BlueCross BlueShield Federal Employee Program.

FEP 2.04.88 Genetic Testing for PTEN Hamartoma Tumor Syndrome

Effective Date: July 15, 2018

Related Policies: None

Genetic Testing for *PTEN* Hamartoma Tumor Syndrome

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. Genetic testing for PTEN can confirm a diagnosis of PHTS.

FDA 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 Amendments (CLIA). Laboratory testing for *PTEN* variants is available under the auspices of the Clinical Laboratory Improvement Amendments. 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.

OBJECTIVE

The objective of this evidence review is to evaluate testing for variants associated with *PTEN* hamartoma syndromes improves the net health outcome in individuals with clinical signs and/or symptoms of a *PTEN* hamartoma tumor syndrome. This review does NOT evaluate testing for at-risk or asymptomatic individuals. (See Benefit Applications)

POLICY STATEMENT

Genetic testing for *PTEN* may be considered **medically necessary** to confirm the diagnosis when a patient has clinical signs of a *PTEN* hamartoma tumor syndrome.

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.

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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

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

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

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.

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

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RATIONALE

Summary of Evidence

For individuals who have clinical signs and/or symptoms of a PHTS, 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 CS and BRRS 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. Most cases of a PHTS occur in individuals with no known family history of PHTS. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Current National Comprehensive Cancer Network guidelines on genetic/familial high-risk assessment for breast and ovarian cancer (v.1.2018)[6] recommend the following for Cowden syndrome management (see Table 1).

Table 1. Guidelines on Genetic/Familial High-Risk Assessment for Breast and Ovarian Cancer

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:
	o Annual mammography and breast MRI screening starting at age 30 to 35 years or 5 to 10 years before the earliest known breast cancer in family (whichever comes first).
	o Age >75, management should be considered on an individual basis.
	• For women with a *PTEN* mutation [disease-associated variant] who are treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue.
	• For endometrial cancer screening, encourage patient education and prompt response to symptoms. Consider annual random endometrial biopsies and/or ultrasound beginning at age 30 to 35 years.
	• Discuss risk-reducing mastectomy and hysterectomy and counsel regarding degree of protection, extent of cancer risk, and reconstructive options
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 breast and thyroid exam.
	• Annual thyroid ultrasound starting at the time of PHTS diagnosis.
	• Colonoscopy, starting at age 35 years, unless symptomatic or a close relative with colon cancer under age 40 years. Colonoscopy should be done every 5 years or more frequently if patient is symptomatic or polyps found.
	• Dermatologic management may be indicated for some patients.
	• 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 at-risk relatives
Reproductive	• For women of reproductive age, advise about options for prenatal diagnosis and assisted

options	reproduction including preimplantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies

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 (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

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POLICY HISTORY

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. Genetic testing for a PTEN mutation is considered investigational for all other indications.
June 2014	Update Policy	Policy updated with literature; reference 1 added. Clarification of testing strategy in Policy Guidelines.
June 2015	Update Policy	Policy updated with literature review. No references added. No change in policy statements.
June 2018	Update Policy	Policy updated with literature review through December 11, 2017; references 1-3 added. Policy statements unchanged. Objective

statement added.