

Lynch Syndrome via *MLH3* Gene Sequencing – Test #705

Brief Description of Clinical Features: Lynch Syndrome (OMIM 120435), also called Hereditary Nonpolyposis Colorectal Cancer (HNPCC), is an inherited cancer syndrome caused by germline mutations in DNA mismatch repair (MMR) genes. MMR genes are responsible for repairing small sequence errors, or mismatches, during DNA replication. Mutations in a single mismatch repair gene can cause widespread genomic instability characterized by the expansion or contraction of short tandem repeat sequences (microsatellites) (reviewed by Grady & Carethers in *Gastroenterology* 135:1079-1099, 2008). This phenomenon of microsatellite instability (MSI) leads to somatic mutations in oncogenes and/or tumor suppressor genes, including *TGFβIIIR* and *NF1* among others (Wang et al. *Hum Genet* 112:117-123, 2003). As a result, Lynch Syndrome is marked by early onset and high lifetime risk of cancer, particularly in the right colon but also in the endometrium, ovary, stomach, bile duct, kidney, bladder, ureter, and brain (Jang & Chung, *Gut and Liver* 4:151-160, 2010). Clinical hallmarks of Lynch Syndrome, as delineated by the Amsterdam criteria, include heritable colorectal (Type I) or extracolonic (Type II) cancer, present in at least three relatives over at least two consecutive generations, with an onset of cancer before the age of 50 in at least one case, and pathological MSI within tumors (Vasen et al. *Gastroenterology* 116:1453-1456, 1999).

Genetics: Lynch Syndrome is an autosomal dominant disease caused by germline mutations in one of six described MMR genes: *MLH1*, *MSH2*, *MSH6*, *MLH3*, *PMS1* and *PMS2* (Peltomaki and Vasen, *Dis Markers* 20:269-276, 2004). Mutations in *MLH1* and *MSH2* account for 80-90% of all Lynch patients and most frequently occur in families meeting the stringent Amsterdam I criteria. Mutations in *MSH6*, *MLH3*, *PMS1* and *PMS2* account for the remaining Lynch patients and are often found in families with atypical HPNCC symptoms, such as low rates of MSI and/or extracolonic carcinomas. Nineteen pathogenic variations have been reported in the *MLH3* gene (OMIM 604395); seventeen are missense mutations, and two are single nucleotide deletions within the coding sequence (Human Gene Mutation Database, www.hgmd.cf.ac.uk).

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 12 exons of the *MLH3* 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_000014.8 mRNA: NM_001040108.1 Protein: NP_001035197.1 (CCDS 32123.1)

Indications for Test: Candidates for this test are patients with Lynch Syndrome, particularly those with atypical symptoms or no detectable mutations in *MLH1* or *MSH2*, and relatives of patients with a verified *MLH3* 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: To date, a mutation in *MLH3* has not been detected in patients that meet the stringent Amsterdam I criteria, but is detected in ~9% of atypical Lynch/HNPCC families (Peltomaki et al. *Dis Markers* 20:269-276, 2004).

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 *MLH3* Gene: \$ 1210

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x24	83898 \$ 370	Sequencing x24	83904 \$ 560
Separation x1	83894 \$ 90	Interpretation/Report x1	83912 \$ 120

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

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