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

EFFECTIVE DATE: 10|15|2015
POLICY LAST UPDATED: 12|18|2018

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 for active surveillance or therapeutic intervention, to guide radiotherapy use ~~or~~ after radical prostatectomy (RP) or to guide medication selection after progression in metastatic castration-resistant prostate cancer.

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
There is no specific CPT coding for some 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.

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 assay will be considered medically necessary when the medical criteria listed above are met.

The Promark and Decipher prostate cancer assays, as well as the Oncotype DX AR-V7 Nuclear Detect are not covered as the evidence is insufficient to determine the effects of the technology on health outcomes.

Commercial Products
Use of gene expression analysis and protein biomarkers to guide management of prostate cancer is considered not medically necessary in all situations as the evidence is insufficient to determine the effects of the technology on health outcomes.

COVERAGE

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

BACKGROUND

Prostate cancer is the second most common noncutaneous cancer diagnosed among men in the United States. 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.

Localized prostate cancers may appear very similar clinically at diagnosis.2 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 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:

- 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 is 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 castrationresistant 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.

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 (GenomeDx Biosciences), and the ProMark™ protein biomarker test (Metamark Genetics) are available under the auspices of CLIA. Laboratories that offer laboratory-developed tests 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.

Prolaris
Prolaris is used to quantify expression levels of 31 cell cycle progression (CCP) genes and 15 housekeeper genes to generate a CCP score.

For individuals who have low- or intermediate-risk clinically localized untreated prostate cancer who receive Prolaris, the evidence includes studies includes retrospective cohort studies of clinical validity using archived samples in patients of mixed risk categories. Relevant outcomes include overall survival, disease-specific survival, quality of life, and treatment-related morbidity. For the low-risk group, the Prostate Testing for Cancer and Treatment (ProtecT) trial showed 99% ten-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 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 localized prostate cancer treated with RP who receive Prolaris, the evidence includes retrospective cohort studies of clinical validity using archived samples. Relevant outcomes include overall survival, disease-specific survival, quality of life, 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.

Oncotype DX Prostate
Oncotype DX® Prostate Cancer Assay is prostate biopsy-based 17-gene RT-PCR assay, representing four molecular pathways (androgen signaling, cellular organization, stromal response and proliferation), that provides a biologic measure of cancer aggressiveness. The assay is indicated for men who are considered candidates for active surveillance (AS) (those with NCCN® very low- and low-risk prostate cancer). The assay is designed to inform decisions between AS and immediate treatment.

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. Relevant outcomes include overall survival, disease-specific survival, quality of life, 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 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.

Oncotype DX Prostate BlueCHiP for Medicare
The potential usefulness of this test 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.

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 a continuous number between 0 and 1, which estimates the probability of "non–GS 6" pathology.

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. Relevant outcomes include overall survival, disease-specific survival, quality of life, 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.

Decipher Prostate Cancer Classifier
The Decipher test classifies as low risk those patients who can delay or defer RT after prostatectomy, or as high risk those who would potentially benefit from early radiation. The GC is a continuous risk score between 0 and 1, with higher risk scores indicating a greater probability of developing metastasis.

For individuals who have localized prostate cancer who are treated with RP and who receive the Decipher 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 overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The clinical validity of the Decipher 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.

Oncotype DX AR-V7 Nuclear Detect
Oncotype DX AR-V7 Nuclear Detect is used to detect nuclear-localized AR-V7 protein in CTCs of men with mCRPC who have failed first-line therapy and are considering additional ARS inhibitor therapy.

For individuals who have metastatic castration-resistant prostate cancer who receive the Oncotype DX AR-V7 Nuclear Detect, the evidence includes a retrospective cohort study of clinical validity using archived samples, and no studies of clinical utility. Relevant outcomes include overall survival, diseasespecific survival, quality of life, and treatment-related morbidity. Current evidence does not support improved outcomes with Oncotype DX AR-V7 Nuclear Detect, given that only a single clinical validity study, meeting inclusion criteria was available. The evidence is insufficient to determine the effects of the technology on health outcomes.

BlueCHiP for Medicare
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
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

The following code requires prior authorization for BlueCHiP for Medicare and is not medically necessary for Commercial Products. This code can be used for the Oncotype DX® Prostate Cancer Assay.
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

The following Unlisted CPT code requires prior authorization for BlueCHiP for Medicare and Commercial Products. The code can be used for any test identified in this policy that does not have a specific CPT code.
81479 Unlisted molecular pathology procedure

RELATED POLICIES
Genetic Testing Services

PUBLISHED
Provider Update, February 2019
Provider Update, November 2017
Provider Update, September 2016
Provider Update, December 2015

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