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

Effective Date: April 15, 2018

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, 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 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 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)[13] 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[13]

Test	Platform	Population	Outcomes	References	MolDX Recommendations
Decipher	Whole transcriptome 1.4	Post RP, adverse pathology/high-risk	Metastasis; prostate cancer–specific	Cooperberg 2015[79]; Den 2014[78]; Den	Cover post-RP for: • pT2 with positive

	RNA expression (44,000 genes) oligonucleotide microarray optimized for FFPE tissue	features	mortality	2015[67]; Erho 2013[82]; Karnes 2013[81]; Klein 2015[77]; Prensner 2014[96]; Ross 2014[80]; Ross 2016[83]; Tomlins 2015[97]; Yamoah 2015[98]	margins • Any pT3 disease • Rising PSA (above nadir)
		Post RP, biochemical recurrence	Metastasis; biochemical failure		
		Post RP, adjuvant or salvage radiotherapy	Metastasis		
Ki-67	IHC	Biopsy, intermediate- to high-risk treated with EBRT	Metastasis	Fisher 2013[99]; Khor 2009[100]; Li 2004[101]; Verhoven 2013[102]	Not recommended
		Biopsy, active surveillance	Prostate cancer–specific mortality		
Oncotype DX	Quantitative RT-PCR for 12 prostate cancer–related genes and 5 housekeeping controls	Biopsy, low- to intermediate-risk treated with RP	Non-organ-confined pT3 or Gleason grade 4 disease on RP	Cullen 2015[55]; Klein 2014[54]	Cover postbiopsy for NCCN very low risk and low-risk prostate cancer before treatment with 10-20 y life expectancy
Prolaris	Quantitative RT-PCR for 31 cell cycle–related genes and 15 housekeeping controls	TURP, active surveillance	Prostate cancer–specific mortality	Bishoff 2014[73]; Cooperberg 2013[57]; Cuzick 2011[47]; Cuzick 2012[44]; Cuzick 2015[42]; Freedland 2013[75]	Cover postbiopsy for NCCN very low risk and low-risk prostate cancer before treatment with at least 10-y life expectancy
		Biopsy, active surveillance	Prostate cancer–specific mortality		
		Biopsy, localized prostate cancer	Biochemical recurrence; metastasis		
		Biopsy, intermediate-risk, treated with EBRT	Biochemical failure		
		RP, node-negative localized prostate cancer	Biochemical recurrence		
ProMark	Multiplex immunofluorescent staining of 8 proteins	Biopsy, Gleason grade 3+3 or 3+4	Non-organ-confined pT3 or Gleason 4 disease on RP	Blume-Jensen 2015[66]	Cover postbiopsy for NCCN very low- and low-risk prostate cancer before treatment with at least 10-y life expectancy
PTEN	Fluorescent in situ hybridization or IHC	TURP, active surveillance	Prostate cancer–specific mortality	Cuzick 2013[103]; Lotan 2011[104]; Lotan 2015[105]	Not recommended
		Biopsy, Gleason grade 3+3	Upgrading to Gleason 4 on RP		
		RP, high-risk localized disease	Biochemical recurrence		

EBRT: external-beam radiation therapy; FFPE: formalin-fixed, paraffin-embedded; IHC: immunohistochemical; NCCN: National Comprehensive Cancer Network; PSA: prostate-specific antigen; pT2: organ-confined; pT3: extraprostatic extension; PTEN: phosphatase and tensin homolog; RNA: ribonucleic acid; RP: radical prostatectomy; RT-PCR: reverse-transcriptase polymerase chain reaction; TURP: transurethral resection of the prostate.

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

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.[106] 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).[107,108]

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POLICY HISTORY

Date	Action	Description
March 2014	New Policy	Microarray-based gene expression analysis to guide management of prostate cancer is considered investigational in all situations.
March 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.”
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 2018	Update Policy	Policy updated with literature review through July 5, 2017. References 14, 50, 60-61, 87, and 89 added. Policy statement unchanged.