Medical Policy

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

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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)
- Local Coverage Article: MolDX: Progensa® PCA3 Assay Coverage Update (A53107)

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)
- 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 variant testing for cancer risk assessment of prostate cancer is considered INVESTIGATIONAL.

Medicare HMO BlueSM and Medicare PPO BlueSM 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.

Local Coverage Article: MolDX: Progensa® PCA3 Assay Coverage Update (A53107)

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

Inpatient
- For services described in this policy, precertification/preauthorization IS REQUIRED for all products if the procedure is performed inpatient.

Outpatient
- For services described in this policy, see below for products where prior authorization might be required if the procedure is performed outpatient.

| Commercial Managed Care (HMO and POS) | This is not a covered service. |
| Commercial PPO and Indemnity | This is not a covered service. |
| Medicare HMO Blue®SM | Prior authorization is not required. |
| Medicare PPO Blue®SM | Prior authorization is not required. |

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>
</tr>
</thead>
<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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<tr>
<td>81551</td>
<td>Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy</td>
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The following CPT and HCPCS codes are considered investigational for Medicare Advantage HMO and Medicare Advantage PPO Members:

<table>
<thead>
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<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>
</tr>
<tr>
<td>0053U</td>
<td>Oncology (prostate cancer), FISH analysis of 4 genes (ASAP1, HDAC9, CHD1 and PTEN), needle biopsy specimen, algorithm reported as probability of higher tumor grade</td>
</tr>
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</table>

**Description**

**PROSTATE CANCER**

Prostate cancer is the second most common cancer in men, with a predicted 161,360 incidence cases and 26,730 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 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 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 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 10.⁶ Numerous genetic alterations associated with 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**

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 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 policy #670. Magnetic resonance imaging-targeted biopsy of suspicious lesions is assessed in policy #747.
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 and 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. In general, the performance of biomarker testing for predicting biopsy referrals compared with clinical examination, including the ratio of free or unbound prostate-specific antigen (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 biomarker tests do not have standardized cutoffs to recommend a 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 being used in practice, because of information about the associated effects on outcomes.

Many test validation populations have included men with a 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 less likely 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.

**Policy History**

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<td>5/2013</td>
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<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


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


