Lynch Syndrome: PMS2 Gene Sequencing

**Condition Description**

Lynch syndrome, caused by a germline mutation in a mismatch repair gene or associated with tumors exhibiting MSI, is characterized by an increased risk of colon cancer and other cancers (e.g., of the endometrium, ovary, stomach, small intestine, hepatobiliary tract, upper urinary tract, brain, skin). Individuals with Lynch syndrome have an approximately 80% lifetime risk for colon cancer. The average age of colorectal cancer diagnosis is 61 years. Women with Lynch syndrome have a 20%-60% lifetime risk of endometrial cancer. The average age of diagnosis of endometrial cancer is age 46-62 years. Among women with Lynch syndrome who develop both colon cancer and endometrial cancer, approximately 50% present first with endometrial cancer. In Lynch syndrome, the mean age of diagnosis of gastric cancer is age 56 years, with intestinal-type adenocarcinoma being the most commonly reported pathology. Lynch syndrome-associated ovarian cancers have a mean age of diagnosis of 42.5 years; approximately 30% are diagnosed before age 40 years.

The diagnosis of Lynch syndrome can be made on the basis of the Amsterdam Clinical Criteria or by molecular genetic testing for germline mutations in one of several mismatch repair (MMR) genes. The Amsterdam Criteria, first established in 1990 for research purposes, were later modified to include the other Lynch syndrome-related cancers for clinical diagnostic purposes. The Amsterdam Criteria are 1) Three or more family members, one of whom is a first-degree relative of the other two, with a confirmed diagnosis of colorectal cancer 2) Two successive affected generations 3) One or more colorectal cancers diagnosed before age 50 years. The modified Amsterdam Criteria replace "colorectal cancer" with "any Lynch syndrome-related cancers." The sensitivity and specificity of the Amsterdam Criteria for identifying a mutation in the mismatch repair genes MSH2 and MLH1 have been reported to be 61% and 67%, respectively. The sensitivity is increased to 78% using the modified Amsterdam Criteria. However, broadening the criteria decreases the specificity.

Lynch syndrome is known to be associated with mutations in four genes involved in the mismatch repair pathway (MLH1, MSH2, MSH6, and PMS2). Germline mutations in MLH1 and MSH2 account for approximately 90% of detected mutations in families with Lynch syndrome. Mutations in MSH6 have been reported in approximately 7%-10% of families with Lynch syndrome. Mutations in PMS2 account for fewer than 5% of mutations in families with Lynch syndrome. Up to 39% of families with mutations in a Lynch syndrome gene do not meet the Amsterdam Criteria. Therefore, families found to have a deleterious mutation in a Lynch syndrome gene should be considered to have Lynch syndrome regardless of the extent of the family history. At least 20% of mutations in MSH2 and 5% of mutations in MLH1 are large deletions or genetic rearrangements.

Lynch syndrome is inherited in an autosomal dominant manner. The majority of individuals diagnosed with Lynch syndrome have inherited the condition from a parent. However, because of incomplete penetrance, variable age of cancer development, cancer risk reduction as a result of screening or prophylactic surgery, or early death, not all individuals with a Lynch syndrome gene mutation have a parent who had cancer.

**Indications**

This test is indicated for:
- Confirmation of a clinical diagnosis of Lynch Syndrome
- Mutation identification after immunohistochemistry analysis positive for loss of PMS2
- Individuals at-risk for Lynch Syndrome due to family history

**Methodology**

Long template PCR amplification is used to isolate the coding gene from genomic DNA, followed by nested PCR. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variants of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

**Detection**

Clinical Sensitivity: Mutations in PMS2 account for fewer than 5% of mutations in families with Lynch syndrome. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

**Specimen Requirements**

*Submit only 1 of the following specimen types*

**Type:** DNA, Isolated

**Specimen Requirements:**
Microtainer
8µg
Isolation using the Perkin Elmer™Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

**Type: Whole Blood (EDTA)**

**Specimen Requirements:**
EDTA (Purple Top)
Infants and Young Children (2 years of age to 10 years old): 3-5 ml
Older Children & Adults: 5-10 ml
Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 24 hours of collection. Do not refrigerate or freeze.

**Type: Saliva**

**Specimen Requirements:**
Oragene™ Saliva Collection Kit
Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

**Specimen Collection and Shipping:**
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

**Special Instructions**
Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

**Related Tests**
- Sequencing of all four Lynch syndrome genes is also available as a panel test.
- Microsatellite instability testing is available.
- Immunohistochemistry for MLH1, MSH2, MSH6, and PMS2 proteins is available, either in a panel or individually.
  - Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to adults who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.