



Louisiana

Genetic Testing for PTEN Hamartoma Tumor Syndrome

Policy # 00417

Original Effective Date: 05/21/2014

Current Effective Date: 06/14/2021

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.

When Services Are 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 genetic testing for a *PTEN* (phosphatase and *tensin* homolog deleted on chromosome 10) to confirm the diagnosis when a patient has clinical signs of a *PTEN* hamartoma tumor syndrome (PHTS) to be **eligible for coverage.****

Based on review of available data, the Company may consider targeted genetic testing for a *PTEN* (phosphatase and *tensin* homolog deleted on chromosome 10) familial variant in a first-degree relative of a proband with a known *PTEN* pathogenic variant to be **eligible for coverage.****

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 genetic testing for a *PTEN* (phosphatase and *tensin* homolog deleted on chromosome 10) for all other indications to be **investigational.***

Policy Guidelines

Testing Strategy to Confirm a Diagnosis in a Proband

The order of testing to optimize yield would be (1) sequencing of *PTEN* exons 1-9 and flanking intronic regions. If no disease-associated variant is identified, perform (2) deletion/duplication analysis. If no disease-associated variant is identified, consider (3) promoter analysis, which detects

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disease-associated variants in approximately 10% of individuals with Cowden syndrome who do not have an identifiable disease-associated variant in the *PTEN* coding region.

Testing a First-Degree Relative

When a *PTEN* disease-associated variant has been identified in the proband, testing of asymptomatic at-risk relatives can identify those family members who have the familial variant, for whom an initial evaluation and ongoing surveillance should be performed.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology - "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" - to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives



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Policy # 00417

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Current Effective Date: 06/14/2021

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

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

***PTEN* Hamartoma Tumor Syndromes**

PTEN hamartoma tumor syndrome (PHTS) is characterized by hamartomatous tumors and *PTEN* germline disease-associated variants. Clinically, PHTS includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), *PTEN*-related Proteus syndrome (PS), and Proteus-like syndrome (PLS).

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Policy # 00417

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CS is a multiple hamartoma syndrome with a high-risk for benign and malignant tumors of the thyroid, breast, and endometrium. Affected individuals usually have macrocephaly, trichilemmomas, and papillomatous papules and present by age late 20s. The lifetime risk of developing breast cancer is 85%, with an average age of diagnosis between 38 and 46 years. The lifetime risk for thyroid cancer, usually follicular carcinoma is approximately 35%. The risk for endometrial cancer is not well-defined but may approach 28%. A 2012 study included 3399 prospectively recruited individuals who met relaxed International Cowden Consortium PHTS criteria; 368 were found to have *PTEN* disease-associated variants. Estimated lifetime cancer risks were: 85.2% for breast (95% confidence interval [CI], 71.4% to 99.1%); 35.2% for thyroid; (95% CI, 19.7% to 50.7%); 28.2% for endometrium (95% CI, 17.1% to 39.3%); 9.0% for colorectal (95% CI, 3.8% to 14.1%); 33.6% for kidney (95% CI, 10.4% to 56.9%); and 6% for melanoma (95% CI, 1.6% to 9.4%). A 2013 study of 154 individuals with a *PTEN* disease-associated variant found cumulative cancer risks at age 70 of 85% (95% CI, 70% to 95%) for any cancer, 77% (95% CI, 59% to 91%) for female breast cancer, and 38% (95% CI, 25% to 56%) for thyroid cancer.

BRRS is characterized by macrocephaly, intestinal hamartomatous polyposis, lipomas, and pigmented macules of the glans penis. Additional features include high birth weight, developmental delay and mental deficiency (50% of affected individuals), a myopathic process in proximal muscles (60%), joint hyperextensibility, pectus excavatum, and scoliosis (50%).

PS is a complex, highly variable disorder involving congenital malformations and hamartomatous overgrowth of multiple tissues, as well as connective tissue nevi, epidermal nevi, and hyperostoses.

PLS is undefined but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS.

CS is the only PHTS disorder associated with a documented predisposition to cancer; however, it has been suggested that patients with other PHTS diagnoses associated with *PTEN* variants should be assumed to have cancer risks similar to CS.

Clinical Diagnosis

A presumptive diagnosis of PHTS is based on clinical findings; however, because of the phenotypic heterogeneity associated with the hamartoma syndromes, the diagnosis of PHTS is made only when a *PTEN* disease-associated variant is identified.

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Diagnostic Criteria for Cowden Syndrome

The International Cowden Consortium has developed criteria for diagnosing CS (see Table 1).

Table 1. Diagnostic Criteria for Cowden Syndrome^a

Diagnostic Criteria
<i>Pathognomonic criteria</i>
Lhermitte-Duclos disease adult defined as the presence of a cerebellar dysplastic gangliocytoma <ul style="list-style-type: none"> • Mucocutaneous lesions: • Trichilemmomas, facial • Acral keratoses • Papillomatous lesions
<i>Major criteria</i>
<ul style="list-style-type: none"> • Breast cancer • Thyroid cancer (papillary or follicular) • Macrocephaly (occipital frontal circumference ≥ 97th percentile) • Endometrial cancer
<i>Minor criteria</i>
<ul style="list-style-type: none"> • Other structural thyroid lesions (eg, adenoma, multinodular goiter) • Mental retardation (ie, IQ ≤ 75) • Gastrointestinal hamartomas • Fibrocystic disease of the breast • Lipomas • Fibromas • Genitourinary tumors (eg, uterine fibroids, renal cell carcinoma) or • Genitourinary structural malformations
<i>Operational diagnosis in an individual</i>
Any of the following: <ol style="list-style-type: none"> 1. Mucocutaneous lesions alone if: <ul style="list-style-type: none"> ○ There are 6 or more facial papules, of which 3 or more must be trichilemmoma, or ○ Cutaneous facial papules and oral mucosal papillomatosis, or ○ Oral mucosal papillomatosis and acral keratoses, or ○ Palmoplantar keratoses, 6 or more

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Policy # 00417

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Current Effective Date: 06/14/2021

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| <ol style="list-style-type: none"> 2. Two or more major criteria, but one must include macrocephaly or Lhermitte-Duclos disease; or 3. One major and 3 minor criteria; or 4. Four minor criteria. |
|--|

Operational diagnosis in a family with a diagnosis of Cowden syndrome

- | |
|---|
| <ol style="list-style-type: none"> 1. One pathognomonic criterion; or 2. Any 1 major criterion with or without minor criteria; or 3. Two minor criteria; or 4. History of Bannayan-Riley-Ruvalcaba syndrome |
|---|

Adapted from Blumenthal et al (2008).

^a These criteria for diagnosing Cowden syndrome have been adopted by the National Comprehensive Cancer Network.

In 2013, a systematic review assessed the clinical features reported in individuals with a *PTEN* disease-associated variant and proposed revised diagnostic criteria. Reviewers concluded that there was insufficient evidence to support inclusion of benign breast disease, uterine fibroids, or genitourinary malformations as diagnostic criteria. There was sufficient evidence to include autism spectrum disorders, colon cancer, esophageal glycogenic acanthosis, penile macules, renal cell carcinoma, testicular lipomatosis, and vascular anomalies, and these clinical features are included in CS testing minor criteria in the National Comprehensive Cancer Network guidelines on genetic/familial high-risk assessment of breast and ovarian (v.2.2021).

Bannayan-Riley-Ruvalcaba Syndrome

Diagnostic criteria for BRRS have not been established. Current diagnostic practices are based heavily on the presence of the cardinal features of macrocephaly, hamartomatous intestinal polyposis, lipomas, and pigmented macules of the glans penis.

Proteus Syndrome

PS appears to affect individuals in a mosaic distribution (ie, only some organs/tissues are affected). Thus, it is frequently misdiagnosed, despite the development of consensus diagnostic criteria. Mandatory general criteria for diagnosis include mosaic distribution of lesions, progressive course, and sporadic occurrence. Additional specific criteria for diagnosis as listed in Table 2.

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Table 2. Diagnostic Criteria for Proteus Syndrome

Additional Diagnostic Criteria
<i>Connective tissue nevi (pathognomonic) OR 2 of the following:</i>
<i>Epidermal nevus</i>
Disproportionate overgrowth (1 or more): <ul style="list-style-type: none"> • Limbs: arms/legs; hands/feet/digits • Skull: hyperostoses • External auditory meatus: hyperostosis • Vertebrae: megaspondylodysplasia • Viscera: spleen/thymus
Specific tumors before end of second decade (either one): <ul style="list-style-type: none"> • Bilateral ovarian cystadenomas • Parotid monomorphic adenoma
<i>OR 3 of the following:</i>
Dysregulated adipose tissue (either one): <ul style="list-style-type: none"> • Lipomas • Regional absence of fat
Vascular malformations (1 or more): <ul style="list-style-type: none"> • Capillary malformation • Venous malformation • Lymphatic malformation
Facial phenotype: <ul style="list-style-type: none"> • Dolichocephaly • Long face • Minor down slanting of palpebral fissures and/or minor ptosis • Low nasal bridge • Wide or anteverted nares • Open mouth at rest

Adapted from Biesecker (2006).

Proteus-Like Syndrome

Proteus-Like Syndrome (PLS) is undefined but describes individuals with significant clinical features of PS not meeting the diagnostic criteria.

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Molecular Diagnosis

PTEN (phosphatase and *tens* in homolog deleted on chromosome 10) is a tumor suppressor gene on chromosome 10q23 and is a dual-specificity phosphatase with multiple but incompletely understood roles in cellular regulation. *PTEN* is the only gene for which disease-associated variants are known to cause PHTS. *PTEN* disease-associated variants are inherited in an autosomal dominant manner.

Most CS cases are simplex. However, because CS is likely underdiagnosed, the actual proportion of simplex cases (ie, individuals with no obvious family history) and familial cases (ie, ≥ 2 related affected individuals) cannot be determined. It is estimated that 50% to 90% of cases of CS are de novo and approximately 10% to 50% of individuals with CS have an affected parent.

Because of the phenotypic heterogeneity associated with the hamartoma syndromes, the diagnosis of PHTS is made only when a *PTEN* disease-associated variant is identified. Up to 85% of patients who meet the clinical criteria for a diagnosis of CS and 65% of patients with a clinical diagnosis of BRRS have a detectable *PTEN* disease-associated variant. Some data have suggested that up to 20% of patients with PS and up to 50% of patients with a PLS have *PTEN* disease-associated variants.

Most of these disease-associated variants can be identified by sequence analysis of the coding and flanking intronic regions of genomic DNA. A smaller number of variants are detected by deletion/duplication or promoter region analysis.

Penetrance

More than 90% of individuals with CS have some clinical manifestation of the disorder by the late 20s. By the third decade, 99% of affected individuals develop the mucocutaneous stigmata, primarily trichilemmomas and papillomatous papules, as well as acral and plantar keratoses.

Management

Treatment

Treatment of the benign and malignant manifestations of PHTS is the same as for their sporadic counterparts (ie, chemotherapy, surgery, and/or radiotherapy as per usual guidelines and clinical practice).

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Surveillance

The most serious consequences of a diagnosis of PHTS relates to the increased risk of cancers, including breast, thyroid, and endometrial, and, to a lesser extent, renal. Therefore, the most important aspect of management of an individual with a *PTEN* disease-associated variant is increased cancer surveillance to detect tumors at the earliest, most treatable stages.

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). Laboratory testing for *PTEN* variants is available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale/Source

The *PTEN* hamartoma tumor syndrome (PHTS) includes several syndromes with heterogeneous clinical symptoms, which may place individuals at an increased risk for the development of certain types of cancer. Genetic testing for *PTEN* can confirm a diagnosis of PHTS.

For individuals who have clinical signs and/or symptoms of a PHTS or who are asymptomatic with a first-degree relative with a PHTS and a known familial variant who receive genetic testing for a *PTEN* familial variant, the evidence includes case series and a large prospective study on the frequency of a *PTEN* variants in individuals meeting clinical criteria for a PHTS, and studies of cancer risk estimates in individuals with a *PTEN* disease-associated variant. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and morbid events. The published clinical validity of testing for the *PTEN* gene is variable. The true clinical validity is difficult to ascertain because the syndrome is defined by the presence of a *PTEN* disease-associated variant. The sensitivity of tests for Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome has been reported to be up to 80% and 60%, respectively. Direct evidence of the clinical utility of genetic testing for *PTEN* is lacking; however, confirming a diagnosis in a patient with clinical signs of a PHTS will lead to changes in clinical management by increasing surveillance to detect cancers associated with PHTS at an early and treatable stage. Although most cases of a PHTS occur in

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Individuals with no known family history of PHTS, testing of at-risk relatives will identify those who should also undergo increased cancer surveillance. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

Reference Library

Current (v.2.2021), National Comprehensive Cancer Network guidelines on genetic/familial high-risk assessment for breast and ovarian cancer include Testing Criteria for Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS) (CRIT-5, v.2.2021) that recommend testing for:

- Individual from a family with a known *PTEN* pathogenic/likely pathogenic variant
- Individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)
- Individual meeting clinical diagnostic criteria for CS/PHTS
- Individual not meeting clinical diagnostic criteria for CS/PHTS with a personal history of: Adult Lhermitte-Duclos disease (cerebellar tumors); or autism spectrum disorder and macrocephaly; or two or more biopsy-proven trichilemmomas; or two or more major criteria (one must be macrocephaly); or three major criteria, without macrocephaly; or one major criteria, without macrocephaly; or one major and ≥ 3 minor criteria; or ≥ 4 minor criteria
- At-risk individual with a relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed. The at-risk individual must have the following: Any one major criterion or two minor criteria.
- *PTEN* pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline analysis.

Additionally, the following is recommended for Cowden syndrome management (see Table 3).

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Table 3. Guidelines on Genetic/Familial High-Risk Assessment for Breast and Ovarian Cancer

Populations	Recommendations
Women	<ul style="list-style-type: none"> Breast awareness starting at age 18 years.
	<ul style="list-style-type: none"> Clinical breast exam every 6 to 12 months, starting at age 25 years or 5 to 10 years before the earliest known breast cancer in the family (whichever comes first).
	<ul style="list-style-type: none"> Breast screening: <ul style="list-style-type: none"> Annual mammography and breast MRI screening starting at age 30 to 35 years or 5 to 10 years before the earliest known breast cancer in family (whichever comes first). Age >75, management should be considered on an individual basis.
	<ul style="list-style-type: none"> For women with a <i>PTEN</i> mutation [disease-associated variant] who are treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue.
	<ul style="list-style-type: none"> For endometrial cancer screening, encourage patient education and prompt response to symptoms. Consider annual random endometrial biopsies and/or ultrasound beginning at age 30 to 35 years.
	<ul style="list-style-type: none"> Discuss risk-reducing mastectomy and hysterectomy and counsel regarding degree of protection, extent of cancer risk, and reconstructive options
Men and women	<ul style="list-style-type: none"> Annual comprehensive physical exam starting at age 18 years or 5 years before the youngest age of diagnosis of a component cancer in the family (whichever comes first), with particular attention to breast and thyroid exam.
	<ul style="list-style-type: none"> Annual thyroid ultrasound starting at starting at age 7. This may also be considered for children at 50% risk of inheriting a known mutation whose parents wish to delay genetic testing until age 18 years.
	<ul style="list-style-type: none"> Colonoscopy, starting at age 35 years, unless symptomatic or a close relative with colon cancer under age 40 years. Colonoscopy should be done every 5 years or more frequently if patient is symptomatic or polyps found.

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	<ul style="list-style-type: none"> • Dermatologic management may be indicated for some patients.
	<ul style="list-style-type: none"> • Consider renal ultrasound starting at age 40 years, then every 1 to 2 years.
	<ul style="list-style-type: none"> • Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms
	<ul style="list-style-type: none"> • Education regarding signs and symptoms of cancer
Relatives	<ul style="list-style-type: none"> • Advise about possible inherited cancer risk to relatives, options for risk assessment, and management
	<ul style="list-style-type: none"> • Recommend genetic counseling and consideration of genetic testing for at-risk relatives
Reproductive options	<ul style="list-style-type: none"> • For women of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including preimplantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies

MRI: magnetic resonance imaging; PHTS: *PTEN* hamartoma tumor syndrome.

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for genetic testing for *PTEN* hamartoma tumor syndrome have been identified.

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

A search of [ClinicalTrials.gov](https://clinicaltrials.gov) in December 2020 did not identify any ongoing or unpublished trials that would likely influence this review.

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05/01/2014 Medical Policy Committee review

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Louisiana

Genetic Testing for PTEN Hamartoma Tumor Syndrome

Policy # 00417

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- 05/21/2014 Medical Policy Implementation Committee approval. New policy.
- 05/07/2015 Medical Policy Committee review
- 05/20/2015 Medical Policy Implementation Committee approval. No change to coverage.
- 08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
- 05/05/2016 Medical Policy Committee review
- 05/18/2016 Medical Policy Implementation Committee approval. No change to coverage.
- 01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
- 05/04/2017 Medical Policy Committee review
- 05/17/2017 Medical Policy Implementation Committee approval. No change to coverage.
- 05/03/2018 Medical Policy Committee review
- 05/16/2018 Medical Policy Implementation Committee approval. Added “pathogenic” to the eligible for coverage statement targeted genetic testing for a *PTEN* familial variant in a first-degree relative of a proband with a known *PTEN*. Moved the Policy Guidelines noted in the coverage section to the Policy Guidelines section.
- 05/02/2019 Medical Policy Committee review
- 05/15/2019 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 05/07/2020 Medical Policy Committee review
- 05/13/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 12/11/2020 Coding update
- 05/06/2021 Medical Policy Committee review
- 05/12/2021 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 05/2022

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 2020 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.

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Louisiana

Genetic Testing for PTEN Hamartoma Tumor Syndrome

Policy # 00417

Original Effective Date: 05/21/2014

Current Effective Date: 06/14/2021

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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	0130U, 81321, 81322, 81323 Code added eff 1/1/2021: 0235U
HCPCS	No codes
ICD-10 Diagnosis	Q85.8, Q85.9, Z82.79

*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,

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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.

****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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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

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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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