MP 2.04.88
Genetic Testing for PTEN Hamartoma Tumor Syndrome

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Policy
Genetic testing for PTEN may be considered medically necessary to confirm the diagnosis when a patient has clinical signs of a PTEN hamartoma tumor syndrome.

Targeted genetic testing for a PTEN familial variant may be considered medically necessary in a first-degree relative of a proband with a known PTEN pathogenic variant.

Genetic testing for PTEN is considered investigational for all other indications.

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 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

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
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</table>

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

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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.

Coding

There are specific CPT codes for PTEN testing:

81321 PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis

81322 known familial variant

81323 duplication/deletion variant.
GENETIC TESTING FOR PTEN HAMARTOMA TUMOR SYNDROME

BENEFIT APPLICATION

BLUE CARD/NATIONAL ACCOUNT ISSUES

Some Plans may have contract or benefit exclusions for genetic testing.

BACKGROUND

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).

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
**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 (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

**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). 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.

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.

Table 2. Diagnostic Criteria for Proteus Syndrome

<table>
<thead>
<tr>
<th>Additional Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connective tissue nevi (pathognomonic) 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: megaspondylo dysplasia</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>
</tbody>
</table>
OR 3 of the following:

<table>
<thead>
<tr>
<th>Dysregulated adipose tissue (either one):</th>
</tr>
</thead>
<tbody>
<tr>
<td>· Lipomas</td>
</tr>
<tr>
<td>· Regional absence of fat</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular malformations (1 or more):</th>
</tr>
</thead>
<tbody>
<tr>
<td>· Capillary malformation</td>
</tr>
<tr>
<td>· Venous malformation</td>
</tr>
<tr>
<td>· Lymphatic malformation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Facial phenotype:</th>
</tr>
</thead>
<tbody>
<tr>
<td>· Dolichocephaly</td>
</tr>
<tr>
<td>· Long face</td>
</tr>
<tr>
<td>· Minor downslanting 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>

Adapted from Biesecker (2006).^7^  

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

**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.\[\]^8^ *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).

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.

Regulatory Status

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. Food and Drug Administration has chosen not to require any regulatory review of this test.

RATIONALE

This evidence review was created in February 2013 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through December 10, 2018.

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 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
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 (eg, 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 Cowden syndrome (CS) and Bannayan-Riley-Ruvalcaba syndrome (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 Proteus-like syndrome. For PTEN-related deletions and duplications, it is up to 10% for BRRS and unknown for CS, Proteus syndrome, and Proteus-like syndrome.

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.

**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 (eg, 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 (eg, 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.

**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.

**SUPPLEMENTAL INFORMATION**

**Practice Guidelines and Position statements**

Current National Comprehensive Cancer Network guidelines on genetic/familial high-risk assessment for breast and ovarian cancer (v.1.2018) recommend the following for Cowden syndrome management (see Table 3).

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

<table>
<thead>
<tr>
<th>Populations</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Women</td>
<td>Breast awareness starting at age 18 years.</td>
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</tbody>
</table>
**Genetic Testing for PTEN Hamartoma Tumor Syndrome**

- 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).
- Breast screening:
  - 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.
- For women with a PTEN mutation [disease-associated variant] who are treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue.
- 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.
- Discuss risk-reducing mastectomy and hysterectomy and counsel regarding degree of protection, extent of cancer risk, and reconstructive options.

**Men and women**
- 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.
- Annual thyroid ultrasound starting at the time of PHTS diagnosis.
- 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.
- Dermatologic management may be indicated for some patients.
- Consider renal ultrasound starting at age 40 years, then every 1 to 2 years.
- Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms.
- Education regarding signs and symptoms of cancer.

**Relatives**
- Advise about possible inherited cancer risk to relatives, options for risk assessment, and management.
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives.

**Reproductive options**
- 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 in December 2019 did not identify any ongoing or unpublished trials that would likely influence this review.

**REFERENCES**


**CODES**

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
</table>
# Genetic Testing for PTEN Hamartoma Tumor Syndrome

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>See Policy Guidelines</td>
</tr>
<tr>
<td>ICD-10-CM</td>
<td>Q85.8 Other phakomatoses, not elsewhere classified</td>
</tr>
<tr>
<td></td>
<td>Q85.9 Phakomatosis, unspecified (includes hamartosis NOS)</td>
</tr>
<tr>
<td></td>
<td>Z13.71 Encounter for nonprocreative screening for genetic disease carrier status</td>
</tr>
<tr>
<td></td>
<td>Z13.79 Encounter for other screening for genetic and chromosomal anomalies</td>
</tr>
</tbody>
</table>

| ICD-10-PCS | Not applicable. ICD-10-PCS codes are only used for inpatient services. There are no ICD procedure codes for laboratory tests. |

<table>
<thead>
<tr>
<th>Type of Service</th>
<th>Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Place of Service</td>
<td>Outpatient</td>
</tr>
</tbody>
</table>

## POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>02/13/14</td>
<td>Replace</td>
<td>Policy updated with literature search through January 9, 2014; reference 1 added. Prenatal testing removed from the investigational statement. Clarification of testing strategy in Policy Guidelines.</td>
</tr>
<tr>
<td>02/12/15</td>
<td>Replace</td>
<td>Policy updated with literature search through January 31, 2015. No references added. No change in policy statements.</td>
</tr>
<tr>
<td>02/11/16</td>
<td>Replace</td>
<td>Policy updated with literature review through December 18, 2015; references 1-3 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>02/24/17</td>
<td>Replace</td>
<td>Policy updated with literature review through January 11, 2017; no references added. The policy is revised with updated genetics nomenclature. Policy statements unchanged.</td>
</tr>
<tr>
<td>02/26/18</td>
<td>Replace</td>
<td>Blue Cross of Idaho adopted changes as noted. Policy updated with literature review through December 11, 2017; no references added. Policy statements unchanged.</td>
</tr>
<tr>
<td>02/21/19</td>
<td>Replace</td>
<td>Blue Cross of Idaho adopted changes as noted, effective 02/21/2019. Policy updated with literature review through December 10, 2018; no references added. Policy statements unchanged.</td>
</tr>
</tbody>
</table>