Genetic Testing for PTEN Hamartoma Tumor Syndrome

Effective: August 1, 2019

Next Review: May 2020
Last Review: June 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

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 variant.

MEDICAL POLICY CRITERIA

I. Genetic testing for PTEN may be considered medically necessary in a first-degree relative of a proband with a known PTEN disease-associated variant.

II. Genetic testing for PTEN, including in the evaluation of PTEN hamartoma tumor syndrome, may be considered medically necessary when any of the following criteria are met:

   A. In a patient with two or more of the following:
      1. Autism spectrum disorder
      2. Breast Cancer
      3. Colon cancer
      4. Endometrial cancer (epithelial)
5. Esophageal glycogenic acanthoses, three or more
6. Gastrointestinal hamartomas (including ganglioneuromas, adenomas, hyperplastic polyps; three or more)
7. Intellectual disability defined as IQ less than or equal to 75
8. Lipomas, three or more
9. Macrocephaly (megalocephaly; defined as greater than or equal to 97th percentile, 58 cm in adult woman, 60 cm in adult men)
10. Macular pigmentation of glans penis
11. Mucocutaneous lesions, three or more with clinical documentation
12. Renal cell carcinoma
13. Testicular lipomatosis
14. Thyroid cancer or thyroid structural lesions (e.g. adenoma, multinodular goiter)
15. Vascular anomalies (including multiple intracranial developmental venous anomalies)

B. In a patient with any of the following:
   1. Two or more biopsy-proven trichilemmomas
   2. Autism spectrum disorder and macrocephaly
   3. Adult Lhermitte-Duclos syndrome

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

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

TESTING IN A FIRST-DEGREE RELATIVE

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

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Current Symptomology
- Documentation of first-degree relative when there is known variant
BACKGROUND

The \textit{PTEN} (phosphatase and tensin homologue) hamartoma tumor syndrome is characterized by hamartomatous tumors and \textit{PTEN} germline disease-associated variants. Clinically, PHTS includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), \textit{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 \textit{PTEN} pathogenic variants should be assumed to have cancer risks similar to those with CS.

CLINICAL DIAGNOSIS

A presumptive diagnosis of PHTS is based on clinical findings (see Policy Guidelines); however, because of the phenotypic heterogeneity associated with the hamartoma syndromes, the diagnosis of PHTS is made only when a \textit{PTEN} disease-associated variant is identified.

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 disease-associated variant is increased cancer surveillance to detect tumors at the earliest, most treatable stages.

MOLECULAR DIAGNOSIS

PTEN is a tumor suppressor gene on chromosome 10q23 and is dual specificity phosphatase with multiple but incompletely understood roles in cellular regulation.[1] PTEN pathogenic variants 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 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 variant. 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 variants.

Most of these pathogenic 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.

REGULATORY STATUS

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 variants 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.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[2] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.
Validation of the clinical use of any genetic test focuses on three main principles:

1. Analytic validity, which refers to the technical accuracy of the test in detecting a pathogenic variant that is present or in excluding a variant that is absent;
2. Clinical validity, which refers to the diagnostic performance of the test (i.e., sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. Clinical utility, which refers to 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.

The focus of this review is on evidence from well designed, studies related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention; and
- Improve health outcomes as a result of those decisions.

**ANALYTIC VALIDITY**

According to a large reference laboratory, analytical sensitivity and specificity for bidirectional sequencing of the *PTEN*-related promoter, coding region and intron-exon boundaries is 99%.[3]

**CLINICAL VALIDITY**

Many reports on the prevalence of the features of Cowden syndrome (CS) and Bannayan-Riley-Ruvalcaba (BRRS) have been based upon 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.[1]

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 Proteus syndrome (PS) and 50% for Proteus-like syndrome (PSL). For *PTEN*-related deletion/duplication, it is up to 10% for BRRS and unknown for CS, PS, and PSL.[3]

Germline *PTEN* variants have been identified in ~80% of patients meeting diagnostic criteria for CS and in 50-60% of patients with a diagnosis of BRRS, using PCR-based sequence analysis of the coding and flanking intronic regions of the gene.[4,5] Marsh screened DNA from 37 CS families and *PTEN* variants were identified in 30 of 37 CS families (81%), including single nucleotide variants, insertions, and deletions.[4] The *PTEN* variant detection rate is much lower in breast cancer patients without other symptoms.[6,7]

Whether the remaining patients have undetected *PTEN* variants or variants in other, unidentified genes, is not known.[8]

A study by Pilarski (2011) determined the clinical features that were most predictive of a disease-associated variant in a cohort of patients tested for *PTEN* variants.[1] 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 and thirty of the 802 patients met diagnostic criteria for a diagnosis of CS. Of these, 79 had a *PTEN* pathogenic variant, for a detection rate of 34%. The authors commented that this 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 variants as previously thought. In contrast, in their study, of the patients meeting diagnostic criteria for BRRS, 23 of 42 (55%) had a pathogenic variant, and seven of nine patients (78%) with diagnostic criteria for both CS and BRRS had a variant, consistent with the literature.

**Section Summary**

Evidence from several small studies indicated that the clinical sensitivity of genetic testing for PTEN variants may be highly variable. This may reflect the phenotypic heterogeneity of the syndromes and an inherent referral bias as 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 variant.

**CLINICAL UTILITY**

The clinical utility of genetic testing can be considered in the following clinical situations:

1. Individuals with suspected PTEN hamartoma tumor syndrome (PHTS)
2. Family members of individuals with PHTS, and
3. Prenatal testing.

**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 pathogenic variant, the medical management focuses on increased cancer surveillance to detect tumors at the earliest, most treatable stages.

- **Family members.**
  
  When a PTEN pathogenic variant has been identified in a proband, testing of at-risk relatives can identify those who also have the pathogenic variant and have PTEN hamartoma tumor syndrome (PHTS). These individuals need initial evaluation and ongoing surveillance.

- **Prenatal screening.**
  
  Prenatal diagnosis is possible for pregnancies at increased risk, by amniocentesis or chorionic villus sampling; the disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Recent studies reporting on the clinical features of individuals with a PTEN pathogenic variant have indicated there is insufficient evidence to support the inclusion of benign breast disease, uterine fibroids, or genitourinary malformations as diagnostic criteria. However, there was sufficient evidence identified to include autism spectrum disorders, colon cancer, esophageal glycogenic acanthosis, penile macules, renal cell carcinoma, testicular lipomatosis and vascular anomalies. These identified clinical features are included in CS testing minor criteria.
Section Summary

Direct evidence for the clinical utility of PTEN testing is lacking. However, the clinical utility of genetic testing for PTEN variants is that genetic testing can confirm the diagnosis in patients with clinical signs and symptoms of PHTS. Management changes include increased surveillance for the cancers associated with these syndromes.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The NCCN guidelines on Genetic/Familial High-Risk Assessment: Breast and Ovarian recommend the following for CS/PHTS management (v3.2019):[9]

For Women:

- Breast awareness starting at age 18 years.
- Clinical breast exam every 6-12 months, starting at age 25 years or 5-10 years before the earliest known breast cancer in the family (whichever comes first).
- Breast screening:
  - Annual mammography with consideration of tomosynthesis and breast MRI [magnetic resonance imaging] screening with contrast starting at age 30-35 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 variant who are treated for breast cancer, and have not had bilateral mastectomy, screening of remaining breast tissue with annual mammography and breast MRI should continue.

- Endometrial cancer screening:
  - Encourage patient education and prompt response to symptoms (eg abnormal bleeding). Patients are encouraged to keep a calendar in order to identify irregularities in their menstrual cycle.
  - Because endometrial cancer can often be detected early based on symptoms, women should be educated regarding the importance of prompt reporting and evaluation of any abnormal uterine bleeding or postmenopausal bleeding. The evaluation of these symptoms should include endometrial biopsy.
  - Endometrial cancer screening does not have proven benefit in women with Cowden syndrome/PHTS. However, endometrial biopsy is both highly sensitive and highly specific as a diagnostic procedure. Screening via endometrial biopsy every 1 to 2 years can be considered.
  - Transvaginal ultrasound to screen for endometrial cancer in postmenopausal women has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but may be considered at the clinician’s discretion. Transvaginal ultrasound is not recommended as a screening tool in premenopausal women due to the wide range of endometrial stripe thickness throughout the normal menstrual cycle.
• Discuss option of hysterectomy upon completion of childbearing and counsel regarding degree of protection, extent of cancer risk, and reproductive desires.

• Discuss risk-reducing mastectomy and hysterectomy and counsel regarding degree of protection, extent of cancer risk, and reconstructive options.

• Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or hysterectomy.

For 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 thyroid exam.

• Annual thyroid ultrasound, starting at the time of PHTS diagnosis, including in childhood.

• Colonoscopy, starting at age 35 years, unless symptomatic or a close relative with colon cancer before age 40 years, then start 5-10 years before earliest known colon cancer in the family. Colonoscopy should be done every 5 years or more frequently if patient is symptomatic or polyps found.

• Consider renal ultrasound starting at age 40 years, then every 1 to 2 years.

• Dermatologic management may be indicated for some patients.

• Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms.

• Education regarding the signs and symptoms of cancer.

For 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.

**SUMMARY**

There is enough research to show that PTEN genetic testing can help to determine appropriate cancer surveillance, leading to improved health outcomes for patients at high risk for PTEN hamartoma tumor syndrome. Clinical guidelines based on research recommend this testing for certain individuals. Therefore, PTEN genetic testing may be considered medically necessary when a presumptive diagnosis of a PTEN hamartoma tumor syndrome has been made, based on clinical signs, and for first-degree relatives of an individual with a known disease-associated PTEN variant.

There is not enough research to show that PTEN genetic testing improves health outcomes for individuals who do not meet the policy criteria. Therefore, genetic testing for a PTEN variant is considered investigational for all other indications.

**REFERENCES**

## CODES

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