Systematic Review of cost-effectiveness models in prostate cancer: exploring new developments in testing and diagnosis

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Abstract

Background

There is currently no formal prostate cancer screening programme in the UK. Early detection using age-based prostate-specific antigen (PSA) testing is unlikely to be cost-effective due to limited mortality benefit and harms associated with overdetection. However, the discovery of new prostate cancer specific biomarkers and more accurate diagnostic strategies (e.g. magnetic resonance imaging (MRI)) could improve the outcomes of screening. A systematic review was conducted to assess the evidence base on cost-effectiveness of such innovations and areas for further development.

Methods

To identify model-based economic evaluations of screening and diagnostic tests for prostate cancer, a systematic review of the literature using the NHS Economic Evaluation Database, Medline, EMBASE, HTA databases, NICE guidelines, and UK National Screening Committee guidance was carried out, between 2009 and 2019. Relevant data were extracted on study type, model inputs, modelling methods and cost-effectiveness conclusions and the results narratively synthesized.

Results

Sixteen studies were included in the review. Seven studies compared the cost-effectiveness of new urinary or blood biomarkers compared to each other or the PSA test and found the biomarkers e.g. the Prostate Health Index (PHI) and SelectMDx, to be the most cost-effective. Seven studies compared newer prostate biopsy methods, including MRI-guided, to TRUS guided biopsy and found MRI-guided methods to be most cost-effective. The newer detection methods showed a reduction in unnecessary biopsies and overtreatment. However, there was uncertainty around the most cost-effective pathway of follow-up strategies (MRI/biomarkers) in men who have a negative initial biopsy. Many studies did not model stage or grade of cancer, cancer progression or the entire testing, screening and treatment pathway. Very few studies fully accounted for uncertainty in their analysis.

Conclusions

This review brings together the cost-effectiveness literature for novel screening and testing methods used in the diagnosis of prostate cancer. Several limitations of the published models were identified. The models generally either compared new biomarkers or new imaging techniques which highlights the importance of future work in this area, as biomarkers and imaging are likely to be used in combination.

1 Background

Prostate cancer is the second most commonly occurring cancer in men worldwide and the fourth most commonly occurring cancer overall.(1) Detection of early disease has historically been achieved using a prostate-specific antigen (PSA) blood test followed by transrectal ultrasound (TRUS) guided biopsy. PSA is not a specific marker for prostate cancer however, and TRUS-guided prostate biopsy is associated with infection and other adverse effects, and can lead to false negative results in up to 25% of cases.(2, 3) Current diagnostic methods, therefore, lead to overdetection of cancers that may not progress to become clinically important in a man's lifetime, but can also miss aggressive, potentially fatal prostate cancer.(4, 5) Overdetection can have a significant effect on the quality of life of the men affected due to the adverse effects associated with testing and unnecessary treatment(6). It is also a poor use of limited healthcare resources. In the absence of robust evidence, current UK policy does not advocate population screening. Several large trials, including the European Randomised Study of Screening for Prostate Cancer (ERSPC)(7), the US Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial(8) and the UK Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) trial(9) have found limited mortality benefit of PSA-based screening when considered overall.(10) Therefore, as it stands, the benefits of screening seem insufficient to outweigh the potential harms of overtreatment.

Recent years have seen the development of biomarker tests to replace or complement PSA-based testing e.g. the Prostate Health Index (PHI), 4Kscore, SelectMDx and PCA3. These tests act as additional reflex tests to aid the decision about when a man should be referred for prostate biopsy. Numerous risk calculators, incorporating factors such as age, family history and digital rectal examination (DRE), alongside blood or urine biomarkers have also been developed with the same goal.(11) Multiparametric magnetic resonance imaging (mpMRI) is another recent development that, when used as a triage test following PSA or other biomarker testing, might allow men with no or likely indolent cancer to avoid unnecessary biopsy and improve diagnostic accuracy with respect to more aggressive disease.(12, 13) There is potential, therefore, for a reduction in overdiagnosis and higher specificity for potentially lethal cancer.(4) However, it is not yet clear if any of these new developments should be implemented either individually or in combination with one another at a national level within a screening programme.

As innovations that aim to address the overdiagnosis associated with prostate cancer screening become available, healthcare policy makers must make informed decisions regarding their use in national screening strategies. As such, it is essential to establish the cost effectiveness of these developments, and their combinations, to make rational decisions about the allocation of limited healthcare resources. Since the early 2000s, several model-based cost-effectiveness analyses have been published assessing the impact of new tests, diagnostic tools and follow-up strategies to improve the outcomes of prostate cancer screening.

The aim of this research is to identify published cost-effectiveness models assessing the impact of these innovations on the costs and outcomes of prostate cancer diagnosis. This review will determine the current evidence base and provide an overview of model characteristics. It will provide information on novel

tests, how they have been modelled, and the data available to populate such models, which will assist the development of new cost-effectiveness models in prostate cancer screening. The review will also assess the limitations of available models, highlighting ways in which a future model may improve on these.

2 Methods

2.3 Study Selection

Study selection proceeded from title/abstract screening against the eligibility criteria through full text review to data extraction. EK was involved at all stages. A second reviewer (JM) independently screened 10% of the titles and abstracts and carried out data extraction on 20% of the included studies. Studies were categorised according to model-based economic evaluation of new (a) biomarkers/tests/risk models for screening in prostate cancer, (b) biopsy methods for definitive diagnosis following an initial triage screening test in prostate cancer and (c) follow-up testing and diagnostic strategies for men initially found to have no or low-risk prostate cancer.

2.1 Search Strategy

In September 2019, studies were identified by searching the National Health Service Economic Evaluation Database (NHS-EED) (2009-2014), Medline, EMBASE, Health Technology Assessment (HTA) databases, National Institute of Clinical Excellence (NICE) guidelines, UK National Screening Committee guidance, and reference lists from relevant studies. The review was restricted to evidence from January 2009 onward to reflect current practice in screening and testing for prostate cancer. Search terms included free text and medical subject headings (MESH) terms (Appendix 1). The search was limited to English language publications.

2.2 Eligibility Criteria

Studies were included if they met the following criteria:

- Model-based economic evaluation of screening or diagnostic strategies for prostate cancer beyond the standard PSA test plus TRUS-biopsy
- Cost-effectiveness, cost-utility analysis, cost-consequence analysis or cost-benefit analysis
- Model-based economic evaluation using primary data from a trial or secondary data from the literature
- Any test for diagnosing or ruling out prostate cancer
- Any subsequent follow-up regime (aside from PSA testing) when prostate cancer has not been identified at initial biopsy
- Any country or type of health system

2.4 Data extraction

Data extraction forms were developed and pilot-tested on a random sample (5%) of included studies and refined accordingly. The data extraction form is shown in Appendix 2.

Information extracted from each study included:

- Context (i.e. the tests compared and country)
- Characteristics of the tests compared (i.e. frequency of testing and threshold for a positive result)
- Population strategy applied to (i.e. screening start and stop age and the prevalence of prostate cancer)
- Outcome measure (e.g. cost per Quality Adjusted Life Year (QALY) gained)
- Cost-effectiveness result
- Characteristics of the model including model type (e.g. decision tree, Markov model) and structure (how clinical pathways are represented)
- Sensitivity analysis (including the extent to which uncertainty in the cost-effectiveness result had been quantified)
- Source of evidence for utility values assigned to health states and costs included in the model
- Source of evidence for accuracy of tests

2.5 Quality assessment

The purpose of the review was to determine the current evidence base and provide an overview of the characteristics of available models. A formal quality checklist was therefore not used to exclude studies from the review. However, existing economic evaluation checklists were used as a guide to reporting the studies(14, 15).

3 Results

In total 979 studies were identified. After removing duplicates and checking for eligibility, 47 full text papers were retrieved (Fig. 1). Sixteen studies were included in the review.

3.1 Study type

Of the sixteen studies, seven compared the cost-effectiveness of new urinary or blood biomarkers compared to each other or to the standard of care (a PSA test) (Table 1). Another seven studies compared different approaches to prostate biopsy. Two studies compared follow-up strategies in men who have a negative initial biopsy result (16, 17). The studies were based in the US (n = 5), UK (n = 4), Netherlands (n = 4), Hong Kong (n = 1), Germany (n = 1) and Canada (n = 1). All but two studies (18, 19) carried out a cost-utility analysis where outcomes were measured in QALYs. The other two were cost-consequence analyses reporting the number of PSA tests and biopsies carried out and expected overall diagnostic costs (19) (18).

Table 1
Studies included following full-text screening

Author	Year	Country	Type of comparison	Tests compared
Bouttell et al(18)	2019	Hong Kong	Biomarker	PHI, PSA
NICE guideline (16)	2019	UK	Follow-up strategy	PSA, PSA velocity, PSA density, % free PSA, PSA doubling time, PSA density intransition zone, PCA3, PHI, mpMRI, no follow-up
Sathianathen al(20)	2018	US	Biomarker	PSA, SelectMDx, PHI, EPI, 4Kscore
Govers et al (21)	2018	US	Biomarker	PSA, SelectMDx
Barnett et al (22)	2018	US	MRI	TRUS biopsy, MRI-guided fusion biopsy, combined biopsy
Faria et al (23)	2018	UK	MRI	TRUS biopsy, mpMRI guided biopsy, template mapping biopsy
Dijkstra et al (24)	2017	Holland	Biomarker	PSA, SelectMDx
Pahwa et al (25)	2017	US	MRI	TRUS biopsy, MRI-guided fusion biopsy, cognitive-targeted biopsy, in-gantry biopsy
Venderink et al (26)	2017	Holland	MRI	TRUS biopsy, MRI TRUS biopsy, in-gantry biopsy
Heijnsdijk et al(27)	2016	Holland	Biomarker	PSA, PHI
Cerantola et al (28)	2016	Canada	MRI	TRUS biopsy, MRI cognitive-targeted biopsy
Nicholson et al (17)	2015	UK	Follow-up strategy	PSA, PCA3, PHI, mpMRI, TRUS biopsy, clinical assessment
de Rooij et al (29)	2013	Holland	MRI	TRUS biopsy, MRI targeted biopsy
Mowatt et al (30)	2013	UK	MRI	T2-MRI, MRS, DCE-MRI, T2-MRI or MRS, T2-MRI or DCE-MRI
Schiffer et al (19)	2012	Germany	Biomarker	PSA, UPA-PC
Nichol et al (31)	2011	US	Biomarker	PSA, PHI

Legend: PHI – Prostate Health Index, PSA – Prostate-Specific Antigen, mpMRI – Multiparametric Magnetic Resonance Imaging, EPI - ExoDx® Prostate(IntelliScore), TRUS – Transrectal Ultrasound, MRI – Magnetic Resonance Imaging, MRS - Magnetic Resonance Spectroscopy, DCE-MRI - Dynamic contrast-enhanced magnetic resonance imaging, DW-MRI - Diffusion-weighted magnetic resonance imaging, UPA-PC - Urinary Proteome Analysis for PCa diagnosis

3.1.1 Strategies compared – biomarkers

The novel diagnostic strategies that were compared to PSA-based testing alone included PSA plus Prostate Health Index (PHI) testing (18, 27, 31), SelectMDx testing(21, 24) and Urinary Proteome Analysis (UPA-PC) testing (19). The definitions of these biomarker tests are given in Appendix 3, Table 1. Most studies considered only one novel test, except Sathianathen et al who compared PHI, the 4Kscore, EPI and SelectMDx.(20) Of the seven studies comparing different biomarkers, six referred to TRUS-guided biopsy to confirm diagnosis and one did not report the biopsy method assumed(27). Only two studies (27, 31) modelled repeat PSA/biomarker testing, assuming annual and 4-yearly screening respectively.

3.1.2 Strategies compared - biopsy methods

Men with a suspicion of prostate cancer indicated by a PSA test or other biomarker are generally referred for a TRUS-guided biopsy. The different biopsy methods the seven studies identified compared included MRI-targeted methods and template mapping biopsy (23). The definitions of biopsy methods are given in Appendix 3, Table 2. Different strategies were compared, including using MRI to decide whether a TRUS guided biopsy is necessary and to target biopsy, and strategies starting with TRUS guided biopsy and using MRI to decide whether a repeat biopsy is necessary. One study(30) compared each separate parameter of mpMRI to standard TRUS imaging, rather than comparing a pathway with MRI to one without. Only one study (22) modelled repeat screening, assuming that men would be screened every 2 years based on the 2013 American Urological Association (AUA) guideline.(32)

3.1.3 Strategies compared – follow-up strategies in men with negative biopsies

Two studies (16, 17) compared follow-up strategies for men with raised PSA, negative MRI and/or negative prostate biopsy. The strategies included various biomarkers (PSA, PSA velocity, PSA density, % free PSA, PSA doubling time, PSA density in transition zone, PCA3, PHI), and MRI imaging techniques.

3.1.4 Patient population

The majority of studies specified that their patient population was biopsy-naïve men with an elevated PSA and/or suspicious DRE (Table 2). Three studies stated that their population of interest was men in whom there is still a suspicion of prostate cancer following a negative initial biopsy result, due to clinical or pathological findings (16, 17, 30). Only two studies modelled screening strategies in a population of test-naïve men (22, 31). Only the NICE guideline justified the start and stop ages used, stating the committee advised an age of 75 to be a realistic upper threshold as the average man would be unlikely to be considered for radical therapy on diagnosis beyond this age. Half the studies did not report the age of the cohort modelled. The modelled prevalence of prostate cancer varied from 10.9% (18) to 66.7% (31), but was usually between 24–30%. Several studies reported the percentage of prostate cancers assumed to be high grade or significant (24) (33) (18, 21), ranging from 26%(18) to 51.2%(24).

Table 2
Assumed prevalence of prostate cancer in included studies

Author	Patient population	Age	Prevalence
Bouttell et al(18)	Chinese men with normal DRE, PSA 4–10 ng/ml	NR	10.9%
Mowatt et al(30)	UK men with suspected PC with a prior negative/inconclusive biopsy, with indications for repeat biopsy (i.e. sustained suspicion of PC as a result of clinical and/or pathological findings)	60	24%
Schiffer et al(19)	German outpatients with PSA > 4 and/or suspicious DRE in a urological outpatient center setting	66	24%
Nicholson et al(17)	UK men who have been referred for a second biopsy because, following a negative initial biopsy result, clinicians still suspect that malignant PCa is present	NR	24%
Cerantola et al(28)	Canadian biopsy-naive men with clinical suspicion of PCa (based on DRE and PSA values 4–10 mg/) with a life expectancy of 20 y	60–65	24%
Venderink et al(26)	Dutch biopsy-naïve men with elevated PSA level or abnormal DRE	NR	25%
de Rooij et al(29)	Dutch men with an elevated PSA level (> 4 ng/ml)	60	25%
Nichol et al(31)	US men with a PSA 2–10 ng/ml	50–75	25%
Nichol et al(31)	US men with PSA 4–10 ng/ml	50–75	25%
Sathianathen et al(20)	US men with PSA > 3	50	29%
Nichol et al(31)	US men with positive PHI at PSA 2–10 ng/ml	50–75	29.6%
Nichol et al(31)	US men with positive PHI at PSA 4–10 ng/ml	50–75	30.3%
Pahwa et al(25)	US biopsy-naive men who have been recommended for prostate biopsy on the basis of abnormal DRE results or elevated PSA levels	41–50	37%
Faria et al(23)	UK men at risk of PCa referred to secondary care for further investigation	NR	38%
Pahwa et al(25)	US biopsy-naive men who have been recommended for prostate biopsy on the basis of abnormal DRE or elevated PSA levels	51–60	44%
Dijkstra et al(24)	Dutch men with PSA > 3 ng/ml	NR	44.4%
Govers et al(21)	US men with elevated PSA or abnormal DRE who under current guidelines would undergo ultrasound guided biopsy	NR	46.4%
Pahwa et al(25)	US biopsy-naive men who have been recommended for prostate biopsy on the basis of abnormal DRE results or elevated PSA levels	41–70	50%
NICE guideline(16)	UK men who have a raised PSA, negative MRI and/or negative prostate biopsy	66	58.2%
Pahwa et al(25)	US biopsy-naive men who have been recommended for prostate biopsy on the basis of abnormal DRE results or elevated PSA levels	61–70	65%
Nichol et al(31)	US men with a PSA > 10 ng/ml	50–75	66.70%

3.1.5 Treatment types

Eight of sixteen studies reported the percentage of men allocated to each type of treatment (Table 3). The percentage of high-grade men allocated to a radical treatment (prostatectomy, radiotherapy, brachytherapy, hormone therapy or androgen deprivation therapy) varied from 65% (29) to 100% (22). The percentage of men with low grade cancer allocated to a radical treatment varied from 20% (24, 29) to 100% (25). Of the other eight studies, three did not include treatment in their timeframe (17–19), four stated that individual treatments were modelled but did not give the allocation ratio (20, 23, 27, 30), and one stated that they did not explicitly model individual treatments (31).

Table 3
Treatment allocation assumed (%)

Study	Dijkstra et al(24)	Govers et al(21)	Barnett et al(22)	Pahwa et al(25)	Venderink et al(26)	Cerantola et al(28)	de Rooij et al(29)	NICE guideline intermediate risk (high risk in brackets)(16)
High Grade/Clinically significant								
RP	70	54	100	32	70	30	40	16 (12)
RT	25	40	-	18	25	30	25	35 (35)
BY	-	-	-	8	-	-	-	3 (1)
BY + EBRT	-	-	-	-	-	10	-	-
ADT	-	-	-	33	-	-	-	-
RT + ADT	-	-	-	-	-	30	-	-
HT	-	-	-	-	-	-	-	22 (48)
WW	5	6	-	2	-	-	18	-
AS	-	-	-	2	5	-	18	25 (5)
Low Grade/Clinically insignificant								
RP	10	50	50	57	40	35	10	18
RT	10	30	-	7	10	35	-	20
BY	-	-	-	16	-	15	10	7
ADT	-	-	-	8	-	-	-	-
HT	-	-	-	-	-	-	-	9
WW	-	-	-	5	-	-	40	-
AS	80	20	50	5	50	15	40	47
Source	(29) expert opinion	(34)	(35)	(36)	expert opinion	(30)	(36), (37), expert opinion	(38)

Legend: RP – Radical Prostatectomy, RT – Radiotherapy, BY – Brachytherapy, EBRT – External Beam Radiotherapy, ADT – Androgen Deprivation Therapy, WW – Watchful Waiting, AS – Active Surveillance, HT – Hormone Therapy

3.2 Model inputs

3.2.1 Accuracy data

All but three studies (17, 28, 31) explicitly reported the sensitivity and specificity of the tests. The assumed sensitivity of a standard biopsy ranged from 0.9 based on ERSPC data (27, 39) to 0.46 based on de Rooij et al (20, 25, 29). The biomarkers were generally either particularly sensitive i.e. good at correctly identifying those with the disease, or particularly specific i.e. good at correctly identifying those without the disease. The SelectMDx test, for example, had the highest sensitivity (0.957, but specificity 0.336) (21, 24, 33) and PHI had the highest specificity (0.974, but sensitivity 0.129) (18, 40). The MRI-targeted biopsy methods generally had a better balance of sensitivity and specificity, ranging from a sensitivity of 0.965 (specificity 0.597) for MRI using a Prostate Imaging–Reporting and Data System (PI-RADS) threshold ≥ 3 (22, 41) to 0.770 (specificity 0.68) using fusion biopsy (20, 26, 42). Appendix 3, Table 3 details the accuracy estimates used along with their evidence sources.

3.2.2 Quality of Life

As detailed in Table 4, all but two studies assigned disutilities to various aspects associated with testing including screening attendance, the biopsy procedure, diagnosis of cancer, treatment, active surveillance, advanced or metastatic cancer, post-treatment or recovery, adverse events associated with biopsy and treatment and palliative therapy. Five of the fourteen studies (17, 21, 22, 24, 26, 27) sourced all utility estimates used in their model from Heijnsdijk et al(6) who in turn obtained their utility estimates from the Cost-Effectiveness Analysis Registry and various additional studies (43–55). The other studies sourced their utility estimates from various unrelated publications, also in different countries and settings. None of the included studies provided Ara et al's recommended level of detail on health state utility values which are sourced from the literature i.e. detail on searches, inclusion/exclusion criteria, the quality

and relevance of included studies, and a justification for the utility values chosen.(56) Only three studies fully reported the uncertainty in the disutility estimates used.(22, 25, 29)

Table 4
Disutility estimates used for prostate cancer states, tests and treatments in the identified economic models (annual values)

Study	Biopsy	Diagnosis	RP	RT	AS	Advanced cancer	Post-treatment	AEs	Other	Source	Report uncertainty
Barnett et al 2018(22)	0.006	0.017	0.247		0.03	0.3	0.05	0.0161 (post-biopsy infection)	0.0002 (PSA screening) 0.00077 (MRI) 0.60 (Palliative therapy)	(6) (75)	Yes
Cerantola et al 2016(28)							0.08		0.22 (relapse)	(76)	No
de Rooij et al 2014(29)			0.33	0.27	0.16					(46)	Yes
Dijkstra et al 2017(24)	0.006	0.017	0.228	0.247	0.03		0.05			(6)	No
Faria et a 2018(23)	0.007 (TPM biopsy)					0.137				(43), PROMIS IPD (4), (77)	Only for TPM biopsy
Govers et al 2018(21)	0.006	0.017	0.228	0.247	0.03		0.05			(6)	No
Heijnsdijk et al 2016(27)	0.006	0.017	0.247	0.228	0.03	0.3	0.05		0.0002 (Screening attendance) 0.60 (Palliative therapy)	(6)	No
Mowatt et al 2013(30)						0.365		0.16 (urinary incontinence) 0.17 (bowel problems 0.12 (erectile Dysfunction)	0.11 (Localised (undiagnosed)) 0.1 (Localised (diagnosed)) 0.19 (Locally advanced (undiagnosed)) 0.18 (Locally advanced (diagnosed))	(78) (79) (80)	Only for cancer states
NICE guideline 2019(16)	0.004, 0.007 (Template mapping biopsy)					0.137			0.027 (low-risk) 0.029 (intermediate-risk) 0.027 (high-risk)	(6, 30, 75, 77, 81, 82)	No
Nichol et al 2012(31)	0.027								0.2 (PCa)	(83) (84) (85)	Only for PCa
Nicholson et al 2015(17)	0.006									(6)	No
Pahwa et al 2017(25)	0.027	Only lifetime QALYs reported								(83)	Yes
Sathianathen et al 2018(20)	0.004		0.14		0.03	0.42	0.05			(6, 86) (83)	Yes
Venderink et al 2017 (26)	0.006	0.02	0.25	0.23	0.03	0.55	0.05			(6)	No

Legend - RP: radical prostatectomy, RT: radiotherapy, AS: active surveillance, AEs: adverse events.

Table 4. *Disutility estimates used for prostate cancer states, tests and treatments in the identified economic models (annual values)*

3.2.3 Resource use

The majority of studies took a healthcare provider perspective for the analysis (only including costs incurred to the provider rather than any wider patient or societal costs) (16, 17, 19–24, 26, 28–30, 57). Two studies stated that a societal perspective was taken but did not refer to the societal costs that were included (27, 31). Only one study included productivity costs in terms of missed days of work when a patient undergoes a biopsy or MRI (25). No study gave a justification for the perspective taken. The main costs included were the cost of testing, biopsy and subsequent management strategy. Ten studies included costs of complications arising from biopsy (16–18, 21–26, 30). Only six studies explicitly stated that costs associated with complications arising from treatment were included (16, 21, 23, 24, 26, 30).

3.3 Modelling methods

3.3.1 Model type

Six combined decision tree/Markov cohort models were identified. In half of these, the decision tree reflected the diagnostic process and the Markov model reflected treatment (21, 23, 29). In the other half, the decision tree captured both diagnosis and treatment and the Markov model was used for post-treatment states (20, 24, 26). Six cohort Markov models (16, 19, 22, 28, 30, 31), 1 continuous time discrete-event microsimulation model (the MISCAN model) (27), and three decision tree models (17, 18, 25) were also identified. No study provided a justification for choosing one model type over another.

The decision trees generally used data on disease prevalence and accuracy of the tests to categorise men into true positives, false positives, true negatives and false negatives(18, 24, 26) with some also incorporating clinical significance of cancer.(21, 23–25, 29) The Markov models captured cancer progression and survival. All but two studies developed a *de novo* model.(22, 27)

3.3.2 Cycle length in cohort Markov models

Seven studies had a one-year cycle length(21, 22, 24, 26, 28, 29, 31), two assumed a cycle length of 3 months(16, 30) and one had a cycle length of 6 months(20). The other two studies did not report the cycle length assumed.(23, 58) Only one study justified the cycle length stating that a cycle length of 3 months is sufficient to reflect possible clinical events associated with prostate cancer.(16)

3.3.3 Time horizon

The time horizon of the models varied from when patients reached the treatment stage (18, 19) to their entire lifetime (20–23, 25, 27, 31). Two studies had a time horizon of 18 years(24, 26) as this was the median follow-up time of survival data for patients with prostate cancer, described in the Scandinavian Prostate Cancer Group-4 (SPCG-4) study. (59) One compared results using a 5, 10, 15 and 20 year time horizon (28), one used a 10 year time horizon because ‘after this period no differences were expected between the strategies’ (29), and one used a 30 year time horizon as ‘by this stage the majority of the modelled cohorts were dead and the additional QALYs per cycle had fallen to < 0.001’ (30).

3.3.4 Sensitivity Analyses

All studies conducted a deterministic sensitivity analysis where input parameters or sets of parameters were varied to see the impact on results. Half of the studies (8/16) also carried out a probabilistic sensitivity analysis where repeated simulations sampled all parameters from their respective distributions to observe the impact on results.(16, 17, 20, 23, 25, 29–31) No study carried out a Value of Information analysis to determine the value of further research in prostate cancer screening.(60)

3.3.5 Model Structure

The structure of a model relates to how different health states are categorised and how patients move between health states. Related to this, the natural history of a disease refers to how a disease progresses in a person over time in the absence of treatment.(61) Only five of the included models (16, 22, 23, 27, 62) took account of how prostate cancer progresses, and how the introduction of a new test might impact on this, and all of these captured this progression differently. Five studies modelled survival only (24) (21) (26) (29) (28). Three did not model beyond diagnosis (15–17). In addition, the definition of clinically significant cancer varied across studies (Table 5). Four of the models did not consider stages or grade of cancer, only presence or absence of cancer(20, 21, 26, 31).

Table 5
Model characteristics

Study	Model type	Progression modelled	Low Risk	Intermediate Risk	High Risk	Time horizon	Cycle length	DSA	PSA
Dijkstra et al(24)	Decision tree/Markov	No	G > 6	-	G ≥ 7	18 years	1 year	Yes	No
Sathianathen et al(20)	Decision tree/Markov	No	-	-	-	Lifetime	6 months	Yes	Yes
Govers et al(21)	Decision tree/Markov	No	G > 6	-	G ≥ 7	Lifetime	1 year	Yes	No
Faria et al(23)	Decision tree/Markov	Yes	PSA < 10, G < 6	PSA 10–15 or G7	G > 8	Lifetime	Not reported	Yes	Yes
Venderink et al(26)	Decision tree/Markov	No	-	-	-	18 years	1 year	Yes	No
de Rooij et al(29)	Decision tree/Markov	No	G3 + 3 or small-size 3 + 4		large tumours with a G3 + 3 or ≥ 3 + 4	10 years	1 year	Yes	No
NICE guideline(16)	Decision tree/Markov	Yes	G ≤ 6, PSA ≤ 10	G = 7 or 10 ≤ PSA < 20	G ≥ 8 and PSA > 20	Lifetime	3 months	Yes	Yes
Nichol et al(31)	Markov cohort	No	-	-	-	Lifetime	1 year	Yes	Yes
Schiffer et al(19)	Markov cohort	No	-	-	-	Up to treatment	Not reported	Yes	Yes
Barnett et al(22)	Markov cohort	Yes	G < 7	G = 7	G > 7	Until death	1 year	Yes	No
Cerantola et al(28)	Markov cohort	No	-	-	-	5, 10, 15, and 20 years	1 year	Yes	No
Mowatt et al(30)	Markov cohort	Yes	G ≤ 6, PSA ≤ 10, ≤T1a	G ≤ 7, PSA ≤ 20, ≤T2b	G > 7, PSA > 20,>T2b	30 years	3 months	Yes	Yes
Pahwa et al(25)	Decision tree	No	G ≤ 6	-	G ≥ 7	Until death	-	Yes	No
Nicholson et al(17)	Decision tree	No	-	-	-	3 years	-	Yes	Yes
Boutell et al(18)	Decision tree	No	-	-	-	Up to biopsy	-	Yes	Yes
Heijnsdijk et al(27)	Microsimulation	Yes	18 stages (combination of T1, T2 and T3+, G < 7, = 7 and > 7)			Lifetime	-	Yes	No

Legend: G = Gleason grade, DSA = Deterministic Sensitivity Analysis, PSA = Probabilistic Sensitivity Analysis, - = not included in model

3.3.6. Data Sources to Inform Progression

Several studies used data from the SPCG-4 study to inform progression risks in diagnosed and undiagnosed men and relative treatment effects in terms of survival (16, 21, 24, 26, 30). SPCG-4 randomly assigned 695 men with localized prostate cancer to watchful waiting or radical prostatectomy from October 1989 through February 1999 and collected follow-up data up to 2017.(63) The studies therefore used data from the watchful waiting arm of SPCG-4 to inform progression in the undiagnosed cases and data from those receiving radical treatments to inform progression and survival in diagnosed cases. Other studies used calibration to prostate cancer specific survival estimates from various studies (64, 65) to estimate the probability of transition through health states (16, 23). Two studies based their transitions through health states on data from the ERSPC(22, 27).

3.4 Cost-effectiveness results

3.4.1 Biomarkers

Of the seven studies that compared PSA testing to testing with PSA plus a new biomarker, four studies found that introducing the new biomarker saves costs and increases QALYs (20, 21, 24, 31). Two did not measure QALYs but found that diagnostic costs were reduced(18, 19). Only Heijndisk et al(27) considered progression through stages or grades of cancer. This study found that PSA + PHI testing saves costs compared to PSA testing and results in the same QALYs (27). The results from all studies were generally driven by a decrease in negative biopsies.

3.4.2 Biopsy methods

Six of the seven studies that compared MRI guided biopsy strategies to each other and to TRUS biopsy found at least one MRI guided strategy to be cost effective (increased costs but also increased QALYs). The exception was Cerantola et al (28) who found that MRI-guided biopsy dominated TRUS guided

biopsy (reduced costs and increased QALYs). Incremental Cost Effectiveness Ratios (ICERs) for MRI-guided biopsy methods compared to standard methods ranged from €323 per QALY(29) to $23,483 per QALY (22), indicating cost-effectiveness according to the £20–30 k threshold recommended by NICE(66). The increased QALYs and reduced costs were generally due to an avoidance of the adverse effects and resource use associated with overdiagnosis.

3.4.3 Follow-up strategies

Neither of the studies comparing follow-up strategies in men with a previous negative biopsy identified a clear indication of cost-effectiveness for any strategy. The NICE guideline (16) concluded that PSA velocity, density and %free PSA may be the best indicators to trigger further diagnostics in higher risk populations however the “no screening” strategy appeared optimal for the lowest-risk subpopulation who had MRI Likert scores of 1 or 2 (very unlikely/unlikely that the patient has prostate cancer that needs to be treated) and 2 previous negative biopsies. Nicholson et al (17) found no strategy to be cost-effective at the threshold recommended by NICE.

3.4.4 Assessing uncertainty in cost-effectiveness results

Four studies found that the results were sensitive to the potential of the tests to identify cancer, particularly clinically significant cancer (21, 23–25, 29). Three studies found results to be sensitive to the assumed prevalence of cancer and significant cancer.(25, 26, 29) The cost of the tests was also stated as an important factor in four of the studies, although in these cases the estimated costs would have to change substantially to impact the results (18, 20, 23, 26). Furthermore, studies found results to be sensitive to probabilities of cancer progression in undiagnosed cases (16, 22), survival rates (16, 26), and quality of life values used for diagnosed cancer states (22, 30).

4 Discussion

The aim of the review was to identify cost-effectiveness models evaluating new diagnostic tests for prostate cancer; provide an overview of the characteristics of these models and their data sources; and assess the limitations of available models, providing guidance on future improvements.

Sixteen studies were identified, all published between 2011 and 2019. Seven compared the cost-effectiveness of new urinary or blood biomarkers to each other or to the standard of care (a PSA test). Another seven compared different approaches to prostate biopsy and two compared follow-up strategies in men who have a negative initial biopsy result. Most models used either a combined decision tree/Markov or purely Markov model structure with only five modelling progression through stages or grades of cancer. Substantial variability was seen in the model pathways of prostate cancer natural history; the data sources used to inform progression; treatment allocation assumed for high and low risk cancers; disutility values assigned to health states; and the assumed accuracy of the tests. All but one study(17) found the introduction of these novel tests to be cost-effective; however, in some cases the benefits may be overestimated due to a failure to take account of overdiagnosis and the natural history of the disease in untested men.

4.1 Limitations Of Included Models

The studies identified had several key limitations. Although they compared novel tests to diagnose prostate cancer, many failed to take into account the complexity of the disease, including stage or grade of cancer and how cancer progresses in diagnosed and undiagnosed cases. This calls into question the reliability of the results as the cost-effectiveness of a new test may be overestimated if the cancers it identifies would never progress to cause symptoms or mortality if not identified. The purpose of screening and testing is to identify cancers at an early stage when they are more amenable to treatment. If cost-effectiveness models do not differentiate between cancer stages it is difficult to measure the effects of early diagnosis.(15)

Only half carried out a probabilistic sensitivity analysis to fully account for the uncertainty in the model parameters. (16, 17, 20, 23, 25, 29–31) Five of the fourteen studies which included QALYs (17, 21, 22, 24, 26, 27) cited Heijnsdijk et al (6) as the source for their utility estimates who in turn obtained their estimates from studies in various countries and settings and using different evaluation techniques. This is against best practice as the values cannot be considered to be equivalent when measured in different populations.(67) However, this approach indicates that there is likely no alternative common source for these utility parameters. Half of the studies did not report uncertainty in their QALY estimates, suggesting that this uncertainty was not accounted for (16, 17, 21, 24, 26–28). As QALY estimates can often have a substantial impact on the intervention considered most cost-effective, it is important that any underlying uncertainty in these estimates is fully accounted for.

Three studies used a time horizon of 3 years or less, modelling only up to biopsy, which is unlikely to be long enough to capture the impact of timely and accurate diagnosis of prostate cancer, due to its long term nature.(17) (18, 19) Only two of the studies included modelled a true screening population of men who have not already been flagged at previous testing.(22, 31) Although most of the models represented the entire diagnostic pathway from test to treatment, the majority of these compared either new biomarkers or new MRI-guided biopsy methods with few comparing combinations of tests. While both biomarker and imaging advancements are important, it seems worthwhile for them to be considered in combination as this is how they are likely to be used in practice. The use of these tests in combination may have the potential to alter the current imbalance in benefits and harms seen with prostate cancer screening. Although several reports have been published on the potential impact of risk-stratified invitation to screening, (68–70) no studies were identified that assessed the cost-effectiveness of this approach.

4.2 Recommendations for future cost-effectiveness models

Any future model should consider the entire diagnostic pathway, which may include both new biomarkers and biopsy methods, to comprehensively assess the ‘true’ cost-effectiveness of these tests within a screening strategy for prostate cancer. When modelling the lifetime cost-effectiveness of a test to diagnose prostate cancer, it is important to consider the natural history of the disease, and how a test may impact on this, to ensure that the benefit of the test is accurately represented and overdiagnosis is considered. The studies identified in this review which modelled the natural history of prostate cancer all did so in different ways, suggesting a lack of clarity in the field. Any future model should consider this carefully with the help of clinical experts.

Although a formal literature review to identify health state utility values has not been carried out, the values used in previous models indicate a potential paucity of information on how prostate cancer treatment and adverse effects impact on quality of life. This should be considered carefully, and uncertainty fully accounted for where it exists, as this could greatly impact the results of a cost-utility model.

4.3 Strengths and Limitations of Review

The strength of this systematic review is that it has provided an overview of cost-effectiveness models published in the last ten years which have compared novel diagnostic methods in prostate cancer. It has offered insight into the data parameters that will be needed to populate a future cost-effectiveness model incorporating new tests and diagnostic strategies in prostate cancer, and potential sources of information for these parameters. It has also highlighted the limitations of previous models. The results from the review have emphasized the importance of accurately estimating factors such as the sensitivity of tests, the prevalence of disease and the progression of the disease. A limitation is that a formal quality checklist has not been used to determine whether studies should be included in the review, however the main purpose of the review was to assess the evidence base on cost-effectiveness of such innovations and areas for further development, using existing economic evaluation checklists.

4.4 Comparison with previous reviews

This is the first study to identify cost-effectiveness models focused on screening and diagnostic strategies beyond standard PSA-based testing. One recent systematic review assessed model-based economic evaluations of PSA-based screening strategies only(67). This review also found significant variation in model pathways to reflect cancer progression in the ten included studies and limited and heterogenous evidence on quality of life. Three older reviews were also identified but all assessed PSA-based screening only.(71–73)

5 Conclusion

The introduction of new biomarkers and MRI guided biopsy methods in the studies identified in this review has been shown to lead to an improvement in health outcomes and a decrease or acceptable increase in costs. (18, 21, 24). Current concerns around implementing PSA-based prostate cancer screening strategies are due to overdiagnosis and overtreatment(74), and these newer methods may lead to a reduction in these factors. This review has highlighted the substantial complexity involved in modelling diagnostic tests in prostate cancer, including whether these strategies should be used at all and if so, how and in what combination. To ensure the cost-effectiveness of any screening strategy pathway is assessed robustly, there is a need to ensure disease progression in diagnosed and undiagnosed cases is accurately represented, uncertainty is fully accounted for, quality of life estimates are measured as accurately as possible, and the possibility of repeat screening and testing in men with a negative diagnosis is considered.

Abbreviations

AUA	**American Urological Association**
CAP	Cluster Randomized Trial of PSA Testing for Prostate Cancer
DRE	Digital Rectal Examination
ERSPC	European Randomised Study of Screening for Prostate Cancer
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
MeSH	Medical subject headings
mpMRI	Multiparametric magnetic resonance imaging
MRI	Magnetic resonance imaging
NHS-EED	National Health Service Economic Evaluation Database
NICE	National Institute of Clinical Excellence
PCPT	Prostate Cancer Prevention Trial
PHI	Prostate Health Index
PI-RADS	Prostate Imaging–Reporting and Data System
PLCO	Prostate, Lung, Colorectal, and Ovarian
PSA	Prostate-specific Antigen
QALY	Quality Adjusted Life Year
SPCG-4	Scandinavian Prostate Cancer Group-4
TRUS	Transrectal Ultrasound
UPA-PC	Urinary Proteome Analysis for prostate cancer

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

None

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Authors' contributions

EK carried out the review, data extraction and analysis of data and wrote the first draft of the manuscript. JM assisted with reviewing and data extraction. SS and HT were involved in the conception of the review. SS, HT, ET, RM contributed to the interpretation of the data and writing of the manuscript. SS, HT, ET, RM critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Figures

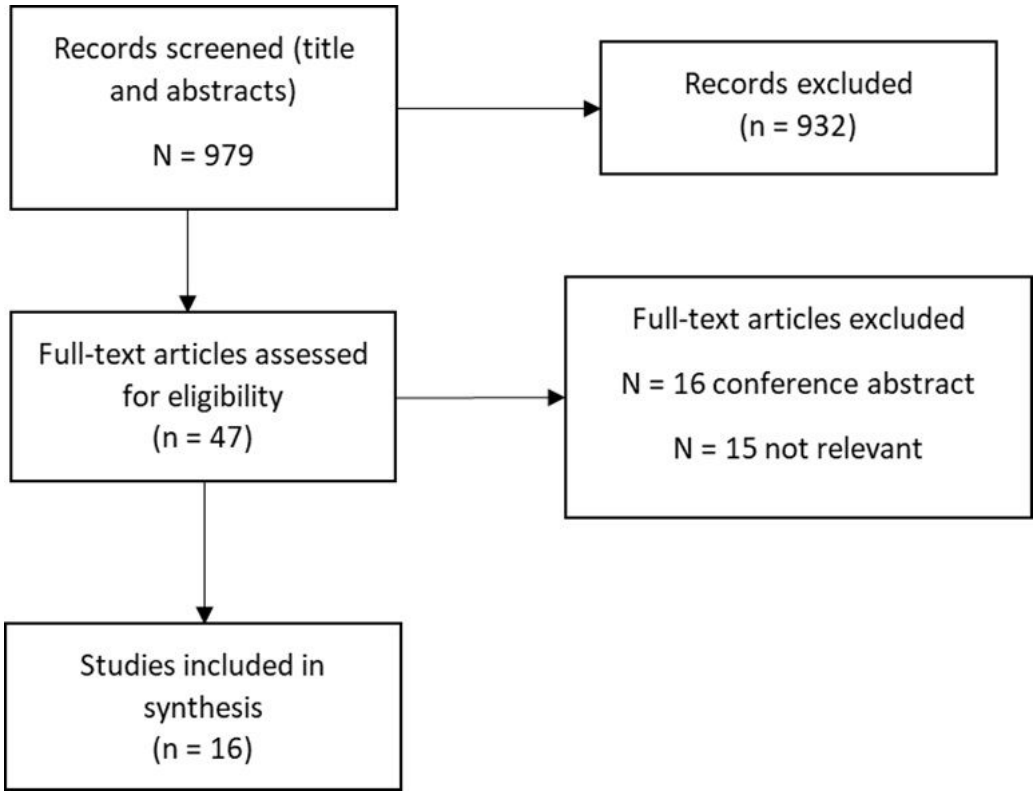

Figure 1

Studies included and excluded from the review

Supplementary Files

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- PRISMA2009checklist.docx
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