

FLETCHER ALLEN HEALTH CARE

PATHOLOGY & LABORATORY MEDICINE

TEST UPDATE: COLORECTAL CANCER TESTING FOR LYNCH SYNDROME

Test Name: Mismatch repair protein immunohistochemistry for screening patients with colorectal cancers for Lynch Syndrome

Assay Information: Since March 15, 2010, the Surgical Pathology Laboratory has been offering mismatch repair protein (MLH1, MSH2, PMS2 and MSH6) immunohistochemistry on colorectal adenocarcinomas. This testing is useful for identifying patients with an autosomal dominant inherited cancer syndrome (Lynch Syndrome) who might benefit from subsequent genetic testing.

For colon cancers that are diagnosed at Fletcher Allen Health Care, mismatch repair protein immunohistochemistry screening will be performed at the written request of the provider after the provider obtains written informed consent from the patient. If the stains show loss of MLH1, reflex testing for BRAF mutation analysis will be performed. As with any reflex testing, you may decline this testing if you believe that it is not medically necessary. This testing is also available for colon cancers diagnosed at other institutions.

If you have any questions regarding this testing, please contact Dr. Anita Iyer at the laboratory (847-2469) or by email (anita.iyer@vtmednet.org)

Clinical Application: Lynch Syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is the most common hereditary colon cancer syndrome, accounting for 3-6% of the total colorectal cancer burden. Microsatellite instability (MSI) is the hallmark of HNPCC. According to the international criteria for HNPCC diagnostics, cancer patients with a family history *or* early onset of colorectal tumors *or* tumors with specific histologic features showing high MSI (MSI-H) should receive genetic counseling and be offered testing for germline mutations in DNA repair genes. Patients with the MSI-H phenotype have germline mutation in one of the several DNA mismatch repair genes (e.g., MLH1, MSH2, PMS2, or MSH6). Therefore, to screen for MSI in a patient's colon cancer, we will look at mismatch repair protein expression in the tumor compared to that in the adjacent normal epithelium. Additional testing for BRAF mutation will be performed by Mayo Medical Laboratories if there is loss of MLH1 protein expression, unless this additional reflex testing is declined.

Method: Immunohistochemical staining (IHC) is used to determine the presence or absence of protein expression for MLH1, MSH2, PMS2, and MSH6. Lymphocytes and normal epithelium exhibit strong nuclear staining and serve as positive internal controls for staining of these proteins.^{1,2}

Limitations: The finding of absent protein expression for one or more of the mismatch repair genes tested does not distinguish between somatic and germline mutations.

Because IHC results may indicate likelihood of a germline alteration, it is recommended that genetic counseling be provided to patients whose tumors exhibit features that raise the possibility of hereditary forms of colon cancer.

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

Medical genetic consultation should also be considered in complex cases or when the diagnosis is atypical or uncertain.

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Test Name: Colorectal Cancer Testing for Lynch Syndrome

Test Code: IPXST (Surgical Section, Special Stain IV)

Sample Preferred sample: Formalin-fixed, paraffin-embedded tissue block Requirements:
Requirements (tissue should have been fixed for at least 24 hours)

Acceptable alternative: 10 unstained sections, nonbaked, on silane coated slides (5-um thick sections). Sections must contain both tumor and normal epithelium.

NOTE: A copy of the pathology report must accompany the block or sections.

EXPECTED VALUE: An interpretive report will be provided.

DAY(S) PERFORMED: Monday - Friday

ANALYTICAL TIME: 24 hours

PRICE: Contact laboratory Customer Service for pricing information, 847-5121 or (800) 991-2799.

CPT CODES: 88342 x 4 for immunohistochemical staining (MLH1, MSH2, PMS2, MSH6)

88342.26 x 4 for interpretation of stains

83898, 83909 x 2, and 83912 for BRAF sent to Mayo Medical Laboratories (Rochester)

EFFECTIVE DATE: March 15, 2010

Test Note:

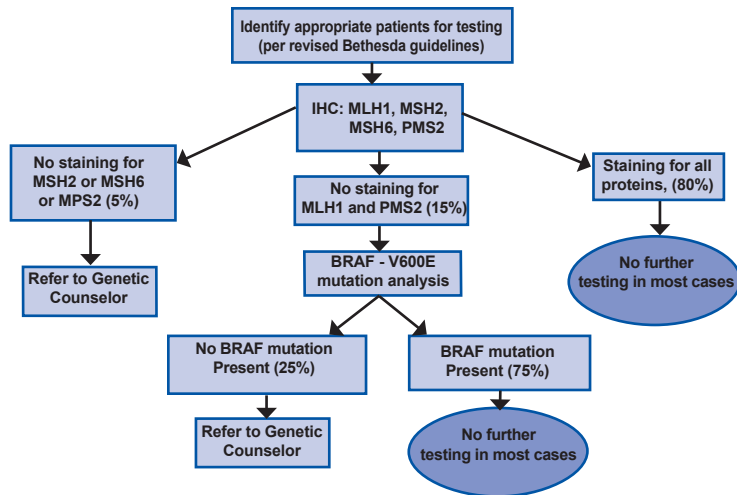
The recommended criteria for mismatch repair protein (MMR) immunohistochemical staining of colorectal cancers for Lynch Syndrome are as follows:

- Colorectal cancer occurring in a patient under 50 years of age.
- Colorectal cancer with HNPCC-related histology in a patient under 60 years of age
 - Mucinous/signet ring cell histology, medullary growth pattern, or microglandular pattern without dirty tumor necrosis
 - Two or more tumor infiltrating lymphocytes per high power field
 - Prominent Crohn's-like peritumoral lymphocytic response
- Colorectal cancer with a synchronous or metachronous HNPCC-related malignancy (colorectal, endometrial, gastric, ovarian, pancreas, ureter, renal pelvis, biliary, small bowel, brain, sebaceous gland adenomas, or keratoacanthomas), regardless of age.
- Family history of Lynch syndrome-associated cancer (per clinical history provided)

* Additional testing for BRAF mutation will be performed at Mayo Medical Laboratories if there is loss of MLH1 protein expression.

As always, you have the option of declining reflex testing if you believe that it is not clinically indicated.

Screening Patients with Colorectal Cancers for Lynch Syndrome Mismatch Repair Protein Immunohistochemistry (IHC) Reflex Algorithm



References

1. Hampel H, Frankel WL, Martin E, et al. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). *N Engl J Med.* 2005;352:1851-1860.
2. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. *J Clin Oncol.* 2005;23:609-618.
3. 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;29:96-104.
4. Lindor NM, Petersen GM, Hadley DW, et al: Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. *JAMA.* 2006;296:1507-1517.



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the University of Vermont*

A Publication of
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