

Corporate Medical Policy

Genetic Testing for PTEN Hamartoma Tumor Syndrome AHS – M2087

File Name: genetic_testing_for_PTEN_hamartoma_tumor_syndrome
Origination: 01/01/2019
Last CAP Review: 07/2019
Next CAP Review: 07/2020
Last Review: 08/2019

Description of Procedure or Service

Phosphatase and tensin homolog (PTEN) hamartoma tumor syndromes (PHTS) are primarily characterized by hamartomatous tumors (disorganized growths of native cells in native tissues) caused by PTEN germline mutations. PHTS include Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), *PTEN*-related Proteus syndrome (PS), and Proteus-like syndrome (PLS) (Charis Eng, 2016; Stanich & Lindor, 2018).

Related Policies

Molecular Panel Testing of Cancers to Identify Targeted Therapy AHS-M2109
General Genetic Testing, Germline Disorders AHS-M2145
General Genetic Testing, Somatic Disorders AHS-M2146

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for genetic testing for PTEN hamartoma tumor syndrome when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for PTEN Hamartoma Tumor Syndrome is covered

1. Genetic testing for a *PTEN* mutation is considered medically necessary to confirm the diagnosis when a patient has clinical signs of Cowden Syndrome/*PTEN* hamartoma tumor syndrome.
 - a. Three or more major criteria, but one must include macrocephaly, Lhermitte-Duclos disease, or gastrointestinal hamartomas; OR
 - b. Two major and three minor criteria

Major Criteria:

- i. Breast Cancer
- ii. Endometrial cancer (epithelial)
- iii. Thyroid Cancer (follicular)

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- iv. Gastrointestinal hamartomas (including ganglioneuromas, adenomas, hyperplastic polyps; ≥ 3)
- v. Lhermitte-Duclos disease (adult)
- vi. Macrocephaly (megalencephaly) (i.e. ≥ 97 th percentile, 58 cm in adult woman, 60 cm in adult men)
- vii. Macular pigmentation of glans penis
- viii. Multiple mucocutaneous lesions (any of the following):
 - Multiple trichilemmomas (≥ 3 , at least one biopsy proven)
 - Acral keratoses (≥ 3 palmoplantar keratotic pits and/or acral hyperkeratotic papules) 4 – GT63
 - Mucocutaneous neuromas (≥ 3)
 - Oral papillomas (particularly on tongue and gingiva), multiple (≥ 3) OR biopsy proven OR dermatologist diagnosed

Minor Criteria:

- i. Autism spectrum disorder
 - ii. Colon cancer
 - iii. ≥ 3 esophageal glycogenic acanthoses
 - iv. Lipomas (≥ 3)
 - v. Intellectual disability (i.e., $IQ \leq 75$)
 - vi. Renal cell carcinoma
 - vii. Testicular lipomatosis
 - viii. Thyroid cancer (papillary or follicular variant of papillary)
 - ix. Thyroid structural lesions (e.g. adenoma, multinodular goiter)
 - x. Vascular anomalies (including multiple intracranial developmental venous anomalies)
2. Genetic testing for a *PTEN* mutation is considered medically necessary in individuals not meeting the clinical diagnostic criteria for Cowden Syndrome/*PTEN* hamartoma tumor syndrome with a personal history of any one of the following:
 - a. Adult Lhermitte-Duclos disease (cerebellar tumors)
 - b. Autism spectrum disorder and macrocephaly
 - c. Two or more biopsy-proven trichilemmomas
 - d. Two or more major criteria (one must be macrocephaly)
 - e. Three major criteria without macrocephaly
 - f. One major and ≥ 3 minor criteria
 - g. ≥ 4 minor criteria
 3. Genetic testing for a *PTEN* mutation is considered medically necessary in individuals with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)
 4. Genetic Testing for a *PTEN* mutation is considered medically necessary in at-risk individuals with a relative with a clinical diagnosis of Cowden Syndrome/*PTEN* Hamartoma Tumor syndrome for whom testing has not been performed AND with either one of the following criteria:
 - a. Any one major criterion, OR
 - b. Two minor criteria
 5. Genetic testing for a *PTEN* mutation is considered medically necessary in a first-degree relative of a proband with a known *PTEN* mutation.

When Genetic Testing for PTEN Hamartoma Tumor Syndrome is not covered

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Genetic testing for a PTEN mutation is considered investigational for all other indications.

See “**Note**” below in the Billing/Coding/Physician Documentation Information section.

Policy Guidelines

Background

The tumor suppressor (Sansal & Sellers, 2004) phosphatase and tensin homolog (PTEN) is an important phosphatase regulator of the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway and the mechanistic target of rapamycin (mTOR) signaling pathway, critical for cell proliferation, cell cycle progression, and apoptosis (Stanich & Lindor, 2018). Loss of function of this gene contributes to an increased risk of both benign and malignant tumors and is implicated in increased lifetime risks of breast, thyroid, uterine, renal, and other cancers. The resulting spectrum of autosomal dominant disorders are known as phosphatase and tensin homolog (PTEN) hamartoma tumor syndromes (PHTS), which include Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), *PTEN*-related Proteus syndrome (PS), and Proteus-like syndrome (PLS) (Charis Eng, 2016).

CS is defined by multiple hamartomas with a high risk for benign and malignant tumors of the thyroid, breast, and endometrium. Besides multiple hamartomas in a variety of tissues, patients have macrocephaly as well as characteristic dermatologic manifestations, such as trichilemmomas and papillomatous papules. The lifetime risk of developing breast cancer is as high as 85%; for thyroid cancer, which is usually follicular carcinoma, is as high as 35%; for endometrial cancer the risk may reach as high as 28% (Charis Eng, 2016). The estimated prevalence of CS is 1 in 200,000 to 250,000, though it is likely underreported (Stanich & Lindor, 2018).

BRRS is characterized by hamartomas along with macrocephaly, lipomas, and pigmented penile macules. It is also associated with high birth weight, developmental delay or deficiency, proximal muscle myopathy, joint hypermobility, high palate, and scoliosis (Stanich & Lindor, 2018). Similar mutations in the *PTEN* gene are found in both CS and BRRS, which are now considered phenotypically distinct presentations of a similar genetic abnormality (Lachlan, Lucassen, Bunyan, & Temple, 2007; Marsh et al., 1999).

PS is characterized by hamartomatous overgrowth of multiple tissues with hyperostoses, vascular malformations, dysregulation of fatty tissues connective tissue nevi, and epidermal nevi. PLS is undefined but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS (Charis Eng, 2016).

Only CS has been documented to confer a predisposition to cancer; however, it has been suggested that any patients with *PTEN* mutations should be assumed to have cancer risks similar to CS (Stanich & Lindor, 2018).

Validity and Utility

All types of mutations have been reported, including missense, nonsense, splice site, insertions, and deletions; therefore, *PTEN* mutation testing usually includes sequence analysis of the entire coding region and deletion/duplication analysis (Charis Eng, 2016; Marsh et al., 1999). Mutations have also been reported in the *PTEN* promoter, and a test for mutations in this region of the gene has become clinically available (Stanich & Lindor, 2018). Germline *PTEN* mutations are found in approximately 20 to 34 percent of individuals who meet clinical criteria for Cowden syndrome or who meet criteria for genetic testing (Pilarski, Stephens, Noss, Fisher, & Prior, 2011; Tan et al., 2011). Mingo et al (2018) recently found that “the frequent occurrence of PTEN gene mutations targeting PTEN N-terminus whose pathogenicity may be related, at least in part, with the retention of PTEN in the nucleus. This could be important for the implementation of precision therapies for patients with alterations in the PTEN pathway (Mingo et al., 2018).”

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Yehia et al (2018) conducted a 4-year multicenter prospective study of incident patients with features of Cowden/Cowden-like (CS/CS-like) and Bannayan-Riley-Ruvalcaba syndromes (BRRS) without PTEN mutations. Exome sequencing and targeted analysis were performed including 59 clinically actionable genes from the American College of Medical Genetics and Genomics (ACMG) and 24 additional genes associated with inherited cancer syndromes. Pathogenic or likely pathogenic cancer susceptibility gene alterations were found in 7 of the 87 (8%) CS/CS-like and BRRS patients and included MUTYH, RET, TSC2, BRCA1, BRCA2, ERCC2 and HRAS (Yehia et al., 2018).”

The diagnosis of PHTS is established by identification of a germline pathogenic variant in PTEN in molecular genetic testing. A single-gene sequence analysis will detect up to 80% of CS cases, 60% of BRRS cases, 50% PLS cases, and 20% cases. Deletion and duplication analysis or promoter region analysis may also detect additional cases, but further research is required. In addition to single gene analysis, gene panels or further comprehensive testing may assist with clinical management (C. Eng, 2016).

Ngeow et al estimated the cost effectiveness of each PTEN mutation detected in CS-like patients using the PTEN Cleveland Clinic (CC) score. The authors found that the cost to detect one PTEN mutation was between \$3720 to \$4573 at a CC score of 15. The authors also concluded that “In sensitivity analyses, CC15 is robustly the most cost-effective strategy for probands who are younger than 60 years (Ngeow et al., 2015)”.

Guidelines and Recommendations

The International Cowden Consortium operational criteria for the diagnosis of Cowden Syndrome *Ver 2000* recommended the following (Pilarski & Eng, 2004):

Pathognomonic criteria

Mucocutaneous lesions

- Trichilemmomas, facial
- Acral keratoses
- Papillomatous papules
- Mucosal lesions

Major criteria

- Breast carcinoma
- Thyroid carcinoma (non-medullary), especially follicular thyroid carcinoma
- Macrocephaly (megalencephaly) (say, ≥ 97 th centile)
- Lhermitte-Duclos disease (LDD)
- Endometrial carcinoma

Minor criteria

- Other thyroid lesions (eg, adenoma or multinodular goitre)
- Mental retardation (say, $IQ \leq 75$)
- GI hamartomas
- Fibrocystic disease of the breast
- Lipomas
- Fibromas
- Genito-urinary tumours (eg, renal cell carcinoma, uterine fibroids) or malformation

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According to the International Cowden Consortium, an operational diagnosis of Cowden Syndrome is made if the individual meets any of the following:

- (1) Mucocutaneous lesions alone if:
 - (a) there are 6 or more facial papules, of which 3 or more must be trichilemmoma, or
 - (b) cutaneous facial papules and oral mucosal papillomatosis, or
 - (c) oral mucosal papillomatosis and acral keratoses, or
 - (d) palmoplantar keratoses, 6 or more
- (2) 2 major criteria but one must include macrocephaly or LDD
- (3) 1 major and 3 minor criteria
- (4) 4 minor criteria

According to the International Cowden Consortium, an operational diagnosis of Cowden Syndrome in a family where one person is diagnostic for Cowden syndrome is made if any of the following criteria are met:

- (1) The pathognomonic mucocutaneous lesion
- (2) Any one major criterion with or without minor criteria
- (3) Two minor criteria

In 2013, Pilarski et al published revised evidence-based criteria covering the spectrum of PTEN-related clinical disorders. The revised guidelines define the operational diagnosis of PTEN Hamartoma Tumor syndrome in an individual who meets either one of the following:

- Three or more major criteria, but one must include macrocephaly, Lhermitte-Duclos disease, or gastrointestinal hamartomas; or
- Two major and three minor criteria

The operational diagnosis in a family where one individual meets the revised PTEN Hamartoma Tumor syndrome clinical diagnostic criteria or has a PTEN mutation is as follows (Pilarski et al., 2013):

- Any two major criteria with our without minor criteria; or
- One major and two minor criteria; or
- Three minor criteria

Pilarski et al defined the major and minor criteria as follows:

Major Criteria:

- Breast Cancer
 - Endometrial cancer (epithelial)
 - Thyroid Cancer (follicular)
 - Gastrointestinal hamartomas (including ganglioneuromas, adenomas, hyperplastic polyps; ≥ 3)
 - Lhermitte-Duclos disease (adult)
 - Macrocephaly (megalcephaly) (i.e. ≥ 97 th percentile, 58 cm in adult woman, 60 cm in adult men)
 - Macular pigmentation of glans penis
 - Multiple mucocutaneous lesions (any of the following):
 - Multiple trichilemmomas (≥ 3 , at least one biopsy proven)
 - Acral keratoses (≥ 3 palmoplantar keratotic pits and/or acral hyperkeratotic papules)
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- Mucocutaneous neuromas (≥ 3)
- Oral papillomas (particularly on tongue and gingiva), multiple (≥ 3) OR biopsy proven OR dermatologist diagnosed

Minor Criteria:

- Autism spectrum disorder
- Colon cancer
- ≥ 3 esophageal glycogenic acanthoses
- Lipomas (≥ 3)
- Intellectual disability (i.e., $IQ \leq 75$)
- Renal cell carcinoma
- Testicular lipomatosis
- Thyroid cancer (papillary or follicular variant of papillary)
- Thyroid structural lesions (e.g. adenoma, multinodular goiter)
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

The **National Comprehensive Cancer Network (NCCN, 2019)** guidelines for Cowden Syndrome/PTEN Hamartoma Tumor syndrome recommends testing in individuals who meet any of the following criteria:

- Individual from a family with a known PTEN pathogenic variant/likely pathogenic variant
- Individuals with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)
- Individuals meeting the clinical diagnostic criteria for CS/PHTS
- Individuals not meeting the clinical diagnostic criteria for Cowden Syndrome/PTEN hamartoma tumor syndrome with a personal history of any one of the following:
 - Adult Lhermitte-Duclos disease (cerebellar tumors)
 - Autism spectrum disorder and macrocephaly
 - Two or more biopsy-proven trichilemmomas
 - Two or more major criteria (one must be macrocephaly)
 - Three major criteria without macrocephaly
 - One major and ≥ 3 minor criteria
 - ≥ 4 minor criteria
- At-risk individuals with a relative with a clinical diagnosis of Cowden Syndrome/PTEN Hamartoma Tumor syndrome for whom testing has not been performed. The at-risk individual must have the following:
 - Any one major criterion, OR
 - Two minor criteria

The major and minor criteria are identical to the ones set forth in 2013 by Pilarski et al.

ClinGen PTEN Expert Panel (2018)

This expert panel was convened by the ClinGen Hereditary Cancer Clinical Domain Working Group to develop PTEN-specific genetic variant interpretations. A total of 42 variants were included in the following categories: benign/likely benign (BEN/LBEN), pathogenic/likely pathogenic (PATH/LPATH), uncertain significance (VUS), and conflicting (CONF) ClinVar assertions.

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The following variants were considered BEN/LBEN: 9C>G, 903G>A, 1026C>A, 1311T>C, 18A>G, 75G>A, 132C>T, 360A>G, 1104T>G, 79+35C>T, 165-13_165-10delGTTT, 254-39G>T, 801+23G>A, and 1026+32T>G.

The following variants were considered PATH/LPATH: 50_51delAA, 511C>T, 892C>T, 964A>T, 987_990delTAAA, 80-1G>C, 165-1G>A, 493-2A>G, 801+1delG, 802-2A>T, 1026+1G, 103A>G, 389G>A, 407G>A, 517C>T, and 737C>T.

The following variants were considered VUS or CONF: 1170C>T, 209+3A>T, 235G>A, 304_306dupAAA, 1052_1054delTAG, 1171C>T, 764G>A, 44G>A, 78C>T, 209+4_209+7delAGTA, 521A>G (Mester et al., 2018).

Applicable Federal Regulations

No FDA-approved tests were found regarding the assessment of hamartomas. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Note: For 5 or more gene tests being run on the same platform, such as multi-gene panel next generation sequencing, please refer to Laboratory Procedures Reimbursement Policy AHS - R2162

Applicable service codes: 81321, 81322, 81323, 81445

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Specialty Matched Consultant Advisory Panel review 7/2019

Medical Director review 7/2019

Policy Implementation/Update Information

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| 1/1/2019 | BCBSNC will provide coverage for genetic testing for PTEN hamartoma tumor syndrome when it is determined to be medically necessary because criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019 (jd) |
| 8/13/2019 | Specialty Matched Consultant Advisory Panel review. 7/2019. Medical Director review 7/2019. (jd) |
| 9/10/2019 | Reviewed by Avalon 2 nd Quarter 2019 CAB. Added Related Policies to the Description section. Reference to "Note" added to the When Not Covered section. Policy guidelines and references updated. "Note" "5 or more gene tests being run on the same platform, such as multi-gene panel next generation sequencing, please refer to Laboratory Procedures Reimbursement Policy AHS |
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- R2162” added to the Billing/Coding section and code table removed. Medical Director review 8/2019. (jd)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.