Overview

Useful For
Evaluation through comparison of both tumor and normal tissue to identify patients at high risk for having hereditary nonpolyposis colorectal cancer (HNPCC)/Lynch syndrome

Evaluation through comparison of both tumor and normal tissue for clinical decision-making purposes given the prognostic implications associated with MSI phenotypes

Genetics Test Information
Only microsatellite instability (MSI) testing is performed.

Additional Tests

<table>
<thead>
<tr>
<th>Test ID</th>
<th>Reporting Name</th>
<th>Available Separately</th>
<th>Always Performed</th>
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<tbody>
<tr>
<td>SLIRV</td>
<td>Slide Review in MG</td>
<td>No, (Bill Only)</td>
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Testing Algorithm
When this test is ordered, slide review 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
A polymerase chain reaction (PCR)-based assay is used to test for tumor microsatellite instability with the use of 5 mononucleotide repeats.

NY State Available
Yes

Specimen

Specimen Type
Varies

Shipping Instructions
Ambient specimen preferred to arrive within 96 hours of draw.

Necessary Information
Pathology report must accompany specimen in order for testing to be performed.

Specimen Required
This test cannot be used to assess tumor tissue unless both tumor and normal tissue are submitted.
If sending multiple blocks, identify individual blocks as normal or tumor.

Paraffin-embedded tissue blocks that have been decalcified are generally unsuccessful and not validated for testing. **If a decalcified specimen is submitted (regardless of decal solution), testing will be canceled.**

**Specimen Type:** Tumor tissue block, formalin-fixed, paraffin-embedded (FFPE) prepared cell block unstained slides

**Specimen Volume:** Approximately 1 cm(2) of tumor is required. This can be 1 cm(2) in aggregate (eg, 5 unstained slides each containing with 0.2 cm(2) of tumor and normal tissue).

**Collection Instructions:**

1. Submit formalin-fixed, paraffin-embedded tissue block with corresponding hematoxylin and eosin (H and E) slides (preferred) or 1 slide stained with H and E and 10 unstained, nonbaked slides (5-micrometer thick sections) of the tumor tissue.

2. Label specimen as Tumor.

**Specimen Type:** Normal tissue block or slide

**Specimen Volume:** Approximately 1 cm(2) of normal tissue is required. This can be 1 cm(2) in aggregate (eg, 5 unstained slides each with 0.2 cm(2) of normal tissue)

**Collection Instructions:**

1. Submit formalin-fixed, paraffin-embedded tissue block with corresponding hematoxylin and eosin (H and E) slides (preferred) or 1 slide stained with H and E and 10 unstained, nonbaked slides (5-micrometer thick sections) of the normal tissue.

2. Label specimen as Normal.

**Additional Information:**

1. Normal tissue does not have to be from the same specimen or tissue source as the tumor specimen submitted for testing. Any normal tissue block, with the exception of tissues composed primarily of adipose tissue, may be submitted. Specimens composed primarily of adipose tissue would not yield a sufficient amount of DNA and if submitted, testing will be canceled.

2. If normal tissue in a formalin-fixed, paraffin-embedded tissue block is not available, whole blood may be submitted instead (see below). A separate FFPE-tumor block is still required for testing if sending in a whole blood specimen for normal.

**Specimen Type:** Normal whole blood (if normal tissue block is not available)

**Container/Tube:** Lavender-top (EDTA) or yellow-top (ACD)

**Acceptable:** Any anticoagulant
Specimen Volume: 3 mL

Collection Instructions:
1. Invert several times to mix blood.
2. Send specimen in original tube.
3. Label specimen as Normal.

Forms
1. Molecular Genetics: Inherited Cancer Syndromes Patient Information (T519) in Special Instructions
2. If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:
   - Oncology Test Request (T729)
   - Gastroenterology and Hepatology Client Test Request (T728)

Reject Due To

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<td>Icterus</td>
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<td>Other</td>
<td>Decalcified specimens, low tumor percentage, insufficient amount of tumor, insufficient amount of normal, adipose tissue, nonformalin fixed, fresh tissue, cytology smears</td>
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Specimen Stability Information

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Clinical and Interpretive

Clinical Information

Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3-prime end of the EPCAM gene have also been associated with HNPCC/Lynch syndrome, as this leads to inactivation of the MSH2 promoter.

Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks
associated with mutations in the other Lynch syndrome related genes and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are less than 15%. Of the 4 mismatch repair genes, mutations within the \textit{PMS2} gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum.

Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of bi-allelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer.

There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of HNPCC/Lynch syndrome. Tumors from individuals with HNPCC/Lynch syndrome demonstrate microsatellite instability (MSI), characterized by numerous alterations in a type of repetitive DNA called microsatellites. Two distinct MSI tumor phenotypes have been described: MSI-H (instability in >30% of microsatellites examined) and MSS/MSI-L (instability in <30% of microsatellites examined). The MSI-H phenotype is associated with germline defects in the \textit{MLH1}, \textit{MSH2}, \textit{MSH6}, or \textit{PMS2} genes, and is the primary phenotype observed in tumors from patients with HNPCC/Lynch syndrome. Immunohistochemistry (IHC) is a complementary testing strategy to MSI testing. Most MSI-H tumors show a loss of protein expression for at least 1 of the 4 mismatch repair genes described above. Loss of expression of 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).

Testing is typically first performed on the tumor of an affected individual and in the context of other risk factors, such as young age at diagnosis or a strong family history of colon cancer or other HNPCC/Lynch syndrome-related cancers. If defective DNA mismatch repair is identified within the tumor, mutation analysis of the associated gene can be performed to identify the causative germline mutation and allow for predictive testing of at-risk individuals.

Of note, MSI-H phenotypes and loss of protein expression by IHC have 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/PMS2 is observed, the BRMLH / \textit{MLH1} Hypermethylation and \textit{BRAF} Mutation Analysis, Tumor or ML1HM / \textit{MLH1} Hypermethylation Analysis, Tumor test may also help to distinguish between a sporadic and germline etiology.

It should be noted that MSI testing is not a genetic test, but rather helps to stratify the risk of having an inherited cancer predisposition syndrome, and identifies patients who might benefit from subsequent genetic testing.

Immunohistochemistry is available as an add-on to this test (IHC / Mismatch Repair [MMR] Protein Immunohistochemistry Only, Tumor). See Lynch Syndrome Testing Algorithm in Special Instructions for additional information.

Evaluation for MSI may also be valuable for clinical decision making. Colon cancers that demonstrate defective DNA mismatch repair (MSI-H) have a significantly better prognosis compared to those with intact mismatch repair
Test Definition: MSI
Microsatellite Instability, Tumor

(MSS/MSI-L). Additionally, current data indicate that stage II and stage III patients with colon cancers characterized by the presence of defective MMR (MSI-H) may not benefit from treatment with fluorouracil (5-FU) alone or in combination with leucovorin (LV). These findings are most likely to impact the management of patients with stage II disease.

Reference Values
An interpretive report will be provided.

Interpretation
The report will include specimen information, assay information, and interpretation of test results. Microsatellite stable (MSS) is reported as MSS/MSI-L (0 or 1 of 5 markers demonstrating instability) or MSI-H (2 or more of 5 markers demonstrating instability).

Cautions
The finding of tumor microsatellite instability does not distinguish between somatic and germline mutations.

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

Supportive Data
Over 1,000 patients who have colon cancer have been evaluated for these genetic alterations.(1/2006)

Clinical Reference

Performance
Method Description

PDF Report
No
Test Definition: MSI
Microsatellite Instability, Tumor

Day(s) and Time(s) Test Performed
Monday, Wednesday; 2 p.m.

Analytic Time
10 days

Maximum Laboratory Time
13 days

Specimen Retention Time
Extracted DNA: 3 months

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
81301-Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed

88381-Microdissection, manual

LOINC® Information

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Test Definition: MSI
Microsatellite Instability, Tumor