Genetic Testing for PTEN Hamartoma Tumor Syndrome

Policy # 00417
Original Effective Date: 05/21/2014
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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.

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* (*p*hosphatase 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* 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* 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 disease-associated variants in approximately 10% of individuals with (CS) 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 deoxyribonucleic acid (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

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

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.

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Background/Overview

PTEN HAMARTOMA TUMOR SYNDROMES

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

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.

Diagnostic Criteria for CS

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

Table 1. Diagnostic Criteria for Cowden Syndrome[a]

Diagnostic Criteria
Pathognomonic criteria
Lhermitte-Duclos disease adult defined as the presence of a cerebellar dysplastic gangliocytoma
Mucocutaneous lesions:
Trichilemmomas, facial
Acral keratoses
Papillomatous lesions
Major criteria
Breast cancer
Thyroid cancer (papillary or follicular)
Macrocephaly (occipital frontal circumference ≥97th percentile)
Endometrial cancer
Minor criteria
Other structural thyroid lesions (e.g., adenoma, multinodular goiter)
Mental retardation (i.e., IQ ≤75)
Gastrointestinal hamartomas
Fibrocystic disease of the breast
Lipomas
Fibromas
Genitourinary tumors (e.g., uterine fibroids, renal cell carcinoma) or
Genitourinary structural malformations
Operational diagnosis in an individual
Any of the following:
1. Mucocutaneous lesions alone if: 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
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
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.1.2018).

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 (i.e., 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.

Table 2. Diagnostic Criteria for Proteus Syndrome

Additional Diagnostic Criteria
Connective tissue nevi (pathognomonic) OR 2 of the following:
Epidermal nevus
Disproportionate overgrowth (1 or more): • 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): • Bilateral ovarian cystadenomas • Parotid monomorphic adenoma
OR 3 of the following:
Dysregulated adipose tissue (either one): • Lipomas • Regional absence of fat
Vascular malformations (1 or more): • Capillary malformation • Venous malformation • Lymphatic malformation
Facial phenotype: • Dolichocephaly • Long face • Minor downslanting 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
PLS is undefined but describes individuals with significant clinical features of PS not meeting the diagnostic criteria.

Molecular Diagnosis
PTEN 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 (i.e., individuals with no obvious family history) and familial cases (i.e., ≥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 (i.e., chemotherapy, surgery, and/or radiotherapy as per usual guidelines and clinical practice).

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

Centers for Medicare and Medicaid Services (CMS)

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.

Rationale/Source

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

TESTING IN PATIENTS WITH SIGNS AND/OR SYMPTOMS OF *PTEN* HAMARTOMA TUMOR SYNDROME

Clinical Context and Test Purpose

The purpose of genetic testing of patients who have signs and/or symptoms of PHTS is to confirm a diagnosis and inform management decisions such as increased cancer surveillance.

The question addressed in this evidence review is: Does genetic testing improve health outcomes in individuals with signs and/or symptoms of PHTS?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients with clinical signs and/or symptoms of a PHTS.

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Interventions
The test being considered is genetic testing for *PTEN*.

Comparators
The following practices are currently being used: standard clinical management without genetic testing for *PTEN*.

Outcomes
The potential beneficial outcomes of primary interest would be improvements in overall survival and disease-specific survival and reductions in morbid events. Increased cancer surveillance in patients with a *PTEN* pathogenic variant is initiated to detect the presence of cancer at earlier and more treatable stages.

Potential harmful outcomes are those resulting from a false-positive or false-negative test. False-positive test results can lead to unnecessary cancer surveillance procedures (e.g., invasive biopsies). False-negative test results can lead to lack of cancer surveillance that might detect cancer at earlier and more treatable stages.

Timing
The primary outcomes of interest are the initiation and frequency of cancer surveillance to affect short-term and long-term survival rates after cancer detection.

Setting
Patients may be referred from primary care to an oncologist or medical geneticist for investigation and management of PHTS. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Simplifying Test Terms
There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predicting a response to therapy.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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 and duplication analysis. If no disease-associated variant is identified, consider (3) promoter analysis.

Clinically Useful
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Many reports on the prevalence of the features of CS and BRRS have been based on data compiled from case reports and studies of small cohorts. Most of these reports were published before adoption of the International Cowden Consortium diagnostic criteria for CS in 1996 (see Table 1), and the true frequencies of the clinical features in CS and BRRS are unknown.

According to a large reference laboratory, the clinical sensitivity of *PTEN*-related disorder sequencing is 80% for CS, 60% for BRRS, 20% for *PTEN*-related Proteus syndrome, and 50% for PLS. For *PTEN*-related deletions and duplications, it is up to 10% for BRRS and unknown for CS, PS, and PLS.

Germline *PTEN* disease-associated variants have been identified in approximately 80% of patients meeting diagnostic criteria for CS and in 50% to 60% of patients with a diagnosis of BRRS, using sequencing analysis using polymerase chain reaction of the coding and flanking intronic regions of the gene. Marsh et al (1998) screened DNA from 37 CS families, and *PTEN* disease-associated variants were identified in 30 (81%) of 37 CS families, including single nucleotide variants, insertions, and deletions. Whether the remaining patients have undetected *PTEN* disease-associated variants or disease-associated variants in other, unidentified genes, is unknown.

A study by Pilarski et al (2011) determined the clinical features most predictive of a disease-associated variant in a cohort of patients undergoing *PTEN* testing. Molecular and clinical data were reviewed for 802 patients referred for *PTEN* analysis to a single laboratory. All patients were classified by whether they met revised International Cowden Consortium diagnostic criteria. Two hundred thirty of the 802 patients met diagnostic criteria for CS. Of these, 79 had a *PTEN* disease-associated variant, for a detection rate of 34%. The authors commented that this disease-associated variant frequency was significantly lower than

previously reported, possibly suggesting that the clinical diagnostic criteria for CS are not as robust at identifying patients with germline *PTEN* disease-associated variants as previously thought. In their study, of the patients meeting diagnostic criteria for BRRS, 23 (55%) of 42 had a disease-associated variant, and 7 (78%) of 9 patients with diagnostic criteria for both CS and BRRS had a disease-associated variant, consistent with the literature.

Section Summary: Clinically Valid
Evidence from several small studies has indicated that the clinical sensitivity of genetic testing for *PTEN* may be highly variable. This may reflect the phenotypic heterogeneity of the syndromes and an inherent referral bias because patients with more clinical features of CS and BRRS are more likely to get tested. The true clinical specificity is uncertain because the syndrome is defined by the disease-associated variant.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

The clinical utility for patients with suspected PHTS depends on the ability of genetic testing to make a definitive diagnosis and for that diagnosis to lead to management changes that improve outcomes. There is no direct evidence for the clinical utility of genetic testing in these patients because no studies were identified describing how a molecular diagnosis of PHTS changed patient management.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

For patients diagnosed with PHTS by identifying a *PTEN* disease-associated variant, the medical management focuses on increased cancer surveillance to detect tumors at the earlier, more treatable stages.

Section Summary: Clinically Useful
Direct evidence of the clinical utility of *PTEN* testing is lacking. However, the clinical utility of genetic testing for *PTEN* is that genetic testing can confirm the diagnosis in patients with clinical signs and/or symptoms of PHTS. Management changes include increased surveillance for the cancers associated with these syndromes.

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FAMILIAL VARIANT TESTING OF ASYMPTOMATIC INDIVIDUALS
Clinical Context and Test Purpose
The purpose of familial variant testing of asymptomatic individuals with a first-degree relative with a PHTS is to screen for the family-specific pathogenic variant to inform management decisions (e.g., increased cancer surveillance) or to exclude asymptomatic individuals from increased cancer surveillance.

The question addressed in this evidence review is: Does genetic testing improve health outcomes in asymptomatic individuals with a first-degree relative who has a PHTS?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is asymptomatic individuals with a first-degree relative who has a PHTS.

Interventions
The test being considered is targeted genetic testing for a *PTEN* familial variant.

Comparators
The following practices are currently being used: standard clinical management without targeted genetic testing for a *PTEN* familial variant.

Outcomes
The potential beneficial outcomes of primary interest would be improvement in overall survival and disease-specific survival and reductions in morbid events. Increased cancer surveillance in patients with a *PTEN* familial variant is initiated to detect the presence of cancer at earlier and more treatable stages. Asymptomatic individuals who test negative for a *PTEN* familial variant can be excluded from increased cancer surveillance.

The potential harmful outcomes are those resulting from a false-positive or false-negative test. False-positive test results can lead to unnecessary cancer surveillance procedures (e.g., invasive biopsies). False-negative test results can lead to lack of cancer surveillance that may detect cancer at earlier and more treatable stages.

Timing
The primary outcomes of interest are the initiation and frequency of cancer surveillance to affect short-term and long-term survival rates after cancer detection.

Setting
Asymptomatic individuals may be referred from primary care to an oncologist or medical geneticist if a *PTEN* familial variant is identified. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes. If targeted genetic testing for a

familial variant is negative, the asymptomatic individual can be excluded from increased cancer surveillance.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

See the discussion in the previous section for patients with sign and/or symptoms of PHTS.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No randomized controlled trials were identified assessing the clinical usefulness of testing asymptomatic individuals with a first-degree relative who has a diagnosis of PHTS.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

When a *PTEN* disease-associated variant has been identified in a proband, testing of first-degree relatives can identify those who also have the familial variant and PHTS. These individuals require an initial evaluation and ongoing cancer surveillance. Alternatively, first-degree relatives who test negative for the familial variant would not require ongoing cancer surveillance.

Section Summary: Clinically Useful
Direct evidence of the clinical utility of familial variant testing in asymptomatic individuals is lacking. However, for first-degree relatives of PHTS in affected individuals, a positive test for a familial variant would confirm the diagnosis of PHTS and result in ongoing cancer surveillance. A negative test for a familial variant would reduce unnecessary cancer surveillance.

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SUMMARY OF EVIDENCE

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 CS and BRRS 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 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.

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05/01/2014	Medical Policy Committee review
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.

Next Scheduled Review Date: 05/2019

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 2017 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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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	81321, 81322, 81323
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, 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.

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.