PTEN Hamartoma Tumor Syndromes Genetic Testing

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Introduction

PTEN hamartoma tumor syndromes (PHTS) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Genomic Unity PTEN analysis	0235U
PTEN deletion/duplication analysis	81323
PTEN known familial mutation analysis	81322
PTEN sequencing	81321

Criteria

Introduction

Requests for PTEN hamartoma tumor syndromes (PHTS) testing are reviewed using the following criteria.

PTEN Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing that would detect the familial mutation, AND
- Diagnostic and Predisposition Testing:

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- Known deleterious family mutation in PTEN identified in 1st, 2nd, or 3rd degree biologic relative(s), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

PTEN Sequencing with Promoter Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous sequencing of PTEN, AND
- Diagnostic Testing for Symptomatic Individuals
  - Personal history of ANY of the following:
    - Bannayan Riley-Ruvalcaba syndrome (BRRS); or
    - Adult Lhermitte-Duclos disease (LDD); or
    - Autism spectrum disorder and macrocephaly; or
    - At least two biopsy-proven trichilemmomas; or
    - At least two major criteria** (one must be macrocephaly); or
    - Three major criteria** without macrocephaly; or
    - One major** and at least three minor criteria***; or
    - Four or more minor criteria***, OR
- Predisposition testing for Presymptomatic/Asymptomatic Individuals:
  - At-risk person with a family history of:
    - A relative (includes first-degree relative or more distant relatives if the first-degree relative is unavailable or unwilling to be tested) with a clinical diagnosis of Cowden syndrome or BRRS (no previous genetic testing); and
    - One major** OR two minor criteria*** in the at-risk person, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

PTEN Deletion/Duplication Analysis:

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - Sequence analysis of PTEN has been performed and resulted negative, and
  - Criteria for PTEN full gene sequencing are met, and
  - No previous deletion/duplication testing, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Criteria for testing purposes are:

**Major:	***Minor:
• Breast cancer • Endometrial cancer • Follicular thyroid cancer • Multiple GI hamartomas or ganglioneuromas • Macrocephaly (at least 97th percentile: 58cm in adult females and 60cm in adult males) • Macular pigmentation of glans penis • Mucocutaneous lesions: one biopsy-proven trichilemmoma, multiple palmoplantar keratoses, multifocal or extensive oral mucosal papillomatosis, multiple cutaneous facial papules (often verrucous)	• Autism spectrum disorder • Colon cancer • ≥ 3 esophageal glycogenic acanthoses • Lipomas • Intellectual disability (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)

Other Considerations

PHTS testing may be performed as part of a multigene, multisyndrome panel. For information on multigene, multisyndrome panel testing, please refer to the guideline *Hereditary Cancer Syndrome Multigene Panels*, as this testing is not addressed here.

For information on germline testing after somatic testing, please refer to the guideline *Hereditary (Germline) Testing After Tumor (Somatic) Testing*, as this testing is not addressed here.

What is PTEN hamartoma tumor syndrome?

PTEN hamartoma tumor syndrome (PHTS) is used to describe the group of conditions caused by PTEN mutations that include hamartomatous growths: Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome and PTEN-related Proteus-like syndrome, and autism spectrum disorder with macrocephaly.[1]

Prevalence

The prevalence is unknown. The prevalence of CS was previously estimated to be 1 in 200,000 individuals, although this is likely low due to underdiagnosis.[1]

Symptoms

Historically, these conditions have been considered clinically distinct but share an underlying genetic etiology, and show some overlap in families.[1]

- **Cowden syndrome** (CS) is characterized by an increased risk for benign and malignant tumors of the breast, endometrium, and thyroid (non-medullary).[1,2]
  - Other common features include macrocephaly and growths on the skin or mucous membranes (mucocutaneous lesions). The lifetime risk for breast cancer is 25-50% with an average age at diagnosis of 38-46 years.[1] However, a 2012 publication by Tan et al. reports that this lifetime risk may be as high as 85%, particularly in individuals with PTEN promoter mutations.[3]
  - The lifetime risk for thyroid cancer can range from 10% to as high as 35%.[1,3] If it occurs, thyroid cancer is usually follicular. It is rarely papillary and is never medullary. Benign thyroid growths are also found in up to 75% of individuals with CS.[1] "However, the high frequency of thyroid disease in the general population means that when taken on their own, thyroid neoplasms have a low predictive value for identifying mutations carriers."[4]
  - Endometrial cancer has a reported lifetime risk of up to 28%.[3]
  - The gastrointestinal polyp risk (often colonic) in individuals with CS may be 80% or higher and the lifetime risk for colorectal cancer is estimated to be 9%.[3]
  - Early onset colorectal cancer has been reported in 13% of individuals with PTEN associated CS indicating earlier and more frequent colonoscopy is warranted in this population.[3,5,6]
  - Additionally, an increased lifetime risk for kidney cancer (approximately 34%) and melanoma (about 5-6%) has been reported.[1-3]
- **Lhermitte-Duclos disease** (LDD) is a rare, benign tumor of the cerebellum called dysplastic gangliocytoma that may present in childhood or adulthood.[1,2] Most adult-onset LDD is caused by a PTEN mutation even when no other signs of CS are present.[1]
- **Bannayan-Riley-Ruvalcaba syndrome** (BRRS) is a genetic disorder characterized by macrocephaly, multiple benign intestinal polyps (hamartomatous type), lipomas, colored spots on the tip of the penis (pigmented macules of the glans penis), and hemangiomas. Some people with BRRS have intellectual disability and/or birth defects. There may be an increased risk for several types of cancer, including breast, thyroid and endometrial.[2]
- **PTEN-related Proteus and PTEN-related Proteus-like syndromes** are highly variable conditions characterized by overgrowth of several different tissues usually in

a patchy asymmetric pattern (mosaic) that is often present from birth but gets worse over time.[1] Clinical signs and symptoms include connective tissue and epidermal nevi (hamartomatous growths), ovarian cystadenomas, parotid monomorphic adenomas, lipomas, capillary/venous/lymphatic malformations, and a characteristic facial dysmorphology.

- **Autism spectrum disorder with macrocephaly** (defined as >2.5 SDs above the age mean or ≥97th percentile) may be caused by a mutation in the PTEN gene.[1]
- **Juvenile polyposis of infancy** may be caused by mutations in PTEN. In this condition, juvenile polyposis is diagnosed before six years of age and the phenotype may be similar to BRRS. “GI manifestations (bleeding, diarrhea, & protein-losing enteropathy) are often severe."[1]

Cause

Pathogenic mutations in the PTEN gene cause PHTS.

- Up to 80% of people with a clinical diagnosis of CS have a PTEN mutation in the coding region.[1] Ten percent of individuals with CS have a PTEN mutation in the promotor region.[1]
- The majority of CS cases are simplex. Approximately 10-50% of individuals with CS have an affected parent.[1] De novo PTEN pathogenic variants occur in 10-44% of individuals with PHTS.
- Nearly all individuals with a PTEN mutation will develop symptoms (complete penetrance).[1,2]
- Up to 71% of individuals with a clinical diagnosis of BRRS have a PTEN mutation.[1] Up to 50% of individuals with Proteus-like syndrome and 20% of individuals with Proteus syndrome have a PTEN mutation.[1] An estimated 10-20% of all individuals with ASD/macrocephaly have a PTEN mutation.[1,7] The likelihood may be greater if other family members have signs and symptoms in the PHTS spectrum.

Inheritance

PHTS are autosomal dominant disorders.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Diagnosis

The diagnosis of PHTS can be established with the identification of a pathogenic mutation in the PTEN gene.

- Sequence analysis of the PTEN gene will detect a mutation in about 80% of people with a clinical diagnosis of CS and 60% of people with a clinical diagnosis of BRRS.[1]
  - **Sequencing of the promoter region** will detect an additional 10% of PTEN mutations that cause CS.[1] As such, it is important to determine whether or not the selected laboratory includes PTEN promoter analysis in their testing.
- The likelihood of identifying a deletion or duplication in people with clinically diagnosed CS is unknown but expected to be relatively low.[1] About 11% of people with BRRS have large PTEN gene deletions.[1]

Clinical diagnostic criteria have been developed. A clinical diagnosis of PHTS is based on the major and minor criteria in the table below.[2]

An operational diagnosis of CS is established if an individual meets any of the following criteria:

- Three or more major criteria* (one must include macrocephaly, Lhermitte-Duclos disease, or GI hamartomas); or
- Two major* and three minor** criteria

If an individual meets the clinical criteria noted above or has a PTEN pathogenic mutation, the family members would meet criteria for an operational diagnosis of CS if they meet one of the following criteria:

- Two major criteria* with or without minor criteria; or
- One major* and two minor criteria**; or
- Three minor** criteria

The major and minor criteria for a clinical diagnosis of PHTS are:[2]

Major:*	Minor:**
• Breast cancer • Endometrial cancer • Follicular thyroid cancer • Three or more GI hamartomas (including ganglioneuromas but excluding hyperplastic polyps) • Adult Lhermitte-Duclos disease • Macrocephaly (at least 97th percentile: 58cm in adult females and 60cm in adult males) • Macular pigmentation of glans penis • Mucocutaneous lesions: ◦ Trichilemmomas: at least three and at least one biopsy proven ◦ Palmoplantar keratotic pits and/or acral hyperkeratotic papules: at least three ◦ Mucocutaneous neuromas: at least three ◦ Oral papillomas (particularly on tongue or gingiva): at least three or one biopsy proven or dermatolologist diagnosed	• Autism spectrum disorder • Colon cancer • At least three esophageal glycogenic acanthoses • At least three lipomas • Intellectual disability (IQ of 75 or less) • Renal cell carcinoma • Testicular lipomatosis • Papillary or follicular variant of papillary thyroid cancer • Thyroid structural lesions (e.g., adenoma, nodule(s), goiter) • Single GI hamartoma or ganglioneuroma • Vascular anomalies (including multiple intracranial developmental venous anomalies)

Management

People with CS need heightened cancer surveillance starting at age 18 years. This may begin earlier if warranted: “For individuals with a family history of a particular cancer type at an early age, screening should be considered five to ten years prior to the youngest diagnosis in the family”.[1] The exception is children should have a yearly thyroid ultrasound starting at age 7 years and skin check with physical examination.[1] Because of the overlap in clinical phenotypes, people with other PTEN-related conditions are advised to follow the same heightened cancer surveillance guidelines as for CS.[8,9]

Survival

Given the phenotypic spectrum of PHTS and underdiagnosis, especially of individuals with non-classic phenotypes, the prognosis for individuals with PHTS is unknown. The increased risk for malignant tumors is the largest factor impacting survival.

Test information

Introduction

Testing for PHTS may include known familial mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2013) issued consensus practice guidelines on the genetics evaluation of autism. They proposed an evaluation scheme with three tiers. The first tier included routine studies such as chromosome analysis and fragile X genetic testing. PTEN gene testing is recommended as a second-tier test when the head circumference is greater than 2.5 SDs above the mean (if no diagnosis is made via first tier testing).[10]

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2025) supported the use of PTEN genetic testing in those with clinical features or a family history. They recommended PTEN genetic testing in any of the following situations:[2]

- Family history of a known PTEN mutation [PTEN known familial mutation testing is appropriate]
- Individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)
- Individual meeting clinical diagnostic criteria, as defined by NCCN, for CS/PHTS
- Individual not meeting clinical diagnostic criteria for CS/PHTS with a personal history of any of the following:
  - Adult-onset Lhermitte-Duclos disease (cerebellar dysplastic gangliocytoma)
  - Autism spectrum disorder and macrocephaly (greater than or equal to 97th percentile)
  - Two or more biopsy proven trichilemmomas
  - Macrocephaly and at least one other major*** criteria
  - Three major*** criteria without macrocephaly
  - One major*** and three or more minor**** criteria
  - Four or more minor**** criteria
- At-risk relative of someone clinically diagnosed with Cowden syndrome or BRRS (who has not had genetic testing), when the at-risk relative has at least one major*** or two minor**** criteria. Ideally, the at-risk person is a first-degree relative (parent, sibling, child) of someone clinically diagnosed, but testing more distant relatives is acceptable if closer relatives are not available or willing to have testing.
- Affected individuals with pathogenic/likely pathogenic variant identified on tumor genomic testing that may have implications if also identified on germline testing. "This should prompt a careful evaluation of personal and family history of the individual to determine the yield of germline sequencing. Somatic PTEN P/LP [pathogenic/likely pathogenic] variants are common in many tumor types in absence of a germline P/LP variant." For information on germline testing after somatic testing, please refer to the guideline *Hereditary (Germline) Testing After Tumor (Somatic) Testing*, as this testing is not addressed here.

The major and minor criteria to determine appropriateness of genetic testing are:

***Major:	****Minor:
• Breast cancer • Endometrial cancer • Follicular thyroid cancer • Multiple GI hamartomas or ganglioneuromas • Lhermitte-Duclos disease (adult) • Macrocephaly (at least 97th percentile: 58 cm in adult females and 60 cm in adult males) • Macular pigmentation of glans penis • Mucocutaneous lesions: one biopsy-proven trichilemmoma, multiple palmoplantar keratoses, multifocal or extensive oral mucosal papillomatosis, multiple cutaneous facial papules (often verrucous)	• Autism spectrum disorder • Colon cancer • 3 or more esophageal glycogenic acanthoses • Lipomas • Intellectual disability (IQ less than or equal to 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)

US Multi-Society Task Force on Colorectal Cancer

The US Multi-Society Task Force on Colorectal Cancer issued a consensus statement on the diagnosis and management of hamartomatous polyposis syndromes that stated:[11]

- "We recommend patients with any of the following undergo a genetic evaluation: 2 or more lifetime hamartomatous polyps, a family history of hamartomatous polyps, or a cancer associated with a hamartomatous polyposis syndrome in first or second-degree relatives. Genetic testing (if indicated) should be performed using a multigene panel test. (Strong recommendation, low quality of evidence)"

Selected Relevant Publication

An expert-authored review of the PHTS stated:[1]

- "Sequence analysis of PTEN is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found. If a pathogenic variant is not identified with deletion/duplication analysis, perform sequence analysis of the PTEN promoter region for variants that decrease PTEN gene expression."
- "The most serious consequences of PHTS relate to the increased risk of cancers including breast, thyroid, endometrial, renal, and to a lesser extent, colon. In this

regard, the most important aspect of management of any individual with a PTEN pathogenic variant is increased cancer surveillance to detect any tumors at the earliest, most treatable stages."

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for PTEN hamartoma tumor syndromes testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

References

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