BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

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

Effective Policy Date: April 1, 2021

Original Policy Date: December 2011

Related Policies:

2.04.111 - Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management
7.01.152 - Magnetic Resonance Imaging-Targeted Biopsy of the Prostate

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

Description

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. Magnetic resonance imaging-targeted biopsy of suspicious lesions is assessed in evidence review 7.01.152.

OBJECTIVE

The objective of this evidence review is to determine whether testing for genetic and protein prostate biomarkers improves the net health outcome in men for whom an initial prostate biopsy or a repeat prostate biopsy is being considered.

POLICY STATEMENT

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

- Kallikrein markers (eg, 4Kscore Test)
- *HOXC6* and *DLX1* testing (eg, SelectMDx)
- 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
- Gene hypermethylation testing (eg, ConfirmMDx)
- Mitochondrial DNA variant testing (eg, Prostate Core Mitomics Test)
- Candidate gene panels.

PCA3 testing (eg, Progensa PCA3 Assay) testing and prostate Health Index (phi) (eg, pro PSA) 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

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, 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.

FDA REGULATORY STATUS

Some Plans may have contract or benefit exclusions for genetic testing.

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 (SelectMDx, ConfirMDx), Innovative Diagnostics (phi™), 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 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 the current standard of care. The Progensa PCA3 Assay should not be used for men with atypical small acinar proliferation on their most recent biopsy. FDA product code: OYM.

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 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.

RATIONALE

Summary of Evidence

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 the 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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Urological Association et al

The American Urological Association (AUA, 2013; confirmed 2018) published guidelines on the early detection of prostate cancer.[67,]The AUA concluded that:

"the literature supporting the efficacy of digital rectal exam (DRE), PSA [prostate-specific antigen] derivatives and isoforms (e.g. free PSA, -2proPSA, prostate health index, hK2, PSA velocity or PSA doubling time) and novel urinary markers and biomarkers (e.g. PCA3) for screening with the goal of reducing prostate cancer mortality provide limited evidence to draw conclusions. While some data suggest use of these secondary screening tools may reduce unnecessary biopsies (i.e. reduce harms) while maintaining the ability to detect aggressive prostate cancer (i.e. maintain the benefits of PSA screening), more research is needed to confirm this."

National Comprehensive Cancer Network

The NCCN guidelines (v.2.2020) recommend that any man with a PSA level greater than 3 ng/mL undergo workup for benign disease, repeat PSA, and digital rectal examination.[68,] The guidelines also recommend consideration of biomarkers that improve the specificity of screening that includes percent free PSA, with consideration of phi, SelectMDx, ExoDx Prostate (IntelliScore) (EPI), or 4Kscore in patients with a PSA level greater than 3 ng/mL who have not yet had a biopsy. Percent free PSA, phi, 4Kscore, PCA3, ExoDx Prostate (IntelliScore) (EPI), and ConfirmMDx might be considered in men who had a negative biopsy but are thought to be at higher risk (category 2A evidence). The NCCN noted that these tests may be especially useful in men with PSA levels between 3 ng/mL and 10 ng/mL. The NCCN considers the Mi-Prostate Score (MiPS) to be investigational at the time of the update. The status of SelectMDx was changed from investigational in 2019 to potentially informative in the 2020 update.

National Institute for Health and Care Excellence

In 2019, the National Institute for Health and Care Excellence (NICE) did not recommend the Progensa PCA3 Assay or the phi test for use in men with suspicion of prostate cancer who had a negative or inconclusive prostate biopsy. [69,]

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (2018) updated recommendations for prostate cancer screening. Genetic and protein biomarkers addressed in this evidence review, including *PCA3*, were not mentioned. [70,]

The U.S. Preventive Services Task Force advises individualized decision making about screening for prostate cancer after discussion with a clinician for men ages 55 to 69 (C recommendation) and recommends against PSA-based screening in men 70 and older (D recommendation).

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. Several MolDx carriers have positive coverage for the ConfirmMDx Epigenetic Molecular Assay and the PCA3 assay. At least 1 LCD will cover percent free PSA, phi, or 4K score once prior to initial biopsy in men who meet criteria.

REFERENCES

1. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014. Bethesda, MD: National Cancer Institute; 2017.
2. 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
3. Bell KJ, Del Mar C, Wright G, et al. Prevalence of incidental prostate cancer: A systematic review of autopsy studies. Int J Cancer. Oct 01 2015; 137(7): 1749-57. PMID 25821151
4. Gleason DF. Classification of prostatic carcinomas. Cancer Chemother Rep. Mar 1966; 50(3): 125-8. PMID 5948714
5. National Cancer Institute. SEER Database. 2018; https://seer.cancer.gov/seerinquiry/index.php?page=view&id=20170036&type=q. Accessed October 26, 2018.
6. Blue Cross and Blue Shield Technology Evaluation Center (TEC). Special report: recent developments in prostate cancer genetics and genetic testing. TEC Assessments. 2008;Volume 23:Tab 7.
7. 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): 621-6. PMID 10625141
8. 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): 581-8. PMID 18423977
9. 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): 2239-46. PMID 15163773
10. 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): 1156-61. PMID 1707140
11. 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): 659-64. PMID 16934392
12. 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): 885-90. PMID 25791513
13. 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): 354-60. PMID 25556937
14. 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): 725-32. PMID 20598634
15. 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): 1320-8. PMID 19297566
16. 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
17. 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
18. 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-biopsy- complications. Accessed October 23, 2017.
19. Lavallee LT, Binette A, Witiuk K, et al. Reducing the Harm of Prostate Cancer Screening: Repeated Prostate-Specific Antigen Testing. Mayo Clin Proc. Jan 2016; 91(1): 17-22. PMID 26688045
20. Ruiz-Aragon J, Marquez-Pelaez S. [Assessment of the PCA3 test for prostate cancer diagnosis: a systematic review and meta-analysis]. Actas Urol Esp. Apr 2010; 34(4): 346-55. PMID 20470697
21. 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): 1033-40. PMID 19642730

22. 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
23. 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): 529-34. PMID 16622122
24. 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): 903-9. PMID 21163642
25. Rosenkrantz AB, Verma S, Choyke P, et al. Prostate Magnetic Resonance Imaging and Magnetic Resonance Imaging Targeted Biopsy in Patients with a Prior Negative Biopsy: A Consensus Statement by AUA and SAR. J Urol. Dec 2016; 196(6): 1613-1618. PMID 27320841
26. Russo GI, Regis F, Castelli T, et al. A Systematic Review and Meta-analysis of the Diagnostic Accuracy of Prostate Health Index and 4-Kallikrein Panel Score in Predicting Overall and High-grade Prostate Cancer. Clin Genitourin Cancer. Aug 2017; 15(4): 429-439.e1. PMID 28111174
27. 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. Sep 2015; 68(3): 464-70. PMID 25454615
28. Stattin P, Vickers AJ, Sjoberg DD, et al. Improving the Specificity of Screening for Lethal Prostate Cancer Using Prostate-specific Antigen and a Panel of Kallikrein Markers: A Nested Case-Control Study. Eur Urol. Aug 2015; 68(2): 207-13. PMID 25682340
29. Loeb S, Shin SS, Broyles DL, et al. Prostate Health Index improves multivariable risk prediction of aggressive prostate cancer. BJU Int. Jul 2017; 120(1): 61-68. PMID 27743489
30. Konety B, Zappala SM, Parekh DJ, et al. The 4Kscore(R) Test Reduces Prostate Biopsy Rates in Community and Academic Urology Practices. Rev Urol. 2015; 17(4): 231-40. PMID 26839521
31. Pecoraro V, Roli L, Plebani M, et al. Clinical utility of the (-2)proPSA and evaluation of the evidence: a systematic review. Clin Chem Lab Med. Jul 01 2016; 54(7): 1123-32. PMID 26609863
32. Catalona WJ, Partin AW, Sanda MG, et al. A multicenter study of [-2]pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/ml prostate specific antigen range. J Urol. May 2011; 185(5): 1650-5. PMID 21419439
33. Tosoian JJ, Druskin SC, Andreas D, et al. Use of the Prostate Health Index for detection of prostate cancer: results from a large academic practice. Prostate Cancer Prostatic Dis. Jun 2017; 20(2): 228-233. PMID 28117387
34. White J, Shenoy BV, Tutrone RF, et al. Clinical utility of the Prostate Health Index (phi) for biopsy decision management in a large group urology practice setting. Prostate Cancer Prostatic Dis. Apr 2018; 21(1): 78-84. PMID 29158509
35. Sanda MG, Feng Z, Howard DH, et al. Association Between Combined TMPRSS2:ERG and PCA3 RNA Urinary Testing and Detection of Aggressive Prostate Cancer. JAMA Oncol. Aug 01 2017; 3(8): 1085-1093. PMID 28520829
36. Tomlins SA, Day JR, Lonigro RJ, et al. Urine TMPRSS2:ERG Plus PCA3 for Individualized Prostate Cancer Risk Assessment. Eur Urol. Jul 2016; 70(1): 45-53. PMID 25985884
37. Ankerst DP, Goros M, Tomlins SA, et al. Incorporation of Urinary Prostate Cancer Antigen 3 and TMPRSS2:ERG into Prostate Cancer Prevention Trial Risk Calculator. Eur Urol Focus. Jan 2019; 5(1): 54-61. PMID 29422418
38. Newcomb LF, Zheng Y, Faino AV, et al. Performance of PCA3 and TMPRSS2:ERG urinary biomarkers in prediction of biopsy outcome in the Canary Prostate Active Surveillance Study (PASS). Prostate Cancer Prostatic Dis. Sep 2019; 22(3): 438-445. PMID 30664734
39. Van Neste L, Hendriks RJ, Dijkstra S, et al. Detection of High-grade Prostate Cancer Using a Urinary Molecular Biomarker-Based Risk Score. Eur Urol. Nov 2016; 70(5): 740-748. PMID 27108162
40. Haese A, Trooskens G, Steyaert S, et al. Multicenter Optimization and Validation of a 2-Gene mRNA Urine Test for Detection of Clinically Significant Prostate Cancer before Initial Prostate Biopsy. J Urol. Aug 2019; 202(2): 256-263. PMID 31026217
41. McKiernan J, Donovan MJ, O'Neill V, et al. A Novel Urine Exosome Gene Expression Assay to Predict High-grade Prostate Cancer at Initial Biopsy. JAMA Oncol. Jul 01 2016; 2(7): 882-9. PMID 27032035
42. Tutrone R, Donovan MJ, Torkler P, et al. Clinical utility of the exosome based ExoDx Prostate(IntelliScore) EPI test in men presenting for initial Biopsy with a PSA 2-10 ng/mL. Prostate Cancer Prostatic Dis. Dec 2020; 23(4): 607-614. PMID 32382078
43. Schipper M, Wang G, Giles N, et al. Novel prostate cancer biomarkers derived from autoantibody signatures. Transl Oncol. Apr 2015; 8(2): 106-11. PMID 25926076
44. Wysock JS, Becher E, Persily J, et al. Concordance and Performance of 4Kscore and SelectMDx for Informing Decision to Perform Prostate Biopsy and Detection of Prostate Cancer. Urology. Jul 2020; 141: 119-124. PMID 32294481
45. Cui Y, Cao W, Li Q, et al. Evaluation of prostate cancer antigen 3 for detecting prostate cancer: a systematic review and meta-analysis. Sci Rep. May 10 2016; 6: 25776. PMID 27161545
46. Rodriguez SVM, Garcia-Perdomo HA. Diagnostic accuracy of prostate cancer antigen 3 (PCA3) prior to first prostate biopsy: A systematic review and meta-analysis. Can Urol Assoc J. May 2020; 14(5): E214-E219. PMID 31793864
47. Nicholson A, Mahon J, Boland A, et al. The clinical effectiveness and cost-effectiveness of the PROGENSA(R) prostate cancer antigen 3 assay and the Prostate Health Index in the diagnosis of prostate cancer: a systematic review and economic evaluation. Health Technol Assess. Oct 2015; 19(87): i-xxxi, 1-191. PMID 26507078

48. Wei JT, Feng Z, Partin AW, et al. Can urinary PCA3 supplement PSA in the early detection of prostate cancer?. J Clin Oncol. Dec 20 2014; 32(36): 4066-72. PMID 25385735
49. Hennenlotter J, Neumann T, Alperowitz S, et al. Age-Adapted Prostate Cancer Gene 3 Score Interpretation - Suggestions for Clinical Use. Clin Lab. Mar 01 2020; 66(3). PMID 32162868
50. Vickers AJ, Gupta A, Savage CJ, et al. A panel of kallikrein marker predicts prostate cancer in a large, population-based cohort followed for 15 years without screening. Cancer Epidemiol Biomarkers Prev. Feb 2011; 20(2): 255-61. PMID 21148123
51. Ruffion A, Devonec M, Champetier D, et al. PCA3 and PCA3-based nomograms improve diagnostic accuracy in patients undergoing first prostate biopsy. Int J Mol Sci. Aug 29 2013; 14(9): 17767-80. PMID 23994838
52. Ruffion A, Perrin P, Devonec M, et al. Additional value of PCA3 density to predict initial prostate biopsy outcome. World J Urol. Aug 2014; 32(4): 917-23. PMID 24500192
53. Merdan S, Tomlins SA, Barnett CL, et al. Assessment of long-term outcomes associated with urinary prostate cancer antigen 3 and TMPRSS2:ERG gene fusion at repeat biopsy. Cancer. Nov 15 2015; 121(22): 4071-9. PMID 26280815
54. Djavan B, Waldert M, Zlotta A, et al. Safety and morbidity of first and repeat transrectal ultrasound guided prostate needle biopsies: results of a prospective European prostate cancer detection study. J Urol. Sep 2001; 166(3): 856-60. PMID 11490233
55. Lujan M, Paez A, Santonja C, et al. Prostate cancer detection and tumor characteristics in men with multiple biopsy sessions. Prostate Cancer Prostatic Dis. 2004; 7(3): 238-42. PMID 15289810
56. Stewart GD, Van Neste L, Delvenne P, et al. Clinical utility of an epigenetic assay to detect occult prostate cancer in histopathologically negative biopsies: results of the MATLOC study. J Urol. Mar 2013; 189(3): 1110-6. PMID 22999998
57. Partin AW, Van Neste L, Klein EA, et al. Clinical validation of an epigenetic assay to predict negative histopathological results in repeat prostate biopsies. J Urol. Oct 2014; 192(4): 1081-7. PMID 24747657
58. Waterhouse RL, Van Neste L, Moses KA, et al. Evaluation of an Epigenetic Assay for Predicting Repeat Prostate Biopsy Outcome in African American Men. Urology. Jun 2019; 128: 62-65. PMID 29660369
59. Van Neste L, Partin AW, Stewart GD, et al. Risk score predicts high-grade prostate cancer in DNA-methylation positive, histopathologically negative biopsies. Prostate. Sep 2016; 76(12): 1078-87. PMID 27121847
60. Partin AW, VAN Criekinge W, Trock BJ, et al. CLINICAL EVALUATION OF AN EPIGENETIC ASSAY TO PREDICT MISSED CANCER IN PROSTATE BIOPSY SPECIMENS. Trans Am Clin Climatol Assoc. 2016; 127: 313-327. PMID 28066067
61. Food and Drug Administration. Summary of Safety and Effectiveness Data. PMA P090026. Quantitative test for determination of [-2]proPSA levels. Silver Spring, MD: Food and Drug Administration; 2012.
62. Aubry W, Lieberthal R, Willis A, et al. Budget impact model: epigenetic assay can help avoid unnecessary repeated prostate biopsies and reduce healthcare spending. Am Health Drug Benefits. Jan 2013; 6(1): 15-24. PMID 24991343
63. Robinson K, Creed J, Reguly B, et al. Accurate prediction of repeat prostate biopsy outcomes by a mitochondrial DNA deletion assay. Prostate Cancer Prostatic Dis. Jun 2010; 13(2): 126-31. PMID 20084081
64. Legisi L, DeSa E, Qureshi MN. Use of the Prostate Core Mitomic Test in Repeated Biopsy Decision-Making: Real-World Assessment of Clinical Utility in a Multicenter Patient Population. Am Health Drug Benefits. Dec 2016; 9(9): 497-502. PMID 28465777
65. Leyten GH, Hessels D, Smit FP, et al. Identification of a Candidate Gene Panel for the Early Diagnosis of Prostate Cancer. Clin Cancer Res. Jul 01 2015; 21(13): 3061-70. PMID 25788493
66. Xiao K, Guo J, Zhang X, et al. Use of two gene panels for prostate cancer diagnosis and patient risk stratification. Tumour Biol. Aug 2016; 37(8): 10115-22. PMID 26820133
67. American Urological Association. Detection of prostate cancer. 2013; http://www.auanet.org/education/guidelines/prostate-cancer-detection.cfm. Accessed August 17, 2020.
68. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: prostate cancer early detection. http://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NCCN clinical practice guidelines in oncology: prostate cancer early detection V.2.2019. National Comprehensive Cancer Network rights reserved. Accessed October 14, 2020.
69. National Institute for Health and Care Excellence (NICE). Prostate cancer: diagnosis and management [NG131]. 2019; https://www.nice.org.uk/guidance/ng131/chapter/Recommendations#assessment-and-diagnosis. Accessed October 14, 2020.
70. U. S. Preventive Services Task Force. Prostate Cancer: Screening. 2018; https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/prostate-cancer-screening1. Accessed October 19, 2020.

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2011	New policy	
June 2013	Replace policy	Policy updated with literature review, references added, policy statement changed PCA3 from investigational to not medically necessary.
June 2014	Replace 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	Replace 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	Replace 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 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.
March 2019	Replace policy	Policy updated with literature review through September 4, 2018; references 6, 32-34, 36-38, 45, 50, 55, and 60 added. The SelectMDx, ExoDx Prostate (IntelliScore), and Apifiny tests added as investigational.
March 2020	Replace policy	Policy updated with literature review through September 18, 2019; references added. Policy statements unchanged.
March 2021	Replace policy	Policy updated with literature review through October 16, 2020; references added. Policy statements unchanged.