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
    - 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 intrinsic 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

<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; gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)</td>
<td>Colon, small bowel, stomach</td>
<td>Hundreds of colonic polyps; gastric polyps; dental and optic anomalies; other rare cancers</td>
<td>&lt;1% of all colorectal cancer</td>
</tr>
<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>
</tr>
<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>
</tr>
<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 (HNPPC)</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>
</tr>
<tr>
<td>MLH1</td>
<td>MutL homologue 1, colon cancer, nonpolyposis type 2</td>
<td>00249</td>
<td>120436</td>
<td>AD</td>
<td>LS/HNPPC</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>
</tr>
<tr>
<td>MSH2</td>
<td>MutS homologue 2, colon cancer, nonpolyposis type 1</td>
<td>00251</td>
<td>609309</td>
<td></td>
<td>Biallelic mutations cause constitutional mismatch repair syndrome (CMMRS)</td>
<td></td>
<td></td>
<td>CMMRS is rare</td>
</tr>
<tr>
<td>MSH6</td>
<td>MutS homologue 6</td>
<td>000179</td>
<td>600678</td>
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</tr>
<tr>
<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>
<td>10-100 colonic polyps</td>
<td>Rare cause of GI cancer</td>
</tr>
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<td>Gene Symbol</td>
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<tr>
<td>PMS2</td>
<td>Postmeiotic segregation increased 2, yeast homologue</td>
<td>000535.5</td>
<td>600259</td>
<td>AD</td>
<td>LS/HNPPC Biallelic mutations cause CMMRS</td>
<td>Colon, stomach, small bowel</td>
<td>Endometrial, ovarian, pancreatic, ureter, renal pelvis, hepatobiliary tract, and CNS cancer; CMMRS</td>
<td>LS causes 2-4% of all colorectal cancer</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>SDHB</td>
<td>Succinate dehydrogenase complex, subunit B, iron sulfur</td>
<td>003000</td>
<td>185470</td>
<td>AD</td>
<td>Hereditary paraganglioma-pheochromocytoma (PGL/PCC)</td>
<td>GI stromal tumors (GISTs)</td>
<td>Paraganglioma; pheochromocytoma; renal cell carcinoma; thyroid cancer</td>
<td>Rare cause of GI cancer</td>
</tr>
<tr>
<td>SDHC</td>
<td>Succinate dehydrogenase complex, subunit C, integral membrane protein</td>
<td>003001</td>
<td>602413</td>
<td>AD</td>
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<tr>
<td>SDHD</td>
<td>Succinate dehydrogenase complex, subunit D, integral membrane protein</td>
<td>003002</td>
<td>602690</td>
<td>AD(^{b})</td>
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<tr>
<td>SMAD4</td>
<td>SMAD, mothers against DPP homologue 4</td>
<td>005359</td>
<td>600993</td>
<td>AD</td>
<td>JPS</td>
<td>Colon, stomach, upper GI</td>
<td>Juvenile GI polyps; epistasis; arteriovenous malformations (AVMs); telangiectasia</td>
<td>Rare cause of GI cancer</td>
</tr>
<tr>
<td>STK11</td>
<td>Serine threonine kinase 11</td>
<td>000455</td>
<td>602216</td>
<td>AD</td>
<td>Peutz-Jeghers syndrome (PJS)</td>
<td>Colon, stomach, small bowel</td>
<td>GI polyps; mucocutaneous hyperpigmentation; gonadal, breast, and pancreatic cancer</td>
<td>Rare cause of GI cancer</td>
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<tr>
<td>TPS3</td>
<td>Tumor protein p53</td>
<td>000546</td>
<td>191170</td>
<td>AD</td>
<td>Li-Fraumeni syndrome (LFS)</td>
<td>Colon</td>
<td>Breast, brain, adrenocortical, renal and other rare cancers; sarcoma; leukemia</td>
<td>Rare cause of GI cancer</td>
</tr>
</tbody>
</table>

\(^{a}\)Deletion/duplication testing only  
\(^{b}\)Parent-of-origin effects  
AD, autosomal dominant; AR, autosomal recessive; Inh., inherited