

PTEN Hamartoma Tumor Syndrome *via* PTEN Gene Sequencing – Test #707

Brief Description of Clinical Features: PTEN Hamartoma Tumor Syndrome (PHTS) is a cluster of related clinical conditions, all caused by germline mutations in the *PTEN* tumor suppressor gene (OMIM 601728). Included in PHTS are Cowden Syndrome (CS; OMIM 158350), Bannayan-Riley-Ruvalcaba Syndrome (BRRS; OMIM 153480), Proteus (PS; OMIM 176920) and Proteus-like Syndromes, and VACTERL Association with Hydrocephalus (OMIM 276950). While each PHTS condition has its own unique pathognomonic features (see for example Blumenthal & Dennis, Eur J Hum Genet 16:1289-1300, 2008), hamartomatous overgrowth, macrocephaly and vascular malformations appear to be common to all conditions (Zhou et al. Lancet 358:210-211, 2001). A presumptive diagnosis of PHTS is typically made based on clinical symptoms, but a definitive diagnosis requires the identification of a heterozygous *PTEN* mutation. Patients with a germline mutation in *PTEN* have a 5-10 fold higher chance of developing cancer at a much earlier age (<30 y/o) than the general population (Eng, Hum Mut 22:183-198, 2003). In addition to confirming the diagnosis of PHTS, testing patients for a germline *PTEN* mutation is essential to accurately assess their risk for cancer and to make appropriate recommendations regarding prevention and treatment of malignancy.

Genetics: PHTS is inherited in an autosomal dominant manner, and *PTEN* is the only known gene to be associated with the disease. In addition to PHTS, germline mutations in *PTEN* have been identified in 16% of patients with Autism Spectrum Disorders (ASD) and macrocephaly, 12.5% of patients with adenomatous and hyperplastic polyps, and 5% of women with at least two different types of cancer (Zbuk & Eng, Nat Rev Cancer 7:35-45, 2007; Lintas & Persico, J Med Genet 46:1-8, 2009). To date, ~230 mutations have been reported for the *PTEN* gene, and most (~95%) are of the type that can be detected by DNA sequencing (Human Gene Mutation Database, www.hgmd.cf.ac.uk). The *PTEN* gene consists of 9 exons and encodes a dual lipid and protein phosphatase. Mutations have been reported throughout the coding region, and sequencing of all 9 exons is recommended (Eng, Hum Mut 22:183-198, 2003). Five mutations have also been reported within the minimal promoter about 800 bp upstream of the start codon and sequencing of this region is also recommended (Teresi et al. Am J Hum Genet 81:756-767, 2007).

Description of This Particular Test: This test involves bidirectional DNA sequencing of the *PTEN* minimal promoter region (positions -1239 to -765 relative to the start codon) and all 9 exons, plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence the promoter region alone or a single exon (Test #100) in family members of patients with a known mutation, or to confirm research results (\$190).

Reference Sequences: Genomic: NC_000010.10 mRNA: NM_000314.4 Protein: NP_000305.3

Indications for Test: Candidates for this test are patients with PHTS or Autism with macrocephaly, women presenting with multiple primary cancers, and relatives of patients with a known germline *PTEN* mutation. This test is specifically designed for heritable germline mutations and is not appropriate for the detection of somatic mutations in tumor tissue.

Sensitivity of Test: This test is predicted to detect causative mutations in ~80% of patients with CS, ~65% of patients with BRRS and ~20% of patients with PS (Eng, Hum Mutat 22:183-198, 2003).

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 3-4 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price:	Sequencing of the <i>PTEN</i> Gene:	\$ 690
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x11	83898 \$ 180	Sequencing x11 83904 \$ 280
Separation x1	83894 \$ 50	Interpretation/Report x1 83912 \$ 110

Accreditation: CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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