Medical Coverage Policy | Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

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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 81313
- 4Kscore (OPKO Health), CPT 81539
- ConfirmMDx (MDx Health), CPT 81551
- ExoDx Prostate IntelliScore (EPI) (Exosome Diagnostics), CPT 0005U
- Apifiny (Exact Sciences), CPT 0021U
- MyProstateScore (MPS) (Lynx Dx), CPT 0113U
- PanGIA Prostate (Genetics Institute of America), CPT 0228U
- SelectMDx (MDx Health), CPT 0339U
- Prostate Health Index (phi) (Beckman Coulter), CPT 84153, 84154, 86316
- Prostate Core Mitomics Test (Mitomics), Unlisted CPT

MEDICAL CRITERIA

Medicare Advantage Plans

Progensa PCA3, CPT 81313

PCA3 testing may be considered medically necessary when the following criteria are met:

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

1. No other relative <u>indication</u> 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] ≥3) (if available)
    c. Positive prior biopsy (cancer Grade Group ≥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)
2. No other relative <u>contraindication</u> 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 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.

4Kscore, CPT 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 5α-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 81551

ConfirmMDx 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 ≤ 75 years of age – Prostate Specific Antigen (PSA) (or adjusted PSA in special populations, i.e., patients taking 5alpha-reductase inhibitors) OR repeat PSA are >3 and <10ng/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 ≥4 and <10ng/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).

    - 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.

ExoDx Prostate IntelliScore (EPI), CPT 0005U
EPI may be considered medically necessary when the following criteria are met:

- The test is ordered only once per year by a physician or other qualified health care professional (i.e., NP, CNS, PA), and;
- For men receiving testing prior to potential biopsy greater than or equal to 50 years of age, and;
- With a PSA of greater than 4ng/ml.

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

Medicare Advantage Plans
Prior authorization is required for the following tests:

- PCA3 testing (eg, Progensa PCA3 Assay)
- 4Kscore
- ConfirmMDx
- ExoDx Prostate IntelliScore

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

Medicare Advantage Plans

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:

- PCA3 testing (eg, Progensa PCA3 Assay)
- 4Kscore
- ConfirmMDx
- ExoDx Prostate IntelliScore

The following genetic and protein biomarkers for the diagnosis of prostate cancer are not covered as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome:

- Apifiny
- MyProstateScore
- PanGIA Prostate
- HOXC6 and DLX1 testing (eg, SelectMDx)
- 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

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 genetic and protein biomarkers for the diagnosis of prostate cancer are considered not medically necessary as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome:

- PCA3 testing (eg, Progensa PCA3 Assay)

- Kallikrein markers (eg, 4Kscore® Test)
- Gene hypermethylation testing (eg, ConfirmMDx)
- PCA3, ERG, and SPDEF RNA expression in exosomes (eg, ExoDx Prostate IntelliScore)
- Autoantibodies ARF 6, NKX3-1, 5¢-UTR-BMI1, CEP 164, 3¢-UTR-Ropporin, Desmocollin, AURKAIP-1, and CSNK2A2 (eg, Apifiny)
- TMPRSS:ERG fusion genes (eg, MyProstateScore {MPS})
- PanGIA Prostate
- HOXC6 and DLX1 testing (eg, SelectMDx)
- Mitochondrial DNA variant testing (eg, Prostate Core Mitomics Test)
- Candidate gene panels

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

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 genetic 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 Progensa® PCA3 Assay (Gen-Probe; now Hologic) was approved by the FDA through the premarket approval process. The Progensa 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 Progensa PCA3 Assay should not be used for men with atypical small acinar proliferation on their most recent biopsy.

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.

For individuals who are being considered for an initial prostate biopsy who receive testing for genetic and protein biomarkers of prostate cancer (eg, kallikreins biomarkers and 4Kscore Test, proPSA and Prostate Health Index, TMPRSS fusion genes and MyProstateScore, 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 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 (eg, 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.

Progensa PCA3 Assay

PCA3 is an mRNA expression assay tested from post-DRE urine. The FDA has approved the PCA3 assay to help decide whether a repeat biopsy in men aged 50 years or older with one or more previous negative prostate biopsies is necessary. In a prospective multicenter study of 466 men with a least one prior negative prostate biopsy scheduled for repeat biopsy based on best clinical judgement, a PCA3 score cutoff of 25 showed a sensitivity of 77.5%, specificity of 57.1%, NPV of 90%, and PPV of 33.6%. Those with a score of <25 were 4.56 times more likely to have a negative repeat biopsy.

4Kscore

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 clinical features of this group of men are poorly defined.

ConfirmMDx
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.

ExoDx Prostate IntelliScore (EPI)
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 Etstranscription factor). EPI uses a proprietary algorithm to translate the level of expression of these three genes into anindividualized 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 conjunctionwith SOC elements such as age, family history, PSA level and DRE results.

Apifiny
Apifiny 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
MyProstateScore measures TMPRSS2-ERG gene fusion and calculates a probability score that incorporates serum PSA or the PCPT, and urineTMPRSS2-ERG and PCA3 scores

PanGIA Prostate
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
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.

Prostate Health Index
The Prostate Health Index (phi; Beckman Coulter) is an assay that combines results of 3 blood serum immunoassays (total PSA, free PSA, [-2]proPSA [p2PSA]) numerically to produce a "phi score." This score is calculated with the phi algorithm using the following formula: ([-2]proPSA/free PSA) x √total PSA. The phi

score is indicated for men 50 years and older with above-normal total PSA readings between 4.0 ng/mL and 10 ng/mL who have had a negative DRE in order to distinguish prostate cancer from benign prostatic conditions.

Medicare Advantage Plans

Progensa PCA3 Assay and ExoDx Prostate IntelliScore (EPI)
While the results of the mostly industry-sponsored validation studies are promising, benefits remain theoretical, namely, that fewer biopsies of men with moderately elevated PSA is inherently a good thing. Certainly, it is good in the short term for men who avoid an "unnecessary" prostate biopsy. Not good, however, are necessary biopsies missed due to false negatives. Moreover, even the definition of "unnecessary" may be evolving. Also, some studies overrepresented men for whom the information is less likely to be helpful (a positive DRE, PSA levels outside the gray zone, or older men not candidates for surgery), or underrepresented others (e.g., high risk groups such as African Americans, etc.). Comparative studies of the many biomarkers are lacking and it is unclear how to use the tests in practice, particularly when test results are contradictory (1). For all these reasons, the long-term benefit of these tests to net health outcomes (i.e., mortality, morbidity, or quality of life) is not yet clear.

4Kscore
In their guidelines, the American Urological Association (AUA) recognizes that the decision to undergo PSA screening in men ages 55 to 69 involves weighing the benefits of reducing the rate of metastatic prostate cancer and prevention of prostate cancer death against the known potential harms associated with screening and treatment. For this reason, shared decision-making is recommended for men 55 to 69 years of age that are considering PSA screening and proceeding based on a man's values and preferences.

The greatest benefit of screening appears to be in men 55 to 69 years of age. Multiple approaches subsequent to a PSA test (e.g., urinary and serum biomarkers, imaging, risk calculators) are available for identifying men more likely to harbor a prostate cancer and/or one with an aggressive phenotype. The use of such tools can be considered in men with a suspicious PSA level to inform prostate biopsy decisions.

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."

ConfirmMDx
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.

CODING
The following CPT codes are covered for Medicare Advantage Plans when medical criteria above are met and are not medically necessary for Commercial Products.

CPT code 81313 is generally used to represent the Progensa® 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 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 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 not covered for Medicare Advantage Plans and are not medically necessary for Commercial Products.

This code can be used for Apifiny:

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 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 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

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 Unlisted CPT code requires prior authorization for Medicare Advantage Plans and Commercial Products. The code can be used for any test identified in this policy that does not have a specific CPT code.

81479 Unlisted molecular pathology procedure

RELATED POLICIES

Genetic Testing Services
Medical Necessity
Proprietary Laboratory Analyses (PLA)

PUBLISHED

Provider Update, February 2023, June 2023
Provider Update, March 2022
Provider Update, May 2020
Provider Update, August 2019
Provider Update, April 2019

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