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

Summary
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. This evidence review will address these types of tests for cancer risk assessment.

FDA REGULATORY STATUS
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. BioReference Laboratories and GenPath Diagnostics (subsidiaries of OPKO Health; 4Kscore®), Metabolon (Prostarix™), ARUP Laboratories, Mayo Medical Laboratories, LabCorp, BioVantra, others (PCA3 assay), Clinical Research Laboratory (Prostate Core Mitomic Test™), MDx Health (ConfirMDx), and Innovative Diagnostics (phi™), are CLIA-certified. 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 FDA through premarket approval process. According to the company’s press release, this assay is “indicated for use in conjunction with other patient information to aid in the decision for repeat biopsy in men 50 years of age or older who have had 1 or more previous negative prostate biopsies and for whom a repeat biopsy would be recommended by a urologist based on the current standard of care, before consideration of Progensa PCA3 assay results.” FDA product code: OYM.

In June 2012, pro-PSA, a blood test used to calculate the Prostate Health Index (phi; Beckman Coulter) was approved by FDA through the premarket approval process. The phi test is indicated as an aid in distinguishing prostate cancer from 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.
2.04.33 Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

POLICY STATEMENT

The following genetic and protein biomarkers for the diagnosis of prostate cancer are considered investigational:
- Kallikrein markers (eg, 4Kscore™ Test)
- Metabolomic profiles (eg, Prostarix™)
- PCA3 testing
- TMPRSS fusion genes
- Candidate gene panels
- Mitochondrial DNA mutation testing (eg, Prostate Core Mitomics Test™)
- Gene hypermethylation testing (eg, ConfirmMDx®)
- Prostate Health Index (phi).

Single-nucleotide polymorphism testing for cancer risk assessment of prostate cancer is considered not medically necessary.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

RATIONALE

Summary of Evidence

For individuals for whom an initial prostate biopsy or a rebiopsy is being considered who receive genetic and protein biomarker testing, the evidence includes systematic reviews and meta-analyses and primarily observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, other test performance measures, resource utilization, hospitalizations, quality of life, and treatment-related mortality and morbidity. The evidence supporting clinical utility varies by test but has not been directly shown for any biomarker test. In general, performance of biomarker testing for predicting biopsy compared with clinical examination, including the ratio of free or unbound prostate-specific antigen (PSA) to total PSA, is lacking. However, procedures for referrals for biopsy based on clinical examination vary, making it difficult to quantify performance characteristics for this comparator. There is considerable variability in biopsy referral practices based on clinical examination alone and many biomarker tests do not have standardized cutoffs to recommend biopsy. Therefore, having prospective, comparative information on how test results are expected to be used or actually being used in practice and the associated effects on outcomes will be needed to determine if the tests improve net health outcomes. Many of the test validation populations have included men with a positive digital rectal exam, prostate-specific antigen (PSA) level outside of the gray zone, or older men for whom the information for test results are less likely to be informative. African Americans have a high burden of morbidity and mortality, but have not been well represented in these study populations. It is unclear how to monitor men with low biomarker risk scores who continue to have symptoms or high or rising PSA levels. Comparative studies of the many biomarkers are lacking and it is unclear how to use the tests in practice, particularly when test results are contradictory. The evidence is insufficient to determine the effects of the technology on health outcomes.
2.04.33 Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network
National Comprehensive Cancer Network guidelines (v.2.2016) recommend that any man with a PSA level greater than 3 ng/mL undergo workup for benign disease, repeat prostate-specific antigen (PSA) and DRE. The guidelines also recommend consideration of %fPSA, phi, and 4Kscore in patients with a PSA level greater than 3 ng/mL who have not yet had a biopsy and consideration of %fPSA, phi, 4Kscore, PCA3, and ConfirmMDx in men who had a negative biopsy but are thought to be at higher risk (category 2A evidence). The panel noted that these tests may be especially useful in men with PSA levels between 3 and 10 ng/mL. Guideline authors note: “The panel believes that no biomarker test can be recommended over any other at this time. The optimal order of biomarker tests and imaging is unknown; and it remains to unclear how to interpret results of multiple tests in individual patients—especially when results are contradictory.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force published recommendations for prostate cancer screening on May 2012. Genetic and protein biomarkers addressed in this evidence review, including PCA3, were not mentioned.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers. Palmetto GBA has issued a local coverage determination for positive coverage for ConfirmMDx Epigenetic Molecular Assay (date effective 11/03/14). Palmetto GBA issued a draft non-coverage policy determination in 2016 for the 4Kscore.

REFERENCES

29. 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. PMID 17105175


55. Boegemann M, Stephan C, Cammann H, et al. The percentage of prostate-specific antigen (PSA) isoform [-2] proPSA and the Prostate Health Index improve the diagnostic accuracy for clinically relevant prostate cancer at initial and repeat biopsy compared with total PSA and percentage free PSA in men aged <65 years. BJU Int. Jan 2016;117(1):72-79. PMID 25818705


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POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>December 2011</td>
<td>New Policy</td>
<td>Policy updated with literature review, references added, policy statement changed PCA3 from investigational to not medically necessary.</td>
</tr>
<tr>
<td>June 2013</td>
<td>Update Policy</td>
<td>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.</td>
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<tr>
<td>June 2014</td>
<td>Update Policy</td>
<td>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.”</td>
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<tr>
<td>December 2016</td>
<td>Replace Policy</td>
<td>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.</td>
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Signature on File

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