MAYO CLINIC LABORATORIES

Test Definition: PMS2

PMS2 Immunostain, Technical Component Only

Overview

Useful For

Identifying patients at high risk for having hereditary nonpolyposis colorectal cancer, also known as Lynch syndrome, in an immunopanel including PMS2 and other mismatch repair markers

Evaluation of tumor tissue to identify patients at risk for having hereditary endometrial carcinoma in an immunopanel including PMS2 and other mismatch repair markers

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
IHTOI	IHC Initial, Tech Only	No	No
IHTOA	IHC Additional, Tech Only	No	No

Testing Algorithm

For the initial technical component only immunohistochemical (IHC) stain performed, the appropriate bill-only test ID will be reflexed and charged (IHTOI). For each additional technical component only IHC stain performed, an additional bill-only test ID will be reflexed and charged (IHTOA).

Method Name

Immunohistochemistry (IHC)

NY State Available

Yes

Specimen

Specimen Type

TECHONLY

Ordering Guidance

This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required, order PATHC / Pathology Consultation.

Shipping Instructions

Attach the green "Attention Pathology" address label (T498) and the pink Immunostain Technical Only label included in the kit to the outside of the transport container.

Necessary Information

If sending normal and tumor blocks; indicate the block number to be stained in performing lab notes (electronic orders) or on the enclosed paperwork (manual orders).

Specimen Required

Supplies: Immunostain Technical Only Envelope (T693)
Specimen Type: Tissue
Container/Tube: Immunostain Technical Only Envelope
Preferred: 2 Unstained positively charged glass slides (25- x 75- x 1-mm) per test ordered; sections 4-microns thick
Acceptable: Formalin-fixed, paraffin-embedded tissue block

Digital Image Access

1. Information on accessing digital images of immunohistochemical (IHC) stains and the manual requisition form can be accessed through this website: https://news.mayocliniclabs.com/pathology/digital-imaging/
2. Clients ordering stains using a manual requisition form will not have access to digital images.
3. Clients wishing to access digital images must place the order for IHC stains electronically. Information regarding digital imaging can be accessed through this website: https://news.mayocliniclabs.com/pathology/digital-imaging/#section3

Forms

If not ordering electronically, complete, print, and send a Immunohistochemical (IHC)/In Situ Hybridization (ISH) Stains Request (T763) with the specimen.

Reject Due To

Wet/frozen tissue Cytology smears Nonformalin fixed tissue Nonparaffin embedded tissue Noncharged slides ProbeOn slides	Reject

Specimen Stability Information

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

Clinical & Interpretive

Clinical Information

Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant hereditary cancer syndrome associated with germline variants in the mismatch repair genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2*.

HNPCC 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* variants (approximately 50%-80%) is generally higher than the risks associated with variants in the other HNPCC-related genes and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include sebaceous neoplasms, 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, variants within the *PMS2* gene confer the lowest risk for any of the tumors within the HNPCC spectrum.

Several clinical variants of HNPCC have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair variants (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 or compound heterozygous mismatch repair alterations, characterized by the presence of biallelic deleterious alterations 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 with a personal or family history of cancer suggestive of HNPCC. Testing tumors from individuals at risk for HNPCC for microsatellite instability (MSI) indicates the presence or absence of defective DNA mismatch repair phenotype within the tumor but does not suggest in which gene the abnormality rests. Tumors from individuals affected by HNPCC usually demonstrate an MSI-H phenotype (MSI >30% of microsatellites examined). The MSI-H phenotype can also be seen in individuals whose tumors have somatic *MLH1* promoter hypermethylation. Tumors from individuals that show the MSS/MSI-L phenotype (MSI at <30% of microsatellites examined), are not likely to have HNPCC or somatic hypermethylation of *MLH1*. Immunohistochemistry (IHC) is a complementary testing strategy to MSI testing. In addition to identifying tumors with defective DNA mismatch repair, IHC analysis is helpful for identifying the gene responsible for the defective DNA mismatch repair within the tumor, because the majority of MSI-H tumors show a loss of expression of at least 1 of the 4 mismatch repair genes described above.

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 HNPCC-related cancers. If defective DNA mismatch repair is identified within the tumor, variant analysis of the associated gene can be performed to identify the causative germline variant 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 families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and germline alterations. 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, BRMLH / *MLH1* Hypermethylation and *BRAF* Mutation Analysis, Tumor or ML1HM / *MLH1* Hypermethylation Analysis, Tumor may also help to distinguish between a sporadic and germline etiology.

It should be noted that this HNPCC screen 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.

Interpretation

This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case.

The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404.

Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Cautions

Age of a cut paraffin section can affect immunoreactivity. Stability thresholds vary widely among published literature and are antigen dependent. Best practice is for paraffin sections to be cut within 6 weeks.

Clinical Reference

1. Burgart LJ. Testing for defective DNA mismatch repair in colorectal carcinoma: a practical guide. Arch Pathol Lab Med. 2005;129(11):1385-1389
2. Klarskov L, Ladelund S, Holck S, et al. Interobserver variability in the evaluation of mismatch repair protein immunostaining. Hum Pathol. 2010;41(10):1387-1396
3. Lanza G, Gafa R, Maestri I, Santini A, Matteuzzi M, Cavazzini L. Immunohistochemical pattern of MLH1/MSH2 expression is related to clinical and pathological features in colorectal adenocarcinomas with microsatellite instability. Mod Pathol. 2002;15(7):741-749
4. Modica I, Soslow RA, Black D, Tornos C, Kauff N, Shia J. Utility of immunohistochemistry in predicting microsatellite instability in endometrial carcinoma. Am J Surg Pathol. 2007;31(5):744-751
5. Mojtahed A, Schrijver I, Ford JM, Longacre TA, Pai RK. A two-antibody mismatch repair protein immunohistochemistry screening approach for colorectal carcinomas, skin sebaceous tumors, and gynecologic tract carcinomas. Mod Pathol. 2011;24(7):1004-1014
6. Rigau V, Sebbagh N, Olschwang S, et al. Microsatellite instability in colorectal carcinoma. The comparison of immunohistochemistry and molecular biology suggests a role for hMSH6 [correction of hMLH6] immunostaining. Arch Pathol Lab Med. 2003;127(6):694-700
7. Shia J. Immunohistochemistry versus microsatellite instability testing for screening colorectal cancer patients at risk for hereditary nonpolyposis colorectal cancer syndrome. Part I. The utility of immunohistochemistry. J Mol Diagn. 2008;10(4):293-300
8. Salem ME, Bodor JN, Puccini A, et al. Relationship between MLH1, PMS2, MSH2 and MSH6 gene-specific alterations and tumor mutational burden in 1057 microsatellite instability-high solid tumors. Int J Cancer. 2020;147(10):2948-2956. doi:10.1002/ijc.33115
9. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

Performance

Method Description
Immunohistochemistry on sections of paraffin-embedded tissue.(Unpublished Mayo method)

PDF Report
No

Day(s) Performed
Monday through Friday

Report Available
1 to 3 days

Specimen Retention Time
Until staining is complete.

Performing Laboratory Location
Rochester

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 using an analyte specific reagent. Its performance characteristics were determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
88342-TC, primary
88341-TC, if additional IHC

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
PMS2	PMS2 IHC, Tech Only	Order only;no result

Test Definition: PMS2

PMS2 Immunostain, Technical Component Only

Result ID	Test Result Name	Result LOINC® Value
70852	PMS2 IHC, Tech Only	Bill only; no result