase the life years gained. When we ran our model with a uniform entry age of 50 years old, the cost-effectiveness of both models improved (Table 4). However, as the diagnostic probabilities were drawn from Göteborg data and not age-stratified these resultsare unlikely to be representative of the true benefit of commencing screening earlier.

Lastly, it should also be pointed out that the unscreened control cohort in the Göteborg study, whilst not formally invited to screening, were not PSA naïve, and still underwent a significant number of PSA tests and TRUS biopsies as a part of random opportunistic screening. In this regard, the Göteborg study, and consequently our model, represents the benefits of a formal population screening program compared to a population exposed to opportunistic screening only. In a truly unscreened, PSA naïve population, it is likely that the mortality differences would be greater still, and the cost per additional QALY considerably more favourable.

5. Conclusions

Our model is a comprehensive cost-utility analysis of a theoretical PSA-based prostate cancerscreening programme in Australia. In our base-case scenario prostate cancer population based screening with aninvitation to participate every 2 years for men aged 50-69 years was not found to be cost effective when compared to a commonly assumed willingness to pay threshold. It was, however, more cost effective per life year gained than the current Australian population screening programme for breast cancer. When the scenario optimised treatment post-diagnosis to focus on active surveillance, rather than primary intervention for low-riskdisease, our screening model was cost-effective after 20 years of follow-up. PSA based population screening maybe cost-effective when compared to opportunistic screening alone if low risk prostate cancer diagnoses can be successfully uncoupled from primary definitive treatment.

6. Compliance with Ethical Standards

6.1 Research Funding

This study was partially funded by a higher research scholarship from the Univeristy of Queensland (UQ). UQ did not have any influence on the subject matter of the study, model design or conclusions. No other external funding was received.

6.2 Conflicts of Interest

The authors: Dr. Andrew Keller, Prof. Christian Gericke, Assoc. Prof. Jennifer Whitty, Dr. John Yaxley, Dr. Boon Kua, Dr. Geoff Coughlin and Dr. Troy Gianduzzo have no conflicts of interest to declare.

6.3 Ethics Approval

Ethics approval was not required for this study.

6.4 Author Contributions

Dr. Andrew Keller created the models, performed the literature review and wrote the paper. Prof. Christain Gericke was involved in paper concept, model design and paper proofing. Assoc Prof. Jennifer Whitty was involved in model design and creation, proofing of paper and assistance with the health economic elements of the paper. Dr. John Yaxley, Dr. Boon Kua and Dr. Geoff Coughlin were involved in model design and proofing of the paper. Dr. Troy Gianduzzo was responsible for the model and paper concept, was involved in model design and paper proofing and literature review.

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8. Legends To Figures

Figure 1. Simplified state transition diagram demonstrating possible cancer diagnoses and treatment decisions that may be made, and subsequent disease states that may be entered by each simulated patient passing through the prostate cancer disease model.

Figure 2. Incremental Cost Effectiveness Ratio (ICER) Tornado diagram of univariate sensitivity analysis of all costs, probabilities and utility values in base case simulation (Scenario 1). The 4 most influential model variables are presented. ICER is represented in Australia dollars per quality adjusted life year gained ($/QALY).

Figure 3. Incremental Cost Effectiveness Ratio (ICER) Tornado diagram of univariate sensitivity analysis of all costs, probabilities and utility values in alternative model (Scenario 2). The 4 most influential model variables are presented. ICER is represented in Australia dollars per quality adjusted life year gained ($/QALY).

Figure 4. Primary Active Surveillance Rate for New Diagnoses of Low Risk Prostate Cancer versus Net Monetary Benefits (NMB = expected QALYs x WTP - expected cost). Discount Rate 5%, Willingness To Pay (WTP) of $50,000, modelled time horizon of 20 years. The screening model becomes cost effective at an active surveillance uptake of 91.9%.

Figure 5. Probabilistic Sensitivity Analysis Scatter Plot, Base Case Scenario (Scenario 1). Output in Incremental Cost Effectiveness, Screening Vs. No-Screening.

Figure 6. Probabilistic Sensitivity Analysis Scatter Plot, Active Surveillance Optimised (Scenario 2) Output in Incremental Cost Effectiveness, Screening Vs. No-Screening.

Figure 7. Cost-Effectiveness Acceptability Curve, Active Surveillance Optimised (Scenario 2). Number of cost-effective iterations versus societal Willingness To Pay (WTP). WTP varied between 0-$100,000 Australian dollars per quality adjusted life year gained. ($AUD/QALY).

9. Tables

9.1 Table 1 Health State Transition Probabilities

State	Event	Transition probability	Standard Error	Source
Screening	Diagnosed Low Risk CaP	0.0045824791	0.0006770141	Hugosson, J. 2010[8]
	Diagnosed Intermediate Risk CaP	0.0027211009	0.0005221863	Hugosson, J. 2010[8]
	Diagnosed High Risk CaP	0.0007103095	2.67E-04	Hugosson, J. 2010[8]
	Diagnosed Advanced CaP	0.000339538	1.85E-04	Hugosson, J. 2010[8]
Non-Screening	Diagnosed Low Risk CaP	0.001567317	0.000396536	Hugosson, J. 2010[8]
	Diagnosed Intermediate Risk CaP	0.0019661929	0.0004440486	Hugosson, J. 2010[8]
	Diagnosed High Risk CaP	0.0009886531	3.15E-04	Hugosson, J. 2010[8]
	Diagnosed Advanced CaP	0.0006812806	2.62E-04	Hugosson, J. 2010[8]
Diagnosed Low Risk CaP	Proceed to EBRT	0.472	0.0352998584	Baade PD, 2012[60]
	Proceed to RRP	0.321	0.0330120433	Baade PD, 2012[60]
	Proceed to WW	0.057	0.0163937488	Baade PD, 2012[60]
	Proceed to AS	#		
Diagnosed Intermediate Risk CaP	Proceed to EBRT	0.4008127208	0.0205988903	Baade PD, 2012[60]
	Proceed to RRP	0.534	0.020967921	Baade PD, 2012[60]
	Proceed to WW	#		
Diagnosed High Risk CaP	Proceed to EBRT	0.4513333333	0.0374038546	Baade PD, 2012[60]
	Proceed to RRP	0.452	0.0374087213	Baade PD, 2012[60]
	Proceed to WW	#		
Active Surveillance <76 years	Develop Advanced Disease whilst on AS	0.00523	0.000425	Koerber F 2014[14]
	Proceed to definitive treatment 1st 5 years	0.0643706623	0.0077606108	Orlendorf DA 2009[20]
	Proceed to definitive treatment 2nd 5 years	0.0323158832	0.0055920986	Orlendorf DA 2009[20]
	Proceed to definitive treatment 3rd 5 years	0.0188410491	0.0042995423	Orlendorf DA 2009[20]
Active Surveillance ≥76 years	Proceed to WW	1	N/A	Campbell-Walsh Urology[21]
AS To Definitive Therapy	Proceed to EBRT	0.2962962963	0.0367957508	Ischia JJ, 2012[17]
	Proceed to RRP	0.6296296296	0.0389135037	Ischia JJ, 2012[17]
	Proceed to WW	#		

Clinical Understaging of Low Risk Disease	Upstaged to Intermediate Risk	0.294	0.0182091154	El Hajj, A. 2013[26]
	Upstaged to High Risk	0.206	0.0161642923	El Hajj, A. 2013[26]
Post Treatment Low Risk	Recurrence	0.0112503069	0.001293151	Hernandez DJ, 2007[22]
Post Treatment Intermediate Risk	Recurrence	0.0797437258	0.0033214409	Hernandez DJ, 2007[22]
Post Treatment High Risk	Recurrence	0.1139901939	0.0038965198	Hernandez DJ, 2007[22]
Post Treatment Recurrence	Progress To Advanced Disease	0.0127	0.0016097136	Boorjian SA, 2011[25]
WW Low Risk Disease	Progress To Advanced Disease	0.0062604731	0.0041172461	Wilt TJ, 2012[24]
WW Intermediate Risk Disease	Progress To Advanced Disease	0.0151549445	0.0063771715	Wilt TJ, 2012[24]
WW High Risk Disease	Progress To Advanced Disease	0.024055818	0.0079981496	Wilt TJ, 2012[24]
Advanced Disease	Die of Advanced CaP	0.224	0.0045832217	PCTCG. 2000[61]
ALL GROUPS	Die Background Mortality	Age dependant	ABS Mortality rates, adjusted for age related prostate cancer mortality	

= Sums to 1.0 with other probabilities in health state.

CaP = Prostate Cancer

RRP = Retro-pubic radical prostatectomy

EBRT = External Beam Radiation Therapy

WW = Watchful waiting

AS = Active Surveillance

9.2 Table 2 Health State Utility Values

State	Utility	Source
Baseline utility value	Age dependant	Banham D. 2014[40]
Screening*	1	Vasarainen H. 2013[34]
Non-Screening*	1	Vasarainen H. 2013[34]
Post Treatment*	0.95	Smith DP. 2009[36]
Advanced Disease*	0.9->0.6 over 5 years	Smith DP. 2009[36], Farkkila N. 2014[39]

*= Values are not absolute, but multipliers of the age dependant baseline utility value.

9.3 Table 3 Health State and Transition Costs

Event	Cost	Source
Screening	$34.89	Fractional cost of PSA tests + TRUS biopsy TOTAL per patient years in Göteborg[8]
Diagnosis Cancer Screening	$1,261.10	CT + Bone Scan + MBS item no. 104 + 105
Diagnosis Cancer Non-Screening	$1,873.56	PSA + TRUS + CT + Bone Scan + MBS item no. 104 + 105
RRP	$14,310	Hall R 2014[62]
EBRT	$15,977.48	MBS item no. 104, 15550, 15562, 15705, 15248, 15263, calculated at 39 fractions, 6 fields + fractional cost of neoadjuvant hormones (.704, Baade PD, 2012[63])
AS	$723.17	Fractional yearly cost of AS protocol over 4 years as per Yaxley J. 2013.[64]
WW	$161.00	105 x2, PSA x 2
Cost Follow-Up Post Rx		Time dependant, limit of 10 years: Year 1 (MBS 105+PSA)x4 Year 2-5 (MBS 105+PSA)x2 Year 6-10 (MBS 105+PSA)
Advanced Disease Year 1	$5,773.51	Bicalutamide + Goserelin x 4 + 105 x2 + CT + Bone Scan
Advanced Disease Year >1	$4,672.08	Bicalutamide + Goserelin x 4 + 105 x2
Prostate Cancer Death	$28,000.00	Carter H. 2014[65]
Non-Prostate Cancer Death	$19,430.62	Canadian Non-Prostate Cancer Death ($36,028.92 Hollander MJ 2009[66])/Canadian Prostate Cancer Death($51,917.21 Krahn MD 2010[67]) X Australian Prostate Cancer Death ($28,000)
ITEMS		
TRUS		
TRUS procedure	$389.95	MBS item no. 37219
Prostate Histology	$210.35	MBS item no. 72827
Ciprofloxacin	$19.13	PBS DPMQ
TRUS sepsis standard	$5,276.00	AR-DRG codes
TRUS sepsis severe	$11,571.00	AR-DRG codes
TRUS sepsis rate	2%	Campbell-Walsh Urology[21]
TRUS TOTAL	$737.71	TRUS + Histology + Ciprofloxacin + 0.02(0.9 TRUS standard + 0.1 TRUS severe)
CT Abdomen/Pelvis	$480.05	MBS item no. 56507

Tc99m Bone Scan	$489.70	MBS item no. 61441
Initital specialist consultation	$85.55	MBS item no. 104
Review specialist consultation	$43.00	MBS item no. 105
PSA	$37.55	MBS item no. 66660
Androgen Deprivation Therapy (ADT)		
Bicalutamide	$131.68	PBS DPMQ
Goserelin	$1,108.97	PBS DPMQ
Neoadjuvant hormones	$2349.62	Bicalutamide x1 + Goserelin x 2

CaP = Prostate Cancer

RRP = Retro-pubic radical prostatectomy

EBRT = External Beam Radiation Therapy

WW = Watchful waiting

AS = Active Surveillance

CT = Computerised Tomography

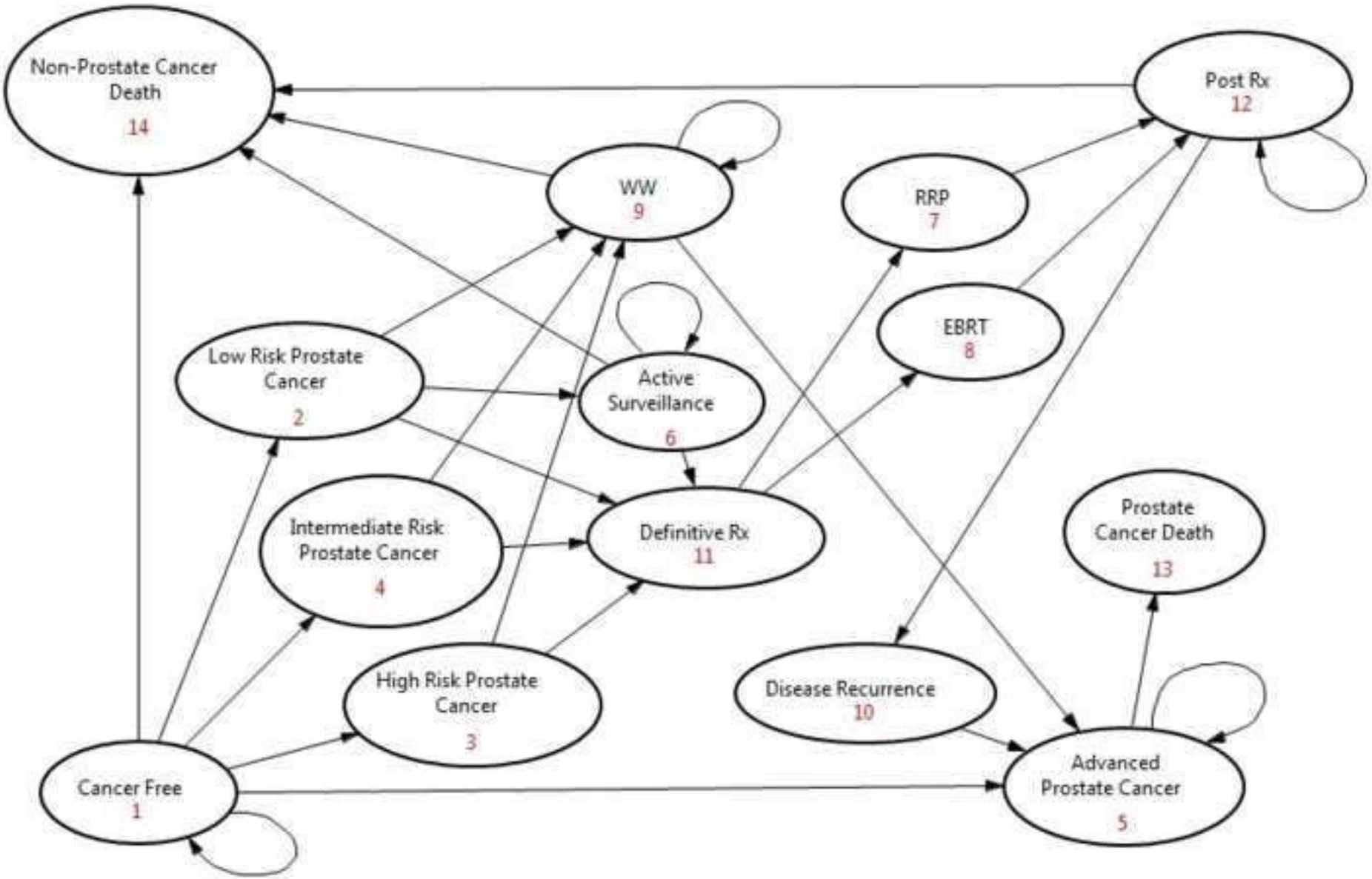
TRUS = Trans-Rectal Ultrasound guided prostate biopsy

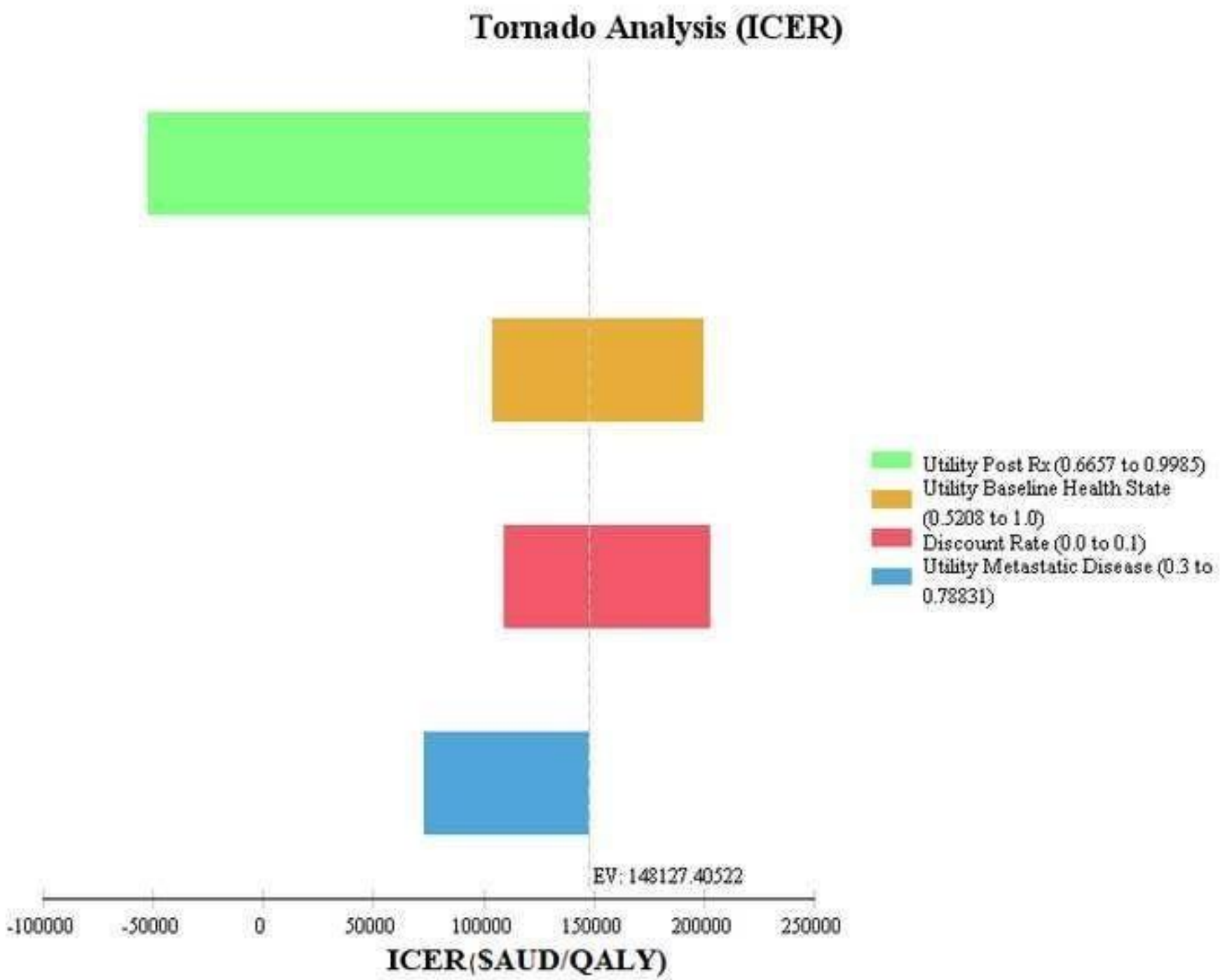
9.4 Table 4: Results

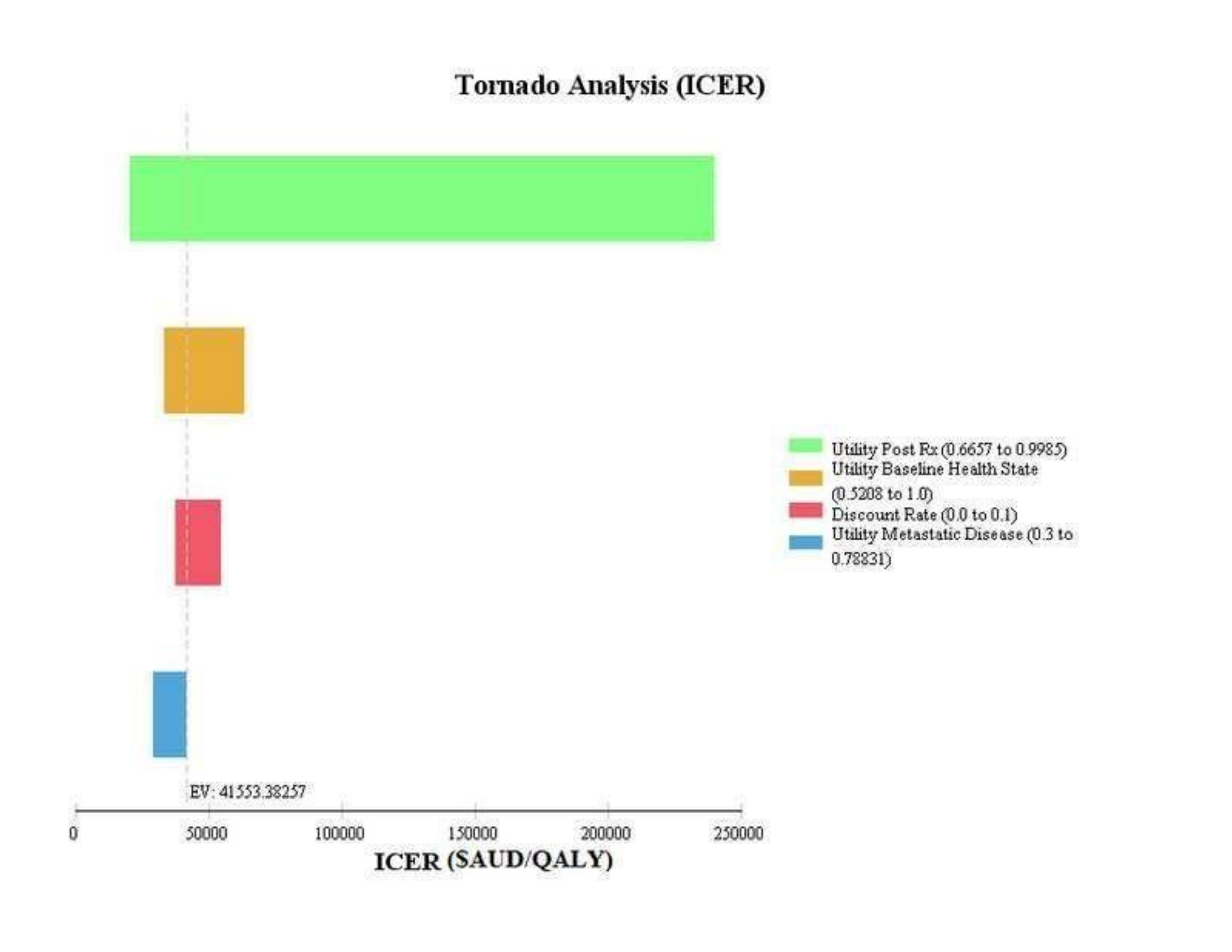
	Cost ($)	QALYs	LYG	Cancer deaths/10,000 men	Non-Cancer deaths/10000 men
MODEL 1: Basecase	**(20 years, 5% discount for both cost and utility)**				
Control	**$4,664.17**	**9.32618**	**11.58002**	**98**	**2809**
Screening	**$5,481.47**	**9.33172**	**11.59783**	**59**	**2816**
Incremental	**$817.30**	**0.00554**	**0.01781**	**-39**	**7**
ICER	**$147,528/QALY**		**$45,890/LYG**		
MODEL 2: Optimised AS	**(20 years, 5% discount for both cost and utility)**				
Control	**$4,524.92**	**9.32974**	**11.57838**	**99**	**2809**
Screening	**$5,085.59**	**9.34196**	**11.59619**	**60**	**2816**
Incremental	**$560.67**	**0.01222**	**0.01781**	**-39**	**7**
ICER	**$45,882/QALY**		**$31,840/LYG**		
MODEL 1: Basecase	**No discount on utilities. 5% discount on costs.**				
Control	**$4,664.17**	**13.78585**	**17.6445**	**98**	**2809**
Screening	**$5,481.47**	**13.79692**	**17.6788**	**59**	**2816**
Incremental	**$817.30**	**0.01107**	**0.0343**	**-39**	**7**
ICER	**$103,965/QALY**		**$23,828/LYG**		
MODEL 2: Optimised AS	**No discount on utilities. 5% discount on costs.**				
Control	**$4,524.92**	**13.79227**	**17.6446**	**99**	**2809**
Screening	**$5,085.59**	**13.81517**	**17.67908**	**60**	**2816**
Incremental	**$560.67**	**0.0229**	**0.03448**	**-39**	**7**
ICER	**$24,483.41/QALY**		**$16,261/LYG**		

9.5 Table 5: Sensitivity Analysis

Variables	**New ICER**	
Discount Rates	**MODEL 1**	**MODEL 2**
2% Discount for both	$122,711/QALY	$40,193/QALY
8% Discount for both	$177,932/QALY	$50,664/QALY
Utility		
Starting Utility 1.0 (Rather than age related)	$103,957/QALY	$33,021/QALY
Utility Post- Treatment 0.9	Net dis-utility for screening cohort	$58,010/QALY
Timeline		
Lifelong timeline	$103,565/QALY	$38,553/QALY
Age of model entry		
All patients start screening at 50	$109,898/QALY	$37,967/QALY


Non-Prostate Cancer Death
14
Post Rx
12
WW
9
RRP
7
EBRT
8
Low Risk Prostate Cancer
2
Active Surveillance
6
Intermediate Risk Prostate Cancer
4
Definitive Rx
11
Prostate Cancer Death
13
High Risk Prostate Cancer
3
Disease Recurrence
10
Cancer Free
1
Advanced Prostate Cancer
5


Tornado Analysis (ICER)
Utility Post Rx (0.6657 to 0.9985)
Utility Baseline Health State (0.5208 to 1.0)
Discount Rate (0.0 to 0.1)
Utility Metastatic Disease (0.3 to 0.78831)
EV: 148127.40522
-100000
-50000
0
50000
100000
150000
200000
250000
ICER(SAUD/QALY)


Tornado Analysis (ICER)
Utility Post Rx (0.6657 to 0.9985)
Utility Baseline Health State (0.5208 to 1.0)
Discount Rate (0.0 to 0.1)
Utility Metastatic Disease (0.3 to 0.78831)
EV: 41553.38257
0
50000
100000
150000
200000
250000
ICER (SAUD/QALY)

Your image file "Figure 4 Univariate NMB 5%.jpg" cannot be opened and processed. Please see the common list of problems, and suggested resolutions below.

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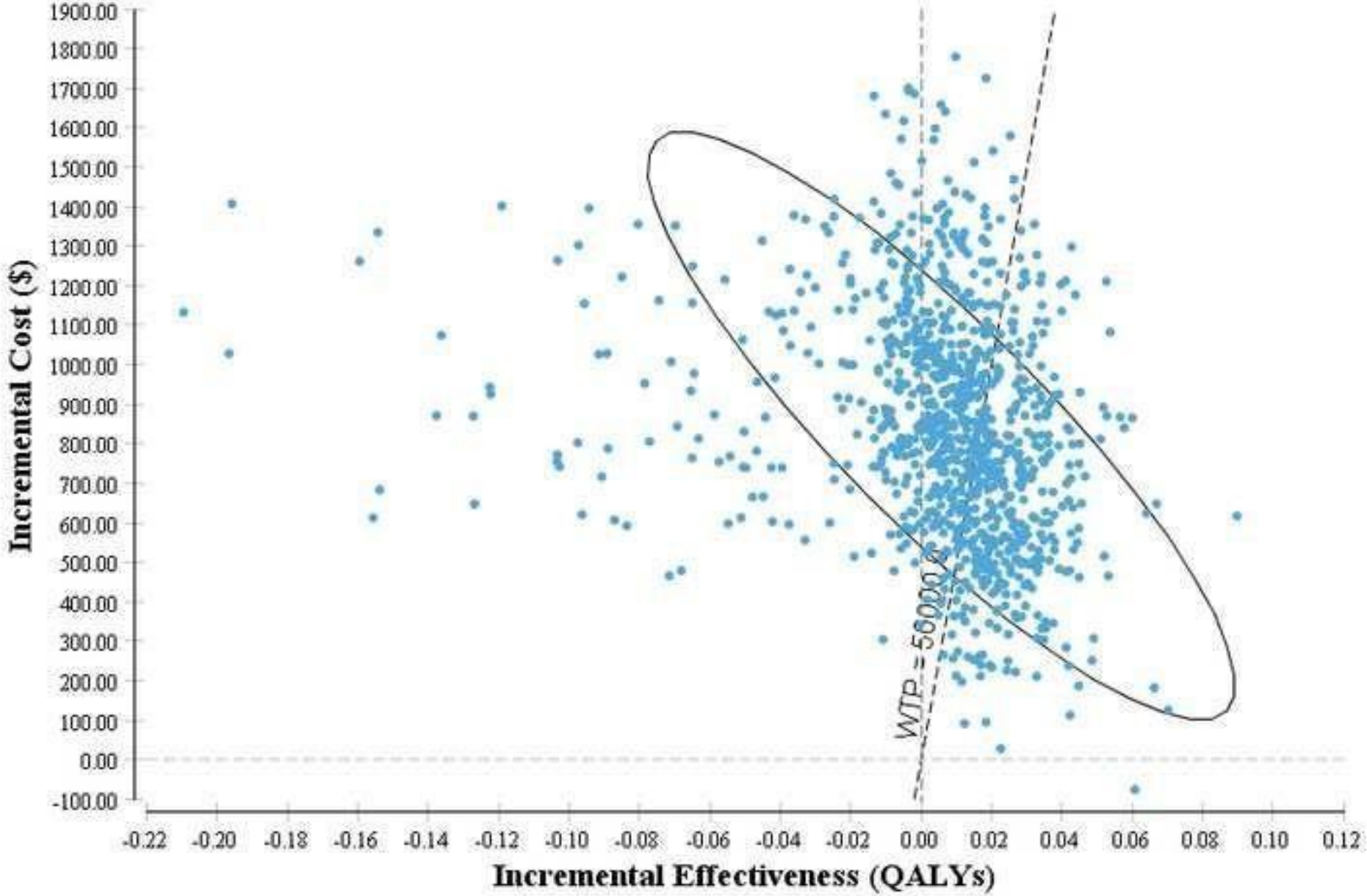
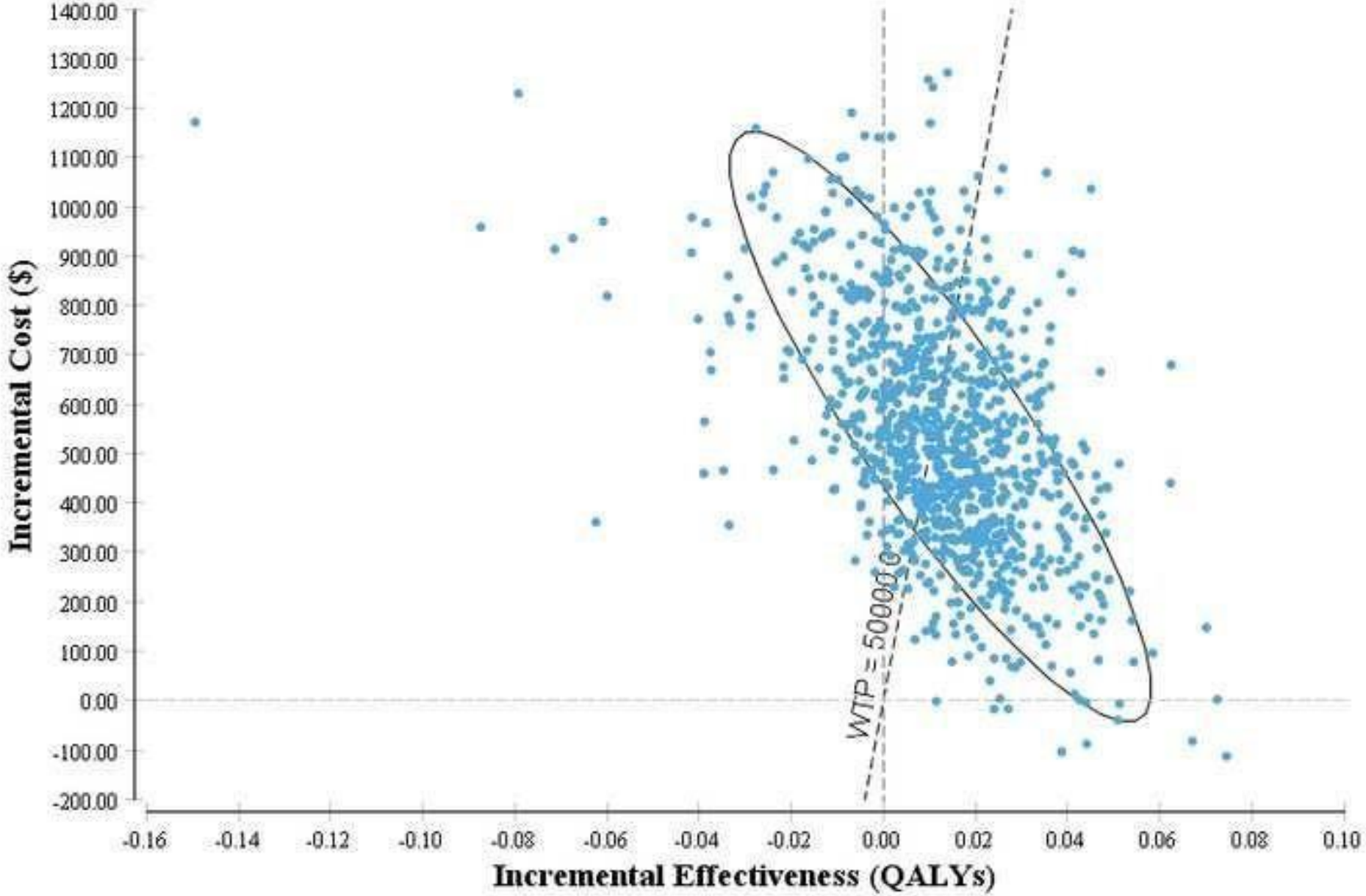
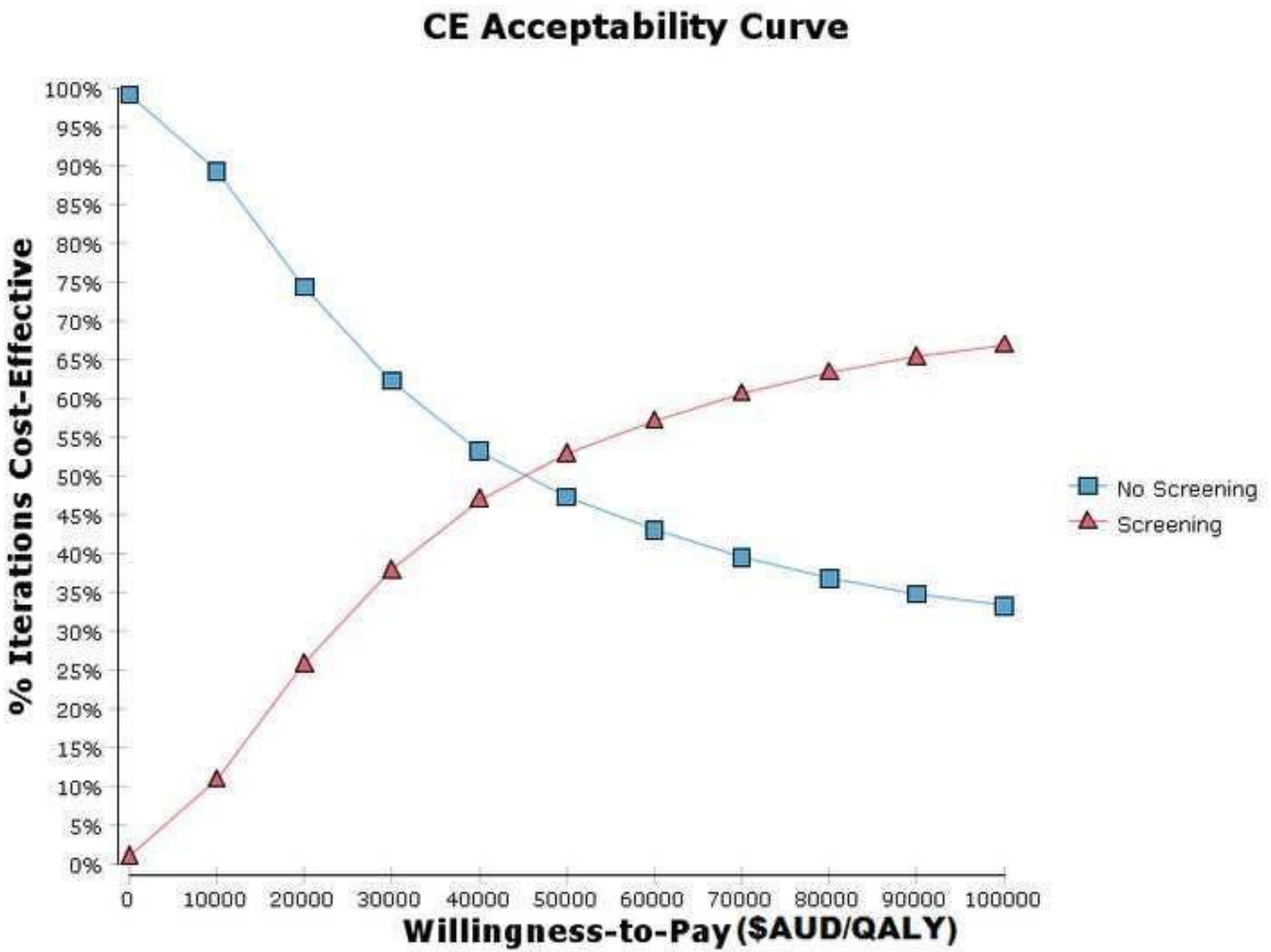
Probabilistic Sensitivity Analysis - Incremental Cost-Effectiveness, Screening v. No Screening



Probabilistic Sensitivity Analysis, Incremental Cost-Effectiveness, Screening v. No Screening




CE Acceptability Curve
% Iterations Cost-Effective
100%
95%
90%
85%
80%
75%
70%
65%
60%
55%
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
0
10000
20000
30000
40000
50000
60000
70000
80000
90000
100000
Willingness-to-Pay ($AUD/QALY)
No Screening
Screening