Regence

Medical Policy Manual Genetic Testing, Policy No. 63

Genetic Testing for PTEN Hamartoma Tumor Syndrome

Effective: September 1, 2026

Next Review: May 2027
Last Review: July 2026

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 developing certain types of cancer. PHTS can be diagnosed with the identification of a *PTEN* variant.

MEDICAL POLICY CRITERIA

Notes: Clinical documentation to support criteria is required (See Required Documentation).

Medically Necessary

I. Genetic testing for *PTEN*, including in the evaluation of *PTEN* hamartoma tumor syndrome, may be considered **medically necessary** when one or more of the following criteria are met:

   A. In a first-degree relative of a proband with a known *PTEN* disease-associated variant

   B. In an individual with any of the following:

1. Two or more biopsy-proven trichilemmomas
2. Autism spectrum disorder and macrocephaly
3. Adult Lhermitte-Duclos syndrome

C. 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)

Investigational

II. Genetic testing for *PTEN* is considered **investigational** when Criterion I. is not met.

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.

REQUIRED 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 pathogenic/likely pathogenic variant

CROSS REFERENCES

1. Genetic Testing for Hereditary Breast and Ovarian Cancer and Li-Fraumeni Syndrome, Genetic Testing, Policy No. 02
2. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
3. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64
4. Biomarkers for Cardiovascular Disease, Laboratory, Policy No. 78

BACKGROUND

The *PTEN* (phosphatase and tensin homologue) hamartoma tumor syndrome 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 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* 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; 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.

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.

CLINICAL VALIDITY

Many reports on the prevalence of the features of Cowden syndrome (CS) and Bannayan-Riley-Ruvalcaba syndrome (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 85% for CS, 65% 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/or CS-like syndrome.[3]

Germline *PTEN* variants have been identified in ~80% of patients meeting diagnostic criteria for CS and in 50 to 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 (1998) 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 in National Comprehensive Cancer Network guidelines (see Policy Guidelines section above) and described in a recent systematic review.[9, 10]

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, Ovarian, Pancreatic, and Prostate recommend the following for CS/PHTS management (3.2026):[10]

For Biologic Females:

- Breast awareness.
- 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 with or without contrast starting at age 30 years or 10 years before the earliest known breast cancer in family (whichever comes first).
    - Age >75 years, management should be considered on an individual basis.
    - For individuals with pathogenic/likely pathogenic *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 as described above.
- Discuss option of risk-reducing mastectomy in individuals with pathogenic/likely pathogenic variants identified. For those with clinical CS/PTHS syndrome, consideration of risk-reducing surgery should be based on family history.
- Endometrial cancer screening, consider starting by age 35 years:
    - 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 CS/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.
- 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 age seven years. This may also be considered for children at 50% risk of inheriting a known mutation whose parents wish to delay genetic testing until age 18 years.
- Colonoscopy, starting at age 35 years, unless symptomatic or a close relative with colon cancer before age 40 years, then start 5 to 10 years before earliest known colon cancer in the family. Colonoscopy should be done every five years or more frequently if patient is symptomatic or polyps found.
- Consider renal ultrasound starting at age 40 years, then every one to two years.
- There may be an increased risk of melanoma, and the prevalence of other skin characteristics with CS/PTHS may independently make routine dermatology evaluations of value. Annual dermatology recommendations are recommended.
- 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.

U.S MULTI-SOCIETY TASK FORCE ON COLORECTAL CANCER

In 2022, the US Multi-Society Task Force on Colorectal Cancer (USMSTF), a group of colorectal cancer (CRC) content experts appointed by the American College of Gastroenterology, American Gastroenterological Association, and American Society for Gastrointestinal Endoscopy, published recommendations on the diagnosis and management of

cancer risk in the gastrointestinal hamartomatous polyposis syndromes, including the following regarding genetic testing:[11]

> We recommend patients with any of the following undergo a genetic evaluation: 2 or more lifetime hamartomatous polyps, a family history of hamartomatous polyps, or a cancer associated with a hamartomatous polyposis syndrome in first- or second-degree relatives. Genetic testing (if indicated) should be performed using a multigene panel test. (Strong recommendation, low quality of evidence).
>
> We recommend genetic evaluation for any individual with the following: 1) 2 or more histologically confirmed Peutz-Jeghers polyps, 2) any number of Peutz-Jeghers polyps in an individual who has a family history of Peutz-Jeghers syndrome in a first-degree relative, 3) characteristic mucocutaneous pigmentation in a person with a family history of Peutz-Jeghers syndrome, 4) any number of Peutz-Jeghers polyps in a person with the characteristic mucocutaneous pigmentation of Peutz-Jeghers syndrome. (Strong recommendation, low quality of evidence).
>
> We recommend genetic evaluation for any individual with 1) 5 or more juvenile polyps of the colon or rectum; or 2) 2 or more juvenile polyps in other parts of the gastrointestinal tract; or (3) any number of juvenile polyps and 1 or more first-degree relatives with juvenile polyposis syndrome. (Strong recommendation, low quality of evidence).
>
> We recommend individuals with multiple gastrointestinal hamartomas or ganglioneuromas undergo genetic evaluation for Cowden's syndrome and related conditions. (Strong recommendation, low quality of evidence).

SUMMARY

Medically Necessary

There is enough research to show that *PTEN* genetic testing can help to determine appropriate cancer surveillance, leading to improved health outcomes for individuals at high risk for *PTEN* hamartoma tumor syndrome. Clinical guidelines based on research recommend this testing for certain people. 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.

Investigational

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

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CODES

Codes	Number	Description
CPT	0235U	*PTEN (phosphatase and tensin homolog)* (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
	81321	*PTEN (phosphatase and tensin homolog)* (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
	81322	;known familial variant
	81323	;duplication/deletion variant
HCPCS	None	

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