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

Policy # 00272
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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.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider select genetic and protein biomarker testing of an individual aged 40-85 prior to an initial prostate biopsy to be **eligible for coverage**** when **ALL** of the selection criteria are met:

- Confirmed moderately elevated PSA > 3 and < 10 ng/mL; AND
- Has not had a prostate biopsy; AND
- One of the following tests is requested as part of a shared decision-making process regarding whether to proceed with prostate biopsy:
    - Prostate Health Index (PHI)
    - 4Kscore®‡ Test
    - SelectMDx (*HOXC6* and *DLX1* testing)
    - ExoDx Prostate IntelliScore (*EPI; PCA3, ERG,* and *SPDEF* RNA expression in exosomes)
    - MyProstateScore (MPS)
    - IsoPSA; AND
- The patient has not been previously tested using the same or similar biomarker test from the same sample or for the same clinical indication, AND

- The patient does not have an established diagnosis of prostate cancer or relative indication for prostate biopsy (e.g., digital rectal examination suspicious for cancer, persistent and significant increase in PSA, positive multiparametric magnetic resonance imaging (MRI), presence of major risk factors for prostate cancer including 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]); AND
- Patient is candidate for prostate biopsy (i.e., has greater than a 10-year life expectancy) and would benefit from treatment of prostate cancer; AND
- The medical records support the medical necessity for the test, including documented evidence of shared decision making between the patient and provider.

Note:
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 Clinical Laboratory Improvement Amendments (CLIA) approved laboratory before considering a biopsy.

The relative indications for prostate biopsy are not absolute. If there is presence of relative indication for prostate biopsy, individual should be encouraged to undergo 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 the provider. This supporting documentation must be provided to the laboratory at the time of ordering the test.

4Kscore Test Algorithm must contain all of the following components:

- *4 Kallikreins proteins (tPSA, fPSA, iPSA and hK2)*
- *Clinical information including age*
- *DRE*
- *Prior biopsy history*

Based on review of available data, the Company may consider select genetic and protein biomarker testing of an individual aged 40 to 85 years prior to repeat prostate biopsy to be **eligible for coverage**** when **ALL** of the selection criteria are met:

- Confirmed moderately elevated PSA > 3 and < 10 ng/mL; AND

- Had negative or non-malignant prostate biopsy and repeat biopsy is considered within 24-months of the prior biopsy; AND
- One of the following tests is requested as part of a shared decision-making process regarding whether to proceed with prostate biopsy:
    - Prostate Health Index (PHI)
    - 4Kscore®‡ Test
    - ExoDx Prostate IntelliScore (EPI)
    - Progensa®‡ PCA3
    - ConfirmMDx (gene hypermethylation testing)
    - MyProstateScore (MPS)
    - IsoPSA; AND
- The patient has not been previously tested using the same or similar biomarker test from the same sample or for the same clinical indication, AND
- The patient does not have an established diagnosis of prostate cancer or relative indication for prostate biopsy (e.g., digital rectal examination suspicious for cancer, persistent and significant increase in PSA, positive multiparametric magnetic resonance imaging (MRI), presence of major risk factors for prostate cancer including 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]); AND
- Patient is candidate for prostate biopsy (i.e., has greater than a 10-year life expectancy) and would benefit from treatment of prostate cancer; AND
- The medical records support the medical necessity for the test, including documented evidence of shared decision making between the patient and provider.

When 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 all other uses of genetic and protein biomarkers for the diagnosis of prostate cancer to be **investigational*,** including but not limited to:

- Autoantibodies ARF 6, NKX3-1, 5' -UTR-BMI1, CEP 164, 3' -UTR-Ropporin, Desmocollin, AURKAIP-1, and CSNK2A2 (eg, Apifiny)
- Sentinel PCa Test

- Mitochondrial DNA variant testing (eg, Prostate Core Mitomics Test)
- PanGIA Prostate
- Candidate gene panels
- NeoLAB™‡ Prostate Liquid Biopsy
- MyProstateScore (MPS) 2.0

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

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 over the age of age 55 and 60% of men over the age of 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. 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 Progensa®‡ PCA3 Assay (Gen-Probe; now Hologic) was approved by the FDA through the premarket approval process. The Progensa PCA3 Assay has been approved by the 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

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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 medical policy addresses these types of tests for cancer risk assessment.

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 MyProstate score, 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 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 (DRE), a prostate-specific antigen (PSA) 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.

NeoLAB™‡ Prostate Liquid Biopsy (NeoGenomics Laboratories, Inc.) is a quantitative real-time PCR (qRT-PCR) test designed to look at expression levels of the genes AR, B2M, ERG, GAPDH, HSPD1, IMPDH2, PCA3, PDLIM5, PSA, PTEN, TMPRSS2, and UAP1 in urine and plasma samples. The expression levels of these genes is used in 2 different algorithms to determine patients prostate cancer risk assessment. It was noted that NeoLAB Prostate differentiates non-cancer and low-risk cancers from high-risk prostate cancer, reducing the need for unnecessary biopsies. Clinical utility studies using this assay results for decision-making for initial biopsy or repeat biopsy were not identified. In addition, no studies were identified that reported on health outcomes such as recurrence or survival of patients that underwent testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

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, MyProstate Score), 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 the longer-term clinical outcomes of the use of genetic and protein biomarkers to decide on repeat prostate biopsy. 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
In 2023, the American Urological Association (AUA) and the Society of Urologic Oncology (SUO) published updated guidelines on the early detection of prostate cancer. Specific guidance related to diagnosis, risk assessment, and utilization of biomarkers are stated in Table 1 below.

Table 1. Relevant AUA/SUO Guideline Statements on Prostate Cancer Screening and Biopsy

Guideline Statement	Evidence Grade and Strength
When screening for prostate cancer, clinicians should use PSA as the first screening test	Strong Recommendation; Evidence Level: Grade A
For people with a newly elevated PSA, clinicians should repeat the PSA prior to a secondary biomarker, imaging, or biopsy	Expert Opinion
Clinicians may use digital rectal exam (DRE) alongside PSA to establish risk of clinically significant prostate cancer	Conditional Recommendation; Evidence Level: Grade C
For people undergoing prostate cancer screening, clinicians should not use PSA velocity as the sole indication for a secondary biomarker, imaging, or biopsy	Strong Recommendation; Evidence Level: Grade B
Clinicians may use adjunctive urine or serum markers when further risk stratification would influence the decision regarding whether to proceed with biopsy.	Conditional Recommendation; Evidence Level: Grade C

After a negative biopsy, clinicians should not solely use a PSA threshold to decide whether to repeat the biopsy	Strong Recommendation; Evidence Level: Grade B
After a negative biopsy, clinicians may use blood-, urine-, or tissue-based biomarkers selectively for further risk stratification if results are likely to influence the decision regarding repeat biopsy or otherwise substantively change the patient's management	Conditional Recommendation; Evidence Level: Grade C
In patients with multifocal HGPIN [high-grade prostatic intraepithelial neoplasia], clinicians may proceed with additional risk evaluation, guided by PSA/DRE and mpMRI findings	Expert Opinion

DRE: digital rectal exam; PSA: prostate-specific antigen; mpMRI: multi-parametric magnetic resonance imaging

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines (v.1.2023) recommend that any man with a PSA level greater than 3 ng/mL undergo workup for benign disease, repeat PSA, and DRE (category 2A evidence).

The NCCN guidelines state that "biomarkers that improve the specificity of detection are not, as yet, mandated as first-line screening tests in conjunction with serum PSA. However, there may be some patients who meet PSA standards for consideration of prostate biopsy, but for whom the patient and/or the physician wish to further define risk". The guidelines recommend that the probability of high-grade cancer (Gleason score ≥3+4, Grade Group 2 or higher) may be further defined utilizing biomarkers that improve the specificity of screening that includes percent free PSA, with consideration of the Prostate Health Index (PHI), SelectMDx, 4K score, ExoDx Prostate Test, MyProstate Score (MPS), and IsoPSA. NCCN also noted that the extent of validation of these tests across diverse populations is variable and 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, ConfirmMDx, ExoDx Prostate Test, MPS, and IsoPSA.

National Institute for Health and Care Excellence
In 2019 and in 2021, when guidelines were updated, 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 medical policy, 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).

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.

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
Ongoing			

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 2023
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	4000	Dec 2023
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
NCT05050084	Parallel Phase III Randomized Trials of Genomic-Risk Stratified Unfavorable Intermediate Risk Prostate Cancer: De-Intensification and Intensification Clinical Trial Evaluation (GUIDANCE)	2050	Apr 2037

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Policy History

Original Effective Date: 10/20/2010
Current Effective Date: 01/01/2024

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.
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.

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

Policy # 00272
Original Effective Date: 10/20/2010
Current Effective Date: 01/01/2024

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 Apifiny 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.
05/05/2022	Medical Policy Committee review
05/11/2022	Medical Policy Implementation Committee approval. NeoLAB Prostate Liquid Biopsy was added as investigational.
10/06/2022	Medical Policy Committee review
10/12/2022	Medical Policy Implementation Committee approval. Coverage changed from investigational to eligible with criteria due to senate bill requirements.
12/01/2022	Medical Policy Committee review
12/14/2022	Medical Policy Implementation Committee approval. Senate bill update. Added MyProstateScore (MPS) and IsoPSA as eligible for coverage.
12/19/2022	Coding update
09/20/2023	Coding update
09/27/2023	Added MyProstateScore (MPS) 2.0 as investigational for all other uses of genetic and protein biomarkers for the diagnosis of prostate cancer.
12/07/2023	Medical Policy Committee review

Policy # 00272
Original Effective Date: 10/20/2010
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12/13/2023 Medical Policy Implementation Committee approval. Policy guidelines removed. Body of policy updated including references. No change to coverage. Added "or relative indication for prostate biopsy (e.g., digital rectal examination suspicious for cancer, persistent and significant increase in PSA, positive multiparametric magnetic resonance imaging (MRI), presence of major risk factors for prostate cancer including 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]);" to criteria bullet for select genetic and protein biomarker testing of an individual aged 40-85 prior to an initial prostate biopsy and repeat biopsy. Added "The relative indications for prostate biopsy are not absolute. If there is presence of relative indication for prostate biopsy, individual should be encouraged to undergo 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 the provider. This supporting documentation must be provided to the laboratory at the time of ordering the test" to the note. New codes effective 01/01/2024 added to policy.
Next Scheduled Review Date: 12/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy

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Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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

Code Type	Code
CPT	0011M, 0005U, 0021U, 0113U, 0228U, 0339U, 0343U, 0359U, 0403U, 81313, 81479, 81539, 81551, 81599 Add code effective 01/01/2024: 0424U, 0433U
HCPCS	No codes
ICD-10 Diagnosis	All related Diagnoses

*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 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 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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**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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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.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.