

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



**EFFECTIVE DATE:** 02|16|2016  
**POLICY LAST UPDATED:** 02|21|2017

## 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.

## MEDICAL CRITERIA

### BlueCHiP for Medicare

The ConfirmMDx<sup>®</sup> gene hypermethylation test is considered medically necessary when the following medical criteria is met:

1. Males aged 40 to 85 years old that have undergone a previous cancer-negative prostate biopsy within 24 months and are being considered for a repeat biopsy due to persistent or elevated cancer-risk factors, and
2. The previous negative prostate biopsy must have collected a minimum of 8 tissue cores (but not have received a saturation biopsy of > 24 tissue cores) and remaining FFPE tissue from all cores is available for testing, and
3. Minimum tissue volume criteria of 20 microns of prostate biopsy core tissue is available (40 microns preferable), and
4. Previous biopsy histology does not include a prior diagnosis of prostate cancer or cellular atypia suspicious for cancer (but may include the presence of high-grade prostatic intraepithelial neoplasia (HGPIN), proliferative inflammatory atrophy (PIA), or glandular inflammation), and
5. Patient is not being managed by active surveillance for low stage prostate cancer, and
6. Tissue was extracted using standard patterned biopsy core extraction (and not transurethral resection of the prostate (TURP)), and
7. Patient has not been previously tested by ConfirmMDx from the same biopsy samples or similar molecular test, and
8. Testing has been ordered by a physician who is certified in the MolDx approved ConfirmMDx Certification and Training Registry (CTR) program.

There is no specific CPT code for this test, so an Unlisted code should be used. See Coding Section.

### Commercial Products

Not applicable

## PRIOR AUTHORIZATION

### BlueCHiP for Medicare

Prior authorization is required for the ConfirmMDx gene hypermethylation test and is obtained via the online tool for participating providers.

### BlueCHiP for Medicare and Commercial Products

Prior authorization is required for BlueCHiP for Medicare and recommended for Commercial products for all tests in this policy filed with an Unlisted CPT code, and is obtained via the online tool for participating providers.

## POLICY STATEMENT

### BlueCHiP for Medicare

The ConfirmMDx gene hypermethylation test is considered medically necessary when the medical criteria above has been met.

The Progenesa PCA3 Assay is considered medically necessary and is covered without a prior authorization requirement.

### **Commercial Products**

Gene hypermethylation testing (ConfirmMDx) and PCA3 testing (Progenesa) are considered not medically necessary due to insufficient peer-reviewed medical literature proving the efficacy of the service.

### **BlueCHiP for Medicare and Commercial Products**

The following genetic, protein biomarkers and non-PSA testing for the diagnosis of prostate cancer are considered not medically necessary due to insufficient peer-reviewed medical literature proving the efficacy of the service.

- Kallikrein markers (e.g., 4Kscore™ Test)
- Metabolomic profiles (e.g., Prostarix™)
- *TMPRSS* fusion genes
- Candidate gene panels
- Mitochondrial DNA mutation testing (e.g., Prostate Core Mitomics Test™)
- Prostate Health Index (phi)
- non-PSA blood testing (e.g., APIFINY®)

Single nucleotide polymorphism (SNPs) testing for cancer risk assessment of prostate cancer is considered not medically necessary due to insufficient peer-reviewed medical literature proving the efficacy of the service.

### **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 coverage/benefits and limitations when services are not medically necessary.

### **BACKGROUND**

Prostate cancer is the second most common cancer in men, with a predicted 181,000 incidence cases and 26,100 deaths expected in United States in 2016. 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 cured 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%, but 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.

The purpose of genetic and protein biomarker testing for prostate cancer is to inform the selection of men who should undergo biopsy or repeat biopsy. Conventional decision-making tools for identifying men for prostate biopsy include serum prostate-specific antigen (PSA), digital rectal exam (DRE), and patient risk factors such as age, race, and family history of prostate cancer.

Commercially available tests to determine candidates for prostate biopsy or repeat biopsy include:

- 4Kscore® (OPKO Lab) Blood test that measures 4 prostate-specific kallikreins, which are combined into an algorithm to produce a score.
- Prostarix™ (Metabolon/Bostwick Laboratories) Urine test that measures several metabolites, which are combined with an algorithm to produce a score.
- Progenesa® (Hologic Gen-Probe, Many labs offer *PCA3* tests [eg, ARUP Laboratories, Mayo Medical Laboratories, and LabCorp]) Urine test that measures *PCA3* mRNA.
- ConfirmMDx® (MDxHealth) Measures hypermethylation of 3 genes in tissue sample.
- Prostate Health Index™ (phi) (Beckman Coulter) Blood test that combines several components of PSA with an algorithm to produce a score
- Prostate Core Mitomics Test™ (PCMT) (Mitomics [formerly Genesis Genomics]) Measures deletions in mitochondrial DNA by polymerase chain reaction in tissue sample

In addition to commercially available tests, single-nucleotide polymorphism 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.

For individuals for whom an initial prostate biopsy or a rebiopsy is being considered who receive genetic and protein biomarker testing, the evidence supporting clinical utility varies by test but has not been directly shown for any biomarker test. In general, performance of biomarker testing for predicting biopsy compared with clinical examination, including the ratio of free or unbound prostate-specific antigen (PSA) to total PSA, is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

### BlueCHiP for Medicare

ConfirmMDx assesses the methylation status of 3 biomarkers (GSTP1, RASSF1, APC) associated with prostate cancer. ConfirmMDx epigenetic assay for prostate cancer (MDxHealth, Irvine, CA) is intended to reduce unnecessary repeat prostate biopsies. While prospective evidence is currently being generated, retrospective evidence of clinical utility supports the potential value of this diagnostic test and serves as adequate evidence of likely clinical utility to support limited coverage.

Progenesa 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.

### 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 Progenesa® 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)

**0005U** Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score (New Code Effective 5/1/2017)

The following CPT code requires prior authorization for BlueCHiP for Medicare and Commercial products. The code can be used for ConfirmMDx® gene hypermethylation test, as well as any test identified in this policy that does not have a specific CPT code.

While the manufacturer of the non-PSA blood test APIFINY®, Armune Bioscience Inc., recommends using CPT codes 83516, 88184, 88185, providers should file with the following Unlisted CPT code.

**81479** Unlisted molecular pathology procedure

The following CPT code is considered not medically necessary for BlueCHiP for Medicare and Commercial products. 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 (Effective 1/1/2017)

## RELATED POLICIES

Genetic Testing Services

## PUBLISHED

Provider Update, May 2017

Provider Update, April 2016

## REFERENCES

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2. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article (LCA): MolDX: PROGENSA® PCA3 Assay Coding and Billing Guidelines (A54462)
3. Parekh DJ, Punnen S, Sjoberg DD, et al. A Multi-institutional Prospective Trial in the USA Confirms that the 4Kscore Accurately Identifies Men with High-grade Prostate Cancer. *Eur Urol*. Oct 27 2014. PMID 25454615
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