Medical Policy
Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

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- Policy: Medicare
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- Coding Information
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Policy Number: 333
BCBSA Reference Number: 2.04.33
NCD/LCD:
- Local Coverage Determination (LCD): MolDX-CDD: ConfirmMDx Epigenetic Molecular Assay (L35632)
- Local Coverage Determination (LCD): 4Kscore Assay (L36763)
- Probensa PCA3 Assay Coding and Billing Guidelines (M00013, V12)

Related Policies
Gene Expression Analysis for Prostate Cancer Management, #670

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

The following genetic and protein biomarkers for the diagnosis of prostate cancer are INVESTIGATIONAL:

- Kallikrein markers (eg, 4Kscore™ Test)
- Metabolomic profiles (eg, Prostarix™)
- PCA3 testing
- TMPRSS fusion genes
- Candidate gene panels
- Mitochondrial DNA mutation testing (eg, Prostate Core Mitomics Test™)
- Gene hypermethylation testing (eg, ConfirmMDx®)
- Prostate Health Index (phi).

Single nucleotide polymorphisms testing for cancer risk assessment of prostate cancer is considered INVESTIGATIONAL.
Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

Local Coverage Determination (LCD): MolDX-CDD: ConfirmMDx Epigenetic Molecular Assay (L35632)

4Kscore™ Assay (CPT code 81539)

4Kscore™ assay is not covered.

Local Coverage Determination (LCD): 4Kscore Assay (L36763)

PCA3 Test (CPT code 81313)

PCA3 test is covered.

Progensa PCA3 Assay Coding and Billing Guidelines (M00013, V12)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required. Yes indicates that prior authorization is required. No indicates that prior authorization is not required. N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>This is not a covered service.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Medicare HMO Blue℠</td>
<td>No</td>
</tr>
<tr>
<td>Medicare PPO Blue℠</td>
<td>No</td>
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</tbody>
</table>

CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following CPT and HCPCS codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:
CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tbody>
<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>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, prognostic algorithm reported as a probability score</td>
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The following CPT and HCPCS codes are considered investigational for Medicare Advantage HMO and Medicare Advantage PPO Members:

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Description

Prostate cancer is the second most common cancer in men, with a predicted 181,000 incidence cases and 26,100 deaths expected in United States in 2016.\textsuperscript{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 cured 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%, but the risk of dying of prostate cancer is 3%.\textsuperscript{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.\textsuperscript{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,\textsuperscript{4} indicating that many cases of cancer are unlikely to pose a threat during a man’s life expectancy.

The most widely used grading scheme for prostate cancer is the Gleason system.\textsuperscript{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 2 to 5 is regarded as normal prostate tissue; 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 rates stratified by Gleason score have been estimated from the Surveillance, Epidemiology, and End Results registry to be about 98% for scores 2 through 6, 92% for a score of 7 with primary pattern 3 and secondary pattern 4 (3+4), 77% for a score of 7 (4+3), and 70% for scores between 8 and 10.\textsuperscript{6}

Numerous genetic alterations associated with development or progression of prostate cancer have been described, with the potential for use of these molecular markers to improve selection of men who should undergo prostate biopsy or rebiopsy after an initial negative biopsy.

CLINICAL CONTEXT AND TEST PURPOSE

The purpose of genetic and protein biomarker testing for prostate cancer is to inform the selection of men who should undergo biopsy or repeat biopsy. Conventional decision-making tools for identifying men for prostate biopsy include digital rectal exam (DRE), serum prostate-specific antigen (PSA), and patient risk factors such as age, race, and family history of prostate cancer.
DRE has relatively low interrater agreement among urologists, with estimated sensitivity, specificity, and positive predictive value (PPV) for diagnosis of prostate cancer of 59%, 94% and 28%, respectively. DRE might have a higher PPV in the setting of elevated PSA.

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 normal DRE, 30% to 35% of men with a PSA level between 4 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. Use of PSA levels in screening has improved detection of prostate cancer. The European Randomized Study of Screening for Prostate Cancer (ERSPC) and Goteborg prostate cancer screening trials demonstrated that biennial PSA screening reduces the risk of being diagnosed with metastatic prostate cancer.

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, the American Cancer Society (ACS) 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 estimated specificity of 91%.

PSA screening in the general population is controversial. The U.S. Preventive Services Task Force recommended against PSA-based screening (D recommendation) in 2012 while guidelines published by ACS and the American Urological Association (AUA) endorsed consideration of PSA screening based on age, other risk factors, and estimated life expectancy. The utility of PSA screening depends on whether screening can lead to management changes that improve net health outcome. Results from the National Institutes for Health-supported Prostate Testing for Cancer and Treatment (ProtecT) trial demonstrated no difference in prostate cancer mortality rates between the treatment strategies of active monitoring, radical prostatectomy, and external-beam radiotherapy in clinically localized prostate cancer that is detected by PSA testing.

These existing screening tools lead to unnecessary prostate biopsies because of their lack of specificity and inability to discriminate low- from high-risk prostate cancer. More than 1 million prostate biopsies are performed annually in the United States with a resulting cancer diagnosis in 20% to 30%. About one-third of men who undergo prostate biopsy experience transient pain, fever, bleeding, and urinary difficulties. Serious biopsy risks (eg, bleeding or infection requiring hospitalization) are rare, with estimated rates ranging from less than 1% to 4%.

Given the risk, discomfort, and burden of biopsy and the low yield for diagnosis, there is a need for noninvasive tests that distinguish potentially aggressive tumors that should be referred for biopsy from clinically insignificant localized tumors that do not need biopsy or other prostatic conditions with the goal of avoiding low-yield biopsy. The following PICOTS were used to select literature that provides evidence relevant to this review.

**Patients**
The relevant populations are men for whom an initial prostate biopsy is being considered because of clinical symptoms (eg, difficulty with urination, elevated PSA) or men for whom a rebiopsy is being considered because the results of an initial prostate biopsy were negative or equivocal and other clinical symptoms remain suspicious.

The population for which these tests would potentially be most informative is men in the indeterminate or “gray zone” range of PSA on repeat testing with unsuspicious DRE findings. Repeat testing of PSA is important because results initially reported to be between 4 and 10 ng/mL are frequently normal. The gray zone for PSA levels is usually between 3 or 4 and 10 ng/mL, but PSA levels vary with age. Age-adjusted normal PSA ranges have been proposed but not standardized or validated.

Screening of men with a life expectancy of less than 10 years is unlikely to be useful because most prostate cancer progresses slowly. However, the age range for which screening is most useful is...
controversial. The ERSPC and Goteborg trials observed benefits of screening only in men up to about 70 years old.

**Interventions**
For assessing future prostate cancer risk, numerous studies have demonstrated the association between many genetic and protein biomarker tests and prostate cancer. Commercially available tests include those described in Table 1.

**Table 1. Commercially Available Tests to Determine Candidate for Prostate Biopsy or Repeat Biopsy**

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>4Kscore®</td>
<td>OPKO lab</td>
<td>Blood test that measures 4 prostate-specific kallikreins, which are combined into an algorithm to produce a score</td>
</tr>
<tr>
<td>ProstarixTM</td>
<td>Metabolon/Bostwick Laboratories</td>
<td>Urine test that measures several metabolites, which are combined with an algorithm to produce a score</td>
</tr>
<tr>
<td>Progensa®</td>
<td>Hologic Gen-Probe</td>
<td>Urine test that measures PCA3 mRNA</td>
</tr>
<tr>
<td></td>
<td>Many labs offer PCA3 tests (eg, ARUP Laboratories, Mayo Medical Laboratories, and LabCorp)</td>
<td></td>
</tr>
<tr>
<td>ConfirmMDx®</td>
<td>MDxHealth</td>
<td>Measures hypermethylation of 3 genes in tissue sample</td>
</tr>
<tr>
<td>Prostate Health IndexTM (phi)</td>
<td>Beckman Coulter</td>
<td>Blood test that combines several components of PSA with an algorithm to produce a score</td>
</tr>
<tr>
<td>Prostate Core Mitomics TestTM (PCMT)</td>
<td>Mitomics (formerly Genesis Genomics)</td>
<td>Measures deletions in mitochondrial DNA by polymerase chain reaction in tissue sample</td>
</tr>
</tbody>
</table>

PSA: prostate specific antigen.

In addition to commercially available tests, single-nucleotide polymorphism testing as part of genome-scanning tests for prostate cancer risk assessment are offered by a variety of laboratories, such as Navigenics (now Life Technologies), LabCorp (23andme), and ARUP Laboratories (deCODE), as laboratory-developed tests.

**Comparators**
Standard clinical examination for determining who goes to biopsy might include DRE, review of history of PSA values, along with consideration of risk factors such as age, race, and family history. The ratio of free or unbound PSA to total PSA (%fPSA) is lower in men who have prostate cancer than in those who do not. A %fPSA cutoff of 25% has been shown to have a sensitivity and specificity of 95% and 20%, respectively, for a group of men with total PSA values between 4.0 and 10.0 ng/mL.\(^{23}\)

The best way to combine all of the risk information to determine who should go to biopsy is not standardized. Risk algorithms have been developed that incorporate clinical risk factors into a risk score or probability. Two examples are the Prostate Cancer Prevention Trial (PCPT) predictive model\(^ {24}\) and the Rotterdam Prostate Cancer risk calculator (also known as the European Research Screening Prostate Cancer Risk Calculator 4 [ERSPC-RC]).\(^ {25}\) The AUA and the Society of Abdominal Radiology recently recommended that high-quality prostate magnetic resonance imaging, if available, should be strongly considered in any patient with a prior negative biopsy who has persistent clinical suspicion for prostate cancer and who is under evaluation for a possible repeat biopsy.\(^ {26}\)
Outcomes
Outcomes of interest are overall survival, disease-specific survival, test accuracy and validity, other test performance measures, resource utilization, hospitalizations, quality of life, and treatment-related mortality and morbidity.

The beneficial outcome of the test is to avoid a biopsy that would be negative for prostate cancer. A harmful outcome is failure to undergo a biopsy that would be positive for prostate cancer, especially when disease is advanced or aggressive. Thus the relevant measures of clinical validity are the sensitivity and negative predictive value. The appropriate reference standard is biopsy. Prostate biopsies are not perfect for diagnosis. Biopsies can miss cancers and repeat biopsies are sometimes needed to confirm diagnosis. Detection rates vary by method used for biopsy and patient characteristics, with published estimates between 14% and 22% for the initial biopsy, 10% and 28% for a second biopsy, and 5% and 10% for a third biopsy.27,28

Time
The timeframe of interest for calculating performance characteristics is time to biopsy result. Men who forgo biopsy based on test results could miss or delay diagnosis of cancer. Longer follow-up would be necessary to determine effects on overall survival.

Setting
Initial screening using PSA levels and DRE may be performed in primary care with referral to specialty (urologist) care for suspicious findings and biopsy. Clinical practice regarding screening methods and frequency vary widely.

Summary
Various genetic and protein biomarkers are associated with prostate cancer. These tests have the potential to improve the accuracy of differentiating which men should undergo prostate biopsy or rebiopsy after a prior negative biopsy. This evidence review will address these types of tests for cancer risk assessment. Testing to determine cancer aggressiveness after a tissue diagnosis of cancer is addressed in policy #670.

For individuals for whom an initial prostate biopsy or a rebiopsy is being considered who receive genetic and protein biomarker testing, the evidence includes systematic reviews and meta-analyses and primarily observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, other test performance measures, resource utilization, hospitalizations, quality of life, and treatment-related mortality and morbidity. The evidence supporting clinical utility varies by test but has not been directly shown for any biomarker test. In general, performance of biomarker testing for predicting biopsy compared with clinical examination, including the ratio of free or unbound prostate-specific antigen (PSA) to total PSA, is lacking. However, procedures for referrals for biopsy based on clinical examination vary, making it difficult to quantify performance characteristics for this comparator. There is considerable variability in biopsy referral practices based on clinical examination alone and many biomarker tests do not have standardized cutoffs to recommend biopsy. Therefore, having prospective, comparative information on how test results are expected to be used or actually being used in practice and the associated effects on outcomes will be needed to determine if the tests improve net health outcomes.

Many of the test validation populations have included men with a positive digital rectal exam, prostate-specific antigen (PSA) level outside of the gray zone, or older men for whom the information for test results are less likely to be informative. African Americans 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.
Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>1/2017</td>
<td>Clarified coding information for the 2017 code changes.</td>
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<td>1/2016</td>
<td>Clarified coding information.</td>
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<td>1/2015</td>
<td>Clarified coding information.</td>
</tr>
<tr>
<td>7/2014</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
<tr>
<td>5/2013</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
<tr>
<td>4/2012</td>
<td>Updated to add new non-covered HCPCS code S3721.</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:

- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

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


