



Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

Policy # 00403

Original Effective Date: 02/19/2014

Current Effective Date: 07/10/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer is addressed separately in medical policy 00272.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider use of tumor-based gene expression molecular assay (i.e., Decipher[®], Oncotype DX[®] Prostate, or Prolaris[®])[†] or ProMark[®][‡] Risk Score assay to be **eligible for coverage**** to guide management of prostate cancer.

Patient Selection Criteria

Coverage eligibility for the use of tumor-based gene expression molecular assay (i.e., Decipher[®], Oncotype DX[®] Prostate, or Prolaris[®])[†] or ProMark[®][‡] Risk Score assay to guide management of prostate cancer will be considered when **ALL** of the criteria are met:

- The test will be used to guide management (e.g., active surveillance versus therapeutic intervention such as radical prostatectomy, radiation therapy, brachytherapy); **AND**
- Needle biopsy confirmed localized adenocarcinoma of prostate with no clinical evidence of lymph node involvement or metastases; **AND**
- Individual has not received pelvic radiation or androgen deprivation therapy prior to the biopsy; **AND**
- Tumor-based gene expression molecular assay or protein biomarker test was not used in past; **AND**

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- For patients with **low or favorable intermediate-risk disease** (see Policy Guidelines section) and an estimated life expectancy of greater than or equal to 10 years, one of the following may be considered for initial risk stratification:
 - Decipher
 - Oncotype DX Prostate
 - Prolaris, or
 - ProMark Risk Score
- For patients with **unfavorable intermediate-risk or high-risk disease** (see Policy Guidelines section) and an estimated life expectancy of greater than or equal to 10 years, one of the following may be considered:
 - Decipher, or
 - Prolaris

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers gene expression analysis and protein biomarkers to guide management of prostate cancer when patient selection criteria are not met and in all other situations, including but not limited to repeat testing, to be **investigational**.*

Policy Guidelines

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:

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Table 1. NCCN Guidelines-Initial Risk Stratification and Staging Workup for Clinically Localized Disease

Risk Group	Clinical/Pathologic Features See Staging (ST-1)		
Very low ^a	Has all of the following: <ul style="list-style-type: none"> • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core • PSA density <0.15 ng/mL/g 		
Low ^a	Has all of the following but does not qualify for very low risk: <ul style="list-style-type: none"> • cT1-cT2a • Grade Group 1 • PSA <10 ng/mL 		
Intermediate	Has all of the following: <ul style="list-style-type: none"> • No high-risk group Features • No very high-risk group features • Has one or more intermediate risk factors (IRFs): <ul style="list-style-type: none"> ○ cT2b-cT2c ○ Grade Group 2 or 3 ○ PSA 10-20 ng/mL 	Favorable intermediate	Has all of the following: <ul style="list-style-type: none"> • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)^b
		Unfavorable intermediate	Has one or more of the following: <ul style="list-style-type: none"> • 2 or 3 IRFs • Grade Group 3 • ≥50% biopsy cores positive

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			(eg, ≥ 6 of 12 cores) ^b
High	Has no very-high-risk features and has exactly one high-risk feature: <ul style="list-style-type: none">• cT3a OR• Grade Group 4 or Grade Group 5 OR• PSA >20 ng/mL		
Very high	Has at least one of the following: <ul style="list-style-type: none">• cT3b-cT4• Primary Gleason pattern 5• 2 or 3 high-risk features• >4 cores with Grade Group 4 or 5		

^e For asymptomatic patients in very-low-, low-, and intermediate-risk groups with life expectancy ≤ 5 years, no imaging or treatment is indicated until the patient becomes symptomatic, at which time imaging can be performed and ADT should be given.

^b An ultrasound- or MRI- or DRE-targeted lesion that is biopsied more than once and demonstrates cancer (regardless of percentage core involvement or number of cores involved) can be considered as a single positive core.

American Joint Committee on Cancer (AJCC)

TNM Staging System For Prostate Cancer (8th ed., 2017)

Definitions for T, N, M

Clinical T (cT)

T Primary Tumor

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Clinically inapparent tumor that is not palpable

T1a Tumor incidental histologic finding in 5% or less of tissue resected

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T1b Tumor incidental histologic finding in more than 5% of tissue resected

T1c Tumor identified by needle biopsy found in one or both sides, but not palpable

T2 Tumor is palpable and confined within prostate

T2a Tumor involves one-half of one side or less

T2b Tumor involves more than one-half of one side but not both sides

T2c Tumor involves both sides

T3 Extraprostatic tumor that is not fixed or does not invade adjacent structures

T3a Extraprostatic extension (unilateral or bilateral)

T3b Tumor invades seminal vesicle(s)

T4 Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall.

Pathological T (pT)

T Primary Tumor

T2 Organ confined

T3 Extraprostatic extension

T3a Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck

T3b Tumor invades seminal vesicle(s)

T4 Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

Note: There is no pathological T1 classification.

Note: Positive surgical margin should be indicated by an R1 descriptor, indicating residual microscopic disease.

N Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed

N0 No positive regional nodes

N1 Metastases in regional node(s)

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M Distant Metastasis

M0 No distant metastasis

M1 Distant metastasis

M1a Nonregional lymph node(s)

M1b Bone(s)

M1c Other site(s) with or without bone disease

Note: When more than one site of metastasis is present, the most advanced category is used. M1c is most advanced.

The 2014 International Society of Urological Pathology (ISUP) consensus conference adopted a new five-tier grading system based on the modified Gleason scores. This new grading (ISUP grade group) system was adopted in the 2016 World Health Organization classification of genitourinary tumors. Tumors are separated into five categories based on the primary and secondary Gleason pattern:

- Grade group 1: Gleason score ≤ 6
- Grade group 2: Gleason score $3+4 = 7$ (hazard ratio [HR] for death 2.8 relative to grade group 1)
- Grade group 3: Gleason score $4+3 = 7$ (HR 6.0 relative to grade group 1)
- Grade group 4: Gleason score = 8 including $4+4 = 8$, $3+5 = 8$, or $5+3 = 8$ (HR 7.1 relative to grade group 1)
- Grade group 5: Gleason scores 9 to 10 including $4+5$, $5+4$, or $5+5$ (HR 12.7 relative to grade group 1)

Background/Overview

Prostate Cancer

Prostate cancer is the second most common noncutaneous cancer diagnosed among men in the U. S. Autopsy studies in the era before the availability of prostate-specific antigen (PSA) screening 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 clinical risk categories (eg, D'Amico criteria) or prognostic tools based on clinical findings, including PSA titers, Gleason grade, or tumor

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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 older men (ages ≥ 70 years) with low-risk disease, comorbidities typically supervene as a cause of death; these men will die with prostate cancer present, rather than from cancer itself. Other very similar appearing low-risk tumors may progress unexpectedly rapidly, quickly disseminating and becoming incurable.

Risk Stratification in Newly Diagnosed Disease

In the U. S., 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:

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

Monitoring After Prostatectomy

All normal prostate tissue and tumor tissue are theoretically removed during radical prostatectomy (RP), so the serum level of PSA should be undetectable following RP. Detectable PSA post-RP indicates residual prostate tissue and presumably persistent or recurrent disease. Prostate-specific antigen is serially measured following RP to detect early disease recurrence. The National Comprehensive Cancer Network recommends monitoring serum PSA every 6 to 12 months for the first 5 years and annually thereafter. Many recurrences following RP can be successfully treated. The American Urological Association recommends that biochemical recurrence be defined as a serum PSA of 0.2 ng/mL or higher, which is confirmed by the second determination with a PSA level of 0.2 ng/mL or higher.

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Castration-Resistant Prostate Cancer

Androgen deprivation therapy (ADT) is generally the initial treatment for patients with advanced prostate cancer. Androgen deprivation therapy can produce tumor response and improve quality of life but most patients will eventually progress on ADT. Disease that progresses while the patient is on ADT is referred to as castration-resistant prostate cancer. After progression, continued ADT is generally used in conjunction with other treatments. Androgen pathways are important in the progression of castration-resistant prostate cancer. Several drugs have been developed that either inhibit enzymes involved in androgen production or inhibit the androgen receptor, such as abiraterone and enzalutamide. Taxane chemotherapy with docetaxel or cabazitaxel may also be used after progression. Immunotherapy (sipuleucel-T) or radium 223 are options for select men.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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). Prolaris[®] (Myriad Genetics), Oncotype DX[®] Prostate and Oncotype DX AR-V7 Nuclear Detect (Genomic Health), Decipher gene expression profiling test (Decipher Corp), and the ProMark[™] protein biomarker test (Metamark Genetics) are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests.

In November 2015, the FDA's Office of Public Health Strategy and Analysis published a report suggesting FDA oversight of laboratory-developed tests. The FDA argued that many tests need more FDA oversight than the regulatory requirements of the CLIA. The CLIA standards relate to laboratory operations but do not address inaccuracies or unreliability of specific tests. Prolaris is among the 20 case studies in the document cited as needing FDA oversight. The report asserted that patients are potentially receiving inappropriate prostate cancer care because there is no evidence that results from the test meaningfully improve clinical outcomes.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration

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approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Gene expression profile analysis and protein biomarkers have been proposed as a means to risk-stratify patients with prostate cancer to guide treatment decisions. These tests are intended to be used either on prostate needle biopsy tissue to guide management decisions for active surveillance or therapeutic intervention, to guide radiotherapy use after radical prostatectomy (RP), or to guide medication selection after progression in metastatic castration-resistant prostate cancer.

Initial Management Decision: Active Surveillance versus Therapeutic Intervention

For individuals who have clinically localized untreated prostate cancer who receive Prolaris, the evidence includes retrospective cohort studies of clinical validity using archived samples in patients of mixed risk categories. Relevant outcomes include overall survival (OS), disease-specific survival, quality of life (QOL), and treatment-related morbidity. For the low-risk group, the Prostate Testing for Cancer and Treatment trial showed 99% 10-year disease-specific survival in mostly low-risk patients receiving active surveillance. The low mortality rate estimated with tight precision makes it unlikely that a test intended to identify a subgroup of low-risk men with a net benefit from immediate treatment instead of active surveillance would find such a group. For the intermediate-risk group, the evidence of improved clinical validity or prognostic accuracy for prostate cancer death using Prolaris Cell Cycle Progression score in patients managed conservatively after a needle biopsy has shown some improvement in areas under the receiver operating characteristic curve over clinicopathologic risk stratification tools. There is limited indirect evidence for potential clinical utility. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have clinically localized untreated prostate cancer who receive Oncotype DX Prostate, the evidence includes case-cohort and retrospective cohort studies of clinical validity using archived samples in patients of mixed risk categories, and a decision-curve analysis examining indirect evidence of clinical utility. Relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. Evidence for clinical validity and potential clinical utility of Oncotype DX Prostate in patients with clinically localized prostate cancer derives from a study predicting adverse pathology after RP. The validity of using tumor pathology as a surrogate for the risk of progression and cancer-specific death is unclear. It is also unclear whether results from an

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RP population can be generalized to an active surveillance population. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have clinically localized untreated prostate cancer who receive Decipher Biopsy, the evidence includes retrospective cohort studies of clinical validity using archived samples in intermediate- and high-risk patients and no studies of clinical utility. Relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. A test designed to identify intermediate-risk men who can receive active surveillance instead of RP or radiotherapy (RT) or high-risk men who can forego androgen deprivation therapy would need to show very high negative predictive value for disease-specific mortality at 10 years and improvement in prediction compared with existing tools used to select such men. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have clinically localized untreated prostate cancer who receive the ProMark protein biomarker test, the evidence includes a retrospective cohort study of clinical validity using archived samples and no studies of clinical utility. Relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. Current evidence does not support improved outcomes with ProMark given that only a single clinical validity study is available. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Management Decision After Radical Prostatectomy

For individuals who have localized prostate cancer treated with RP who receive Prolaris, the evidence includes retrospective cohort studies of clinical validity using archived samples. Relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. No direct evidence is available to support the clinical utility of Prolaris for improving net outcomes of patients with localized prostate cancer following RP. The chain of evidence is also incomplete. Decision-curve analysis did not provide convincing evidence of meaningful improvement in net benefit by incorporating the cell cycle progression (CCP) score. Evidence of improved clinical validity or prognostic accuracy for prostate cancer death using the Prolaris Cell Cycle Progression score in patients after prostatectomy has shown some improvement in areas under the receiver operating characteristic curve over clinicopathologic risk stratification tools. Although Prolaris CCP score may have an association with biochemical recurrence (BCR), disease-specific survival outcomes were reported in only 1 analysis. A larger number of disease-specific survival events and precision

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estimates for discrimination measures are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have localized prostate cancer who are treated with RP and who receive the Decipher RP prostate cancer classifier, the evidence includes a study of analytic validity, prospective and retrospective studies of clinical validity using overlapping archived samples, decision-curve analyses examining indirect evidence of clinical utility, and prospective decision-impact studies without pathology or clinical outcomes. Relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. The clinical validity of the Decipher RP genomic classifier has been evaluated in samples of patients with high-risk prostate cancer undergoing different interventions following RP. Studies reported some incremental improvement in discrimination. However, it is unclear whether there is consistently improved reclassification-particularly to higher risk categories-or whether the test could be used to predict which men will benefit from radiotherapy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Management Decision in Castration-Resistant Prostate Cancer

For individuals who have metastatic castration-resistant prostate cancer who receive the Oncotype DX AR-V7 Nuclear Detect, the evidence includes 1 prospective cohort study, 1 retrospective cohort study of clinical validity using archived samples, and no studies of clinical utility. Relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. Current evidence does not support improved outcomes with Oncotype DX AR-V7 Nuclear Detect, given that only 2 clinical validity studies meeting inclusion criteria were available. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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American Society of Clinical Oncology

In 2020, the American Society of Clinical Oncology (ASCO) published a guideline on molecular biomarkers in localized prostate cancer.¹⁰⁸ The guidelines state, "Currently, there are no strong data or expert guidelines to support active surveillance in otherwise healthy men with Grade Group 3 or higher cancer; therefore, we would consider the use of genomic biomarkers only in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect a physician's recommendation or a patient's choice for surveillance versus treatment, but they should not be used routinely."

Specific recommendations included the following:

Molecular biomarkers to identify patients with prostate cancer who are most likely to benefit from active surveillance:

- Recommendation 1.1. Commercially available molecular biomarkers (i.e. Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).
- Recommendation 1.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

Molecular biomarkers to diagnose clinically significant prostate cancer:

- Recommendation 2.1. Commercially available molecular biomarkers (i.e. Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Recommendation: Moderate).
- Recommendation 2.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

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Molecular biomarkers to guide the decision of post prostatectomy adjuvant versus salvage radiation:

- Recommendation 3.1. The Expert Panel recommends consideration of a commercially available molecular biomarker (eg, Decipher Genomic Classifier) in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. In the absence of prospective clinical trial data, routine use of genomic biomarkers in the postprostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).
- Recommendation 3.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

“Although the routine use of molecular biomarkers is not recommended, the Expert Panel recognized that there may be scenarios in which biomarkers may be helpful to inform prognostication or to guide management decisions. For instance, men who are considering active surveillance of newly diagnosed prostate cancer with higher-risk features for progression (eg, high-volume Grade Group 1, low volume Grade Group 2, or high PSA density) may benefit from a biomarker, although the committee recognizes that a relative minority of men will attain clear actionable data as test results are often equivocal in this scenario.

For men struggling to determine whether adjuvant versus early salvage postprostatectomy RT is most appropriate, biomarker data may provide additional data to integrate into the final decision. Which of the available commercial biomarkers is best (if any) in these settings cannot be determined as these assays have not been sufficiently compared head to head in properly designed studies. However, the extent of supporting data significantly varied among the assays. Furthermore, understanding their use in the context of MRI imaging is also of great importance (Question 4). There are insufficient data to support a consensus statement on the relative value of genomics versus MRI; however, for an individual patient, MRI or genomic testing may ultimately provide overlapping, complementary, or discordant information. Comprehensive studies with comparative data, costs, and clinical implications would be valuable.”

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American Urological Association and American Society for Radiation Oncology

Radiation Oncology

The American Urological Association and American Society for Radiation Oncology published guidelines on clinically localized prostate cancer. The guidelines included the following statements on risk assessment:

1. "Clinicians should use clinical T stage, serum PSA, Grade Group (Gleason score), and tumor volume on biopsy to risk stratify patients with newly diagnosed prostate cancer. (Strong Recommendation; Evidence Level: Grade B)"
2. "Clinicians may selectively use tissue-based genomic biomarkers when added risk stratification may alter clinical decision-making. (Expert Opinion)"
3. "Clinicians should not routinely use tissue-based genomic biomarkers for risk stratification or clinical decision-making. (Moderate Recommendation; Evidence Level: Grade B)"

The American Urological Association (2018) published guidelines for castration-resistant prostate cancer. The guidelines do not mention AR-V7 assays.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines for prostate cancer (v. 1.2023) provide a table of tissue-based tests for prostate cancer prognosis.

The guidelines include the following statements related to risk stratification:

- Patients with NCCN low, favorable intermediate, unfavorable intermediate, or high-risk disease and life expectancy ≥ 10 y may consider the use of the following tumor-based molecular assays: Decipher, Oncotype DX Prostate, and Prolaris.
- Decipher may be considered to inform adjuvant treatment if adverse features are found after radical prostatectomy and during workup for radical prostatectomy PSA persistence or recurrence (category 2B for the latter setting)

The panel also recommended that "the use of AR-V7 tests in circulating tumor cells can be considered to help guide selection of therapy in the post-abiraterone/enzalutamide metastatic castration-resistant prostate cancer setting."

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National Institute for Health and Care Excellence

In 2019, the National Institute for Health and Care Excellence updated its guidance on the diagnosis and management of prostate cancer. The guidance did not address gene expression profile testing.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
<i>Prolaris</i>			
NCT03152448 ^a	Two-Part Prospective Study to Measure Impact of Prolaris ^{®‡} Testing Added to Treatment Decision Following Biopsy in Newly Diagnosed Prostate Cancer Patients to Measure Prediction of Progression/Recurrence in Men Treated at VAMC	1511	Mar 2022
NCT03290508 ^a	Long-Term Prospective Registry to Evaluate Treatment Decisions and Clinical Outcomes in Patients With Favorable Intermediate-Risk Localized Prostate Cancer Following Cell Cycle Progression (CCP) Testing (Prolaris ^{®‡} Test)	524	Jan 2022

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NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT04404894 ^a	Long-Term Prospective Registry to Evaluate Treatment Decisions and Clinical Outcomes in Prostate Cancer Patients From Diverse Urology Practice Settings Following Prolaris ^{®†} Testing	500	Nov 2029
<i>Decipher</i>			
NCT02723734	Validation Study on the Impact of Decipher Testing - VANDAAM Study	250	May 2024
NCT04396808	Genomics in Michigan to AdJust Outcomes in Prostate cancer (G-MAJOR): A Randomized Multi-center Study for Men With Newly Diagnosed Favorable Risk Prostate Cancer	900	Nov 2023
NCT05050084 ^a	Parallel Phase III Randomized Trials of Genomic-Risk Stratified Unfavorable Intermediate Risk Prostate Cancer: De-Intensification and Intensification Clinical Trial Evaluation (GUIDANCE)	2050	Apr 2037
NCT04484818	A Phase III Double Blinded Study of Early Intervention After RADICAL ProstaTEctomy With Androgen Deprivation Therapy With or Without Darolutamide vs. Placebo in Men at Highest Risk of Prostate Cancer Metastasis by Genomic Stratification (ERADICATE)	810	May 2028
NCT04513717	Parallel Phase III Randomized Trials for High Risk Prostate Cancer Evaluating De-Intensification for Lower Genomic Risk and Intensification of Concurrent Therapy for Higher Genomic Risk With Radiation (PREDICT-RT*)	2478	Dec 2033

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NCT No.	Trial Name	Planned Enrollment	Completion Date
Prolaris or Decipher or Oncotype			
NCT04396808	Genomics in Michigan to AdJust Outcomes in Prostate cancer (G-MAJOR): A Randomized Multi-center Study for Men With Newly Diagnosed Favorable Risk Prostate Cancer	900	Nov 2023

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

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Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

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02/06/2014	Medical Policy Committee review
02/19/2014	Medical Policy Implementation Committee approval. New policy.
06/04/2015	Medical Policy Committee review
06/17/2015	Medical Policy Implementation Committee approval. Policy statement unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
06/02/2016	Medical Policy Committee review
06/20/2016	Medical Policy Implementation Committee approval. Promark and Decipher tests added to the policy. Policy statement updated by adding "protein biomarkers". Title change.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes and CPT coding update
06/01/2017	Medical Policy Committee review
06/21/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Extensive updates to rationale and references.
08/01/2017	Coding update
06/07/2018	Medical Policy Committee review
06/20/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/01/2018	Coding update
08/07/2018	Coding update
06/06/2019	Medical Policy Committee review
06/19/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/11/2019	Coding update
06/04/2020	Medical Policy Committee review
06/10/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/08/2020	Coding update
03/24/2021	Coding update
06/03/2021	Medical Policy Committee review

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06/09/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/09/2022	Coding update
06/02/2022	Medical Policy Committee review
06/08/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/06/2022	Medical Policy Committee review
10/11/2022	Medical Policy Implementation Committee approval. Extensive revisions to the coverage section and throughout the policy. Added a Policy Guidelines section.
12/01/2022	Medical Policy Committee review
12/14/2022	Medical Policy Implementation Committee approval. Extensive revisions to the coverage section and throughout the policy. Added a Policy Guidelines section. Updated the Supplemental Information section and an NCCN reference.
12/16/2022	Coding update
06/01/2023	Medical Policy Committee review
06/06/2023	Coding update
06/14/2023	Medical Policy Implementation Committee approval. Added a new five-tier grading system to the Policy Guidelines section based on modified Gleason Scores and adopted by the International Society of Urological Pathology consensus conference. Coverage eligibility unchanged.

Next Scheduled Review Date: 06/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0047U, 81479, 81541, 81542, 81599, 84999 Delete code effective 01/01/2023: 0343U Delete code effective 07/01/2023: 0053U
HCPCS	No codes
ICD-10 Diagnosis	C61

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

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1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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