**Protocol**

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

(20433)

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<th>Medical Benefit</th>
<th>Effective Date: 07/01/16</th>
<th>Next Review Date: 05/17</th>
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<tr>
<td>Preauthorization</td>
<td>No</td>
<td>Review Dates: 09/09, 09/10, 07/11, 07/12, 05/13, 05/14, 05/15, 05/16</td>
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This Protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

**Description**

There are a variety of genetic and protein biomarkers 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 Protocol will address these types of tests, as well as single nucleotide polymorphisms (SNPs) testing for cancer risk assessment.

**Summary of Evidence**

Evidence on the clinical validity of genetic and protein biomarker tests related to prostate cancer is variable and incomplete, leaving considerable uncertainty regarding clinical performance characteristics such as sensitivity, specificity, and predictive value. Some tests show evidence for predictive ability in the diagnosis of prostate cancer; however, incremental accuracy in comparison with currently available tests has not been consistently demonstrated. In addition, these data do not demonstrate clinical utility, i.e., that using a test will change treatment decisions and improve subsequent outcomes.

Numerous studies have demonstrated the association of many different single nucleotide polymorphisms (SNPs) with prostate cancer, and these studies generally show a modest degree of association with future risk for prostate cancer. However, the clinical utility of these tests is uncertain; there is no evidence that information obtained from SNP testing can be used to change management in ways that will improve outcomes.

**Policy**

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

- Kallikrein markers (e.g., 4Kscore™ Test)
- Metabolomic profiles (e.g., Prostarix™)
- PCA3 testing
- TMPRSS fusion genes
• Candidate gene panels
• Mitochondrial DNA mutation testing (e.g., Prostate Core Mitomics Test™)
• Gene hypermethylation testing (e.g., ConfirmMDx®)

Single nucleotide polymorphisms (SNPs) testing for cancer risk assessment of prostate cancer is considered investigational.

**Medicare Advantage**

For Medicare Advantage the ConfirmMDx epigenetic molecular assay is considered *medically necessary* under the following conditions:

1. Males aged 40 to 85 years old that have undergone a previous cancer-negative prostate biopsy within 24 months and are being considered for a repeat biopsy due to persistent or elevated cancer-risk factors, and
2. The previous negative prostate biopsy must have collected a minimum of eight tissue cores (but not have received a saturation biopsy of > 24 tissue cores) and remaining FFPE tissue from all cores is available for testing, and
3. Minimum tissue volume criteria of 20 microns of prostate biopsy core tissue is available (40 microns preferable), and
4. Previous biopsy histology does not include a prior diagnosis of prostate cancer or cellular atypia suspicious for cancer (but may include the presence of high-grade prostatic intraepithelial neoplasia (HGPIN), proliferative inflammatory atrophy (PIA), or glandular inflammation), and
5. Patient is not being managed by active surveillance for low stage prostate cancer, and
6. Tissue was extracted using standard patterned biopsy core extraction (and not transurethral resection of the prostate (TURP)), and
7. Patient has not been previously tested by ConfirmMDx from the same biopsy samples or similar molecular test, and
8. Testing has been ordered by a physician who is certified in the MolDx approved ConfirmMDx Certification and Training Registry (CTR) program*.

**Medicare Advantage Policy Guidelines**

*Because of the complicated nature of management decisions utilizing the ConfirmMDX assay and the potential for missing early prostate cancer, testing must be furnished only by physicians who are enrolled in a MolDx approved CTR program. Healthcare providers who order ConfirmMDX must be registered and certified in the ConfirmMDX CTR program. Coverage for ConfirmMDX testing is available only through these providers.

The ConfirmMDX epigenetic molecular assay may also available through the PASCUAL clinical trial. Participation in the PASCUAL trial is not a prerequisite to the limited coverage.

**Background**

Conventional decision-making tools for identifying men who should undergo prostate biopsy include serum prostate-specific antigen (PSA), digital rectal exam (DRE) and patient risk factors such as age, race, and family
history of prostate cancer. However, these screening tools lead to unnecessary prostate biopsies because of their lack of specificity and inability to discriminate low- from high-risk prostate cancer.

Prostate cancer is a complex, heterogeneous disease, in which numerous genetic alterations have been described, with the potential for use of these molecular markers to improve decision making as to whom should undergo prostate biopsy or rebiopsy after an initial negative biopsy.

For assessing future prostate cancer risk, numerous studies have demonstrated the association of many different SNPs with prostate cancer, and these studies generally show a modest degree of association with future risk for prostate cancer.

Commercially available tests include:

- **4Kscore Test** (OPKO Lab), a blood test that measures four prostate-specific kallikreins, which are combined into an algorithm to decide whether a patient should proceed to prostate biopsy.
- **Prostarix** (Metabolon/Bostwick Laboratories) is a post-DRE urine test based on several metabolites and an algorithm to decide whether a patient should proceed to prostate biopsy or undergo repeat biopsy after an initial negative biopsy.
- The **PCA3** test is offered in the United States by a number of reference laboratories including ARUP, Mayo Medical Laboratories, and LabCorp. Reagents used in testing are developed by Gen-Probe.
- **Prostate Core Mitomics Test** (Mitomics [formerly Genesis Genomics]), which measures mitochondrial DNA mutations in a negative prostate biopsy to determine whether a patient should undergo repeat biopsy.
- **ConfirmMDx** (MDxHealth) measures hypermethylation of three genes in a negative prostate biopsy to determine whether a patient should undergo repeat biopsy.
- **SNP testing** as part of genome-scanning tests for prostate cancer risk assessment are offered by a variety of laboratories, such as Navigenics (now Life Technologies), LabCorp (23andme), and ARUP (deCode), as laboratory-developed tests.

**Regulatory Status**

Only one **PCA3** test has been submitted to the U.S. Food and Drug Administration (FDA) for premarket approval. The Gen-Probe Progensa® **PCA3** Assay was approved by FDA on February 15, 2012, through the 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 one 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.

Other tests mentioned in this Protocol, if available, are offered as laboratory-developed tests under the Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet general regulatory standards of the Clinical Laboratory Improvement Act and must be licensed by CLIA for high-complexity testing.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are
considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

**References**

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


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<tr>
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<th>Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer</th>
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<td>76.</td>
<td>Recommendations from the EGAPP Working Group: does PCA3 testing for the diagnosis and management of prostate cancer improve patient health outcomes? Genet Med. Sep 26 2013. PMID 24071797</td>
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<td>78.</td>
<td>Local Coverage Determination (LCD): MolDX-CDD: ConfirmMDx Epigenetic Molecular Assay (L36326). For services performed on or after 10/01/2015.</td>
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