

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, 2024

Last Revised: Dec. 26, 2023


Replaces: 12.04.33

RELATED MEDICAL POLICIES:

None

Select a hyperlink below to be directed to that section.

[POLICY CRITERIA](#) | [CODING](#) | [RELATED INFORMATION](#)
[EVIDENCE REVIEW](#) | [REFERENCES](#) | [HISTORY](#)

 Clicking this icon returns you to the hyperlinks menu above.

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	<p>The following protein biomarkers for the diagnosis of prostate cancer are considered investigational:</p> <ul style="list-style-type: none"> • Autoantibodies ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2 (e.g., Apifyny) • Kallikrein markers (e.g., 4Kscore Test)

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 (Apifyny)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

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 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 United States; 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 age 55 and 60% of men age 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 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 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 prostate cancer (defined as a Gleason score ≥ 7) if a prostate biopsy were performed.
Apifyn	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



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 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.

Apify 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.

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 Apify), 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			
NCT00773773	A Study to Assess if a Combination of Serum Measurements of Molecular Biomarkers and Serum Protein Profiling Can be Used to Predict Which Patients Undergoing Prostatic Biopsy Will be Diagnosed With Cancer	500	Oct 2023
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 2023
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 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 4 below.^{74,75}

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



Guideline Statement	Evidence Grade and Strength
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 (v.1.2023) recommend that any man with a PSA level greater than 3 ng/mL undergo workup for benign disease, repeat PSA, and digital rectal examination.⁷⁶

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 National Institute for Health and Care Excellence (NICE) did not recommend the Progenesa PCA3 Assay or the PHI test for use in men with suspicion of prostate cancer who had a negative or inconclusive prostate biopsy.⁷⁷



U.S. 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.⁷⁸

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).

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), 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.

References

1. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014. Bethesda, MD: National Cancer Institute; 2017.
2. Odedina FT, Akinremi TO, Chinegwundoh F, et al. Prostate cancer disparities in Black men of African descent: a comparative literature review of prostate cancer burden among Black men in the United States, Caribbean, United Kingdom, and West Africa. *Infect Agent Cancer*. Feb 10 2009; 4 Suppl 1(Suppl 1): S2. PMID 19208207



3. Bell KJ, Del Mar C, Wright G, et al. Prevalence of incidental prostate cancer: A systematic review of autopsy studies. *Int J Cancer*. Oct 01 2015; 137(7): 1749-57. PMID 25821151
4. Gleason DF. Classification of prostatic carcinomas. *Cancer Chemother Rep*. Mar 1966; 50(3): 125-8. PMID 5948714
5. National Cancer Institute. SEER Database.
<https://seer.cancer.gov/seerquery/index.php?page=view&id=20170036&type=q>. Accessed December 4, 2023.
6. Hoogendam A, Buntinx F, de Vet HC. The diagnostic value of digital rectal examination in primary care screening for prostate cancer: a meta-analysis. *Fam Pract*. Dec 1999; 16(6): 621-6. PMID 10625141
7. Gosselaar C, Roobol MJ, Roemeling S, et al. The role of the digital rectal examination in subsequent screening visits in the European randomized study of screening for prostate cancer (ERSPC), Rotterdam. *Eur Urol*. Sep 2008; 54(3): 581-8. PMID 18423977
8. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level or =4.0 ng per milliliter. *N Engl J Med*. May 27 2004; 350(22): 2239-46. PMID 15163773
9. Catalona WJ, Smith DS, Ratliff TL, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. *N Engl J Med*. Apr 25 1991; 324(17): 1156-61. PMID 1707140
10. Aus G, Bergdahl S, Lodding P, et al. Prostate cancer screening decreases the absolute risk of being diagnosed with advanced prostate cancer--results from a prospective, population-based randomized controlled trial. *Eur Urol*. Mar 2007; 51(3): 659-64. PMID 16934392
11. Buzzoni C, Auvinen A, Roobol MJ, et al. Metastatic Prostate Cancer Incidence and Prostate-specific Antigen Testing: New Insights from the European Randomized Study of Screening for Prostate Cancer. *Eur Urol*. Nov 2015; 68(5): 885-90. PMID 25791513
12. Arnsrud Godtman R, Holmberg E, Lilja H, et al. Opportunistic testing versus organized prostate-specific antigen screening: outcome after 18 years in the Göteborg randomized population-based prostate cancer screening trial. *Eur Urol*. Sep 2015; 68(3): 354-60. PMID 25556937
13. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol*. Aug 2010; 11(8): 725-32. PMID 20598634
14. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med*. Mar 26 2009; 360(13): 1320-8. PMID 19297566
15. Wolf AM, Wender RC, Etzioni RB, et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. *CA Cancer J Clin*. 2010; 60(2): 70-98. PMID 20200110
16. Rosario DJ, Lane JA, Metcalfe C, et al. Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within ProtecT study. *BMJ*. Jan 09 2012; 344: d7894. PMID 22232535
17. Liss M, Ehdai B, Loeb S, et al. The Prevention and Treatment of the More Common Complications Related to Prostate Biopsy Update. 2012; updated 2016; <https://www.auanet.org/guidelines-and-quality/guidelines/best-practice-statements-and-whitepapers/prostate-needle-biopsy-complications>. Accessed December 4, 2023.
18. Lavallée LT, Binette A, Witiuk K, et al. Reducing the Harm of Prostate Cancer Screening: Repeated Prostate-Specific Antigen Testing. *Mayo Clin Proc*. Jan 2016; 91(1): 17-22. PMID 26688045
19. Ruiz-Aragón J, Márquez-Peláez S. [Assessment of the PCA3 test for prostate cancer diagnosis: a systematic review and meta-analysis]. *Actas Urol Esp*. Apr 2010; 34(4): 346-55. PMID 20470697
20. Mackinnon AC, Yan BC, Joseph LJ, et al. Molecular biology underlying the clinical heterogeneity of prostate cancer: an update. *Arch Pathol Lab Med*. Jul 2009; 133(7): 1033-40. PMID 19642730
21. Partin AW, Brawer MK, Subong EN, et al. Prospective evaluation of percent free-PSA and complexed-PSA for early detection of prostate cancer. *Prostate Cancer Prostatic Dis*. Jun 1998; 1(4): 197-203. PMID 12496895



22. Thompson IM, Ankerst DP, Chi C, et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. *J Natl Cancer Inst.* Apr 19 2006; 98(8): 529-34. PMID 16622122
23. van Vugt HA, Roobol MJ, Kranse R, et al. Prediction of prostate cancer in unscreened men: external validation of a risk calculator. *Eur J Cancer.* Apr 2011; 47(6): 903-9. PMID 21163642
24. Rosenkrantz AB, Verma S, Choyke P, et al. Prostate Magnetic Resonance Imaging and Magnetic Resonance Imaging Targeted Biopsy in Patients with a Prior Negative Biopsy: A Consensus Statement by AUA and SAR. *J Urol.* Dec 2016; 196(6): 1613-1618. PMID 27320841
25. Mi C, Bai L, Yang Y, et al. 4Kscore diagnostic value in patients with high-grade prostate cancer using cutoff values of 7.5% to 10%: A meta-analysis. *Urol Oncol.* Jun 2021; 39(6): 366.e1-366.e10. PMID 33685800
26. Russo GI, Regis F, Castelli T, et al. A Systematic Review and Meta-analysis of the Diagnostic Accuracy of Prostate Health Index and 4-Kallikrein Panel Score in Predicting Overall and High-grade Prostate Cancer. *Clin Genitourin Cancer.* Aug 2017; 15(4): 429-439.e1. PMID 28111174
27. Parekh DJ, Punnen S, Sjoberg DD, et al. A multi-institutional prospective trial in the USA confirms that the 4Kscore accurately identifies men with high-grade prostate cancer. *Eur Urol.* Sep 2015; 68(3): 464-70. PMID 25454615
28. Punnen S, Freedland SJ, Polascik TJ, et al. A Multi-Institutional Prospective Trial Confirms Noninvasive Blood Test Maintains Predictive Value in African American Men. *J Urol.* Jun 2018; 199(6): 1459-1463. PMID 29223389
29. Bhattu AS, Zappala SM, Parekh DJ, et al. A 4Kscore Cut-off of 7.5% for Prostate Biopsy Decisions Provides High Sensitivity and Negative Predictive Value for Significant Prostate Cancer. *Urology.* Feb 2021; 148: 53-58. PMID 33217456
30. Stattin P, Vickers AJ, Sjoberg DD, et al. Improving the Specificity of Screening for Lethal Prostate Cancer Using Prostate-specific Antigen and a Panel of Kallikrein Markers: A Nested Case-Control Study. *Eur Urol.* Aug 2015; 68(2): 207-13. PMID 25682340
31. Loeb S, Shin SS, Broyles DL, et al. Prostate Health Index improves multivariable risk prediction of aggressive prostate cancer. *BJU Int.* Jul 2017; 120(1): 61-68. PMID 27743489
32. Konety B, Zappala SM, Parekh DJ, et al. The 4Kscore Test Reduces Prostate Biopsy Rates in Community and Academic Urology Practices. *Rev Urol.* 2015; 17(4): 231-40. PMID 26839521
33. Pecoraro V, Roli L, Plebani M, et al. Clinical utility of the (-2)proPSA and evaluation of the evidence: a systematic review. *Clin Chem Lab Med.* Jul 01 2016; 54(7): 1123-32. PMID 26609863
34. Anyango R, Ojwando J, Mwita C, et al. Diagnostic accuracy of [-2]proPSA versus Gleason score and Prostate Health Index versus Gleason score for the determination of aggressive prostate cancer: a systematic review. *JBIM Evid Synth.* Jun 2021; 19(6): 1263-1291. PMID 33741840
35. Catalona WJ, Partin AW, Sanda MG, et al. A multicenter study of [-2]pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/ml prostate specific antigen range. *J Urol.* May 2011; 185(5): 1650-5. PMID 21419439
36. Tosoian JJ, Druskin SC, Andreas D, et al. Use of the Prostate Health Index for detection of prostate cancer: results from a large academic practice. *Prostate Cancer Prostatic Dis.* Jun 2017; 20(2): 228-233. PMID 28117387
37. White J, Shenoy BV, Tutrone RF, et al. Clinical utility of the Prostate Health Index (phi) for biopsy decision management in a large group urology practice setting. *Prostate Cancer Prostatic Dis.* Apr 2018; 21(1): 78-84. PMID 29158509
38. Sanda MG, Feng Z, Howard DH, et al. Association Between Combined TMPRSS2:ERG and PCA3 RNA Urinary Testing and Detection of Aggressive Prostate Cancer. *JAMA Oncol.* Aug 01 2017; 3(8): 1085-1093. PMID 28520829
39. Tomlins SA, Day JR, Lonigro RJ, et al. Urine TMPRSS2:ERG Plus PCA3 for Individualized Prostate Cancer Risk Assessment. *Eur Urol.* Jul 2016; 70(1): 45-53. PMID 25985884
40. Ankerst DP, Goros M, Tomlins SA, et al. Incorporation of Urinary Prostate Cancer Antigen 3 and TMPRSS2:ERG into Prostate Cancer Prevention Trial Risk Calculator. *Eur Urol Focus.* Jan 2019; 5(1): 54-61. PMID 29422418



41. Tosoian JJ, Trock BJ, Morgan TM, et al. Use of the MyProstateScore Test to Rule Out Clinically Significant Cancer: Validation of a Straightforward Clinical Testing Approach. *J Urol.* Mar 2021; 205(3): 732-739. PMID 33080150
42. Newcomb LF, Zheng Y, Faino AV, et al. Performance of PCA3 and TMPRSS2:ERG urinary biomarkers in prediction of biopsy outcome in the Canary Prostate Active Surveillance Study (PASS). *Prostate Cancer Prostatic Dis.* Sep 2019; 22(3): 438-445. PMID 30664734
43. Van Neste L, Hendriks RJ, Dijkstra S, et al. Detection of High-grade Prostate Cancer Using a Urinary Molecular Biomarker-Based Risk Score. *Eur Urol.* Nov 2016; 70(5): 740-748. PMID 27108162
44. Haese A, Trooskens G, Steyaert S, et al. Multicenter Optimization and Validation of a 2-Gene mRNA Urine Test for Detection of Clinically Significant Prostate Cancer before Initial Prostate Biopsy. *J Urol.* Aug 2019; 202(2): 256-263. PMID 31026217
45. Hendriks RJ, van der Leest MMG, Israël B, et al. Clinical use of the SelectMDx urinary-biomarker test with or without mpMRI in prostate cancer diagnosis: a prospective, multicenter study in biopsy-naïve men. *Prostate Cancer Prostatic Dis.* Dec 2021; 24(4): 1110-1119. PMID 33941866
46. McKiernan J, Donovan MJ, O'Neill V, et al. A Novel Urine Exosome Gene Expression Assay to Predict High-grade Prostate Cancer at Initial Biopsy. *JAMA Oncol.* Jul 01 2016; 2(7): 882-9. PMID 27032035
47. Tutrone R, Donovan MJ, Torkler P, et al. Clinical utility of the exosome based ExoDx Prostate(IntelliScore) EPI test in men presenting for initial Biopsy with a PSA 2-10 ng/mL. *Prostate Cancer Prostatic Dis.* Dec 2020; 23(4): 607-614. PMID 32382078
48. Tutrone R, Lowentritt B, Neuman B, et al. ExoDx prostate test as a predictor of outcomes of high-grade prostate cancer - an interim analysis. *Prostate Cancer Prostatic Dis.* Sep 2023; 26(3): 596-601. PMID 37193776
49. Schipper M, Wang G, Giles N, et al. Novel prostate cancer biomarkers derived from autoantibody signatures. *Transl Oncol.* Apr 2015; 8(2): 106-11. PMID 25926076
50. Wysock JS, Becher E, Persily J, et al. Concordance and Performance of 4Kscore and SelectMDx for Informing Decision to Perform Prostate Biopsy and Detection of Prostate Cancer. *Urology.* Jul 2020; 141: 119-124. PMID 32294481
51. Cui Y, Cao W, Li Q, et al. Evaluation of prostate cancer antigen 3 for detecting prostate cancer: a systematic review and meta-analysis. *Sci Rep.* May 10 2016; 6: 25776. PMID 27161545
52. Rodríguez SVM, García-Perdomo HA. Diagnostic accuracy of prostate cancer antigen 3 (PCA3) prior to first prostate biopsy: A systematic review and meta-analysis. *Can Urol Assoc J.* May 2020; 14(5): E214-E219. PMID 31793864
53. Nicholson A, Mahon J, Boland A, et al. The clinical effectiveness and cost-effectiveness of the PROGENSA prostate cancer antigen 3 assay and the Prostate Health Index in the diagnosis of prostate cancer: a systematic review and economic evaluation. *Health Technol Assess.* Oct 2015; 19(87): i-xxxi, 1-191. PMID 26507078
54. Wei JT, Feng Z, Partin AW, et al. Can urinary PCA3 supplement PSA in the early detection of prostate cancer?. *J Clin Oncol.* Dec 20 2014; 32(36): 4066-72. PMID 25385735
55. Hennenlotter J, Neumann T, Alperowitz S, et al. Age-Adapted Prostate Cancer Gene 3 Score Interpretation - Suggestions for Clinical Use. *Clin Lab.* Mar 01 2020; 66(3). PMID 32162868
56. Vickers AJ, Gupta A, Savage CJ, et al. A panel of kallikrein marker predicts prostate cancer in a large, population-based cohort followed for 15 years without screening. *Cancer Epidemiol Biomarkers Prev.* Feb 2011; 20(2): 255-61. PMID 21148123
57. Ruffion A, Devonec M, Champetier D, et al. PCA3 and PCA3-based nomograms improve diagnostic accuracy in patients undergoing first prostate biopsy. *Int J Mol Sci.* Aug 29 2013; 14(9): 17767-80. PMID 23994838
58. Ruffion A, Perrin P, Devonec M, et al. Additional value of PCA3 density to predict initial prostate biopsy outcome. *World J Urol.* Aug 2014; 32(4): 917-23. PMID 24500192
59. Merdan S, Tomlins SA, Barnett CL, et al. Assessment of long-term outcomes associated with urinary prostate cancer antigen 3 and TMPRSS2:ERG gene fusion at repeat biopsy. *Cancer.* Nov 15 2015; 121(22): 4071-9. PMID 26280815



60. Djavan B, Waldert M, Zlotta A, et al. Safety and morbidity of first and repeat transrectal ultrasound guided prostate needle biopsies: results of a prospective European prostate cancer detection study. *J Urol.* Sep 2001; 166(3): 856-60. PMID 11490233
61. Lujan M, Paez A, Santonja C, et al. Prostate cancer detection and tumor characteristics in men with multiple biopsy sessions. *Prostate Cancer Prostatic Dis.* 2004; 7(3): 238-42. PMID 15289810Li
62. Stewart GD, Van Neste L, Delvenne P, et al. Clinical utility of an epigenetic assay to detect occult prostate cancer in histopathologically negative biopsies: results of the MATLOC study. *J Urol.* Mar 2013; 189(3): 1110-6. PMID 22999998
63. Partin AW, Van Neste L, Klein EA, et al. Clinical validation of an epigenetic assay to predict negative histopathological results in repeat prostate biopsies. *J Urol.* Oct 2014; 192(4): 1081-7. PMID 24747657
64. Waterhouse RL, Van Neste L, Moses KA, et al. Evaluation of an Epigenetic Assay for Predicting Repeat Prostate Biopsy Outcome in African American Men. *Urology.* Jun 2019; 128: 62-65. PMID 29660369
65. Van Neste L, Partin AW, Stewart GD, et al. Risk score predicts high-grade prostate cancer in DNA-methylation positive, histopathologically negative biopsies. *Prostate.* Sep 2016; 76(12): 1078-87. PMID 27121847
66. Partin AW, VAN CRIEKINGE W, TROCK BJ, et al. CLINICAL EVALUATION OF AN EPIGENETIC ASSAY TO PREDICT MISSED CANCER IN PROSTATE BIOPSY SPECIMENS. *Trans Am Clin Climatol Assoc.* 2016; 127: 313-327. PMID 28066067
67. Food and Drug Administration. Summary of Safety and Effectiveness Data. PMA P090026. Quantitative test for determination of [-2]proPSA levels. Silver Spring, MD: Food and Drug Administration; 2012.
68. Aubry W, Lieberthal R, Willis A, et al. Budget impact model: epigenetic assay can help avoid unnecessary repeated prostate biopsies and reduce healthcare spending. *Am Health Drug Benefits.* Jan 2013; 6(1): 15-24. PMID 24991343
69. Robinson K, Creed J, Reguly B, et al. Accurate prediction of repeat prostate biopsy outcomes by a mitochondrial DNA deletion assay. *Prostate Cancer Prostatic Dis.* Jun 2010; 13(2): 126-31. PMID 20084081
70. Legisi L, DeSa E, Qureshi MN. Use of the Prostate Core Mitomic Test in Repeated Biopsy Decision-Making: Real-World Assessment of Clinical Utility in a Multicenter Patient Population. *Am Health Drug Benefits.* Dec 2016; 9(9): 497-502. PMID 28465777
71. Leyten GH, Hessels D, Smit FP, et al. Identification of a Candidate Gene Panel for the Early Diagnosis of Prostate Cancer. *Clin Cancer Res.* Jul 01 2015; 21(13): 3061-70. PMID 25788493
72. Xiao K, Guo J, Zhang X, et al. Use of two gene panels for prostate cancer diagnosis and patient risk stratification. *Tumour Biol.* Aug 2016; 37(8): 10115-22. PMID 26820133
73. Tosoian JJ, Sessine MS, Trock BJ, et al. MyProstateScore in men considering repeat biopsy: validation of a simple testing approach. *Prostate Cancer Prostatic Dis.* Sep 2023; 26(3): 563-567. PMID 36585434
74. Wei JT, Barocas D, Carlsson S, et al. Early Detection of Prostate Cancer: AUA/SUO Guideline Part II: Considerations for a Prostate Biopsy. *J Urol.* Jul 2023; 210(1): 54-63. PMID 37096575
75. Wei JT, Barocas D, Carlsson S, et al. Early Detection of Prostate Cancer: AUA/SUO Guideline Part I: Prostate Cancer Screening. *J Urol.* Jul 2023; 210(1): 46-53. PMID 37096582
76. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: prostate cancer early detection V.1.2023. https://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf. Accessed September 25, 2023.
77. National Institute for Health and Care Excellence (NICE). Prostate cancer: diagnosis and management [NG131]. 2019. Updated December 15, 2021; <https://www.nice.org.uk/guidance/ng131/chapter/Recommendations#assessment-and-diagnosis>. Accessed December 4, 2023.
78. U. S. Preventive Services Task Force. Prostate Cancer: Screening. 2018; <https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/prostate-cancer-screening1>. Accessed December 4, 2023.



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 (Progenesa) ExoDx Prostate IntelliScore, Prostate Health Index (phi), Select MDx, and TMRSS 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".
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.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2024 Premera All Rights Reserved.

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.



Discrimination is Against the Law

Premera Blue Cross (Premera) complies with applicable Federal and Washington state civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, sex, gender identity, or sexual orientation. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability, sex, gender identity, or sexual orientation. Premera provides free aids and services to people with disabilities to communicate effectively with us, such as qualified sign language interpreters and written information in other formats (large print, audio, accessible electronic formats, other formats). Premera provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, contact the Civil Rights Coordinator. If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, sex, gender identity, or sexual orientation, you can file a grievance with: Civil Rights Coordinator — Complaints and Appeals, PO Box 91102, Seattle, WA 98111, Toll free: 855-332-4535, Fax: 425-918-5592, TTY: 711, Email AppealsDepartmentInquiries@Premera.com. You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Ave SW, Room 509F, HHH Building, Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD). Complaint forms are available at <http://www.hhs.gov/ocr/office/file/index.html>.

Washington residents: You can also file a civil rights complaint with the Washington State Office of the Insurance Commissioner, electronically through the Office of the Insurance Commissioner Complaint Portal available at <https://www.insurance.wa.gov/file-complaint-or-check-your-complaint-status>, or by phone at 800-562-6900, 360-586-0241 (TDD). Complaint forms are available at <https://fortress.wa.gov/oic/online-services/cc/pub/complaintinformation.aspx>.

Alaska residents: Contact the Alaska Division of Insurance via email at insurance@alaska.gov, or by phone at 907-269-7900 or 1-800-INSURAK (in-state, outside Anchorage).

Language Assistance

ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 800-722-1471 (TTY: 711).

PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nang walang bayad. Tumawag sa 800-722-1471 (TTY: 711).

注意: 如果您使用繁體中文，您可以免費獲得語言援助服務。請致電 800-722-1471 (TTY: 711)。

CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 800-722-1471 (TTY: 711).

주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다. 800-722-1471 (TTY: 711) 번으로 전화해 주십시오.

ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода. Звоните 800-722-1471 (телетайп: 711).

LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 800-722-1471 (TTY: 711).

MO LOU SILAFIA: Afai e te tautala Gagana fa'a Sāmoa, o loo iai auunaga fesoasoan, e fai fua e leai se totagi, mo oe, Telefoni mai: 800-722-1471 (TTY: 711).

ໂປດອຸລາ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ, ໂດຍບໍ່ເສັຽຄ່າ, ຄມມນມີພ້ອມໃຫ້ທ່ານ. ໂທ 800-722-1471 (TTY: 711).

注意事項: 日本語を話される場合、無料の言語支援をご利用いただけます。800-722-1471 (TTY:711) まで、お電話にてご連絡ください。

PAKDAAR: Nu saritaem ti Ilocano, ti serbisyo para ti baddang ti lengguahe nga awanan bayadna, ket sidadaan para kenyam. Awagan ti 800-722-1471 (TTY: 711).

УВАГА! Якщо ви розмовляєте українською мовою, ви можете звернутися до безкоштовної служби мовної підтримки. Телефонуйте за номером 800-722-1471 (телетайп: 711).

ប្រយ័ត្ន: បើសិនជាអ្នកនិយាយ ភាសាខ្មែរ, សេវាជំនួយផ្នែកភាសា ដោយមិនគិតលុយ គឺអាចមានសំរាប់អ្នក។ ចូរ ទូរស័ព្ទ 800-722-1471 (TTY: 711)។

ማስታወሻ: የሚናገሩት ቋንቋ አማርኛ ከሆነ የትርጉም አርዳታ ድርጅቶች: በነጻ ሊያግኙዎት ተዘጋጅተዋል: ወደ ሚከተለው ቁጥር ይደውሉ 800-722-1471 (መስማት ለተሳናቸው: 711).

XIYYEEFFANNAA: Afaan dubbattu Oroomiffa, tajaajjila gargaarsa afaanii, kanfaltiidhaan ala, ni argama. Bilbilaa 800-722-1471 (TTY: 711).

ملحوظة: إذا كنت تتحدث اذكر اللغة، فإن خدمات المساعدة اللغوية تتوافر لك بالمجان. اتصل برقم 800-722-1471 (رقم هاتف الصم والبكم: 711).

ਧਿਆਨ ਦਿਓ: ਜੇ ਤੁਸੀਂ ਪੰਜਾਬੀ ਬੋਲਦੇ ਹੋ, ਤਾਂ ਭਾਸ਼ਾ ਵਿੱਚ ਸਹਾਇਤਾ ਸੇਵਾ ਤੁਹਾਡੇ ਲਈ ਮੁਫਤ ਉਪਲਬਧ ਹੈ। 800-722-1471 (TTY: 711) 'ਤੇ ਕਾਲ ਕਰੋ।

ထိစား: ถ้าคุณพูดภาษาไทยคุณสามารถใช้บริการช่วยเหลือทางภาษาได้ฟรี โทร 800-722-1471 (TTY: 711).

ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zur Verfügung. Rufnummer: 800-722-1471 (TTY: 711).

UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer 800-722-1471 (TTY: 711).

ATANSYON: Si w pale Kreyòl Ayisyen, gen sèvis èd pou lang ki disponib gratis pou ou. Rele 800-722-1471 (TTY: 711).

ATTENTION: Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 800-722-1471 (ATS: 711).

ATENÇÃO: Se fala português, encontram-se disponíveis serviços linguísticos, grátis. Ligue para 800-722-1471 (TTY: 711).

ATTENZIONE: In caso la lingua parlata sia l'italiano, sono disponibili servizi di assistenza linguistica gratuiti. Chiamare il numero 800-722-1471 (TTY: 711).

توجہ: اگر بہ زبان فارسی گفتگو می کنید، تسهیلات زبانی بصورت رایگان برای شما فراهم می باشد. با 800-722-1471 (TTY: 711) تماس بگیرید.