## Title

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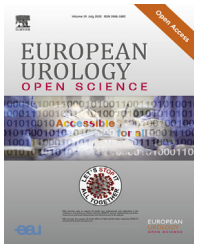

European Association of Urology

Review – Prostate Cancer

# Health Economic Evidence for Liquid- and Tissue-based Molecular Tests that Inform Decisions on Prostate Biopsies and Treatment of Localised Prostate Cancer: A Systematic Review

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**Abstract**

***Context:*** Several liquid- and tissue-based biomarker tests (LTBTs) are available to inform the need for prostate biopsies and treatment of localised prostate cancer (PCa) through risk stratification, but translation into routine practice requires evidence of their clinical utility and economic impact.

***Objective:*** To review and summarise the health economic evidence on the ability of LTBTs to inform decisions on prostate biopsies and treatment of localised PCa through risk stratification.

***Evidence acquisition:*** A systematic search was performed in the EMBASE, MEDLINE, Health Technology Assessment, and National Health Service Health Economic Evaluation databases. Eligible publications were those presenting health economic evaluations of an LTBT to select individuals for biopsy or risk-stratify PCa patients for treatment. Data on the study objectives, context, methodology, clinical utility, and outcomes were extracted and summarised.

***Evidence synthesis:*** Of the 22 studies included, 14 were focused on test-informed biopsies and eight on treatment selection. Most studies performed cost-effectiveness analyses ($n$ = 7), followed by costing ($n$ = 4) or budget impact analyses ($n$ = 3). Most (18 of 22) studies concluded that biomarker tests could decrease health care

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costs or would be cost-effective. However, downstream consequences and long-term outcomes were typically not included in studies that evaluated LTBT to inform biopsies. Long-term effectiveness was modelled by linking evidence from different sources instead of using data from prospective studies.
***Conclusions:*** Although studies concluded that LTBTs would probably be cost-saving or -effective, the strength of this evidence is disputable because of concerns around the validity and transparency of the assumptions made. This warrants prospective interventional trials to inform health economic analyses to ensure collection of direct evidence of clinical outcomes based on LTBT use.
***Patient summary:*** We reviewed studies that evaluated whether blood, urine, and tissue tests can reduce the health and economic burden of prostate cancer. Results indicate that these tests could be cost-effective, but clinical studies of long-term outcomes are needed to confirm the findings.


## 1. Introduction

Distinguishing between indolent and aggressive tumours remains a challenge in the diagnosis and management of localised prostate cancer (PCa). Existing clinical prognostic assays, such as digital rectal examination (DRE) and serum levels of prostate-specific antigen (PSA), have limited specificity and sensitivity for early identification of aggressive tumours. Together with the lack of comprehensive liquid biopsies in PCa care, this is leading to many tissue biopsies and repeat biopsies that have substantial cost and clinical complications, such as bleeding and infection, leading to major health and economic burdens on patients and society. Given that a minority of all PCas diagnosed represent life-threatening disease and that tissue biopsies have limited precision in predicting the clinical course of the disease, the health and economic burden for PCa patients and society is further increased by overdiagnosis that may lead to overtreatment [1,2].

To reduce the burden of PCa, prospective evidence suggests that patients with low and favourable intermediate risk PCa (PSA $<$10 ng/ml and Gleason $\leq$ 3 + 4 [grade group 2]) may be managed through active surveillance (AS) [3,4]. The ProtecT study randomised 1643 patients with screen-detected PCa, of whom approximately 80% had low or favourable intermediate risk, to AS, radical prostatectomy, or radiotherapy as the initial management strategy [5]. After median follow-up of 10 yr, radical treatment reduced the risk of disease progression, but a significant difference in PCa-specific or overall survival was not observed. Despite these results and the common complications associated with radical treatments that substantially impact quality of life [5], several real-world studies have shown that only 30–50% of patients with low risk and 10–15% of those with intermediate risk are initially managed with AS in the USA, Germany, and Australia [6–10]. This suggests that both under- and overtreatment of PCa continue to pose a substantial health and economic burden on patients and society.

To better target treatment and to reduce the number of tissue biopsies, liquid and tissue-based biomarker tests (LTBTs) have been developed to improve risk stratification of (suspected) localised PCa. These tests have two specific applications in the context of localised PCa by predicting whether patients harbour an aggressive tumour: (1) they indicate which patients should undergo a repeat biopsy after an initial negative biopsy and (2) they indicate which patients are candidates for AS and which are most likely to benefit from active treatment, such as radical or systemic treatment. Although several LTBTs are authorised on the basis of extensive validation studies and are commercially available, they have not yet been studied in prospective interventional trials and are not strongly recommended for localised disease in clinical guidelines of leading professional societies, such as the European Association of Urology, American Urology Association, and American Society for Clinical Oncology [3,11]. The National Comprehensive Cancer Network (NCCN) recommends consideration of biomarkers in selecting individuals for a prostate biopsy to improve the specificity of screening [12]. The NCCN does not recommend routine use of biomarkers for informing decisions on treatment, but suggests that patients with low- and favourable intermediate-risk PCa may consider use of the tissue-based Decipher, Oncotype Dx, and Prolaris tests during initial risk stratification [13].

In addition to evidence on the clinical utility of LTBTs in improving outcomes, health economic evidence is required to justify the costs of these tests to ensure successful translation to widespread clinical use. Many countries around the world, such as the UK, Canada, and Australia, require evidence on the cost-effectiveness or "value for money" of health care technologies before their use is reimbursed by public health care systems. Although recent clinical-evidence reviews of these tests have suggested the need to include cost-effectiveness [14–16], a formal appraisal of the health economic evidence for test-informed management of PCa is lacking. We sought to fill this gap and provide a basis for future study design enabling economic evaluations of LTBT by reviewing the current health economic evidence on the use of LTBTs to inform the need for a (repeat) biopsy or treatment decisions for localised PCa.

## 2. Evidence acquisition

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [17,18]. A protocol for this review was not published before it was conducted.

### 2.1. Eligibility criteria

Eligible publications were those reporting on model- or trial-based health economic evaluations of a liquid- (including urine and blood) or tissue-based test to select individuals for a prostate biopsy or to risk-stratify patients with localised PCa for treatment. The study was not limited to full economic evaluations such as cost-benefit and -effectiveness analyses, and included costing studies (ie, cost per patient as the main outcome) and budget impact analyses (ie, population-level cost as the outcome). A test was considered to inform biopsies if it informed the decision to perform prostate biopsies in PCa patients or individuals who are suspected of having PCa based on PSA and DRE. This included the use of tests to inform the need for biopsies for patients on AS following diagnosis of a presumed clinically insignificant cancer. A test was considered to risk-stratify patients for treatment if it informed treatment decisions, including decisions regarding adjuvant treatment. Only full-text publications written in English were included. Publications investigating standard PSA only were not eligible for inclusion. Studies investigating PSA-based tests beyond standard PSA, such as percent free PSA and PSA density, were eligible for inclusion. Other publications not eligible for inclusion were those focusing on screening or metastatic disease, cost-of-illness studies, reviews, commentaries, letters, conference abstracts, and those evaluating management options only. No restrictions regarding the year of publication were applied.

### 2.2. Search strategy and study selection

The literature search was performed on September 16, 2020 using the Ovid platform to access the EMBASE, MEDLINE, Health Technology Assessment, and National Health Service Health Economic Evaluation Database platforms. Each database was searched individually using four sets of free-text terms to identify publications on (1) PCa, (2) economic evaluations, and (3) tests, and (4) to exclude publications on screening and metastatic PCa. Only generic terms were used to identify LTBTs; no specific biomarker or test names were used to avoid selection bias based on prior knowledge of certain biomarkers or tests. Subject headings were considered but were not included in the final search strategy. No exclusion criteria were enforced during the search to avoid erroneous exclusion of eligible publications. The final database-specific searches are presented in Supplementary Tables 1–4.

Two reviewers (K.D. and A.P.S.) independently screened titles and abstracts of 150 publications to check for consistency, after which one reviewer (K.D.) completed the screening. The full texts of included publications were independently reviewed by the same two reviewers for final inclusion or exclusion. Disagreements between reviewers were resolved via consensus. Publications were excluded if they were not full-text articles (eg, conference abstract), not about PCa, not a health economic evaluation of a LTBT, or if they focussed on imaging only. The references of publications included were screened for further articles of interest.

### 2.3. Data extraction and synthesis

One reviewer (K.D.) extracted data from all the publications included using a predefined data extraction template. Information was extracted for year of publication, journal of publication, source(s) of funding, conflict(s) of interest, test(s) considered, test application (ie, inform biopsies or treatment), patient population, type of health economic analysis, health outcomes considered, strategies compared, study perspective, geographical location, type of analysis (ie, trial- or model-based), time horizon, cost indexing year, discount rates, modelling technique, model structure, model validation efforts, sensitivity analyses performed, uncertainty analyses performed, evidence approach, evidence for diagnostic performance, evidence for health outcomes, evidence for impact on clinical management, evidence on patient preferences, economic outcomes, and health outcomes.

In terms of data synthesis, journals of publication were classified according to their subject areas as medical, health policy, or multidisciplinary according to their subject area and category on SCImago Journal & Country Rank (www.scimagojr.com/). Potential conflicts of interests were determined according to the (industry) funding source and whether any author had industry or consultancy affiliations. The health economic analyses were categorised as costing, budget impact, or cost-effectiveness analyses, with multiple categories potentially applicable per publication. Comparators were classified as standard of care (SOC), including a test, or other (eg, when including imaging only). Health and economic outcomes were summarised according to whether test use increased or decreased costs and health outcomes and, for cost-effectiveness studies, whether their use was considered cost-effective by the original authors. Increases in health outcomes of less than 0.05 quality-adjusted life years (QALYs) were considered negligible increases. Although arbitrary, this threshold was selected and used to synthesise the evidence into a format informative to readers, in other words, to indicate whether the difference was considered meaningful. The threshold is not a measure of statistical significance, as significance would relate to the certainty rather than the magnitude of the difference in QALYs.

### 2.4. Risk of bias and quality of evidence

In the absence of an established method for assessing bias and methodological quality in health economic studies, the risk of bias in publications and the appropriateness of the methods was assessed as part of the evidence synthesis on the basis of the study methods and evidence used. The

Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist was used to assess the quality of reporting [19]. Although the CHEERS checklist was developed as a checklist rather than a quality scoring tool, it has been widely used to assess the quality of reporting for health economic studies in the absence of better alternatives. For each publication, we assessed which CHEERS items were applicable and whether those were reported. A score for the quality of reporting of a publication on a scale from 0% to 100% was defined as the proportion of applicable items reported compared to the total number of applicable CHEERS items.

## 3. Evidence synthesis

The literature search yielded 1535 publications, of which 317 were identified as duplicates (Fig. 1 and Supplementary Tables 1–4). Of the 1218 unique publications, 1140 were excluded on the basis of title and abstract. After assessment of the full text of the remaining 78 publications, 58 were excluded for varying reasons, most commonly because of an inappropriate article format or because it was a study only evaluating multiparametric magnetic resonance imaging (mpMRI; Fig. 1). After adding two publications to the sample based on cross-referencing, the final number of publications included for data extraction was 22.

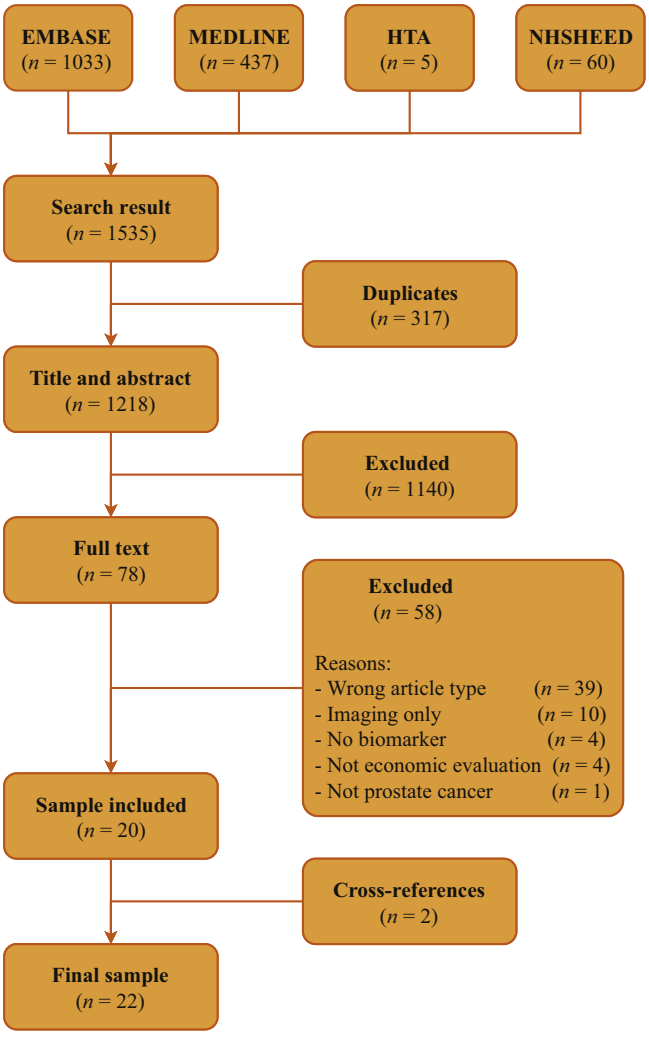


**Fig. 1 – PRISMA flowchart of the study selection process. HTA = Health Technology Assessment; NHSHEED = National Health Service Health Economic Evaluation Database.**

### 3.1. Characteristics of the studies included

Fourteen studies (64%) focused on the use of tests to inform biopsies [20–33], that is, whether an initial or repeat biopsy was to be performed, whereas eight studies (36%) focused on the use of tests for risk stratification to inform treatment decisions [34–41]. Tables 1 and 2 provide an overview of a subset of the data extracted for tests aimed at informing biopsies and treatment of PCa, respectively. An overview of all the data extracted is provided in Supplementary Tables 5 and 6. An overview of the tests evaluated and their characteristics is provided in Table 3. Note that one study considered a hypothetical test [32], which is not included in this table.

Tests were mostly evaluated for use in the USA (10/22 studies, 45%) [35,22,26–28,36–38,40,41], followed by France ($n$ = 3, 14%) [23,30,31] and then Germany [21,30], Spain [20,30], and the UK [33,34] ($n$ = 2, each, 9%). Canada [39], England and Wales [24], Hong Kong [29], Italy [30], The Netherlands [25], and Sweden [32] were each the perspective in one study. Nine studies (41%) reported industry funding [23,26,30,31,33–35,37,40]. Another six studies (27%) did not disclose any funding source [22,25,27,28,36,38], but three of these studies included authors with industry or consultancy affiliations [22,27,38]. Eleven studies (50%) were published relatively recently, from 2017 onwards. Most publications were in medical journals ($n$ = 15, 68%) [20,21,25,27,28,30,31,33–35,37,38,40,41], followed by health policy journals ($n$ = 6, 27%) [22–24,32,36,39] and multidisciplinary journals ($n$ = 1, 5%) [29].

### 3.2. Quality of reporting

Detailed scoring of the studies according to the CHEERS checklist is presented in Supplementary Table 7. On average, the studies included reported 81% of the applicable items (median 80%, range 64–100%). CHEERS items that were not appropriately reported by 20% or more of the studies to which they were applicable included: title; setting and location; effectiveness measure; health-related quality-of-life population; currency and conversion; characterisation of uncertainty; source of funding; and conflicts of interest. On average, publications in health policy journals reported more CHEERS items (87%) compared to papers in medical and multidisciplinary journals (79%). Although this finding is concordant with previous reviews of health economic studies [42,43], lower completeness of reporting is not necessarily associated with lower methodological quality.

**Table 1 – Overview of the data extracted for 14 health economic studies on liquid- or tissue-based tests to inform decisions on the need for a prostate biopsy**

| Publication | Analysis | Test(s) considered | DMA | Patient population | Comparison category | Health outcome | Geographical location | Evidence approach [a] | Diagnostic performance evidence | Impact of test(s) on costs | Impact of test(s) on health outcome | Cost-effectiveness judgement [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bermudez-Tamayo et al, 2007 [20] | CEA | pfPSA | Initial Bx | Low risk | Test vs SOC | CCs detected, prognostic utility, actual cases | Spain | MBSS with observational cost data | Literature | Decrease | Decrease | Cost-effective |
| Schiffer et al, 2012 [21] | CA | UPA-PC | Initial Bx | Low risk or higher | Test vs SOC | NA | Germany | MBSS | Observational validation study | Decrease | NA | NA |
| Aubry et al, 2013 [22] [b] | BIA | ConfirmMDx | Repeat Bx | Repeat Bx candidate | Test vs SOC | NA | USA | MBSS | Observational validation study | Decrease | NA | NA |
| Malavaud et al, 2013 [23] | BIA | PCA3 Score | Repeat Bx | Repeat Bx candidate | Test vs SOC | NA | France | Chart review with simulated test results | | Decrease | NA | NA |
| Nicholson et al, 2015 [24] | CEA | PCA3 Score, PHI | Repeat Bx | Repeat Bx candidate | Test vs SOC vs other | QALYs | England and Wales | MBSS with modelled impact | Observational validation studies | Increase | Negligible increase | Not cost-effective |
| Dijkstra et al, 2017 [25] | CEA | SelectMDx | Initial Bx | Low risk or higher | Test vs SOC | QALYs | Netherlands | MBSS | Observational validation study | Decrease | Negligible increase | Dominant |
| Sanda et al, 2017 [26] | CA | T2:ERG, PCA3 Score | Initial Bx | Low risk or higher | Test vs SOC vs other | NA | USA | MBSS | Observational validation study | Decrease | NA | NA |
| Voigt et al, 2017 [27] [b] | BIA | 4Kscore | Initial Bx | Low risk or higher | Test vs SOC | NA | USA | Observational study with modelled impact | | Decrease | NA | NA |
| Sathianathen et al, 2018 [28] | CEA | PHI, 4Kscore, SelectMDx, EPI | Initial Bx | Low risk or higher | Test vs SOC | QALYs | USA | MBSS | Observational validation studies | Decrease | Negligible increase | Cost-effective |
| Boutell et al, 2019 [29] | CEA | PHI | Initial Bx | Low risk | Test vs SOC | CCs missed, unnecessary Bx | Hong Kong | MBSS | Observational validation study | Decrease | Increase in CCs missed, decrease in unnecessary Bx | Inconclusive |
| Govers et al, 2019 [30] | CEA | SelectMDx | Initial Bx | Bx candidate | Test vs SOC | QALYs | France, Germany, Italy, Spain | MBSS | Observational validation study | Decrease | Negligible increase | Dominant |
| Mathieu et al, 2019 [31] | CA | PHI | Initial Bx | Low risk | Test vs SOC | NA | France | Observational study with MBSS | Observational validation study | Increase | NA | NA |
| Fridhammer et al, 2020 [32] | CEA | Hypothetical | Initial Bx | Low risk | Test vs SOC | QALYs | Sweden | MBSS | Assumption | Decrease (PSA 3.0–9.9 or 2.0–9.9 ng/ml) Increase (PSA 2.0–2.9 ng/ml) | Decrease (PSA 3.0–9.9 ng/ml) Increase (PSA 2.0–2.9 or 2.0–9.9 ng/ml) | Cost-effective |
| Kim et al, 2020 [33] | CA | PSAd, PHI | Initial Bx | Bx candidate | Test vs other | NA | UK | Observational study with modelled impact | Observational validation study | Decrease | NA | NA |

BIA = budget-impact analysis; CA = cost analysis; CEA = cost-effectiveness analysis; DMA = decision-making aim; Bx = biopsy; NA = not applicable; PSA = prostate-specific antigen; pfPSA = percent free PSA; UPA-P = urinary proteome analysis for prostate cancer; PHI = Prostate Health Index; EPI = ExoDx Prostate Intelli-Score; PSAd = PSA density; SOC = standard of care; mpMRI = multiparametric magnetic resonance imaging; CCs = cancer cases; QALYs = quality-adjusted life years; MBSS = modelling based on sensitivity and specificity; DT = decision tree; STM = state-transition model; DES = discrete event simulation.

[a] Impact here refers to both health and economic outcomes for CEAs and economic outcomes for CAs or BIAs.

[b] Obtained via cross-referencing.

[c] A dominant strategy improves health outcomes at lower costs, so it is better in terms of health and economic outcomes, whereas a cost-effective strategy improves health outcomes at higher costs, but the increase in costs is considered proportionate to the improvement in health, so the improvement in health is worth the increase in costs.

**Table 2 – Overview of data extracted data for eight health economic studies on liquid- or tissue-based tests to facilitate treatment decisions for localised prostate cancer**

| Publication | Analysis | Test(s) considered | DMA | Patient population | Comparison category | Health outcome | Geographical location | Evidence approach [a] | Diagnostic performance evidence | Impact of test(s) on costs | Impact of test(s) on health outcome | Cost-effectiveness judgment [b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Calvert et al, 2003 [34] | CEA | DNA-Ploidy | Initial TS | Localised NOS | Test vs other | QALYs | UK | Modelling based on sensitivity and specificity | Assumption | Increase | Increase | Cost-effective |
| Zubek and Konski, 2009 [35] | CEA | ProstatePx | Adjuvant TS | Received RP | Test vs SOC | QALYs | USA | OBS with modelled impact | NA | Increase | Increase | Cost-effective |
| Reed et al, 2014 [36] | CEA | NADiA ProsVue Slope | Adjuvant TS | IR and HR of recurrence | Test vs SOC | QALYs | USA | Retrospective study with modelled impact | NA | Increase | Negligible increase | Not cost-effective |
| Roth et al, 2015 [37] | CEA | ProMark | Initial TS | LR and IR of recurrence | Test vs SOC | QALYs | USA | OBS with modelled impact | Observational validation study | Decrease | Negligible increase | Dominant |
| Albala et al, 2016 [38] | CA | OncotypeDX | Initial TS | Favourable IR or LR | Test vs SOC | NA | USA | OBS with historical cohort | NA | Decrease (LR) Increase (IR) | NA | NA |
| Health Quality Ontario, 2017 [39] | BIA | Prolaris | Initial TS | LR and IR | Test vs SOC | NA | Canada | OBS | NA | Increase | NA | NA |
| Lobo et al, 2017 [40] | CEA | Decipher | Adjuvant TS | Received RP | Test vs SOC vs other | QALYs | USA | OBS with clinical vignette study | NA | Increase | Increase | Cost-effective |
| Chang et al, 2019 [41] | CEA | OncotypeDX | Initial TS | Favourable IR or LR | Test vs SOC | QALYs | USA | OBS with historical cohort | NA | Increase | Increase | Cost-effective |

BIA = budget-impact analysis; CA = cost analysis; CEA = cost-effectiveness analysis; DMA = decision-making analysis; TS = treatment strategy; NA = not applicable; NOS = not otherwise specified; RP = radical prostatectomy; HR = high risk; IR = intermediate risk; LR = low risk; SOC = standard of care; QALYs = quality-adjusted life years; OBS = observational study; DT: decision tree, STM: state-transition model.

[a] Impact here refers to both health and economic outcomes for CEAs and economic outcomes for CAs or BIAs.

[b] A dominant strategy improves health outcomes at lower costs, so it is better in terms of health and economic outcomes, whereas a cost-effective strategy improves health outcomes at increased costs, but the increase in costs is considered proportionate to the improvement in health, so the improvement in health is worth the increase in costs.

**Table 3 – Overview of the liquid- and tissue-based biomarker tests evaluated in the health economic studies included in the review**

| Test name | Sample type | Biomarker(s) | DMA | Studies, *n* (%) | References |
|---|---|---|---|---|---|
| Prostate Health Index | Blood | Total PSA, free PSA, proPSA | Biopsy | 5 (23) | [24,28,29,31,33] |
| PCA3 Score/PROGENSA | Urine | Relative levels of *PCA3* and *KLK3* RNA | Biopsy | 3 (14) | [23,24,26] |
| SelectMDx | Urine | *DLX1*, *HOXC6* and *KLK3* mRNA (this test also considers clinical variables) | Biopsy | 3 (14) | [25,28,30] |
| 4Kscore | Blood | Total PSA, free PSA, intact PSA, and human glandular kallikrein 2 | Biopsy | 2 (9) | [27,28] |
| OncotypeDx | Tissue | mRNA levels of 12 cancer-related genes (and 5 reference genes) involved in stromal response, androgen signalling, cellular organisation, and proliferation | Treatment | 2 (9) | [38,41] |
| ConfirmMDx | Tissue | Methylated *GSTP1*, *APC*, and *RASSF1* | Biopsy | 1 (5) | [22] |
| Decipher | Tissue | mRNA levels of 22 genes involved in cell differentiation, proliferation, adhesion, motility, structure, cell-cycle progression, mitosis, immune modulation, and other unknown function | Treatment | 1 (5) | [40] |
| DNA-Ploidy | Tissue | Amount of DNA in the nuclei of prostate cancer cells | Treatment | 1 (5) | [34] |
| ExoDx Prostate Intelli-Score | Urine | Exosomal RNA for *PCA3*, *SPDEF*, and *ERG* | Biopsy | 1 (5) | [28] |
| NADiA ProsVue Slope | Blood | Supersensitive PSA kinetics | Treatment | 1 (5) | [36] |
| Percent free PSA | Blood | Free PSA, total PSA | Biopsy | 1 (5) | [20] |
| Prolaris | Tissue | mRNA levels of 31 cell-cycle progression genes and 15 control genes | Treatment | 1 (5) | [39] |
| ProMark | Tissue | Relative expression of 8 proteins (CUL2, DERL1, FUS, HSPA9, PDSS2, SMAD4, S6(P), and YBX1) | Treatment | 1 (5) | [37] |
| ProstatePx | Tissue | Morphometric and antigen expression profile of prostate cancer cells | Treatment | 1 (5) | [35] |
| PSA density | Blood | Total PSA, prostate volume | Biopsy | 1 (5) | [33] |
| T2:ERG | Urine | Relative levels of *TMPRSS2:ERG* and *KLK3* mRNA | Biopsy | 1 (5) | [26] |
| Urinary proteome analysis | Urine | 12 urinary peptides, total PSA, free PSA | Biopsy | 1 (5) | [21] |

DMA = decision-making aim; PSA = prostate-specific antigen.

### 3.3. *LTBTs to inform the need for prostate biopsies*

Of the 14 studies focusing on the use of tests to provide information on the need for a biopsy, 11 (79%) focused on the need for an initial biopsy [20,21,25–33] and three (21%) on the need for a repeat biopsy after an initial negative tissue biopsy [22–24]. Thirteen studies (93%) compared the use of a test to SOC, one of which also included a strategy without biopsies [26] and another additionally investigated the combination of tests [24]. One study compared several strategies including tests and imaging [33].

Most studies were cost-effectiveness analyses ($n$ = 7, 50%) [20,24,25,28–30,32], followed by cost analyses ($n$ = 4, 29%) [21,26,31,33] and budget impact analyses ($n$ = 3, 21%) [22,23,27]. Five of the cost-effectiveness analyses used QALYs as the effectiveness outcome, which is the gold-standard effectiveness outcome in health economics as it allows for comparison across diseases. Twelve of 14 studies adopted a health care payer perspective. Nine studies (64%) considered a time horizon of 3 yr or shorter. All studies were model-based, with decision tree analysis the technique most frequently used ($n$ = 7, 50%). Six studies considered treatments in their model structure [25–28,30,32]. No study presented model validation efforts. Three studies (21%) performed uncertainty analyses [24,28,32].

Eleven out of 14 studies (79%) modelled test outcomes and subsequent management decisions based on the sensitivity and specificity of the tests and linked those test outcomes to health and economic outcomes, whereas two studies used observational data on diagnosis patterns and linked those to health and economic outcomes [27,33]. One study performed a chart review for which test results were simulated to estimate how many biopsies could have been avoided [23]. For the 12 studies that used sensitivity and specificity, ten derived the diagnostic performance from observational studies [21,22,24–26,28–31,33] and single studies derived this from literature [20] or made an assumption because they investigated a hypothetical test [32]. Of the seven cost-effectiveness analyses, effectiveness outcomes were modelled based on literature in six [20,24,25,28,30,32] and based on observational data in one study [29], although for that study the effectiveness outcome was not QALYs but the number of missed cancer cases and unnecessary biopsies. All studies assumed perfect compliance with the test recommendations, that is, clinician or patient preferences and practice variations were not considered.

Eleven out of 13 studies (85%) found the use of tests to be cost-saving [20–23,25–30,33], of which those performing cost-effectiveness analyses found the use of tests cost-effective or dominant, that is, preferable in terms of effectiveness and costs. Two of these 13 studies (15%) found that the use of tests would increase costs [24,31]. One of these was the only official health technology assessment report, concluding that the use of two tests (evaluated separately) was not cost-effective [24]. The study that evaluated a hypothetical test for different subgroups found mixed results, but overall concluded that use of a test would be cost-effective [32].

### 3.4. LTBTs to inform treatment decisions for confirmed PCa

Of the eight studies on the use of tests to inform treatment decisions, five (63%) focused on the initial treatment after diagnosis [34,37–39,41] and three (38%) on postprostatectomy adjuvant treatment [35,36,40]. Four studies (50%) focused on a low- and intermediate-risk population [37–39,41] and one study focused on an intermediate- and high-risk cohort [36], whereas others defined the population of interest as having undergone prostatectomy ($n$ = 2, 25%) [35,40] or having localised disease ($n$ = 1, 13%) [34]. Seven studies (88%) compared the use of a test to SOC [35–41], one of which also included a strategy in which all patients would receive adjuvant treatment [40]. One study compared a test-informed strategy to strategies in which all patients would either enrol in a surveillance strategy or undergo prostatectomy in the initial treatment phase [34].

Six of the eight studies were cost-effectiveness analyses (75%) [34–37,40,41] and single studies presented a budget impact [39] or costing analysis [38]. All cost-effectiveness analyses were performed using QALYs as the effectiveness outcome. All studies adopted a health care payer perspective. Single studies considered a time horizon of 180 d [38] or 5 yr [39], whereas all other studies considered a time horizon of 10 yr or more [34–37,40,41]. Seven of the eight studies (88%) were model-based, with state-transition modelling the technique most frequently used ($n$ = 6, 86%) [34–37,40,41]. All state-transition models were structured according to health states, whereas the structure of the decision tree was mainly defined by the different treatment options. Three of the seven model-based analyses (43%) presented external validation for specific parts of the model [36,37,41]. Four of the eight studies (50%) performed some sort of uncertainty analysis [35,35,36,37,40].

Seven of the eight studies (88%) mainly used observational data to link health and economic outcomes to observed treatment decisions based on test results [35–41], whereas one study (13%) modelled test outcomes and subsequent treatment decisions based on the sensitivity and specificity of the test [34]. Of the studies using observational data, one used historical data for the control strategy [38]. All six cost-effectiveness analyses modelled effectiveness outcomes based on the literature. Two studies (25%) assumed perfect compliance with test recommendations [34,35], that is, clinician or patient preferences as a source of practice variation were not considered, which is not expected to be realistic. The other studies accounted for variation in following test recommendations in the real world, but to varying extents: five modelled treatment patterns as found in the observational data used [36–39,41] and one used a clinical vignette study in which participants stated what their choice would be in varying scenarios [40]. No study explicitly considered patient preferences regarding treatment options, but the observational data used in four studies do include this real-world variation [37,37,38,39,41].

Six of the eight studies (75%) found that use of a test would increase the total costs of care [34–36,39–41], one study (13%) found a decrease in costs [37], and one study found cost savings for a low-risk cohort but an increase in costs for an intermediate-risk population [38]. All cost-effectiveness analyses found that LTBT use results in better health outcomes, although this increase was considered to be relatively small in magnitude for two studies by the reviewers [36,37]. Five of the six cost-effectiveness analyses found that use of tests was cost-effective or dominant [34,35,37,40,41], whereas one study found that test use was not cost-effective [36].

### 3.5. Discussion

We systematically reviewed 22 health economic studies evaluating 17 different molecular tests aimed at informing the need for a (repeat) biopsy or treatment decisions for localised PCa. Overall, these studies suggest that LTBT use to inform the need for prostate biopsies and the treatment of PCa can be either cost-saving or -effective. In particular, tests aimed at informing biopsy decisions were found to result in cost savings because of a lower number of prostate tissue biopsies performed. LTBT use to inform treatment decisions could potentially be cost-effective, that is, they improve health outcomes at an acceptable increase in cost, according to the authors. The encouraging results from these studies, however, do not align with the current uptake of tests in clinical guidelines or routine practice outside the USA. This discordance is likely to be caused by the absence of prospective interventional clinical studies on which health economic evaluations should be based. In addition, our review identified methodological challenges explaining why the current studies provide insufficient evidence for health care decision-makers to justify the incremental costs. These mainly relate to the short time horizons for which outcomes are evaluated, including how use of these tests will impact clinical management in subsequent stages of the disease, and several structural model assumptions.

The studies that evaluated LTBT use to inform the need for invasive tissue biopsies had a particularly narrow focus in terms of downstream health outcomes and costs. For example, most of these studies adopted short-term time horizons and ignored the impact of false-negative test results or accounted for it in a limited way. The clinical utility of LTBTs in changing management was not considered in these studies at all and only indirectly in some studies focusing on PCa treatment. Ignoring these aspects may results in cost-effectiveness estimates that are biased in favour of tests, as a previous modelling study in advanced PCa demonstrated that compliance with test results may have a substantial impact on health economic outcomes [44]. Although studies focusing on treatment of PCa overall more extensively accounted for downstream consequences, the number of studies was low and they focused on specific tests, leaving the overall judgement on the cost-effectiveness of tests in this context uncertain.

Given the lack of prospective comparative evidence, the studies reviewed can be considered early-stage health economic evaluations that are neither designed nor suitable for providing definitive evidence for reimbursement. Nevertheless, these early economic models can inform

further translation of tests and treatments by prioritising additional clinical studies [45]. Despite being early-stage evaluations, overall the studies appraised provided insufficient justification of the evidence, model structures, and techniques used. This is in line with other reviews of health economic studies in oncology [43,46]. Willis et al [47] reviewed five full economic evaluations of mpMRI for the diagnosis prostate cancer and found substantial heterogeneity in the questions posed, pathways modelled, and assumptions made. They concluded that there is a need for a better standard of reporting around key modelling assumptions and a wider range of sensitivity analyses to explore the impact of structural assumptions and to reflect uncertainty around data inputs for the model parameters. We suggest that transparent reporting may be even more important for early-stage analyses specifically, as these often require a larger number and intensity of assumptions based on more limited evidence. Previous studies have additionally discussed a deficiency of policies for health economic analyses, as well as a lack of reviewers with knowledge of health economics, urging journals to provide authors and reviewers with guidance on cost-effectiveness studies [42]. Given that the vast majority of studies included in this review were published in medical journals and that reporting quality was found to be lower in those journals compared to health policy journals according to the CHEERS checklist, this may have contributed to the lack of justification identified.

Despite the overall positive findings, the issues highlighted above suggest that health economic estimates may be overoptimistic and that, consequently, the cost-effectiveness of test-informed management of PCa is promising but warrants additional research through prospective interventional studies. The observation that three out of eight studies without industry involvement had an overall negative conclusion (38%) compared to only one out of 14 studies with clear industry involvement (7%) may further add to scepticism about the strength of the currently available health economic evidence. This also highlights the need for investigator-initiated clinical studies to strengthen the evidence base for long-term health outcomes. Although controlled interventional studies are as necessary for biomarkers as they are for pharmaceuticals from a health economic perspective, consideration should be given to appropriate regulatory protection to ensure investments are protected following positive study results.

To advance the translation of tests on the basis of health economic evidence, future studies should be aware of several opportunities, most of which relate to the perception that tests should not be considered in isolation but as part of the broader clinical pathway. First, economic evaluations should be considered from an early stage in the development process to collect as much relevant information along the way, which could reduce the number of assumptions that need to be made in the health economic evaluation. Second, studies focusing on the use of tests in the diagnostic process should collect data on how the test will be used in practice, or at least explore the impact of compliance to test results in sensitivity analyses, and realistically account for downstream consequences of false-negative test results. Third, studies focusing on the management of PCa should at least aim to collect data on the impact on actual decisions made and consequent long-term health through observational studies. Fourth, uncertainty in outcomes should be explored and reported more transparently in terms of both model parameters and model assumptions and structure, rather than just in terms of one-way sensitivity analysis of selected parameters. Finally, studies should use existing reporting checklists, such as the CHEERS checklist [19], to improve reporting on health economic evaluations.

Further research could also investigate the potential of LTBTs to identify asymptomatic metastatic disease during the diagnostic process. Such early detection could lead to downstaging and, hence, better long-term health outcomes.

This review has certain limitations. Its findings are subject to publication bias, as not all studies may have been published, especially studies with negative findings regarding the cost-effectiveness of tests. The risk of publication bias is highlighted by the substantial number of conference abstracts that were excluded during full-text screening, as full-text publications may not have been pursued for studies with negative findings. The CHEERS checklist was used to appraise the reporting quality of publications in the absence of a better alternative, but this checklist was not designed to score publications and using it to do so may be considered subjective. In terms of data extraction, the lack of clear reporting and justification of methods, modelling assumptions, and analyses performed might have resulted in categorisations that readers or the authors of the original papers might not fully agree with. Finally, some studies presented a range of analyses that had to be summarised into a single cost-effectiveness judgement at the discretion of the reviewers.

## 4. Conclusions

This review found that most health economic studies concluded that LTBTs can be cost-saving or -effective when used to select individuals for prostate biopsies or to inform decisions on the treatment of confirmed localised PCa through risk stratification. These findings warrant further research through prospective interventional studies to provide robust data on clinical utility and long-term health outcomes that will be essential to strengthen the health economic evidence base. Such information will be crucial to optimise reimbursement of the most cost-effective tests by public health care systems so that outcomes can be improved for the broader population.

***Author contributions:*** Koen Degeling had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* IJzerman.
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*Drafting of the manuscript:* Degeling.
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*Statistical analysis:* Degeling.
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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euros.2021.03.002.

## References

[1] Andriole GL, Crawford ED, Grubb RL, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009;360:1310–9.
[2] Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360:1320–8.
[3] Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: risk stratification, shared decision making, and care options. J Urol 2018;199:683–90.
[4] Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer–2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2021;79:243–62.
[5] Hamdy FC, Donovan JL, Lane JA, et al. Active monitoring, radical prostatectomy and radical radiotherapy in PSA-detected clinically localised prostate cancer: the ProtecT three-arm RCT. Health Technol Assess 2020;24:1–176.
[6] Cooperberg MR, Carroll PR. Trends in management for patients with localized prostate cancer, 1990–2013. JAMA 2015;314:80–2.
[7] Ingimarsson JP, Celaya MO, Laviolette M, Rees JR, Hyams ES. Trends in initial management of prostate cancer in New Hampshire. Cancer Causes Control 2015;26:923–9.
[8] Womble PR, Montie JE, Ye Z, Linsell SM, Lane BR, Miller DC. Contemporary use of initial active surveillance among men in Michigan with low-risk prostate cancer. Eur Urol 2015;67:44–50.
[9] Ruseckaite R, Beckmann K, O'Callaghan M, et al. A retrospective analysis of Victorian and South Australian clinical registries for prostate cancer: trends in clinical presentation and management of the disease. BMC Cancer 2016;16:607.
[10] Löppenberg B, Sood A, Dalela D, et al. Variation in locoregional prostate cancer care and treatment trends at commission on cancer designated facilities: a National Cancer Data Base analysis 2004 to 2013. Clin Genitourin Cancer 2017;15:e955–68.
[11] Eggener SE, Rumble RB, Armstrong AJ, et al. Molecular biomarkers in localized prostate cancer: ASCO guideline. J Clin Oncol 2019;38:1474–94.
[12] Carroll PH, Mohler JL. NCCN guidelines updates: prostate cancer and prostate cancer early detection. J Natl Compr Canc Netw 2018;16 (5 Suppl):620–3.
[13] Mohler JL, Antonarakis ES, Armstrong AJ, et al. Prostate cancer, version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2019;17:479–505.
[14] Olleik G, Kassouf W, Aprikian A, et al. Evaluation of new tests and interventions for prostate cancer management: a systematic review. J Natl Compr Canc Netw 2018;16:1340–51.
[15] Fine ND, LaPolla F, Epstein M, Loeb S, Dani H. Genomic classifiers for treatment selection in newly diagnosed prostate cancer. BJU Int 2019;124:578–86.
[16] Becerra MF, Atluri VS, Bhattu AS, Punnen S. Serum and urine biomarkers for detecting clinically significant prostate cancer. Urol Oncol. In press. https://doi.org/10.1016/j.urolonc.2020.02.018.
[17] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100.
[18] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
[19] Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health 2013;16:231–50.
[20] Bermudez-Tamayo C, Martin Martin JJ, Del Puerto Lopez Del Amo Gonzalez M, Perez Romero C. Cost-effectiveness of percent free PSA for prostate cancer detection in men with a total PSA of 4–10 ng/ml. Urol Int 2007;79:336–44.
[21] Schiffer E, Bick C, Grizelj B, Pietzker S, Schofer W. Urinary proteome analysis for prostate cancer diagnosis: cost-effective application in routine clinical practice in Germany. Int J Urol 2012;19:118–25.
[22] Aubry W, Lieberthal R, Willis A, Bagley G, Willis 3rd SM, Layton A. Budget impact model: epigenetic assay can help avoid unnecessary repeated prostate biopsies and reduce healthcare spending. Am Health Drug Benefits 2013;6:15–24.
[23] Malavaud B, Cussenot O, Mottet N, et al. Impact of adoption of a decision algorithm including PCA3 for repeat biopsy on the costs for prostate cancer diagnosis in France. J Med Econ 2013;16:358–63.
[24] Nicholson A, Mahon J, Boland A, et al. The clinical effectiveness and cost-effectiveness of the PROGENSA prostate cancer antigen 3 assay and the Prostate Health Index in the diagnosis of prostate cancer: a systematic review and economic evaluation. Health Technol Assess 2015;19:1–191.
[25] Dijkstra S, Govers TM, Hendriks RJ, et al. Cost-effectiveness of a new urinary biomarker-based risk score compared to standard of care in prostate cancer diagnostics – a decision analytical model. BJU Int 2017;120:659–65.

[26] Sanda MG, Feng Z, Howard DH, et al. Association between combined TMPRSS2:ERG and PCA3 RNA urinary testing and detection of aggressive prostate cancer. JAMA Oncol 2017;3:1085–93.
[27] Voigt JD, Dong Y, Linder V, Zappala S. Use of the 4Kscore test to predict the risk of aggressive prostate cancer prior to prostate biopsy: overall cost savings and improved quality of care to the US healthcare system. Rev Urol 2017;19:1–10.
[28] Sathianathen NJ, Kuntz KM, Alarid-Escudero F, et al. Incorporating biomarkers into the primary prostate biopsy setting: a cost-effectiveness analysis. J Urol 2018;200:1215–20.
[29] Bouttell J, Teoh J, Chiu PK, et al. Economic evaluation of the introduction of the Prostate Health Index as a rule-out test to avoid unnecessary biopsies in men with prostate specific antigen levels of 4–10 in Hong Kong. PLoS One 2019;14:e0215279.
[30] Govers TM, Hessels D, Vlaeminck-Guillem V, et al. Cost-effectiveness of SelectMDx for prostate cancer in four European countries: a comparative modeling study. Prostate Cancer Prostat Dis 2019;22:101–9.
[31] Mathieu R, Castelli C, Fardoun T, et al. Cost analysis of prostate cancer detection including the Prostate Health Index (PHI). World J Urol 2019;37:481–7.
[32] Fridhammar A, Axelsson U, Persson U, Bjartell A, Borrebaeck CAK. The value of a new diagnostic test for prostate cancer: a cost-utility analysis in early stage of development. Pharmacoecon Open 2020;5:77–88.
[33] Kim L, Boxall N, George A, et al. Clinical utility and cost modelling of the phi test to triage referrals into image-based diagnostic services for suspected prostate cancer: the PRIM (Phi to RefIne Mri) study. BMC Med 2020;18:95.
[34] Calvert NW, Morgan AB, Catto JWF, et al. Effectiveness and cost-effectiveness of prognostic markers in prostate cancer. Br J Cancer 2003;88:31–5.
[35] Zubek VB, Konski A. Cost effectiveness of risk-prediction tools in selecting patients for immediate post-prostatectomy treatment. Mol Diagn Ther 2009;13:31–47.
[36] Reed SD, Stewart SB, Scales Jr CD, Moul JW. A framework to evaluate the cost-effectiveness of the NADiA ProsVue slope to guide adjuvant radiotherapy among men with high-risk characteristics following prostatectomy for prostate cancer. Value Health 2014;17:545–54.
[37] Roth JA, Ramsey SD, Carlson JJ. Cost-effectiveness of a biopsy-based 8-protein prostate cancer prognostic assay to optimize treatment decision making in Gleason 3 + 3 and 3 + 4 early stage prostate cancer. Oncologist 2015;20:1355–64.
[38] Albala D, Kemeter MJ, Febbo PG, et al. Health economic impact and prospective clinical utility of Oncotype DX Genomic Prostate Score. Rev Urol 2016;18:123–32.
[39] Health Quality Ontario. Prolaris Cell Cycle Progression test for localized prostate cancer: a health technology assessment. Ontario Health Technol Assess Ser 2017;17:1–75.
[40] Lobo JM, Trifiletti DM, Sturz VN, et al. Cost-effectiveness of the Decipher Genomic Classifier to guide individualized decisions for early radiation therapy after prostatectomy for prostate cancer. Clin Genitourin Cancer 2017;15:e299–309.
[41] Chang EM, Punglia RS, Steinberg ML, Raldow AC. Cost-effectiveness of the Oncotype DX Genomic Prostate Score for guiding treatment decisions in patients with early stage prostate cancer. Urology 2019;126:89–95.
[42] Leung HW, Chan AL, Leung MS, Lu CL. Systematic review and quality assessment of cost-effectiveness analysis of pharmaceutical therapies for advanced colorectal cancer. Ann Pharmacother 2013;47:506–18.
[43] Degeling K, Vu M, Koffijberg H, et al. Health economic models for metastatic colorectal cancer: a methodological review. Pharmacoeconomics 2020;38:683–713.
[44] Degeling K, Schivo S, Mehra N, et al. Comparison of timed automata with discrete event simulation for modeling of biomarker-based treatment decisions: an illustration for metastatic castration-resistant prostate cancer. Value Health 2017;20:1411–9.
[45] IJzerman MJ, Koffijberg H, Fenwick E, Krahn M. Emerging use of early health technology assessment in medical product development: a scoping review of the literature. Pharmacoeconomics 2017;35:727–40.
[46] Bullement A, Cranmer HL, Shields GE. A review of recent decision-analytic models used to evaluate the economic value of cancer treatments. Appl Health Econ Health Policy 2019;17:771–80.
[47] Willis SR, van der Meulen J, Valerio M, Miners A, Ahmed HU, Emberton M. A review of economic evaluations of diagnostic strategies using imaging in men at risk of prostate cancer. Curr Opin Urol 2015;25:483–9.