**Medical Coverage Policy |** Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

**EFFECTIVE DATE:** 07|01|2019
**POLICY LAST UPDATED:** 06|04|2019

## OVERVIEW

Various genetic and protein biomarkers are associated with prostate cancer. These tests have the potential to improve the accuracy of differentiating which men should undergo prostate biopsy or rebiopsy after a prior negative biopsy.

**For coverage of tests filed with PLA codes (0005U ExoDx Prostate IntelliScore and 0021U Apifiny), please refer to the related policy "Proprietary Laboratory Analyses (PLA)."**

## MEDICAL CRITERIA

**BlueCHiP for Medicare and Commercial Products**

Not applicable

## PRIOR AUTHORIZATION

**BlueCHiP for Medicare and Commercial Products**

There is no specific CPT coding for some of the services referenced in this policy. Therefore, an Unlisted CPT code should be used (see Coding Section for details). All Unlisted genetic testing CPT codes require prior authorization to determine what service is being rendered and if the service is covered or not medically necessary. See the Related Policies section.

Prior authorization is required for BlueCHiP for Medicare and recommended for Commercial Products and is obtained via the online tool for participating providers. See the Related Policies section.

## POLICY STATEMENT

**BlueCHiP for Medicare**

The following tests are considered medically necessary and are covered without a prior authorization requirement:

- Progensa® PCA3 Assay
- 4Kscore® Test (Effective 12/1/2018)
- Prostate Health Index (phi) (Effective 12/1/2018)

The following genetic and protein biomarkers for the diagnosis of prostate cancer are not covered as the evidence is insufficient to determine the effects of the technology on health outcomes:

- HOXC6 and DLX1 testing (eg, SelectMDx)
- TMPRSS:ERG fusion genes (eg, MiPS)
- Gene hypermethylation testing (eg, ConfirmMDx)
- Mitochondrial DNA variant testing (eg, Prostate Core Mitomics Test)
- Candidate gene panels

Single nucleotide variant testing for cancer risk assessment of prostate cancer is not covered as the evidence is insufficient to determine the effects of the technology on health outcomes.

**Commercial Products**
The following genetic and protein biomarkers for the diagnosis of prostate cancer are considered not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes:

- Kallikrein markers (eg, 4Kscore® Test)
- Prostate Health Index (phi)
- HOXC6 and DLX1 testing (eg, SelectMDx)
- PCA3 testing (eg, Progensa PCA3 Assay)
- TMPRSS:ERG fusion genes (eg, MiPS)
- Gene hypermethylation testing (eg, ConfirmMDx)
- Mitochondrial DNA variant testing (eg, Prostate Core Mitomics Test)
- Candidate gene panels

Single nucleotide variant testing for cancer risk assessment of prostate cancer is considered not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes.

## COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate section of the Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for applicable genetic testing and not medically necessary/not covered benefits/coverage.

## BACKGROUND

Prostate cancer is the second most common cancer in men, with a predicted 161,360 incidence cases and 26,730 deaths expected in the United States in 2017.

Prostate cancer is a complex, heterogeneous disease, ranging from microscopic tumors unlikely to be life-threatening to aggressive tumors that can metastasize, leading to morbidity or death. Early localized disease can usually be treated with surgery and radiotherapy, although active surveillance may be adopted in men whose cancer is unlikely to cause major health problems during their lifespan or for whom the treatment might be dangerous. In patients with inoperable or metastatic disease, treatment consists of hormonal therapy and possibly chemotherapy. The lifetime risk of being diagnosed with prostate cancer for men in the United States is approximately 16%, while the risk of dying of prostate cancer is 3%. African-American men have the highest prostate cancer risk in the United States; the incidence of prostate cancer is about 60% higher and the mortality rate is more than 2 to 3 times greater than that of white men. Autopsy results have suggested that about 30% of men age 55 and 60% of men age 80 who die of other causes have incidental prostate cancer, indicating that many cases of cancer are unlikely to pose a threat during a man's life expectancy.

**Grading**
The most widely used grading scheme for prostate cancer is the Gleason system. It is an architectural grading system ranging from 1 (well differentiated) to 5 (poorly differentiated); the score is the sum of the primary and secondary patterns. A Gleason score of 6 or less is low-grade prostate cancer that usually grows slowly; 7 is an intermediate grade; 8 to 10 is high-grade cancer that grows more quickly. A revised prostate cancer grading system has been adopted by the National Cancer Institute and the World Health Organization.

Numerous genetic alterations associated with development or progression of prostate cancer have been described, with the potential for the use of these molecular markers to improve the selection process of men who should undergo prostate biopsy or rebiopsy after an initial negative biopsy.

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 (SelectMDx, ConfirMDx), Innovative Diagnostics (phiTM), and ExoDx® Prostate (Exosome Diagnostics). 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 Progensa® PCA3 Assay (Gen-Probe; now Hologic) was approved by the FDA through the premarket approval process. The Progensa PCA3 Assay (Hologic Gen-Probe) has been approved by the FDA to aid in the decision for repeat biopsy in men 50 years or older who have had one or more negative prostate biopsies and for whom a repeat biopsy would be recommended based on current standard of care. The Progensa PCA3 Assay should not be used for men with atypical small acinar proliferation on their most recent biopsy.

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 prostatespecific 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.

For individuals who are being considered for an initial prostate biopsy 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 Mi-Prostate Score, SelectMDx for Prostate Cancer, ExoDx Prostate, Apifiny, PCA3 score), 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 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, a prostate-specific antigen 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 the effects of the technology on health outcomes.

For individuals who are being considered for repeat biopsy who receive testing for genetic and protein biomarkers of prostate cancer (eg, Gene Hypermethylation and ConfirmMDx test, Prostate Core Mitomics Test), 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 did not compare performance characteristics with standard risk prediction models. Direct evidence supporting clinical utility has not been shown. No data are currently available on physician decisions on rebiopsy or on the longer term clinical outcomes of men who did not have biopsy based on test results. The evidence is insufficient to determine the effects of the technology on health outcomes.

**BlueCHiP for Medicare**

Progensa PCA3 Assay, an FDA approved test by Gen-Probe Incorporated, is an mRNA expression assay used alone or in combination with other molecular tests for prostate cancer determination to identify patients with increased risk of prostate cancer. PCA3 may help to improve the specificity of prostate cancer detection providing additional information about the risk of prostate cancer over the use of the PSA test alone. Based on the ratio of PCA3 mRNA/PSA mRNA x1000, the PCA3 assay is performed on the first urine collected following an attentive digital rectal examination.

The 4Kscore combines data from serum levels of four kallikrein proteins (fPSA, tPSA, iPSA, human kalilkrein 2 (hK2)), along with clinical information (age, DRE, prior negative biopsy) to estimate the percent likelihood of HGPCa on biopsy using a proprietary algorithm. The 4K score is not FDA approved, but rather a Laboratory Developed Test (LDT) through one CLIA-accredited testing laboratory in Nashville, TN.

The Prostate Health Index (phi; Beckman Coulter) is an assay that combines results of 3 blood serum immunoassays (total PSA, free PSA, [-2]proPSA [p2PSA]) numerically to produce a "phi score." This score is calculated with the phi algorithm using the following formula: ([-2]proPSA/free PSA) x √total PSA. The phi score is indicated for men 50 years and older with above-normal total PSA readings between 4.0 ng/mL and 10 ng/mL who have had a negative DRE in order to distinguish prostate cancer from benign prostatic conditions.

## CODING

The following CPT codes are covered for BlueCHiP for Medicare and not medically necessary for Commercial Products.
CPT code 81313 is generally used to represent the Progensa® PCA3 Assay, but can also be used for non-brand name testing.
**81313** PCA3/KLK3 (prostate specific antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)

This code can be used for 4Kscore® Test.
**81539** Oncology (high-grade prostate cancer), biochemical assay of four proteins (total PSA, free PSA, intact PSA and human kallikrein 2 [hK2]) plus patient age, digital rectal examination status, and no history of positive prostate biopsy, utilizing plasma, prognostic algorithm reported as a probability score

The following CPT codes are not covered for BlueCHiP for Medicare and not medically necessary for Commercial products.

This code can be used for the ConfirmMDx® gene hypermethylation test.
**81551** Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy ~~(New Code Effective 1/1/2018)~~

The following Unlisted CPT code requires prior authorization for BlueCHiP for Medicare and Commercial Products. The code can be used for any test identified in this policy that does not have a specific CPT code.
**81479** Unlisted molecular pathology procedure

## RELATED POLICIES

Genetic Testing Services
Proprietary Laboratory Analyses (PLA)

## PUBLISHED

Provider Update, August 2019
Provider Update, April 2019
Provider Update, February 2019
Provider Update, May 2017
Provider Update, April 2016

## REFERENCES


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2. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD):

Biomarkers Testing (Prior to Initial Biopsy) for Prostate Cancer Diagnosis (L37733)
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