FEP 2.04.111 Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

Effective Date: April 1, 2019

Related Policies:
2.04.33 Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

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, to guide radiotherapy use after radical prostatectomy (RP), or to guide medication selection after progression in metastatic castration-resistant prostate cancer.

Objective
The objective of this evidence review is to determine whether, compared with clinicopathologic risk stratification or when used with clinicopathologic risk stratification, tests of gene expression profiles and protein biomarkers improve outcomes in men with prostate cancer. The specific tests considered are the commercially available versions of Prolaris, Oncotype DX Prostate, ProMark, Decipher, and Oncotype DX AR-V7 Nuclear Detect.

Policy Statement
Use of gene expression analysis and protein biomarkers to guide management of prostate cancer is considered investigational in all situations.

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).
FDA REGULATORY STATUS

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.

In November 2015, the FDA’s Office of Public Health Strategy and Analysis published a report suggesting FDA oversight of laboratory-developed tests.15 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 report asserted that patients are potentially receiving inappropriate prostate cancer care because there is no evidence that results from the test meaningfully improve clinical outcomes.

RATIONALE

Summary of Evidence

Initial Management Decision: Active Surveillance vs Therapeutic Intervention

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 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 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 and no studies 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.

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.

Management Decision after Radical Prostatectomy
For individuals who have localized prostate cancer treated with RP who receive ProMark, 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 ProMark 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.

Management Decision in Castration-Resistant Prostate Cancer
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, disease-specific 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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements
The National Comprehensive Cancer Network guidelines for prostate cancer (v.4.2018) provide a table of tissue-based tests for prostate cancer prognosis (see Table 1).12

The Network panel suggested that men with low or favorable intermediate clinically localized disease may consider Decipher, Oncotype DX Prostate, Prolaris, or ProMark during initial risk stratification and Decipher may be considered during workup for radical prostatectomy, although the panel warned that the utility of these assays has not been fully assessed in randomized controlled trials. The guidelines also state that AR-V7 assays are promising predictors of abiraterone and enzalutamide resistance, but they have not yet been validated prospectively and externally.
Table 1. Available Tissue-Based Tests for Prostate Cancer Prognosis 12

<table>
<thead>
<tr>
<th>Test</th>
<th>Platform</th>
<th>Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decipher</strong></td>
<td>Whole transcriptome 1.4 RNA expression (44,000 genes)</td>
<td>Post RP, adverse pathology/high-risk features</td>
<td>Metastasis; prostate cancer specific mortality</td>
</tr>
<tr>
<td></td>
<td>oligonucleotide microarray optimized for FFPE tissue</td>
<td>Post RP, biochemical recurrence</td>
<td>Metastasis; biochemical failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post RP, adjuvant or salvage radiotherapy</td>
<td>Metastasis</td>
</tr>
<tr>
<td><strong>Ki-67</strong></td>
<td>IHC</td>
<td>Biopsy, intermediate-to high-risk treated with EBRT</td>
<td>Metastasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biopsy, active surveillance</td>
<td>Prostate cancer specific mortality</td>
</tr>
<tr>
<td><strong>Oncotype DX</strong></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>
</tr>
<tr>
<td><strong>ProLaris</strong></td>
<td>Quantitative RT-PCR for 31 cell cyclerelated genes and 15 housekeeping controls</td>
<td>TURP, active surveillance</td>
<td>Prostate cancer specific mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biopsy, active surveillance</td>
<td>Prostate cancer specific mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biopsy, localized prostate cancer</td>
<td>Biochemical recurrence; metastasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biopsy, intermediate-risk, treated with EBRT</td>
<td>Biochemical failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RP, node-negative localized prostate cancer</td>
<td>Biochemical recurrence</td>
</tr>
<tr>
<td><strong>ProMark</strong></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>
</tr>
<tr>
<td><strong>PTEN</strong></td>
<td>Fluorescent in situ hybridization or IHC</td>
<td>TURP, active surveillance</td>
<td>Prostate cancer specific mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biopsy, Gleason grade 3+3</td>
<td>Upgrading to Gleason 4 on RP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RP, high-risk localized disease</td>
<td>Biochemical recurrence</td>
</tr>
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</table>


American Urological Association et al
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The guidelines stated that among most low-risk localized prostate cancer patients, genomic biomarkers have not demonstrated a clear role in the selection of active surveillance or in the follow-up of patients on active surveillance.


National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (2014) updated its guidance on the diagnosis and management of prostate cancer. The guidance did not address gene expression profile testing.

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

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers. 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


The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
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16 Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Gene Expression Analysis for Prostate Cancer Management. TEC Assessments. 2014;Volume 28:Tab 11. PMID

17 Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Gene Expression Profiling for Prostate Cancer Management. TEC Assessments. 2015;Volume 29:Tab 9. PMID


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POLICY HISTORY

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<tr>
<th>Date</th>
<th>Action</th>
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March 2014  New Policy  Microarray-based gene expression analysis to guide management of prostate cancer is considered investigational in all situations.


September 2015  Update Policy  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.”

March 2017  Update Policy  Policy updated with literature review; Numerous references changed. Policy statement unchanged.


March 2019  Update Policy  Policy updated with literature review through September 4, 2018. Numerous references added. A new investigational indication was added for assays that detect androgen-receptor splice variant 7 messenger RNA (AR-V7) in circulating tumor cells from men with metastatic castration-resistant prostate cancer to predict resistance to androgen receptor signaling (ARS) inhibitors, such as abiraterone or enzalutamide. Policy statement unchanged.

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