BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.88 Genetic Testing for PTEN Hamartoma Tumor Syndrome

Annual Effective Policy Date: January 1, 2025

Original Policy Date: September 2013

Related Policies:

None

Genetic Testing for PTEN Hamartoma Tumor Syndrome

Description

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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.

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing improves the net health outcome in individuals with clinical signs and/or symptoms of a *PTEN* hamartoma tumor syndrome or asymptomatic or at-risk individuals with a known familial variant.

POLICY STATEMENT

Genetic testing for *PTEN* may be considered **medically necessary** to confirm the diagnosis when an individual 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.

POLICY GUIDELINES

Testing Strategy to Confirm a Diagnosis in a Proband

The order of testing to optimize yield would be (1) sequencing of *PTEN* exons 1-9 and flanking intronic regions. If no disease-associated variant is identified, perform (2) deletion/duplication analysis. If no disease-associated variant is identified, consider (3) promoter analysis, which detects disease-associated variants in approximately 10% of individuals with Cowden syndrome who do not have an identifiable disease-associated variant in the *PTEN* coding region.

Testing a First-Degree Relative

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

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology - "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" - to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratory testing for *PTEN* variants is available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the 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.

RATIONALE

Summary of Evidence

For individuals who have clinical signs and/or symptoms of a *PTEN* hamartoma tumor syndrome (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 a 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 morbid events. The published clinical validity of testing for the *PTEN* gene 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 has 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 an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

Current (v.2.2024), National Comprehensive Cancer Network guidelines on genetic/familial high-risk assessment for breast and ovarian cancer[6], include Testing Criteria for Cowden Syndrome (CS)/*PTEN* Hamartoma Tumor Syndrome (PHTS) (CRIT-8) that recommend testing for:

- Individual from a family with a known *PTEN* pathogenic/likely pathogenic variant
- Individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)
- Individual meeting clinical diagnostic criteria for CS/PHTS
- Individual not meeting clinical diagnostic criteria for CS/PHTS with a personal history of: Adult Lhermitte-Duclos disease (cerebellar tumors); or autism spectrum disorder and macrocephaly; or 2 or more biopsy-proven trichilemmomas; or 2 or more major criteria (1 must be macrocephaly); or 3 major criteria, without macrocephaly; or 1 major and ≥3 minor criteria; or ≥4 minor criteria
- At-risk individual with a relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed. The at-risk individual must have the following: Any 1 major criterion or 2 minor criteria.
- *PTEN* pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline analysis.

Additionally, the following is recommended for Cowden syndrome management (see Table 1).

Table 1. NCCN Guidelines on Cowden Syndrome / *PTEN* Hamartoma Tumor Syndrome Management

Populations	Recommendations
Women	• Breast awareness starting at age 18 years.
	• 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 and without contrast starting at age 30 years or 10 years before the earliest known breast cancer in the family (whichever comes first).
	• Age >75, management should be considered on an individual basis.
	• For individuals with a PTEN pathogenic/likely pathogenic variant who are treated for breast cancer, and have not had a bilateral mastectomy, screening with annual mammogram 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/PHTS syndrome, consideration of risk-reducing surgery should be based on family history. Discuss risk-reducing mastectomy and hysterectomy and counsel regarding degree of protection, extent of cancer risk, and reconstructive options

	• Counseling should include a discussion regarding degree of protection, reconstruction options, and risks. In addition, the family history and residual breast cancer risk with age and life expectancy should be considered during counseling.
	• For 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, individuals 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 individuals 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.
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 7. This may also be considered for children at 50% risk of inheriting a known pathogenic/likely pathogenic 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 under age 40 years, then start 5 to 10 years before the earliest known colon cancer in the family. Colonoscopy should be done every 5 years or more frequently if patient is symptomatic or polyps found.
	• 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 exams are recommended.
	• Consider renal ultrasound starting at age 40 years, then every 1 to 2 years.
	• Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms

	• Education regarding signs and symptoms of cancer
Relatives	• Advise about possible inherited cancer risk to relatives, options for risk assessment, and management
	• Recommend genetic counseling and consideration of genetic testing for family members
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

CS: Cowden Syndrome; MRI: magnetic resonance imaging; PHTS: *PTEN* hamartoma tumor syndrome.

U.S. Preventive Services Task Force Recommendations

No **U.S. Preventive Services Task Force** recommendations for genetic testing for *PTEN* hamartoma tumor syndrome have been identified.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
September 2013	New policy	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.
June 2014	Replace policy	Policy updated with literature; reference 1 added. Clarification of testing strategy in Policy Guidelines.
June 2015	Replace policy	Policy updated with literature review; no references added. Policy statements unchanged.
June 2018	Replace policy	Policy updated with literature review through December 11, 2017; references 1-3 added. Objective Statement added. Policy statements unchanged.
June 2019	Replace policy	Policy updated with literature review through December 10, 2018; no references added. Policy statements unchanged.
June 2020	Replace policy	Policy updated with literature review through December 10, 2019; no references added. Added NCCN testing criteria for Cowden Syndrome/PTEN Hamartoma Tumor Syndrome (Version 1.2020). Policy statement unchanged.
June 2021	Replace policy	Policy updated with literature review through December 14, 2020; no references added. Updated NCCN testing criteria for Cowden Syndrome/PTEN Hamartoma Tumor Syndrome (Version 2.2021). Policy statement unchanged.
June 2022	Replace policy	Policy updated with literature review through November 15, 2021; no references added. Updated NCCN testing criteria for Cowden Syndrome/PTEN Hamartoma Tumor Syndrome. Policy statements unchanged.
June 2023	Replace policy	Policy updated with literature review through November 14, 2023; no references added. Minor editorial refinements to policy statements; intent unchanged.
December 2024	Replace policy	Policy updated with literature review through December 21, 2023; no references added. Policy statements unchanged.