

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

A Cost Utility Analysis of Prostate Cancer Screening in Australia

Dr. Andrew Keller^{1,2}, Prof. Christian Gericke^{1,2}, Assoc. Prof. Jennifer A Whitty¹, Dr. John Yaxley³,
Dr. Boon Kua³, Dr Geoff Coughlin³ and Dr. Troy Gianduzzo^{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 both prostate cancer and background mortality in the Göteborg study. The incremental cost per quality-adjusted life-year (QALY) for PSA screening was \$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 screening dramatically.

Key Points for Decision Makers:

- PSA-based prostate cancer screening is not cost effective in an Australian population with current treatment patterns.
- Increased utilisation of active surveillance (AS) enhances the cost-effectiveness of prostate cancer 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
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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 Practitioners' (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-cancer screening 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]

1 Active surveillance (AS), an approach of monitoring rather than immediately treating low risk PC, has been
2 demonstrated to decrease the harm of overtreatment, whilst preserving the benefits of screening.[12] Decision
3 analyses investigating the cost-effectiveness of AS protocols compared to primary intervention for low risk
4 prostate cancer found that AS dominated primary intervention at all modelled time horizons.[13, 14]
5
6
7
8
9
10

11 **1. Aim**

12 We aimed to investigate the predicted cost utility of a theoretical Australian PSA-based population screening
13 programme. In our model, prostate cancer diagnoses were risk stratified, and any subsequent treatment based
14 upon current Australian treatment patterns. The accumulated costs, utilities and cancer specific mortality rates
15 between hypothetical screening and non-screening cohorts were recorded and compared. We aimed to compare
16 two systematic screening strategies to current opportunistic screening practices: (i) a screening strategy where
17 any cancer diagnoses would be treated in accordance with current Australian treatment patterns and (ii) an
18 active surveillance-optimised strategy where any low risk PC diagnoses were followed with an active
19 surveillance protocol instead of receiving primary intervention until clinical disease progression.
20
21
22
23
24
25
26
27

28 **2. Methodology**

29 **2.1 Study Population**

30 The model evaluated the outcomes of a uniformly distributed Australian male cohorts aged between 50-69
31 years. A uniform distribution was selected to better reflect the recruitment method of the Göteborg study, as
32 opposed to all men entering the model at a set age, as is commonly employed in other decision models.[9-11]
33
34
35
36
37
38

39 **2.2 Screening Strategies**

40 The model assessed the cost-utility of two screening strategies for prostate cancer: strategy 1) Asystematic
41 population screening strategy, with invitation for screening with a serum PSA test every 2 years, with any supra-
42 threshold PSA tests offered a Trans-Rectal Ultrasound guided biopsy (TRUS); strategy 2) Opportunistic prostate
43 cancer screening, representing current standard practice.
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 Two separate scenarios were created utilising the same two screening strategies. The first scenario, or base case,
2 compared both screening programmes with any subsequent prostate cancer diagnoses being treated in
3 accordance with current Australian clinical practices, with treatment strategies determined by both cancer risk
4 stratification and patient preference. The second scenario, or the AS-optimised model, differed in that
5 subsequent low risk prostate cancer diagnoses were all treated initially with AS instead of the majority of cases
6 receiving primary intervention. Those on active surveillance that had PSA progression ($PSA \geq 10\text{ng/mL}$) or PC
7 upgrading (Gleason score >6) on subsequent TRUS biopsy would proceed to definitive intervention based upon
8 their new risk stratification.
9
10
11
12
13
14
15
16
17
18
19

20 **2.3 Markov Model Structure and Health States**

21 To investigate the cost-utility of a PSA based screening programme in a simulated Australian population we
22 built a decision model utilising Markov processes in TreeAge Pro 2014 software suite. (TreeAge Software Inc.,
23 Williamstown, MA, USA)
24
25
26

27 All men entered the model in a cancer-free/pre-diagnosis health state. Literature based probabilities saw men
28 either remain 1) disease free, 2) die of background (non-PC) causes or diagnosed with 3) low-risk, 4)
29 intermediate-risk, 5) high-risk or 6) advanced (metastatic) PC.
30
31
32
33
34
35

36 Following diagnosis of non-metastatic PC the patient would either undergo AS (surveillance with curative
37 intent, limited to those with low risk diagnoses), surgery, radiation or watchful waiting (WW; surveillance with
38 palliative intent, limited to those with a life expectancy less than 10 years or contraindications to curative
39 therapy). Curative treatment options were limited to the most commonly available Australian treatment options
40 of Radical Retro-pubic Prostatectomy (RRP) and External Beam Radiation Therapy (EBRT). Following
41 diagnosis and treatment men would stay in risk stratified post-treatment health states until natural death or
42 development of metastatic disease. (Figure 1)
43
44
45
46
47
48
49
50

51 In line with the Göteborg study, PSA screening would cease once a patient reached age 69 years, but they would
52 continue to cycle through the model.[8] A one year cycle length was selected to best represent the slow natural
53 history of PC. A 20 year time horizon was selected owing to the paucity of quality literature on both the natural
54 history of PC and EBRT failure rates after this length of time.
55
56
57
58
59
60
61
62
63
64
65

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 of transition 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, individual papers 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 $\leq T1a$, Intermediate risk – Gleason score ≤ 7 , PSA ≤ 20 , clinical stage $\leq T2b$, 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 base case (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).

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

4
5
6 A treatment threshold of equal or greater to 76 years old was selected as described in Campbell-Walsh Urology.
7
8 At this age all patients currently in the AS health state would transition to the WW health state.[21]

9
10 Probabilities of disease recurrence for each risk stratification following definitive treatment were derived from
11 analysis of 6,652 D'Amico risk stratified men receiving PC therapy at a high volume centre.[22]

12
13
14 Probability of disease progression to metastasis for those in watchful waiting disease states was drawn from the
15 Prostate Intervention Versus Observation Trial (PIVOT), being more contemporaneous (published 2012 vs
16 2002), with longer median follow-up (10 years vs 6.2) and having more participants in the observation arm (367
17 vs 349 men) than the next largest study published by Holmberg et al.[23,24]

18
19
20 Risk of progression to the advanced disease state following post-treatment recurrence was drawn from an
21 international study which followed 2,426 men with biochemical recurrence after RRP with a median follow-up
22 of 6.6 years.[25]

23
24
25 Adjustment for the possibility of initial clinical under-staging of low risk disease was performed, utilizing the
26 results of the largest published prostatectomy specimen series of 626 patients meeting the strict Prostate Cancer
27 Research International: Active Surveillance (PRIAS) criteria.[26]

28
29
30 Probabilities of background mortality were drawn from Australian Bureau of Statistics age related mortality
31 rates, and adjustments made for age related prostate cancer specific death rates.[27, 28] Although there is
32 evidence androgen deprivation therapy (ADT) might increase the rate of cardiovascular events, an increase in
33 cardiovascular mortality has not been conclusively demonstrated conclusively with significant discordance in
34 results between published trials.[29-31] Additionally, in our model ADT was only initiated when metastases
35 were present, reflecting more conservative practice and resulting in lower total ADT exposure. As such, we did
36 not adjust the transition probability to non-cancer related death for those in the metastatic disease state. We also
37 did not adjust for peri-operative mortality in the RRP group, however, Björklund et al's paper demonstrated that
38 the 90 day peri-operative mortality in >22,000 men receiving RRP was lower than the age-matched cohort
39 (<0.2%).[32]

2.4.3 Utility Values

1
2 Health states were each assigned a utility value representing the health-related quality of life of an average
3 patient inhabiting that disease state. All health state utility values were derived from Australian data where
4 possible. (Table 2)
5
6

7
8
9 PC screening has been criticised as increasing anxiety and reducing health related quality of life (HRQoL)
10 during and after diagnosis.[4] However, in the Dutch and Finnish centres of the ERSPC it was shown that
11 screening does not induce short term HRQoL effect.[33, 34] Even those patients who had false positive results
12 tended to regard screening as a positive experience.[35] Likewise participating in an active surveillance protocol
13 does not appear to impact HRQoL or increase anxiety when compared to controls, with participants' HRQoL
14 similar to age adjusted controls.[34, 36, 37] Utility scores were consequently unaffected by screening or AS in
15 our model.
16
17
18
19
20
21

22
23 We elected to use a single Australian study for our post-treatment utility scores. Smith et al. followed the same
24 large cohort (1500) of 50-69 year old men for 3 years before and after definitive treatment, comparing their
25 utility directly against an age and pre-morbidity matched control cohort over the same three year period, using
26 the same health instrument. This study utilised the University of California, prostate cancer index, a validated
27 instrument which includes all 12 components of the commonly used 12-item short form (SF-12) questionnaire.
28 They demonstrated a relative utility value of 0.95 when compared to age-matched controls at 3 years following
29 treatment.[36]
30
31
32
33
34
35
36

37
38
39 Despite widely ranging protocols for administration of androgen deprivation therapy our model conservatively
40 initiated its usage only when patients transitioned to the metastatic health state. Of the treatment options
41 androgen deprivation therapy is widely regarded as having the greatest effect on HRQoL, however, this may
42 reflect the poor baseline of patients selected for androgen deprivation therapy.[36, 38] The metastatic health
43 state utility value was drawn from a combination of Australian and international studies. [36, 39] Smith et al's
44 Australian HRQoL study demonstrated a utility of 0.9 at initiation of androgen deprivation therapy, however
45 follow-up was inadequate to assess the utility of terminal prostate cancer.[36] The utility of PC at its terminal
46 stage was drawn from Farkilla et al, which assessed HRQoL using multiple health instruments (15D, EQ-5D,
47 VAS, EORTC QLQ-C30) from which our utility value of terminal PC of 0.6 was synthesized.[39] The utility of
48 the advanced disease state thus fell from 0.9 to 0.6 over a five year period to represent deteriorating wellbeing
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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

3
4 All utility values for disease-states listed above used above were not absolute values, but were multipliers for
5 the age related baseline utility in a contemporary Australian male population.[40]
6

7 8 9 10 11 **2.4.4 Costs**

12
13
14
15 Costs were accumulated by both being in a specific disease state (state costs) as well discrete events (transition
16 costs), such as having surgery.

17
18
19 A health system perspective was used to assign costs for screening, AS and treatment, as the model aims to
20 approximate the costs of a government-run screening programme. Out of pocket and time costs for programme
21

22
23
24 participants were therefore not included. Transition and state costings were derived from a combination of
25 Australian studies, Medicare Benefits Schedule (MBS), Pharmaceutical Benefits Scheme (PBS) and Australian
26 Refined – Diagnosis Related Groups (AR-DRGs). (Table 3) All costs were inflated to 10 July 2015 dollars using
27 annual inflation rates from the Reserve Bank of Australia.
28
29

30
31
32
33
34 The cost of annual screening was calculated from the overall number of PSA blood tests and TRUS biopsies
35 performed in the Göteborg study. A fractional annual test frequency per patient was calculated after adjusting
36 for model dropout for either natural death or reaching the age limit of screening. The Australian costs of a serum
37 PSA test and a TRUS biopsy, allowing for a 2% rate of post-TRUS sepsis were then used to arrive at the final
38 cost of screening per man aged 50-69 in the screening cohort.[21]
39
40
41
42

43 44 45 46 47 **2.5 Model Outcomes**

48
49
50
51 The primary model output was Quality Adjusted Life Years (QALYs) for each screening strategy over 20 years.
52 Costs effectiveness was measured as an Incremental Cost Effectiveness Ratio (ICER) and expressed in
53 \$/QALY. Life Years Gained (LYG) was used as an alternative model output to allow comparison with other
54 cost-analyses that did not use the QALY metric.
55
56
57
58
59
60
61
62
63
64
65

1 All future costs, QALYs and LYGs were discounted 5% and compared to a societal willingness to pay (WTP) of
2 \$50,000/QALY in line with Pharmaceutical Benefits Advisory Committee guidelines and a half-cycle correction
3 was applied to all Markov processes. [41] Undiscounted QALYs and LYGs are also presented due to ongoing
4 controversy regarding the discounting of future health outcomes, particularly for screening and prevention
5 programmes.[42, 43] Cancer-specific mortalities, and interventions saved per 10,000 men was also used to
6 compare treatment strategies.
7
8
9
10

11 **2.6.1 Univariate Sensitivity Analysis**

12 We conducted univariate sensitivity analyses of all probabilities, cost and utility values to determine the effect
13 of uncertainty of each variable upon the models output. All cost and utility values were varied 20% above and
14 below the base case value. Transition probabilities were varied within their 95% confidence intervals.
15 Simulations were also run with a lifelong timeline and a cohort start age of 50 to assess possible impact on
16 model outcomes.
17
18
19
20
21
22
23
24
25
26

27 Univariate sensitivity analysis outside of the confidence intervals was performed for the probability of entering
28 the active surveillance health state following a diagnosis of low risk PC. This was done to determine what rate
29 of primary active surveillance was required in order to achieve an increase in QALYs at a sub-threshold WTP
30 value.
31
32
33
34
35
36
37
38
39
40

41 **2.6.2 Probabilistic Sensitivity Analysis**

42 Multivariate probabilistic sensitivity analysis was performed for all variables in the both scenarios to assess
43 overall model uncertainty. A second order Monte Carlo analysis was performed with all variables drawn
44 simultaneously. Beta and gamma distributions were estimated for utility and costings values respectively from
45 normal distributions with standard deviations of 20% above and below the base case values. A combination of
46 Dirichlet and beta distributions were drawn for probability values based on their standard error values, as per
47 Table 1. 10,000 samples were drawn for each probabilistic sensitivity analysis.
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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, discount rate and the utility of advanced disease. Cost variability within 20% of the base case value had little effect on overall model output with almost all transition probabilities being more influential. Reducing the age of model entry to 50 years old, rather than utilising a uniform distribution between ages 50-69, had the effect of reducing the 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

1
2 Probabilistic sensitivity analysis was performed for base model (Scenario 1) in order to ascertain the proportion
3
4 of simulations in which it proved cost-effective. Assuming a willingness-to-pay threshold of
5
6 \$AU50,000/QALY the base case model was cost effective in 38% of simulations, delivered improved QALYs at
7
8 supra-threshold WTP in 38%, and decreased QALYs in 24.5% of simulations. (Figure 5)

9
10 For Scenario 2, Optimised Active Surveillance, the probabilistic sensitivity analysis demonstrated cost-
11
12 effectiveness in 53% of all simulations, provided an increase in QALYs at a supra-threshold WTP in 27% of
13
14 simulations and decreased QALYs in 19% of simulations. (Figure 6)

15
16
17 A cost-effectiveness acceptability curve was plotted for scenario 2 to demonstrate the effect of increasing WTP
18
19 on the number of cost-effective iterations, at a WTP of \$100,000/QALY screening was cost effective in 66% of
20
21 all iterations. (Figure 7)

4.1 Discussion

22
23
24
25
26
27
28
29
30 Our model is the first to explore the effectiveness and the cost of instituting a PSA-based populationscreening
31
32 programme based on the results of the Göteborg Randomised Population-based prostate-cancer screening trial.
33
34 Other CEAs to date have based their assumptions upon the results of the PLCO or ERSPC trials, however, the
35
36 protocols of both trials were flawed.[5]

37
38
39 In our base case scenario, screening was not found to be cost effective as although it increased QALYs, it did so
40
41 at an incremental cost of \$147,528/QALY, which was well above our nominal willingness to pay(WTP)of
42
43 \$50,000/QALY.

44
45
46 When the results are viewed with a LYG metric the results appear more favourable, with a cost of
47
48 \$45,890/LYG. It must be stressed that the seemingly large difference between the cost/QALY and cost/LYG is
49
50 not due simply to patient disutility following treatment. Rather, as evidenced by the univariate sensitivity
51
52 analysis, two of most influential model variables were the pre-morbid utility score and the discount rate of
53
54 future outcomes/costs, consequently multiple lives needed to be extended in order to generate a single additional
55
56 QALY. The cost-effectiveness of our model compares favourably with other CEAs, which have demonstrated
57
58 highly variable results.[9]

1 Pataky et al., in an ERSPC-based Canadian micro-simulation study, found screening strategies cost between
2 \$27,000 - \$54,000/LYG compared to non-screening strategies.[9] They also found that all strategies resulted in
3 decreased QALYs for the screened population, however, this result was very sensitive to the utility values
4 used.[9]
5

6
7
8 An American CEA based upon the NNT of the ERSPC (48 men) found at 9 years follow-up that screening was
9 not cost-effective based upon their societal WTP of \$100,000/LYG.[11] However, they found that screening
10 became cost effective when the NNT was less than 21, which compares favourably with the Göteborg's NNT of
11 12.
12
13
14

15 Only one CEA is published that aims to model an Australian prostate cancer screening programme, and it is
16 based upon the 9 year follow-up data from the ERSPC.[10] This model failed to demonstrate cost-utility for a
17 population screening model in Australia, with a cost of \$291,817/QALY at 10 years follow-up, however, this
18 analysis disregards the role of active surveillance completely.[10] Furthermore, every man in this model
19 diagnosed with PC assumed a 0.05 disutility and all lifetime treatment costs immediately. This model also
20 arguably overestimates costs by assuming the cost accrual of 100% screening compliance while assuming the
21 compliance-unadjusted mortality reduction of the ERSPC which had only 82% of screened men having at least
22 one PSA test, and 86% of men undergoing TRUS when recommended.[7]
23
24
25

26 Whilst our model suggests population-based screening at current AS uptake rates is not cost-effective when
27 compared to Australia's WTP, it does appear to compare favourably with established Australian screening
28 programmes. BreastScreen Australia have not performed a comprehensive cost-utility analysis to directly
29 compare cost/QALY against.[44] They have, however, performed a CEA, with the Markov model output unit
30 being cost per LYG. Similar to our model, BreastScreen Australia also focused on a population of 50-69 year
31 olds, used a biennial screening test and a 5% discount rate for future costs and benefits. After adjusting for
32 inflation, the estimated cost per LYG over a 20 year time horizon was \$47,776/LYG.[44] Using the same LYG
33 metric, a 5% discount rate at a 20 year time horizon PSA based screening was more cost-effective at
34 \$45,890/LYG.
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50

51 Similarly, no true cost-utility analyses of the established Australian colon cancer screening programme have
52 been performed, however, a CEA examining cost/LYG has been undertaken.[45] The projected cost of
53 \$53,989/LYG, after adjustment to today's dollars, was higher than for our prostate cancer model, however, the
54 time horizon the authors in this study selected was only 10 years. [46]
55
56
57
58
59
60
61
62
63
64
65

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

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29 The AS uptake rate required for cost effectiveness in our model was 92%, which whilst high, may not be
30 unattainable. Data from the Victorian Prostate Cancer Registry (VPCR) demonstrates increasing AS utilisation
31 in recent years, with 36% of all new low risk diagnoses initially selecting AS.[50] In Sweden, AS is now the
32 most commonly selected primary treatment for low risk PC, with 72% of all new diagnoses initially managed
33 with AS.[51]

34
35
36
37
38
39
40 Concerns about clinical under-grading and under-staging of prostate cancer exist and are perhaps contributing to
41 under-utilisation of AS as a treatment option for low risk prostate cancer.[26, 52] However, the clinical effect of
42 an initial under-grading of prostate cancer in AS patients is yet to be established and it is not reason enough to
43 deny patients the option of AS. The un-marrying of PC diagnosis and its immediate treatment and the increased
44 utilisation of AS as a treatment option are crucial to the cost-effectiveness of PSA based prostate cancer
45 screening and essential in reducing screening-related harm.[53, 54]

46
47
48
49
50
51
52
53 This difficulty in establishing a disconnection between PC diagnosis and treatment might be alleviated by the
54 increasing utilisation of multi-parametric Magnetic Resonance Imaging (mpMRI).[55]. MpMRI has shown
55 utility as a second line diagnostic tool in lieu of TRUS biopsy.[55] It allows preferential detection of those
56 intermediate and high risk prostate cancers more likely to benefit from intervention, thereby avoiding detection
57
58
59
60
61
62
63
64
65

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 is highly 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 a societal 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 sensitivity analysis, 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, and for development of metastases following disease recurrence. However, sensitivity analysis reveals the model to be relatively insensitive to these variables, and consequently it is unlikely this affected 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
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 results are unlikely to be representative of the true benefit of commencing screening earlier.

25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
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 cancer screening programme in Australia. In our base-case scenario prostate cancer population based screening with an invitation 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-risk disease, our screening model was cost-effective after 20 years of follow-up. PSA based population screening may be 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 University 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.

7. References

1. Welfare AIoHa. Cancer in Australia: an overview 2012. Cancer series no 74 Cat no CAN 70 Canberra: AIHW [cited 13/06/2014] Available from: www.aihw.gov.au.
2. Ferlay J SI, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013 Available from: <http://globocan.iarc.fr>, [cited on 16/10/2014].
3. AIHW. Multiple causes of death in Australia: an analysis of all natural and selected chronic disease causes of death 1997-2007. AIHW bulletin no 105 Cat no AUS 159 Canberra: AIHW. 2012.
4. RACGP. Guidelines for preventive activities in general practice, 8th edn. East Melbourne: Royal Australian College of General Practitioners. 2012.
5. Eckersberger E FJ, Sadri H, , Margreiter M TS, Lepor H, Djavan B. Screening for Prostate Cancer: A Review of the ERSPC and PLCO Trials. *Reviews in Urology*. 2009;11(3):127-33.
6. Andriole GL, Crawford ED, Grubb RL, 3rd, Buys SS, Chia D, Church TR, et al. Mortality results from a randomized prostate-cancer screening trial. *The New England journal of medicine*. 2009 Mar 26;360(13):1310-9.
7. Schröder F HJ, Roobol M, , Tammela T CSea. Screening and Prostate-Cancer Mortality in a Randomized European Study. *NEJM*. 2009;360(13):1320-8.
8. Hugosson J CS, Aus G, Bergdahl S, Khatami A, Lodding P, Pihl C, Stranne J, Holmberg E, L H. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. *The lancet oncology*. 2010;11:725-32.
9. Pataky R, Gulati R, Etzioni R, Black P, Chi KN, Coldman AJ, et al. Is prostate cancer screening cost-effective? A microsimulation model of prostate-specific antigen-based screening for British Columbia, Canada. *International journal of cancer Journal international du cancer*. 2014 Jan 20.
10. Martin AJ, Lord SJ, Verry HE, Stockler MR, Emery JD. Risk assessment to guide prostate cancer screening decisions: a cost-effectiveness analysis. *The Medical journal of Australia*. 2013 Jun 3;198(10):546-50.
11. Shteynshlyuger A, Andriole GL. Cost-effectiveness of prostate specific antigen screening in the United States: extrapolating from the European study of screening for prostate cancer. *The Journal of urology*. 2011 Mar;185(3):828-32.

12. Klotz L. Active surveillance for prostate cancer: patient selection and management. *Curr Oncol.* 2010 Sep;17 Suppl 2:S11-7.
13. Hayes JH, Ollendorf DA, Pearson SD, Barry MJ, Kantoff PW, Stewart ST, et al. Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis. *Jama.* 2010 Dec 1;304(21):2373-80.
14. Koerber F, Waidelich R, Stollenwerk B, Rogowski W. The cost-utility of open prostatectomy compared with active surveillance in early localised prostate cancer. *BMC health services research.* 2014;14(1):163.
15. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *Jama.* 1998 Sep 16;280(11):969-74.
16. Baade PD, Youlden DR, Gardiner RA, Ferguson M, Aitken JF, Yaxley J, et al. Factors associated with treatment received by men diagnosed with prostate cancer in Queensland, Australia. *BJU international.* 2012 Dec;110(11 Pt B):E712-9.
17. Ischia JJ, Pang CY, Tay YK, Suen CF, Aw HC, Frydenberg M. Active surveillance for prostate cancer: an Australian experience. *BJU international.* 2012 Apr;109 Suppl 3:40-3.
18. Prostate Cancer Foundation of Australia and Cancer Council Australia PSA Testing Guidelines Expert Advisory Panel. Draft clinical practice guidelines PSA Testing and Early Management of Test-Detected Prostate Cancer. [PDF on Internet] Sydney: Cancer Council Australia. [cited 2015 Jun 13]. Available from: http://wiki.cancer.org.au/australia/Guidelines:PSA_Testing/Active_surveillance.
19. Mottet N BJ, Briers E, van den Bergh R.C.N., Bolla M vCNJ, Cornford P., Culine S JS, Lam T, Mason M.D, Matveev V., van der Poel H vdKTH, Rouvière O, Wiegel T. Guidelines on Prostate Cancer. *European Association of Urology.* 2015.
20. Orlendorf DA HJ, McMahon P, Pearson SD, . Active Surveillance and radical prostatectomy for the management of low risk, clinically-localized prostate cancer - Final Appraisal Document. *Institute for Clinical and Economic Review.* 2009.
21. Wein AJ KL, Novick AC, Partin AW, Peters CA. *Campbell-Walsh Urology 10th Edition: Elsevier Saunders;* 2012.
22. Hernandez DJ, Nielsen ME, Han M, Partin AW. Contemporary evaluation of the D'amico risk classification of prostate cancer. *Urology.* 2007 Nov;70(5):931-5.
23. Holmberg L, Bill-Axelsson A, Helgesen F, Salo JO, Folmerz P, Haggman M, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. *The New England journal of medicine.* 2002 Sep 12;347(11):781-9.
24. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al. Radical prostatectomy versus observation for localized prostate cancer. *The New England journal of medicine.* 2012 Jul 19;367(3):203-13.
25. Boorjian SA, Thompson RH, Tollefson MK, Rangel LJ, Bergstralh EJ, Blute ML, et al. Long-term risk of clinical progression after biochemical recurrence following radical prostatectomy: the impact of time from surgery to recurrence. *European urology.* 2011 Jun;59(6):893-9.
26. El Hajj A, Ploussard G, de la Taille A, Allory Y, Vordos D, Hoznek A, et al. Analysis of outcomes after radical prostatectomy in patients eligible for active surveillance (PRIAS). *BJU international.* 2013 Jan;111(1):53-9.
27. AIHW. Australian Institute of Health and Welfare (AIHW) 2014. Australian Cancer Incidence and Mortality (ACIM) books: Prostate cancer. Canberra: AIHW. [Cited 13/07/2015] Available from: <http://www.aihw.gov.au/acim-books;> 2014.
28. Australian Bureau of Statistics DiAPoICCoA, [Cited 21 July 2015] Available from: [http://www.ausstats.abs.gov.au/ausstats/subscriber.nsf/0/83A6580246688CEBCA2578840012A073/\\$File/33030_2009.pdf](http://www.ausstats.abs.gov.au/ausstats/subscriber.nsf/0/83A6580246688CEBCA2578840012A073/$File/33030_2009.pdf). Deaths, Australia. 2009.
29. Carneiro A, Sasse AD, Wagner AA, Peixoto G, Kataguirri A, Neto AS, et al. Cardiovascular events associated with androgen deprivation therapy in patients with prostate cancer: a systematic review and meta-analysis. *World journal of urology.* 2014 Nov 12.
30. Jespersen CG, Norgaard M, Borre M. Androgen-deprivation therapy in treatment of prostate cancer and risk of myocardial infarction and stroke: a nationwide Danish population-based cohort study. *European urology.* 2014 Apr;65(4):704-9.
31. Voog JC, Paulus R, Shipley WU, Smith MR, McGowan DG, Jones CU, et al. Cardiovascular Mortality Following Short-term Androgen Deprivation in Clinically Localized Prostate Cancer: An Analysis of RTOG 94-08. *European urology.* 2016 Feb;69(2):204-10.
32. Bjorklund J, Folkvaljon Y, Cole A, Carlsson S, Robinson D, Loeb S, et al. Postoperative mortality 90 days after robot-assisted laparoscopic prostatectomy and retropubic radical prostatectomy: a nationwide population-based study. *BJU international.* 2016 Jan 13.

33. Essink-Bot ML, de Koning HJ, Nijs HG, Kirkels WJ, van der Maas PJ, Schroder FH. Short-term effects of population-based screening for prostate cancer on health-related quality of life. *Journal of the National Cancer Institute*. 1998 Jun 17;90(12):925-31.
34. Vasarainen H, Malmi H, Maattanen L, Ruutu M, Tammela T, Taari K, et al. Effects of prostate cancer screening on health-related quality of life: results of the Finnish arm of the European randomized screening trial (ERSPC). *Acta oncologica*. 2013 Nov;52(8):1615-21.
35. Essink-Bot ML, Korfage IJ, De Koning HJ. Including the quality-of-life effects in the evaluation of prostate cancer screening: expert opinions revisited? *BJU international*. 2003 Dec;92 Suppl 2:101-5.
36. Smith DP, King MT, Egger S, Berry MP, Stricker PD, Cozzi P, et al. Quality of life three years after diagnosis of localised prostate cancer: population based cohort study. *BMJ*. 2009;339:b4817.
37. Wilcox CB, Gilbourd D, Louie-Johnsun M. Anxiety and health-related quality of life (HRQL) in patients undergoing active surveillance of prostate cancer in an Australian centre. *BJU international*. 2014 Mar;113 Suppl 2:64-8.
38. Cooperberg MR, Ramakrishna NR, Duff SB, Hughes KE, Sadownik S, Smith JA, et al. Primary treatments for clinically localised prostate cancer: a comprehensive lifetime cost-utility analysis. *BJU international*. 2013 Mar;111(3):437-50.
39. Farkkila N, Torvinen S, Roine RP, Sintonen H, Hanninen J, Taari K, et al. Health-related quality of life among breast, prostate, and colorectal cancer patients with end-stage disease. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*. 2014 May;23(4):1387-94.
40. Banham D, Hawthorne G, Goldney R, Ratcliffe J. Health-Related Quality of Life (HRQoL) changes in South Australia: comparison of burden of disease morbidity and survey-based health utility estimates. *Health and quality of life outcomes*. 2014 Aug 5;12(1):113.
41. Pharmaceutical Benefits Advisory Committee. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.5). Canberra: DoHA, January 2014.
42. Severens JL, Milne RJ. Discounting health outcomes in economic evaluation: the ongoing debate. *Value Health*. 2004 Jul-Aug;7(4):397-401.
43. Oliver A. A normative perspective on discounting health outcomes. *J Health Serv Res Policy*. 2013 Jul;18(3):186-9.
44. Australia B. BreastScreen Australia Evaluation - Evaluation Final Report. 2009.
45. O'Leary BA, Olynyk JK, Neville AM, Platell CF. Cost-effectiveness of colorectal cancer screening: comparison of community-based flexible sigmoidoscopy with fecal occult blood testing and colonoscopy. *Journal of gastroenterology and hepatology*. 2004 Jan;19(1):38-47.
46. Albert M, Tempany CM, Schultz D, Chen MH, Cormack RA, Kumar S, et al. Late genitourinary and gastrointestinal toxicity after magnetic resonance image-guided prostate brachytherapy with or without neoadjuvant external beam radiation therapy. *Cancer*. 2003 Sep 1;98(5):949-54.
47. Loeb S, Bjurlin MA, Nicholson J, Tammela TL, Penson DF, Carter HB, et al. Overdiagnosis and overtreatment of prostate cancer. *European urology*. 2014 Jun;65(6):1046-55.
48. Murphy DG, Loeb S. Prostate cancer: Growth of AS in the USA signals reduction in overtreatment. *Nature reviews Urology*. 2015 Sep 22.
49. Godtman RA, Holmberg E, Khatami A, Stranne J, Hugosson J. Outcome following active surveillance of men with screen-detected prostate cancer. Results from the Göteborg randomised population-based prostate cancer screening trial. *European urology*. 2013 Jan;63(1):101-7.
50. Weerakoon M, Papa N, Lawrentschuk N, Evans S, Millar J, Frydenberg M, et al. The current use of active surveillance in an Australian cohort of men: a pattern of care analysis from the Victorian Prostate Cancer Registry. *BJU international*. 2015 Apr;115 Suppl 5:50-6.
51. Loeb S, Folkvaljon Y, Makarov DV, Bratt O, Bill-Axelsson A, Stattin P. Five-year nationwide follow-up study of active surveillance for prostate cancer. *European urology*. 2015 Feb;67(2):233-8.
52. Oliveira IS, Pontes-Junior J, Abe DK, Crippa A, Dall'oglio MF, Nesralah AJ, et al. Undergrading and understaging in patients with clinically insignificant prostate cancer who underwent radical prostatectomy. *International braz j urol : official journal of the Brazilian Society of Urology*. 2010 May-Jun;36(3):292-9.
53. Sartor O. Expert Editorial: The PSA Screening Conundrum Revisited [Cited 17/10/2014] Available from: <http://gucasym.org/expert-editorial-psa-screening-conundrum-revisited>.
54. Murphy DG, Ahlering T, Catalona WJ, Crowe H, Crowe J, Clarke N, et al. The Melbourne Consensus Statement on the early detection of prostate cancer. *BJU international*. 2014 Feb;113(2):186-8.
55. Pokorny MR, de Rooij M, Duncan E, Schroder FH, Parkinson R, Barentsz JO, et al. Prospective Study of Diagnostic Accuracy Comparing Prostate Cancer Detection by Transrectal Ultrasound-Guided Biopsy Versus Magnetic Resonance (MR) Imaging with Subsequent MR-guided Biopsy in Men Without Previous Prostate Biopsies. *European urology*. 2014 Jul;66(1):22-9.

56. de Rooij M, Crienen S, Witjes JA, Barentsz JO, Rovers MM, Grutters JP. Cost-effectiveness of Magnetic Resonance (MR) Imaging and MR-guided Targeted Biopsy Versus Systematic Transrectal Ultrasound-Guided Biopsy in Diagnosing Prostate Cancer: A Modelling Study from a Health Care Perspective. *European urology*. 2013 Dec 21.
57. Turkbey B, Mani H, Aras O, Ho J, Hoang A, Rastinehad AR, et al. Prostate cancer: can multiparametric MR imaging help identify patients who are candidates for active surveillance? *Radiology*. 2013 Jul;268(1):144-52.
58. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2014 Sep 13.
59. Drummond MF SM, Torrance, GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes 3rd Edition*: Oxford University Press;2005.
60. Baade PD, Aitken JF, Ferguson M, Gardiner RA, Chambers SK. Diagnostic and treatment pathways for men with prostate cancer in Queensland: investigating spatial and demographic inequalities. *BMC Cancer*. 2010;10:452.
61. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. *Lancet*. 2000 Apr 29;355(9214):1491-8.
62. Hall RM, Linklater N, Coughlin G. Robotic and open radical prostatectomy in the public health sector: cost comparison. *ANZ journal of surgery*. 2014 Jun;84(6):477-80.
63. Baade PD, Gardiner RA, Ferguson M, Youlden DR, Aitken JF, Yaxley J, et al. Factors associated with diagnostic and treatment intervals for prostate cancer in Queensland, Australia: a large cohort study. *Cancer Causes Control*. 2012 Apr;23(4):625-34.
64. Yaxley J, Yaxley J, Gardiner R, Yaxley W. Prostate cancer - active surveillance as a management option. *Australian family physician*. 2013 Jan-Feb;42(1-2):74-6.
65. Carter HE, Martin A, Schofield D, Duchesne G, Haworth A, Hornby C, et al. A decision model to estimate the cost-effectiveness of intensity modulated radiation therapy (IMRT) compared to three dimensional conformal radiation therapy (3DCRT) in patients receiving radiotherapy to the prostate bed. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2014 Jun 11.
66. Hollander MJ. Costs of end-of-life care: findings from the province of Saskatchewan. *Healthcare quarterly*. 2009;12(3):50-8.
67. Krahn MD, Zagorski B, Laporte A, Alibhai SM, Bremner KE, Tomlinson G, et al. Healthcare costs associated with prostate cancer: estimates from a population-based study. *BJU international*. 2010 Feb;105(3):338-46.

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 ($NMB = \text{expected QALYs} \times WTP - \text{expected cost}$). 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	Upstaged to Intermediate Risk	0.294	0.0182091154	El Hajj, A. 2013[26]
Understaging of Low Risk Disease	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 healthstate.

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	\$1,261.1	CT + Bone Scan + MBS item no. 104 + 105
Screening	0	
Diagnosis Cancer	\$1,873.5	PSA + TRUS + CT + Bone Scan + MBS item no. 104 + 105
Non-Screening	6	
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		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)
Post Rx		
Advanced Disease	\$5,773.5	Bicalutamide + Goserelin x 4 + 105 x2 + CT + Bone Scan
Year 1	1	
Advanced Disease	\$4,672.0	Bicalutamide + Goserelin x 4 + 105 x2
Year >1	8	
Prostate Cancer	\$28,000.	Carter H. 2014[65]
Death	00	
Non-Prostate	\$19,430.	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)
Cancer Death	62	
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	\$5,276.0	AR-DRG codes
standard	0	
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
Initial 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	\$1,108.9 7	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

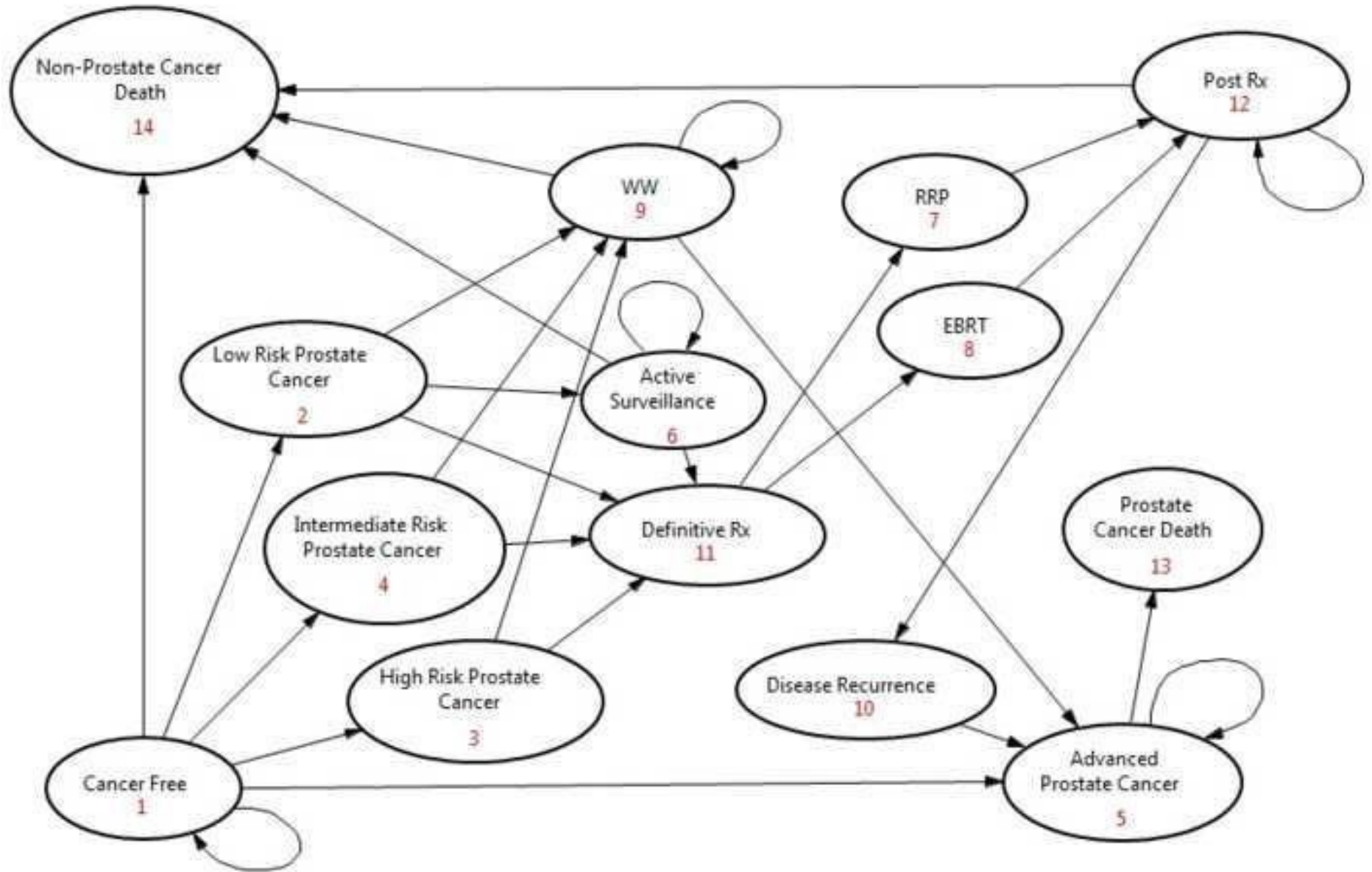
TRUS = Trans-Rectal Ultrasound guided prostate biopsy

9.4 Table 4: Results

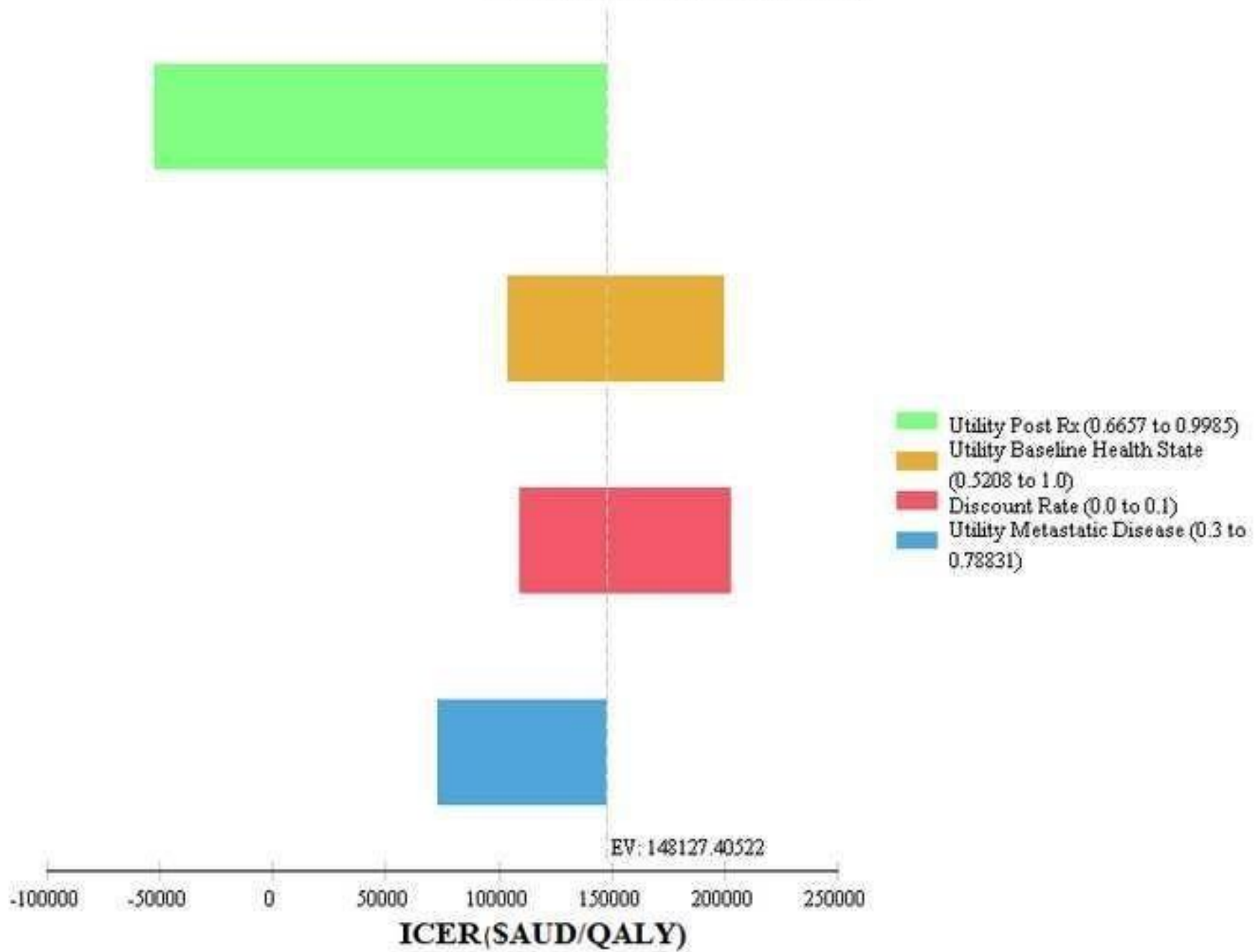
	Cost (\$)	QALYs	LYG	Cancer deaths/10,000 men	Non-Cancer deaths/10000 men
MODEL 1: Basecase	(20 years, 5% discount for both cost and utility)				
Control	\$4,664.17	9.32618	11.58002	98	2809
Screening	\$5,481.47	9.33172	11.59783	59	2816
<i>Incremental</i>	\$817.30	0.00554	0.01781	-39	7
<i>ICER</i>	\$147,528/QALY		\$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
<i>Incremental</i>	\$560.67	0.01222	0.01781	-39	7
<i>ICER</i>	\$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
<i>Incremental</i>	\$817.30	0.01107	0.0343	-39	7
<i>ICER</i>	\$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
<i>Incremental</i>	\$560.67	0.0229	0.03448	-39	7
<i>ICER</i>	\$24,483.41/QALY		\$16,261/LYG		

9.5 Table 5: Sensitivity Analysis

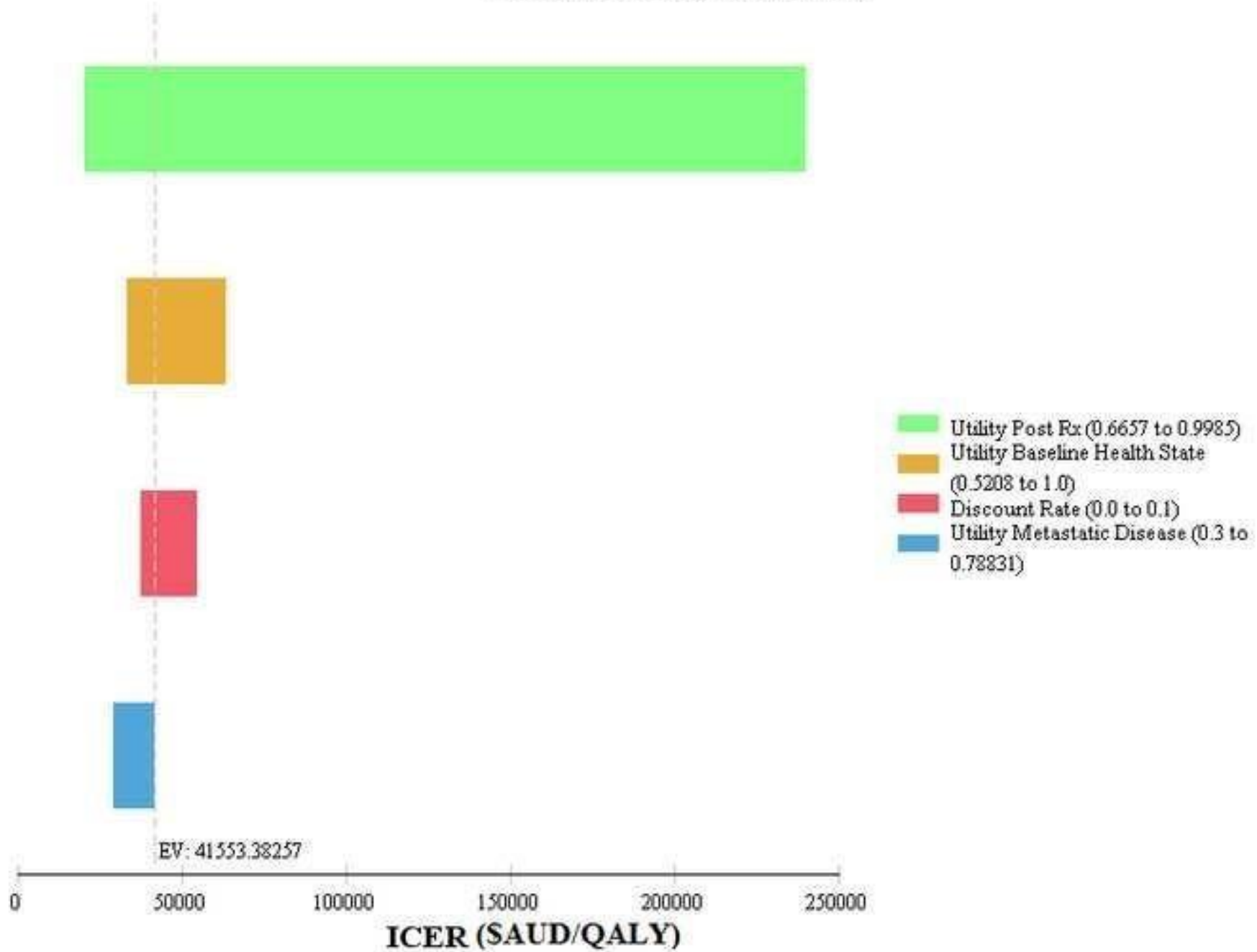
Variables	New ICER	
Discount Rates	MODEL 1	MODEL 2
2% Discount for both	\$122,711/QALY	\$40,193/QALY
8% Discount for both	\$177,932/QALY	\$50,664/QALY
Utility		
Starting Utility 1.0 (Rather than age related)	\$103,957/QALY	\$33,021/QALY
Utility Post- Treatment 0.9	Net dis-utility for screening cohort	\$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



Tornado Analysis (ICER)



Tornado Analysis (ICER)



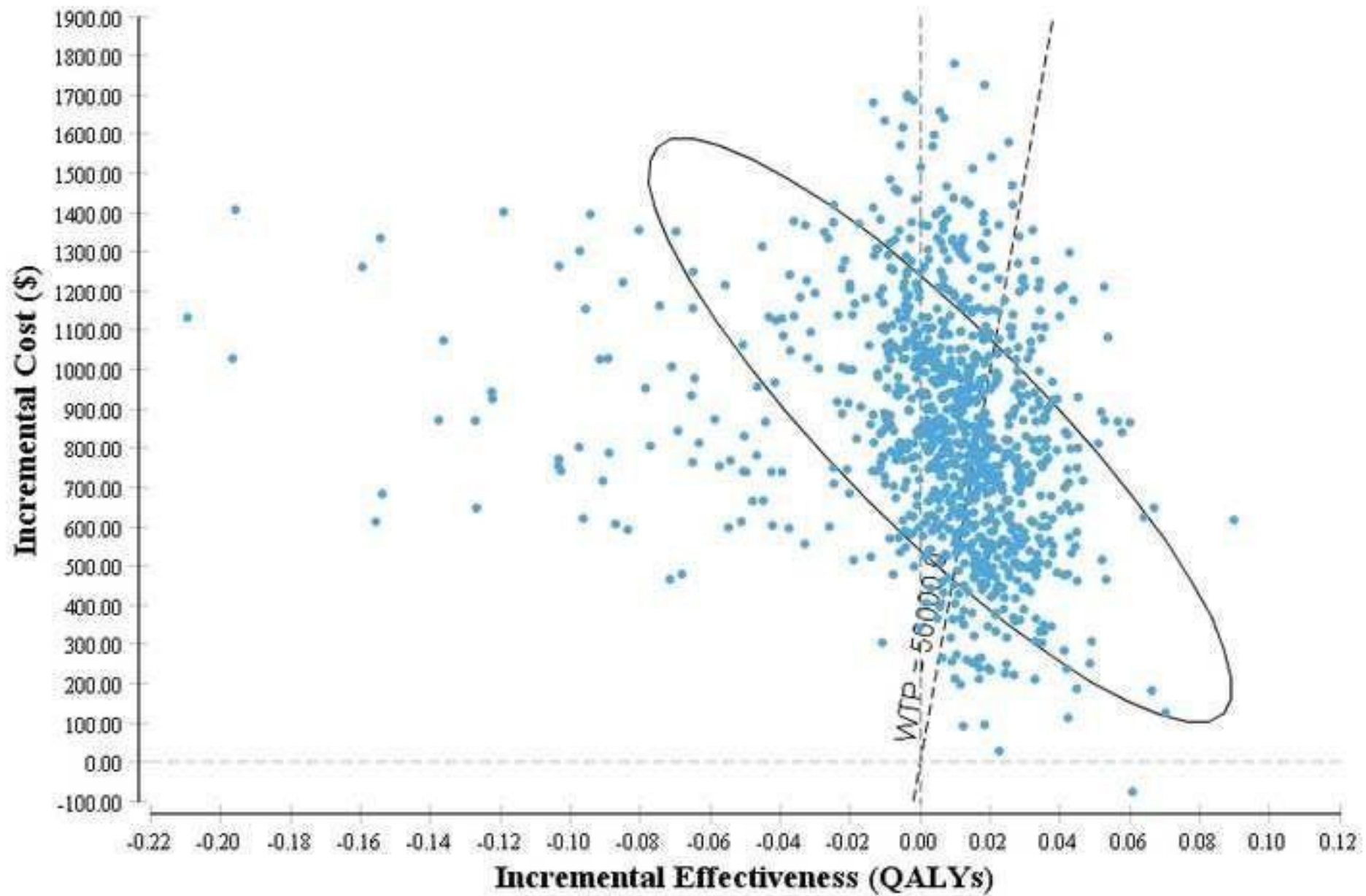
Your image file "Figure 4 Univariate NMB 5%.jpg" cannot be opened and processed. Please see the common list of problems, and suggested resolutions below.

Reason: The image file is corrupt or invalid. Please check and resubmit.

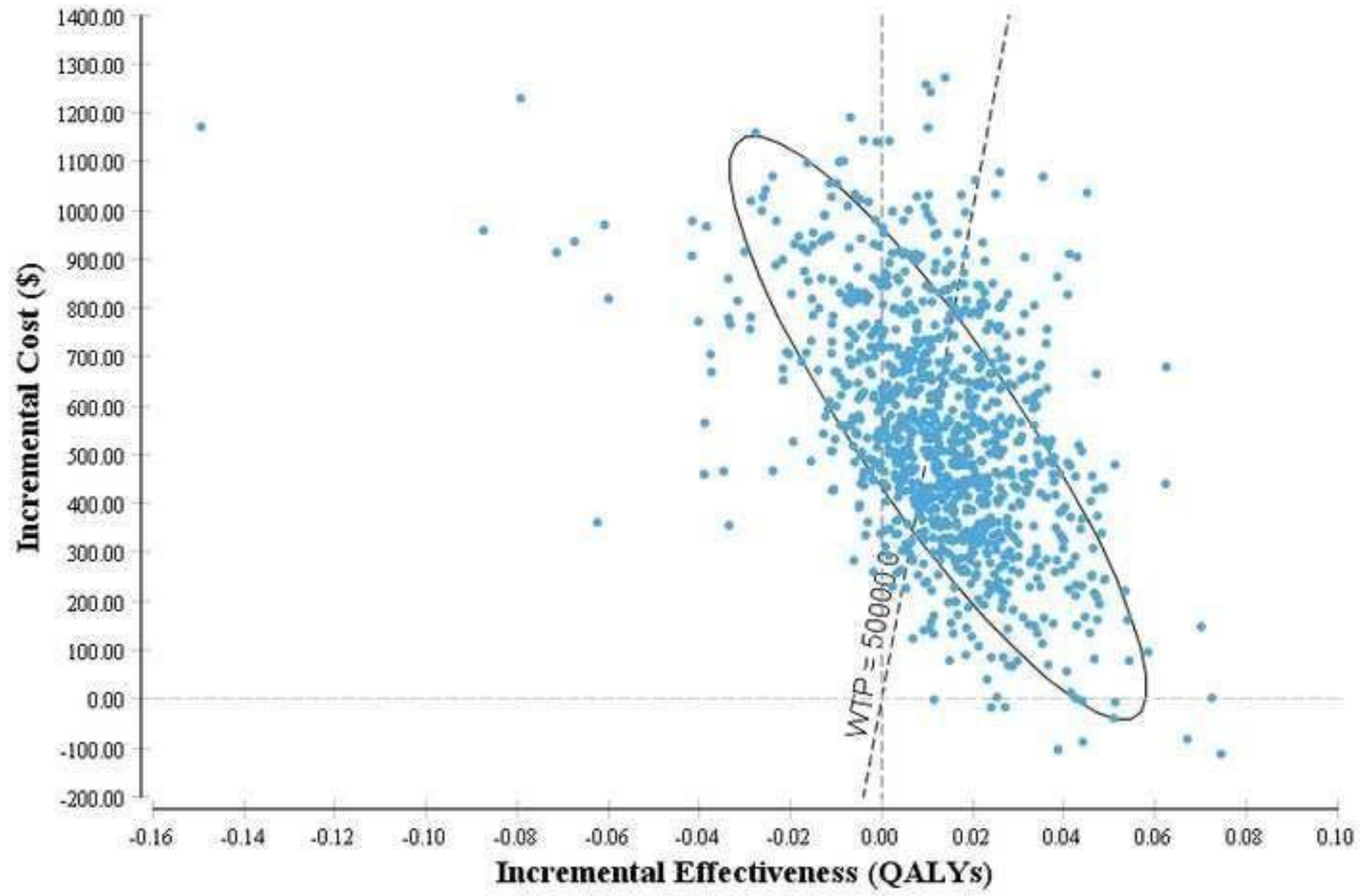
Other Common Problems When Creating a PDF from an image file

You will need to convert your image file to another format or fix the current image, then re-submit it.

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



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



CE Acceptability Curve

