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 MLH1, MSH2, MSH6, PMS2, and 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:
  - SDHD – autosomal dominant with paternal parent-of-origin effect
  - MUTYH – autosomal recessive but may also have autosomal dominant risks that are not well defined
  - MSH3 and 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:
  - MLH1 – 50% (Smith, 2016)
  - MSH2 – 40% (Smith, 2016)
  - MSH6 – 7-10% (Miyaki, 1997; Berends, 2002; Petomaki, 2003)
  - PMS2 – <5% (Senter, 2008)
  - EPCAM – ~1-3% (Kuiper, 2011)
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>
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<tr>
<td>Deletions 11-44 bp</td>
<td>100</td>
<td>87.8-100</td>
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<tr>
<td>Insertions 1-10 bp</td>
<td>94.8</td>
<td>86.8-98.5</td>
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<tr>
<td>Insertions 11-23 bp</td>
<td>100</td>
<td>62.1-100</td>
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</tbody>
</table>

*a 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) Attenuated FAP (AFAP) Associated cancer(s)/tumor(s): colon, duodenal, thyroid, pancreas, stomach, medulloblastoma, hepatoblastoma</td>
<td>AD</td>
</tr>
<tr>
<td>AXIN2</td>
<td>604025</td>
<td>Oligodontia-colorectal cancer syndrome (OSCRCS) Associated cancer(s): colon</td>
<td>AD</td>
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<tr>
<td>BMPR1A</td>
<td>601299</td>
<td>Juvenile polyposis syndrome (JPS) Associated cancer(s)/tumor(s): colon, stomach, small intestine, pancreas</td>
<td>AD</td>
</tr>
<tr>
<td>CDH1</td>
<td>192090</td>
<td>Hereditary diffuse gastric cancer (HDGC) Associated cancer(s)/tumor(s): diffuse gastric, lobular breast</td>
<td>AD</td>
</tr>
<tr>
<td>CHEK2</td>
<td>604373</td>
<td>Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others</td>
<td>AD</td>
</tr>
<tr>
<td>EPCAM</td>
<td>185535</td>
<td>Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others</td>
<td>AD</td>
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<tr>
<td>MLH1</td>
<td>120436</td>
<td>Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others</td>
<td>AD</td>
</tr>
<tr>
<td>MSH2</td>
<td>609309</td>
<td>Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others</td>
<td>AD</td>
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<tr>
<td>MSH3</td>
<td>600887</td>
<td>Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others</td>
<td>AR</td>
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<tr>
<td>MSH6</td>
<td>600678</td>
<td>Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others</td>
<td>AD</td>
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<tr>
<td>MUTYH</td>
<td>604933</td>
<td>Associated cancer(s)/tumor(s): breast</td>
<td>AD</td>
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<tr>
<td>NTHL1</td>
<td>602656</td>
<td>Associated cancer(s)/tumor(s): polyposis</td>
<td>AR</td>
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<tr>
<td>PMS2</td>
<td>600259</td>
<td>Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others</td>
<td>AD</td>
</tr>
<tr>
<td>POLD1</td>
<td>174761</td>
<td>Polymerase proofreading-associated polyposis (PPAP) Associated cancer(s)/tumor(s): polyposis, colorectal</td>
<td>AD</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 Associated cancer(s)/tumor(s): breast, endometrial, thyroid, colon, renal cell carcinoma</td>
<td>AD</td>
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<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>
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<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>
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<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>Gene</td>
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</tr>
<tr>
<td>SMAD4</td>
<td>600993</td>
<td>Juvenile polyposis syndrome (JPS); hereditary hemorrhagic telangiectasia (HHT) syndrome Associated cancer(s)/tumor(s): colon, stomach, small intestine, pancreas</td>
<td>AD</td>
</tr>
<tr>
<td>STK11</td>
<td>602216</td>
<td>Peutz-Jeghers syndrome (PJS) 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) Associated cancer(s)/tumor(s): soft tissue sarcoma, osteosarcoma, central nervous system (CNS) tumor, breast, adrenocortical carcinoma, choroid plexus carcinoma, rhabdomyosarcoma</td>
<td>AD</td>
</tr>
</tbody>
</table>

a Association is suggested but not well-established at this time
b 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