

Corporate Medical Policy

Genetic Testing for PTEN Hamartoma Tumor Syndrome AHS – M2087

File Name: genetic_testing_for_PTEN_hamartoma_tumor_syndrome
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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 includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), *PTEN*-related Proteus syndrome (PS), and Proteus-like syndrome (PLS) (C. Eng, 2016; Stanich & Roberts, 2023).

Genetic counseling is strongly recommended for individuals pursuing genetic testing for PHTS.

Related Policies

Genetic Testing for Breast, Ovarian, Pancreatic, and Prostate Cancers AHS-M2003
Molecular Markers in Fine Needle Aspirates of the Thyroid AHS-M2108

*****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

All major and minor criteria are defined in Note 1.

1. For asymptomatic individuals who are in a family with a known pathogenic *PTEN* mutation, reimbursement is allowed for the following testing:
 - a. Testing restricted to the known familial mutation.
 - b. Comprehensive *PTEN* gene sequencing when the specific *PTEN* mutation is unknown.
2. For individuals suspected of having Cowden Syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS), genetic testing for a *PTEN* mutation is considered medically necessary when at least one of the following clinical signs is present:

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- a. Three or more major criteria (one must be macrocephaly, Lhermitte-Duclos disease, or gastrointestinal hamartomas).
 - b. Two major and three minor criteria.
3. For individuals not meeting the clinical diagnostic criteria above, genetic testing for a *PTEN* mutation is considered medically necessary when the individual has 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. Two major and two or more minor criteria (for individuals without macrocephaly).
 - g. One major and three or more minor criteria.
 - h. Four or more minor criteria.
4. For individuals with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS), genetic testing for a *PTEN* mutation is considered medically necessary.
5. For at-risk individuals with a relative who has been clinically but not genetically diagnosed with CS/PHTS or BRRS, genetic testing for a *PTEN* mutation is considered medically necessary when at least **one** of the following conditions are met:
- a. The at-risk individual has any one major criterion.
 - b. The at-risk individuals has two minor criteria.
6. Reimbursement is allowed for genetic testing for a *PTEN* mutation in individuals with a *PTEN* pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline analysis.

NOTES

Note 1: The NCCN provides the following major and minor testing criteria for Cowden Syndrome/PTEN Hamartoma Tumor Syndrome (Category 2A recommendation: based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate):

Major Testing Criteria

- Breast cancer
- Endometrial cancer
- Follicular thyroid cancer
- Multiple GI hamartomas or ganglioneuromas
- Macrocephaly (megalcephaly) (ie, $\geq 97\%$, 58 cm in adult female, 60 cm in adult male)
- Macular pigmentation of glans penis
- Mucocutaneous lesions (any of the following):
 - One biopsy-proven trichilemmoma
 - Multiple palmoplantar keratoses
 - Multifocal or extensive oral mucosal papillomatosis

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- Multiple cutaneous facial papules (often verrucous)

Minor Testing Criteria

- Autism spectrum disorder
- Colon cancer
- ≥ 3 Esophageal glycogenic acanthoses
- Lipomas
- Intellectual disability (i.e., $IQ \leq 75$)
- Papillary or follicular variant of papillary thyroid cancer
- Thyroid structural lesions (e.g., adenoma nodule[s], goiter)
- Renal cell carcinoma
- Single GI hamartoma or ganglioneuroma
- Testicular lipomatosis
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

When Genetic Testing for PTEN Hamartoma Tumor Syndrome is not covered

For all other situations not described above, genetic testing for a *PTEN* mutation is considered investigational.

Policy Guidelines

Background

Tumor suppressor genes serve several purposes within the body; these genes are able to regulate cell division, restore DNA errors, and tell cells when to die (a process known as apoptosis). Communication of these processes occurs via various cell signaling pathways. In particular, the tumor suppressor gene known as 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 (Sansal & Sellers, 2004; Stanich & Roberts, 2023). The PI3K/AKT and mTOR signaling pathways are critical for cell proliferation, cell cycle progression, and apoptosis.

Loss of function of the *PTEN* 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; patients may also display clinical features such as cognitive changes, skin changes, macrocephaly (enlarged head) and intestinal polyposis (Ngeow & Eng, 2020). Further, loss of *PTEN* gene functionality results in a spectrum of autosomal dominant disorders known as *PTEN* hamartoma tumor syndromes (PHTS); this includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), *PTEN*-related Proteus syndrome (PS), and Proteus-like syndrome (PLS) (C. Eng, 2016; Charis Eng, 2016). Autism spectrum disorders (ASDs) with macrocephaly and adult Lhermitte-Duclos disease (LDD) have also been associated with PHTS (Pilarski, 2019; Stanich & Roberts, 2023).

A diagnosis of PHTS is established by identification of a germline pathogenic variant in *PTEN* via 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% of PS 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). All types of mutations have been reported including missense, nonsense, splice site, insertions, and deletions; therefore, *PTEN* mutation testing usually requires sequence analysis of the entire coding region and deletion/duplication analysis (C. 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 & Roberts, 2023). Mingo et al. (2018) recently found that the pathogenicity of frequent *PTEN* mutations targeting the N-terminus “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.” Germline *PTEN* mutations are found in approximately 20 to 34% of individuals who

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meet clinical criteria for CS or who meet criteria for genetic testing (Pilarski, 2019; Pilarski et al., 2011; Tan et al., 2011). This number seems to be highly variable as Giorgianni et al. (2013) state that approximately 80% of CS patients have a *PTEN* mutation at locus 10q23.2.

Cowden Syndrome (CS)

Cowden Syndrome is defined by multiple hamartomas with a high risk for benign and malignant tumors in the thyroid, breast, and endometrium. Besides multiple hamartomas in a variety of tissues, patients typically exhibit macrocephaly as well as characteristic dermatologic manifestations, such as trichilemmomas (benign tumors originating from hair follicles) and papillomatous papules (wart-like growths) (Garofola & Gross, 2024). For individuals with CS, the lifetime risk of developing breast cancer is as high as 85%; for thyroid cancer, which is usually follicular carcinoma, the lifetime risk is as high as 35%; finally, for endometrial cancer, the risk may reach as high as 28% (C. Eng, 2016; Charis Eng, 2016). The estimated prevalence of CS is 1 in 200,000 to 250,000, though it is likely underreported (Stanich & Roberts, 2023). Of all PHTS, 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 & Roberts, 2023).

Bannayan-Riley-Ruvalcaba Syndrome (BRRS)

Bannayan-Riley-Ruvalcaba Syndrome 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 & Roberts, 2023). 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 et al., 2007; Marsh et al., 1999).

PTEN-related Proteus Syndrome (PS)

PTEN-related Proteus Syndrome is characterized by hamartomatous overgrowth of multiple tissues with hyperostosis (excessive bone growth), vascular malformations, dysregulation of fatty tissues, connective tissue nevi, and epidermal nevi. Phenotypic features of PS are usually present at birth and progress over an individual's lifetime (Hobert & Eng, 2009).

Proteus-like Syndrome (PLS)

Proteus-like Syndrome is undefined but typically refers to individuals with similar clinical features to PS who do not meet the diagnostic criteria (C. Eng, 2016; Charis Eng, 2016; Hobert & Eng, 2009). Overall, limited information is available on PLS. Stanich and Roberts (2023) report that PLS cases typically exhibit “a distinct type of epidermal nevus (also referred to as segmental overgrowth, lipomatosis, arteriovenous malformation, and epidermal nevus (SOLAMEN) syndrome or type 2 segmental Cowden syndrome).”

Autism Spectrum Disorders (ASDs)

Autism Spectrum Disorders are a collection of disorders presenting with common abnormalities associated with social and communication behaviors. A few studies have been published which research the relationship between *PTEN* mutations and ASDs. Schaefer and Mendelsohn (2013) completed a literature review of at least seven different studies and determined that 15 of 318 (5%) individuals with an ASD diagnosis had a pathogenic *PTEN* mutation; further, macrocephaly was present in all 15 cases.

Lhermitte-Duclos Disease (LDD)

Lhermitte-Duclos Disease is a rare disease characteristic of benign tumor development in the granule cells of the cerebellum. It has been reported that “Most LDD patients appear to have a germline loss of the *PTEN* allele and go on to lose the remaining *PTEN* allele at some point, thereby allowing abnormal growth of the

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granule cells” (Giorgianni et al., 2013). LDD often develops in conjunction with CS, but may also develop singularly (Stanich & Roberts, 2023).

Proprietary Testing

Ambry Genetics, GeneDx, Invitae, and Blueprint Genetics all have genetic tests for *PTEN* mutations. Invitae and Blueprint Genetics both use a next-generation sequencing (NGS) assay that performs full *PTEN* gene sequencing and deletion/duplication analysis (Ambry, 2024; Blueprint, 2024; GeneDx, 2024; Invitae, 2022). The Invitae assay “achieves >99% analytical sensitivity and specificity for single nucleotide variants, insertions, and deletions <15bp [base pair] in length, and exon-level deletions and duplications.” The Blueprint Genetics NGS sequencing assay for single genes performs similarly with a >99% specificity and sensitivity for single nucleotide variants, including insertions, deletions, and indels up to 50 bp. The Invitae assay has a clinical sensitivity of 85% for CS, 70% for BRRS, 20-50% for Proteus-Like Syndrome, and 10% for *PTEN*-related macrocephalic autism spectrum disorder. The clinical sensitivity is not provided by Blueprint Genetics; however, clinical sensitivity is said to vary based on patient clinical presentation (Blueprint, 2024; Invitae, 2022).

GeneDx utilizes a PCR-amplified assay with capillary sequencing to confirm variants of clinical or uncertain significance. Their assay also performs deletion/duplication testing using “either exon-level CGH [comparative genomic hybridization] or MLPA [multiplex ligation-dependent probe amplification]. Confirmation of copy number changes is performed by MLPA, qPCR [quantitative polymerase chain reaction], or repeat aCGH [array CGH] analysis.” GeneDx has found that “for those probands with Cowden syndrome, sequence analysis of the coding and promoter regions is expected to detect 47-80% of causative variants, while large deletions and duplications have been reported. For individuals with Bannayan-Riley-Ruvalcaba syndrome, ~60% of causative pathogenic variants will be detected by sequencing while 11% will be detected by deletion/duplication analysis” (GeneDx, 2024). Ambry Genetics also utilizes a PCR-amplified assay with NGS, as well as Sanger Sequencing for any regions “missing or with insufficient read depth coverage for reliable heterozygous variant detection.” Their assay also performs gross deletion and duplication analysis, with any copy number changes detected from NGS confirmed by targeted chromosomal microarray or MLPA. Their analytical sensitivity is >99.9% for described mutations in the *PTEN* gene when present and has an identical clinical sensitivity to that described by Invitae (Ambry, 2024).

Clinical Utility and Validity

Yehia et al. (2018) conducted a four-year multicenter study; all participants had suspected BRRS or Cowden/Cowden-like (CS/CS-like) syndromes without *PTEN* mutations. Exome sequencing and targeted analysis was completed on 59 genes supported by the American College of Medical Genetics and Genomics (ACMG), as well as on 24 additional genes known to be associated with inherited cancer syndromes. “Pathogenic or likely pathogenic cancer susceptibility gene alterations were found in seven of the 87 (8%) CS/CS-like and BRRS patients and included *MUTYH*, *RET*, *TSC2*, *BRCA1*, *BRCA2*, *ERCC2* and *HRAS*” (Yehia et al., 2018).

Ngeow et al. (2015) estimated the cost effectiveness of each *PTEN* mutation detected in CS-like patients using the *PTEN* Cleveland Clinic (CC) score. This is a risk assessment tool which helps to estimate an individual’s risk of having a *PTEN* mutation. Several questions are answered through an online survey, and a total risk score between 0 and 100 is provided (CC, 2020). The authors found that the cost to detect one *PTEN* mutation was between \$3720 to \$4573 at a CC score of 15 (CC15). 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).

Isik et al. (2020) researched the genotype to phenotype correlation of patients with *PTEN* mutations. A total of 10 molecularly confirmed PHTS patients participated in this study; these participants originated from seven different families. The authors note that “Macrocephaly was the most common clinical finding, involving all patients. This was followed by skin lesions, neurodevelopmental delay, and pathologic cranial magnetic resonance imaging findings” (Isik et al., 2020). Further, sequencing of the *PTEN* gene identified seven different *PTEN* variants; four variants were located in exon five. The authors conclude by highlighting

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the importance of screening for *PTEN* mutations in patients with macrocephaly, particularly due to an increased risk of cancer.

Jonker et al. (2020) conducted an extensive literature search to identify evidence to support a thyroid carcinoma surveillance program among children with PHTS. They found that children with PHTS were at an increased risk of developing differentiated thyroid carcinoma (DTC), “with 4 years being the youngest age reported at presentation and FTC [follicular thyroid carcinoma] being overrepresented.” This finding supports genetic testing for *PTEN* mutations, as that could provide guidance and awareness for potential thyroid cancer development at an early age and reduce morbidity with early diagnosis. “Consensus within the study team was reached to recommend surveillance from the age of 10 years onwards, since at that age the incidence of DTC seems to reach 5%” (Jonker et al., 2020). This recommendation was also supported by Baran et al. (2021), who further retrospectively investigated patients at the Children’s Hospital of Philadelphia with a PHTS diagnosis between January 2003 and June 2019. They found “the most common clinical feature at presentation was macrocephaly (85.1%), followed by impaired development (42.0%), skin/oral lesions (30.9%), and autism spectrum disorder (27.2%),” which also appears to corroborate the physical findings of Isik et al. (2020).

Cummings et al. (2022) conducted a systematic review and meta-analysis of the behavioral and psychological features associated with *PTEN* mutations and the prevalence of autism spectrum disorder characteristics. Using a random effects model, the researchers estimated a pooled prevalence of ASD at 25%, with frequent reporting of intellectual disability and developmental delay, including issues that pertained globally, to motor, and to speech and language. Less frequently were mentions of emotional difficulties and impaired cognitive functioning. This indicates that further research using appropriate comparison groups may provide greater depth of the association with aberrations affecting *PTEN*.

Guidelines and Recommendations

The International Cowden Consortium Operational Criteria for the Diagnosis of Cowden Syndrome Ver 2000

The following recommendations were provided:

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 (e.g., adenoma or multinodular goitre)
- Mental retardation (say, IQ
- GI hamartomas
- Fibrocystic disease of the breast
- Lipomas

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- Fibromas
- Genito-urinary tumours (e.g., renal cell carcinoma, uterine fibroids) or malformation

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 six or more facial papules, of which three 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, six or more
- (2) Two major criteria but one must include macrocephaly or LDD
- (3) One major and 3 minor criteria
- (4) Four 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

Pilarski et al. (2013) 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 or without minor criteria; or
- One major and two minor criteria; or
- Three minor criteria

Pilarski et al. (2013) 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 women, 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) 4 – GT63
 - 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

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- ≥ 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)

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Cowden Syndrome/PTEN Hamartoma Tumor syndrome recommend testing in individuals who meet any of the following criteria:

- “Individual from a family with a known *PTE*^{cc} P/LP variant
 - Individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)
 - Individual meeting clinical diagnostic criteria^{mm} for CS/PHTS
 - Individual not meeting the clinical diagnostic criteria^{mm} for CS/PHTS with a personal history of:
 - Adult Lhermitte-Duclos disease (cerebellar tumors); or
 - Autism spectrum disorder and macrocephaly; or
 - Two or more biopsy-proven trichilemmomas; or
 - Two or more major criteria (one must be macrocephaly); or
 - Three major criteria, without macrocephaly; or
 - One major and ≥ 3 minor criteria;ⁿⁿ or
 - ≥ 4 minor criteria
 - individual with a relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed
 - individual must have the following:
 - Any one major criterion, OR
 - Two minor criteria
2. *PTEN* P/LP variant detected by tumor genomic testing on any tumor type in the absence of germline analysis^{oo}”

The relevant superscripts are captured below.

^{cc}When this gene is included as part of a multi-gene panel, an individual does not need to meet these testing criteria if testing criteria on other testing criteria pages are met.

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^{mm}If an individual has two or more major criteria, such as breast cancer and nonmedullary thyroid cancer, but does not have macrocephaly, one of the major criteria may be included as one of the three minor criteria to meet testing criteria.

^{oo}This should prompt a careful evaluation of personal and family history of the individual to determine the yield of germline sequencing. Somatic PTEN pathogenic/likely pathogenic variants are common in many tumor types in absence of germline pathogenic/likely pathogenic variant” (NCCN, 2024).

Aforementioned major and minor testing criteria are reported below.

“Major Testing Criteria:

- Breast cancer
- Endometrial cancer
- Follicular thyroid cancer
- Multiple GI hamartomas or ganglioneuromas^{pp}
- Macrocephaly (megalcephaly) (ie, $\geq 97\%$, 58 cm in adult female, 60 cm in adult male)^{qq}
- Macular pigmentation of glans penis
- Mucocutaneous lesions^{rr} (any of the following):
 - One biopsy-proven trichilemmoma
 - Multiple palmoplantar keratoses
 - Multifocal or extensive oral mucosal papillomatosis
 - Multiple cutaneous facial papules (often verrucous)

Minor Testing Criteria:^{ss}

- Autism spectrum disorder
- Colon cancer
- ≥ 3 Esophageal glycogenic acanthoses
- Lipomas
- Intellectual disability (ie, $\text{IQ} \leq 75$)
- Papillary or follicular variant of papillary thyroid cancer
- Thyroid structural lesions (e.g., adenoma nodule[s], goiter)

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- Renal cell carcinoma
- Single GI hamartoma or ganglioneuroma
- Testicular lipomatosis
- Vascular anomalies (including multiple intracranial developmental venous anomalies)” (NCCN, 2024)

The relevant superscripts are captured below.

^{pp}Multiple polyp types are often seen in patients with PHTS, and less commonly may include adenomas, hyperplastic polyps, and other histologies.

^{rr}The literature available on mucocutaneous lesions is not adequate to accurately specify the number or extent of mucocutaneous lesions required to be a major criterion for CS/PHTS. Clinical judgment should be used.

^{ss}evidence exists in the literature to include fibrocystic disease of the breast, fibromas, and uterine fibroids as diagnostic criteria” (NCCN, 2024)

The NCCN also notes that “Other cancers associated with PTEN but not in the testing criteria include: colorectal, kidney cancer, and melanoma.”

In their section outlining the “REVISED CLINICAL DIAGNOSTIC CRITERIA FOR PTEN HAMARTOMA TUMOR SYNDROME,” the NCCN recommends the following:

“Operational diagnosis in an individual (either of the following):

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

Operational diagnosis in a family where one individual meets revised PTEN hamartoma tumor syndrome clinical diagnostic criteria or has a *PTEN* P/LP variant:

1. Any two major criteria with or without minor criteria; or
2. One major and two minor criteria; or
3. Three minor criteria” (NCCN, 2024).

ClinGen PTEN Expert Panel

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.

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.

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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).

American College of Medical Genetics (ACMG)

In 2013, the ACMG published guidelines for identifying the etiology of autism spectrum disorders (ASDs). These guidelines state that “*PTEN* testing [should] be reserved for patients with ASDs with a head circumference above the 98th percentile” (Schaefer & Mendelsohn, 2013). The authors then suggest that of all ASD-related genetic evaluations, about 5% of testing will be due to *PTEN* mutations.

National Organization for Rare Disorders (NORD)

The NORD asserts that “The primary findings in PHTS include increased risk for certain types of cancer, benign tumors and tumor-like malformations (hamartomas) and neurodevelopmental disorders. The symptoms of PHTS vary greatly from person to person and can develop at any age.” However, some noteworthy sign and symptoms that indicate *PTEN* genetic testing are captured below.

- “A small percentage of adults develop a rare tumor known as a cerebellar dysplastic gangliocytoma (Lhermitte-Duclos disease). Symptoms of Lhermitte-Duclos disease include increased intracranial pressure, impaired ability to coordinate voluntary movements (ataxia) and seizures. It is rare when a person with adult-onset Lhermitte-Duclos does not have an underlying *PTEN* variant, and observing this tumor type is an automatic indicator for *PTEN* genetic testing.”
- “Macrocephaly (large head size) is found in 94% of measured patients with PHTS and can be a helpful screening tool to identify patients for *PTEN* genetic testing. In most patients, large head size is caused by overgrowth of brain tissue. The head shape may also be longer than average relative to width in some individuals (dolicocephaly).”

The authors go further to state that “Sotos syndrome is a rare genetic disorder characterized by excessive growth that occurs prior to and after birth (prenatally and postnatally)...The overlap of neurodevelopmental disabilities and macrocephaly in both PHTS and Sotos syndrome indicates the need for genetic testing to avoid misdiagnosis” (NORD, 2023). Genetic counseling is also suggested.

The authors report that “A diagnosis of PHTS may be suspected based upon a thorough clinical evaluation, a detailed patient history and the presence of characteristic findings. Recently, a variant risk calculator has been developed which can estimate the risk for adults to have a *PTEN* variant based on their personal history characteristics; this tool is available online at <https://www.lerner.ccf.org/gmi/ccscore/>. The diagnosis can only be confirmed when a variant of the *PTEN* gene is identified (NORD, 2023).

The current suggested screening regimens by age include:

“Children (under age 18)

- Yearly thyroid ultrasound starting at 7 years of age
- Yearly skin check with physical examination
- Consider neurodevelopmental evaluation

Adults

- Monthly breast self-examination starting at age 18 years
- Yearly thyroid ultrasound and dermatologic evaluation

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- Females: breast screening (at minimum mammogram) yearly beginning at age 35; MRI may also be incorporated
- Females: consider endometrial cancer screening starting at age 35 years. Personalized management including endometrial biopsy every 1-2 years and transvaginal ultrasound as needed (postmenopausal)
- Colonoscopy beginning at age 35 (unless symptomatic or close relative with colon cancer before age 40 years); colonoscopy frequency every 5 years; more frequently if symptomatic or polyps are found
- Biannual (every other year) renal imaging (CT or MRI preferred) beginning at age 40

For patients with a family history of a particular cancer type, screening may be considered 5-10 years prior to the youngest diagnosis in the family. For example, a patient whose mother developed breast cancer at 30 may begin breast surveillance at age 25-30” (NORD, 2023).

American College of Gastroenterology (ACG)

In 2015, the ACG published guidelines on genetic testing and management of hereditary gastrointestinal cancer syndromes. These guidelines clearly state that the “Genetic evaluation of a patient with possible CS should include testing for *PTEN* mutations... CS is caused by mutations in the *PTEN* gene. Once a disease-causing mutation is identified in a patient with CS or related conditions, other family members should undergo mutation-specific testing to determine whether the disease is present or absent so that appropriate surveillance can be undertaken” (Syngal et al., 2015). Further, the ACG also notes that “Surveillance in affected or at-risk CS patients should include screening for colon, stomach, small bowel, thyroid, breast, uterine, kidney, and skin (melanoma) cancers (conditional recommendation, low quality of evidence)” (Syngal et al., 2015).

State and Federal Guidelines, as applicable

Food and Drug Administration (FDA)

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; 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.

Applicable service codes: 81321, 81322, 81323, 0235U

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

Genetic Testing for PTEN Hamartoma Tumor Syndrome AHS – M2087

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Specialty Matched Consultant Advisory Panel review 7/2019

Medical Director review 7/2019

Specialty Matched Consultant Advisory Panel review 7/2020

Medical Director review 7/2020

Specialty Matched Consultant Advisory Panel review 7/2021

Medical Director review 7/2021

Medical Director review 7/2022

Medical Director review 11/2023

Medical Director review 7/2024

Policy Implementation/Update Information

- 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 2nd 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 - 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)
- 7/28/20 Updated Related Policies. The following changes were made to the When Covered section: Added Item 1 reimbursement language for genetic counseling; item 2, iv. under Major Criteria, removed “adenomas” and added “but excluding”; added items 6-7 reimbursement language, and reformatted as applicable. Updated policy guidelines and references. The following codes were added to the Billing/Coding section: 96040, S0265, and Note added as follows: **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”.

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Specialty Matched Consultant Advisory Panel review 7/2020. Medical Director review 7/2020. (jd)

- 10/1/21 Reviewed by Avalon 2nd Quarter 2021 CAB. Added the following indication to item #5 under the When Covered section: “or Bannayan-Riley-Ruvalcaba syndrome (BRRS)”. Description, Policy Guidelines, and Reference sections updated. Added PLA code 0235U to Billing/Coding section effective 10/1/21. Specialty Matched Consultant Advisory Panel review 7/2021. Medical Director review 7/2021. (jd)
- 9/13/22 Reviewed by Avalon 2nd Quarter 2022 CAB. Updated description, background, policy guidelines and references. Removed related policy titled Molecular Panel Testing of Cancers for Diagnosis, Prognosis, and Identification of Targeted Therapy AHS-M2109 due to archival. Billing/coding section updated. When Covered section edited for clarity and updated: Major and Minor criteria were moved from item 2 to Note 1, added item 2c, item 8 removed and added as sub criteria "a" to item 6. Medical Director review 7/2022. (tm)
- 12/5/23 Reviewed by Avalon 3rd Quarter 2023 CAB. Updated Description, Policy Guidelines and References sections. The following changes were made to the When Covered section: Previous coverage criteria 1 regarding recommendation for genetic counseling moved into policy description. Previous coverage criteria 6 moved to coverage criteria 1 with coverage expanded to all members of a family with a known PTEN mutation. Former coverage criteria 2.c. was moved into coverage criteria 3 and adjusted to match NCCN language and now reads 3. “f. Two major and two or more minor criteria (for individuals without macrocephaly).” Not Covered section edited for clarity. Medical Director review 11/2023. (tm)
- 9/4/24 Reviewed by Avalon 2nd Quarter 2024 CAB. Description, Policy Guidelines and References sections updated. Codes 96040 and S0265 removed from Billing/Coding section. Medical Director review 7/2024. (tm)

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