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## OVERVIEW

Various genetic and protein biomarkers are 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.

The following tests are addressed in this policy:

- ProgenSA PCA3 Assay (Hologic), CPT Code 81313
- 4Kscore (OPKO Health), CPT Code 81539
- ConfirmMDx (MDx Health), CPT Code 81551
- ExoDx Prostate IntelliScore (EPI) (Exosome Diagnostics), CPT Code 0005U
- Apify (Exact Sciences), CPT Code 0021U
- MyProstateScore (MPS) (Lynx Dx), CPT Code 0113U
- PanGIA Prostate (Genetics Institute of America), CPT Code 0228U
- SelectMDx (MDx Health), CPT Code 0339U
- Prostate Health Index (phi) (Beckman Coulter), CPT Code 81479
- Prostate Core Mitomics Test (Mitomics), CPT Code 81479
- Immunoassay for tumor antigen, other antigen, quantitative (eg, CA 50, 72-4, 549), each, CPT code 86316

## MEDICAL CRITERIA

### Medicare Advantage Plans and Commercial Products

#### 4Kscore, CPT Code 81539

The 4Kscore test will be considered medically reasonable and necessary when all the following are met:

1. When all of the components of the algorithm are present.
2. Testing of men 45 years of age and older, prior to an initial biopsy or following a negative biopsy, who have a confirmed\* moderately elevated PSA (greater than 3 and less than 10 ng/mL; greater than or equal to 4 and less than 10 ng/mL in men greater than 75 years of age) when BOTH of the following are present:
  - No other relative indication\*\* for prostate biopsy including ANY of the following: (this may not be an all-inclusive list)
    - DRE suspicious for cancer should be encouraged to undergo biopsy
    - Persistent and significant increase in PSA should be encouraged to undergo biopsy
    - Positive multiparametric magnetic resonance imaging (MRI) (if done)
    - Other major risk factor for prostate cancer including: (this may not be an all inclusive list)
      - Ethnicity at higher risk for prostate cancer
      - First-degree relative with prostate cancer
      - High-penetrance prostate cancer risk gene(s) per the National Comprehensive Cancer Network (NCCN) (if known)
  - No other relative contraindication\*\* for prostate biopsy including ANY of the following:
    - Less than a 10-year life expectancy
    - Benign disease not ruled out.
3. Presence of shared decision making between the ordering provider and the beneficiary concerning the 4Kscore testing.

\* PSA elevation should be verified after a few weeks under standardized conditions (e.g. no ejaculation, manipulations, and urinary tract infections, no medications such as 5 $\alpha$ -reductase) in the same laboratory or other CLIA approved laboratory before considering a biopsy.

\*\* The relative indications and contraindications are not absolute. When it is determined that the 4Kscore test is medically reasonable and necessary in a beneficiary with one of the relative indications or contraindications for prostate biopsy the medical record must support the medical necessity for the test and there must be documented evidence of shared decision making between the patient and provider. This supporting documentation must be provided to the laboratory at the time of ordering the test.

### **ConfirmMDx, CPT Code 81551**

### **SelectMDx, CPT Code 0339U**

ConfirmMDx and SelectMDx may be considered medically necessary when ALL of the following criteria are met:

1. The patient must not have an established diagnosis of prostate cancer.
2. The beneficiary is a candidate for prostate biopsy or repeat prostate biopsy, according to a consensus guideline [(i.e., National Comprehensive Cancer Network® (NCCN), American Society of Clinical Oncology®(ASCO), American Urological Association (AUA)].
  - a. For men  $\leq$  75 years of age – Prostate Specific Antigen (PSA) (or adjusted PSA in special populations, i.e., patients taking 5 $\alpha$ -reductase inhibitors) OR repeat PSA are  $>3$  and  $<10$ ng/mL AND/OR Digital Rectal Exam (DRE) findings are very suspicious for cancer
  - b. For men  $>$  75 years of age – PSA (or adjusted PSA in special populations, i.e., patients taking 5- $\alpha$ -reductase inhibitors) OR repeat PSA are  $\geq 4$  and  $<10$ ng/mL AND/OR DRE findings are very suspicious for cancer.

EXCEPTION: a molecular biomarker test may be performed in men with PSA levels  $>10$  ng/mL who are being considered for repeat biopsy IF appropriate according to consensus guidelines AND according to the following: the specific biomarker test has been validated in men with PSA levels  $>10$  ng/mL AND a Multiparametric MRI (mpMRI) is negative, *if performed*.

3. The beneficiary has not had a prostate biopsy OR has had a previous negative or non-malignant but abnormal histopathology finding (i.e., atypical small acinar proliferation (ASAP) or high-grade prostatic intraepithelial neoplasia (HGPIN) on prostate biopsy).
  - o Patients under consideration for a repeat biopsy have first undergone repeat PSA and/or DRE testing as recommended by consensus guidelines
4. The beneficiary would benefit from treatment of prostate cancer and patient management will be impacted by use of a biomarker in a manner already demonstrated in the peer-reviewed published literature to improve patient outcomes.
5. The medical record supports the medical necessity for the biomarker test.
6. Testing is performed according to the intended use of the test in the intended patient population for which the test was developed and validated.
7. Testing must be performed according to Clinical Laboratory Improvement Amendments (CLIA) and/or Food and Drug Administration (FDA) regulations in an accredited laboratory.
8. For a given clinical indication (pre-OR post-biopsy), only one molecular biomarker may be performed UNLESS a second test, meeting all the criteria established herein, is reasonable and necessary as an adjunct to the first test, according to criteria established in this policy.
9. If the test relies on an algorithm which may range in complexity from a threshold determination of a single numeric value to a complex mathematical or computational function, the algorithm must be validated in a cohort that is not a development cohort for the algorithm.
10. The analytes measured have demonstrated clinical validity and clinical utility (i.e., improved detection or discrimination of cancer or high-grade cancer or reduction in the need for biopsy) in the peer-reviewed published literature, establishing a clear and significant biological/molecular basis for stratifying patients and subsequently selecting (either positively or negatively) their clinical management decision within a clearly defined population.
11. The test is ordered by a physician specialist in the management of prostate cancer, such as a urologist or oncologist. An exception may be made in geographic locations where the specialist(s) cannot be reasonably reached by the beneficiary and the ordering provider is located closer to the beneficiary's

place of residence than the nearest specialist. We would generally expect that beneficiaries for whom the test is ordered under this exception to be living in rural locations, islands, or some other location where access to care is limited.

### **MyProstateScore (MPS), CPT Code 0113U**

MPS may be considered medically necessary when the following criteria for numbers 1 through 3 are met:

1. The test is ordered only once per year by a physician or other qualified health care professional (i.e., NP, CNS, PA) AND one of the following:
  - a. Prior to potential biopsy for men >/ 45 years old; OR
  - b. Men who need a repeat biopsy in the setting of individuals thought to be at higher risk despite a prior negative biopsy with confirmed moderately elevated PSA (>3ng/ml and <10ng/ml; or PSA >/4ng/ml and < 10ng/ml in men > 75 years of age)

\*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.
2. AND no other relative indication for prostate biopsy including ANY of the following:
  - a. DRE suspicious for cancer (e.g., nodules, induration, or asymmetry)
  - b. Positive multiparametric MRI (Prostate Imaging Reporting and Data System [PI-RADS]  $\geq$ 3) (if available)
  - c. Positive prior biopsy (cancer Grade Group  $\geq$ 1, intraductal carcinoma (IDC), atypical intraductal proliferation (AIP))
  - 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)
3. AND no other relative contraindication for prostate biopsy including ANY of the following:
  - a. <10 year life expectancy, or otherwise not a candidate for prostate cancer treatment
  - b. Invasive treatment for benign prostatic disease or taking medications that influence serum PSA levels within 6 months.
  - c. Active prostatitis on antibiotics

### **Medicare Advantage Plans and Commercial Products**

Unless otherwise noted, for any test filed with an Unlisted CPT code, the medical necessity criteria in the Genetic Testing Services policy would be used. Please see the Related Policies section.

### **PRIOR AUTHORIZATION**

Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products and is obtained via the online tool for participating providers for the following tests:

- 4Kscore
- ConfirmMDx
- MyProstateScore (MPS)
- SelectMDx

### **Medicare Advantage Plans and Commercial Products**

There is no specific CPT coding for some of the services referenced in this policy. Therefore, an Unlisted CPT code should be used (see Coding Section for details). All Unlisted genetic testing CPT codes require prior authorization to determine what service is being rendered and if the service is covered or not medically necessary. See the Related Policies section.

Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products and is obtained via the online tool for participating providers. See the Related Policies section.

**Note:** Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

### **POLICY STATEMENT**

The following test(s) are covered:

- ExoDx Prostate IntelliScore (EPI)
- ProgenSA PCA3

The following test is covered, but due to the instruction to file an Unlisted CPT code, prior authorization is required:

- Prostate Health Index (phi)

The following tests are considered medically necessary when the medical criteria above are met:

- 4Kscore
- ConfirmMDx
- MyProstateScore (MPS)
- SelectMDx

The following test is considered not covered when filed with one of the ICD-10-CM codes listed in the Coding section of this policy.

- Immunoassay for tumor antigen, other antigen, quantitative (eg, CA 50, 72-4, 549), each

The following genetic and protein biomarkers for the diagnosis of prostate cancer are considered not covered for Medicare Advantage Plans and not medically necessary for Commercial Products as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome:

- Apifyny
- PanGIA Prostate
- Mitochondrial DNA variant testing (eg, Prostate Core Mitomics Test)
- Candidate gene panels

Single nucleotide variant testing for cancer risk assessment of prostate cancer is not covered as the evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

### **Commercial Products**

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. §27-19-81 described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

## COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate section of the Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for applicable laboratory testing and not medically necessary/not covered benefits/coverage.

## BACKGROUND

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 United States is approximately 16%, while 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 2 to 3 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.

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.

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 (CLIA). Laboratories that offer laboratory-developed tests must be licensed under the CLIA for high-complexity testing. The following laboratories are certified under the CLIA: 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 (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 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 biopsies and for whom a repeat biopsy would be recommended based on current standard of care. The Progenesa PCA3 Assay should not be used for men with atypical small acinar proliferation on their most recent biopsy.

The 4Kscore test measures blood levels of four Kallikreins protein biomarkers (total prostate-specific antigen [tPSA], free PSA [fPSA], intact PSA [iPSA], and human Kallikrein-related peptidase 2 [hK2]) in addition to other clinical information, including age, digital rectal examination (DRE) and prior biopsy history. All of these components are placed into a proprietary algorithm to provide a percent risk for a high-grade Gleason score greater than or equal to 7 cancer on biopsy. The 4Kscore test algorithm's goal is to refine patient selection for biopsies to reduce unnecessary biopsies in men being considered for biopsy of the prostate for potential cancer.

The NCCN updated guidelines states that the 4Kscore test may be considered prior to biopsy for those with prior negative biopsy who are thought to be at risk for clinically significant prostate cancer. The NCCN notes that it is important for patients and their urologists to understand that no optimal cutoff threshold has been established for the 4Kscore test. It is recommended that the 4Kscore test may be considered before biopsy in men with serum PSA levels greater than 3ng/ml who desire more specificity. With a recommendation for specific clinical scenarios, coupled with documented shared decision making, the AUA and NCCN organizations both state that biomarkers specifically 4Kscore “can be considered in men with a suspicious PSA level to inform prostate biopsy decisions.”

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.

ConfirmMDx® is a multi-gene test that uses prostate biopsy tissue to assess the methylation status of 3 biomarkers (GSTP1, RASSF1, APC) associated with prostate cancer. The performance of this assay in large, blinded clinical validation studies demonstrated a NPV of 90% for all prostate cancer and 96% for high-grade disease, considerably higher than that afforded by standard histopathology review. A field observation study conducted in 138 patients with negative biopsies found a repeat biopsy rate of 4.3%, significantly lower than the 40% repeat biopsy rate reported in the PLCO trial, for patients with an initial negative biopsy.

Biomarkers can help stratify men who have an elevated PSA into those more likely versus less likely to have aggressive disease. These non-invasive biomarker tests have demonstrated that they can (1) reduce the need for unnecessary biopsies in men unlikely to have prostate cancer or high-grade prostate cancer and/or (2) better define men at risk for higher-grade prostate cancer. There is adequate evidence to show that the incremental information provided by validated molecular biomarker tests for prostate cancer in samples of patients whose findings can be generalized to the Medicare population, changes physician management in a way that improves outcomes.

EPI is a urine-based 3-gene exosomal RNA expression assay. The EPI gene signature and score incorporates levels of PCA3 (PCa antigen 3), ERG (v-ets erythroblastosis virus E26 oncogene homologs) and SPDEF (SAM-pointed domain-containing Ets transcription factor). EPI uses a proprietary algorithm to translate the level of expression of these three genes into an individualized risk score that predicts the presence of HGPC, with a higher EPI score indicative of a higher probability of high-grade disease. EPI does not incorporate PSA and other SOC factors into the score, but is intended to be used in conjunction with SOC elements such as age, family history, PSA level and DRE results.

Apify uses an algorithm to score the detection of 8 autoantibodies (ARF 6, NKX3-1, 5' -UTR-BMI1, CEP 164, 3' -UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2) in serum. The identified biomarkers play a role in processes such as androgen response regulation and cellular structural integrity and are proteins that are thought to play a role in prostate tumorigenesis.

MyProstateScore measures TMPRSS2-ERG gene fusion and calculates a probability score that incorporates serum PSA or the PCPT, and urine TMPRSS2-ERG and PCA3 scores.

PanGIA Prostate is a urine test that uses a device with binding pockets for small molecules, proteins, and cells. Results are uploaded to the cloud and a machine learning algorithm compares the results with a signature from patients who have had a positive biopsy and patients who have had a negative prostate biopsy. The report includes a diagnosis with the level of confidence in the diagnosis.

SelectMDx for prostate cancer uses a model that combines HOXC6 and DLX1 gene expression with traditional risk assessment models. HOXC6 and DLX1 mRNA is measured in post-DRE urine against kallikrein-related peptidase 3 as an internal reference.

For individuals who are being considered for an initial prostate biopsy who receive testing for genetic and protein biomarkers of prostate cancer (eg, 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 test. Comparative studies 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 (eg, 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.

## **CODING**

The following CPT code(s) are covered

CPT code 81313 is generally used to represent the Progenesa® PCA3 Assay but can also be used for non-brand name testing.

**81313** PCA3/KLK3 (prostate specific antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)

This code can be used for ExoDx Prostate IntelliScore (EPI):

**0005U** Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score

The following CPT code(s) are covered when medical criteria above are met.

This code can be used for 4Kscore® Test:

**81539** Oncology (high-grade prostate cancer), biochemical assay of four proteins (total PSA, free PSA, intact PSA and human kallikrein 2 [hK2]) plus patient age, digital rectal examination status, and no history of positive prostate biopsy, utilizing plasma, prognostic algorithm reported as a probability score

This code can be used for the ConfirmMDx® gene hypermethylation test.

**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

This code can be used for MyProstateScore (MPS):

**0113U** Oncology (prostate), measurement of PCA3 and TMPRSS2-ERG in urine and PSA in serum following prostatic massage, by RNA amplification and fluorescence-based detection, algorithm reported as risk score

This code can be used for SelectMDx:

**0339U** Oncology (prostate), mRNA expression profiling of HOXC6 and DLX1, reverse transcription polymerase chain reaction (RT-PCR), first-void urine following digital rectal examination, algorithm reported as probability of high-grade cancer (New Code Effective 10/1/2022)  
**(For Dates of Service prior to 10/1/2022, an Unlisted CPT code must be used.)**

The following CPT code(s) are not covered for Medicare Advantage Plans and are not medically necessary for Commercial Products.

This code can be used for Apifyn:

**0021U** Oncology (prostate), detection of 8 autoantibodies (ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2), multiplexed immunoassay and flow cytometry serum, algorithm reported as risk score

This code can be used for PanGIA Prostate:

**0228U** Oncology (prostate), multianalyte molecular profile by photometric detection of macromolecules adsorbed on nanosponge array slides with machine learning, utilizing first morning voided urine, algorithm reported as likelihood of prostate cancer

If the following CPT code is filed for prostate testing, it is considered not covered for Medicare Advantage Plans and not medically necessary for Commercial Products when filed with one of the ICD-10-CM codes, listed below:

Note: This CPT code can be used for testing for more conditions/diagnoses than are referenced in this policy. Please see the Related Policies section for other not covered and not medically necessary conditions/diagnoses.

**86316** Immunoassay for tumor antigen, other antigen, quantitative (eg, CA 50, 72-4, 549), each

## ICD-10-CM

C61

The following Unlisted CPT code requires prior authorization. The code can be used for any test identified in this policy that does not have a specific CPT code, including Prostate Health Index (phi).

**81479** Unlisted molecular pathology procedure

## RELATED POLICIES

Biomarker Testing Mandate

Genetic Testing Services

Medical Necessity

Proprietary Laboratory Analyses (PLA)

Serum Tumor Markers for Breast and Gastrointestinal Malignancies

Unlisted Procedures

Urinary Biomarkers for Cancer Screening, Diagnosis and Surveillance

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4. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: MolDX: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer (L39005)



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