Genetic Testing for PTEN Hamartoma Tumor Syndrome

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I. Policy Description

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).[1,2]

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

Terms such as male and female are used when necessary to refer to sex assigned at birth.

II. Related Policies

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

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

All major and minor criteria are defined in Note 1

1) Genetic counseling **IS REQUIRED** for individuals prior to and after undergoing genetic testing for PTEN hamartoma tumor syndrome (PHTS).

~~1)~~2) For asymptomatic individuals who are in a family with a known pathogenic *PTEN* mutation, the following testing **MEETS COVERAGE CRITERIA**:

a) Testing restricted to the known familial mutation.

b) Comprehensive *PTEN* gene sequencing when the specific *PTEN* mutation is unknown.

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~~2)~~3)For individuals suspected of having Cowden Syndrome (CS)/~~PTEN hamartoma tumor syndrome (~~PHTS~~),~~ genetic testing for a *PTEN* mutation **MEETS COVERAGE CRITERIA** when at least one of the following clinical signs is present:

a) Three or more major criteria (one must be macrocephaly, Lhermitte-Duclos disease, or gastrointestinal hamartomas).

b) Two major and three minor criteria.

~~3)~~4)For individuals not meeting the clinical diagnostic criteria above, genetic testing for a *PTEN* mutation **MEETS COVERAGE CRITERIA** 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)~~5)For individuals with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS), genetic testing for a *PTEN* mutation **MEETS COVERAGE CRITERIA**.

~~5)~~6)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 **MEETS COVERAGE CRITERIA** 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)~~7)For individuals with a *PTEN* pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline analysis, genetic testing for a *PTEN* mutation **MEETS COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

~~7)~~8)For all other situations not described above, genetic testing for a PTEN mutation **DOES NOT MEET COVERAGE CRITERIA**.

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):[3]

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Major Testing Criteria

- Breast cancer
- Endometrial cancer (epithelial)
- Follicular thyroid cancer
- Three or more GI hamartomas or ganglioneuromas
- Lhermitte-Duclos disease (adult)
- Macrocephaly (megalocephaly) (ie, ≥97%, 58 cm in adult female, 60 cm in adult male)
- Macular pigmentation of glans penis
- Mucocutaneous lesions (any of the following):
  - Trichilemmoma (three or more, at least one biopsy-proven)
  - Three or more palmoplantar keratotic pits and/or acral hyperkeratotic papules
  - Three or more mucocutaneous neuromas
  - Oral papillomas, particularly on tongue and gingiva (three or more papillomas **or** one biopsy-proven or dermatologist diagnosed papilloma)

Minor Testing Criteria

- Autism spectrum disorder
- Colon cancer
- Three or more esophageal glycogenic acanthoses
- Three or more lipomas
- Intellectual disability (i.e., IQ ≤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)

IV. Table of Terminology

Term	Definition
ACG	American College of Gastroenterology
aCGH	Array comparative genomic hybridization
ACMG	American College of Medical Genetics and Genomics
AKT	Protein Kinase B
ALK	*Anaplastic lymphoma kinase gene*
ASDs	Autism spectrum disorders
BEN	Benign
BP	Base pair
BRCA1	*Breast cancer type 1 gene*
BRCA2	*Breast cancer type 2 gene*
BRRS	Bannayan-Riley-Ruvalcaba syndrome
CC	Cleveland Clinic
CC15	Cleveland Clinic Score of 15

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CGH	Comparative genomic hybridization
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid Services
CONF	Conflicting
CS	Cowden Syndrome
DNA	Deoxyribonucleic acid
DTC	Differentiated thyroid carcinoma
ERCC2	*ERCC excision repair 2 gene*
FDA	Food and Drug Administration
FTC	Follicular thyroid carcinoma
GI	Gastrointestinal
HRAS	*HRas proto-oncogene*
IQ	Intelligence quotient
LBEN	Likely benign
LDD	Lhermitte-Duclos disease
LDT	Laboratory-developed test
LPATH	Likely pathogenic
MLPA	Multiplex ligation-dependent probe amplification
mTOR	Mechanistic Target of Rapamycin
MUTYH	*mutY DNA glycosylase*
NCCN	National Comprehensive Cancer Network
NGS	Next generation sequencing
NORD	National Organization for Rare Disorders
PATH	Pathogenic
PCR	Polymerase chain reaction
PHTS	PTEN Hamartoma Tumor Syndromes
PI3K	Phosphatidylinositol 3-Kinase
PLS	Proteus-Like Syndrome
PS	Proteus Syndrome
PTEN	*Phosphatase and tensin homolog*
qPCR	Quantitative polymerase chain Reaction
RET	*Ret proto-oncogene*
RNA	Ribonucleic acid
SOLAMEN	Segmental Overgrowth, Lipomatosis, Arteriovenous Malformation, and Epidermal Nevus
TSC2	*Tuberous sclerosis complex 2 gene*
VUS	Variant of uncertain significance

V. Scientific 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

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phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway and the mechanistic target of rapamycin (mTOR) signaling pathway.[2,4] 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.[5] Dental malformations have also been identified in 27% of pediatric PHTS patients.[6] Further, loss of *PTEN* gene functionality results in a spectrum of autosomal dominant disorders known *PTEN* hamartoma tumor syndromes (PHTS); this includes CS, Bannayan-Riley-Ruvalcaba syndrome (BRRS), *PTEN*-related PS, and PLS.[1,7] Autism spectrum disorders (ASDs) with macrocephaly and adult Lhermitte-Duclos disease (LDD) have also been associated with PHTS.[2,8]

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 85% of CS cases, 65% 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.[1] 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.[1,9] Mutations have also been reported in the *PTEN* promoter, and a test for mutations in this region of the gene has become clinically available.[2] 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 meet clinical criteria for CS or who meet criteria for genetic testing.[8,11,12] 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. Recently genotype-phenotype correlations identified that 72% of PTEN mutations are located in the tensin-type C2 domain.[6]

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).[14] 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%.[1,7] The estimated prevalence of CS is 1 in 200,000 to 250,000, though it is likely underreported.[2] 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.[2]

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.[2] Similar

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mutations in the *PTEN* gene are found in both CS and BRRS, which are now considered phenotypically distinct presentations of a similar genetic abnormality.[9,15]

PTEN-related *Proteus Syndrome (PS)*

PTEN-related PS 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.[16]

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.[1,7,16] 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)."[2]

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.[17]

Moreno Fernandes, et al. (2026) reported a novel *PTEN* frameshift variant in a four year old girl presenting with congenital hypothyroidism, progressive macrocephaly, and ASD.[18] Genetic testing enabled identification of a previously undescribed pathogenic *PTEN* variant, confirming a diagnosis of PHTS. In pediatric patients, the combination of progressive macrocephaly and neurodevelopmental disorders, particularly ASD, should be considered a clinical red flag for underlying genetic conditions such as PHTS.[18] Because oncologic manifestations typically arise later in life, early neurodevelopmental presentations may represent the first opportunity for diagnosis.[18] This case reinforces the importance of *PTEN* sequencing when clinical suspicion arises, as early diagnosis informs genetic counseling and enables timely implementation of cancer surveillance strategies. Identification of novel pathogenic *PTEN* variants also expands understanding of genotype–phenotype correlations in PHTS. Early identification is critical to initiate surveillance, including thyroid palpation and ultrasound during childhood, in accordance with published recommendations.[18]

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 granule cells."[13] LDD often develops in conjunction with CS, but may also develop singularly.[2]

Proprietary Testing

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Ambry Genetics, GeneDx, LabCorp 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.[18-21]19-22 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 PLS, 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.[20,21]21,22

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."[19]20 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."[19]20 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.[18]19

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.*"[22]23

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.[24]25 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."[23]24

Isik, et al. (2020) researched the genotype to phenotype correlation of patients with *PTEN* mutations. A total of ten 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

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pathologic cranial magnetic resonance imaging findings."[25][26] Further, sequencing of the *PTEN* gene identified seven different *PTEN* variants; four variants were located in exon five. The authors conclude by highlighting the importance of screening for *PTEN* mutations in patients with macrocephaly, particularly due to an increased risk of cancer.[25][26]

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%."[26][27] 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%),"[26,27][27,28] 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 ad impaired cognitive functioning. This indicates that further research using appropriate comparison groups may provide greater depth of the association with aberrations affecting *PTEN*.[28][29]

VI. Guidelines and Recommendations

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

The International Cowden Consortium established the operational criteria for diagnosing CS in 1995 and updated them in 2000, categorizing features into Pathognomonic, Major, and Minor criteria.

- Pathognomonic criteria include mucocutaneous lesions such as facial trichilemmomas, acral keratoses, papillomatous lesions, and mucosal lesions.
- Major criteria include significant features such as breast carcinoma, thyroid carcinoma, macrocephaly, endometrial carcinoma, and LDD.
- Minor criteria include thyroid lesions, intellectual disabilities, gastrointestinal hamartomas, fibrocystic disease of the breast, lipomas, fibromas, and genitourinary tumors or malformations.[29,30][30,31]

For operational diagnosis in a person, mucocutaneous lesions alone can be sufficient if specific conditions are met, such as having six or more facial papules with three or more being trichilemmomas, or combinations of cutaneous facial papules, oral mucosal papillomatosis, and acral keratoses. Alternatively, diagnosis can be based on two major criteria, one major and three minor criteria, or four minor criteria.[29,30][30,31]

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For operational diagnosis in a family, the presence of pathognomonic criteria, any one major criterion with or without minor criteria, or two minor criteria can be sufficient.[2930]

The National Comprehensive Cancer Network (NCCN) adopted these criteria to ensure accurate diagnosis and management of CS, The NCCN continues to refine them based on new clinical and genetic information and currently hold the most up-to-date criteria for diagnosing CS and other PHTS disorders.[3,29,313,30,32]

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 (PHTS) in an individual who meets either one of the following:

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

The operational diagnosis in a family where one individual meets the revised PHTS clinical diagnostic criteria or has a PTEN mutation is as follows:

- Any two major criteria with or without minor criteria; or
- One major and two minor criteria; or
- Three minor criteria[3233]

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)
- LDD (adult)
- Macrocephaly (megalocephaly) (i.e., ≥97th 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
- ≥3 esophageal glycogenic acanthoses
- Lipomas (≥3)
- Intellectual disability (i.e., IQ ≤75)
- Renal cell carcinoma

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- 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)[32][33]

The National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Cowden Syndrome/PHTS recommend testing in individuals who meet any of the following criteria:

- "Individual from a family with a known *PTEN*[ff] P/LP variant
- Individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)
- Individual meeting clinical diagnostic criteria for CS/PHTS
- Individual not meeting the clinical diagnostic criteria 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;[qq] 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
- *PTEN* P/LP variant detected by tumor genomic testing on any tumor type in the absence of germline analysis[rr]"[3]

The relevant superscripts are captured below.

"[ff]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.

[qq]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.

[rr]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."[3]

Aforementioned major and minor testing criteria are reported below.

"Major Testing Criteria:

- Breast cancer

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- Endometrial cancer (epithelial)
- Follicular thyroid cancer
- ≥3 GI hamartomas or ganglioneuromas[ss]
- Macrocephaly (megalocephaly) (ie, ≥97%, 58 cm in adult female, 60 cm in adult male)
- Macular pigmentation of glans penis
- Mucocutaneous lesions[uu]
  - Trichilemmoma (≥3, at least 1 biopsy-proven)
  - ≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules)
  - ≥3 mucocutaneous neuromas
  - Oral papillomas (particularly on tongue and gingiva)(≥3 or 1 biopsy-proven or dermatologist diagnosed)

Minor Testing Criteria:[vv]

- Autism spectrum disorder
- Colon cancer
- ≥3 Esophageal glycogenic acanthoses
- ≥3 Lipomas
- Intellectual disability (ie, IQ ≤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)"[3]

The relevant superscripts are captured below.

"[ss]Multiple polyp types are often seen in patients with PHTS, and less commonly may include adenomas, hyperplastic polyps, and other histologies.

[uu]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.

[vv]~~evidence~~[zz]Insufficient evidence exists in the literature to include fibrocystic disease of the breast, fibromas, and uterine fibroids as diagnostic criteria"[3]

The NCCN also notes that "Melanoma is also associated with PTEN but is not included in the testing criteria."[3]

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.

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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."[3]

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.

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.[~~33~~34]

American College of Medical Genetics (ACMG)

In 2013, the ACMG published guidelines for identifying the etiology of ASDs. These guidelines state that "*PTEN* testing [should] be reserved for patients with ASDs with a head circumference above the 98th percentile."[17] 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."[~~34~~35] 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)."[~~34~~35]

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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."[34][35] 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.[34][35]

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
- 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."[34][35]

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."[35][36] 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)."[35][36]

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The Japan Society of Coloproctology

The Japan Society for Coloproctology, in conjunction with several leading Japanese medical institutions, has developed a comprehensive set of guidelines for the diagnosis and management of Cowden Syndrome/PHTS in children and adults. These guidelines incorporate contributions from specialists in gastroenterology, oncology, pediatrics, dermatology, genetic medicine, and other related fields.

"This guideline adopted the NCCN criteria for diagnosis of CS/PHTS, which included 8 major criteria and 10 minor criteria, including clinical manifestations and *PTEN* testing criteria."[36~~36~~37]

Key recommendations from the joint guideline include the following:

- "We strongly recommend referral to a dermatologist to assess the presence of mucocutaneous lesions associated with PHTS.
- As the risk of developing colorectal cancer is higher in patients with this syndrome than in the general population, resection of colorectal polyps, which are considered precancerous lesions, is weakly recommended. There is no existing evidence to confirm whether resection of colorectal polyps inhibits the development of colorectal cancer and improves its prognosis.
- Owing to the high risk of developing breast cancer in women with this syndrome, breast surveillance using mammography or contrast-enhanced MRI is strongly recommended.
- Genetic testing for PTEN is recommended for patients with suspected CS/PHTS, considering the benefits for definitive diagnosis of this syndrome and for cancer surveillance."[36~~36~~37]

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

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.

VIII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

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This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

IX. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
0235U	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions Proprietary test: Genomic Unity® PTEN Analysis Lab/Manufacturer: Variantyx Inc

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

X. Evidence-based Scientific References

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XI. Revision History

Revision Date	Summary of Changes
06/03/2026	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: Addition of new CC1 requiring genetic counseling: "1) Genetic counseling IS REQUIRED for individuals prior to and after undergoing genetic testing for PTEN hamartoma tumor syndrome (PHTS)." CC3 edited for clarity

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