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: 12|18|2018

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® 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.

Prior to 1/1/2018 there is no specific CPT code for this test, so an Unlisted code should be used. Effective 1/1/2018, there is a specific CPT code for this testing. Please see Coding Section for details.

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

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

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:

- Kallikrein markers (eg, 4Kscore® Test)
- Prostate Health Index (phi)
- 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, Apifiny)
- TMPRSS:ERG fusion genes
- 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
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- PCA3 testing (eg, Progensa PCA3 Assay)
- TMPRSS:ERG fusion genes
- Gene hypermethylation testing (eg, ConfirmMDx)
- Mitochondrial DNA variant testing (eg, Prostate Core Mitomics Test)
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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

ConfirmM Dx 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.

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.

CODING

The following CPT code is 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)

The following CPT code requires prior authorization for BlueCHiP for Medicare and is considered 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

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

This code can be used for ExoDx® Prostate IntelliScore.
0005U Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score

This code can be used for Apifiny®.
0021U Oncology (prostate), detection of 8 autoantibodies (ARF 6, NKX3-1, 5'- UTR-BMI1, CEP 164, 3'-UTRRopporin, Desmocollin, AURKAIP-1, CSNK2A2), multiplexed immunoassay and flow cytometry serum, algorithm reported as risk score

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

PUBLISHED
Provider Update, February 2019
Provider Update, May 2017
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. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. Jan 2017;67(1):7-30. PMID 28055103
4. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014. Bethesda, MD: National Cancer Institute; 2017.
5. Odedina FT, Akinremi TO, Chinegwundoh F, et al. Prostate cancer disparities in Black men of African descent: a comparative literature review of prostate cancer burden among Black men in the United States, Caribbean, United Kingdom, and West Africa. Infect Agent Cancer. Feb 10 2009;4 Suppl 1:S2. PMID 19208207
6. Bell KJ, Del Mar C, Wright G, et al. Prevalence of incidental prostate cancer: A systematic review of autopsy studies. Int J Cancer. Oct 1 2015;137(7):1749-1757. PMID 25821151
7. Gleason DF. Classification of prostatic carcinomas. Cancer Chemother Rep. Mar 1966;50(3):125-128. PMID 5948714

8. National Cancer Institute. SEER Database. 2018; https://seer.cancer.gov/seerinquiry/index.php?page=view&id=20170036&type=q. Accessed October 26, 2018.
9. Hoogendam A, Buntinx F, de Vet HC. The diagnostic value of digital rectal examination in primary care screening for prostate cancer: a meta-analysis. Fam Pract. Dec 1999;16(6):621-626. PMID 10625141
10. Gosselaar C, Roobol MJ, Roemeling S, et al. The role of the digital rectal examination in subsequent screening visits in the European Randomized Study of Screening for Prostate Cancer (ERSPC), Rotterdam. Eur Urol. Sep 2008;54(3):581-588. PMID 18423977
11. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med. May 27 2004;350(22):2239-2246. PMID 15163773
12. Catalona WJ, Smith DS, Ratliff TL, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. N Engl J Med. Apr 25 1991;324(17):1156-1161. PMID 1707140
13. Aus G, Bergdahl S, Lodding P, et al. Prostate cancer screening decreases the absolute risk of being diagnosed with advanced prostate cancer--results from a prospective, population-based randomized controlled trial. Eur Urol. Mar 2007;51(3):659-664. PMID 16934392
14. Buzzoni C, Auvinen A, Roobol MJ, et al. Metastatic prostate cancer incidence and prostate-specific antigen testing: new insights from the European randomized study of screening for prostate cancer. Eur Urol. Nov 2015;68(5):885-890. PMID 25791513
15. Arnsrud Godtman R, Holmberg E, Lilja H, et al. Opportunistic testing versus organized prostate-specific antigen screening: outcome after 18 years in the Goteborg randomized population-based prostate cancer screening trial. Eur Urol. Sep 2015;68(3):354-360. PMID 25556937
16. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. Lancet Oncol. Aug 2010;11(8):725-732. PMID 20598634
17. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. Mar 26 2009;360(13):1320-1328. PMID 19297566
18. Wolf AM, Wender RC, Etzioni RB, et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. CA Cancer J Clin. Mar-Apr 2010;60(2):70-98. PMID 20200110
19. Rosario DJ, Lane JA, Metcalfe C, et al. Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within ProtecT study. BMJ. Jan 09 2012;344:d7894. PMID 22232535
20. Liss M, Ehdaie B, Loeb S, et al. The Prevention and Treatment of the More Common Complications Related to Prostate Biopsy Update. 2012; updated 2016; https://www.auanet.org/guidelines/prostate-needle-biopsycomplications. Accessed October 19, 2018.
21. Lavallee LT, Binette A, Witiuk K, et al. Reducing the harm of prostate cancer screening: repeated prostatespecific antigen testing. Mayo Clin Proc. Jan 2016;91(1):17-22. PMID 26688045
22. Mackinnon AC, Yan BC, Joseph LJ, et al. Molecular biology underlying the clinical heterogeneity of prostate cancer: an update. Arch Pathol Lab Med. Jul 2009;133(7):1033-1040. PMID 19642730
23. Ruiz-Aragon J, Marquez-Pelaez S. [Assessment of the PCA3 test for prostate cancer diagnosis: a systematic review and meta-analysis] [Spanish]. Actas Urol Esp. Apr 2010;34(4):346-355. PMID 20470697
24. Partin AW, Brawer MK, Subong EN, et al. Prospective evaluation of percent free-PSA and complexed-PSA for early detection of prostate cancer. Prostate Cancer Prostatic Dis. Jun 1998;1(4):197-203. PMID 12496895
25. Thompson IM, Ankerst DP, Chi C, et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. J Natl Cancer Inst. Apr 19 2006;98(8):529-534. PMID 16622122
26. van Vugt HA, Roobol MJ, Kranse R, et al. Prediction of prostate cancer in unscreened men: external validation of a risk calculator. Eur J Cancer. Apr 2011;47(6):903-909. PMID 21163642

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