UAB MEDICAL GENOMICS LABORATORY

Sanger Sequencing of *PTEN* Only for Related Disorders (PTEN1)

Ordering Information

Acceptable specimen types:

- Fresh blood sample (3-6 ml EDTA; no time limitations associated with receipt)
- Saliva (OGR-575 DNA Genotek; kits are provided upon request)
- DNA (extracted from lymphocyte cells; a minimum volume of 25µL at 3µg; O.D. of 260:280nm ≥1.8; must be extracted in a CLIA or equivalent certified lab)

Turnaround time:

15 working days

Price, CPT codes, and Z code:

$1,100* (USD – institutional/self-pay);

CPT: 81321 and 81323

Z code: ZB6AH

*$800 if mutation is identified during sequencing

Candidates for this test:

Patients suspected to have *PTEN*-related disorders or who seek confirmation of a clinical diagnosis

Specimen shipping and handling:

- Please find acceptable specimen type above.

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www.uab.edu/medicine/genetics/medical-genomics-laboratory

- All submitted specimens must be sent at room temperature. DO NOT ship on ice.
- Specimens must be packaged to prevent breakage and absorbent material must be included in the package to absorb liquids in the event that breakage occurs. Also, the package must be shipped in double watertight containers (e.g. a specimen pouch + the shipping company's diagnostic envelope).
- To request a sample collection kit, please visit the website or email medgenomics@uabmc.edu to complete the specimen request form.
- Please contact the MGL (via email at medgenomics@uabmc.edu, or via phone at 205-934-5562) prior to sample shipment and provide us with the date of shipment and tracking number of the package so that we can better ensure receipt of the samples.

Required forms:

- Test Requisition Form
- Form for Customs (for international shipments)

Note: Detailed and accurate completion of this document is necessary for reporting purposes. The Medical Genomics Laboratory issues its clinical reports based on the demographic data provided by the referring institution on the lab requisition form. It is the responsibility of the referring institution to provide accurate information. If an amended report is necessary due to inaccurate or illegible documentation, additional reports will be drafted with charge.

Requests for testing may not be accepted for the following reasons:

- No label (patients full name and date of collection) on the specimens
- No referring physician's or genetic counselor's names and addresses
- No billing information
- DNA samples must be extracted in a CLIA or equivalent certified lab

For more information, test requisition forms, or sample collection and mailing kits, please call: 205-934-5562.

Disorder Background

PTEN hamartoma tumor syndrome (PHTS) includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome (PS), and Proteus-like syndrome. This group of disorders shares significant clinical overlap [Eng, 2003]. Each of these disorders is inherited in an autosomal dominant manner, and de novo mutations are common.

1. CS is a multiple hamartoma syndrome with a high risk of benign and malignant tumors of the thyroid (10%), breast (25-50%), and endometrium (10%). Most patients usually have macrocephaly and pathognomonic mucocutaneous lesions, including trichilemmomas, papillomatous papules, and acaral and plantar keratoses. Other tumors include harmartomatous polyps of the GI tract, fibrocystic disease of the breast, fibromas, cerebellar dysplastic gangliocytoma (Lhermitte-Duclos disease), skin cancers, renal cell carcinomas, uterine leiomyoma, and brain tumors as well as vascular malformations affecting any organ.

2. BRRS is characterized by macrocephaly, intestinal polyposis, lipomas, and pigmented macules of the glans penis. Other common features include developmental delay, mental retardation, hamartomatous polyps of the GI tract, a myopathic process in proximal muscles, joint hyperextensibility, pectus excavatum, and scoliosis. Individuals with BRRS who have *PTEN* gene mutations are thought to have the same cancer risks as individuals with CS.

3. PS is a complex, highly variable disorder consisting variably of disproportionate, asymmetric overgrowth of body parts; cerebriform connective tissue nevi; epidermal nevi; vascular malformations of the capillary, venous, and lymphatic types; dysregulated adipose tissue; and hyperostoses[Cohen, 2005]. Unusual tumor types have been observed, such as cystadenoma of the ovary, various types of testicular tumors, central nervous system tumors, and parotid monomporphoic adenomas. Somatic mosaicism, lethal in the nonmosaic state, is the present hypothesis for PS.

4. Proteus-like syndrome is undefined but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS.

5. Macrocephaly/Autism Syndrome is one of *PTEN*-related disorders. Autism is associated with macrocephaly in approximately 20% of cases. Several studies have shown that *PTEN* mutations can be found in a subset of individuals who present with autism and macrocephaly, with or without the presence of other features of *PTEN*-related tumor syndrome [Butler et al. 2005, Buxbaum et al. 2007, Goffin et al. 2001, Herman et al. 2007]. Therefore, *PTEN* sequence analysis may be considered as additional testing when other genetic causes of autism have been ruled out through the autism panel.

Test Description

The ***PTEN*-only by Sanger** sequencing starts with extraction of DNA from the blood sample of the patient, followed by direct sequencing of the entire coding region. MLPA analysis to detect copy number changes is performed. Mutations screened for include truncating mutations (nonsense, frameshift, splicing mutations), missense mutations, multi-exon deletions and total gene deletions.

Test sensitivity varies depending on the clinical diagnosis. The sequencing approach used by MGL will identify >99% of intragenic minor lesion mutations in the *PTEN* gene. Partial or whole gene deletions/duplications can be detected by MLPA copy number analysis.

REFERENCES available on website.