Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

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 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.

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®, 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 November 2015, the FDA’s Office of Public Health Strategy and Analysis published a document on public health evidence for FDA oversight of LDTs.4 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 improve clinical outcomes.

POLICY STATEMENT

Use of gene expression analysis and protein biomarker to guide management of prostate cancer is considered investigational in all situations.
FEP POLICY 2.04.111 Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

BENEFIT APPLICATION

The BCBS FEP contract affects coverage for genetic screening and testing. Refer to the current FEP Service Benefit Plan brochure for additional information and guidance.

RATIONALE

Summary of Evidence

Initial Management Decision: Active Surveillance vs Therapeutic Intervention

For individuals who have clinically localized prostate cancer who receive Prolaris, the evidence includes 1 study of analytic validity and retrospective cohort studies of clinical validity using archived samples 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 clinically localized prostate cancer who receive Oncotype DX Prostate, the includes 2 studies of analytic validity, case-cohort and retrospective cohort studies of clinical validity using archived samples, 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 radical prostatectomy. 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 radical prostatectomy 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 clinically localized prostate cancer who receive the ProMark protein biomarker test, the evidence includes 1 study of analytic validity, 1 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. There is insufficient evidence to 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 intermediate- or low-risk prostate cancer after radical prostatectomy who receive Prolaris, the evidence includes 1 study of analytic validity and retrospective cohort 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 postprostatectomy 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 high-risk prostate cancer after radical prostatectomy who receive the Decipher prostate cancer classifier, the evidence includes 1 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, 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. All validation studies are Simon category C. 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 (NCCN) guidelines for prostate cancer (v.3.2016) 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 believes that men with clinically localized disease may consider these assays, though 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 RNA expression (44,000 genes) oligonucleotide microarray optimized for FFPE tissue</td>
<td>Post RP, adverse pathology/high-risk features</td>
<td>Metastasis; prostate cancer–specific mortality</td>
<td>Cooperberg 2015&lt;sup&gt;12&lt;/sup&gt;; Den 2014&lt;sup&gt;17&lt;/sup&gt;; Den 2015&lt;sup&gt;46&lt;/sup&gt;; Erho 2013&lt;sup&gt;36&lt;/sup&gt;; Karnes 2013&lt;sup&gt;35&lt;/sup&gt;; Klein 2015&lt;sup&gt;31&lt;/sup&gt;; Prensner 2014&lt;sup&gt;32&lt;/sup&gt;; Ross 2014&lt;sup&gt;34&lt;/sup&gt;; Ross 2015&lt;sup&gt;47&lt;/sup&gt;; Tomlins 2015&lt;sup&gt;36&lt;/sup&gt;; Yamoah 2015&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Cover post-RP for: • pT2 with positive margins • Any pT3 disease • Rising PSA (above nadir)</td>
</tr>
<tr>
<td>Ki-67</td>
<td>IHC</td>
<td>Biopsy, intermediate-to high-risk treated with EBRT</td>
<td>Metastasis</td>
<td>Fisher 2013&lt;sup&gt;32&lt;/sup&gt;; Khor 2009&lt;sup&gt;31&lt;/sup&gt;; Li 2004&lt;sup&gt;33&lt;/sup&gt;; Verhoven 2013&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Oncotype DX</td>
<td>Quantitative RT-PCR for 12 prostate cancer-related genes and 5 housekeeping controls</td>
<td>Biopsy, low- to intermediate-risk treated with RP</td>
<td>Non-organ-confined pT3 or Gleason grade 4 disease on RP</td>
<td>Cullen 2015&lt;sup&gt;52&lt;/sup&gt;; Klein 2014&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Cover postbiopsy for NCCN very low risk and low-risk prostate cancer at diagnosis with 10-20 y of life expectancy</td>
</tr>
<tr>
<td>Prolaris</td>
<td>Quantitative RT-PCR for 31 cell cycle-related genes and 15 housekeeping controls</td>
<td>TURP, active surveillance</td>
<td>Prostate cancer–specific mortality</td>
<td>Bishoff 2014&lt;sup&gt;49&lt;/sup&gt;; Cooperberg 2013&lt;sup&gt;45&lt;/sup&gt;; Cuzick 2011&lt;sup&gt;46&lt;/sup&gt;; Cuzick 2012&lt;sup&gt;47&lt;/sup&gt;; Cuzick 2015&lt;sup&gt;48&lt;/sup&gt;; Freedland 2013&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Cover postbiopsy for NCCN very low risk and low-risk prostate cancer at diagnosis with at least 10 y of life expectancy</td>
</tr>
<tr>
<td>Promark</td>
<td>Multiplex immunofluorescent staining of 8 proteins</td>
<td>Biopsy, Gleason grade 3+3 or 3+4</td>
<td>Non-organ-confined pT3 or Gleason 4 disease on RP</td>
<td>Blume-Jensen 2015&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Not reviewed</td>
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<tr>
<td>PTEN</td>
<td>Fluorescent in situ hybridization or IHC</td>
<td>TURP, active surveillance</td>
<td>Prostate cancer–specific mortality</td>
<td>Cuzick 2013&lt;sup&gt;49&lt;/sup&gt;; Lotan 2011&lt;sup&gt;50&lt;/sup&gt;; Lotan 2015&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Not recommended</td>
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In 2007, the American Urological Association (AUA) published guidelines on the management of clinically localized prostate cancer.\textsuperscript{21} AUA reviewed and confirmed the validity of these guidelines in 2011. The guidelines do not address gene expression profile analysis.

The National Institute for Health and Care Excellence (NICE) published an updated guidance on the diagnosis and management of prostate cancer in January 2014.\textsuperscript{97} NICE guidelines did not address gene expression profile analysis.

Not applicable.

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\textsuperscript{®} (03/02/15), Decipher\textsuperscript{®} (03/02/15), Oncotype DX Prostate (10/05/15), and ProMark (10/10/2016).\textsuperscript{98,99}


## POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<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>September 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>
</tr>
<tr>
<td>March 2017</td>
<td>Update Policy</td>
<td>Policy updated with literature review; Numerous references changed. Policy statement unchanged.</td>
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