Test Definition: MSI

Microsatellite Instability, Tumor

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

Test ID	Reporting Name	Available Separately	Always Performed
SLIRV	Slide Review in MG	No, (Bill Only)	Yes

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

Other	Decalcified specimens, low tumor percentage, insufficient amount of tumor, insufficient amount of normal, adipose tissue, nonformalin fixed, fresh tissue, cytology smears

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Frozen		
	Refrigerated		

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 *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 *MLH1*, *MSH2*, *MSH6*, or *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 / *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 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 (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

1. Baudhuin LM, Burgart LJ, Lentovich O, Thibodeau SN: Use of microsatellite instability and immunohistochemistry testing for the identification of individuals at risk for Lynch Syndrome. Fam Cancer 2005;4(3):255-265

2. Terdiman JP, Gum JR Jr, Conrad PG, et al: Efficient detection of hereditary nonpolyposis colorectal cancer gene carriers by screening for tumor microsatellite instability before germline genetic testing. Gastroenterology 2001 January;120(1):21-30

3. Popat S, Hubner R, Houlston RS: Systematic review of microsatellite instability and colorectal cancer prognosis. JCO 2005 23(3):609-618

4. Ribic CM, Sargent DJ, Moore MJ, et al: Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N Engl J Med 2003 349:247-257

5. Kohlmann W, Gruber SB: Lynch Syndrome. In GeneReviews. Updated 2014 May 22. Edited by RA Pagon, MP Adam, HH Ardinger, et al: Seattle WA. University of Washington, Seattle; 1993-2014. Available at www.ncbi.nlm.nih.gov/books/NBK1211/

Performance

Method Description

A PCR-based assay using capillary electrophoresis is used to test the tumor for microsatellite instability with the use of 5 mononucleotide repeats (BAT25, BAT26, NR-21, NR-24 and MONO-27).(Package insert: Promega MSI Analysis Kit; Bacher JW, Flanagan LA, Smalley RL, et al: Development of a fluorescent multiplex assay for detection of MSI-High tumors. Dis Markers 2004;20:237-250)

PDF Report

No

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

Test ID	Test Order Name	Order LOINC Value
MSI	Microsatellite Instability, Tumor	43368-0

Result ID	Test Result Name	Result LOINC Value
53306	Result Summary	50397-9
53307	Result	43368-0
53308	Interpretation	69047-9
53309	Specimen	31208-2
53310	Source	31208-2
54448	Tissue ID	80398-1
53311	Released By	18771-6