Preauthorization is not 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.

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 protocol addresses these types of tests for cancer risk assessment. Magnetic resonance imaging-targeted biopsy of suspicious lesions is assessed in the Magnetic Resonance Imaging–Targeted Biopsy of the Prostate Protocol.

POLICY

Multigene expression (Prolaris™; Oncotype Dx) assay on prostate cancer tissue is considered medically necessary to determine prognosis when the following clinical conditions are met:

- Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), AND
- FFPE prostate biopsy specimen with at least 0.5 mm of cancer length, AND
- Patient Stage as defined by one of the following:
  - Very Low Risk Disease (T1c AND Gleason Score ≤ six AND PSA ≤ 10 ng/mL AND < three prostate cores with tumor AND ≤ 50% cancer in any core AND PSA density of < 0.15 ng/mL/g) OR
  - Low Risk Disease (T1-T2a AND Gleason Score ≤ six AND PSA ≤ 10 ng/mL), AND
- Patient has an estimated life expectancy of greater than or equal to 10 years, AND
- Patient is a candidate for and is considering conservative therapy and would be eligible for definitive therapy (radical prostatectomy, radiation therapy or brachytherapy), AND
- Result will be used to determine treatment between definitive therapy and conservative management AND
- Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy.

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.

ConfirmMDx and other prostate tissue gene methylation testing are considered **investigational** in all other situations.

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 (other than ConfirmMDx when meeting the medically necessary criteria above)
- Prostate Health Index (PHI)
- The autoantibody serum (phage-protein microarray) test
- The prostate skin test (e.g., epidermal genetic information retrieval or EGIR)
- Liquid Biopsy
- Gene expression assays to predict recurrence or response to therapy.

Gene expression assays to determine prognosis (e.g., Decipher Prostate Cancer Classifier and Promark™) are considered **investigational**.

Single nucleotide polymorphism (SNPs) testing for cancer risk assessment of prostate cancer is considered **investigational**.
POLICY GUIDELINES

GENETICS NOMENCLATURE UPDATE

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing protocol updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. 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 is 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.
ConfirmMDx

For Medicare Advantage the ConfirmMDx epigenetic molecular assay is considered medically necessary when the above medically necessary criteria are met AND 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

PROSTATE CANCER

Prostate cancer is the second most common cancer in men, with a predicted 161,360 incidence cases and 26,730 deaths expected in United States in 2017.

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 cured 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 United States is approximately 16%, but the risk of dying of prostate cancer is 3%. African-American men have the highest prostate cancer risk in the United States; 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 one (well differentiated) to five (poorly differentiated); the score is the sum of the primary and secondary patterns. A Gleason score of two to five is regarded as normal prostate tissue; six is low-grade prostate cancer that usually grows slowly; seven is an intermediate grade; eight to 10 is high-grade cancer that grows more quickly. Ten-year survival rates stratified by Gleason score have been estimated from the Surveillance, Epidemiology, and End Results registry to be about 98% for scores two through six, 92% for a score of seven with primary pattern 3 and secondary pattern 4 (3+4), 77% for a score of seven (4+3), and 70% for scores between eight and 10.

Numerous genetic alterations associated with development or progression of prostate cancer have been described, with the potential for use of these molecular markers to improve selection 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 (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, Marlborough, MA) was approved by the 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 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.

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 four 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 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.


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


100. Wojno KJ, Costa FJ, Cornell RJ, et al. Reduced rate of repeated prostate biopsies observed in ConfirmMDx clinical utility field study. Am Health Drug Benefits. May 2014;7(3):129-134. PMID 24991397


123. National Government Services, Inc. (Primary Geographic Jurisdiction - Illinois, New York - Entire State, Connecticut, Massachusetts, Maine, New Hampshire, Rhode Island, Vermont, Wisconsin, Minnesota) Local Coverage Determination (LCD): MOLECULAR Pathology Procedures (L35000), Revision Effective Date for services performed on or after 01/01/2018.

124. Noridian Healthcare Solutions, LLC (Jurisdiction - California - Entire State, American Samoa, Guam, Hawaii, Northern Mariana Islands, Nevada) Local Coverage Determination (LCD): MolDX-CDD: CONFIRMMDX Epigenetic Molecular Assay (L36327), Revision Effective Date for services performed on or after 01/01/2018.