Health economic model report

HE.1 General

The economic approach to provide evidence to support decision making around a clinical review question begins with a systematic search of the literature. The aim of this is to source any published economic evaluations of relevance to the topic of interest. At this stage it may become apparent that evidence exists in the literature which exactly meets the review question criteria and therefore there is no need for original economic analysis. If this proves not to be the case it may be decided that economic modelling can generate some useful analysis. The aim is to produce a cost-utility analysis in order to weigh up the benefits and harms of comparable interventions. The extent to which this is possible will be driven by the availability of evidence upon which to parameterise the clinical pathway and disease natural history.

HE.2 RQ8: Managing people at increased risk of prostate cancer

HE.2.1 Decision problem

Table HE01: Research questions

RQ 8	What is the most clinically- and cost-effective follow-up protocol for people who have a raised PSA, negative MRI and/ or negative biopsy?

Men who have had a negative MRI and/or a negative biopsy may still have prostate cancer. Factors that might indicate undetected prostate cancer include a raised PSA, abnormal digital rectal examination (DRE), abnormal results of other PSA-based tests, such as free PSA to total PSA expressed as a percentage (free-to-total PSA%), PSA density and PSA velocity and new biomarkers, such as the prostate cancer gene 3 (PCA3) assessed prior to initial biopsy, Table HE01 and Table HE02.

Table HE02: Research questions

Population	People who have a raised PSA, negative MRI and/ or negative biopsy
Intervention	Different follow-up strategies, including screening test, based on PSA and its derivatives (PSA density, velocity and % free forms) at given intervals, that trigger further investigation
Comparator	Different follow up protocols Standard of care
Outcomes	A cost-utility analysis was constructed based on the quality of life (in quality adjusted life years [QALYs]) and costs of different follow up protocols

HE.2.2 Methods

As none of the studies identified in our systematic search were found to be relevant, a de novo economic model was required, as the committee identified this question as its top priority for original modelling. There is substantial variability of practice, especially since MRI became a routine part of the diagnostic pathway, with little certainty about the long-term follow-up of people with apparently negative findings.

HE.2.2.1 Overview of the model

Modelled population(s) and intervention(s)

The model aims to identify the most clinically and cost-effective follow-up protocol for people who have a raised PSA, negative MRI and/or negative prostate biopsy. A follow-up protocol is defined as a strategy that combines screening tests over a follow-up time and, if the screening test is positive, a diagnostic procedure. Prostate cancer diagnosis is determined by a positive prostate biopsy. The modelled population follows the same population the research question addresses.

The model uses a patient perspective for outcomes and an NHS and PSS perspective for costs, in line with Developing NICE guidelines (NICE, 2014). Health outcomes and costs are discounted applying a discount rate at 3.5% per year. The key health economic outcomes, used to determine cost effectiveness, are incremental costs and QALYs, and the resulting ICER.

Prostate cancer is much less likely in men under the age of 50 years, and 86% of cases occur in men aged 65 years and over (Patel et al., 2009). Within studies that provided the source data for our model, the mean or median age was between 62 and 73 years old. As such, a baseline age of 66 is likely to be representative. Patients entering the model pass through a series of discrete health states over time. This allows costs and QALYs to be accrued for each cycle spent in each particular health state, for the duration of the model. The model structure was developed in collaboration with the guideline committee to reflect the relevant clinical states that people with prostate cancer may potentially experience.

Model structure

We built a Markov model with 3-monthly cycle to predict lifetime costs and health outcomes for people who have a raised PSA and negative finding on prostate imaging and/or biopsy. In Markov models, the modelled cohort moves between health states, and it is assumed that state membership remains constant during a discrete time (cycle). The committee confirmed that a cycle length of 3 months is sufficient to reflect possible clinical events a person with prostate cancer may experience. The model was designed as a simplified representation of the pathway of different follow-up strategies for patients who have a raised PSA and negative prostate findings. The model comprised two strata of health states:

The top stratum comprised 3 *macro-states* reflecting true and diagnosed cancer status. Everyone enters the decision problem with a negative diagnosis, though some are **true negative** (no cancer) and some are **false negative**, (undetected cancer). People with no cancer (true negative) are at risk of developing prostate cancer (becoming false negative); at some point, those with undetected prostate cancer are likely to be captured and hence move to the **true positive** (detected prostate cancer), the 3rd macro-state. We assume that diagnostic strategies, i.e. prostate biopsies, are perfectly specific; hence, a false-positive macro-state is not modelled (this assumption has been made in previous studies, e.g. Faria et al., 2018).

The second stratum – applying only to people with (diagnosed or undiagnosed) prostate cancer – comprised a series of *micro-states* reflecting the progression and prognosis of the disease. These micro-states are risk-stratified: **low-**, **intermediate-** and **high-risk** for localised prostate cancer, and a further micro-state for patients with **metastases**. This is to capture the principle that effective follow-up regimens would detect cancer at a stage when it is more likely to be amenable to treatment, whereas ineffective approaches would detect cases ‘too late’, as reflected in worse prognosis. Once the prostate cancer is diagnosed, patients move to the ‘true positive’ macro-state and their progression is modelled from the micro-state they have been diagnosed at. People are assumed to die from prostate cancer only if they had developed metastases, whereas people at other states were at risk of all-cause death.

States labelled as negative, truly or falsely, are duplicated to make the distinction between two populations: prostate biopsy naïve and experienced. The former represents people who received mpMRI only. This is to reflect that subsequent prostate biopsies are likely to become less sensitive in capturing the disease (Roehl et al., 2002; Schoots et al., 2015; Sidana et al., 2018).

The model addresses the scenario where people require further diagnostic tests owing to symptomatic or incidental findings, e.g., urinary symptoms that may indicate prostate pathology and skeletal pain that may indicate metastatic disease as triggers that would lead to a potential diagnosis regardless of other markers.

The modelled cohort are undergoing follow-up strategies and then directed to diagnostic approaches that should conclude with a positive biopsy, so that patients are judged as having prostate cancer. Otherwise, patients would return to be followed up. The model structure allows the comparison of different follow-up strategies. Follow-up strategies that capture the disease in the best timing before severe progression occurred were identified, Table HE03 and Figure HE01.

Definition of significant prostate cancer

Clinically significant prostate cancer is defined as Gleason score ≥ 3+4 (i.e. any score of 7 or greater) or cancer core length ≥ 4 mm. The guideline committee decided to use this definition as it captures the most sensitive cases. The Gleason grade, determined by a prostate biopsy, gives an indication of the aggressiveness of prostate cancer. It ranges from 1 to 5, with the least describing tissues that look healthy and the highest describing abnormal tissues. As prostate tumours comprise cancerous cells with different grades, the modern system of grading, post 2014, is to use the commonest plus the highest in core biopsies. Some studies use the commonest plus the second commonest. Thus, typical Gleason scores assigned to prostate cancer range from 6 to 10. The terms used for health states in the model follow the cancer risk categories recommended by NICE (CG175 2014). Low-risk state represents clinically non-significant cancer, Gleason score ≤ 6 and PSA ≤ 10. Intermediate- and high-risk states are those that meet the criteria in the definition above with Gleason at 7; PSA within the range of (10 to 20), and Gleason ≥ 8; PSA > 20, respectively.

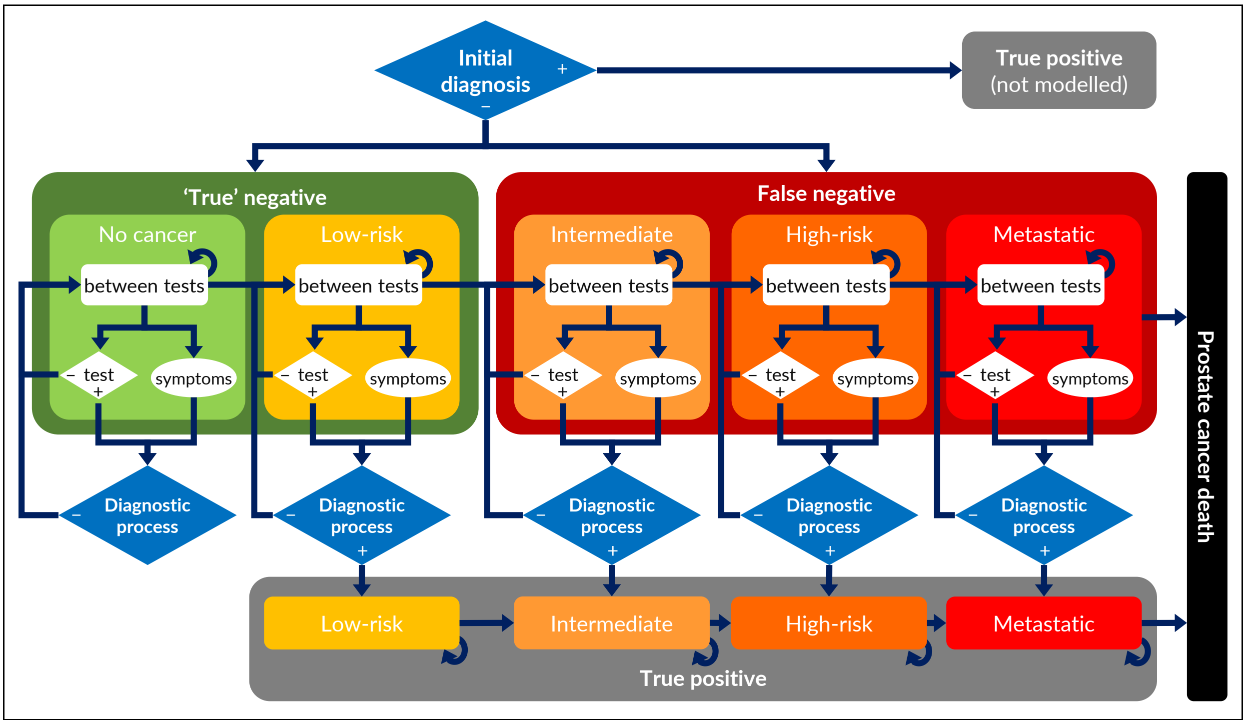
Table HE03: Modelled health states

Health States	
TN – no cancer*	True negative, those truly diagnosed as having no cancer
TN – low-risk*	Those who have clinically non-significant prostate cancer but diagnosed as no cancer. TN used to reflect that even if they were captured the treatment would not add benefits
FN – intermediate-risk*	Cases with intermediate-risk localised prostate cancer but were misclassified as having no cancer.
FN – high-risk*	Cases with high-risk localised prostate cancer but were misclassified as having no cancer.
FN – metastatic*	Cases where the disease spread outside the prostate and still not captured
TP – low-risk	People with low-risk cancer and were truly captured
TP – intermediate-risk	People with intermediate-risk cancer and were truly captured, receiving relevant treatments
TP – high-risk	People with high-risk cancer and were truly captured, receiving relevant treatments
TP – metastatic	People with metastases truly captured and receiving relevant treatments
Death from PCa	Allowed only from diagnosed metastatic prostate cancer
Death from other causes	Allowed from any other alive states and sourced from life table data

Health States

* *At the model start, each of these states had previous negative diagnosis, either negative mpMRI only or negative biopsy and/or mpMRI*

Figure HE01 provides a schematic depiction of the model structure.



All-cause mortality is possible from any state

Figure HE01: Schematic depiction of original health economic model

Key assumptions

There were a number of assumptions built into the economic model which needed to be considered when analysing the results generated. These are summarised in Table HE04.

Table HE04: Key assumptions of original cost–utility model

- baseline population with negative prostate findings comprises true negative and false negative based on previous diagnostics;
- people in true negative developing the disease move to low-risk prostate cancer
- people diagnosed with prostate cancer, moving to true positive states, must pass through false negative, having the disease not identified;
- people with prostate cancer (diagnosed and undiagnosed) are at continuous risk of progression;
- progression occurs subsequently i.e. from low to intermediate to high and then to metastases;
- two types of prostate biopsies are included (TRUS and TPM) and assumed perfectly specific, and TPM biopsy is perfectly sensitive too;
- cases with localised prostate cancer are not at risk of prostate cancer death;
- prostate cancer specific death occurs only among metastatic patients.
- Apart from subsequent TRUS, we assumed screening tests still have the same accuracy data when applied subsequently.

HE.2.2 Parameters – general approach

Identifying sources of parameters

With the exception of diagnostic procedures' accuracy data, which were drawn from the systematic review conducted for this research question (see below), the majority of model inputs have been derived from the key UK or European studies in the area of prostate cancer, supplemented by data from other US studies. Ahmed et al. (2017) reported findings from PROMIS that is a paired-cohort confirmatory study to assess diagnostic accuracy of multi-parametric magnetic resonance imaging (mpMRI) and trans-rectal ultrasound guided biopsy (TRUS) against template prostate mapping biopsy (TPM) as the reference test. PROMIS's estimates of mpMRI and TRUS performance to capture the disease together with the estimates of true prevalence of prostate cancer informed the baseline population distribution in our model. Kasivisvanathan et al.'s (2018) findings from PRECISION (a multicentre randomised controlled trial evaluating the performance of mpMRI-influenced TRUS compared with TRUS only) provided data on the relative sensitivity of mpMRI-influenced TRUS compared with TRUS only (that is, the extent to which using mpMRI to inform biopsy improves the sensitivity of the test). Prostate cancer specific mortality was sourced from STAMPEDE trial, where James et al. (2016) reported findings on the overall survival for people with metastatic prostate cancer. A study by Gnanapragasam et al. (2016) analysed UK registry data on people with localised prostate cancer and reported disease specific mortality according to risk groups. They also reported the primary treatment received by people at each risk group. The rates of adverse events associated with prostate cancer primary treatments were sourced from ProtecT study, by Donovan et al. (2016) for localised disease and from STAMPEDE for metastatic prostate cancer. Findings on metastases risk rates from different risk groups of localised prostate cancer were reported in the Scandinavian Prostate Cancer Group 4 trial (SPCG4), by Bill-Axelson et al. (2014), where participants were assigned either to radical prostatectomy or watchful waiting. Because this kind of watchful waiting represents a low-intensity approach to managing localised disease, the committee agreed that it stands as a good proxy for the natural history of occult prostate cancer (which, by definition, will never be studied empirically).

We asked the committee to identify papers of relevance. During the review (see Evidence review E), we retrieved articles that did not meet the formal inclusion criteria, but appeared to be promising sources of evidence for our model. In particular, we identified studies that potentially supplied data on developing symptoms for people with or without prostate cancer being diagnosed. We studied the reference lists of articles retrieved through any of these approaches to identify any further publications of interest.

When searching for quality of life, resource use and cost parameters in particular, searches were conducted in specific databases designed for this purpose, the CEA (Cost-Effectiveness Analysis) Registry and the NHS Economic Evaluation Database (NHS EED), for example.

In cases where there was paucity of published literature for values essential to parameterise key aspects of the model, data were obtained from unpublished sources; further details are provided below.

Selecting parameters

Our overriding selection criteria were as follows:

- The selected studies should report outcomes that correspond as closely as possible to the health states and events simulated in the model.
- The selected studies should report a population that closely matches the UK population (ideally, they should be drawn from the UK population).

- All other things being equal, more powerful studies (based on sample size and/or number of events) were preferred.
- Where there was no reason to discriminate between multiple possible sources for a given parameter, we gave consideration to quantitative synthesis (meta-analysis), to provide a single summary estimate.

HE.2.3 Parameters

HE.2.4 – cohort parameters and natural history

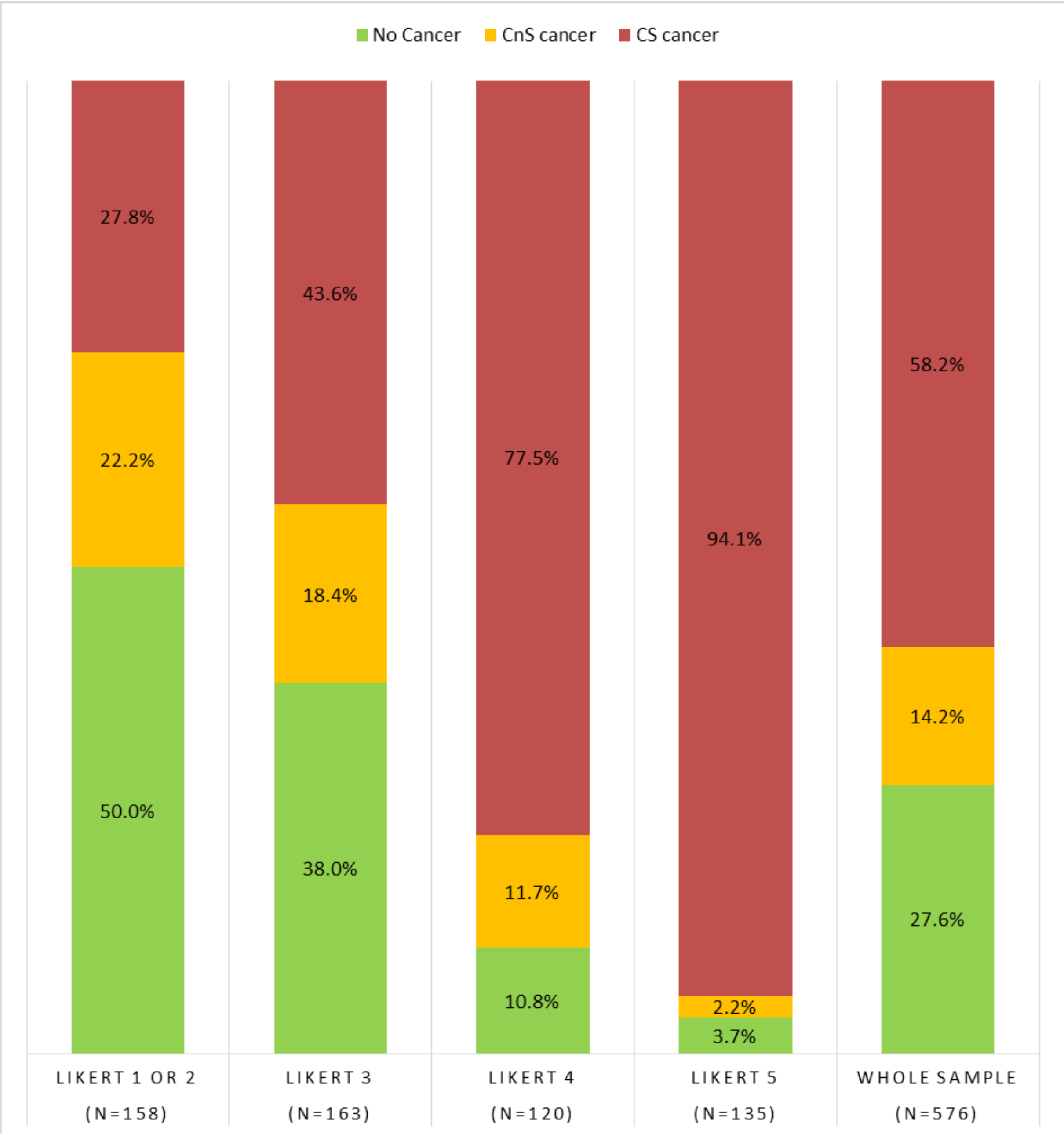
Natural history

Epidemiological parameters were obtained via a literature review of published studies and exploring available national statistics and health outcome databases.

The base-case modelled cohort comprises men at age 66 with suspected prostate cancer and prior negative findings on mpMRI and/or 1 or 2 biopsies. Therefore, the model addresses different baseline populations based on diagnostic history, and each has a different starting distribution of people with true negative and false negative status, as shown in Table HE06. Evidence to calculate these probabilities was predominantly drawn from evidence review D of this update, which investigates the optimal diagnostic pathway for people with suspected prostate cancer, with particular reliance on PROMIS (Ahmed et al., (2017) and PRECISION (Kasivisvanathan et al., 2018). The prevalence of clinically significant prostate cancer was based on that reported in PROMIS, as the committee indicated that the eligibility criteria for the study are representative of the population of interest for this question. Ahmed et al. analysed the diagnostic accuracy of TRUS and mpMRI judged against transperineal mapping biopsy using 24 cores. They used Likert categorical score (1 to 5, with 1 for not likely and 5 for very likely) to mark the findings of prostate imaging.

PROMIS reports results using 2 definitions of clinically significant prostate cancer. The committee advised that the ‘secondary’ definition is more relevant for our decision-space, both because it corresponds with the definition of disease of at least intermediate grade in the risk stratification used in the guideline and also because it is more representative of the approach to risk stratification that will have informed the treatment decisions for people in the evidence we use to estimate the treated history of true positive disease (see below). This is not to say that it is a better definition of disease that truly is clinically significant; rather that is a definition that accords well with the other evidence in the model.

The prevalence rates of significant prostate cancer, using the secondary definition, reported in PROMIS were different based on the Likert score. They were 27.8%, 43.6%, 77.5% and 94.8% for people with Likert score at 1 or 2, 3, 4 and 5, respectively. As the number of people with Likert 1, reported in PROMIS, was small (n =23) and only 5 men with true disease, Likert 1 and Likert 2 were grouped in one Likert grade (1 or 2), including 158 men. We assumed that the disease prevalence for the sub-population who had previous negative biopsies but did not receive mpMRI, is the average of prevalence rates across all Likert grades in PROMIS (58.2%), Figure HE02. It also shows the prevalence of clinically non-significant cancer, as 22.2%, 18.4%, 11.7%, 2.2% and 14.2% in people with Likert 1 or 2, Likert 3, Likert 4, Likert 5 and those who did not receive mpMRI, respectively.



The whole sample estimates is the average of all Likert scores assigned for those who did not receive mpMRI in our model.

CnS: Clinically non-significant; CS: Clinically significant

Figure HE02: The prevalence of clinically significant and non-significant prostate cancer obtained from PROMIS

Modelling approach to define the baseline population based on previous diagnosis

As the evidence shows that people have different prevalence rates of the disease based on their diagnostic history, it was necessary to address our decision problem in a number of subpopulations. Further, the recommendations, made based on evidence review D for prostate cancer diagnosis, potentially lead to 11 sub-populations that the current analysis should address. These are based on the Likert score (1 or 2, 3, 4 and 5), if people receive mpMRI, and on the number of biopsies (1 or 2). There is a possibility that people with Likert score of 1 or 2 do not receive biopsy. It is also possible that there are still people who received 1 or 2 biopsy but not mpMRI. Thus, the baseline population is distributed between truly and falsely negative based on their Likert score if they receive mpMRI and the number of previous biopsies (1 or 2); falsely negative population is further distributed between clinically non-significant and significant cancer, based on PROMIS findings.

We developed a decision tree model to quantify the distribution of baseline populations based on their diagnostic history. The model was sourced with data on the disease prevalence and TRUS accuracy data.

The PROMIS trialists provided us with further analysis estimating the systematic TRUS biopsy sensitivity to capture the clinically significant and non-significant prostate cancers stratified based on Likert score. TRUS biopsy was performed blind to and reported independently of the mpMRI test during the study. Thus, for people who received mpMRI, we had to derive the relative sensitivity of MRI-influenced TRUS compared with systematic TRUS from other sources. This was sourced from our clinical review performed in evidence review D and heavily relying on PRECISION. These values, affecting the sensitivity of TRUS in people with Likert ≥3, were 1.79 and 0.39 for clinically significant and non-significant cancer, respectively. For people, who did not receive mpMRI or their Likert score was less than 3, the TRUS sensitivity did not change. Further, for people who had two previous negative biopsies, we had to derive the sensitivity of subsequent TRUS from other sources. There was a paucity of evidence on this estimate. One of the sources identified was a study by Roehl et al. (2002), who reported data on prostate biopsies performed subsequently on a cohort of people with suspicion of prostate cancer. We derived the relative sensitivity of subsequent biopsy compared to the first one. These values, applied on the sensitivity of systematic TRUS obtained from PROMIS, were 0.44 and 0.70 for clinically significant and non-significant cancer, respectively, Table HE05. To avoid obtaining mathematically implausible values (sensitivity cannot be greater than 1 or less than 0), the relative sensitivity was applied as rates and then converted to probabilities.

Table HE05: The sensitivity of TRUS to capture clinically significant and non-significant cancer derived from PROMIS and then adjusted based on MRI influence or subsequent TRUS

MRI Likert score	Clinically significant			Clinically non-significant		
	Sensitivity from PROMIS	Estimated sensitivity of MRI-influenced TRUS		Sensitivity from PROMIS	Estimated sensitivity of MRI-influenced TRUS	
		1st TRUS[a]	2nd TRUS[b]		1st TRUS[a]	2nd TRUS[b]
1 or 2	29.5%	29.5%[c]	14.4%[c]	40.0%	40.0%[c]	29.9%[c]
3	52.1%	73.2%	44.3%	30.0%	13.0%	9.2%
4	60.2%	80.8%	51.9%	14.3%	5.8%	4.1%
5	76.4%	92.4%	68.2%	33.3%	14.6%	10.4%
no MRI	60.6%	60.6%[d]	33.9%[d]	31.7%	31.7%[d]	23.3%[d]

[a] *PROMIS estimate multiplied by relative sensitivity of MRI-influenced TRUS compared with systematic TRUS from clinical review where appropriate*
[b] *The value of first TRUS sensitivity (a) multiplied by the relative sensitivity of subsequent TRUS to initial TRUS derived from Roehl et al (2002)*
[c] *MRI does not influence TRUS in LIKERT <3, as it does not provide a target*
[d] *TRUS sensitivity unaltered in absence of MRI*

The decision tree model was run for the 11 sub-populations, and it produced the related baseline distribution as people either with no cancer, with clinically non-significant cancer or with clinically significant cancer, Table HE06. People diagnosed with clinically non-significant prostate cancer were labelled as having low-risk disease in our model. People with clinically significant prostate cancer can be in intermediate- or high-risk states. The proportion of each risk group was obtained from PROMIS.

Table HE06: Baseline distribution of the modelled population based on previous diagnostic tests

MRI Likert score	No. of previous negative biopsies	Baseline distribution of the modelled population		
		No cancer	Clinically non-significant	Clinically significant
1 or 2	0	50.0%	22.2%	27.8%
	1	68.1%	18.1%	13.8%
	2	78.4%	14.6%	7.0%
3	1	61.1%	25.7%	13.2%
	2	68.2%	26.0%	5.8%
4	1	36.8%	37.3%	25.9%
	2	46.6%	45.3%	8.1%
5	1	39.4%	20.2%	40.4%
	2	61.3%	28.1%	10.6%
no MRI	1	54.8%	19.3%	25.9%
	2	69.1%	18.7%	12.2%

Developing prostate cancer

People who were truly diagnosed with no prostate cancer are still at a risk of developing prostate cancer. The likelihood of patients moving from the true negative state in the model and developing low-risk prostate cancer would be ideally informed by studies that follow-up people with raised PSA and have had their prostate biopsy checked using a perfect test. However, such data seem to be scarce. We identified an alternative source of data to inform the probability of developing low-risk prostate cancer within the population of interest. Andriol et al. (2010) reported data on the effectiveness of dutasteride to reduce the risk of prostate cancer on people with raised PSA and previous negative prostate biopsy. The study is a randomised controlled trial whereby participants were assigned to either dutasteride or placebo and followed up for 4 years. The primary outcome was the number of prostate cancer incidences. The findings were 625 out of 3424 patients in the placebo arm developed low-risk prostate cancer (18.25%) diagnosed using 10-core TRUS at 4 years. The study seemed relevant based on the population. However, the negative findings obtained using 10 to 12 core biopsy, which is an imperfect test, included cases with prostate cancer that were misclassified as negative. To use this study’s estimates to inform the transition from true negative (no cancer) to false negative, its results needed to be adjusted, based on the estimated prevalence of low-risk disease and the TRUS sensitivity to capture it, the method is outlined below.

Schoots et al. (2015) reported accuracy data on the performance of TRUS and MRI-informed TRUS, meta-analysed from 16 studies, to capture significant and non-significant prostate cancer within 2 populations: biopsy-naïve and people who had previous negative biopsy. Their finding that could inform the transition from true negative to low-risk prostate cancer in our model was: the prevalence of non-significant prostate cancer (low-risk in our model) within people with previous negative biopsy was 9%. We obtained the sensitivity of TRUS to capture the low-risk disease from data provided by PROMIS team (0.31). These findings were used to adjust the percentage of people, who developed low-risk prostate cancer in the placebo arm over 4 years, reported by Andriol et al. (2010).

Modelling approach for progression in undiagnosed cases:

Ideally, the model would be informed by a study that recruited people with prostate cancer who do not receive any intervention and monitored their progression. The Scandinavian Prostate Cancer Group 4 (SPCG4) study appeared to be relevant. This trial recruited 695 men with early prostate cancer between 1989 and 1999, who were randomly allocated to watchful waiting and radical prostatectomy. The watchful waiting arm is our main interest, as it represents a non-curative strategy. The SPCG4's reported outcomes were time to metastases, prostate cancer death and overall survival from up to 18 years of follow-up. Time to metastases was reported based on risk groups. The cumulative incidence of metastases over 18 years was 35 out of 131, 59 out of 133 and 44 out of 84 for low-, intermediate- and high-risk, respectively. However, we assumed in our model that there were underlying transitions by which patients could not move from low-risk, for example, to metastases, rather they have to pass through the intermediate- and high-risk stages.

We built a Markov model with 5 health states: low-, intermediate-, high-risk, metastases and death, evaluated by calibration. The model was calibrated to the cumulative incidence of metastases at 18 years for each risk group, obtained from the Scandinavian trial SPCG4, starting from high-risk and working backwards (see Table HE07). The calibration of the Markov model takes into consideration the risk of death, obtained from Swedish life table dated back to 1999 ("Source: Statistics Sweden") to reflect life expectancy at that time. First, we calculate the transition probability from high-risk disease to metastases (accounting for the competing hazard of all-cause mortality). This then allows us to estimate the transition probability from intermediate-risk to high-risk disease in a similar way and, once those parameters are estimated, the transition from low-risk to intermediate-risk disease can be derived. We used numerical optimisation (the generalised reduced gradient nonlinear algorithm used by the Solver add-in in Excel) to estimate the optimal value of the parameters by minimising the error in the total number of people developing metastases (before dying) after 18 years.

Development of symptoms in people with undiagnosed prostate cancer

People with undiagnosed prostate cancer may experience disease-related symptoms that trigger diagnostic procedures. The likelihood of these symptoms are different based on the risk groups of prostate cancer. Sources identified to inform the likelihood of symptoms were:

The rate of developing symptoms in people who did not have the disease and those with undiagnosed low-risk prostate cancer was sourced from Kirby et al. (2003). They reported data from PREDICT trial on the occurrence of acute urinary retention and/or transurethral resection of the prostate in people with benign prostatic hyperplasia randomised to doxazocin/finasteride or placebo. The population in this study had PSA level between 4.1 and 10 ng/ml with negative prostate biopsy. The outcome of the placebo arm of this trial informed the model on the proportion of people with no disease or with low-risk prostate cancer developing urinary symptoms that direct them to diagnostic procedures. The findings were 7 out of 269 participants (2.6%) developed the symptoms over a year.

For people with undiagnosed intermediate- or high-risk prostate cancer, Studer et al. (2005) reported data from EORTC trial on time to first symptomatic progression for people with localised prostate cancer randomly assigned to either receive immediate androgen deprivation therapy or on the onset of symptoms, including increase in pain score due to prostate cancer by more than or equal to two categories, deterioration in WHO performance status by two levels due to prostate cancer or evidence of ureteric obstruction caused either by the primary tumour or metastases. Time to first symptomatic progression in the deferred treatment arm may inform the model on the proportion of people with intermediate- or high-risk prostate cancer experiencing symptoms that trigger diagnostic procedures. The findings were 140 out of 493 participants (28.4%) developed the symptoms over 5 years.

For people with undiagnosed metastases, James et al. (2016) reported data from the TRAPEZE trial on time to first skeletal related event within people who had metastatic prostate cancer, randomly assigned to zoledronic acid and/or strontium-89 or placebo. The population in this trial received docetaxel and prednisolone. We assumed that these treatments do not affect the chance of developing skeletal symptoms. The study informed the model about the proportion of undiagnosed metastatic patients developing skeletal symptoms. The findings were 234 out of 381 participants (61.4%) developed the symptoms over 22 months.

Modelling approach for diagnostic procedures

The simulated follow-up strategies were formed based on screening and diagnostic tests that the committee considered clinically meaningful. They ranged from the least intensive strategies, i.e. no screening and waiting for symptoms, to the most rigorous ones, i.e. performing a transperineal template mapping (TPM) biopsy, assumed to be perfectly sensitive, for all people. In the base case, all follow-up strategies stopped when the modelled cohort reached 75 years, which the committee advised was a realistic upper threshold (mostly because the average person would be unlikely to be considered for radical therapy on diagnosis beyond this age).

People with a negative diagnosis, either falsely or truly, were subject to follow-up strategies that could lead to subsequent diagnostic procedures. This might be triggered by symptoms or applied in specific time intervals within the model. A follow-up strategy may consist of up to 3 main stages with associated decision points:

- Screening stage made up of the following decision points:
    - Frequency of testing;
    - Type of screening test (mostly based on PSA and its derivatives);
    - Threshold at which cases identified as positive; and if this was positive;
- Diagnostic stage that may include imaging the prostate using MRI techniques that we needed to define the threshold, at which people directed to biopsy, and if this was positive;
- Prostate biopsy that labelled cases as diagnosed, if positive, otherwise they returned to be subject to a potentially next follow-up.

In a situation where people developed symptoms, they were eligible to receive diagnostic procedure using MRI and/or biopsy directly, as a screening test was not required. Every time patients were directed to a follow-up, there was a chance that they move to the diagnosed cases based on the follow-up strategy accuracy data. This was reflected as transition probabilities in the model, which was the test sensitivity multiplied by the probability of developing or not developing symptoms.

Modelling approach for progression in diagnosed cases:

The Markov model for diagnosed cases, evaluated by calibration, comprised six health states. It included the same health states as the model of undiagnosed cases and the 6th health state was prostate cancer specific death. The Markov model was calibrated to the cumulative incidence of prostate cancer specific death at 10 years for each risk group of localised prostate cancer, obtained from the prognostic modelling study by Gnanapragasam et al. (2016). It was also calibrated to the overall survival obtained from STAMPEDE at 43 months for people with metastases (James et al .2016).

Gnanapragasam et al. performed a cohort study that utilised data of 10,139 men with non-metastatic prostate cancer that were available from the Public Health England National Cancer Registration Service Eastern Office. The data were closely representative of real-world contemporary clinical practice, as primary sources of information included electronic and paper-based reports, clinical notes, and pathology results from 10 hospitals, of which only 2 were academic centres. The population was initially categorised as low, intermediate, or high risk based on the NICE risk stratification system. The primary outcome of interest in this study was prostate cancer specific mortality. In addition, this study reported the uptake of different treatment types in each risk group across the whole cohort, which reflect the UK clinical practice.

STAMPEDE is a UK randomised controlled trial that reported overall survival for people with metastases who received standard of care only or standard of care plus docetaxel; the median follow-up was 43 months.

Based on the assumption that people experience underlying transitions to metastases in order to die from prostate cancer, transition probabilities from low- to intermediate-, from intermediate- to high-risk and from high-risk to metastases were estimated, taking into account the treatment received by people at each risk group as reported in the two studies. As a source of general mortality for the model calibration, we used UK life table back dated to 2010 to 2012 to correspond to the time when people in STAMPEDE were followed-up, Table HE07.

Table HE07: Natural history parameters

Parameter	Value (95%CI)	Source
Probability of developing low-risk prostate cancer	0.008 (0.0075 to 0.009)	Andriol (2010), Schoots (2015), Roehl (2002) and Brown (2018)
Parameters used in model calibration for undiagnosed cases		
Low-risk		
Mean age	64.6 (63.7 to 65.5)	Bill-Axelson
Metastases cumulative incidence at 18 years	26.72% (19.52 to 34.59%)	
Intermediate-risk		
Mean age	64 (63.2 to 64.8)	Bill-Axelson
Metastases cumulative incidence at 18 years	44.36% (36.04 to 52.84%)	
High-risk		
Mean age	65.2 (64.0 to 66.4)	Bill-Axelson
Metastases cumulative incidence at 18 years	52.38% (41.74 to 62.92%)	
Parameters used in model calibration for diagnosed cases		
Low-risk		
Mean age	66.2 (58.74 to 74.34)	Gnanapragasam (2016)
PCa death cumulative incidence at 10 years	2.2% (1.2 to 3.4%)	
Intermediate-risk		
Mean age	70.08 (62.54 to 77.97)	Gnanapragasam (2016)
PCa death cumulative incidence at 10 years	7.4% (5.7 to 9.3%)	
High-risk		
Mean age	72.18 (65.16 to 79.46)	Gnanapragasam (2016)
PCa death cumulative incidence at 10 years	19.6% (17.2 to 22.1%)	
Metastases		
Median age (IQR)	65 (61 to 71)	James (2016)
Overall mortality at 43 months (SoC arm)	50.0% (46.4 to 53.6%)	
Overall mortality at 43 months (SoC + DOC[a])	37.5% (32.7 to 42.6%)	
Parameters derived from models calibration		
Progression 3-month probabilities in undiagnosed cases		

Parameter	Value (95%CI)	Source
From low to intermediate-risk	0.038 (0.028 to 0.052)	Model calibration
From intermediate- to high-risk	0.085 (0.043 to 0.161)	
From high-risk to metastases	0.014 (0.010 to 0.020)	
Progression 3-month probabilities in diagnosed cases		
From low to intermediate-risk	0.035 (0.019 to 0.064)	Model calibration
From intermediate- to high-risk	0.031 (0.021 to 0.046)	
From high-risk to metastases	0.008 (0.007 to 0.009)	
Hazard ratio of death for people with metastases **not** receiving docetaxel	13.38 (12.05 to 14.86)	
Hazard ratio of death for people with metastases receiving docetaxel	9.07 (7.67 to 10.71)	
Probability of developing symptoms for people undiagnosed (not treated): lower urinary tract symptoms for localised disease or skeletal related events for metastases		
People without PCa or with low-risk PCa at one year	2.6% (1.0 to 4.8%)	Kirby (2003)
Intermediate- or high risk PCa at 5 years	28.4% (24.5 to 32.5%)	Studer (2005)
Metastatic at 22 months	61.4% (56.5 to 66.2%)	James (2016)

[(a)] *Standard of care and docetaxel*

Treatments used in the diagnosed cases

Treatments used for diagnosed cases were obtained from Gnanapragasam et al. (2016). Active surveillance is a conservative strategy, followed by the majority (47%) of people with low-risk disease. A smaller group of people (25%) with intermediate-risk disease received active surveillance, and 5% of people with high-risk disease chose this strategy as a primary option. Brachytherapy was received by a minority of people, 7%, 3% and 0.5% in low-, intermediate and high-risk groups respectively.

Groups of low- (9%), intermediate (22%) and high-risk (48%) disease received androgen deprivation therapy (ADT). Data on the ADT treatment, used by each risk-group, were obtained from Mowatt et al. (2013). Low- and intermediate-risk groups were assumed to receive a triptorelin 11.5 mg injection (Decapeptyl) following to bicalutamide 50 mg tablets course for 21 days; one injection covers a 3-month period. The high-risk group received the same treatments, but with 8 injections covering the period of two years (every 3 months).

Radical prostatectomy was received by 18%, 16% and 12% of low-, intermediate- and high-risk groups. Radical radiotherapy technique, received by 20% of low-risk group and by 35% of intermediate- and high-risk groups, was assumed to be intensity-modulated radiotherapy, delivered over 20 and 37 fractions for people with low-/intermediate- and high-risk respectively, Table HE08.

Table HE08: Treatments used in localised disease based on risk groups reported in Gnanapragasam (2016)

Risk group	Active surveillance	Brachytherapy	Hormone therapy	Radical prostatectomy	External radiotherapy
Low-risk	46.7% (44.3 to 49.0%)	6.7% (5.5 to 7.9%)	8.6% (7.3 to 10.0%)	17.8% (16.0 to 19.6%)	20.3% (18.5 to 22.3%)

Risk group	Active surveillance	Brachytherapy	Hormone therapy	Radical prostatectomy	External radiotherapy
Intermediate-risk	25.3% (23.9 to 26.7%)	2.9% (2.3 to 3.4%)	21.6% (20.3 to 22.9%)	15.6% (14.4 to 16.8%)	34.7% (33.2 to 36.3%)
High-risk	5.4% (4.8 to 6.1%)	0.6% (0.36 to 0.81%)	47.8% (46.4 to 49.3%)	11.6% (10.7 to 12.5%)	34.6% (33.2 to 36.0%)

People with metastases were assumed to receive ADT for 3 years and docetaxel for 6 3-weekly cycles at a dose of 75 mg/m2. Based on STAMPEDE data by James et al., we assumed that 28% and 14% of people with metastases, who developed progression to castration resistant stage in an average of two years, received abiraterone and docetaxel as life extending treatments, respectively. People were assumed to receive abiraterone for a mean duration of 8 months (COU-AA-301), and docetaxel over 9.5 cycles (James et al. 2016).

Mortality

Mortality from all other causes, which are not represented explicitly within the model, are estimated using national mortality statistics.

Prostate cancer specific death is only allowed for people with metastases in the model. As disease specific mortality data were not explicitly reported in STAMPEDE study, overall survival is used to reflect the mortality of metastatic people. Based on the model calibration explained above, the hazard ratio of death for people with metastatic prostate cancer, compared to all other health states, which experienced population level mortality, was estimated. The hazard ratio obtained from docetaxel arm was used in our model to reflect current practice, where people with metastases are most likely to receive docetaxel and other life extending treatments, such as abiraterone. For people with undiagnosed metastases, the hazard ratio of prostate cancer death was obtained from the standard of care arm in STAMPEDE.

HE.2.2.5 – Diagnostic accuracy data

The model population was potentially followed-up by screening procedures. People were directed to further diagnostic procedures, such as prostate biopsies if the screening results were positive. The prostate specific antigen (PSA) and its derivatives, although not perfect, are mainly used as biomarkers to identify possible prostate cancer. There are rather more sophisticated biomarkers recently used within the primary care settings, including prostate cancer antigen 3 (PCA3) assay and prostate health index (PHI). Multi-parametric MRI is an imaging diagnostic increasingly used to detect if people need more invasive diagnostic procedures, such as prostate biopsy. These follow-up strategies' cost-effectiveness were evaluated in our model. The accuracy parameters of these procedures, including sensitivity and specificity were drawn from the clinical evidence review, Table HE09.

Table HE09: Accuracy parameters of diagnostics at different thresholds used in the model

Test	Threshold	Sensitivity (95% CIs)	Specificity(95% CIs)	Correlation*
Total PSA	4 ng/ml	0.90 (0.78, 0.96)	0.10 (0.03, 0.27)	0.673
	5 ng/ml	0.92 (0.86, 0.96)	0.12 (0.10, 0.14)	
	6 ng/ml	0.83 (0.75, 0.89)	0.30 (0.13, 0.56)	
	7 ng/ml	0.75 (0.65, 0.83)	0.33 (0.27, 0.40)	
	8.5 ng/ml	0.30(0.19, 0.43)	0.72(0.67, 0.77)	
PSA velocity	0.28 ng/ml/year	0.95 (0.84, 0.99)	0.05 (0.02, 0.12)	0.631
	0.75 ng/ml/year	0.69 (0.57, 0.79)	0.56 (0.43, 0.68)	

Test	Threshold	Sensitivity (95% CIs)	Specificity(95% CIs)	Correlation*
	1.19 ng/ml/year	0.75 (0.60, 0.86)	0.42 (0.32, 0.53)	
PSA density	0.09 ng/mi/ml	0.95 (0.89, 0.98)	0.15 (0.12, 0.17)	0.588
	0.12 ng/mi/ml	0.92 (0.86, 0.95)	0.22 (0.19, 0.25)	
	0.15 ng/mi/ml	0.73 (0.64, 0.80)	0.52 (0.42, 0.62)	
	0.30 ng/mi/ml	0.66 (0.54, 0.76)	0.76 (0.57, 0.88)	
% free PSA	10%	0.51 (0.18, 0.82)	0.67 (0.18, 0.95)	0.507
	15%	0.59 (0.40, 0.75)	0.67 (0.47, 0.82)	
	20%	0.67 (0.45, 0.84)	0.52 (0.31, 0.72)	
	25%	0.86 (0.76, 0.93)	0.28 (0.17, 0.42)	0.827
	30%	0.83 (0.72, 0.90)	0.28 (0.17, 0.44)	0.791
	35%	0.95 (0.88, 0.98)	0.34 (0.30, 0.37)	
	38%	0.90 (0.82, 0.98)	0.50 (0.47, 0.53)	
PSA doubling time	24 months	0.47 (0.35, 0.60)	0.36 (0.31, 0.42)	0.631
	30 months	0.37 (0.21, 0.56)	0.40 (0.14 to 0.41)	
	50 months	0.30 (0.16, 0.49)	0.42 (0.29 to 0.56)	
	70 months	0.11 (0.04, 0.29)	0.42 (0.29 to 0.56)	
PSA density in transition zone	0.20 ng/mi/ml	0.95 (0.89, 0.98)	0.21 (0.19, 0.24)	0.588
	0.25 ng/mi/ml	0.91 (0.84, 0.95)	0.23 (0.14, 0.35)	
PCA3	20	0.89 (0.82, 0.93)	0.30 (0.24, 0.41)	0.777
	35	0.71 (0.59, 0.81)	0.57 (0.46, 0.66)	0.696
	50	0.65(0.53, 0.75)	0.67 (0.57, 0.76)	0.521
PHI	25	0.90 (0.73, 0.97)	0.08 (0.03, 0.17)	0.507
	30	0.90 (0.81, 0.95)	0.25 (0.19, 0.33)	
	35	0.80 (0.62, 0.91)	0.48 (0.36, 0.60)	
	40	0.62 (0.50, 0.72)	0.60 (0.52, 0.67)	
	48.9	0.40 (0.28, 0.54)	0.78 (0.70, 0.85)	
	62	0.30 (0.20, 0.41)	0.91 (0.85, 0.94)	
DRE	+/-	0.23 (0.14, 0.35)	0.89 (0.80, 0.94)	0.848
mpMRI	Likert of ≥3	0.94 (0.91, 0.96)	0.32 (0.24, 0.41)	0.721
	Likert of ≥4	0.87 (0.71, 0.95)	0.72 (0.65, 0.79)	

* *The correlation between test sensitivity and its false positive rate was derived from the bivariate meta-analysis, if available*.

It was not possible to obtain comparable pooled accuracy estimates for all diagnostic tests. PHI and PSA doubling time at the different thresholds were extracted from individual studies, Scattoni (2003), Lazzeri (2012), Porpiglia (2014), Ciatto (2008) and Shimbo (2009).

The correlation between a test sensitivity and its false positive rate was taken into consideration when the model ran probabilistically. For every screening test, where there were five studies or more, the correlation factor between the sensitivity and false positive rate (1 – specificity) was obtained from the bivariate meta-analysis; for more details see evidence review E. However, if the number of studies sourcing the evidence on the test accuracy data at a given threshold was less than 5, the correlation factor was assumed the same as one derived from the synthesis at a different threshold. There were several tests, including PSA doubling time, PSA density in the transition zone and PHI, where the number of studies was less than 5 at all thresholds. We assumed the correlation factor for these three tests to be the same as the PSA velocity test at a threshold of 0.75 ng/ml/year, the PSA density and % free PSA test at a threshold of 15%, respectively.

There is evidence that subsequent TRUSs are less sensitive than initial ones in capturing prostate cancer (Roehl et al., 2002, Schoots et al., 2015, and Sidana et al., 2018). However, there was a lack of evidence on absolute accuracy data of TRUS to identify prostate cancer within the model population (people with previous negative biopsy). Roehl et al. (2002) performed a cohort study of 2,526 volunteers 40 years old or older with one or more negative prostate biopsy and raised PSA from 1991 to 2000. They reported data on up to 10 prostate biopsy findings. They estimated the prevalence of any prostate cancer as 0.38 based on the number of cancers detected over the 10 biopsies (963) divided by the number of participants (2,526). At the second biopsy, the number of participants was 837, and the number of any prostate cancer detected was 143. The serious issues with the use of this study findings were that in addition to the study being outdated, as the TRUS techniques have changed in terms of the number of cores (4 to 6 vs 10 to 12), the accuracy of TRUS was not judged against a reference test such as TPM.

A further study that reported data on the performance of TRUS to capture prostate cancer within people with previous negative biopsy was Schoots et al. (2015). It is a systematic review and meta-analysis that compared the performance of TRUS with MRI-informed TRUS. The findings were that the sensitivity of TRUS to capture any prostate cancer in people with previous negative biopsy was 0.54 (95% CI 0.32 to 0.75). The authors reported more details on the sensitivity of TRUS based on significant and non-significant prostate cancer that were 0.56 (95% CI 0.39 to 0.72) and 0.68 (95% CI 0.09 to 0.98). This study limitations that undermined the use of its findings were due to the absence of a reference diagnostic test, e.g. TPM, and the small sample size in studies that sourced the TRUS sensitivity for non-significant disease (n = 11). Instead of assigning an absolute value to the sensitivity of subsequent TRUS, we obtained the relationship between sensitivity of the initial and subsequent biopsies from Roehl et al. (2002). We applied this relative reduction in the sensitivity of subsequent TRUS to the estimates obtained from PROMIS.

The parameters used for the relative sensitivity of MRI-informed TRUS compared with TRUS only were obtained from our clinical review, heavily relying on PRECISION's findings reported by Kasivisvanathan et al. (2018). These were 1.79 and 0.39 for clinically significant and clinically non-significant prostate cancer, respectively.

Follow-up strategies

Based on the number of tests reported in Table HE09, we could theoretically evaluate a huge number of possible follow-up strategies. However, we confined our analysis to a number of strategies that the guideline committee found meaningful, taking into consideration the procedures prescribed in primary care settings. The committee found that the PSA density test at a threshold of 0.30 is irrelevant, as the threshold is too high, and the evidence on this test was obtained from two Japanese studies that affected its applicability. In addition, we did not include strategies with screening tests that appeared to have poor accuracy data. For example, PSA doubling time tests, representing PSA kinetics measures, perform worse than PSA velocity. Further, we excluded screening test based on low-quality evidence. The evidence, sourcing the accuracy data of the % free PSA test at a threshold of 35% and the PSA density in transition zone, was obtained from a study that does not show consistency in reporting data on a test at two different thresholds. This study reported the sensitivity and specificity of the % free PSA test at a threshold of 35% and 38% as 0.95, 0.34 and 0.90, 0.50 respectively, which is not consistent with the test performance at different thresholds, reported in the other studies.

The follow-up strategies simulated in our model varied from the least intensive strategy (i.e. waiting for symptoms that trigger further investigation) to a rigorous strategy that can be performing template mapping biopsy to all candidates. An example of follow-up protocols simulated in our model is shown in Table HE10.

A follow-up strategy involved clinically feasible combinations of screening and/or imaging test and biopsy. It entailed a number of decision points as follows:

- Type of screening test and the related threshold (e.g. PSA derivatives);
- Frequency of the screening test;
- Determining biopsy if the previous test positive;
- Stopping rule; the relevant time, for which a person suspected with prostate cancer would be receiving this follow-up strategy. The follow-up strategy could stop at a specific age or after a number of years.

Table HE10: An example of a follow-up strategy components

Decision point	Strategy components
Type of test and the related threshold	PSA density threshold at 0.12 ng/mi/ml
How often	every 6 months
Second test if the previous positive	mpMRI at Likert of ≥3
Determining biopsy if the previous positive	TRUS
When to stop	at age 75

Complications of prostate biopsy

Data on adverse events associated with prostate biopsy were sourced from three studies: Rosario et al (2012) reporting data from ProtecT and other two cohort studies by Nam et al. (2010) and Hoeks et al. (2012), Table HE11.

Complications of treatments for diagnosed cases

Common adverse events associated with prostate cancer treatments were modelled. Data on radical prostatectomy and radiotherapy complications, including erectile dysfunction, urinary incontinence and bowel problems, were sourced from ProtecT study (Donovan et al. 2016). Treatments for metastases, including ADT and docetaxel, were associated with adverse events reported from STAMPEDE by James et al. (2016), Table HE11.

Table HE11: Complications associated with TRUS biopsy and treatments used in the model

Complication	Probability (95% CIs)	Source	Notes
AEs associated with TRUS biopsy			
Hospital admission	1.4% (0.7 to 2.5%)	Rosario (2012)	Beta distribution
Reasons for hospital admission			
Urinary infection	72% (68 to 75%)	Nam (2010)	Dirichlet distribution
Urinary bleeding	19% (16 to 22%)	Nam (2010)	Dirichlet distribution
Urinary obstruction	9% (7.1 to 11.2%)	Nam (2010)	Dirichlet distribution
Sepsis	0.4%	Hoeks (2012)	Fixed value
AEs associated with radical prostatectomy			
Erectile dysfunction	88.0% (84.2 to 91.2%	ProtecT: 1 year follow-up	Beta distribution
Urinary incontinence	71.0% (66.7 to 75.0%)	ProtecT: 1 year follow-up	Beta distribution
Bowel dysfunction	3.3% (1.7 to 5.7%)	ProtecT: 6-month follow-up	Beta distribution
AEs associated with radical radiotherapy			
Erectile dysfunction	77.8% (73.0 to 82.1%)	ProtecT: 1 year follow-up	Beta distribution
Urinary incontinence	5.7% (3.8 to 8.2%)	ProtecT: 1 year follow-up	Beta distribution
Bowel dysfunction	10.4% (7.4 to 14.2%)	ProtecT: 6-month follow-up	Beta distribution
AEs associated with ADT plus docetaxel			
Erectile dysfunction	10.4% (7.9 to 13.2%)	STAMPEDE	Beta distribution

Complication	Probability (95% CIs)	Source	Notes
Febrile neutropenia	15.3% (12.4 to 18.6%)	STAMPEDE	Beta distribution
Neutropenia	12.0% (9.4 to 15%)	STAMPEDE	Beta distribution
General disorders	6.2% (4.3 to 8.5%)	STAMPEDE	Beta distribution
Musculoskeletal disorders	5.8% (4.3 to 8.5%)	STAMPEDE	Beta distribution
Gastrointestinal disorders	8.2% (6.0 to 10.8%)	STAMPEDE	Beta distribution
Urinary infection	4.2% (2.7 to 6.2%)	STAMPEDE	Beta distribution
Respiratory disorders	5.3% (3.6 to 7.5%)	STAMPEDE	Beta distribution
Cardiac disorders	2.9% (1.7 to 4.7%)	STAMPEDE	Beta distribution
Nervous system disorders	3.5% (2.1 to 5.3%)	STAMPEDE	Beta distribution

HE.2.2.6 – resource use

The information to allocate appropriate resource use to the treatment elements of the model was sourced from the primary evidence base, where available. In the absence of this data a literature review was conducted to locate published economic evaluations or costing studies which may provide UK-specific resource use information of interest. Any remaining gaps in the resource use evidence were filled with estimates from the experts within the guideline committee, for which we could then apply appropriate unit costs.

Rosario et al. (2012) reported data on a group of participants (119 out of 1147), who received biopsy-related consultations. These were modelled as 77%, 12% and 10% received GP consultations, urology department nurse and other NHS direct, respectively.

Resources required to perform mpMRI were included in the model by following the approach reported by Mowatt et al (2013). They reported resources, including two radiographers spending about an hour and a consultant-led appointment for 45 minutes. They included also the capital and equipment cost per patient, Table HE12.

Resources used for active surveillance were obtained from Ramsay et al. and included 4 three-monthly PSA measures plus 4 three-monthly nurse-led outpatient appointments and 2 six-monthly GP appointments for digital rectal examination over the 1st year.

HE.2.2.7 – costs

The costs of each of the resource use elements within the model were obtained from a number of standard sources. Where these sources did not provide the unit cost needed to parameterise the cost of a resource use variable within the model then a search was conducted for unit costs generated from costing studies or within trials. Where the parameter was a key component of the model, a tailored systematic review can be conducted to locate the most appropriate unit cost.

The Prescription Pricing Authority drug tariff database was used for prices of drugs. The database was updated monthly therefore a single month's tariff was used for all analysis to maintain consistency.

NHS Reference costs (2016/17) were used as the source of unit costs for inpatient and outpatient procedures as well as hospital stay information. The Personal Social Services

Research Unit (PSSRU) generates the Unit Costs for Health and Social Care report which includes costs for both community and hospital-based healthcare staff.

Where an appropriate reference cost could not be sourced from national tariffs and the cost variable used was from a relevant published study, the value was inflated to current prices using the HCIS inflation indices for the financial year of 2016/17.

The cost included in the model comprised the costs of screening and diagnostic tests and the cost of treatments or strategies received by people once diagnosed with the disease. The treatment costs entailed:

- the transition cost, implying the cost of the full treatment related protocol, which can be any of the treatments reported by Gnanapragasam et al. (2016) for localised disease and hormone therapy plus docetaxel for people with metastases;
- the monitoring cost, which included procedures people received according to their disease severity. We assumed that everyone received the following:
    - PSA test every three months for the 1st year and then bi-annually;
    - Nurse-led outpatient appointment every three months for the 1st year and then bi-annually;

People with high-risk localised and people with metastases were subject to additional monitoring tests:

- CT scan once annually; then every six months for metastatic cases only;
- Bone scan once annually; then every six months for metastatic cases only.

The costs of primary treatments used in the model for diagnosed cases were sourced from the NHS reference cost, when possible.

The cost of radical prostatectomy included a first and a follow-up surgery consultation, and it was obtained as the weighted average of elective patients with and without excess bed-days. The cost of external radiotherapy, delivered using the IMRT technique, included the cost of delivery and the preparation of 20 and 37 fractions for outpatient session (weighted average of with and without technical support) for low-/intermediate and high-risk disease respectively.

The brachytherapy cost was obtained from the NHS reference costs, where the costs of the preparation and delivery of a fraction of interstitial radiotherapy were reported. We obtained the weighted average of inpatient, day case and outpatient, assuming that the therapy included only a single fraction.

A main component of hormone therapy used in the model was triptorelin injection (Decapeptyl 11.5 mg), delivered by a practice nurse in primary care setting. Thus, the administration costs were included.

The expected costs of complications associated with radical prostatectomy and radiotherapy were included. We assumed that the adverse events data of external radiotherapy extracted from ProtecT were applied to brachytherapy.

The cost of chemotherapy received by metastatic patients was obtained from an economic evaluation of docetaxel performed by Woods et al. (2018). They utilised data from STAMPEDE study and reported the cost of a six-cycle course of docetaxel, including the acquisition, administration and monitoring costs for different age groups. People with metastases who progressed to castrate-resistant stage were eligible to receive life-extending treatments, including abiraterone and a further 9.5-cycle course of docetaxel. The recommended dose of abiraterone was 1000 mg a day and the mean duration was 8 months, extracted from De Bono et al. (2011) who reported data from COU-AA-301. The costs of life extending treatments were discounted for two years accounting for the average time people stayed at the metastases state without having these medications (James et al. 2016).

1 **Table HE12: Costs used within the model**

Parameter	Unit cost (£)	Source	Notes
PSA measure	19.03	Mowatt et al (2013)	£6.73 (PSA test kit)+£12.30 (nurse consultation)
Resources used for mpMRI			
Radiographer 1 (£/hour)	56.60	Mowatt et al. (2013)	Updated using PSSRU 2017
Radiographer 2 (£/hour)	60.50	Mowatt et al. (2013)	Updated using PSSRU 2017
Consultant (£/hour)	138.00	Mowatt et al. (2013)	Updated using PSSRU 2017
Equipment cost per patient	90.72	Mowatt et al. (2013)	Updated to 2016/17
admin and consumable cost per patient	34.62	Mowatt et al. (2013)	Updated to 2016/17
TRUS			
TRUS only	286.74	NHS reference costs 2016/17	
Histopathology	113.81	Nicholson et al. (2015)	Updated to 2016/17
Consultations potentially associated with TRUS			
GP	38.00	PSSRU 2017	Per patient contact lasting 9.22 minutes
Specialist nurse	103.00	NHS reference costs 2016/17	WF01A: Face-to-Face Attendance, Follow-up, urology
Other NHS direct	20.98	Mowatt et al. (2013)	Updated to 2016/17
Trans-perineal template biopsy	1,401.16	NHS reference costs 2016/17	LB77: Weighted average of elective, day case and outpatients (histopathology cost and AEs associated with TPM assumed the same as TRUS)
Treatments or strategies used in the model for localised disease when diagnosed (including a cost of one-year follow-up equals to AS cost and costs of related adverse events)			
Active surveillance			
PSA test every 3 months for 1st year	19.03	Mowatt et al. (2013)	
DRE every 6 months	38.00	PSSRU 2017	GP appointment
Nurse-led outpatient appointments every 3 months for 1st year	43.67	PSSRU 2017	Cost per hour of patient contact =131 (assumed 20 minutes)
Brachytherapy	1,403.78	NHS reference costs 2016/17	Weighted average of inpatient, day case and outpatient (AEs assumed the same as external radiotherapy)
External radiotherapy (IMRT over 37 fractions)	4,901.05	NHS reference costs 2016/17	Costs of: Deliver a Fraction of Treatment on a Superficial or Orthovoltage Machine; Preparation for Intensity Modulated Radiation Therapy (weighted average of with/without technical support). All multiplied by 37 fractions

Parameter	Unit cost (£)	Source	Notes
Radical prostatectomy	5,270.37	NHS reference costs 2016/17	LB21: Weighted average of elective patients
First surgery consultation appointment	129.58	NHS reference costs 2016/17	WF01B: Non-Admitted Face-to-Face Attendance, First
Follow-up surgery consultation appointment	103.05	NHS reference costs 2016/17	WF01A: Non-Admitted Face-to-Face Attendance, Follow-up
LHRH treatment: Decapeptyl 11.25 injection (3-month dose)	207.00	BNF	One dose for low/intermediate risk. 2-year treatment for high-risk (8 doses). 3-year treatment for metastatic (12 doses)
Delivered by a practice nurse	21.00	PSSRU 2017	(£42/hour) assumed 30 minutes
Bicalutamide 50	5.72	BNF	One tablet daily for 21 days
Treatments used in the model for metastases when diagnosed (including costs of related adverse events)			
Docetaxel for age less than 60	1,846.04	Woods et al. (2018)	Acquisition at dose of 75mg/m2, administration and monitoring for 6 cycles (STAMPEDE), weighted average of different WHO
Docetaxel for age 60-64	1,909.41	Woods et al. (2018)	Acquisition at dose of 75mg/m2, administration and monitoring for 6 cycles (STAMPEDE), weighted average of different WHO
Docetaxel for age 65-69	1,891.65	Woods et al. (2018)	Acquisition at dose of 75mg/m2, administration and monitoring for 6 cycles (STAMPEDE), weighted average of different WHO
Docetaxel for age greater than 69	1,670.74	Woods et al. (2018)	Acquisition at dose of 75mg/m2, administration and monitoring for 6 cycles (STAMPEDE), weighted average of different WHO
Further life extending treatments used in the model for metastases in hormone resistant stage			
Abiraterone 250 mg	1,950.00	BNF (box of 120 tablets)	mean treatment duration 8 months; with daily dose of 1 g (COU-AA-301)
Docetaxel for age less than 60	2,728.56	Woods et al. (2018)	Acquisition at dose of 75mg/m2, administration and monitoring for 9.5 cycles (STAMPEDE), weighted average of different WHO
Docetaxel for age 60-64	2,822.22	Woods et al. (2018)	Acquisition at dose of 75mg/m2, administration and monitoring for 9.5 cycles (STAMPEDE), weighted average of different WHO
Docetaxel for age 65-69	2,795.97	Woods et al. (2018)	Acquisition at dose of 75mg/m2, administration and monitoring for 9.5 cycles (STAMPEDE), weighted average of different WHO
Docetaxel for age greater than 69	2,469.45	Woods et al. (2018)	Acquisition at dose of 75mg/m2, administration and monitoring for 9.5 cycles (STAMPEDE), weighted average of different WHO
AEs associated with biopsy and treatments			
Urinary infection	429.25	NHS reference	LA04S: Kidney or Urinary Tract

Parameter	Unit cost (£)	Source	Notes
		costs 2016/17	Infections, without Interventions, with CC Score 0-1 (non-elective short stay)
Urinary bleeding	523.81	NHS reference costs 2016/17	LB18Z: Attention to Suprapubic Bladder Catheter (non-elective short stay)
Urinary obstruction	1,503.70	NHS reference costs 2016/17	LB09D: Intermediate Endoscopic Ureter Procedures, 19 years and over (non-elective short stay)
Sepsis	2,053.35	NHS reference costs 2016/17	Weighted average of non-elective patients
Erectile dysfunction	113.70	NHS reference costs 2016/17	LB43: Weighted average
Urinary incontinence	291.21	NICE CG 175 (2014)	Managed by containment pads. Updated to 2016/17
Bowel dysfunction	1,780.22	NICE CG 175 (2014)	Mean weighted cost including costs associated with sigmoidoscopy, laser therapy, enemas and blood transfusion
Neutropenia	6,292.20	NHS reference costs 2016/17	PM45: Weighted average of non-elective patients
Musculoskeletal disorders	1,002.52	NHS reference costs 2016/17	HD26: Weighted average of non-elective patients
Gastrointestinal disorders	1,166.19	NHS reference costs 2016/17	FD10: Weighted average of non-elective patients
Respiratory disorders	608.93	NHS reference costs 2016/17	DZ19: Weighted average of non-elective patients
Cardiac disorders	1,513.24	NHS reference costs 2016/17	EB10: Weighted average of non-elective patients
Nervous system disorders	1,390.61	NHS reference costs 2016/17	AA26: Weighted average of non-elective patients
Resources used for monitoring high-risk and metastases			
CT scan	98.28	NHS reference costs 2016/17	RD21A
Bone scan	81.15	NHS reference costs 2016/17	RD50Z

Once the cost of every treatment potentially received by people with diagnosed prostate cancer in the model, the expected costs of treatments received by people in each risk group were derived. The expected costs of adverse events were also included.

Table HE13 shows the expected costs of diagnostic tests and treatments based on risk groups. These costs were derived based on the unit costs shown in Table HE12.

Table HE13: Tests and treatments costs based on risk groups used in the model

Test/Treatment	Average cost (£) (95% CIs)
Diagnostics costs	
PCA3	178.70 (145.40 to 215.39)
PSA measures	19.03 (fixed value)
% free PSA	36.51 (29.71 to 44.00)
PHI (not including capital or maintenance costs)	105.78 (86.07 to 127.50)

Test/Treatment	Average cost (£) (95% CIs)
DRE	38.00 (fixed value)
GP appointment once symptoms developed	38.00 (fixed value)
TRUS including histopathology and expected associated AEs	412.83 (407.11 to 421.38)
Post-MRI TRUS including histopathology, expected associated AEs and fusion	444.39 (438.67 to 452.95)
mpMRI	313.41 (254.99 to 377.75)
Trans-perineal template biopsy, including histopathology, expected associated AEs	1,527.25 (1,248.59 to 1,761.72)
Treatments costs including expected associated AEs applied once disease captured	
Low-risk	2,101.56 (1,586.45 to 2,474.59)
Intermediate-risk	2,394.84 (1,758.69 to 2,471.43)
High-risk	3,498.21 (2,504.14 to 3,995.70)
Metastases	13,331.41 (10,700.15 to 16,496.64)
Monitoring costs (3-monthly)	
Low-risk	31.35 (fixed value)
Intermediate-risk	31.35 (fixed value)
High-risk	76.21 (fixed value)
Metastases	121.06 (fixed value)

HE.2.2.8 – quality of life

Health-related quality of life assigned to people with no cancer in the model was obtained from Kind et al. 1999, who analysed EQ-5D survey, completed by 3,395 people aged 18 or over in the UK, and reported age-related utility values. Localised prostate cancer was assumed to have no effect on quality of life. Thus, men with localised disease (diagnosed or undiagnosed) were assumed to have the same age-related utility as their counterparts with no cancer. However, developing metastatic prostate cancer was associated with a decrement in health-related quality of life that was derived from Torvinen et al. (2013). They reported health related quality of life estimates using EQ-5D for people in different stages of prostate cancer. The decrement in health related quality of life caused by metastases calculated as (-0.137) was the difference between the weighted average of the local disease and the metastatic disease EQ-5D scores.

Further, there was evidence on prostate biopsies affecting health-related quality of life temporarily, due to potentially adverse events (Brown et al., 2018, and Li et al., 2016). However, Brown et al. obtained their estimates from EQ-5D questionnaire completed by PROMIS participants who underwent two types of biopsy, TRUS and TPM, concomitantly. They found that there was a decrement in health-related quality of life of -0.176, assumed to last for two weeks. However, this evidence could not inform the effect of each procedure on quality of life. Similar to Brown et al., we assumed this decrement is associated with TPM. The decrement in health-related quality of life caused by TRUS was sourced from two studies, Heijnsdijk et al. (2012) and Li et al (2016). The former used a proxy value obtained from a study that focused on breast cancer biopsy, reflecting pain and short-term adverse events associated with biopsy. In the absence of directly applicable estimates of TRUS effects on quality of life, we followed Heijnsdijk et al. approach of assigning 0.1 decrement of quality of life caused by TRUS and assumed to last for two weeks. In addition, we used Li et al. findings on the quality of life affected by infections associated with TRUS, weighted by the probability of developing infections obtained from other studies (Rosario et al., Nam et al. and Hoeks et al).

Short-term complications due to radical treatments, including radical prostatectomy and radiotherapy, are also associated with decrement in health-related quality of life. We used Donovan et al.'s findings from ProtecT to source our model with probability of developing erectile dysfunction, urinary incontinence (duration of one year) and bowel dysfunction (duration of six months). The decrement in quality of life due to these types of complications was derived from Mowatt et al. Table HE14 shows the health-related quality of life estimates used in the model.

Table HE14: Decrements in health-related quality of life used in the model

State / event	Value	Source
Decrement associated with metastases	-0.137	Torvinen (2013)
Decrement associated with TPM (2 weeks)	-0.176	Brown et al. (2018)
Decrement associated with TRUS (2 weeks)	-0.101	Heijnsdijk (2012), Li (2016)
QALY loss due to transition to TP-low-risk	-0.027	Donovan et al. (2016), Mowatt et al. (2013)
QALY loss due to transition to TP-intermediate-risk	-0.029	Donovan et al. (2016), Mowatt et al. (2013)
QALY loss due to transition to TP-high-risk	-0.027	Donovan et al. (2016), Mowatt et al. (2013)

HE.2.2.9 Sensitivity analyses

The impact of changes in parameter estimates individually on the model results was explored by performing one-way sensitivity analyses. The mean of the input parameter of interest was replaced by the lower and upper bound of the 95% confidence interval, when available, otherwise it was altered by a plausible range. The impact of these changes on the expected incremental net benefits in a pairwise comparison is reported in a tornado diagram.

HE.2.2.10 Probabilistic sensitivity analyses

We configured the models to perform probabilistic sensitivity analysis to quantify uncertainty in the true values of input parameters. Probability distributions were estimated for all input variables with the exception of the direct costs, assigned to a number of resources. Distribution parameters were sourced from the study in which the value was obtained, where possible, or were estimated based on the usual properties of data of that type.

The distribution for each of the parameters used within the probabilistic sensitivity analysis was driven by the variable type and the availability of reported information. Beta distributions were used for variables denoting a probability, including developing symptoms and possible complications associated with prostate biopsy and with treatments. Dirichlet distributions, however, were assigned to branching probabilities to ensure that they sum to 1 at each iteration. A beta distribution was also estimated for the utility values, which also traditionally confined to values between 0 and 1. Costs data, obtained from the NHS reference costs, were assigned gamma distribution, if there were data on the sample size (number of data submissions) that allowed the estimation of standard errors.

The accuracy data parameters, including sensitivity and specificity, of the screening tests used in the model were assigned multivariate normal distributions. This was to account for the possible correlation between sensitivity and specificity. We obtained the correlation factor from the variance/covariance matrix derived from the evidence synthesis performed within the clinical review for this question.

The model calibration performed to estimate progression probabilities for people with undiagnosed and diagnosed prostate cancer was run for 1000 times to address the uncertainty within the data used for calibration. At each iteration, the model was calibrated based on a simulated value from a beta distribution assigned to the cumulative incidence of metastases reported in the watchful waiting arm in SPCG4 study for each risk group for the undiagnosed cohort, and to the cumulative incidence of disease specific mortality reported for each risk group by Gnanapragasam et al. for people with diagnosed disease. We followed the approach reported by Ren et al. (2018) to account for the ordered parameters whilst sampling, i.e. the risk of metastasis or prostate cancer death increases according to the risk (low-, intermediate- and to high-risk). This should ensure that the values simulated at each iteration are clinically meaningful. Then, when the model ran probabilistically, the probabilities of progression, obtained from model calibration, were simulated from multivariate normal distributions, taking into consideration the possible correlation between the probabilities of progression from different risk groups. The correlation factors were obtained from the model calibration output, by transforming the probabilities to the log odds, and then deriving the variance/covariance matrices.

HE.3 Results

Base-case cost–utility results

The results reported in the tables for each population in the main document exclude TPM strategies. The tables with the full results including TPM strategies are reported in the Appendix HE.6. Based on the number of screening tests that the guidelines committee considered clinically meaningful and plausible frequencies to perform these tests, we simulated 191 possible strategies. The cost-effectiveness of these strategies was assessed in 11 sub-populations, based on their diagnostic history.

To report the results for this number of strategies and populations in an efficient way that helps informing decision making, we followed the following approach:

For every population, the baseline population distribution is represented in a decision tree figure that shows, the disease prevalence estimates, the diagnostic tests people underwent and the resulting population distribution that enter the Markov model.

Then, the model dynamics are depicted in figures that show the natural disease history, labelled as “no screening” strategy, for the related population. These figures trace the population in two ways: First, the disease severity, as “no cancer”, low-, intermediate-, high-risk and metastatic. Second, the true status, as true negative (TN) assigned to people with no cancer and people with undiagnosed low-risk cancer, false negative (FN) assigned to people with undiagnosed clinically significant cancer and true positive (TP) assigned to people with diagnosed cancer. In addition, the model dynamics figures demonstrate the impact of a number of screening strategies on disease progression. These strategies were selected to indicate the mechanism of the model in capturing the modelled cohort progression. For every population, we selected 4 strategies: 2 that were found to be optimal at the two cost-effectiveness thresholds, £20,000 and £30,000 per QALY; the strategy where all candidates receive an immediate TRUS and no subsequent follow-up; and finally the more invasive strategy where all candidates receive an immediate TPM and no subsequent follow-up.

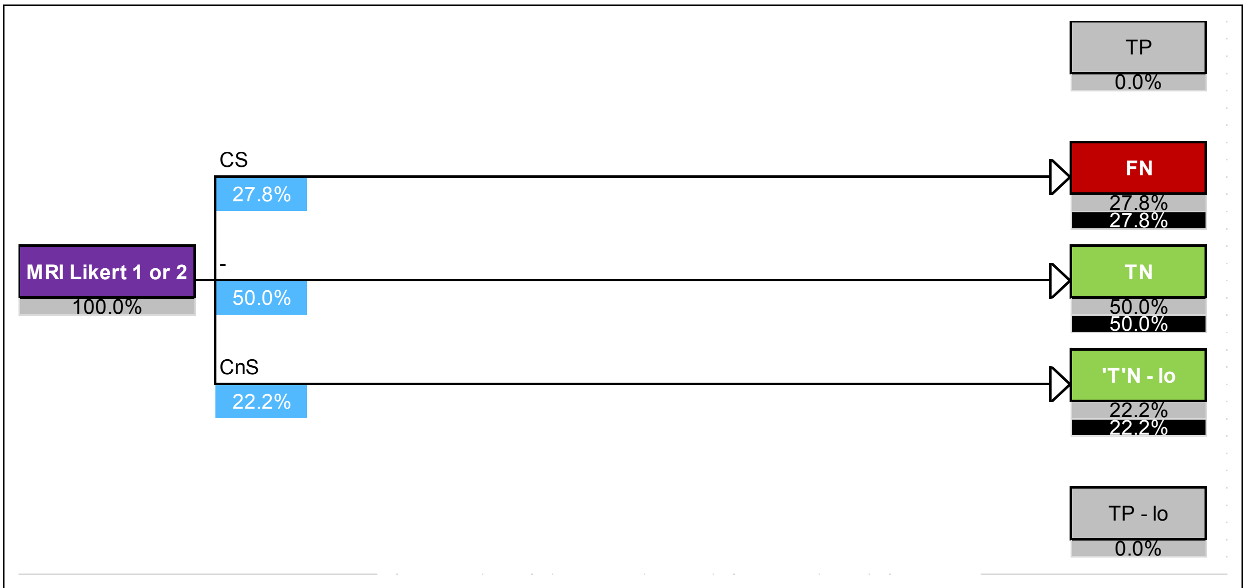
We also report the incremental deterministic analysis results for every population. The strategies are ordered from the least to the most expensive, and every strategy found to be dominated (more expensive and less effective than the next best one) or extendedly dominated (the ICER is greater than the next best one) was excluded. We also tabulate the top 10 strategies that generate the greatest health benefits at two cost-effectiveness thresholds: £20,000 and £30,000 per QALY. In this table, a number of findings for the top 10 strategies are also detailed; these are: the total costs and QALYs, treatment costs, screening costs, the average number of unnecessary biopsies, cumulative incidence of prostate cancer death and the life years associated with the related strategy.

To demonstrate the uncertainty surrounding the results, one-way sensitivity analysis, using Tornado diagrams, is reported for every population. In addition, the probabilistic results are depicted in the cost-effectiveness acceptability curve.

HE.3.1 MRI Likert 1 or 2; 0 biopsies

Baseline population

The population of interest here is people who received mpMRI with Likert score at 1 or 2 and did not receive prostate biopsy. The baseline population distribution is 50%, 22.2% and 27.8% for people with truly no cancer, people with missed clinically non-significant cancer and people with missed clinically significant cancer, respectively, Figure HE03.



Percentages in blue boxes indicate probabilities at each branch of the tree. Percentages in grey boxes indicate proportion of whole tested population at each stage. Percentages in black boxes indicate proportion of people receiving a negative diagnosis who fall into each category (note that the NPV of the algorithm is given by 1 – the proportion in the black box under 'FN'). CS: Clinically significant; CnS: Clinically non-significant; FN: False negative CS disease; TN: true negative; 'T'N-lo: missed CnS disease; TP and TP-lo: Truly positive CS and CnS disease, respectively.

Figure HE03: The decision tree to derive the baseline population distribution (Likert 1 or 2 with no previous biopsy)

Model dynamics

Figure HE04 demonstrates the modelled cohort over 30 years. On the left side, it shows the disease development, starting as low-risk and then progressing to intermediate-, then to high-risk and then to metastatic disease. On the right side, it shows the performance of diagnostics capturing the disease within people misclassified as false negative. This is shown for the least intensive "no screening" strategy, at the top, where people prostate biopsy only if they develop symptoms, to the most invasive strategy at the bottom, where all candidates receive an immediate TPM and not followed-up subsequently. In between, the impact of applying 3 follow-up strategies on disease progression and their performance in identifying missed disease is demonstrated over time. This is shown for: the strategy where people receive 6-monthly %free PSA; if level <15%, they are directed to TRUS biopsy, the strategy where people receive 3-monthly %free PSA; if level <15%, they are directed to TRUS biopsy and the strategy where people receive an immediate TRUS and they are not followed-up subsequently.

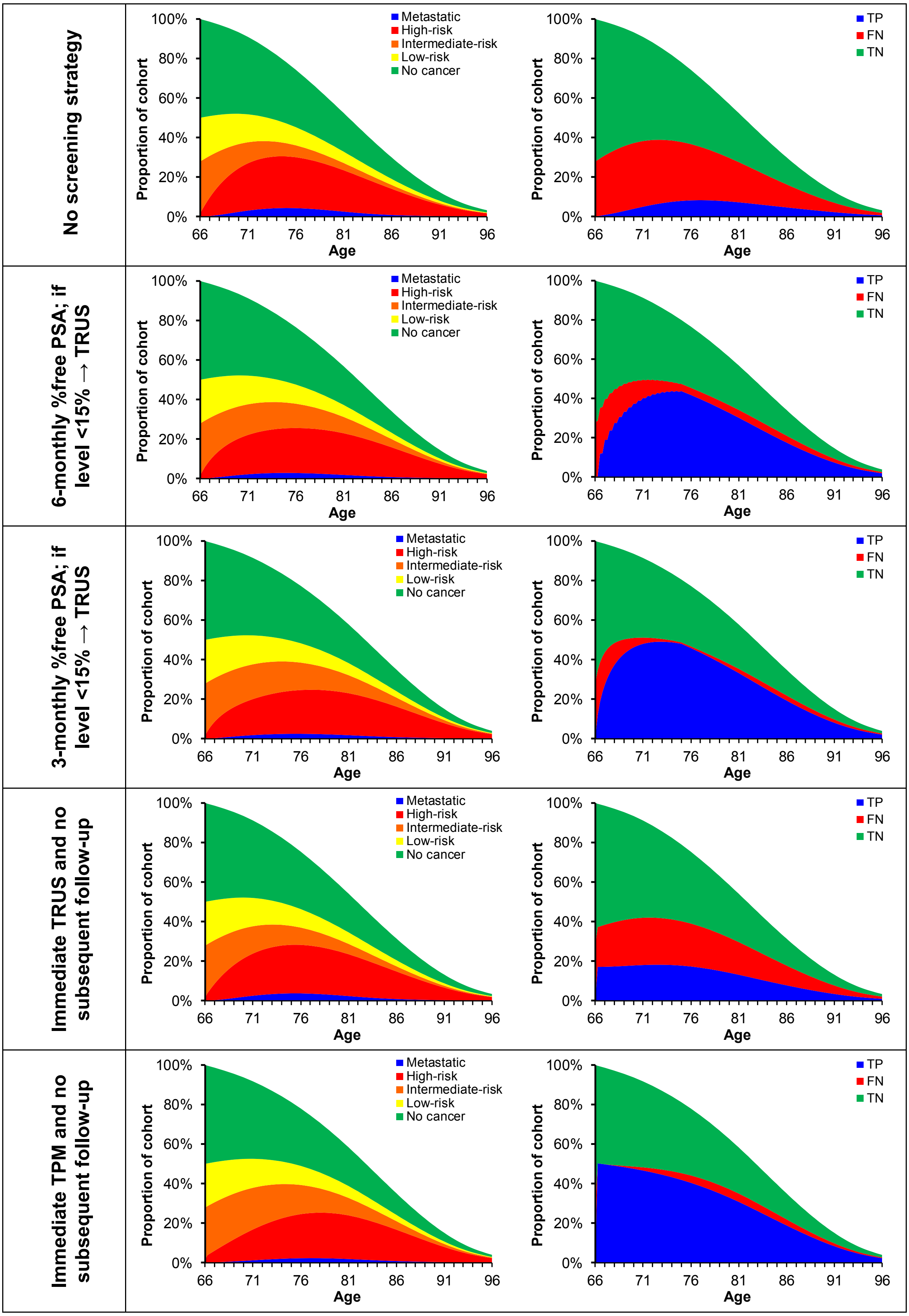


Figure HE04: Tracking the modelled cohort over 30 years, tracing the disease progression on the left hand, and reflecting the diagnosed cases overtime on the right hand for a given strategy

Incremental deterministic analysis

Table HE15 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, where all candidates receive an immediate TRUS and no subsequent follow-up, seems optimal. At a slightly higher threshold, performing strategies that include 6-monthly screening tests using PSA velocity at a threshold of 0.75 ng/ml/year or the percentage of free PSA at a threshold of 15% seems to be optimal.

Table HE15: Base-case deterministic cost-utility results (excluding TPM) for people with Likert <3 and no biopsies

	Absolute		Incremental		
Strategy	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£1,961	8.881			
TRUS everyone	£3,250	8.989	£1,290	0.108	£11,954
6-monthly %free PSA; if level <15% → TRUS	£6,508	9.132	£3,258	0.143	£22,752
6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£6,822	9.146	£314	0.014	£23,184
3-monthly %free PSA; if level <15% → TRUS	£8,358	9.191	£1,536	0.045	£34,491
3-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£8,746	9.195	£388	0.004	£87,514
3-monthly PSA; if density ≥ 0.15ng/ml/ml → TRUS	£8,987	9.196	£241	0.001	£195,856
3-monthly PHI; if level ≥ 35 → TRUS	£10,596	9.200	£1,610	0.003	£463,713

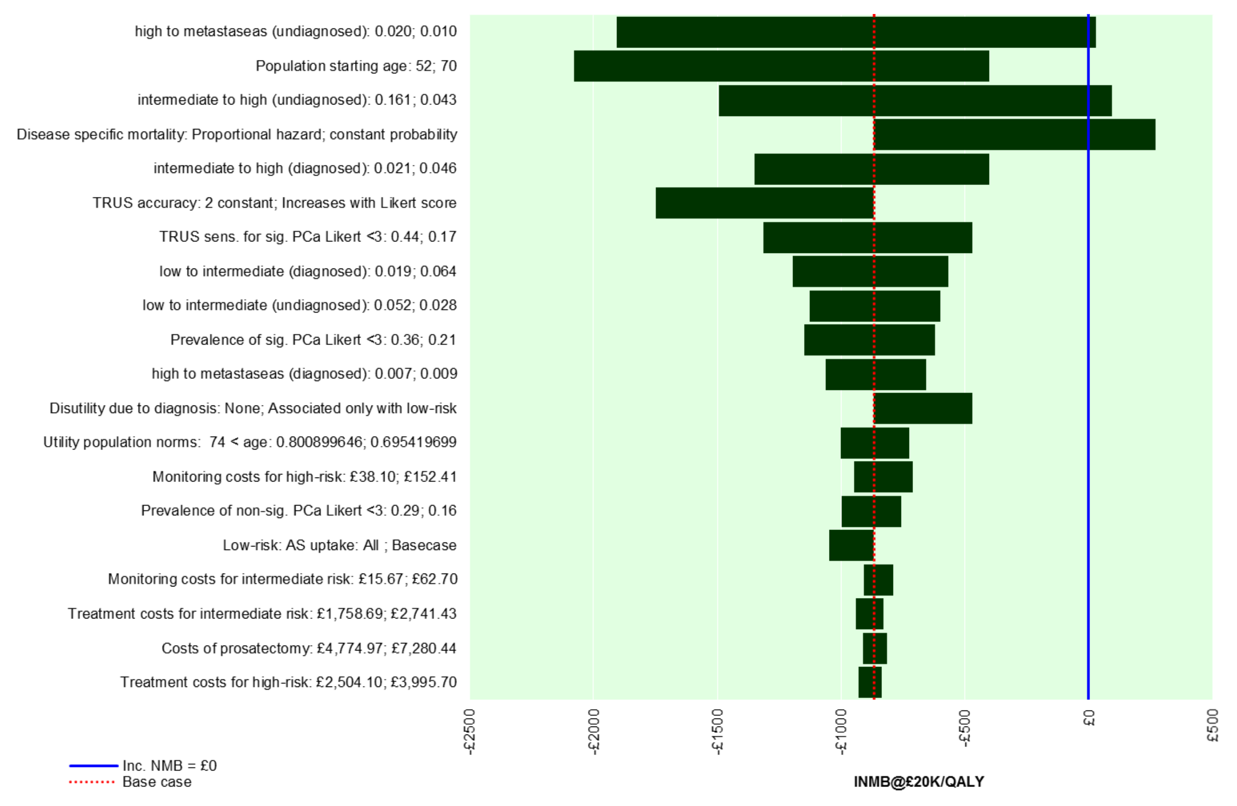
Table HE16 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The strategy including the 6-monthly % free PSA test at a threshold of 15% is ranked as the 5th and 3rd at cost-effectiveness thresholds of £20,000 and £30,000 per QALY, respectively. However, performing this strategy 3-monthly brings it down to the 4th position at the higher cost-effectiveness threshold, while at a cost-effectiveness threshold of £20,000 per QALY, this strategy's rank is 64. The table also shows the significant increase in the number of unnecessary biopsies and the screening cost between the two test frequencies.

Table HE16: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY (excluding TPM) for people with Likert <3 and no biopsies

						Absolute		Rank at thresholds of	
Strategy	**Life-years**	**PC deaths**	**Unnecessary biopsies**	**Screening costs (£)**	**Treatment costs (£)**	**Costs (£)**	**Effects (QALYs)**	**£20k/ QALY**	**£30k/ QALY**
TRUS everyone	16.04	20.2%	0.93	£0	£2,652	£3,250	8.989	1	19
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.29	17.2%	2.27	£98	£3,829	£5,229	9.073	2	8
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.30	17.1%	2.43	£97	£3,894	£5,361	9.079	3	6
1-yearly %free PSA; if level <15% → TRUS	16.24	17.7%	1.84	£193	£3,653	£4,961	9.058	4	16
6-monthly %free PSA; if level <15% → TRUS	16.44	15.7%	3.22	£345	£4,413	£6,508	9.132	5	3
2-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.10	19.2%	1.28	£49	£3,082	£3,944	9.004	6	28
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.09	19.3%	1.21	£49	£3,030	£3,856	8.999	7	29
6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.48	15.3%	4.04	£174	£4,573	£6,822	9.146	8	1
2-yearly %free PSA; if level <15% → TRUS	16.06	19.7%	1.00	£96	£2,894	£3,669	8.987	9	31
2-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	16.15	18.6%	1.81	£48	£3,308	£4,398	9.023	10	23
6-monthly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.50	15.1%	4.34	£172	£4,627	£6,992	9.151	13	2
3-monthly %free PSA; if level <15% → TRUS	16.61	14.1%	5.74	£603	£4,996	£8,358	9.191	64	4
3-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.64	13.9%	7.35	£305	£5,090	£8,746	9.195	87	5
6-monthly PSA; if level ≥ 6ng/ml → TRUS	16.53	14.8%	5.95	£168	£4,745	£7,701	9.156	67	7
3-monthly DRE; if abnormal → TRUS	16.37	16.4%	2.37	£757	£4,133	£6,288	9.108	25	9
1-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	16.37	16.4%	3.56	£93	£4,160	£6,074	9.100	19	10

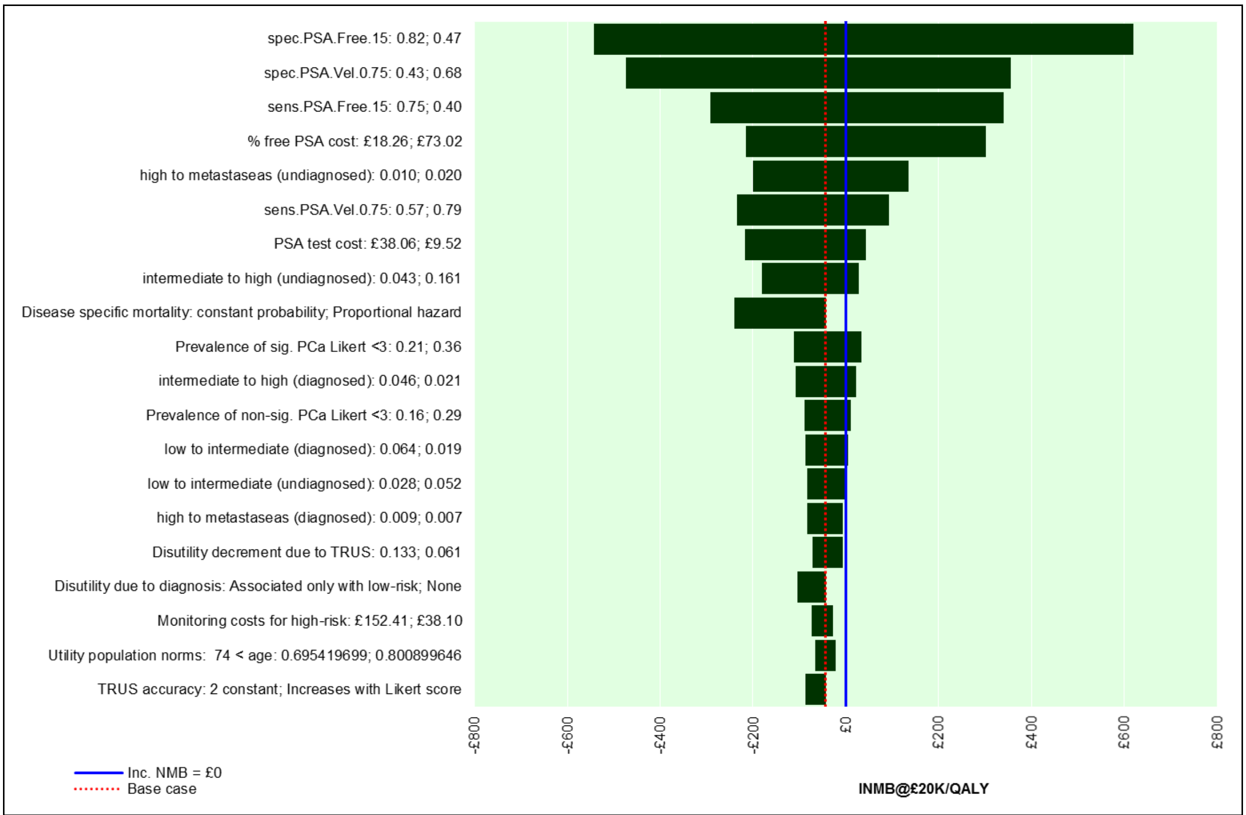
One-way sensitivity analysis

Figure HE05 shows the impact of changing the value of a parameter on the results of a pairwise comparison between “no screening strategy and the strategy where people receive an immediate TRUS biopsy and not followed-up subsequently. It shows that the results are sensitive to probabilities of progression from intermediate- to high-risk and from high-risk to metastatic in undiagnosed cases. It shows also the significant impact of assigning a constant probability to prostate cancer death on the results, where “no screening” strategy becomes more beneficial.



Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

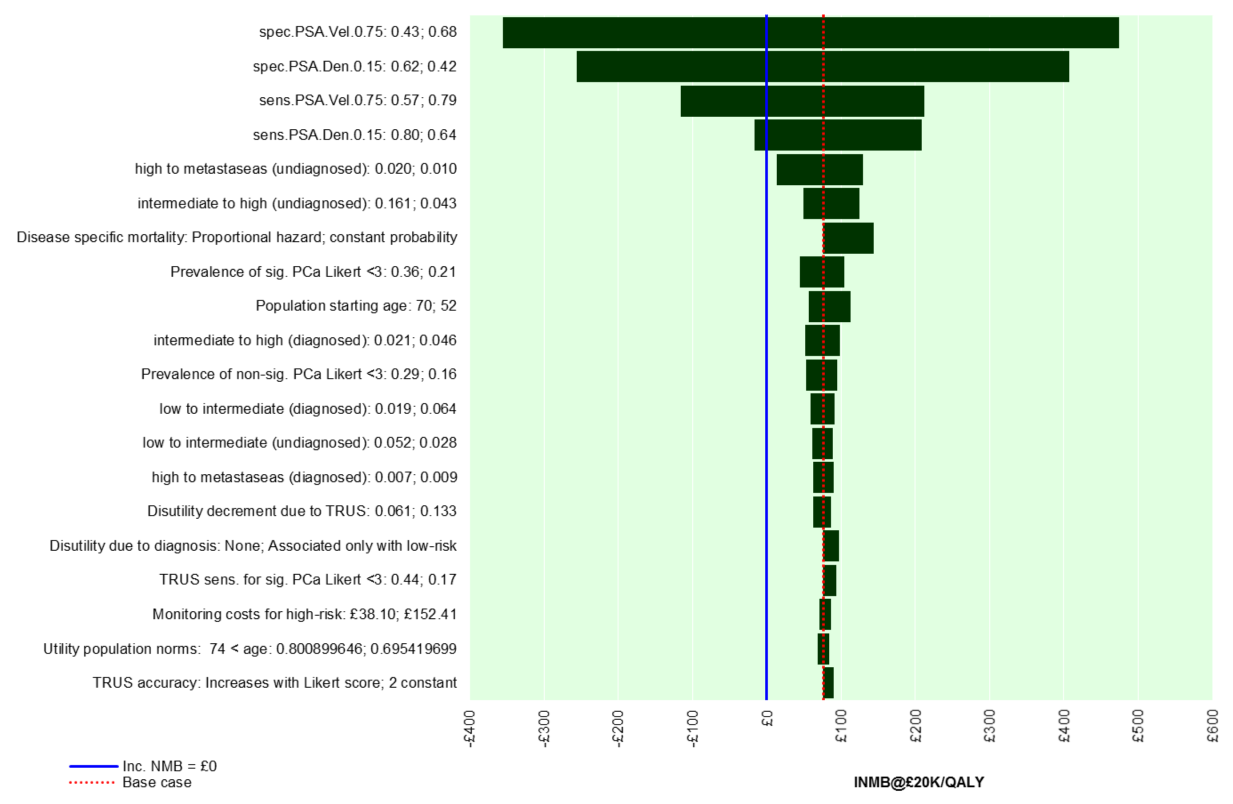
Figure HE05: One-way sensitivity analysis “no screening” vs “TRUS everyone” based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY



Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE06: One-way sensitivity analysis "6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS" vs "6-monthly %free PSA; if level <15% → TRUS" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Figure HE06 shows the comparison between the strategy including 6-monthly PSA velocity test at a threshold of 0.75 ng/ml/year and the one including 6-monthly % free PSA test at a threshold of 15%. It shows that given the 95% confidence interval of the two tests' accuracy data, there is not any significant difference between the two tests' performance. The costs of tests, in particular the cost of free PSA test, seem to be having a considerable impact on the results.



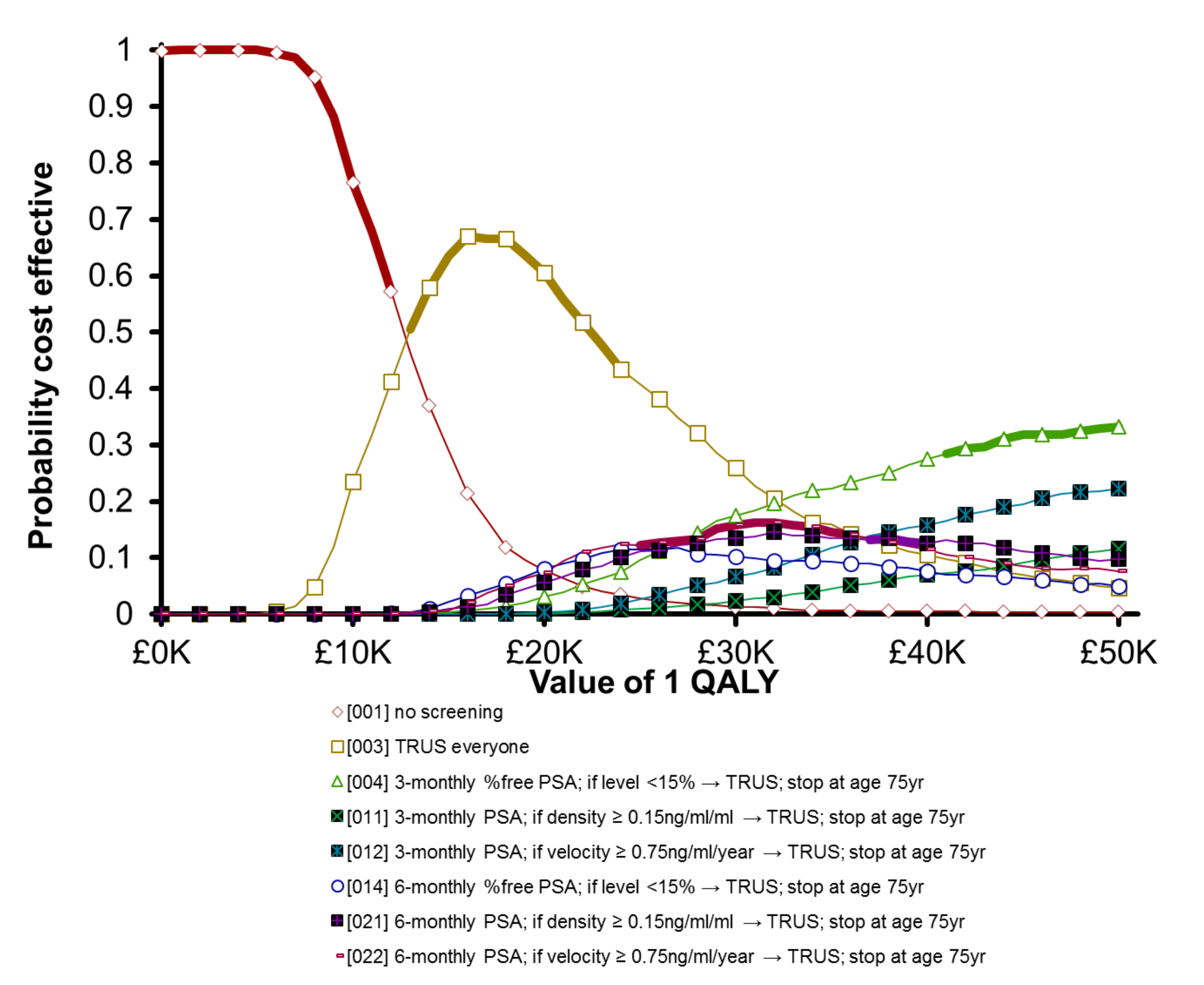
Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE07: One-way sensitivity analysis "6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS" vs "6-monthly PSA; if density ≥ 0.15ng/ml/ml → TRUS" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Figure HE07 shows the comparison between the strategy including 6-monthly PSA velocity test at a threshold of 0.75 ng/ml/year and the one including 6-monthly PSA density test at a threshold of 0.15 ng/ml/ml. It shows that given the 95% confidence interval of the two tests' accuracy data, there is not any significant difference between the two tests' performance.

Probabilistic results

Figure HE08 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY, excluding strategies with TPM. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. The strategy where people receive an immediate TRUS seem to be cost-effective at a threshold of £20,000 per QALY with a probability of about 70%. The probability of the strategy including 6-monthly PSA velocity test at a threshold of 0.75 ng/ml/year being cost-effective at a threshold of £30,000 per QALY is about 20%. At a cost-effectiveness threshold between £40,000 and £50,000 per QALY, the strategy including 3-monthly % free PSA test at a threshold of 15% seems to be cost effective with a probability of about 35%.



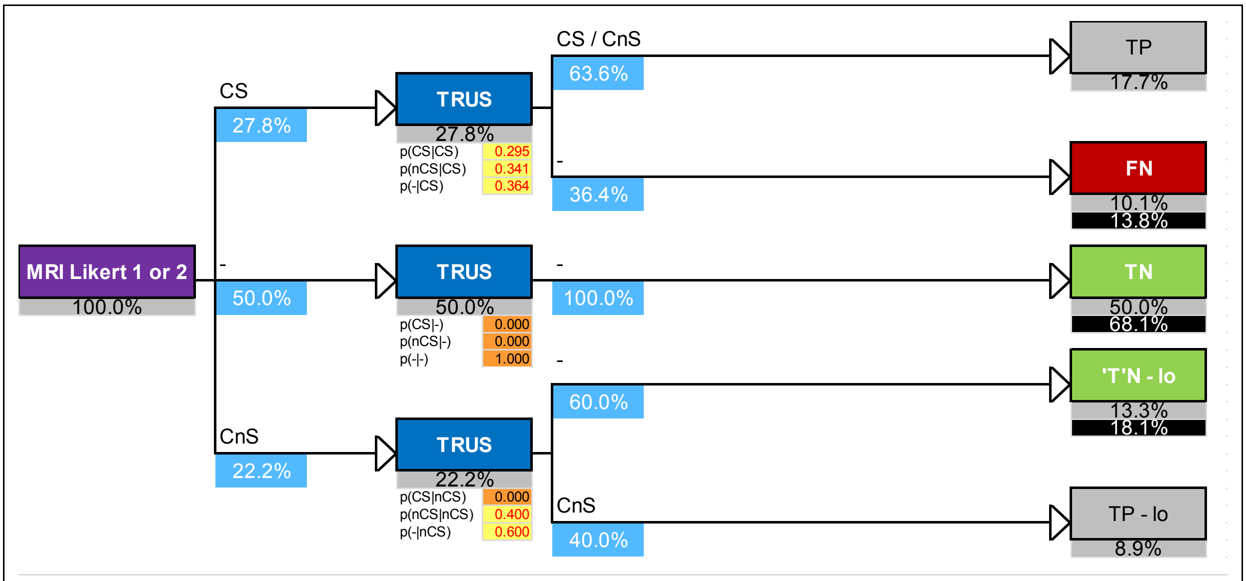
Bold line indicates cost effectiveness acceptability frontier

Figure HE08: Cost-effectiveness acceptability curve excluding TPM strategies

HE.32 MRI Likert 1 or 2; 1 biopsy

Baseline population

The population of interest here is people who received mpMRI with Likert score at 1 or 2 and one prostate biopsy (TRUS). Applying the prevalence obtained from PROMIS and the accuracy data of TRUS results in the baseline population distribution being 68.1%, 18.1% and 13.8% for people with truly no cancer, people with missed clinically non-significant cancer and people with missed clinically significant cancer, respectively, Figure HE09.



Bold line indicates Baseline population distribution (Likert 1 or 2 with one previous biopsy): Percentages in blue boxes indicate probabilities at each branch of the tree. Percentages in grey boxes indicate proportion of whole tested population at each stage. Percentages in black boxes indicate proportion of people receiving a negative diagnosis who fall into each category (note that the NPV of the algorithm is given by 1 – the proportion in the black box under 'FN'). Figures in yellow and orange boxes indicate conditional probabilities of each diagnosis, given true status. CS: Clinically significant; CnS: Clinically non-significant; FN: False negative CS disease; TN: true negative; 'T'N-lo: missed CnS disease; TP and TP-lo: Truly positive CS and CnS disease, respectively.

Figure HE09: The decision tree to derive the baseline population distribution (Likert 1 or 2 with 1 previous biopsy)

Model dynamics

Figure HE10 demonstrates the modelled cohort over 30 years. On the left side, it shows the disease development, starting as low-risk and then progressing to intermediate-, then to high-risk and then to metastatic disease. On the right side, it shows the performance of diagnostics capturing the disease within people misclassified as false negative. This is shown for the least intensive "no screening" strategy, at the top, where people prostate biopsy only if they develop symptoms, to the most invasive strategy at the bottom, where all candidates receive an immediate TPM and not followed-up subsequently. In between, the impact of applying 3 follow-up strategies on disease progression and their performance in identifying missed disease is demonstrated over time. This is shown for: the strategy where people receive a yearly PSA test; if velocity ≥0.75 ng/ml/year, they are directed to TRUS biopsy, the strategy where people receive a yearly PSA test; if density ≥0.15, they are directed to TRUS biopsy and the strategy where people receive an immediate TRUS and they are not followed-up subsequently.

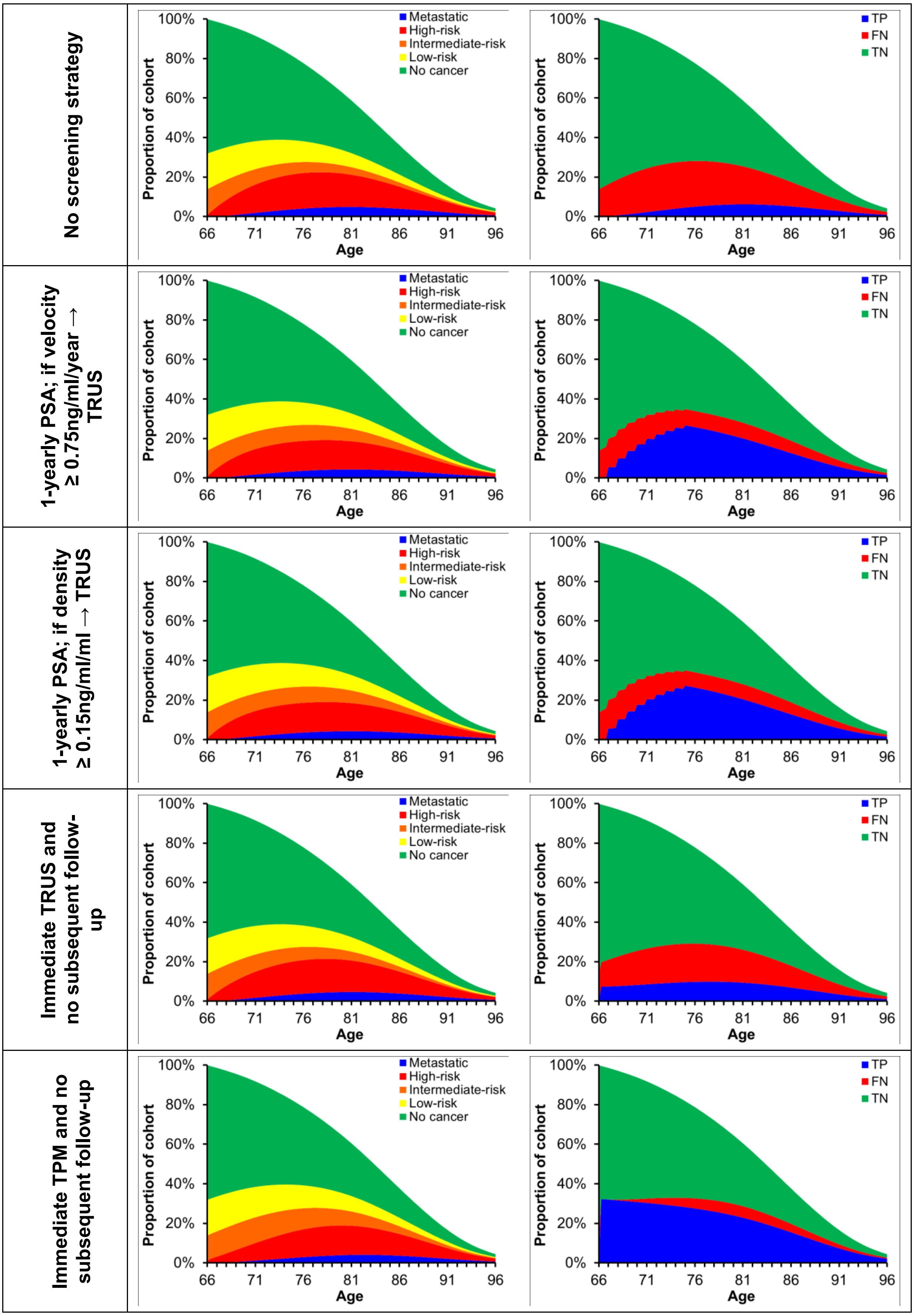


Figure HE10: Tracking the modelled cohort over 30 years, tracing the disease progression on the left hand, and reflecting the diagnosed cases overtime on the right hand for a given strategy

Incremental deterministic analysis

Table HE17 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, where all candidates receive an immediate TRUS and no subsequent follow-up, seems optimal. At a slightly higher threshold, performing strategies that include a yearly screening tests using PSA velocity at a threshold of 0.75 ng/ml/year seems to be optimal.

Table HE17: Base-case deterministic cost-utility results (excluding TPM) for people with Likert <3 and one biopsy

Strategy	Absolute		Incremental		
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£1,249	9.151			
TRUS everyone	£2,138	9.196	£889	0.046	£19,534
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£4,150	9.274	£2,012	0.078	£25,794
6-monthly %free PSA; if level <15% → TRUS	£5,450	9.316	£1,300	0.042	£30,853
6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£5,805	9.324	£355	0.008	£44,946
3-monthly %free PSA; if level <15% → TRUS	£7,550	9.352	£1,745	0.027	£63,720
3-monthly PCA3; if level ≥ 50 → TRUS	£10,435	9.357	£2,885	0.006	£499,120

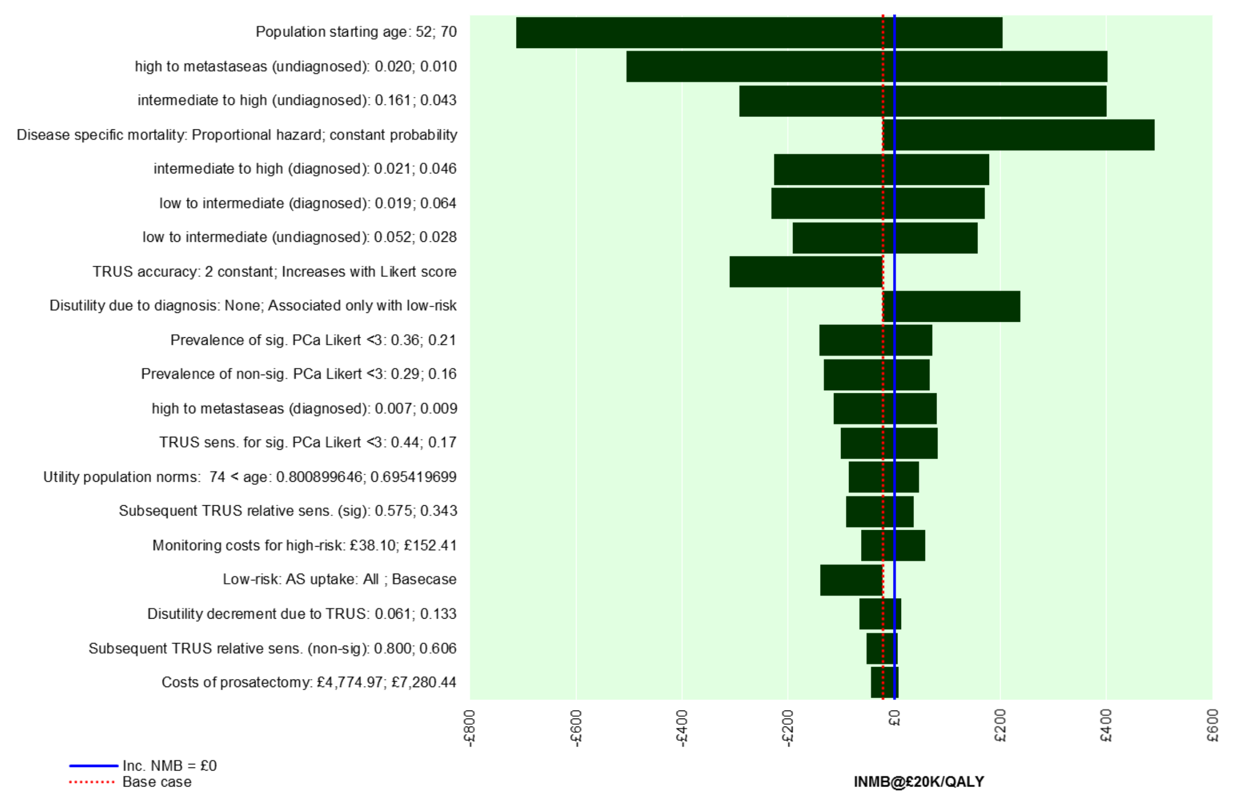
Table HE18 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The two strategies including a yearly PSA velocity test at a threshold of 0.75ng/ml/year and a yearly PSA density test at a threshold of 0.15 ng/ml/ml are ranked as the 1st and 2nd at cost-effectiveness thresholds of £30,000 per QALY, respectively. However, the number of unnecessary biopsies and the screening cost associated with these two tests are very similar.

Table HE18: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY (excluding TPM) for people with Likert <3 and one biopsy

Strategy	Life-years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
TRUS everyone	16.48	15.7%	1.14	£0	£1,537	£2,138	9.196	1	11
no screening	16.36	16.9%	0.29	£0	£1,037	£1,249	9.151	2	51
3-yearly DRE; if abnormal → TRUS	16.41	16.3%	0.54	£79	£1,287	£1,705	9.169	3	38
2-yearly DRE; if abnormal → TRUS	16.44	16.0%	0.64	£112	£1,384	£1,884	9.177	4	31
3-yearly %free PSA; if level <15% → TRUS	16.49	15.4%	0.99	£74	£1,644	£2,268	9.194	5	24
2-yearly %free PSA; if level <15% → TRUS	16.54	14.9%	1.26	£104	£1,850	£2,632	9.212	6	12
3-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.51	15.2%	1.19	£39	£1,735	£2,406	9.200	7	20
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.56	14.6%	1.53	£54	£1,965	£2,810	9.221	8	8
3-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.52	15.1%	1.26	£38	£1,771	£2,473	9.203	9	19
2-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.57	14.5%	1.63	£54	£2,009	£2,895	9.224	10	6
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.72	12.8%	2.93	£111	£2,653	£4,150	9.274	30	1
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.73	12.7%	3.14	£110	£2,709	£4,288	9.278	38	2
6-monthly %free PSA; if level <15% → TRUS	16.84	11.6%	4.17	£402	£3,145	£5,450	9.316	65	3
1-yearly %free PSA; if level <15% → TRUS	16.68	13.2%	2.35	£217	£2,499	£3,875	9.263	22	4
6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.87	11.2%	5.28	£205	£3,282	£5,805	9.324	77	5
[6-monthly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.88	11.1%	5.69	£204	£3,328	£6,000	9.327	81	7
6-monthly DRE; if abnormal → TRUS	16.63	13.8%	1.76	£469	£2,261	£3,644	9.247	37	9
3-monthly DRE; if abnormal → TRUS	16.78	12.2%	3.04	£872	£2,899	£5,237	9.300	72	10

One-way sensitivity analysis

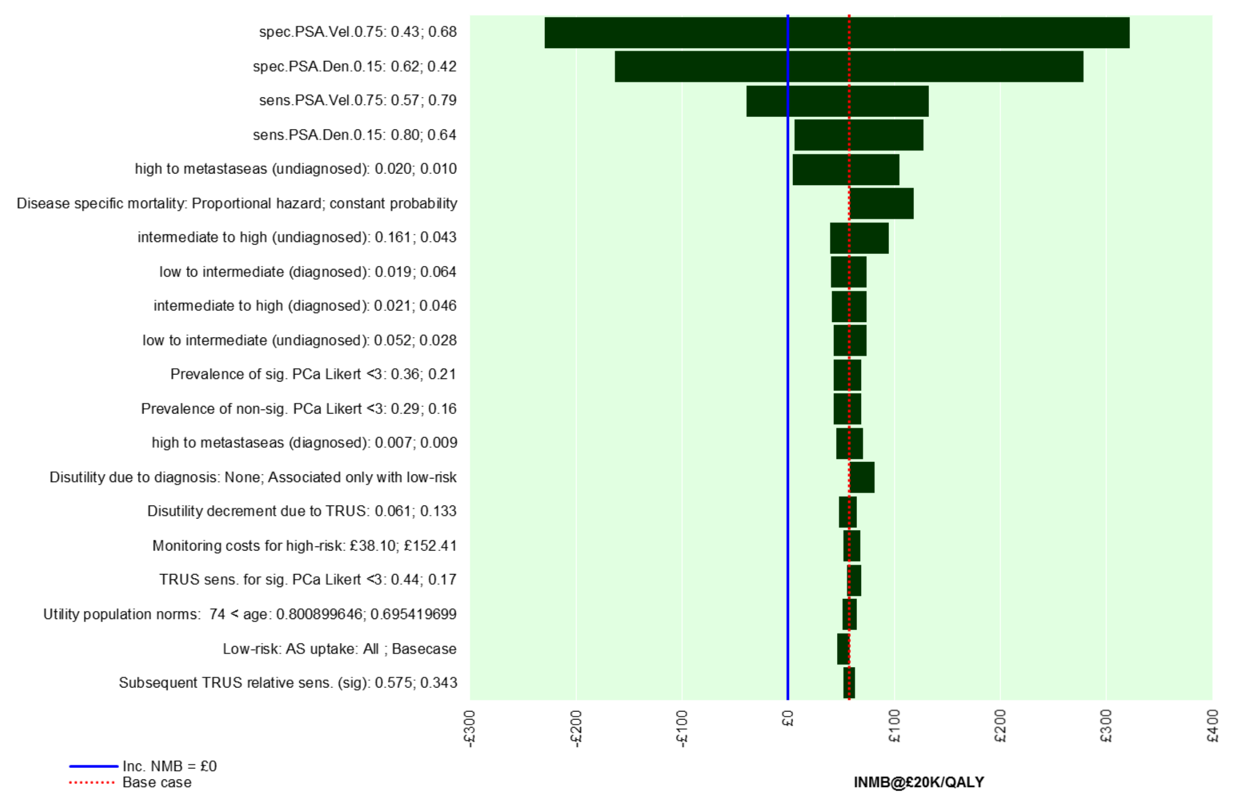
Figure HE11 shows the impact of changing the value of a parameter on the results of a pairwise comparison between "no screening strategy and the strategy where people receive an immediate TRUS biopsy and not followed-up subsequently. It shows that the results are sensitive to probabilities of progression in undiagnosed and diagnosed cases. It shows also the significant impact of assigning a constant probability to prostate cancer death or starting the model with older age (70 years old) on the results, where "no screening" strategy becomes more beneficial. Further, applying disutility on people with low-risk cancer once diagnosed results in the "no screening" strategy being more beneficial.



Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE11: One-way sensitivity analysis "no screening" vs "TRUS everyone" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Figure HE12 shows the comparison between the strategy including a yearly PSA velocity test at a threshold of 0.75 ng/ml/year and the one including a yearly PSA density test at a threshold of 0.15 ng/ml/ml. It shows that given the 95% confidence interval of the two tests' accuracy data, there is not any significant difference between the two tests' performance.

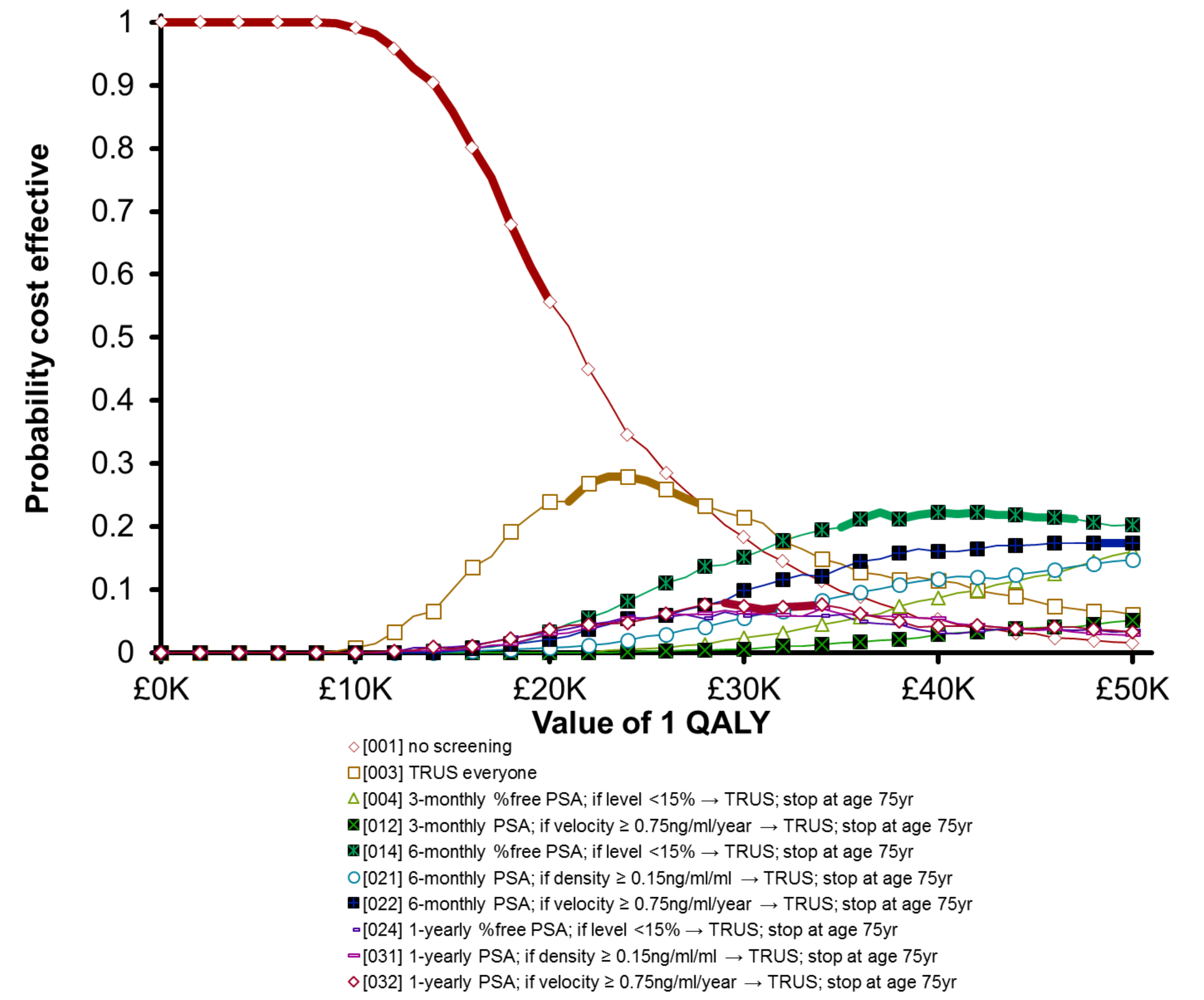


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE12: One-way sensitivity analysis "1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS" vs "1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Probabilistic results

Figure HE13 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY, excluding strategies with TPM. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. The strategy where people receive an immediate TRUS seem to be cost-effective at a threshold of £20,000 per QALY with a probability of about 30%. The probability of the strategy including a yearly PSA velocity test at a threshold of 0.75 ng/ml/year being cost-effective at a threshold of £30,000 per QALY is just less than 10%. At a cost-effectiveness threshold between £40,000 and £50,000 per QALY, the strategy including 6-monthly % free PSA test at a threshold of 15% seems to be cost effective with a probability of about 20%.



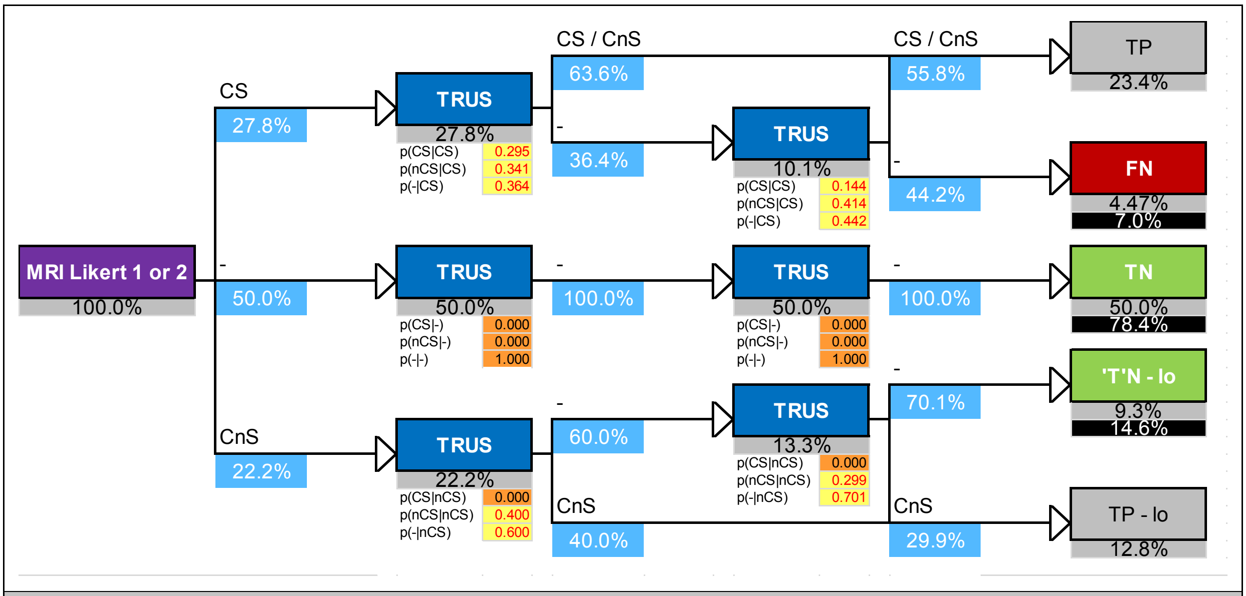
Bold line indicates cost effectiveness acceptability frontier

Figure HE13: Cost-effectiveness acceptability curve excluding TPM strategies

HE.33 MRI Likert 1 or 2; 2 biopsies

Baseline population

The population of interest here is people who received mpMRI with Likert score at 1 or 2 and two prostate biopsies (TRUS). Applying the prevalence obtained from PROMIS and the accuracy data of TRUS results in the baseline population distribution being 78.4%, 14.6% and 7.0% for people with truly no cancer, people with missed clinically non-significant cancer and people with missed clinically significant cancer, respectively, Figure HE14.



Percentages in blue boxes indicate probabilities at each branch of the tree. Percentages in grey boxes indicate proportion of whole tested population at each stage. Percentages in black boxes indicate proportion of people receiving a negative diagnosis who fall into each category (note that the NPV of the algorithm is given by 1 – the proportion in the black box under 'FN'). Figures in yellow and orange boxes indicate conditional probabilities of each diagnosis, given true status. CS: Clinically significant; CnS: Clinically non-significant; FN: False negative CS disease; TN: true negative; 'T'N-lo: missed CnS disease; TP and TP-lo: Truly positive CS and CnS disease, respectively.

Figure HE14: The decision tree to derive the baseline population distribution (Likert 1 or 2 with 2 previous biopsies)

Model dynamics

Figure HE15 demonstrates the modelled cohort over 30 years. On the left side, it shows the disease development, starting as low-risk and then progressing to intermediate-, then to high-risk and then to metastatic disease. On the right side, it shows the performance of diagnostics capturing the disease within people misclassified as false negative. This is shown for the least intensive "no screening" strategy, at the top, where people receive prostate biopsy only if they develop symptoms, to the most invasive strategy at the bottom, where all candidates receive an immediate TPM and not followed-up subsequently. In between, the impact of applying 3 follow-up strategies on disease progression and their performance in identifying missed disease is demonstrated over time. This is shown for: the strategy where people receive a 2-yearly PSA test; if velocity ≥0.75 ng/ml/year, they are directed to TRUS biopsy, the strategy where people receive a 2-yearly % free PSA test; if level <15%, they are directed to TRUS biopsy and the strategy where people receive an immediate TRUS and they are not followed-up subsequently.

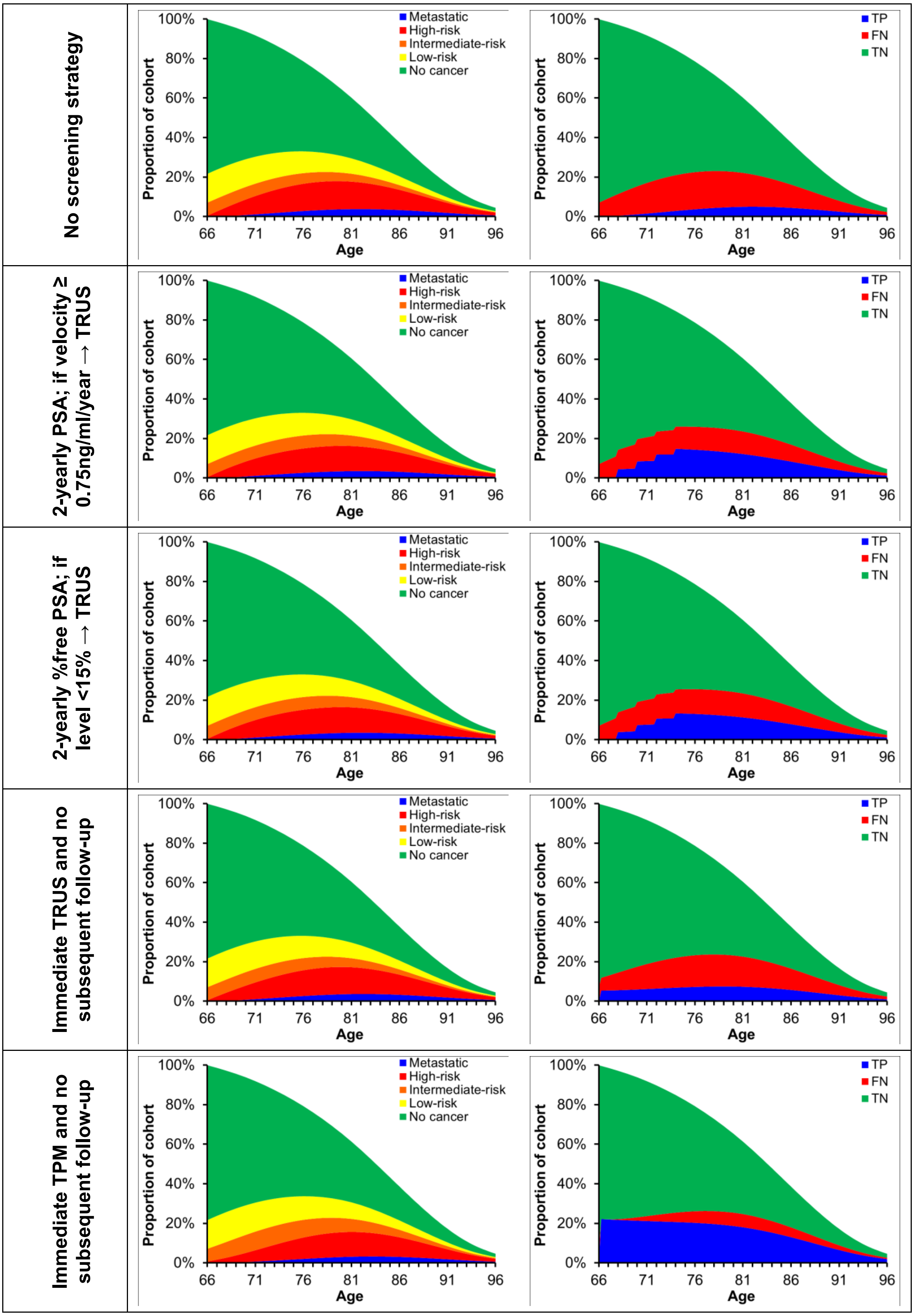


Figure HE15: Tracking the modelled cohort over 30 years, tracing the disease progression on the left hand, and reflecting the diagnosed cases overtime on the right hand for a given strategy

Incremental deterministic analysis

Table HE19 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, none of the strategies seems to be worthwhile. At a higher threshold, the strategy, where all candidates receive an immediate TRUS and no subsequent follow-up, seems optimal. Also, performing strategies that include a 2-yearly screening test using PSA velocity at a threshold of 0.75 ng/ml/year or the % free PSA test at a threshold of 15% seems to be optimal.

Table HE19: Base-case deterministic cost-utility results (excluding TPM) for people with Likert <3 and two biopsies

	Absolute		Incremental		
Strategy	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£981	9.305			
TRUS everyone	£1,744	9.335	£764	0.030	£25,489
2-yearly %free PSA; if level <15% → TRUS	£2,223	9.352	£478	0.018	£26,988
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£2,386	9.358	£164	0.006	£27,013
1-yearly %free PSA; if level <15% → TRUS	£3,365	9.390	£979	0.032	£30,936
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£3,628	9.397	£263	0.007	£36,025
6-monthly %free PSA; if level <15% → TRUS	£4,876	9.426	£1,248	0.029	£43,392
6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£5,244	9.430	£368	0.004	£101,540
3-monthly %free PSA; if level <15% → TRUS	£7,065	9.444	£1,820	0.014	£125,963
3-monthly PCA3; if level ≥ 50 → TRUS	£10,206	9.448	£3,141	0.004	£768,180

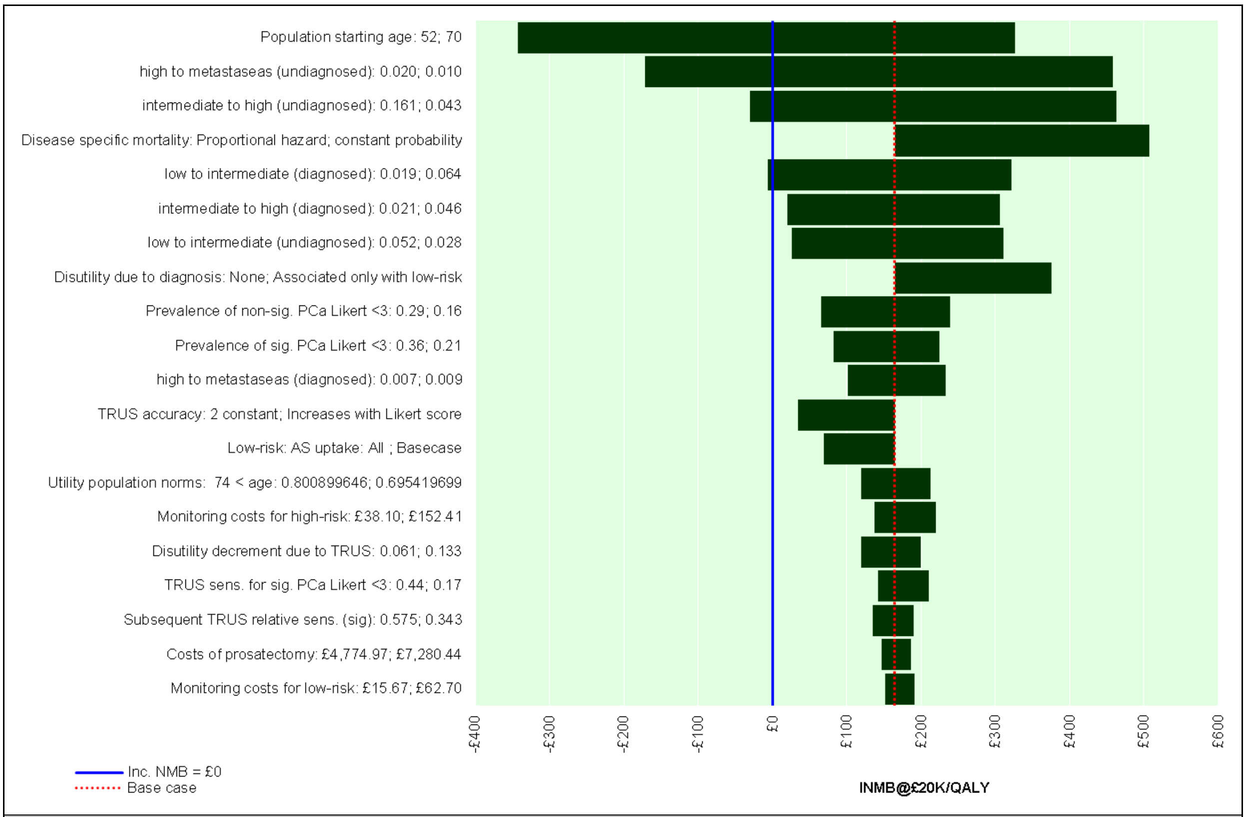
Table HE20shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The two strategies including a 2-yearly PSA velocity test at a threshold of 0.75ng/ml/year and a 2-yearly PSA density test at a threshold of 0.15 ng/ml/ml are ranked as the 1st and 2nd at cost-effectiveness thresholds of £30,000 per QALY, respectively. However, the number of unnecessary biopsies and the screening cost associated with these two tests are very similar.

Table HE20: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY (excluding TPM) for people with Likert <3 and two biopsies

Strategy	Life-years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
no screening	16.70	13.5%	0.32	£0	£783	£981	9.305	1	18
3-yearly DRE; if abnormal → TRUS	16.74	13.0%	0.60	£81	£996	£1,395	9.319	2	14
2-yearly DRE; if abnormal → TRUS	16.76	12.8%	0.70	£114	£1,073	£1,553	9.325	3	12
TRUS everyone	16.79	12.6%	1.24	£0	£1,151	£1,744	9.335	4	5
3-yearly %free PSA; if level <15% → TRUS	16.80	12.2%	1.10	£76	£1,299	£1,904	9.339	5	9
3-yearly DRE; if abnormal → mpMRI; if Likert ≥4 → TRUS	16.73	13.1%	0.25	£81	£942	£1,463	9.317	6	33
3-yearly PHI; if level ≥ 62 → TRUS	16.76	12.8%	0.58	£223	£1,058	£1,604	9.323	7	28
3-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.82	12.0%	1.32	£39	£1,377	£2,032	9.344	8	7
2-yearly DRE; if abnormal → mpMRI; if Likert ≥4 → TRUS	16.75	12.9%	0.30	£114	£1,011	£1,627	9.323	9	32
2-yearly %free PSA; if level <15% → TRUS	16.84	11.8%	1.39	£106	£1,462	£2,223	9.352	10	3
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.86	11.5%	1.70	£55	£1,558	£2,386	9.358	14	1
2-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.87	11.4%	1.81	£55	£1,594	£2,467	9.361	16	2
1-yearly %free PSA; if level <15% → TRUS	16.96	10.4%	2.60	£226	£1,996	£3,365	9.390	41	4
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.98	10.1%	3.26	£116	£2,123	£3,628	9.397	52	6
3-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.83	11.9%	1.40	£39	£1,408	£2,094	9.346	11	8
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.99	10.0%	3.49	£115	£2,169	£3,763	9.400	58	10

One-way sensitivity analysis

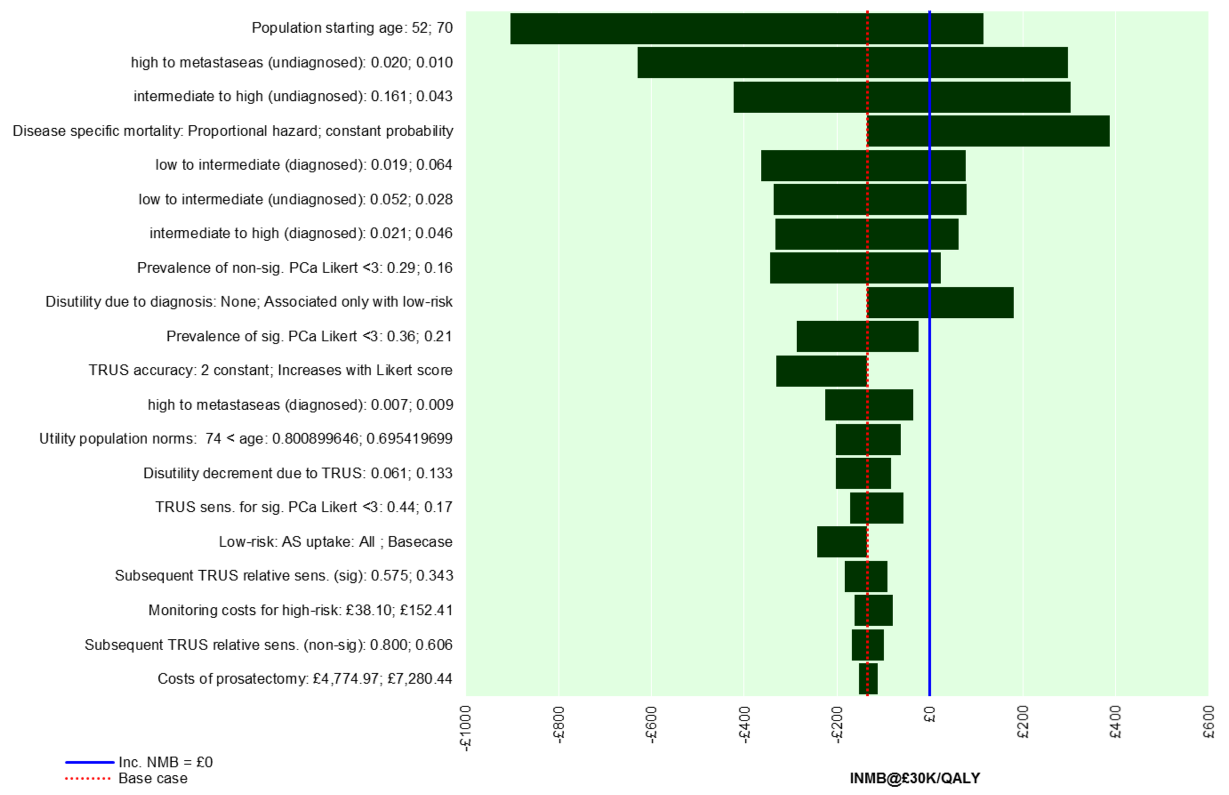
Figure HE16 shows the impact of changing the value of a parameter on the results of a pairwise comparison between “no screening strategy and the strategy where people receive an immediate TRUS biopsy and not followed-up subsequently. The strategy of “no screening” remains optimal unless the starting age is younger (52 years old), or the disease progression is faster, in particular, in the undiagnosed cases.



Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE16: One-way sensitivity analysis “no screening” vs “TRUS everyone” based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

In contrast, at a threshold of £30,000 per QALY, the strategy, where people receive an immediate TRUS biopsy and not followed-up subsequently, is more cost-effective than “no screening”, unless the starting age is older (70) and the disease progression is slower, Figure HE17. The figure also shows that “no screening” becomes more cost-effective, if the prevalence of clinically non-significant prostate cancer is lower (the lower bound of the 95% confidence interval) or a disutility of 0.05 is applied on people with clinically non-significant cancer once diagnosed.

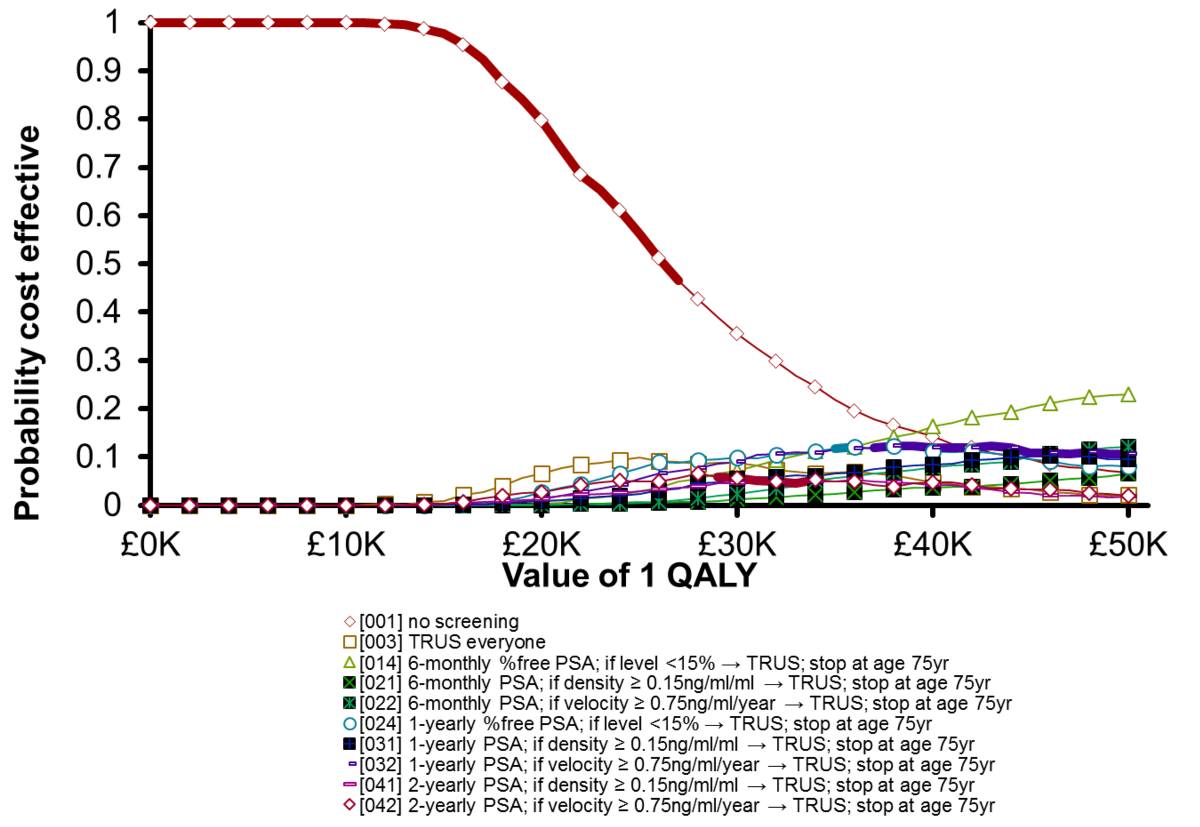


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE17: One-way sensitivity analysis “no screening” vs “TRUS everyone” based on the incremental net monetary benefits at cost-effectiveness threshold of £30,000 per QALY

Probabilistic results

Figure HE18 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY, excluding strategies with TPM. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. The probability of the strategy including a 2-yearly PSA velocity test at a threshold of 0.75 ng/ml/year being cost-effective at a threshold of £30,000 per QALY is about 5%. At a cost-effectiveness threshold between £40,000 and £50,000 per QALY, the same strategy applied yearly instead of 2-yearly seems to be cost effective with a probability of about 10%.



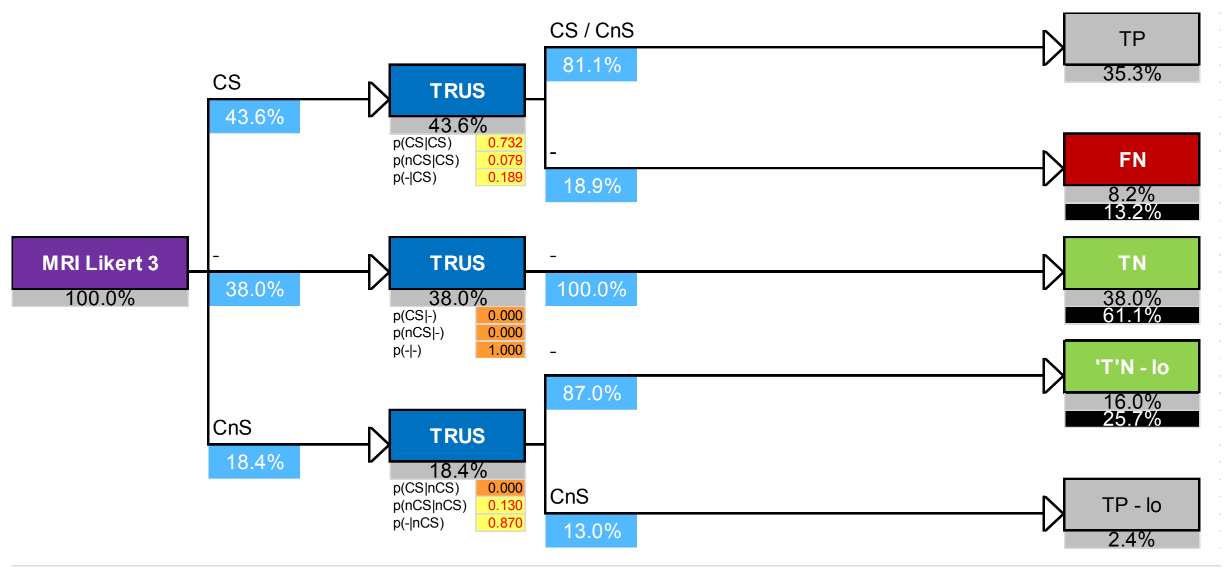
Bold line indicates cost effectiveness acceptability frontier

Figure HE18: Cost-effectiveness acceptability curve excluding TPM strategies

HE.33 MRI Likert 3; 1 biopsy

Baseline population

The population of interest here is people who received mpMRI with Likert score at 3 and 1 prostate biopsy (TRUS). Applying the prevalence obtained from PROMIS and the accuracy data of TRUS, influenced by the mpMRI, results in the baseline population distribution being 61.1%, 25.7% and 13.2% for people with truly no cancer, people with missed clinically non-significant cancer and people with missed clinically significant cancer, respectively, Figure HE19.



Bold line indicates Baseline population distribution (Likert 3 with one previous biopsy): Percentages in blue boxes indicate probabilities at each branch of the tree. Percentages in grey boxes indicate proportion of whole tested population at each stage. Percentages in black boxes indicate proportion of people receiving a negative diagnosis who fall into each category (note that the NPV of the algorithm is given by 1 – the proportion in the black box under 'FN'). Figures in yellow and orange boxes indicate conditional probabilities of each diagnosis, given true status. CS: Clinically significant; CnS: Clinically non-significant; FN: False negative CS disease; TN: true negative; 'T'N-lo: missed CnS disease; TP and TP-lo: Truly positive CS and CnS disease, respectively.

Figure HE19: The decision tree to derive the baseline population distribution (Likert 3 with 1 previous biopsy)

Model dynamics

Figure HE20 demonstrates the modelled cohort over 30 years. On the left side, it shows the disease development, starting as low-risk and then progressing to intermediate-, then to high-risk and then to metastatic disease. On the right side, it shows the performance of diagnostics capturing the disease within people misclassified as false negative. This is shown for the least intensive "no screening" strategy, at the top, where people receive prostate biopsy only if they develop symptoms, to the most invasive strategy at the bottom, where all candidates receive an immediate TPM and not followed-up subsequently. In between, the impact of applying 3 follow-up strategies on disease progression and their performance in identifying missed disease is demonstrated over time. This is shown for: the strategy where people receive a 2-yearly PSA test; if density ≥0.15 ng/ml/ml, they are directed to TRUS biopsy, the strategy where people receive a yearly PSA test; if velocity ≥0.75 ng/ml/year, they are directed to TRUS biopsy and the strategy where people receive an immediate TRUS and they are not followed-up subsequently.

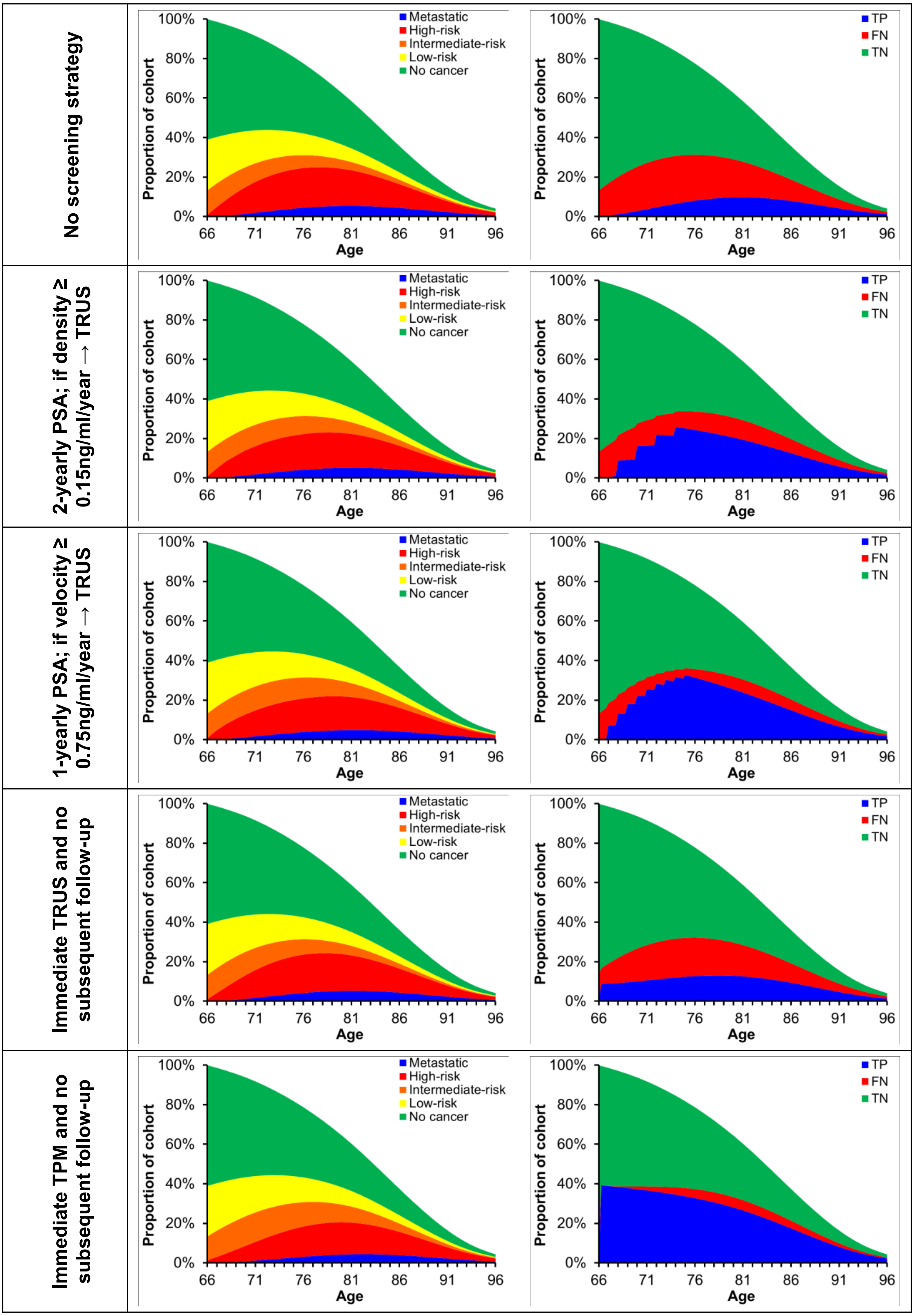


Figure HE20: Tracking the modelled cohort over 30 years, tracing the disease progression on the left hand, and reflecting the diagnosed cases overtime on the right hand for a given strategy

Table HE21: Base-case deterministic cost-utility results (excluding TPM) for people with Likert 3 and one biopsy

Strategy	Absolute		Incremental		
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£1,683	9.124			
TRUS everyone	£2,591	9.187	£908	0.063	£14,382
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£3,496	9.243	£905	0.056	£16,240
2-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	£3,585	9.247	£89	0.005	£18,776
1-yearly %free PSA; if level <15% → TRUS	£4,513	9.292	£928	0.045	£20,718
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£4,768	9.304	£255	0.012	£21,946
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	£4,896	9.308	£128	0.004	£31,525
6-monthly %free PSA; if level <15% → TRUS	£5,972	9.337	£1,076	0.029	£36,719
6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£6,315	9.342	£343	0.005	£67,716
6-monthly PSA; if density ≥ 0.15ng/ml/ml → TRUS	£6,505	9.344	£190	0.002	£124,020
3-monthly %free PSA; if level <15% → TRUS	£8,092	9.356	£1,587	0.012	£132,139
3-monthly PCA3; if level ≥ 50 → TRUS	£10,914	9.359	£2,822	0.003	£827,094

Incremental deterministic analysis

Table HE21 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategies, including 2-yearly PSA screening tests, using density at a threshold of 0.15 ng/ml/ml or velocity at a threshold of 0.75 ng/ml/year, seem to be optimal. At a higher cost-effectiveness threshold (£30,000 per QALY), the same strategies, applied yearly instead of 2-yearly seem optimal.

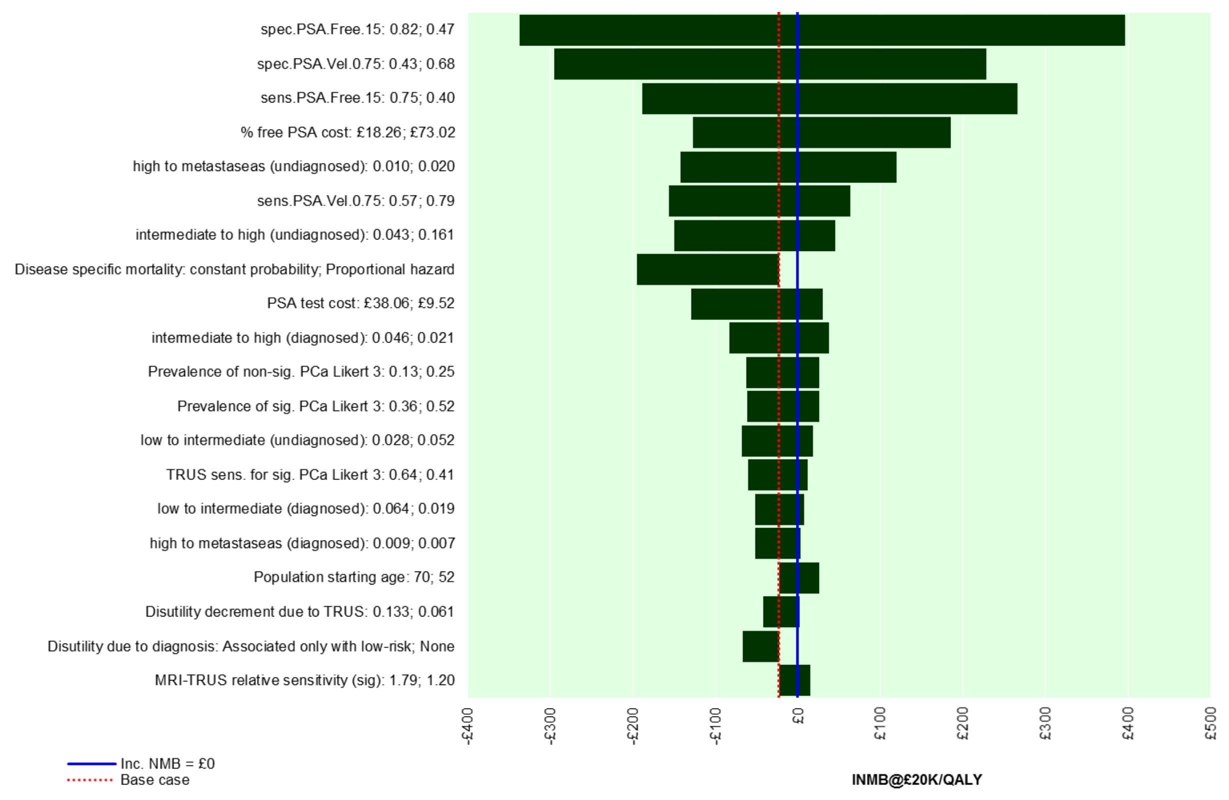
Table HE22 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The two strategies including a 2-yearly PSA density test at a threshold of 0.15 ng/ml/ml and a 2-yearly PSA velocity test at a threshold of 0.75ng/ml/year are ranked as the 1st and 2nd at cost-effectiveness thresholds of £20,000 per QALY, respectively. The same strategies applied yearly have the same rank at a cost-effectiveness threshold of £30,000 per QALY, and the two strategies have very similar number of the associated unnecessary biopsies, screening costs and treatments costs.

Table HE22: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY (excluding TPM) for people with Likert 3 and one biopsy

Strategy	Life-years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
2-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.62	14.2%	1.66	£52	£2,673	£3,585	9.247	1	13
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.61	14.3%	1.55	£52	£2,626	£3,496	9.243	2	17
1-yearly %free PSA; if level <15% → TRUS	16.74	13.0%	2.48	£208	£3,099	£4,513	9.292	3	3
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.78	12.6%	3.07	£106	£3,224	£4,768	9.304	4	1
2-yearly %free PSA; if level <15% → TRUS	16.58	14.7%	1.28	£100	£2,501	£3,305	9.230	5	20
2-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	16.68	13.6%	2.34	£50	£2,872	£4,060	9.266	6	8
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.79	12.5%	3.29	£106	£3,267	£4,896	9.308	7	2
2-yearly PSA; if level ≥ 6ng/ml → TRUS	16.65	13.9%	2.14	£51	£2,782	£3,886	9.257	8	14
2-yearly PSA; if density ≥ 0.09ng/ml/ml → TRUS	16.69	13.6%	2.49	£50	£2,900	£4,148	9.269	9	9
3-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.55	14.8%	1.25	£37	£2,454	£3,173	9.220	10	28
6-monthly %free PSA; if level <15% → TRUS	16.87	11.6%	4.54	£387	£3,567	£5,972	9.337	52	4
1-yearly PSA; if level ≥ 6ng/ml → TRUS	16.82	12.2%	4.34	£104	£3,364	£5,400	9.314	37	5
1-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	16.84	12.0%	4.78	£103	£3,439	£5,642	9.321	54	6
6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.90	11.4%	5.66	£198	£3,663	£6,315	9.342	80	7
1-yearly PHI; if level ≥ 35 → TRUS	16.81	12.3%	3.53	£581	£3,337	£5,538	9.315	55	10

One-way sensitivity analysis

Figure HE21 shows the impact of changing the value of a parameter on the results of a pairwise comparison between the strategy including a yearly PSA velocity test at a threshold of 0.75 ng/ml/year and the one including a yearly % free PSA test at a threshold of 15%. It shows that given the 95% confidence interval of the two tests' accuracy data, there is not any significant difference between the two tests' performance. The tests' costs, in particular % free PSA test, have an impact as well.

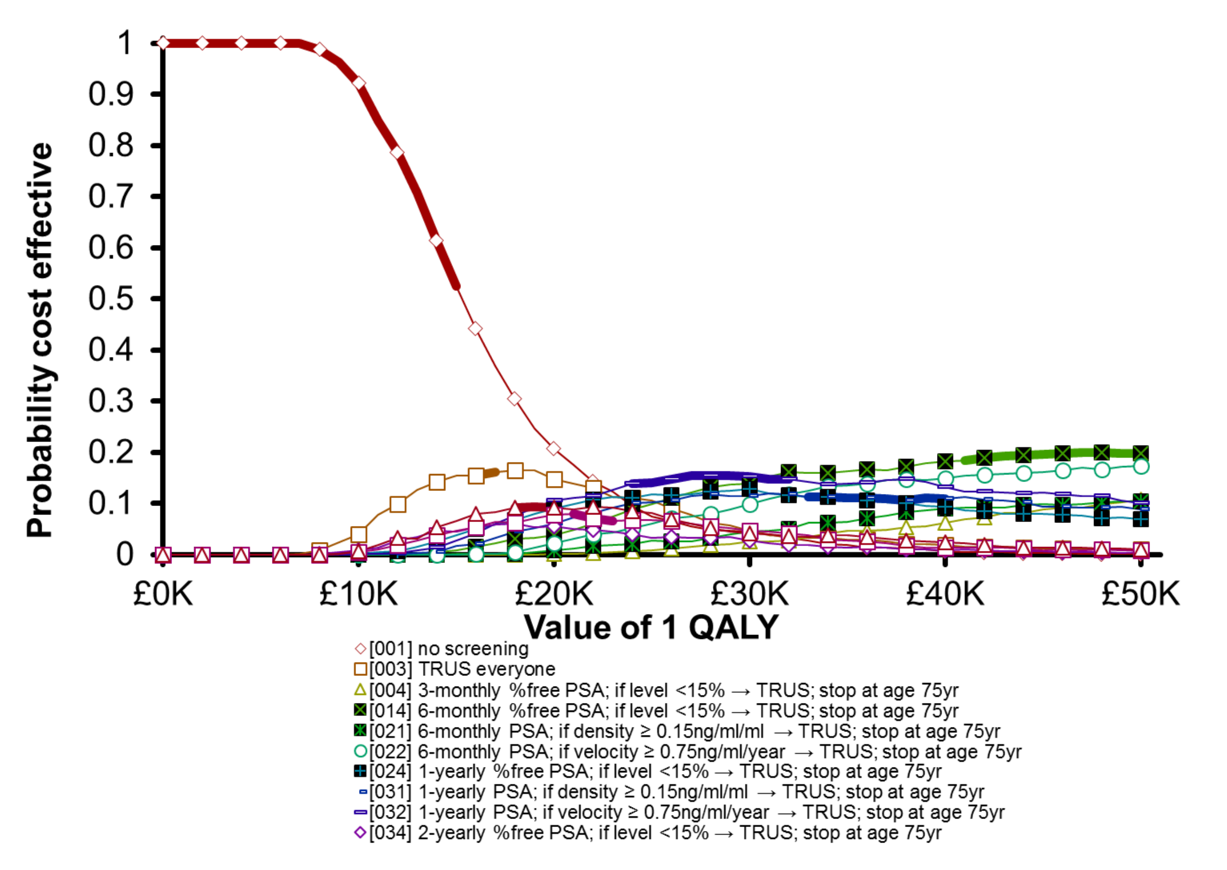


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE21: One-way sensitivity analysis "1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS" vs "1-yearly %free PSA; if level <15% → TRUS" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Probabilistic results

Figure HE22 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY, excluding strategies with TPM. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. The probability of the strategy including a yearly PSA velocity test at a threshold of 0.75 ng/ml/year being cost-effective at a threshold between £20,000 and £30,000 per QALY is just less than 20%. At a cost-effectiveness threshold between £40,000 and £50,000 per QALY, the strategy including 6-monthly % free PSA test at a threshold of 15% seems to be cost effective with a probability of 20%.



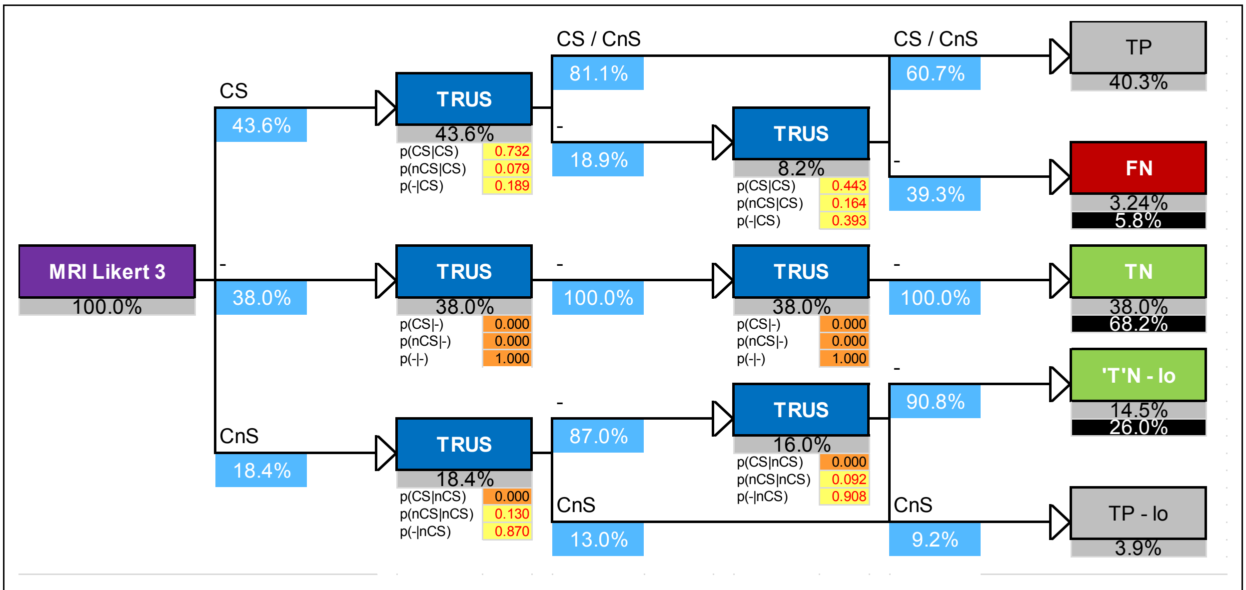
Bold line indicates cost effectiveness acceptability frontier

Figure HE22: Cost-effectiveness acceptability curve excluding TPM strategies

HE.35 MRI Likert 3; 2 biopsies

Baseline population

The population of interest here is people who received mpMRI with Likert score at 3 and 2 prostate biopsies (TRUS). Applying the prevalence obtained from PROMIS and the accuracy data of TRUS, influenced by the mpMRI, results in the baseline population distribution being 68.2%, 26.0% and 5.8% for people with truly no cancer, people with missed clinically non-significant cancer and people with missed clinically significant cancer, respectively, Figure HE23.



Bold line indicates Baseline population distribution (Likert 3 with two previous biopsies): Percentages in blue boxes indicate probabilities at each branch of the tree. Percentages in grey boxes indicate proportion of whole tested population at each stage. Percentages in black boxes indicate proportion of people receiving a negative diagnosis who fall into each category (note that the NPV of the algorithm is given by 1 – the proportion in the black box under 'FN'). Figures in yellow and orange boxes indicate conditional probabilities of each diagnosis, given true status. CS: Clinically significant; CnS: Clinically non-significant; FN: False negative CS disease; TN: true negative; 'T'N-lo: missed CnS disease; TP and TP-lo: Truly positive CS and CnS disease, respectively.

Figure HE23: The decision tree to derive the baseline population distribution (Likert 3 with 2 previous biopsies)

Model dynamics

Figure HE24 demonstrates the modelled cohort over 30 years. On the left side, it shows the disease development, starting as low-risk and then progressing to intermediate-, then to high-risk and then to metastatic disease. On the right side, it shows the performance of diagnostics capturing the disease within people misclassified as false negative. This is shown for the least intensive "no screening" strategy, at the top, where people receive prostate biopsy only if they develop symptoms, to the most invasive strategy at the bottom, where all candidates receive an immediate TPM and not followed-up subsequently. In between, the impact of applying 3 follow-up strategies on disease progression and their performance in identifying missed disease is demonstrated over time. This is shown for: the strategy where people receive a 2-yearly PSA test; if density ≥0.15 ng/ml/ml, they are directed to TRUS biopsy, the strategy where people receive a 6-monthly % free PSA test; if level <15%, they are directed to TRUS biopsy and the strategy where people receive an immediate TRUS and they are not followed-up subsequently.

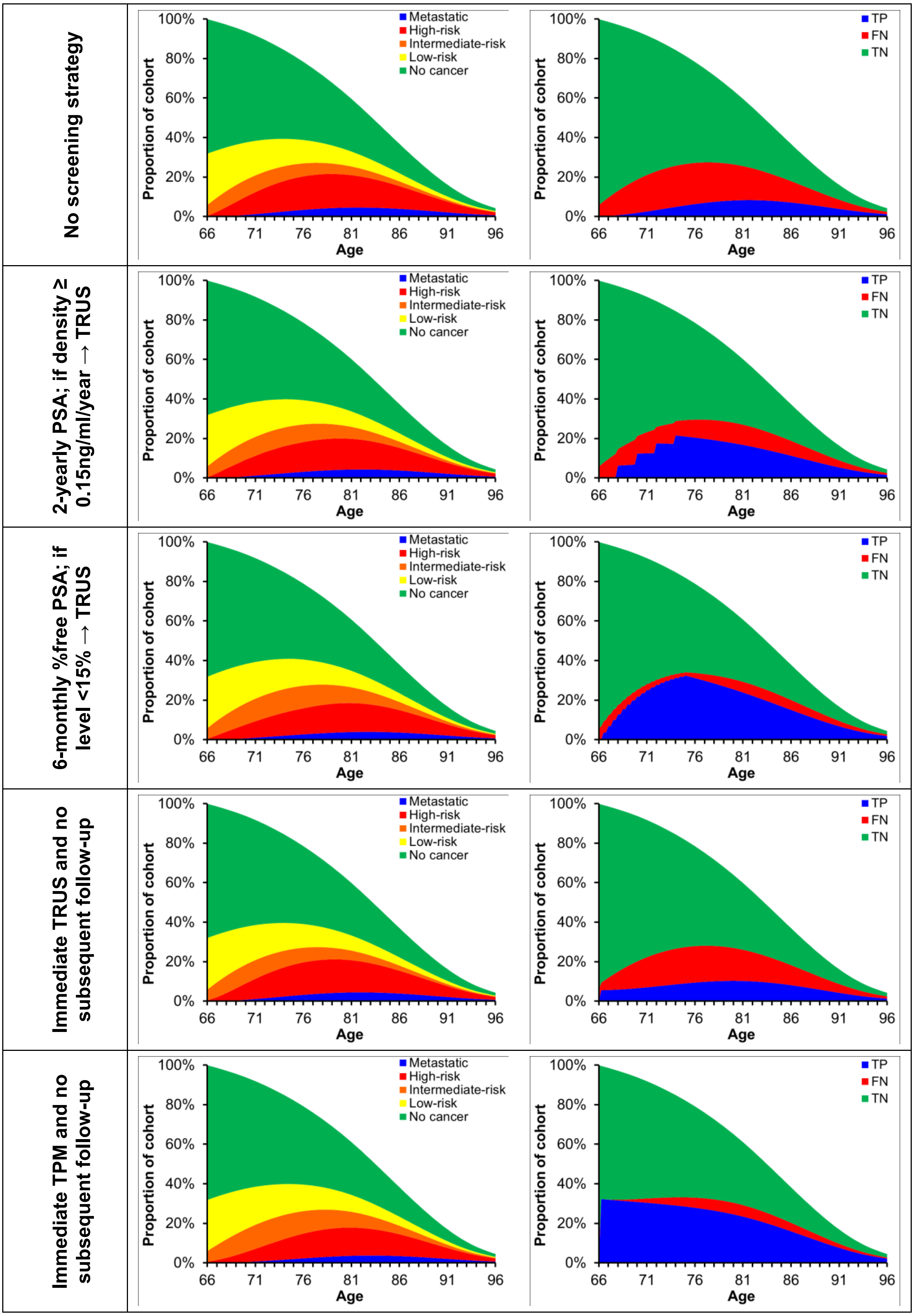


Figure HE24: Tracking the modelled cohort over 30 years, tracing the disease progression on the left hand, and reflecting the diagnosed cases overtime on the right hand for a given strategy

Incremental deterministic analysis

Table HE23 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, including 2-yearly PSA screening tests, using velocity at a threshold of 0.75 ng/ml/year, seem to be optimal. At a higher cost-effectiveness threshold (£30,000 per QALY), the same strategy, applied yearly instead of 2-yearly seems optimal.

Table HE23: Base-case deterministic cost-utility results (excluding TPM) for people with Likert 3 and two biopsies

Strategy	Absolute		Incremental		
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£1,396	9.248			
3-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£2,671	9.322	£1,275	0.074	£17,160
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£3,025	9.341	£354	0.019	£18,427
2-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	£3,110	9.345	£85	0.004	£22,776
1-yearly %free PSA; if level <15% → TRUS	£4,011	9.380	£901	0.035	£26,071
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£4,269	9.388	£258	0.009	£29,311
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	£4,401	9.391	£132	0.003	£42,781
6-monthly %free PSA; if level <15% → TRUS	£5,512	9.413	£1,111	0.021	£51,873
6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£5,882	9.416	£371	0.003	£137,248
3-monthly %free PSA; if level <15% → TRUS	£7,794	9.423	£1,912	0.007	£268,630
3-monthly PCA3; if level ≥ 50 → TRUS	£10,857	9.425	£3,063	0.003	£1,130,820

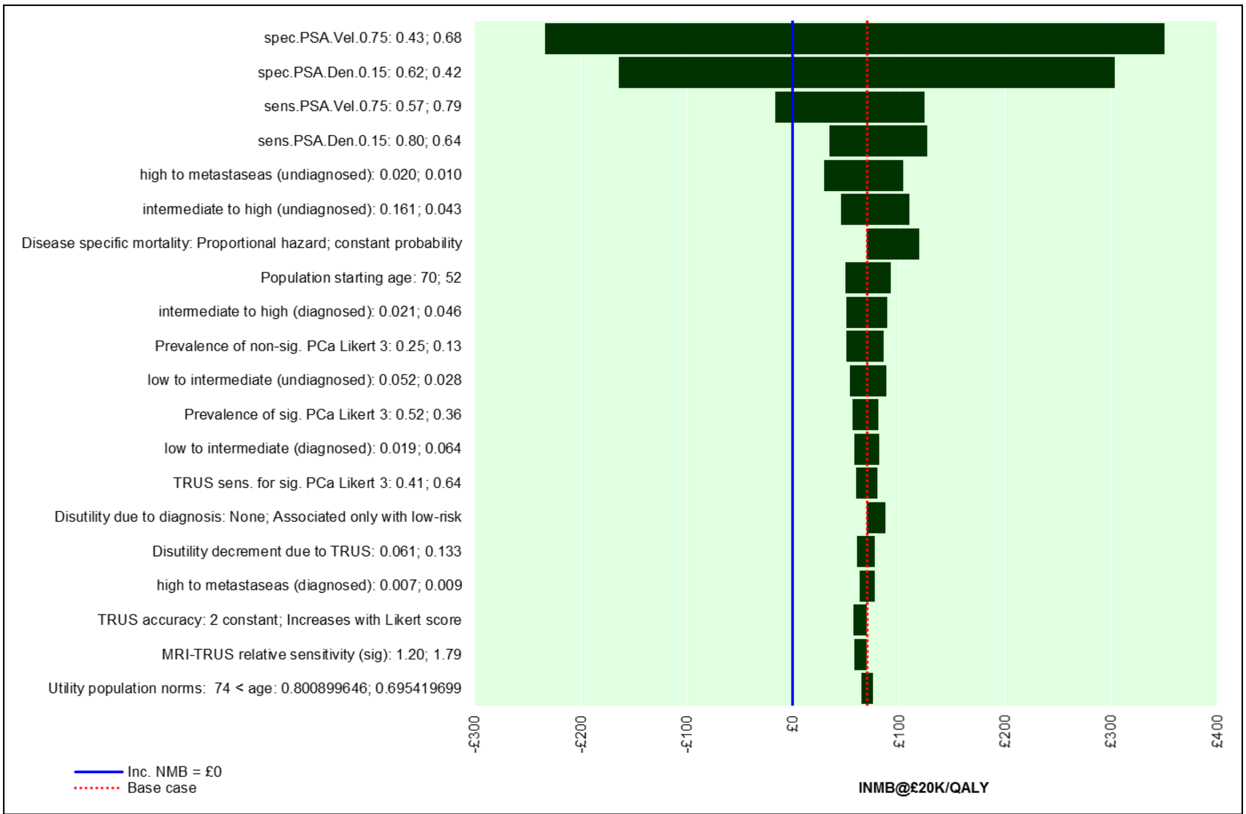
Table HE24 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The strategies including screening tests using PSA density at a threshold of 0.15 ng/ml/ml, PSA velocity at a threshold of 0.75ng/ml/year and % free PSA at a threshold of 15% seem to be optimal if applied 2-yearly or yearly at the cost-effectiveness thresholds of £20,000 or £30,000 per QALY, respectively.

Table HE24: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY (excluding TPM) for people with Likert 3 and two biopsies

Strategy	Life-years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.82	12.3%	1.70	£54	£2,145	£3,025	9.341	1	5
2-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.83	12.2%	1.81	£53	£2,185	£3,110	9.345	2	4
2-yearly %free PSA; if level <15% → TRUS	16.79	12.6%	1.40	£104	£2,039	£2,847	9.331	3	9
3-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.77	12.7%	1.30	£38	£1,980	£2,671	9.322	4	16
3-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.78	12.6%	1.37	£38	£2,017	£2,740	9.325	5	14
3-yearly %free PSA; if level <15% → TRUS	16.75	13.0%	1.08	£74	£1,884	£2,523	9.313	6	21
3-yearly PSA; if level ≥ 6ng/ml → TRUS	16.80	12.4%	1.75	£38	£2,106	£2,977	9.333	7	15
3-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	16.82	12.2%	1.92	£38	£2,181	£3,118	9.340	8	10
3-yearly PSA; if density ≥ 0.09ng/ml/ml → TRUS	16.83	12.1%	2.04	£38	£2,205	£3,188	9.342	9	12
2-yearly PSA; if level ≥ 6ng/ml → TRUS	16.85	11.9%	2.34	£53	£2,278	£3,412	9.352	10	8
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.96	10.8%	3.36	£112	£2,667	£4,269	9.388	29	1
1-yearly %free PSA; if level <15% → TRUS	16.93	11.1%	2.71	£219	£2,555	£4,011	9.380	16	2
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.97	10.7%	3.60	£112	£2,706	£4,401	9.391	36	3
2-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	16.88	11.7%	2.57	£53	£2,355	£3,580	9.360	14	6
2-yearly PSA; if density ≥ 0.09ng/ml/ml → TRUS	16.88	11.6%	2.74	£52	£2,379	£3,670	9.361	19	7

One-way sensitivity analysis

Figure HE25 shows the impact of changing the value of a parameter on the results of a pairwise comparison between the strategy including a yearly PSA velocity test at a threshold of 0.75 ng/ml/year and the one including a yearly PSA density test at a threshold of 0.15 ng/ml/ml. It shows that given the 95% confidence interval of the two tests' accuracy data, there is not any significant difference between the two tests' performance.

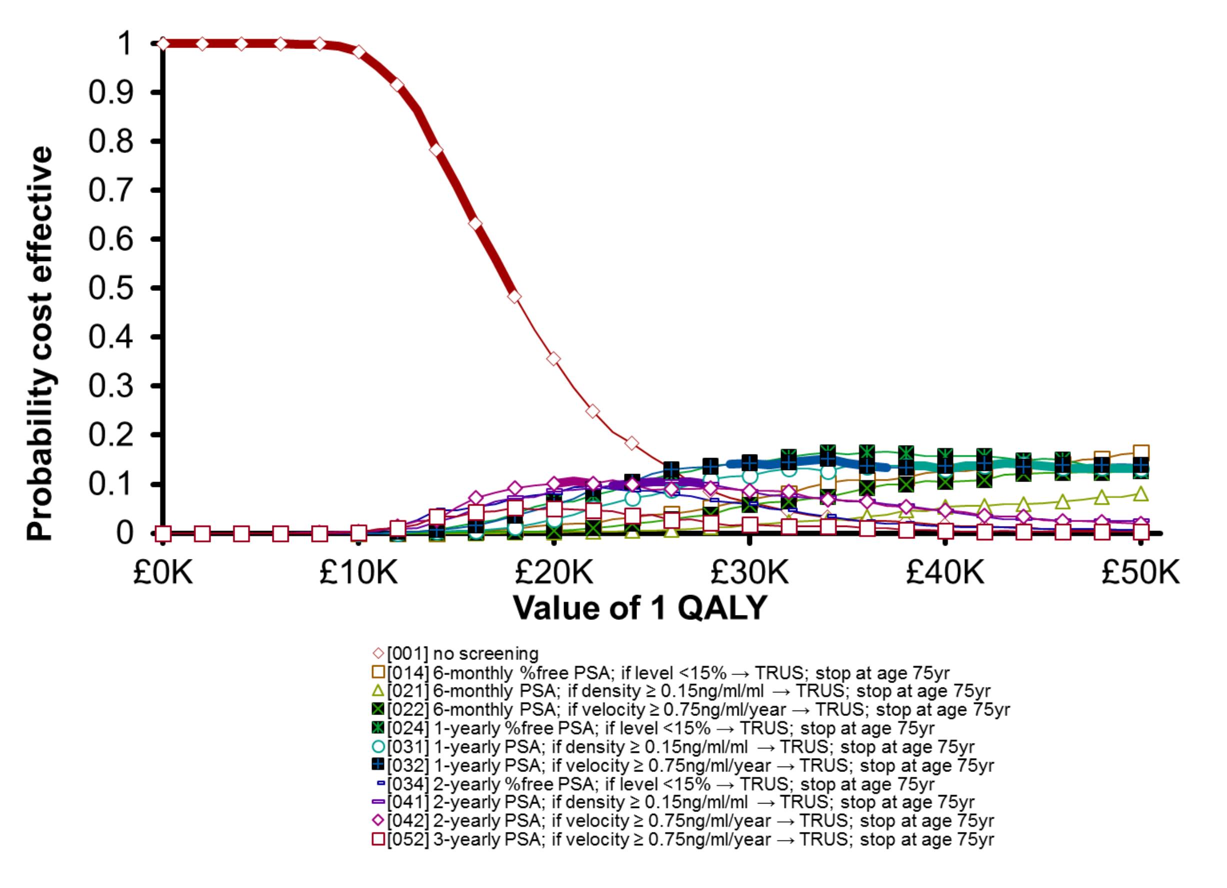


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE25: One-way sensitivity analysis "1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS" vs "1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Probabilistic results

Figure HE26 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY, excluding strategies with TPM. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. The probability of the strategy including a 2-yearly PSA velocity test at a threshold of 0.75 ng/ml/year or 2-yearly PSA density test at a threshold of 0.15 ng/ml/ml, being cost-effective at a threshold between £20,000 and £30,000 per QALY is about 10%.



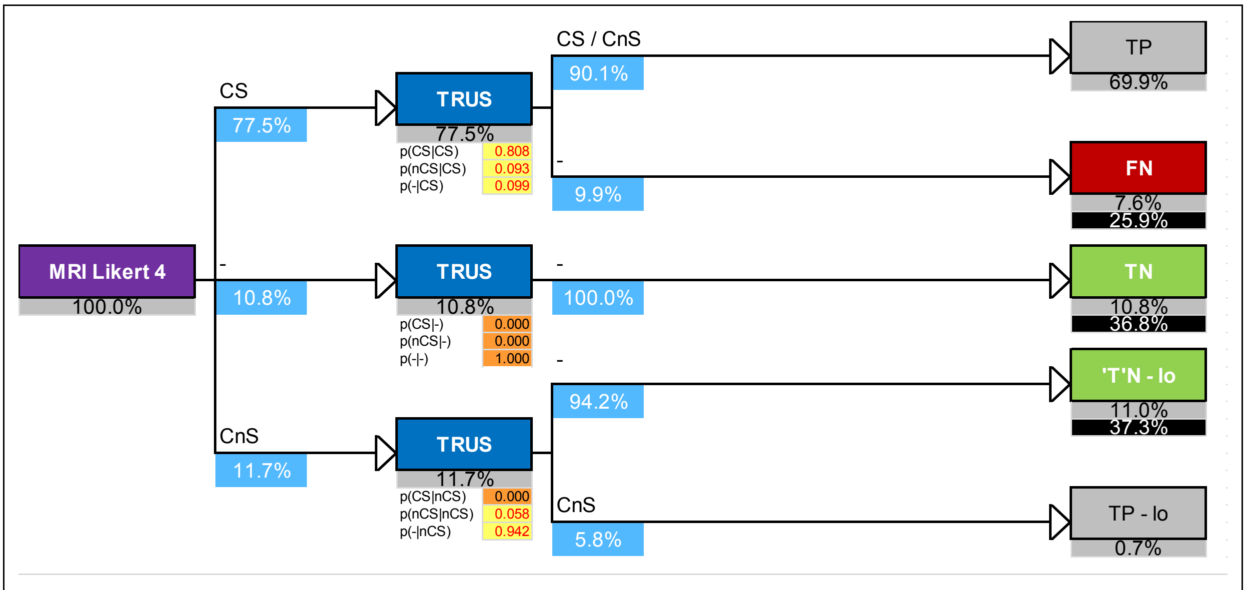
Bold line indicates cost effectiveness acceptability frontier

Figure HE26: Cost-effectiveness acceptability curve excluding TPM strategies

HE.36 MRI Likert 4; 1 biopsy

Baseline population

The population of interest here is people who received mpMRI with Likert score at 4 and 1 prostate biopsy (TRUS). Applying the prevalence obtained from PROMIS and the accuracy data of TRUS, influenced by the mpMRI, results in the baseline population distribution being 36.8%, 37.3% and 25.9% for people with truly no cancer, people with missed clinically non-significant cancer and people with missed clinically significant cancer, respectively, Figure HE27.



Bold line indicates Baseline population distribution (Likert 4 with one previous biopsy): Percentages in blue boxes indicate probabilities at each branch of the tree. Percentages in grey boxes indicate proportion of whole tested population at each stage. Percentages in black boxes indicate proportion of people receiving a negative diagnosis who fall into each category (note that the NPV of the algorithm is given by 1 – the proportion in the black box under 'FN'). Figures in yellow and orange boxes indicate conditional probabilities of each diagnosis, given true status. CS: Clinically significant; CnS: Clinically non-significant; FN: False negative CS disease; TN: true negative; 'T'N-lo: missed CnS disease; TP and TP-lo: Truly positive CS and CnS disease, respectively.

Figure HE27: The decision tree to derive the baseline population distribution (Likert 4 with 1 previous biopsy)

Model dynamics

Figure HE28 demonstrates the modelled cohort over 30 years. On the left side, it shows the disease development, starting as low-risk and then progressing to intermediate-, then to high-risk and then to metastatic disease. On the right side, it shows the performance of diagnostics capturing the disease within people misclassified as false negative. This is shown for the least intensive "no screening" strategy, at the top, where people receive prostate biopsy only if they develop symptoms, to the most invasive strategy at the bottom, where all candidates receive an immediate TPM and not followed-up subsequently. In between, the impact of applying 3 follow-up strategies on disease progression and their performance in identifying missed disease is demonstrated over time. This is shown for: the strategy where people receive a yearly PSA test; if density ≥0.15 ng/ml/ml, they are directed to TRUS biopsy, the strategy where people receive a 6-monthly PSA test; if velocity ≥0.75 ng/ml/year, they are directed to TRUS biopsy and the strategy where people receive an immediate TRUS and they are not followed-up subsequently.

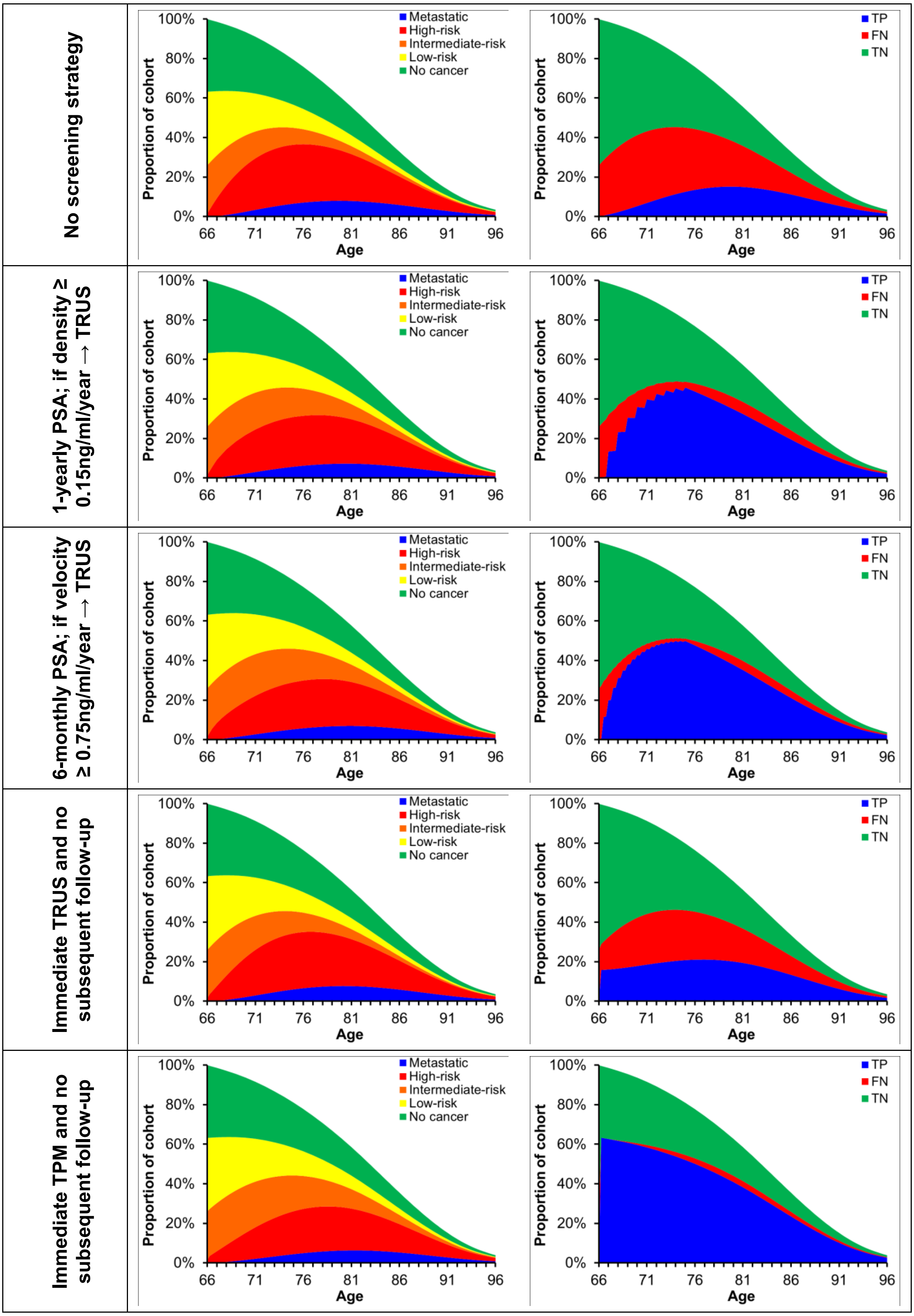


Figure HE28: Tracking the modelled cohort over 30 years, tracing the disease progression on the left hand, and reflecting the diagnosed cases overtime on the right hand for a given strategy

Incremental deterministic analysis

Table HE25 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, including a yearly PSA screening tests, using velocity at a threshold of 0.75 ng/ml/year, seem to be optimal. At a higher cost-effectiveness threshold (£30,000 per QALY), the same strategy, applied 6-monthly instead of yearly seems optimal.

Table HE25: Base-case deterministic cost-utility results (excluding TPM) for people with Likert 4 and one biopsy

Strategy	Absolute		Incremental		
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£2,530	8.818			
TRUS everyone	£3,767	8.945	£1,237	0.127	£9,748
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£6,154	9.106	£2,388	0.161	£14,865
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	£6,268	9.112	£114	0.006	£18,422
6-monthly %free PSA; if level <15% → TRUS	£7,286	9.154	£1,018	0.042	£24,346
6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£7,558	9.164	£272	0.010	£27,370
6-monthly PSA; if density ≥ 0.15ng/ml/ml → TRUS	£7,713	9.167	£155	0.003	£48,636
3-monthly %free PSA; if level <15% → TRUS	£9,186	9.187	£1,473	0.020	£72,320
3-monthly PCA3; if level ≥ 50 → TRUS	£11,545	9.192	£2,359	0.004	£556,406

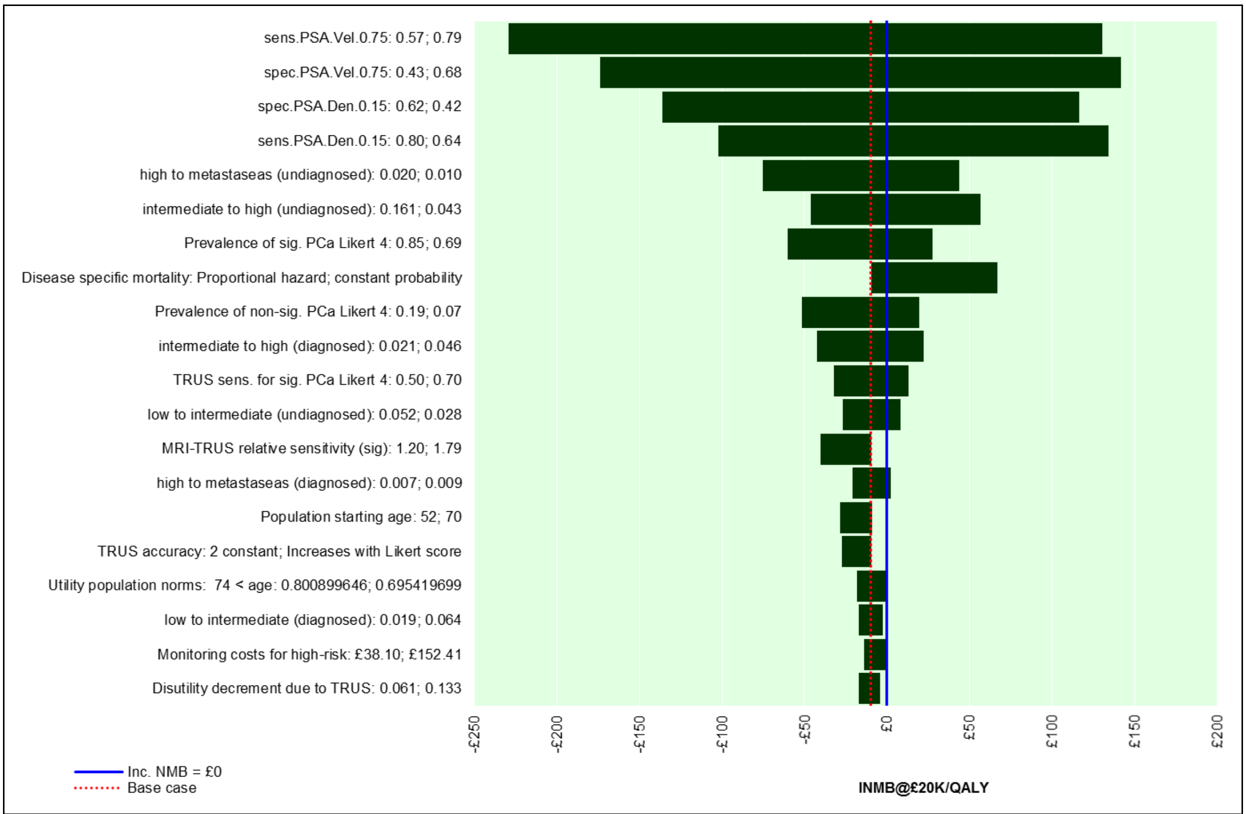
Table HE26 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The strategies including screening tests using PSA density at a threshold of 0.15 ng/ml/ml, PSA velocity at a threshold of 0.75ng/ml/year and % free PSA at a threshold of 15% seem to be optimal if applied yearly or 6-monthly at the cost-effectiveness thresholds of £20,000 or £30,000 per QALY, respectively. However, the number of associated unnecessary biopsies and screening costs increased significantly.

Table HE26: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY (excluding TPM) for people with Likert 4 and one biopsy

Strategy	Life-years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.36	17.2%	2.70	£91	£4,762	£6,268	9.112	1	6
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.34	17.4%	2.53	£91	£4,715	£6,154	9.106	2	8
1-yearly %free PSA; if level <15% → TRUS	16.29	17.8%	2.08	£180	£4,575	£5,923	9.088	3	12
1-yearly PSA; if level ≥ 6ng/ml → TRUS	16.39	16.9%	3.43	£88	£4,865	£6,654	9.124	4	7
1-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	16.42	16.6%	3.77	£87	£4,942	£6,865	9.134	5	4
6-monthly %free PSA; if level <15% → TRUS	16.47	16.2%	3.91	£324	£5,062	£7,286	9.154	6	2
1-yearly PSA; if density ≥ 0.09ng/ml/ml → TRUS	16.43	16.6%	4.00	£86	£4,965	£6,976	9.136	7	5
6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.50	15.9%	4.77	£164	£5,158	£7,558	9.164	8	1
2-yearly PSA; if density ≥ 0.09ng/ml/ml → TRUS	16.22	18.5%	1.92	£45	£4,367	£5,501	9.057	9	19
2-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	16.21	18.6%	1.82	£45	£4,332	£5,424	9.053	10	20
6-monthly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.51	15.8%	5.09	£163	£5,190	£7,713	9.167	11	3
1-yearly PHI; if level ≥ 35 → TRUS	16.38	17.0%	2.91	£495	£4,836	£6,833	9.122	12	9
3-monthly DRE; if abnormal → TRUS	16.40	16.9%	2.97	£711	£4,868	£7,111	9.131	14	10

One-way sensitivity analysis

Figure HE29 shows the impact of changing the value of a parameter on the results of a pairwise comparison between the strategy including a yearly PSA velocity test at a threshold of 0.75 ng/ml/year and the one including a yearly PSA density test at a threshold of 0.15 ng/ml/ml. It shows that given the 95% confidence interval of the two tests' accuracy data, there is not any significant difference between the two tests' performance.

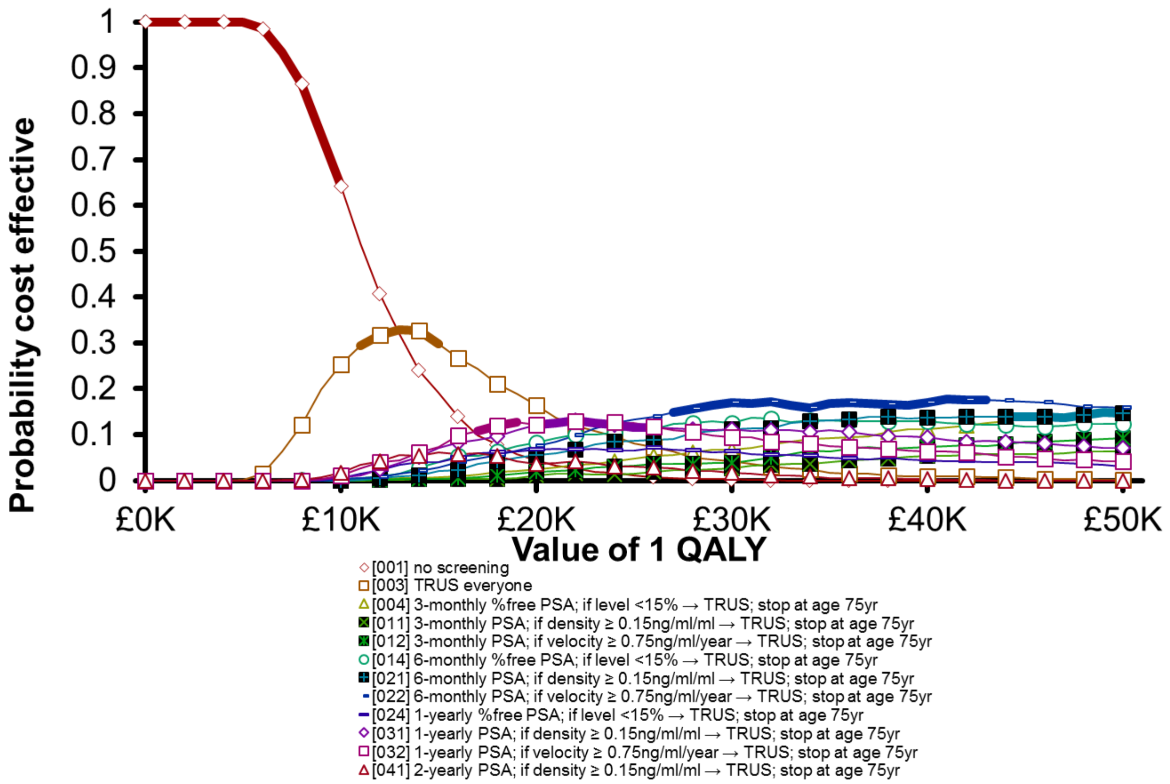


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE29: One-way sensitivity analysis "1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS" vs "1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Probabilistic results

Figure HE30 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY, excluding strategies with TPM. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. At a cost-effectiveness threshold of £10,000 per QALY, the strategy where people receive an immediate TRUS seems optimal with a probability of 30%. The probability of the strategy including a yearly PSA velocity test at a threshold of 0.75 ng/ml/year or yearly PSA density test at a threshold of 0.15 ng/ml/ml, being cost-effective at a threshold of £20,000 per QALY is about 10%.



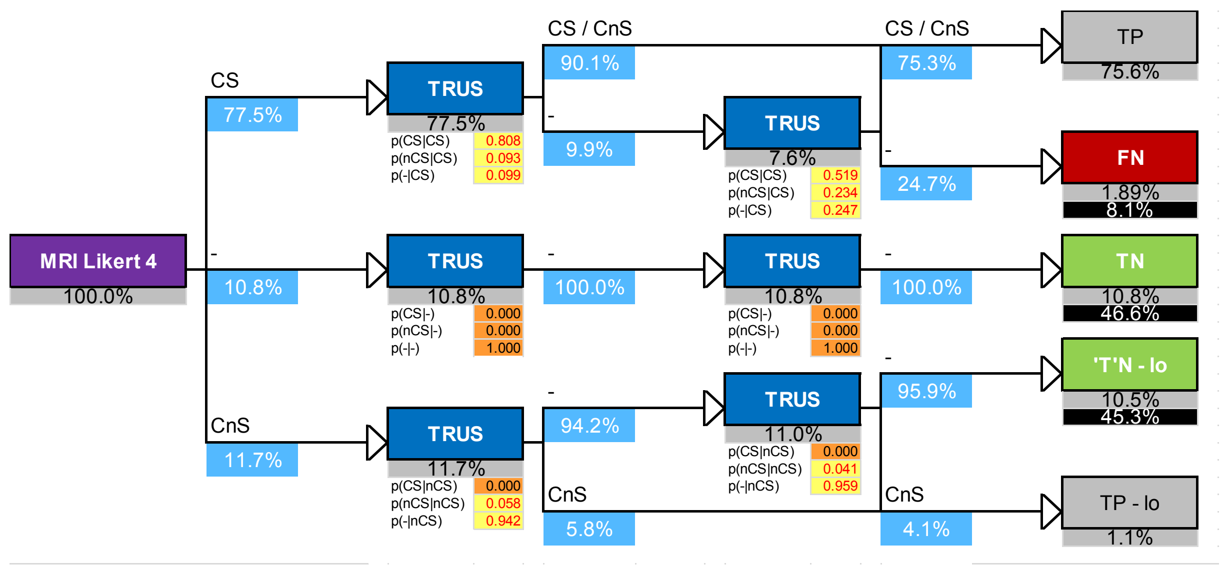
Bold line indicates cost effectiveness acceptability frontier

Figure HE30: Cost-effectiveness acceptability curve excluding TPM strategies

HE.37 MRI Likert 4; 2 biopsies

Baseline population

The population of interest here is people who received mpMRI with Likert score at 4 and 2 prostate biopsies (TRUS). Applying the prevalence obtained from PROMIS and the accuracy data of TRUS, influenced by the mpMRI, results in the baseline population distribution being 46.6%, 45.3% and 8.1% for people with truly no cancer, people with missed clinically non-significant cancer and people with missed clinically significant cancer, respectively, Figure HE31.



Bold line indicates Baseline population distribution (Likert 4 with two previous biopsies): Percentages in blue boxes indicate probabilities at each branch of the tree. Percentages in grey boxes indicate proportion of whole tested population at each stage. Percentages in black boxes indicate proportion of people receiving a negative diagnosis who fall into each category (note that the NPV of the algorithm is given by 1 – the proportion in the black box under 'FN'). Figures in yellow and orange boxes indicate conditional probabilities of each diagnosis, given true status. CS: Clinically significant; CnS: Clinically non-significant; FN: False negative CS disease; TN: true negative; 'T'N-lo: missed CnS disease; TP and TP-lo: Truly positive CS and CnS disease, respectively.

Figure HE31: The decision tree to derive the baseline population distribution (Likert 4 with 2 previous biopsies)

Model dynamics

Figure HE32 demonstrates the modelled cohort over 30 years. On the left side, it shows the disease development, starting as low-risk and then progressing to intermediate-, then to high-risk and then to metastatic disease. On the right side, it shows the performance of diagnostics capturing the disease within people misclassified as false negative. This is shown for the least intensive "no screening" strategy, at the top, where people receive prostate biopsy only if they develop symptoms, to the most invasive strategy at the bottom, where all candidates receive an immediate TPM and not followed-up subsequently. In between, the impact of applying 3 follow-up strategies on disease progression and their performance in identifying missed disease is demonstrated over time. This is shown for: the strategy where people receive a 2-yearly PSA test; if density ≥0.12 ng/ml/ml, they are directed to TRUS biopsy, the strategy where people receive a yearly PSA test; if density ≥0.15 ng/ml/ml, they are directed to TRUS biopsy and the strategy where people receive an immediate TRUS and they are not followed-up subsequently.

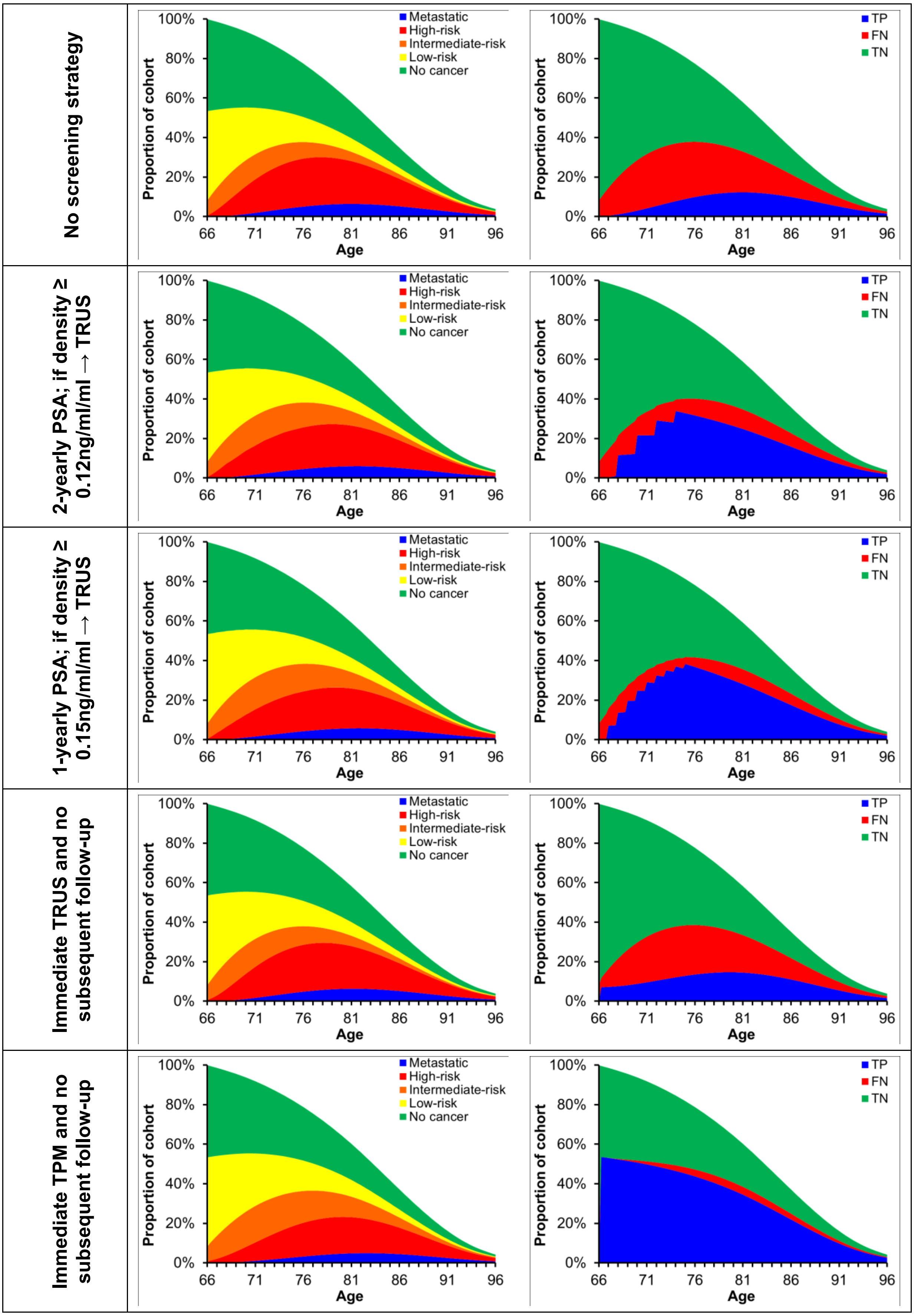


Figure HE32: Tracking the modelled cohort over 30 years, tracing the disease progression on the left hand, and reflecting the diagnosed cases overtime on the right hand for a given strategy

Incremental deterministic analysis

Table HE27 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, including a 2-yearly PSA screening tests, using density at a threshold of 0.15 ng/ml/ml, seem to be optimal. At a higher cost-effectiveness threshold (£30,000 per QALY), the same strategy, applied yearly seems optimal.

Table HE27: Base-case deterministic cost-utility results (excluding TPM) for people with Likert 4 and two biopsies

Strategy	Absolute		Incremental		
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£1,965	9.052			
3-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£3,572	9.169	£1,607	0.117	£13,713
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£3,970	9.198	£398	0.029	£13,742
2-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	£4,061	9.204	£91	0.006	£16,088
2-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	£4,521	9.227	£461	0.023	£20,037
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£5,264	9.264	£743	0.037	£20,040
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	£5,389	9.268	£125	0.005	£27,230
6-monthly %free PSA; if level <15% → TRUS	£6,530	9.296	£1,141	0.027	£41,646
6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£6,858	9.302	£328	0.006	£53,631
6-monthly PSA; if density ≥ 0.15ng/ml/ml → TRUS	£7,044	9.304	£187	0.002	£99,158
3-monthly %free PSA; if level <15% → TRUS	£8,810	9.314	£1,766	0.010	£175,409
3-monthly PCA3; if level ≥ 50 → TRUS	£11,653	9.317	£2,843	0.003	£970,889

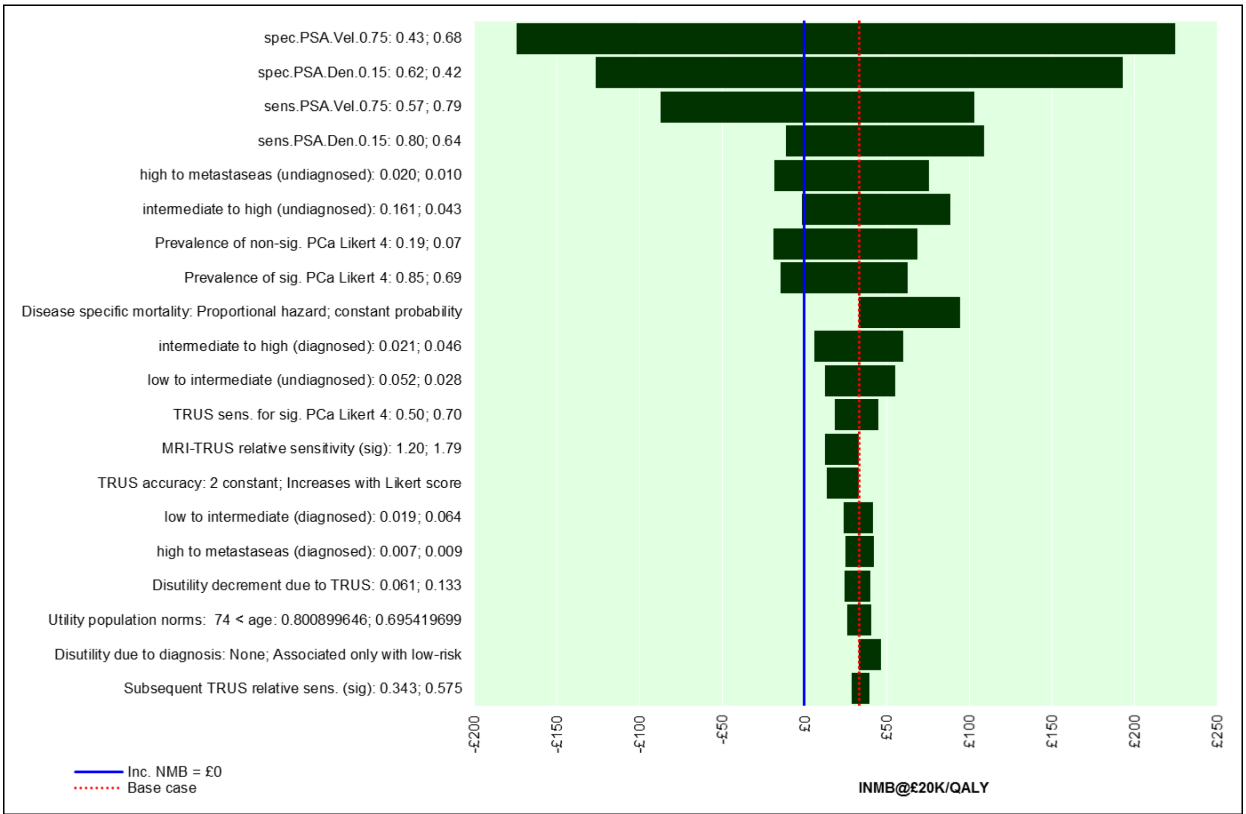
Table HE28 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The strategies including 2-yearly screening tests using PSA density at thresholds of 0.15 ng/ml/ml and 0.12 ng/ml/ml, have the first and second positions at a cost-effectiveness threshold of £20,000 per QALY. However, the number of associated unnecessary biopsies increased significantly from 1.65 to 2.27 using the lower test threshold.

Table HE28: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY (excluding TPM) for people with Likert 4 and two biopsies

Strategy	Life-years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
2-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.51	15.9%	1.65	£51	£3,127	£4,061	9.204	1	14
2-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	16.57	15.2%	2.27	£49	£3,338	£4,521	9.227	2	9
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.67	14.2%	3.15	£104	£3,669	£5,264	9.264	3	2
2-yearly PSA; if density ≥ 0.09ng/ml/ml → TRUS	16.58	15.1%	2.40	£49	£3,367	£4,602	9.230	4	8
1-yearly %free PSA; if level <15% → TRUS	16.64	14.6%	2.59	£203	£3,545	£5,018	9.251	5	3
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.50	16.0%	1.56	£51	£3,077	£3,970	9.198	6	17
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.69	14.1%	3.36	£103	£3,712	£5,389	9.268	7	1
2-yearly PSA; if level ≥ 6ng/ml → TRUS	16.55	15.5%	2.07	£50	£3,244	£4,344	9.216	8	12
1-yearly PSA; if level ≥ 6ng/ml → TRUS	16.72	13.8%	4.28	£101	£3,806	£5,837	9.276	9	21
1-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	16.74	13.5%	4.71	£100	£3,878	£6,075	9.284	10	19
1-yearly PSA; if density ≥ 0.09ng/ml/ml → TRUS	16.75	13.5%	4.99	£100	£3,900	£6,207	9.285	19	4
6-monthly %free PSA; if level <15% → TRUS	16.77	13.2%	4.86	£379	£3,985	£6,530	9.296	21	5
1-yearly PHI; if level ≥ 35 → TRUS	16.71	13.8%	3.63	£567	£3,780	£6,025	9.276	28	6

One-way sensitivity analysis

Figure HE33 shows the impact of changing the value of a parameter on the results of a pairwise comparison between the strategy including a yearly PSA velocity test at a threshold of 0.75 ng/ml/year and the one including a yearly PSA density test at a threshold of 0.15 ng/ml/ml. It shows that given the 95% confidence interval of the two tests' accuracy data, there is not any significant difference between the two tests' performance.

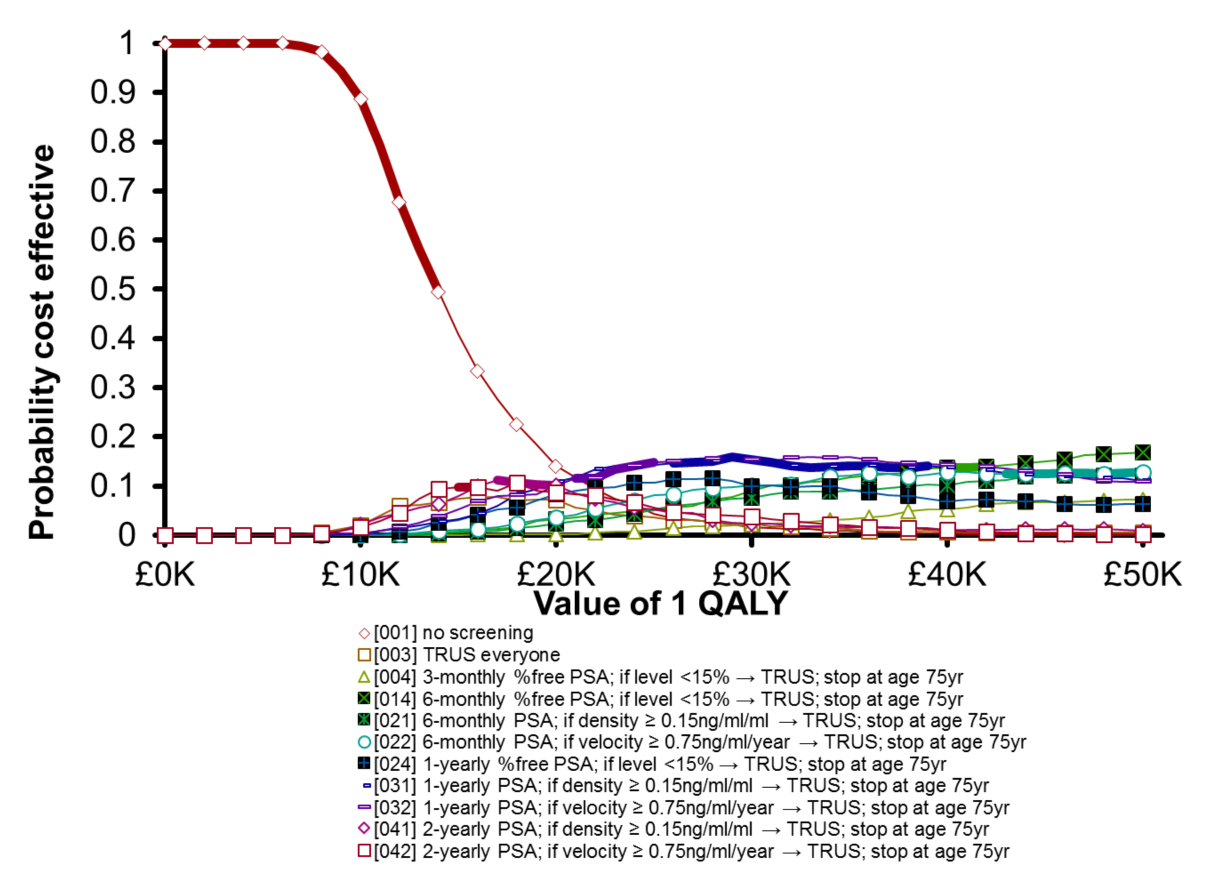


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE33: One-way sensitivity analysis "1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS" vs "1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Probabilistic results

Figure HE34 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY, excluding strategies with TPM. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. At a cost-effectiveness threshold of £20,000 per QALY, the strategy including a 2-yearly PSA velocity test at a threshold of 0.75 ng/ml/year seems cost-effective with a probability of 10%. At a cost-effectiveness threshold of £30,000 per QALY, the strategy including a yearly PSA density test at a threshold of 0.15 ng/ml/ml, seems cost-effective with a probability of 15%.



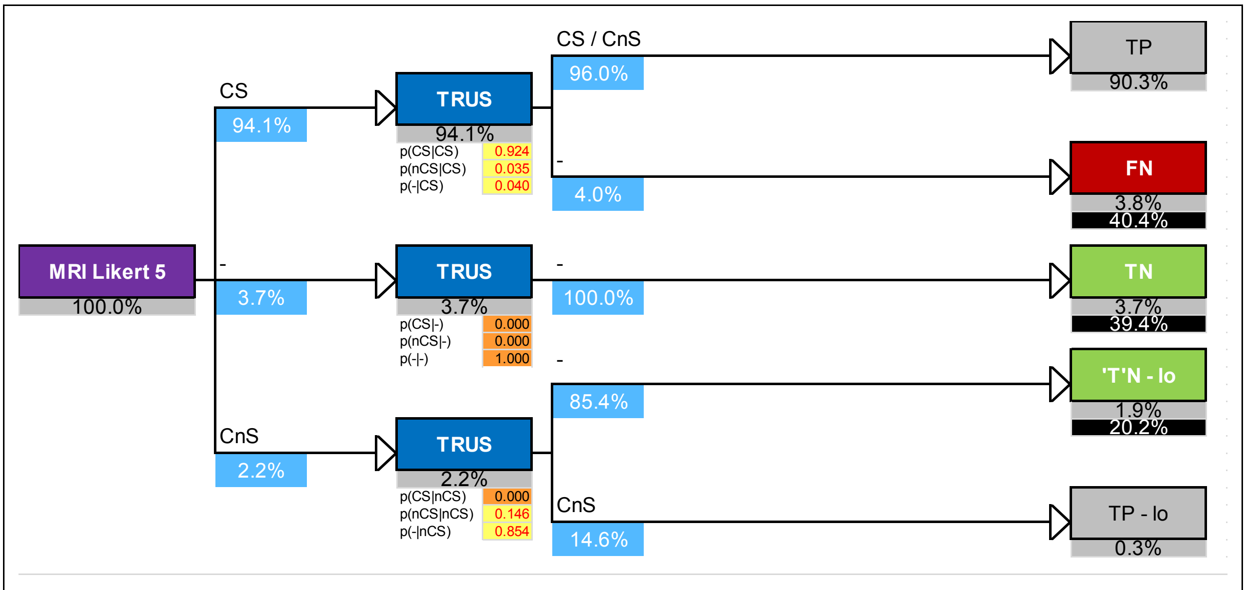
Bold line indicates cost effectiveness acceptability frontier

Figure HE34: Cost-effectiveness acceptability curve excluding TPM strategies

HE.33 MRI Likert 5; 1 biopsy

Baseline population

The population of interest here is people who received mpMRI with Likert score at 5 and 1 prostate biopsies (TRUS). Applying the prevalence obtained from PROMIS and the accuracy data of TRUS, influenced by the mpMRI, results in the baseline population distribution being 39.4%, 20.2% and 40.4% for people with truly no cancer, people with missed clinically non-significant cancer and people with missed clinically significant cancer, respectively, Figure HE35.



Bold line indicates Baseline population distribution (Likert 5 with one previous biopsy): Percentages in blue boxes indicate probabilities at each branch of the tree. Percentages in grey boxes indicate proportion of whole tested population at each stage. Percentages in black boxes indicate proportion of people receiving a negative diagnosis who fall into each category (note that the NPV of the algorithm is given by 1 – the proportion in the black box under 'FN'). Figures in yellow and orange boxes indicate conditional probabilities of each diagnosis, given true status. CS: Clinically significant; CnS: Clinically non-significant; FN: False negative CS disease; TN: true negative; 'T'N-lo: missed CnS disease; TP and TP-lo: Truly positive CS and CnS disease, respectively.

Figure HE35: The decision tree to derive the baseline population distribution (Likert 5 with 1 previous biopsy)

Model dynamics

Figure HE36 demonstrates the modelled cohort over 30 years. On the left side, it shows the disease development, starting as low-risk and then progressing to intermediate-, then to high-risk and then to metastatic disease. On the right side, it shows the performance of diagnostics capturing the disease within people misclassified as false negative. This is shown for the least intensive "no screening" strategy, at the top, where people receive prostate biopsy only if they develop symptoms, to the most invasive strategy at the bottom, where all candidates receive an immediate TPM and not followed-up subsequently. In between, the impact of applying 3 follow-up strategies on disease progression and their performance in identifying missed disease is demonstrated over time. This is shown for: the strategy where people receive a 6-monthly % free PSA test; if level <15%, they are directed to TRUS biopsy, the strategy where people receive a 6-monthly PSA test; if velocity ≥0.75 ng/ml/year, they are directed to TRUS biopsy and the strategy where people receive an immediate TRUS and they are not followed-up subsequently.

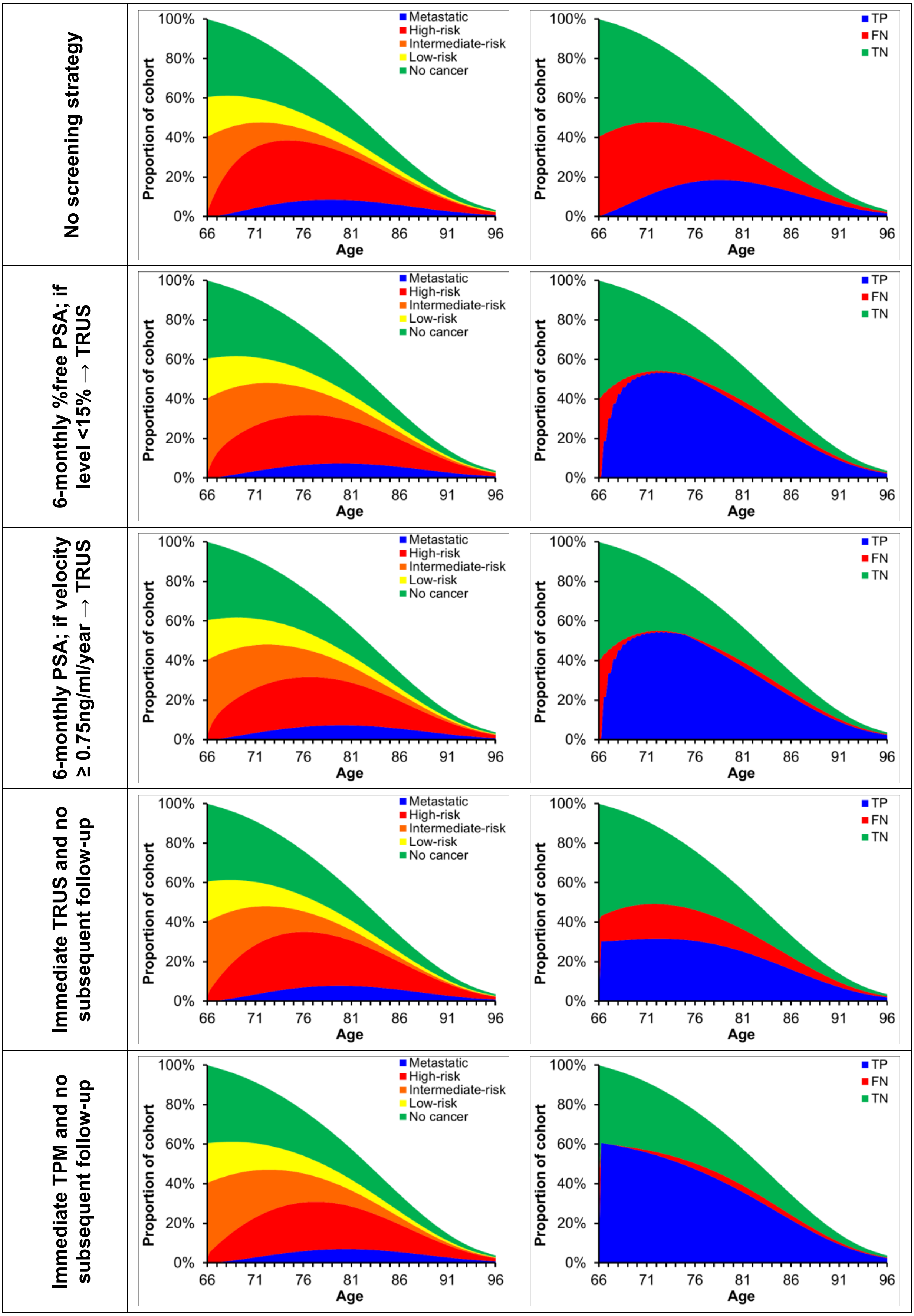


Figure HE36: Tracking the modelled cohort over 30 years, tracing the disease progression on the left hand, and reflecting the diagnosed cases overtime on the right hand for a given strategy

Incremental deterministic analysis

Table HE29 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, including a 6-monthly % free PSA test at a threshold of 15%, seems to be optimal. At a higher cost-effectiveness threshold (£30,000 per QALY), the strategy, including 6-monthly PSA velocity test at a threshold of 0.75 ng/ml/year, seems optimal.

Table HE29: Base-case deterministic cost-utility results (excluding TPM) for people with Likert 5 and one biopsy

Strategy	Absolute		Incremental		
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£3,012	8.746			
TRUS everyone	£4,856	8.984	£1,844	0.238	£7,741
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	£6,679	9.083	£1,822	0.099	£18,462
6-monthly %free PSA; if level <15% → TRUS	£7,455	9.123	£776	0.041	£19,105
6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£7,678	9.132	£223	0.008	£26,740
6-monthly PSA; if density ≥ 0.15ng/ml/ml → TRUS	£7,805	9.134	£127	0.003	£47,970
3-monthly %free PSA; if level <15% → TRUS	£8,884	9.154	£1,078	0.019	£55,403
3-monthly PCA3; if level ≥ 50 → TRUS	£10,809	9.158	£1,925	0.004	£487,035

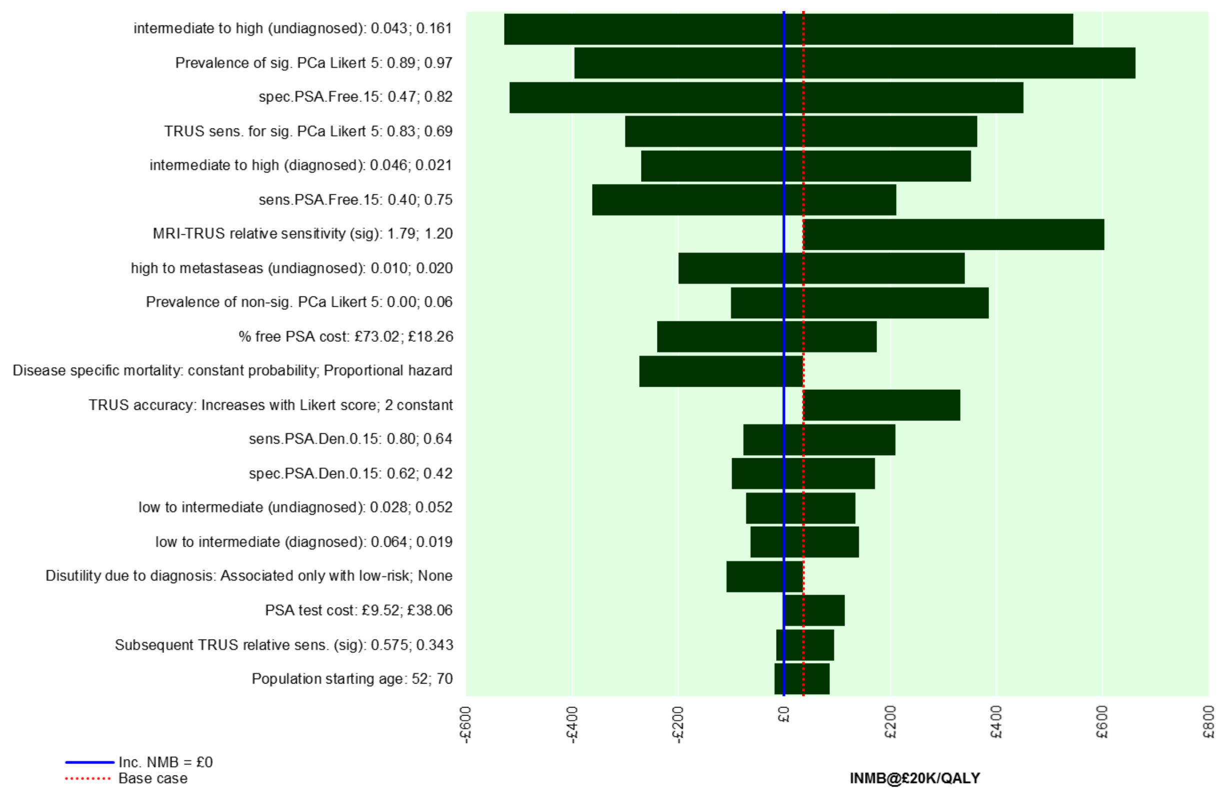
Table HE30 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The strategy, including a 6-monthly % free PSA test at a threshold of 15%, and the strategy, including a yearly PSA density test at a threshold of 0.15 ng/ml/ml, have the first and second positions at a cost-effectiveness threshold of £20,000 per QALY, respectively. However, the number of associated unnecessary biopsies increased significantly from 2.20 to 3.04 with the use of the % free PSA test.

Table HE30: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY (excluding TPM) for people with Likert 5 and one biopsy

						Absolute		Rank at thresholds of	
Strategy	**Life-years**	**PC deaths**	**Unnecessary biopsies**	**Screening costs (£)**	**Treatment costs (£)**	**Costs (£)**	**Effects (QALYs)**	**£20k/ QALY**	**£30k/ QALY**
6-monthly %free PSA; if level <15% → TRUS	16.41	16.5%	3.04	£276	£5,682	£7,455	9.123	1	2
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.31	17.3%	2.20	£78	£5,434	£6,679	9.083	2	6
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.30	17.5%	2.06	£79	£5,396	£6,586	9.077	3	10
6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.44	16.2%	3.77	£139	£5,757	£7,678	9.132	4	1
6-monthly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.44	16.1%	4.04	£138	£5,783	£7,805	9.134	5	3
1-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	16.36	16.8%	3.18	£74	£5,576	£7,195	9.102	6	4
1-yearly PSA; if level ≥ 6ng/ml → TRUS	16.34	17.1%	2.89	£76	£5,516	£7,024	9.093	7	8
TRUS everyone	16.04	20.3%	0.77	£0	£4,263	£4,856	8.984	8	26
1-yearly %free PSA; if level <15% → TRUS	16.25	17.8%	1.67	£157	£5,282	£6,398	9.061	9	15
1-yearly PSA; if density ≥ 0.09ng/ml/ml → TRUS	16.37	16.8%	3.39	£74	£5,595	£7,295	9.104	10	5
3-monthly DRE; if abnormal → TRUS	16.36	16.9%	2.26	£607	£5,534	£7,340	9.105	11	7
3-monthly %free PSA; if level <15% → TRUS	16.50	15.6%	5.44	£489	£5,963	£8,884	9.154	22	9

One-way sensitivity analysis

Figure HE37 shows the impact of changing the value of a parameter on the results of a pairwise comparison between the strategy including a yearly PSA density test at a threshold of 0.15 ng/ml/ml and the one including a 6-monthly % free PSA test at a threshold of 15%. It shows that the results are very sensitive to a number of parameters if altered by the 95% confidence interval.

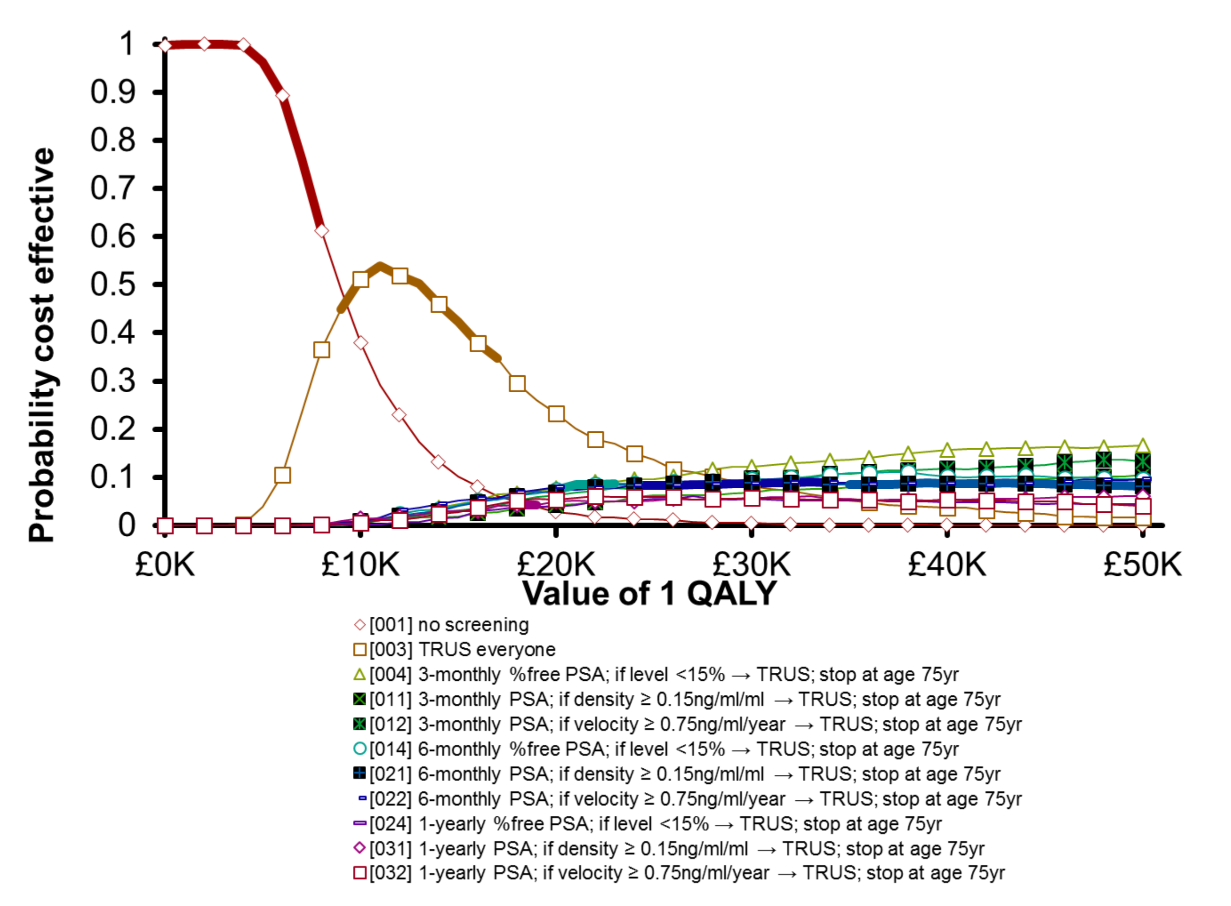


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE37: One-way sensitivity analysis "6-monthly %free PSA; if level <15% → TRUS" vs "1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Probabilistic results

Figure HE38 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY, excluding strategies with TPM. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. At a cost-effectiveness threshold of £10,000 per QALY, the strategy, where people receive an immediate TRUS, seems optimal with a probability of 50%. At a cost-effectiveness threshold of £20,000 per QALY, the strategies including a yearly PSA density at a threshold of 0.15 ng/ml/ml, or 6-monthly % free PSA test, seem cost-effective with a probability of less than 10%.



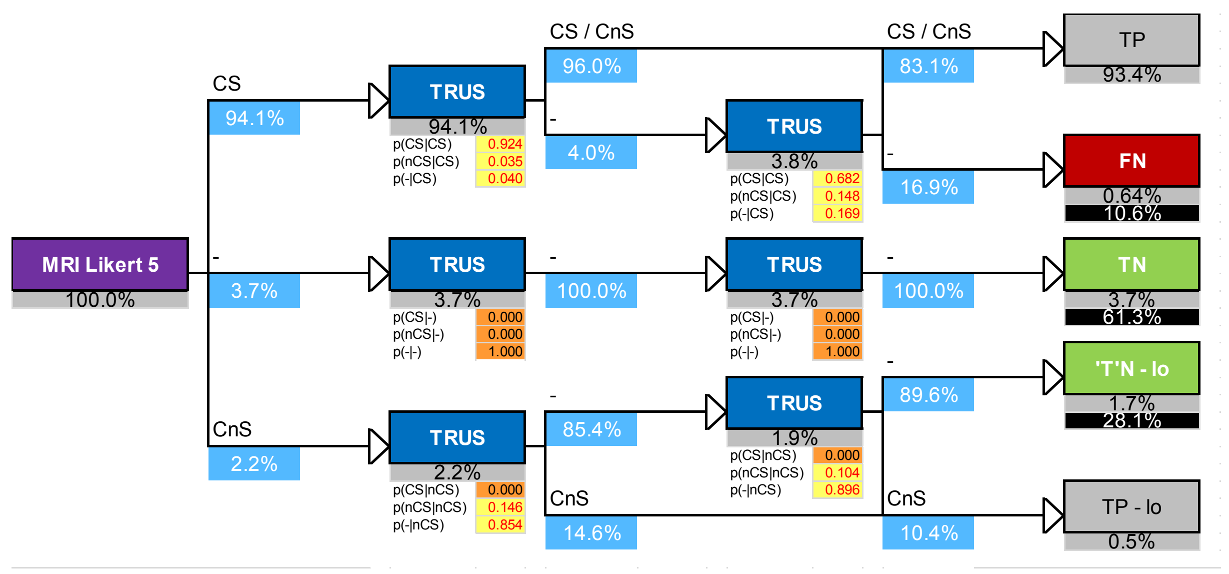
Bold line indicates cost effectiveness acceptability frontier

Figure HE38: Cost-effectiveness acceptability curve excluding TPM strategies

HE.39 MRI Likert 5; 2 biopsies

Baseline population

The population of interest here is people who received mpMRI with Likert score at 5 and 2 prostate biopsies (TRUS). Applying the prevalence obtained from PROMIS and the accuracy data of TRUS, influenced by the mpMRI, results in the baseline population distribution being 61.3%, 28.1% and 10.6% for people with truly no cancer, people with missed clinically non-significant cancer and people with missed clinically significant cancer, respectively, Figure HE39.



Bold line indicates Baseline population distribution (Likert 5 with two previous biopsies): Percentages in blue boxes indicate probabilities at each branch of the tree. Percentages in grey boxes indicate proportion of whole tested population at each stage. Percentages in black boxes indicate proportion of people receiving a negative diagnosis who fall into each category (note that the NPV of the algorithm is given by 1 – the proportion in the black box under 'FN'). Figures in yellow and orange boxes indicate conditional probabilities of each diagnosis, given true status. CS: Clinically significant; CnS: Clinically non-significant; FN: False negative CS disease; TN: true negative; 'T'N-lo: missed CnS disease; TP and TP-lo: Truly positive CS and CnS disease, respectively.

Figure HE39: The decision tree to derive the baseline population distribution (Likert 5 with 2 previous biopsies)

Model dynamics

Figure HE40 demonstrates the modelled cohort over 30 years. On the left side, it shows the disease development, starting as low-risk and then progressing to intermediate-, then to high-risk and then to metastatic disease. On the right side, it shows the performance of diagnostics capturing the disease within people misclassified as false negative. This is shown for the least intensive "no screening" strategy, at the top, where people receive prostate biopsy only if they develop symptoms, to the most invasive strategy at the bottom, where all candidates receive an immediate TPM and not followed-up subsequently. In between, the impact of applying 3 follow-up strategies on disease progression and their performance in identifying missed disease is demonstrated over time. This is shown for: the strategy where people receive a 2-yearly PSA test; if density ≥0.15 ng/ml/ml, they are directed to TRUS biopsy, the strategy where people receive a yearly PSA test; if velocity ≥0.75 ng/ml/year, they are directed to TRUS biopsy and the strategy where people receive an immediate TRUS and they are not followed-up subsequently.

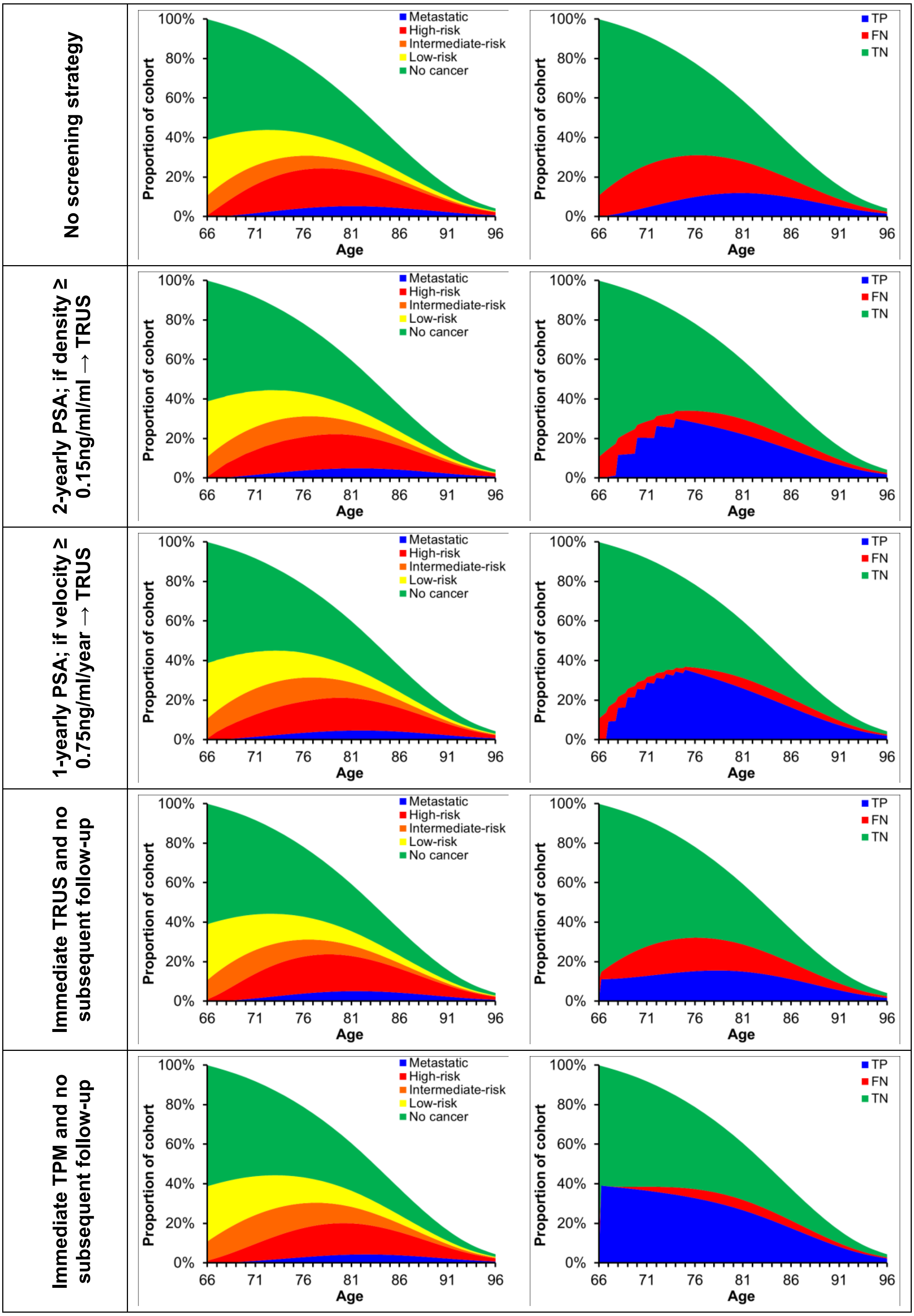


Figure HE40: Tracking the modelled cohort over 30 years, tracing the disease progression on the left hand, and reflecting the diagnosed cases overtime on the right hand for a given strategy

Incremental deterministic analysis

Table HE31 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, including a 2-yearly PSA density test at a threshold of 0.15 ng/ml/ml, seems to be optimal. At a higher cost-effectiveness threshold (£30,000 per QALY), the strategy, including a yearly PSA velocity test at a threshold of 0.75 ng/ml/year, seems optimal.

Table HE31: Base-case deterministic cost-utility results (excluding TPM) for people with Likert 5 and two biopsies

	Absolute		Incremental		
Strategy	**Costs (£)**	**Effects (QALYs)**	**Costs (£)**	**Effects (QALYs)**	**ICER (£/QALY)**
no screening	£1,869	9.170			
TRUS everyone	£2,839	9.245	£970	0.075	£12,964
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£3,756	9.308	£918	0.063	£14,505
2-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	£3,839	9.313	£82	0.005	£17,903
1-yearly %free PSA; if level <15% → TRUS	£4,653	9.349	£814	0.036	£22,581
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£4,879	9.358	£226	0.009	£25,707
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	£4,995	9.361	£116	0.003	£39,421
6-monthly %free PSA; if level <15% → TRUS	£5,984	9.379	£989	0.018	£54,708
6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£6,311	9.381	£327	0.002	£169,700
3-monthly PHI; if level ≥ 62 → TRUS	£7,305	9.384	£994	0.003	£344,079
3-monthly %free PSA; if level <15% → TRUS	£8,033	9.385	£728	0.001	£629,842
3-monthly PCA3; if level ≥ 50 → TRUS	£10,810	9.387	£2,777	0.002	£1,334,003

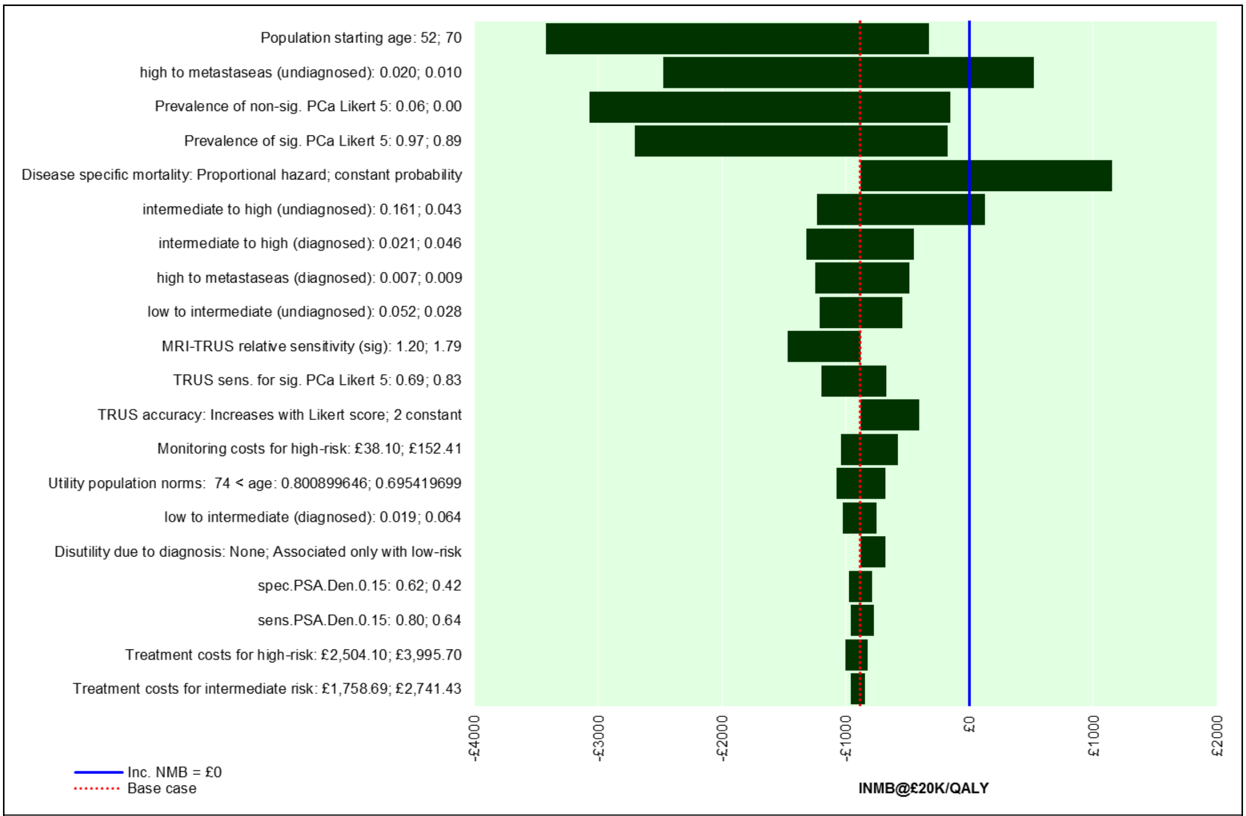
Table HE32 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The strategies, including PSA density test at a threshold of 0.15 ng/ml/ml, PSA velocity tests at a threshold of 0.75 ng/ml/year and % free PSA tests at a threshold of 15%, seem to have the first 3 positions if applied 2-yearly or yearly at cost-effectiveness thresholds of £20,000 or £30,000 per QALY, respectively.

Table HE32: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY (excluding TPM) for people with Likert 5 and two biopsies

Strategy	Life-years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
2-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.77	12.7%	1.69	£50	£2,973	£3,839	9.313	1	6
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.76	12.8%	1.59	£50	£2,931	£3,756	9.308	2	8
2-yearly %free PSA; if level <15% → TRUS	16.73	13.2%	1.31	£98	£2,815	£3,578	9.296	3	17
2-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	16.82	12.2%	2.38	£49	£3,143	£4,277	9.330	4	4
1-yearly %free PSA; if level <15% → TRUS	16.87	11.7%	2.53	£201	£3,306	£4,653	9.349	5	3
2-yearly PSA; if level ≥ 6ng/ml → TRUS	16.80	12.4%	2.17	£49	£3,068	£4,122	9.322	6	7
2-yearly PSA; if density ≥ 0.09ng/ml/ml → TRUS	16.83	12.1%	2.53	£49	£3,166	£4,359	9.333	7	5
3-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	16.76	12.7%	1.77	£35	£2,976	£3,847	9.306	8	16
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.90	11.4%	3.12	£103	£3,403	£4,879	9.358	9	1
3-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.71	13.3%	1.28	£36	£2,792	£3,472	9.287	10	25
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.91	11.3%	3.34	£103	£3,437	£4,995	9.361	15	2
1-yearly PSA; if level ≥ 6ng/ml → TRUS	16.93	11.1%	4.40	£101	£3,510	£5,474	9.364	49	9
2-yearly PHI; if level ≥ 35 → TRUS	16.79	12.5%	1.81	£276	£3,041	£4,180	9.321	14	10

One-way sensitivity analysis

Figure HE41 shows the impact of changing the value of a parameter on the results of a pairwise comparison between the “no screening” strategy and the strategy, including 2-yearly PSA density tests at a threshold of 0.15 ng/ml/ml. It shows that the latter strategy remains worthwhile unless the disease progression in undiagnosed cases is slower. Applying the prostate cancer death as a constant probability in the model results in the results always in favour of the less intensive strategy.

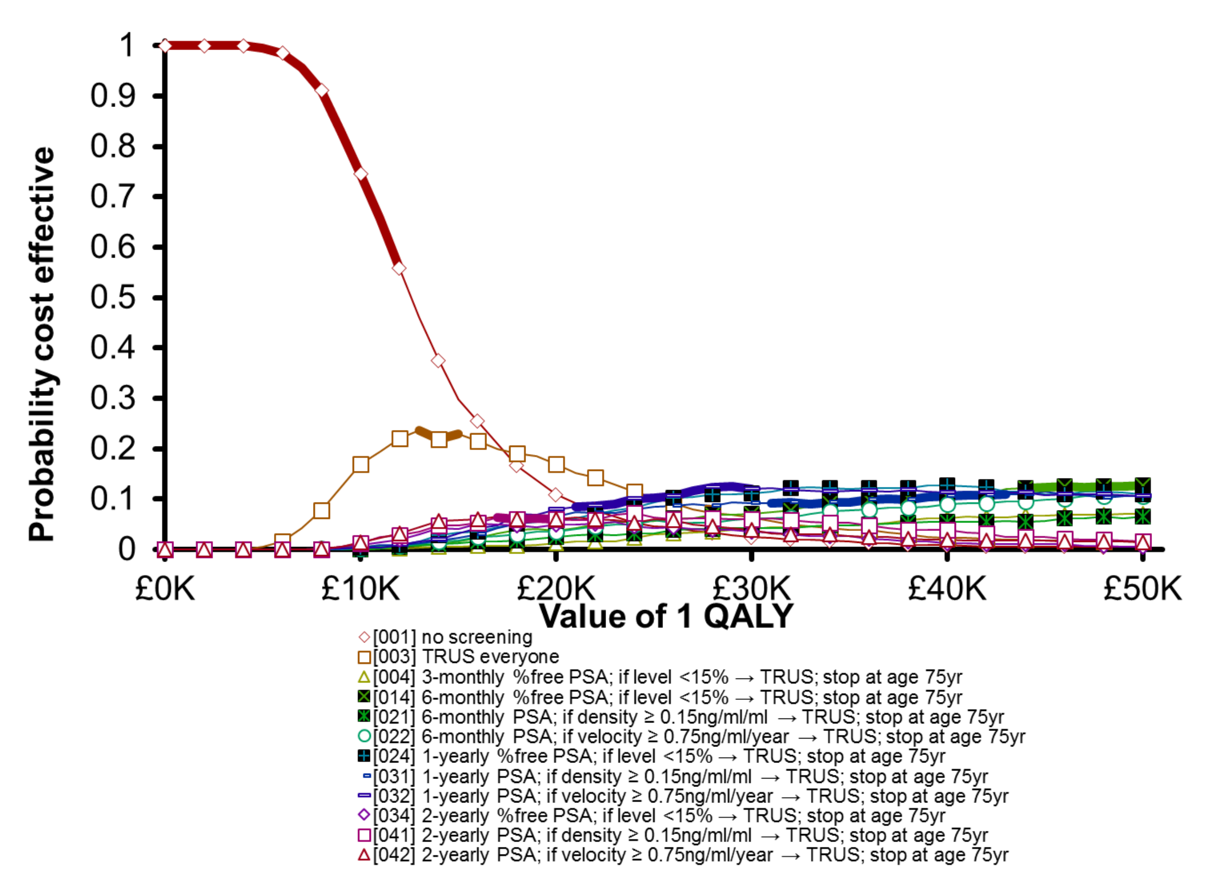


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE41: One-way sensitivity analysis “no screening” vs “2-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS” based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Probabilistic results

Figure HE42 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY, excluding strategies with TPM. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. At a cost-effectiveness threshold of £20,000 per QALY, the strategies including 2-yearly PSA density tests at a threshold of 0.15 ng/ml/ml, or PSA velocity tests at a threshold of 0.75 ng/ml/year, seem cost-effective with a probability of less than 10%. The same strategies, if applied yearly are found to be optimal at a cost-effectiveness threshold of £30,000 per QALY with a probability of just greater than 10%.



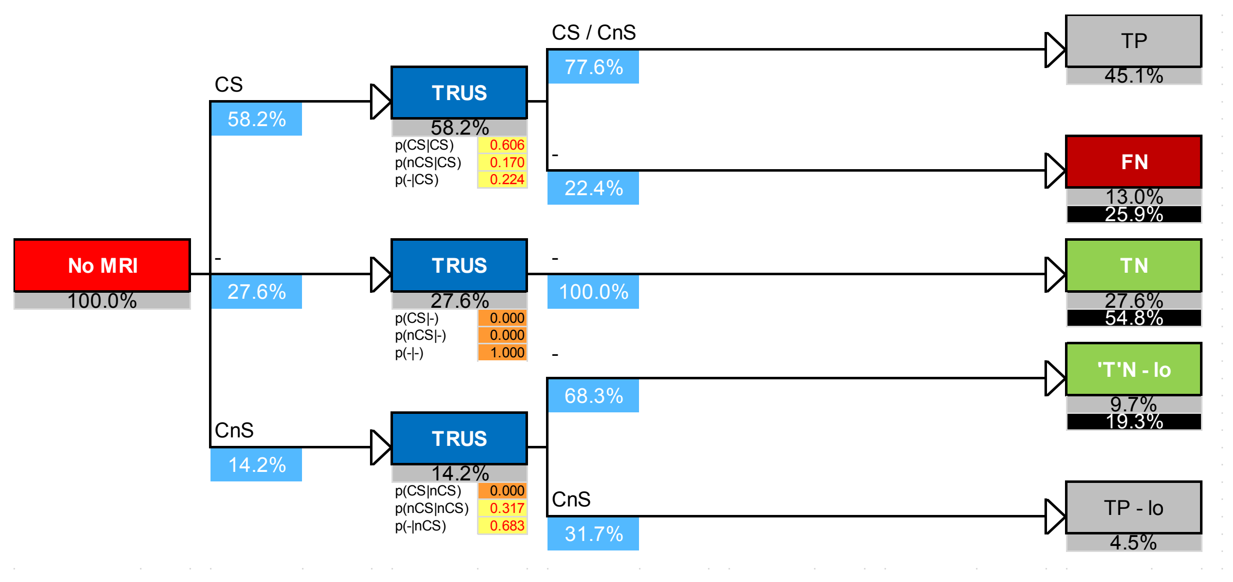
Bold line indicates cost effectiveness acceptability frontier

Figure HE42: Cost-effectiveness acceptability curve excluding TPM strategies

HE.3.10 1 biopsy; no mpMRI

Baseline population

The population of interest here is people who received 1 prostate biopsy (TRUS) and did not receive mpMRI. The average estimates for the prevalence and the accuracy data of TRUS obtained from the whole sample in PROMIS is assumed applicable for this population. This results in the baseline population distribution being 54.8%, 19.3% and 25.9% for people with truly no cancer, people with missed clinically non-significant cancer and people with missed clinically significant cancer, respectively, Figure HE43.



Bold line indicates Baseline population distribution (one previous biopsy and no mpMRI): Percentages in blue boxes indicate probabilities at each branch of the tree. Percentages in grey boxes indicate proportion of whole tested population at each stage. Percentages in black boxes indicate proportion of people receiving a negative diagnosis who fall into each category (note that the NPV of the algorithm is given by 1 – the proportion in the black box under 'FN'). Figures in yellow and orange boxes indicate conditional probabilities of each diagnosis, given true status. CS: Clinically significant; CnS: Clinically non-significant; FN: False negative CS disease; TN: true negative; 'T'N-lo: missed CnS disease; TP and TP-lo: Truly positive CS and CnS disease, respectively.

Figure HE43: The decision tree to derive the baseline population distribution (1 previous biopsy and no mpMRI)

Model dynamics

Figure HE44 demonstrates the modelled cohort over 30 years. On the left side, it shows the disease development, starting as low-risk and then progressing to intermediate-, then to high-risk and then to metastatic disease. On the right side, it shows the performance of diagnostics capturing the disease within people misclassified as false negative. This is shown for the least intensive "no screening" strategy, at the top, where people receive prostate biopsy only if they develop symptoms, to the most invasive strategy at the bottom, where all candidates receive an immediate TPM and not followed-up subsequently. In between, the impact of applying 3 follow-up strategies on disease progression and their performance in identifying missed disease is demonstrated over time. This is shown for: the strategy where people receive yearly PSA tests; if density ≥0.15 ng/ml/ml, they are directed to TRUS biopsy, the strategy where people receive 6-monthly PSA tests; if velocity ≥0.75 ng/ml/year, they are directed to TRUS biopsy and the strategy where people receive an immediate TRUS and they are not followed-up subsequently.

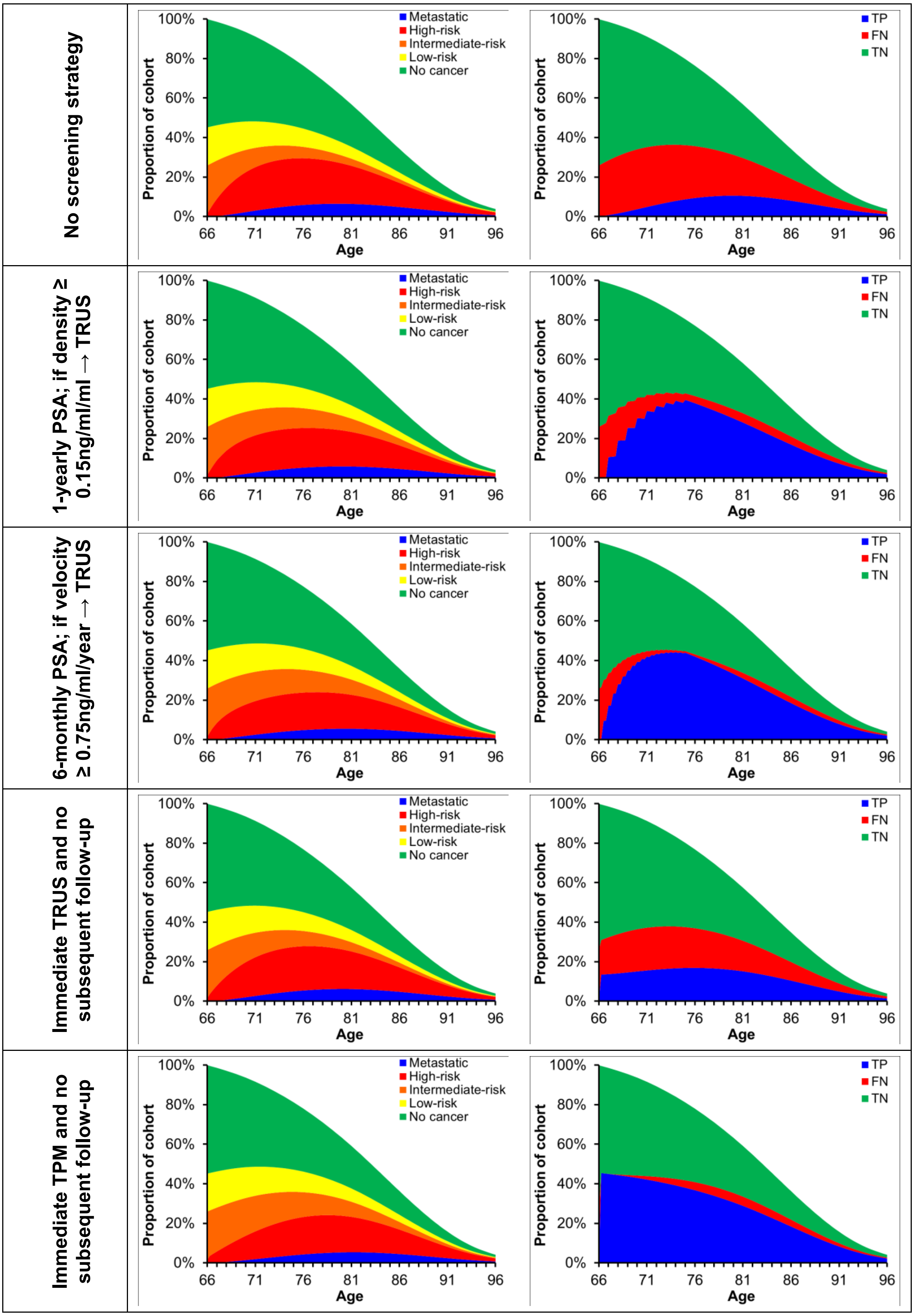


Figure HE44: Tracking the modelled cohort over 30 years, tracing the disease progression on the left hand, and reflecting the diagnosed cases overtime on the right hand for a given strategy

Incremental deterministic analysis

Table HE33 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, including yearly PSA velocity tests at a threshold of 0.75 ng/ml/ml, seems to be optimal. At a higher cost-effectiveness threshold (£30,000 per QALY), the strategy, including 6-monthly PSA velocity tests at a threshold of 0.75 ng/ml/year, seems optimal.

Table HE33: Base-case deterministic cost-utility results (excluding TPM) for people with one biopsy but no MRI

	Absolute		Incremental		
Strategy	**Costs (£)**	**Effects (QALYs)**	**Costs (£)**	**Effects (QALYs)**	**ICER (£/QALY)**
no screening	£1,924	8.950			
TRUS everyone	£3,103	9.052	£1,179	0.102	£11,553
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£5,312	9.175	£2,209	0.124	£17,862
6-monthly %free PSA; if level <15% → TRUS	£6,427	9.228	£1,115	0.052	£21,243
6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£6,701	9.237	£274	0.009	£29,162
6-monthly PSA; if density ≥ 0.15ng/ml/ml → TRUS	£6,855	9.240	£155	0.003	£51,560
3-monthly %free PSA; if level <15% → TRUS	£8,091	9.264	£1,235	0.024	£52,460
3-monthly PCA3; if level ≥ 50 → TRUS	£10,474	9.269	£2,383	0.005	£484,103

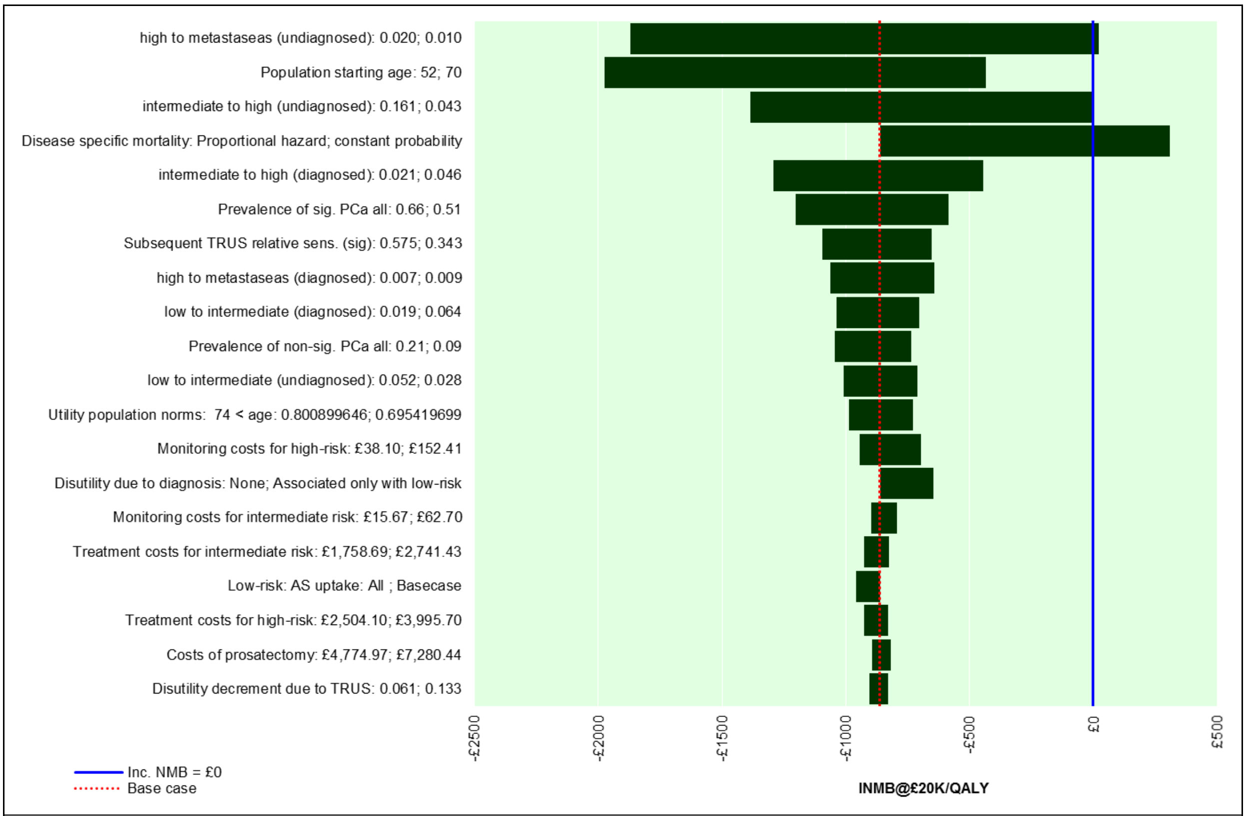
Table HE34 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The strategies, including PSA density test at a threshold of 0.15 ng/ml/ml, PSA velocity tests at a threshold of 0.75 ng/ml/year and % free PSA tests at a threshold of 15%, seem to have the first 3 positions if applied yearly or 6-monthly at cost-effectiveness thresholds of £20,000 or £30,000 per QALY, respectively. However, the strategy including 6-monthly % free PSA tests at a threshold of 15% is found the 3rd and the 2nd at the two cost-effectiveness thresholds £20,000 and £30,000 per QALY, respectively, with the average number of unnecessary biopsies at 3.57.

Table HE34: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY (excluding TPM) for people with one biopsy but no MRI

Strategy	Life-years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.51	14.9%	2.50	£98	£3,971	£5,312	9.175	1	5
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.53	14.8%	2.67	£97	£4,029	£5,436	9.181	2	4
6-monthly %free PSA; if level <15% → TRUS	16.65	13.7%	3.57	£343	£4,427	£6,427	9.228	3	2
1-yearly %free PSA; if level <15% → TRUS	16.47	15.4%	2.02	£193	£3,802	£5,054	9.159	4	11
2-yearly PSA; if density ≥ 0.12ng/ml/ml → mpMRI; if Likert ≥4 → TRUS	16.42	16.0%	0.87	£48	£3,509	£4,920	9.151	5	16
2-yearly PSA; if density ≥ 0.09ng/ml/ml → mpMRI; if Likert ≥4 → TRUS	16.43	15.9%	0.92	£48	£3,540	£5,009	9.154	6	15
2-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TRUS	16.36	16.6%	0.65	£49	£3,285	£4,417	9.125	7	27
2-yearly mpMRI; if Likert ≥4 → TRUS	16.45	15.8%	1.01	£0	£3,589	£5,129	9.160	8	13
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TRUS	16.34	16.8%	0.62	£49	£3,231	£4,319	9.119	9	33
2-yearly PSA; if level ≥ 6ng/ml → mpMRI; if Likert ≥4 → TRUS	16.39	16.3%	0.80	£48	£3,409	£4,730	9.139	10	22
6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.68	13.4%	4.49	£173	£4,537	£6,701	9.237	11	1
6-monthly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.69	13.3%	4.82	£172	£4,574	£6,855	9.240	14	3
3-monthly DRE; if abnormal → TRUS	16.59	14.3%	2.63	£752	£4,204	£6,266	9.207	26	6
1-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	16.59	14.2%	3.92	£93	£4,255	£6,116	9.201	20	7
1-yearly PSA; if density ≥ 0.09ng/ml/ml → TRUS	16.60	14.1%	4.21	£92	£4,284	£6,247	9.203	36	8
1-yearly PSA; if level ≥ 6ng/ml → TRUS	16.56	14.4%	3.58	£94	£4,158	£5,892	9.192	16	9
3-monthly %free PSA; if level <15% → TRUS	16.76	12.6%	6.40	£612	£4,796	£8,091	9.264	82	10

One-way sensitivity analysis

Figure HE45 shows the impact of changing the value of a parameter on the results of a pairwise comparison between the “no screening” strategy and the strategy, where people receive an immediate TRUS. It shows that the latter strategy remains worthwhile unless the disease progression in undiagnosed cases is slower. Applying the prostate cancer death as a constant probability in the model results in the results always in favour of the less intensive strategy.

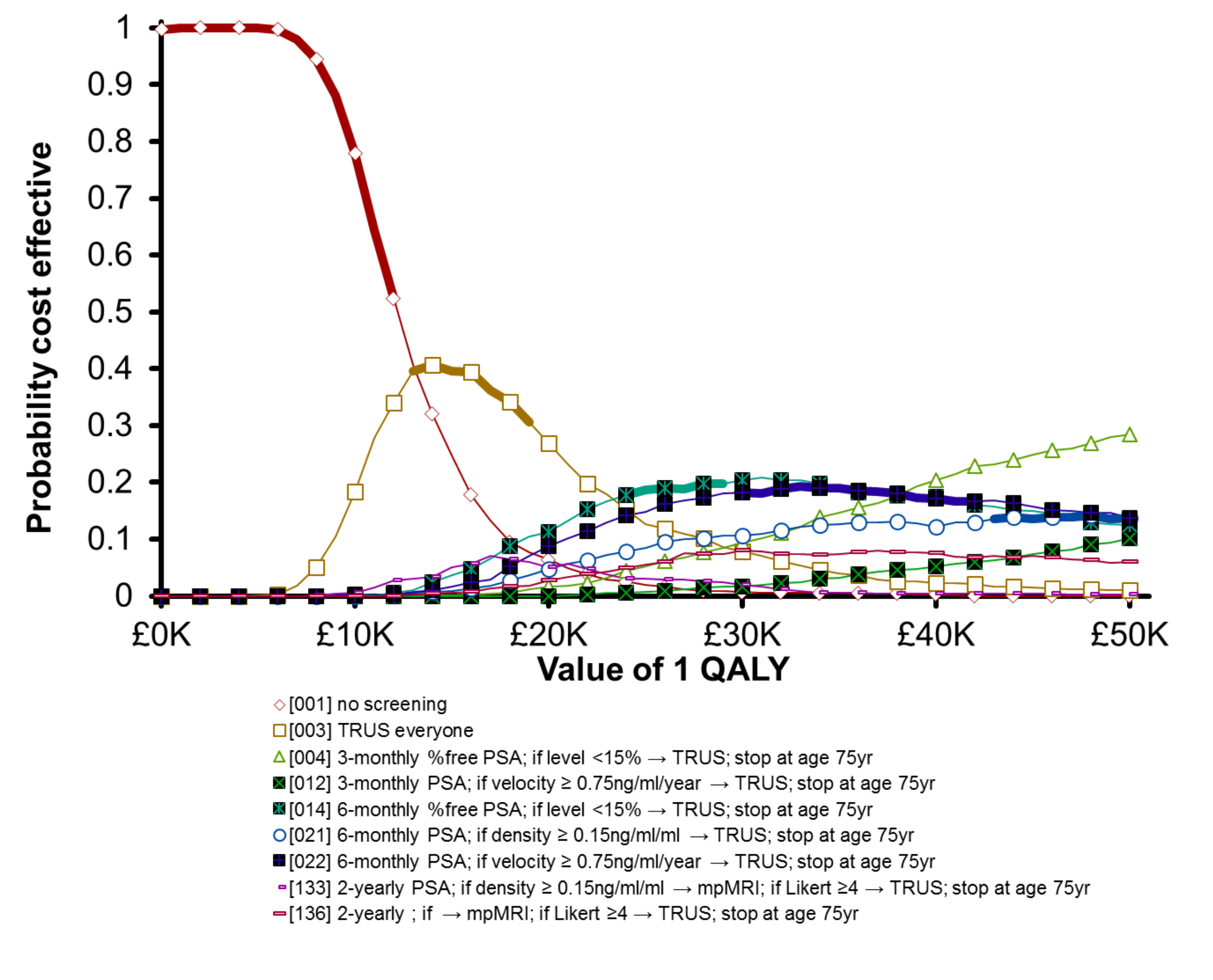


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE45: One-way sensitivity analysis “no screening” vs “TRUS everyone” based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Probabilistic results

Figure HE46 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY, excluding strategies with TPM. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. At a cost-effectiveness threshold between £10,000 and £20,000 per QALY, the strategy, where people receive an immediate TRUS seems optimal with a probability of 40%. At a cost-effectiveness threshold of £30,000 per QALY, the strategy, including 6-monthly % free PSA test at a threshold of 15%, seems cost-effective with a probability of 20%. At a cost-effectiveness threshold between £30,000 and £40,000 per QALY, the strategy, including 6-monthly PSA velocity test at a threshold of 0.75 ng/ml/year is found to be optimal with a probability of 20%.



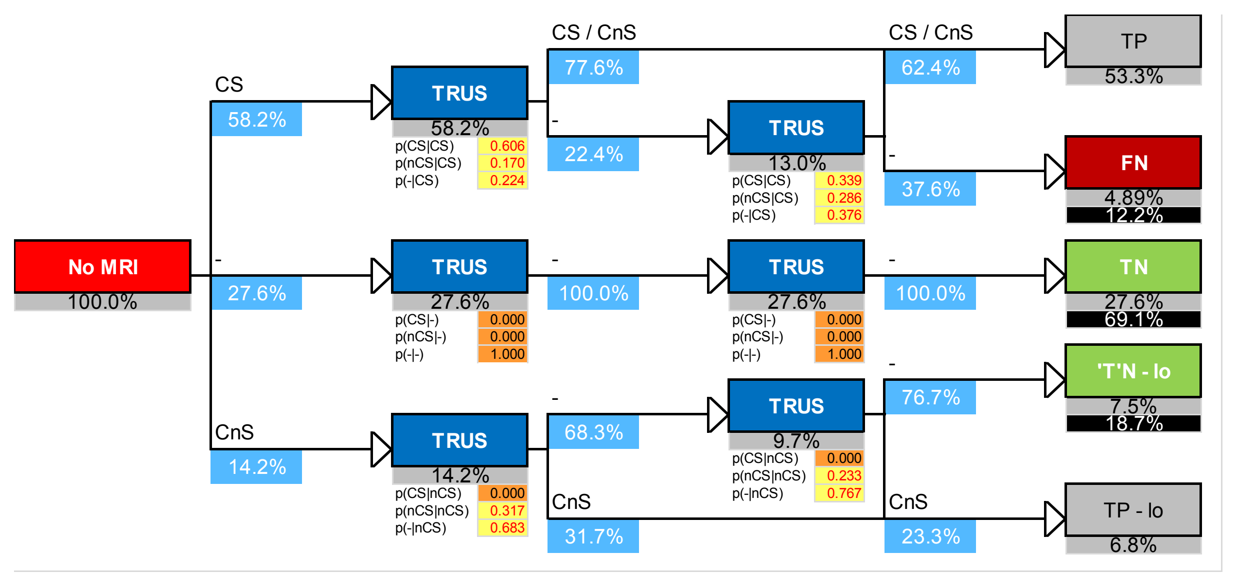
Bold line indicates cost effectiveness acceptability frontier

Figure HE46: Cost-effectiveness acceptability curve excluding TPM strategies

HE.3.11 2 biopsies; no mpMRI

Baseline population

The population of interest here is people who received 1 prostate biopsy (TRUS) and did not receive mpMRI. The average estimates for the prevalence and the accuracy data of TRUS obtained from the whole sample in PROMIS is assumed applicable for this population. This results in the baseline population distribution being 69.1%, 18.7% and 12.2% for people with truly no cancer, people with missed clinically non-significant cancer and people with missed clinically significant cancer, respectively, Figure HE47.



Bold line indicates Baseline population distribution (two previous biopsies and no mpMRI): Percentages in blue boxes indicate probabilities at each branch of the tree. Percentages in grey boxes indicate proportion of whole tested population at each stage. Percentages in black boxes indicate proportion of people receiving a negative diagnosis who fall into each category (note that the NPV of the algorithm is given by 1 – the proportion in the black box under 'FN'). Figures in yellow and orange boxes indicate conditional probabilities of each diagnosis, given true status. CS: Clinically significant; CnS: Clinically non-significant; FN: False negative CS disease; TN: true negative; 'T'N-lo: missed CnS disease; TP and TP-lo: Truly positive CS and CnS disease, respectively.

Figure HE47: The decision tree to derive the baseline population distribution (2 previous biopsies and no mpMRI)

Model dynamics

Figure HE48 demonstrates the modelled cohort over 30 years. On the left side, it shows the disease development, starting as low-risk and then progressing to intermediate-, then to high-risk and then to metastatic disease. On the right side, it shows the performance of diagnostics capturing the disease within people misclassified as false negative. This is shown for the least intensive "no screening" strategy, at the top, where people receive prostate biopsy only if they develop symptoms, to the most invasive strategy at the bottom, where all candidates receive an immediate TPM and not followed-up subsequently. In between, the impact of applying 3 follow-up strategies on disease progression and their performance in identifying missed disease is demonstrated over time. This is shown for: the strategy where people receive 2-yearly PSA tests; if velocity ≥0.75 ng/ml/year, they are directed to TRUS biopsy, the strategy where people receive yearly PSA tests; if velocity ≥0.75 ng/ml/year, they are directed to TRUS biopsy and the strategy where people receive an immediate TRUS and they are not followed-up subsequently:

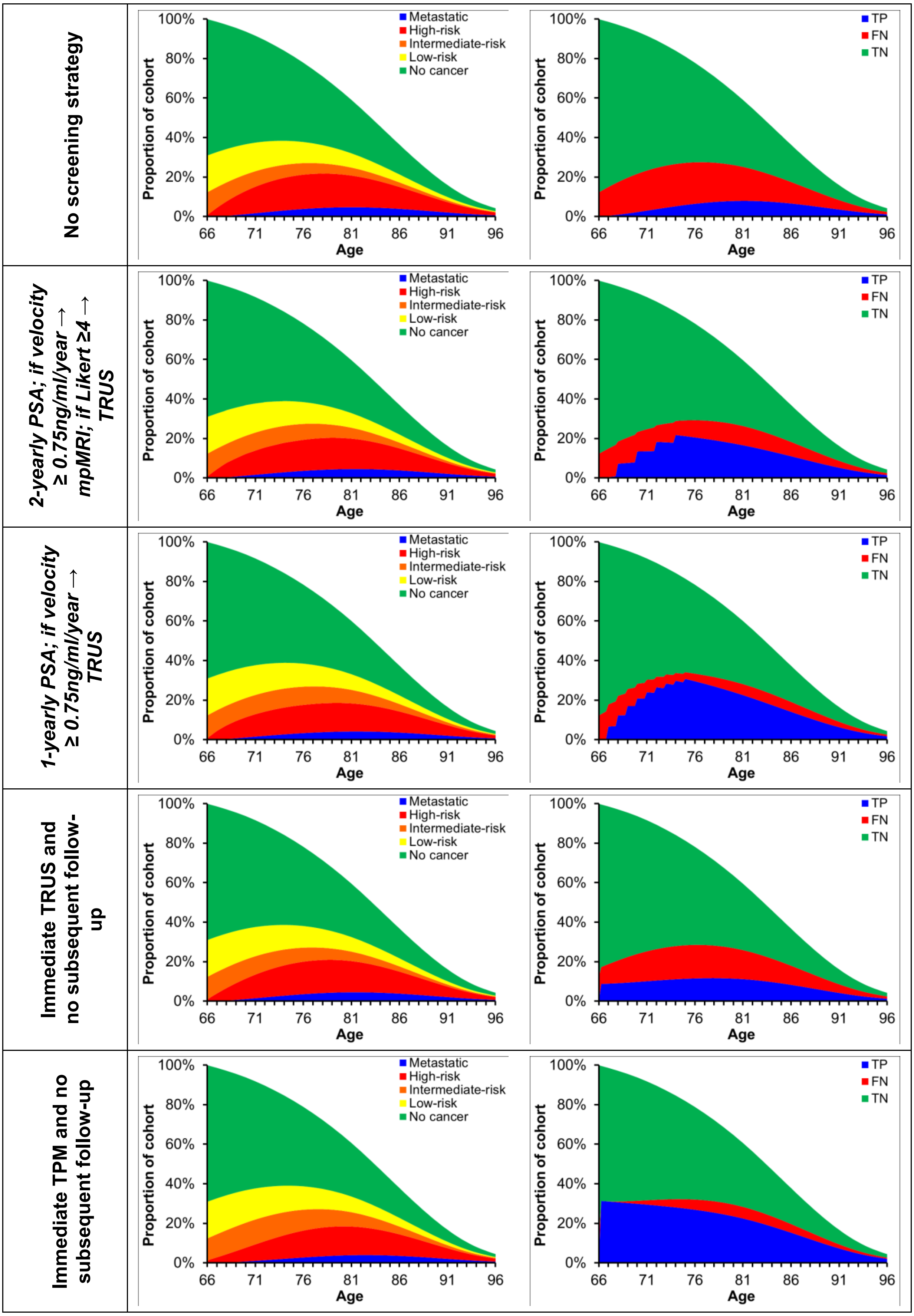


Figure HE48: Tracking the modelled cohort over 30 years, tracing the disease progression on the left hand, and reflecting the diagnosed cases overtime on the right hand for a given strategy

Incremental deterministic analysis

Table HE35 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, where people receive 2-yearly PSA tests, and if velocity ≥0.75 ng/ml/ml, they are directed to mpMRI that detects, if Likert ≥4, the need for a prostate biopsy, seems to be optimal. At a higher cost-effectiveness threshold (£30,000 per QALY), the strategy, including yearly PSA velocity tests at a threshold of 0.75 ng/ml/year and then prostate biopsy, seems optimal.

Table HE35: Base-case deterministic cost-utility results (excluding TPM) for people with two biopsies but no MRI

Strategy	Absolute		Incremental		
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£1,413	9.193			
TRUS everyone	£2,331	9.251	£918	0.058	£15,757
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TRUS	£3,350	9.307	£1,019	0.057	£18,012
2-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TRUS	£3,439	9.312	£90	0.004	£20,942
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£4,382	9.349	£943	0.037	£25,527
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	£4,509	9.352	£127	0.004	£33,689
6-monthly %free PSA; if level <15% → TRUS	£5,521	9.382	£1,012	0.029	£34,356
6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£5,837	9.386	£316	0.004	£76,949
3-monthly %free PSA; if level <15% → TRUS	£7,440	9.398	£1,604	0.012	£133,263
3-monthly PCA3; if level ≥ 50 → TRUS	£10,264	9.401	£2,824	0.003	£869,012

Table HE36 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The strategies, including PSA density test at a threshold of 0.15 ng/ml/ml, PSA velocity tests at a threshold of 0.75 ng/ml/year and % free PSA tests at a threshold of 15%, seem to have the first 3 positions if applied 2-yearly and combined with mpMRI at Likert score ≥4, at a cost-effectiveness threshold of £20,000. The strategies including the same screening tests, applied yearly and excluding the mpMRI, win the first 3 positions at a cost-effectiveness threshold of £30,000 per QALY. However, the strategies applied yearly and excluding the mpMRI were associated with a significantly increased number of associated unnecessary biopsies (more than 4 times).

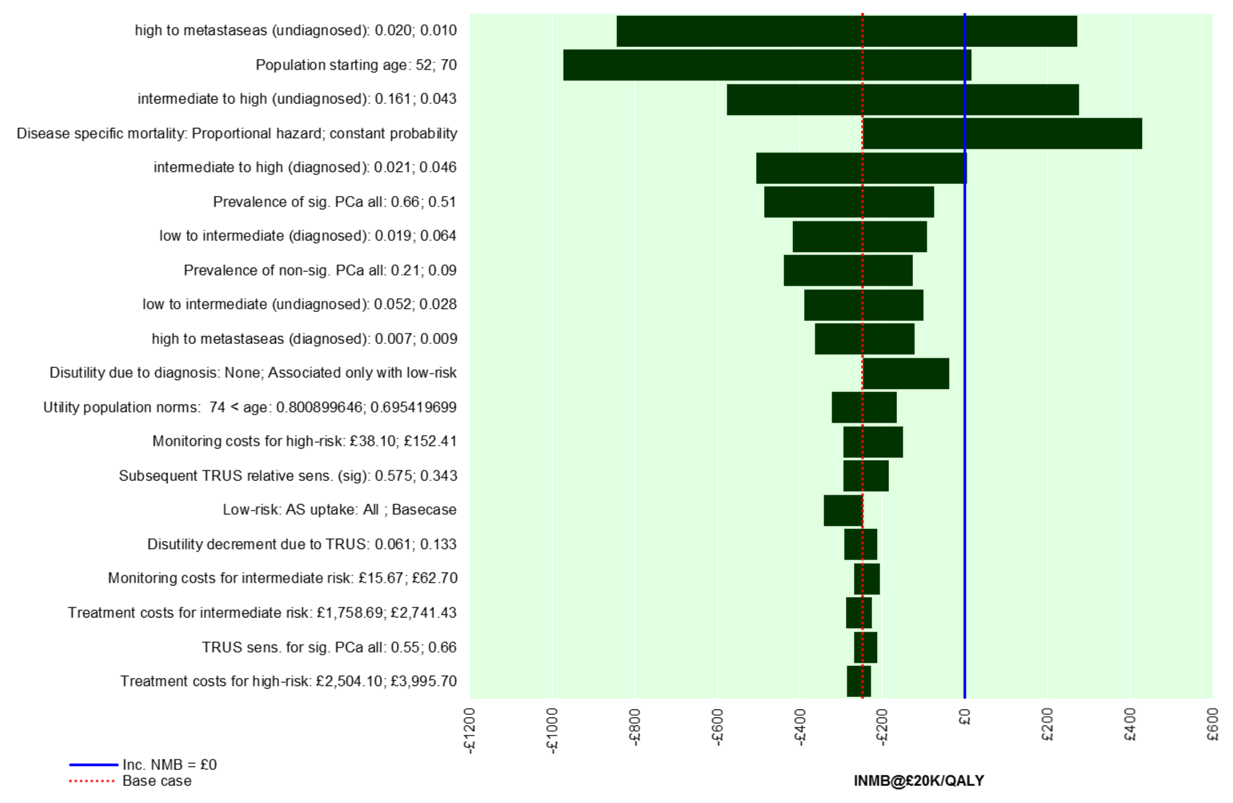
Table HE36: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY (excluding TPM) for people with two biopsies but no MRI

Strategy	Life-years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TRUS	16.74	12.8%	0.71	£53	£2,289	£3,350	9.307	1	10
2-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TRUS	16.75	12.7%	0.75	£53	£2,328	£3,439	9.312	2	8
2-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TRUS	16.71	13.1%	0.60	£102	£2,182	£3,158	9.296	3	15
3-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TRUS	16.70	13.2%	0.57	£38	£2,149	£3,034	9.288	4	36
3-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TRUS	16.69	13.3%	0.54	£38	£2,111	£2,960	9.284	5	38
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.72	12.9%	1.58	£53	£2,318	£3,122	9.291	6	32
2-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.74	12.8%	1.68	£52	£2,366	£3,209	9.295	7	27
TRUS everyone	16.61	14.4%	1.16	£0	£1,742	£2,331	9.251	8	66
3-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TRUS	16.66	13.6%	0.46	£73	£2,014	£2,799	9.274	9	51
[040] 2-yearly %free PSA; if level <15% → TRUS	16.69	13.3%	1.30	£102	£2,192	£2,936	9.281	10	48
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.88	11.2%	3.03	£108	£2,967	£4,382	9.349	27	1
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.90	11.1%	3.25	£107	£3,015	£4,509	9.352	35	2
1-yearly %free PSA; if level <15% → TRUS	16.85	11.6%	2.44	£211	£2,831	£4,130	9.338	17	3
2-yearly PSA; if density ≥ 0.12ng/ml/ml → mpMRI; if Likert ≥4 → TRUS	16.80	12.2%	1.02	£52	£2,496	£3,930	9.330	12	4
2-yearly PSA; if density ≥ 0.09ng/ml/ml → mpMRI; if Likert ≥4 → TRUS	16.81	12.2%	1.07	£52	£2,520	£4,022	9.332	20	5
6-monthly %free PSA; if level <15% → TRUS	16.98	10.2%	4.35	£390	£3,338	£5,521	9.382	74	6

Strategy	Life-years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
2-yearly mpMRI; if Likert ≥4 → TRUS	16.82	12.0%	1.18	£0	£2,558	£4,150	9.336	31	7
2-yearly PSA; if level ≥ 6ng/ml → mpMRI; if Likert ≥4 → TRUS	16.78	12.4%	0.93	£52	£2,421	£3,753	9.321	11	9

One-way sensitivity analysis

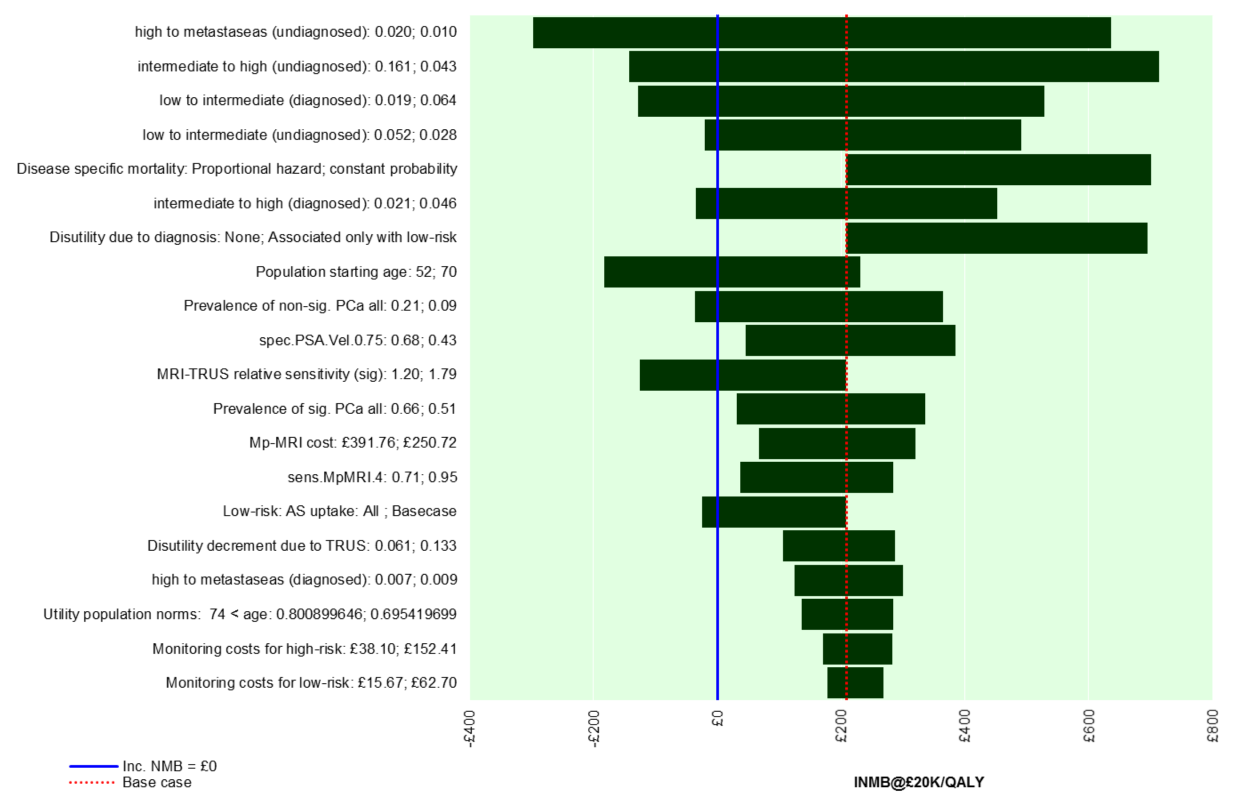
Figure HE49 shows the impact of changing the value of a parameter on the results of a pairwise comparison between the “no screening” strategy and the strategy, where people receive an immediate TRUS. It shows that the latter strategy remains worthwhile unless the disease progression in undiagnosed cases is slower, or the modelled cohort starting age is 70. Applying the prostate cancer death as a constant probability in the model results in the results always in favour of the less intensive strategy.



Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE49: One-way sensitivity analysis “no screening” vs “TRUS everyone” based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Figure HE50 shows the impact of changing the value of a parameter on the results of a pairwise comparison between the strategy, where people receive 2-yearly PSA tests, and if velocity ≥0.75 ng/ml/ml, they are directed to mpMRI that detects, if Likert ≥4, the need for a prostate biopsy, and the strategy applying the same PSA velocity test yearly and excluding the mpMRI. It shows that the latter strategy becomes more cost-effective at a threshold of £20,000 per QALY if the disease progression is faster, or the modelled cohort starting age is younger (52), or the relative sensitivity of MRI-influenced TRUS is lower (1.20 obtained from Schoots et al.), or the diagnosed low-risk people receive all active surveillance.

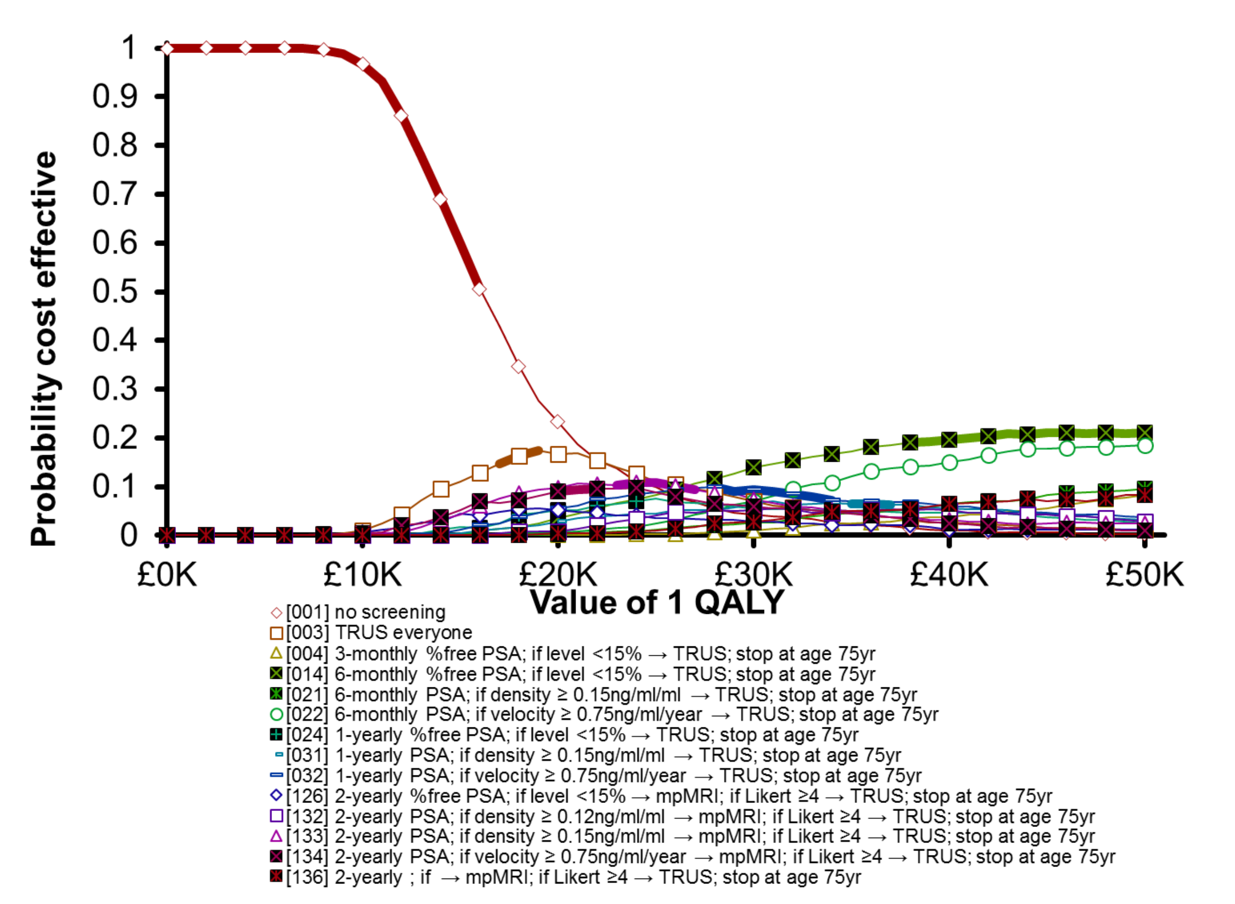


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE50: One-way sensitivity analysis "2-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TRUS" vs "1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Probabilistic results

Figure HE51 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY, excluding strategies with TPM. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, where people receive 2-yearly PSA tests, and if velocity ≥0.75 ng/ml/ml, they are directed to mpMRI that detects, if Likert ≥4, the need for a prostate biopsy, seems optimal with a probability of 10%. At a cost-effectiveness threshold of £30,000 per QALY, the strategy, applying the same PSA velocity test yearly and excluding the mpMRI, seems optimal with a probability of just less than 10%. At a cost-effectiveness threshold of £40,000 per QALY, the strategy, including 6-monthly % free PSA test at a threshold of 15%, seems cost-effective with a probability of 20%.



Bold line indicates cost effectiveness acceptability frontier

Figure HE51: Cost-effectiveness acceptability curve excluding TPM strategies

HE.4 Discussion

The model results suggest follow-up protocols found to be optimal for people with previous negative findings using mpMRI and/or prostate biopsy. The analysis addressed 11 sub-population based on previous diagnosis using Likert score for people who received mpMRI and the number of previous negative biopsies, either 1 or 2.

The strategy where people receive an immediate TPM biopsy seemed to be the most optimal in the majority of the sub-populations. However, this type of biopsy was assumed to be perfectly sensitive in the model, which may not be the case in clinical practice. In addition, it would be associated with overdiagnosis, which means people with clinically non-significant disease would be identified causing them anxiety and probably exposing them to treatments that are not likely to provide any extended survival. This may cause potential harms that the base case model may underestimate.

Having excluded strategies with TPM biopsy, measures derived from PSA tests, including velocity at a threshold of 0.75 ng/ml/year, density at a threshold of 0.15 ng/ml/ml and the percentage of free PSA at a threshold of 15% appeared to be reliable indicators that trigger further diagnostics within the majority of subpopulations. However, “no screening” strategy appears optimal for the lowest-risk subpopulation who had MRI Likert scores of 1 or 2 and 2 previous negative biopsies, unless QALYs are valued at a little over £20,000 each. The model generates consistent results, as the optimal frequency of tests changes proportionally with the potential risk of disease. For example, within the population who had negative mpMRI (Likert 1 or 2), the optimal frequency of the PSA velocity test was every 6 months, every year or 2-yearly for people who had no biopsy, 1 biopsy or 2 biopsies, respectively (when QALYs are valued at £30,000).

However, the one-way sensitivity analysis shows high uncertainty surrounding the results. The hazard of prostate cancer death is proportional to general mortality in the model base-case, as the model seems to fit the data well. Assigning a constant probability with time to the disease specific mortality has a significant impact on the results, leading to fewer deaths. The strategy where all candidates receive an immediate TRUS and no subsequent follow-up was found optimal in the majority of sub-populations when prostate cancer death was assigned a constant probability with time. Further, the uncertainty in disease progression, in particular the transitions from intermediate- to high-risk disease and from high-risk disease to metastases within undiagnosed cases, affects the model conclusions.

The impact on the model results occurred due to assigning a constant probability over time to disease specific death can be explained. The probability of prostate cancer death and probabilities of progression in diagnosed cases were derived from a model calibration that used two sources: 1) disease specific death from metastatic population reported in STAMPEDE, and 2) disease specific death from localised disease reported in Gnanapragasam et al. (2016). This led to the progression probabilities being different according to the disease-specific death whether it was assigned a proportional hazard or a constant probability over time. In the base-case, the hazard of prostate cancer death for diagnosed people was 9 times the hazard of death in general population; this implies that the probability of prostate cancer death for people at age 79 for example is 11.2%, whereas the constant probability of prostate cancer death was 3%. Further, assigning a constant probability to disease-specific death was associated with treatments being less effective; the disease progression from high-risk to metastases was 0.8% in the base-case compared to 1.4% in the scenario where the prostate cancer death was assigned a constant probability over time.

The pairwise sensitivity analysis between the strategies that include PSA velocity at a threshold of 0.75 ng/ml/year, PSA density at a threshold of 0.15 ng/ml/ml or the percentage of free PSA at a threshold of 15% shows that they perform similarly, given the 95% confidence interval of the accuracy estimates.

Model validation

When compared with disease specific mortality at 10 years reported by Gnanapragasam et al. (2016) that analysed UK registry data on people with localised prostate cancer, the model delivers comparable results when the baseline population start at diagnosed states. In their study, the cumulative incidence of prostate cancer death was 2%, 7% and 20% for people with low-, intermediate- and high-risk disease, compared to 1.6%, 6.1% and 17.4% for the same risk groups respectively. When assigned a constant probability with time, prostate cancer death at 10 years was 1.6%, 5.6% and 15.3% for people with low-, intermediate- and high-risk disease, respectively.

When compared with the 10-year mortality reported by Hamdy et al. (2016) from the overall arms in ProtecT, the model delivers somewhat divergent results. The cumulative incidence of total death and disease specific death was 10% and 1%, respectively in ProtecT. However, the figures were 16.2% and 2.5% for total deaths and prostate cancer death, respectively in our model, and when assigned a constant probability over time to disease specific death, the difference in figures was larger, 17.1% and 3.5% for all deaths and prostate cancer deaths, respectively. However, the disparity between the figures in ProtecT and our model can be justified. The population was considered healthy in ProtecT compared with the general population, as the 10-year cumulative incidence of all cause death for people starting at age 62 was 10%, which is relatively low. Further, the population in ProtecT was recruited from a screening program, which implies that the disease was identified in its very early stage. In our model, the disease progression probabilities were obtained from a UK registry data that is more likely to reflect the real world.

When compared with the intervention arm in the Scandinavian study, SPCG4, our model delivers comparable results when baseline populations start at diagnosed states. The 18-year cumulative incidence of disease specific death was 10.2%, 15.1% and 33.1%, compared to 8.1%, 16.1% and 29.1% in our model for people with low-, intermediate- and high-risk disease, respectively. When disease specific mortality was assigned a constant probability over time, the figure in our model were 6.3%, 14.9% and 28.8% for low-, intermediate- and high-risk groups, respectively.

However, when compared with the watchful waiting arm in the Scandinavian study, the results were more divergent and the disparity between our model base-case results and our model when disease specific death was assigned a constant probability over time was even more noticeable. The 18-year disease specific death was 14%, 39.3% and 35.7% in the watchful waiting arm in the Scandinavian study compared to 20.3%, 35.2% and 43.5% in our model when the baseline population started at undiagnosed states and were not-followed up for people with low-, intermediate- and high-risk disease, respectively. However, these figures were 12%, 23.2% and 31% in our model when disease specific death was assigned a constant probability over time for low-, intermediate- and high-risk groups. It is noteworthy that the results reported in the Scandinavian study shows inconsistency, as the cumulative incidence of prostate cancer death in people with high-risk disease is less than it in the intermediate-risk group (35.7% vs 39.3%).

The economic evaluation performed by Faria et al based on PROMIS showed that the optimal strategy to diagnose prostate cancer was to offer people mpMRI and, if it shows positive findings, up to 2 TRUS. In addition to the apparent difference between populations in PROMIS and our analysis that addresses people with previous negative findings, there are further differences in our approach that worth noting. To address the heterogeneity within people with different findings on mpMRI, the disease prevalence used in our analysis is different according to Likert score. Further, the TRUS performance varies according to Likert score, based on evidence obtained from PROMIS. Our approach of addressing populations based on Likert score allows to deploy the relevant TRUS accuracy data based on Likert score. Using the average TRUS sensitivity obtained from all Likert score leads to the TRUS performance being overestimated when applied to people with Liker score 1 or 2.

Faria et al. obtained the disease progression probabilities from a model calibration that used outcomes from a US study by Wilt et al. (2012) that reported findings from PIVOT. It is a randomised clinical trial, where people were randomly assigned to active monitoring or radical prostatectomy. In this study, the inclusion criteria required people to be 75 years old or younger with life expectancy of at least 10 years and are fit to prostate surgery. This implies that population is potentially considered healthier than what would be expected in real life. Thus, the disease is less aggressive in PROMIS economic evaluation than in our analysis with a yearly transition probability from high-risk to metastases at 2.2% and 0.8% vs 5.6% and 3.2% for undiagnosed and diagnosed cases, respectively. Further, the prostate cancer death was assigned a constant probability over time with a yearly probability of 14.7% and 14.3% for people with undiagnosed and diagnosed metastatic prostate cancer in PROMIS economic evaluation. The base case in our analysis deploys disease specific mortality as a proportional hazard to general mortality. However, we assigned a constant probability to the disease specific mortality in a scenario analysis; the yearly probabilities of prostate cancer death were 16.7% and 11.4% for people with undiagnosed and diagnosed metastatic prostate cancer, respectively.

HE.5 References

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HE.6 Appendix

HE.6.1 Base-case cost–utility results including TPM strategies

The results reported in this section include TPM strategies.

HE.6.1.1 MRI Likert 1 or 2; 0 biopsies

Incremental deterministic analysis

Table HE37 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, where all candidates receive an immediate TPM and no subsequent follow-up, seems optimal.

Table HE37: Base-case deterministic cost-utility results for people with Likert <3 and no biopsies

Strategy	Absolute		Incremental		
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£1,961	8.881			
TRUS everyone	£3,250	8.989	£1,290	0.108	£11,954
TPM everyone	£6,878	9.277	£3,627	0.288	£12,610

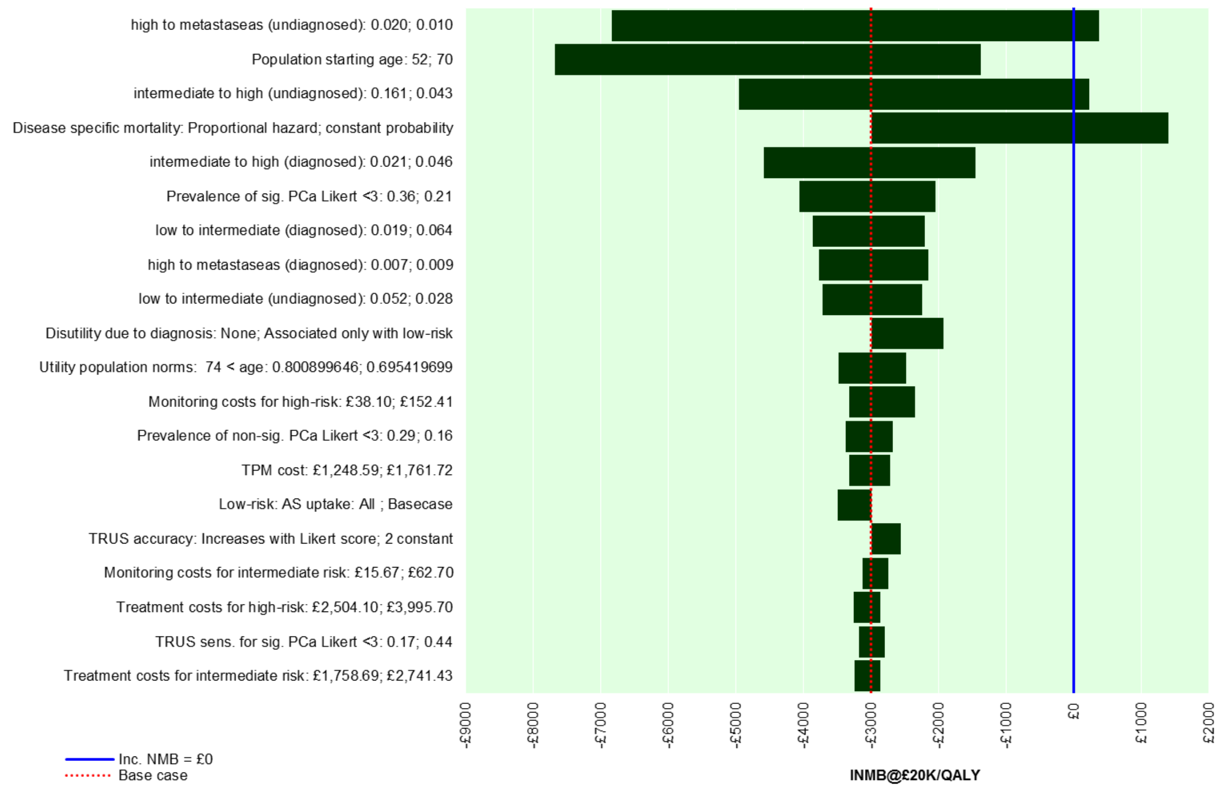
Table HE38 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The strategy, where people receive 2-yearly PSA tests, and if density ≥0.15 ng/ml/ml, they receive mpMRI, and if Likert score ≥4, they are directed to TPM, wins the second position at a cost-effectiveness threshold of £20,000 per QALY. However, the same strategy with a lower PSA density threshold (0.12 ng/ml/ml) maintains the same rank at a cost-effectiveness threshold of £30,000 per QALY.

Table HE38: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY for people with Likert <3 and no biopsies

Strategy	Life years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
TPM everyone	16.72	13.4%	0.91	£0	£5,081	£6,878	9.277	1	1
2-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.56	14.4%	0.48	£39	£4,843	£6,446	9.199	2	7
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TPM	16.54	14.6%	0.45	£39	£4,797	£6,352	9.193	3	9
2-yearly PSA; if density ≥ 0.12ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.61	14.0%	0.63	£37	£5,007	£6,942	9.219	4	2
2-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM	16.51	14.9%	0.39	£78	£4,661	£6,117	9.177	5	15
2-yearly PSA; if level ≥ 6ng/ml → mpMRI; if Likert ≥4 → TPM	16.59	14.2%	0.59	£38	£4,939	£6,780	9.210	6	6
2-yearly PHI; if level ≥ 35 → mpMRI; if Likert ≥4 → TPM	16.58	14.3%	0.50	£211	£4,912	£6,742	9.207	7	8
2-yearly PSA; if density ≥ 0.09ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.61	13.9%	0.66	£37	£5,028	£7,036	9.221	8	3
2-yearly mpMRI; if Likert ≥4 → TPM	16.62	13.9%	0.73	£0	£5,058	£7,186	9.225	9	4
2-yearly %free PSA; if level <15% → TPM	16.55	14.5%	0.90	£75	£4,806	£6,556	9.190	10	16
6-monthly PHI; if level ≥ 62 → TPM	16.68	13.4%	1.08	£836	£5,194	£7,936	9.249	29	5
6-monthly DRE; if abnormal → TPM	16.64	13.7%	1.20	£315	£5,070	£7,465	9.230	23	10

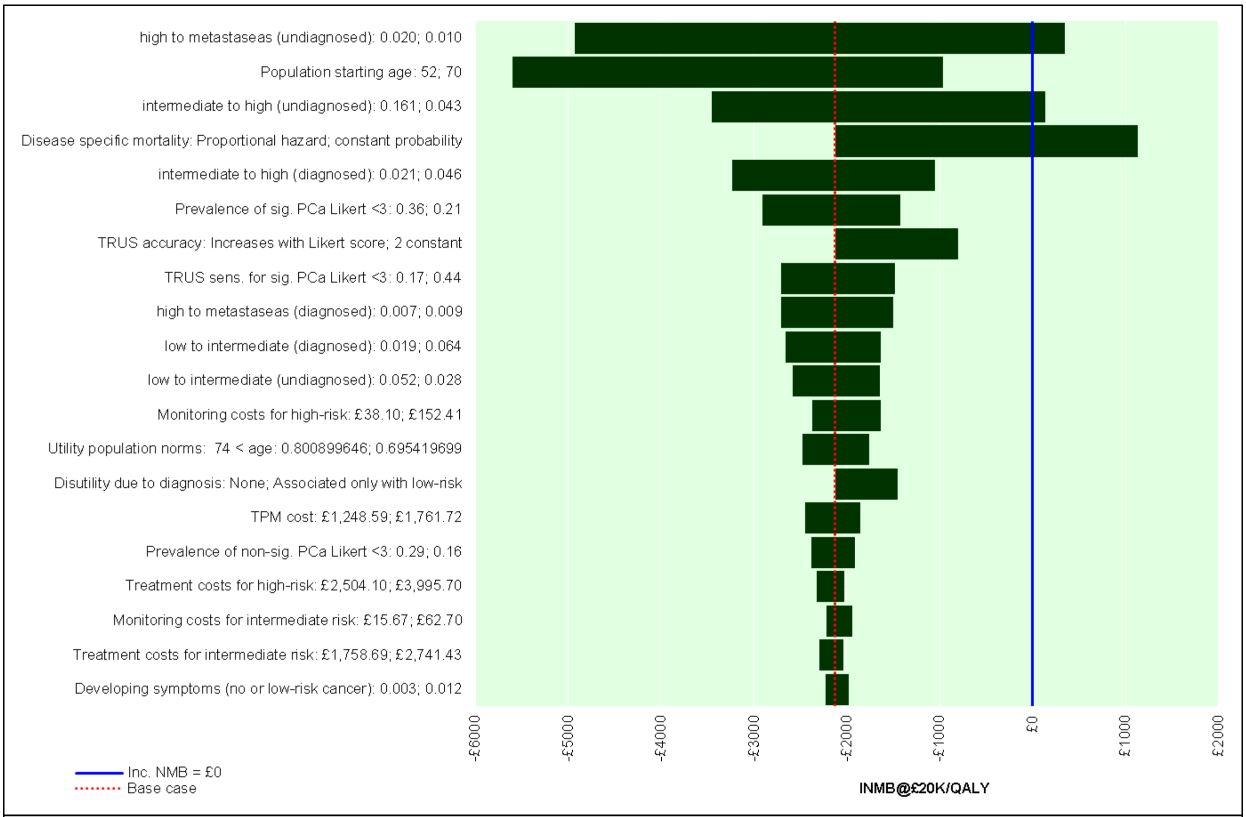
One-way sensitivity analysis

Figure HE52 shows the impact of changing the value of a parameter on the results of a pairwise comparison between “no screening” strategy and the strategy where people receive an immediate TPM biopsy and not followed-up subsequently. It shows that the results are sensitive to probabilities of progression from intermediate- to high-risk and from high-risk to metastatic in undiagnosed cases. It shows also the significant impact of assigning a constant probability to prostate cancer death on the results, where “no screening” strategy becomes more beneficial.



Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE52: One-way sensitivity analysis “no screening” vs “TPM everyone”based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

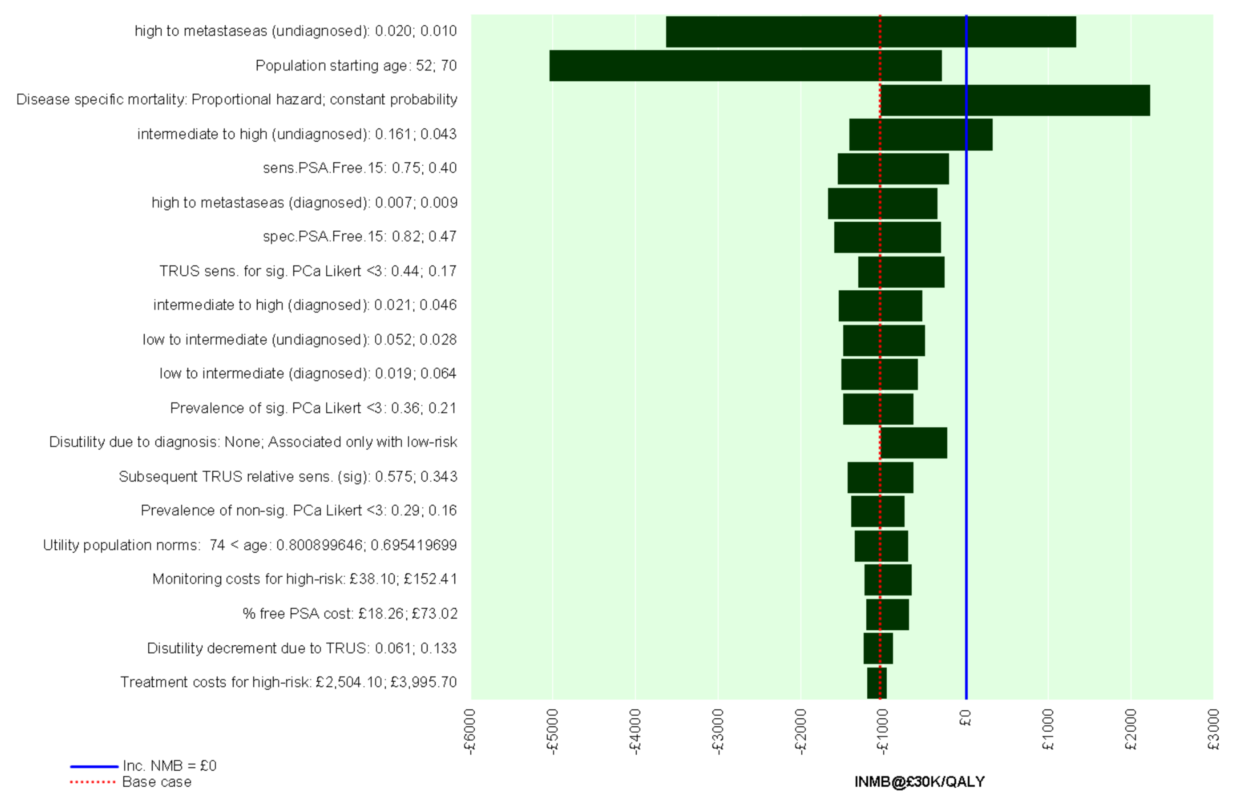


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE53: One-way sensitivity analysis "TRUS everyone" vs "TPM everyone" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Figure HE53 shows the impact of changing the value of a parameter on the results of a pairwise comparison between "TRUS everyone" strategy and the strategy where people receive an immediate TPM biopsy and not followed-up subsequently. It shows that the results are sensitive to probabilities of progression from high-risk to metastatic in undiagnosed cases. It shows also the significant impact of assigning a constant probability to prostate cancer death on the results, where "TRUS everyone" strategy becomes more beneficial.

Figure HE54 shows the impact of changing the value of a parameter on the results of a pairwise comparison between "TRUS everyone" strategy and the strategy where people receive 6-monthly % free PSA test at a threshold of 15%, and then a TRUS biopsy. It shows that the results are sensitive to probabilities of progression from intermediate- to high-risk and from high-risk to metastatic in undiagnosed cases. It shows also the significant impact of assigning a constant probability to prostate cancer death on the results, where "no screening" strategy becomes more beneficial.

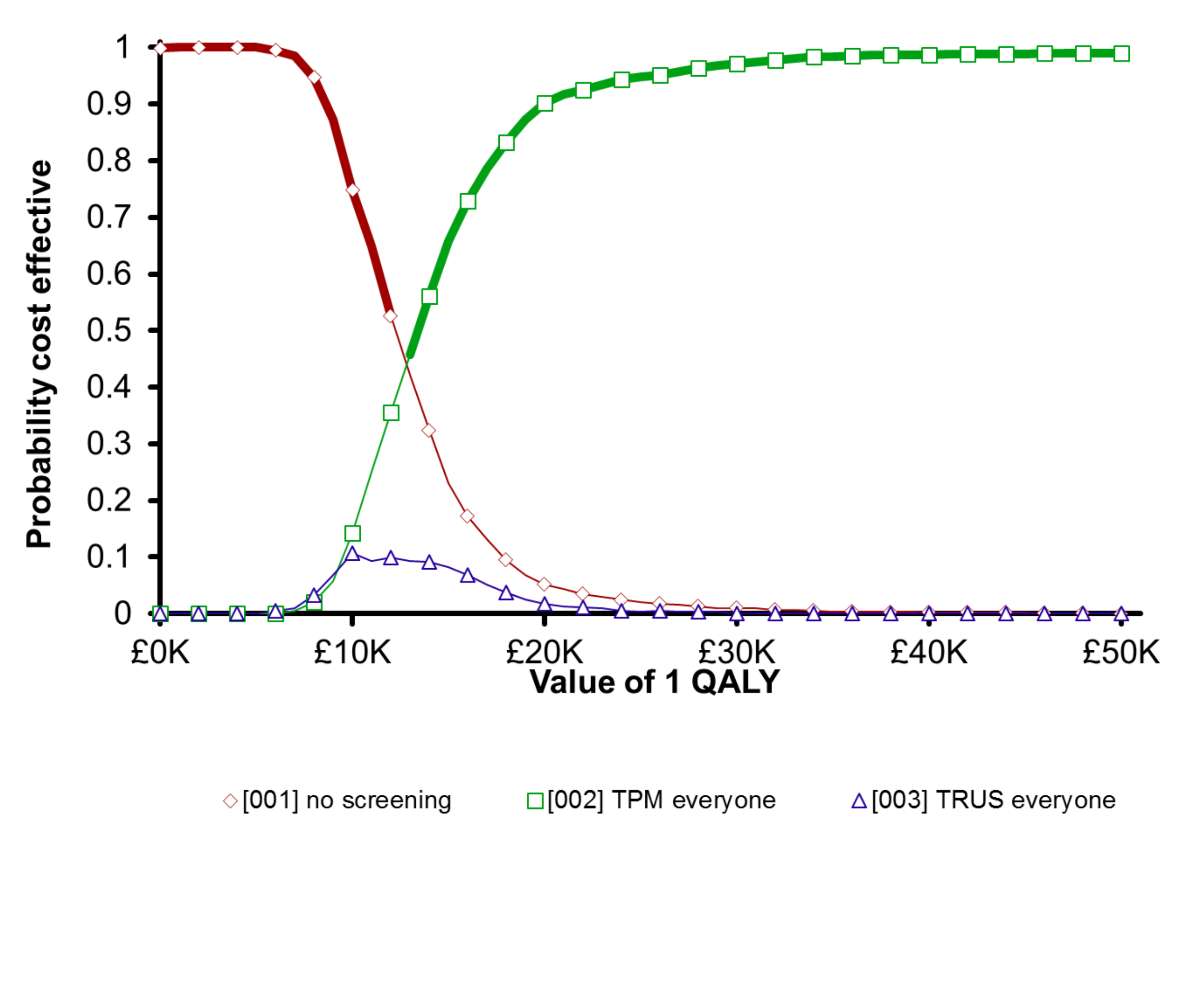


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE54: One-way sensitivity analysis “TRUS everyone” vs “6-monthly %free PSA; if level <15% → TRUS” based on the incremental net monetary benefits at cost-effectiveness threshold of £30,000 per QALY

Probabilistic results

Figure HE55 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. The strategy where people receive an immediate TPM seems to be cost-effective at a threshold of £20,000 per QALY with a probability of about 90%.



Bold line indicates cost effectiveness acceptability frontier

Figure HE55: Cost-effectiveness acceptability curve

HE.6.12 MRI Likert 1 or 2; 1 biopsy

Incremental deterministic analysis

Table HE39 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, where all candidates receive an immediate TPM and no subsequent follow-up, seems optimal.

Table HE39: Base-case deterministic cost-utility results for people with Likert <3 and one biopsy

Strategy	Absolute		Incremental		
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£1,249	9.151			
2-yearly DRE; if abnormal → mpMRI; if Likert ≥4 → TPM; stop at age 75yr	£3,677	9.302	£2,428	0.152	£16,019
TPM everyone	£5,389	9.406	£1,711	0.104	£16,532
3-monthly PHI; if level ≥ 62 → TPM; stop at	£9,224	9.423	£3,835	0.017	£221,379

age 75yr					

Table HE40 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The strategies including 2-yearly % free PSA test at a threshold of 15%, 2-yearly PSA velocity test at a threshold of 0.75ng/ml/year or 2-yearly PSA density test at a threshold of 0.15 ng/ml/ml, if reached the thresholds, followed by mpMRI, if Likert ≥4, people receive TPM, win the best positions following the strategy, where all receive an immediate TPM.

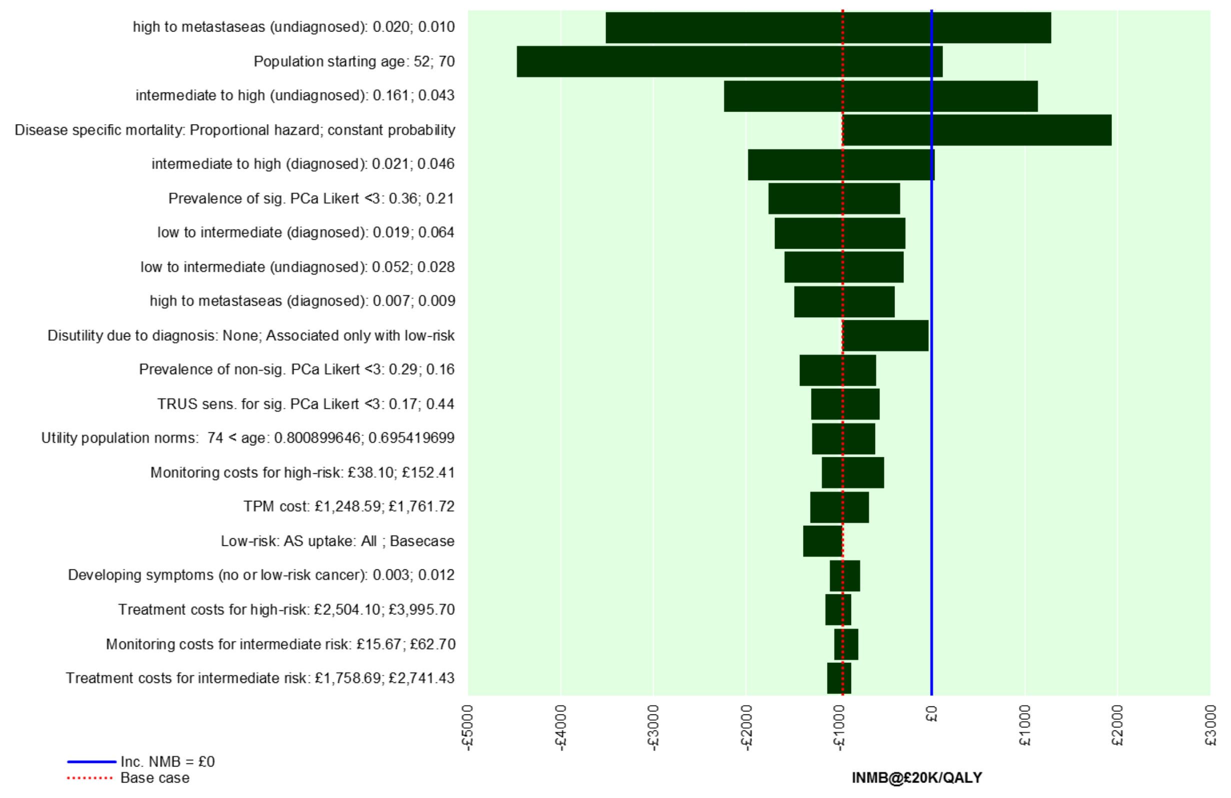
Table HE40: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY for people with Likert <3 and one biopsy

Strategy	Life years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
TPM everyone	17.00	10.3%	1.12	£0	£3,494	£5,389	9.406	1	1
2-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM	16.92	10.7%	0.46	£89	£3,415	£4,806	9.370	2	4
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TPM	16.95	10.4%	0.54	£45	£3,524	£5,042	9.381	3	3
2-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.95	10.3%	0.57	£45	£3,560	£5,140	9.385	4	2
3-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TPM	16.89	10.9%	0.44	£33	£3,324	£4,609	9.355	5	13
3-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.90	10.8%	0.47	£33	£3,369	£4,701	9.359	6	11
3-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM	16.85	11.2%	0.38	£65	£3,197	£4,382	9.343	7	19
2-yearly DRE; if abnormal → mpMRI; if Likert ≥4 → TPM	16.75	12.4%	0.26	£101	£2,722	£3,677	9.302	8	47
2-yearly PHI; if level ≥ 62 → mpMRI; if Likert ≥4 → TPM	16.79	12.0%	0.26	£276	£2,905	£4,048	9.320	9	38
3-yearly PHI; if level ≥ 35 → mpMRI; if Likert ≥4 → TPM	16.91	10.6%	0.49	£181	£3,441	£4,973	9.366	10	16
2-yearly PHI; if level ≥ 35 → mpMRI; if Likert ≥4 → TPM	16.97	10.2%	0.60	£246	£3,616	£5,463	9.391	11	5
2-yearly PSA; if level ≥ 6ng/ml → mpMRI; if Likert ≥4 → TPM	16.97	10.1%	0.72	£44	£3,637	£5,532	9.392	15	6

2-yearly PSA; if density ≥ 0.12ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.99	10.0%	0.77	£43	£3,694	£5,707	9.398	19	7
2-yearly PSA; if density ≥ 0.09ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.99	9.9%	0.82	£43	£3,710	£5,822	9.399	27	8
2-yearly PCA3; if level ≥ 50 → mpMRI; if Likert ≥4 → TPM	16.94	10.5%	0.47	£428	£3,483	£5,227	9.377	14	9
3-yearly PSA; if density ≥ 0.12ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.94	10.3%	0.62	£32	£3,545	£5,193	9.376	13	10

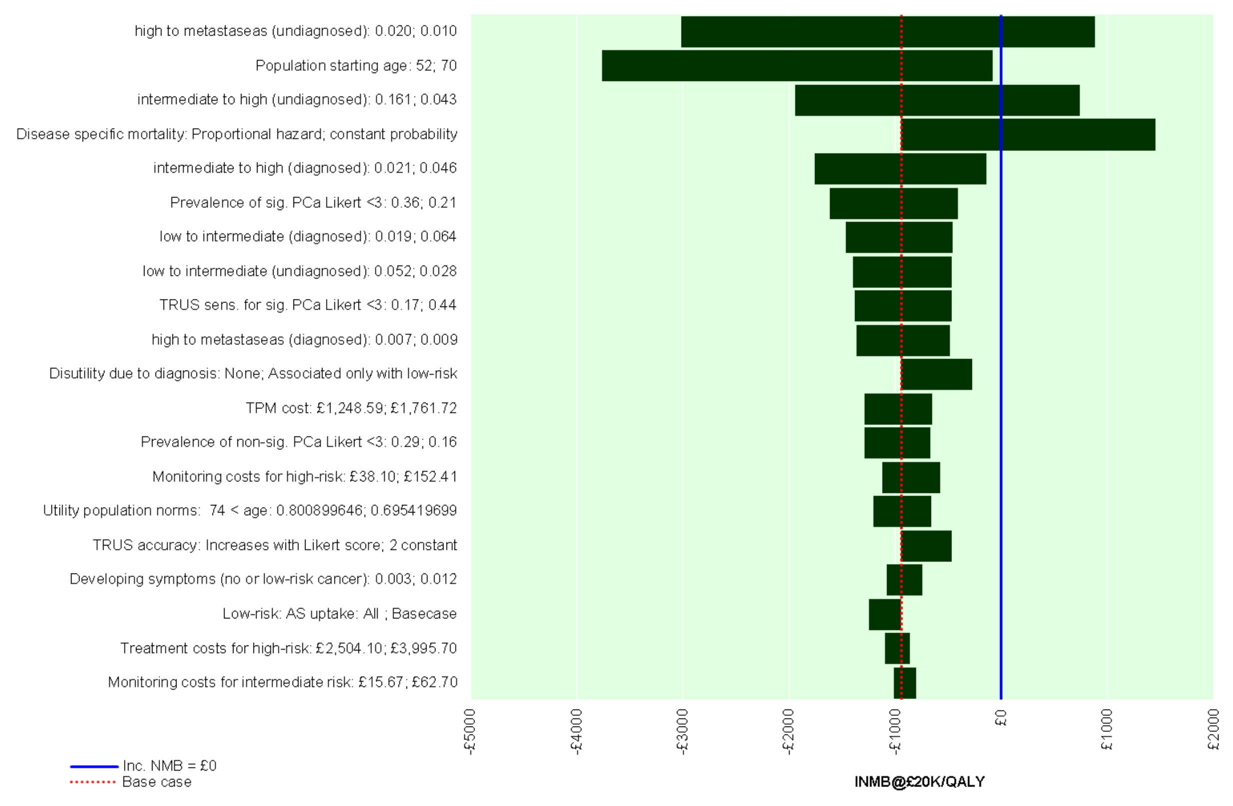
One-way sensitivity analysis

Figure HE56 shows the impact of changing the value of a parameter on the results of a pairwise comparison between “no screening” strategy and the strategy where people receive an immediate TPM biopsy and not followed-up subsequently. It shows that the results are sensitive to probabilities of progression from intermediate- to high-risk and from high-risk to metastatic in undiagnosed cases. It shows also the significant impact of assigning a constant probability to prostate cancer death on the results, where “no screening” strategy becomes more beneficial**.** Starting the model at an older age (70) disadvantages the interventional strategy.



Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE56: One-way sensitivity analysis “no screening” vs “TPM everyone” based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

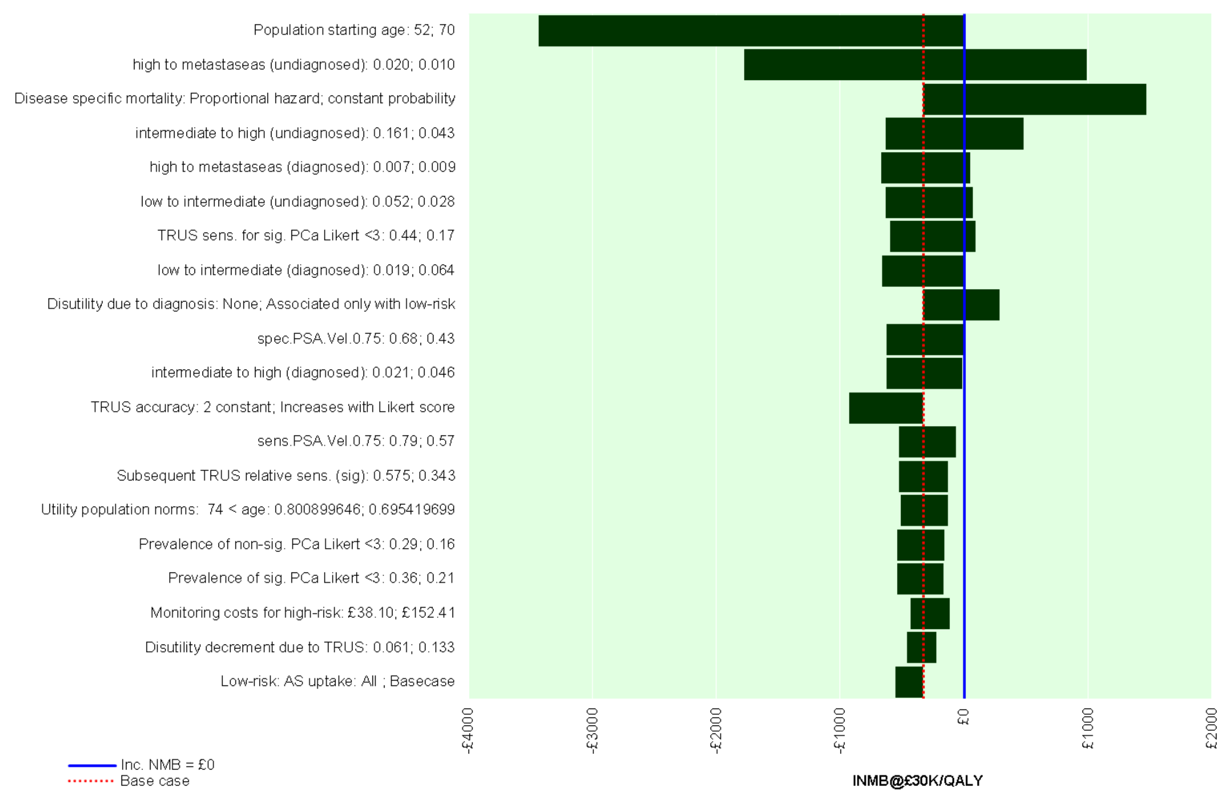


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE57: One-way sensitivity analysis "TRUS everyone" vs "TPM everyone" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Figure HE57 shows the impact of changing the value of a parameter on the results of a pairwise comparison between "TRUS everyone" strategy and the strategy where people receive an immediate TPM biopsy and not followed-up subsequently. It shows that the results are sensitive to probabilities of progression from intermediate- to high-risk and from high-risk to metastatic in undiagnosed cases. It shows also the significant impact of assigning a constant probability to prostate cancer death on the results, where "TRUS everyone" strategy becomes more beneficial.

Figure HE58 shows the impact of changing the value of a parameter on the results of a pairwise comparison between "TRUS everyone" strategy and the strategy where people receive yearly PSA tests; if velocity ≥ 0.75ng/ml/year, directed to TRUS. It shows that the results are sensitive to probabilities of progression in undiagnosed and diagnosed cases. It shows also the significant impact of assigning a constant probability to prostate cancer death on the results, where "TRUS everyone" strategy becomes more beneficial. Also, assigning a disutility for people with low-risk disease once diagnosed disadvantages the follow-up protocol.

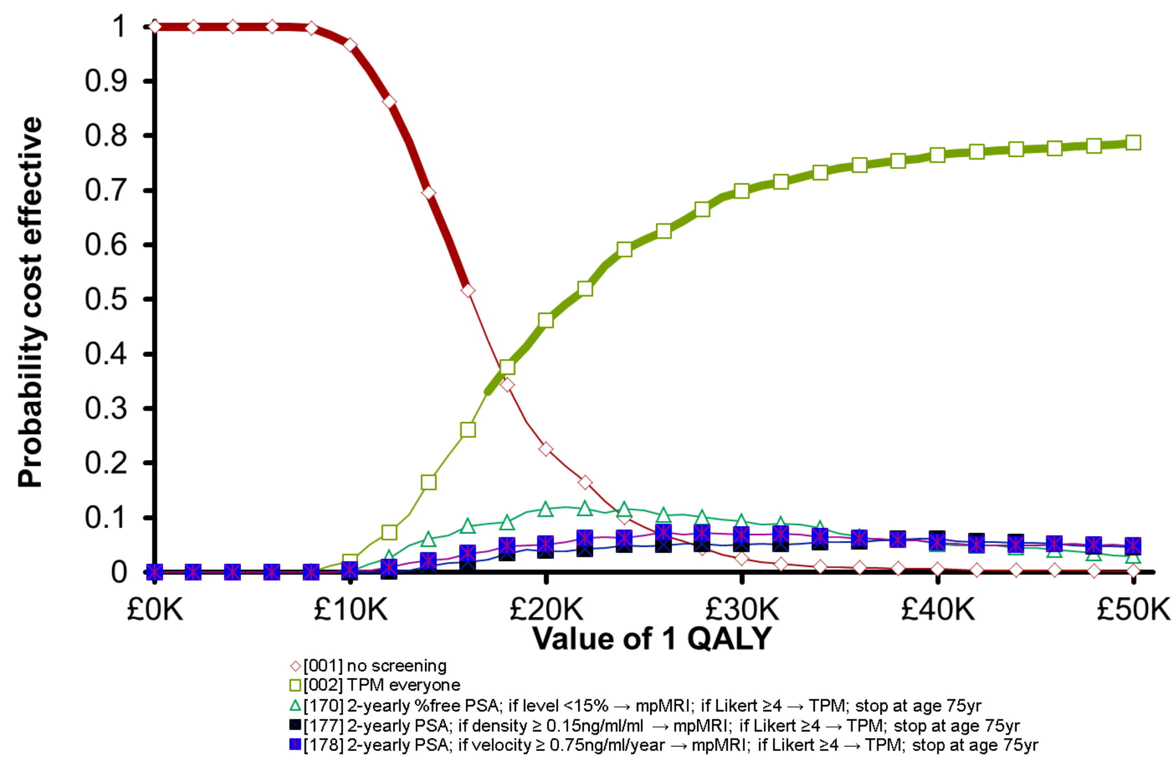


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE58: One-way sensitivity analysis "TRUS everyone" vs "1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS" based on the incremental net monetary benefits at cost-effectiveness threshold of £30,000 per QALY

Probabilistic results

Figure HE59 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. The strategy where people receive an immediate TPM seems to be cost-effective at a threshold of £20,000 per QALY with a probability of about 40%.



Bold line indicates cost effectiveness acceptability frontier

Figure HE59: Cost-effectiveness acceptability curve

HE.6.13 MRI Likert 1 or 2; 2 biopsies

Incremental deterministic analysis

Table HE41 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, where 3-yearly % free PSA tests direct candidates to mpMRI that in turn direct people to TPM, if Likert score ≥4, seems optimal. At a slightly higher cost-effectiveness threshold, the same strategy applied 2-yearly seems to be optimal.

Table HE41: Base-case deterministic cost-utility results for people with Likert <3 and two biopsies

Strategy	Absolute		Incremental		
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£981	9.305			
2-yearly DRE; if abnormal → mpMRI; if Likert ≥4 → TPM	£3,045	9.419	£2,064	0.115	£17,957
3-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM	£3,700	9.452	£656	0.033	£19,953
2-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM	£4,076	9.471	£376	0.019	£20,237
2-yearly PSA; if velocity ≥ 0.75ng/ml/year →	£4,313	9.479	£237	0.008	£29,720

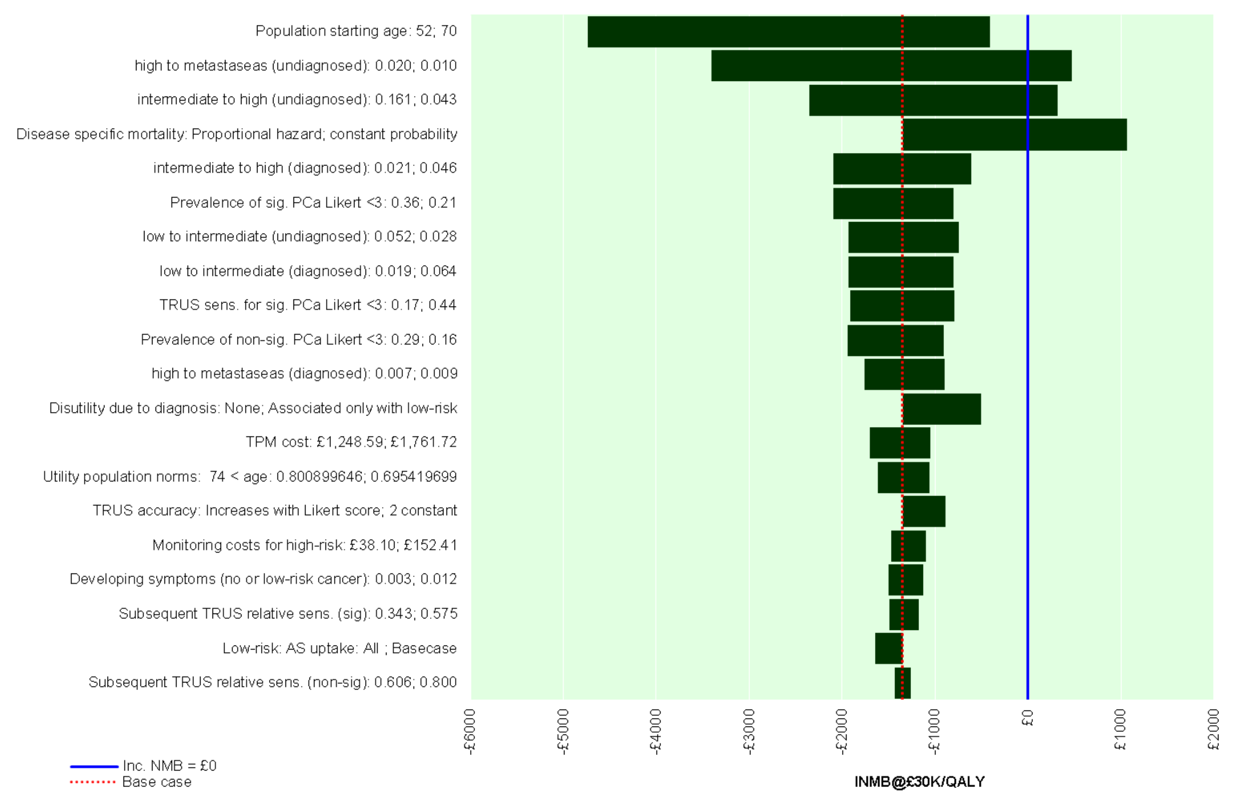
mpMRI; if Likert ≥4 → TPM					
2-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TPM	£4,413	9.482	£100	0.003	£36,868
2-yearly PSA; if density ≥ 0.12ng/ml/ml → mpMRI; if Likert ≥4 → TPM	£5,021	9.491	£608	0.009	£66,189
2-yearly PSA; if density ≥ 0.09ng/ml/ml → mpMRI; if Likert ≥4 → TPM	£5,148	9.492	£127	0.001	£133,790
2-yearly mpMRI; if Likert ≥4 → TPM	£5,363	9.493	£215	0.001	£178,041
6-monthly PHI; if level ≥ 62 → TPM	£6,392	9.497	£1,029	0.004	£281,234
3-monthly PHI; if level ≥ 62 → TPM	£8,959	9.500	£2,567	0.004	£662,879

Table HE42 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The strategy including 2-yearly PSA velocity test at a threshold of 0.75 ng/ml/year, if reached the threshold, followed by mpMRI, if Likert ≥4, people receive TPM, win the 1st position at the cost-effectiveness threshold of £30,000 per QALY.

Table HE42: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY for people with Likert <3 and two biopsies

Strategy	Life years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
3-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM	17.09	8.8%	0.41	£69	£2,562	£3,700	9.452	1	6
2-yearly DRE; if abnormal → mpMRI; if Likert ≥4 → TPM	17.00	9.8%	0.27	£106	£2,148	£3,045	9.419	2	20
2-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM	17.13	8.4%	0.50	£95	£2,723	£4,076	9.471	3	2
3-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TPM	17.11	8.5%	0.48	£35	£2,670	£3,917	9.462	4	5
3-yearly DRE; if abnormal → mpMRI; if Likert ≥4 → TPM	16.96	10.2%	0.23	£75	£2,001	£2,784	9.404	5	36
3-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TPM	17.12	8.4%	0.50	£35	£2,709	£4,007	9.465	6	4
2-yearly PHI; if level ≥ 62 → mpMRI; if Likert ≥4 → TPM	17.03	9.5%	0.28	£290	£2,298	£3,381	9.433	7	18
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TPM	17.15	8.2%	0.59	£49	£2,815	£4,313	9.479	8	1
3-yearly PHI; if level ≥ 62 → mpMRI; if Likert ≥4 → TPM	16.99	9.9%	0.24	£207	£2,134	£3,057	9.416	9	28
2-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TPM	17.16	8.1%	0.62	£48	£2,846	£4,413	9.482	10	3
3-yearly PHI; if level ≥ 35 → mpMRI; if Likert ≥4 → TPM	17.14	8.3%	0.53	£193	£2,770	£4,283	9.470	11	7
2-yearly PHI; if level ≥ 35 → mpMRI; if Likert ≥4 → TPM	17.17	8.0%	0.65	£266	£2,895	£4,752	9.486	27	8

3-yearly PSA; if density ≥ 0.12ng/ml/ml → mpMRI; if Likert ≥4 → TPM	17.16	8.1%	0.67	£34	£2,860	£4,514	9.478	23	9
3-yearly PSA; if level ≥ 6ng/ml → mpMRI; if Likert ≥4 → TPM	17.14	8.2%	0.62	£35	£2,795	£4,348	9.472	17	10



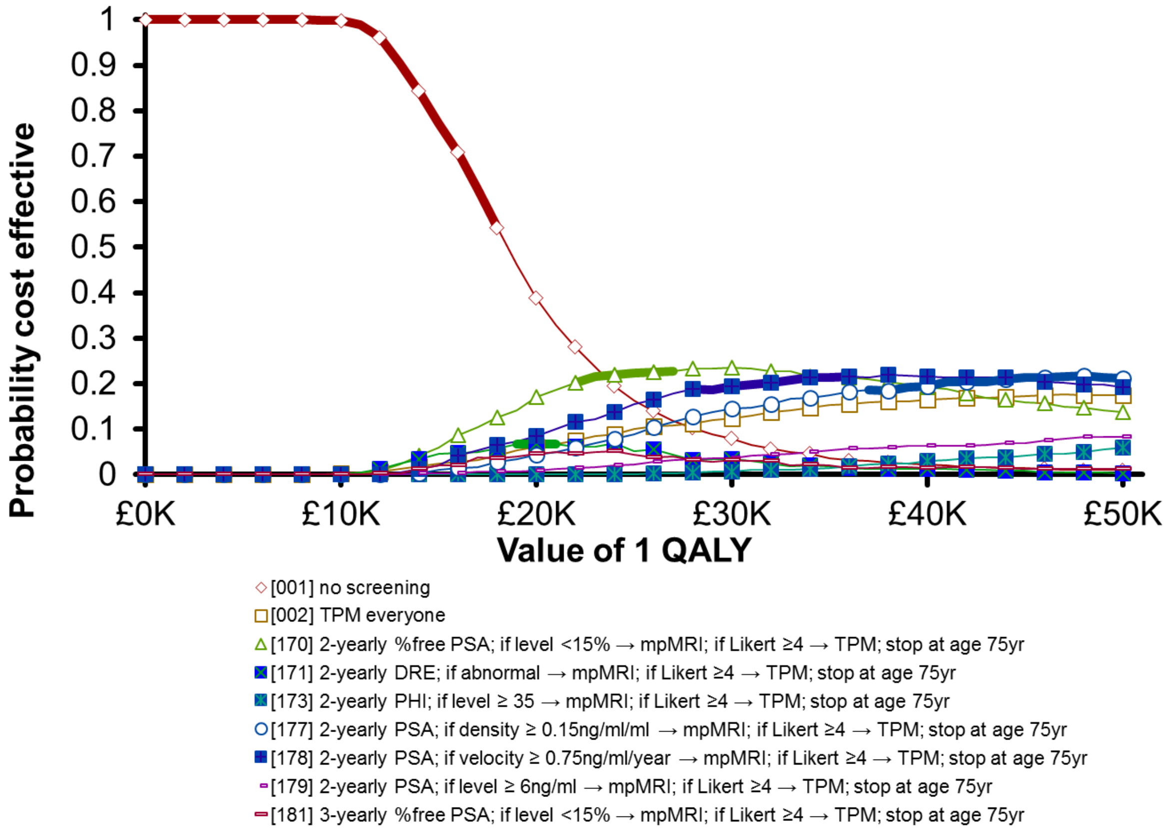
Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE60: One-way sensitivity analysis "TRUS everyone" vs "TPM everyone" based on the incremental net monetary benefits at cost-effectiveness threshold of £30,000 per QALY

Figure HE60 shows the impact of changing the value of a parameter on the results of a pairwise comparison between "TRUS everyone" strategy and the strategy where people receive an immediate TPM biopsy and not followed-up subsequently. It shows that the results are sensitive to probabilities of progression from intermediate- to high-risk and from high-risk to metastatic in undiagnosed cases. It shows also the significant impact of assigning a constant probability to prostate cancer death on the results, where "TRUS everyone" strategy becomes more beneficial.

Probabilistic results

Figure HE61 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. The two strategies, 2-yearly % free PSA tests or PSA velocity tests that direct candidates to mpMRI that in turn direct people to TPM, if Likert score ≥4, seem to be cost-effective at a threshold between £20,000 and £30,000 per QALY with a probability of about 20%.



Bold line indicates cost effectiveness acceptability frontier

Figure HE61: Cost-effectiveness acceptability curve

HE.6.14 MRI Likert 3; 1 biopsy

Table HE43 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, where all candidates receive an immediate TPM and no subsequent follow-up, seems optimal.

Table HE43: Base-case deterministic cost-utility results for people with Likert 3 and one biopsy

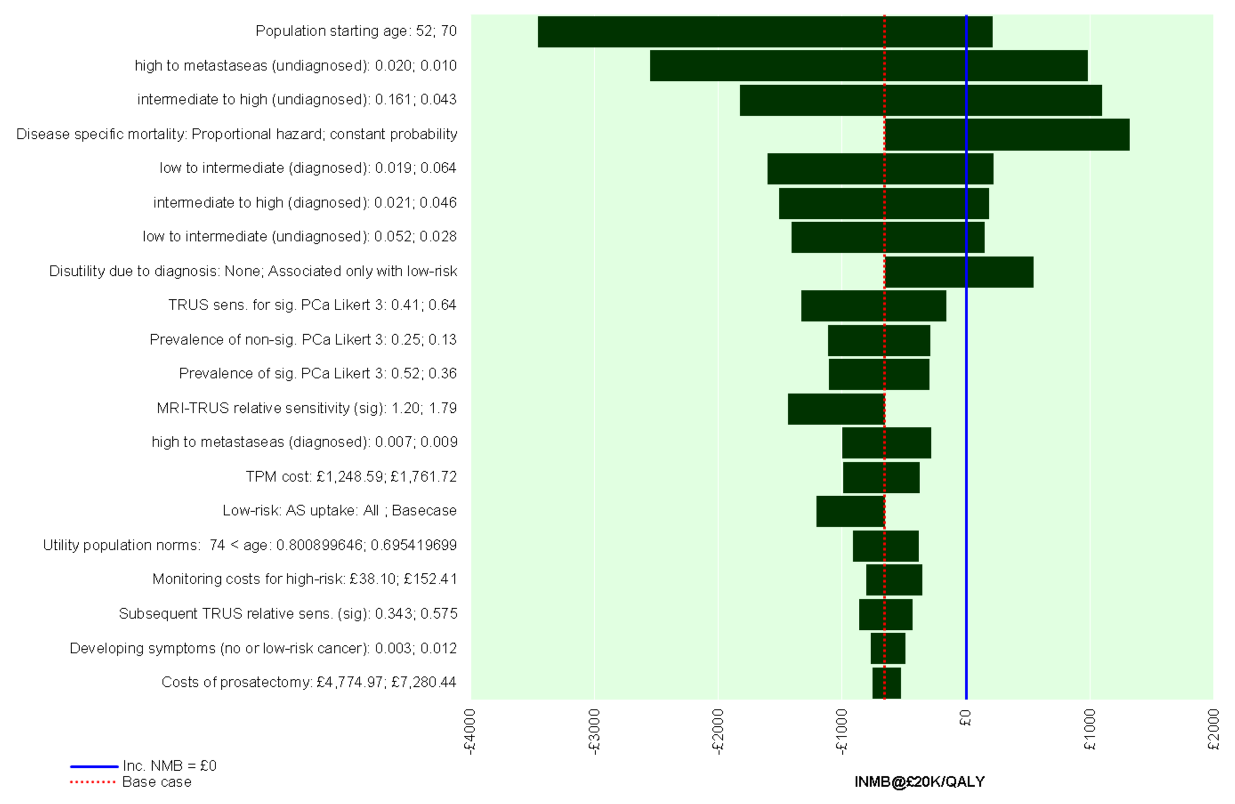
Strategy	Absolute		Incremental		
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£1,683	9.124			
TRUS everyone	£2,591	9.187	£908	0.063	£14,382
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£3,496	9.243	£905	0.056	£16,240
TPM everyone	£5,905	9.385	£2,409	0.143	£16,882
3-monthly PHI; if level ≥ 62 → TPM	£9,347	9.399	£3,442	0.014	£244,450

Table HE44 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The strategies including 2-yearly % free PSA test at a threshold of 15%, 2-yearly PSA velocity test at a threshold of 0.75ng/ml/year or 2-yearly PSA density test at a threshold of 0.15 ng/ml/ml, if reached the thresholds, followed by mpMRI, if Likert ≥4, people receive TPM, win the best positions following the strategy, where all receive an immediate TPM.

Table HE44: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY for people with Likert 3 and one biopsy

Strategy	Life years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
TPM everyone	16.95	10.9%	1.10	£0	£4,048	£5,905	9.385	1	1
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TPM	16.88	11.2%	0.55	£43	£3,943	£5,475	9.353	2	3
2-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM	16.85	11.5%	0.47	£85	£3,823	£5,238	9.341	3	7
2-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.89	11.1%	0.57	£43	£3,983	£5,572	9.357	4	2
3-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.83	11.6%	0.47	£32	£3,755	£5,108	9.328	5	14
3-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TPM	16.81	11.8%	0.45	£32	£3,705	£5,015	9.323	6	18
3-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM	16.78	12.1%	0.39	£62	£3,564	£4,781	9.309	7	25
2-yearly PHI; if level ≥ 35 → mpMRI; if Likert ≥4 → TPM	16.91	10.9%	0.61	£233	£4,044	£5,885	9.363	8	5
2-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.62	14.2%	1.66	£52	£2,673	£3,585	9.247	9	74
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.61	14.3%	1.55	£52	£2,626	£3,496	9.243	10	80
2-yearly PSA; if density ≥ 0.12ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.93	10.7%	0.76	£41	£4,129	£6,111	9.371	17	4
2-yearly PSA; if level ≥ 6ng/ml → mpMRI; if Likert ≥4 →	16.92	10.9%	0.71	£42	£4,067	£5,941	9.365	11	6

TPM									
2-yearly PSA; if density ≥ 0.09ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.94	10.7%	0.80	£41	£4,146	£6,218	9.373	26	8
2-yearly ; if → mpMRI; if Likert ≥4 → TPM	16.94	10.6%	0.88	£0	£4,174	£6,393	9.375	48	9
3-yearly PSA; if density ≥ 0.12ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.88	11.2%	0.61	£30	£3,947	£5,592	9.346	12	10

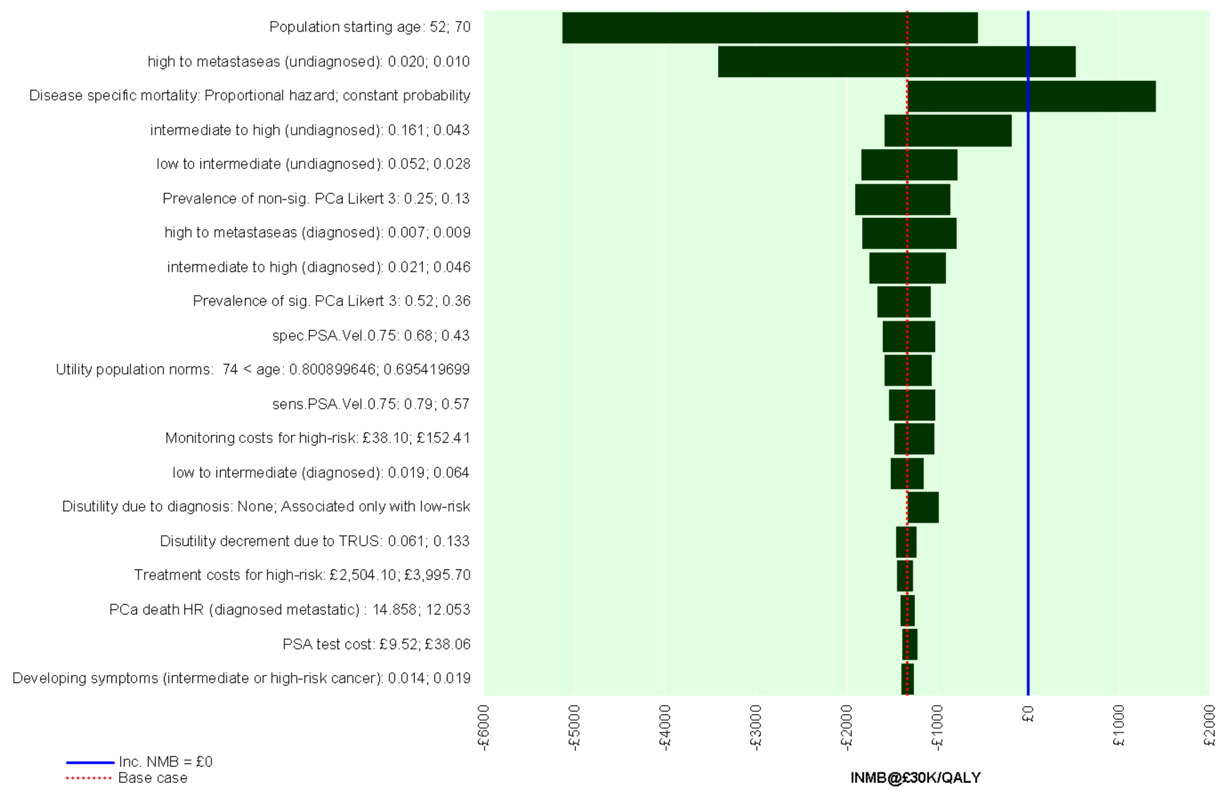


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE62: One-way sensitivity analysis "TRUS everyone" vs "TPM everyone" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Figure HE62 shows the impact of changing the value of a parameter on the results of a pairwise comparison between "TRUS everyone" strategy and the "TPM everyone" strategy. It shows that the results are sensitive to probabilities of progression in undiagnosed and diagnosed cases. It shows also the significant impact of assigning a constant probability to prostate cancer death on the results, where "TRUS everyone" strategy becomes more beneficial. Also, assigning a disutility for people with low-risk disease once diagnosed disadvantages the "TPM everyone" strategy.

Figure HE63 shows the impact of changing the value of a parameter on the results of a pairwise comparison between "TRUS everyone" strategy and the strategy where people receive yearly PSA tests; if velocity ≥ 0.75ng/ml/year, directed to TRUS. It shows that the results are sensitive to the probability of progression from high-risk to metastases in undiagnosed cases. It shows also that assigning a constant probability to prostate cancer death disadvantages the follow-up strategy.

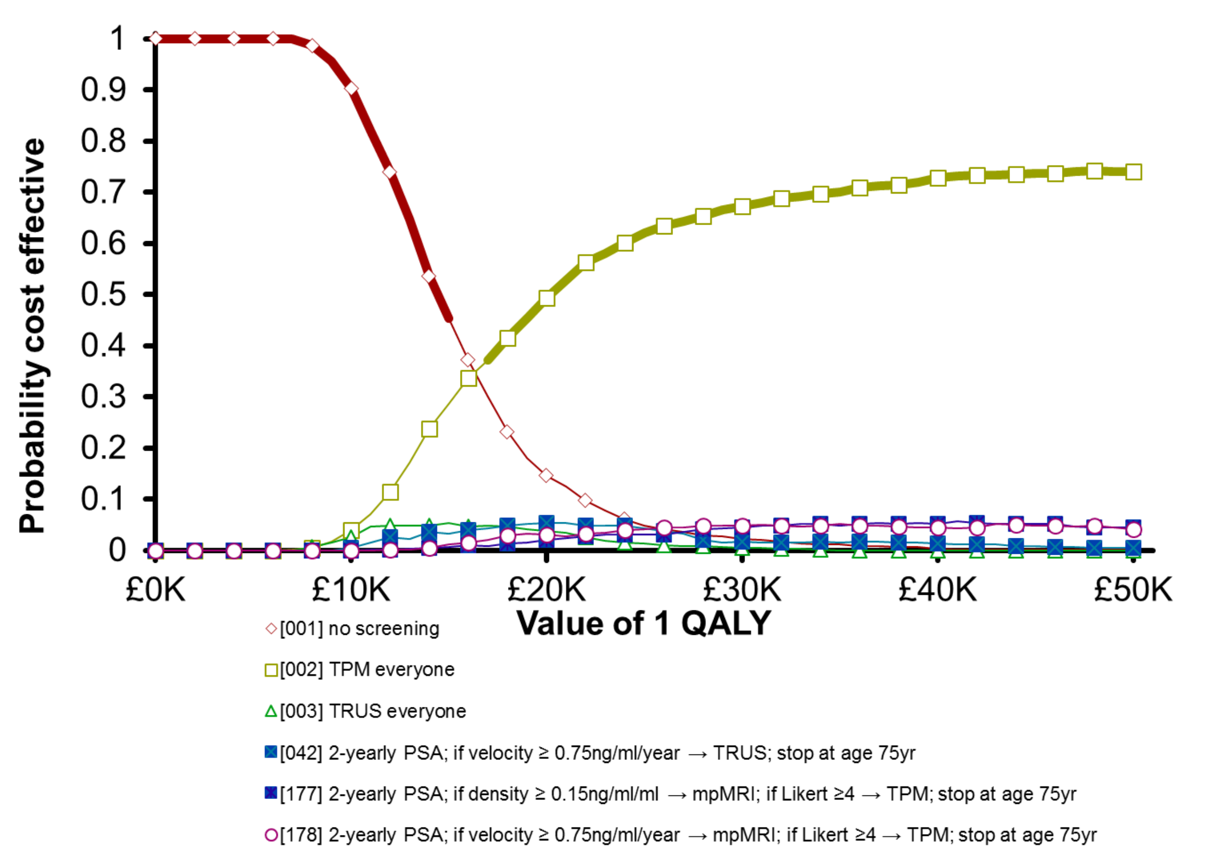


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

1 **Figure HE63: One-way sensitivity analysis "TRUS everyone" vs "1-yearly PSA; if**
2 **velocity ≥ 0.75ng/ml/year → TRUS" based on the incremental net**
3 **monetary benefits at cost-effectiveness threshold of £30,000 per QALY**

4 **Probabilistic results**

5 Figure HE64 shows the uncertainty surrounding the model results for this population at a
6 range of cost-effectiveness thresholds from 0 to £50,000 per QALY. The bold line indicates
7 the strategy that generates the greatest health monetary benefits at a given threshold. The
8 strategy where people receive an immediate TPM seems to be cost-effective at a threshold
9 of £20,000 per QALY with a probability of about 50%.



Bold line indicates cost effectiveness acceptability frontier

Figure HE64: Cost-effectiveness acceptability curve

HE.6.12 MRI Likert 3; 2 biopsies

Table HE45 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, where 2-yearly % free PSA tests direct candidates to mpMRI that in turn direct people to TPM, if Likert score ≥4, seems optimal.

Table HE45: Base-case deterministic cost-utility results for people with Likert 3 and two biopsies

Strategy	Absolute		Incremental		
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£1,396	9.248			
3-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£2,671	9.322	£1,275	0.074	£17,160
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£3,025	9.341	£354	0.019	£18,427
2-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM	£4,701	9.430	£1,676	0.089	£18,794
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TPM	£4,939	9.440	£238	0.010	£24,486

2-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TPM	£5,037	9.443	£98	0.003	£30,041
2-yearly PSA; if density ≥ 0.12ng/ml/ml → mpMRI; if Likert ≥4 → TPM	£5,604	9.455	£568	0.011	£50,746
2-yearly PSA; if density ≥ 0.09ng/ml/ml → mpMRI; if Likert ≥4 → TPM	£5,719	9.456	£115	0.001	£95,689
2-yearly ; if → mpMRI; if Likert ≥4 → TPM	£5,911	9.457	£191	0.002	£118,199
6-monthly PHI; if level ≥ 62 → TPM	£6,847	9.462	£936	0.005	£200,282
3-monthly PHI; if level ≥ 62 → TPM	£9,134	9.468	£2,287	0.006	£387,723

Table HE46 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The strategies, including 2-yearly % free PSA test at a threshold of 15% or 2-yearly PSA velocity test at a threshold of 0.75ng/ml/year, if reached the thresholds, followed by mpMRI, if Likert ≥4, people receive TPM, win the best positions.

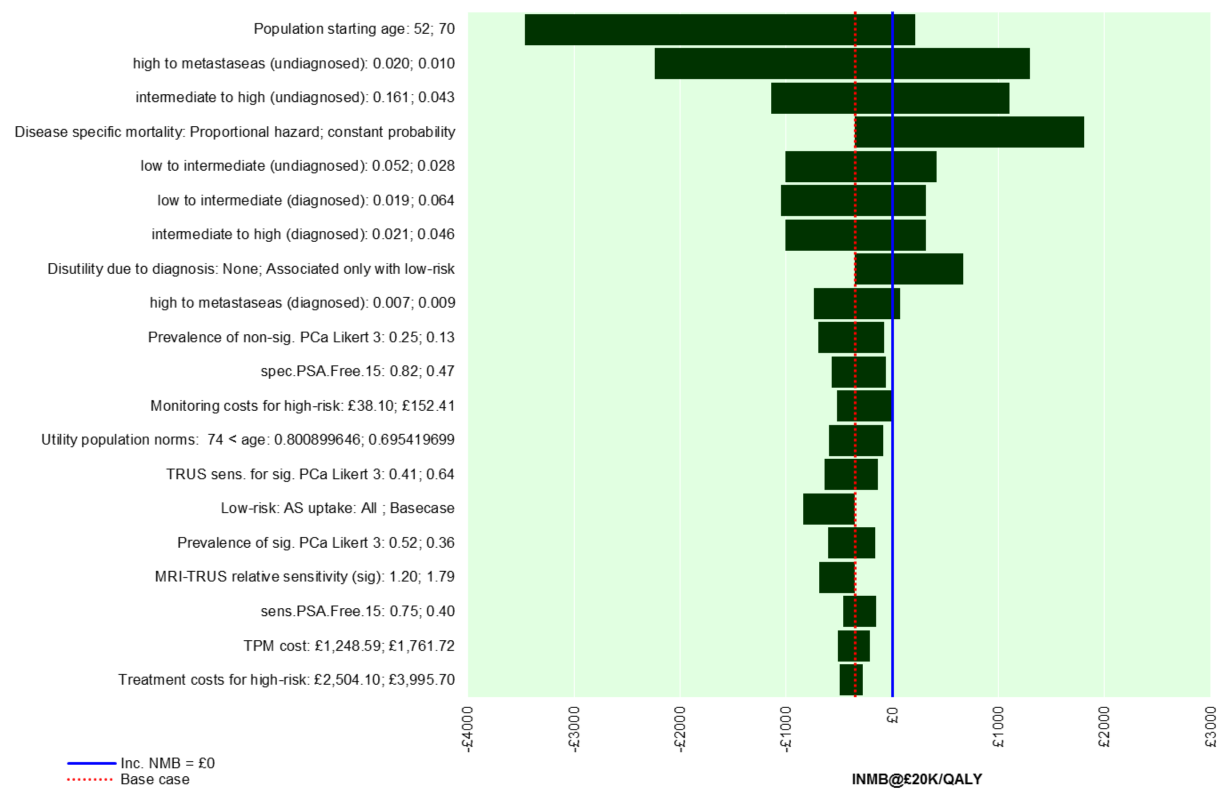
Table HE46: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY for people with Likert 3 and two biopsies

Strategy	Life years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
2-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM	17.05	9.5%	0.51	£89	£3,311	£4,701	9.430	1	3
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TPM	17.07	9.3%	0.59	£45	£3,420	£4,939	9.440	2	1
3-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM	16.99	10.1%	0.42	£65	£3,091	£4,275	9.407	3	17
3-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TPM	17.02	9.7%	0.48	£33	£3,220	£4,503	9.418	4	9
3-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TPM	17.03	9.6%	0.51	£33	£3,266	£4,596	9.422	5	5
2-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TPM	17.08	9.2%	0.62	£45	£3,457	£5,037	9.443	6	2
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.82	12.3%	1.70	£54	£2,145	£3,025	9.341	7	57
2-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.83	12.2%	1.81	£53	£2,185	£3,110	9.345	8	56
2-yearly %free PSA; if level <15% → TRUS	16.79	12.6%	1.40	£104	£2,039	£2,847	9.331	9	67
2-yearly DRE; if abnormal → mpMRI; if Likert ≥4 → TPM	16.88	11.3%	0.29	£102	£2,606	£3,556	9.367	10	43
2-yearly PHI; if level ≥ 35 → mpMRI; if Likert ≥4 → TPM	17.09	9.0%	0.66	£247	£3,513	£5,361	9.449	33	4
2-yearly PSA; if level ≥ 6ng/ml → mpMRI; if Likert ≥4 → TPM	17.10	9.0%	0.77	£44	£3,534	£5,429	9.450	40	6

TPM everyone	17.08	9.5%	1.20	£0	£3,408	£5,302	9.445	35	7
3-yearly PSA; if density ≥ 0.12ng/ml/ml → mpMRI; if Likert ≥4 → TPM	17.07	9.2%	0.66	£32	£3,441	£5,090	9.438	21	8
2-yearly PSA; if density ≥ 0.12ng/ml/ml → mpMRI; if Likert ≥4 → TPM	17.11	8.9%	0.83	£44	£3,591	£5,604	9.455	61	10

One-way sensitivity analysis

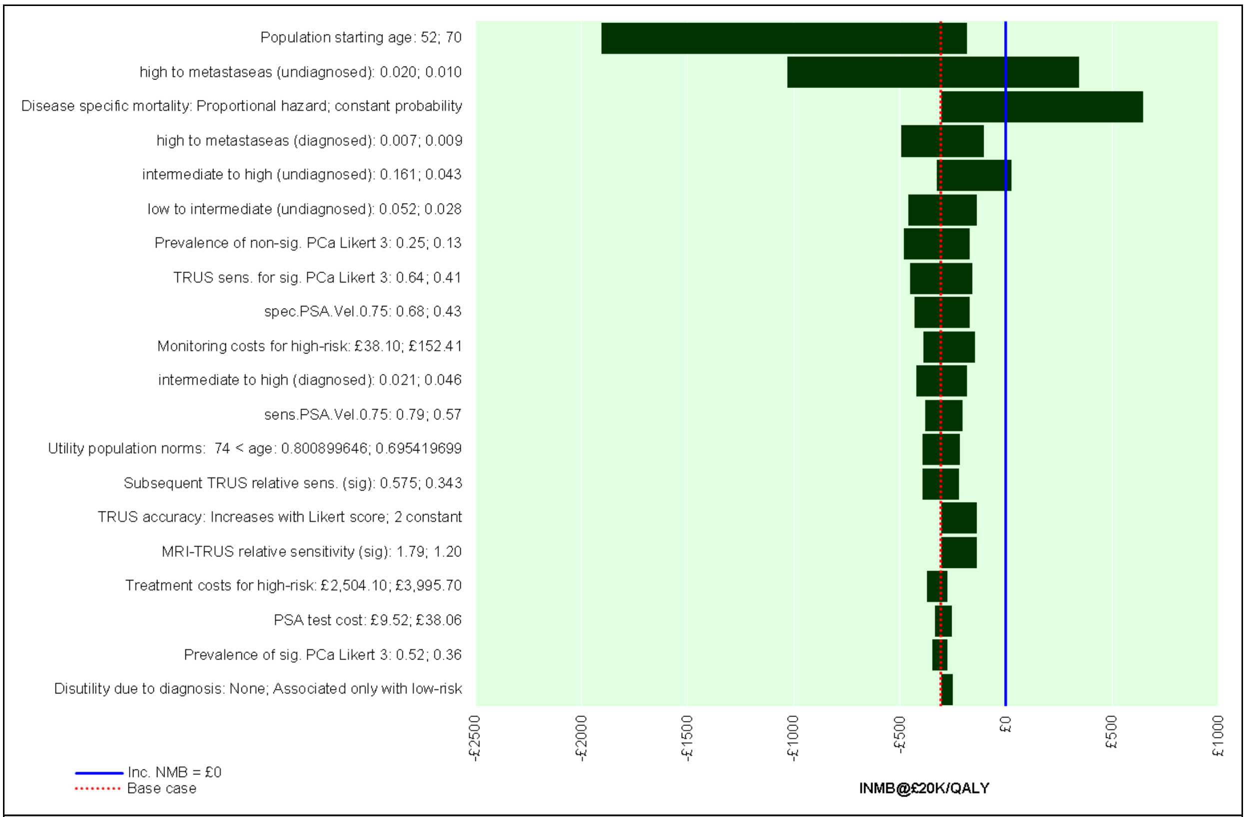
Figure HE65 shows the impact of changing the value of a parameter on the results of a pairwise comparison between “no screening” strategy and the strategy, where 2-yearly % free PSA tests direct candidates to mpMRI that in turn direct people to TPM, if Likert score ≥4. It shows that the results are sensitive to probabilities of progression from intermediate- to high-risk and from high-risk to metastatic in undiagnosed cases. It shows also the significant impact of assigning a constant probability to prostate cancer death on the results, where “no screening” strategy becomes more beneficial**.** Starting the model at an older age (70) disadvantages the interventional strategy. Applying disutility on people with low-risk disease once diagnosed leads to the screening strategy becoming disadvantageous.



Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE65: One-way sensitivity analysis “no screening” vs “2-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM” based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Figure HE66 shows the impact of changing the value of a parameter on the results of a pairwise comparison between “TRUS everyone” strategy and the strategy where people receive 2-yearly PSA tests; if velocity ≥ 0.75ng/ml/year, directed to TRUS. It shows that the results are sensitive to the probability of progression from high-risk to metastases in undiagnosed cases. It shows also that assigning a constant probability to prostate cancer death disadvantages the follow-up strategy.

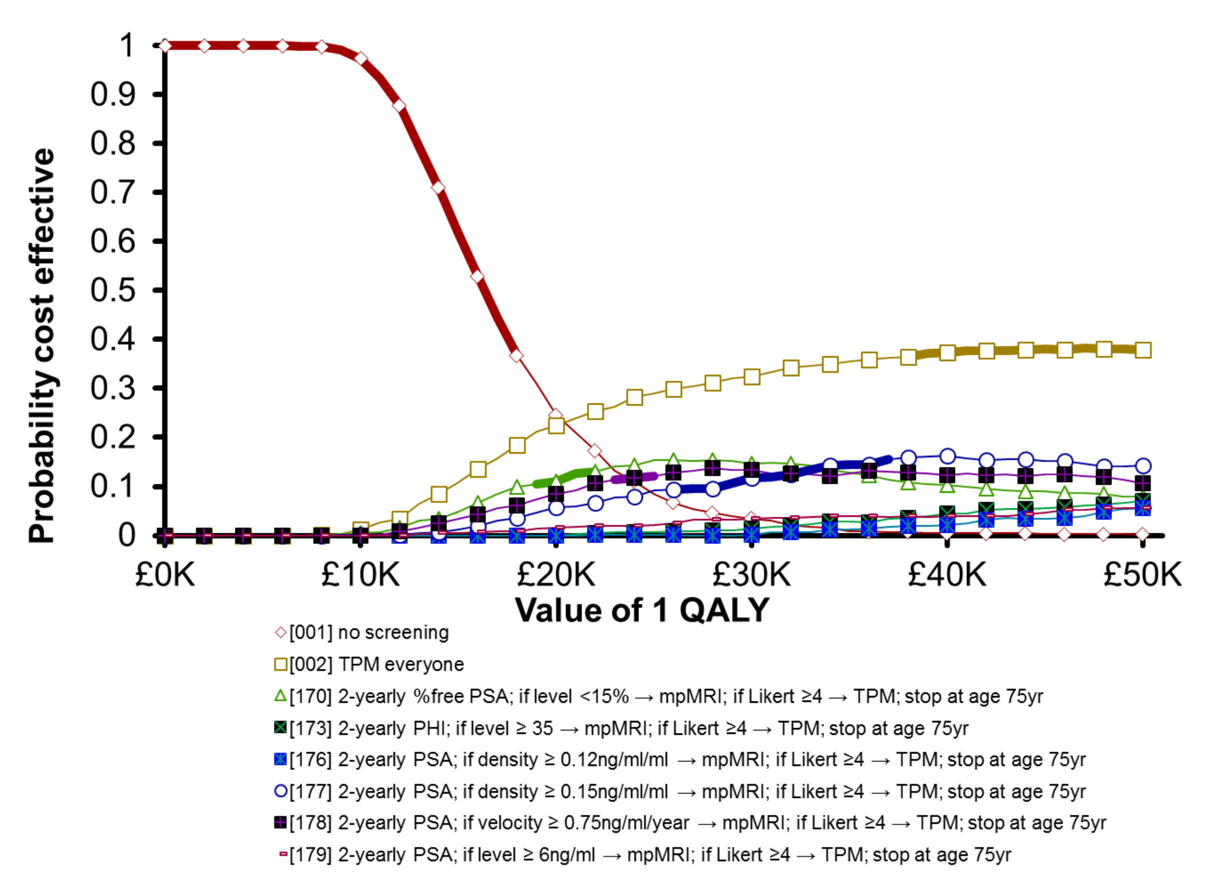


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line "TRUS everyone" vs "2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS"

Figure HE66: One-way sensitivity analysis "TRUS everyone" vs "2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Probabilistic results

Figure HE67 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. The strategy, where 2-yearly % free PSA tests direct candidates to mpMRI that in turn direct people to TPM, if Likert score ≥4, seems to be cost-effective at a threshold of £20,000 per QALY with a probability of about 10%



Bold line indicates cost effectiveness acceptability frontier

Figure HE67: Cost-effectiveness acceptability curve

HE.6.12 MRI Likert 4; 1 biopsy

Table HE47 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, where all candidates receive an immediate TPM and no subsequent follow-up, seems optimal.

Table HE47: Base-case deterministic cost-utility results for people with Likert 4 and one biopsy

Strategy	Absolute		Incremental		
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£2,530	8.818			
TRUS everyone	£3,767	8.945	£1,237	0.127	£9,748
TPM everyone	£7,840	9.242	£4,074	0.297	£13,712

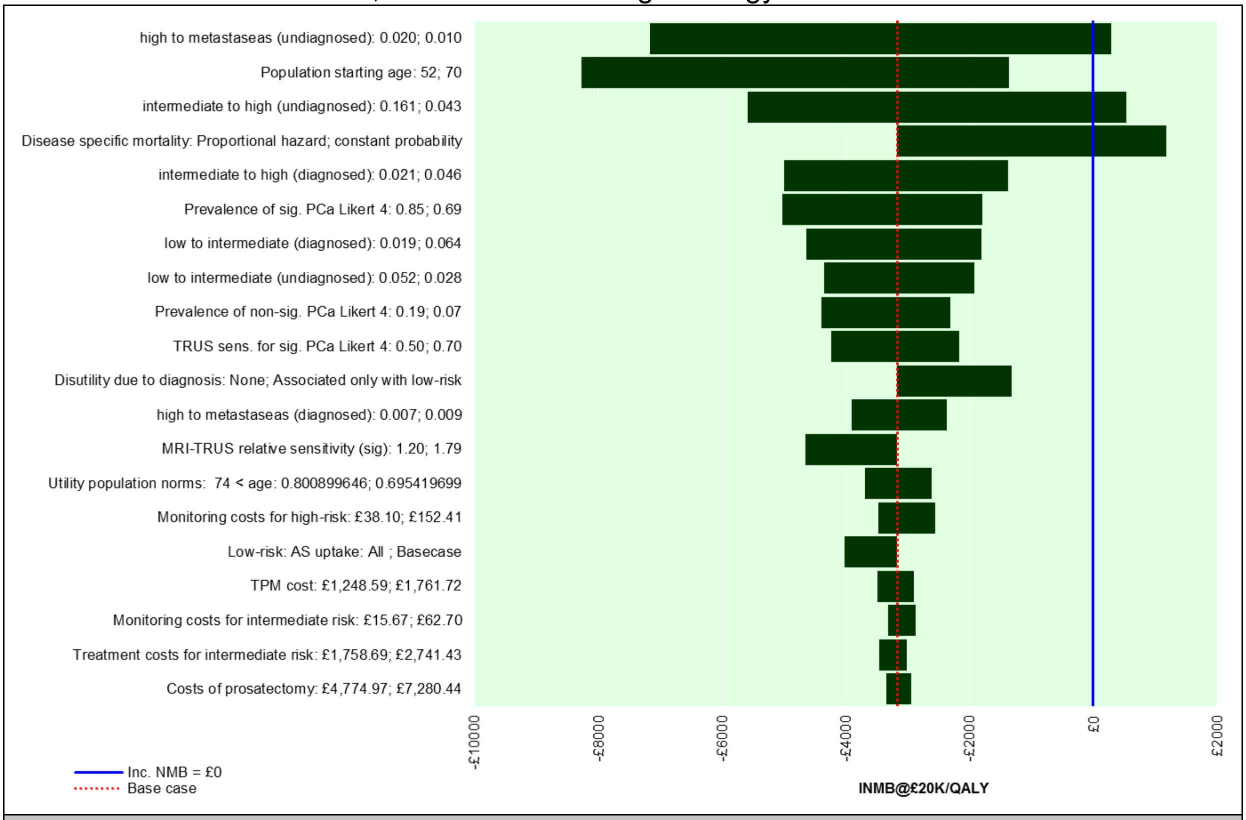
Table HE48 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The strategies including yearly % free PSA tests at a threshold of 15%, yearly PSA velocity tests at a threshold of 0.75ng/ml/year or yearly PSA density tests at a threshold of 0.15 ng/ml/ml, if reached the thresholds, people receive TPM, win the best positions following the strategy, where all receive an immediate TPM.

Table HE48: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY for people with Likert 4 and one biopsy

Strategy	Life years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
TPM everyone	16.65	14.4%	0.88	£0	£6,115	£7,840	9.242	1	1
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.36	17.2%	2.70	£91	£4,762	£6,268	9.112	2	28
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.34	17.4%	2.53	£91	£4,715	£6,154	9.106	3	38
1-yearly %free PSA; if level <15% → TRUS	16.29	17.8%	2.08	£180	£4,575	£5,923	9.088	4	55
1-yearly PSA; if level ≥ 6ng/ml → TRUS	16.39	16.9%	3.43	£88	£4,865	£6,654	9.124	5	34
1-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	16.42	16.6%	3.77	£87	£4,942	£6,865	9.134	6	23
2-yearly PSA; if density ≥ 0.12ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.51	15.3%	0.61	£32	£5,816	£7,692	9.175	7	6
6-monthly %free PSA; if level <15% → TRUS	16.47	16.2%	3.91	£324	£5,062	£7,286	9.154	8	11
2-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.46	15.8%	0.49	£35	£5,628	£7,248	9.152	9	14
2-yearly PSA; if density ≥ 0.09ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.52	15.2%	0.63	£32	£5,838	£7,770	9.177	10	5
6-monthly PHI; if level ≥ 62 → TPM	16.59	14.7%	0.96	£696	£6,044	£8,520	9.206	26	2
1-yearly %free PSA; if level <15% → TPM	16.58	14.7%	1.35	£119	£6,051	£8,454	9.202	28	3
2-yearly ; if → mpMRI; if Likert ≥4 → TPM	16.53	15.1%	0.69	£0	£5,873	£7,890	9.182	14	4
6-monthly DRE; if abnormal → TPM	16.54	15.0%	1.04	£268	£5,901	£8,069	9.186	17	7

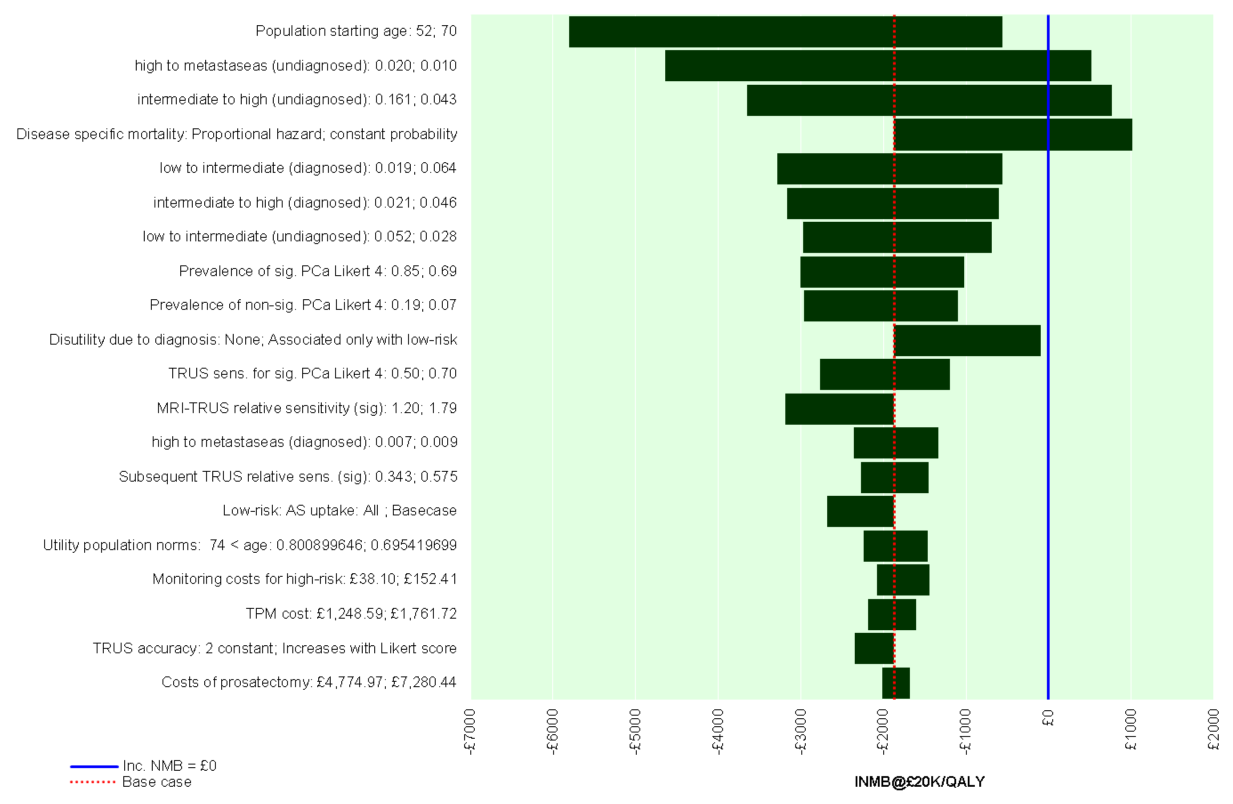
One-way sensitivity analysis

Figure HE68 shows the impact of changing the value of a parameter on the results of a pairwise comparison between “no screening” strategy and the strategy where people receive an immediate TPM biopsy and not followed-up subsequently. It shows that the interventional strategy is always worthwhile unless the disease progression is low in the undiagnosed cases. It shows also the significant impact of assigning a constant probability to prostate cancer death on the results, where “no screening” strategy becomes more beneficial**.**



Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE68: One-way sensitivity analysis “no screening” vs “TPM everyone” based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

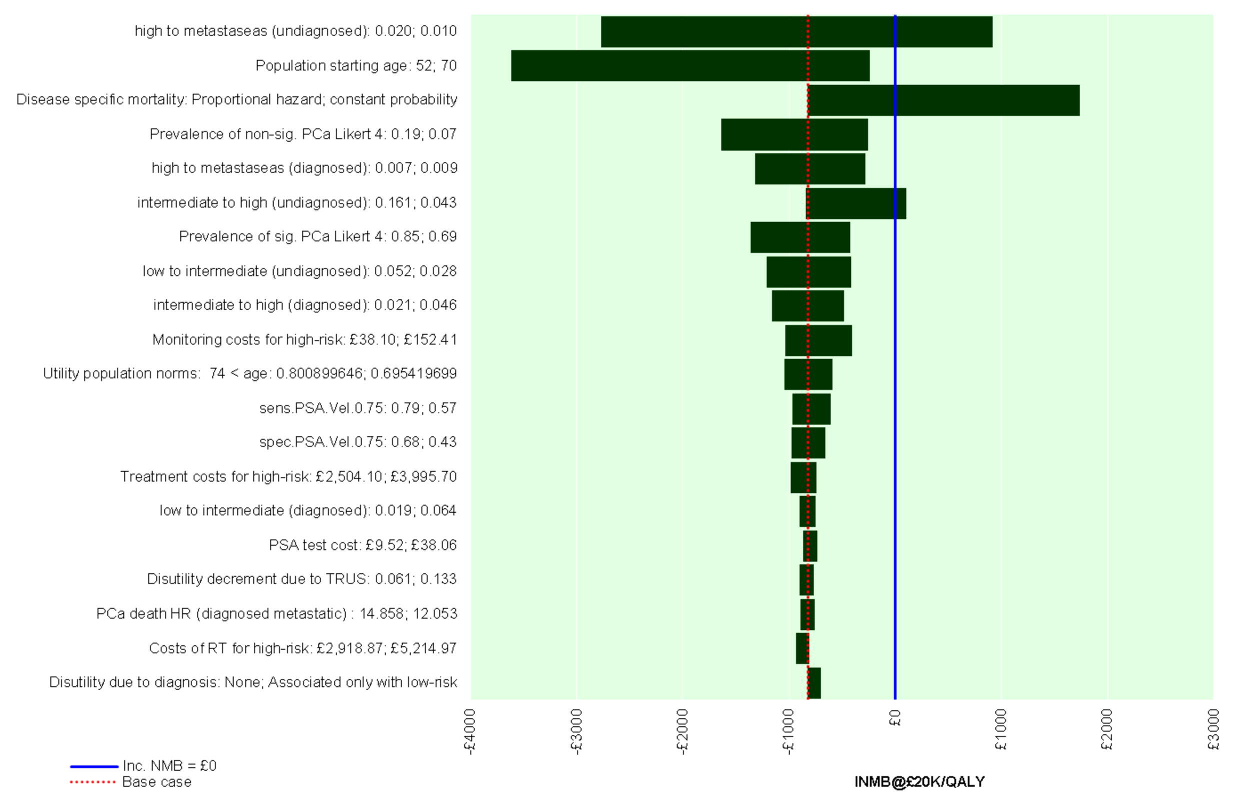


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE69: One-way sensitivity analysis “TRUS everyone” vs “TPM everyone” based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Figure HE69 shows the impact of changing the value of a parameter on the results of a pairwise comparison between “TRUS everyone” strategy and the “TPM everyone” strategy. It shows that the results are sensitive to probabilities of progression in undiagnosed cases. It shows also the significant impact of assigning a constant probability to prostate cancer death on the results, where “TRUS everyone” strategy becomes more beneficial.

Figure HE70 shows the impact of changing the value of a parameter on the results of a pairwise comparison between “TRUS everyone” strategy and the “1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS” strategy. It shows that the results are sensitive to probabilities of progression in undiagnosed cases. It shows also the significant impact of assigning a constant probability to prostate cancer death on the results, where “TRUS everyone” strategy becomes more beneficial.

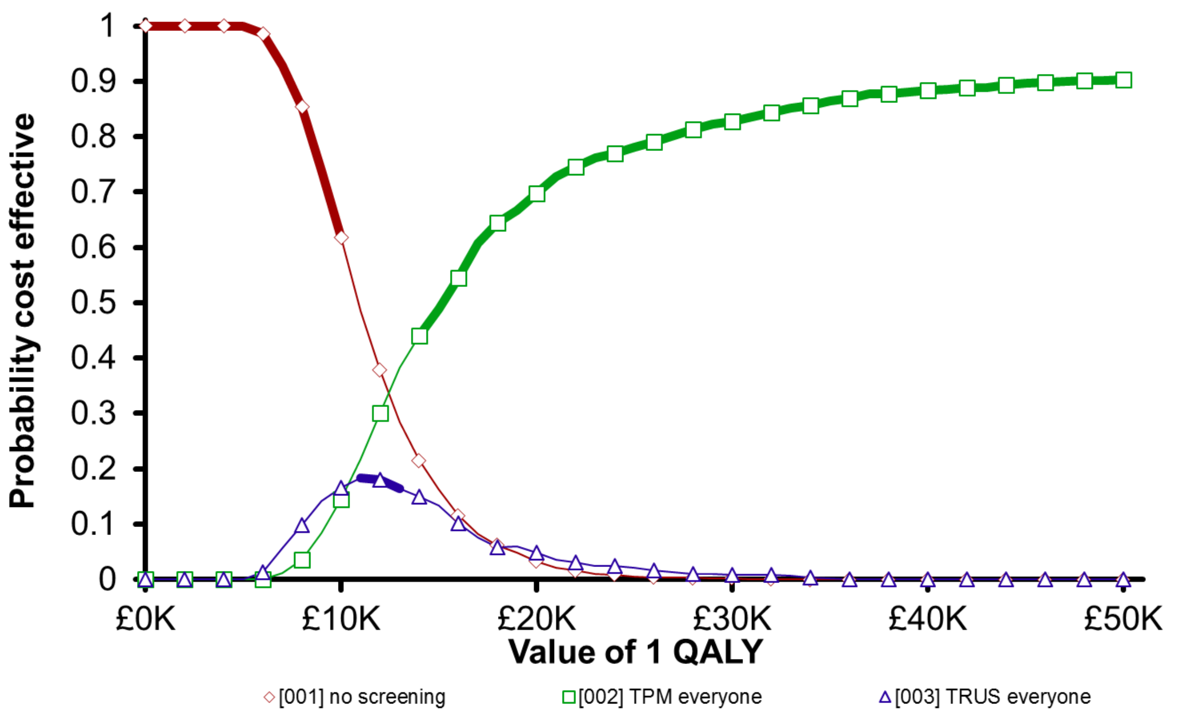


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line TRUS everyone vs 1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS

Figure HE70: One-way sensitivity analysis “TRUS everyone” vs “1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS” based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Probabilistic results

Figure HE71 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. The strategy where people receive an immediate TPM seems to be cost-effective at a threshold of £20,000 per QALY with a probability of about 60%.



Bold line indicates cost effectiveness acceptability frontier

Figure HE71: Cost-effectiveness acceptability curve

HE.6.12 MRI Likert 4; 2 biopsies

Table HE49 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, where all candidates receive an immediate TPM and no subsequent follow-up, seems optimal.

Table HE49: Base-case deterministic cost-utility results for people with Likert 4 and two biopsies

Strategy	Absolute		Incremental		
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£1,965	9.052			
3-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£3,572	9.169	£1,607	0.117	£13,713
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£3,970	9.198	£398	0.029	£13,742
2-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	£4,061	9.204	£91	0.006	£16,088
TPM everyone	£6,928	9.362	£2,867	0.158	£18,092
3-monthly PHI; if level ≥ 62 → TPM	£9,557	9.372	£2,629	0.010	£260,329

Table HE50 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The strategies including 2-yearly % free PSA tests at a threshold of 15%, 2-yearly PSA velocity tests at a threshold of 0.75ng/ml/year or 2-yearly PSA density tests at a threshold of 0.15 ng/ml/ml, if reached the thresholds, followed by mpMRI, if Likert ≥4, people receive TPM, win the best positions following the strategy, where all receive an immediate TPM.

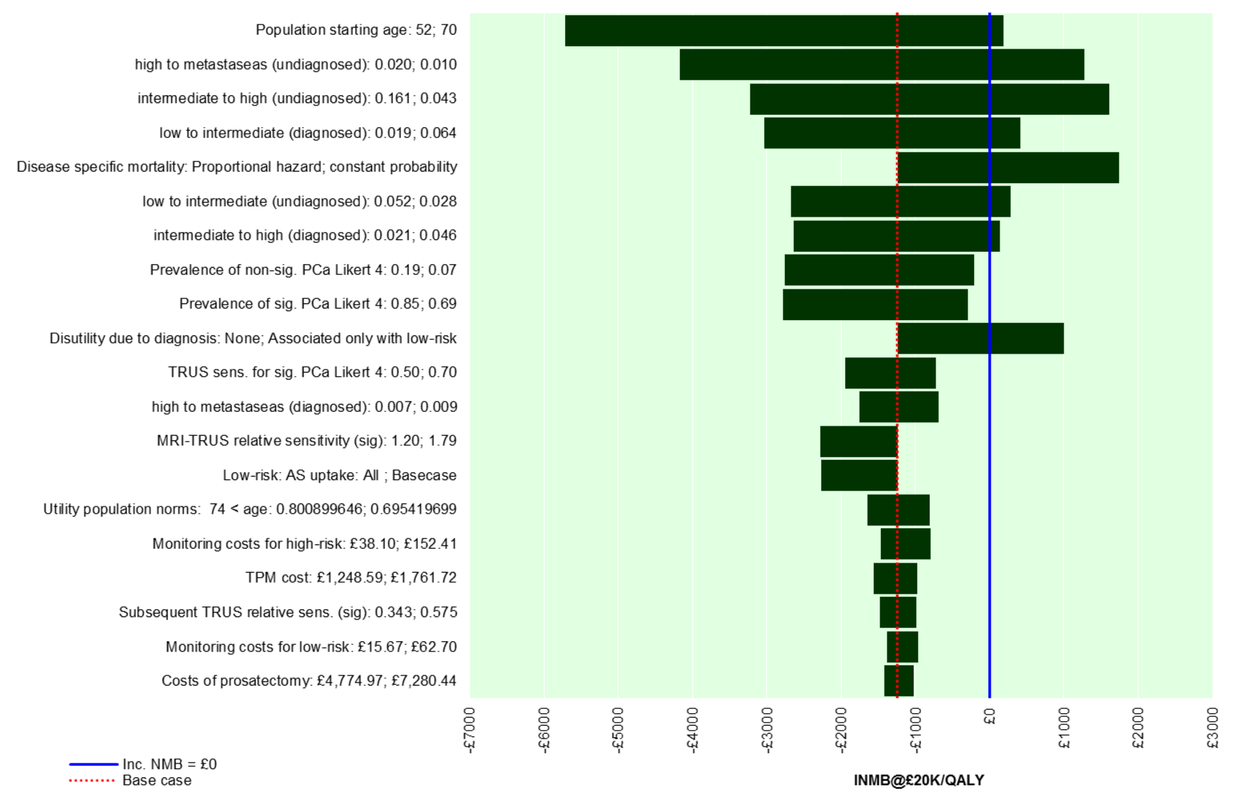
Table HE50: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY for people with Likert 4 and two biopsies

Strategy	Life years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
TPM everyone	16.91	11.7%	1.09	£0	£5,150	£6,928	9.362	1	1
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TPM	16.82	12.2%	0.58	£39	£4,758	£6,318	9.323	2	6
2-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.83	12.1%	0.60	£38	£4,805	£6,412	9.327	3	3
2-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM	16.78	12.6%	0.51	£77	£4,614	£6,079	9.309	4	9
2-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.51	15.9%	1.65	£51	£3,127	£4,061	9.204	5	78
2-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	16.57	15.2%	2.27	£49	£3,338	£4,521	9.227	6	70
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.67	14.2%	3.15	£104	£3,669	£5,264	9.264	7	48
2-yearly PSA; if level ≥ 6ng/ml → mpMRI; if Likert ≥4 → TPM	16.85	11.9%	0.71	£37	£4,905	£6,736	9.337	8	5
2-yearly PSA; if density ≥ 0.09ng/ml/ml → TRUS	16.58	15.1%	2.40	£49	£3,367	£4,602	9.230	9	69
1-yearly %free PSA; if level <15% → TRUS	16.64	14.6%	2.59	£203	£3,545	£5,018	9.251	10	58
2-yearly PSA; if density ≥ 0.12ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.87	11.7%	0.76	£36	£4,976	£6,895	9.344	13	2
2-yearly PSA; if density ≥ 0.09ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.88	11.7%	0.79	£36	£4,997	£6,985	9.346	19	4
2-yearly PHI; if level ≥ 35 → mpMRI; if Likert ≥4 → TPM	16.85	12.0%	0.63	£207	£4,878	£6,706	9.335	12	7

2-yearly mpMRI; if Likert ≥4 → TPM	16.88	11.6%	0.86	£0	£5,028	£7,127	9.348	30	8
3-yearly mpMRI; if Likert ≥4 → TPM	16.82	12.1%	0.69	£0	£4,800	£6,567	9.323	25	10

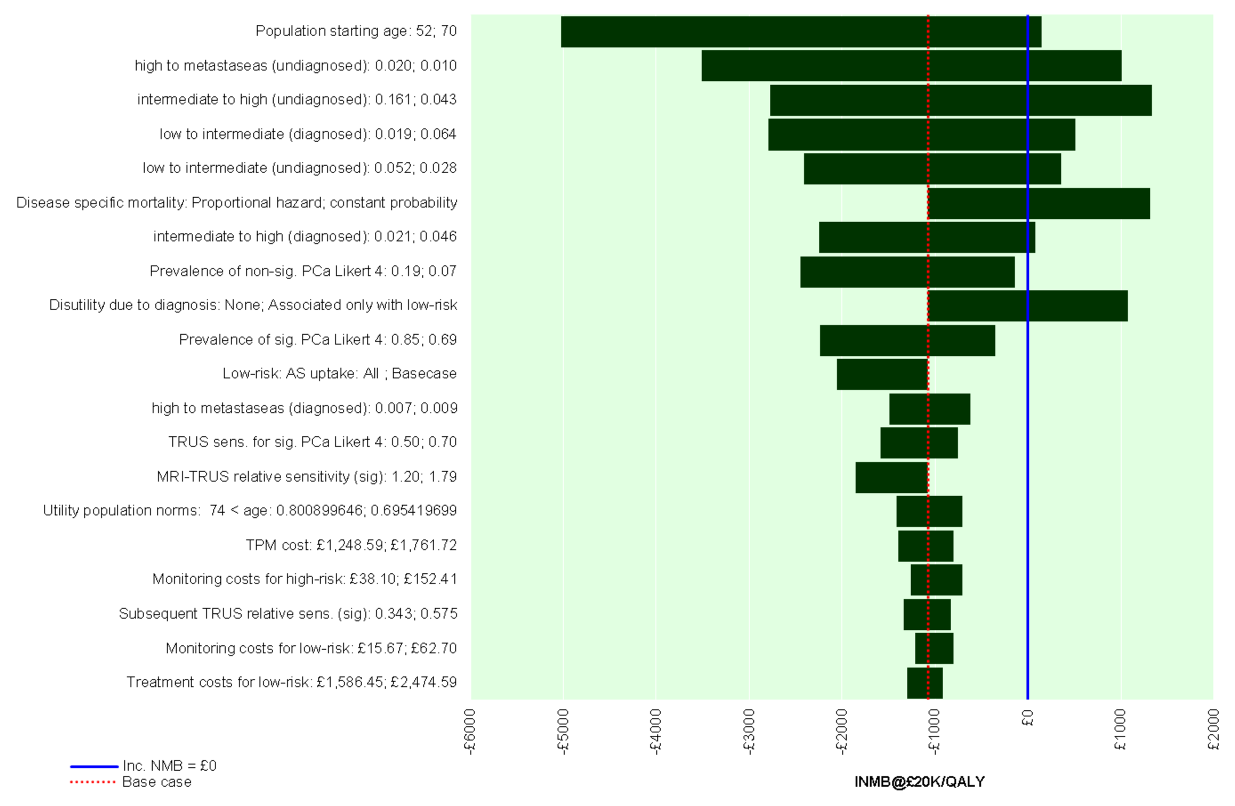
One-way sensitivity analysis

Figure HE72 shows the impact of changing the value of a parameter on the results of a pairwise comparison between “no screening” strategy and the strategy where people receive an immediate TPM biopsy and not followed-up subsequently. It shows that the results are very sensitive to a number of parameters, mainly related to the disease progression. It shows also the significant impact of assigning a constant probability to prostate cancer death on the results, where “no screening” strategy becomes more beneficial. Starting the model with older age (70) disadvantages the interventional strategy.



Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line “no screening” vs “TPM everyone”

Figure HE72: One-way sensitivity analysis “no screening” vs “TPM everyone” based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

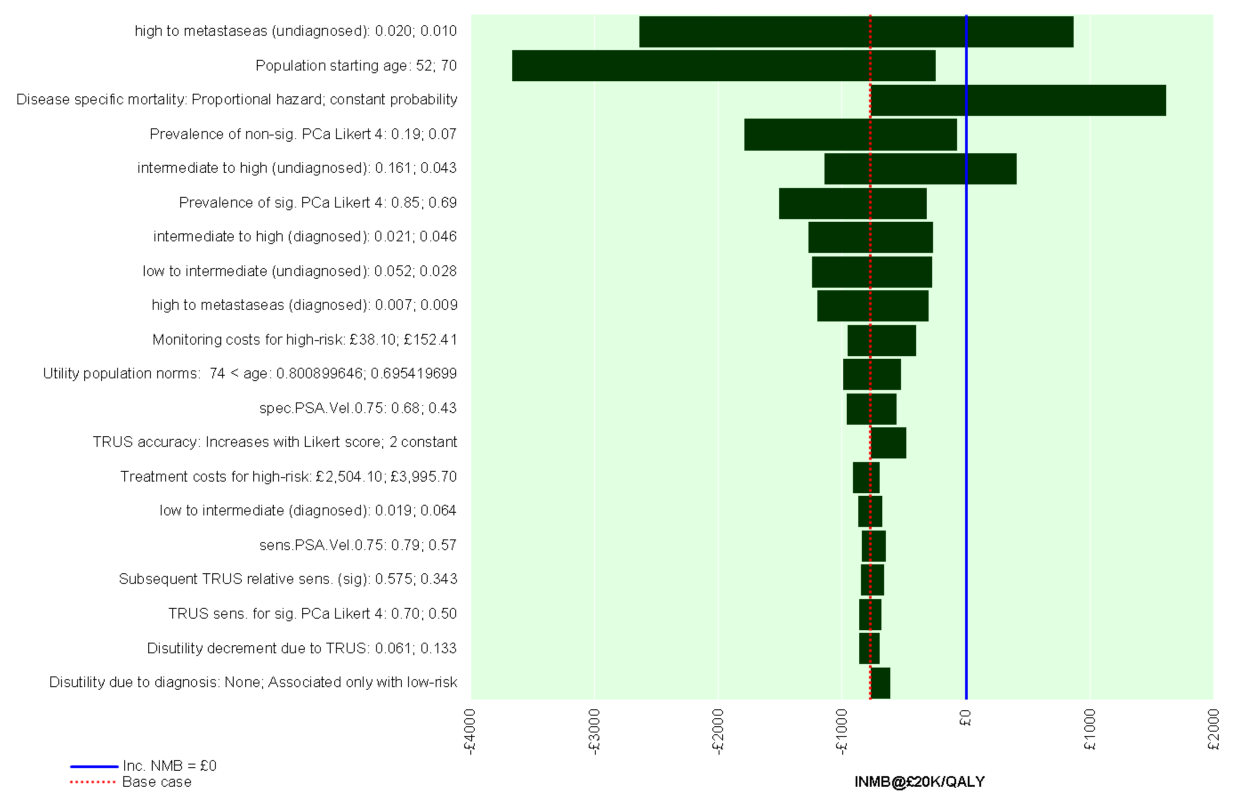


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line "TRUS everyone" vs "TPM everyone"

Figure HE73: One-way sensitivity analysis "TRUS everyone" vs "TPM everyone" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Figure HE73 shows the impact of changing the value of a parameter on the results of a pairwise comparison between "TRUS everyone" strategy and the "TPM everyone" strategy. It shows that the results are sensitive to probabilities of progression in undiagnosed and diagnosed cases. It shows also the significant impact of assigning a constant probability to prostate cancer death on the results, where "TRUS everyone" strategy becomes more beneficial. Also, assigning a disutility for people with low-risk disease once diagnosed disadvantages the "TPM everyone" strategy.

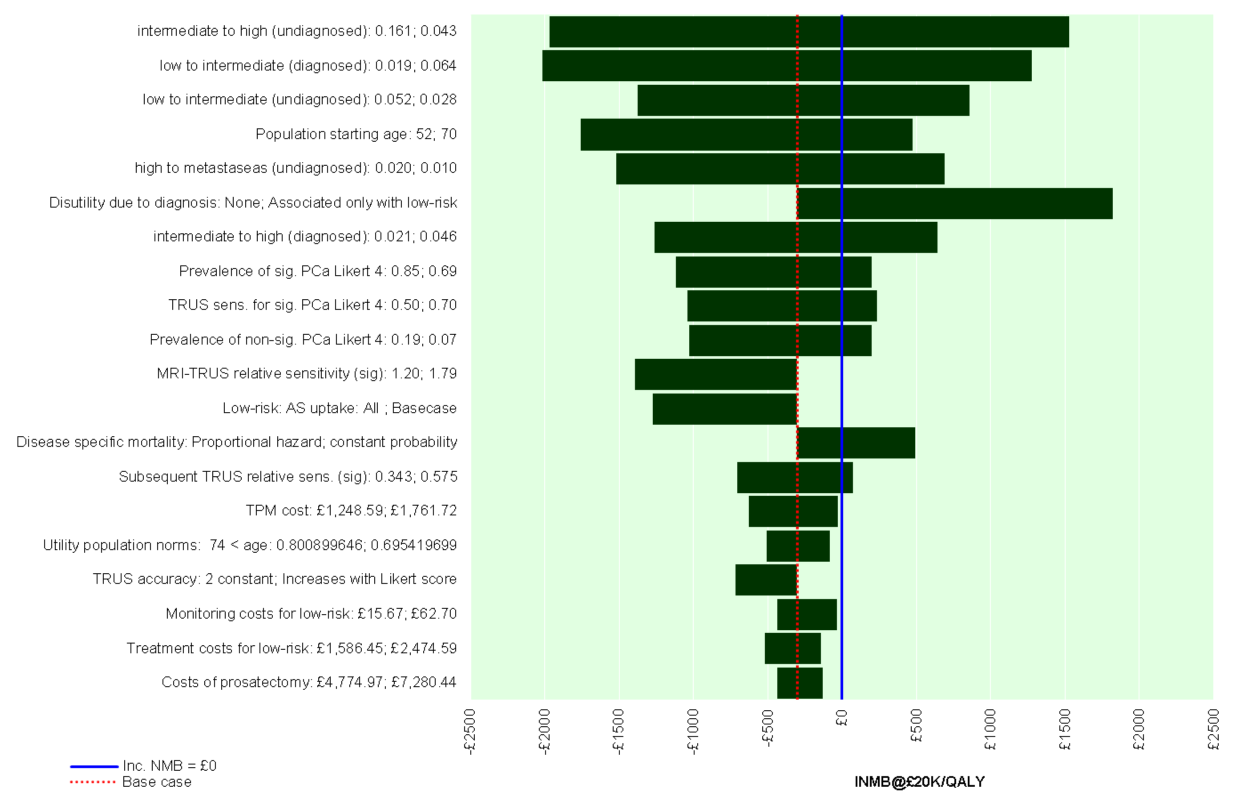
Figure HE74 shows the impact of changing the value of a parameter on the results of a pairwise comparison between "TRUS everyone" strategy and the strategy where people receive 1-yearly PSA tests; if velocity ≥ 0.75ng/ml/year, directed to TRUS. It shows that the results are sensitive to the probability of progression from intermediate to high-risk and from high-risk to metastases in undiagnosed cases. It shows also that assigning a constant probability to prostate cancer death disadvantages the follow-up strategy.



Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line "TRUS everyone" vs "1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS"

Figure HE74: One-way sensitivity analysis "TRUS everyone" vs "1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Figure HE75 shows the impact of changing the value of a parameter on the results of a pairwise comparison between the strategy where people receive 2-yearly PSA tests; if velocity ≥ 0.75ng/ml/year, directed to TRUS and the "TPM everyone" strategy. It shows that the results are sensitive to a number of key parameters, mainly probabilities of disease progression in undiagnosed and diagnosed cases, the disease prevalence and TRUS accuracy. It shows also that assigning a constant probability to prostate cancer death disadvantages the "TPM everyone" strategy. Also, applying disutility on people with low-risk disease once diagnosed disadvantages the "TPM everyone" strategy.

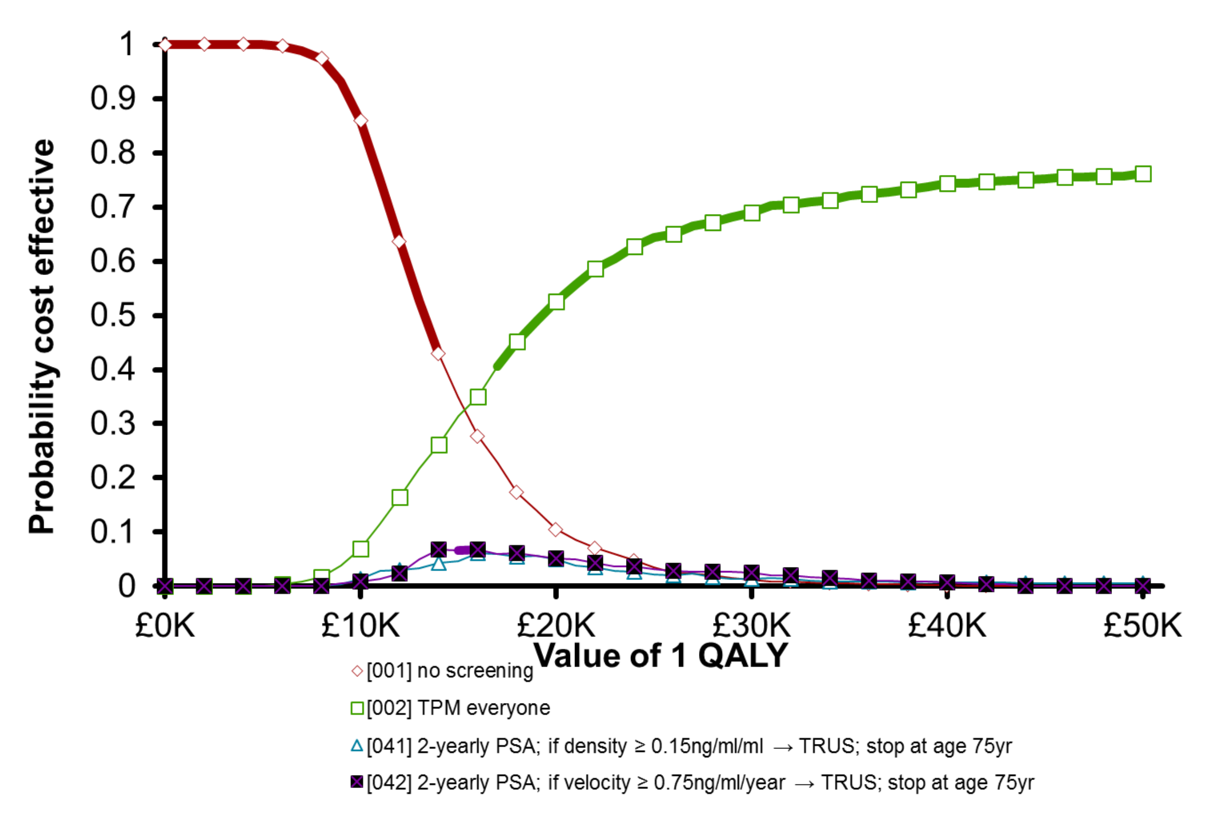


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line “2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS” vs “TPM everyone”

1 **Figure HE75: One-way sensitivity analysis “2-yearly PSA; if velocity ≥ 0.75ng/ml/year**
2 **→ TRUS” vs “TPM everyone” based on the incremental net monetary**
3 **benefits at cost-effectiveness threshold of £20,000 per QALY**

4 **Probabilistic results**

5 Figure HE76 shows the uncertainty surrounding the model results for this population at a
6 range of cost-effectiveness thresholds from 0 to £50,000 per QALY. The bold line indicates
7 the strategy that generates the greatest health monetary benefits at a given threshold. The
8 strategy where people receive an immediate TPM seems to be cost-effective at a threshold
9 of £20,000 per QALY with a probability of about 45%.



Bold line indicates cost effectiveness acceptability frontier

Figure HE76: Cost-effectiveness acceptability curve

HE.6.12 MRI Likert 5; 1 biopsy

Table HE51 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, where all candidates receive an immediate TPM and no subsequent follow-up, seems optimal.

Table HE51: Base-case deterministic cost-utility results for people with Likert 5 and one biopsy

Strategy	Absolute		Incremental		
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£3,012	8.746			
TRUS everyone	£4,856	8.984	£1,844	0.238	£7,741
TPM everyone	£7,791	9.181	£2,934	0.197	£14,927

Table HE52 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The strategies including 6-monthly % free PSA tests at a threshold of 15%, yearly PSA velocity tests at a threshold of 0.75ng/ml/year or yearly PSA density tests at a threshold of 0.15 ng/ml/ml, if reached the thresholds, people receive TRUS, win the best positions following the strategy, where all receive an immediate TPM.

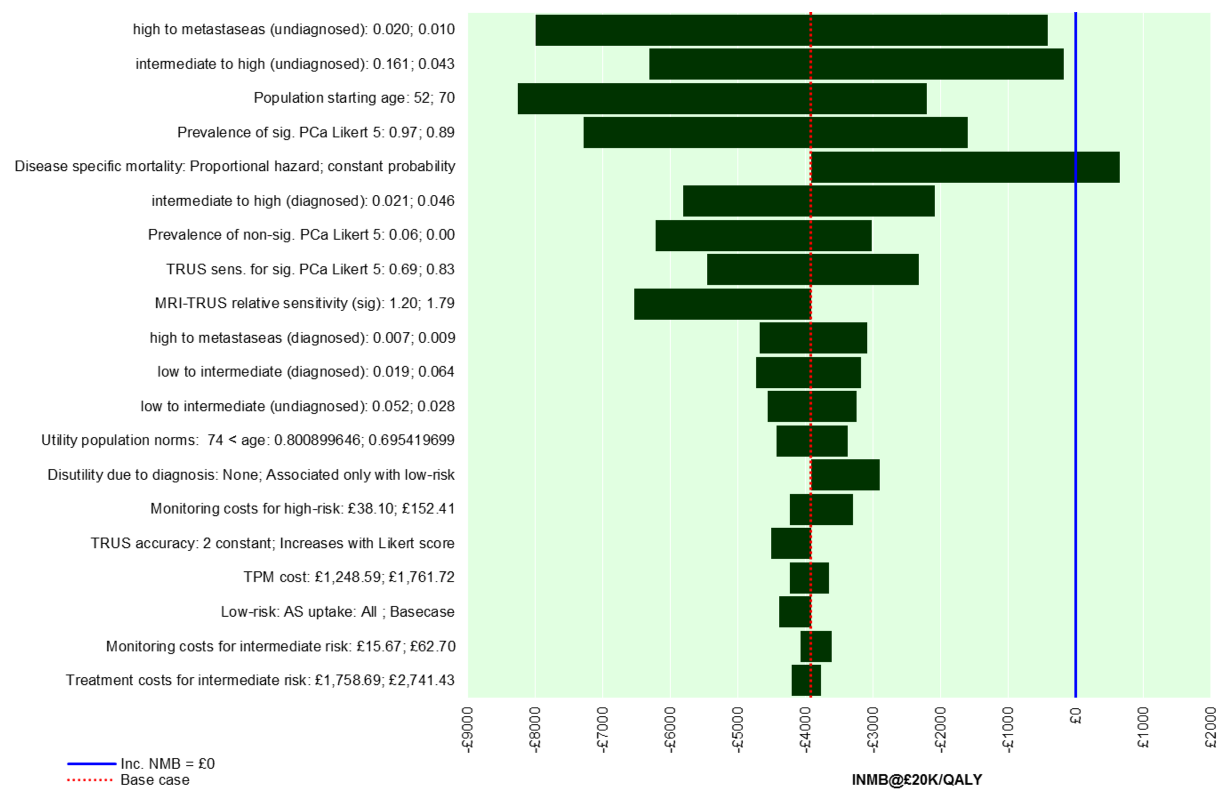
1 **Table HE52: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for**
2 **additional QALY for people with Likert 5 and one biopsy**

Strategy	Life years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
TPM everyone	16.51	15.6%	0.74	£0	£6,051	£7,791	9.181	1	1
6-monthly %free PSA; if level <15% → TRUS	16.41	16.5%	3.04	£276	£5,682	£7,455	9.123	2	3
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.31	17.3%	2.20	£78	£5,434	£6,679	9.083	3	7
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.30	17.5%	2.06	£79	£5,396	£6,586	9.077	4	11
6-monthly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.44	16.2%	3.77	£139	£5,757	£7,678	9.132	5	2
6-monthly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.44	16.1%	4.04	£138	£5,783	£7,805	9.134	6	4
1-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	16.36	16.8%	3.18	£74	£5,576	£7,195	9.102	7	5
1-yearly PSA; if level ≥ 6ng/ml → TRUS	16.34	17.1%	2.89	£76	£5,516	£7,024	9.093	8	9
TRUS everyone	16.04	20.3%	0.77	£0	£4,263	£4,856	8.984	9	38
1-yearly %free PSA; if level <15% → TRUS	16.25	17.8%	1.67	£157	£5,282	£6,398	9.061	10	16
1-yearly PSA; if density ≥ 0.09ng/ml/ml → TRUS	16.37	16.8%	3.39	£74	£5,595	£7,295	9.104	11	6
3-monthly DRE; if abnormal → TRUS	16.36	16.9%	2.26	£607	£5,534	£7,340	9.105	12	8
3-monthly %free PSA; if level <15% → TRUS	16.50	15.6%	5.44	£489	£5,963	£8,884	9.154	23	10

3

One-way sensitivity analysis

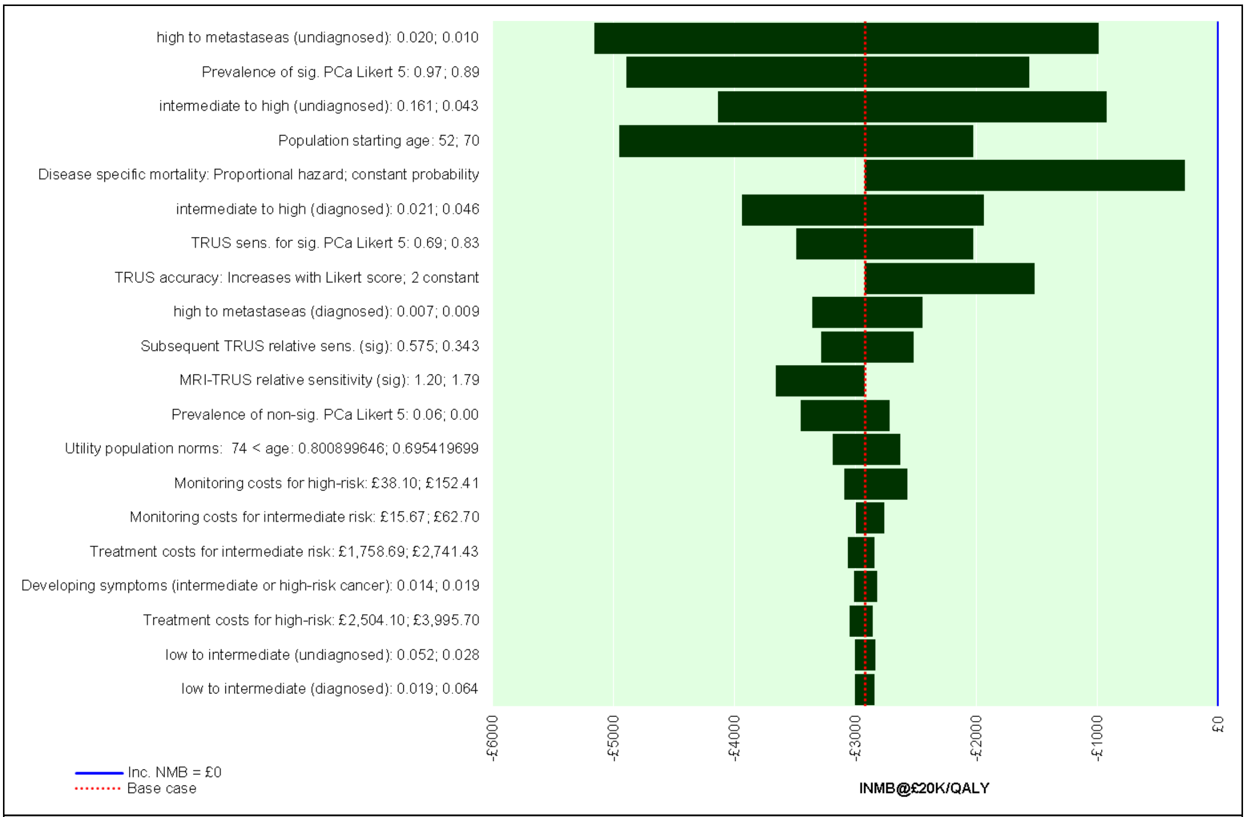
Figure HE77 shows the impact of changing the value of a parameter on the results of a pairwise comparison between "no screening" strategy and the strategy where people receive an immediate TPM biopsy and not followed-up subsequently. It shows that the latter strategy is always worthwhile unless prostate cancer death is assigned a constant probability.



Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line "no screening" vs "TPM everyone"

Figure HE77: One-way sensitivity analysis "no screening" vs "TPM everyone" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

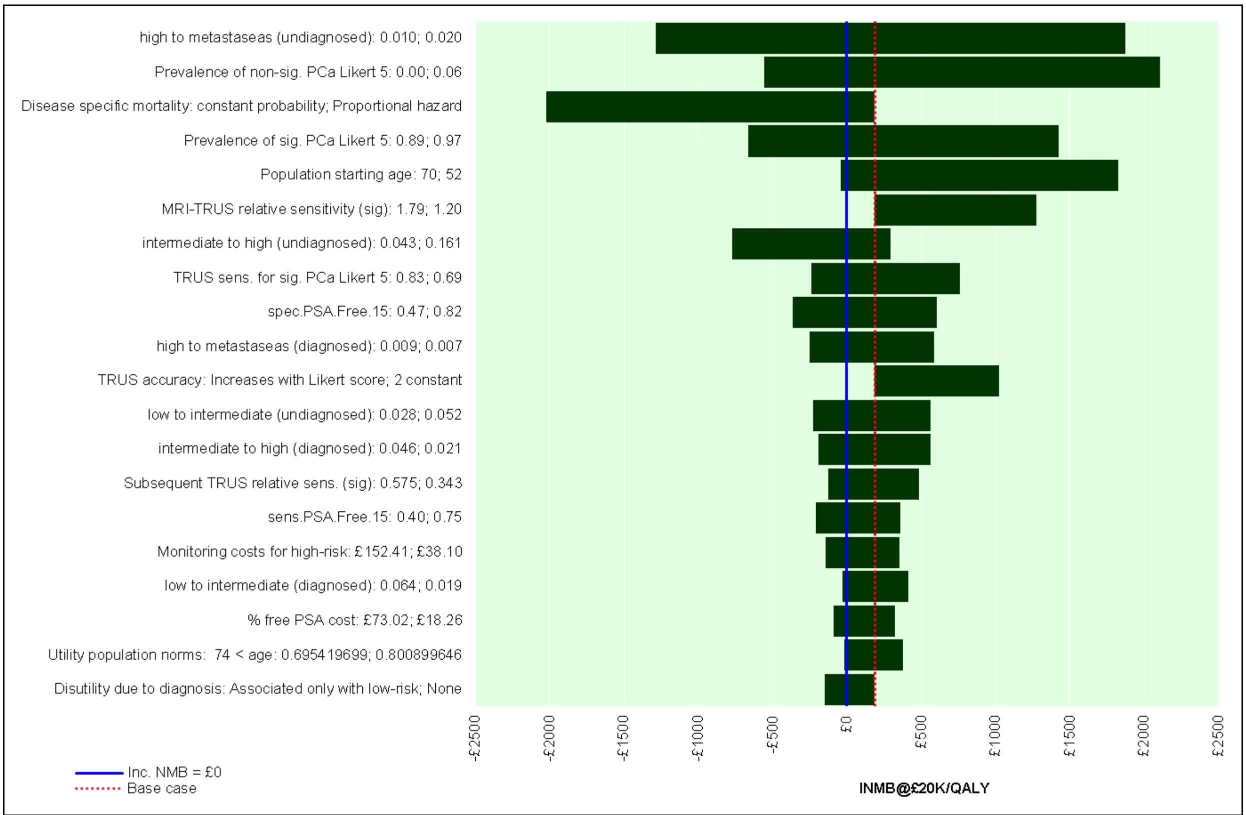
Figure HE78 shows the impact of changing the value of a parameter on the results of a pairwise comparison between "no screening" strategy and the strategy where people receive an immediate TRUS biopsy and not followed-up subsequently. It shows that the latter strategy is always worthwhile.



Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line "no screening" vs "TRUS everyone"

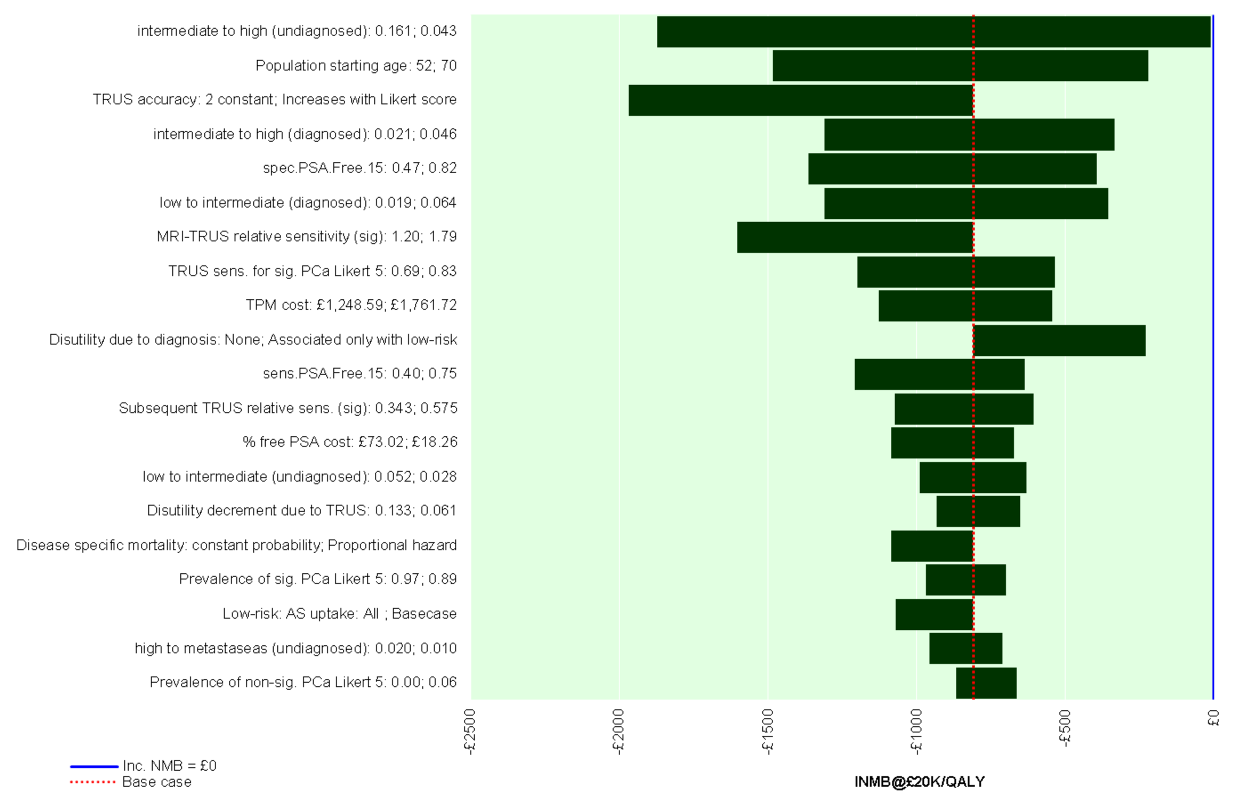
Figure HE78: One-way sensitivity analysis "no screening" vs "TRUS everyone" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Figure HE79 shows the impact of changing the value of a parameter on the results of a pairwise comparison between "6-monthly %free PSA; if level <15% → TRUS" strategy and the strategy where people receive an immediate TRUS biopsy and not followed-up subsequently. It shows that the given the 95% confidence interval assigned to a number og key parameters, the performance of the two strategies is similar. However, Figure HE80 shows that "TPM everyone" strategy always worthwhile when compared to the same follow-up protocole.



Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line "6-monthly %free PSA; if level <15% → TRUS" vs "TRUS everyone"

Figure HE79: One-way sensitivity analysis "6-monthly %free PSA; if level <15% → TRUS" vs "TRUS everyone" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

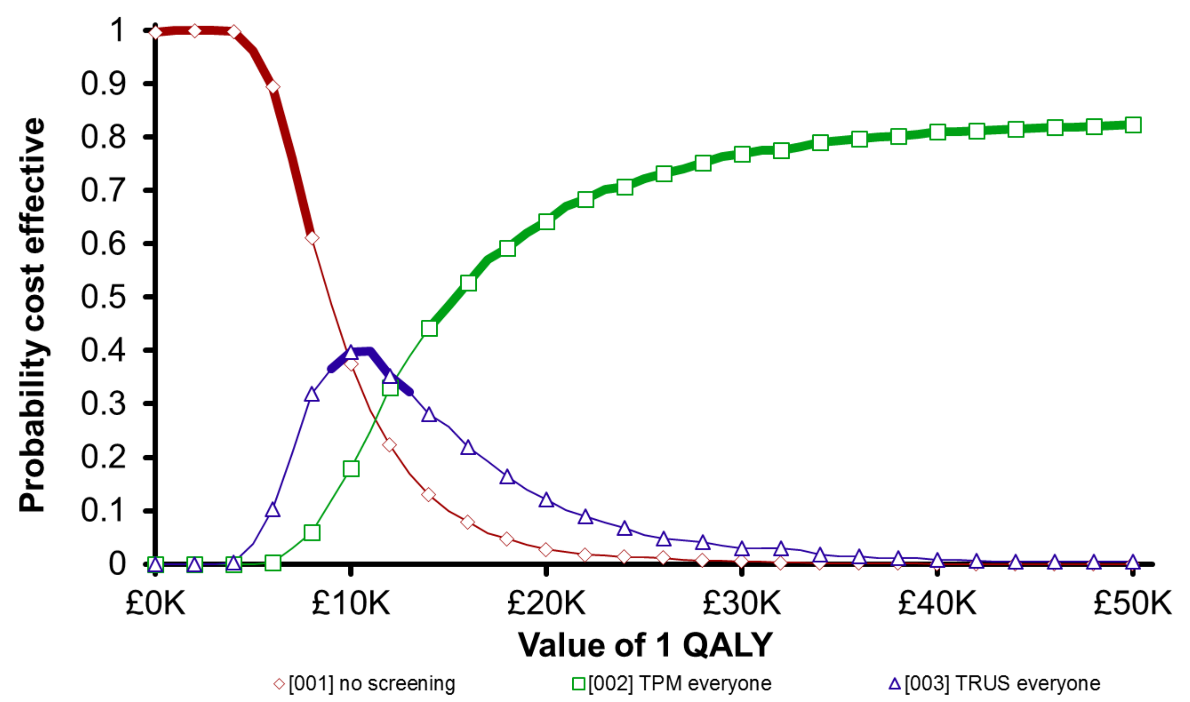


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line “6-monthly %free PSA; if level <15% → TRUS” vs “TPM everyone”

Figure HE80: One-way sensitivity analysis “6-monthly %free PSA; if level <15% → TRUS” vs “TPM everyone” based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Probabilistic results

Figure HE81 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. The strategy where people receive an immediate TPM seems to be cost-effective at a threshold of £20,000 per QALY with a probability of about 60%.



Bold line indicates cost effectiveness acceptability frontier

Figure HE81: Cost-effectiveness acceptability curve

HE.6.12 MRI Likert 5; 2 biopsies

Table HE53 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, including 2-yearly PSA density test at a threshold of 0.15 ng/ml/ml that direct people to TRUS, seems optimal. At a slightly higher cost-effectiveness threshold, the strategy, where all candidates receive an immediate TPM and no subsequent follow-up, seems optimal.

Table HE53: Base-case deterministic cost-utility results for people with Likert 5 and two biopsies

Strategy	Absolute		Incremental		
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£1,869	9.170			
TRUS everyone	£2,839	9.245	£970	0.075	£12,964
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	£3,756	9.308	£918	0.063	£14,505
2-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	£3,839	9.313	£82	0.005	£17,903
1-yearly %free PSA; if level <15% → TRUS	£4,653	9.349	£814	0.036	£22,581
TPM everyone	£5,864	9.399	£1,211	0.050	£24,410
3-monthly PHI; if level ≥ 62 → TPM	£9,315	9.415	£3,451	0.016	£216,067

Table HE54 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The strategies including 2-yearly % free PSA tests at a threshold of 15%, 2-yearly PSA velocity tests at a threshold of 0.75ng/ml/year or 2-yearly PSA density tests at a threshold of 0.15 ng/ml/ml, if reached the thresholds, people receive TRUS, win the best positions at a cost-effectiveness threshold of £20,000 per QALY. At a cost-effectiveness threshold of £30,000 per QALY, the same strategies, applied yearly, win the best positions, following the strategy, where all receive an immediate TPM.

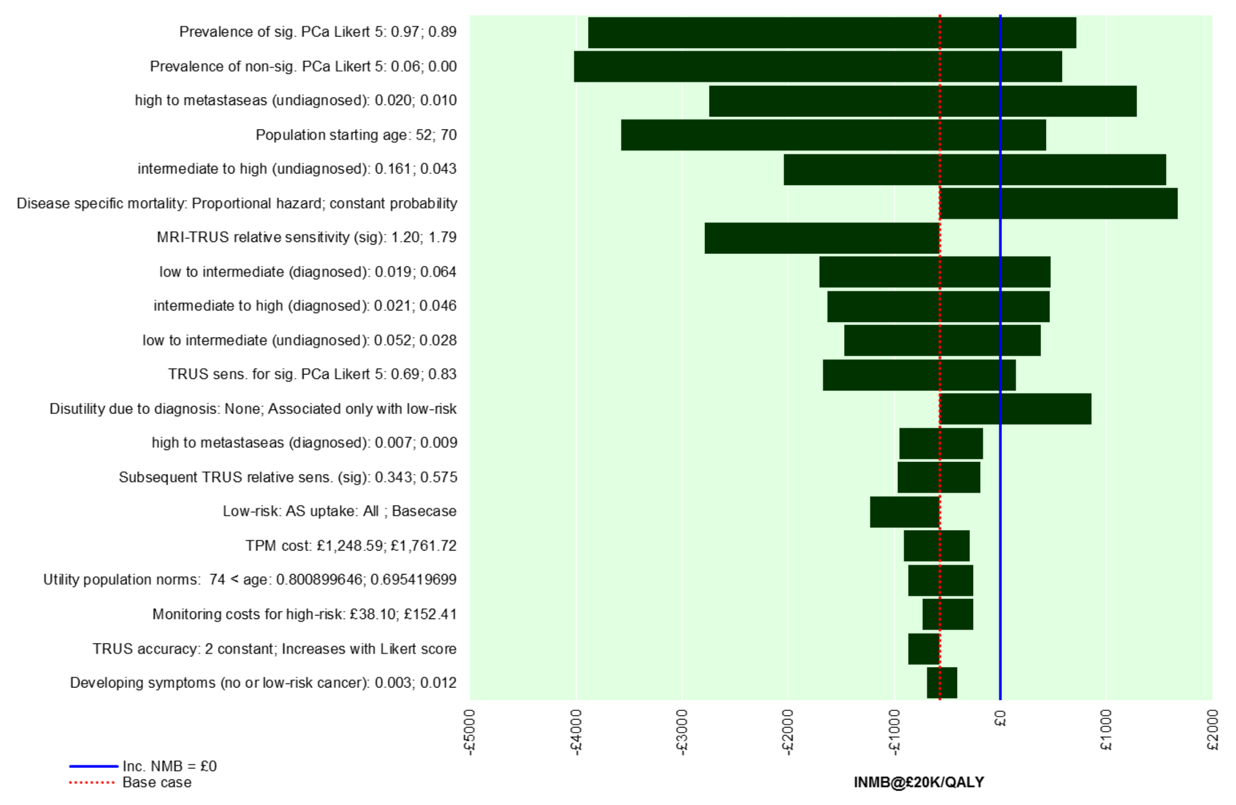
Table HE54: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY for people with Likert 5 and two biopsies

Strategy	Life years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
2-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.77	12.7%	1.69	£50	£2,973	£3,839	9.313	1	14
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.76	12.8%	1.59	£50	£2,931	£3,756	9.308	2	16
2-yearly %free PSA; if level <15% → TRUS	16.73	13.2%	1.31	£98	£2,815	£3,578	9.296	3	35
2-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	16.82	12.2%	2.38	£49	£3,143	£4,277	9.330	4	9
1-yearly %free PSA; if level <15% → TRUS	16.87	11.7%	2.53	£201	£3,306	£4,653	9.349	5	4
2-yearly PSA; if level ≥ 6ng/ml → TRUS	16.80	12.4%	2.17	£49	£3,068	£4,122	9.322	6	15
2-yearly PSA; if density ≥ 0.09ng/ml/ml → TRUS	16.83	12.1%	2.53	£49	£3,166	£4,359	9.333	7	12
3-yearly PSA; if density ≥ 0.12ng/ml/ml → TRUS	16.76	12.7%	1.77	£35	£2,976	£3,847	9.306	8	33
1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS	16.90	11.4%	3.12	£103	£3,403	£4,879	9.358	9	2
3-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.71	13.3%	1.28	£36	£2,792	£3,472	9.287	10	50
TPM everyone	16.98	10.6%	1.12	£0	£4,006	£5,864	9.399	19	1
1-yearly PSA; if density ≥ 0.15ng/ml/ml → TRUS	16.91	11.3%	3.34	£103	£3,437	£4,995	9.361	15	3
2-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.94	10.7%	0.59	£43	£3,939	£5,527	9.376	30	5
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TPM	16.93	10.8%	0.56	£43	£3,899	£5,430	9.373	26	6
2-yearly PSA; if density ≥ 0.12ng/ml/ml → mpMRI; if Likert	16.97	10.3%	0.78	£41	£4,084	£6,068	9.390	73	7

≥4 → TPM									
2-yearly PHI; if level ≥ 35 → mpMRI; if Likert ≥4 → TPM	16.95	10.5%	0.62	£234	£4,000	£5,841	9.383	56	8
2-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM	16.90	11.1%	0.49	£85	£3,779	£5,193	9.361	25	10

One-way sensitivity analysis

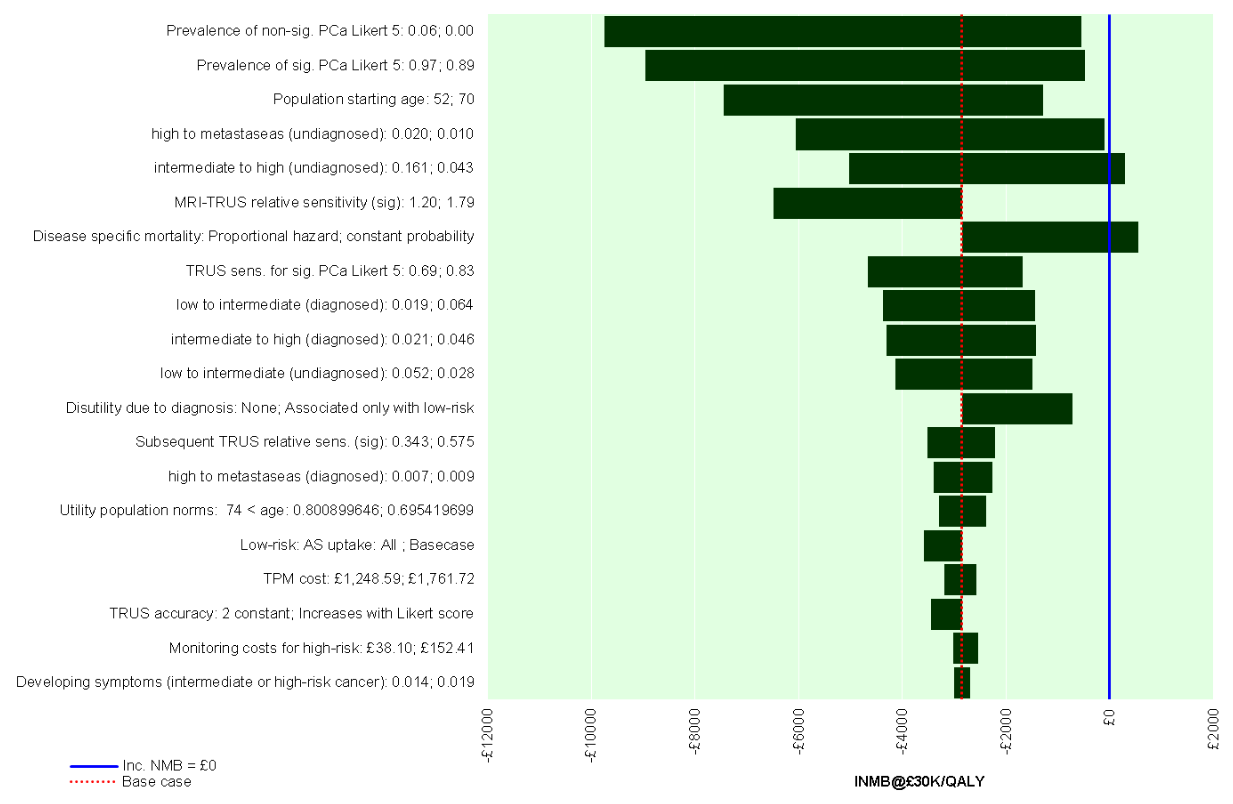
Figure HE82 shows the impact of changing the value of a parameter on the results of a pairwise comparison between “no screening” strategy and the strategy where people receive an immediate TPM biopsy and not followed-up subsequently at a cost-effectiveness threshold of £20,000 per QALY. It shows that the results are very sensitive to a number of parameters that are related mainly to the prevalence estimates, TRUS sensitivity and the disease progression. It shows also the significant impact of assigning a constant probability to prostate cancer death on the results, where “no screening” strategy becomes more beneficial. Starting the model with older age (70) disadvantages the interventional strategy.



Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line “no screening” vs “TPM everyone”

Figure HE82: One-way sensitivity analysis “no screening” vs “TPM everyone” based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

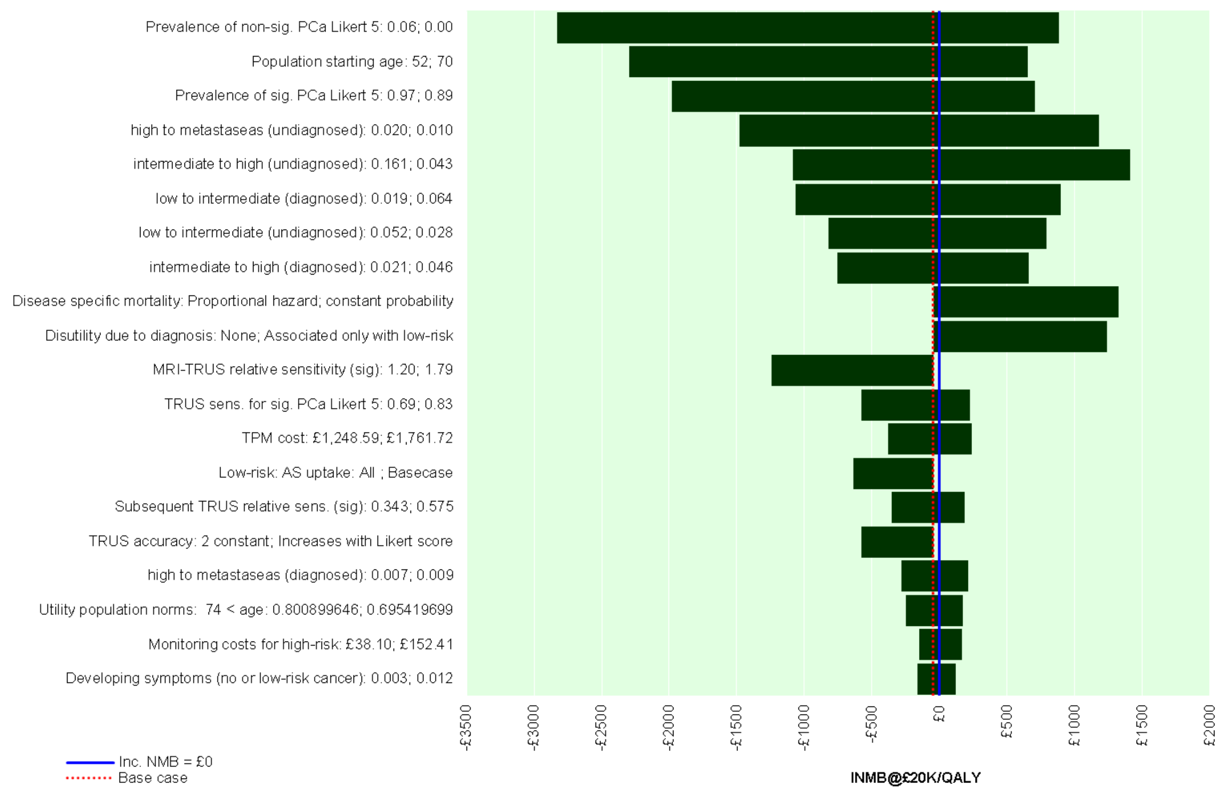
At a cost-effectiveness threshold of £30,000 per QALY, Figure HE83 shows the impact of changing the value of a parameter on the results of a pairwise comparison between “no screening” strategy and the strategy where people receive an immediate TPM biopsy and not followed-up subsequently. It shows that the latter strategy is always worthwhile unless prostate cancer death is assigned a constant probability and the disease progression from intermediate to high-risk is significantly slower in the undiagnosed cases.



Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line "no screening" vs "TPM everyone"

Figure HE83: One-way sensitivity analysis "no screening" vs "TPM everyone" based on the incremental net monetary benefits at cost-effectiveness threshold of £30,000 per QALY

Figure HE84 shows that "TRUS everyone" and "TPM everyone" strategies perform similarly, given the uncertainty surrounding a number of key parameters.

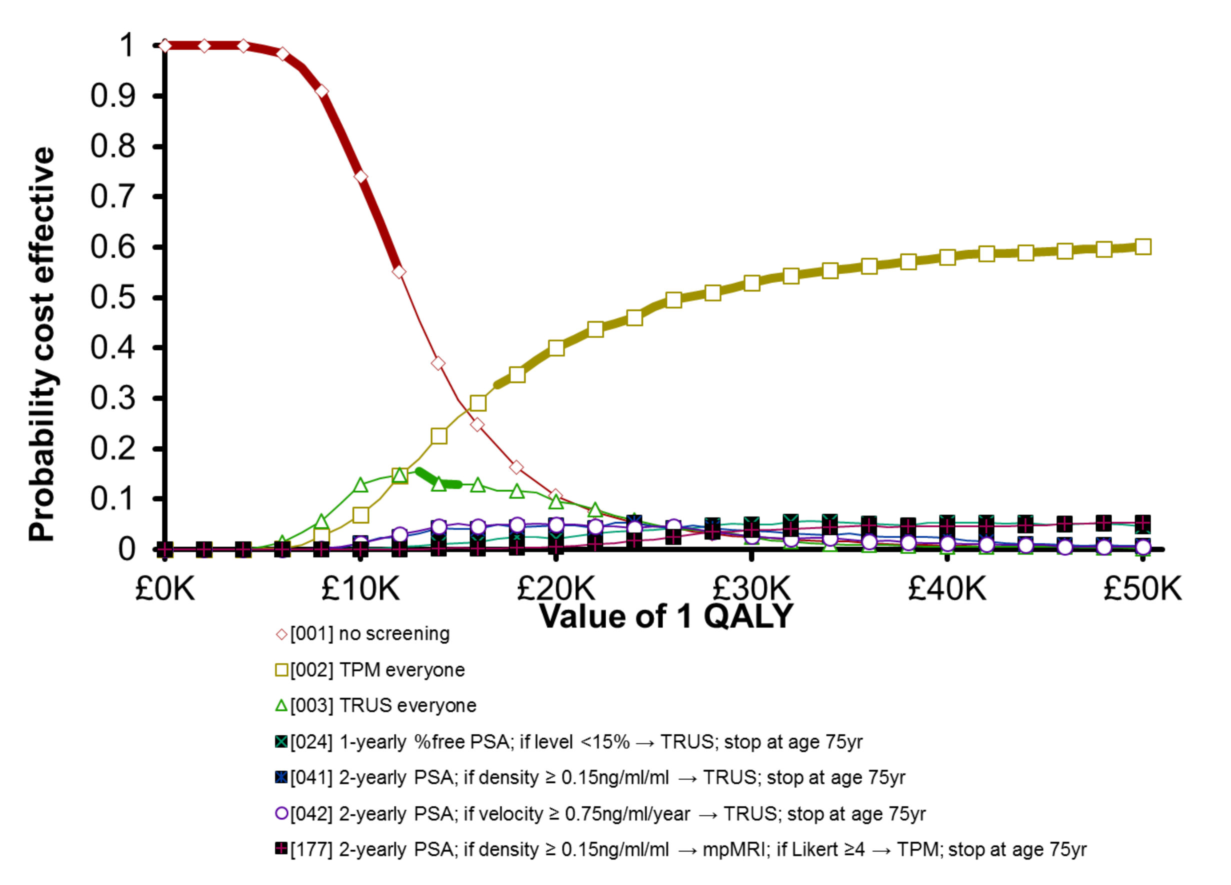


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line "TRUS everyone" vs "TPM everyone"

Figure HE84: One-way sensitivity analysis "TRUS everyone" vs "TPM everyone" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Probabilistic results

Figure HE85 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. The strategy where people receive an immediate TPM seems to be cost-effective at a threshold of £20,000 per QALY with a probability of about 40%.



Bold line indicates cost effectiveness acceptability frontier

Figure HE85: Cost-effectiveness acceptability curve

HE.6.1.10 1 biopsy; no mpMRI

Table HE55 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, where all candidates receive an immediate TPM and no subsequent follow-up, seems optimal.

Table HE55: Base-case deterministic cost-utility results for people with one biopsy but no MRI

Strategy	Absolute		Incremental		
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£1,924	8.950			
TRUS everyone	£3,103	9.052	£1,179	0.102	£11,553
TPM everyone	£6,499	9.303	£3,396	0.251	£13,526
3-monthly PHI; if level ≥ 62 → TPM	£9,602	9.305	£3,103	0.002	£1,477,812

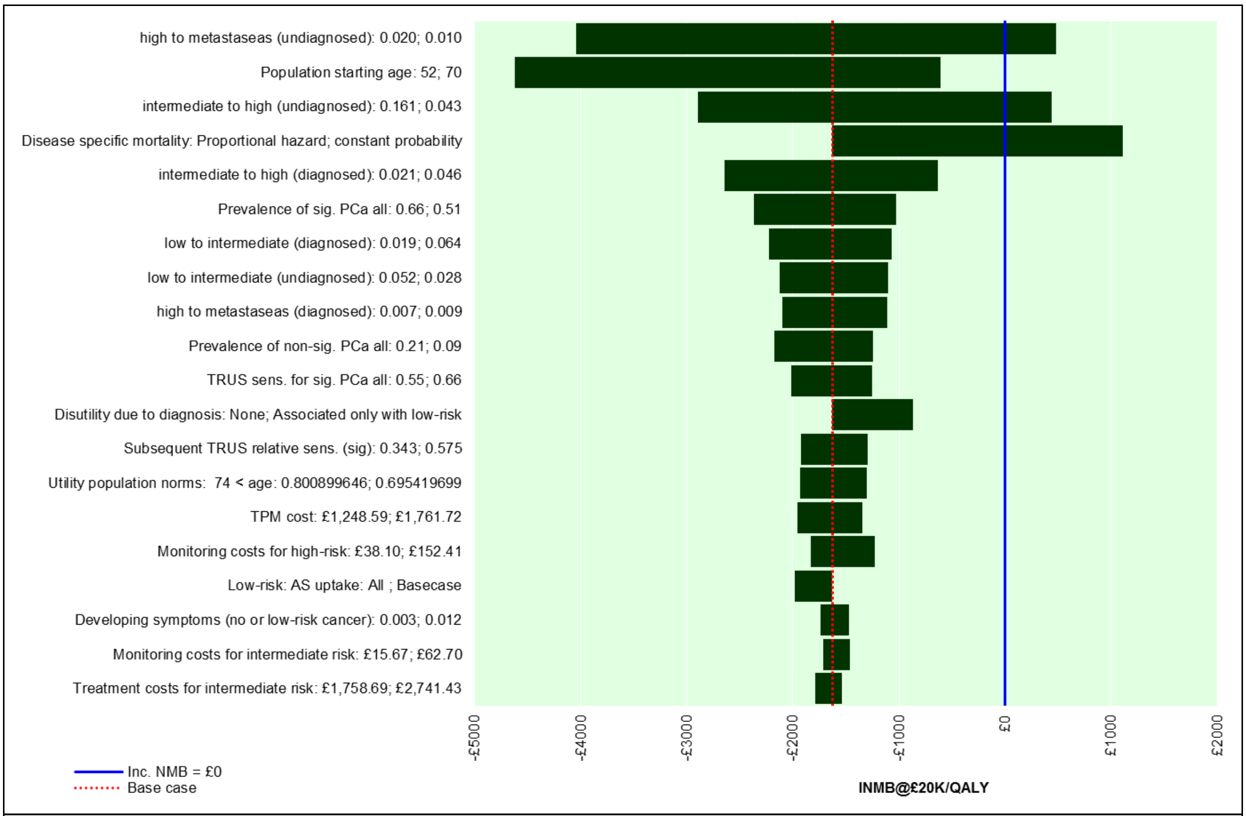
Table HE56 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The strategies, including, 2-yearly PSA density test at a threshold of 0.15 ng/ml/ml , 2-yearly PSA velocity test at a threshold of 0.75ng/ml/year or 2-yearly % free PSA test at a threshold of 15%, if reached the thresholds, followed by mpMRI, if Likert ≥4, people receive TPM, win the best positions following the strategy, where all receive an immediate TPM at a cost-effectiveness threshold of £20,000 per QALY.

Table HE56: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY for people with one biopsy but no MRI

Strategy	Life years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
TPM everyone	16.78	12.7%	0.95	£0	£4,676	£6,499	9.303	1	1
2-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.64	13.6%	0.49	£40	£4,523	£6,120	9.235	2	4
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TPM	16.62	13.7%	0.47	£41	£4,480	£6,025	9.230	3	7
2-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM	16.59	14.0%	0.40	£81	£4,351	£5,789	9.215	4	11
2-yearly PSA; if density ≥ 0.12ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.68	13.2%	0.65	£39	£4,679	£6,635	9.254	5	2
2-yearly PSA; if level ≥ 6ng/ml → mpMRI; if Likert ≥4 → TPM	16.66	13.3%	0.61	£39	£4,614	£6,470	9.246	6	5
2-yearly PHI; if level ≥ 35 → mpMRI; if Likert ≥4 → TPM	16.66	13.4%	0.52	£220	£4,589	£6,423	9.243	7	8
2-yearly PSA; if density ≥ 0.09ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.69	13.1%	0.69	£38	£4,698	£6,734	9.256	8	3
2-yearly PCA3; if level ≥ 50 → mpMRI; if Likert ≥4 → TPM	16.61	13.8%	0.41	£387	£4,432	£6,194	9.225	9	14
2-yearly ; if → mpMRI; if Likert ≥4 → TPM	16.70	13.0%	0.77	£0	£4,728	£6,895	9.260	10	6
6-monthly PHI; if level ≥ 62 → TPM	16.75	12.6%	1.14	£887	£4,853	£7,692	9.281	58	9
6-monthly DRE; if abnormal → TPM	16.71	12.9%	1.28	£333	£4,734	£7,213	9.263	40	10

One-way sensitivity analysis

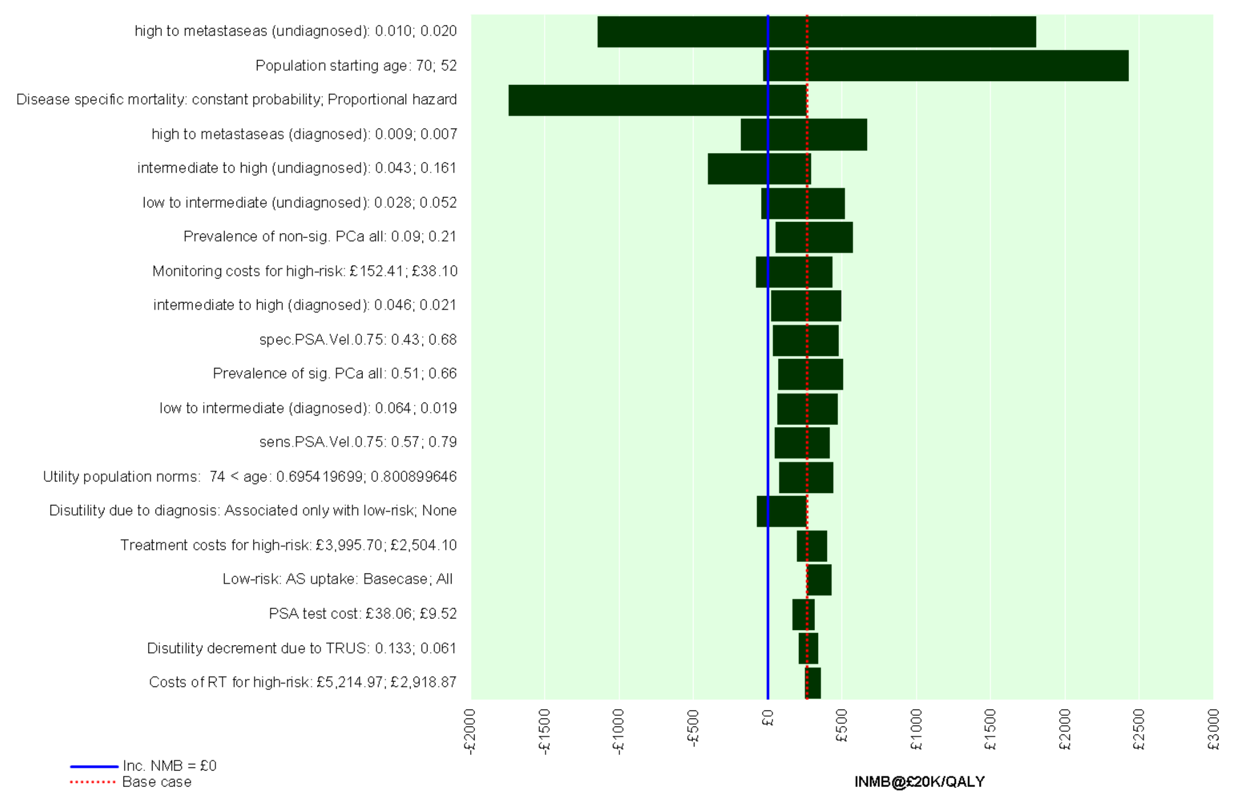
Figure HE86 shows the impact of changing the value of a parameter on the results of a pairwise comparison between “no screening” strategy and the strategy where people receive an immediate TPM biopsy and not followed-up subsequently. It shows that the latter strategy is always worthwhile unless prostate cancer death is assigned a constant probability or disease progression is significantly slower in the undiagnosed cases.



Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line “TRUS everyone” vs “TPM everyone”

Figure HE86: One-way sensitivity analysis “TRUS everyone” vs “TPM everyone” based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Figure HE87 shows the impact of changing the value of a parameter on the results of a pairwise comparison between “1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS” strategy and the strategy where people receive an immediate TRUS biopsy and not followed-up subsequently. It shows that the results are sensitive to a number of parameters, mainly disease progression. It shows also the significant impact of assigning a constant probability to prostate cancer death on the results, where “TRUS everyone” strategy becomes more beneficial.

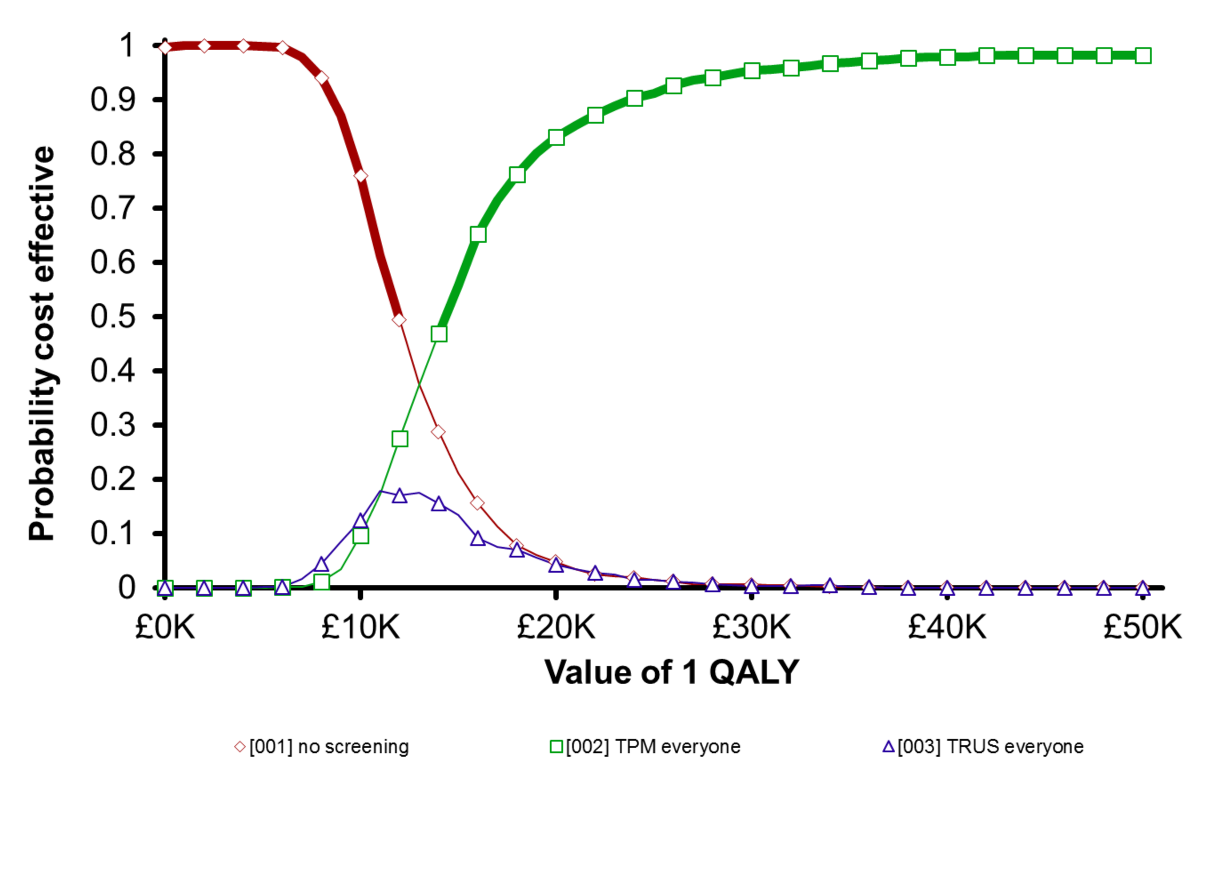


Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line "1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS" vs "TRUS everyone"

Figure HE87: One-way sensitivity analysis "1-yearly PSA; if velocity ≥ 0.75ng/ml/year → TRUS" vs "TRUS everyone" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Probabilistic Results

Figure HE88 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. The strategy where people receive an immediate TPM seems to be cost-effective at a threshold of £20,000 per QALY with a probability of about 80%.



Bold line indicates cost effectiveness acceptability frontier

Figure HE88: Cost-effectiveness acceptability curve

HE.6.1.11 2 biopsies; no mpMRI

Table HE57 shows the incremental analysis results of strategies appeared to have health benefits. At a cost-effectiveness threshold of £20,000 per QALY, the strategy, where all candidates receive an immediate TPM and no subsequent follow-up, seems optimal.

Table HE57: Base-case deterministic cost-utility results for people with two biopsies but no MRI

Strategy	Absolute		Incremental		
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
no screening	£1,413	9.193			
TRUS everyone	£2,331	9.251	£918	0.058	£15,757
2-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM	£4,724	9.387	£2,394	0.136	£17,618
TPM everyone	£5,299	9.417	£575	0.030	£19,137
6-monthly PHI; if level ≥ 62 → TPM	£6,879	9.425	£1,580	0.009	£180,561
3-monthly PHI; if level ≥ 62 → TPM	£9,188	9.436	£2,309	0.010	£227,388

Table HE58 shows the top 10 strategies that generate the greatest health monetary benefits at two cost-effectiveness thresholds £20,000 and £30,000 per QALY. The strategies, including, 2-yearly % free PSA test at a threshold of 15%, 2-yearly PSA velocity test at a threshold of 0.75ng/ml/year or 2-yearly PSA density test at a threshold of 0.15 ng/ml/ml, if reached the thresholds, followed by mpMRI, if Likert ≥4, people receive TPM, win the best positions following the strategy, where all receive an immediate TPM at the both cost-effectiveness thresholds, £20,000 and £30,000 per QALY.

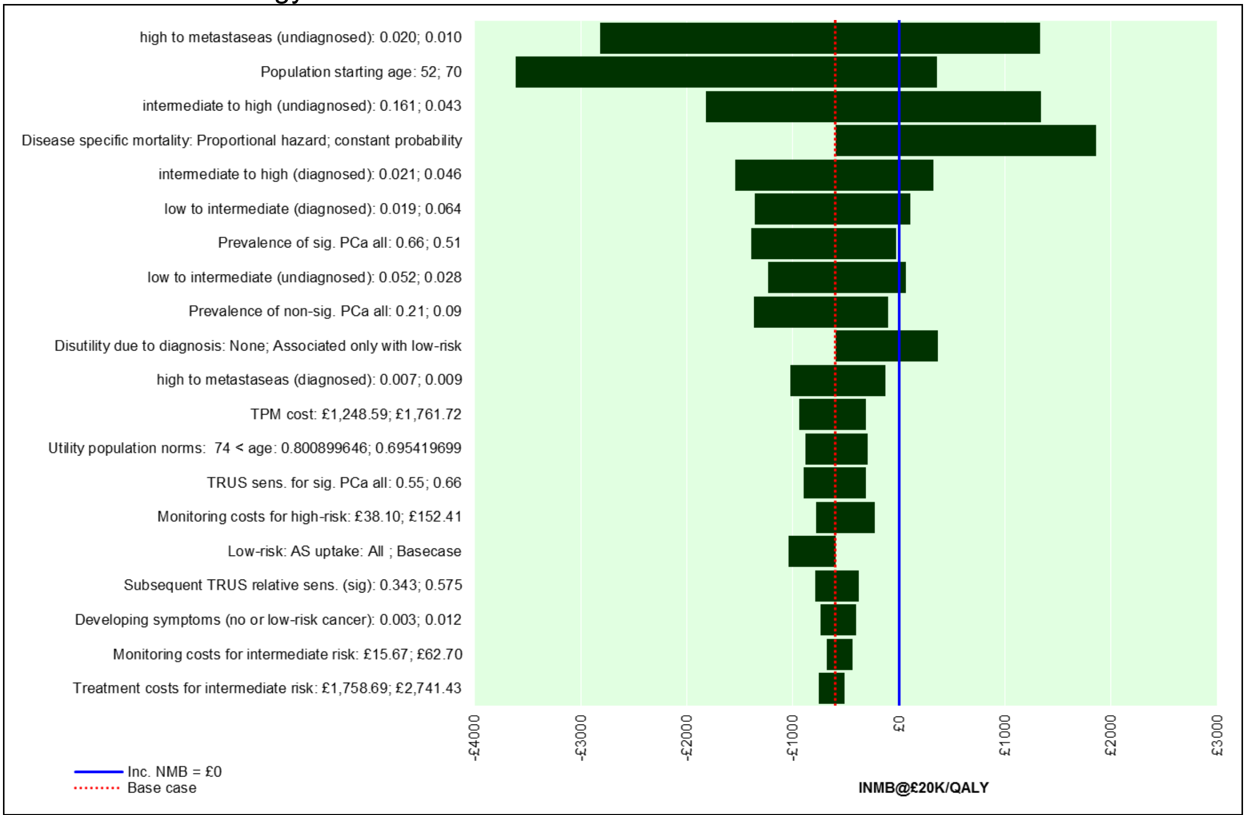
Table HE58: Base-case top strategies based on net health benefits ranked for two thresholds of maximum willingness to pay for additional QALY for people with two biopsies but no MRI

Strategy	Life years	PC deaths	Unnecessary biopsies	Screening costs (£)	Treatment costs (£)	Absolute		Rank at thresholds of	
						Costs (£)	Effects (QALYs)	£20k/ QALY	£30k/ QALY
TPM everyone	17.02	10.1%	1.14	£0	£3,400	£5,299	9.417	1	1
2-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM	16.95	10.3%	0.47	£89	£3,337	£4,724	9.387	2	4
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TPM	16.98	10.0%	0.55	£46	£3,444	£4,961	9.397	3	3
2-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.99	10.0%	0.58	£45	£3,480	£5,059	9.401	4	2
3-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TPM	16.92	10.5%	0.45	£33	£3,250	£4,531	9.372	5	12
3-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.93	10.4%	0.47	£33	£3,294	£4,623	9.376	6	9
3-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM	16.89	10.9%	0.39	£65	£3,124	£4,305	9.360	7	18
2-yearly DRE; if abnormal → mpMRI; if Likert ≥4 → TPM	16.79	12.0%	0.26	£102	£2,654	£3,603	9.321	8	46
2-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TRUS	16.74	12.8%	0.71	£53	£2,289	£3,350	9.307	9	63
2-yearly PSA; if density ≥ 0.15ng/ml/ml → mpMRI; if Likert ≥4 → TRUS	16.75	12.7%	0.75	£53	£2,328	£3,439	9.312	10	57
2-yearly PHI; if level ≥ 35 → mpMRI; if Likert ≥4 → TPM	17.00	9.8%	0.62	£248	£3,535	£5,384	9.406	15	5

2-yearly PSA; if level ≥ 6ng/ml → mpMRI; if Likert ≥4 → TPM	17.01	9.8%	0.73	£44	£3,557	£5,454	9.408	24	6
2-yearly PSA; if density ≥ 0.12ng/ml/ml → mpMRI; if Likert ≥4 → TPM	17.02	9.6%	0.79	£44	£3,612	£5,630	9.413	38	7
2-yearly PSA; if density ≥ 0.09ng/ml/ml → mpMRI; if Likert ≥4 → TPM	17.03	9.6%	0.83	£44	£3,628	£5,746	9.414	65	8
3-yearly PSA; if density ≥ 0.12ng/ml/ml → mpMRI; if Likert ≥4 → TPM	16.98	10.0%	0.63	£32	£3,467	£5,117	9.393	16	10

One-way sensitivity analysis

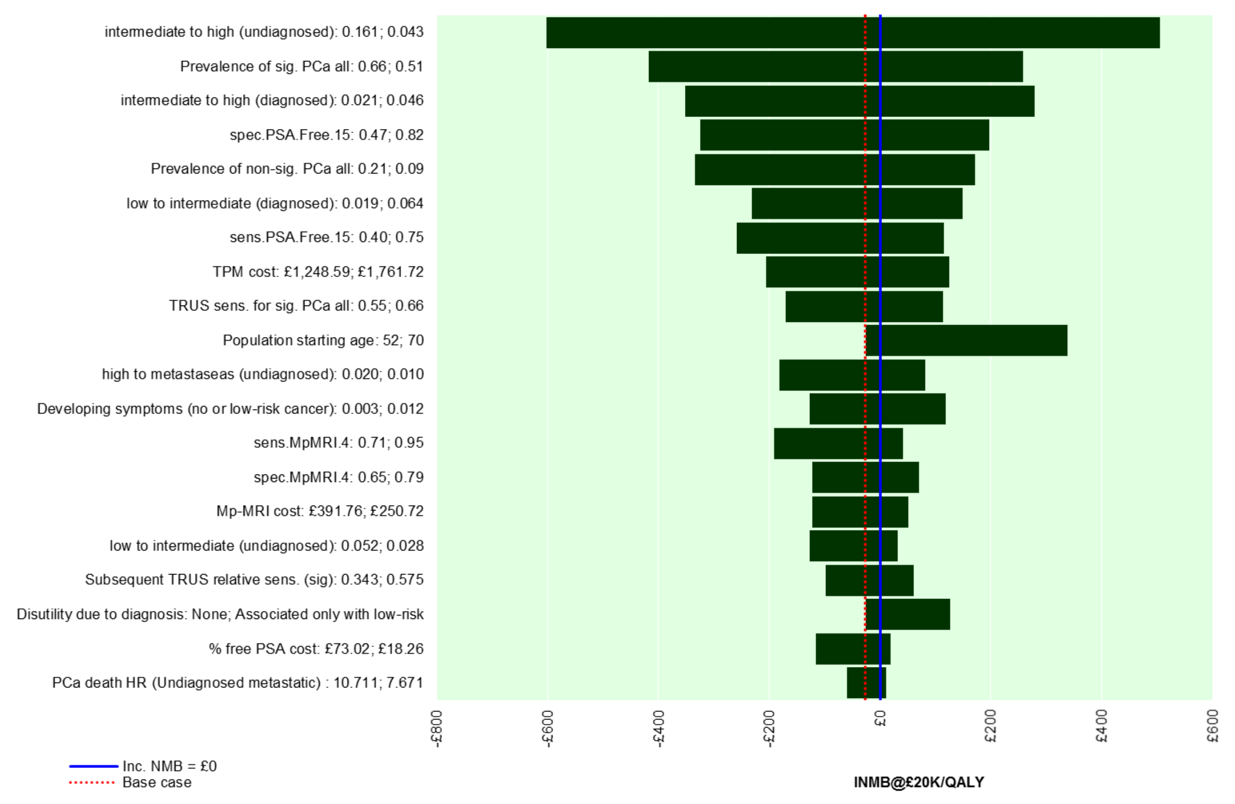
Figure HE89 shows the impact of changing the value of a parameter on the results of a pairwise comparison between "no screening" strategy and the strategy where people receive an immediate TPM biopsy and not followed-up subsequently at a cost-effectiveness threshold of £20,000 per QALY. It shows that the results are very sensitive to a number of parameters that are related mainly to the disease progression. It shows also the significant impact of assigning a constant probability to prostate cancer death on the results, where "no screening" strategy becomes more beneficial. Starting the model with older age (70) or applying disutility on people with low-risk disease once diagnosed disadvantages the interventional strategy.



Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line "no screening" vs "TPM everyone"

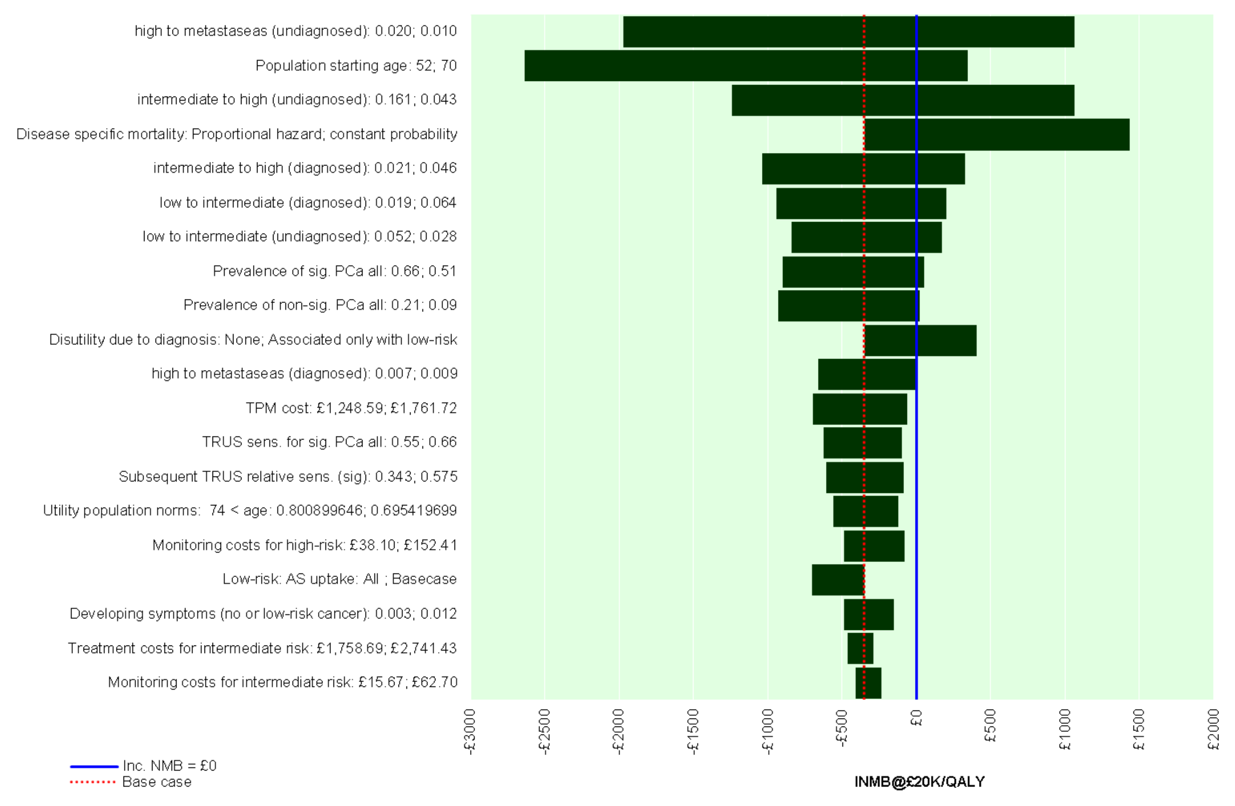
Figure HE89: One-way sensitivity analysis "no screening" vs "TPM everyone" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY

Figure HE90 shows the impact of changing the value of a parameter on the results of a pairwise comparison between the strategy where people receive 2-yearly % free PSA test, if level <15%, they receive mpMRI, if Likert score ≥4, they receive TPM, and the strategy where people receive an immediate TPM biopsy and not followed-up subsequently at a cost-effectiveness threshold of £20,000 per QALY. It shows that given the 95% confidence interval assigned to a number of parameters, including disease progression probabilities, disease prevalence, diagnostic tests accuracy data and the test costs, there is not a significant difference between the two strategies.



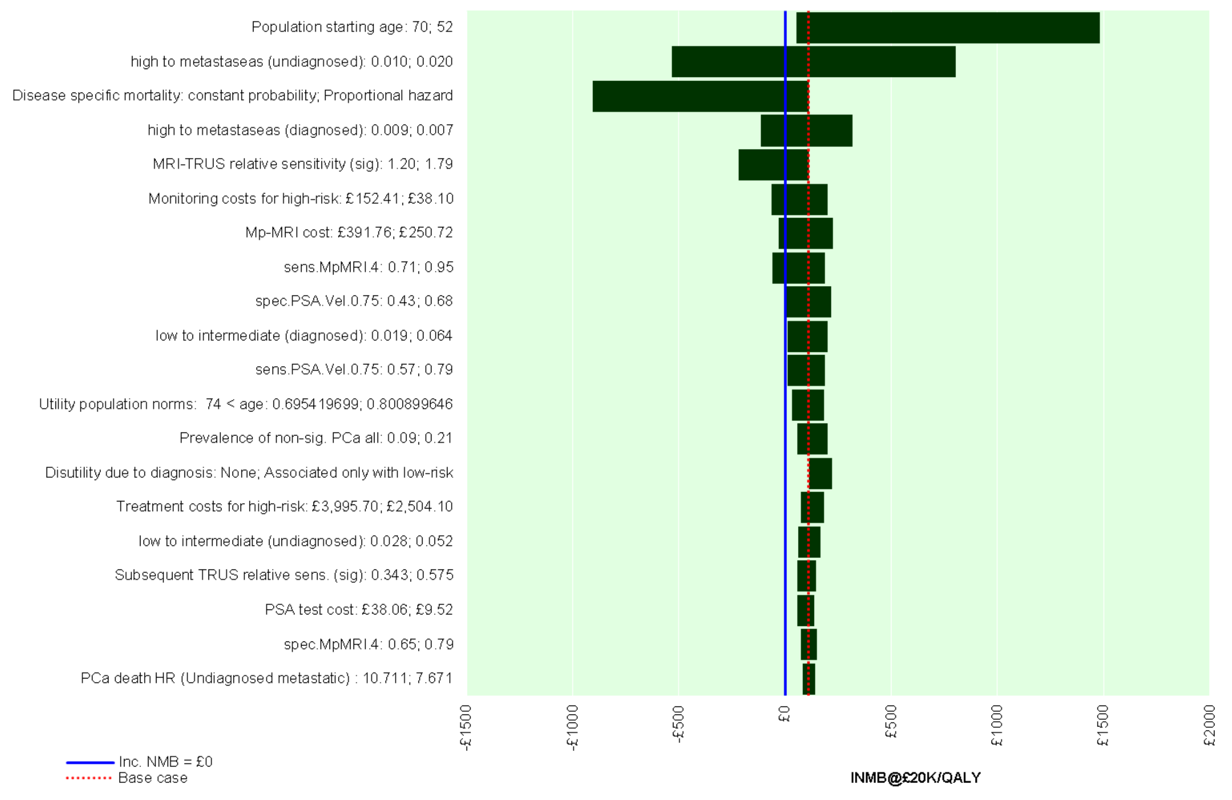
Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line

Figure HE90: One-way sensitivity analysis “2-yearly %free PSA; if level <15% → mpMRI; if Likert ≥4 → TPM” vs “TPM everyone” based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY



Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line "TRUS everyone" vs "TPM everyone"

Figure HE91: One-way sensitivity analysis "TRUS everyone" vs "TPM everyone" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY



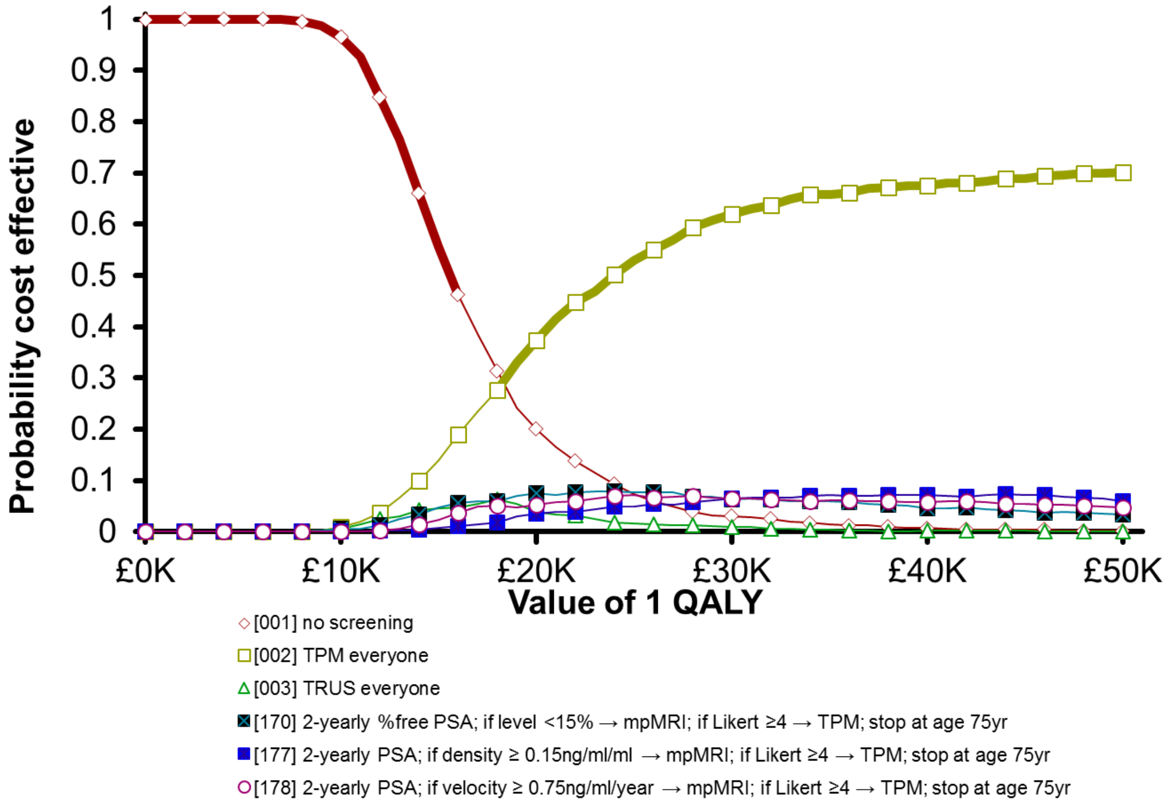
Tornado diagram: the dotted red line represents the base-case results; the bars on its sides represent the results if the parameter is altered by the values described on the left side; if the change has a significant impact on the conclusion, the related bar exceeds the blue line "2-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TRUS " vs "TRUS everyone"

1 **Figure HE92: One-way sensitivity analysis 2-yearly PSA; if velocity ≥ 0.75ng/ml/year → mpMRI; if Likert ≥4 → TRUS " vs "TRUS everyone" based on the incremental net monetary benefits at cost-effectiveness threshold of £20,000 per QALY**

5 **Probabilistic results**

6 Figure HE93 shows the uncertainty surrounding the model results for this population at a range of cost-effectiveness thresholds from 0 to £50,000 per QALY. The bold line indicates the strategy that generates the greatest health monetary benefits at a given threshold. The strategy where people receive an immediate TPM seems to be cost-effective at a threshold of £20,000 per QALY with a probability of about 40%.

11



Bold line indicates cost effectiveness acceptability frontier

1 **Figure HE93: Cost-effectiveness acceptability curve**

2