EFFECTIVE DATE: 11|01|2026
POLICY LAST REVIEWED: 07|15|2026

OVERVIEW

ProMark® is a biopsy-based prostate cancer prognostic test that utilizes an automated, quantitative protein-based multiplex immunofluorescent in situ imaging platform to evaluate standard formalin-fixed, paraffin-embedded (FFPE) prostate tissue to differentiate indolent from aggressive prostate cancer. ProMark® technology allows for analysis of proteins directly from the cancerous regions of interest. The test has shown the ability to predict prostate cancer aggressiveness.

MEDICAL CRITERIA

Medicare Advantage Plans and Commercial Products

ProMark assay is considered medically necessary when ALL of the following medical criteria is met:

- Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement); AND,
- Stage as defined by the ONE of the following:
  - Very Low Risk Disease (T1c AND Gleason Score ≤ 6 AND PSA ≤ 10 ng/mL AND ≤ 50% cancer in any core AND PSA density of < 0.15 ng/mL/g); OR,
  - Low Risk Disease (T1-T2a AND Gleason Score ≤ 6 AND PSA ≤ 10 ng/mL); AND,
- Estimated life expectancy of greater than or equal to 10 years; AND,
- Is a candidate for and is considering conservative therapy and yet and would be eligible for definitive therapy (radical prostatectomy, radiation therapy or brachytherapy); AND,
- Has not received pelvic radiation or androgen deprivation therapy prior to the biopsy; AND,
- Is monitored for disease progression according to active surveillance guidelines as recorded in NCCN guidelines.

PRIOR AUTHORIZATION

There is no specific CPT coding for testing referenced in this policy. Therefore, an Unlisted CPT code should be used (See Coding Section for details). All Unlisted genetic testing CPT codes require prior authorization to determine what service is being rendered and if the service is covered or not medically necessary. See the Related Policies section.

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

The following test(s) are considered medically necessary for Medicare Advantage Plans and Commercial Products when the medical criteria above is met.

- ProMark

The following test(s) are considered not covered for Medicare Advantage Plans and not medically necessary for Commercial Products when the medical criteria above is not met as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome:

- ProMark

Commercial Products

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L**. §27-19-81** described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for applicable laboratory testing and not medically necessary/not covered benefits/coverage.

BACKGROUND

ProMark® is a biopsy-based prostate cancer prognostic test that utilizes an automated, quantitative protein-based multiplex immunofluorescent in situ imaging platform to evaluate standard formalin-fixed, paraffin-embedded (FFPE) prostate tissue to differentiate indolent from aggressive prostate cancer. The assay measures the signal intensity of 8 protein biomarkers (i.e., CUL2, DERL1, FUS, HSPA9, PDSS2, pS6, SMAD4 and YBX1) in tumor and benign prostate glands on FFPE biopsy tissue sections to generate an algorithmically derived risk score indicating the likelihood of having high-risk disease. Unlike deoxyribonucleic acid (DNA)/ribonucleic Acid (RNA)-based tests that require biopsy tissue to be homogenized prior to analysis, ProMark® technology allows for analysis of proteins directly from the cancerous regions of interest. The test has shown the ability to predict prostate cancer aggressiveness regardless from which region the prostate biopsy was taken, a key feature and benefit given the considerable heterogeneity that exists in biopsied tissue.

Traditionally, clinicopathologic characteristics are utilized to determine risk and subsequent treatment. Several nomograms have been introduced to try to determine who is at risk of developing metastatic disease and who, if treated early, could avoid this outcome. A representative nomogram taken from the National Comprehensive Cancer Network (NCCN) and American Urological Association (AUA), divides early prostate cancer into several groups based initially on life expectancy, with a second stratification using clinical exam, reassessment of life expectancy, biopsy (Gleason score), prostate-specific antigen (PSA) and imaging after 5 years.

These groups are detailed below:

	Risk Category			
	Very Low	**Low**	**Intermediate**	**High**

Clinicopathologic Findings	• T1c AND • Gleason score ≤ 6 AND • PSA ≤ 10 ng/mL AND • < 3 prostate cores with tumor AND • ≤ 50% tumor in any core AND • PSA density of <0.15 ng/mL/g	• T1-T2a AND • Gleason score ≤ 6/Gleason grade group 1 AND • PSA ≤ 10 ng/mL	• T2b-T2c OR • Gleason score 3+4=7/Gleason grade group 2 OR • Gleason score 4+3=7/Gleason grade group 3 OR • PSA 10-20 ng/mL	• T3a OR • Gleason Score 8/Gleason grade group 4 OR • Gleason score 9-10/Gleason grade group 5 OR • PSA > 20 ng/mL
Treatment Options				
≥ 20 y life expectancy	• Active Surveillance • RT or Brachy • RP (± LND)			
≥ 10 y life expectancy	• Active Surveillance	• Active Surveillance • RT or Brachy • RP (± LND	• RP (± LND) • RT or Brachy ± Adj Horm	• RT + Adj Horm • RT + Brachy • RP + LND ± RT, ADT
< 10 y life expectancy	• Observation	• Observation	• RT or Brachy ± Adj Horm • Observation	• N/A

Table 1: NCCN 2017 V2 - Localized Prostate Cancer Risk Stratification and Treatment
(PSA – Prostate Specific Antigen; RT –Radiation Therapy; RP – Radical Prostatectomy; LND – lymph node dissection; Adj Horm – Adjuvant Androgen Deprivation)

The intended use of ProMark® is to categorize an individual to favorable versus non-favorable disease pathology based on the risk score on the specificity curve. The positive predictive value (PPV) for favorable pathology, at a risk score of≤0.33, was 83.6% (specificity, 90%). Conversely, at a risk score of >0.80, 76.9% had non-favorable disease (i.e., only 23.1% of patients in the high-risk score category had favorable disease). This translates to 39% of patients in this study population having risk scores ≤0.33 or >0.8, of which 81% were correctly identified by ProMark®. Of patients with intermediate risk scores (0.33< risk score ≤0.8), 58.3% had favorable disease. The PPV of ProMark® was also compared with those of the NCCN and D'Amico risk categories. The PPV for favorable pathology, at a risk score of ≤0.33, was 75% for patients in the NCCN intermediate-risk category; 81.5% for NCCN low-risk patients, and 95% for NCCN very low-risk, with an overall PPV for favorable pathology of 85%. This contrasts favorably with the PPVs obtained for the NCCN risk categories alone, which were 40.9% for intermediate risk, 63.8% for low-risk, and 80.3% for very low-risk.

Findings suggest that the ProMark® risk score provides additional confidence that a patient categorized to the NCCN very low-risk group indeed has a favorable pathology based on his biopsy from 80.3% to 95%. Conversely, the predictive value for non-favorable pathology was 76.9% at a risk score >0.8, but reached 100% at a risk score cutoff point of >0.9. For all NCCN and D'Amico risk categories, a higher ProMark®

risk score correlated with decreased frequency of favorable cases. The evidence is sufficient to determine the effects of the technology on health outcomes.

CODING

Medicare Advantage Plans and Commercial Products

The following code(s) are medically necessary when the medical criteria above is met:

81479 Unlisted molecular pathology procedure

RELATED POLICIES

Biomarker Testing Mandate
Unlisted Procedures

PUBLISHED

Provider Update, September 2026
Provider Update, July 2025
Provider Update, September 2024
Provider Update, November 2023
Provider Update, June 2022

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