Overview

Useful For

Providing a comprehensive evaluation for hereditary colon cancer in patients with a personal or family history suggestive of a hereditary colon cancer syndrome

Serving as a second-tier test for patients in whom previous targeted gene variant analyses for specific hereditary colorectal cancer-related genes were negative

Establishing a diagnosis of a hereditary colon cancer syndrome in some cases, allowing for targeted cancer surveillance of associated extra-colonic organs known to be at increased risk for cancer

Identifying variants within genes known to be associated with increased risk for colon cancer allowing for predictive testing of at-risk 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 the genes listed on the panel.

Prior Authorization is available for this assay; see Special Instructions

See Targeted Gene Regions Interrogated by Hereditary Colon Cancer Panel in Special Instructions for details regarding the targeted gene regions identified by this test.

Testing Algorithm

The following algorithms are available in Special Instructions:

-Lynch Syndrome Testing Algorithm

-Colonic Polyposis Syndromes Testing Algorithm

Special Instructions

- Molecular Genetics: Inherited Cancer Syndromes Patient Information
- Informed Consent for Genetic Testing
- Colonic Polyposis Syndromes Testing Algorithm
- Hereditary Colon Cancer Multi-Gene Panel Prior Authorization Ordering Instructions
- Targeted Genes Interrogated by Hereditary Colon Cancer Panel
- 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 preferred to arrive within 96 hours of collection.

Specimen Required

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

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: 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.

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. Hereditary Colon Cancer Multi-Gene Panel Prior Authorization Ordering Instructions in Special Instructions

Specimen Minimum Volume

1 mL

Reject Due To

All specimens will be evaluated at 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

Colorectal cancer occurs in approximately 5% to 6% of individuals in the general population. In rare cases, individuals with a family history of colorectal cancer may be at increased risk for colon and other cancers due to a single-gene predisposition syndrome, known as hereditary colorectal cancer. The 2 most common hereditary colorectal cancer syndromes are Lynch syndrome and familial adenomatous polyposis (FAP). However, there are multiple other genes that are also known to cause to hereditary colorectal cancer or contribute to an increased risk for colorectal cancer. This panel uses next-generation sequencing (NGS), array comparative genomic hybridization (aCGH), and other technologies to evaluate for germline variants in 17 genes known to be associated with an increased risk for colon cancer development. Two of the genes listed, *CHEK2* and *MLH3*, are not associated with a known hereditary cancer syndrome defined by a distinct spectrum of tumors. However, literature suggests that variants in these genes may confer an increased risk for colon cancer and, therefore, are predicted to contribute to cancer risk in patients and families.

Gene	**Known association**
MLH1	Lynch syndrome
MSH2	Lynch syndrome
MSH6	Lynch syndrome
PMS2	Lynch syndrome
EPCAM	Lynch syndrome
APC	Familial adenomatous polyposis
MYH/MutYH	*MYH*-associated polyposis
SCG5/GREM1	Hereditary mixed polyposis syndrome
STK11	Peutz-Jeghers syndrome
SMAD4	Juvenile polyposis syndrome
BMPR1A	Juvenile polyposis syndrome
PTEN	*PTEN* hamartoma tumor syndrome (ie, Cowden syndrome)
CDH1	Hereditary diffuse gastric cancer
AXIN2	Oligodontia-colorectal cancer syndrome
TP53	Li-Fraumeni syndrome
CHEK2	Low-risk gene
MLH3	Low-risk gene

Indications for testing include but are not limited to:

-Patients in whom no specific colorectal cancer syndrome is evident but for whom there is a clear familial component

-Patients whose family history is consistent with familial colorectal cancer type X(1)

-Patients with a strong suspicion for a single-gene hereditary colon cancer syndrome based on an autosomal dominant pattern of colon cancer in the family

-Patients with a personal or family history of colonic polyposis

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(2) 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 involvement of 1 or more of the genes on the panel may have a variant that is not identified by the methods performed (eg, promoter alterations, deep intronic alterations). The absence of a variant, therefore, does not eliminate the possibility of a hereditary colorectal cancer syndrome or other heritable risk for colon cancer. For predictive testing of asymptomatic individuals, it is important to first document the presence of a gene variant in an affected family member.

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

Technical Limitations:

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

Due to the limitations of next-generation sequencing, small deletions and insertions greater than 8 nucleotides in length will not be detected by this test. If a diagnosis of one of the syndromes on this panel is still suspected, consider full gene sequencing using traditional Sanger methods. Single or multi-exon deletions as well as whole gene deletions will be detected by array comparative genomic hybridization (aCGH).

Rare alterations 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.

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.

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 alterations identified for this patient are available upon request.

Reclassification of Variants-Policy:

At this time, it is not standard practice for the laboratory to systematically 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. Lindor NM, Rabe K, Petersen GM, et al: Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. JAMA. 2005;293(16):1979-1985

2. 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

3. Lindor NM, McMaster ML, Lindor CJ, Greene MH, National Cancer Institute, Division of Cancer Prevention, Community Oncology and Prevention Trials Research Group: Concise handbook of familial cancer susceptibility syndromes-second edition. J Natl Cancer Inst Monogr. 2008;(38):1-93

4. Masciari S, Syngal S: The role of *p53* in colorectal cancer. In: Potter JD, Lindor NM, eds. Genetics of Colorectal Cancer. Springer Verlag; 2009:213-217

5. Jaeger E, Leedham S, Lewis A, et al: Hereditary mixed polyposis syndrome is caused by a 40-kb upstream duplication that leads to increased and ectopic expression of the BMP antagonist *GREM1*. Nat Genet. 2012;44(6):699-703

6. Ligtenberg MJL, Kuiper RP, Chan TL, et al: Heritable somatic methylation and inactivation of *MSH2* in families with Lynch syndrome due to deletion of the 3' exons of *TACSTD1*. Nat Genet. 2009;41(1):112-117

7. Lammi L, Arte S, Somer M, et al: Mutations in *AXIN2* cause familial tooth agenesis and predispose to colorectal cancer. Am J Hum Genet. 2004;74:1043-1050

8. Liu HX, Zhou XL, Liu T, et al: The role of hMLH3 in familial colorectal cancer. Cancer Res. 2003;63(8):1894-1899

Performance

Method Description

Next-generation sequencing and/or Sanger sequencing is performed to test for the presence of a variant in the *APC*, *AXIN2*, *BMPR1A*, *CDH1*, *CHEK2*, *MLH1*, *MLH3*, *MSH2*, *MSH6*, *MYHlMutYH*, *TP53*, *PTEN* (including analysis of the promoter), *SMAD4*, and *STK11* genes. Additionally, array comparative genomic hybridization (aCGH) is used to test for the presence of large deletions and duplications in the *APC* (including analysis of promoter 1A and 1B), *AXIN2*, *BMPR1A*, *CDH1*, *CHEK2* (excluding exons 12-15), *EPCAM*, *MLH1*, *MLH3*, *MSH2*, *MSH6, TP53*, *PTEN*, *SMAD4*,

and *STK11* genes. Additionally, aCGH is used to test for the presence of large deletions and duplications in the 3' end of the *ECAPM* gene and to assess for the presence of the reported 40-kb duplication in *SCG5/GREM1*.(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; 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)

Bidirectional sequence analysis with long-range polymerase chain reaction (PCR) is performed to test for the presence of a variant in all coding regions and intron/exon boundaries of the *PMS2* gene. Gene dosage analysis by multiplex ligation-dependent probe amplification 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, Swensen JJ: Avoidance of pseudogene interference in the detection of 3' deletions in *PMS2*. Hum Mutat. 2011;32:1063-1071)

All reported alterations detected by next-generation sequencing are confirmed using Sanger sequencing or other PCR-based assay.

PDF Report

No

Day(s) and Time(s) Test Performed

Performed weekly; Varies

Analytic Time

4 weeks

Maximum Laboratory Time

5 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

81435

81436

81228

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
HCRC	Hereditary Colon Cancer Panel	In Process

Result ID	Test Result Name	Result LOINC Value
52588	Result Summary	50397-9
52589	Result	82939-0
52590	Interpretation	69047-9
52591	Additional Information	48767-8
52592	Specimen	31208-2
52593	Source	31208-2
52594	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.