Lynch Syndrome: *EPCAM* Gene Deletion/Duplication

**Test Code:** DEPCA  
**Turnaround time:** 2 weeks  
**CPT Codes:** 81403 x1

### Condition Description

Deletions of the 3’ end of the *EPCAM* gene (2q21) (also known as the TACSTD1 gene) cause Lynch syndrome by methylating and inactivating the *MSH2* gene. Kovacs et al. (2009) identified deletions of the *EPCAM* gene in five of 27 families tested that did not have a mutation in the *MLH1* or *MSH2* genes. The phenotype of individuals with deletions of the *EPCAM* gene differs slightly from the classic Lynch syndrome phenotype. These individuals tend to be diagnosed with colorectal cancer only. The age at disease onset (25-63 years) is similar to those with mutations of the *MSH2* gene.

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 an Lynch syndrome gene do not meet the Amsterdam Criteria. Therefore, families found to have a deleterious mutation in an 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.


**References:**

- GeneReviews  
- OMIM #185535: EPCAM gene  
- OMIM #120435: Lynch syndrome

### Genes

**EPCAM**

### Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of Lynch syndrome.  
- Individuals at-risk for Lynch syndrome due to family history.

### Methodology

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient’s phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

### Detection

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Kovacs et al. (2009) identified deletions of the EPCAM gene in five of 27 families tested that did not have a mutation in the MLH1 or MSH2 genes. Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

Related Tests

- Sequence analysis of the MLH1, MSH2, MSH6, and PMS2 genes is available as a panel or individually.
- Deletion/duplication analysis of the MLH1, MSH2, and MSH6 genes is available as a panel or individually for those individuals in whom sequence analysis is negative.
- Immunohistochemistry for the MLH1, MSH2, MSH6, and PMS2 proteins is available individually.
- Microsatellite instability testing is available and is recommended before immunohistochemistry.