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).

II. 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 Section VII of this policy document.

All major and minor criteria are defined in Note 1

1) Genetic counseling for *PTEN* mutation testing **MEETS COVERAGE CRITERIA** and is recommended**.**

2) Genetic testing for a *PTEN* mutation **MEETS COVERAGE CRITERIA** 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; OR
   c) Three major and two minor criteria, in an individual without macrocephaly

3) Genetic testing for a *PTEN* mutation **MEETS COVERAGE CRITERIA** 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

4) Genetic testing for a *PTEN* mutation **MEETS COVERAGE CRITERIA** in individuals with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS).

5) Genetic Testing for a *PTEN* mutation **MEETS COVERAGE CRITERIA** in at-risk individuals with a relative with a clinical diagnosis of Cowden Syndrome/PTEN Hamartoma Tumor syndrome or Bannayan-Riley-Ruvalcaba syndrome (BRRS) 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
6) In first-degree relatives of an individual with a known *PTEN* mutation, genetic testing for a *PTEN* mutation **MEETS COVERAGE CRITERIA**.
    a) Comprehensive *PTEN* mutation testing **MEETS COVERAGE CRITERIA** if the familial pathogenic/likely pathogenic variant is not known.
7) Genetic testing for a *PTEN* mutation **MEETS COVERAGE CRITERIA** in individuals with *PTEN* pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline analysis.

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 a patient's illness.

8) Genetic testing for a *PTEN* mutation **DOES NOT MEET COVERAGE CRITERIA** for all other indications.

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 (megalocephaly) (ie, ≥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
    - Multiple cutaneous facial papules (often verrucuous)

Minor Testing Criteria

- Autism spectrum disorder
- Colon cancer
- ≥3 Esophageal glycogenic acanthoses
- 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)

III. 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
CGH	Comparative genomic hybridization
CLIA ’88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid
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
LDTs	Laboratory-developed tests
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

IV. 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 phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway and the mechanistic target of rapamycin (mTOR) signaling pathway. 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. Further, loss of *PTEN* gene functionality results in a spectrum of autosomal dominant disorders known *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). Autism spectrum disorders (ASDs) with macrocephaly and adult Lhermitte-Duclos disease (LDD) have also been associated with PHTS.

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. 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. Mutations have also been reported in the *PTEN* promoter, and a test for mutations in this region of the gene has become clinically available. 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. 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)

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

Bannayan-Riley-Ruvalcaba Syndrome (BRRS)

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. 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.

PTEN-related *Proteus Syndrome (PS)*

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.

Proteus-like Syndrome (PLS)

PLS is undefined but typically refers to individuals with similar clinical features to PS who do not meet the diagnostic criteria. Overall, limited information is available on PLS. Stanich (2021) 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)

ASDs 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)

LDD 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.” LDD often develops in conjunction with CS, but may also develop singularly.

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. 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.

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”. 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.

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.”*

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."

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." 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.

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 ad impaired cognitive functioning. This indicates

V. Guidelines and Recommendations

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

The following recommended were provided:

<u>Pathognomonic criteria</u>

Mucocutaneous lesions

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

<u>Major criteria</u>

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

Minor criteria

- Other thyroid lesions (eg, adenoma or multinodular goitre)
- Mental retardation (say, IQ
- GI hamartomas
- Fibrocystic disease of the breast
- Lipomas
- Fibromas
- Genito-urinary tumours (eg, 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 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:

- Any two major criteria with our 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 (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
- 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 *PTEN*[t] pathogenic variant/likely pathogenic variant
- Individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)
- Individual meeting the 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;[bb] or
    - ≥4 minor criteria

- At-risk individual with a relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed. The at-risk individual must have the following:
  - Any one major criterion, OR
  - Two minor criteria

- *PTEN* pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline analysis[cc]

[t]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.

[bb]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.

[cc]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.

Major Testing Criteria

- Breast cancer
- Endometrial cancer
- Follicular thyroid cancer
- Multiple GI hamartomas or ganglioneuromas[dd]
- Macrocephaly (megalocephaly) (ie, ≥97%, 58 cm in adult female, 60 cm in adult male)[ee]
- Macular pigmentation of glans penis
- Mucocutaneous lesions[ff] (any of the following):
  - One biopsy-proven trichilemmoma
  - Multiple palmoplantar keratoses
  - Multifocal or extensive oral mucosal papillomatosis
  - Multiple cutaneous facial papules (often verrucuous)

Minor Testing Criteria[gg]

- Autism spectrum disorder
- Colon cancer
- ≥3 Esophageal glycogenic acanthoses
- 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)

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. [In these criteria], the terms males and females refer to sex assigned at birth.

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

[ff]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.

[gg]Insufficient evidence exists in the literature to include fibrocystic disease of the breast, fibromas, and uterine fibroids as diagnostic criteria."

"<u>Operational diagnosis in an individual (either of the following):</u>

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.

<u>Operational diagnosis in a family where one individual meets revised PTEN hamartoma tumor syndrome clinical diagnostic criteria or has a *PTEN* pathogenic/likely pathogenic variant:</u>

1. Any two major criteria with or without minor criteria; or
2. One major and two minor criteria; or
3. Three minor criteria."

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 (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." 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 states 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." Genetic counseling is also suggested.

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." 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)."

VI. 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: http://www.cms.gov/medic-are-coverage-database/overview-and-quick-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.

VII. 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.

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 Integration 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).

VIII. Evidence-based Scientific References

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IX. Policy History

Policy approved by Medical Directors	9/20/2022
Policy approved at UMC	12/16/2022
Policy effective	6/1/2023