



Policy

Medical Policy Manual

Approved Revision: Do Not Implement Until 12/31/26

Prostate Cancer Biomarkers Testing

page 1

DESCRIPTION

Biomarkers are "chemicals" found in blood, urine or tissue that can indicate both normal and abnormal processes. One of the most well-known biomarker tests is the PSA, which detects abnormally high blood levels of prostate specific antigen to screen for cancer. Although PSA testing can help detect prostate cancer at an early stage, having an elevated PSA (> 3 mg/ml) does not mean that an individual has cancer.

The use of PSA testing has traditionally focused on the amount of PSA found circulating in the free or unbound (fPSA) form. When expressed as a ratio of total prostate-specific antigen (tPSA) to free prostate-specific antigen, it can improve early detection, staging and monitoring of prostate cancer. The proportion of free PSA to total PSA, using a cut-off of 25%, is more sensitive and specific than the traditional PSA test.

Other combination serum tests that have a high predictive value are:

- The Prostate Health Index (PHI) is a serum test for PSA, free PSA and p2PSA where results are combined to calculate the probability of prostate cancer.
- The Kallikrein markers (i.e., 4Kscore) test measures fPSA, tPSA, human kallikrein-related peptidase 2 (hK2) and intact PSA. This test also considers age, digital rectal exam results and prior biopsy status.

PSA exists not only in unbound but also in several complex forms. Prostate cancer antigen 3 (PCA3) is a non-protein-coding messenger RNA (mRNA) that is highly overexpressed in prostate cancer tissue. A urine test was developed to measure PCA3 levels (e.g., ProgenSA® PCA3 Assay) given the strong association between PCA3 mRNA levels and prostate cancer. The PCA3 has a high negative predictive value for men with a prior negative biopsy using a PCA3 cut-off score of >25 .

An epigenetic (biologic mechanism that activates/de-activates a gene) assay that may improve the stratification of individuals being considered for repeat prostate biopsy is testing for hypermethylation of GSTP1, APC, and RASSF1 (e.g., ConfirmMDx®) on the tissue from a biopsied prostate tumor. This test may help determine which individuals should consider subsequent biopsies.

POLICY

- **Prostate** biomarker testing for the diagnosis **or suspicion** of prostate cancer is considered **medically necessary** if the medical appropriateness criteria are met. (**See Medical Appropriateness below.**)
- All other **prostate** biomarker testing for the screening, detection, stratification, and management of prostate cancer are considered **investigational**.

MEDICAL APPROPRIATENESS

- **Prostate** biomarker testing for the diagnosis **or suspicion** of prostate cancer is considered **medically appropriate** if **ANY ONE** of the following are met:



Policy

Medical Policy Manual

Approved Revision: Do Not Implement Until 12/31/26

Prostate Cancer Biomarkers Testing

page 2

- Prior to initial biopsy if **ALL** of the following are met:
 - PSA greater than 3 ng/mL
 - **The test is being used to assist in assessing the risk of clinically significant prostate cancer and to support shared decision-making regarding the need for an initial biopsy**
 - **ONE or more** of the following biomarker tests are used:
 - Percent free PSA (%fPSA)
 - Prostate Health Index (PHI)
 - Kallikrein markers (i.e., 4Kscore)
 - **Other guideline-supported serum or urine biomarkers with comparable intended use (testing names are not all inclusive).**
- Individual with at least one negative biopsy and **ALL** of the following are met:
 - **Ongoing** clinical suspicion of prostate cancer
 - **Biomarker testing is being used to help determine the need for repeat biopsy or additional diagnostic evaluation**
 - **ONE or more** of the following tests are used:
 - Percent free PSA (%fPSA)
 - Prostate Health Index (PHI)
 - Kallikrein markers (i.e., 4Kscore)
 - PCA3
 - **Prostate cancer methylation assays (e.g., GSTP1, APC, and RASSF1 hypermethylation testing such as ConfirmMDx®)**
 - **Other guideline-supported serum, urine, tissue, or epigenetic biomarkers intended to improve selection for repeat biopsy**

IMPORTANT REMINDERS

- Any specific products referenced in this policy are just examples and are intended for illustrative purposes only. It is not intended to be a recommendation of one product over another and is not intended to represent a complete listing of all products available. These examples are contained in the parenthetical e.g. statement.
- We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the Medical Policy and a health plan or government program (e.g., TennCare), the express terms of the health plan or government program will govern.

ADDITIONAL INFORMATION

Biomarker testing should be used as an adjunct to, and not a replacement for, clinical evaluation, PSA testing, digital rectal examination, imaging findings, and shared decision-making.

Examples listed above are not all-inclusive. Equivalent biomarker assays with similar clinical indications and evidence may be reviewed using the same criteria.



Medical Policy Manual

Approved Revision: Do Not Implement Until 12/31/26

Prostate Cancer Biomarkers Testing

page 3

These criteria are intended to align with contemporary recommendations from NCCN, AUA, SUO, and other relevant professional societies recognizing the use of validated biomarkers to refine prostate cancer risk assessment and biopsy decision-making.

SOURCES

- American Urological Association (AUA) / American Society for Radiation Oncology (ASTRO) / Society of Urologic Oncology (SUO). (2022). *Clinically localized prostate cancer*: AUA/ASTRO/SUO guideline. Retrieved February 16, 2023 from www.auanet.org/guidelines.
- American Urological Association (AUA) / American Society for Radiation Oncology (ASTRO) / Society of Urologic Oncology (SUO). (2023, June). *Early detection of prostate cancer*: AUA guideline. Retrieved July 18, 2025 from www.auanet.org/guidelines.
- BlueCross BlueShield Association. Evidence Positioning System. (12:2025). *Genetic and protein biomarkers for the diagnosis and cancer risk assessment of prostate cancer* (2.04.33). Retrieved September 14, 2026 from <https://www.bcbsaoca.com/eps/>. (75 articles and/or guidelines reviewed)
- Bryant, R. J., Sjoberg, D. D., Vickers, A. J., Robinson, M. C., Kumar, R., Marsden, L., et al. (2015). Predicting high-grade cancer at ten-core prostate biopsy using four kallikrein markers measured in blood in the ProtecT Study. *Journal of the National Cancer Institute*, 107 (7), 1-9. (Level 4 evidence)
- Carlsson, S., Maschino, A., Schroder, F., Bangma, C., Steyerberg, E., van der Kwast, T., et al. (2013). Predictive value of four kallikrein markers for pathologically insignificant compared with aggressive prostate cancer in radical prostatectomy specimens: results from the European randomized study of screening for prostate cancer section Rotterdam. *European Urology*, 64 (5), 693-699. (Level 2 evidence)
- European Association of Urology (EAU). (2025). *Guidelines on prostate cancer*. Retrieved July 18, 2025 from <https://uroweb.org>.
- Fenton, J.J., Weyrich, M.S., Durbin, S., Liu, Y., Bang, H., & Melnikow, J. (2018). Prostate-specific antigen-based screening for prostate cancer evidence report and systematic review for the US preventive service task force. *JAMA*, 319 (18), 1901-1913. (Level 1 evidence)
- Konety, B., Zappala, S. M., Parekh, D. J., Osterhout, D., Schock, J., Chudler, R. M., (2015). The 4Kscore® Test reduces prostate biopsy rates in community and academic urology practices. *Reviews in Urology*, 17 (4), 231-240. (Level 1 evidence)
- National Comprehensive Cancer Network. (2026, February). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). *Prostate cancer early detection*. (V.2.2026). Retrieved February 18, 2026 from the National Comprehensive Cancer Network.
- Prostate Cancer Prostatic Diseases*. 23 (4), 607-614. [E-pub ahead of print] doi: 10.1038/s41391-020-0237-z. (Level 1 evidence)
- Punnen, S., Pavan, N., & Parekh, D. (2015). Finding the wolf in sheep's clothing: the 4Kscore is a novel blood test that can accurately identify the risk of aggressive prostate cancer. *Reviews in Urology*, 17 (1), 3-13. (Level 2 evidence)
- Tutrone, R., Donovan, M.J., Torkler, P., Tadigotla, V., Mclain, T., & Noerholm, M., et al. (2020). Clinical utility of the exosome based ExoDx prostate (IntelliScore) EPI test in men presenting for initial biopsy with a PSA 2–10 ng/mL.
- U. S. Food and Drug Administration. (2012, February). Center for Devices and Radiological Health. *Pre-market approval decisions for February 2012 (Progenesa® PCA3 Assay)*. Retrieved August 26, 2016 from <http://www.accessdata.fda.gov>.



BlueCross BlueShield
of Tennessee

Policy

Medical Policy Manual

Approved Revision: Do Not Implement Until 12/31/26

Prostate Cancer Biomarkers Testing

page 4

Wei, J. T., Feng, Z., Partin, A. W., Brown, E., Thompson, I., Sokoll, L., (2014). Can urinary PCA3 supplement PSA in the early detection of prostate cancer? *Journal of Clinical Oncology*, 32 (36), 4066-4072. (Level 1 evidence)

EFFECTIVE DATE 12/31/2026

ID_BT