MAYO CLINIC LABORATORIES

Test Definition: IHC

Mismatch Repair (MMR) Protein Immunohistochemistry Only, Tumor

Overview

Useful For

Evaluating tumor tissue to identify patients at risk for having hereditary nonpolyposis colon cancer/Lynch syndrome

Additional Tests

Test Id	Reporting Name	Available Separately	Always Performed
MLH1I	MLH-1, Immunostain	No, (Bill only)	Yes
MSH2I	MSH-2, Immunostain	No, (Bill only)	Yes
MSH6I	MSH-6, Immunostain	No, (Bill only)	Yes
PMS2I	PMS-2, Immunostain	No, (Bill only)	Yes

Testing Algorithm

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

For more information see Lynch Syndrome Testing Algorithm.

Special Instructions

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

Method Name

Immunohistochemistry (IHC)

NY State Available

Yes

Specimen

Specimen Type

Varies

Necessary Information

Pathology report (final or preliminary), at minimum containing the following information, **must accompany specimen for testing to be performed:**

1. Patient name
2. Block number-must be on all blocks, slides, and paperwork (can be handwritten on the paperwork)
3. Tissue collection date

4. Source of the tissue

Specimen Required

Tumor tissue is required.

Preferred: Submit both of the following specimens.
Acceptable: Submit **at least one** of the following specimens.

Specimen Type: Tissue block
Collection Instructions: Submit a formalin-fixed, paraffin-embedded tissue block with acceptable amount of tumor tissue.

Specimen Type: Tissue slide
Slides: 1 Hematoxylin and eosin-stained and 10 unstained
Collection Instructions:
Submit the followings slides:
1 Slide stained with hematoxylin and eosin
AND
10 Unstained, nonbaked slides with 5-micron thick sections of the tumor tissue.
Note: The total amount of required tumor nuclei can be obtained by scraping up to 10 slides from the same block.
Additional Information: Hematoxylin and eosin-stained and unstained slides will not be returned.

Forms

1. Molecular Genetics: Inherited Cancer Syndromes Patient Information (T519)
2. If not ordering electronically, complete, print, and send an Oncology Test Request (T729) with the specimen.

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

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

Clinical & 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).

Immunohistochemistry 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.

For more information see Lynch Syndrome Testing Algorithm.

Reference Values
An interpretive report will be provided.

Interpretation
The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Cautions
The finding of absent protein expression for 1 or more of the mismatch repair genes tested does not distinguish

between somatic variants 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 1000 patients who have colorectal cancer have been evaluated for these genetic alterations by our laboratory staff (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. doi:10.1007/s10689-004-1447-6
2. Shia J, Klimstra DS, Nafa K, et al. Value of immunohistochemical detection of DNA mismatch repair proteins in predicting germline mutation in hereditary colorectal neoplasms. Am J Surg Pathol. 2005;29(1):96-104
3. Idos G, Valle L. Lynch syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews (Internet). University of Washington, Seattle; 2004. Updated February 2, 2021. Accessed July 16, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1211/

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 internal controls for staining of these proteins.(Cunningham JM, Kim CY, Christensen ER, et al. The frequency of hereditary defective mismatch repair in a prospective series of unselected colorectal carcinomas. Am J Hum Genet. 2001;69[4]:780-790; Gill S, Lindor NM, Burgart LJ, et al. Isolated loss of PMS2 expression in colorectal cancers: frequency, patient age, and familial aggregation. Clin Cancer Res. 2005;11[18]:6466-6471)

PDF Report
No

Day(s) Performed
Varies

Report Available
5 to 8 days

Specimen Retention Time
Tissue blocks: Unused portions of blocks will be returned; Tissue slides: Hematoxylin and eosin-stained and unstained

slides will not be returned. Unused slides are stored for at least 5 years.

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

Fees & 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 account representative. 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. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

88341 MLH1, MLH2, or MLH6 (if appropriate)
88342 PMS2 (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
IHC	MMR Protein, IHC Only, Tumor	In Process

Result ID	Test Result Name	Result LOINC® Value
53258	Result Summary	50397-9
53259	Result	In Process
54443	Interpretation	59465-5
53260	Specimen	31208-2
53261	Source	31208-2
54444	Tissue ID	80398-1
53262	MLH1 IHC	81691-8
53263	MSH2 IHC	81692-6
53264	MSH6 IHC	81693-4
53265	PMS2 IHC	81694-2
53266	Released By	18771-6