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

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Policy Number: 670
BCBSA Reference Number: 2.04.111
NCD/LCD:
- Local Coverage Determination (LCD): MolDX-CDD: Decipher Prostate Cancer Classifier Assay (L35868)
- Local Coverage Determination (LCD): MolDX: Prolaris Prostate Cancer Genomic Assay for Men with Favorable Intermediate Risk Disease (L37043)
- Local Coverage Determination (LCD): MolDX-CDD: Genomic Health Oncotype DX Prostate Cancer Assay (L36153)
- Local Coverage Determination (LCD): MolDX- CDD: ProMark Risk Score (L36665)
- Local Coverage Determination (LCD): MolDX: Oncotype DX® Genomic Prostate Score for Men with Favorable Intermediate Risk Prostate Cancer (L37262)

Related Policies
Gene-Based Tests for Screening, Detection, and/or Management of Prostate Cancer, #333

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Gene expression analysis and protein biomarker to guide management of prostate cancer are considered INVESTIGATIONAL in all situations.

Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the links below.

Local Coverage Determination (LCD): MolDX-CDD: Decipher® Prostate Cancer Classifier Assay (L35868)

Local Coverage Determination (LCD): MolDX-CDD: Prolaris™ Prostate Cancer Genomic Assay (L35869)
Local Coverage Determination (LCD): MolDX: Prolaris™ Prostate Cancer Genomic Assay for Men with Favorable Intermediate Risk Disease (L37043)

Local Coverage Determination (LCD): MolDX-CDD: Genomic Health™ Oncotype DX® Prostate Cancer Assay (L36153)

Local Coverage Determination (LCD): MolDX- CDD: ProMark Risk Score (L36665)

Local Coverage Determination (LCD): MolDX: Oncotype DX® Genomic Prostate Score for Men with Favorable Intermediate Risk Prostate Cancer (L37262)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Inpatient</th>
<th>Outpatient</th>
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<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Medicare HMO Blue℠</td>
<td>No</td>
</tr>
<tr>
<td>Medicare PPO Blue℠</td>
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CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81541</td>
<td>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</td>
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<tr>
<td>0011M</td>
<td>Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and/or urine, algorithms to predict high-grade prostate cancer risk</td>
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</table>

Description
Prostate cancer is the second most common cancer diagnosed among men in the United States. According to the National Cancer Institute (NCI), nearly 240,000 new cases are expected to be diagnosed in the United States in 2013 and are associated with around 30,000 deaths. Autopsy studies in the pre-
PSA screening era have identified incidental cancerous foci in 30% of men 50 years of age, with incidence reaching 75% at age 80 years. However, NCI Surveillance Epidemiology and End Results data show age-adjusted cancer-specific mortality rates for men with prostate cancer have declined from 40 per 100,000 in 1992 to 22 per 100,000 in 2010. This decline has been attributed to a combination of earlier detection via PSA screening and improved therapies.

Localized prostate cancers may appear very similar clinically at diagnosis. However, they often exhibit diverse risk of progression that may not be captured by accepted clinical risk categories (eg, D'Amico criteria) or prognostic tools that are 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 elderly men (70 years) with this type of low-risk disease, comorbidities typically supervene as a cause of death; these men will die with prostate cancer present, rather than from the cancer. 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 or not to treat immediately. A patient may choose definitive treatment upfront. Surgery (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. 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 which 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). 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 biological indolence or aggressiveness of individual lesions, and thus inform management decisions. 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.

After RP, accurate risk stratification can identify those patients at high risk of prostate specific-cancer mortality who would most likely benefit from additional therapy versus those patients who may be cured by surgery alone and could be spared the potential impact of additional treatment.
The optimal timing of radiotherapy (RT) after RP is a debate. Adjuvant RT may maximize cancer control outcomes, however, salvage RT can minimize overtreatment and still lead to acceptable oncologic outcomes. Several analyses have shown conflicting conclusions as to whether adjuvant RT is favored over salvage RT (with salvage RT typically being initiated at a post-RP PSA level of 0.3 to 0.6 ng/mL).

Decipher® (GenomeDx Biosciences, Vancouver, BC, Canada) is a tissue-based tumor 22-biomarker gene expression profile test that is intended to guide the use of radiation after RP. The Decipher test classifies patients as low risk, who can delay or defer radiation 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 metastasis.

Summary
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 intended to be used in combination with accepted clinical criteria (Gleason score, prostate-specific antigen [PSA], 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.

The evidence for Prolaris® Cell Cycle Progression score in patients who have clinically localized prostate cancer includes 1 study of analytic validity and 2 retrospective cohort studies using archived samples examining clinical validity. The evidence for Prolaris® cell cycle progression score in men post prostatectomy with intermediate or lower risk disease includes 3 retrospective cohort studies using archived samples examining clinical validity, and a decision curve analysis from 1 study providing indirect evidence for clinical utility. Evidence of improved clinical validity or prognostic accuracy for prostate cancer death using Prolaris® in patients managed conservatively after needle biopsy or for recurrence in patients postprostatectomy shows some improvement in areas under the receiver operator characteristic curve over clinicopathologic risk stratification tools. There is limited indirect evidence for potential clinical utility.

The evidence for Oncotype Dx® Prostate in patients who have clinically localized prostate cancer includes 2 studies of analytic validity, 1 case-cohort analysis using archived samples examining clinical validity, and a decision curve analysis from 1 study examining indirect evidence for clinical utility. 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 following radical prostatectomy. Although a relevant intermediate outcome, it is necessary to establish generalizability to an active surveillance population.

The evidence for the ProMark™ protein biomarker test in patients who have clinically localized prostate cancer includes 1 study of analytic validity, 1 retrospective cohort study using archived samples examining clinical validity, and no studies of clinical utility. There is insufficient evidence to support improved outcomes with ProMark™ given that only a single clinical validity study was available.

The evidence for the Decipher® prostate cancer classifier in patients who have high-risk prostate cancer post radical prostatectomy includes 1 study of analytic validity, 8 studies using archived samples (7 prospective-retrospective designs, 1 case-control) examining clinical validity, and 6 decision curve analyses examining indirect evidence for clinical utility, and 1 prospective decision impact study. Relevant outcomes include overall survival, disease-specific survival, test accuracy, test validity, 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 radical prostatectomy. Studies reported some incremental improvement in discrimination. However, it is unclear
whether there is consistent improved reclassification—particularly to higher risk categories—or whether the test could be used to predict which men will benefit from radiotherapy.

Relevant outcomes for tests include overall survival, disease-specific survival, test accuracy and validity, quality of life, and treatment-related morbidity.

According to the Simon et al framework for study classification and levels of evidence (LOE) for prognostic studies using archived specimens, identified studies for all tests are considered “category C”—prospective observational registry, treatment, and follow-up not dictated. As noted by Simon et al (2009): “[c]ategory C studies may be validated to LOE II if two or more subsequent studies provide similar results. However, it is unlikely that category C studies would ever be sufficient to change practice, except under particularly compelling circumstances.”

Given the magnitudes of improved discrimination (clinical validity) reported and limited indirect evidence for clinical utility, the evidence is insufficient to determine the effects of the technologies on health outcomes.

**Policy History**

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<th>Action</th>
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<td>1/2018</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>9/2016</td>
<td>BCBSA National medical policy review. Corrections made to study description in and Section Summary of Prolaris section. References added.</td>
</tr>
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<td>10/2015</td>
<td>Local Coverage Determination (LCD): MolDX: Genomic Health™ Oncotype DX® Prostate Cancer Assay (L36153) added. 10/1/2015</td>
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<td>8/2015</td>
<td>BCBSA national medical policy review. Investigational indications clarified. Title changed to “Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management.” 8/1/2015</td>
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<td></td>
<td>Local Coverage Determination (LCD): MolDX: Prolaris™ Prostate Cancer Genomic Assay (L35629) added. 8/2015</td>
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<td>12/2014</td>
<td>New references added from BCBSA National medical policy.</td>
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**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

**References**

43. MAQC Consortium. The MicroArray Quality Control (MAQC) project shows inter- and intraplatform reproducibility of gene expression measurements. *Nat Biotechnol*. Sep 2006;24(9):1151-1161. PMID 16964229


