Hereditary Gastrointestinal Cancer Panel, Sequencing and Deletion/Duplication, 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
  - Sanger sequencing is performed as necessary to fill in regions of low coverage and confirm reported variants; see below for further technical limitations
- 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

Hereditary Gastrointestinal Cancer Panel, Sequencing and Deletion/ Duplication 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
APC	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
BMPR1A	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
CDH1	Cadherin 1, E-cadherin	004360	192090	AD	Hereditary diffuse gastric cancer (HDGC)	Diffuse gastric, colon	Lobular breast cancer	1-3% of all gastric cancers
EPCAM[a]	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
MLH1	MutL homologue 1, colon cancer, nonpolyposis type 2	000249	120436	AD	LS/HNPCC 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
MSH2	MutS homologue 2, colon cancer, nonpolyposis type 1	000251	609309					
MSH6	MutS homologue 6	000179	600678					
MUTYH	MutY homologue	00128425	604933	AR	*MUTYH*-associated polyposis (MAP)	Colon	10-100 colonic polyps	Rare cause of GI cancer

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
PMS2	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
PTEN	Phosphatase and tensin homolog	000314	601728	AD	*PTEN* 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
SDHB	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
SDHC	Succinate dehydrogenase complex, subunit C, integral membrane protein	003001	602413	AD				
SDHD	Succinate dehydrogenase complex, subunit D, integral membrane protein	003002	602690	AD[b]				
SMAD4	SMAD, mothers against DPP homologue 4	005359	600993	AD	JPS	Colon, stomach, upper GI	Juvenile GI polyps; epistasis; arteriovenous malformations (AVMs); telangiectasia	Rare cause of GI cancer
STK11	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
TP53	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

[a]Deletion/duplication testing only
[b]Parent-of-origin effects
AD, autosomal dominant; AR, autosomal recessive; Inh., inherited