



Louisiana

Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

Policy # 00272

Original Effective Date: 10/20/2010

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Microarray-based Gene Expression Analysis for Prostate Cancer Management is addressed separately in medical policy 00403.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the following genetic and protein biomarkers for the diagnosis of prostate cancer to be **investigational***:

- Kallikrein markers (eg, 4Kscore Test)
- Prostate Health Index (phi)
- *HOXC6* and *DLX1* testing (eg, SelectMDx)
- 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, Apifyny)
- *PCA3* testing (eg, ProgenSA PCA3 Assay)
- *TMPRSS:ERG* fusion genes
- Gene hypermethylation testing (eg, ConfirmMDx)
- Mitochondrial DNA variant testing (eg, Prostate Core Mitomics Test)
- PanGIA Prostate
- Candidate gene panels.

Based on review of available data, the Company considers single nucleotide variant testing for cancer risk assessment of prostate cancer to be **investigational.***

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Policy Guidelines

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview

Prostate Cancer

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 U. S. is approximately 16%, while the risk of dying of prostate cancer is 3%. African American men have the highest prostate cancer risk in the U. S.; 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

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quickly. A revised prostate cancer grading system has been adopted by the National Cancer Institute and the World Health Organization. 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 the 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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. FDA has chosen not to require any regulatory review of these tests. In February 2012, the Progen[®][‡] PCA3 Assay (Gen-Probe; now Hologic) was approved by the FDA through the premarket approval process. The Progen[®] PCA3 Assay has been approved by the

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FDA to aid in the decision for repeat biopsy in men 50 years or older who have had 1 or more negative prostate biopsies and for whom a repeat biopsy would be recommended based on the 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.

Rationale/Source

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 Mi-Prostate Score, SelectMDx for Prostate Cancer, ExoDx Prostate, Apify, 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 the 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

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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.

Supplemental Information

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Urological Association et al

The American Urological Association (AUA, 2013; confirmed 2018) published guidelines on the early detection of prostate cancer. The AUA concluded that:

“the literature supporting the efficacy of digital rectal exam (DRE), PSA [prostate-specific antigen] derivatives and isoforms (e.g. free PSA, -2proPSA, prostate health index, hK2, PSA velocity or PSA doubling time) and novel urinary markers and biomarkers (e.g. PCA3) for screening with the goal of reducing prostate cancer mortality provide limited evidence to draw conclusions. While some data suggest use of these secondary screening tools may reduce unnecessary biopsies (i.e. reduce harms) while maintaining the ability to detect aggressive prostate cancer (i.e. maintain the benefits of PSA screening), more research is needed to confirm this.”

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National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines (v.1.2021) recommend that any man with a PSA level greater than 3 ng/mL undergo workup for benign disease, repeat PSA, and digital rectal examination.

The guidelines recommend as part of the workup for benign disease, consider biomarkers that improve the specificity of screening that includes percent free PSA, with consideration of the Prostate Health Index (PHI), SelectMDx, 4K score, and ExoDx Prostate IntelliScore (EPI) in patients who have not yet had a biopsy. NCCN noted that these tests may be especially useful in men with PSA levels between 3 ng/mL and 10 ng/mL. NCCN also noted that it is not yet known how these tests could be applied in optimal combination with magnetic resonance imaging (MRI).

For men who had a negative biopsy but are thought to be at higher risk, NCCN recommends to consider biomarkers that improve the specificity of screening (category 2A evidence). Tests that should be considered in the post-biopsy setting include percent free PSA 4Kscore, PHI, PCA3, ExoDx Prostate IntelliScore (EPI), and ConfirmMDx. The NCCN considers the Mi-Prostate Score (MiPS) to be investigational at the time of the update.

National Institute for Health and Care Excellence

In 2019, the National Institute for Health and Care Excellence (NICE) did not recommend the ProgenSA PCA3 Assay or the phi test for use in men with suspicion of prostate cancer who had a negative or inconclusive prostate biopsy.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (2018) updated recommendations for prostate cancer screening. Genetic and protein biomarkers addressed in this evidence review, including *PCA3*, were not mentioned.

The U.S. Preventive Services Task Force advises individualized decision making about screening for prostate cancer after discussion with a clinician for men ages 55 to 69 (C recommendation) and recommends against PSA-based screening in men 70 and older (D recommendation).

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Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers. Several MolDx carriers have positive coverage for the ConfirmMDx Epigenetic Molecular Assay and the PCA3 assay. At least 1 LCD will cover 1 biomarker test (percent free PSA, phi, 4K score or EPI) prior to initial biopsy in men who meet criteria.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT00773773	A Study to Assess if a Combination of Serum Measurements of Molecular Biomarkers and Serum Protein Profiling Can be Used to Predict Which Patients Undergoing Prostatic Biopsy Will be Diagnosed With Cancer	500	Oct 2021
NCT04357717 ^a	Clinical Evaluation of ExoDx™‡ Prostate (IntelliScore) in Men With Prior Negative Prostate Biopsy Presenting for a Repeat Biopsy	350	Jul 2021
NCT04100811 ^a	Validating the miR Scientific Sentinel™‡ Platform (Sentinel PCC4 Assay) in Men Undergoing Core Needle Biopsy Due to Suspicion of Prostate Cancer for Distinguishing Between no Cancer, Low-, Intermediate- and High-Risk Prostate Cancer	2,000	Dec 2022
NCT01739062	Prostate Cancer Risk Assessment Using Genetic Markers in General Practice (ProCaRis)	5,000	Oct 2031

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NCT04079699	Predicting Prostate Cancer Using a Panel of Plasma and Urine Biomarkers Combined in an Algorithm in Elderly Men Above 70 Years	700	Oct 2039
<i>Unpublished</i>			
NCT03082274 ^a	Prospective Validation of Prostate Biomarkers for Repeat Biopsy: The PRIORITY Study	1,000	Dec 2019
NCT01632930	Medical Economics of Urinary PCSA3 Test for Prostate Cancer Diagnosis	962	Nov 2020 (status unknown)

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

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Policy History

Original Effective Date: 10/20/2010

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- 10/14/2010 Medical Policy Committee review
- 10/20/2010 Medical Policy Implementation Committee approval. New policy.
- 10/06/2011 Medical Policy Committee review
- 10/19/2011 Medical Policy Implementation Committee approval. Minor change to coverage statement (“prognosis” added to the investigational statement on PCA3).
- 10/11/2012 Medical Policy Committee review
- 10/31/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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- 02/19/2013 Coding updated
- 10/03/2013 Medical Policy Committee review
- 10/16/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 12/04/2014 Medical Policy Committee review
- 12/17/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 08/06/2015 Medical Policy Committee review
- 08/19/2015 Medical Policy Implementation Committee approval. Added Kallikrein markers (4Kscore test), metabolomics profiles (Prostarix), candidate gene panels, mitochondrial DNA mutation testing (Prostate Core Mitomics test), and gene hypermethylation testing (ConfirmMDx) to INV statement. Title change.
- 10/06/2016 Medical Policy Committee review
- 10/19/2016 Medical Policy Implementation Committee approval. No change to coverage.
- 01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes and CPT coding update
- 01/05/2017 Medical Policy Committee review
- 01/18/2017 Medical Policy Implementation Committee approval. Added Prostate Health Index (phi) to investigational statement and rationale. Updated rationale and references.
- 01/04/2018 Medical Policy Committee review
- 01/17/2018 Medical Policy Implementation Committee approval. Policy revised to separate initial biopsy and repeat biopsy populations, policy statement otherwise unchanged.
- 10/29/2018 Coding update
- 01/10/2019 Medical Policy Committee review
- 01/23/2019 Medical Policy Implementation Committee approval. The SelectMDx, ExoDx Prostate (IntelliScore), and Apify tests added as investigational.
- 01/03/2020 Medical Policy Committee review
- 01/08/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged
- 02/04/2021 Medical Policy Committee review
- 02/10/2021 Medical Policy Implementation Committee approval. Coverage eligibility unchanged
- 05/06/2021 Medical Policy Committee review
- 05/12/2021 Medical Policy Implementation Committee approval. PanGIA Prostate added as investigational.

Next Scheduled Review Date: 05/2022

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Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0005U, 0021U, 0113U, 81313, 81479, 81539, 81551, 81599 Code added eff 1/1/2021: 0228U
HCPCS	No codes
ICD-10 Diagnosis	C61, Z12.5

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into

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standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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