Protocol

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

Medical Benefit
Effective Date: 02/01/22
Next Review Date: 01/23

Preauthorization
Yes
Review Dates: 09/09, 09/10, 07/11, 07/12, 05/13, 05/14, 05/15, 05/16, 05/17, 09/17, 05/18, 01/19, 05/19, 11/19, 01/20, 03/21, 01/22

Preauthorization is required.
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.

RELATED PROTOCOL
Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

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<td>Interventions of interest are: • Testing for genetic and protein biomarkers of prostate cancer</td>
<td>Comparators of interest are: • Standard clinical examination including measurement of percent free prostate-specific antigen</td>
<td>Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Resource utilization • Quality of life</td>
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<td>Individuals: • Who are being considered for repeat prostate biopsy</td>
<td>Interventions of interest are: • Testing for genetic and protein biomarkers of prostate cancer</td>
<td>Comparators of interest are: • Standard clinical examination including measurement of percent free prostate-specific antigen</td>
<td>Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Resource utilization • Quality of life</td>
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DESCRIPTION
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 the Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management Protocol.

SUMMARY OF EVIDENCE
For individuals who are being considered for an initial prostate biopsy who receive testing for genetic and protein biomarkers of prostate cancer (e.g., kallikreins biomarkers and 4Kscore Test, proPSA and Prostate Health

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Index, TMPRSS fusion genes and Mi-Prostate Score, 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, a prostate-specific antigen 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 (e.g., PCA3 score, Gene Hypermethylation and ConfirmMDx test, Prostate Core Mitomics Test), 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 physician decisions on rebiopsy or on the longer-term clinical outcomes of men who did not have a biopsy based on test results. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**POLICY**

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

- Kallikrein markers (e.g., 4Kscore™ Test)
- Prostate Health Index (PHI)
- HOXC6 and DLX1 testing (e.g., SelectMDx)
- PCA3, ERG, and SPDEF RNA expression in exosomes (e.g., ExoDx Prostate IntelliScore [EPI])
- Autoantibodies ARF 6, NKX3-1, 5’-UTR-BMI1, CEP 164, 3’-UTR-Ropporin, Desmocollin, AURKAIP-1, and CSNK2A2 (e.g., Apifiny)
- PCA3 testing (e.g., Progensa PCA3 Assay)
- TMPRSS: ERG fusion genes
- Gene hypermethylation testing (e.g., ConfirmMDx)
- Mitochondrial DNA variant testing (e.g., Prostate Core Mitomics Test™)
- PanGIA Prostate
- Candidate gene panels

Single nucleotide variant testing for cancer risk assessment of prostate cancer is considered **investigational**.
POLICY GUIDELINES

GENETIC COUNSELING

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

MEDICARE ADVANTAGE

PCA3

For Medicare Advantage PCA3 testing may be considered medically necessary only when all biopsies in previous encounter(s) are negative for prostatic cancer, the subsequent prostate specific antigen (PSA) is rising, and when the patient or physician wants to avoid repeat biopsy (“watchful waiting”).

When the physician plans to biopsy the prostate, a PCA3 test is considered not medically necessary.

All other indications for PCA3 are considered not medically necessary.

For Medicare Advantage, each biomarker test (% fPSA, PHI, 4Kscore, or EPI) may be considered medically necessary ONCE in men ≥45 years old, prior to initial biopsy, with confirmed* moderately elevated PSA (>3 and <10 ng/mL; ≥4 and <10 ng/mL in men >75 years old) with BOTH the following:

1. No other relative indication for prostate biopsy including ANY of the following:
   a. DRE suspicious for cancer
   b. Positive multiparametric MRI (if done)
   c. Other major risk factor for prostate cancer including:
      i. Ethnicity at higher risk for prostate cancer**
      ii. First-degree relative with prostate cancer**
      iii. High-penetrance prostate cancer risk gene(s) per NCCN (if known)

2. No other relative contraindication for prostate biopsy including ANY of the following:
   a. <10 year life expectancy
   b. Invasive treatment for benign prostatic disease or taking medications that influence serum PSA levels within 6 mo.
   c. Active prostatitis on antibiotics

*PSA elevation should be confirmed after a few weeks under standardized conditions (i.e., no ejaculation, manipulations, and urinary tract infections) in the same laboratory before considering a biopsy.

**Limitation does not apply to EPI
CONFIRMMDX
For Medicare Advantage ConfirmMDx may be considered medically necessary when all of the following conditions are met:

- 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
- 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
- Minimum tissue volume criteria of 20 microns of prostate biopsy core tissue is available (40 microns preferable), AND
- 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
- Patient is not being managed by active surveillance for low stage prostate cancer, AND
- Tissue was extracted using standard patterned biopsy core extraction (and not transurethral resection of the prostate (TURP)), AND
- Patient has not been previously tested by CONFIRMMDX from the same biopsy samples or similar molecular test.

BACKGROUND
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%. 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 two to three times greater than that of white men. Autopsy results have suggested that about 30% of men age 55 and 60% of men age 80 who die of other causes have incidental prostate cancer, 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. 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. A cross-walk of these grading systems is shown in Table 1.
Numerous genetic alterations associated with development or progression of prostate cancer have been described, with the potential for the use of these molecular markers to improve the selection process of men who should undergo prostate biopsy or rebiopsy after an initial negative biopsy.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed under the Clinical Laboratory Improvement Amendments for high-complexity testing. The following laboratories are certified under the Clinical Laboratory Improvement Amendments: BioReference Laboratories and GenPath Diagnostics (subsidiaries of OPKO Health; 4Kscore®), ARUP Laboratories, Mayo Medical Laboratories, LabCorp, BioVantra, others (PCA3 assay), Clinical Research Laboratory (Prostate Core Mitomic Test™), MDx Health (SelectMDx, ConfiMDx), Innovative Diagnostics (phi™), and ExoDx® Prostate (Exosome Diagnostics). To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests.

In February 2012, the Progensa® PCA3 Assay (Gen-Probe; now Hologic) was approved by the FDA through the premarket approval process. The Progensa PCA3 Assay has been approved by the FDA to aid in the decision for repeat biopsy in men 50 years or older who have had one or more negative prostate biopsies and for whom a repeat biopsy would be recommended based on the current standard of care. The Progensa PCA3 Assay should not be used for men with atypical small acinar proliferation on their most recent biopsy. FDA product code: OYM.

In June 2012, proPSA, a blood test used to calculate the Prostate Health Index (phi; Beckman Coulter) was approved by the FDA through the premarket approval process. The phi test is indicated as an aid to distinguish prostate cancer from a 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.

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

33. 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


70. National Government Services, Inc. (Primary Geographic Jurisdiction 06 & K - Illinois, Minnesota, Wisconsin, Connecticut, New York - Entire State, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont) Local Coverage Determination (LCD): Biomarker Testing (Prior to Initial Biopsy) for Prostate Cancer Diagnosis L37733, Revision Effective Date for services performed on or after 08/01/2021.


72. Noridian Healthcare Solutions, LLC, (Jurisdiction E - California - Entire State, American Samoa, Guam, Hawaii, Northern Mariana Islands, Nevada) (Jurisdiction F - Alaska, Arizona, Idaho, Montana, North Dakota, Oregon, South Dakota, Utah, Washington, and Wyoming) Local Coverage Determination (LCD): MolDX: CONFIRM MDX Epigenetic Molecular Assay (L36327) and (L36329), Revision Effective Date or services performed on or after 12/10/2020.
73. Palmetto GBA (Jurisdiction J & M: Alabama, Georgia, Tennessee, North Carolina, South Carolina, West Virginia, Virginia) Local Coverage Determination (LCD): MolDX: CONFIRMMDX Epigenetic Molecular Assay (L35632), revision Effective Date for services performed on or after 12/17/2020.


75. CGS Administrators, LLC, (Jurisdiction 15 - Kentucky, Ohio) Local Coverage Determination (LCD): MolDX-CDD: CONFIRMMDX Epigenetic Molecular Assay (L36006), Revision Effective Date for services performed on or after 04/22/2021.