Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

**Description**
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, or to guide radiotherapy use after radical prostatectomy (RP).

**FDA REGULATORY STATUS**
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® (Myriad Genetics, Salt Lake City, UT), Oncotype DX® Prostate (Genomic Health, Redwood City, CA), and Decipher® gene expression profiling test (GenomeDx Biosciences, Vancouver, BC), and the ProMark™ protein biomarker test (Metamark Genetics, Cambridge, MA) 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 November 2015, the FDA’s Office of Public Health Strategy and Analysis published a document on public health evidence for FDA oversight of LDTs.16 FDA argued that many tests need more FDA oversight than the regulatory requirements of CLIA. 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 document asserted that patients are potentially receiving inappropriate prostate cancer care because there is no evidence that results from the test meaningfully improves clinical outcomes.

**POLICY STATEMENT**
Use of gene expression analysis and protein biomarker to guide management of prostate cancer is considered investigational in all situations.
POLICY GUIDELINES

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

RATIONALE

Summary of Evidence

Initial Management Decision: Active Surveillance vs Therapeutic Intervention

For individuals who have low-risk clinically localized untreated prostate cancer who receive Prolaris, Oncotype DX Prostate, or ProMark protein biomarker test, the evidence includes studies of analytic validity and studies of clinical validity using archived samples from patients in mixed risk categories. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, quality of life, and treatment-related morbidity. The 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 individuals who have intermediate-risk clinically localized untreated prostate cancer who receive Prolaris, the evidence includes a study of analytic validity and retrospective cohort studies of clinical validity using archived samples in patients of mixed risk categories and a decision-curve analysis providing indirect evidence of clinical utility. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, quality of life, and treatment-related morbidity. 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. All validation studies are Simon category C. 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 2 studies of analytic validity, 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, test accuracy and validity, 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. All validation studies are Simon category C or D. 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 study of analytic validity, a retrospective cohort study of clinical validity using archived samples, and no studies of clinical utility. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, quality of life, and treatment-related morbidity. Current evidence does not support improved outcomes with ProMark given that only a single clinical validity study was 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 who are treated with RP who receive Prolaris, the evidence includes a study of analytic validity, and retrospective studies of clinical validity using archived samples. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, 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. All validation studies are Simon category C or D. 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 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, test accuracy and 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 RP. 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. All validation studies are Simon category C or D. The evidence is insufficient to determine the effects of the technology on health outcomes.

**SUPPLEMENTAL INFORMATION**

**Practice Guidelines and Position Statements**

The National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (v.2.2017) provide a table of tissue-based tests for prostate cancer prognosis, along with evidence information and Molecular Diagnostic Services Program (MolDX) recommendations (see Table 1). The NCCN panel suggested that men with clinically localized disease may consider these assays, although the panel warned that the utility of these assays has not been fully assessed in randomized clinical trials.

**Table 1: Available Tissue-Based Tests for Prostate Cancer Prognosis**

<table>
<thead>
<tr>
<th>Test</th>
<th>Platform</th>
<th>Population</th>
<th>Outcomes</th>
<th>References</th>
<th>MolDX Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decipher</td>
<td>Whole transcriptome 1.4</td>
<td>Post RP, adverse</td>
<td>Metastasis; prostate</td>
<td>Cooperberg 2014&lt;sup&gt;13&lt;/sup&gt;; Den 2016&lt;sup&gt;2&lt;/sup&gt;; Den</td>
<td>Cover post-RP for: pT2 with positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pathology/high-risk</td>
<td>cancer–specific</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Oncotype DX</th>
<th>Ki-67</th>
<th>ProMark</th>
<th>PTEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantitative RT-PCR for 12 prostate cancer-related genes and 5 housekeeping controls</td>
<td>IHC</td>
<td>Multiplex immunofluorescent staining of 8 proteins</td>
<td>Fluorescent in situ hybridization or IHC</td>
</tr>
<tr>
<td>Biopsy, active surveillance</td>
<td>Biopsy, low-to-intermediate-risk treated with RP</td>
<td>Biopsy, Gleason grade 3+3 or 3+4</td>
<td>Biopsy, Gleason grade 3+3 or 3+4</td>
</tr>
<tr>
<td>Non-organ-confined pT3 or Gleason grade 4 disease on RP</td>
<td>Prostate cancer-specific mortality</td>
<td>Non-organ-confined pT3 or Gleason 4 disease on RP</td>
<td>Prostate cancer-specific mortality</td>
</tr>
<tr>
<td>Cover postbiopsy for NCCN very low risk and low-risk prostate cancer before treatment with 10-20 y life expectancy</td>
<td>Not recommended</td>
<td>Cover postbiopsy for NCCN very low risk and low-risk prostate cancer before treatment with at least 10-y life expectancy</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>


American Urological Association et al

In 2017, the American Urological Association, American Society for Radiation Oncology, and the Society of Urologic Oncology published joint guidelines on the management of clinically localized prostate cancer.[14] The guidelines stated that among most low-risk localized prostate cancer patients, genomic analysis of tumors has the potential to predict which patients will benefit from adjuvant therapy and which patients can safely be observed without immediate treatment.

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biomarkers have not demonstrated a clear role in the selection of active surveillance or in follow-up of patients on active surveillance.

**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 2014. The guidance did not address gene expression profile analysis.

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**Medicare National Coverage**
Palmetto GBA, a local carrier, issued "limited coverage" determinations under the auspices of a Coverage with Data Development mechanism for the following tests (date effective): Prolaris (03/02/15), Decipher (03/02/15), Oncotype DX Prostate (10/05/15), and ProMark (10/10/2016).

**REFERENCES**


Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management


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


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POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2014</td>
<td>New Policy</td>
<td>Microarray-based gene expression analysis to guide management of prostate cancer is considered investigational in all situations.</td>
</tr>
<tr>
<td>March 2015</td>
<td>Update Policy</td>
<td>Policy updated with literature review; references 24-25 and 40-51 added. Promark and Decipher tests added to policy. Change in policy title. Policy statement unchanged. Title change to “Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management.”</td>
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