MEDICAL POLICY – 12.04.33
Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

BCBSA Ref. Policy: 2.04.33

<table>
<thead>
<tr>
<th>Effective Date:</th>
<th>Jan. 1, 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last Revised:</td>
<td>June 1, 2018</td>
</tr>
<tr>
<td>Replaces:</td>
<td>2.04.33</td>
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</table>

RELATED MEDICAL POLICIES:
- 12.04.111 Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

Select a hyperlink below to be directed to that section.

- POLICY CRITERIA
- CODING
- RELATED INFORMATION
- EVIDENCE REVIEW
- REFERENCES
- HISTORY

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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 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 | Investigational
--- | ---
**Genetic and protein biomarkers** | The following genetic and protein biomarkers for the diagnosis of prostate cancer are considered investigational:
- Candidate gene panels
- Gene hypermethylation testing (eg, ConfirmMDx®)
- Kallikrein markers (eg, 4Kscore™ Test)
- Mitochondrial DNA mutation testing (eg, Prostate Core Mitomics Test™)
- PCA3 testing
- Prostate Health Index (phi)
- SelectMDx
- TMPRSS fusion genes

**Single nucleotide polymorphisms testing** | Single nucleotide polymorphisms (SNPs) testing for cancer risk assessment of prostate cancer is considered investigational.

Note: Prolaris and Oncotype DX Prostate, gene expression analysis tests for prostate cancer management, are addressed in a separate medical policy (see Related Policies).

**Coding**

<table>
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<th>Code</th>
<th>Description</th>
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<tr>
<td><strong>CPT</strong></td>
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<tr>
<td>81229</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities</td>
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<tr>
<td>81313</td>
<td>PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)</td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>81539</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,</td>
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### Code

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<th>Description</th>
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<tr>
<td>81541</td>
<td>Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score (new code effective 1/1/18)</td>
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</table>

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### Related Information

**Genetic Counseling**

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients. Genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

### Evidence Review

**Background**

Various genetic and protein biomarkers are associated with prostate cancer. These tests have the potential for determining which men should undergo prostate biopsy or rebiopsy after a prior negative biopsy. This evidence review addresses these types of tests for cancer risk assessment. Testing to determine cancer aggressiveness after a tissue diagnosis of cancer is addressed in a related policy (see Related Policies).
Prostate Cancer

Prostate cancer is the second most common cancer in men with a predicted 161,360 cases and 26,700 deaths expected in the United States in 2017.¹

Prostate cancer is a complex, heterogeneous disease, ranging from microscopic tumors that are 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, and 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%, but 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 Although the lifetime risk of being diagnosed with prostate cancer is 16%, autopsy results have suggested that about 30% of men age 55 and 60% of men age 80 who have died of other causes have incidental prostate cancer.⁴ This indicates that many cases of prostate cancer are present but 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 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. Ten-year survival stratified by Gleason score has been estimated from the Surveillance, Epidemiology, and End Results to be about 98% for scores 2 through 6, 92% for score 7 with primary pattern 3 and secondary pattern 4 (3+4), 77% for score 7 (4+3), and 70% for scores 8 to 10.⁶

Numerous genetic alterations associated with the development or progression of prostate cancer have been described. These molecular markers have been used to help decide which men 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 or a repeat biopsy who receive testing for genetic and 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 accuracy, test validity, other test performance measures, resource utilization, hospitalizations, and quality of life. The evidence supporting clinical utility varies by test but has not been directly shown for any biomarker test. In general, the performance of biomarker testing for predicting biopsy referrals compared with clinical examination, including the ratio of free or unbound PSA to total PSA, is lacking. Procedures for referrals for biopsy based on clinical examination vary, making it difficult to quantify performance characteristics for this comparator. There is also considerable variability in biopsy referral practices based on clinical examination alone, and many of the biomarker tests do not have standardized cutoffs to recommend biopsy. Therefore, to determine whether the tests improve the net health outcome, prospective comparative data are needed on how test results are expected to be used vs how they are actually being used in practice. Many 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 PSA test results are to be informative. African American men have a high burden of morbidity and mortality, but have not been well represented in these study populations. It is unclear how to monitor men with low biomarker risk scores who continue to have symptoms or high or rising PSA levels. Comparative studies of the many biomarkers are lacking, and it is unclear how to use the tests in practice, particularly when test results are contradictory. 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, the American Urological Association published guidelines for the early detection of prostate cancer. Based on a systematic review of the literature to 2013, the Association recognized that novel urinary markers, such as PCA3 protein biomarker and TMPRSS2-ERG, may be “used as adjuncts for informing decisions about the need for a prostate biopsy—or repeat
biopsy—after PSA [prostate-specific antigen] screening,” but emphasized the lack of evidence “that these tests will increase the ratio of benefit to harm.”

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.27 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.

**Evaluation of Genomic Applications in Practice and Prevention**

In 2013, the Evaluation of Genomic Applications in Practice and Prevention working group published the following recommendations for PCA3 testing in prostate cancer,121 based on the Agency for Healthcare Quality and Research comparative effectiveness review62:

- Evidence was insufficient to recommend “PCA3 testing to inform decisions for when to re-biopsy previously biopsy-negative patients for prostate cancer, [or] to inform decisions to conduct initial biopsies for prostate cancer in at-risk men (eg, previous elevated PSA or suspicious DRE [digital rectal examination])…”

- Evidence was “insufficient ... to recommend PCA3 testing in men with cancer-positive biopsies to determine if the disease is indolent or aggressive in order to develop an optimal treatment plan.”

- “…[T]he overall certainty of clinical validity to predict the diagnosis of prostate cancer using PCA3 is deemed ‘low.’ ... [C]linical use for diagnosis is discouraged unless further evidence supports improved clinical validity.”

- “…[T]he overall certainty of net health benefit is deemed ‘low.’ [C]linical use [is discouraged] unless further evidence supports improved clinical outcomes.”
**National Comprehensive Cancer Network**

National Comprehensive Cancer Network (NCCN) guidelines (v.1.2017) recommend that any man with a PSA level greater than 3 ng/mL undergo workup for benign disease, repeat PSA and digital rectal examination. The guidelines also recommend consideration of percent free PSA, phi, 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 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 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 published recommendations for Prostate Cancer Screening on May 2012. Genetic and protein biomarkers addressed in this policy, including PCA3, were not mentioned.

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers. Palmetto GBA has issued a local coverage determination for positive coverage for the following test (date effective): ConfirmMDx Epigenetic Molecular Assay (effective 2014). Palmetto GBA issued a draft noncoverage policy determination in 2016 for the 4Kscore.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this policy are listed in Table1.
Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td><strong>Ongoing</strong></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 2017</td>
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<tr>
<td>NCT02241122</td>
<td>Improved Prostate Cancer Diagnosis - Combination of Magnetic Resonance Imaging Targeted Biopsies and Biomarkers (Multi-IMPROD)</td>
<td>400</td>
<td>Nov 2017</td>
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<tr>
<td>NCT02250313a</td>
<td>PASCUAL (Prostate Assay Specific Clinical Utility at Launch) Study</td>
<td>600</td>
<td>Mar 2018</td>
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<tr>
<td>NCT01739062</td>
<td>Prostate Cancer Risk Assessment Using Genetic Markers in General Practice</td>
<td>4500</td>
<td>Jan 2021</td>
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<tr>
<td>NCT01632930</td>
<td>Medical Economics of Urinary PCSA3 Test for Prostate Cancer Diagnosis</td>
<td>900</td>
<td>Dec 2021</td>
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</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®), ARUP Laboratories, Mayo Medical Laboratories, LabCorp, BioVantra, others (PCA3 assay), Clinical Research Laboratory (Prostate Core Mitomic Test™), MDx Health (ConfirMDx), and Innovative Diagnostics (phiTM). To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.
In February 2012, the Progensa® PCA3 Assay (Gen-Probe; now Hologic, Marlborough, MA) was approved by the FDA through the premarket approval process. According to the company’s press release, this assay is “indicated for use in conjunction with other patient information to aid in the decision for repeat biopsy in men 50 years of age or older who have had 1 or more previous negative prostate biopsies and for whom a repeat biopsy would be recommended by a urologist based on the current standard of care, before consideration of Progensa PCA3 assay results.” FDA product code: OYM.

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

References


55. Boegemann M, Stephan C, Cammann H, et al. The percentage of prostate-specific antigen (PSA) isoform [-2]proPSA and the Prostate Health Index improve the diagnostic accuracy for clinically relevant prostate cancer at initial and repeat biopsy compared with total PSA and percentage free PSA in men aged <\=65 years. BJU Int. Jan 2016;117(1):72-79. PMID 25818705


100. Wojno KJ, Costa FJ, Cornell RJ, et al. Reduced rate of repeated prostate biopsies observed in ConfirmMDx clinical utility field study. Am Health Drug Benefits. May 2014;7(3):129-134. PMID 24991397


## History

<table>
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<tr>
<th>Date</th>
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<td>06/10/13</td>
<td>New policy. Add to Genetic Testing section. Policy renumbered from 2.04.33 to 12.04.33, to align with Genetic Testing section.</td>
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<td>01/03/14</td>
<td>Update Related Policies; add 12.04.111, effective 12/9/13.</td>
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<td>02/10/14</td>
<td>Interim Review. Interim review to add ConfirmMDx to Description section. Reference added. Note added to policy statement that Prolaris and Oncotype Dx Prostate are addressed in another policy. CPT code 82119 was incorrectly listed; the code was corrected to 81229; deleted code 83890-92 removed.</td>
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<td>06/19/14</td>
<td>Annual Review. Policy updated with literature review through March 16, 2014; references 1, 12-13, 31-46, 60-65, 67-70, and 82-88 added. No change to policy statement.</td>
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<td>01/12/15</td>
<td>Coding update. New CPT code 81313, effective 1/1/15, added to policy. Update related policy title, 12.04.111.</td>
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<td>06/09/15</td>
<td>Annual Review. Title changed “Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer.” Policy revised to focus on diagnostic testing (as well as SNP testing for cancer risk assessment). Policy statements revised to include an expanded list of diagnostic genetic and protein biomarker tests as investigational. Prognostic testing is being moved to Policy No. 12.04.111. List of commercially available tests moved to Policy Guidelines from Description section. Policy updated with literature review through March 16, 2015. References extensively revised. Policy statements changed as noted. ICD-9 and ICD-10 diagnosis codes</td>
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<td>Date removed, as these were informational only. CPT code 0010M added to the policy.</td>
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<td>08/01/16</td>
<td>Update Related Policies. Remove 12.04.64 as it was archived.</td>
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<td>02/10/17</td>
<td>Policy moved into new format; no change to policy statements.</td>
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<td>04/11/17</td>
<td>Coding update; removed HCPCS code S3721 as it was terminated in 2016. Minor formatting update. Added BCBSA reference policy.</td>
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<tr>
<td>05/12/17</td>
<td>Coding update; removed CPT code 0010M which was terminated 01/2017 and replaced by 81539.</td>
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<tr>
<td>07/01/17</td>
<td>Minor update, added SelectMDx as an example of Metabolomic profiles in the Policy Coverage Criteria section. Removed Appendix.</td>
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<td>01/01/18</td>
<td>Annual Review, approved December 6, 2017. Policy updated with literature review through July 2017; input received by the BCBSA Medical Advisory Panel in September 2017; Policy revised to separate initial biopsy and repeat biopsy populations; references 1-2 and 22 updated; reference 1, 22, and 27 added; Prostarix test removed from policy and policy statement; policy statement otherwise unchanged.</td>
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<td>04/13/18</td>
<td>Coding update, added CPT code 81541 (new code effective 1/1/18).</td>
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<td>06/01/18</td>
<td>Minor update. Added SelectMDx to policy coverage criteria as it was noted above (07/01/17) but had not been added.</td>
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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
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