MASSACHUSETTS

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Medical Policy

Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

Table of Contents

Policy Number: 336

BCBSA Reference Number: 2.04.33 (For Plan internal use only)

Related Policies

Magnetic Resonance Imaging–Targeted Biopsy of the Prostate, #747

Policy

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

The following biomarkers for the diagnosis of prostate cancer are considered **INVESTIGATIONAL**:

- Kallikrein markers (eg, 4Kscore™ Test)
- Prostate Health Index (phi)
- Autoantibodies ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, and CSNK2A2 (eg, Apifiny)

Single-nucleotide variant testing for cancer risk assessment of prostate cancer is considered **INVESTIGATIONAL**.

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**.

	Outpatient
Commercial Managed Care (HMO and POS)	This is **not** a covered service.
Commercial PPO and Indemnity	This is **not** a covered service.

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 codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity, Medicare Advantage HMO and Medicare Advantage PPO Members:

CPT Codes

CPT codes:	Code Description
0021U	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
0053U	Oncology (prostate cancer), FISH analysis of 4 genes (ASAP1, HDAC9, CHD1 and PTEN), needle biopsy specimen, algorithm reported as probability of higher tumor grade

The following CPT code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

CPT Codes

CPT codes:	Code Description
81539	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

The above medical necessity criteria MUST be met for the following code to be covered for Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
81539	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

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 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-walk of these grading systems is shown in Table 1.

Table 1. Prostate Cancer Grading Systems

Grade Group	Gleason Score (Primary and Secondary Pattern)	Cells
1	6 or less	Well differentiated (low grade)
2	7 (3 + 4)	Moderately differentiated (moderate grade)
3	7 (4 + 3)	Poorly differentiated (high grade)
4	8	Undifferentiated (high grade)
5	9-10	Undifferentiated (high grade)

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. 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

Date	Action
1/2021	Medicare information removed. See MP #132 Medicare Advantage Management for local coverage determination and national coverage determination reference.

4/2019	Annual policy review. New investigational tests described. Clarified coding information. Effective 4/1/2019.
1/2019	Ongoing investigational indications described. For coverage information on the following tests, see medical policy #954, AIM Genetic Testing Management Program and medical policy #957, AIM Genetic Testing Management Program CPT and HCPCS Codes. Effective 1/1/2019. Clarified coding information. • Genetic Testing for TMPRSS Fusion Genes in Prostate Cancer (using PCR) • Genetic Testing for Mitochondrial DNA Mutation Testing (eg, Prostate Core Mitomics Test™) • Candidate Gene Panels • PCA3 Testing • Gene Hypermethylation Testing (eg, ConfirmMDx®).
7/2018	Clarified coding information.
4/2018	Annual policy review. Prostarix test removed from policy and policy statement. Effective 4/1/2018.
1/2018	Clarified coding information.
3/2017	Annual medical policy review. New investigational indications described. Clarified coding information. Effective 3/1/2017.
1/2017	Clarified coding information for the 2017 code changes.
1/2016	Clarified coding information.
9/2015	Annual medical policy review. New investigational indications described; title changed. Effective 9/1/2015.
1/2015	Clarified coding information.
7/2014	Annual policy review. New references added.
3/2014	Annual policy review. New references added.
5/2013	Annual policy review. New references added.
4/2012	Updated to add new non-covered HCPCS code S3721.
12/1/2011	New medical policy describing ongoing non-coverage. Effective 12/01/2011.

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

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