Medical Coverage Policy | Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management (formerly: Prostate Cancer Genomic Assays)

Blue Cross Blue Shield of Rhode Island

EFFECTIVE DATE: 10|15|2015
POLICY LAST UPDATED: 09|05|2017

OVERVIEW

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 regarding active surveillance versus therapeutic intervention, or after radical prostatectomy (RP) to guide radiotherapy use.

Two gene expression profiling tests, Prolaris and Oncotype DX Prostate, are each intended to be used in combination with accepted clinical criteria (Gleason score, prostate-specific antigen, clinical stage) to stratify needle biopsy–diagnosed localized prostate cancer according to biological aggressiveness, and direct initial patient management. The ProMark protein biomarker test uses immunofluorescence and automated quantitative images in intact biopsy tissue to risk-stratify patients to active surveillance or therapeutic intervention.

MEDICAL CRITERIA
BlueCHiP for Medicare
PROLARIS
The Prolaris™ assay is covered only when the following clinical conditions are met:
- Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), **and**
- FFPE prostate biopsy specimen with at least 0.5 mm of cancer length, **and**
- Patient Stage as defined by the one of the following:
  - Very Low Risk Disease (T1c **AND** Gleason Score ≤ 6 **AND** PSA ≤ 10 ng/mL **AND** <3 prostate cores with tumor **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**
- Patient has an estimated life expectancy of greater than or equal to 10 years, **and**
- Patient is a candidate for and is considering conservative therapy and yet and would be eligible for definitive therapy (radical prostectomy, radiation therapy or brachytherapy), **and**
- Result will be used to determine treatment between definitive therapy and conservative management, **and**
- Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy, **and**
- Test is ordered by a physician certified in the Myriad **PROLARIS™** Certification and Training Registry (CTR), **and**
- Patient is monitored for disease progression according to established standard of care.

ONCOTYPEDX
The Oncotype DX® Prostate Cancer Assay is covered only when the following clinical conditions are met:
- Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), **and**
- Patient stage as defined by the one of the following:
  - Very Low Risk Disease (T1c AND Gleason Score = 6 AND PSA = 10 ng/mL **AND** <3 prostate cores with tumor **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**
- Patient has an estimated life expectancy of ≥ 10 years, **and**
- Patient 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**
- Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy, **and**
- Test is ordered by a physician certified in the Genomic Health™ Oncotype DX® Prostate Cancer Assay Certification and Training Registry (CTR), **and**
- Patient is monitored for disease progression according to active surveillance guidelines as recorded in NNCN guidelines.

Commercial Products
Not applicable

PRIOR AUTHORIZATION
BlueCHiP for Medicare and Commercial Products
Prior authorization is required for BlueCHiP for Medicare and recommended for Commercial products and is obtained via the online tool for participating providers. See the Related Policies section.

POLICY STATEMENT
BlueCHiP for Medicare
The Prolaris and Oncotype DX prostate cancer assays will be considered medically necessary when the medical criteria listed above are met.

The Promark and Decipher prostate cancer assays are considered not medically necessary because there is insufficient peer-reviewed literature proving the efficacy of the service.

Commercial Products
Gene expression analysis and protein biomarker to guide management of prostate cancer, including those brand name tests identified in this policy, are considered not medically necessary because direct evidence is insufficient to establish the analytical and clinical validity, or the clinical utility of the services.

COVERAGE
Benefits may vary between groups/contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for limitations of benefits/coverage for laboratory tests or when services are not medically necessary.

BACKGROUND
Prostate cancer is the second most common noncutaneous cancer diagnosed among men in the United States. According to the National Cancer Institute, nearly 180,000 new cases are expected to be diagnosed in the United States in 2016 and are associated with approximately 26,000 deaths. Autopsy studies in the era prior to the availability of prostate-specific antigen screening have identified incidental cancerous foci in 30% of men 50 years of age, with incidence reaching 75% at age 80 years. However,
between 1975 and 1991 prostate cancer mortality rose and subsequently dropped 39% by 2007. The rise in mortality is unexplained, though it has been suggested as due to how cause of death was assigned. Regarding the subsequent decline, a number of potential explanations have been suggested as underlying reasons: improvements in treatment and screening, changes in assigning causes of death, and risk of cardiovascular death among men with prostate cancer treated with hormonal therapy.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Prolaris®, Oncotype DX® Prostate, and Decipher® gene expression profiling test, and the ProMark™ protein biomarker test are available under the auspices of CLIA.

Laboratories that offer LDTs must be licensed by 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 men newly diagnosed with clinically localized prostate cancer, the purpose of gene expression profiling and protein biomarkers tests is to inform a decision whether to undergo immediate therapy versus forego immediate therapy and begin active surveillance. 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 prostate-specific antigen (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 (ages greater than or equal to 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 the cancer itself. Other very similar appearing low-risk tumors may progress unexpectedly rapidly, quickly disseminating and becoming incurable.

The divergent behavior of localized prostate cancers creates uncertainty whether to treat immediately. A patient may choose potentially curative treatment upfront. Surgery including radical prostatectomy (RP) or external-beam radiotherapy (EBRT) are most commonly used to treat patients with localized prostate cancer. Complications most commonly reported with RP or EBRT and with the greatest variability are incontinence (0%-73%) and other genitourinary toxicities (irritative and obstructive symptoms); hematuria (typically ≤5%); gastrointestinal and bowel toxicity, including nausea and loose stools (25%-50%); proctopathy, including rectal pain and bleeding (10%-39%); and erectile dysfunction, including impotence (50%-90%).

American Urological Association guidelines suggest patients with low- and intermediate-risk disease have the option of "active surveillance," taking into account patient age, patient preferences, and health conditions related to urinary, sexual, and bowel function. With this approach the patient will forgo immediate therapy and continue regular monitoring until signs or symptoms of disease progression are evident, at which point curative treatment is instituted.

Given the unpredictable behavior of early prostate cancer, additional prognostic methods to biologically stratify this disease are under investigation. These include gene expression profiling, which refers to analysis of mRNA expression levels of many genes simultaneously in a tumor specimen, and protein biomarkers.

The purpose of gene expression profiling and protein biomarkers tests in patients who have prostate cancer and who have undergone RP is to inform a management decisions.

Two gene expression profiling tests and 1 protein biomarker test are intended to biologically stratify prostate cancers diagnosed on prostate needle biopsy: Prolaris (Myriad Genetics, Salt Lake City, UT) and Oncotype Dx Prostate Cancer Assay (Genomic Health, Redwood City, CA) are gene expression profiling tests that use archived tumor specimens as the mRNA source, reverse transcriptase polymerase chain reaction (RT-PCR) amplification, and the TaqMan low-density array platform (Applied Biosystems, Foster City, CA). A protein biomarker test, ProMark (Metamark Genetics, Cambridge, MA), is an automated quantitative imaging method to measure protein biomarkers by immunofluorescent staining in defined areas in intact formalin-fixed paraffin-embedded biopsy tissue, in order to provide independent prognostic information to aid in the stratification of patients with prostate cancer to active surveillance or therapy.

Prolaris
Prolaris is used to quantify expression levels of 31 cell cycle progression (CCP) genes and 15 housekeeper genes to generate a CCP score. Oncotype DX Prostate is used to quantify expression levels of 12 cancer-related and 5 reference genes to generate a Genomic Prostate Score (GPS). In the final analysis, the CCP score or GPS is combined in proprietary algorithms with clinical risk criteria (PSA, Gleason grade, tumor

stage) to generate new risk categories (ie, reclassification) intended to reflect biologic indolence or aggressiveness of individual lesions, and thus inform management decisions.

Oncotype DX Prostate
The Oncotype Dx Prostate assay includes 5 reference genes and 12 cancer genes that represent 4 molecular pathways of prostate cancer oncogenesis: androgen receptor, cellular organization, stromal response, and proliferation. The assay results are combined to produce a GPS, which ranges from 0 to 100. Higher GPS scores indicate more risk.

ProMark Protein Biomarker Test
The ProMark assay includes 8 biomarkers that predict prostate pathology aggressiveness and lethal outcomes: *DERL1*, *PDSS2*, *pS6*, *YBX1*, *HSPA9*, *FUS*, *SMAD4*, and *CUL2*. The assay results are combined using predefined coefficients for each marker from a logistic regression model to calculate a risk score. The risk score is continuous number between 0 and 1, which estimates the probability of "non–GS 6" pathology.

Decipher Prostate Cancer Classifier
Decipher is a tissue-based tumor 22-biomarker gene expression profiling test intended to classify high risk individuals who have undergone RP. The Decipher test classifies patients as low risk, who can delay or defer RT after prostatectomy, or high risk, as those who would potentially benefit from early radiation. The gene expression classifier is a continuous risk score between 0 and 1, with higher risk scores indicating a greater probability of developing metastasis.

For individuals who have clinically localized prostate cancer, or intermediate- or low-risk prostate cancer after radical prostatectomy, who receive Prolaris, the evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have clinically localized prostate cancer who receive Oncotype DX Prostate or the ProMark protein biomarker test, the evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have high-risk prostate cancer after radical prostatectomy who receive the Decipher prostate cancer classifier, the evidence is insufficient to determine the effects of the technology on health outcomes.

Therefore, all tests are considered not medically necessary.

The potential usefulness of Prolaris is that it allows physicians to determine which patients with early prostate cancer are candidates for active surveillance or observation and are more likely to have a good outcome without needing to receive definitive treatment.

The potential usefulness of the Oncotype DX prostate cancer assay is that it allows physicians to determine which patients with early prostate cancer are candidates for active surveillance and are more likely to have a good outcome without needing to receive definitive treatment.

CODING
BlueCHiP for Medicare and Commercial Products
There is not a specific CPT code for most testing in this policy. Therefore, the unlisted molecular pathology procedure code 81479 should be used when appropriate.

The following CPT code requires prior authorization.
81479 Unlisted molecular pathology procedure

The following CPT code can be used for the Prolaris® assay. It requires prior authorization for BlueCHiP for Medicare and is considered not medically necessary for Commercial Products.

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 (New Code Effective 1/1/2018)

RELATED POLICIES
Genetic Testing Services

PUBLISHED
Provider Update, November 2017
Provider Update, September 2016
Provider Update, December 2015

REFERENCES

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2. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: PROLARIS™ Prostate Cancer Genomic Assay (L36350)

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