Genetic Testing for PTEN Hamartoma Tumor Syndrome

Policy #    00417
Original Effective Date:   05/21/2014
Current Effective Date:    05/17/2017

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) variant to confirm the diagnosis when a patient has clinical signs of a PTEN (phosphatase and tensin homolog deleted on chromosome 10) hamartoma tumor syndrome 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 (phosphatase and tensin homolog deleted on chromosome 10) variant to be eligible for coverage.

Note:
- **Testing strategy for confirming the diagnosis in a proband**
  The order of testing to optimize yield would be (1) Sequencing of PTEN exons 1-9 and flanking intron 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 Cowden syndrome (CS) who do not have an identifiable disease-associated variant in the PTEN coding region.

Note:
- **Testing in 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 family variant, for whom an initial evaluation and ongoing surveillance should be performed.

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) variant for all other indications to be investigational.*
Genetic Testing for PTEN Hamartoma Tumor Syndrome

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Background/Overview
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 a PTEN mutation can confirm a diagnosis of PHTS.

PTEN hamartoma tumor syndrome 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).

Cowden syndrome 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, which is 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 deleterious 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 deleterious PTEN mutation were found to have cumulative cancer risks at age 70 of 85% for any cancer (95% CI, 70% to 95%), 77% for female breast cancer (95% CI, 59% to 91%), and 38% for thyroid cancer (95% CI, 25% to 56%).

Bannayan-Riley-Ruvalcaba syndrome (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%).

PTEN-related Proteus syndrome (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.

Proteus-like syndrome (PLS) is undefined but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS.

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

Table 1. International Cowden Consortium Diagnostic Criteria for Cowden Syndrome

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathognomonic criteria</strong></td>
</tr>
<tr>
<td>Lhermitte-Duclos disease adult defined as the presence of a cerebellar dysplastic gangliocytoma</td>
</tr>
<tr>
<td>Mucocutaneous lesions;</td>
</tr>
<tr>
<td>Trichilemmomas, facial</td>
</tr>
<tr>
<td>Acral keratoses</td>
</tr>
<tr>
<td>Papillomatous lesions</td>
</tr>
<tr>
<td><strong>Major criteria</strong></td>
</tr>
<tr>
<td>Breast cancer</td>
</tr>
<tr>
<td>Thyroid cancer (papillary or follicular)</td>
</tr>
<tr>
<td>Macrocephaly (occipital frontal circumference ≥97th percentile)</td>
</tr>
<tr>
<td>Endometrial cancer</td>
</tr>
<tr>
<td><strong>Minor criteria</strong></td>
</tr>
<tr>
<td>Other structural thyroid lesions (eg, adenoma, multinodular goiter)</td>
</tr>
<tr>
<td>Mental retardation (ie, IQ ≤75)</td>
</tr>
<tr>
<td>Gastrointestinal hamartomas</td>
</tr>
<tr>
<td>Fibrocystic disease of the breast</td>
</tr>
<tr>
<td>Lipomas</td>
</tr>
<tr>
<td>Fibromas</td>
</tr>
<tr>
<td>Genitourinary tumors (eg, uterine fibroids, renal cell carcinoma) or</td>
</tr>
<tr>
<td>Genitourinary structural malformations</td>
</tr>
<tr>
<td><strong>Operational diagnosis in an individual</strong></td>
</tr>
<tr>
<td>Any of the following:</td>
</tr>
<tr>
<td>1. Mucocutaneous lesions alone if:</td>
</tr>
<tr>
<td>There are 6 or more facial papules, of which 3 or more must be trichilemmoma, or</td>
</tr>
<tr>
<td>Cutaneous facial papules and oral mucosal papillomatosis, or</td>
</tr>
<tr>
<td>Oral mucosal papillomatosis and acral keratoses, or</td>
</tr>
<tr>
<td>Palmoplantar keratoses, 6 or more</td>
</tr>
<tr>
<td>2. Two or more major criteria, but one must include macrocephaly or Lhermitte-Duclos disease; or</td>
</tr>
<tr>
<td>3. One major and 3 minor criteria; or</td>
</tr>
<tr>
<td>4. Four minor criteria.</td>
</tr>
<tr>
<td><strong>Operational diagnosis in a family with a diagnosis of Cowden syndrome</strong></td>
</tr>
<tr>
<td>1. One pathognomonic criterion; or</td>
</tr>
<tr>
<td>2. Any 1 major criterion with or without minor criteria; or</td>
</tr>
<tr>
<td>3. Two minor criteria; or</td>
</tr>
<tr>
<td>4. History of Bannayan-Riley-Ruvalcaba syndrome</td>
</tr>
</tbody>
</table>

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

In 2013, a systematic review was conducted related to the clinical features reported in individuals with a PTEN mutation, and revised diagnostic criteria were proposed. The authors 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,
Genetic Testing for PTEN Hamartoma Tumor Syndrome

Policy # 00417
Original Effective Date: 05/21/2014
Current Effective Date: 05/17/2017

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 NCCN guidelines Genetic/Familial High Risk Assessment: Breast and Ovarian (v2.2015).

Bannayan-Riley-Ruvalcaba Syndrome
Diagnostic criteria for BRRS have not been set but 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
Proteus syndrome is highly variable and 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.

Table 2. Additional Criteria for Diagnosis of Proteus Syndrome

<table>
<thead>
<tr>
<th>Additional Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connective tissue nevi (pathognomonic)</td>
</tr>
<tr>
<td>OR 2 of the following:</td>
</tr>
<tr>
<td>Epidermal nevus</td>
</tr>
<tr>
<td>Disproportionate overgrowth (1 or more):</td>
</tr>
<tr>
<td>• Limbs: arms/legs; hands/feet/digits</td>
</tr>
<tr>
<td>• Skull: hyperostoses</td>
</tr>
<tr>
<td>• External auditory meatus: hyperostosis</td>
</tr>
<tr>
<td>• Vertebrae: megaspondylodyplasia</td>
</tr>
<tr>
<td>• Viscera: spleen/thymus</td>
</tr>
<tr>
<td>Specific tumors before end of second decade (either one):</td>
</tr>
<tr>
<td>• Bilateral ovarian cystadenomas</td>
</tr>
<tr>
<td>• Parotid monomorphic adenoma</td>
</tr>
<tr>
<td>OR 3 of the following:</td>
</tr>
<tr>
<td>Dysregulated adipose tissue (either one):</td>
</tr>
<tr>
<td>• Lipomas</td>
</tr>
<tr>
<td>• Regional absence of fat</td>
</tr>
<tr>
<td>Vascular malformations (1 or more):</td>
</tr>
<tr>
<td>• Capillary malformation</td>
</tr>
<tr>
<td>• Venous malformation</td>
</tr>
<tr>
<td>• Lymphatic malformation</td>
</tr>
<tr>
<td>Facial phenotype:</td>
</tr>
<tr>
<td>• Dolichocephaly</td>
</tr>
<tr>
<td>• Long face</td>
</tr>
<tr>
<td>• Minor downsloping of palpebral fissures and/or minor ptosis</td>
</tr>
<tr>
<td>• Low nasal bridge</td>
</tr>
<tr>
<td>• Wide or anteverted nares</td>
</tr>
<tr>
<td>• Open mouth at rest</td>
</tr>
</tbody>
</table>
Genetic Testing for PTEN Hamartoma Tumor Syndrome

Policy # 00417

Original Effective Date: 05/21/2014
Current Effective Date: 05/17/2017

Proteus-Like Syndrome
Proteus-Like Syndrome is undefined but describes individuals with significant clinical features of PS but who do not meet the diagnostic criteria.

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).

Surveillance
The most serious consequences of PHTS relate 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 mutation is increased cancer surveillance to detect tumors at the earliest, most treatable stages.

Molecular Diagnosis
PTEN (phosphatase and tensin 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.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
Genetic Testing for PTEN Hamartoma Tumor Syndrome

Policy # 00417
Original Effective Date: 05/21/2014
Current Effective Date: 05/17/2017

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratory testing for PTEN mutations is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by 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.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source
The evaluation of a genetic test focuses on 3 main principles: (1) analytic validity (technical accuracy of a test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (diagnostic performance of a test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility.

PTEN 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 PTEN hamartoma tumor syndrome (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.

Interventions
Genetic testing for PTEN.

Comparators
Standard clinical management without genetic testing for PTEN.

Outcomes
The general outcomes of interest are overall survival (OS), disease-specific survival, and morbid events. The potential beneficial outcomes of primary interest would be improvements in OS 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 results. False-positive test results can lead to unnecessary cancer surveillance procedures such as invasive biopsies.
False-negative test results can lead to lack of cancer surveillance that might detect cancer at earlier and more treatable stages.

**Time**
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.

**Analytic Validity**
Analytic validity is the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent. Measures of analytic validity include sensitivity (detection rate), specificity (false-positive rate), precision (repeatability of test results), and assay robustness (resistance to small changes in preanalytic or analytic variables). Analytic validity must be demonstrated in multiple sites and across populations of interest.

According to a large reference laboratory, analytic sensitivity and specificity for polymerase chain reaction (PCR) sequencing PTEN-related disorders is 99%, and analytical sensitivity and specificity of testing for deletions/duplications by multiplex ligation-dependent probe amplification is 90% and 98%, respectively.

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

**Clinical Validity**
Clinical validity is the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease.

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, and the true frequencies of the clinical features in CS and BRRS are not known.

According to a large reference laboratory, the clinical sensitivity of PTEN-related disorders sequencing is 80% for CS, 60% for BRRS, 20% for PTEN-related PS, and 50% for PLS. For PTEN-related deletion/duplication, it is up to 10% for BRRS and unknown for CS, PS, and PLS.

Germline PTEN mutations 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 PCR-based mutation analysis of the
Genetic Testing for PTEN Hamartoma Tumor Syndrome

Policy # 00417
Original Effective Date: 05/21/2014
Current Effective Date: 05/17/2017

coding and flanking intronic regions of the gene. Marsh et al screened DNA from 37 CS families, and PTEN mutations were identified in 30 of 37 CS families (81%), including point mutations, insertions, and deletions.

Whether the remaining patients have undetected PTEN mutations or mutations in other, unidentified genes, is not known.

A 2011 study by Pilarski et al determined the clinical features most predictive of a mutation in a cohort of patients tested for PTEN mutations. Molecular and clinical data were reviewed for 802 patients referred for PTEN analysis by a single laboratory. All of the patients were classified as to whether they met revised International Cowden Consortium Diagnostic criteria. Two hundred thirty of the 802 patients met diagnostic criteria for a diagnosis of CS. Of these, 79 had a PTEN disease-associated variant, for a detection rate of 34%. The authors commented that this mutation 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 mutations as previously thought. In contrast, in their study, of the patients meeting diagnostic criteria for BRRS, 23 of 42 (55%) had a mutation, and 7 of 9 patients (78%) with diagnostic criteria for both CS and BRRS had a mutation, consistent with the literature.

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

Clinical Utility
Clinical utility is how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Genetic testing could have utility if it could confirm the diagnosis of PHTS when the diagnosis cannot be made clinically, or if it were used to confirm a diagnosis earlier than would otherwise be possible without genetic testing, and if earlier diagnosis led to management changes that improve outcomes.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Preferred evidence comes from randomized controlled trials (RCTs). No such trials were identified.

Chain of Evidence
A chain of 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.
Genetic Testing for PTEN Hamartoma Tumor Syndrome

Policy # 00417
Original Effective Date: 05/21/2014
Current Effective Date: 05/17/2017

Individuals with Suspected PHTS
The clinical utility for these patients 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 as no studies were identified that described how a molecular diagnosis of PHTS changed patient management.

However, for patients who are diagnosed with PHTS by identifying a PTEN disease-associated variant, the medical management focuses on increased cancer surveillance to detect tumors at the earliest, most treatable stages.

Section Summary: Clinical Utility
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.

PTEN 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 with 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 with a PHTS.

Interventions
Targeted genetic testing for a PTEN familial variant.

Comparators
Standard clinical management without targeted genetic testing for a PTEN familial variant.

Outcomes
The general outcomes of interest are OS, disease-specific survival, and morbid events. The potential beneficial outcomes of primary interest would be improvement in OS 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.
Genetic Testing for PTEN Hamartoma Tumor Syndrome

Policy # 00417
Original Effective Date: 05/21/2014
Current Effective Date: 05/17/2017

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

Time
Same as above for patients with sign and/or symptoms of PHTS.

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.

Analytic Validity
Same as the previous section for patients with sign and/or symptoms of PHTS.

Clinical Validity
Same as the previous section for patients with sign and/or symptoms of PHTS.

Clinical Utility
Clinical utility is how the results of a diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Preferred evidence comes from RCTs. No such trials were identified.

Chain of Evidence
A chain of 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.

Family Members
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: Clinical Utility
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
Genetic Testing for PTEN Hamartoma Tumor Syndrome

Policy # 00417
Original Effective Date: 05/21/2014
Current Effective Date: 05/17/2017

comfirm the diagnosis of PHTS and result in ongoing cancer surveillance. A negative test for a familial variant would reduce unnecessary cancer surveillance.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
A search of ClinicalTrials.gov in January 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

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, the evidence includes case series and 1 large prospective study on the frequency of a PTEN variant 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 reported analytic validity for PTEN genetic testing is high. The published clinical validity of testing for PTEN 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 have 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.

References
Genetic Testing for PTEN Hamartoma Tumor Syndrome

Policy # 00417
Original Effective Date: 05/21/2014
Current Effective Date: 05/17/2017


**Policy History**

Original Effective Date: 05/21/2014
Current Effective Date: 05/17/2017

- 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.

Next Scheduled Review Date: 05/2018

**Coding**

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

<table>
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<tr>
<th>Code Type</th>
<th>Code</th>
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<tbody>
<tr>
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<td>81321, 81322, 81323</td>
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<tr>
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<td>ICD-10 Diagnosis</td>
<td>Q85.8  Q85.9  Z82.79</td>
</tr>
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</table>
Genetic Testing for PTEN Hamartoma Tumor Syndrome

Policy #  00417
Original Effective Date:  05/21/2014
Current Effective Date:  05/17/2017

*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. 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.

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