BlueCross BlueShield of Vermont

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Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management
Corporate Medical Policy

File Name: Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management
File Code: 10.99.VT86
Origination: 09/01/2024
Last Review: 10/2025
Next Review: 09/2026
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Description/Summary

Prostate Cancer
Prostate cancer is the second most common cancer diagnosed among men in the U.S. Autopsy studies in the pre-prostate-specific antigen (PSA) screening era have identified incidental cancerous foci in 30% of men 50 years of age, with incidence reaching 75% at age 80 years.

Localized prostate cancers may appear very similar clinically at diagnosis. However, they often exhibit diverse risk of progression that may not be captured by accepted clinical risk categories (e.g., D'Amico criteria) or prognostic tools that are based on clinical findings, including PSA titers, Gleason grade, or tumor stage. In studies of conservative management, the risk of localized disease progression based on prostate cancer-specific survival rates at 10 years may range from 15% to 20% to perhaps 27% at 20-year follow-up/ Among elderly men (70 years or more) with this type of low-risk disease, comorbidities typically supervene as a cause of death; these men will die with prostate cancer present, rather than from the cancer. Other very similar-appearing low-risk tumors may progress unexpectedly rapidly, quickly disseminating and becoming incurable.

Risk Stratification in Newly Diagnosed Disease
In the United States, most prostate cancers are clinically localized at diagnosis due in part to the widespread use of PSA testing. Clinicopathologic characteristics are used to stratify patients by risk based on the extent of the primary tumor (T category), nearby lymph node involvement (N category), metastasis (M category), PSA level and Gleason score. The National Comprehensive Cancer Network and American Urological Association risk categories for clinically localized prostate cancer are similar, derived from the D'Amico criteria and broadly include low-, intermediate-, or high-risk as follows as well as subcategories within these groups:

1. Low: T1-T2a and Gleason score ≤6 grade group 1 and PSA level ≤10 ng/mL;

2. Intermediate: T2b-T2c or Gleason score 3+4=7/Gleason grade group 2 or Gleason score 4+3=7/Gleason grade group 3 or PSA level 10-20 ng/mL;
3. High: T3a or Gleason score 8/Gleason grade group 4 or Gleason score 9-10/Gleason grade group 5 or PSA level >20 ng/mL.

Risk stratification is combined with patient age, life expectancy, and treatment preferences to make initial therapy decisions.

Gene Expression Profile Analysis
Gene expression profiling is the measurement of the activity (i.e., expression) of thousands of genes at once, to create a global picture of cellular function. These profiles may distinguish between cells that are actively dividing, or show how the cells react to a particular treatment. Many experiments of this sort measure an entire genome simultaneously, that is, every gene present in a particular cell.
Several transcriptomics technologies can be used to generate the necessary data to analyze. DNA microarrays measure the relative activity of previously identified target genes. Sequence based techniques, like RNA-Seq, provide information on the sequences of genes in addition to their expression level.

The safety and effectiveness of gene expression analysis to guide management of prostate cancer has been established. It may be considered a useful option when indicated.

Policy

Coding Information

Click the links below for attachments, coding tables & instructions.

Attachment I

When a service may be considered medically necessary

Decipher may be considered **medically necessary** for the following:

- Individuals with NCCN very-low-risk, low-risk, and favorable intermediate-risk, and unfavorable intermediate-risk prostate cancer who have a greater than 10-year life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy; **OR**
- Individuals with intermediate-risk prostate cancer when deciding whether to add androgen-deprivation therapy to radiation; **OR**
- Individuals post-radical prostatectomy:
    - for pT2 with positive margins;
    - any pT3 disease;
    - rising PSA (above nadir)

Oncotype DX Genomic Prostate Score, Prolaris or **ProMark** may be considered **medically necessary** for the following**:**

- Individuals with NCCN very-low-risk, low-risk, and favorable intermediate-risk prostate cancer who have a greater than 10-year life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy; **OR**
- Individuals with intermediate-risk prostate cancer when deciding whether to add androgen-deprivation therapy to radiation

AR-V7 testing may be considered **medically necessary** for the following:

- To help guide selection of therapy in individuals in the post abiraterone/enzalutamide metastatic castration-resistant prostate cancer (CRPC setting).

When a service is considered investigational

- The use of more than one type of test to assess risk of prostate cancer progression (**Oncotype DX Genomic Prostate Score, Decipher, Prolaris**, or **ProMark**, etc.) is considered **investigational**.
- All other indications that are not listed as medically necessary are considered **investigational**.

Reference Resources

1. Blue Cross Blue Shield Blue Care Network of Michigan Medical Policy: Gene Expression Profile Analysis for Risk Stratification for Prostate Cancer Management. Effective 3/1/2025. Accessed October 2025.
2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 2.2020. Accessed September 2024.
3. American Urological Association (AUA). Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Accessed September 2024.
4. Eggener SE, Rumble RB, Armstrong AJ, Morgan TM, Crispino T, Cornford P, van der Kwast T, Grignon DJ, Rai AJ, Agarwal N, Klein EA, Den RB, Beltran H. Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline. J Clin Oncol. 2020 May 1;38(13):1474-1494. PMID: 31829902. Accessed September 2024.

Document Precedence

Blue Cross and Blue Shield of Vermont (Blue Cross VT) Medical Policies are developed to provide clinical guidance and are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. The applicable group/individual contract and member certificate language, or employer's benefit plan if an ASO group, determines benefits that are in effect at the time of service. Since medical practices and knowledge are constantly evolving, Blue Cross VT reserves the right to review and revise its medical policies periodically. To the extent that there may be any conflict between medical policy and contract/employer benefit plan language, the member's contract/employer benefit plan language takes precedence.

Audit Information

Blue Cross VT reserves the right to conduct audits on any provider and/or facility to ensure compliance with the guidelines stated in the medical policy. If an audit identifies instances of non-compliance with this medical policy, Blue Cross VT reserves the right to recoup all non-compliant payments.

Administrative and Contractual Guidance

Benefit Determination Guidance

Prior approval is required and benefits are subject to all terms, limitations and conditions of the subscriber contract.

Incomplete authorization requests may result in a delay of decision pending submission of missing information. To be considered compete, see policy guidelines above.

NEHP/ABNE members may have different benefits for services listed in this policy. To confirm benefits, please contact the customer service department at the member's health plan.

Federal Employee Program (FEP): Members may have different benefits that apply. For further information please contact FEP customer service or refer to the FEP Service Benefit Plan Brochure. It is important to verify the member's benefits prior to providing the service to determine if benefits are available or if there is a specific exclusion in the member's benefit.

Coverage varies according to the member's group or individual contract. Not all groups are required to follow the Vermont legislative mandates. Member Contract language takes precedence over medical policy when there is a conflict.

If the member receives benefits through an Administrative Services Only (ASO) group, benefits may vary or not apply. To verify benefit information, please refer to the member's employer benefit plan documents or contact the customer service department. Language in the employer benefit plan documents takes precedence over medical policy when there is a conflict.

Policy Implementation/Update information

09/2024	New policy. Medical necessity criteria established for use of gene expression profiling and protein biomarker testing for management of prostate cancer.
10/2025	Added "unfavorable intermediate-risk" as eligible for testing by Decipher. Updated Oncotype DX Prostate name to Oncotype DX Genomic Prostate Score. Conflicting Reference Policy reference removed. References updated.

Eligible providers

Qualified healthcare professionals practicing within the scope of their license(s).

Approved by Blue Cross VT Medical Directors

Tom Weigel, MD, MBA
Vice President and Chief Medical Officer

Tammaji P. Kulkarni, MD
Senior Medical Director

Attachment I

Code Type	Number	Brief Description	Policy Instructions
The following codes will be considered as medically necessary when applicable criteria have been met.			
CPT®	0047U	Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score	Requires Prior Authorization
CPT®	81479	Unlisted molecular pathology procedure	Requires Prior Authorization
CPT®	81541	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	Requires Prior Authorization
CPT®	81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score	Requires Prior Authorization
CPT®	81551	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	Requires Prior Authorization
CPT®	81599	Unlisted multianalyte assay with algorithmic analysis	Requires Prior Authorization