

Gastrointestinal Hereditary Cancer Panel, Including Lynch Syndrome

Indications for Ordering

Confirm a diagnosis of hereditary gastrointestinal (GI) cancer in individuals with a personal or family history of GI cancer and/or polyposis

Test Description

- Targeted capture of all coding exons and intron/exon junctions of 15 genes (excluding *PMS2*) followed by massively parallel sequencing
 - See table for list of genes tested
- Deletion/duplication analysis of 15 genes by tiled, custom-designed comparative genomic hybridization (CGH) array (excludes *PMS2*)
- Sanger sequencing and multiplex ligation probe amplification (MLPA) of *PMS2*

Tests to Consider

Primary test

[Gastrointestinal Hereditary Cancer Panel, Sequencing and Deletion/ Duplication, 16 Genes 2013449](#)

- Preferred test for individuals with suspected Lynch syndrome or another hereditary GI cancer syndrome
- Analysis of specific genes included in this panel may be available individually at ARUP
 - For test availability and further information, see [ARUP's Genetics site](#) (www.aruplab.com/genetics)

Related test

[Familial Mutation, Targeted Sequencing 2001961](#)

- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Incidence

- >190,000 new cases of GI cancer (colon, esophageal, rectal, stomach, and small bowel) each year in the U.S.
- 5-10% of GI cancers are hereditary
- Individuals with a pathogenic germline variant associated with a hereditary GI cancer syndrome
 - Are at increased risk for GI cancer
 - May be at risk for other types of cancers

Symptoms

- Common signs of a hereditary GI cancer syndrome
 - Early onset of GI cancer (<50 years of age)
 - Multiple GI polyps
 - Multiple and/or rare tumors in a single individual
 - Family history of GI or related cancers
- See table for common hereditary GI cancer syndromes and associated clinical features
- Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]) is associated with an increased risk for the following cancers
 - Colorectal
 - Endometrial
 - Ovarian
 - Gastric
 - Urinary tract
 - Pancreatic
 - Hepatobiliary
 - Small intestine
 - CNS
- Constitutional mismatch repair syndrome (CMMRS) is associated with
 - Childhood onset of colon or small bowel cancer
 - Hematologic cancer
 - Brain tumors
 - Café-au-lait macules

Genetics

Genes – see table for genes tested and for gene-specific information

Test Interpretation

Results

- Positive
 - One pathogenic variant detected in *APC*, *BMPR1A*, *CDH1*, *PTEN*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *STK11*, or *TP53* gene
 - Confirms diagnosis of a hereditary GI cancer syndrome
 - Predicts increased risk for GI cancer
 - One pathogenic variant detected in *EPCAM*, *MLH1*, *MSH2*, *MSH6*, or *PMS2* gene confirms a diagnosis of Lynch syndrome
 - Predicts increased risk for Lynch-associated cancers
 - Homozygosity or compound heterozygosity for pathogenic variant(s) in *MLH1*, *MSH2*, *MSH6*, or *PMS2* gene
 - Consistent with diagnosis of constitutional mismatch repair syndrome
 - Two pathogenic variants detected in *MUTYH* gene
 - Confirms diagnosis of *MUTYH*-associated polyposis
 - One pathogenic variant detected in *MUTYH* gene
 - Predicts carrier status for *MUTYH*-associated polyposis
- Negative
 - No pathogenic variants detected in the genes analyzed
 - Reduces, but does not exclude, the risk of a hereditary form of GI cancer in individual
- Inconclusive – variants of unknown clinical significance may be identified

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Not determined or evaluated
 - Variants in genes not included on the panel
 - Deep intronic and regulatory region variants
 - Breakpoints for large deletions/duplications
 - Sequence changes in *EPCAM* gene
- Deletions/duplications may not be detected in
 - Exon 9 in *BMPR1A* gene
 - Exon 1 in *CDH1* and *MSH2* genes
 - Exon 8 in *PMS2* gene
 - Exons 4, 6, and 7 in *STK11* gene
- Individuals with hematological malignancy and/or a previous allogenic bone marrow transplant should not undergo molecular genetic testing on peripheral blood specimen
 - Testing of cultured fibroblasts or buccal specimen is required for accurate interpretation of test results
 - Not all predisposing genes are analyzed

Gene Symbol	Gene Name	NM #	OMIM #	Inh.	Associated Syndromes/ Phenotypes	Associated GI Cancers	Other Clinical Features and Tumors	Frequency of Disorder Due to Pathogenic Gene Variants
<i>APC</i>	Adenomatous polyposis coli	ex1b: 001127511 ex1a-15: 001127510	611731	AD	Familial adenomatous polyposis (FAP); attenuated FAP; Turcot syndrome; Gardner syndrome; gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)	Colon, small bowel, stomach	Hundreds of colonic polyps; gastric polyps; dental and optic anomalies; other rare cancers	<1% of all colorectal cancer
<i>BMPR1A</i>	Bone morphogenetic protein receptor, type 1A	004329	601299	AD	Juvenile polyposis syndrome (JPS)	Colon, stomach, upper GI	Juvenile GI polyps	Rare cause of GI cancer
<i>CDH1</i>	Cadherin 1, E-cadherin	004360	192090	AD	Hereditary diffuse gastric cancer (HDGC)	Diffuse gastric, colon	Lobular breast cancer	1-3% of all gastric cancers
<i>EPCAM</i> *	Epithelial cell adhesion molecule	002354	185535	AD	Lynch syndrome (LS)/hereditary nonpolyposis colorectal cancer (HNPCC)	Colon, stomach, small bowel	Endometrial, ovarian, pancreatic, ureter, renal pelvis, hepatobiliary tract, and CNS cancer	LS causes 2-4% of all colorectal cancer
<i>MLH1</i>	MutL homologue 1, colon cancer, nonpolyposis type 2	000249	120436	AD	Biallelic mutations cause constitutional mismatch repair syndrome (CMMRS)	Colon, stomach, small bowel	Endometrial, ovarian, pancreatic, ureter, renal pelvis, hepatobiliary tract, and CNS cancer; CMMRS	LS causes 2-4% of all colorectal cancer CMMRS is rare
<i>MSH2</i>	MutS homologue 2, colon cancer, nonpolyposis type 1	000251	609309					
<i>MSH6</i>	MutS homologue 6	000179	600678					
<i>MUTYH</i>	MutS homologue	00128425	604933	AR	<i>MUTYH</i> -associated polyposis (MAP)	Colon	10-100 colonic polyps	Rare cause of GI cancer

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<i>PMS2</i>	Postmeiotic segregation increased 2, yeast homologue	000535.5	600259	AD	LS/HNPCC Biallelic mutations cause CMMRS	Colon, stomach, small bowel	Endometrial, ovarian, pancreatic, ureter, renal pelvis, hepatobiliary tract, and CNS cancer; CMMRS	LS causes 2-4% of all colorectal cancer
<i>PTEN</i>	Phosphatase and tensin homolog	000314	601728	AD	<i>PTEN</i> hamartoma tumor syndrome; Cowden syndrome (CS); Bannayan-Riley-Ruvalcaba syndrome (BRRS); Proteus syndrome (PS); Proteus-like syndrome (PLS)	Colon	Breast, endometrial, thyroid, CNS, skin, and renal cancer; macrocephaly; GI polyps; mucocutaneous lesions; benign breast, thyroid, and endometrial disease; developmental delay; tissue overgrowth	Rare cause of GI cancer
<i>SDHB</i>	Succinate dehydrogenase complex, subunit B, iron sulfur	003000	185470	AD	Hereditary paraganglioma-pheochromocytoma (PGL/PCC)	GI stromal tumors (GISTs)	Paraganglioma; pheochromocytoma; renal cell carcinoma; thyroid cancer	Rare cause of GI cancer
<i>SDHC</i>	Succinate dehydrogenase complex, subunit C, integral membrane protein	003001	602413	AD				
<i>SDHD</i>	Succinate dehydrogenase complex, subunit D, integral membrane protein	003002	602690	AD**				
<i>SMAD4</i>	SMAD, mothers against DPP homologue 4	005359	600993	AD	JPS	Colon, stomach, upper GI	Juvenile GI polyps; epistaxis; arteriovenous malformations (AVMs); telangiectasia	Rare cause of GI cancer
<i>STK11</i>	Serine threonine kinase 11	000455	602216	AD	Peutz-Jeghers syndrome (PJS)	Colon, stomach, small bowel	GI polyps; mucocutaneous hyperpigmentation; gonadal, breast, and pancreatic cancer	Rare cause of GI cancer
<i>TP53</i>	Tumor protein p53	000546	191170	AD	Li-Fraumeni syndrome (LFS)	Colon	Breast, brain, adrenocortical, renal and other rare cancers; sarcoma; leukemia	Rare cause of GI cancer