## Condition Description

**PTEN** Hamartoma Tumor Syndrome (PHTS) is characterized by hamartomatous tumors and germline PTEN mutations. Clinically, PHTS includes Cowden Syndrome (CS), Bannayan-Riley-Ruvalcaba Syndrome (BRRS), Proteus Syndrome (PS), and Proteus-Like Syndrome.

Cowden Syndrome (CS) is a multiple hamartoma syndrome with a high risk of benign and malignant tumors of the thyroid, breast, and endometrium. Affected individuals usually have macrocephaly, trichilemmomas, and papillomatous papules, and present by the late 20s. The lifetime risk of developing breast cancer is 25%-50%, with an average age of diagnosis between 38 and 46 years; the lifetime risk for thyroid cancer (usually follicular, rarely papillary, but never medullary thyroid cancer) is around 10%, and the risk for endometrial cancer may approach 5%-10%.

Bannayan-Riley-Ruvalcaba Syndrome (BRRS) is a congenital disorder characterized by macrocephaly, intestinal polyposis, lipomas, and pigmented macules of the glans penis.

Proteus Syndrome (PS) is a complex, highly variable disorder involving congenital malformations and hamartomatous overgrowth of multiple tissues, as well as connective tissue nevi, epidermal nevi, and hyperostoses.

Proteus-Like Syndrome is undefined, but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS.

A presumptive diagnosis of PHTS is based on clinical signs. The actual diagnosis of PHTS is made only when a PTEN mutation is identified. Approximately 80% of individuals who meet the diagnostic criteria for CS and 60% of individuals with a clinical diagnosis of BRRS have a detectable PTEN gene mutation. Approximately 10% of individuals with BRRS who do not have a mutation detected in the PTEN coding sequence have large deletions within or encompassing PTEN. Preliminary data also suggest that up to 50% of individuals with a Proteus-like syndrome and up to 20% of individuals with Proteus syndrome have PTEN mutations.

The PTEN gene (10q23.3) has 9 exons. It appears that nuclear PTEN mediates cell cycle arrest, while cytoplasmic PTEN is required for apoptosis. The majority (76%) of germline mutations in PTEN result in either truncated protein, lack of protein (haploinsufficiency), or dysfunctional protein. Many missense mutations are functionally null and several act as dominant negatives. When PTEN is absent, decreased, or dysfunctional, phosphorylation of Akt is un inhibited, leading to the inability to activate cell cycle arrest and/or to undergo apoptosis. In addition, through lack of protein phosphatase activity, the mitogen-activated protein kinase (MAPK) pathway is dysregulated, leading to abnormal cell survival.

Sequencing of the PTEN gene is recommended after a clinical diagnosis consistent with PHTS, and provides a complementary method to confirm the presence of mutations in a proband, identify at-risk individuals among the proband's relatives, and provide prenatal diagnosis in families with known mutations. For patients with suspected PHTS, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.


## Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Indications</th>
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<tbody>
<tr>
<td><strong>PTEN</strong></td>
<td>This test is indicated for:</td>
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<tr>
<td></td>
<td>• Confirmation of a clinical diagnosis of PHTS in an individual in whom sequence analysis was negative.</td>
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<tr>
<td></td>
<td>• Individuals at-risk for PHTS due to family history in whom sequence analysis was negative.</td>
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## Methodology

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

## Detection

Approximately 10% of individuals with BRRS who do not have a mutation detected in the PTEN coding sequence have large deletions within/encompassing PTEN. Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations.

Results of molecular analysis should be interpreted in the context of the patient's clinical presentation and family history.

## Specimen Requirements
Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Please submit copies of pedigree or other family history information along with the sample. Contact the laboratory if further information is needed. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition form.

**Related Tests**

- Cowden Syndrome: PTEN Gene Sequencing (OY) is required before deletion/duplication analysis.
- Prenatal Custom Diagnostics is available to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.