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

#### Test

<table>
<thead>
<tr>
<th>Protein biomarkers</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td></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>
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</table>

#### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<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
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 rebiopsy after a prior negative biopsy. This policy addresses these types of tests for cancer risk assessment.

Background

Prostate Cancer

Prostate cancer is the second most common cancer in men with a predicted 161,360 incidence cases and 26,700 deaths expected in the United States in 2017.\(^1\)

Prostate cancer is a complex, heterogeneous disease, ranging from microscopic tumors unlikely to be life-threatening to aggressive tumors which 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.\(^6\) A cross-reference of the 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, the evidence includes systematic reviews and meta-analyses and primarily observational studies. Relevant outcomes are overall survival, disease-
specific survival, test validity, other test performance measures, resource utilization, and quality of life. The evidence supporting clinical utility varies by 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, 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 and meta-analyses and primarily observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measures, 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 the men who did not have 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

In 2013 (confirmed in 2018), the American Urological Association published guidelines on the early detection of prostate cancer.58 The association concluded that “the literature supporting the efficacy of digital rectal exam (DRE), PSA 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 published joint guidelines in 2016 on prostate magnetic resonance imaging (MRI) and MRI-targeted biopsy.²⁶ 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.

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) guidelines (v.2.2018) recommend that any man with a PSA level greater than 3 ng/mL undergo workup for benign disease, repeat PSA, and digital rectal examination.⁵⁹ The guidelines also recommend consideration of biomarkers that improve the specificity of screening including percent free PSA, phi, 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, and ConfirmMDx in men who had a negative biopsy but are thought to be at higher risk (category 2A evidence). NCCN noted that these tests may be especially useful in men with PSA levels between 3 ng/mL and 10 ng/mL. NCCN considers ExoDx Prostate (IntelliScore) 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.
U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force updated recommendations for prostate cancer screening in 2018. 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). Guidelines published by the American Cancer Society and the American Urological Association (AUA) have endorsed consideration of PSA screening based on age, other risk factors, and estimated life expectancy.\textsuperscript{17,62,63}

Medicare National Coverage

There is no national coverage determination.

Ongoing and Unpublished Clinical Trials

Some currently 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>
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<tbody>
<tr>
<td>Ongoing</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 2018</td>
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<tr>
<td>NCT03082274\textsuperscript{a}</td>
<td>Prospective Validation of Prostate Biomarkers for Repeat Biopsy: The PRIORITY Study</td>
<td>1000</td>
<td>Dec 2019</td>
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<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
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<tr>
<td>--------------</td>
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</tr>
<tr>
<td>NCT01739062</td>
<td>Prostate Cancer Risk Assessment Using Genetic Markers in General Practice</td>
<td>4500</td>
<td>Jan 2021</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>
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**Unpublished**

<table>
<thead>
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<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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</thead>
<tbody>
<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>
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<tr>
<td>NCT02250313a</td>
<td>PASCUAL (Prostate Assay Specific Clinical Utility at Launch) Study (ConfirmMDx)</td>
<td>600</td>
<td>Mar 2018 (terminated)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

*a 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®). To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests.

**References**


<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</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>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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<tr>
<td>05/01/19</td>
<td>Minor update, History section updated for clarity.</td>
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200 Independence Avenue SW, Room 509F, HHH Building
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