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
Limitations

- Diagnostic errors can occur due to rare sequence variations

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene Name</th>
<th>NM #</th>
<th>OMIM #</th>
<th>Inh.</th>
<th>Associated Syndromes/Phenotypes</th>
<th>Associated GI Cancers</th>
<th>Other Clinical Features and Tumors</th>
<th>Frequency of Disorder Due to Pathogenic Gene Variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>Adenomatous polyposis coli</td>
<td>ex1b: 001127511 ex1a-15: 001127510</td>
<td>611731</td>
<td>AD</td>
<td>Familial adenomatous polyposis (FAP); attenuated FAP; Turcot syndrome; Gardner syndrome</td>
<td>Colon, small bowel</td>
<td>Hundreds of colonic polyps; gastric polyps; dental and optic anomalies; other rare cancers</td>
<td>&lt;1% of all colorectal cancer</td>
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<tr>
<td>BMPR1A</td>
<td>Bone morphogenetic protein receptor, type 1A</td>
<td>004329</td>
<td>601299</td>
<td>AD</td>
<td>Juvenile polyposis syndrome (JPS)</td>
<td>Colon, stomach, upper GI</td>
<td>Juvenile GI polyps</td>
<td>Rare cause of GI cancer</td>
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<tr>
<td>CDH1</td>
<td>Cadherin 1, E-cadherin</td>
<td>004360</td>
<td>192090</td>
<td>AD</td>
<td>Hereditary diffuse gastric cancer (HDGC)</td>
<td>Diffuse gastric, colon</td>
<td>Lobular breast cancer</td>
<td>1-3% of all gastric cancers</td>
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<tr>
<td>EPCAM*</td>
<td>Epithelial cell adhesion molecule</td>
<td>002354</td>
<td>185535</td>
<td>AD</td>
<td>Lynch syndrome (LS)/hereditary nonpolyposis colorectal cancer (HNPCC)</td>
<td>Colon, stomach, small bowel</td>
<td>Endometrial, ovarian, pancreatic, ureter, renal pelvis, hepatobiliary tract, and CNS cancer</td>
<td>LS causes 2-4% of all colorectal cancer</td>
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<tr>
<td>MLH1</td>
<td>Mutt homologue 1, colon cancer, nonpolyposis type 2</td>
<td>000249</td>
<td>120436</td>
<td>AD</td>
<td>LS/HNPCC; Biallelic mutations cause constitutional mismatch repair syndrome (CMMRS)</td>
<td>Colon, stomach, small bowel</td>
<td>Endometrial, ovarian, pancreatic, ureter, renal pelvis, hepatobiliary tract, and CNS cancer</td>
<td>LS causes 2-4% of all colorectal cancer</td>
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<tr>
<td>MSH2</td>
<td>Muts homologue 2, colon cancer, nonpolyposis type 1</td>
<td>000251</td>
<td>609309</td>
<td>AD</td>
<td>Biallelic mutations cause constitutional mismatch repair syndrome (CMMRS)</td>
<td>Colon, stomach, small bowel</td>
<td>Endometrial, ovarian, pancreatic, ureter, renal pelvis, hepatobiliary tract, and CNS cancer</td>
<td>CMMRS is rare</td>
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<tr>
<td>MSH6</td>
<td>Muts homologue 6</td>
<td>000179</td>
<td>600678</td>
<td>AR</td>
<td>MUTYH-associated polyposis (MAP)</td>
<td>Colon</td>
<td>10-100 colonic polyps</td>
<td>Rare cause of GI cancer</td>
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<td>MUTYH</td>
<td>MutY homologue</td>
<td>00128425</td>
<td>604933</td>
<td>AR</td>
<td>MUTYH-associated polyposis (MAP)</td>
<td>Colon</td>
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<td>PMS2</td>
<td>Postmeiotic segregation increased 2, yeast homologue</td>
<td>000535.5</td>
<td>600259</td>
<td>AD</td>
<td>LS/HNPCC; Biallelic mutations cause CMMRS</td>
<td>Colon, stomach, small bowel</td>
<td>Endometrial, ovarian, pancreatic, ureter, renal pelvis, hepatobiliary tract, and CNS cancer</td>
<td>LS causes 2-4% of all colorectal cancer</td>
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<td>PTEN</td>
<td>Phosphatase and tensin homolog</td>
<td>000314</td>
<td>601728</td>
<td>AD</td>
<td>PTEN hamartoma tumor syndrome; Cowden syndrome (CS); Bannayan-Riley-Ruvalcaba syndrome (BRRS); Proteus syndrome (PS); Proteus-like syndrome (PLS)</td>
<td>Colon</td>
<td>Breast, endometrial, thyroid, CNS, skin, and renal cancer; macrocephaly; GI polyps; mucocutaneous lesions; benign breast, thyroid, and endometrial disease; developmental delay; tissue overgrowth</td>
<td>Rare cause of GI cancer</td>
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<td>SDHB</td>
<td>Succinate dehydrogenase complex, subunit B</td>
<td>003000</td>
<td>185470</td>
<td>AD</td>
<td>Hereditary paraganglioma-</td>
<td>GI stromal tumors (GISTs)</td>
<td>Paraganglioma; pheochromocytoma; renal</td>
<td>Rare cause of GI cancer</td>
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<td>Inh.</td>
<td>SDHC</td>
<td>Succinate dehydrogenase complex, subunit C, integral membrane protein</td>
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<td></td>
<td>SDHD</td>
<td>Succinate dehydrogenase complex, subunit D, integral membrane protein</td>
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<td>602690</td>
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<td>SMAD4</td>
<td>SMAD, mothers against DPP homologue 4</td>
<td>005359</td>
<td>600993</td>
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<td>Serine threonine kinase 11</td>
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<td>7TP3</td>
<td>Tumor protein p53</td>
<td>000546</td>
<td>191170</td>
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</table>

| Inh. = inheritance, AD = autosomal dominant, AR = autosomal recessive, * = deletion/duplication testing only, ** = parent-of-origin effects | iron sulfur | pheochromocytoma (PGL/PCC) | cell carcinoma; thyroid cancer | Succinate dehydrogenase complex, subunit C, integral membrane protein | Succinate dehydrogenase complex, subunit D, integral membrane protein | SMAD, mothers against DPP homologue 4 | Peutz-Jeghers syndrome (PJS) | Colon, stomach, small bowel | Juvenile GI polyps; epistasis; arteriovenous malformations (AVMs); telangiectasia | Colon, stomach, upper GI | Juvenile GI polyps; epistasis; arteriovenous malformations (AVMs); telangiectasia | Colon, stomach, small bowel | GI polyps; mucocutaneous hyperpigmentation; gonadal, breast, and pancreatic cancer | Colon | Breast, brain, adrenocortical, renal and other rare cancers; sarcoma; leukemia | Rare cause of GI cancer | Rare cause of GI cancer | Rare cause of GI cancer | Rare cause of GI cancer | Rare cause of GI cancer | Rare cause of GI cancer |