Medical Policy
Genetic Testing for PTEN Hamartoma Tumor Syndrome

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- Policy: Medicare
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Policy Number: 615
BCBSA Reference Number: 2.04.88
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

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.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Plan</th>
<th>Outpatient</th>
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<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>No</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
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<tr>
<td>Medicare HMO Blue℠</td>
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<tr>
<td>Medicare PPO Blue℠</td>
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CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81321</td>
<td>PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis</td>
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<tr>
<td>81322</td>
<td>PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant</td>
</tr>
<tr>
<td>81323</td>
<td>PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant</td>
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ICD-9 Diagnosis Codes

<table>
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<th>ICD-9 Diagnosis codes:</th>
<th>Code Description</th>
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<tr>
<td>759.6</td>
<td>Other hamartoses, NEC</td>
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<tr>
<td>V18.9</td>
<td>Family history of, genetic disease carrier</td>
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ICD-10-CM Diagnosis Code

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<th>ICD-10-CM Diagnosis codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>Q85.8</td>
<td>Other phakomatoses, not elsewhere classified</td>
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<tr>
<td>Q85.9</td>
<td>Phakomatosis, unspecified</td>
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<td>Z84.81</td>
<td>Family history of carrier of genetic disease</td>
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Description

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.¹ 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 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.

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

Table 1. International Cowden Consortium 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 (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

*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.5 Reviewers concluded that there was insufficient evidence to support inclusion of benign breast disease, uterine fibroids, or genitourinary malformations as diagnostic criteria. There was sufficient evidence to include autism spectrum disorders, colon cancer, esophageal glycogenic acanthosis, penile macules, renal cell carcinoma, testicular lipomatosis, and vascular anomalies, and these clinical features are included in CS testing minor criteria in the National Comprehensive Cancer Network guidelines on genetic/familial high-risk assessment of breast and ovarian (v.2.2017).6

**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 2.7

**Table 2. Additional Criteria for Diagnosis of 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: megaspodyldysplasia
- 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

**Proteus-Like Syndrome**
PLS 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 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.

**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, \( \geq 2 \) 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.

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

For individuals who have clinical signs and/or symptoms of a PHTS or who are asymptomatic with a first-degree relative with a PHTS and a known familial variant who receive genetic testing for a *PTEN* familial variant, the evidence includes case series and 1 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 morbidity 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 Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome 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.

**Policy History**

<table>
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<th>Date</th>
<th>Action</th>
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<tr>
<td>4/2017</td>
<td>BCBSA National medical policy review. Policy clarified. Policy statements unchanged. 4/1/2017</td>
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<tr>
<td>6/2015</td>
<td>Local Coverage Determination (LCD): Molecular Pathology Procedures (L34506) added.</td>
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<tr>
<td>7/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
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<tr>
<td>9/2013</td>
<td>New references from BCBSA National medical policy.</td>
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**Information Pertaining to All Blue Cross Blue Shield Medical Policies**
Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References