Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

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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.

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 in all situations to be **investigational.***

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 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. PSA 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 has recommended 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.

Castration-Resistant Prostate Cancer

Androgen deprivation therapy (ADT) is generally the initial treatment for patients with advanced prostate cancer. ADT 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 this test.

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

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 vs Therapeutic Intervention

For individuals who have low- or intermediate-risk 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. The 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 the effects of the technology on health outcomes.

For individuals who have low- or intermediate-risk 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. The 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 RP population can be generalized to an active surveillance population. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have low- or intermediate-risk clinically localized untreated prostate cancer who receive Decipher Biopsy, the evidence includes retrospective cohort studies of clinical validity using archived samples in intermediate-risk patients and no studies of clinical utility. The relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. For intermediate-risk men, a test designed to identify men who can receive active surveillance instead of RP or RT would need to show very high negative predictive value for disease-specific mortality at ten years and improvement in prediction compared with existing tools used to select such men. Clinical validity studies of Decipher Biopsy reported prostate cancer metastases at five years but did

not report survival outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have low- or intermediate-risk 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. The 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 the effects of the technology on health outcomes.

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. The relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

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.

The 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 the effects of the technology on health outcomes.

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 one prospective cohort study, one retrospective cohort study of clinical validity using archived samples, and no studies of clinical utility. The 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 two clinical validity studies meeting inclusion criteria were available. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

National Comprehensive Cancer Network
The National Comprehensive Cancer Network guidelines for prostate cancer (v.4.2019) provide a table of tissue-based tests for prostate cancer prognosis. The Network panel suggested that men with low or favorable intermediate clinically localized disease may consider Decipher, Oncotype DX Prostate, Prolaris, or ProMark during initial risk stratification and Decipher may be considered during workup for radical prostatectomy, although the panel warned that the utility of these assays has not been fully assessed in randomized controlled trials. 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."

American Urological Association et al
The American Urological Association, American Society for Radiation Oncology, and the Society of Urologic Oncology (2017, 2018) published joint guidelines on the management of clinically localized prostate cancer. The guidelines stated that among most low-risk localized prostate cancer patients, genomic biomarkers have not demonstrated a clear role in the selection of active surveillance or in the follow-up of patients on active surveillance.

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

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence updated its guidance on the diagnosis and management of prostate cancer in 2019. 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 and unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Prolaris			
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	1500	Jan 2024
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)	6000	Sep 2027
Oncotype DX			

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02668276[a]	The Impact of a Gene Expression Profile on Treatment Choice and Outcome Among Minority Men Newly Diagnosed With Prostate Cancer: A Randomized Trial	300	Aug 2022
Decipher			
NCT03770351	Precision Medicine for Early Prostate Cancer: Integrating Biological and Patient Complexity Variables to Predict Treatment Response	693	Jun 2019
NCT02609269	Decipher Genomics Resource Information Database (GIRD)	10,000	Dec 2020
NCT02723734	Validation Study on the Impact of Decipher Testing - VANDAAM Study	240	May 2021
Unpublished			
Prolaris			
NCT03511235[a]	Clinical Outcomes in Men With Prostate Cancer Who Selected Active Surveillance Using Prolaris Testing	850	Aug 2018 (completed)
Decipher			

NCT: national clinical trial; PTEN: phosphatase and tensin homolog.
[a] Denotes industry-sponsored or cosponsored trial.

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Policy History

Original Effective Date: 02/19/2014
Current Effective Date: 07/13/2020

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.

Policy # 00403
Original Effective Date: 02/19/2014
Current Effective Date: 07/13/2020

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

Next Scheduled Review Date: 06/2021

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 2019 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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CPT is a registered trademark of the American Medical Association.

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

Code Type	Code
CPT	0005U, 0047U, 81479, 81541, 81599, 84999 Code added eff 1/1/2020: 81542
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:

A. 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
B. 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:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.