Hereditary Gastrointestinal Cancer Panel, Including Lynch Syndrome

Pathogenic variants in multiple genes have been implicated in hereditary gastrointestinal (GI) cancer. Hereditary cancer predisposition is often characterized by early age of onset (typically before age 50) and multiple, multifocal, and/or similar cancers in a single individual or in a closely related family member. Pathogenic variants in the genes analyzed by this panel cause variable phenotypes and cancer risks, including non-GI cancers. Lynch syndrome, the most common hereditary predisposition to colon cancer, is caused by pathogenic variants in the \textit{MLH1}, \textit{MSH2}, \textit{MSH6}, \textit{PMS2}, and \textit{EPCAM} genes.

**DISEASE OVERVIEW**

**Associated Disorder**

Lynch syndrome

Individuals with Lynch syndrome are at increased risk for colorectal, endometrial, stomach, ovarian, and other cancers.

**Etiology**

At least 2-4% of colorectal cancers are associated with a hereditary cause.

**Prevalence**

- 1/440 individuals from the general population are estimated to have Lynch syndrome.
- Prevalence of pathogenic variants in the additional genes on this panel is largely unknown.

**Inheritance**

- All genes tested on the Hereditary GI Cancer Panel are autosomal dominant with the exception of:
  - \textit{SDHD} – autosomal dominant with paternal parent-of-origin effect
  - \textit{MUTYH} – autosomal recessive but may also have autosomal dominant risks that are not well defined
  - \textit{MSH3} and \textit{NTHL1} – autosomal recessive
- Some genes are associated with autosomal recessive childhood cancer predisposition or other syndromes.

**TEST DESCRIPTION**

See [Genes Tested] table for genes included in the panel.

**Clinical Sensitivity**

- Variable, dependent on phenotype/condition
- Proportion of Lynch syndrome attributed to pathogenic variants in specific mismatch repair (MMR) gene:
  - \textit{MLH1} – 50%
  - \textit{MSH2} – 40%
  - \textit{MSH6} – 7-10%
  - \textit{PMS2} – <5%
  - \textit{EPCAM} – ~1-3%

---

**TESTS TO CONSIDER**

**Hereditary Gastrointestinal Cancer Panel, Sequencing and Deletion/Duplication 2013449**

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray/Sequencing/Multiplex Ligation-dependent Probe Amplification

**Indication for testing:**

- Recommended test to confirm a diagnosis of hereditary GI cancer in individuals with a personal or family history of GI cancer and/or polyposis.
- When a relative has a previously identified pathogenic sequence variant, see Familial Mutation, Targeted Sequencing (2001961).

**Familial Mutation, Targeted Sequencing 2001961**

Method: Polymerase Chain Reaction/Sequencing

**Indication for testing:**

- Recommended test if there is a known familial sequence variant previously identified in a family member.
- A copy of the family member’s test result documenting the familial variant is required.

See Related Tests
Testing Strategy

Contraindications for Ordering

- Should not be ordered to detect somatic variants associated with malignancy as sensitivity for mosaic variants is low with methodology used for germline assays.
- 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 is required for accurate interpretation of test results.
- When a relative has a previously identified pathogenic variant, see Familial Mutation, Targeted Sequencing (2001961).

Limitations

- A negative result does not exclude a heritable form of cancer.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this individual has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted genes
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Deletions/duplications in AXIN2 and MSH3
  - Sequence variants in EPCAM
  - Noncoding transcripts
  - The following exons are not sequenced due to technical limitations of the assay:
    - **CHEK2** (NM_001349956) 4; (NM_001005735) 3; (NM_007194) 10,12,13,14,15
    - **SDHC** (NM_001035511) 5
    - **SDHD** (NM_001276506) 4
  - The following may not be detected:
    - Deletions/duplications/insertions of any size by massively parallel sequencing
    - Deletions/duplications less than 1kb in the targeted genes by array
    - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
    - Low-level somatic variants
    - Single exon deletions/duplications in the following exons:
      - **APC** (NM_001127511) 1
      - **BMPR1A** (NM_004329) 9
      - **CDH1** (NM_004360) 1
      - **CHEK2** (NM_001005735) 3; (NM_007194) 11, 12, 14, 15
      - **MSH2** (NM_000251) 1; (NM_001258281) 2
      - **MSH6** (NM_000179) 10
      - **MUTYH** (NM_001128425) 1
      - **NTHL1** (NM_002528) 3, 4, 5, 6
      - **POLD1** (NM_002691) 6, 18, 25
      - **PTEN** (NM_000314) 8, 9; (NM_001304717) 1
      - **SDHD** (NM_001276506) 4
      - **TP53** (NM_001126113) 10; (NM_001126114) 10

Analytical Sensitivity

- For Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA) of **PMS2**: 99%
- For massively parallel sequencing:

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytical Sensitivity (PPA) Estimate (%)</th>
<th>Analytical Sensitivity (PPA) 95% Credibility Region (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>99.2</td>
<td>96.9-99.4</td>
</tr>
<tr>
<td>Deletions 1-10 bp</td>
<td>93.8</td>
<td>84.3-98.2</td>
</tr>
<tr>
<td>Deletions 11-44 bp</td>
<td>100</td>
<td>87.8-100</td>
</tr>
<tr>
<td>Insertions 1-10 bp</td>
<td>94.8</td>
<td>86.8-98.5</td>
</tr>
<tr>
<td>Insertions 11-23 bp</td>
<td>100</td>
<td>62.1-100</td>
</tr>
</tbody>
</table>

Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants
<table>
<thead>
<tr>
<th>Gene</th>
<th>MIM Number</th>
<th>Disorder/Associated Cancer(s)/Tumor(s)</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>611731</td>
<td>Familial adenomatous polyposis (FAP)</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Attenuated FAP (AFAP)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated cancer(s)/tumor(s): colon, duodenal, thyroid, pancreas, stomach, medulloblastoma, hepatoblastoma</td>
<td></td>
</tr>
<tr>
<td>AXIN2</td>
<td>604025</td>
<td>Oligodontia-colorectal cancer syndrome (OSCRCS)</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated cancer(s): colon</td>
<td></td>
</tr>
<tr>
<td>BMPR1A</td>
<td>601299</td>
<td>Juvenile polyposis syndrome (JPS)</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated cancer(s)/tumor(s): colon, stomach, small intestine, pancreas</td>
<td></td>
</tr>
<tr>
<td>CDH1</td>
<td>192090</td>
<td>Hereditary diffuse gastric cancer (HDGC)</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated cancer(s)/tumor(s): diffuse gastric, lobular breast</td>
<td></td>
</tr>
<tr>
<td>CHEK2</td>
<td>604373</td>
<td>Associated cancer(s)/tumor(s): breast, colorectal, prostate, thyroid</td>
<td>AD</td>
</tr>
<tr>
<td>EPCAM</td>
<td>185535</td>
<td>Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC)</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others</td>
<td></td>
</tr>
<tr>
<td>MLH1</td>
<td>120436</td>
<td>Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC)</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Constitutional mismatch repair deficiency (CMMRD)</td>
<td></td>
</tr>
<tr>
<td>MSH2</td>
<td>609309</td>
<td>Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC)</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Constitutional mismatch repair deficiency (CMMRD)</td>
<td></td>
</tr>
<tr>
<td>MSH3</td>
<td>600887</td>
<td>Associated cancer(s)/tumor(s): polyposis</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Constitutional mismatch repair deficiency (CMMRD)</td>
<td></td>
</tr>
<tr>
<td>MSH6</td>
<td>600678</td>
<td>Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC)</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Constitutional mismatch repair deficiency (CMMRD)</td>
<td></td>
</tr>
<tr>
<td>MUTYH</td>
<td>604933</td>
<td>Associated cancer(s)/tumor(s): breast</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MUTYH-associated polyposis (MAP)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated cancer(s)/tumor(s): colon, duodenal</td>
<td></td>
</tr>
<tr>
<td>NTHL1</td>
<td>602656</td>
<td>Associated cancer(s)/tumor(s): polyposis</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Constitutional mismatch repair deficiency (CMMRD)</td>
<td></td>
</tr>
<tr>
<td>PMS2</td>
<td>600259</td>
<td>Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC)</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Constitutional mismatch repair deficiency (CMMRD)</td>
<td></td>
</tr>
<tr>
<td>POLD1</td>
<td>174761</td>
<td>Polymerase proofreading-associated polyposis (PPAP)</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated cancer(s)/tumor(s): polyposis, colorectal</td>
<td></td>
</tr>
<tr>
<td>POLE</td>
<td>174762</td>
<td>Associated cancer(s)/tumor(s): polyposis, colorectal</td>
<td>AD</td>
</tr>
<tr>
<td>PTEN</td>
<td>601728</td>
<td>Cowden syndrome/PTEN hamartoma tumor syndrome</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated cancer(s)/tumor(s): breast, endometrial, thyroid, colon, renal cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>SDHB</td>
<td>185470</td>
<td>Associated cancer(s)/tumor(s): paraganglioma, pheochromocytoma, GIST, pulmonary chondroma, renal clear cell carcinoma</td>
<td>AD</td>
</tr>
<tr>
<td>SDHC</td>
<td>602413</td>
<td>Associated cancer(s)/tumor(s): paraganglioma, pheochromocytoma, GIST, pulmonary chondroma, renal clear cell carcinoma</td>
<td>AD</td>
</tr>
<tr>
<td>SDHD</td>
<td>602690</td>
<td>Associated cancer(s)/tumor(s): paraganglioma, pheochromocytoma, GIST, pulmonary chondroma, renal clear cell carcinoma</td>
<td>AD</td>
</tr>
<tr>
<td>SMAD4</td>
<td>600993</td>
<td>Juvenile polyposis syndrome (JPS); hereditary hemorrhagic telangiectasia (HHT) syndrome</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated cancer(s)/tumor(s): colon, stomach, small intestine, pancreas</td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>MIM Number</td>
<td>Disorder/Associated Cancer(s)/Tumor(s)</td>
<td>Inheritance</td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
<td>-------------------------------------------------------------------------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>STK11</td>
<td>602216</td>
<td>Peutz-Jeghers syndrome (PJS)&lt;br&gt;Associated cancer(s)/tumor(s): breast, colon, stomach, small intestine, pancreas, ovary, testes, lung</td>
<td>AD</td>
</tr>
<tr>
<td>TP53</td>
<td>191170</td>
<td>Li-Fraumeni syndrome (LFS)&lt;br&gt;Associated cancer(s)/tumor(s): soft tissue sarcoma, osteosarcoma, central nervous system (CNS) tumor, breast, adenocortical carcinoma, choroid plexus carcinoma, rhabdomyosarcoma</td>
<td>AD</td>
</tr>
</tbody>
</table>

*Association is suggested but not well-established at this time

Paternal parent-of-origin effect

AD, autosomal dominant; AR, autosomal recessive

REFERENCES


RELATED INFORMATION

Colorectal Cancer
Gastrointestinal Stromal Tumors - GISTs
Lynch Syndrome - Hereditary Nonpolyposis Colorectal Cancer (HNPCC)
Tumor Markers

RELATED TESTS

Familial Adenomatous Polyposis Panel: (APC) Sequencing and Deletion/Duplication, (MUTYH) 2 Mutations 2004915
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Hereditary Cancer Panel, Sequencing and Deletion/Duplication 2012032
Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

Hereditary Paraganglioma-Pheochromocytoma (SDHB, SDHC, and SDHD) Sequencing and Deletion/Duplication Panel 2007167
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

HNPCC/Lynch Syndrome (MLH1) Sequencing and Deletion/Duplication 0051650
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

HNPCC/Lynch Syndrome (MSH2) Sequencing and Deletion/Duplication 0051654
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

HNPCC/Lynch Syndrome (MSH6) Sequencing and Deletion/Duplication 0051656
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

HNPCC/Lynch Syndrome (PMS2) Sequencing and Deletion/Duplication 0051737
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Juvenile Polyposis (SMAD4) Sequencing and Deletion/Duplication 2001971
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Juvenile Polyposis Syndrome (BMPR1A) Sequencing and Deletion/Duplication 2004992
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Li-Fraumeni (TP53) Sequencing and Deletion/Duplication 2009313
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Peutz-Jeghers Syndrome (STK11) Sequencing and Deletion/Duplication 2008398
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

PTEN-Related Disorders (PTEN) Sequencing and Deletion/Duplication 2002470
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification