



FEP Medical Policy Manual

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

Annual Effective Policy Date: April 1, 2024

Original Policy Date: December 2011

Related Policies:

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

7.01.152 - Magnetic Resonance Imaging-Targeted Biopsy of the Prostate

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

Description

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Various genetic and protein biomarkers are associated with prostate cancer. These tests have the potential to improve the accuracy of differentiating between which men should undergo prostate biopsy and which rebiopsy after a prior negative biopsy. This evidence review addresses these types of tests for cancer risk assessment. Testing to determine cancer aggressiveness after a tissue diagnosis of cancer is addressed in evidence review 2.04.111. Magnetic resonance imaging-targeted biopsy of suspicious lesions is assessed in evidence review 7.01.152.

OBJECTIVE

The objective of this evidence review is to determine whether testing for genetic and protein prostate biomarkers improves the net health outcome in men for whom an initial prostate biopsy or a repeat prostate biopsy is being considered.

POLICY STATEMENT

The following genetic and protein biomarkers for the diagnosis of prostate cancer are considered **investigational**:

- Kallikrein markers (eg, 4Kscore Test)
- *HOXC6* and *DLX1* testing (eg, SelectMDx)
- PCA3, ERG, and SPDEF RNA expression in exosomes (eg, ExoDx Prostate IntelliScore)
- Autoantibodies ARF 6, NKX3-1, 5' -UTR-BMI1, CEP 164, 3' -UTR-Ropporin, Desmocollin, AURKAIP-1, and CSNK2A2 (eg, Apifyny)
- *TMPRSS:ERG* fusion genes (eg, MyProstate Score)
- Gene hypermethylation testing (eg, ConfirmMDx)
- Mitochondrial DNA variant testing (eg, Prostate Core Mitomics Test)
- PanGIA Prostate
- Candidate gene panels.

PCA3 testing (eg, ProgenSA PCA3 Assay), Prostate Health Index (phi), *PCA3*, ERG, and SPDEF RNA expression in exosomes (eg, ExoDx Prostate IntelliScore) for cancer risk assessment of prostate cancer is considered **not medically necessary**.

Single nucleotide variant testing for cancer risk assessment of prostate cancer is considered **investigational**.

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). Laboratories that offer laboratory-developed tests must be licensed under the CLIA for high-complexity testing. The following laboratories are certified under the CLIA : BioReference Laboratories and GenPath Diagnostics (subsidiaries of OPKO Health; 4Kscore), ARUP Laboratories, Mayo Medical Laboratories, LabCorp, BioVantra, others (PCA3 assay), Clinical Research Laboratory (Prostate Core Mitomic Test™), MDx Health (SelectMDx, ConfirMDx), Innovative Diagnostics (phi™), and ExoDx Prostate (Exosome Diagnostics). To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests.

In February 2012, the ProgenSA PCA3 Assay (Gen-Probe; now Hologic) was approved by the FDA through the premarket approval process. The ProgenSA PCA3 Assay has been approved by the FDA to aid in the decision for repeat biopsy in men 50 years or older who have had 1 or more negative prostate biopsies and for whom a repeat biopsy would be recommended based on the current standard of care. The ProgenSA PCA3 Assay should not be used for men with atypical small acinar proliferation on their most recent biopsy. FDA product code: OYM.

In June 2012, proPSA, a blood test used to calculate the Prostate Health Index (PHI ; Beckman Coulter) was approved by the FDA through the premarket approval process. The PHI test is indicated as an aid to distinguish prostate cancer from a benign prostatic condition in men ages 50 and older with prostate-specific antigen levels of 4 to 10 ng/mL and with digital rectal exam findings that are not suspicious. According to the manufacturer, the test reduces the number of prostate biopsies. FDA product code: OYA.

RATIONALE

Summary of Evidence

For individuals who are being considered for an initial prostate biopsy who receive testing for genetic and protein biomarkers of prostate cancer (eg, kallikreins biomarkers and 4Kscore Test, proPSA and Prostate Health Index, TMPRSS fusion genes and MyProstateScore, SelectMDx for Prostate Cancer, ExoDx Prostate, Apify, PCA3 score, and PanGIA Prostate), the evidence includes systematic reviews, meta-analyses, and primarily observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, resource utilization, and quality of life. The evidence supporting clinical utility varies by the test but has not been directly shown for any biomarker test. Absent direct evidence of clinical utility, a chain of evidence might be constructed. However, the performance of biomarker testing for directing biopsy referrals is uncertain. While some studies have shown a reduction or delay in biopsy based on testing, a chain of evidence for clinical utility cannot be constructed due to limitations in clinical validity. Test validation populations have included men with a positive digital rectal exam (DRE), a prostate-specific antigen (PSA) level outside of the gray zone (between 3 or 4 ng/mL and 10 ng/mL), or older men for whom the information from test results are less likely to be informative. Many biomarker tests do not have standardized cutoffs to recommend a biopsy. In addition, comparative studies of the many biomarkers are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are being considered for repeat biopsy who receive testing for genetic and protein biomarkers of prostate cancer (eg, PCA3 score, Gene Hypermethylation and ConfirmMDx test, Prostate Core Mitomics Test, MyProstate Score), the evidence includes systematic reviews and meta-analyses and primarily observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, resource utilization, and quality of life. The performance of biomarker testing for guiding rebiopsy decisions is lacking. The tests are associated with a diagnosis of prostate cancer and aggressive prostate cancer, but studies on clinical validity are limited and do not compare performance characteristics with standard risk prediction models. Direct evidence supporting clinical utility has not been shown. No data are currently available on the longer-term clinical outcomes of the use of genetic and protein biomarkers to decide on repeat prostate biopsy. 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 Urological Association et al

In 2023, the American Urological Association (AUA) and the Society of Urologic Oncology (SUO) published updated guidelines on the early detection of prostate cancer. Specific guidance related to diagnosis, risk assessment, and utilization of biomarkers are stated in Table 1 below.^{74,75}

Table 1. Relevant AUA/SUO Guideline Statements on Prostate Cancer Screening and Biopsy

Guideline Statement	Evidence Grade and Strength
When screening for prostate cancer, clinicians should use PSA as the first screening test	Strong Recommendation; Evidence Level: Grade A
For people with a newly elevated PSA, clinicians should repeat the PSA prior to a secondary biomarker, imaging, or biopsy	Expert Opinion
Clinicians may use digital rectal exam (DRE) alongside PSA to establish risk of clinically significant prostate cancer	Conditional Recommendation; Evidence Level: Grade C
For people undergoing prostate cancer screening, clinicians should not use PSA velocity as the sole indication for a secondary biomarker, imaging, or biopsy	Strong Recommendation; Evidence Level: Grade B
Clinicians may use adjunctive urine or serum markers when further risk stratification would influence the decision regarding whether to proceed with biopsy.	Conditional Recommendation; Evidence Level: Grade C
After a negative biopsy, clinicians should not solely use a PSA threshold to decide whether to repeat the biopsy	Strong Recommendation; Evidence Level: Grade B
After a negative biopsy, clinicians may use blood-, urine-, or tissue-based biomarkers selectively for further risk stratification if results are likely to influence the decision regarding repeat biopsy or otherwise substantively change the patient's management	Conditional Recommendation; Evidence Level: Grade C
In patients with multifocal HGPIN [high-grade prostatic intraepithelial neoplasia], clinicians may proceed with additional risk evaluation, guided by PSA/DRE and mpMRI findings	Expert Opinion

DRE: digital rectal exam; PSA: prostate-specific antigen; mpMRI: multi-parametric magnetic resonance imaging

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines (v.1.2023) recommend that any man with a PSA level greater than 3 ng/mL undergo workup for benign disease, repeat PSA, and DRE (category 2A evidence).⁷⁶

The NCCN guidelines state that "biomarkers that improve the specificity of detection are not, as yet, mandated as first-line screening tests in conjunction with serum PSA. However, there may be some patients who meet PSA standards for consideration of prostate biopsy, but for whom the patient and/or the physician wish to further define risk". The guidelines recommend that the probability of high-grade cancer (Gleason score $\geq 3+4$, Grade Group 2 or higher) may be further defined utilizing biomarkers that improve the specificity of screening that includes percent free PSA, with consideration of the Prostate Health Index (PHI), SelectMDx, 4K score, ExoDx Prostate Test , MyProstate Score (MPS), and IsoPSA. NCCN also noted that the extent of validation of these tests across diverse populations is variable and is not yet known how these tests could be applied in optimal combination with magnetic resonance imaging (MRI).

For men who had a negative biopsy but are thought to be at higher risk, NCCN recommends to consider biomarkers that improve the specificity of screening (category 2A evidence). Tests that should be considered in the post-biopsy setting include percent-free PSA, 4Kscore, PHI, PCA3, ConfirmMDx, ExoDx Prostate Test, MPS, and IsoPSA..

National Institute for Health and Care Excellence

In 2019 and in 2021, when guidelines were updated, the NICE guidelines did not recommend the ProgenSA PCA3 Assay or the PHI test for use in men with suspicion of prostate cancer who had a negative or inconclusive prostate biopsy.⁷⁷

U.S. Preventive Services Task Force Recommendations

The **U.S. Preventive Services Task Force** (2018) updated recommendations for prostate cancer screening. Genetic and protein biomarkers addressed in this evidence review, including *PCA3*, were not mentioned.⁷⁸

The **U.S. Preventive Services Task Force** advises individualized decision making about screening for prostate cancer after discussion with a clinician for men ages 55 to 69 (C recommendation) and recommends against PSA-based screening in men 70 and older (D recommendation).

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
December 2011	New policy	
June 2013	Replace policy	Policy updated with literature review, references added, policy statement changed PCA3 from investigational to not medically necessary.
June 2014	Replace policy	Policy updated with literature review through March 16, 2014; references 1, 12-13, 31-46, 60-65, 67-70, 82-88 added. No change to policy statement.
June 2015	Replace policy	Policy updated with literature review through March 16, 2015. Policy revised to focus on diagnostic testing (as well as SNP testing for cancer risk assessment). Policy statements revised to include an expanded list of diagnostic genetic and protein biomarker tests as investigational. Prognostic testing is being moved to Policy No. 2.04.111. References extensively revised. Title changed "Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer.,
December 2016	Replace policy	Policy updated with literature review through August 26, 2016; references 1-28, 31-44, 46-57, 60-65, 82, 96-99, 102, 104, 107, 110-111, and 117-118 added. Prostate Health Index (phi) biomarker test added to review and policy statement.
March 2018	Replace policy	Policy updated with literature review through July 26, 2017; references 1-2 and 22 updated; reference 1, 22, and 27 added; Prostarix test removed from policy and policy statement; policy statement corrected due to FDA premarket approval status to change PCA3 and Prostate Health Index (phi) biomarker tests from investigational to not medically necessary, otherwise policy statement unchanged.
March 2019	Replace policy	Policy updated with literature review through September 4, 2018; references 6, 32-34, 36-38, 45, 50, 55, and 60 added. The SelectMDx, ExoDx Prostate (IntelliScore), and Apify tests added as investigational.
March 2020	Replace policy	Policy updated with literature review through September 18, 2019; references added. Policy statements unchanged.
March 2021	Replace policy	Policy updated with literature review through October 16, 2020; references added. Policy statements unchanged.
June 2021	Replace policy	Policy updated with literature review through February 19, 2021. PanGIA Prostate added as investigational.
March 2022	Replace policy	Policy updated with literature review through October 6, 2021; references added. MyProstateScore (renamed from MiPS) added as an example of a TMRSS:ERG fusion gene test. Policy statements otherwise unchanged.
March 2023	Replace policy	Policy updated with literature review through September 19, 2022; references added. Policy statements unchanged.
March 2024	Replace policy	Policy updated with literature review through September 26, 2023; references added. Policy statements unchanged.

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