GUIDELINES
This policy does not certify benefits or authorization of benefits, which is designated by each individual policyholder contract. Paramount applies coding edits to all medical claims through coding logic software to evaluate the accuracy and adherence to accepted national standards. This guideline is solely for explaining correct procedure reporting and does not imply coverage and reimbursement.

DESCRIPTION
Prostate cancer is the second most common cancer diagnosed among men in the United States. Many individuals do not need treatment for their prostate cancer in as much as their prognosis is excellent even without treatment. However, physicians and patients struggle to know who can safely be observed versus the subgroup that needs more aggressive treatment to achieve cure, and recognize that definitive treatment for localized prostate cancer can have lifelong morbidities.

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 regarding active surveillance versus therapeutic intervention, or after radical prostatectomy (RP) to guide radiotherapy use.

Progsensa® PCA3 Assay, an FDA approved test by Gen-Probe Incorporated, is an mRNA expression assay used alone or in combination with other molecular tests for prostate cancer determination to identify patients with increased risk of prostate cancer. PCA3 may help to improve the specificity of prostate cancer detection providing additional information about the risk of prostate cancer over the use of the PSA test alone. Based on the ratio of PCA3 mRNA/PSA mRNA x1000, the PCA3 assay is performed on the first urine collected following an attentive digital rectal examination.

Oncotype DX® Prostate Cancer Assay is prostate biopsy-based 17-gene RT-PCR assay, representing four molecular pathways (androgen signaling, cellular organization, stromal response and proliferation), that provides a biologic measure of cancer aggressiveness. The assay is indicated for men who are considered candidates for active surveillance (AS) (those with National Comprehensive Cancer Network (NCCN®) very low- and low-risk prostate cancer). The assay is designed to inform decisions between AS and immediate treatment.

Prolaris™ is an RNA based assay measuring the expression of 31 cell cycle progression (CCP) genes and 15 “housekeeping” genes that act as internal controls and normalization standards in each patient sample. The assay is performed on formalin fixed paraffin-embedded (FFPE) prostate cancer blocks. The assay results are reported as a numerical score along with accompanying interpretive information.

The Decipher® prostate cancer assay, a 22-biomarker expression signature using oligonucleotide microarray technology, interrogates 1.4 million RNAs extracted from a formalin-fixed paraffin embedded (FFPE) tissue block of the index lesion (defined by highest tumor stage or histological Gleason grade) from the RP specimen. The biomarkers that comprise the Decipher classifier include cell cycle progression, androgen signaling, cell adhesion, tumor cell motility, migration and immune evasion functions.

ConfirmMDx assesses the methylation status of 3 biomarkers (GSTP1, RASSF1, APC) associated with prostate cancer. ConfirmMDx is intended for use in patients with high-risk factors such as elevated/rising prostate-specific antigen (PSA) or abnormal digital rectal examination (DRE), with a negative or non-malignant abnormal histopathology finding (e.g., atypical cell or high grade prostate intraepithelial neoplasia (HGPIN)) in the previous biopsy, and is being considered for repeat biopsy. Several case/control studies in archived biopsy core tissue blocks demonstrated the sensitivity, specificity and high negative predictive value (NPV) of these biomarkers to predict cancer detection in a repeat biopsy procedure. Single biopsy cores, using as little as 20 microns from formalin-fixed, paraffin embedded (FFPE) tissue blocks or sections cut from blocks fixed on glass slides are used in this assay.

4Kscore Test measures the blood plasma levels of four different prostate-derived kallikrein proteins [total prostate-specific antigen (PSA), free PSA, intact PSA and human kallikrein2 (hK2)] and combines results in an algorithm
with age, digital rectal exam (nodules, no nodules) and prior biopsy results. The result purports to identify an individual's specific probability for finding a high-grade, Gleason score seven or higher prostate cancer upon biopsy.

**POLICY**

**Progensa® PCA3 Assay (81313) requires prior authorization for all product lines.**

These genetic and protein biomarkers for prostate cancer are non-covered for HMO, PPO, Individual Marketplace, Advantage:

- Oncotype DX® Prostate (0047U)
- Prolaris® (81541)
- Decipher® (81479)
- ConfirmMDx® (81551)

These genetic and protein biomarkers for prostate cancer require prior authorization for Elite:

- Oncotype DX® Prostate (0047U)
- Prolaris® (81541)
- Decipher® (81479)
- ConfirmMDx® (81551)

**4Kscore Test (81539) is non-covered for HMO, PPO, Individual Marketplace, Elite.**

**4Kscore Test (81539) requires prior authorization for Advantage.**

Other genetic and protein biomarkers for prostate cancer are non-covered for all product lines (this list may not be all-inclusive):

- TMPRSS2-ERG gene fusion
- percent free PSA
- Prostate Health Index (PHI)
- CCP Score
- DD3
- Glutathione S-transferase Gene (GSTP1, pi-class) Methylation Assay
- Proveri Prostate Cancer Assay (PPCA™)
- uPM3 Test
- ExosomeDx® Prostate (IntelliScore) (0005U)
- SelectMDx

**Progensa® PCA3 Assay (81313)**

PCA3 testing is covered ONLY when all biopsies in previous encounter(s) are negative and when the patient or physician wants to avoid repeat biopsy (watchful waiting).

When the physician plans to biopsy the prostate, Paramount will consider a PCA3 test as investigational and thus, not a covered benefit. Paramount considers all other indications for PCA3 not reasonable and necessary.

Medical record documentation must indicate the rationale to perform a PCA3 assay. Providers who report a PCA3 service AND perform a biopsy may be referred for additional action.

**Non-Covered**

Paramount has determined these genetic and protein biomarkers for prostate cancer are experimental and investigational and therefore non-covered because there is insufficient evidence in the peer-reviewed medical literature of the effectiveness of these procedures (this list may not be all-inclusive):

- TMPRSS2-ERG gene fusion
- percent free PSA
- Prostate Health Index (PHI)
- CCP Score
- DD3
- Glutathione S-transferase Gene (GSTP1, pi-class) Methylation Assay
- Proveri Prostate Cancer Assay (PPCA™)
- uPM3 Test
- ExosomeDx® Prostate (IntelliScore) (0005U)
- SelectMDx

**HMO, PPO, Individual Marketplace**

Paramount has determined that Oncotype DX Prostate Cancer (0047U), Prolaris® (81541), Decipher® (81479), ConfirmMDx® (81551), 4Kscore Test (81539) for prostate cancer are experimental and investigational and therefore non-covered because there is insufficient evidence in the peer-reviewed medical literature of the effectiveness of these procedures.

**Advantage**

4Kscore Test (81539) is covered for prostate cancer when results will impact medical management and PSA >3.0 ng/mL with or without previous benign prostate biopsy

Paramount has determined that Oncotype DX Prostate Cancer (0047U), Prolaris® (81541), Decipher® (81479), ConfirmMDx® (81551) for prostate cancer are experimental and investigational and therefore non-covered because there is insufficient evidence in the peer-reviewed medical literature of the effectiveness of these procedures.

**Elite**

**Oncotype DX® Prostate (0047U) and Prolaris® (81541)**

The Oncotype DX® Prostate Cancer Assay and Prolaris™ assay are covered only when ALL of the following clinical conditions are met:

- Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), and
- Patient stage as defined by the one of the following:
  - Very Low Risk Disease (T1c AND Gleason Score = 6 AND PSA = 10 ng/mL AND <3 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 = 6 AND PSA = 10 ng/mL), Patient has an estimated life expectancy of greater than or equal to 10 years, 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 yet and would be eligible for definitive therapy (radical prostatectomy, radiation therapy or brachytherapy), and
- Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy, and
- Test is ordered by a physician certified in the Certification and Training Registry (CTR) of the test ordered, and
- Patient is monitored for disease progression according to established standard of care, and
- Physician must report the development of metastasis or prostate cancer deaths in patients not treated definitively who were deemed low risk by the assay.

**Decipher® (81479)**

The Decipher GC assay is covered only when ALL of the following clinical conditions are met:

- Patient with prostate cancer who has undergone a RP within the previous 60 months and is being considered for postoperative secondary therapy due to one or more cancer-recurrence risk factors, and
- Patient must have achieved initial PSA nadir (defined as PSA at or below 0.2 ng/ml) within 120 days of RP surgery, and
- Patient must not have any evidence of distant metastasis, and
- Patient must not have received any neo-adjuvant treatment prior to surgery, and
- Decipher GC is performed on a patient’s RP specimen, and
- Patient’s surgical pathology report or medical records must have documented presence of adverse pathology:
  - Pathological stage T2 disease with a positive surgical margin, or
  - Pathological stage T3 disease (e.g., extraprostatic extension, seminal vesicle invasion, bladder neck invasion), or
  - Rising PSA after initial PSA nadir, and
- Testing has been ordered by a physician who is certified in the GenomeDX Decipher Certification and Training Registry (CTR)

**ConfirmMDx® (81551)**

ConfirmMDx is covered when ALL of the following conditions are met:

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 8 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.

Paramount has determined that 4Kscore Test (81539) for prostate cancer is experimental and investigational and therefore non-covered because there is insufficient evidence in the peer-reviewed medical literature of the effectiveness of this procedure.

**CODING/BILLING INFORMATION**

The appearance of a code in this section does not necessarily indicate coverage. Codes that are covered may have selection criteria that must be met. Payment for supplies may be included in payment for other services rendered.

**CPT CODES**

- **81313** PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)
- **81479** Unlisted molecular pathology procedure
- **81539** Oncology (high-grade prostate cancer), biochemical assay of four proteins (Total PSA, Free PSA, Intact PSA and human kallikrein-2 [hK2]), utilizing plasma or serum, prognostic algorithm reported as a probability score
- **81541** Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin embedded tissue, algorithm reported as a disease-specific mortality risk score (Effective 01/01/2018)
- **81551** Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy (Effective 01/01/2018)
- **0005U** Oncology (prostate) mRNA gene expression profile by real-time RT-PCR of 3 genes (ERP, PCA3, and SPDEF), urine, algorithm reported as risk score
- **0047U** Oncology (prostate), mRNA, gene expression profile by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score

**TAWG REVIEW DATES:** 08/26/2016, 04/21/2017, 01/25/2018, 08/23/2018, 09/27/2018

**REVISION HISTORY EXPLANATION**

**08/26/16:** Policy created to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).

**04/21/17:** Added tests TMPRSS2-ERG gene fusion, percent free PSA, Prostate Health Index (PHI), CCP Score, DD3, Glutathione S-transferase Gene (GSTP1, pi-class) Methylation Assay, Proveri Prostate Cancer Assay (PPCA™), uPM3 Test to policy as non-covered. Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).

**01/25/18:** Changed title from Gene Expression Analysis for Prostate Cancer to Genetic and Protein Biomarkers for Diagnosis and Risk Assessment of Prostate Cancer. Added 4Kscore Test (81539) as non-covered for HMO, PPO, Individual Marketplace, Elite and covered for Advantage per ODM guidelines. Added ExosomeDx® Prostate (IntelliScore) (0005U) as non-covered for all product lines. Added effective 01/01/2018 new codes 81541 (Prolaris) & 81551 (ConfirmMDx) as covered with prior authorization for all product lines. Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).

**08/23/18:** Added effective 07/01/2018 new code 0047U. Oncotype DX Prostate Cancer (0047U), Prolaris® (81541), Decipher® (81479), & ConfirmMDx® (81551) are now non-covered for HMO, PPO, Individual Marketplace, & Advantage. Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).

**09/27/18:** Added SelectMDx as non-covered for all product lines. Policy updated per CMS guidelines. Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).
REFERENCES/RESOURCES
Centers for Medicare and Medicaid Services, CMS Manual System and other CMS publications and services
Ohio Department of Medicaid http://jfs.ohio.gov/
Centers for Medicare and Medicaid Services, Healthcare Common Procedure Coding System, HCPCS Release and Code Sets
Industry Standard Review
Hayes, Inc.