Lynch Syndrome (HNPCC), *MSH2* Sequencing

**Test Code:** 2032  
**Department:** Molecular Genetics  
**CPT Code(s):**  
83891  
83892 x 17  
83898 x 17  
83904 x 17  
83909 x 17

**Test Synonyms:**  
*MSH2* full gene sequencing  
Lynch Syndrome sequencing

**Background:**  
Lynch syndrome (also known as Hereditary Non-Polyposis Colon Cancer, HNPCC), is an autosomal dominant hereditary cancer syndrome that accounts for 3-5% of all colon cancers. Lynch syndrome-associated tumors are characterized by microsatellite instability (MSI) and are caused by germline mutations in any of four mismatch repair (MMR) genes (*MLH1*, *MSH6*, *MSH2*, *PMS2*). The risk of colon and gastric cancers are increased in both sexes, and women with Lynch syndrome have an increased risk for endometrial and ovarian cancers. The testing strategy for Lynch syndrome includes screening by MSI analysis followed by immunohistochemistry (IHC) testing of MMR proteins. Full gene sequencing can then be performed to identify germline mutations in the putative mutated gene(s) identified by IHC. (Please contact Client Services at (855) 535-1522 for more information regarding MSI and IHC testing). Germline mutations in *MLH1* and *MSH2* account for 90% of Lynch syndrome cases while mutations of *MSH6* and *PMS2* comprise the remaining fractions. While one study indicated that 65% of *MSH2* and 87% of *MLH1* variants were point mutations (the rest being gross deletions/duplications), comprehensive clinical sensitivity of *MSH2*, *MLH1*, and *MSH6* sequencing is unknown.

**Reasons for Referral:**  
- Identification of inherited genetic defects in MMR gene(s) in colorectal cancer patients with tumors testing positive by IHC and/or MSI  
- Confirmation of a suspected diagnosis with a positive family history of early onset colon cancer when familial mutation is known  
- Predispositional testing for asymptomatic family members with a positive family history of colorectal cancer

**Methodology:**  
Sequencing for *MSH2* is carried out by amplification of all exons and intron/exon boundaries followed by bi-directional Sanger sequencing. Full gene sequencing is expected to have a yield greater than 95% for single nucleotide substitutions and small insertions/deletions. All nucleotide changes are analyzed within the context of current databases and literature to predict pathogenicity. MMR genes may be sequenced individually or as a panel.

**Specimen Requirements:**  
- **Blood:** EDTA or ACD (Solution A or B):  
  - Adult: 5 mL  
  - Child: 5 mL  
  - Infant: 2-3 mL

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Q11-TSD-100.01
A REQUISITION FORM MUST ACCOMPANY ALL SAMPLES. Please include detailed clinical information, including ethnicity, clinical history, and family history.

Test Performed (Days):
Weekly

Turn Around Time:
14 – 21 days

Shipment Sensitivity Requirements:
Package and ship specimen to remain cold, but not frozen. Ship via overnight express, using the FedEx priority overnight label provided. Contact Client Services for shipping kits and instructions at (855) 535-1522.

References: