 Approved: Do Not Implement Until 3/1/18

Novel Biomarkers for the Diagnosis and Management of Prostate Cancer

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 prostate-specific antigen (PSA). The PSA test, which detects abnormally high blood levels of PSA, has been used for decades to screen for prostate cancer. Although (Prostate Specific Antigen) PSA testing can help catch prostate cancer at an early stage, having an elevated PSA (> 3 ng/ml) doesn't necessarily mean that an individual has cancer.

The use of PSA for early detection of prostate cancer 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) which is a serum test for PSA, free PSA and p2PSA where results are combined to calculate the probability of prostate cancer.
- Kallikrein markers (i.e., 4Kscore) test measures fPSA, tPSA, human kallikrein 2 (hk2) and intact PSA; this test also considers age, digital rectal exam results and prior biopsy status.

PSA exists not only unbound but also in several complex forms. PSA3 (e.g. Progensa® PCA3 Assay) is a urine test for prostate tissue specific RNA that is overexpressed in 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 (biological mechanisms 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 individuals with a negative biopsy but elevated clinical risk factors determine the need for subsequent biopsies.

POLICY

- Biomarker testing for percent free PSA (%fPSA), and/or Prostate Health Index (PHI), and/or kallikrein markers (i.e., 4Kscore) prior to initial biopsy and/or repeat biopsy is considered ***medically necessary*** if the medical appropriateness criteria are met. **(See Medical Appropriateness below.)**

- PCA3 testing and/or gene *(GSTP1, APC,* and *RASSF1*) hypermethylation testing (e.g.,ConfirmMDx®) testing following a biopsy are considered ***medically necessary*** if the medical appropriateness criteria are met. **(See Medical Appropriateness below.)**

- All other novel biomarker tests for the screening, detection, stratification, and management of prostate cancer are considered ***investigational.***

See also:

- Gene Expression Profile Analysis for Prostate Cancer Management
- Prostate Specific Antigen (PSA)

MEDICAL APPROPRIATENESS

- Biomarker testing is considered ***medically appropriate*** if **ANY ONE** of the following are met:
    - Percent free PSA (%fPSA), and/or Prostate Health Index (PHI), and/or Kallikrein markers (i.e., 4Kscore) for initial and/or repeat biopsy when the PSA greater than 3ng/mL
    - PCA3 test and/or gene *(GSTP1, APC,* and *RASSF1*) hypermethylation testing (e.g.,ConfirmMDx®) testing prior to repeat biopsy when **ALL** of the following are met:
        - One prior negative prostate biopsy
        - Clinical suspicion of prostate cancer

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, the express terms of the health plan will govern.

ADDITIONAL INFORMATION

Detection of aggressive prostate cancer permits identification of those individual most likely to benefit from aggressive intervention. Conversely, those men harboring non-life-threatening disease would be able to avoid unnecessary interventions. While the list of other biomarker tests (e.g., SelectMDx™, ExoDx™ Prostate, Mi-Prostate™ Score) is growing rapidly, validation through further testing is needed.

SOURCES

American Urological Association (AUA) / American Society for Radiation Oncology (ASTRO) / Society of Urologic Oncology (SUO) (2017, April) *Clinically localized prostate cancer*: AUA/ASTRO/SUO guideline. Retrieved December 4, 2017 from www.auanet.org/guidelines

Aubin, S. M., Reid, J., Sarno, M.J., Blase, A., Aussie, J., Rittenhouse, H., et al. (2010). PCA3 molecular urine test for predicting repeat prostate biopsy outcome in populations at risk: validation in the placebo arm of the dutasteride REDUCE trial. *Journal of Urology,* 184 (5), 1947-1952. Abstract retrieved August 18, 2016 from PubMed database.

Auprich, M., Bjartell, A., Chun, F., de la Taille, A., Freedland, S., Haese, A., et al. (2011). Contemporary role of prostate cancer antigen 3 in the management of prostate cancer. *European Urology,* 60 (5), 1045-1054. Abstract retrieved August 18, 2016 from PubMed database.

BlueCross BlueShield Association. Medical Policy Reference Manual. (10:2016). *Genetic and protein biomarkers for the diagnosis and cancer risk assessment of prostate cancer* (2.04.33). Retrieved October 27, 2017 from BlueWeb. (124 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)

Cary, C. and Cooperberg, M (2013) Biomarkers in prostate cancer surveillance and screening: past, present, and future. *Therapeutic Advances in Urology,* 5 (6), 318-329. (Level 5 evidence)

Gittelman, M. C., Hertzman, B., Bailen, J., Williams, T., Kozoil, I., Henderson, R. J., et al. (2013). PCA3 molecular urine test as a predictor of repeat prostate biopsy outcome in men with previous negative biopsies: a prospective multicenter clinical study. *Journal of Urology,* 190 (1), 64-69. Abstract retrieved August 18, 2016 from PubMed database.

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. (2017, February). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). *Prostate cancer early detection*. (V.2.2017). Retrieved October 27, 2017 from https://www.nccn.org .

National Institute for Health and Care Excellence (2014, January) *Prostate cancer: diagnosis and management.* Retrieved October 30, 2017 from www.nice.org.ok

Parekh, D., Punnen, S., Sjoberg, D., Asroff, S., Bailen, J., Cochran, J., et al. (2015). A multi-institutional prospective trial in the USA confirms that the 4Kscore accurately identifies men with high-grade prostate cancer. *European Urology,* 68, 464-470. Abstract retrieved August 18, 2016 from PubMed database.

Partin, A. W., Van Neste, L., Klein, E. A., Marks, L. S., Gee, J. R., Troyer, D. A., et al. (2014). Clinical validation of an epigenetic assay to predict negative histopathological results in repeat prostate biopsies. *Journal of Urology*, 192 (4), 1081-1087. Abstract retrieved August 18, 2016 from PubMed database.

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)

Stewart, G. D., Van Neste, L., Delvenne, P., Delrée, P., Delga, A., McNeill, S. A., et al. (2013). Clinical utility of an epigenetic assay to detect occult prostate cancer in histopathologically negative biopsies: results of the MATLOC study. *Journal of Urology,* 189 (3), 1110-1116. Abstract retrieved August 18, 2016 from PubMed database.

U. S. Food and Drug Administration. (2012, February). Center for Devices and Radiological Health. *Pre-market approval decisions for February 2012 (Progensa® PCA3 Assay).* Retrieved August 26, 2016 from http://www.accessdata.fda.gov

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)

Winifred S. Hayes, Inc. Genetic Test Evaluation (GTE) Report. (2014, June; last update search May 2015). *PCA3 detection test for prostate cancer.* Retrieved August 19, 2016 from www.Hayesinc.com/subscribers .(96 articles and/or guidelines reviewed)

EFFECTIVE DATE 3/1/2018

ID_BT