**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/encompassing *PTEN*. Preliminary data also suggest that up to 50% of individuals with Proteus-like syndrome and up to 20% of individuals with Proteus syndrome have *PTEN* mutations.

Germline *PTEN* mutations have been identified in individuals with autism/pervasive developmental disorder and macrocephaly, especially in the presence of other personal or family history consistent with CS/BRRS. Approximately 20% of individuals with autism spectrum disorders and macrocephaly have germline *PTEN* mutations. The 10%-20% prevalence of germline *PTEN* mutations in autism spectrum disorders with macrocephaly has now been confirmed by several independent groups.

The *PTEN* gene (10q23.3) has 9 exons. It appears that nuclear *PTEN* mediates cell cycle arrest, while cytoplasmic *PTEN* is required for phosphatase activity, the mitogen-activated protein kinase (MAPK) pathway is dysregulated, leading to abnormal cell survival. 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 uninhibited, leading to the inability to activate cell cycle arrest and/or to undergo apoptosis. In addition, through lack of protein phosphorylation, 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.

Please [click here](http://www.ThinkGenetic.com) for patient-friendly information on Cowden syndrome.

**Genes**

*PTEN*

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of PHTS or autism with macrocephaly.
- Individuals at-risk for PHTS or autism with macrocephaly due to family history.

**Methodology**

PCR amplification of 9 exons contained in the *PTEN* gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions using automated fluorescence dye-exchange sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and will not detect large deletions.

**Detection**

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/encompassing PTEN. Preliminary data also suggest that up to 50% of individuals with Proteus-like syndrome and up to 20% of individuals with Proteus syndrome have PTEN mutations. Approximately 20% of individuals with autism spectrum disorders and macrocephaly have germline PTEN mutations. Mutations in the promoter region, some mutations in the introns, other regulatory element mutations, and large deletions cannot be detected by this analysis.

Analytical Sensitivity: ~99%.

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple 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 EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Cowden Syndrome: PTEN Gene Deletion/Duplication (OW) is available for those individuals in whom sequence analysis is negative.
- Known Mutation Analysis (KM) is available to family members if mutations are identified by sequencing.
- 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.