Test Definition: PMS2Z

PMS2 Gene, Full Gene Analysis

Overview

Useful For

Establishing a diagnosis of Lynch syndrome/hereditary nonpolyposis colorectal cancer

Determining whether absence of PMS2 protein in tumor tissue, as demonstrated by immunohistochemistry, is associated with a germline mutation in the affected individual

Identification of familial *PMS2* mutation to allow for predictive testing in family members

Genetics Test Information

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 (PMS2) Full Gene Analysis Prior Authorization Ordering Instructions
- Lynch Syndrome Testing Algorithm
- Informed Consent for Genetic Testing (Spanish)

Method Name

Polymerase Chain Reaction (PCR) followed by DNA Sequence Analysis and Gene Dosage Analysis by Multiplex Ligation-Dependent Probe Amplification (MLPA)

NY State Available

Yes

Specimen

Specimen Type

Varies

Shipping Instructions

Specimen preferred to 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: 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 (*PMS2*) Full Gene Analysis Prior Authorization Ordering Instructions in Special Instructions

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

Reject Due To

No specimen should be rejected.

Specimen Stability Information

Specimen Type	Temperature	Time
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, and 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 and 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 and/or immunohistochemistry for the presence or absence of defective DNA mismatch repair. Tumors that demonstrate absence of expression of PMS2 are more likely to have a germline mutation in the *PMS2* gene.

Reference Values

An interpretative 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 *PMS2*-related Lynch syndrome may have a mutation that is not identified by this method (eg, deep intronic mutations, promoter mutations). The absence of a mutation, therefore, does not eliminate the possibility of a diagnosis of Lynch syndrome. For predictive testing of asymptomatic individuals, it is important to first document the presence of a *PMS2* gene mutation in an affected family member.

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

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

Predictive testing of an asymptomatic child is not recommended.

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.

In addition to disease-related probes, the multiplex ligation-dependent probe amplification technique utilizes probes localized to other chromosomal regions as internal controls. In certain circumstances, these control probes may detect other diseases or conditions for which this test was not specifically intended. Results of the control probes are not normally reported. However, in cases where clinically relevant information is identified, the ordering physician will be informed of the result and provided with recommendations for any appropriate follow-up testing.

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. 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

3. 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

4. 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

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. Lynch Syndrome-GeneReviews-NCBI Bookshelf. Available at www.ncbi.nlm.nih.gov/books/NBK1211/

Performance

Method Description

Bidirectional sequence analysis is performed to test for the presence of a mutation in all coding regions and intron/exon boundaries of the *PMS2* gene. Additionally, gene dosage analysis (multiplex ligation-dependent probe amplification) is used to test for the presence of large deletions and duplications in this gene.(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)

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

81317-*PMS2* (*postmeiotic segregation increased 2 [S. cerevisiae])* (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

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

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
PMS2Z	PMS2 Gene, Full Gene Analysis	79417-2

Result ID	Test Result Name	Result LOINC Value
53540	Result Summary	50397-9
53541	Result	79417-2
53542	Interpretation	69047-9
53543	Additional Information	48767-8
53544	Specimen	31208-2
53545	Source	31208-2
53546	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.