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FEP Medical Policy Manual

FEP 2.04.111 Gene Expression Profiling, Protein Biomarkers, and Multimodal Artificial Intelligence for Prostate Cancer Management

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Related Policies:

2.04.33 - Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

Gene Expression Profiling, Protein Biomarkers, and Multimodal Artificial Intelligence for Prostate Cancer Management

Description

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Gene expression profile analysis and protein biomarkers have been proposed as a means to risk-stratify individuals 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, protein biomarkers, and multimodal artificial intelligence (MMAI) improve outcomes in individuals with prostate cancer. The specific tests considered are the commercially available versions of Prolaris, Oncotype DX Prostate, ProMark, Decipher, Oncotype DX AR-V7 Nuclear Detect, and ArteraAI Prostate Test.

POLICY STATEMENT

Use of gene expression analysis, protein biomarkers, and multimodal artificial intelligence (MMAI) to guide management of prostate cancer is considered **investigational** in all situations.

POLICY GUIDELINES

None

BENEFIT APPLICATION

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

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.

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 (Decipher Corp), the ProMark™ protein biomarker test (Metamark Genetics), and Artera Prostate Test are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests.

In November 2015, the FDA"s Office of Public Health Strategy and Analysis published a report suggesting FDA oversight of laboratory-developed tests.[17,] The FDA argued that many tests need more FDA oversight than the regulatory requirements of the CLIA. The 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 versus Therapeutic Intervention

For individuals who have clinically localized untreated prostate cancer who receive Prolaris, the evidence includes retrospective cohort studies of clinical validity using archived samples in patients of mixed risk categories. Relevant outcomes include overall survival (OS), disease-specific survival, quality of life (QOL), and treatment-related morbidity. For the low-risk group, the Prostate Testing for Cancer and Treatment trial showed 99% 10-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 a 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 that the technology results in an improvement in the net health outcome.

For individuals who have 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 in patients of mixed risk categories, and a decision-curve analysis examining indirect evidence of clinical utility. Relevant outcomes include OS, disease-specific survival, QOL, 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 the 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 that the technology results in an improvement in the net health outcome.

For individuals who have clinically localized untreated prostate cancer who receive Decipher Biopsy, the evidence includes retrospective cohort studies of clinical validity using archived samples in intermediate- and high-risk patients and no studies of clinical utility. Relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. A test designed to identify intermediate-risk men who can receive active surveillance instead of RP or radiotherapy (RT) or high-risk men who can forego androgen deprivation therapy would need to show very high negative predictive value for disease-specific mortality at 10 years and improvement in prediction compared with existing tools used to select such men. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have 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 OS, disease-specific survival, QOL, 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 that the technology results in an improvement in the net health outcome.

For individuals who have clinically localized untreated prostate cancer who receive ArteraAI Prostate Test, the evidence includes 1 meta-analysis and 5 retrospective analyses on archived samples from randomized clinical trials on prostate cancer patients of mixed risk categories to assess clinical validity and utility. Relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. Evidence for clinical validity and potential clinical utility of ArteraAI Prostate Test in patients with clinically localized prostate cancer derives from a handful of studies comparing relevant outcomes against comparators like National Comprehensive Cancer Network (NCCN) and standard clinicopathologic risk-stratification tools. Multimodal artificial intelligence (MMAI) algorithms, that form the foundation of ArteraAI, have shown they can outperform comparators at prognosticating 10-year outcomes of interest (OS, distant metastasis [DM], biochemical failure [BF], and prostate cancer-specific survival [PCSS]). Additionally, MMAI was able to demonstrate it is predictive for short-term androgen deprivation therapy (ST-ADT) and can determine if prostate cancer patients would have a better net health outcome on RT alone or RT plus ST-ADT. Limitations of these studies are synonymous with retrospective analysis, including but not limited to, clinical heterogeneity of study populations, variability in data recording, and different conditions under which measurements occurred. No study reported management changes made in response to ArteraAI Prostate Test results, but current NCCN management algorithms recommend MMAI testing with ArteraAI for prostate cancer patients with NCCN intermediate-risk scores to indicate patients that should undergo ST-ADT regardless of RT dose or type. Moreover, NCCN notes that MMAI testing with ArteraAI may provide more accurate risk stratification to enable better management of cancer patients; however, it remains unclear on how this could be used in clinical practice as specific MMAI cutoff values have not been published. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Management Decision After Radical Prostatectomy

For individuals who have localized prostate cancer treated with radical prostatectomy (RP) who receive Prolaris, the evidence includes retrospective cohort studies of clinical validity using archived samples. Relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. No direct evidence is available to support the clinical utility of Prolaris for improving net outcomes of patients with localized prostate cancer following RP. The chain of evidence is also incomplete. Decision-curve analysis did not provide convincing evidence of meaningful improvement in net benefit by incorporating the cell cycle progression (CCP) score. 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. Although Prolaris CCP score may have an association with biochemical recurrence (BCR), disease-specific survival outcomes were reported in only 1 analysis. A larger number of disease-specific survival events and precision estimates for discrimination measures are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have localized prostate cancer who are treated with RP and who receive the Decipher RP 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 OS, disease-specific survival, QOL, and treatment-related morbidity. The clinical validity of the Decipher RP 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 consistently improved reclassification-particularly to higher risk categories-or whether the test could be used to predict which men will benefit from RT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have localized prostate cancer treated with RP who receive ArteraAI Prostate Test, the evidence includes 2 retrospective cohort studies of clinical validity using archived samples. Relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. ArteraAI proved to be prognostic for RP-specific endpoints of BCR and adverse pathology given the statistically significant association. Disease-specific survival outcomes were reported in both studies and the evidence of clinical validity and prognostic accuracy for MMAI scores via ArteraAI testing in patients after RP demonstrated statistically improved PCSM and OS when compared to standard clinicopathologic risk stratification tools. Limitations of these studies are synonymous with retrospective analysis, including but not limited to, clinical heterogeneity of study populations, variability in data recording, and different conditions under which measurements occurred. No study reported management changes made in response to ArteraAI Prostate Test results. Overall, ArteraAI Prostate Test is validated for disease-specific outcomes for prostate cancer patients who underwent RP and can provide additional prognostic information that may guide postoperative management, but further studies are needed to determine if MMAI can be used to decide specific treatment regimens that improve health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 1 prospective cohort study, 1 retrospective cohort study of clinical validity using archived samples, and no studies of clinical utility. Relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. Current evidence does not support improved outcomes with Oncotype DX AR-V7 Nuclear Detect, given that only 2 clinical validity studies meeting inclusion criteria were available. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Management Decision in Castration-Sensitive Prostate Cancer

For individuals who have metastatic castration-sensitive prostate cancer (mCSPC) who receive ArteraAI Prostate Test, the evidence includes 2 retrospective cohort studies of clinical validity using archived samples. Relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. MMAI was able to estimate treatment effects and determine that MMAI high-risk mCRPC patients would derive benefit from metastasis-directed therapy (MDT) when compared to observation. Limitations of these studies are synonymous with retrospective analysis, including but not limited to, clinical heterogeneity of study populations, variability in data recording, and different conditions under which measurements occurred. No study reported management changes made in response to ArteraAI Prostate Test results. Overall, ArteraAI Prostate Test is prognostic for mCSPC patients and has the potential to guide treatment management, but further studies are needed to determine if MMAI can be used to decide specific treatment regimens that improve net health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society of Clinical Oncology

In 2020, the American Society of Clinical Oncology (ASCO) published a guideline on molecular biomarkers in localized prostate cancer.[122,] The guidelines state, "Currently, there are no strong data or expert guidelines to support active surveillance in otherwise healthy men with Grade Group 3 or higher cancer; therefore, we would consider the use of genomic biomarkers only in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect a physician"s recommendation or a patient"s choice for surveillance versus treatment, but they should not be used routinely."

Specific recommendations included the following:

Molecular biomarkers to identify patients with prostate cancer who are most likely to benefit from active surveillance:

- Recommendation 1.1. Commercially available molecular biomarkers (i.e. Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).
- Recommendation 1.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

Molecular biomarkers to diagnose clinically significant prostate cancer:

- Recommendation 2.1. Commercially available molecular biomarkers (i.e. Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Recommendation: Moderate).
- Recommendation 2.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

Molecular biomarkers to guide the decision of post prostatectomy adjuvant versus salvage radiation:

Recommendation 3.1. The Expert Panel recommends consideration of a commercially available molecular biomarker (eg, Decipher Genomic Classifier) in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. In the absence of prospective clinical trial data, routine use of genomic biomarkers in the postprostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Recommendation 3.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

American Urological Association and American Society for Radiation Oncology

The American Urological Association and American Society for Radiation Oncology published guidelines on clinically localized prostate cancer.[14,] The guidelines included the following statements on risk assessment:

1. "Clinicians should use clinical T stage, serum PSA, Grade Group (Gleason score), and tumor volume on biopsy to risk stratify patients with newly diagnosed prostate cancer. (Strong Recommendation; Evidence Level: Grade B)."
2. "Clinicians may selectively use tissue-based genomic biomarkers when added risk stratification may alter clinical decision-making. (Expert Opinion)."
3. "Clinicians should not routinely use tissue-based genomic biomarkers for risk stratification or clinical decision-making. (Moderate Recommendation; Evidence Level: Grade B)."

The American Urological Association (2018) published guidelines for castration-resistant prostate cancer.[123,] The guidelines do not mention AR-V7 assays.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (v.1.2025) provide a table of tissue-based tests for prostate cancer prognosis.[13,]Guidelines are updated frequently; refer to the source document for current recommendations. The most recent guidelines (v.1.2025) include the following recommendations and statements related to risk-stratification and testing for biomarkers:

22-gene genomic classifier (GC) (Decipher)

- "RT alone may be considered for patients with a low GC score and NCCN intermediate-risk disease."
- "The addition of ST-ADT should be considered for patients with a high GC score given their increased risk of DM and significant benefit of ST-ADT on DM, irrespective of RT dose or brachytherapy boost."

- "Patients with a GC low-risk score should be counseled that the absolute benefit of LT-ADT over ST-ADT is smaller than for patients with GC high-risk scores and when accounting for patient age, comorbidities, and patient preferences, it may be reasonable with shared decision-making to use a duration shorter than LT-ADT."
- "For patients with node-negative disease post-RP planned for early secondary RT (PSA ≤ 0.5 ng/mL) with GC low or intermediate risk, use of RT alone should be considered."
- "For patients planned for early secondary RT with a GC high-risk tumor, use of secondary RT with ADT is recommended."

ArteraAI Prostate Test

- Patients with intermediate-risk prostate cancer planning to receive RT, those with biomarker-positive disease, and especially those with unfavorable intermediate-risk disease, should be recommended for the addition of ST-ADT regardless of RT dose or type, notwithstanding contraindications to ADT. Those with biomarker (-) tumors, especially tumors with more favorable prognostic risk, may consider the use of RT alone.
- "Specific MMAI cut points have not been published to date to precisely guide specific treatment decisions. Rather, the test may be used to provide more accurate risk stratification to enable improved shared decision-making."

The discussion section in the guidelines, which is pending update as of April 2024, includes the following statements related to risk stratification:

- Patients with low or favorable intermediate disease and life expectancy greater than or equal to 10 years may consider the use of Decipher, Oncotype DX Prostate, or Prolaris during initial risk stratification. Patients with unfavorable intermediate- and high-risk disease and life expectancy greater than or equal to 10 years may consider the use of Decipher or Prolaris.
- Decipher may be considered to inform adjuvant treatment if adverse features are found after radical prostatectomy and during workup for radical prostatectomy PSA persistence or recurrence (NCCN category 2A; Simon et al [2019] category 2B).

The panel also stated that "the use of AR-V7 tests in circulating tumor cells can be considered to help guide selection of therapy in the post-abiraterone/enzalutamide metastatic castration-resistant prostate cancer setting."

Of note, in the April 2024 version of the NCCN guideline, the following footnotes were noted to be removed, but the related discussion sections are still pending update:

- "Decipher molecular assay should be considered if not previously performed to inform adjuvant treatment if adverse features are found post-RP."
- "Consider AR-V7 testing to help guide selection of therapy.

National Institute for Health and Care Excellence

In 2019 (updated 2021), the National Institute for Health and Care Excellence updated its guidance on the diagnosis and management of prostate cancer.[124,] 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. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2014	New Policy	
March 2015	Replace policy	Microarray-based gene expression analysis to guide management of prostate cancer is considered investigational in all situations.
September 2015	Replace policy	Policy updated with literature review. References 26-27 and 33-36 added; policy statement unchanged. Policy title updated.
March 2017	Replace 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.€š
March 2018	Replace policy	Policy updated with literature review through July 5, 2017. References 14, 50, 60-61, 87, and 89 added. Policy statement unchanged.
March 2019	Replace 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.
March 2020	Replace policy	Policy updated with literature review through October 8, 2019; references added. Added indication and reorganized evidence review to distinguish Decipher Biopsy and Decipher RP tests; no new studies of Decipher added. Policy statement unchanged.
March 2021	Replace policy	Policy updated with literature review through October 11, 2020; references added. Policy statement unchanged.
March 2022	Replace policy	Policy updated with literature review through October 8, 2021; references added. Policy statement unchanged.
March 2023	Replace policy	Policy updated with literature review through September 26, 2022; reference added. Policy statement unchanged.
March 2024	Replace policy	Policy updated with literature review through October 11, 2023; no references added. Policy statement unchanged.
December 2024	Replace policy	Policy updated with literature review through July 19, 2024; references added. Policy statement unchanged.
March 2026	Replace policy	Policy updated with literature review through March 13, 2025; references added. Title changed with the addition of 3 new indications for the ArteraAI Prostate Test with accompanying evidence. Added NCCN definitions for test in prostate cancer to the rationale section. Multimodal artificial intelligence (MMAI) testing is considered investigational.