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Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

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State Guidelines

Applicable Medi-Cal guidelines as of the publication of this policy (**this guideline supersedes the criteria in the Policy Statement section below**):

- I. Department of Managed Health Care (DMHC) All Plan Letter (APL) Guideline:
 - N/A
- II. Department of Health Care Services (DHCS) Provider Manual Guideline:
 - [Pathology: Molecular Pathology \(path molec\)](#)

Below is an excerpt of the guideline language. Please refer to the specific Provider Manual in the link above for the complete guideline.

Biomarker and Pharmacogenetic Testing

Medi-Cal covers medically necessary biomarker and pharmacogenomic testing, as described in the manual section Proprietary Laboratory Analyses (PLA). Medi-Cal may not cover all CPT and HCPCS codes associated with a particular biomarker or pharmacogenomic test.

Biomarker Testing

Biomarker testing is used to diagnose, treat, manage, or monitor a Medi-Cal member's disease or condition to guide treatment decisions. As defined by Section 14132.09 of the Welfare and Institutions Code, biomarker testing is the analysis of an individual's tissue, blood or other biospecimen for the presence of a biomarker. Biomarker testing includes, but is not limited to, single-analyte tests, multiplex panel tests and whole genome sequencing. Biomarkers are a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a specific therapeutic intervention. A biomarker includes, but is not limited to, gene mutations or protein expression. Medically necessary biomarker testing is subject to utilization controls and evidence-based clinical practice guidelines.

When testing for biomarkers, all Medi-Cal providers must ensure that they are provided in a manner that limits disruptions to care. As with all Medi-Cal benefits, restricted or denied use of biomarker testing for the purpose of diagnosis, treatment or ongoing monitoring of any medical condition is subject to Medi-Cal's grievance, appeal and State Fair Hearing processes, as well as any additional processes established specifically for Medi-Cal managed care plans.

- III. Department of Health Care Services (DHCS) All Plan Letter (APL) Guideline:
 - [APL 22-010 – Cancer Biomarker Testing](#)

Below is an excerpt of the guideline language. Please refer to the specific All Plan Letter in the link above for the complete guideline.

For the purposes of this APL, "Biomarker test" is defined as a diagnostic test, single or multigene, of an individual's biospecimen, such as tissue, blood, or other bodily fluids, for DNA or RNA alterations, including phenotypic characteristics of a malignancy, to identify an individual with a subtype of cancer, in order to guide treatment. Biomarkers, also called tumor markers, are substances found in higher-than-normal levels in the cancer itself, or in blood, urine, or tissues of some individuals with cancer. Biomarkers can determine the likelihood some types of cancer will spread. They can also help doctors choose the best treatment.

Medi-Cal managed care health plans (MCPs) are required to cover medically necessary biomarker testing for members with:

- Advanced or metastatic stage 3 or 4 cancer.
- Cancer progression or recurrence in the member with advanced or metastatic stage 3 or 4 cancer.

MCPs are prohibited from imposing prior authorization requirements on biomarker testing that is associated with a federal Food and Drug Administration (FDA)-approved therapy for advanced or metastatic stage 3 or 4 cancer. If the biomarker test is not associated with an FDA-approved cancer therapy for advanced or metastatic stage 3 or 4 cancer, MCPs may still require prior authorization for such testing.

Policy Statement

Any criteria that are not specifically addressed in the above APL and Provider Manual, please refer to the criteria below.

- I. The following genetic and protein biomarkers for the diagnosis of prostate cancer are considered **investigational**:
 - A. Kallikrein markers (e.g., 4Kscore Test)
 - B. Prostate Health Index (PHI)
 - C. *HOXC6* and *DLX1* testing (e.g., SelectMDx)
 - D. PCA3, ERG, and SPDEF RNA expression in exosomes (e.g., ExoDx Prostate IntelliScore)
 - E. Autoantibodies ARF 6, NKX3-1, 5' -UTR-BMI1, CEP 164, 3' -UTR-Ropporin, Desmocollin, AURKAIP-1, and CSNK2A2 (e.g., Apifiny)
 - F. *PCA3* testing (e.g., Progensa PCA3 Assay)
 - G. *TMPRSS:ERG* fusion genes (e.g., MyProstate Score)
 - H. Gene hypermethylation testing (e.g., ConfirmMDx)
 - I. Mitochondrial DNA variant testing (e.g., Prostate Core Mitomics Test)
 - J. PanGIA Prostate
 - K. Candidate gene panels
- II. Single nucleotide variant testing for cancer risk assessment of prostate cancer is considered **investigational**.

Note: For individuals enrolled in health plans subject to the Biomarker Testing Law (Health & Safety Code Section 1367.667 and the Insurance Code Section 10123.209), Centers for Medicare & Medicaid Services (CMS) Local Coverage Determination (LCD) may also apply. Please refer to the [Medicare National and Local Coverage](#) section of this policy and to [MoLDx: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer](#) for reference.

Policy Guidelines

Coding

See the [Codes table](#) for details.

Description

Various genetic and protein biomarkers are associated with prostate cancer. These tests have the potential to improve the accuracy of differentiating between which men should undergo prostate biopsy and which should undergo rebiopsy after a prior negative biopsy. This evidence review addresses these types of tests for cancer risk assessment. Testing to determine cancer aggressiveness after a tissue diagnosis of cancer is addressed in Blue Shield of California Medical Policy: Gene Expression Profiling, Protein Biomarkers, and Multimodal Artificial Intelligence for Prostate Cancer Management.

Summary of Evidence

For individuals who are being considered for an initial prostate biopsy who receive testing for genetic and protein biomarkers of prostate cancer (e.g., kallikreins biomarkers and 4Kscore Test, proPSA and Prostate Health Index, TMPRSS fusion genes and MyProstateScore, SelectMDx for Prostate Cancer, ExoDx Prostate, Apifiny, PCA3 score, and PanGIA Prostate), the evidence includes systematic reviews, meta-analyses, and primarily observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, resource utilization, and quality of life. The evidence supporting clinical utility varies by the test but has not been directly shown for any biomarker test. Absent direct evidence of clinical utility, a chain of evidence might be constructed. However, the performance of biomarker testing for directing biopsy referrals is uncertain. While some studies have shown a reduction or delay in biopsy based on testing, a chain of evidence for clinical utility cannot be constructed due to limitations in clinical validity. Test validation populations have included men with a positive digital rectal exam (DRE), a prostate-specific antigen (PSA) level outside of the gray zone (between 3 or 4 ng/mL and 10 ng/mL), or older men for whom the information from test results are less likely to be informative. Many biomarker tests do not have standardized cutoffs to recommend a biopsy. In addition, comparative studies of the many biomarkers are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are being considered for repeat biopsy who receive testing for genetic and protein biomarkers of prostate cancer (e.g., PCA3 score, Gene Hypermethylation and ConfirmMDx test, Prostate Core Mitomics Test, MyProstate Score), the evidence includes systematic reviews and meta-analyses and primarily observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, resource utilization, and quality of life. The performance of biomarker testing for guiding rebiopsy decisions is lacking. The tests are associated with a diagnosis of prostate cancer and aggressive prostate cancer, but studies on clinical validity are limited and do not compare performance characteristics with standard risk prediction models. Direct evidence supporting clinical utility has not been shown. No data are currently available on the longer-term clinical outcomes of the use of genetic and protein biomarkers to decide on repeat prostate biopsy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

Not applicable

Related Policies

- Gene Expression Profiling, Protein Biomarkers, and Multimodal Artificial Intelligence for Prostate Cancer Management

Benefit Application

Blue Shield of California Promise Health Plan is contracted with L.A. Care Health Plan for Los Angeles County and the Department of Health Care Services for San Diego County to provide Medi-Cal health benefits to its Medi-Cal recipients. In order to provide the best health care services and practices, Blue Shield of California Promise Health Plan has an extensive network of Medi-Cal primary care providers and specialists. Recognizing the rich diversity of its membership, our providers are given training and educational materials to assist in understanding the health needs of their patients as it could be affected by a member's cultural heritage.

The benefit designs associated with the Blue Shield of California Promise Medi-Cal plans are described in the Member Handbook (also called Evidence of Coverage).

Regulatory Status

Cal. Health & Safety Code §1367.667, Insurance Code Section 10123.209, and Welfare and Institutions Code 14132.09

California laws that require insurers to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed.

Laboratory-Developed Tests (LDTs) and CLIA Certification

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed under the CLIA for high-complexity testing. The following laboratories are certified under the CLIA: BioReference Laboratories and GenPath Diagnostics (subsidiaries of OPKO Health; 4Kscore®), ARUP Laboratories, Mayo Medical Laboratories, LabCorp, BioVantra, others (PCA3 assay), Clinical Research Laboratory (Prostate Core Mitomic Test™), MDx Health (SelectMDx, ConfirmMDx), Innovative Diagnostics (PHI™), and ExoDx® Prostate (Exosome Diagnostics). To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests.

FDA Approval of Progensa® PCA3 Assay

In February 2012, the Progensa® PCA3 Assay (Gen-Probe; now Hologic) was approved by the FDA through the premarket approval process. The Progensa PCA3 Assay has been approved by the FDA to aid in the decision for repeat biopsy in men 50 years or older who have had 1 or more negative prostate biopsies and for whom a repeat biopsy would be recommended based on the current standard of care. The Progensa PCA3 Assay should not be used for men with atypical small acinar proliferation on their most recent biopsy. FDA product code: OYM.

FDA Approval of Prostate Health Index (PHI) Test

In June 2012, proPSA, a blood test used to calculate the Prostate Health Index (PHI; Beckman Coulter) was approved by the FDA through the premarket approval process. The PHI test is indicated as an aid to distinguish prostate cancer from a benign prostatic condition in men ages 50 and older with prostate-specific antigen levels of 4 to 10 ng/mL and with digital rectal exam findings that are not suspicious. According to the manufacturer, the test reduces the number of prostate biopsies. FDA product code: OYA.

Health Equity Statement

Blue Shield of California Promise Health Plan's mission is to transform its health care delivery system into one that is worthy of families and friends. Blue Shield of California Promise Health Plan seeks to advance health equity in support of achieving Blue Shield of California Promise Health Plan's mission.

Blue Shield of California Promise Health Plan ensures all Covered Services are available and accessible to all members regardless of sex, race, color, religion, ancestry, national origin, ethnic group identification, age, mental disability, physical disability, medical condition, genetic information, marital status, gender, gender identity, or sexual orientation, or identification with any other persons or groups defined in Penal Code section 422.56, and that all Covered Services are provided in a culturally and linguistically appropriate manner.

Rationale

Background

Prostate Cancer

Prostate cancer is the most common cancer, and the second most common cause of cancer death in men. Prostate cancer is a complex, heterogeneous disease, ranging from microscopic tumors unlikely to be life-threatening to aggressive tumors that can metastasize, leading to morbidity or death. Early localized disease can usually be treated with surgery and radiotherapy, although active surveillance may be adopted in men whose cancer is unlikely to cause major health problems during their lifespan or for whom the treatment might be dangerous. In patients with inoperable or metastatic disease, treatment consists of hormonal therapy and possibly chemotherapy. The lifetime risk of being diagnosed with prostate cancer for men in the U.S. is approximately 16%, while the risk of dying of prostate cancer is 3%.¹ African American men have the highest prostate cancer risk in the U.S.; the incidence of prostate cancer is about 60% higher and the mortality rate is more than 2 to 3 times greater than that of White men.² Autopsy results have suggested that about 30% of men over the age of 55 and 60% of men over the age of 80 who die of other causes have incidental prostate cancer³, indicating that many cases of cancer are unlikely to pose a threat during a man's life expectancy.

Grading

The most widely used grading scheme for prostate cancer is the Gleason system.⁴ It is an architectural grading system ranging from 1 (well-differentiated) to 5 (undifferentiated); the score is the sum of the primary and secondary patterns. A Gleason score of 6 or less is low-grade prostate cancer that usually grows slowly; 7 is an intermediate grade; 8 to 10 is high-grade cancer that grows more quickly. A revised prostate cancer grading system has been adopted by the National Cancer Institute and the World Health Organization.⁵ A cross-walk of these grading systems is shown in Table 1.

Table 1. Prostate Cancer Grading Systems

Grade Group	Gleason Score (Primary and Secondary Pattern)	Cells
1	6 or less	Well-differentiated (low grade)
2	7 (3 + 4)	Moderately differentiated (moderate grade)
3	7 (4 + 3)	Poorly differentiated (high grade)
4	8	Undifferentiated (high grade)
5	9 to 10	Undifferentiated (high grade)

Numerous genetic alterations associated with the development or progression of prostate cancer have been described, with the potential for the use of these molecular markers to improve the

selection process of men who should undergo prostate biopsy or rebiopsy after an initial negative biopsy.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Genetic and protein biomarker tests are best evaluated within the framework of a diagnostic or prognostic test because such frameworks provide diagnostic and prognostic information that assists in clinical management decisions. Because these tests are used as an adjunct to the usual diagnostic workup, it is important to evaluate whether the tests provide incremental information above the standard workup to determine whether the tests have utility in clinical practice.

Biomarker Testing for Selection of Men for Initial Prostate Biopsy

Clinical Context and Test Purpose

The purpose of genetic and protein biomarker testing for prostate cancer is to inform the selection of men who should undergo an initial biopsy. Conventional decision-making tools for identifying men for prostate biopsy include a digital rectal exam (DRE), serum prostate-specific antigen (PSA), and patient risk factors such as age, race, and family history of prostate cancer.

Digital rectal examination has a relatively low interrater agreement among urologists, with an estimated sensitivity, specificity, and positive predictive value (PPV) for diagnosis of prostate cancer of 59%, 94%, and 28%, respectively.⁶ Digital rectal examination might have a higher PPV in the setting of elevated PSA.⁷

The risk of prostate cancer increases with increasing PSA levels; an estimated 15% of men with a PSA level of 4 ng/mL or less and a normal DRE, 30% to 35% of men with a PSA level between 4 ng/mL and 10 ng/mL, and more than 67% of men with a PSA level greater than 10 ng/mL will have biopsy-detectable prostate cancer.^{8,9} Use of PSA levels in screening has improved the detection of prostate cancer. The European Randomized Study of Screening for Prostate Cancer (ERSPC) trial and Göteborg Randomised Prostate Cancer Screening Trial demonstrated that biennial PSA screening reduces the risk of being diagnosed with metastatic prostate cancer.^{10,11,12,13,14} However, elevated PSA levels are not specific to prostate cancer; levels can be elevated due to infection, inflammation, trauma, or ejaculation. In addition, there are no clear cutoffs for cancer positivity with PSA. Using a common PSA level cutoff of 4.0 ng/mL, Wolf et al (2010), on behalf of the American Cancer Society, systematically reviewed the literature and calculated pooled estimates of elevated PSA sensitivity of 21% for detecting any prostate cancer and 5% for detecting high-grade cancers with an estimated specificity of 91%.¹⁵

Existing screening tools have led to unnecessary prostate biopsies. More than 1 million prostate biopsies are performed annually in the U.S., with a resulting cancer diagnosis in 20% to 30% of men. About one-third of men who undergo prostate biopsy experience transient pain, fever, bleeding, and urinary difficulties. Serious biopsy risks (e.g., bleeding or infection requiring hospitalization) have estimated rates ranging from less than 1% to 3%.^{16,17}

Given the risk, discomfort, burden of biopsy, and low diagnostic yield, there is a need for noninvasive tests that distinguish potentially aggressive tumors that should be referred for biopsy from clinically insignificant localized tumors or other prostatic conditions that do not need biopsy with the goal of avoiding low-yield biopsy.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are men for whom an initial prostate biopsy is being considered because of clinical symptoms (e.g., difficulty with urination, elevated PSA).

The population for which these tests could be most informative is men in the indeterminate or "gray zone" range of PSA level on repeat testing with unsuspicious DRE findings. Repeat PSA testing is important because results initially reported being between 4 ng/mL and 10 ng/mL frequently revert to normal.¹⁸ The gray zone for PSA levels is usually between 3 or 4 ng/mL and 10 ng/mL, but PSA levels vary with age. Age-adjusted normal PSA ranges have been proposed but not standardized or validated.

Screening of men with a life expectancy of fewer than 10 years is unlikely to be useful because most prostate cancer progresses slowly. However, the age range for which screening is most useful is controversial. The ERSPC and Rotterdam trials observed benefits of screening only in men up to about 70 years old.

Interventions

For assessing future prostate cancer risk, numerous studies have demonstrated the association between many genetic and protein biomarker tests and prostate cancer. Commercially available tests for the selection of men for initial prostate biopsy include those described in Table 2.

Table 2. Commercially Available Tests to Determine Candidates for Initial Prostate Biopsy

Test	Manufacturer	Description
4Kscore	OPKO lab	Blood test that measures 4 prostate-specific kallikreins, which are combined into an algorithm to produce a risk score estimating the probability of finding high-grade prostate cancer (defined as a Gleason score ≥ 7) if a prostate biopsy were performed.
Prostate Health Index (phi)	Beckman Coulter	Blood assay that combines several components of PSA (total PSA, free PSA, [-2] proPSA) in an algorithm that includes patient age.
Mi-Prostate (MiPS) renamed MyProstate score 2021	University of Michigan MLabs renamed LynxDx	Measures <i>TMPRSS2-ERG</i> gene fusion and calculates a probability score that incorporates serum PSA or the PCPT, and urine <i>TMPRSS2-ERG</i> and PCA3 scores
SelectMDx	MDxHealth	Clinical model that combines post-DRE urinary panel for <i>HOXC6</i> and <i>DLX1</i> gene expression with other risk factors
ExoDx Prostate IntelliScore (EPI)	Exosome Diagnostics	Urine panel for <i>PCA3</i> , <i>ERG</i> , and <i>SPDEF</i> RNA expression in exosomes
Apifiny	Armune BioScience (acquired by Exact Sciences in 2017)	Algorithm with detection of 8 autoantibodies (ARF 6, NKX3-1, 5' -UTR-BMI1, CEP 164, 3' -UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2) in serum
PCA3 score (e.g., Progensa)	<ul style="list-style-type: none">Hologic Gen-ProbeMany labs offer PCA3 tests (e.g., ARUP Laboratories,	Measures <i>PCA3</i> mRNA in urine samples after prostate massage. <i>PCA3</i> mRNA may be normalized using PSA level to account for prostate cells.

Test	Manufacturer	Description
	Mayo Medical Laboratories, LabCorp)	
PanGIA Prostate	Genetics Institute of America	Analysis of a signature of small molecules, proteins, and cells with a proprietary machine learning algorithm.

DRE: digital rectal exam; mRNA: messenger ribonucleic acid; PCPT: Prostate Cancer Prevention Trial; PSA: prostate-specific antigen.

Prostate-specific kallikreins (e.g., 4Kscore) are a subgroup of enzymes that cleave peptide bonds in proteins. The intact PSA and human kallikrein 2 tests are immunoassays that employ distinct mouse monoclonal antibodies. The score combines the measurement of 4 prostate-specific kallikreins (total PSA, free PSA, intact PSA, human kallikrein), with an algorithm including patient age, DRE (nodules or no nodules), and a prior negative prostate biopsy. The 4K algorithm generates a risk score estimating the probability of finding high-grade prostate cancer (defined as a Gleason score ≥ 7) if a prostate biopsy were performed. The intended use of the test is to aid in a decision whether to proceed with a prostate biopsy. The test is not intended for patients with a previous diagnosis of prostate cancer, who have had a DRE in the previous 4 days, who have received 5 α reductase inhibitor therapy in the previous 6 months, or who have undergone treatment for symptomatic benign prostatic hypertrophy in the previous 6 months.

The Prostate Health Index (phi; Beckman Coulter) is an assay that combines results of 3 blood serum immunoassays (total PSA, free PSA, [-2]proPSA [p2PSA]) numerically to produce a "PHI score." This score is calculated with the PHI algorithm using the following formula: $([-2]\text{proPSA}/\text{free PSA}) \times \sqrt{\text{total PSA}}$. The phi score is indicated for men 50 years and older with above-normal total PSA readings between 4.0 ng/mL and 10 ng/mL who have had a negative DRE in order to distinguish prostate cancer from benign prostatic conditions.

TMPRSS2 is an androgen-regulated transmembrane serine protease that is preferentially expressed in the normal prostate tissue. In prostate cancer, it may be fused to an E26 transformation-specific (ETS) family transcription factor (*ERG*, *ETV1*, *ETV4*, *ETV5*), which modulates transcription of target genes involved in cell growth, transformation, and apoptosis. The result of gene fusion with an ETS transcription gene (e.g., MyProstate Score) is that the androgen-responsive promoter of *TMPRSS2* upregulates expression of the ETS gene, suggesting a mechanism for neoplastic transformation. Fusion genes may be detected in tissue, serum, or urine.

TMPRSS2-ERG gene rearrangements have been reported in 50% or more of primary prostate cancer samples.¹⁹ Although *ERG* appears to be the most common ETS family transcription factor involved in the development of fusion genes, not all are associated with *TMPRSS2*. About 6% of observed rearrangements are seen with *SLC45A3*, and about 5% appear to involve other types of rearrangement.²⁰

SelectMDx for prostate cancer uses a model that combines *HOXC6* and *DLX7* gene expression with traditional risk assessment models. *HOXC6* and *DLX7* mRNA is measured in post-DRE urine against kallikrein-related peptidase 3 as an internal reference.

ExoDx Prostate (IntelliScore), also called EPI, evaluates a urine-based 3-gene exosome expression assay using *PCA3* and *ERGRNA* in urine, normalized to *SPDEF*. Evidence on the association between the *PCA3* gene and prostate cancer aggressiveness is described in the next section on repeat biopsy. Measurement in exosomes, which are small double-lipid membrane vesicles that are secreted from cells, is novel. Exosomes encapsulate a portion of the parent cell cytoplasm and contain proteins and mRNA. They are shed into biofluids (e.g., blood, urine). This test does not require DRE.

Apifiny uses an algorithm to score the detection of 8 autoantibodies (ARF 6, NKX3-1, 5' -UTR-BMI1, CEP 164, 3' -UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2) in serum. The identified biomarkers play a role in processes such as androgen response regulation and cellular structural integrity and are proteins that are thought to play a role in prostate tumorigenesis.

PanGIA Prostate is a urine test that uses a device with binding pockets for small molecules, proteins, and cells. Results are uploaded to the cloud and a machine learning algorithm compares the results with a signature from patients who have had a positive biopsy and patients who have had a negative prostate biopsy. The report includes a diagnosis with the level of confidence in the diagnosis.

Comparators

Standard clinical examination for determining who requires a biopsy might include DRE, review of the history of PSA levels, along with consideration of risk factors such as age, race, and family history. The ratio of free (or unbound) PSA to total PSA (percent free PSA) is lower in men who have prostate cancer than in those who do not. A percent free PSA cutoff of 25% has been shown to have a sensitivity and specificity of 95% and 20%, respectively, for men with total PSA levels between 4.0 ng/mL and 10.0 ng/mL.²¹

The best way to combine all risk information to determine who should go to biopsy is not standardized. Risk algorithms have been developed that incorporate clinical risk factors into a risk score or probability. Two examples are the Prostate Cancer Prevention Trial (PCPT) predictive model²² and the Rotterdam Prostate Cancer risk calculator (also known as the ERSPC-Risk Calculator 4 [ERSPC-RC]).²³ The American Urological Association and the Society of Abdominal Radiology (2016) recommend that high-quality prostate magnetic resonance imaging, if available, should be strongly considered in any patient with a prior negative biopsy who has persistent clinical suspicion for prostate cancer and who is under evaluation for a possible repeat biopsy.²⁴

Outcomes

The beneficial outcome of the test is to avoid a negative biopsy for prostate cancer. A harmful outcome is a failure to undergo a biopsy that would be positive for prostate cancer, especially when the disease is advanced or aggressive. Thus the relevant measures of clinical validity are the sensitivity and negative predictive value (NPV). The appropriate reference standard is a biopsy, though prostate biopsy is an imperfect diagnostic tool. Biopsies can miss cancers and repeat biopsies are sometimes needed to confirm the diagnosis. Detection rates vary by biopsy method and patient characteristics.

The timeframe of interest for calculating performance characteristics is time to biopsy results. Men who forgo biopsy based on test results could miss or delay the diagnosis of cancer. Longer follow-up would be necessary to determine the effects on overall survival (OS).

Study Selection Criteria

For the evaluation of clinical validity, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Studies were excluded from the evaluation of the clinical validity of the test because they did not use the marketed version of the test, did not include information needed to calculate performance characteristics, did not use an appropriate reference standard or the reference standard was

unclear, did not adequately describe the patient characteristics, or did not adequately describe patient selection criteria.

Kallikreins Biomarkers and 4Kscore Test

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews

Russo et al (2017) performed a systematic review of studies that evaluated the diagnostic accuracy of the 4Kscore test in patients undergoing biopsy with a PSA level between 2 ng/mL and 20 ng/mL (Table 3). Results of the DRE were not described. The NPV to exclude any type of cancer ranged from 28% to 64% (Table 4). The NPV of the 4Kscore test to exclude high-grade (Gleason score ≥ 7) cancer ranged from 95% to 99%.

Mi et al (2021) performed a systematic review and meta-analysis of studies reporting the diagnostic accuracy of the 4Kscore test to detect high-grade prostate cancer using cutoff values of 7.5% to 10%.²⁵ Pooled analyses found acceptable diagnostic accuracy (see Table 4). However, significant heterogeneity among the included studies lowered confidence in the results.

Kawada et al (2024) performed a systematic review and meta-analysis of 49 studies reporting on the diagnostic accuracy of liquid biomarkers for the detection of clinically significant prostate cancer; investigators did not explicitly define "clinically significant" prostate cancer.²⁶ Ten prospective studies (n=11,586) specifically evaluated the 4Kscore. Pooled analyses found acceptable diagnostic accuracy (see Table 4). Additionally, in subgroup analyses that included 6 studies in the biopsy-naïve setting (n=9283), the sensitivity, specificity, PPV, and NPV were 87% (95% CI, 81 to 91), 57% (95% CI, 50 to 63), 29% (95% CI, 19 to 41), and 96% (95% CI, 92 to 98), respectively.

Table 3. Characteristics of Systematic Reviews Assessing the Clinical Validity of the 4Kscore for Diagnosing Prostate Cancer

Study	Studies, Design	Dates	Key Inclusion Criteria	Reference Studies Included
Russo et al (2017) ²⁷	10 Observational cohort	2010-2015	Blood samples were collected before biopsy; indication for biopsy was independent of 4K results	Biopsy for prostate cancer detection (overall or high grade with Gleason score ≥ 7)
Mi et al (2021) ²⁵	Observational cohort 7 retrospective, 2 prospective	Searches through December 2019	Cohort or case-control studies of the diagnostic accuracy of the 4Kscore using biopsy as the gold standard and providing data to calculate test characteristics. Studies not using cutoff values of 7.5% to 10% were excluded.	Biopsy for detection of high-grade prostate cancer (Gleason score ≥ 7)
Kawada et al (2024) ²⁶	49 total; 10 prospective cohorts evaluating the 4Kscore	Searches through March 2023	Studies on the diagnostic accuracy of the 4Kscore using biopsy as the gold standard and providing data to calculate test characteristics; patients in included studies were suspected of harboring prostate cancer or any reason	Systematic biopsy and image-targeted biopsy

Table 4. Results of Systematic Reviews Assessing the Clinical Validity of 4Kscore for Diagnosing Prostate Cancer

Study	Studies Included	N	Outcomes	Sens (95% CI), %	Spec (95% CI), %	PPV Range %	NPV Range %	OR (95% CI)	AUC (95% CI)
Russo et al (2017) ²⁷	10	NR	Diagnostic performance for any prostate cancer	74 (73 to 76)	60 (59 to 61)	59 to 92	28 to 64	4.6 (3.5 to 6.1)	NR
Russo et al (2017) ²⁷ (subgroup analysis)	10	NR	Diagnostic performance for high-grade prostate cancer	87 (85 to 89)	61 (60 to 62)	8 to 43	95 to 99	10.2 (8.1 to 12.8)	NR
Mi et al (2021) ²⁵	7 retrospective, 2 prospective	9847	Diagnostic performance for high-grade prostate cancer	90 (86 to 92)	44 (36 to 52)	NR	NR	7 (5 to 8)	0.81 (0.77 to 0.84)
Kawada et al (2024) ²⁶	10 prospective cohorts	11,586	Diagnostic performance for prostate cancer	87 (83 to 91)	58 (49 to 66)	19 to 40	92 to 98	8.84 (6.17 to 12.68)	0.83 (NR)

AUC: area under the curve; CI: confidence interval; NR: not reported; NPV: negative predictive value; OR: odds ratio; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

Prospective Studies

Additional prospective validation study of the 4Kscore test conducted in different populations has been published (Tables 5 and 6).

Bhattu et al (2021) conducted a retrospective exploratory analysis using data from the 2 previously published validation studies, to determine test performance with a cut-off of 7.5% as the indication to proceed with biopsy.²⁸

Tables 7 and 8 summarize the relevance and design and conduct limitations. A major limitation was the inclusion of patients outside the indeterminate range of PSA. Although Bhattu reported test characteristics in the subgroup of patients with PSA between 3 and 10, this study was limited by its retrospective design.

Longer-term data on the incidence of prostate cancer in men who do not have a biopsy following testing with the marketed version of 4Kscore are not available. However, a case-control study by Stattin et al (2015), which was a nested cohort study of more than 17,000 Swedish men, estimated that, for men age 60 with PSA levels of 3 or higher and a kallikrein-related peptidase 3 risk score less than 10%, the risk of metastasis at 20 years was 1.95% (95% confidence interval [CI], 0.64% to 4.66%).²⁹

Table 5. Characteristics of Clinical Validity Studies Assessing the 4Kscore Test

Study	Study Population	Design	Reference Standard	Timing of Reference and Index Tests	Blinding of Assessors	Comment
Bhattu et al (2021) ²⁸	Combined analysis of patients from the above 2 studies, evaluating the test at a cut off of 7.5% as the indication to proceed with biopsy.	Retrospective exploratory analysis of data from the above 2 studies	Prostate biopsy with ≥ 10 cores	Blood sample taken prior to biopsy	Yes	

DRE: digital rectal exam; PSA: prostate-specific antigen.

Table 6. Results of Clinical Validity Studies Assessing the 4Kscore Test

Study	Initial N	Final N	Performance Characteristics (95% CI)			
			4Kscore Sens (%)	Comparators Spec (%)	PPV (%)	NPV (%)
Bhattu et al (2021) ²⁸						
• All patients (N = 1378)	• 1378	• 1378	• 94	• 42	• 37	• 95
• African Americans (n = 290)		• 290	• 95	• 39	• 49	• 93
• non-African Americans (n = 1088)		• 1088	• 94	• 42	• 33	• 96
• Patients ages 45 to 75 years with PSA 3 to 10 (n = 920)		• 920	• 92	• 35	• 31	• 94

AUC: area under the curve; CI: confidence interval; hK2: human kallikrein 2 (kallikreins are a subgroup of enzymes that cleave peptide bonds in proteins); NPV: negative predictive value; NR: not reported; PCPT: Prostate Cancer Prevention Trial; PPV: positive predictive value; PSA: prostate-specific antigen; Sens: sensitivity; Spec: specificity.

Table 7. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Bhattu et al (2021) ²⁸					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

PSA: prostate-specific antigen.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 8. Study Design and Conduct Limitations

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Bhattu et al (2021) ²⁸				Retrospective, exploratory analysis		1. Confidence intervals for test characteristics not reported.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Retrospective Studies

Verbeek et al (2019) conducted a retrospective comparison of the discriminatory ability of the 4Kscore test compared to the Rotterdam Prostate Cancer Risk Calculator.³⁰ The cohort included 2872 men with a PSA ≥ 3.0 from the European Randomized Study of Screening for Prostate Cancer Rotterdam. The 4K panel was measured in frozen serum samples. The areas under the curve (AUCs) were similar, with an AUC of 0.88 for the 4K score and 0.87 for the Rotterdam Prostate Cancer Risk Calculator ($p=.41$). Addition of the 4K score to the Rotterdam Prostate Cancer Risk Calculator had a modest, though statistically significant improvement in discriminatory ability with an AUC of 0.89. A limitation of this study is that men were included who had a PSA outside of the levels of interest, which would be between 3 and 10 ng/ml.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No RCTs reporting direct evidence of utility for clinical outcomes were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Various cutoffs for the kallikrein-related peptidase 3 probability score were used in decision-curve analyses to estimate the number of biopsies versus cancers missed. Parekh et al (2015) estimated that 307 biopsies could have been avoided and 24 cancer diagnoses would have been delayed with a 9% 4Kscore cutoff for biopsy, and 591 biopsies would have been avoided with 48 diagnoses delayed with a 15% cutoff.³¹ However, inferences on clinical utility cannot be made due to deficiencies in estimating the clinical validity that is described in the previous section.

Konety et al (2015) reported on the results of a survey of 35 U.S. urologists identified through the 4Kscore database at OPKO Lab as belonging to practices that were large users of the test.³² All 611 patients of participating urologists to whom men were referred for an abnormal PSA level or DRE and had a 4Kscore test were included. Urologists, who received the 4Kscore as a continuous risk percentage, were retrospectively asked about their plans for biopsy before and after receiving the test results and whether the 4Kscore test results influenced their decisions. The physicians reported that the 4Kscore results influenced decisions in 89% of men and led to a 64.6% reduction in prostate biopsies. The 4Kscore risk categories (low-risk: <7.5%, intermediate risk: 7.5% to 19.9%, high-risk: $\geq 20\%$) correlated highly ($p<.001$) with biopsy outcomes in 171 men with biopsy results.

Subsection Summary: Kallikreins Biomarkers and 4Kscore Test

There is uncertainty regarding clinical performance characteristics such as sensitivity, specificity, and predictive value due to the following factors: a lack of standardization of cutoffs to recommend biopsy, study populations including men with low (<4 ng/mL) and high (>10 ng/mL) baseline PSA levels, positive DRE results likely outside the intended use population, and lack of comparison with models using information from a standard clinical examination. Very few data are available on longer-term clinical outcomes of men who are not biopsied based on 4Kscore results. The evidence needed to conclude the test has clinical validity is insufficient.

Absent direct evidence of clinical utility, a chain of evidence might be constructed. The 4Kscore test is associated with a diagnosis of aggressive prostate cancer. The incremental value of the 4Kscore concerning clinical examination and risk calculators in the intended use population is unknown due to deficiencies in estimating clinical validity. There is no prospective evidence that the use of 4Kscore changes management decisions. Given that the test manufacturer's website states the test is for men with inconclusive results, the inclusion of men with PSA levels greater than 10 ng/mL and a positive DRE in the validation studies are likely not reflective of the intended use population. The chain of evidence is incomplete.

proPSA and Prostate Health Index

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews

Several systematic reviews and meta-analyses have evaluated the clinical validity of p2PSA (proPSA) and PHI tests. The characteristics of the most relevant and comprehensive reviews are shown in Table 9. All primary studies were observational and most were retrospective. Reviews included studies of men with a positive, negative, or inconclusive DRE; Pecoraro et al (2016)³³ restricted eligibility to studies including PSA levels between 2 ng/mL and 10 ng/mL, while Russo et al (2017)²⁷ restricted eligibility to studies including PSA levels between 2 ng/mL and 20 ng/mL. Anyango and Kawada (previously introduced) included studies in men of any age with any range of PSA levels and Anyango reported results according to different cutoffs.^{34,26}

Pecoraro et al (2016) rated most of the 17 primary studies as low quality due to the design (most were retrospective), lack of blinding of outcome assessors to reference standard results, lack of clear cutoffs for diagnosis, and lack of explicit diagnostic question.³³ Russo et al (2017) included 23 studies that were mostly prospective and rated as moderate quality.²⁷ Kawada et al (2024) included 22 studies that were mostly prospective cohorts; 14 studies included patients in the initial biopsy setting and 8 included patients in both initial and repeat biopsy settings.²⁶ Overall, there was high heterogeneity across studies but pooled estimates showed generally low NPV (5% to 91%) and low specificity (25% to 52%) when sensitivity was 85% to 93% (Table 10). In a subgroup analysis, Kawada et al (2024) pooled data from 6 studies comprising patients in the biopsy-naïve setting; the pooled sensitivity, specificity, PPV, and NPV, were 87% (95% CI, 81 to 91), 57% (95% CI, 50 to 63), 36% (95% CI, 27 to 46), and 92% (95% CI, 87 to 95), respectively.²⁶

Table 9. Characteristics of Systematic Reviews Assessing the Clinical Validity of the PHI Test for Diagnosing Prostate Cancer

Study	Studies Included	Dates	Key Inclusion Criteria ^a	Design	Reference Studies Included
Pecoraro et al (2016) ³³	17	2003 to 2014	PSA level 2 to 10 ng/mL	Prospective, retrospective, and mixed prospective/retrospective, observational	
Russo et al (2017) ²⁷	23	2010 to 2015	Blood samples were collected before biopsy; PSA level 2 to 20 ng/mL; indication for biopsy was independent of PHI results	Mostly retrospective, observational	Biopsy for prostate cancer detection (overall or high grade with Gleason score ≥ 7)
Anyango et al (2021) ³⁴	12	2015 to 2018	Studies that enrolled men of any age who had a diagnosis of aggressive	Observational cross-sectional, cohort, or case-control designs	Gleason score

Study	Studies Included	Dates	Key Inclusion Criteria ^a	Design	Reference Studies Included
			PCa as determined from biopsy specimens, and with any range of PSA levels	in which the index and reference tests were interpreted in the same group of participants.	
Kawada et al (2024) ²⁶	49 total; 22 evaluating the PHI test	Searches through March 2023	Studies on the diagnostic accuracy of PHI using biopsy as the gold standard and providing data to calculate test characteristics; patients in included studies were suspected of harboring prostate cancer or any reason	Prospective, retrospective	Systematic biopsy and image-targeted biopsy

PCa: prostate cancer; PHI: Prostate Health Index; PSA: prostate-specific antigen.

^a Results from all studies were with or without digital rectal exam.

Table 10. Results of Systematic Reviews on the Clinical Validity of the PHI Test for Diagnosing Prostate Cancer

Study	Studies/N (Range)	Outcomes	Sens (95% CI), %	Spec (95% CI), %	PPV Range, %	NPV Range, %	OR (95% CI), %
Pecoraro et al (2016) ³³	17/6912 (63 to 1091)	Diagnostic performance for any prostate cancer	Set at 90	Phi: 31 (29 to 33) Total PSA: 25 (23 to 27)			
Russo et al (2017) ²⁷	23	Diagnostic performance for any prostate cancer	89 (88 to 90)	34 (32 to 35)	76 to 98	15 to 63	4.4 (3.3 to 5.8)
Russo et al (2017) ²⁷ (subset)	7	Diagnostic performance for high-grade prostate cancer	93 (90 to 95)	26 (25 to 28)	88 to 99	5 to 31	3.5 (2.5 to 5.0)
Anyango et al (2021) ³⁴	Total 12/8462 PHI \leq 25: 3/3222 PHI 26 to 35: 6/6030 PHI \geq 36: 5/1476	Diagnostic accuracy in determining the aggressiveness of prostate cancer	PHI \leq 25: 97 (95 to 98) PHI 26 to 35: 87 (8 to 91) PHI \geq 36: 72 (64 to 79)	PHI \leq 25: 10 (6 to 16) PHI 26 to 35: 45 (39 to 50) PHI \geq 36: 74 (68 to 80)			
Kawada et al (2024) ²⁶	22/8652 (77 to 1538)	Diagnostic performance for clinically significant prostate cancer	85 (80 to 89)	52 (43 to 60)	38 (31 to 45)	91 (87 to 93)	6.28 (4.79 to 8.24)

CI: confidence interval; NPV: negative predictive value; OR: odds ratio; PHI: Prostate Health Index; PPV: positive predictive value; PSA: prostate-specific antigen; Sens: sensitivity; Spec: specificity.

Retrospective Studies

Loeb et al (2017) conducted a modeling study to compare established risk calculators with and without the PHI test.³⁰ The population for this retrospective analysis included 728 men from the

prospective multicenter clinical trial of PHI (Catalona et al, 2011).³⁵ The probability of aggressive prostate cancer was evaluated at each value of PHI from 1 to 100. The addition of PHI to the PCPT 2.0 risk calculator increased the AUC for the discrimination of aggressive prostate cancer from 0.575 to 0.696 ($p < .001$), while the addition of phi to the ERSPC 4 plus DRE risk calculator increased the AUC from 0.650 to 0.711 ($p = .014$).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs directly measuring the effect of the PHI test on clinical outcomes were found.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

A chain of evidence might be used to demonstrate clinical utility if each link in the chain is intact. Two observational studies have shown a reduction or delay in biopsy procedures for men with PSA levels in the 4 to 10 ng/mL range, nonsuspicious DRE findings, and a low PHI score. Tosoian et al (2017) found a 9% reduction in the rate of biopsy among 345 men who underwent PHI testing compared with 1318 men who did not.³⁶ There was an associated 8% reduction in the incidence of negative biopsies in men who had PHI testing, but the interpretation of results is limited because the use of the PHI test was based solely on provider discretion. A prospective multicenter study by White et al (2018) evaluated physician recommendations for biopsy before and after receiving the PHI test result.³⁷ The PHI score affected the physician's management plan in 73% of cases, with biopsy deferrals when the PHI score was low and the decision to perform biopsies when the PHI score was 36 or more. A chain of evidence requires evidence that the test could be used to affect health outcomes, and that the test is clinically valid. Due to questions about the clinical validity of the test, a chain of evidence cannot be constructed.

Subsection Summary: proPSA and Prostate Health Index

Many studies and systematic reviews of these studies have reported on the clinical validity of PHI. Primary studies included men with positive, negative, and inconclusive DRE and men with PSA levels outside of the 4- to 10-ng/mL range. There is no standardization of cutoffs used in a clinical setting for diagnosis. With sensitivity around 90% for the detection of any prostate cancer, specificity ranged from 25% to 52% and NPV, which would indicate an absence of disease and allow patients to forego biopsy, ranged from 5% to 91%. For high-grade disease, the sensitivity of the PHI test was 93%, with a NPV ranging from 5% to 31%.

The PHI test is associated with a diagnosis of prostate cancer. Although observational studies have shown a reduction or delay in a biopsy with PHI testing, a chain of evidence cannot be constructed about an improvement in health outcomes due to limitations in clinical validity. The chain of evidence is incomplete.

TMRSS Fusion Genes and MyProstate Score

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Validation studies on the combined 2-gene test (*TMPPRSS2-ERG* and *PCA3*) are shown in Table 11. Sanda et al (2017), from the National Cancer Institute Early Detection Research Network, reported separate developmental and validation cohorts for high-grade prostate cancer in men undergoing initial prostate biopsy.³⁸ For the validation cohort, any of the following was considered a positive result: PSA level greater than 10 ng/mL, urine *TMPPRSS2-ERG* score greater than 8, or urine *PCA3* score greater than 20. Performance characteristics of this algorithm, compared with the individual markers, are shown in Table 12. Analysis showed that specificity could be increased from 17% to 33% compared with PSA alone, without loss of sensitivity. The difference in specificity was statistically significant, with a prespecified 1-sided p-value of .04 (lower bound of 1-sided 95% CI, 0.73%).

In the study by Tomlins et al (2016), 80% of the 1244 patients were undergoing initial biopsy due to elevated PSA levels (Table 11).³⁹ Thresholds were not defined and the AUCs for predicting any cancer using PSA alone, PCPT risk calculator alone, or the Mi-Prostate Score (MiPS) alone are shown in Table 12. The AUC for MiPS was significantly improved compared with the PCPT risk calculator ($p < .001$). However, a study by Ankerst et al (2019) found that adding *TMPPRSS2-ERG* to a PCPT risk calculator plus *PCA3* did not improve the AUC.⁴⁰ The online PCPT risk calculator now includes both the *PCA3* and *TMPPRSS2-ERG* scores, which will be used for further validation.

Tosoian et al (2021) reported on a study to establish and validate a threshold for the MyProstateScore test (previously named MiPS) to rule out Gleason Group ≥ 2 prostate cancer.⁴¹ A threshold of ≤ 10 was identified in a training cohort and validated using a combined dataset that included 977 biopsy naïve men from the validation study previously reported in Tomlins et al (2016) and 548 biopsy naïve men prospectively enrolled as part of an Early Detection Research Network study that did not evaluate the MyProstateScore. In the overall cohort, sensitivity was 97.0%, specificity was 32.6%, NPV was 97.5%, and PPV was 29.1%. Results were similar in the subgroup of men with PSA between 3 and 10 or with PSA < 3 with suspicious DRE. The study authors are co-founders and have equity in LynDx, which has licensed the urine biomarkers evaluated in the study.

The multiinstitutional Canary Prostate Surveillance Study (PASS) was reported by Newcomb et al (2019).⁴² The study included 782 men under active surveillance (2,069 urine samples) to examine the association of urinary *PCA3* and *TMPPRSS2-ERG* with biopsy-based reclassification. *TMPPRSS2-ERG* was not associated with short-term reclassification at the first surveillance biopsy.

Table 11. Characteristics of Studies Assessing the Clinical Validity of the Combined *TMPPRSS2-ERG* and *PCA3* Score

Study; Study Trial	Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors	Comment
Sanda et al (2017) ³⁸	561 men who had initial prostate biopsy	4-center PRoBE criteria	HG (Gleason score ≥ 7) prostate cancer on biopsy	Algorithm with PSA level > 10 ng/mL; <i>T2:ERG</i> score > 8 ; or <i>PCA3</i> score > 20	Samples collected after DRE and prior to biopsy	Yes	A separate developmental cohort of 516 men is reported
Tomlins et al (2016) ³⁹	1244 men who had initial (80%) or repeat biopsy due to elevated PSA	7-center prospective	Any cancer or HG cancer (Gleason score ≥ 7)		Samples collected after DRE and prior to biopsy	Yes	A MiPS score threshold was not provided, so sensitivity and NPV were not calculated

DRE: digital rectal exam; HG: high-grade; MiPS: Mi-Prostate Score; NPV: negative predictive value; PRoBE: prospective-specimen-collection, retrospective-blinded-evaluation; PSA: prostate-specific antigen; *T2:ERG*: *TMPRSS2-ERG*.

Table 12. Results of Studies Assessing the Clinical Validity of the Combined *TMPRSS2-ERG* and *PCA3* Score

Study	Initial N	Final N	Threshold	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	p ^a
Sanda et al (2017) ³⁸	561	561						
PSA level, ng/mL			3	91.2 (86.6 to 95.8)	16.7 (13.1 to 20.3)	28.2 (28.9 to 29.5)	84.1 (75.1 to 90.3)	
<i>PCA3</i>			7	96.6 (93.7 to 99.5)	18.4 (14.7 to 22.1)	29.8 (28.6 to 30.9)	93.8 (86.2 to 97.3)	
<i>PCA3, T2:ERG</i>			20, 8	90.5 (85.8 to 95.2)	35.4 (30.8 to 40.0)	33.4 (31.5 to 35.4)	91.2 (86.1 to 94.6)	
PSA level >10 ng/mL; <i>T2:ERG</i> score >8; or <i>PCA3</i> score >20				92.6 (88.4 to 96.8)	33.4 (28.8 to 37.9)	33.2 (31.4 to 35.1)	92.6 (87.5 to 95.8)	
				AUC (95% CI not reported)				
				Excluded Samples	PSA Alone	PCPT Risk Calculator	PSA Plus <i>PCA3</i>	MiPS
Tomlins et al (2016) ³⁹	1244	1225	19 with insufficient samples for analysis					
Any cancer				0.59	0.64	0.73	0.75	<.001
High-grade cancer				0.65	0.71	0.75	0.77	<.001

AUC: area under the curve; CI: confidence interval; MiPS: Mi-Prostate Score; NPV: negative predictive value; PCPT: Prostate Cancer Prevention Trial; PPV: positive predictive value; PSA: prostate-specific antigen; Sens: sensitivity; Spec: specificity; *T2:ERG*: *TMPRSS2-ERG*.

^a P-value for MiPS vs PCPT risk calculator.

Tables 13 and 14 summarize relevance and design and conduct limitations for each study.

Table 13. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Sanda et al (2017) ³⁸	4. Some patients were 70 y, 16% had an abnormal DRE; median PSA level was 4.8 ng/mL				
Tomlins et al (2016) ³⁹	4. 25% were >70 y, 23% had an abnormal DRE; median PSA level was 4.7 ng/mL		3. Not compared with most current (v2) PCPT risk calculator		

DRE: digital rectal exam; PCPT: Prostate Cancer Prevention Trial; PSA: prostate-specific antigen.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 14. Study Design and Conduct Limitations

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Sanda et al (2017) ³⁸						
Tomlins et al (2016) ³⁹					1. Confidence intervals not reported	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Sanda et al (2017) calculated that restricting biopsy to participants with positive findings on *TMPRSS2-ERG* score, *PCA3* score, or PSA level at thresholds of 8, 20, and 10, respectively, would have avoided 42% of unnecessary biopsies (true negative) and 12% of low-grade cancers.³⁸ It was estimated that 7% of cancers would be missed using the combined threshold, compared with 21% using a *PCA3* threshold of 7.

Tomlins et al (2016) also used decision-curve analysis to estimate the number of biopsies that would have been performed and cancers that would have been missed using a MiPS risk cutoff for biopsy in their cohort.³⁹ Compared with a biopsy-all strategy, using a MiPS cutoff for aggressive cancer of 15% would have avoided 36% of biopsies while missing 7% of any prostate cancer and 1.6% of high-grade prostate cancer diagnoses. Using the PCPT risk calculator cutoff of 15% for aggressive cancer would have avoided 68% of biopsies while missing 25% of any cancer and 8% of high-grade cancer.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

No studies were found that directly show the effects of using MiPS results on clinical outcomes. Given the lack of direct evidence of utility, a chain of evidence would be needed to demonstrate clinical utility. The MiPS test is associated with a diagnosis of prostate cancer and aggressive prostate cancer. The clinical validity study of the MiPS test included men with relevant PSA levels but also included men with a positive DRE who would not likely forego biopsy.

Subsection Summary: TMPRSS Fusion Genes and MyProstate Score

Concomitant detection of *TMPRSS2-ERG* and *PCA3* in addition to the multivariate PCPT risk calculator may more accurately identify men with prostate cancer than with PSA level alone or the PCPT risk calculator alone. However, adding *TMPRSS2-ERG* score to PSA level plus *PCA3* score only resulted in a 0.02 difference in the AUC compared with the combination of PSA plus *PCA3*, with a maximum AUC of 0.77 for the detection of high-grade cancer. In a study from the National Cancer Institute Early Detection Research Network, using either/or thresholds of *TMPRSS2-ERG* plus *PCA3* score or PSA level improved specificity compared with PSA alone, without a loss in sensitivity. It does not appear from this study that an algorithm that combines *TMPRSS2-ERG*, *PCA3*, or PSA level has any incremental improvement in NPV of 92.6% (95% CI, 87.5% to 95.8%) over *PCA3* score alone 93.8% (95% CI, 86.2% to 97.3%).

Current evidence on the *TMPRSS2-ERG* and *PCA3* scores is insufficient to support its use. The MiPS test has data suggesting an improved AUC compared with the PCPT risk calculator in a validation study, and improved specificity compared with PSA level in another study, but improvement in diagnostic accuracy compared to individual components of the algorithm at similar thresholds has not been reported. Data on clinical utility are lacking. No prospective data are available on using the MiPS score for decision making. The chain of evidence is incomplete.

SelectMDx for Prostate Cancer

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews

The previously introduced systematic review by Kawada et al (2024) included 9 studies evaluating the clinical validity of SelectMDx in patients with clinically significant prostate cancer.²⁶ The characteristics of the review and results are provided in Tables 15 and 16, respectively. In subgroup analyses that included 7 studies in the biopsy-naïve setting, the pooled sensitivity, specificity, PPV, and NPV were 85% (95% CI, 72 to 92), 54% (95% CI, 38 to 69), 39% (95% CI, 29 to 50), and 90% (95% CI, 82 to 95), respectively.

Table 15. Characteristics of Systematic Reviews Assessing the Clinical Validity of SelectMDx for Diagnosing Prostate Cancer

Study	Studies Included	Dates	Key Inclusion Criteria ^a	Design	Reference Studies Included
Kawada et al (2024) ²⁶	49 total; 9 evaluating SelectMDx	Searches through March 2023	Studies on the diagnostic accuracy of SelectMDx using biopsy as the gold standard and providing data to calculate test characteristics; patients in included studies were suspected of harboring prostate cancer or any reason	Prospective, retrospective	Systematic biopsy and image-targeted biopsy

Table 16. Results of Systematic Reviews on the Clinical Validity of SelectMDx for Diagnosing Prostate Cancer

Study	Studies/N (Range)	Outcomes	Sens (95% CI), %	Spec (95% CI), %	PPV Range, %	NPV Range, %	OR (95% CI), %
Kawada et al (2024) ²⁶	9/2609	Diagnostic performance for prostate cancer	82% (69 to 91)	56% (41 to 70)	39% (30% to 49%)	90% (82% to 95%)	6.16 (2.62 to 14.49)

CI: confidence interval; NPV: negative predictive value; OR: odds ratio; PPV: positive predictive value; PSA: prostate-specific antigen; Sens: sensitivity; Spec: specificity.

Prospective Studies

Van Neste et al (2016) evaluated a risk calculator that added *HOXC6* and *DLX7* expression to a clinical risk model that included DRE, PSA density, and previous cancer negative biopsies (Table 17).⁴³ A training set in 519 men and an independent validation set in 386 men were assessed. When evaluating the risk model in men who were in the "gray zone" of PSA level between 3 ng/mL and 10 ng/mL, the AUC was significantly higher than a clinical risk model alone, Prostate Cancer Prevention Trial Risk Calculator (PCPTRC) for detection of any cancer or for detection of high-grade cancer (Table 18). Limitations of this study is the inclusion of men with an abnormal DRE (Tables 19 and 20), which was the strongest predictor of prostate cancer in the training set (odds ratio [OR]=5.53; 95% CI, 2.89 to 10.56) and inclusion of men who were scheduled for either initial or repeat biopsy. The OR for *HOXC6* and *DLX7* expression in this model was 1.68 (95% CI, 1.38 to 2.05; p<.003).

Table 17. Characteristics of Clinical Validity Studies Assessing SelectMDx for Prostate Cancer

Study	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Van Neste et al (2016) ⁴³	386 men with PSA level >3 ng/mL scheduled for initial (89%) or repeat biopsy	Prospective	Prostate cancer on biopsy	NR	Urine sample taken after DRE and prior to biopsy	NR

DRE: digital rectal exam; NR: not reported; PSA: prostate-specific antigen.

Table 18. Results of Clinical Validity Studies Assessing SelectMDx for Prostate Cancer

Study	Total N	N With PSA Level <10 ng/mL	N with PSA Level <10 ng/mL and Normal DRE	AUC for the Risk Score in Patients With PSA Level <10 ng/mL (95% CI)			
				Any Cancer	HG Cancer	PCPTRC	p
Van Neste et al (2016) ⁴³	386	264		0.90 (0.85 to 0.96)	0.78 (0.68 to 0.88)	0.66 (0.57 to 0.75)	.001

AUC: area under the curve; CI: confidence interval; DRE: digital rectal exam; HG: high-grade; IQR: interquartile range; MRI: magnetic resonance imaging; NPV: negative predictive value; NR: not reported; PCPTRC: Prostate Cancer Prevention Trial Risk Calculator; PPV: positive predictive value; PSA: prostate-specific antigen; Sens: sensitivity; Spec: specificity.

Table 19. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Van Neste et al (2016) ⁴³	4. 31% of men had abnormal DRE and men were undergoing either initial or repeat biopsy. The study was conducted in Europe and not representative of the U.S. population	3. The clinical risk model was changed for the Haese et al (2019) publication			

DRE: digital rectal exam; PCPTR: Prostate Cancer Prevention Trial Risk; PSA: prostate specific antigen; %fPSA: percent free PSA.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not

explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

• Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 20. Study Design and Conduct Limitations

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Van Neste et al (2016) ⁴³		1. Blinding not reported			1. Inadequate description of indeterminate samples	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No trials were identified that compared health outcomes for patients managed with and without the test.

Van Neste et al (2016) estimated that when using a cutoff of 98% NPV for high-grade (Gleason ≥ 7) prostate cancer, there would be a total reduction in biopsies by 42% and a decrease in unnecessary biopsies by 53%.⁴³

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. Current evidence on clinical validity is insufficient.

Because the clinical validity of SelectMDx for Prostate Cancer has not been established, a chain of evidence supporting the clinical utility of this test cannot be constructed.

Subsection Summary: SelectMDx for Prostate Cancer

A systematic review evaluating SelectMDx among other liquid biomarkers in patients suspected of harboring prostate cancer or any reason reported a sensitivity and specificity of 82% and 56%, respectively. One validation from 2019 reported that a risk model that added an expression of *HOX6* and *DLX7* to a newly revised clinical risk model (patient age, DRE, and PSA density) increased the AUC

for the detection of high-grade cancer. However, men who are in the "gray zone" who have a PSA level between 3 ng/mL and 10 ng/mL and normal DRE are the patients who would most likely be considered for this test. Comparison with the PCPTR was not reported for this population of interest, limiting the interpretation of this study. It is also not known whether SelectMDx would provide additional specificity when compared to percent free PSA (%fPSA). An additional limitation is that the study was conducted in a European population, which is primarily Caucasian and would not be representative of the U.S. population. A more recent study from 2021 found that use of the SelectMDx test in biopsy-naïve men resulted in a 38% reduction of biopsy procedures, a 35% reduction of overdiagnosis of low-grade prostate cancer and could save 38% of MRIs, at the cost of missing 10% of high-grade prostate cancers compared to biopsy for all patients. However, the use of MRI alone in all patients to select for prostate biopsy had the highest net benefit as a prebiopsy stratification tool.

No trials identified have compared health outcomes for patients managed with and without the SelectMDx for Prostate Cancer. A chain of evidence depends on clinical validity. Current evidence on adding *HOXC6* and *DLX7* expression to a clinical risk model is insufficient to support its use. Data on SelectMDx have suggested an improved AUC (0.78) compared with the PCPTR (0.66) in 1 validation study that included men with PSA levels in the indeterminate range. Sensitivity and specificity rates have not been reported. No prospective data are available on using SelectMDx for decision making. Present studies on clinical validity are insufficient to establish a chain of evidence. The chain of evidence is incomplete.

ExoDx Prostate (IntelliScore)

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

McKiernan et al (2016) conducted a multicenter validation study of urine exosome *PCA3*, *ERG*, and *SPDEF* RNA expression to predict high-grade (Gleason score ≥ 7) prostate cancer (Table 21).⁴⁴ The threshold for a positive test was derived from a training set separate from the validation set. The assay improved on the standard of care alone, with an AUC of 0.73 compared with 0.63 for the standard of care ($p < .001$) and 0.62 for the PCPTR (Table 22). Diagnostic performance is shown in Table 22, with a sensitivity of 97% and NPV of 96%.

Table 21. Characteristics of Clinical Validity Studies Assessing ExoDx Prostate (IntelliScore)

Study	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
McKiernan et al (2016) ⁴⁴	1064 men ≥ 50 y with PSA level 2 to 10 ng/mL and scheduled for initial biopsy	Multicenter prospective	Gleason score ≥ 7 prostate cancer on biopsy	15.6 derived from a separate training set	Urine collection prior to biopsy	Yes

PSA: prostate-specific antigen.

Table 22. Results of Clinical Validity Studies Assessing ExoDx Prostate (IntelliScore)

Study	Initial N	Final N	Excluded Samples	Area Under the Curve (95% CI)			
				ExoDx + SOC	SOC Alone	PCPTR	p
McKiernan et al (2016) ⁴⁴	1064	519 in intended use population	Technical reasons or failure to meet study criteria	0.73 (0.68 to 0.77)	0.63 (0.58 to 0.68)	0.62 (0.57 to 0.67)	<.001
Diagnostic Performance (95% CI), %							

Study	Initial N	Final N	Excluded Samples	Area Under the Curve (95% CI)			
				Sensitivity	Specificity	PPV	NPV
				97.44 (93.93 to 100)	27.68 (21.09 to 34.28)	37.25 (30.62 to 43.89)	96.08 (90.75 to 100)

CI: confidence interval; NPV: negative predictive value; PCPTRC: Prostate Cancer Prevention Trial Risk Calculator; PPV: positive predictive value; PSA: prostate-specific antigen; SOC: standard of care.

Tables 23 and 24 summarize relevance and design and conduct limitations in each study.

Table 23. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
McKiernan et al (2016) ⁴⁴	4. Study population included patients with suspicious DRE		3. Standard of care did not include DRE or free PSA results		

DRE: digital rectal exam; PSA: prostate-specific antigen.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 24. Study Design and Conduct Limitations

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
McKiernan et al (2016) ⁴⁴			1. The timing of urine sampling was not described			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Tutrone et al (2020) reported a trial that evaluated the effect of ExoDx Prostate on the decision to biopsy (Tables 25 through 28).⁴⁵ This multicenter, prospective, blinded RCT was conducted in

partnership with CareFirst BlueCross/BlueShield of Maryland and included 1094 men with a PSA 2 to 10 ng/ml who were considered for prostate biopsy based on clinical criteria. All patients had the test, but only patients randomized to the ExoDx Prostate arm received the test results. The primary outcome of the study was to determine if ExoDX Prostate could reduce initial biopsies. The secondary endpoint was the successful diagnosis of high-grade prostate cancer. A total of 942 patients (86.1%) had complete data and usable samples. In the ExoDx Prostate arm, 93 patients received low-risk test results and 106 patients (23%) received recommendations to defer biopsy. High-risk ExoDx Prostate scores led to a recommendation for biopsy in 87% of the 365 ExoDx Prostate-positive patients. Compliance with a recommendation for biopsy was 72% in the ExoDx Prostate arm compared to about 40% in the control arm, leading to increased biopsy rates in the ExoDx Prostate arm (58%) compared to controls (39%). In African-American patients, who represented 23% of the patient population, 91% had high-risk scores. The study did not meet its primary endpoint. The main effect of the test was to increase biopsies with an increase in the number of at least Grade Group 2 cancers, but there was also an increase in the number of men biopsied who had no cancer or low-grade cancer compared to the control arm. Additional limitations of the study are the inclusion of men with very low PSA (2 ng/ml) and the lack of information on what screening had preceded the referral for biopsy. It is unclear if the standard of care for repeat PSA and %fPSA were assessed prior to the decision to biopsy, if controls received this standard of care, or if the test was intended as a replacement for repeat PSA and %fPSA.

Tutrone et al (2023) reported on a retrospective outcome analysis follow-up study of the initial 2020 study reported above.⁴⁶ Of the original 1094 cohort, 833 patients had complete follow-up data at 2.5 years. In this analysis, patients returned to routine standard of care after enrollment in the clinical utility trial, and a retrospective outcome analysis was conducted. The average time from ExoDX Prostate testing to the first biopsy was significantly longer in the low-risk ExoDX Prostate arm (216 days) compared to high-risk ExoDX Prostate arm (68.7 days; $p < .001$) and when compared to low-risk ExoDX Prostate patients in the standard of care arm (79.4 days; $p < .001$). In the ExoDx Prostate arm, low-risk patients had significantly fewer biopsies than high-risk patients (44.6% vs 79.0%, $p < .001$); in the standard of care arm the decision to defer was independent of ExoDx Prostate score and, as a result, did not differ between low-risk and high-risk scores. Patients in both arms with low-risk ExoDx Prostate scores had lower rates of high-grade prostate cancer at 2.5 years than high-risk ExoDx Prostate score patients (7.9% vs. 26.8%; $p < .001$), and the ExoDx Prostate arm discovered 21.8% (106 vs 87) more high-grade prostate cancer than the standard of care arm. Limitations of this interim analysis mimic limitations that were described in the above study; the study was also retrospective in nature.

Table 25. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					<i>Active</i>	<i>Comparator</i>
Tutrone et al (2020) ⁴⁵	U.S.	24	2017-2018	1094 men aged > 50 with PSA 2 to 10 ng/ml who were considered for biopsy based on clinical criteria	458 patients received EPI results	484 patients had the test but did not receive the test results

EPI: ExoDx Prostate (Intelliscore); PSA: prostate specific antigen; RCT: randomized controlled trial; NR: not reported

Table 26. Summary of Key RCT Results

Study	Biopsy Rate n(%)	No Cancer Rate n(%)	Grade 1 Cancer Rate n(%)	GG2 to GG4 Cancer Rate n(%)
Tutrone et al (2020) ⁴⁵				
EPI	264 (57.5%)	113 (42.8%)	73 (27.7%)	78 (29.5%)
Control	190 (39.3%)	83 (43.7%)	47 (24.7%)	60 (31.6%)

Study	Biopsy Rate n(%)	No Cancer Rate n(%)	Grade 1 Cancer Rate n(%)	GG2 to GG4 Cancer Rate n(%)
Tutrone et al (2023)				

EPI: ExoDx Prostate (IntelliScore); GG: Grade Group; RCT: randomized controlled trial.

Table 27. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Tutrone et al (2020) ⁴⁵	4. Included men with very low PSA levels (e.g., 2 ng/ml)		1. Standard of care was not defined.	1. The primary outcome was not achieved. The study found an increase in compliance without a decrease in the rate of no cancers or GG1 cancers	

GG: Grade Group; PSA: prostate specific antigen.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms

Table 28. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Tutrone et al (2020) ⁴⁵	3. Randomization procedures were not described	1. Pathologists were blinded, but patients and clinicians were not blinded to treatment assignment when test results were revealed.	2. The high number of false positives in patients with no cancer or low grade cancer was not discussed.			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Subsection Summary: ExoDx Prostate (IntelliScore)

The ExoDx Prostate (IntelliScore) assay showed a sensitivity of 97% and NPV of 96% for high-grade prostate cancer in men over 50 years of age who had PSA levels between 2 ng/mL and 10 ng/mL.

The primary limitation of the study was that patients with a suspicious DRE were enrolled in the study, but DRE or free PSA were not included in the comparison prediction.

One RCT was identified on ExoDx Prostate. It is unclear from this report whether the test is intended to be used in addition to repeat PSA and %fPSA, or if the test is intended to be used as a replacement for the current standard of care. In either event, the study did not meet its primary endpoint of decreasing unnecessary biopsies. The main impact of the test was to increase biopsies overall, without decreasing the percentage of no cancer or low-grade cancer identified on biopsy. Because of the increase in biopsy rates, there is a potential for this test to lead to overtreatment of slow-growing prostate cancer.

Apifiny

Schipper et al (2015) identified 8 autoantibodies associated with prostate cancer in a case-control study of men 40 to 70 years old with prostate cancer and PSA levels between 2.5 ng/mL and 20 ng/mL, compared to healthy men 25 to 40 years of age with PSA levels less than 1.0 ng/mL.⁴⁷ When the algorithm was applied to an independent validation set, the AUC was 0.69 (95% CI, 0.62 to 0.75).

Subsection Summary: Apifiny

Evidence on Apifiny is preliminary. In a validation set, the AUC was 0.69. The threshold for a positive test has not been determined and the sensitivity, specificity, PPV, and NPV rates compared with established tests have not been reported. Studies validating the diagnostic performance of Apifiny are needed.

PanGIA Prostate

No studies were identified on PanGIA Prostate.

Comparative Studies

4Kscore and SelectMDx

Wysock et al (2020) compared the performance of 4Kscore and SelectMDx to inform decisions of whether to perform a prostate biopsy.⁴⁸ New referrals (N=128) with elevated PSA were advised to undergo both 4Kscore and SelectMDx; 114 men underwent both tests. There was poor concordance between the 2 tests, with discordant guidance in 45.6% of the population. Since biomarker results were used to determine which patients should undergo biopsy (i.e., the reference test was not obtained for all patients), it cannot be determined which of the tests was more accurate.

Initial or Repeat Biopsy

PCA3 Score (e.g., Progensa PCA3 Assay)

Some studies have assessed men who are scheduled for an initial biopsy, although the U.S. Food and Drug Administration (FDA) approved indication for the Progensa PCA3 Assay is to aid in the decision for repeat biopsy in men 50 years or older who have had 1 or more negative prostate biopsies and for whom a repeat biopsy would be recommended based on current standard of care. Evaluation of the PCA3 score is relevant to both initial and repeat prostate biopsy.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews

Several systematic reviews and meta-analyses have described the clinical validity of the PCA3 Assay. The characteristics of the reviews are described in Table 29. All primary studies were observational, with 1 study using the placebo arm from an RCT. Reviewers selected studies of men with positive, negative, or inconclusive DRE without restrictions on PSA levels. Kawada et al (2024) and Cui et al (2016) both reported on the results of a systematic review of case-control or cohort studies.^{49,26} In both

reviews, studies assessed both initial and repeat biopsy. Studies in the review by Cui et al (2016) had a quality rating of moderate to high, whereas the quality of included studies in the review by Kawada et al (2024) was not reported. Rodriguez et al (2020) conducted a systematic review of PCA3 in men who had not yet undergone biopsy.⁵⁰ Nine studies in men without prior biopsy were identified, and 5 studies that used a cutoff of 35 were included in the meta-analysis. The assessment by Nicholson et al (2015) for the National Institute for Health and Care Excellence included 11 cohorts of men for whom initial prostate biopsy results were negative or equivocal.⁵¹

Results from the systematic reviews are shown in Table 30. In the meta-analysis by Cui et al (2016), the most common PCA3 assay cutoff for categorizing low- and high-risk was 35 (25 of 46 studies).⁴⁹ The estimates of AUC were lower for studies that included men having repeated (0.68) versus initial (0.80) biopsies. A PCA3 assay cutoff was not provided by Kawada et al (2024), and the pooled sensitivity and specificity were 85% and 37%, respectively; the majority of data were from patients in the initial biopsy setting.²⁶

Rodriguez et al (2020) found a pooled sensitivity of 69% and specificity of 65% in the 5 studies that used a cutoff of 35 in men without prior biopsy.⁵⁰ The studies were all prospective cohorts and rated as having a low risk of bias, except for uncertainty in flow and timing.

Nicholson et al (2015) included 13 reports describing 11 cohorts, including 1 from the placebo arm of an RCT.⁵¹ Referral criteria for repeat biopsy, were varied, often unclear, and differed based on whether normal or abnormal DREs were included. The mean or median PSA, when reported, ranged from 4.9 to 11.0 ng/mL and the prevalence of cancer on repeat biopsy varied from 11.4% to 68.3%. Meta-analyses were not performed due to heterogeneity. The addition of PCA3 to clinical assessment, as a continuous or categorical variable, generally led to an improvement in AUC, but studies that fixed sensitivity and derived specificity and those that reported decision-curve analysis had mixed results.

Table 29. Characteristics of Systematic Reviews Assessing the Clinical Validity of Progensa PCA3 Assay for Diagnosing Prostate Cancer

Study	Studies	Dates	Key Inclusion Criteria	Design	Reference Studies Included
Kawada et al (2024) ²⁶	49 total; 7 evaluating PCA3	Searches through March 2023	Studies on the diagnostic accuracy of PCA3 using biopsy as the gold standard and providing data to calculate test characteristics; patients in included studies were suspected of harboring prostate cancer or any reason	Prospective and retrospective cohort	Biopsy as reference standard
Rodriguez et al 2020 ⁵⁰	5	2007-2014	PCA3 cutoff of 35 in men without prior biopsy	Prospective cohort	Biopsy as reference standard
Cui et al (2016) ⁴⁹	46	Up to 2014		Prospective, retrospective (case-control or cohort) OBS	Biopsy as reference standard
Nicholson et al (2015) ⁵¹	11	2000-2014	Initial prostate biopsy negative or equivocal, 6+ cores in initial biopsy, with or without DRE	Prospective and mixed (prospective/retrospective) OBS (1 included a cohort from a RCT)	Biopsy as reference standard

DRE: digital rectal exam; OBS: observational; RCT: randomized controlled trial.

Table 30. Results of Systematic Reviews Assessing the Clinical Validity of Progensa PCA3 Assay for Diagnosing Prostate Cancer

Study	Studies	N (Range)	Outcomes	Sens (95% CI), %	Spec (95% CI), %	AUC (95% CI) or Range
Kawada et al (2024) ²⁶	7	2833 (128 to 692)	Any prostate cancer on initial or repeat biopsy	85% (74% to 92%)	37% (21% to 57%)	0.73 (NR)
Rodriguez et al 2020 ⁵⁰	5	2,083 (80 to 692)	Any prostate cancer on initial biopsy	Pooled 69% (61% to 75%)	65% (55% to 73%)	0.73 (0.67 to 0.80)
Cui et al (2016) ⁴⁹	46	12,295 (NR)	Any prostate cancer on initial or repeat biopsy	Pooled: 65% (63% to 66%) Range: 47% to 95%	• Pooled: 73% (72% to 74%) • Range: 22% to 100%	0.75 (0.74 to 0.77)
Nicholson et al (2015) ⁵¹	11	3336 (41 to 1072)	Any prostate cancer on repeat biopsy	CA alone range, 44% to 48% CA plus PCA3 range, 39% to 46%	Fixed at 80% • CA alone: 0.55 to 0.75 • CA plus PCA3: 0.61 to 0.76	0.73 (0.67 to 0.80)

AUC: area under the curve; CA: clinical assessment; CI: confidence interval; NR: not reported; Sens: sensitivity; Spec: specificity.

Prospective Studies

Not included in the systematic reviews was a prospective trial from the National Cancer Institute on the clinical validity of the PCA3 assay to complement PSA-based detection of prostate cancer (Tables 31 and 32).⁵² The trial was designed to evaluate whether PCA3 greater than 60 could improve the PPV of an initial biopsy and whether PCA3 less than 20 could improve the NPV of a repeat biopsy. Of the 859 men in the study, 562 were presenting for their initial prostate biopsy and 297 were presenting for repeat biopsy. For the detection of high-grade cancer, the performance of the PCPT risk calculator was modestly improved by adding PCA3 assay results to the risk calculator factors, with an AUC improvement from 0.74 to 0.78 for initial biopsy and 0.74 to 0.79 on repeat biopsy ($p \leq .003$). The PPV of the PCA3 assay at a threshold of 60 ng/mL to detect prostate cancer in an initial biopsy was 80% (95% CI, 72% to 86%), while the NPV of the PCA3 assay at a threshold of 20 ng/mL for prostate cancer in men undergoing repeat biopsy was 88% (95% CI, 81% to 93%). Estimates of biopsies avoided and cancer missed at this threshold is described in the section on clinical utility.

A similar validation study was published by Ankerst et al (2018) in 854 men who underwent a diagnostic biopsy.⁴⁰ The addition of PCA3 to the PCPTRC increased the AUC (95% CI) from 70% (66.0% to 74.0%) to 76.4% (72.8% to 80.0%). The AUC with *TMPRSS2:ERG* added to both was 77.1% (73.6% to 80.6%). These have been added to the online risk tool for further validation. Investigators have also been assessing the effect of age on PCA3 values, finding that age adjusted values improve the diagnostic performance of the test.⁵³

The prospective multi-institutional Canary PASS was reported by Newcomb et al (2019).⁴² The study included 782 men under active surveillance (2,069 urine samples) to examine the association of urinary PCA3 and *TMPRSS2:ERG* with biopsy-based reclassification. Under the PASS protocol, PSA is measured every 3 months and ultrasound-guided biopsies are performed 12 and 24 months after diagnosis, then every 2 years. Post-DRE urine samples were collected every 6 months. Modeling showed minimal benefit of adding PCA3 to a model with clinical variables, improving the AUC from 0.743 to 0.753.

Table 31. Characteristics of Clinical Validity Studies Assessing the Progensa PCA3 Assay

Study	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Wei et al (2014) ⁵²	910 men scheduled for a diagnostic prostate biopsy (initial or repeat)	Prospective	Any prostate cancer on biopsy or HG prostate cancer (Gleason score >6)	Determined a priori at thresholds of <20 and >60	Urine samples collected following DRE and prior to biopsy	Yes

DRE: digital rectal exam; HG: high-grade.

Table 32. Results of Clinical Validity Studies Assessing the Progensa PCA3 Assay

Study	Initial N	Final N	Excluded Samples	Clinical Validity (95% Confidence Interval), %			
	N			Sens	Spec	PPV	NPV
Wei et al (2014) ⁵⁴	910	859	27				
Initial biopsy PCA3 >60		562		42 (36 to 48)	91 (87 to 94)	80 (72 to 86)	
Repeat biopsy PCA3 <20		297		76 (64 to 86)	52 (45 to 58)		88 (81 to 93)

NPV: negative predictive value; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

No notable limitations were identified for study relevance or design and conduct.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Clinical utility studies using assay results for decision making for an initial biopsy, repeat biopsy, or treatment have not been reported, nor have studies of the effects of using assay results on clinical outcomes.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Several studies using decision analysis to estimate the cost-benefit tradeoff between a reduction in unnecessary biopsies and missed prostate cancers have been published. One group reported potential reductions in unnecessary biopsies of 48% to 52%, with attendant increases in missed prostate cancers of 6% to 15% using either a PCA3-based nomogram⁵⁵ or PCA3 level corrected for prostate volume (PCA3 density).⁵⁶ Merdan et al (2015) used decision analysis to simulate long-term outcomes associated with the use of the PCA3 score to trigger repeat biopsy compared with the PCPT risk calculator in men with at least 1 previous negative biopsy and elevated PSA levels.⁵⁷ They estimated that incorporating the PCA3 score of 25 (biopsy threshold) into the decision to recommend repeat biopsy could avoid 55.4% of repeat biopsies, with a 0.93% reduction in the 10-year survival rate. Wei et al (2014) calculated that for men with a PCA3 score less than 20 and PSA less than 4 ng/mL, 8% of men would have avoided a repeat biopsy with 9% of low-grade cancers missed and no

high-grade cancers missed.⁵² If only PCA3 scores less than 20 were taken into account, 46% of men would have avoided rebiopsy but 12% would have undiagnosed cancer and 3% would have undiagnosed high-grade cancer. For patients undergoing an initial biopsy, 13% of aggressive cancers would have been underdiagnosed.

Subsection Summary: PCA3 Score (e.g., Progensa PCA3 Assay)

At least 47 studies have evaluated the clinical validity of PCA3 mRNA to facilitate decision making for initial or repeat prostate biopsy, and there are systematic reviews of those studies. Studies of the PCA3 score as a diagnostic test for prostate cancer have reported sensitivities and specificities mostly in the moderate range (e.g., 76% sensitivity, 52% specificity). One systematic review that focused on studies of repeat biopsy found mixed results regarding whether the PCA3 assay could improve diagnostic accuracy over clinical assessment alone. Other systematic reviews found an AUC of 0.73 in men having an initial biopsy compared to 0.68 for the PCA3 assay in men having repeat biopsies. Other recent studies have reported minimal benefit of adding PCA3 to a model with clinical variables.

Given the lack of direct evidence of utility, a chain of evidence would be needed to demonstrate clinical utility. Studies of the PCA3 score as a diagnostic test for prostate cancer have reported sensitivities and specificities in the moderate range. Consideration of rebiopsy based only on PCA3 scores was estimated to miss 3% of aggressive cancers. One estimate suggested that adding a PCA3 score to PSA level would reduce rebiopsy rates by 8%, while another analysis suggested that over half of rebiopsies could be avoided by adding the PCA3 score to the PCPT risk calculator. No prospective studies were found describing differences in management based on PCA3 risk assessment. The clinical utility of the PCA3 test is uncertain because it is not clear whether its use can change management in ways that improve patient outcomes. The chain of evidence is incomplete.

Biomarker Testing for Selection of Men for Repeat Prostate Biopsy

Clinical Context and Test Purpose

The purpose of genetic and protein biomarker testing for prostate cancer is to inform the selection of men who should undergo repeat biopsy. The conventional decision-making tools for identifying men for prostate biopsy include DRE, serum PSA, and patient risk factors such as age, race, and family history of prostate cancer and are described in the previous section on selecting men for initial prostate biopsy.

Given the risk, discomfort, burden of biopsy, and the low diagnostic yield, there is a need for noninvasive tests that distinguish potentially aggressive tumors that should be referred for rebiopsy from clinically insignificant localized tumors or other prostatic conditions that do not need rebiopsy, with the goal of avoiding low-yield biopsy.

The following PICO was used to select literature that provides evidence relevant to this review.

Populations

The relevant population of interest are men for whom a rebiopsy is being considered because the results of an initial prostate biopsy were negative or equivocal and other clinical symptoms remain suspicious.

Interventions

For assessing future prostate cancer risk, numerous studies have demonstrated the association between many genetic and protein biomarker tests and prostate cancer. Commercially available tests for selection of men for repeat prostate biopsy include those described in Table 33.

Table 33. Commercially Available Tests to Determine Candidates for Repeat Prostate Biopsy

Test	Manufacturer	Description
PCA3 Score (e.g., Progensa PCA3 Assay)	<ul style="list-style-type: none"> • Hologic Gen-Probe • Many labs offer PCA3 tests (e.g., ARUP Laboratories, Mayo Medical Laboratories, LabCorp) 	Measures PCA3 mRNA in urine samples after prostate massage. PCA3 mRNA may be normalized using PSA to account for prostate cells.
ConfirmMDx	MDxHealth	Measures methylation of the genes <i>GSTP1</i> , <i>APC</i> , and <i>RASSF1</i> in tissue sample
Prostate Core Mitomics Test (PCMT)	Mitomics (formerly Genesis Genomics)	Measures deletions in mitochondrial DNA by polymerase chain reaction in tissue sample
Gene panel testing	Many labs offer SNV testing, such as Life Technologies, LabCorp (23andme), and ARUP Laboratories (deCODE)	Panel tests for prostate cancer risk are offered as laboratory-developed tests
MyProstate Score 2.0	LynxDx	Urine test designed to predict the presence of clinically significant prostate cancer (Grade Group ≥ 2 or Gleason score ≥ 7) by analyzing a comprehensive array of 18 unique gene transcripts

mRNA: messenger ribonucleic acid; PCA3: prostate cancer antigen 3; PSA: prostate-specific antigen; SNV: single nucleotide variant.

PCA3 is a noncoding long-chain RNA that is highly overexpressed in prostate cancer compared with noncancerous prostate tissue and is detectable in urine. The Progensa PCA3 Assay is approved by the FDA to facilitate decision making among men with prior negative prostate biopsies.

Epigenetic changes—chromatin protein modifications that do not involve changes to the underlying DNA sequence but can change gene expression—have been identified in specific genes. An extensive literature has reported significant associations between epigenetic DNA modifications and prostate cancer. ConfirmMDx (MDxHealth) is a commercially available test for gene methylation intended to distinguish true- from false-negative prostate biopsies to avoid the need for repeat biopsy.

The Prostate Core Mitomics Test (PCMT; Mitomics; formerly Genesis Genomics) is a proprietary test intended to determine whether a patient has prostate cancer, despite a negative prostate biopsy, by assessing a 3.4-kilobases deletion in mitochondrial DNA by polymerase chain reaction to detect “tumor field effect.” The test is performed on the initial negative prostate biopsy tissue and is being evaluated in men who have had an initial negative biopsy. A negative PCMT result is intended to confirm the result of the negative biopsy so that the patient can avoid a second biopsy, while a positive PCMT is intended to indicate that the patient is at high-risk of undiagnosed prostate cancer.

Single nucleotide variants (SNVs) occur when a single nucleotide is replaced with another, and are the most common type of genetic variation in humans. They occur normally throughout the genome and can act as biologic markers for disease association. Genome-wide association studies have identified correlations between prostate cancer risk and specific SNVs. However, it is widely accepted that, individually, SNV-associated disease risk is low and of no value in screening, although multiple SNVs in combination may account for a higher proportion of prostate cancer. Investigators have begun to explore the use of algorithms incorporating information from multiple SNVs to increase the clinical value of testing.

Comparators

Standard clinical examination for determining who requires a biopsy might include DRE, a review of the history of PSA values, and consideration of risk factors such as age, race, and family history. The ratio of free (unbound) PSA to total PSA is lower in men who have prostate cancer than in those who do not. A percent free PSA cutoff of 25% has been shown to have a sensitivity and specificity of 95% and 20%, respectively, for men with total PSA levels between 4.0 ng/mL and 10.0 ng/mL.²¹

The best way to combine all of the risk information to determine who should go to biopsy is not standardized. Risk algorithms have been developed that incorporate clinical risk factors into a risk score or probability. Two examples are the PCPT predictive model²² and the ERSPC-RC.²³ The American Urological Association and the Society of Abdominal Radiology recently recommended that high-quality prostate magnetic resonance imaging, if available, should be strongly considered in any patient with a prior negative biopsy who has persistent clinical suspicion for prostate cancer and who is under evaluation for a possible repeat biopsy.²⁴

Outcomes

The beneficial outcome of the test is to avoid a negative biopsy for prostate cancer. A harmful outcome is a failure to undergo a biopsy that would be positive for prostate cancer, especially when the disease is advanced or aggressive. Thus, the relevant measures of clinical validity are sensitivity and NPV. The appropriate reference standard is a biopsy, though prostate biopsy is an imperfect diagnostic tool. Biopsies can miss cancers and repeat biopsies are sometimes needed to confirm the diagnosis. Detection rates vary by biopsy method and patient characteristics, with published estimates between 10% and 28% for a second biopsy and 5% and 10% for a third biopsy.^{58,59} The timeframe of interest for calculating performance characteristics is time to biopsy results. Men who forego biopsy based on test results could miss or delay the diagnosis of cancer. Longer follow-up would be necessary to determine the effects on OS.

Study Selection Criteria

For the evaluation of clinical validity, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Studies were excluded from the evaluation of the clinical validity of the test because they did not use the marketed version of the test, did not include information needed to calculate performance characteristics, did not use an appropriate reference standard or the reference standard was unclear, did not adequately describe the patient characteristics, or did not adequately describe patient selection criteria.

Gene Hypermethylation and ConfirmMDx

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Three blinded multicenter validation studies of the ConfirmMDx test have been performed, 1 of which was conducted in African American men (Tables 34 and 35).^{60,61,62} For the cases that had a positive second biopsy after an initial negative biopsy, sensitivity ranged from 62% to 74%, with an NPV for a negative second biopsy ranging from 79% to 90%. Multivariate analysis of potential predictors of cancer on repeat biopsy, corrected for age, PSA, DRE, and first biopsy histopathology characteristics, showed that the ConfirmMDx test was the most significant independent predictor of patient outcome in both the Detection of Cancer Using Methylated Events in Negative Tissue (DOCUMENT) (OR=2.69; 95% CI, 1.60 to 4.51) and Methylation Analysis to Locate Occult Cancer (MATLOC) (OR=3.17; 95% CI, 1.81 to 5.53) studies.

Van Neste et al (2016) and Partin et al (2016) reported on results of combined data from the DOCUMENT and MATLOC studies for patients with high-grade (Gleason score, ≥ 7) prostate

cancer.^{63,64} DNA methylation was the most significant and important predictor of high-grade cancer, with an NPV of 96% (precision not reported) and an OR of 9.80 (95% CI, 2.12 to 45.23).

Table 34. Characteristics of Clinical Validity Studies Assessing ConfirmMDx

Study	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors	Comment
Waterhouse et al (2018) ⁶²	Archived, cancer-negative prostate biopsy core tissue samples from 211 African American men from 7 U.S. urology centers	Retrospective, ConfirmMDx performed on first biopsy	Repeat biopsy	NR	<30 mo	Yes	55% of men had a normal DRE; median PSA level was 6.2 ng/mL
Partin et al (2014) ⁶¹ DOCUMENT	Archived, cancer-negative prostate biopsy core tissue samples from 350 men from 5 U.S. urology centers	Retrospective, case-control with assay performed on archived samples	Repeat biopsy	NR	<24 mo	Yes	60% of men had a normal DRE; median PSA level was 5.3 ng/mL
Stewart et al (2013) ⁶⁰ MATLOC	Archived cancer-negative prostate biopsy core tissue samples from 498 men from the U.K. and Belgium	Retrospective ConfirmMDx performed on first biopsy	Repeat biopsy	NR	<30 mo	Yes	73% of men had benign DRE; median PSA level was 5.9 ng/mL

DOCUMENT: Detection of Cancer Using Methylated Events in Negative Tissue study; DRE: digital rectal exam; MATLOC: Methylation Analysis to Locate Occult Cancer study; NR: not reported; PSA: prostate-specific antigen.

Table 35. Results of Clinical Validity Studies Assessing ConfirmMDx

Study; Trial	Initial N	Final N	Excluded Samples	Prevalence of Condition	Clinical Validity (95% CI), %			
					Sens	Spec	PPV	NPV
Waterhouse et al (2018) ⁶²	NR	211	NR	81 had positive second biopsy (cases), 130 had negative second biopsy (controls)	74 (63 to 83)	60 (51 to 69)	54 (47 to 60)	79 (72 to 85)
Partin et al (2014) ⁶¹ DOCUMENT	350	320	30	92 had positive second biopsy (cases), 228 had negative second biopsy (controls)	62 (51 to 72)	64 (57 to 70)		88 (85 to 91)
Stewart et al (2013) ⁶⁰ MATLOC	498	483	15	87 had positive second biopsy, 396 had negative second biopsy (controls)	68 (57 to 77)	64 (59 to 69)		90 (87 to 93)
Summary					51 to 83	51 to 70	54	72 to 93

CI: confidence interval; DOCUMENT: Detection of Cancer Using Methylated Events in Negative Tissue study; MATLOC: Methylation Analysis to Locate Occult Cancer study; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

Tables 36 and 37 summarize the relevance and design and conduct limitations in each study.

Table 36. Study Relevance Limitations

Study; Trial	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Waterhouse et al (2018) ⁶²		1. Classification thresholds not described (proprietary)			

Study; Trial	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Partin et al (2014) ⁶¹ ; DOCUMENT		1. Classification thresholds not described (proprietary)			
Stewart et al (2013) ⁶⁰ ; MATLOC		1. Classification thresholds not defined. Training set with a stepwise approach to maximize NPV			

DOCUMENT: Detection of Cancer Using Methylated Events in Negative Tissue study; MATLOC: Methylation Analysis to Locate Occult Cancer study; NPV: negative predictive value.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 37. Study Design and Conduct Limitations

Study; Trial	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Waterhouse et al (2018) ³³	1. Selection not described				1. Inadequate description of indeterminate and missing samples	
Partin et al (2014) ⁵¹ ; DOCUMENT						
Stewart et al (2013) ⁶⁵ ; MATLOC						

DOCUMENT: Detection of Cancer Using Methylated Events in Negative Tissue study; MATLOC: Methylation Analysis to Locate Occult Cancer study;

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Aubry et al (2013) estimated the reduction in biopsies associated with ConfirmMDx use.⁶⁶ Using the performance characteristics from MATLOC, the authors estimated that 1106 biopsies per 1 million people would be avoided. The study did not include a decision analysis comparing the tradeoff in a reduction in biopsies and missed cancers.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of ConfirmMDx has not been established, a chain of evidence supporting the clinical utility of this test cannot be constructed.

Subsection Summary: Gene Hypermethylation and ConfirmMDx

Three retrospective clinical validation studies have reported on the ConfirmMDx score in men who have undergone repeat biopsy. The studies did not provide estimates of validity compared with other risk prediction models. ConfirmMDx was shown to be the most significant predictor of patient outcome in a multivariate model that included age, PSA level, DRE, and first biopsy histopathology characteristics. Sensitivity ranged from 62% to 74% and NPV from 79% to 90%. In a subsequent analysis of ConfirmMDx in men with high-grade prostate cancer on rebiopsy, the NPV was 96%, but the precision of the estimate was not reported.

No studies were found that directly show the effects of using ConfirmMDx test results on clinical outcomes. Given the lack of direct evidence of utility, a chain of evidence would be needed to demonstrate clinical utility. The ConfirmMDx test is associated with a diagnosis of prostate cancer and aggressive prostate cancer, but studies did not compare performance characteristics with standard risk prediction models. No data are currently available on the longer-term clinical outcomes of the men who did not have biopsy based on ConfirmMDx results. The chain of evidence is incomplete.

Prostate Core Mitomics Test

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Robinson et al (2010) assessed the clinical value of a 3.4-kilobase mitochondrial deletion in predicting rebiopsy outcomes.⁶⁷ Levels of the deletion were measured by a quantitative polymerase chain reaction in prostate biopsies negative for cancer from 101 men who underwent repeat biopsy within 1 year and had known outcomes. The clinical performance of the deletion was calculated with the use of an empirically established cycle threshold cutoff, the lowest cycle threshold as diagnostic of prostate cancer, and the histopathologic diagnosis on the second biopsy. Final data were based on 94 patients, who on the second biopsy had 20 malignant and 74 benign diagnoses. The cycle cutoff gave a sensitivity and specificity of 84% and 54%, respectively, with an area under the receiving operating curve of 0.75. The NPV was 91%.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Legisi et al (2016) queried a pathology services database to identify (1) men who had a negative initial prostate biopsy and a negative PCMT (n=644), and (2) men who had a negative initial prostate biopsy and a repeat biopsy (n=823). Of the 644 patients with a negative PCMT, 35 had a repeat biopsy and 5 (14.2%) were false-negatives who were found to have cancer on rebiopsy. The number of false-negatives of the patients who did not have a repeat biopsy cannot be determined from this study.⁶⁸ Of the second group of 823 men who had a repeat biopsy, 132 had a PCMT. Changes in physician decision-making led to earlier detection of prostate cancer by 2.5 months and an increase in cancer detection rates, but this was only observed when men with atypical small acinar proliferation on index biopsy were not included. Interpretation of these results is limited because testing was not random or consecutive.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of PCMT has not been established, a chain of evidence supporting the clinical utility of this test cannot be constructed.

Subsection Summary: Prostate Core Mitomics Test

The PCMT has preliminary data on its performance characteristics in a small validation study, showing a sensitivity of 84%, specificity of 91%, and NPV of 91%.

No studies were found that directly show the effects of using PCMT results on clinical outcomes. Given the lack of direct evidence of utility, a chain of evidence would be needed to demonstrate clinical utility. The PCMT has preliminary data on performance characteristics in a small validation study, but independent confirmation of clinical validity is needed. The studies did not provide estimates of validity compared with clinical examination and standard risk scores. Changes in physician decision-making led to earlier detection of prostate cancer and an increase in cancer detection rates, but the interpretation of these results is limited by potential selection bias. No data are available on long-term clinical outcomes. Data on clinical utility are lacking.

Candidate Gene Panels

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

A 3-gene panel (*HOXC6, TDRD1, DLX1*) developed by Leyten et al (2015) is now commercially available as SelectMDx (see above).⁶⁹ Xiao et al (2016) reported the development of an 8-gene panel (*PMP22, HPN, LMTK2, FN1, EZH2, GOLM1, PCA3, GSTP1*) that distinguished high-grade prostate cancer from indolent prostate cancer with a sensitivity of 93% and NPV of 61% (Tables 38 and 39).⁷⁰ Validation of this panel is needed.

Table 38. Characteristics of Clinical Validity Studies Assessing Candidate Gene Panels

Study	Study Population	Design	Reference Standard
Xiao et al (2016) ⁷⁰	Specimens from 158 men	Retrospective	High-grade prostate cancer on biopsy

Table 39. Results of Clinical Validity Studies Assessing Candidate Gene Panels

Study	N	Clinical Validity (95% CI), %			
		Sens	Spec	PPV	NPV
Xiao et al (2016) ⁷⁰ ; 8-gene panel	158	93 (88 to 97)	70 (36 to 104)	98 (95 to 100)	61 (25 to 97)

CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of these multigene tests has not been established, a chain of evidence supporting the clinical utility of these tests cannot be constructed.

Subsection Summary: Candidate Gene Panels

Numerous studies have demonstrated the association between SNVs and prostate cancer. Gene panels that evaluate the likelihood of prostate cancer on biopsy are in development.

MyProstate Score

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Tosoian et al (2023) evaluated the MyProstate Score test in men with persistent risk of Grade Group ≥ 2 cancer after a negative biopsy who are being considered for repeat biopsy.⁷¹ A total of 422 men underwent repeat biopsy in the primary study cohort; the validation cohort consisted of 268 men. Thresholds of 15 and 40 met pre-defined performance criteria in the primary cohort (median PSA 6.4; IQR, 4.3 to 9.1); upon biopsy, 58 men (14%) were found to have Grade Group ≥ 2 cancer, and 25 men (5.9%) had Grade Group ≥ 3 cancer. In the validation cohort, repeat biopsy was negative in 205 men (76%), and revealed Grade Group 1 cancer in 38 men (14%); it also demonstrated Grade Group ≥ 2 cancer in 25 men (9.3%). The rule-out threshold of 15 provided 100% NPV and 100% sensitivity for Grade Group ≥ 2 cancer. Using the upper threshold of 40 to rule-in biopsies for only men at highest risk would have avoided 179 biopsies (67%) maintained a 95% NPV value.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Clinical utility studies using MyProstate Score results for decision making for repeat biopsy or treatment have not been reported.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of MyProstate Score has not been established, a chain of evidence supporting the clinical utility of this test cannot be constructed.

Subsection Summary: MyProstate Score

One recent prospective study reports sensitivity and specificity data for the MyProstate Score test. No studies were found that directly show the effects of using MyProstate test results on clinical outcomes.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a U.S. professional society, an international society with U.S. representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Urological Association et al

In 2023, the American Urological Association (AUA) and the Society of Urologic Oncology (SUO) published updated guidelines on the early detection of prostate cancer. Specific guidance related to diagnosis, risk assessment, and utilization of biomarkers are stated in Table 40 below.⁷²

Table 40. Relevant AUA/SUO Guideline Statements on Prostate Cancer Screening and Biopsy

Guideline Statement	Evidence Grade and Strength
When screening for prostate cancer, clinicians should use PSA as the first screening test	Strong Recommendation; Evidence Level: Grade A
For people with a newly elevated PSA, clinicians should repeat the PSA prior to a secondary biomarker, imaging, or biopsy	Expert Opinion
Clinicians may use digital rectal exam (DRE) alongside PSA to establish risk of clinically significant prostate cancer	Conditional Recommendation; Evidence Level: Grade C
For people undergoing prostate cancer screening, clinicians should not use PSA velocity as the sole indication for a secondary biomarker, imaging, or biopsy	Strong Recommendation; Evidence Level: Grade B
Clinicians may use adjunctive urine or serum markers when further risk stratification would influence the decision regarding whether to proceed with biopsy.	Conditional Recommendation; Evidence Level: Grade C
After a negative biopsy, clinicians should not solely use a PSA threshold to decide whether to repeat the biopsy	Strong Recommendation; Evidence Level: Grade B
After a negative biopsy, clinicians may use blood-, urine-, or tissue-based biomarkers selectively for further risk stratification if results are likely to influence the decision regarding repeat biopsy or otherwise substantively change the patient's management	Conditional Recommendation; Evidence Level: Grade C
In patients with multifocal HGPIN [high-grade prostatic intraepithelial neoplasia], clinicians may proceed with	Expert Opinion

Guideline Statement	Evidence Grade and Strength
additional risk evaluation, guided by PSA/DRE and mpMRI findings DRE: digital rectal exam; PSA: prostate-specific antigen; mpMRI: multi-parametric magnetic resonance imaging	

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer early detection (v.2.2024) recommend that any man with a PSA level greater than 3 ng/mL undergo workup for benign disease, repeat PSA, and DRE (category 2A evidence).⁷³

The NCCN guidelines state that "biomarkers that improve the specificity of detection are not, as yet, mandated as first-line screening tests in conjunction with serum PSA. However, there may be some patients who meet PSA standards for consideration of prostate biopsy, but for whom the patient and/or the physician wish to further define risk". The guidelines recommend that the probability of high-grade cancer (Gleason score $\geq 3+4$, Grade Group 2 or higher) may be further defined utilizing biomarkers that improve the specificity of screening that includes percent free PSA, with consideration of the Prostate Health Index (PHI), SelectMDx, 4K score, ExoDx Prostate Test, MyProstate Score (MPS), and IsoPSA. NCCN also noted that the extent of validation of these tests across diverse populations is variable and is not yet known how these tests could be applied in optimal combination with magnetic resonance imaging (MRI).

For men who had a negative biopsy but are thought to be at higher risk, NCCN recommends to consider biomarkers that improve the specificity of screening (category 2A evidence). Tests that should be considered in the post-biopsy setting include percent-free PSA, 4Kscore, PHI, PCA3, ConfirmMDx, ExoDx Prostate Test, MPS, and IsoPSA.

National Institute for Health and Care Excellence

In 2019 and in 2021, when guidelines were updated, the NICE guidelines did not recommend the Progensa PCA3 Assay or the PHI test for use in men with suspicion of prostate cancer who had a negative or inconclusive prostate biopsy.⁷⁴

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (2018) updated recommendations for prostate cancer screening. Genetic and protein biomarkers addressed in this evidence review, including *PCA3*, were not mentioned.⁷⁵

The U.S. Preventive Services Task Force advises individualized decision making about screening for prostate cancer after discussion with a clinician for men ages 55 to 69 (C recommendation) and recommends against PSA-based screening in men 70 and older (D recommendation). An update of these recommendations is pending.

Medicare National and Local Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Local coverage guidance for California is provided by the Molecular Diagnostic Services Program (MolDX®) program in the document [MolDX: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer](#)⁷⁶ and the associated [Billing and Coding: MolDX: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer](#).⁷⁷

MolDX identifies two applications of molecular biomarkers to risk-stratify patients at increased risk for prostate cancer:

- I. A non-invasive or minimally invasive test, the results of which are obtained to inform the decision to perform an initial biopsy (pre-biopsy).

- II. A test performed to further refine risk when a biopsy has been performed but does not clearly indicate malignancy on histopathologic examination (post-biopsy). Such a test can potentially obviate the need for a repeat biopsy.

MolDx provides limited coverage for molecular Deoxyribonucleic acid/ribonucleic acid (DNA/RNA) biomarker tests for the diagnosis of prostate cancer that help differentiate men who may or may not benefit from a prostate biopsy when ALL of the following conditions are met:

1. The patient must not have an established diagnosis of prostate cancer.
2. The beneficiary is a candidate for prostate biopsy or repeat prostate biopsy, according to a consensus guideline [(i.e., National Comprehensive Cancer Network® (NCCN), American Society of Clinical Oncology® (ASCO), American Urological Association (AUA)].
 - a. For men \leq 75 years of age - Prostate Specific Antigen (PSA) (or adjusted PSA in special populations, i.e., patients taking 5alpha-reductase inhibitors) OR repeat PSA are >3 and <10 ng/mL AND/OR Digital Rectal Exam (DRE) findings are very suspicious for cancer.
 - b. For men >75 years of age - PSA (or adjusted PSA in special populations, i.e., patients taking 5-alpha-reductase inhibitors) OR repeat PSA are ≥ 4 and <10 ng/mL AND/OR DRE findings are very suspicious for cancer.

EXCEPTION: a molecular biomarker test may be performed in men with PSA levels >10 ng/mL who are being considered for repeat biopsy IF appropriate according to consensus guidelines AND according to the following: the specific biomarker test has been validated in men with PSA levels >10 ng/mL AND a Multiparametric MRI (mpMRI) is negative, *if performed*.

3. The beneficiary has not had a prostate biopsy OR has had a previous negative or non-malignant but abnormal histopathology finding (i.e., atypical small acinar proliferation (ASAP) or high-grade prostatic intraepithelial neoplasia (HGPIN) on prostate biopsy).
 - o Patients under consideration for a repeat biopsy have first undergone repeat PSA and/or DRE testing as recommended by consensus guidelines
4. The beneficiary would benefit from treatment of prostate cancer and patient management will be impacted by use of a biomarker in a manner already demonstrated in the peer-reviewed published literature to improve patient outcomes.
5. The medical record supports the medical necessity for the biomarker test.
6. Testing is performed according to the intended use of the test in the intended patient population for which the test was developed and validated.
7. Testing must be performed according to Clinical Laboratory Improvement Amendments (CLIA) and/or Food and Drug Administration (FDA) regulations in an accredited laboratory.
8. For a given clinical indication (pre-OR post-biopsy), only one molecular biomarker may be performed UNLESS a second test, meeting all the criteria established herein, is reasonable and necessary as an adjunct to the first test, according to criteria established in this policy.
9. If the test relies on an algorithm which may range in complexity from a threshold determination of a single numeric value to a complex mathematical or computational function, the algorithm must be validated in a cohort that is not a development cohort for the algorithm.
10. The analytes measured have demonstrated clinical validity and clinical utility (i.e., improved detection or discrimination of cancer or high-grade cancer or reduction in the need for biopsy) in the peer-reviewed published literature, establishing a clear and significant biological/molecular basis for stratifying patients and subsequently selecting (either positively or negatively) their clinical management decision within a clearly defined population.
11. The test is ordered by a physician specialist in the management of prostate cancer, such as a urologist or oncologist. An exception may be made in geographic locations where the specialist(s) cannot be reasonably reached by the beneficiary and the ordering provider is located closer to the beneficiary's place of residence than the nearest specialist. We would

generally expect that beneficiaries for whom the test is ordered under this exception to be living in rural locations, islands, or some other location where access to care is limited.

The following coding guidance is included in MolDx [Billing and Coding: MolDx: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer](#).⁷⁷

The following tests may be billed in the post-biopsy setting (after a negative or non-malignant biopsy, as defined in the policy) for individuals contemplating a repeat biopsy:

- Progensa PCA3 assay (CPT 81313), performed on post-digital rectal exam (DRE) urine specimens
- ConfirmMDx assay (CPT 81551), performed on formalin-fixed, paraffin embedded (FFPE) tissue specimens.
- MyProstate Score 2.0 (MPS 2.0) (PLA 0403U), performed on first catch urine specimens

The following test may be billed in the pre-biopsy setting as defined in the policy:

- SelectMDx assay (PLA 0339U), performed on post-digital rectal exam (DRE) urine specimens

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 41.

Table 41. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT04100811 ^a	Validating the miR Scientific Sentinel™ Platform (Sentinel PCC4 Assay) in Men Undergoing Core Needle Biopsy Due to Suspicion of Prostate Cancer for Distinguishing Between no Cancer, Low-, Intermediate- and High-Risk Prostate Cancer	4000	Dec 2024
NCT04079699	Predicting Prostate Cancer Using a Panel of Plasma and Urine Biomarkers Combined in an Algorithm in Elderly Men Above 70 Years	700	Oct 2039
NCT05050084	Parallel Phase III Randomized Trials of Genomic-Risk Stratified Unfavorable Intermediate Risk Prostate Cancer: De-Intensification and Intensification Clinical Trial Evaluation (GUIDANCE)	2050	Apr 2037

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
 - PSA level/density
 - Pertinent comorbidities
 - Biopsy Gleason score
 - Number of biopsy cores with presence of disease including cancer involvement
- Test requested and reason for test
- Documentation that individual is a candidate for active surveillance or definitive therapy
- Prior treatment (if applicable) including prostatectomy if applicable

Post Service (in addition to the above, please include the following):

- Laboratory report/results

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	0005U	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score <i>(Includes ExosomeDx® Prostate (IntelliScore), Exosome Diagnostics, Inc)</i>
	0021U	Oncology (prostate), detection of 8 autoantibodies (ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2), multiplexed immunoassay and flow cytometry serum, algorithm reported as risk score <i>(Includes Apifin®, Armune BioScience, Inc)</i>
	0113U	Oncology (prostate), measurement of PCA3 and TMPRSS2-ERG in urine and PSA in serum following prostatic massage, by RNA amplification and fluorescence-based detection, algorithm reported as risk score <i>(Includes MyProstateScore, Lynx DX)</i>
	0228U	Oncology (prostate), multianalyte molecular profile by photometric detection of macromolecules adsorbed on nanospunge array slides with machine learning, utilizing first morning voided urine, algorithm reported as likelihood of prostate cancer <i>(Includes PanGIA Prostate, Genetics Institute of America, Entopsis, LLC)</i>
	0339U	Oncology (prostate), mRNA expression profiling of HOXC6 and DLX1, reverse transcription polymerase chain reaction (RT-PCR), first-void urine following digital rectal examination, algorithm reported as probability of high-grade cancer

Type	Code	Description
		<i>(Includes SelectMDx® for Prostate Cancer, MDxHealth®, Inc)</i>
	0343U	Oncology (prostate), exosome-based analysis of 442 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as molecular evidence of no-, low-, intermediate- or high-risk of prostate cancer <i>(Includes miR Sentinel™ Prostate Cancer Test, miR Scientific, LLC)</i>
	0403U	Oncology (prostate), mRNA, gene expression profiling of 18 genes, first-catch urine, algorithm reported as percentage of likelihood of detecting clinically significant prostate cancer <i>(Includes MyProstateScore 2.0, LynxDX)</i>
	0424U	Oncology (prostate), exosome-based analysis of 53 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as no molecular evidence, low-, moderate- or elevated-risk of prostate cancer <i>(Includes miR Sentinel™ Prostate Cancer Test, miR Scientific®, LLC)</i>
	0495U	Oncology (prostate), analysis of circulating plasma proteins (tPSA, fPSA, KLK2, PSP94, and GDF15), germline polygenic risk score (60 variants), clinical information (age, family history of prostate cancer, prior negative prostate biopsy), algorithm reported as risk of likelihood of detecting clinically significant prostate cancer <i>(Includes Stockholm3, BioAgilytix Diagnostics)</i>
	81313	PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (e.g., prostate cancer)
	81539	Oncology (high-grade prostate cancer), biochemical assay of four proteins (Total PSA, Free PSA, Intact PSA, and human kallikrein-2 [hK2]), utilizing plasma or serum, prognostic algorithm reported as a probability score
	81551	Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy
	84153	Prostate specific antigen (PSA); total
	84154	Prostate specific antigen (PSA); free
	86316	Immunoassay for tumor antigen, other antigen, quantitative (e.g., CA 50, 72-4, 549), each
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
02/01/2026	New policy.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary or Medical Necessity means reasonable and necessary services to protect life, to prevent significant illness or significant disability, or alleviate severe pain through the diagnosis or treatment of disease, illness, or injury, as required under W&I section 14059.5(a) and 22 CCR section 51303(a). Medically Necessary services must include services necessary to achieve age-appropriate growth and development, and attain, maintain, or regain functional capacity.

For Members less than 21 years of age, a service is Medically Necessary if it meets the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) standard of Medical Necessity set forth in 42 USC section 1396d(r)(5), as required by W&I sections 14059.5(b) and 14132(v). Without limitation, Medically Necessary services for Members less than 21 years of age include all services necessary to achieve or maintain age-appropriate growth and development, attain, regain or maintain functional capacity, or improve, support, or maintain the Member's current health condition. Contractor must determine Medical Necessity on a case-by-case basis, taking into account the individual needs of the Child.

Criteria Determining Experimental/Investigational Status

In making a determination that any procedure, treatment, therapy, drug, biological product, facility, equipment, device, or supply is "experimental or investigational" by the Plan, the Plan shall refer to evidence from the national medical community, which may include one or more of the following sources:

1. Evidence from national medical organizations, such as the National Centers of Health Service Research.
2. Peer-reviewed medical and scientific literature.
3. Publications from organizations, such as the American Medical Association (AMA).
4. Professionals, specialists, and experts.
5. Written protocols and consent forms used by the proposed treating facility or other facility administering substantially the same drug, device, or medical treatment.
6. An expert physician panel selected by one of two organizations, the Managed Care Ombudsman Program of the Medical Care Management Corporation or the Department of Managed Health Care.

Feedback

Blue Shield of California Promise Health Plan is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/en/bsp/providers.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Blue Shield of California Promise Health Plan Prior Authorization Department at (800) 468-9935, or the Complex Case Management Department at (855) 699-5557 (TTY 711) for San Diego County and (800) 605-2556 (TTY 711) for Los Angeles County or visit the provider portal at www.blueshieldca.com/en/bsp/providers.

Disclaimer: Blue Shield of California Promise Health Plan may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield of California Promise Health Plan reserves the right to review and update policies as appropriate.