MEDICAL POLICY – 2.04.514
Protein Biomarkers for Diagnosis and Risk Assessment of Prostate Cancer

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 patients 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

<table>
<thead>
<tr>
<th>Test</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein biomarkers</td>
<td>The following protein biomarkers for the diagnosis of prostate cancer are considered investigational:</td>
</tr>
<tr>
<td></td>
<td>- Autoantibodies ARF 6, NKX3-1, 5′-UTR-BMI1, CEP 164, 3′-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2 (eg, Apinifi)</td>
</tr>
<tr>
<td></td>
<td>- Kallikrein markers (eg, 4Kscore™ Test)</td>
</tr>
</tbody>
</table>

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>CPT</td>
<td>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)</td>
</tr>
<tr>
<td>81539</td>
<td>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 (Apinifi)</td>
</tr>
</tbody>
</table>

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### 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, with a predicted 174,650 incidence cases and 31,620 deaths expected in the United States in 2019.\(^1\)

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 United States is approximately 16%, while the risk of dying of prostate cancer is 3%.\(^2\) 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.\(^3\) 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,\(^4\) 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.\(^5\) It is an architectural grading system ranging from 1 (well-differentiated) to 5 (poorly-differentiated); 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. A cross-walk of these grading systems is shown in Table 1.

Table 1. Prostate Cancer Grading Systems

<table>
<thead>
<tr>
<th>Grade Group</th>
<th>Gleason Score (Primary and Secondary Pattern)</th>
<th>Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 or less</td>
<td>Well-differentiated (low grade)</td>
</tr>
<tr>
<td>2</td>
<td>7 (3 + 4)</td>
<td>Moderately differentiated (moderate grade)</td>
</tr>
<tr>
<td>3</td>
<td>7 (4 + 3)</td>
<td>Poorly differentiated (high grade)</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>Undifferentiated (high grade)</td>
</tr>
<tr>
<td>5</td>
<td>9-10</td>
<td>Undifferentiated (high grade)</td>
</tr>
</tbody>
</table>

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.

Summary of Evidence

For individuals who are being considered for an initial prostate biopsy who receive testing for protein biomarkers of prostate cancer (eg, 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 positive digital rectal exam (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 the effects of the technology on health outcomes.

For individuals who are being considered for repeat biopsy who receive testing for protein biomarkers of prostate cancer, 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 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 did not compare performance characteristics with standard risk prediction models. Direct evidence supporting clinical utility has not been shown. No data are currently available on physician decisions on rebiopsy or on the longer-term clinical outcomes of men who did not have a biopsy based on test results. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American Urological Association et al

The American Urological Association (2013; confirmed in 2018) published guidelines on the early detection of prostate cancer. The association concluded that “the literature supporting the efficacy of digital rectal exam (DRE), PSA [prostate-specific antigen] derivatives and isoforms (eg, free PSA, -2proPSA, prostate health index, hK2, PSA velocity or PSA doubling time) and novel urinary markers and biomarkers (eg, PCA3) for screening with the goal of reducing prostate cancer mortality provide limited evidence to draw conclusions. While some data suggest use of these secondary screening tools may reduce unnecessary biopsies (ie, reduce harms) while maintaining the ability to detect aggressive prostate cancer (ie, maintain the benefits of PSA screening), more research is needed to confirm this.”

The American Urological Association and the Society of Abdominal Radiology (2016) published joint guidelines on prostate magnetic resonance imaging and magnetic resonance imaging-targeted biopsy. The associations recommended:

In patients with negative or low suspicion magnetic resonance imaging (PI-RADS [Prostate Imaging Reporting and Data System] assessment category of 1 or 2, respectively), other ancillary markers (ie, PSA [prostate-specific antigen], PSAD [PSA...
density], PSAV [PSA velocity], PCA3, PHI, 4K) may be of value in identifying patients warranting repeat systematic biopsy, although further data are needed on this topic.

Guidelines published by the American Cancer Society and the American Urological Association have endorsed consideration of PSA screening based on age, other risk factors, and estimated life expectancy.\textsuperscript{17,64,65}

**National Comprehensive Cancer Network**

The National Comprehensive Cancer Network (NCCN) guidelines (v.2.2019) recommend that any man with a PSA level greater than 3 ng/mL undergo workup for benign disease, repeat PSA, and digital rectal examination.\textsuperscript{1} The guidelines also recommend consideration of biomarkers that improve the specificity of screening including percent free PSA, phi, ExoDx Prostate (IntelliScore) (EPI), and 4Kscore in patients with a PSA level greater than 3 ng/mL who have not yet had a biopsy, and consideration of percent free PSA, phi, 4Kscore, PCA3, ExoDx Prostate (IntelliScore) (EPI), and ConfirmMDx in men who had a negative biopsy but are thought to be at higher risk (category 2A evidence). The NCCN noted that these tests may be especially useful in men with PSA levels between 3 ng/mL and 10 ng/mL. The NCCN considers the Mi-Prostate Score (MiPS) and Select MDx to be investigational at the time of the update. NCCN indicated that:

... no biomarker test can be recommended over any other at this time. The optimal order of biomarker tests and imaging is unknown; and it remains unclear how to interpret results of multiple tests in individual patients – especially when results are contradictory.

**National Institute for Health and Care Excellence**

The National Institute for Health and Care Excellence (2019) 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.\textsuperscript{66}

**U.S. Preventive Services Task Force Recommendations**

The U.S. Preventive Services Task Force (2018) updated recommendations for prostate cancer screening.\textsuperscript{67} Protein biomarkers addressed in this policy, including PCA3, were not mentioned.
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).

**Medicare National Coverage**

There is no national coverage determination. At least one LCD will cover percent free PSA, phi, or 4K score once prior to initial biopsy in men who meet criteria.

**Ongoing and Unpublished Clinical Trials**

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 2.

**Table 2. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT00773773</td>
<td>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</td>
<td>500</td>
<td>Oct 2019</td>
</tr>
<tr>
<td>NCT03082274*</td>
<td>Prospective Validation of Prostate Biomarkers for Repeat Biopsy: The PRIORITY Study</td>
<td>1000</td>
<td>Dec 2019</td>
</tr>
<tr>
<td>NCT01739062</td>
<td>Prostate Cancer Risk Assessment Using Genetic Markers in General Practice (ProCaRis)</td>
<td>5000</td>
<td>Jan 2024</td>
</tr>
<tr>
<td>NCT01632930</td>
<td>Medical Economics of Urinary PCSA3 Test for Prostate Cancer Diagnosis</td>
<td>962</td>
<td>Nov 2020</td>
</tr>
<tr>
<td>NCT04079699</td>
<td>Predicting Prostate Cancer Using a Panel of Plasma and Urine Biomarkers Combined in an Algorithm in Elderly Men Above 70 Years</td>
<td>700</td>
<td>Oct 2039</td>
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<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>------------</td>
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<td>--------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>NCT02241122</td>
<td>Improved Prostate Cancer Diagnosis - Combination of Magnetic Resonance Imaging Targeted Biopsies and Biomarkers (Multi-IMPROD)</td>
<td>350</td>
<td>Apr 2018 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

Denotes industry-sponsored or cosponsored trial.

**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. Laboratories that offer laboratory-developed tests must be licensed under the Clinical Laboratory Improvement Amendments for high-complexity testing. The following laboratories are certified under the Clinical Laboratory Improvement Amendments: 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 (phiTM), 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**


31. Loeb S, Shin SS, Broyles DL et al. Prostate Health Index improves multivariable risk prediction of aggressive prostate cancer. BJU Int., 2016 Oct 16;120(1). PMID 27743489


34. 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., 2011 Mar 23;185(5). PMID 21419439


36. 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.


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/04/19</td>
<td>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 codes 81229, 81313, 81479, 81541, and 81551 as they are now reviewed by AIM Specialty Health.</td>
</tr>
<tr>
<td>02/01/19</td>
<td>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”.</td>
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<td>05/01/19</td>
<td>Minor update, History section updated for clarity.</td>
</tr>
<tr>
<td>01/01/20</td>
<td>Annual Review, approved December 10, 2019. Policy updated with literature review through September 2019; references added. Policy statements unchanged.</td>
</tr>
</tbody>
</table>

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