Medical Policy
Genetic Testing for PTEN Hamartoma Tumor Syndrome

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Policy Number: 615
BCBSA Reference Number: 2.04.88

Related Policies
None

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

Genetic testing for a PTEN mutation may be considered MEDICALLY NECESSARY to confirm the diagnosis when a patient has clinical signs of a PTEN hamartoma tumor syndrome.

Genetic testing for a PTEN mutation may be considered MEDICALLY NECESSARY in a first-degree relative of a proband with a known PTEN mutation.

Genetic testing for a PTEN mutation is considered INVESTIGATIONAL for all other indications.

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.

<table>
<thead>
<tr>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
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<tr>
<td>Medicare HMO BlueSM</td>
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<td>Medicare PPO BlueSM</td>
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</tbody>
</table>

CPT Codes / HCPCS Codes / ICD-9 Codes
The following codes are included below for informational purposes. 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. A draft of future ICD-10 Coding related to this document, as it might look today, is included below for your reference.

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>
</tr>
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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>
</tr>
<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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</tbody>
</table>

**ICD-9 Diagnosis Codes**

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

**ICD-10-CM Diagnosis Code**

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

**Description**

The PTEN hamartoma tumor syndrome (PHTS) includes several syndromes with heterogeneous clinical symptoms, which may place individuals at an increased risk of the development of certain types of cancer. PHTS can be diagnosed with the identification of a PTEN mutation.

**Background**

The *PTEN* (‘phosphatase and *tensin* homologue on chromosome 10’) hamartoma tumor syndrome (PHTS) is characterized by hamartomatous tumors and PTEN germline mutations. 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 the late 20s. The lifetime risk of developing breast cancer is 25-50%, with an average age of diagnosis between 38 and 46 years. The lifetime risk for thyroid cancer, which is usually follicular carcinoma, is approximately 10%. The risk for endometrial cancer is not well defined, but may approach 5-10%.

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.

Proteus-like syndrome 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 mutation is identified.

International Cowden Consortium diagnostic criteria for the diagnosis of Cowden Syndrome

Pathognomonic criteria
- Lhermitte-Duclos disease (LDD) — 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:
   a. There are six or more facial papules, of which three or more must be trichilemmoma, or
   b. Cutaneous facial papules and oral mucosal papillomatosis, or
   c. Oral mucosal papillomatosis and acral keratoses, or
   d. Palmoplantar keratoses, six or more
2. Two or more major criteria, but one must include macrocephaly or LDD; or
3. One major and three minor criteria; or
4. Four minor criteria.

Operational diagnosis in a family where one individual is diagnostic for Cowden
1. One pathognomonic criterion; or
2. Any one major criterion with or without minor criteria; or
3. Two minor criteria; or
History of Bannayan–Riley–Ruvalcaba syndrome

(National Comprehensive Cancer Network)

Bannayan-Riley-Ruvalcaba syndrome (BRRS). 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 (PS) is highly variable and 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 include:

- Connective tissue nevi (pathognomonic)

OR two of the following:

- Epidermal nevus
- Disproportionate overgrowth (one or more)
  - Limbs: arms/legs; hands/feet/digits
  - Skull: hyperostosis
  - External auditory meatus: hyperostosis
  - Vertebrae: megaspondylosplasia
  - Viscera: spleen/thymus
- Specific tumors before end of second decade (either one)
  - Bilateral ovarian cystadenomas
  - Parotid monomorphic adenoma

OR three of the following:

- Dysregulated adipose tissue (either one)
  - Lipomas
  - Regional absence of fat
- Vascular malformations (one 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 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.

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 homologue on chromosome 10’) is a tumor suppressor gene on chromosome 10q23 and is dual specificity phosphatase with multiple but incompletely understood roles in cellular regulation. (1) PTEN mutations are inherited in an autosomal dominant manner.

Because CS is likely underdiagnosed, the actual proportion of simplex cases (defined as individuals with no obvious family history) and familial cases (defined as ≥2 related affected individuals) cannot be determined. The majority of CS cases are simplex. It is estimated that 50-90% of cases of CS are de novo and approximately 10-50% 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 mutation 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 mutation. Some data suggest the up to 20% of patients with Proteus syndrome and up to 50% of patients with a Proteus-like syndrome have PTEN mutations.

**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.

PTEN is the only gene in which mutations are known to cause PHTS.

**Summary**
A *PTEN* mutation can be identified in up to 85% of patients who meet the clinical criteria for a diagnosis of Cowden syndrome (CS) and 65% of patients with a clinical diagnosis of Bannayan-Riley-Ruvalcaba syndrome. Most of these mutations can be identified by sequence analysis of the coding and flanking intronic regions of genomic DNA. A smaller number of mutations are detected by deletion/duplication or promoter region analysis. However, the published clinical validity of testing for *PTEN* mutations is variable, and the true clinical validity is difficult to ascertain, as the syndrome is defined by the presence of a *PTEN* mutation.

The clinical utility of genetic testing for a *PTEN* mutation is high, in that confirming a diagnosis in a patient with clinical signs of a *PTEN* hamartoma tumor syndrome (PHTS) will lead to changes in clinical management by increasing surveillance to detect cancers known to be 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. Therefore, genetic testing for a *PTEN* mutation may be considered medically necessary when a presumptive diagnosis of a PHTS has been made, based on clinical signs and also in first-degree relatives of a probands with a known *PTEN* mutation.

**Policy History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>7/2014</td>
<td>BCBSA National medical policy review.</td>
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<tr>
<td></td>
<td>Prenatal testing removed from the investigational statement. Effective 7/1/2014.</td>
</tr>
<tr>
<td>7/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
</tr>
<tr>
<td>9/2013</td>
<td>New references from BCBSA National medical policy.</td>
</tr>
<tr>
<td>8/2013</td>
<td>BCBSA National medical policy review.</td>
</tr>
<tr>
<td></td>
<td>New policy describing medically necessary and investigational indications. Effective 8/1/2013.</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