Overview

Useful For
Evaluation of tumor tissue to identify patients at risk for having hereditary nonpolyposis colon cancer/Lynch syndrome

Additional Tests

<table>
<thead>
<tr>
<th>Test ID</th>
<th>Reporting Name</th>
<th>Available Separately</th>
<th>Always Performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSH2I</td>
<td>MSH-2, Immunostain</td>
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<tr>
<td>MSH6I</td>
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<td>PMS2I</td>
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<td>MLH1I</td>
<td>MLH-1, Immunostain</td>
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</tbody>
</table>

Testing Algorithm
When this test is ordered, MLH1, MSH2, MSH6, and PMS2 stains will always be performed at an additional charge.

See Lynch Syndrome Testing Algorithm in Special Instructions.

Special Instructions
- Molecular Genetics: Inherited Cancer Syndromes Patient Information
- Lynch Syndrome Testing Algorithm

Method Name
Immunohistochemical Staining

NY State Available
Yes

Specimen

Specimen Type
Varies

Specimen Required
Tumor tissue is required.

Specimen Type: Tissue block and slide

Collection Instructions:
1. Submit formalin-fixed, paraffin-embedded tissue block (preferred) or 1 slide stained with hematoxylin and eosin and 10 unstained, nonbaked slides (5-micron thick sections) of the tumor tissue.

2. Sections should contain tumor tissue.
**Forms**

1. **Molecular Genetics: Inherited Cancer Syndromes Patient Information** (T519) in Special Instructions

2. If not ordering electronically, complete, print, and send an **Oncology Test Request** (T729) with the specimen.

**Reject Due To**

| Other                  | Specimens that have been decalcified (all methods); specimens that have not been formalin-fixed, paraffin-embedded; bone marrow in EDTA |

**Specimen Stability Information**

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Temperature</th>
<th>Time</th>
<th>Special Container</th>
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<tbody>
<tr>
<td>Varies</td>
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<tr>
<td></td>
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<tr>
<td></td>
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**Clinical and Interpretive**

**Clinical Information**

Hereditary nonpolyposis colon cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant inherited cancer syndrome that predisposes individuals to the development of colorectal, endometrial, gastric, upper urinary tract, and other cancers. Individuals with HNPCC/Lynch syndrome have a germline mutation in 1 of several genes involved in DNA mismatch repair. The majority of mutations associated with HNPCC/Lynch syndrome occur in **MSH2** and **MLH1**; however, mutations in **MSH6** and **PMS2** have also been identified.

There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of HNPCC/Lynch syndrome. Typically, the first step is to evaluate tumors for the characteristics common to individuals with HNPCC/Lynch syndrome, which include microsatellite instability (presence of numerous alterations in a type of repetitive DNA called microsatellites) and loss of protein expression of 1 or more of the genes associated with HNPCC/Lynch syndrome.

Microsatellite instability (MSI) and immunohistochemistry (IHC) are commonly interpreted together to evaluate risk for HNPCC/Lynch syndrome. High levels of MSI within a tumor are suggestive of defective DNA mismatch repair, however, this finding does not provide information about which gene is involved. IHC is a complementary testing strategy used to evaluate the expression of the MLH1, MSH2, MSH6, and PMS2 proteins in HNPCC/Lynch syndrome-related cancers. Loss of expression of 1 or more of these proteins within the tumor is helpful in identifying which corresponding genes to target for mutation analysis. Although MSI and IHC are best interpreted together, they are also available separately to accommodate clinical situations in which there are barriers to performing these tests concurrently (eg, financial concerns, specimen requirements).

IHC alone can determine retention or loss of MLH1, MSH2, MSH6, and PMS2 protein expression. If all 4 proteins are present, the likelihood of HNPCC/Lynch syndrome is reduced, but not eliminated, because approximately 5% of
tumors that display MSI also have normal protein expression for these 4 genes. Loss of 1 or more proteins by IHC is suggestive of defective DNA mismatch repair within the tumor and the likelihood of HNPCC/Lynch syndrome is increased. Germline testing (ie, mutation analysis) for the corresponding genes can then be performed to identify the causative germline mutation and allow for predictive testing of at risk individuals.

Of note, loss of protein expression by IHC has also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical HNPCC/Lynch syndrome families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and germline mutations. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these 2 possibilities. In addition, when absence of MLH1 and PMS2 are observed, the BRMLH / MLH1 Hypermethylation and BRAF Mutation Analysis, Tumor or ML1HM / MLH1 Hypermethylation Analysis, Tumor test may also help to distinguish between a sporadic and germline etiology. It should be noted that this is not a genetic test, but rather stratifies the risk of having an inherited cancer predisposition syndrome, and identifies patients who might benefit from subsequent genetic testing.

See Lynch Syndrome Testing Algorithm in Special Instructions for additional information.

Reference Values
An interpretive report will be provided.

Interpretation
An interpretive report will be provided.

Cautions
The finding of absent protein expression for 1 or more of the MMR genes tested does not distinguish between somatic and germline mutations.

Because immunohistochemistry (IHC) results may indicate likelihood of a germline alteration, it is recommended that genetic counseling be provided prior to IHC testing.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors may occur in our interpretation of results if information given to us is inaccurate or incomplete.

Supportive Data
Over 1,000 patients who have colorectal cancer have been evaluated for these genetic alterations by our laboratory staff (1/2006).

Clinical Reference


Performance

Method Description
Immunohistochemistry staining is used to determine the presence or absence of protein expression for MLH1, MSH2, MSH6, and PMS2. Lymphocytes and normal epithelium exhibit strong nuclear staining and serve as positive

PDF Report
No

Day(s) Performed
Monday through Friday

Report Available
5 to 8 days

Specimen Retention Time
Unused portions of blocks will be returned. Unused slides are stored indefinitely.

Performing Laboratory Location
Rochester

Fees and Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information
MLH-1, Immunostain
88341 (if appropriate)

MSH-2, Immunostain
88341 (if appropriate)

MSH-6, Immunostain
88341 (if appropriate)

PMS-2, Immunostain
88342 (if appropriate)

LOINC® Information
## Test Definition: IHC
MMR Protein, IHC Only, Tumor

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