# 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.

## 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

- 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

- 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

## 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.[1]

### Prevalence

1/279 individuals from the general population are estimated to have Lynch syndrome.[2]

### 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*: 15-40%[3]
  - *MSH2*: 20-40%[3]
  - *MSH6*: 12-35%[3]
  - *PMS2*: 5-25%[3]
  - *EPCAM*: <10%[3]

## 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 hematologic 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:

| Variant Class | Analytical Sensitivity (PPA) Estimate[a] (%) | Analytical Sensitivity (PPA) 95% Credibility Region[a] (%) |
|---|---|---|

[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

| Variant Class | Analytical Sensitivity (PPA) Estimate[a] (%) | Analytical Sensitivity (PPA) 95% Credibility Region[a] (%) |
|---|---|---|
| SNVs | 99.2 | 96.9-99.4 |
| Deletions 1-10 bp | 93.8 | 84.3-98.2 |
| Deletions 11-44 bp | 100 | 87.8-100 |
| Insertions 1-10 bp | 94.8 | 86.8-98.5 |
| Insertions 11-23 bp | 100 | 62.1-100 |

[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

## Genes Tested

| Gene | MIM Number | Disorder/Associated Cancer(s)/Tumor(s) | Inheritance |
|---|---|---|---|
| *APC* | 611731 | FAP<br>AFAP<br>GAPPS<br>Associated cancer(s)/tumor(s): colorectal adenomas and cancer, duodenal adenomas and cancer, fundic gland polyps, osteomas, thyroid, pancreas, and others | AD |
| *AXIN2* | 604025 | ODCRCS<br>Associated cancer(s): polyposis, colorectal[a] | AD |
| *BMPR1A* | 601299 | JPS<br>Associated cancer(s)/tumor(s): juvenile polyps, colorectal, stomach, small intestine, pancreas | AD |
| *CDH1* | 192090 | HDGC<br>Associated cancer(s)/tumor(s): diffuse gastric, lobular breast | AD |
| *CHEK2* | 604373 | Associated cancer(s)/tumor(s): breast, prostate, colorectal, thyroid[a] | AD |
| *EPCAM* | 185535 | Lynch syndrome/HNPCC<br>Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, pancreas, ovarian,[a] breast,[a] and others | AD |
| *MLH1* | 120436 | Lynch syndrome/HNPCC<br>Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, panceas, breast,[a] and others | AD |
| | | CMMRD | AR |

[a]Association is suggested but not well-established at this time.

[b]Paternal parent-of-origin effect.

AD, autosomal dominant; AFAP, attenuated FAP; AR, autosomal recessive; CMMRD, constitutional mismatch repair deficiency; CNS, central nervous system; FAP, familial adenomatous polyposis; GAPPS, gastric adenocarcinoma and proximal polyposis of the stomach; HDGC, hereditary diffuse gastric cancer; HHT, hereditary hemorrhagic telangiectasia; HNPCC, hereditary nonpolyposis colorectal cancer; JPS, juvenile polyposis syndrome; LFS, Li-Fraumeni syndrome; MAP, MUTYH-associated polyposis; ODCRCS, oligodontia-colorectal cancer syndrome; PJS, Peutz-Jeghers syndrome; PPAP, polymerase proofreading-associated polyposis

| Gene | MIM Number | Disorder/Associated Cancer(s)/Tumor(s) | Inheritance |
|---|---|---|---|
| *MSH2* | 609309 | Lynch syndrome/HNPCC<br>Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, pancreas, breast,[a] and others | AD |
| | | CMMRD | AR |
| *MSH3* | 600887 | Associated cancer(s)/tumor(s): polyposis, colorectal[a] | AR |
| *MSH6* | 600678 | Lynch syndrome/HNPCC<br>Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, pancreas, breast,[a] and others | AD |
| | | CMMRD | AR |
| *MUTYH* | 604933 | Associated cancer(s)/tumor(s): breast,[a] colorectal[a] | AD |
| | | MAP<br>Associated cancer(s)/tumor(s): colorectal adenomas and cancer, duodenal adenomas and cancer | AR |
| *NTHL1* | 602656 | Associated cancer(s)/tumor(s): polyposis, colorectal[a] | AR |
| *PMS2* | 600259 | Lynch syndrome/HNPCC<br>Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian,[a] breast,[a] and others | AD |
| | | CMMRD | AR |
| *POLD1* | 174761 | PPAP<br>Associated cancer(s)/tumor(s): polyposis, colorectal[a] | AD |
| *POLE* | 174762 | PPAP<br>Associated cancer(s)/tumor(s): polyposis, colorectal[a] | AD |
| *PTEN* | 601728 | Cowden syndrome/*PTEN* hamartoma tumor syndrome<br>Associated cancer(s)/tumor(s): breast, endometrial, thyroid, colorectal, renal cell carcinoma | AD |
| *SDHB* | 185470 | Associated cancer(s)/tumor(s): paraganglioma, pheochromocytoma, GIST, pulmonary chondroma, renal clear cell carcinoma | AD |
| *SDHC* | 602413 | Associated cancer(s)/tumor(s): paraganglioma, pheochromocytoma, GIST, pulmonary chondroma, renal clear cell carcinoma | AD |
| *SDHD* | 602690 | Associated cancer(s)/tumor(s): paraganglioma, pheochromocytoma, GIST, pulmonary chondroma, renal clear cell carcinoma | AD[b] |
| *SMAD4* | 600993 | JPS, HHT syndrome<br>Associated cancer(s)/tumor(s): juvenile polyps, colorectal, stomach, small intestine, pancreas | AD |

[a]Association is suggested but not well-established at this time.

[b]Paternal parent-of-origin effect.

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| Gene | MIM Number | Disorder/Associated Cancer(s)/Tumor(s) | Inheritance |
|---|---|---|---|
| *STK11* | 602216 | PJS<br>Associated cancer(s)/tumor(s): Peutz-Jeghers-type hamartomatous polyps, breast, colorectal, stomach, small intestine, pancreas, ovarian, testes, lung | AD |
| *TP53* | 191170 | LFS<br>Associated cancer(s)/tumor(s): soft tissue sarcoma, osteosarcoma, CNS tumor, breast, colorectal, pancreas,[a] adrenocortical carcinoma, choroid plexus carcinoma, rhabdomyosarcoma | AD |

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[b]Paternal parent-of-origin effect.

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## References


1. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology, genetic/familial high-risk assessment: colorectal, Version 1.2020. [Updated: Jul 2020; Accessed: Feb 2021]

2. Win AK, Jenkins MA, Dowty JG, et al. Prevalence and penetrance of major genes and polygenes for colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2017;26(3):404-412. PubMed

3. Idos G, Valle L. Lynch syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2021. [Last revision: Feb 2021; Accessed: Feb 2021]


## Additional Resources

Doros L, Schultz KA, Stewart DR, et al. *DICER1*-related disorders. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2021. [Last update: Apr 2020; Accessed: Jun 2020]

Hegde M, Ferber M, Mao R, et al. ACMG technical standards and guidelines for genetic testing for inherited colorectal cancer (Lynch syndrome, familial adenomatous polyposis, and MYH-associated polyposis). Genet Med. 2014;16(1):101-116. PubMed

Jasperson KW, Patel SG, Ahnen DJ. APC-associated polyposis conditions. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2021. [Last Update: Feb 2017; Accessed: Feb 2020]

Larsen Haidle J, Howe JR. Juvenile polyposis syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2021. [Last update: Mar 2017; Accessed: Oct 2020]

National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: gastrointestinal stromal tumors (GIST), Version 1.2021. [Last update: Oct 2020; Accessed: April 2021]

## Related Information

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

## Related Tests

Familial Adenomatous Polyposis Panel: (APC) Sequencing and Deletion/Duplication, (MUTYH) 2 Mutations (Extended TAT as of 11/20/20-no referral available) 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 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

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