The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Preauthorization is required. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

Description

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. PHTS can be diagnosed with the identification of a PTEN mutation.

Background

The PTEN (phosphatase and tensin homolog deleted 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% to 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% to 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.

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 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 1 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
4. History of Bannayan-Riley-Ruvalcaba syndrome

(International Cowden Consortium diagnostic criteria for the diagnosis of Cowden syndrome have been adopted by the National Comprehensive Cancer Network [NCCN])

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. (1) The authors concluded that there was insufficient
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 Cowden syndrome testing minor criteria in NCCN guidelines (v4.2013). Available online at: http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf.

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 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: hyperostoses
  - External auditory meatus: hyperostosis
  - Vertebrae: megaspondylodysplasia
  - Viscera: spleen/thymus
- Specific tumors before end of second decade (either one)
  - Bilateral ovarian cystadenomas
  - Parotid monomorphic adenoma

**OR 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 homolog deleted 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. (2) 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% 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 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 PS and up to 50% of patients with a PLS 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.

**Regulatory Status**

No U.S. Food and Drug Administration–cleared molecular diagnostic tests were found. Thus, molecular evaluation is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

**Policy (Formerly Corporate Medical Guideline)**

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.
Policy Guideline

Testing strategy for confirming the diagnosis in a proband

The order of testing to optimize yield would be (1) sequencing of PTEN exons one to nine and flanking intron regions. If no mutation is identified, perform (2) deletion/duplication analysis. If no mutation is identified, consider, (3) promoter analysis, which detects mutations in ~10% of individuals with CS who do not have an identifiable mutation in the PTEN coding region.

Testing a first-degree relative

When a PTEN mutation has been identified in the proband, testing of asymptomatic at-risk relatives can identify those family members who have the family-specific mutation, for whom an initial evaluation and ongoing surveillance should be performed.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


