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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)
- 4Kscore (OPKO Health)
- ConfirmMDx (MDx Health)
- ExoDx Prostate IntelliScore (Exosome Diagnostics)
- Apify (Exact Sciences)
- MyProstateScore (MPS) (Lynx Dx)
- PanGIA Prostate (Genetics Institute of America)
- Prostate Health Index (phi) (Beckman Coulter)
- SelectMDx (MDx Health)
- Prostate Core Mitomics Test (Mitomics)

MEDICAL CRITERIA

Medicare Advantage Programs

ProgenSA PCA3

PCA3 testing will be considered medically reasonable and necessary when all the following are met:

- 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”)

4Kscore

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 α -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

ConfirmMDx is covered 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 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.

ExoDx Prostate IntelliScore (EPI)

EPI is covered ONCE in men ≥ 50 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. Positive multiparametric MRI (if done)
 - c. Other major risk factor for prostate cancer including:
 - i. 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. 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.

Apifyn, MyProstateScore and PanGIA Prostate

Apifyn, MyProstateScore and PanGIA Prostate may be considered medically necessary when the Medicare Advantage Plans medical necessity criteria is used for review, found in the Medical Necessity policy. Please see Related Policies section.

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
- Apifyn

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 without a prior authorization requirement:

- 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 tests may be considered medically necessary when the medical criteria in the Medical Necessity policy are met:

- Apifyn
- MyProstateScore
- PanGIA Prostate

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 outcomes:

- 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 without a prior authorization requirement:

- 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 outcomes.

- 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, Apifyn)
- TMPRSS:ERG fusion genes (eg, MyProstateScore {MPS})
- HOXC6 and DLX1 testing (eg, SelectMDx)
- Mitochondrial DNA variant testing (eg, Prostate Core Mitomics Test)
- PanGIA Prostate
- 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 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.

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, TMRSS fusion genes and MyProstateScore, SelectMDx for Prostate Cancer, ExoDx Prostate, Apifyny, 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 did 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.

Medicare Advantage Plans

ProgenSA PCA3 Assay

ProgenSA 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 $\times 1000$, the PCA3 assay is performed on the first urine collected following an attentive digital rectal examination.

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.

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

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 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 standard of care (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.

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: $([-2]proPSA/free PSA) \times \sqrt{total PSA}$. 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.

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 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 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:

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 codes are covered for Medicare Advantage Plans when medical criteria found in the Medical Necessity policy are met and are not medically necessary for Commercial Products.

This code can be used for Apify:

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

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, March 2022

Provider Update, May 2020

Provider Update, August 2019

Provider Update, April 2019

Provider Update, February 2019

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