MEDICAL POLICY – 2.04.514

Protein Biomarkers for Diagnosis and Risk Assessment of Prostate Cancer

BCBSA Ref. Policy: 2.04.33

Effective Date:	Jan. 1, 2026	RELATED MEDICAL POLICIES:
Last Revised:	Dec. 9, 2025	None
Replaces:	12.04.33	

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Introduction

A biomarker is a chemical in the body. Certain biomarkers can show when something unusual is going on with certain bodily processes. One of the most commonly known and tested biomarkers is prostate specific antigen (PSA). Higher levels of PSA in the blood indicate a problem with the prostate. The difficulty is that the PSA test doesn't tell us what kind of problem is affecting the prostate – whether it's simply an enlarged prostate or cancer. If the PSA is high, the usual next step is a biopsy. A biopsy is taking small bits of tissue to see if cancer is present. Other biomarker tests have been developed in recent years with the hope of telling doctors which individuals should have a biopsy and who can skip it. Published medical studies about these newer prostate biomarker tests are contradictory. That means some studies show the tests detect what they're supposed to, and other studies don't. At this time, there is not enough medical evidence to show that newer prostate cancer biomarker tests are effective.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Test	Investigational
Protein biomarkers	**The following protein biomarkers for the diagnosis of prostate cancer are considered investigational:** • Autoantibodies ARF 6, NKX3-1, 5′-UTR-BMI1, CEP 164, 3′-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2 (e.g., Apinify) • Kallikrein markers (e.g., 4Kscore Test) • MiCheck Prostate

Coding

Code	Description
CPT	
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 (4KScore)
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 (Apifiny)
0591U	Oncology (prostate cancer), biochemical analysis of 3 proteins (total PSA, free PSA, and HE4), plasma, serum, prognostic algorithm incorporating 3 proteins and digital rectal examination, results reported as a probability score for clinically significant prostate cancer (new code effective 10/01/25)

Related Information

N/A

Evidence Review

Description

Various 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 policy addresses these types of tests for cancer risk assessment.

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 individuals 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 United States (US) 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 US; 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 cancer,[3] indicating that many cases of prostate 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 crosswalk 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	9-10	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.

Biomarker Testing for Selection of Men for Initial Prostate Biopsy

The purpose of 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 individual risk factors such as age, race, and family history of prostate cancer.

DRE 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] DRE 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 US, 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.

Interventions

For assessing future prostate cancer risk, numerous studies have demonstrated the association between protein biomarker tests and prostate cancer. Commercially available tests for the selection of men for initial prostate biopsy reviewed in this policy are 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

Test	Manufacturer	Description
		prostate cancer (defined as a Gleason score ≥7) if a prostate biopsy were performed.
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
MiCheck Prostate	Minomic Inc.	Algorithm based test that incorporates data from immunoassays for total prostate specific antigen (tPSA), free PSA (fPSA), and Human Epididymal Protein 4 (HE4) and the patient's age.

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 individual 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 individuals with a previous diagnosis of prostate cancer, who have had a DRE in the previous 4 days, who have received 5α reductase inhibitor therapy in the previous 6 months, or who have undergone treatment for symptomatic benign prostatic hypertrophy in the previous 6 months.

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.

MiCheck Prostate is an algorithm that combines the testing results of three Abbott ARCHITECT™ serum immunoassays (total prostate specific antigen [tPSA], free PSA [fPSA] and Human Epididymal Protein 4 [HE4]) and one clinical factor (i.e. the patient's Age). The MiCheck Prostate algorithm combines these results to calculate a Percentage Risk Score, which provides an indication of the likelihood of the presence of clinically significant Prostate Cancer (csPCa) (Gleason score >3+4) and is called the MiCheck %Risk of csPCa.

Summary of Evidence

For individuals who are being considered for an initial prostate biopsy who receive testing for protein biomarkers of prostate cancer (e.g., kallikreins biomarkers and 4Kscore Test and Apifiny), the evidence includes systematic reviews, meta-analyses, and primarily observational studies. The 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 DRE, a 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.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in **Table 3**.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
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

NCT No.	Trial Name	Planned Enrollment	Completion Date
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.

Practice Guidelines and Position Statements

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

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or the 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 4 below.[72]

Table 4. 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 additional risk evaluation, guided by PSA/DRE and mpMRI findings	Expert Opinion

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 digital rectal examination (category 2A evidence).[74]

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 ≥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 National Institute for Health and Care Excellence (NICE) 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.[75]

US Preventive Services Task Force Recommendations

The US Preventive Services Task Force (USPSTF; 2018) updated recommendations for prostate cancer screening. Protein biomarkers addressed in this policy, including PCA3, were not mentioned.[76]

The USPSTF 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 Coverage

There is no national coverage determination.

Regulatory Status

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, ConfirMDx), Innovative Diagnostics (PHI), MiCheck Prostate (Minomic Inc.), 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.

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History

Date	Comments
01/04/19	New policy, approved December 13, 2018, effective January 4, 2019. This policy replaces policy 12.04.33. Policy updated with literature review through September 2018; references 6, 32-34, and 39, added. Apinifi added as investigational. Candidate gene panels, ConfirmMDx, Prostate Core Mitomics test, PCA3 (Progensa) ExoDx Prostate IntelliScore, Prostate Health Index (phi), Select MDx, and TMPRSS ERG fusion gene removed from policy. Removed CPT codes 81229, 81313, 81479, 81541, and 81551 as they are now reviewed by AIM Specialty Health.
02/01/19	Minor update, title changed from “Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer“ to “Protein Biomarkers for Diagnosis and Risk Assessment of Prostate Cancer“.

Date	Comments
05/01/19	Minor update, History section updated for clarity.
01/01/20	Annual Review, approved December 10, 2019. Policy updated with literature review through September 2019; references added. Policy statements unchanged.
01/01/21	Annual Review, approved December 1, 2020. Policy updated with literature review through October 16, 2020; references added. Policy statements unchanged.
06/01/21	Annual Review, approved May 4, 2021. Policy updated with literature review through February 19, 2021. Policy statements unchanged.
01/01/23	Annual Review, approved December 23, 2022. Policy updated with literature review through September 19, 2022; references added. Policy statements unchanged.
01/01/24	Annual Review, approved December 26, 2023. Policy updated with literature review through September 26, 2023; references added. Policy statements unchanged.
01/01/25	Annual Review, approved December 23, 2024. Policy updated with literature review through September 16, 2024; references added. Policy statements unchanged.
01/01/26	Annual Review, approved December 9, 2025. Policy updated with literature review through September 25, 2025; References added. Added MiCheck prostate to the list of protein biomarkers for the diagnosis of prostate cancer that are considered investigational. Added CPT code 0591U; moved to this policy from policy 2.04.520 Laboratory Testing Investigational Services.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.