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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.

Gene expression profile analysis and protein biomarkers have been proposed as a means to risk-stratify patients with prostate cancer to guide treatment decisions. These tests are intended to be used either on prostate needle biopsy tissue to guide management decisions for active surveillance or therapeutic intervention, to guide radiotherapy use after radical prostatectomy (RP), or to guide medication selection after progression in metastatic castration-resistant prostate cancer.

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 the 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.

The Oncotype DX AR-V7 Nuclear Detect test may be considered **medically necessary** when ALL of the following conditions are met:

1. Patients with progressive, metastatic castration-resistant prostate cancer, (mCRPC) as defined by the Prostate Cancer Working Group 2 guidelines (a minimum of 2 rising prostate-specific antigen (PSA) levels 1 or more weeks apart, new lesions by bone scintigraphy, and/or new or enlarging soft tissue lesions by computed tomography (CT) or magnetic resonance imaging (MRI))
2. Patients who have failed one androgen receptor signaling (ARS) inhibitor, specifically Enzalutamide (Xtandi) or Abiraterone (Zytiga)
3. Patients who are considered appropriate for treatment by their treating physician for the alternative ARS inhibitor (ARSi), specifically Enzalutamide (Xtandi) or Abiraterone (Zytiga), as a single agent.

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™)
- HOXC6 and DLX1 testing (e.g., SelectMDx)
- PCA3, ERG, and SPDEF RNA expression in exosomes (e.g., ExoDx Prostate IntelliScore)
- PCA3 testing (e.g., ProgenSA PCA3 Assay)
- TMPRSS: ERG 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
- Autoantibodies ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, and CSNK2A2 (e.g., Apifyny)
- 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 Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

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

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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

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**.

Prolaris

For Medicare Advantage the Prolaris assay may be considered **medically necessary** when the above medically necessary criteria are met AND the test is ordered by a physician certified in the Myriad PROLARIS™ Certification and Training Registry (CTR).

Biomarker Testing

ONE biomarker test (%fPSA, PHI, or 4Kscore) 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. Persistently elevated PSA
 - c. Positive multiparametric MRI (if done)
 - d. 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. Benign disease not ruled out

*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 (1).

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 the United States in 2017.¹

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 United States is approximately 16%, while the risk of dying of prostate cancer is 3%.² 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 men⁴ indicating that many cases of cancer are unlikely to pose a threat during a man's life expectancy.

Localized prostate cancers may appear very similar clinically at diagnosis.² However, they often exhibit diverse risk of progression that may not be captured by clinical risk categories (e.g., D'Amico criteria) or prognostic tools based on clinical findings, including PSA titers, Gleason grade, or tumor stage.³⁻⁷ In studies of conservative management, the risk of localized disease progression based on prostate cancer-specific survival rates at 10 years may range from 15%^{8,9} to 20%¹⁰ to perhaps 27% at 20-year follow-up.¹¹ Among older men (ages 70 years or older) with low-risk disease, comorbidities typically supervene as a cause of death; these men will die with prostate cancer present, rather than from cancer itself. Other very similar appearing low-risk tumors may progress unexpectedly rapidly, quickly disseminating and becoming incurable.

Grading

The most widely used grading scheme for prostate cancer is the Gleason system.⁵ It is an architectural grading system ranging from 1 (well differentiated) to 5 (poorly differentiated); 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.⁶ A cross-walk of these grading systems is shown in Table 1.

Table 1. Prostate Cancer Grading Systems

Grade Group	Gleason Score) (Primary and Secondary Pattern)	Cells
1	6 or less	Well differentiated (low grade)
2	7 (3+4)	Moderately differentiated (moderate grade)
3	7(4+3)	Poorly differentiated (high grade)
4	8	Undifferentiated (high grade)
5	9-10	Undifferentiated (high grade)

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.

Risk Stratification in Newly Diagnosed Disease

In the United States, most prostate cancers are clinically localized at diagnosis due in part to the widespread use of PSA testing. Clinicopathologic characteristics are used to stratify patients by risk based on the extent of the primary tumor (T category), nearby lymph node involvement (N category), metastasis (M category), PSA level and Gleason score. The National Comprehensive Cancer Network and American Urological Association risk cate-

gories for clinically localized prostate cancer are similar, derived from the D'Amico criteria and broadly include low-, intermediate-, or high-risk as follows as well as subcategories within these groups^{12,13}:

- Low: T1-T2a and Gleason score ≤ 6 /Gleason grade group 1 and PSA level ≤ 10 ng/mL;
- Intermediate: T2b-T2c or Gleason score 3+4=7/Gleason grade group 2 or Gleason score 4+3=7/Gleason grade group 3 or PSA level 10-20 ng/mL;
- High: T3a or Gleason score 8/Gleason grade group 4 or Gleason score 9-10/Gleason grade group 5 or PSA level >20 ng/mL.

Risk stratification is combined with patient age, life expectancy, and treatment preferences to make initial therapy decisions.

Monitoring After Prostatectomy

All normal prostate tissue and tumor tissue is theoretically removed during radical prostatectomy (RP), so the serum level of PSA should be undetectable following RP. Detectable PSA post-RP indicates residual prostate tissue and presumably persistent or recurrent disease. PSA is serially measured following RP to detect early disease recurrence. The National Comprehensive Cancer Network recommends monitoring serum PSA every six to 12 months for the first five years and annually thereafter.¹² Many recurrences following RP can be successfully treated. The American Urological Association has recommended that biochemical recurrence be defined as a serum PSA of 0.2 ng/mL or higher, which is confirmed by the second determination with a PSA level of 0.2 ng/mL or higher.¹⁴

Castration-Resistant Prostate Cancer

Androgen deprivation therapy (ADT) is generally the initial treatment for patients with advanced prostate cancer. ADT can produce tumor response and improve quality of life but most patients will eventually progress on ADT. Disease that progresses while the patient is on ADT is referred to as castration-resistant prostate cancer. After progression, continued ADT is generally used in conjunction with other treatments. Androgen pathways are important in the progression of castration-resistant prostate cancer. Several drugs have been developed that either inhibit enzymes involved in androgen production or inhibit the androgen receptor, such as abiraterone and enzalutamide. Taxane chemotherapy with docetaxel or cabazitaxel may also be used after progression. Immunotherapy (sipuleucel-T) or radium 223 are options for select men.

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 under the CLIA 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, ConfirMDx), Innovative Diagnostics (phiTM), and ExoDx[®] Prostate (Exosome Diagnostics). Prolaris[®] (Myriad Genetics), Oncotype DX[®] Prostate and Oncotype DX AR-V7 Nuclear Detect (Genomic Health), Decipher[®] gene expression profiling test (GenomeDx Biosciences), and the ProMark[™] protein biomarker test (Metamark Genetics) are available under the auspices of CLIA. 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 Progenesa[®] PCA3 Assay (Gen-Probe; now Hologic) was approved by the FDA through the premarket approval process. The Progenesa PCA3 Assay (Hologic Gen-Probe) 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 biop-

sies and for whom a repeat biopsy would be recommended based on 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.

In November 2015, the FDA's Office of Public Health Strategy and Analysis published a report suggesting FDA oversight of LDTs.¹⁵ The FDA argued that many tests need more FDA oversight than the regulatory requirements of CLIA. CLIA standards relate to laboratory operations but do not address inaccuracies or unreliability of specific tests. Prolaris is among the 20 case studies in the document cited as needing FDA oversight. The report asserted that patients are potentially receiving inappropriate prostate cancer care because there is no evidence that results from the test meaningfully improve clinical outcomes.

RELATED PROTOCOL

Magnetic Resonance Imaging–Targeted Biopsy of the Prostate

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.**

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