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Horizon BCBSNJ
Uniform Medical Policy Manual

Section:	Pathology
Policy Number:	030
Effective Date:	02/02/2019
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Subject:
Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

Description:

IMPORTANT NOTE:

The purpose of this policy is to provide general information applicable to the administration of health benefits that Horizon Blue Cross Blue Shield of New Jersey and Horizon Healthcare of New Jersey, Inc. (collectively "Horizon BCBSNJ") insures or administers. If the member's contract benefits differ from the medical policy, the contract prevails. Although a service, supply or procedure may be medically necessary, it may be subject to limitations and/or exclusions under a member's benefit plan. If a service, supply or procedure is not covered and the member proceeds to obtain the service, supply or procedure, the member may be responsible for the cost. Decisions regarding treatment and treatment plans are the responsibility of the physician. This policy is not intended to direct the course of clinical care a physician provides to a member, and it does not replace a physician's independent professional clinical judgment or duty to exercise special knowledge and skill in the treatment of Horizon BCBSNJ members. Horizon BCBSNJ is not responsible for, does not provide, and does not hold itself out as a provider of medical care. The physician remains responsible for the quality and type of health care services provided to a Horizon BCBSNJ member.

Horizon BCBSNJ medical policies do not constitute medical advice, authorization, certification, approval, explanation of benefits, offer of coverage, contract or guarantee of payment.

Various genetic and protein biomarkers are associated with prostate cancer. These tests have the potential to improve the accuracy of differentiating between which men should undergo prostate biopsy and which rebiopsy after a prior negative biopsy. This policy addresses these types of tests for cancer risk assessment. Testing to determine cancer aggressiveness after a tissue diagnosis of cancer is addressed in a separate policy on 'Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management' (Policy #096 in the Pathology Section).

Populations	Interventions	Comparators	Outcomes
Individuals: · Who are being	Interventions of interest are: · Testing for genetic	Comparators of interest are: · Standard clinical	Relevant outcomes include: · Overall survival

considered for initial prostate biopsy	and protein biomarkers of prostate cancer	examination including measurement of percent free prostate-specific antigen	· Disease-specific survival · Test validity · Resource utilization · Quality of life
Individuals: · Who are being considered for repeat prostate biopsy	Interventions of interest are: · Testing for genetic and protein biomarkers of prostate cancer	Comparators of interest are: · Standard clinical examination including measurement of percent free prostate-specific antigen	Relevant outcomes include: · Overall survival · Disease-specific survival · Test validity · Resource utilization · Quality of life

Background

Prostate Cancer

Prostate cancer is the second most common cancer in men, with a predicted 161,360 incidence cases and 26,730 deaths expected in the United States in 2017.[1]

Prostate cancer is a complex, heterogeneous disease, ranging from microscopic tumors unlikely to be life-threatening to aggressive tumors that can metastasize, leading to morbidity or death. Early localized disease can usually be treated with surgery and radiotherapy, although active surveillance may be adopted in men whose cancer is unlikely to cause major health problems during their lifespan or for whom the treatment might be dangerous. In patients with inoperable or metastatic disease, treatment consists of hormonal therapy and possibly chemotherapy. The lifetime risk of being diagnosed with prostate cancer for men in the United States is approximately 16%, while the risk of dying of prostate cancer is 3%.[2] African American men have the highest prostate cancer risk in the United States; the incidence of prostate cancer is about 60% higher and the mortality rate is more than 2 to 3 times greater than that of white men.[3] 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,[4] 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.[5] It is an architectural grading system ranging from 1 (well differentiated) to 5 (poorly differentiated); the score is the sum of the primary and secondary patterns. A Gleason score of 6 or less is low-grade prostate cancer that usually grows slowly; 7 is an intermediate grade; 8 to 10 is high-grade cancer that grows more quickly. A revised prostate cancer grading system has been adopted by the National Cancer Institute and the World Health Organization.[6] A cross-walk of these grading systems is shown in Table 1.

Table 1. Prostate Cancer Grading Systems

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

Numerous genetic alterations associated with development or progression of prostate cancer have been described, with the potential for the use of these molecular markers to improve the selection process of men who should undergo prostate biopsy or rebiopsy after an initial negative biopsy.

Regulatory Status
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. Laboratories that offer laboratory-developed tests must be licensed under the Clinical Laboratory Improvement Amendments for high-complexity testing. The following laboratories are certified under the Clinical Laboratory Improvement Amendments: BioReference Laboratories and GenPath Diagnostics (subsidiaries of OPKO Health; 4Kscore®), ARUP Laboratories, Mayo Medical Laboratories, LabCorp, BioVantra, others (PCA3 assay), Clinical Research Laboratory (Prostate Core Mitomic Test™), MDx Health (SelectMDx, ConfirMDx), Innovative Diagnostics (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 this test.

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. FDA product code: OYM.

In June 2012, proPSA, a blood test used to calculate the Prostate Health Index (phi; Beckman Coulter) was approved by the FDA through the premarket approval process. The phi test is indicated as an aid to distinguish prostate cancer from a benign prostatic condition in men ages 50 and older with prostate-specific antigen levels of 4 to 10 ng/mL and with digital rectal exam findings that are not suspicious. According to the manufacturer, the test reduces the number of prostate biopsies. FDA product code: OYA.

Related Policies

- Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management (Policy #096 in the Pathology Section)

Policy:

*(**NOTE**: For services provided **August 1, 2017** and after, Horizon Blue Cross Blue Shield of New Jersey collaborates with eviCore healthcare to conduct Medical Necessity Determination for certain molecular and genomic testing services for members enrolled in Horizon BCBSNJ fully insured products as well as Administrative Services Only (ASO) accounts that have **elected** to participate in the Molecular and Genomic Testing Program ("the Program"). Beginning August 1, 2017, the criteria and guidelines included in this policy apply to members enrolled in plans that have **NOT elected** to participate in the Program.*

*To access guidelines that apply for services provided **August 1, 2017** and after to members enrolled in plans that **HAVE elected** to participate in the Program, please visit www.evicore.com/healthplan/Horizon_Lab.*

For Medicare Advantage, please refer to the Medicare Coverage Section below for coverage guidance.)

1. 4Kscore testing is considered ***medically necessary*** when all of the following criteria are met:
   · No previous 4Kscore testing performed after the most recent negative biopsy when a result was successfully obtained, AND
   · No previous ConfirmMDx testing on the most recent negative biopsy when a result was successfully obtained, AND
   · Member is not under active surveillance for low stage prostate cancer, AND
   · Negative prostate biopsy within the past 24 months, AND
   · Member is considered at higher risk for prostate cancer by one or more of the following:
      o Family history of 1st degree relative with prostate cancer diagnosed younger than age 65 years, and/or
      o African American race, and/or
      o Known mutation in a gene associated with increased risk of prostate cancer (e.g., BRCA 1/2, HOXB13 (G84E mutation carriers), MLH1, MSH2, MSH6, PMS2, EPCAM)

2. ConfirmMDx testing is considered ***medically necessary*** when all of the following criteria are met:
   · No previous ConfirmMDx testing on the same sample when a result was successfully obtained, AND
   · No previous 4Kscore testing performed after the most recent negative biopsy when a result was successfully obtained, AND
   · Member is not under active surveillance for low stage prostate cancer, AND
   · Negative prostate biopsy within the past 24 months, AND
   · Member is considered at higher risk for prostate cancer by one or more of the following:
      o Family history of 1st degree relative with prostate cancer diagnosed younger than age 65 years, and/or

o African American race, and/or
o Known mutation in a gene associated with increased risk of prostate cancer (e.g., BRCA 1/2, HOXB13 (G84E mutation carriers), MLH1, MSH2, MSH6, PMS2, EPCAM)

3. Prostate cancer antigen 3 (PCA3) testing is considered ***medically necessary*** when all of the following criteria are met:

· Age >50 years, AND
· One or more previous negative prostate biopsies, AND
· Continued clinical suspicion of prostate cancer based on DRE or elevation of PSA of >3 ng/mL, and for whom a repeat biopsy would be recommended by a urologist based on current standard of care, AND
· Atypical small acinar proliferation (ASAP) was NOT identified on the most recent biopsy.

4. The following genetic and protein biomarkers for the diagnosis of prostate cancer are considered ***investigational***:

- Metabolomic profiles (eg, Prostarix™)
- *TMPRSS* fusion genes
- Candidate gene panels
- Mitochondrial DNA mutation testing (eg, Prostate Core Mitomics Test™)
- Prostate Health Index (phi)
- HOXC6 and DLX1 testing (e.g., Select MDx)
- PCA3, ERG, and SPDEF RNA expression in exosomes (e.g., ExoDx Prostate IntelliScore)
- Autoantibodies ARF5, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocolin, AURKAIP-1, CSNK2A2 (e.g., Apinify).

5. Single nucleotide polymorphisms (SNPs) testing for cancer risk assessment of prostate cancer is considered ***investigational***.

Medicare Coverage:

There is no National Coverage Determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of Local Medicare Carriers. Novitas Solutions, Inc, the Local Medicare Carrier for jurisdiction JL, has determined that the PROGENSA® PCA3 Assay is covered for certain limited diagnosis. For additional information and eligibility for PROGENSA® PCA3 Assay, refer to Local Coverage Determination (LCD): Biomarkers for Oncology (L35396). Available to be accessed at Novitas Solutions, Inc., Medical Policy Search page: https://www.novitas-solutions.com/webcenter/portal/MedicareJL/LcdSearch?_afrLoop=90769712476969#!%40%40%3F_afrLoop%3D90769712476969%26centerWidth%3D100%2525%26leftWidth%3D0%2525%26rightWidth%3D0%2525%26showFooter%3Dfalse%26showHeader%3Dfalse%26_adf.ctrl-state%3D63y7eftob_46.

Noridian Healthcare Solutions, LLC, the Local Medicare Carrier for jurisdiction J-E, is providing limited coverage for the ConfirmMDx epigenetic assay for prostate cancer

(MDxHealth, Irvine, CA) when LCD L36327 criteria is met. Coverage is limited to providers enrolled in the ConfirmMDx Certification and Training Registry (CTR) program. For additional information and eligibility, refer to Local Coverage Determination (LCD): MolDX-CDD: ConfirmMDx Epigenetic Molecular Assay (L36327). Available to be accessed at CMS Local Coverage Determinations by State Index search page: https://www.cms.gov/medicare-coverage-database/indexes/lcd-state-index.aspx.

There is no National Coverage Determination (NCD) or applicable Local Coverage Determination (LCD) for the below tests. Therefore, Medicare Advantage Products will follow the Horizon BCBSNJ Medical Policy for these tests:
• Metabolomic profiles (eg, Prostarix™)
• TMPRSS fusion genes
• Candidate gene panels
• Mitochondrial DNA mutation testing (eg, Prostate Core Mitomics Test™)
• Prostate Health Index (phi).

PROPRIETARY LABS (Labs that are the sole source for the diagnostic lab test)
For labs which are proprietary (that is, the sole source for the diagnostic lab test involved), Medicare Advantage Products will follow the Medicare Local Coverage Determination of the State where the proprietary lab is located.

Per FUTURE Local Coverage Determination (LCD): 4Kscore Test Algorithm (L37792), effective 3/21/19, the use of the 4Kscore test algorithm is non-covered. The available published clinical evidence on the 4Kscore Test does not support improved health outcomes in the Medicare patient population.

For additional information, refer to FUTURE Local Coverage Determination (LCD): 4Kscore Test Algorithm (L37792). Available to be accessed at Novitas Solutions, Inc., Medical Policy Search page: https://www.novitas-solutions.com/webcenter/portal/MedicareJL/LcdSearch?_afrLoop=90769712476969#!%40%40%3F_afrLoop%3D90769712476969%26centerWidth%3D100%2525%26leftWidth%3D0%2525%26rightWidth%3D0%2525%26showFooter%3Dfalse%26showHeader%3Dfalse%26_adf.ctrl-state%3D63y7eftob_46.

Horizon BCBSNJ Medical Policy Development Process:

This Horizon BCBSNJ Medical Policy (the "Medical Policy") has been developed by Horizon BCBSNJ's Medical Policy Committee (the "Committee") consistent with generally accepted standards of medical practice, and reflects Horizon BCBSNJ's view of the subject health care services, supplies or procedures, and in what circumstances they are deemed to be medically necessary or experimental/ investigational in nature. This Medical Policy also considers whether and to what degree the subject health care services, supplies or procedures are clinically appropriate, in terms of type, frequency, extent, site and duration and if they are considered effective for the illnesses, injuries or diseases discussed. Where relevant, this Medical Policy considers whether the subject health care services, supplies or procedures are being requested primarily for the convenience of the covered person or the health care provider. It may also consider whether the services, supplies or procedures are more costly than an alternative service or sequence of services, supplies or procedures that are at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the relevant illness, injury or disease. In reaching its conclusion regarding what it considers to be the generally accepted standards of medical practice, the Committee

reviews and considers the following: all credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, physician and health care provider specialty society recommendations, the views of physicians and health care providers practicing in relevant clinical areas (including, but not limited to, the prevailing opinion within the appropriate specialty) and any other relevant factor as determined by applicable State and Federal laws and regulations.

Index:
Prostate Cancer, PCA Test

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Codes:

(The list of codes is not intended to be all-inclusive and is included below for informational purposes only. Inclusion or exclusion of a procedure, diagnosis, drug or device code(s) does not constitute or imply authorization, certification, approval, offer of coverage or guarantee of payment.)

CPT*

81313
81479
81539
81551
81599
0005U
0021U

HCPCS

American Medical Association.

Medical policies can be highly technical and are designed for use by the Horizon BCBSNJ professional staff in making coverage determinations. Members referring to this policy should discuss it with their treating physician, and should refer to their specific benefit plan for the terms, conditions, limitations and exclusions of their coverage.
