

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

**Effective Date:** April 15, 2018

**Related Policies:**

2.04.111 Gene Expression Analysis for Prostate Cancer Management

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

#### Description

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.

#### 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. Laboratories that offer laboratory-developed tests must be licensed under the Clinical Laboratory Improvement Amendments for high-complexity testing. The following laboratories are certified under the Clinical Laboratory Improvement Amendments: 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 (ConfirMDx), and Innovative Diagnostics (phi™). In addition to commercially available tests, single-nucleotide variant (SNV) testing as part of genome-scanning tests for prostate cancer risk assessment are offered by a variety of laboratories, such as Navigenics (now Life Technologies), LabCorp (23andme), and ARUP Laboratories (deCODE), as laboratory-developed tests. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

In February 2012, the Progenesa® PCA3 Assay (Gen-Probe; now Hologic, Marlborough, MA) was approved by FDA through the premarket approval process. According to the company's press release, this assay is "indicated for use in conjunction with other patient information to aid in the decision for repeat biopsy in men 50 years of age or older who have had 1 or more previous negative prostate biopsies and for whom a repeat biopsy would be recommended by a urologist based on the current standard of care, before consideration of Progenesa PCA3 assay results." FDA product code: OYM.

In June 2012, proPSA, a blood test used to calculate the Prostate Health Index (phi; Beckman Coulter, Brea, CA) was approved by 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

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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.

### POLICY STATEMENT

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

- Kallikrein markers (eg, 4Kscore™ Test)
- *TMPRSS* fusion genes
- Candidate gene panels
- Mitochondrial DNA variant testing (eg, Prostate Core Mitomics Test™)
- Gene hypermethylation testing (eg, ConfirmMDx®)

*PCA3* testing and prostate Health Index (phi) 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

#### Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUMAN Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

**Table PG1. Nomenclature to Report on Variants Found in DNA**

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

**Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification**

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

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### 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

For individuals who are being considered for an initial prostate biopsy or a repeat biopsy who receive testing for genetic and protein biomarkers of prostate cancer, the evidence includes systematic reviews and meta-analyses and primarily observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, other test performance measures, resource utilization, and quality of life. The evidence supporting clinical utility varies by test but has not been directly shown for any biomarker test. In general, the performance of biomarker testing for predicting biopsy referrals compared with clinical examination, including the ratio of free or unbound PSA to total PSA, is lacking. Procedures for referrals for biopsy based on clinical examination vary, making it difficult to quantify performance characteristics for this comparator. There is also considerable variability in biopsy referral practices based on clinical examination alone, and many biomarker tests do not have standardized cutoffs to recommend a biopsy. Therefore, to determine whether the tests improve the net health outcome, prospective, comparative data are needed on how test results are expected to be used vs how they are being used in practice, because of information about the associated effects on outcomes. Many test validation populations have included men with a positive digital rectal exam, 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 PSA test results are less likely to be informative. African American men have a high burden of morbidity and mortality, but have not been well represented in these study populations. It is unclear how to monitor men with low biomarker risk scores who continue to have symptoms or high or rising PSA levels. Comparative studies of the many biomarkers are lacking, and it is unclear how to use the tests in practice, particularly when test results are contradictory. The evidence is insufficient to determine the effects of the technology on health outcomes.

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### SUPPLEMENTAL INFORMATION

#### Practice Guidelines and Position Statements

##### American Urological Association et al

In 2013, the American Urological Association published guidelines on the early detection of prostate cancer.<sup>120</sup> Based on a systematic review of the literature to 2013, the Association recognized that novel urinary markers, such as PCA3 protein biomarker and *TMPRSS2-ERG* fusion gene, may be “used as adjuncts for informing decisions about the need for a prostate biopsy—or repeat biopsy—after PSA [prostate-specific antigen] screening,” but emphasized the lack of evidence “that these tests will increase the ratio of benefit to harm.”

The American Urological Association and the Society of Abdominal Radiology published joint guidelines in 2016 on prostate magnetic resonance imaging (MRI) and MRI-targeted biopsy.<sup>27</sup> The associations recommended:

“In patients with negative or low suspicion magnetic resonance imaging (PI-RADS [Prostate Imaging Reporting and Data System] assessment category of 1 or 2, respectively), other ancillary markers (ie PSA [prostate-specific antigen], PSAD [PSA density], PSAV [PSA velocity], PCA3, PHI, 4K) may be of value in identifying patients warranting repeat systematic biopsy, although further data are needed on this topic.”

##### Evaluation of Genomic Applications in Practice and Prevention

In 2013, the Evaluation of Genomic Applications in Practice and Prevention working group published the following recommendations for *PCA3* testing in prostate cancer,<sup>121</sup> based on the Agency for Healthcare Quality and Research comparative effectiveness review,<sup>62</sup> summarized earlier:

- Evidence was insufficient to recommend “PCA3 testing to inform decisions for when to rebiopsy previously biopsy-negative patients for prostate cancer, [or] to inform decisions to conduct initial biopsies for prostate cancer in at-risk men (e.g., previous elevated PSA or suspicious DRE [digital rectal examination])....”
- Evidence was “insufficient ... to recommend PCA3 testing in men with cancer-positive biopsies to determine if the disease is indolent or aggressive in order to develop an optimal treatment plan.”
- “...[T]he overall certainty of clinical validity to predict the diagnosis of prostate cancer using PCA3 is deemed ‘low.’... [C]linical use for diagnosis is discouraged unless further evidence supports improved clinical validity.”
- “...[T]he overall certainty of net health benefit is deemed ‘low.’... [C]linical use [is discouraged] unless further evidence supports improved clinical outcomes.”

##### National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) guidelines (v.2.2017) recommend that any man with a PSA level greater than 3 ng/mL undergo workup for benign disease, repeat PSA, and digital rectal examination.<sup>122</sup> The guidelines also recommend consideration of percent free PSA, phi, and 4Kscore in patients with a PSA level greater than 3 ng/mL who have not yet had a biopsy, and consideration of percent free PSA, phi, 4Kscore, PCA3, and ConfirmMDx in men who had a negative biopsy but are thought to be at higher risk (category 2A evidence). NCCN noted that these tests may be especially useful in men with PSA levels between 3 ng/mL and 10 ng/mL. NCCN indicated that:

“... no biomarker test can be recommended over any other at this time. The optimal order of biomarker tests and imaging is unknown; and it remains unclear how to interpret results of multiple tests in individual patients – especially when results are contradictory.”

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### U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force published recommendations for prostate cancer screening in 2012.<sup>18</sup> Genetic and protein biomarkers addressed in this evidence review, including PCA3, were not mentioned.

### 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. Palmetto GBA has issued a local coverage determination for positive coverage for ConfirmMDx Epigenetic Molecular Assay (effective 2014). Palmetto GBA issued a draft noncoverage policy determination in 2016 for the 4Kscore.

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### POLICY HISTORY

Date	Action	Description
December 2011	New Policy	
June 2013	Update Policy	Policy updated with literature review, references added, policy statement changed PCA3 from investigational to not medically necessary.
June 2014	Update 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	Update 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	Update 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

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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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.

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