Test Definition: MLH1Z

MLH1 Gene, Full Gene Analysis

Overview

Useful For

Determining whether absence of MLH1 protein, by immunohistochemistry in tumor tissue, is associated with a germline mutation in the affected individual

Establishing a diagnosis of Lynch syndrome/hereditary nonpolyposis colorectal cancer

Identification of familial *MLH1* mutation to allow for predictive testing in family members

Genetics Test Information

Prior Authorization is available for this assay; see Special Instructions.

Additional Tests

Test ID	Reporting Name	Available Separately	Always Performed
COLAB	Hereditary Colon Cancer CGH Array	Yes, (Order FMTT)	Yes

Testing Algorithm

When this test is ordered, comparative genomic hybridization array 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
- Informed Consent for Genetic Testing
- Lynch Syndrome (MLH1) Full Gene Analysis Prior Authorization Ordering Instructions
- Lynch Syndrome Testing Algorithm
- Informed Consent for Genetic Testing (Spanish)

Method Name

Polymerase Chain Reaction (PCR) Amplification/DNA Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Shipping Instructions

Specimen preferred to arrive within 96 hours of draw.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call

800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Specimen Type: Whole blood

Container/Tube:

Preferred: 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.

Additional Information: Prior Authorization is available for this test. **Submit the required form with the specimen.**

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing-Spanish (T826)

2. Molecular Genetics: Inherited Cancer Syndromes Patient Information (T519) in Special Instructions

3. Lynch Syndrome (*MLH1*) Full Gene Analysis Prior Authorization Ordering Instructions in Special Instructions

4. If not ordering electronically, complete, print, and send an Oncology Test Request (T729) with the specimen.

Specimen Minimum Volume

1 mL

Reject Due To

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

Specimen Stability Information

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

Clinical and Interpretive

Clinical Information

Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC) 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 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. 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 <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/central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of biallelic 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 Lynch syndrome. One such strategy involves testing the tumors from suspected individuals for microsatellite instability (MSI) and immunohistochemistry (IHC) for the presence or absence of defective DNA mismatch repair. Tumors that demonstrate absence of expression of MLH1 and PMS2 are more likely to have a germline mutation in the *MLH1* gene.

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Some individuals who have a diagnosis of *MLH1*-related Lynch syndrome may have a mutation that is not identified by this method (eg, promoter mutations, deep intronic mutations). The absence of a mutation, therefore, does not eliminate the possibility a diagnosis of Lynch syndrome. For predictive testing, it is important to first document the presence of an *MLH1* gene mutation in an affected family member.

In some cases, DNA alterations of undetermined significance may be identified.

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

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 is inaccurate or incomplete.

We strongly recommend that patients undergoing predictive testing receive genetic counseling both prior to testing and after results are available.

Somatic alterations (eg, promoter hypermethylation) have been identified in individuals with an absence of MLH1 protein expression in tumor tissue. Therefore, an MSI-H phenotype (>30% of microsatellites) and the absence of protein expression for MLH1 may be the result of a somatic alteration, rather than a germline mutation. Testing for *MLH1* promoter hypermethylation and the *BRAF V600E* mutation (BRMLH / *MLH1* Hypermethylation and *BRAF* Mutation Analysis, Tumor) in a colon tumor from an affected individual may help to confirm or rule out this possibility. Additionally, evaluation of other affected family members' tumors for the presence or absence of defective mismatch repair may be helpful in evaluating the hereditary nature of the disorder.

Supportive Data

Samples from approximately 100 patients were tested by DNA sequence analysis and the results compared to those obtained by other techniques (CSGE, manual DNA sequence) utilized in the laboratory.

Clinical Reference

1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May;17(5):405-424

2. 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;4:255-265

3. Umar A, Baland CR, Terdiman JP, et al: Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004;261-268

4. Lynch HT, de le Chapelle A: Hereditary colorectal cancer. N Engl J Med 2003;348:919-932

5. International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer. Mutation Database. Available at www.insight-group.org/

Performance

Method Description

Bidirectional sequence analysis is used to test for the presence of a mutation in all coding regions and intron/exon boundaries of the *MLH1* gene. Additionally, array comparative genomic hybridization (aCGH) is used to test for the presence of large deletions and duplications.(Aradhya S, Lewis R, Bonaga T, et al: Exon-level array CGH in a large clinical cohort demonstrates increased sensitivity of diagnostic testing for Mendelian disorders. Genet Med 2012;14[6]:594-603)

PDF Report

No

Day(s) and Time(s) Test Performed

Performed weekly, Varies

Analytic Time

14 days

Maximum Laboratory Time

20 days

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

81292-MLHI1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81228-Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, Bacterial Artificial Chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
MLH1Z	MLH1 Gene, Full Gene Analysis	92676-6

Result ID	Test Result Name	Result LOINC Value
53576	Result Summary	50397-9
53577	Result	82939-0
53578	Interpretation	69047-9
53579	Additional Information	48767-8
53580	Specimen	31208-2
53581	Source	31208-2
53582	Array Billed?	No LOINC Needed
53583	Released By	18771-6

Prior Authorization

Insurance preauthorization is available for this testing; forms are available in Special Instructions.

Patient financial assistance may be available to those who qualify.Patients who receive a bill from Mayo Clinic Laboratories will receive information on eligibility and how to apply.