

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



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OVERVIEW

There are a variety of genetic and protein biomarkers 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. This policy will address these types of tests, as well as single nucleotide polymorphisms (SNPs) testing for cancer risk assessment.

MEDICAL CRITERIA

BlueCHiP for Medicare

The ConfirmMDx[®] 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.

Commercial Products

Not applicable

PRIOR AUTHORIZATION

BlueCHiP for Medicare and Commercial Products

Prior authorization is required for BlueCHiP for Medicare and recommended for Commercial products and is obtained via the online tool for participating providers for all tests identified in this policy. See the Related Policies section.

Note: PCA3 testing (Progenesa[®]), filed with CPT code 81313, does not require prior authorization.

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 and protein biomarkers 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™)

Single nucleotide polymorphisms (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/contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for applicable genetic testing coverage/benefits and limitations when services are not medically necessary.

BACKGROUND

Conventional decision-making tools for identifying men who should undergo 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. However, these screening tools lead to unnecessary prostate biopsies because of their lack of specificity and inability to discriminate low- from high-risk prostate cancer.

Prostate cancer is a complex, heterogeneous disease, in which numerous genetic alterations have been described, with the potential for use of these molecular markers to improve decision making as to whom should undergo prostate biopsy or rebiopsy after an initial negative biopsy.

For assessing future prostate cancer risk, numerous studies have demonstrated the association of many different SNPs with prostate cancer, and these studies generally show a modest degree of association with future risk for prostate cancer.

Commercially available tests include:

- 4Kscore Test (OPKO Lab), a blood test that measures 4 prostate-specific kallikreins, which are combined into an algorithm to decide whether a patient should proceed to prostate biopsy.
- Prostarix (Metabolon/Bostwick Laboratories) is a post-DRE urine test based on several metabolites and an algorithm to decide whether a patient should proceed to prostate biopsy or undergo repeat biopsy after an initial negative biopsy.
- The *PCA3* test is offered in the United States by a number of reference laboratories including ARUP, Mayo Medical Laboratories, and LabCorp. Reagents used in testing are developed by Gen-Probe.
- Prostate Core Mitomics Test (Mitomics [formerly Genesis Genomics]), which measures mitochondrial DNA mutations in a negative prostate biopsy to determine whether a patient should undergo repeat biopsy.

- ConfirmMDx (MDxHealth) measures hypermethylation of 3 genes in a negative prostate biopsy to determine whether a patient should undergo repeat biopsy.
- SNP 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 (deCode), as laboratory-developed tests.

Only 1 *PCA3* test has been submitted to the U.S. Food and Drug Administration (FDA) for premarket approval. The Gen-Probe Progenesa® *PCA3* Assay was approved by FDA on February 15, 2012, 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.

Other tests mentioned in this policy, if available, are offered as laboratory-developed tests under the Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet general regulatory standards of the Clinical Laboratory Improvement Act and must be licensed by CLIA for high-complexity testing.

Evidence on the clinical validity of genetic and protein biomarkers related to prostate cancer diagnosis is variable and incomplete, leaving considerable uncertainty regarding clinical performance characteristics such as sensitivity, specificity, and predictive value. Some tests show evidence for predictive ability in the diagnosis of prostate cancer; however, incremental accuracy in comparison with currently available tests has not been consistently demonstrated. In addition, these data do not demonstrate clinical utility, i.e., that using a test will change treatment decisions and improve subsequent outcomes. Therefore, use of genetic and protein biomarkers for the diagnosis of prostate cancer is considered not medically necessary.

Numerous studies have demonstrated the association of many different SNPs with prostate cancer, and these studies generally show a modest degree of association with future risk for prostate cancer. However, the clinical utility of these tests is uncertain; there is no evidence that information obtained from SNPs testing can be used to change management in ways that will improve outcomes. Therefore, SNPs testing for cancer risk assessment of prostate cancer is considered not medically necessary.

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 code is covered for BlueCHiP for Medicare and not medically necessary for Commercial products.

81313

The following CPT code requires prior authorization for BlueCHIP for Medicare and Commercial products.
81479

RELATED POLICIES

Preauthorization via Web-Based Tool for Genetic Testing

PUBLISHED

Provider Update, April 2016

REFERENCES

1. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: CONFIRMMDX Epigenetic Molecular Assay (L35796)
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
4. Sreekumar A, Poisson LM, Rajendiran TM, et al. Metabolomic profiles delineate potential role for sarcosine in prostate cancer progression. *Nature.* Feb 12 2009;457(7231):910-914. PMID 19212411
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6. van Gils MP, Cornel EB, Hessels D, et al. Molecular PCA3 diagnostics on prostatic fluid. *Prostate.* Jun 1 2007;67(8):881-887. PMID 17440939
7. Groskopf J, Aubin SM, Deras IL, et al. APTIMA PCA3 molecular urine test: development of a method to aid in the diagnosis of prostate cancer. *Clin Chem.* Jun 2006;52(6):1089-1095. PMID 16627561
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