Review – Prostate Cancer

Molecular Biomarkers for the Detection of Clinically Significant Prostate Cancer: A Systematic Review and Meta-analysis

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Abstract

Context: Prostate cancer (PCa) is the second most common type of cancer in men. Individualized risk stratification is crucial to adjust decision-making. A variety of molecular biomarkers have been developed in order to identify patients at risk of clinically significant PCa (csPCa) defined by the most common PCa risk stratification systems.

Objective: The present study aims to examine the effectiveness (diagnostic accuracy) of blood or urine-based PCa biomarkers to identify patients at high risk of csPCa.

Evidence acquisition: A systematic review of the literature was conducted. Medline and EMBASE were searched from inception to March 2021. Randomized or non-randomized clinical trials, and cohort and case-control studies were eligible for inclusion. Risk of bias was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. Pooled estimates of sensitivity, specificity, and area under the curve were obtained.

Evidence synthesis: Sixty-five studies (N = 34 287) were included. Not all studies included prostate-specific antigen-selected patients. The pooled data showed that the Prostate Health Index (PHI), with any cutoff point between 15 and 30, had sensitivity of 0.95–1.00 and specificity of 0.14–0.33 for csPCa detection. The pooled estimates for SelectMDx test sensitivity and specificity were 0.84 and 0.49, respectively.

Conclusions: The PHI test has a high diagnostic accuracy rate for csPCa detection, and its incorporation in the diagnostic process could reduce unnecessary biopsies.

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Prostate cancer (PCa) is a major health problem, with approximately 1.4 million cases diagnosed worldwide each year [1]. It is the second most common cancer in males after lung cancer worldwide [2], and its prevalence increases with each additional year of age [3]. The mean age of PCa onset is 65 yr and the majority of PCa patients are diagnosed from then onwards, with the age group of 70–75 yr having the highest incidence rate [4].

PCa often progresses slowly and has a prolonged preclinical phase. Therefore, many men with PCa die from causes other than PCa and without evidence of pathological manifestation [3].

Traditionally, diagnosis and staging of PCa have been based on prostate-specific antigen (PSA) level, digital rectal examination (DRE), and transrectal ultrasound guided prostate biopsy.

Serum PSA measurement is the reference standard for the early detection of PCa. However, PSA level does not exclusively increase in malignant pathology, as high levels can also be observed in benign prostatic pathologies such as benign prostatic hyperplasia, prostatitis, other urinary tract infections, and even acute urine retention. Moreover, PSA cannot discriminate between indolent PCa (iPCa) and aggressive tumors.

Most men with positive screening results (elevated PSA levels or abnormal DRE) who undergo prostate biopsy will not have PCa. Approximately two-thirds of men with an elevated PSA level can expect a false positive test result [5]. Moreover, biopsy procedures are related to complications such as pain, bleeding, and sepsis, and the related consequences on the utilization of health resources. However, the most serious harm of PCa screening may be overdiagnosis, which may result in subsequent overtreatment [6]. Consequently, strategies to differentiate iPCa from aggressive tumors are necessary [1]. Current European Urological Association guidelines recommend the use of risk stratification tools, such as risk calculators and magnetic resonance imaging (MRI), and biomarker tests for the prediction of a positive prostate biopsy as reflex tests after an elevated PSA level [7].

Recently, there has been an expansion in the availability of new molecular blood and urine test biomarkers that can be used to support prostate biopsy decisions, providing more individualized risks for PCa, distinguishing between clinically significant PCa (csPCa) and iPCa, or predicting the prognosis of patients already diagnosed [8]. However, no consensus has been reached on the use of these tests in routine clinical practice.

The objective of the present study is to examine the diagnostic accuracy of the biomarker tests in the identification of patients with csPCa.

2. Evidence acquisition

A systematic review (SR) of the literature was carried out following the Cochrane Collaboration methodology [9] with reporting in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [10]. The prespecified protocol for this review was registered in PROSPERO (registration number CRD42021240638).

2.1. Data sources and searches

The following electronic databases were searched (from 2010 to March 1, 2021): Medline (Ovid platform) and EMBASE (Elsevier interface). The search strategy included both controlled vocabulary and text-word terms related to PCa and molecular biomarker. Searches were limited to the English and Spanish languages. The complete search strategy is available in Supplementary Table 1. We also examined the reference lists of included articles and, through search in Google Scholar, articles that referenced the included studies.

2.2. Selection criteria and study selection

Studies were eligible for inclusion if they fulfilled the following criteria:

1. Design: randomized or nonrandomized clinical trials (RCTs or non-RCTs) were eligible for inclusion. In the absence of such designs, cohort and case-control studies that performed an evaluation of the diagnostic validity of the tests were considered.

2. Population: adult men (≥18 yr) with clinical factors that suggested csPCa comprised the study population. Studies with a heterogeneous group of patients (eg, patients with suspected PCa, either iPCa or csPCa) were included only if the results for patients meeting the inclusion criteria were reported separately.

3. Index tests: any blood or urine test based on biomarkers aimed at distinguishing csPCa from iPCa was performed.

4. Reference standard: it included alternative tests, biopsy, magnetic resonance, or usual care.

However, there is a lack of evidence on patient-important outcomes and thus more research is needed.

Patient summary: It has been possible to verify that the application of biomarkers could help detect prostate cancer (PCa) patients with a higher risk of poorer evolution. The Prostate Health Index shows an ability to identify 95–100 for every 100 patients suffering from clinically significant PCa who take the test, preventing unnecessary biopsies in 14–33% of men without PCa or insignificant PCa. © 2022 The Authors. Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
Fig. 1 – PRISMA flow chart detailing the screening process. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.
| Study          | Country                          | Funded* | Design        | Biomarker | Test                          | Biopsy                | Outcome |
|---------------|----------------------------------|---------|---------------|-----------|-------------------------------|-----------------------|---------|
| Abate (2015)  | France, Germany, Italy, Spain, and UK | Y       | Nested case-control | PHI       | Beckman Coulter              | ≥12-cylinder TRUS guided | N N Y   |
| Babajide (2021) | USA                             | N       | Case-control  | PHI       | Beckman Coulter              | NR                   | Y Y Y   |
| Barsiene (2020) | Lithuania                        | Y       | Prospective   | PHI, PHID | Beckman Coulter              | NR                   | Y Y Y   |
| Bertok (2020)  | Austria                          | N       | Retrospective | PHI       | Beckman Coulter TRUS guided or systematic | N N Y   |
| Boeckermann (2016) | Germany and France         | N       | Prospective   | PHI       | Beckman Coulter              | 8-cylinder TRUS guided | N N Y   |
| Busetto (2020) | Italy                           | Y       | Prospective   | PHI       | Beckman Coulter              | ≥10-cylinder TRUS guided | Y Y Y   |
| Cao (2018)     | USA                             | N       | Retrospective | PHI       | Beckman Coulter              | ≥12 cylinder         | Y N Y   |
| Catalina (2011) | USA                             | Y       | Case-control  | PHI       | Beckman Coulter              | ≥12 cylinder         | Y Y Y   |
| Chiu (2016)    | China                           | Y       | Prospective   | PHI       | Beckman Coulter              | ≥10 cylinder TRUS guided | N Y N   |
| Chiu (2016)    | China                           | Y       | Prospective   | PHI       | Beckman Coulter              | ≥10 cylinder TRUS guided | N Y Y   |
| Chiu (2019)    | China, France, Singapore, China, and Taiwan | Y       | Prospective   | PHI       | Beckman Coulter              | TRUS guided         | Y Y N   |
| Choi (2020)    | South Korea                     | NR      | Retrospective | PHI       | Beckman Coulter Transrectal or transperineal | Y Y N   |
| De La Calle (2015) | USA                        | N       | Prospective   | PHI       | Beckman Coulter              | TRUS guided         | Y Y Y   |
| Druskin (2018) | USA                             | N       | Retrospective | PHID      | Beckman Coulter              | TRUS guided         | Y Y Y   |
| Falagario (2021) | USA                        | NR      | Retrospective | PHI       | Total PSA, free PSA, intact PSA, and HR2 | 4Kscore test | mpMRI fusion and 12-cylinder systematic | N N Y   |
| Fan (2019)     | Taiwan                          | N       | Prospective   | PHI       | Beckman Coulter              | ≥12-cylinder TRUS guided | Y Y N   |
| Filella (2014) | Spain                           | N       | Ambispective  | PHI       | Beckman Coulter              | NR                   | N N Y   |
| Foj (2020)     | Spain                           | N       | Retrospective | PHI       | Beckman Coulter              | ≥10-cylinder TRUS guided | N N Y   |
| Foley (2016)   | Ireland                         | N       | Retrospective | PHI       | Beckman Coulter              | 12-cylinder TRUS guided | N N Y   |
| Furuya (2017)  | Japan                           | NR      | Retrospective | PHI + MRI | Beckman Coulter              | ≥16-cylinder transperineal ultrasound guided | Y Y Y   |
| Guazzoni (2011) | Italy                           | Y       | Prospective   | PHI       | Beckman Coulter              | ≥10-cylinder TRUS guided | N N Y   |
| Haese (2019)   | The Netherlands, France, and Germany | N       | Retrospective | PHI       | Beckman Coulter              | ≥10-cylinder TRUS guided | Y Y Y   |
| Hansen (2013)  | USA                             | Y       | Retrospective | PHI       | Beckman Coulter              | ≥10-cylinder TRUS-TRUS guided | N Y Y   |
| Hsieh (2020)   | Taiwan                          | N       | Prospective   | PHI       | Beckman Coulter              | 12-cylinder TRUS guided | Y Y Y   |
| Kim (2020)     | UK                              | Y       | Prospective   | PHI       | Beckman Coulter Transrectal or transperineal | Y Y N   |
| Kotova (2020)  | Russia                          | N       | Prospective   | PHI       | Beckman Coulter              | ≥12-cylinder TRUS guided | N N Y   |
| Lazzeri (2013) | Italy, Germany, France, Spain, and UK | Y       | Prospective   | PHI       | Beckman Coulter              | ≥12-cylinder TRUS guided | N N Y   |
| Lazzeri (2016) | Italy, France, Spain, Germany, and UK | Y       | Nested case-control | PHI  | Beckman Coulter              | ≥10-cylinder TRUS guided | N N Y   |
| Leyten (2015)  | The Netherlands                 | Y       | Retrospective | PHI       | Beckman Coulter              | ≥10-cylinder TRUS guided | N N Y   |
| Study                  | Country          | Funded†     | Design          | Biomarker          | Test                      | Biopsy       | Outcome |
|-----------------------|------------------|-------------|-----------------|--------------------|---------------------------|--------------|---------|
| Loeb (2015) [29]      | USA              | Y           | Prospective     | PHI                | Beckman Coulter           | ≥10 cylinder | Y       |
| Loeb (2017) [30]      | USA              | Y           | Prospective     | PHI                | Beckman Coulter           | ≥6 cylinder  | Y        |
| McKiernan (2016) [31] | USA              | Y           | Prospective     | ERG and PCA3       | ExoDx Prostate            | NR           | Y       |
| Meamin (2014) [59]    | Italy            | NR          | Prospective     | PHI                | Beckman Coulter           | TRUS guided  | N        |
| Morote (2016) [47]    | Spain            | NR          | Prospective     | PHI                | Beckman Coulter           | ≥12-cylinder | TRUS     |
| Morerezai (2021) [70] | Sweden           | N           | Prospective     | Clinical variables, total PSA, free PSA, HK2, MSMB, and HOXB13 | Stockholm3 test | TRUS guided and mpMRI | N        |
| Na (2014) [76]        | China            | Y           | Prospective     | PHI                | Beckman Coulter           | 10-cylinder   | TRUS     |
| Na (2017) [65]        | China            | N           | Prospective     | PHI                | Beckman Coulter           | 10–14-cylinder TRUS guided | Y        |
| Nordström (2015) [93] | Sweden           | N           | Case-control    | PHI                | Beckman Coulter           | 10–12-cylinder TRUS guided | N        |
| Nygård (2016) [95]    | Norway           | N           | Prospective     | PCA3               | Progensa PCA3             | Extended 10 cylinder | Y        |
| O’Malley (2017) [33]  | USA              | N           | Prospective     | PCA3               | Progensa PCA3             | TRUS guided  | N        |
| Park (2018) [62]      | South Korea      | N           | Prospective     | PHI                | Beckman Coulter           | TRUS guided  | N        |
| Punnen (2018) [34]    | France           | Y           | Prospective     | Total PSA, free PSA, intact PSA, and HK2 | 4Kscore test | ≥10-cylinder TRUS guided | N        |
| Roumigué (2020) [49]  | France           | N           | Retrospective   | Clinical variables, total PSA, free PSA, intact PSA, and HK2 | HoXC6 and DLX1 | SelectMDx | TRUS guided and mpMRI fusion | Y        |
| Ruffion (2013) [50]   | France           | NR          | Prospective     | PCA3               | Progensa PCA3             | TRUS guided  | N        |
| Ruffion (2014) [51]   | France           | NR          | Prospective     | PCA3               | Progensa PCA3             | TRUS guided  | Y        |
| Sanchis-Bonet (2018)  | Spain            | N           | Prospective     | PHI                | Beckman Coulter           | NR           | N        |
| Sanda (2017) [35]     | USA              | Y           | Retrospective   | PCA3               | Progensa PCA3             | 12-cylinder TRUS guided | Y        |
| Schulze (2020) [20]   | Germany          | N           | Prospective     | PHI                | Beckman Coulter           | 10–14 cylinder | Y        |
| Seisen (2015) [52]    | France           | Y           | Prospective     | PHI                | Beckman Coulter           | ≥12-cylinder TRUS guided | Y        |
| Shore (2019) [36]     | USA              | N           | Retrospective   | PHI                | Beckman Coulter           | 10–12-cylinder TRUS guided | Y        |
| Steuber (2022) [21]   | Germany          | Y           | Prospective     | Thrombospondin-1, cathepsin D, total PSA, free PSA, and patient age | Proclarix test | 10–12-cylinder TRUS guided and mpMRI fusion | Y        |
| Tan (2017) [67]       | Singapore        | N           | Prospective     | PHI                | Beckman Coulter           | ≥12-cylinder TRUS guided | Y        |
| Tomlins (2016) [37]   | USA              | Y           | Prospective     | PCA3, T2:ERG, and serum PSA level | TMPRSS2 and ERG | MyProstateScore | TRUS guided | N        |
| Tosoian (2017) [94]   | USA              | N           | Prospective     | PHI                | Beckman Coulter           | NR           | N        |
| Tosoian (2017) [38]   | USA              | N           | Prospective     | PHI                | Beckman Coulter           | NR           | Y        |
| Tosoian (2021) [40]   | USA              | N           | Prospective     | PCA3, TMPRSS2, and serum PSA level | MyProstateScore | TRUS guided | Y        |
| Van Neste (2016) [55] | The Netherlands   | Y           | Prospective     | PCA3               | Progensa PCA3             | 10-cylinder TRUS guided | N        |
| Wang (2017) [82]      | China            | N           | Prospective     | PCA3               | Progensa PCA3             | 10–12-cylinder TRUS guided | N        |
| Wei (2014) [41]       | USA              | Y           | Prospective     | PCA3               | Progensa PCA3             | TRUS guided  | N        |
| Woo (2020) [81]       | USA and Spain    | N           | Prospective     | PCA3, PCA3 and T2:ERG | NR                       | NR           | N        |

(continued on next page)
5. Target conditions: csPCa (Gleason score ≥7, International Society of Urological Pathology ≥2, and intermediate- or high-risk localized PCa using the D’Amico Classification System for PCa or according to the European Association of Urology).

6. Outcomes: studies that reported any of the following outcome measures were included: cancer-specific survival, metastasis, change in treatment decisions, and adverse effects. In diagnostic performance studies, measures of sensitivity, specificity, and area under the curve (AUC) with 95% confidence intervals (CIs) were also included, if available.

7. Language: only studies published in English or Spanish were included.

8. Publication type: only full original publications were considered.

9. Date of publication: due to the fact that biomarker-based tests have emerged in the last decade, only studies published from 2010 were considered.

Two reviewers (D.I.-V. and A.A.C.) screened retrieved references independently and in duplicate, starting with titles and abstracts. The full texts of all articles deemed potentially relevant were then screened to confirm eligibility. Disagreements between the reviewers were checked by a third reviewer (T.P.-S.).

2.3. Data extraction process and risk of bias assessment

Data extraction and risk of bias (RoB) assessment were also conducted independently and in duplicate. Discrepancies were discussed and, when no consensus was reached, a third reviewer was consulted. Data extracted include general information, study design, sample characteristics, test details (biomarker and cutoff point), reference standard, and results.

RoB was assessed using either the Cochrane Risk of Bias tools for RCT (RoB 2.0) [11], or the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) revised tool [12].

2.4. Assessment of publication bias

Potential publication bias was explored by constructing the Deeks asymmetry graphs and computing the Egger test [13], with the significance level set at 0.05, using metafunnel and metabias commands, respectively, in STATA version 16.

2.5. Data synthesis

We built 2 × 2 tables summarizing true positive (TP), false positive, true negative, and false negative (FN) values to calculate sensitivity and specificity for detecting csPCa. Review Manager (RevMan, version 5.4.1., 2020; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) was used to show the sensitivity and specificity measurements at the study level. Pooled estimates with 95% CIs were performed by bivariate random-effect meta-analyses using the midas command in STATA version 16 [14]. A continuity correction was used in trials that reported zero cells in a 2 × 2 table (eg, when TP or FN is zero). Heterogeneity was assessed by visually analyzing forest plots and through the Higgins I² statistic [15]. Several sources of heterogeneity were anticipated, including the type of diagnostic test, cutoff point, definition of csPCa, and ethnic origin. When reported in studies, the effect using a subgroup analysis was explored.

2.6. Certainty of evidence assessment

An assessment of the certainty of evidence per outcome was performed for tests included in the meta-analysis, based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. We developed evidence profiles and rated the overall certainty of evidence as high, moderate, low, or very low [16].

3. Evidence synthesis

The results of the literature search and study selection process are shown in Figure 1. Our search identified 2954 references, of which 336 studies were selected for full text assessment. Three of these could not be retrieved [17–19]. Sixty-five studies [20–84], reported in 69 articles [20–88], finally fulfilled the pre-established selection criteria. The list of studies excluded at the full-text level and the reasons for exclusion are provided in Supplementary Table 2.
| Study         | N | N PCa | Clinically significant PCa | Age | Inclusion criteria                                      | Exclusion criteria                                           | Ethnicity       | PSA (ng/ml)                  |
|--------------|---|-------|-----------------------------|-----|--------------------------------------------------------|-------------------------------------------------------------|----------------|-----------------------------|
| Abrate (2015) | 142| 65    | 44                          | 65.40 | 7.52<sup>*</sup> NR                                    | 1. >45 yr  
2. With or without suspect DRE  
3. Obese (BMI ≥30) | NR | 6.80 (4.40–10.10)            |
| Babajide (2021) | 293| 158   | 52                          | NR   | NR                                                    | 1. Background of PCa  
2. Treated with 5-alpha reductase inhibitors  
3. Suspicious DRE  
4. PSA >10.00 ng/ml  
5. Previous prostate biopsy | African Americans (100) | NR | 4.32 ± 1.85<sup>†</sup>   |
| Barisiene (2020) | 210| 112   | 40                          | 63   | 7.09<sup>†</sup> NR                                    | 1. >50 yr  
2. Elevated PSA (2.50–10.00 ng/ml)  
3. Negative DRE | NR | 4.60 (4.40–4.71)<sup>†</sup>  |
| Bertok (2020) | 140| 70    | 42                          | 62.15 | NR                                                    | 1. Elevated PSA  
2. TRUS-guided prostate biopsy | NR | 2.00–10.00<sup>‡</sup>  |
| Boegemann (2016) | 769| 347   | 111                         | 59   | 39–65<sup>‡</sup>                                        | 1. Acute or chronic prostatitis  
2. UTI  
3. Treated with 5-alpha reductase inhibitors (previous 6 mo) | NR | 6.80 ± 3.90 (1.00–19.90)<sup>‡</sup> |
| Busetto (2020) | 52 | 17    | 7                           | 64   | 8.70<sup>‡</sup>                                        | 1. Elevated PSA (1.60–8.00 ng/ml)  
2. With or without suspect DRE | NR | 4.40 ± 2.71 (1.00–19.90)  |
| Cao (2018) | 271| 77    | 52                          | 63   | NR                                                    | 1. Biopsy results not available | African Americans (14.4) | NR | 5.40 ± 1.90 (2.00–10.00)  |
| Catalona (2011) | 892| 430   | 139                         | 62.80 | 7.00<sup>‡</sup>                                        | 1. PSA outside 2.00–10.00 ng/ml  
2. Medical treatment known to affect serum PSA levels  
3. Previous interventions such as transurethral resection of the prostate  
4. Acute prostatitis  
5. UTI  
6. Blood collection or biopsy at inappropriate time interval  
7. Previous androgen replacement therapy | NR | 13.27 ± 2.71 (9.95–20.01)<sup>‡</sup> |

(continued on next page)
| Study          | N  | PCa | Clinically significant PCa | Age | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Ethnicity | PSA (ng/ml) |
|---------------|----|-----|---------------------------|-----|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----------|-------------|
| Chiu (2016)   | 569| 62  | 16                        | 66  | 1. Elevated PSA (4.00–10.00 ng/ml) and negative DRE                               | 1. Background of PCa 2. Any suspicious rectal finding 3. Withdrawal therapy or 5-alpha reductase inhibitors |
|               |    |     |                           |     | 2. With or without lower urinary tract symptoms                                  |                                                                                   | Asians    | 6.73 (5.64–8.03) |
|               |    |     |                           |     | 3. Before the prostate biopsy                                                     |                                                                                   |           |             |
|               |    |     |                           |     | 1. TRUS-guided prostate biopsy from 10 to 12 cylinders 2.                         |                                                                                   |           |             |
|               |    |     |                           |     | Elevated PSA (2.00–20.00 ng/ml)                                                  |                                                                                   |           |             |
| Chiu (2019)   | 503| 1149| 115                       | 63  | 1. Timed to biopsy by PSA 4.00–10.00 ng/ml with or without a suspicious DRE or PSA < 4 ng/ml and a suspicious DRE | 1. Acute prostatitis or UTI 2. Treated with 5-alpha reductase inhibitors (previous 3 mo) 3. Previous prostate biopsy 4. Previous transurethral resection of the prostate |
|               |    | 262 | 66                        | 65  | 1. Biopsied with previous PSA and PHI                                              |                                                                                   | Caucasians| 2.00–10.00  |
|               |    | 151 | 66                        |     | 2. Elevated PSA (2.50–10.00 ng/ml)                                               |                                                                                   | Asians    | 2.00–10.00  |
|               |    | 66  | 61–71                     |     | 1. Elevated PSA (<10.00 ng/ml) and negative DRE                                   |                                                                                   |           |             |
|               |    |     |                           |     | and negative DRE                                                                  |                                                                                   |           |             |
| Choi (2020)   | 114| 37  | 28                        | 62.81 | 7.87 | 6.17 (1.92–36.90) |                                                                                   | Caucasians|             |
|               |    |     |                           | 87.8 | 4.20 | 8.50 |                                                                                   |           |             |
| De La Calle (2015) | 561 | 233 | 114                       | 62.10 | 8.30 | 38–87 | 1. Biopsy and blood draw completed                                                | African Americans |             |
|               |    |     |                           |     | 2. Elevated PSA (4.00–10.00 ng/ml)                                               |                                                                                   | Hispanic  |             |
|               |    |     |                           |     | and negative DRE                                                                  |                                                                                   | Hispanic  |             |
|               |    |     |                           |     | 1. Background of PCa                                                              |                                                                                   | Hispanic  |             |
|               |    |     |                           |     | 2. Positive previous prostate biopsy                                               |                                                                                   | Other ethnicities |             |
|               |    |     |                           |     | 1. Elevated PSA (4.00–10.00 ng/ml)                                               |                                                                                   |           |             |
|               |    |     |                           |     | and negative DRE                                                                  |                                                                                   |           |             |
|               |    |     |                           |     | 1. Suspicious DRE                                                                 |                                                                                   |           |             |
|               |    |     |                           |     | 1. Elevated PSA (<10.00 ng/ml) and negative DRE                                   |                                                                                   |           |             |
| Druskin       | 241|     |                           | 65  | 59.3–70.8                                                                         | 1. Elevated PSA (4.00–10.00 ng/ml)                                               | African Americans | 7.00 (4.90–10.20) |
| (2018)        |    |     |                           |     | and negative DRE                                                                  |                                                                                   |           |             |
|               |    |     |                           |     | 1. Suspicious DRE                                                                 |                                                                                   |           |             |
| Falagario     | 256| 153 | 94                        | 66  | 60–70.9                                                                           | 1. Acute prostatitis or UTI 2. Treated with 5-alpha reductase inhibitors (previous 3 mo) 3. Previous prostate biopsy 4. Previous transurethral resection of the prostate |
| (2021)        |    |     |                           |     | and negative DRE                                                                  |                                                                                   | Asians    | 4.00–10.00  |
| Fan (2019)    | 307| 95  | 52                        | 66  | 57.67–74.33                                                                       | 1. Medical treatment known to affect serum PSA levels 2. Acute prostatitis or UTI 3. Invasive treatment for BPH |
| (2019)        |    |     |                           |     | and negative DRE                                                                  |                                                                                   | NR (Spanish) | 6.17 (1.92–36.90) |
| Filella (2014)| 354| 175 | 80                        | 68  | 38–88                                                                             | 1. Elevated PSA < 10.00 ng/ml and negative DRE                                    |           |             |
| Study          | N  | N PCa | Clinically significant PCa | Age | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Ethnicity (%) | PSA (ng/ml) |
|---------------|----|-------|--------------------------|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------|-------------|
| Foj (2020)    | 276| 151   | 80                       | 66.65 | 7.29 | 1. Timed to biopsy by elevated PSA or suspicious DRE                                  | 1. Medical treatment known to affect serum PSA levels                               | NR (Spanish) | 6.14 (0.50–36.90) |
| Foley (2016)  | 250| 112   | 77                       | 63.87 | NR  | 1. Availability of a biobank serum sample prior to biopsy                             | 1. Invasive treatment for BPH                                                       | NR           | 6.40 (0.50–1400.00) |
| Furuya (2017) | 50 | 33    | 21                       | 68.50 | NR  | 1. Elevated PSA (2.00–10.0 ng/ml)                                                     | 1. Bacterial prostatitis (previous 3 mo)                                           | NR           | 6.92 ± 1.69 (3.74–9.96) |
| Guazzoni      | 268| 107   | 52                       | 63.30 | 8.20 | 1. Elevated PSA (2.00–10.0 ng/ml)                                                     | 1. Acute or chronic bacterial prostatitis                                           | NR           | 5.70 (2.00–9.90) |
| Haese (2019)  | 1039| 916   | 521                      | 64   | NR  | 60–70                                  | 1. Background of PCa 2. Medical treatment known to affect serum PSA levels (previous 6 mo) | NR           | 6.20 (4.60–9.40) |
| Hansen (2013) | 692| 318   | 137                      | 65   | NR  | 60–70                                  | 1. Background of PCa 2. Medical treatment known to affect serum PSA levels (previous 6 months) | NR           | 5.20 (4.30–7.20) |
| Hsieh (2020)  | 102| 39    | 24                       | 65.50 | NR  | 60–70                                  | 1. Background of PCa 2. Medical treatment known to affect serum PSA levels (previous 6 months) | Asians       | 7.78 (6.12–11.80) |
| Kim (2020)    | 545| 349   | 258                      | NR   | NR  | 1. Elevated PSA (≥2.00 ng/ml)                                                         | 1. Previous prostate biopsy                                                       | NR           | 8.00 (6.00–13.00) |
| Kotova (2020) | 128| 61    | 33                       | 66   | NR  | 44–88                                  | 1. Previous treatment with antiandrogens                                           | NR           | 8 (2.06–76.80) |
| Lazzeri (2013)| 646| 264   | 139                      | 64.20 | 7.50 | 1. Elevated PSA (≥2.00 ng/ml)                                                         | 1. Bacterial prostatitis (previous 3 mo)                                           | Caucasians   | 5.80 (4.30–7.70) |

(continued on next page)
| Study            | N  | N PCa | Clinically significant PCa | Age | Inclusion criteria                                                                 | Exclusion criteria                                                                 |
|------------------|----|-------|-----------------------------|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Lazzeri (2016)   | 262| 136   | 106                         | 67.30| 1. >45 yr 2. PSA 4.00–10.00 ng/ml 3. With or without suspect DRE 4. With or without previous negative biopsy | 1. Bacterial prostatitis 2. Previous prostate endoscopic surgery 3. Treated with dutasteride or finasteride 4. Chronic renal failure 5. Marked alterations in blood proteins (normal plasma range: 6–8 g/d), hemophiliacs, or with multiple previous transfusions |
| Leyten (2015)    | 358| 157   | 93                          | 65  | 1. Background of PCa 2. Medical treatment known to affect serum PSA levels (previous 6 mo) 3. Prostate biopsies (previous 3 mo) 4. Invasive treatment for BPH (previous 6 mo) |
| Loeb (2015)      | 658| 324   | 160                         | 63  | 1. >50 yr 2. PSA 2.00–10.00 ng/ml 3. Negative DRE                                  | NR                                                                                 |
| Loeb (2017)      | 728| 334   | 118                         | 62.80| 1. Elevated PSA (2.00–10.00 ng/ml) and negative DRE 2. Prostate biopsy with ≥6 casts <6 mo after blood collection | 1. Prostate surgery 2. UTI 3. Medical treatment known to affect serum PSA levels (eg, 5-alpha reductase inhibitors) |
| McKiernan (2016) | 255| 120   | 78                          | 62  | 1. >50 yr 2. Timed to biopsy (initial or repeated) by elevated PSA (2.00–20.00 ng/ml) or suspicious DRE | 1. Invasive treatment for BPH (previous 6 mo) 2. Medical treatment known to affect serum PSA levels (previous 3–6 mo) |
|                  | 519| 250   | 148                         | 63  | 1. History of invasive treatment for benign prostate disease in the previous 6 mo 2. Medical treatment known to affect serum PSA levels (previous 3–6 mo) | 1. History of invasive treatment for benign prostate disease in the previous 6 mo 2. Medical treatment known to affect serum PSA levels (previous 3–6 mo) |

**Note:** PSA, prostate-specific antigen; DRE, digital rectal examination; NR, not reported.
| Study                  | N  | N PCa | Clinically significant PCa | Age       | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Ethnicity | PSA (ng/ml) |
|-----------------------|----|-------|----------------------------|-----------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------|-------------|
| Mareini (2014)        | 275| 86    | 26                         | 65.40     | 1. Elevated PSA (2.00–10.00 ng/ml)                                                 | 1. Acute or chronic prostatitis 2. Surgery or previous prostate biopsy 3. Medical treatment known to affect serum PSA levels | NR        | 4.50        |
| Morote (2016)         | 183| 68    | 45                         | 67        | 1. <75 yr                                                                           | 1. Serious diseases such as metastatic cancers, severe cardiovascular disease, or dementia | NR (Spanish) | 5.10        |
| Mortezavi (2021)      | 532| 291   | 194                        | 64        | 1. 45–75 yr                                                                         | 1. Participación en un ensayo para enfermedad de la próstata 2. Biopsia de próstata (previous 6 mo) y exposición previa a la prueba de PCA3 3 Previous prostate biopsy | NR        | 6.10        |
| Na (2014)             | 636| 274   | 158                        | 68        | 1. PSA >4.00 ng/ml 2. Ratio of fPSA <0.16 3. Density of PSA >0.15 4. Presence of prostate nodules detected by DRE or TRUS | NR                                                                                           | Asians    | 7.20        |
| Na (2017)             | 1538| 618   | 488                        | 66.95     | 1. PSA >10.00 ng/ml 2. PSA >4.00 ng after 2–3 mo 3. XfPSA <0.16 when patients had a total level of total PSA >4.00 ng/ml 4. Suspicious lesions detected on DRE or TRUS with any PSA level | NR                                                                                           | Asians    | 11.42       |
| Nordström (2015)      | 531| 271   | 134                        | NR        | 1. Elevated PSA (3.00–15.00 ng/ml)                                                 | NR                                                                                           | NR        | 4.2 ± 2.3   |
| Nordström (2021)      | 1544| 509   | 213                        | 64.20     | 1. Elevated PSA (>3.00 ng/ml)                                                      | NR                                                                                           | NR        |             |
| Nygård (2016)         | 124| 70    | 49                         | 65.10*    | 1. Elevated PSA (3.00–25.00 ng/ml)                                                 | NR                                                                                           | NR        | 7.20        |
| O'Malley (2017)       | 718| 518   | 194                        | 63        | 1. Elevated PSA and/or in progression, <15% free PSA 2. Family history of PCa 3. Previous atypical small acinar proliferation or high-grade intraepithelial neoplasia of the prostate or suspicious for DRE | NR                                                                                           | African Americans 10 Non-African Americans 90 | 5.10        |
| Park (2018)           | 246| 125   | 29                         | 69.60     | 1. Elevated PSA (>3.50 ng/ml) and negative DRE                                     | 1. Background of PCa or other urogenital cancers 2. Previous endoscopic surgery of the prostate, acute or chronic prostatitis (previous 3 mo), or untreated UTI 3. Previous prostate biopsy | NR        | 7.80        |

(continued on next page)
| Study                  | N  | PCa | Clinically significant PCa | Age | Inclusion criteria                   | Exclusion criteria                                               | Ethnicity                  | PSA (ng/ml)            |
|-----------------------|----|-----|----------------------------|-----|--------------------------------------|------------------------------------------------------------------|---------------------------|------------------------|
|                       |    |     |                            |     |                                      |                                                                  |                           |                        |
| Punnen (2018) [34]    | 366| 215 | ISUP grade ≥2              | NR  | 1. Prostate biopsy with ≥10 nuclei  | 1. Background of PCa 2. DRE within 96 h of phlebotomy 3. Invasive treatment of the prostate 4. Treated with 5-alpha reductase inhibitors (previous 3 mo) | African Americans (56) Caucasians (40) Other ethnicities (4) |                        |
|                       |    |     |                            | NR  |                                      |                                                                  |                           |                        |
|                       |    |     |                            | NR  |                                      |                                                                  |                           |                        |
|                       |    |     |                            | NR  |                                      |                                                                  |                           |                        |
| Roumigié (2020) [49]  | 117| 64  | ISUP grade ≥2              | 65  | 1. Elevated PSA or suspicious DRE   | NR                                                               | NR                       | 7.00 (6.50–8.00)        |
|                       |    |     |                            |     |                                      |                                                                  |                           |                        |
| Ruffion (2013) [50]   | 594| 276 | Gleason ≥7                 | 63  | 1. >55 yr 2. Informed consent       | 1. PSA >20.00 ng/ml 2. Previous prostate biopsy 3. Medical treatment known to affect serum PSA levels 4. Previous prostate surgery for BPH 5. <55 yr | French                    | 5.90 (4.70–7.90)        |
|                       |    |     |                            |     |                                      |                                                                  |                           |                        |
| Ruffion (2014) [51]   | 595| 274 | Gleason ≥7                 | 63  | 1. Elevated PSA or suspicious DRE or family history of PCa | 1. PSA >20.00 ng/ml 2. >T2b 3. Previous surgery 4. Treated with 5-alpha reductase inhibitors | NR                       | 5.90 (4.70–7.90)        |
|                       |    |     |                            |     |                                      |                                                                  |                           |                        |
| Sanchis-Bonet (2018)  [48] | 197| 85  | Gleason ≥7                 | 68  | 1. Elevated PSA (2.00–20.00 ng/ml) or suspicious DRE 2. >45 yr | 1. Treated with 5-alpha reductase inhibitors (previous 6 mo) 2. UUT or urinary tract manipulation (previous 3 mo) | NR (Spanish)             | 5.80 (4.40–7.80)        |
|                       |    |     |                            |     |                                      |                                                                  |                           |                        |
| Sanda (2017) [35]     | 516| 254 | Gleason ≥7                 | 62  | 1. Scheduled to biopsy for the first time 2. Informed consent 3. Posturinary samples after rectal examination (DRE) prior to biopsy | 1. Background of PCa 2. Previous prostate biopsy 3. Previous prostatectomy 4. Other cancer diagnosis 5. Inability to provide a post-DRE urine sample | Caucasians (81) African Americans (10) Asians (4) Other ethnicities (5) | 4.80 (0.30–460.40)       |
|                       |    |     |                            |     |                                      |                                                                  |                           |                        |
|                       |    |     |                            |     |                                      |                                                                  |                           |                        |
|                       | 561| 264 | 148                        | 62  | 27–86                                |                                                                  | Caucasians (79) African Americans (14) Asians (2) Other ethnicities (5) | 5.30 (0.20–274.90)       |
| Study              | N PCa | N Clinically significant PCa | Age | Inclusion criteria | Exclusion criteria | Ethnicity (%) | PSA (ng/ml) |
|-------------------|-------|-----------------------------|-----|-------------------|-------------------|---------------|-------------|
| Schulze (2020)    | 122   | 76 50                       | 65.41 | NR | 41–81 | 1. Timed to biopsy due to elevated PSA or in progression or suspicious DRE | NR | 9.55 (1.91–82.90) |
| Seisen (2015)     | 138   | 62 39                       | NR | NR | NR | 1. Elevated PSA (4.00–20.00 ng/ml) or suspicious DRE | NR | 7.80 (0.70–19.80) |
| Shore (2019)      | 80    | 27 21                       | 67 62–72 | NR | 1. Scheduled to biopsy | NR | Caucasians (90) African Americans (9) Other ethnicities (1) |
| Steuber (2022)    | 362   | NR 103                       | 64 | NR | 7.79 | 1. Elevated PSA (2.00–10.00 ng/ml) 2. Suspicious DRE (≥35 cm³) | NR | 6.12 (4.61–7.65) |
| Tan (2017)        | 157   | 30 19                       | 65.40 | 6.46 | NR | 1. 50–75 yr 2. Suspicious DRE 3. Elevated PSA (4.00–10.00 ng/ml) | NR | Asians (99) Other ethnicities (1) |
| Tomlins (2016)    | 711   | NR NR                       | NR | NR | NR | 1. Scheduled for biopsy and urine evaluation T2; EKG and PCA3 1. Pretreatment for PCa 2. Surgical treatment of the prostate within 6 mo prior to urine collection 3. Prostate biopsy (previous 6 wk) | NR | NR |
| Tomlins (2017)    | 1225  | 518 224                     | 64 | 58–70 | 1. Scheduled for biopsy | NR | Caucasians (73) Non-Caucasians (27) |
| Tosoian (2017)    | 135   | 75 46                       | 64.30 | NR | 58.90–70.10 | 1. Elevated PSA, PSA kinetics, and/or abnormal rectal examination | NR | African Americans (36) |
| Tosoian (2017)    | 118   | 47 35                       | NR | NR | 58.90–71.20 | 1. Elevated PSA and PSA kinetics 1. Suspicious DRE | NR | African Americans (10) |
| Tosoian (2021)    | 548   | 262 146                     | NR | NR | 56–67 | 1. Scheduled for biopsy | NR | African Americans (4) |
| Tosoian (2021)    | 516   | 253 156                     | 61 | 56–67 | NR | NR | African Americans (10) |

(continued on next page)
Table 2 (continued)

| Study              | N   | N PCa | Clinically significant PCa | Age | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Ethnicity                  | PSA (ng/ml) |
|--------------------|-----|-------|----------------------------|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|----------------------------|-------------|
|                     |     |       | N                          | Definition                  | Mean/median SD/IQR Range                                                                 |                                                                                     |                           |             |
| Van Neste (2016)   | 386 | 181   | 90                         | Gleason ≥7                  | 64.90 60–70                                                                 | 1. Timed to biopsy (initial or repeated) by elevated PSA (3.00 ng/ml), suspicious DRE, or family history of PCa | African Americans (7.5) | 4.50 (3.10–6.00) |
| Wang (2017)        | 519 | 212   | 109                        | NR                          | 64.70 60–70                                                                 | 1. Elevated PSA (≥4.00 ng/ml) or suspicious DRE 2. Recent instrumentation or catheterization of the urethra 3. Treated with finasteride or hormonal treatment | NR                         | 7.30 (5.20–10.90) |
| Wei (2014)         | 562 | 264   | 148                        | Gleason ≥7                  | 62 8 NR                                                                 | 1. Timed to biopsy (initial) 2. Elevated PSA or in progression, <15% free PSA3 3. Family history of PCa 4. Previous atypical small acinar proliferation or suspicious or high-grade DRE prostate intraepithelial neoplasia | Caucasians (79)  African Americans (14) Other ethnicities (7) | 7.00 ± 15.00 |
| Woo (2020)         | 297 | 67    | 26                         | NR                          | 64 8                                                                 | 1. Scheduled to biopsy by elevated PSA or suspicious DRE 2. Participation in a trial for prostate disease 3. Previous prostate surgery 4. Previous prostate biopsy (previous 6 mo) 5. Previous PCA3 | NR                         | 10.00 ± 10.00 |
| Wu (2019)          | 165 | 107   | 83                         | NR                          | 66.50 47–82                                                                 | 1. Lack of essential clinical data: age, PSA, % fPSA (free PSA divided by PSA), p2PSA or PV | Caucasians (82)  African Americans (11) Other ethnicities (7) | 8.60 (1.50–39.20) |
| Wysock (2020)      | 635 | 272   | 207                        | Gleason ≥7                  | 69 61–76 NR                                                                 | 1. Elevated PSA 1. Previous biopsy | Asians | 13.30 (7.60–31.50) |
|                    | 1045| 449   | 347                        | NR                          | 68 62–74                                                                 | NR                                                                                     | NR                         | 11.70 (7.00–25.70) |
|                    | 50  | 26    | 22                         | ISUP grade ≥2               | 63 52–74 NR                                                                 | 1. Elevated PSA 1. Previous biopsy | Caucasians (74)  African Americans (14) | 5.25 (3.80–8.13) |
Table 2 (continued)

| Study          | N   | N PCa | Clinically significant PCa | Age | Inclusion criteria | Exclusion criteria | Ethnicity (%) | PSA (ng/ml) |
|----------------|-----|-------|---------------------------|-----|-------------------|-------------------|---------------|-------------|
|                |     |       |                           |     |                   |                   |               |             |
| Yu (2016) [83] | 261 | 67    | Gleason 4 + 3 and ≥8      | 67  | NR 25–91          | 1. Elevated PSA (>4 ng/ml)  
2. % ratio of fPSA <0.16  
3. PSAD >0.15  
4. Presence of prostate nodules detected by DRE or TRUS | NR | Hispanic (4) Other ethnecities (8) |
| Zappala (2017) [44] | 1012 | 470 | 231 | 66 | NR 61–72 | 1. 10-cylinder TRUS-guided prostate biopsy  
2. DRE within 96 h prior to phlebotomy 3. Treated with 5-alpha reductase inhibitors (previous 6 mo)  
4. Invasive urological procedures that can affect serum PSA levels (previous 6 mo) | Caucasians (87) African Americans (8.5) Hispanic (4) Other ethnecities (0.5) | NR | 10.67 (0.41–2006.25) |

BMI = body mass index; BPH = benign prostatic hyperplasia; DRE = digital rectal examination; fPSA = free prostate-specific antigen; IQR = interquartile range; ISUP = International Society of Urological Pathology; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; NR = not reported; p2PSA = (-2) pro–prostate-specific antigen; PCa = prostate cancer; PCA3 = prostate cancer antigen 3; PHI = Prostate Health Index; PSA = prostate-specific antigen; PSAD = PSA density; PV = prostate volume; T2: ERG = gene fusion between transmembrane serine protease 2 (TMPRSS2) and the transcription factor ERG; SD = standard deviation; TRUS = transrectal ultrasound; UTI = urinary tract infection.

a Own calculation.
b Median (interquartile range).
c Mean ± SD.
d Range.
e Mean ± SD (range).
3.1 Characteristics of included studies

The main characteristics of the selected studies are summarized in Tables 1 and 2.

Only diagnostic performance studies with an observational design were included: 43 prospective, 13 retrospective, two ambispective, two with a retrospective analysis of prospectively collected data, three case-control studies, and two nested case-control studies. Ten studies contained two [25,31,35,37,41,55,78,81,89] or three [40] different populations and data were treated as separate studies.

The diagnostic tests analyzed were Prostate Health Index (PHI), a mathematical combination of free and total PSA and the [-2]pro-PSA isoform (Beckman Coulter, Inc.), in 37 studies [20,22,24,25,29,30,32,38,43,46–48,52,54,58–62,64,65,67,72–77,80,83,87,89–94]; Progensa prostate cancer antigen 3 (PCA3; Gen-Probe Incorporated) in 12 studies [23,28,41,50–53,55,66,81,82,95]; PHI density in five studies [20,26,38,59,90]; SelectMDx in five studies [36,42,49,57,78]; 4K score test (OPKO Health, Inc.) in four studies [27,34,42,44]; MyProstateScore (MLabs) in three studies [37,40,81]; TMPRSS2:ERG in two studies [37,40]; Stockholm 3 in two studies [69,70]; ExoDx Prostate IntelliScore in one study [31]; and Proclarix test in one study [21]. All of these compared the performance of the tests with prostate biopsy (Table 1).

Included studies involved 34,287 men, 14,792 (43.14%) diagnosed with PCa and 7,905 (23.06%) with csPCa. Not all studies included PSA-selected patients [23,25,78,84,87,27,34–37,40,53,74]. The selection criteria and main characteristics of participants are summarized in Table 2.

3.2 RoB in included studies

The RoB assessment is summarized in Figures 2A and 2B.

Out of the 65 studies identified, only one was classified as having a low RoB in all domains. In the remaining studies, the most common methodological concerns involved the domains for the patient selection (19 studies at a high RoB), the index test domain (47 studies and the training cohorts in the studies by Sanda et al. [35], Tosoian et al. [40], and Woo et al. [81] at a high RoB), and the flow and timing (22 studies at a high RoB). The detailed judgments for each domain are available in Supplementary Table 3.

3.3 Quality of evidence

The overall quality of the evidence for PHI and SelectMDx was considered low (Supplementary Tables 4 and 5 provide the evidence profiles, respectively).

3.4 Synthesis of results

Diagnostic accuracy results of selected studies are listed in Supplementary Table 6.

Out of the 65 included studies, only 21 remained for a quantitative analysis for PHI and SelectMDx [36,42,49,57,78]. The results of all meta-analyses and subgroups analyses are available in Supplementary Table 7.

3.4.1 Urine tests

3.4.1.1 Progensa PCA3. Cutoff points ranged from 5 to 35. For the cutoff point 15, the test yielded sensitivity ranging between 93% and 99%, and specificity of 37%. The cutoff point 20 showed sensitivity between 89% and 99%, and specificity of 51%. Finally, at the cutoff point 35, the sensitivity ranged between 62% and 71%, while the specificity increased to 59–66%. The AUC ranged from 0.59 to 0.83.

3.4.1.2 SelectMDx test. Pooled sensitivity and specificity were 84% (95% CI: 71–92%; I² = 79.7%; k = 5; n = 1957) and 49% (95% CI: 26–72%; I² = 93.9%; k = 5; n = 1957), respectively (see Fig. 3A). Pooled AUC was 0.79 (95% CI: 0.75–0.82; k = 5; n = 1957). Figure 3B shows the hierarchic summary ROC plot with 95% CI area and summary point.

3.4.1.3 TMPRSS2:ERG. Reported AUC ranged from 0.64 to 0.75. No data related to the sensitivity and specificity of TMPRSS2:ERG was reported.

3.4.1.4 MyProstateScore. With a cutoff point of ≥10, sensitivity ranged between 96.6% and 97.4%, and specificity between 28.6% and 34.6%. For cutoff points >10, the sensitivity ranged from 95.5% to 96.7%, while the specificity remains between 29% and 33.3% [40]. Reported AUC ranged between 0.60 and 0.80 [37,81].

3.4.1.5 ExoDx Prostate IntelliScore. The sensitivity and specificity ranged from 91.8% to 97.4% and from 35.7% to 37.25%, respectively. The AUC ranged from 0.73 to 0.78 [31].
3.4.2. Blood tests
3.4.2.1. Prostate Health Index. Only 16 out of 37 selected studies on PHI were included in meta-analyses. Cutoff points ranged from 15 to 55. Subgroup analyses could be conducted by cutoff point and ethnic origin.

3.4.2.1.1. Cutoff point 15–20. Pooled sensitivity and specificity were 99% (95% CI: 97–100%; $I^2 = 76.26%$; $k = 4$; $n = 2994$) and 14% (95% CI: 9–19%; $I^2 = 87.03%$; $k = 4$; $n = 2994$), respectively (Fig. 4A). Pooled AUC was 0.53 (95% CI: 0.49–0.57; $k = 4$; $n = 2994$; Fig. 4B).

PHI showed higher sensitivity and specificity in patients of Asian origin (sensitivity = 100%; 95% CI: 99–100%; specificity = 13%; 95% CI: 8–19%; $k = 3$; $n = 1428$)

3.4.2.1.2. Cutoff point 20–25. Pooled sensitivity and specificity were 96% (95% CI: 94–98%; $I^2 = 73.26%$; $k = 7$; $n = 6698$) and 24% (95% CI: 18–30%; $I^2 = 95.57%$; $k = 7$; $n = 6698$), respectively (Fig. 4C). The AUC obtained was 0.71 (95% CI: 0.67–0.75; $k = 7$; $n = 6698$; Fig. 4D).

Again, higher accuracy was obtained in Asian patients (sensitivity = 99%; 95% CI: 97–100%; specificity = 30%; 95% CI: 20–39%; $k = 3$; $n = 2744$) than in European patients (sensitivity = 95%; 95% CI: 93–97%; specificity = 21%; 95% CI: 16–26%; $k = 4$; $n = 3954$).

3.4.2.1.3. Cutoff point 25–30. Pooled sensitivity and specificity were 95% (95% CI: 89–98%; $I^2 = 85.72%$; $k = 9$; $n = 6321$) and 33% (95% CI: 23–45%; $I^2 = 98.27%$; $k = 9$; $n = 6321$), respectively (Fig. 4E). The derived AUC showed an accuracy of 0.76 (95% CI: 0.72–0.79; $k = 9$; $n = 6321$; Fig. 4F).

Sensitivity was higher in Asian patients (98%; 95% CI: 94–100%; $k = 5$; $n = 3680$) than in African-American (94%; 95% CI: 83–100%; $k = 1$; $n = 293$) and European (93%; 95% CI: 87–100%; $k = 4$; $n = 2348$) patients. Specificity was higher in Asian patients (41%; 95% CI: 25–58%; $k = 5$; $n = 3680$), followed by European (30%; 95% CI: 15–44%; $k = 4$; $n = 2348$) and African-American patients (15%; 95% CI: 5–34%; $k = 1$; $n = 293$) patients.

3.4.2.1.4. Cutoff point 30–35. Pooled sensitivity and specificity were 87% (95% CI: 81–91%; $I^2 = 88.94%$; $k = 9$; $n = 5964$) and 49% (95% CI: 41–58%; $I^2 = 95.53%$; $k = 9$; $n = 5964$), respectively. Pooled AUC was 0.76 (95% CI: 0.72–0.80; $k = 9$; $n = 5964$).

Sensitivity was higher in Asian patients (98%; 95% CI: 94–100%; $k = 5$; $n = 3680$) than in African-American (94%; 95% CI: 83–100%; $k = 1$; $n = 293$) and European (93%; 95% CI: 87–100%; $k = 4$; $n = 2348$) patients. Specificity was higher in Asian patients (58%; 95% CI: 46–70%; $k = 5$; $n = 3680$), followed by European (49%; 95% CI: 41–57%; $k = 5$; $n = 2877$) and African-American (26%; 95% CI: 11–41%; $k = 1$; $n = 293$) patients.

3.4.2.1.5. Cutoff point 35–40. Pooled sensitivity and specificity were 79% (95% CI: 66–88%; $I^2 = 83.13%$; $k = 5$; $n = 1164$) and 56% (95% CI: 48–64%; $I^2 = 81.78%$; $k = 5$; $n = 1164$), respectively. The AUC obtained was 0.69 (95% CI: 0.64–0.72; $k = 0$; $n = 5964$). Despite the high level of heterogeneity between studies, no differences were observed between Asian and European patients ($p = 0.14$).

3.4.2.1.6. Cutoff point 55. The sensitivity was 42% (95% CI: 32–53%; $I^2 = 73.61%$; $k = 3$; $n = 2028$), while the specificity was 87% (95% CI: 72–95%; $I^2 = 98.28%$; $k = 3$; $n = 2028$).
Pooled AUC showed an accuracy of 0.60 (95% CI: 0.56–0.64; \( k = 3; n = 2028 \)). No subgroup analysis could be performed by ethnic origin.

3.4.2.2. PHI density. Among the studies included for this test [20,26,38,59,90], the range for sensitivity was 90–97% and that for specificity was 32–39%.

3.4.2.3. 4Kscore test. Four studies provided data on this test [27,34,42,44]. Assuming a risk of suffering csPCa of \( \geq7.5\%\), the sensitivity was 95.5% and the specificity was 32.1%, whereas when a risk of 12% was assumed, the sensitivity decreased to 90.1% and the specificity increased to 53.5%. The AUC ranged from 0.72 to 0.87.

3.4.2.4. Stockholm3 test. Studies identified do not report sensitivity and specificity data [69,70]. The AUC ranged from 0.77 to 0.86.

3.4.2.5. Proclarix. The only included study obtained sensitivity and specificity of 91% and 22%, respectively [21].

3.5. Publication bias

No publication bias was identified, except in the PHI analysis with a cutoff point between 30 and 35 (\( p = 0.02 \)). The results of the Egger tests and Deeks asymmetry graphs are available in Supplementary Table 7 and Supplementary Figure 1, respectively.

3.6. Discussion

The assessment of molecular biomarkers for the detection of csPCa is based on the data derived from 65 studies...
\( N = 34,287 \), which evaluate their diagnostic accuracy in a population undergoing initial biopsy for suspected csPCa due to high PSA levels, family history, abnormal DRE, or altered multiparametric MRI. Quality of evidence for the tests included in the meta-analysis (PHI and SelectMDx) has been rated as low.

Included studies present high variability in terms of the assessed tests. Most (37) assessed the performance of the PHI [20,22,24,25,29,30,32,38,43,46–48,52,54,58–62,64,65,67,72–77,80,83,87,89–94], although only 16 of them could be included in the meta-analysis. Other blood tests assessed were PHI density [20,26,38,59,90], 4Kscore test [27,34,42,44], Stockholm3 test [69,70], and Proclarix test [21]. The diagnostic test based on the analysis of urine samples assessed by the highest number of studies was Progensa PCA3 [23,28,41,50–53,55,66,81,82,95]. Other urine tests assessed were SelectMDx [36,42,49,57,78], MyProstateScore [33,35,37,40,81], TMPRSS2:ERG [37,40], and ExoDx Prostate Intelliscore [31].

Approximately 77% of biopsies performed in men included in this SR did not yield a positive csPCa result. Furthermore, a 20% received a diagnosis of iPCa, placing them at risk of overdiagnosis, biopsy-related complications, and wasted health care resources, evidencing the need for better risk stratification.
Results of the assessed tests are measured on a continuous scale so that their behavior depends on where the cutoff point is set. However, information on established cutoff points was not provided in 25 of the included studies [22,27–32,34,37,38,41,46,48,55,58,59,62,69,75,76,80–82,87,89,91,93,94], and variability in terms of selected cutoffs is present among studies assessing the same test. Since the optimal 4Kscore, PCA3, and PHI cutoff points for the diagnosis of csPCa are not established, a comparison of diagnostic accuracy at different cutoff points was performed.

The results indicate that four analyzed tests (two urine tests and two blood tests) show an ability to identify ≥95% patients with csPCa: Progensa PCA3, with cutoff point 15; My-Prostate Score, using a cutoff point of >10; PHI, with any cutoff point between 15 and 30; and 4Kscore test, assuming a risk of csPCa of ≥7.5%. Using these tests and cutoff points, the ability to prevent unnecessary biopsies ranged between 14% and 37% [22,24,25,28–30,40,42,47,51,64,65,67,72,73,77] which shows that these could be useful as a non-invasive method of supporting the decision on whether or not the first prostate biopsy is necessary and, consequently, reducing the total number of unnecessary biopsies. However, it should be taken into account that only the results related to PHI are pooled effect estimates. The biomarker-based tests considered in this SR (particularly, PHI) would be included with triaging purposes in the diagnostic pathway for patients with a high clinical suspicion of csPCa but negative MRI results, in order to prevent unnecessary biopsies.

Of the nine SRs on biomarker-based tests for the management of PCa published to date to the best of our knowledge [62,96–103], only two focused on evaluating the use of these tests in discerning iPca from csPCa and, consequently, in improving the decision-making process for first biopsies and treatment planning. Nevertheless, neither of them analyzes the available scientific evidence for all available tests, but rather for specific tests. Russo et al. [96] obtained for PHI and 4Kscore tests, sensitivity for the detection of csPCa of 93% and 87%, respectively, and specificity of 34% and 61%, respectively. Zappala et al. [101] evaluated the predictive precision of 4Kscore to discriminate between patients with and without csPCa, obtaining a pooled estimate for AUC of 0.80. Our results are consistent with these previous results.

One aspect to consider is the difference in test accuracy depending on the ethnic origin of patients. The evidence has shown possible improved performance of these tests in Asian populations, followed by Caucasian and African-American men. Confirmation of this finding would support the need for research on the best cutoff points based on patient ethnicity.

Available evidence exclusively consists of studies that evaluate the diagnostic validity of tests. However, using new tests with evidence of diagnostic utility does not directly imply improving decisions related to the diagnosis and treatment of PCa. Therefore, further research is needed to determine what effect the implementation of these tests would have on clinical decision making and patient-important health outcomes (eg, complications, recurrence-free survival, cancer survival, morbidity, and quality of life).

The main limitation of the present review is the methodological differences among studies, mainly the diversity or the lack of information about cutoff values. Moreover, a subgroup analysis to explore this issue could not always be performed. Another potential limitation is the possibility that some studies have not been included because those are not written in English or Spanish or because those are not indexed in the consulted databases. However, to the best of our knowledge, our SR is the most extensive review carried out to date on the effectiveness of the incorporation of tests, based on biomarkers in samples of blood or urine, for the identification of patients at high risk of csPCa. Methodologically, the SR benefits from rigorous methods following the fundamental principles of transparency and replicability; a comprehensive search, a peer selection, data extraction, and RoB assessment; and an assessment of the certainty of evidence on the basis of a structured and explicit approach.

4. Conclusions

Our findings indicate that PHI has high diagnostic accuracy for csPCa detection, and its incorporation in the diagnostic pathway could reduce unnecessary biopsies. However, there is a lack of evidence on the effects on patient consequences, supporting the need for well-conducted test-treatment RCTs in which investigators allocate patients to receive a PHI test or a control diagnostic approach (no test), and measure patient-important outcomes. Based on the pooled sensitivity estimate for SelectDMx, it is possible that the use of this test for the identification of patients with csPCa is not the best option. Finally, according to the limited available evidence, it is not possible to reach a clear conclusion on the other tests evaluated.

Author contributions: Tasmania del Pino-Sedeño 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.

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References

[1] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J Clin 2021;71:209–49.
[2] Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends—an update. Cancer Epidemiol Biomarkers Prev 2016;25:16–27.
[3] Bell KJ, Del Mar C, Wright G, Dickinson J, Glasziou P. Prevalence of incidental prostate cancer: a systematic review of autopsy studies. Int J Cancer 2015;137:1749–57.
[4] Ferlay J, Ervik M, Lam F, et al. Global cancer observatory: cancer today. Lyon, France: International Agency for Research on Cancer; 2020. p. 419.
[5] National Cancer Institute. SEER cancer stat facts. Bethesda, MD: National Institutes of Health; 2019. https://seer.cancer.gov/statfacts/html/mulmy.html.
[6] Fenton J, Weyrich M, Durbin S, Liu Y, Bang H, Melnikow J. Prostate-specific antigen-based screening for prostate cancer: evidence report and a systematic review for the U.S. Preventive Services Task Force. JAMA 2018;319:1914–31.
[7] Mottet N, Bellmunt J, Briers E, et al. EAU-ENAM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer. 2021.
[8] Loeb S, Dani H. Whom to biopsy: prediagnostic risk stratification with biomarkers, nomograms, and risk calculators. Urol Clin North Am 2017;44:517–24.
[9] Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. Cochrane Collaboration; 2011.
[10] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
[11] Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Br Med J 2019;366:i4898.
[12] Whiting PF, Rutjes AWS, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–36.
[13] Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 2005;58:882–93.
[14] Dwamena B. MIDAS: Sta ta module for meta-analytical integration of diagnostic test accuracy studies. Statistical Software Components 2007.
[15] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Br Med J 2003;327:557–60.
[16] Schünemann HJ, Mustafa RA, Brozek J, et al. GRADE guidelines: 22. The GRADE approach for tests and strategies—from test accuracy to patient-important outcomes and recommendations. J Clin Epidemiol 2019;111:69–82.
[17] Parekh D, Punnen S, Sjoberg D, et al. A multi-institutional prospective trial in the USA confirms that the 4Kscore accurately identifies men with high-grade prostate cancer. Eur Urol 2015;68:464–70.
[18] Bollito E, De Luca S, Ciciliano M, et al. Prostate cancer gene 3 urine assay cutoff in diagnosis of prostate cancer: a validation study on an Italian patient population undergoing first and repeat biopsy. Anal Quant Cytol Histol 2012;34:96–104.
[19] Wennmiller J, Neumann T, Alperowitz S, et al. Age-adapted prostate cancer gene 3 score interpretation—suggestions for clinical use. Clin Lab 2020;66.
[20] Schulze A, Christoph F, Sachs M, et al. Use of the Prostate Health Index and density in 3 outpatient centers to avoid unnecessary prostate biopsies. Urol Int 2020;104:181–6.
[21] Steuber T, Heidegger I, Kafka M, et al. PROPOSe: a real-life prospective study of ProclariX, a novel blood-based test to support challenging biopsy decision-making in prostate cancer. Eur Urol Oncol 2022;5:321–7.
[22] Babajide R, Carbunaru S, Nettey OS, et al. Performance of Prostate Health Index in biopsy naive black men. J Urol 2021;205:718–24.
[23] Lee CH, Ninh HY, Handly BC, Wagner EA, Meng QH. Combination of prostate cancer antigen 3 and prostate-specific antigen improves diagnostic accuracy in men at risk of prostate cancer. Arch Pathol Lab Med 2018;142:1106–12.
[24] Catalana WJ, Partin AW, Sanda MG, et al. A multi-center study of [–2]pro-prostate-specific antigen (PSA) in combination with PSA and free PSA for prostate cancer detection in the 2.0 to 10.0 ng/ml PSA range. J Urol 2011;185:1650–5.
[25] De La Calle C, Patil D, Wei JT, et al. Multicenter evaluation of the prostate health index to detect aggressive prostate cancer in biopsy naive men. J Urol 2015;194:65–72.
[26] Druskin SC, Tossoian JJ, Young A, et al. Combining Prostate Health Index density, magnetic resonance imaging and prior negative biopsy status to improve the detection of clinically significant prostate cancer. BJU Int 2018;121:619–26.
[27] Falagario UG, Lantzi A, Jambor I, et al. Using biomarkers in patients with positive multiparametric magnetic resonance imaging: 4Kscore predicts the presence of cancer outside the index lesion. Int J Urol 2021;28:47–52.
[28] Hansen J, Auprich M, Abyai SA, et al. Initial prostate biopsy: development and internal validation of a biopsy-specific nomogram based on the prostate cancer antigen 3 assay. Eur Urol 2013;63:201–9.
[29] Loeb S, Senda MG, Broyles DL, et al. The prostate health index selectively identifies clinically significant prostate cancer. J Urol 2015;193:1163–9.
[30] Loeb S, Shin SS, Broyles DL, et al. Prostate Health Index improves multivariable risk prediction of aggressive prostate cancer. BJU Int 2017;120:61–8.
[31] McKiernan J, Donovan MJ, O’Neill V, et al. A novel urine exosome gene expression assay to predict high-grade prostate cancer at initial biopsy. JAMA Oncol 2016;2:882–9.
[32] Bertok T, Jane E, Bertokova A, et al. Validating fPSA glycoprofile as a prostate cancer biomarker to avoid unnecessary biopsies and re-biopsies. Cancers (Basel) 2020;12:2988.
[33] O’Malley PG, Nguyen DP, Al Hussein Al Awamlh B, et al. Racial variation in the utility of urinary biomarkers PCA3 and T2ERG in a large multicenter study. J Urol 2017;198:42–9.
[34] Punnern S, Freedland SJ, Polascik TJ, et al. A multi-institutional prospective trial confirms noninvasive blood test maintains predictive value in African American men. J Urol 2018;199:1459–63.
[35] Senda MG, Feng Z, Howard DH, et al. Association between combined TMPPRSS2:ERG and PCA3 RNA urinary testing and detection of aggressive prostate cancer. JAMA Oncol 2017;3:1085–93.
[36] Shore N, Hafaron J, Langford T, et al. Urinary biomarker test impacts prostate biopsy decision making in clinical practice. Urol Pract 2019;6:256–60.
[37] Tomlins SA, Day JR, Lonigro RJ, et al. Urine TMPPRSS2:ERG plus PCA III for individualized prostate cancer risk assessment. Eur Urol 2016;70:45–53.
[38] Tossoian JJ, Druskin SC, Andrews D, et al. Prostate Health Index density improves detection of clinically significant prostate cancer. BJU Int 2017;120:793–8.
Tosoian JJ, Patel HD, Mamawala M, et al. Longitudinal assessment of urinary PCA3 for predicting prostate cancer grade reclassification in favorable-risk men during active surveillance. Prostate Cancer Prostatic Dis 2017;20:339–42.

Tosoian JJ, Teck PG, Morgan TM, et al. Use of the MyProstateScore test to rule out clinically significant cancer: validation of a straightforward clinical testing approach. J Urol 2021;205:732–9.

Wei JT, Feng Z, Partin AW, et al. Can urinary PCA3 supplement PSA in the early detection of prostate cancer? J Clin Oncol 2014;32: 4066–72.

Wysocz JS, Becher E, Persily J, Loeb S, Lepor H. Concordance and performance of 4Kscore and SelectMDx for informing decision to perform prostate biopsy and detection of prostate cancer. Urology 2020;141:119–24.

Chiu PK, Teoh JYC, Lee WM, et al. Extended use of prostate health index and percentage of [−2]pro–prostate-specific antigen in Chinese men with prostate-specific antigen 10–20 ng/mL and normal digital rectal examination. Investig Clin Urol 2016;57:336–42.

Zappa MA, Tong Y, Linder V, et al. The 4Kscore blood test accurately identifies men with aggressive prostate cancer prior to prostate biopsy with or without DRE information. Int J Clin Pract 2017;71: 1–10, e4943.

Filella X, Foj L, Alcover J, Augé JM, Molina R, Jiménez W. The influence of prostate volume in prostate health index performance in patients with total PSA lower than 10 ng/mL. Clin Chim Acta 2014;436:303–7.

Foj L, Filella X. Development and internal validation of a novel PHI- nomogram to identify aggressive prostate cancer. Clin Chim Acta 2020;501:174–8.

Morote J, Celma A, Planas J, et al. Eficacia del índice de salud prostática para identificar cánceres de próstata agresivos. Una validación institucional. Actas Urol Esp 2016;40:378–85.

Sanchis-Bonet A, Barriouneau-González M, Bajo-Chueca AM, et al. Validation of the prostate health index in a predictive model of prostate cancer. Actas Urol Esp 2018;42:25–32.

Roumiuguié M, Ploussard G, Nogueira L, et al. Independent evaluation of the respective predictive values for high-grade prostate cancer of clinical information and RNA biomarkers after upfront MRI and image-guided biopsies. Cancers (Basel) 2020;12:285.

Ruffon A, Devonec M, Champetier D, et al. PCA3 and PCA3-based nomograms improve diagnostic accuracy in patients undergoing first prostate biopsy. Int J Mol Sci 2013;14:17767–80.

Ruffon A, Perrin P, Devonec M, et al. Additional value of PCA3 density to predict initial prostate biopsy outcome. World J Urol 2014;32:917–23.

Seisen T, Roupé T, Braudt D, et al. Accuracy of the prostate health index versus validation of prostate cancer antigen 3 score to predict overall and significant prostate cancer at initial biopsy. Prostate 2015;75:103–11.

Leuten GHJM, Hessels D, Smit FP, et al. Identification of a candidate gene panel for the early diagnosis of prostate cancer. Clin Cancer Res 2015;21:3061–70.

Chiu PK, Roobol MJ, Teoh JY, et al. Prostate Health Index (PHI) and prostate-specific antigen (PSA) predictive models for prostate cancer in the Chinese population and the role of digital rectal examination–estimated prostate volume. Int Urol Nephrol 2016;48:1631–7.

Van Neste L, Hendriks RJ, Dijkstra S, et al. Detection of high-grade prostate cancer using a urinary molecular biomarker–based risk score. Eur Urol 2016;70:740–8.

Foley RW, Maweni RM, Gorman L, et al. European Randomised Study of Screening for Prostate Cancer (ERSPC) risk calculators significantly outperform the Prostate Cancer Prevention Trial (PCPT) 2.0 in the prediction of prostate cancer: a multi-institutional study. BJU Int 2016;118:706–13.

Busetto GM, Del Giudice F, Maggi M, et al. Prospective assessment of two–gene urinary test with multiparametric magnetic resonance imaging of the prostate for men undergoing primary prostate biopsy. World J Urol 2020;39:1869–77.

Guazzoni G, Nava L, Lazzeri M, et al. Prostate-specific antigen (PSA) isoform [−2]proPSA significantly improves the prediction of prostate cancer at initial extended prostate biopsies in patients with total PSA between 2.0 and 10 ng/ml: results of a prospective study in a clinical setting. Eur Urol 2011;60:214–22.

Mearini L, Ferri C, Lazzeri M, et al. Evaluation of prostate-specific antigen isoform p2PSA and its derivatives, [2]p2PSA, prostate health index and prostate dimension–adjusted related index in the detection of prostate cancer at first biopsy: an exploratory, multi-institutional study. Urology 2014;93:135–45.

Furuya K, Kawahara T, Narahara M, et al. Measurement of serum isoform [−2]proPSA derivatives shows superior accuracy to magnetic resonance imaging in the diagnosis of prostate cancer in patients with a total prostate-specific antigen level of 2–10 ng/mL. Scand J Urol 2017;51:257–62.

Choi J, Kang M, Sun H, et al. Comparison between Gleason score distribution and prostate health index in patients with prostate-specific antigen values of 2.5–10 ng/mL. Investig Clin Urol 2020;61:582–7.

Park H, Lee SW, Song G, et al. Diagnostic performance of [−2]proPSA and Prostate Health Index for prostate cancer: prospective, multi-institutional study. J Korean Med Sci 2018;33:e94.

Barisiene M, Bakavicius A, Stanciute D, et al. Prostate Health Index and Prostate Health Index density as diagnostic tools for improved prostate cancer detection. Biomed Res Int 2020;2020:9872146.

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.

Na R, Ye D, Qi J, et al. Prostate Health Index significantly reduced unnecessary prostate biopsies in patients with PSA 2–10 ng/mL and PSA >10 ng/mL: results from a multicenter study in China. Prostate 2017;77:1221–9.

Kotova ES, Savochkina VA, Doludin YV, et al. Identification of clinically significant prostate cancer by combined PCA3 and AMACR mRNA detection in urine samples. Res Reports Urol 2020;12:403–13.

Tan LG, Tan YK, Tai BC, et al. Prostate Health Index and PCA3 in the early detection of prostate cancer? J Clin Oncol 2014;32:4066–72.

Ngard Y, Haukaas SA, Eide GE, et al. Prostate cancer antigen-3 (PCA3) and PCA3-based nomograms in the diagnosis of prostate cancer: an external validation of Hansen’s nomogram on a Norwegian cohort. Scand J Urol 2015;49:8–15.

Hisjel PF, Li WJ, Lin WC, et al. Combining prostate health index and multiparametric magnetic resonance imaging in the diagnosis of clinically significant prostate cancer in an Asian population. World J Urol 2020;38:1207–14.

Fan Y-H-F, Po-Hsun P, Tzu-Ping L, et al. Prostate Health Index outperforms other PSA derivatives in predicting a positive biopsy in men with tPSA <10 ng/mL: Largest prospective cohort in Taiwan. J Chin Med Assoc 2019;82:772–7.

Abrate A, Lazzeri M, Lughezzani G, et al. Clinical performance of the Prostate Health Index (PHI) for the prediction of prostate cancer in obese men: data from the PROMetheus project, a multicentre European prospective study. BJU Int 2015;115:537–45.

Boegemann M, Stephan C, Cammann H, et al. The percentage of prostate-specific antigen (PSA) isoform [−2]proPSA and the Prostate Health Index improve the diagnostic accuracy for clinically relevant prostate cancer at initial and repeat biopsy compared with total PSA and percentage free PSA in men. BJU Int 2016;117:72–9.

Na R, Ye D, Liu F, et al. Performance of serum prostate–specific antigen isoform [−2]proPSA (p2PSA) and the Prostate Health Index (PHI) in a Chinese hospital-based biopsy population. Prostate 2014;74:1569–75.

Chiu PK, Ng CF, Semjonov A, et al. Multicentre evaluation of the role of the Prostate Health Index (PHI) in regions with differing prevalence of prostate cancer: adjustment of PHI reference ranges is needed for European and Asian settings. Eur Urol 2019;75:558–61.
Scattoni V, Trooekens G, Steyaert S, et al. Multicenter optimization and validation of a 2-Gene mRNA urine test for detection of clinically significant prostate cancer before initial prostate biopsy. J Urol 2019;202:256–62.

Lazzeri M, Lughezzani G, Haese A, et al. Clinical performance of prostate health index and urinary PCA3 for predicting cancer at initial or repeat biopsy. J Urol 2013;190:496–501.

Lazzeri M, Lughezzani G, Haese A, et al. Clinical performance of prostate health index in men with tPSA>10 ng/ml: results from a multicentric European study. Urol Oncol 2016;34:415.e13–e19.

Woo J, Santausasagna S, Banks J, et al. Urine extracellular vesicle GATA2 mRNA discriminates biopsy result in men with suspicion of prostate cancer. J Urol 2020;204:691–700.

Wang FB, Chen R, Ren SC, et al. Prostate cancer antigen 3 moderately improves diagnostic accuracy in Chinese patients undergoing first prostate biopsy. Asian J Androl 2017;19:238–43.

Yu GP, Na R, Ye DW, et al. Performance of the Prostate Health Index in predicting prostate biopsy outcomes among men with a negative digital rectal examination and transrectal ultrasonography. Asian J Androl 2016;18:633–8.

Wu ZY, Yang C, Luo J, Deng SL, Wu B, Chen M. Establishment of reference intervals for serum [-2]proPSA (P2PSA), %P2PSA and Prostate Health Index in healthy men. Onco Targets Ther 2019;12:6453–60.

Grönberg H, Eklund M, Picker W, et al. Prostate cancer diagnostics using a combination of the Stockholm3 blood test and multiparametric magnetic resonance imaging. Eur Urol 2018;74:722–8.

Hendriks RJ, van der Leest MMG, Dijkstra S, et al. A urinary biomarker-based risk score correlates with multiparametric MRI for prostate cancer detection. Prostate 2017;77:1401–7.

Foley RW, Gorman L, Sharifi N, et al. Improving multivariable prostate cancer risk assessment using the Prostate Health Index. BJU Int 2016;117:409–17.

Huang D, Yang X, Wu Y, et al. Cost-effectiveness analysis of Prostate Health Index in decision making for initial prostate biopsy. Front Oncol 2020;10:565382.

Wu YS, Fu XJ, Na R, et al. PHI-based risk calculators performed better in the prediction of prostate cancer in the Chinese population. Asian J Androl 2019;21:592–7.

Barisiene M, Bakavicius A, Stanciute D, et al. Prostate Health Index and Prostate Health Index Density as diagnostic tools for improved prostate cancer detection. BJU Int 2021;2020:718–24.

Filella X, Foj L, Augé JM, Molina R, Alcover J. Clinical utility of %p2PSA and prostate health index in the detection of prostate cancer. Clin Chem Lab Med 2014;52:1347–55.

Lazzeri M, Haese A, De La Taille A, et al. Serum isoform [-2]proPSA derivatives significantly improve prediction of prostate cancer at initial biopsy in a total PSA range of 2–10 ng/ml: a multicentric European study. Eur Urol 2013;63:986–94.

Nordstrom T, Vickers A, Assel M, Lilja H, Grönberg H, Eklund M. Comparison between the four-kallikrein panel and prostate health index for predicting prostate cancer. Eur Urol 2015;68:139–46.

Tosoian JJ, Druskin SC, Andreas D, et al. Use of the Prostate Health Index for detection of prostate cancer: results from a large academic practice. Prostate Cancer Prostatic Dis 2017;20:228–33.

Nygård Y, Haukaas SA, Halvorsen OJ, et al. A positive real-time elastography (RTE) combined with a Prostate Cancer Gene 3 (PCA3) score above 35 convey a high probability of intermediate- or high-risk prostate cancer in patient admitted for primary prostate biopsy. BMC Urol 2016;16:1–8.

Russo GI, Regis F, Castelli T, et al. A systematic review and meta-analysis of the diagnostic accuracy of Prostate Health Index and 4-Kallikrein Panel score in predicting overall and high-grade prostate cancer. Clin Genitourin Cancer 2017;15:429–439.e1.

Muñoz Rodríguez SV, García-Perdomo HA. Diagnostic accuracy of prostate cancer antigen 3 (PCA3) prior to first prostate biopsy: a systematic review and meta-analysis. Can Urol Assoc J 2020;14:1–6.

Lee D, Shim SR, Ahn ST, et al. Diagnostic performance of the prostate cancer antigen 3 test in prostate cancer: systematic review and meta-analysis. Clin Genitourin Cancer 2020;18:402–408.e5.

García-Perdomo HA, Chaves MJ, Osorio JC, Sanchez A. Association between TMPRSS2-ERG fusion gene and the prostate cancer: systematic review and meta-analysis. Cent Eur J Urol 2018;71:410–9.

Filella X, Giménez N. Evaluation of [-2]proPSA and prostate health index (phi) for the detection of prostate cancer: a systematic review and meta-analysis. Clin Chem Lab Med 2013;51:729–39.

Zappala SM, Scardino PT, Okrongly D, Linder V, Dong Y. Clinical performance of the 4Kscore test to predict high-grade prostate cancer at biopsy: a meta-analysis of us and European clinical validation study results. Rev Urol 2017;19:149–55.

Acosta N, Varela R, Mesa JA, Serrano López ML, Cómbita AL, Sanabria-Salas MC. Biomarcadores de pronóstico en pacientes con cáncer de próstata localizado. Rev Colomb Cancerol 2017;21:113–25.

Olleik G, Kasouf W, Apríkian A, et al. Evaluation of new tests and interventions for prostate cancer management: a systematic review. JNCCN J Natl Compr Cancer Netw 2018;16:1340–51.