MEDICAL POLICY

POLICY TITLE	**GENETIC AND PROTEIN BIOMARKERS FOR THE DIAGNOSIS AND CANCER RISK ASSESSMENT OF PROSTATE CANCER**
POLICY NUMBER	**MP 2.280**

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**4/1/2026**

POLICY

Genetic and protein biomarkers for the diagnosis of prostate cancer, including, but not limited to the following, are considered **investigational**:

- Kallikrein markers (e.g., 4KscoreTest)
- Prostate Health Index (PHI)
- *HOXC6* and *DLX1* testing (e.g., SelectMDx)
- PCA3, ERG, and SPDEF RNA expression in exosomes (e.g., ExoDx Prostate IntelliScore)
- Autoantibodies ARF 6, NKX3-1, 5-UTR-BMI1, CEP 164, 3-UTR-Ropporin, Desmocollin, AURKAIP-1, and CSNK2A2 (e.g., Apifiny)
- *PCA3* testing (e.g., Progensa PCA3 Assay)
- *TMPRSS: ERG* fusion genes (e.g., MyProstate Score)
- Gene hypermethylation testing (e.g., ConfirmMDx)
- Mitochondrial DNA mutation testing (e.g., Prostate Core Mitomics Test)
- PanGIA Prostate
- Candidate gene panels

Single nucleotide variant testing for cancer risk assessment of prostate cancer is considered **investigational**. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with the above procedures.

Cross-References

MP 2.259 Molecular Panel Testing of Cancers to Identify Targeted Therapies
MP 2.263 Gene Expression Profiling, Protein Biomarkers, and Multimodal Artificial Intelligence for Prostate Cancer Management
MP 2.267 Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
MP 2.277 Investigational Miscellaneous Genetic and Molecular Tests

MEDICAL POLICY

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PRODUCT VARIATIONS

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations. Please see additional information below.

FEP PPO: Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

DESCRIPTION/BACKGROUND

PROSTATE CANCER

Prostate cancer is the most common cancer, and the second most common cause of cancer death in men. 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 U.S. is approximately 16%, while the risk of dying of prostate cancer is 3%. African American men have the highest prostate cancer risk in the U.S.; 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. Autopsy results have suggested that about 30% of men over the age of 55 and 60% of men over the age of 80 who die of other causes have incidental prostate cancer, 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. It is an architectural grading system ranging from 1 (well-differentiated) to 5 (undifferentiated); 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. 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 to 10	Undifferentiated (high grade)

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.

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 (CLIA). Laboratories that offer laboratory-developed tests must be licensed under the CLIA for high-complexity testing. The following laboratories are certified under the CLIA: 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 (SelectMDx, ConfirMDx), Innovative Diagnostics (PHI™), and ExoDx® Prostate (Exosome Diagnostics). To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests.

In February 2012, the Progensa® PCA3 Assay (Gen-Probe; now Hologic) was approved by the FDA through the premarket approval process. The Progensa PCA3 Assay has been approved by the FDA to aid in the decision for repeat biopsy in men 50 years or older who have had 1 or more negative prostate biopsies and for whom a repeat biopsy would be recommended based on the current standard of care. The Progensa PCA3 Assay should not be used for men with atypical small acinar proliferation on their most recent biopsy. FDA product code: OYM.

In June 2012, proPSA, a blood test used to calculate the Prostate Health Index (PHI ; Beckman Coulter) was approved by the FDA through the premarket approval process. The PHI test is indicated as an aid to distinguish prostate cancer from a benign prostatic condition in men ages 50 and older with prostate-specific antigen levels 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.

RATIONALE

Summary of Evidence

For individuals who are being considered for an initial prostate biopsy who receive testing for genetic and protein biomarkers of prostate cancer (e.g., kallikreins biomarkers and 4Kscore Test, proPSA and Prostate Health Index, TMPRSS fusion genes and MyProstateScore, SelectMDx for Prostate Cancer, ExoDx Prostate, Apifiny, PCA3 score, and PanGIA Prostate),

the evidence includes systematic reviews, meta-analyses, and primarily observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, resource utilization, and quality of life. The evidence supporting clinical utility varies by the 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 a positive digital rectal exam (DRE), a prostate-specific antigen (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 that the technology results in an improvement in the net health outcome.

For individuals who are being considered for repeat biopsy who receive testing for genetic and protein biomarkers of prostate cancer (e.g., PCA3 score, Gene Hypermethylation and ConfirmMDx test, Prostate Core Mitomics Test, MyProstate Score), the evidence includes systematic reviews and meta-analyses and primarily observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, 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 do not compare performance characteristics with standard risk prediction models. Direct evidence supporting clinical utility has not been shown. No data is currently available on the longer-term clinical outcomes of the use of genetic and protein biomarkers to decide on repeat prostate biopsy, The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

DEFINITIONS

NA

DISCLAIMER

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as permitted by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These polices are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

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CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational for the diagnosis and cancer risk assessment of prostate cancer, therefore, not covered:

CPT Codes®								
81313	81479	81539	81551	0011M	0005U	0021U	0113U	0228U
0339U	0343U	0359U	0403U	0424U	0433U	0495U	0497U	0534U
0550U	0609U							

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POLICY HISTORY

MP 2.280	**01/01/2020 Administrative Update.** Added new codes effective 01/01/2020: 81552, 81559, 0011M, 0005U, 0021U, 0053U, and 0113U.
	08/19/2020 Consensus Review. No change in policy statement. Removed codes 81552 and 81559. Added Genetic counseling segment under policy guidelines. References and background updated.
	11/30/2020 Major Review. Added medically necessary criteria for Gene expression profile analysis for the evaluation of prostate cancer based on NCCN Biomarker Compendium. Revised, statement, guidelines, references, and coding.

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	12/29/2021 Minor Review. Changed title of policy. Updated MN criteria for management of prostate cancer as well as policy guidelines. Updated FEP, Background, and references. Added code 81542 to MN coding table.
	08/29/2022 Minor Review. Removed Promark as MN. Other management testing is now NMN. miR Sentinel™ test added to INV diagnosis tests. Updated guidelines, FEP, background, rationale, and references. Added 0228U, 0339U, and 0343U to INV coding table.
	12/01/2022 Administrative Update. Added new code 0359U effective 01/01/2023
	06/13/2023 Administrative Update. Deleted 0053U effective 07/01/2023
	09/07/2023 Administrative Update. Added new code 0403U. Effective date 10/01/2023.
	12/08/2023 Consensus Review. Updated cross-references and references. No changes to coding.
	12/12/2023 Administrative Update. Added codes 0424U and 0433U.
	09/18/2024 Administrative Update. New codes 0495U, 0497U, 0513U added effective 10/01/2024.
	10/21/2024 Minor Review. Modified criteria for management tests. Added INV statement for multimodal artificial intelligence assays. Updated coding table; added 0376U. Updated background, rationale, and references.
	03/12/2025 Administrative Update. New codes 0534U and 0550U added. Effective date 04/01/2025
	10/10/2025 Minor Review. Removed management test statements and procedure codes to MP 2.263. Diagnosis and Cancer Risk Assessment tests still remain investigational. Updated background, cross-references, rationale, coding table, and references.
	12/11/2025 Administrative Update. Added new code 0609U. Eff date 01/01/2026