Test Definition: LYNCH

Lynch Syndrome Panel

Overview

Useful For

Establishing a diagnosis of Lynch syndrome

Identification of familial *MLH1, MSH2, MSH6, PMS2*, or *EPCAM* mutations to allow for predictive testing in family members

Genetics Test Information

This test includes next-generation sequencing, Sanger sequencing, array comparative genomic hybridization, and multiplex ligation-dependent probe amplification to evaluate for mutations and large deletions/duplications in the *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* genes. Sanger sequencing may also be performed to confirm detected variants.

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

Testing Algorithm

See Lynch Syndrome Testing Algorithm in Special Instructions.

Special Instructions

- Molecular Genetics: Inherited Cancer Syndromes Patient Information
- Informed Consent for Genetic Testing
- Lynch Syndrome Panel (LYNCH) Prior Authorization Ordering Instructions
- Lynch Syndrome Testing Algorithm
- Informed Consent for Genetic Testing (Spanish)

Method Name

Custom Sequence Capture and Targeted Next Generation Sequencing Followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing and Gene Dosage Analysis by Array Comparative Genomic Hybridization (aCGH) or Multiplex Ligation-Dependent Probe Amplification (MLPA)

NY State Available

Yes

Specimen

Specimen Type

Varies

Shipping Instructions

Specimen should arrive within 96 hours of collection.

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:

1. To ensure minimum volume and concentration of DNA is met, the preferred volume of blood must be submitted. Testing may be canceled if DNA requirements are inadequate.

2. Prior Authorization is available for this assay; see Special Instructions. **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. Lynch Syndrome Panel (LYNCH) Prior Authorization Ordering Instructions in Special Instructions

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

4. 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)

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

While the risk for colorectal cancer in the general population is 6%, rarely colon cancer is attributable to hereditary factors associated with a single abnormal gene that predisposes individuals to increased risks for cancer in a family.

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' end of the *EPCAM* gene, which lead to inactivation of the *MSH2* promotor, have also been associated with Lynch syndrome.

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 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.

The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with Lynch syndrome.

Reference Values

An interpretive report will be provided.

Interpretation

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

Cautions

Clinical Correlations:

Some individuals who have a hereditary susceptibility to breast cancer 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 of a hereditary susceptibility to breast cancer in the individual or family. For predictive testing, it is important to first document the presence of a gene mutation in an affected family member.

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.

Technical Limitations:

In some cases, DNA variants of undetermined significance may be identified. Due to the limitations of next-generation sequencing, we can detect greater than 93% of insertions and deletions up to 20 bases and 43 bases, respectively. If a diagnosis is still suspected, consider full gene sequencing using traditional Sanger methods. Single

or multiexon deletions as well as whole gene deletions will be detected by array comparative genomic hybridization (aCGH) or multiplex ligation-dependent probe amplification (MLPA). 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.

Evaluation Tools:

Multiple in-silico evaluation tools were used to assist in the interpretation of these results. These tools are updated regularly; therefore, changes to these algorithms may result in different predictions for a given alteration. Additionally, the predictability of these tools for the determination of pathogenicity is currently not validated.

Unless reported or predicted to cause disease, alterations found deep in the intron or alterations that do not result in an amino acid substitution are not reported. These and common polymorphisms identified for this patient are available upon request.

Reclassification of Variants-Policy:

All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. At this time, it is not standard practice for the laboratory to systematically re-review likely deleterious alterations or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

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. Lindor NM, McMaster ML, Lindor CJ, et al: Concise Handbook of Familial Cancer Susceptibility Syndromes. Second edition. J Natl Cancer Inst Monogr 2008;(38):1-93

3. Lynch Syndrome-GeneReviews-NCBI Bookshelf. Accessed 6/1/2015. Available at www.ncbi.nlm.nih.gov/books/NBK1211/

4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Genetic/Familial High-Risk Assessment: Colorectal Version 2.2014. Accessed 6/1/2015. Available at www.nccn.org

5. Vasen HFA, Moslein G, Alonso A, et al: Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). J Med Genet 2007;44:353-362

6. Baglietto L, Lindor NM, Dowty JG, et al: Risks of Lynch syndrome cancers for MSH6 mutation carriers. J Natl Cancer Inst 2010 Feb3;102(3):193-201

7. Senter L, Clendenning M, Sotamaa K, et al: The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. Gastroenterology 2008;135:419-428

8. Vaughn CP, Hart J, Samowitz WS, Swensen JJ: Avoidance of pseudogene interference in the detection of 3' deletions in PMS2. Hum Mutat 2011;32:1063-1071

9. Clendenning M, Hampel H, LaJeunesse J, et al: Long-range PCR facilitates the identification of PMS2-specific mutations. Hum Mutat 2006;27(5):490-495

Performance

Method Description

Next-generation sequencing is performed to test for the presence of a mutation in the *MLH1*, *MSH2*, and *MSH6* genes.(Pritchard CC, Smith C, Salipante SJ, et al: ColoSeq provides comprehensive Lynch and polyposis syndrome mutational analysis using massively parallel sequencing. J Mol Diagn 2012;14[4]:357-366)

Gene dosage analysis by array comparative genomic hybridization (aCGH) is used to test for the presence of large deletions and duplications in the *MLH1*, *MSH2*, *MSH6*, and *EPCAM* genes.(Swaroop A, 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)

Bidirectional sequence analysis with long-range PCR is performed to test for the presence of a mutation in all coding regions and intron/exon boundaries of the *PMS2* gene. Gene dosage analysis by multiplex ligation-dependent probe amplification (MLPA) is used to test for the presence of large deletions and duplications in the PMS2 gene.(Clendenning M, Hampel H, LaJeunesse J, et al: Long-range PCR facilitates the identification of PMS2-specific mutations. Hum Mutat 2006;27[5]:490-495; Vaughn CP, Hart KJ, Samowitz WS, et al: Avoidance of pseudogene interference in the detection of 3' deletions in PMS2. Hum Mutat 2011;32:1063-1071)

Reported variants detected by next-generation sequencing will be confirmed by Sanger sequencing.

PDF Report

No

Day(s) and Time(s) Test Performed

Varies

Analytic Time

3 weeks

Maximum Laboratory Time

4 weeks

Specimen Retention Time

Whole Blood: 2 weeks (if available) Extracted DNA: Indefinitely

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-MLH1

81295-MSH2

81298-MSH6

81317-PMS2

81319-*PMS2* (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81403-EPCAM

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
LYNCH	Lynch Syndrome Panel	In Process

Result ID	Test Result Name	Result LOINC Value
37830	Result Summary	50397-9
37831	Result	82939-0
37832	Interpretation	69047-9
37833	Additional Information	48767-8
37834	Specimen	31208-2
37835	Source	31208-2
37836	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.