MASSACHUSETTS

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Medical Policy

Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

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Policy Number: 336

BCBSA Reference Number: 2.04.33 (For Plan internal use only)

Related Policies

N/A

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

The following biomarkers for the diagnosis of prostate cancer are considered **INVESTIGATIONAL**:

- Kallikrein markers (eg, 4Kscore™ Test)
- Prostate Health Index (phi)
- Autoantibodies ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, and CSNK2A2 (eg, Apifiny)

Single-nucleotide variant testing for cancer risk assessment of prostate cancer is considered **INVESTIGATIONAL**.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	This is **not** a covered service.
Commercial PPO and Indemnity	This is **not** a covered service.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity, Medicare Advantage HMO and Medicare Advantage PPO Members:

CPT Codes

CPT codes:	Code Description
0021U	Oncology (prostate), detection of 8 autoantibodies (ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2), multiplexed immunoassay and flow cytometry serum, algorithm reported as risk score

The following CPT code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

CPT Codes

CPT codes:	Code Description
81539	Oncology (high-grade prostate cancer), biochemical assay of four proteins (Total PSA, Free PSA, Intact PSA, and human kallikrein-2 [hK2]), utilizing plasma or serum, prognostic algorithm reported as a probability score

The ~~above~~ medical necessity criteria MUST be met for the following code to be covered for Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
81539	Oncology (high-grade prostate cancer), biochemical assay of four proteins (Total PSA, Free PSA, Intact PSA, and human kallikrein-2 [hK2]), utilizing plasma or serum, prognostic algorithm reported as a probability score

Description

PROSTATE CANCER

Prostate cancer is the most common cancer, and the second most common cause of cancer death in men. 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 U.S. is approximately 16%, while the risk of dying of prostate cancer is 3%.[1,] African American men have the highest prostate cancer risk in the U.S.; 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.[2,] Autopsy results have suggested that about 30% of men over the age of 55 and 60% of men over the age of 80 who die of other causes have incidental prostate cancer[3,], 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.[4,] It is an architectural grading system ranging from 1 (well-differentiated) to 5 (undifferentiated); 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.[5,] A cross-walk of these grading systems is shown in Table 1.

Table 1. Prostate Cancer Grading Systems

Grade Group	Gleason Score (Primary and Secondary Pattern)	Cells
1	6 or less	Well differentiated (low grade)
2	7 (3 + 4)	Moderately differentiated (moderate grade)
3	7 (4 + 3)	Poorly differentiated (high grade)
4	8	Undifferentiated (high grade)
5	9-10	Undifferentiated (high grade)

Summary

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.

For individuals who are being considered for an initial prostate 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 MyProstateScore, SelectMDx for Prostate Cancer, ExoDx Prostate, Apifiny, PCA3 score, and PanGIA Prostate), 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 (DRE), a prostate-specific antigen (PSA) 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 that the technology results in an improvement in the net health outcome.

For individuals who are being considered for repeat biopsy who receive testing for genetic and protein biomarkers of prostate cancer (eg, PCA3 score, Gene Hypermethylation and ConfirmMDx test, Prostate Core Mitomics Test, MyProstate Score), 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 do not compare performance characteristics with standard risk prediction models. Direct evidence supporting clinical utility has not been shown. No data are currently available on the longer-term clinical outcomes of the use of genetic and protein biomarkers to decide on repeat prostate biopsy, The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Policy History

Date	Action
1/2024	Annual policy review. Description, summary, and references updated. Policy statement unchanged.
7/2023	Clarified coding information.

3/2023	AIM Specialty Health changed its name to Carelon Medical Benefits Management.
1/2023	Annual policy review. Description, summary, and references updated. Policy statement unchanged.
1/2021	Medicare information removed. See MP #132 Medicare Advantage Management for local coverage determination and national coverage determination reference.
4/2019	Annual policy review. New investigational tests described. Clarified coding information. Effective 4/1/2019.
1/2019	Ongoing investigational indications described. For coverage information on the following tests, see medical policy #954 Carelon Genetic Testing Management Program and medical policy #957, Carelon Genetic Testing Management Program CPT and HCPCS Codes. Effective 1/1/2019. Clarified coding information. • Genetic Testing for TMPRSS Fusion Genes in Prostate Cancer (using PCR) • Genetic Testing for Mitochondrial DNA Mutation Testing (eg, Prostate Core Mitomics Test™) • Candidate Gene Panels • PCA3 Testing • Gene Hypermethylation Testing (eg, ConfirmMDx®).
7/2018	Clarified coding information.
4/2018	Annual policy review. Prostarix test removed from policy and policy statement. Effective 4/1/2018.
1/2018	Clarified coding information.
3/2017	Annual medical policy review. New investigational indications described. Clarified coding information. Effective 3/1/2017.
1/2017	Clarified coding information for the 2017 code changes.
1/2016	Clarified coding information.
9/2015	Annual medical policy review. New investigational indications described; title changed. Effective 9/1/2015.
1/2015	Clarified coding information.
7/2014	Annual policy review. New references added.
3/2014	Annual policy review. New references added.
5/2013	Annual policy review. New references added.
4/2012	Updated to add new non-covered HCPCS code S3721.
12/1/2011	New medical policy describing ongoing non-coverage. Effective 12/01/2011.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

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(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. https://seer.cancer.gov/seerinquiry/index.php?page=view&id=20170036&type=q. Accessed September 19, 2022.
6. 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
7. 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
8. 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
9. 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
10. 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
11. 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
12. Arnsrud Godtman R, Holmberg E, Lilja H, et al. Opportunistic testing versus organized prostate-specific antigen screening: outcome after 18 years in the Göteborg randomized population-based prostate cancer screening trial. Eur Urol. Sep 2015; 68(3): 354-60. PMID 25556937
13. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. Lancet Oncol. Aug 2010; 11(8): 725-32. PMID 20598634
14. Schröder 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
15. 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. 2010; 60(2): 70-98. PMID 20200110
16. 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
17. 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-and-quality/guidelines/best-practice-statements-and-whitepapers/prostate-needle-biopsy-complications. Accessed September 19, 2022.
18. Lavallée 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
19. Ruiz-Aragón J, Márquez-Peláez 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
20. 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
21. 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
22. 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
23. 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
24. 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
25. Mi C, Bai L, Yang Y, et al. 4Kscore diagnostic value in patients with high-grade prostate cancer using cutoff values of 7.5% to 10%: A meta-analysis. Urol Oncol. Jun 2021; 39(6): 366.e1-366.e10. PMID 33685800

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. Punnen S, Freedland SJ, Polascik TJ, et al. A Multi-Institutional Prospective Trial Confirms Noninvasive Blood Test Maintains Predictive Value in African American Men. J Urol. Jun 2018; 199(6): 1459-1463. PMID 29223389
29. Bhattu AS, Zappala SM, Parekh DJ, et al. A 4Kscore Cut-off of 7.5% for Prostate Biopsy Decisions Provides High Sensitivity and Negative Predictive Value for Significant Prostate Cancer. Urology. Feb 2021; 148: 53-58. PMID 33217456
30. 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
31. 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
32. Konety B, Zappala SM, Parekh DJ, et al. The 4Kscore® Test Reduces Prostate Biopsy Rates in Community and Academic Urology Practices. Rev Urol. 2015; 17(4): 231-40. PMID 26839521
33. 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
34. Anyango R, Ojwando J, Mwita C, et al. Diagnostic accuracy of [-2]proPSA versus Gleason score and Prostate Health Index versus Gleason score for the determination of aggressive prostate cancer: a systematic review. JBI Evid Synth. Jun 2021; 19(6): 1263-1291. PMID 33741840
35. 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
36. 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
37. 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
38. 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
39. 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
40. 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
41. Tosoian JJ, Trock BJ, Morgan TM, et al. Use of the MyProstateScore Test to Rule Out Clinically Significant Cancer: Validation of a Straightforward Clinical Testing Approach. J Urol. Mar 2021; 205(3): 732-739. PMID 33080150
42. 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
43. 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
44. 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
45. Hendriks RJ, van der Leest MMG, Israël B, et al. Clinical use of the SelectMDx urinary-biomarker test with or without mpMRI in prostate cancer diagnosis: a prospective, multicenter study in biopsy-naïve men. Prostate Cancer Prostatic Dis. Dec 2021; 24(4): 1110-1119. PMID 33941866

46. 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
47. 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
48. Tutrone R, Lowentritt B, Neuman B, et al. ExoDx prostate test as a predictor of outcomes of high-grade prostate cancer - an interim analysis. Prostate Cancer Prostatic Dis. Sep 2023; 26(3): 596-601. PMID 37193776
49. 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
50. 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
51. 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
52. Rodríguez SVM, García-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
53. Nicholson A, Mahon J, Boland A, et al. The clinical effectiveness and cost-effectiveness of the PROGENSA® 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
54. 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
55. 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
56. 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
57. 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
58. 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
59. 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
60. 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
61. 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
62. 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
63. 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
64. 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
65. 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

66. 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
67. 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.
68. 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
69. 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
70. 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
71. 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
72. 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
73. Tosoian JJ, Sessine MS, Trock BJ, et al. MyProstateScore in men considering repeat biopsy: validation of a simple testing approach. Prostate Cancer Prostatic Dis. Sep 2023; 26(3): 563-567. PMID 36585434
74. Wei JT, Barocas D, Carlsson S, et al. Early Detection of Prostate Cancer: AUA/SUO Guideline Part II: Considerations for a Prostate Biopsy. J Urol. Jul 2023; 210(1): 54-63. PMID 37096575
75. Wei JT, Barocas D, Carlsson S, et al. Early Detection of Prostate Cancer: AUA/SUO Guideline Part I: Prostate Cancer Screening. J Urol. Jul 2023; 210(1): 46-53. PMID 37096582
76. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: prostate cancer early detection V.1.2023. https://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf. Accessed September 25, 2023.
77. National Institute for Health and Care Excellence (NICE). Prostate cancer: diagnosis and management [NG131]. 2019. Updated December 15, 2021; https://www.nice.org.uk/guidance/ng131/chapter/Recommendations#assessment-and-diagnosis. Accessed September 25, 2023.
78. U. S. Preventive Services Task Force. Prostate Cancer: Screening. 2018; https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/prostate-cancer-screening1. Accessed September 26, 2023.