

Peutz-Jeghers Syndrome via *STK11* Gene Sequencing – Test #711

Brief Description of Clinical Features: Peutz-Jeghers Syndrome (PJS; OMIM 175200) is an autosomal dominant disorder characterized by hamartomatous polyps in the gastrointestinal tract and melanin pigmentation around the mouth, eyes, nostrils, buccal mucosa, fingers, toes and other sites. PJS patients typically present in early childhood with pigmentation or with complications of polyposis, such as intussusception, bowel obstruction and/or bleeding. Compared to the general population, patients with PJS have an increased risk of intestinal and various extra-intestinal malignancies, including breast, pancreatic, ovarian, testicular and cervical cancer; their lifetime risk is ~4 fold higher for gastrointestinal cancer and ~6 fold higher for breast cancer compared to individuals without PJS (Hearle et al. *Clin Cancer Res* 12:3209-3215, 2006). Approximately 75% of PJS cases are known to be familial while the remainder appears to be sporadic (Lim et al. *Br. J Cancer* 89:308-313, 2003).

Genetics: PJS is caused by heterozygous germline mutations in the tumor suppressor gene *STK11* (OMIM 602216). *STK11*, also called *LKB1*, consists of 9 exons and encodes a serine/threonine kinase that inhibits cellular proliferation by promoting cell-cycle arrest (Tiainen et al. *PNAS* 96:9248-9251, 1999). Second hit mutations in *STK11* ultimately lead to unfettered growth and tumorigenesis. To date, ~100 unique mutations have been described throughout the *STK11* gene (Human Gene Mutation Database, www.hgmd.cf.ac.uk). Most (80%) are truncating mutations (i.e. frameshift, nonsense, splice-site, or exonic deletions) that result in early protein termination (Hearle et al. *Clin Cancer Res* 12:3209-3215, 2006). The rest are missense or in-frame deletions. One large genomic deletion encompassing *STK11* has also been described.

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 9 exons of the *STK11* gene, plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence a single exon (Test #100) in family members of patients with a known mutation, or to confirm research results (\$190).

Reference Sequences: Genomic: NC_000019.9 mRNA: NM_000455.4 Protein: NP_000446.1 CCDS 45896.1

Indications for Test: Candidates for this test are patients with Peutz-Jeghers Syndrome. 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 ~70% of patients with PJS (Hearle et al. *Clin Cancer Res* 12:3209-3215, 2006). Of all the documented *STK11* mutations, 95% are of the type that can be detected by DNA sequencing.

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price:	Sequencing of the <i>STK11</i> Gene:	\$ 640
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x9	83898 \$ 180	Sequencing x9 83904 \$ 260
Separation x1	83894 \$ 40	Interpretation/Report x1 83912 \$ 90

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

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