

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR PTEN HAMARTOMA TUMOR SYNDROME
POLICY NUMBER	MP 2.255

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	RETIRED 7/1/2026

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I. POLICY

Genetic testing for a *PTEN* mutation 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. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

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

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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.

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II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital BlueCross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO – Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at <https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>.

III. DESCRIPTION/BACKGROUND

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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.

***PTEN* Hamartoma Tumor Syndromes**

PTEN hamartoma tumor syndrome (PHTS) 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 age late 20s. The lifetime risk of developing breast cancer is 85%, with an average age of diagnosis between 38 and 46 years. The lifetime risk for thyroid cancer, usually follicular carcinoma, is approximately 35%. The risk for endometrial cancer is not well-defined but may approach 28%. A 2012 study included 3399 prospectively recruited individuals who met relaxed International Cowden Consortium PHTS criteria; 368 were found to have *PTEN* disease-associated variants. Estimated lifetime cancer risks were: 85.2% for breast (95% confidence interval [CI], 71.4% to 99.1%); 35.2% for thyroid; (95% CI, 19.7% to 50.7%); 28.2% for endometrium (95% CI, 17.1% to 39.3%); 9.0% for colorectal (95% CI, 3.8% to 14.1%); 33.6% for kidney (95% CI, 10.4% to 56.9%); and 6% for melanoma (95% CI, 1.6% to 9.4%). A 2013 study of 154 individuals with a *PTEN* disease-associated variant found cumulative cancer risks at age 70 of 85% (95% CI, 70% to 95%) for any cancer, 77% (95% CI, 59% to 91%) for female breast cancer, and 38% (95% CI, 25% to 56%) for thyroid cancer.

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%).

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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* variants 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* disease-associated variant is identified.

Diagnostic Criteria

Cowden Syndrome

The International Cowden Consortium has developed criteria for diagnosing CS (see Table 1).

Table 1. Diagnostic Criteria for Cowden Syndrome^a

Diagnostic Criteria
Pathognomonic criteria
Lhermitte-Duclos disease 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

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Any of the following:

1. Mucocutaneous lesions alone if:
 - There are 6 or more facial papules, of which 3 or more must be trichilemmoma, or
 - Cutaneous facial papules and oral mucosal papillomatosis, or
 - Oral mucosal papillomatosis and acral keratoses, or
 - Palmoplantar keratoses, 6 or more
2. Two or more major criteria, but one must include macrocephaly or Lhermitte-Duclos disease; or
3. One major and 3 minor criteria; or
4. Four minor criteria.

Operational diagnosis in a family with a diagnosis of Cowden syndrome

1. One pathognomonic criterion; or
2. Any 1 major criterion with or without minor criteria; or
3. Two minor criteria; or
4. History of Bannayan-Riley-Ruvalcaba syndrome

Adapted from Blumenthal et al (2008)

^aThese criteria for diagnosing Cowden syndrome have been adopted by the National Comprehensive Cancer Network.

In 2013, a systematic review assessed the clinical features reported in individuals with a *PTEN* disease-associated variant and proposed revised diagnostic criteria. Reviewers concluded that there was insufficient evidence to support inclusion of benign breast disease, uterine fibroids, or genitourinary malformations as diagnostic criteria. 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 many of these clinical features are included in CS testing minor criteria in the National Comprehensive Cancer Network guidelines on genetic/familial high-risk assessment of breast and ovarian (v.2.2024).

Bannayan-Riley-Ruvalcaba Syndrome

Diagnostic criteria for BRRS have not been established. Current diagnostic practices 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

PS 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 as listed in Table 2.

Table 2. Diagnostic Criteria for Proteus Syndrome

Additional Diagnostic Criteria
Connective tissue nevi (pathognomonic) OR 2 of the following:
Epidermal nevus

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Disproportionate overgrowth (1 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 3 of the following:
Dysregulated adipose tissue (either one): • Lipomas • Regional absence of fat
Vascular malformations (1 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

Adapted from Biesecker (2006)

Proteus-Like Syndrome

Proteus-Like Syndrome (PLS) is undefined but describes individuals with significant clinical features of PS not meeting the diagnostic criteria.

Molecular Diagnosis

PTEN (phosphatase and *tens* in homolog deleted on chromosome 10) is a tumor suppressor gene on chromosome 10q23 and is a dual-specificity phosphatase with multiple but incompletely understood roles in cellular regulation. *PTEN* is the only gene for which disease-associated variants are known to cause PHTS. *PTEN* disease-associated variants are inherited in an autosomal dominant manner.

Most CS cases are simplex. However, because CS is likely underdiagnosed, the actual proportion of simplex cases (i.e., individuals with no obvious family history) and familial cases (i.e., ≥ 2 related affected individuals) cannot be determined. 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.

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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* disease-associated variant. Some data have suggested that up to 20% of patients with PS and up to 50% of patients with a PLS have *PTEN* disease-associated variants.

Most of these disease-associated 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.

Management

Treatment

Treatment of the benign and malignant manifestations of PHTS is the same as for their sporadic counterparts (i.e., chemotherapy, surgery, and/or radiotherapy as per usual guidelines and clinical practice).

Surveillance

The most serious consequences of a diagnosis of PHTS relates 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.

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.

IV. RATIONALE

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Summary of Evidence

For individuals who have clinical signs and/or symptoms of a 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

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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. 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.

V. DEFINITIONS

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N/A

VI. Benefit Variations

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations are based on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross' medical policies are developed to assist in administering a member's benefits. These medical policies do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. Coding Information

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

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Covered When Medically Necessary:

Procedure Codes							
0235U	81321	81322	81323				

ICD-10-CM Diagnosis Code	Description
Q85.81	PTEN hamartoma tumor syndrome
Q85.82	Other Cowden syndrome
Q85.89	Other phakomatoses, not elsewhere classified
Q85.9	Phakomatosis, unspecified
Z13.71	Encounter for nonprocreative screening for genetic disease carrier status
Z13.79	Encounter for other screening for genetic and chromosomal anomalies

IX. References

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12. Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.88, Genetic Testing for PTEN Hamartoma Tumor Syndrome. March 2024

X. POLICY HISTORY

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MP 2.255	03/13/2020 Consensus Review. Policy statement remains unchanged. References reviewed and updated. Added NCCN testing criteria for Cowden Syndrome/PTEN Hamartoma Tumor Syndrome (Version 1.2021).
	10/16/2020 Administrative Update. New PLA code 0235U added, effective 01/01/2021. Policy statement remains unchanged.
	04/23/2021 Consensus Review. Policy statement unchanged. Addition of NCCN statement. References updated.
	03/18/2022 Consensus Review. No change to policy statement. FEP language, Background, and References updated.
	08/16/2022 Administrative Update. ICD10 codes Q85.81, Q85.82, and Q85.89 added to policy; effective 10/01/2022
	03/10/2023 Consensus Review. No change to policy statement. Product Variation, Background and References updated.
	09/11/2023 Administrative Update. ICD10 code definitions revised due to new code. Effective 10/01/2023
	03/19/2024 Consensus Review. No change to policy statement. References updated.
	11/19/2024 Administrative Update. Removed NCCN statement.
	02/28/2025 Consensus Review. No change to policy statement.
	03/06/2026 Retirement Review. EviCore delegation.

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