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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)

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 massively parallel sequencing:

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	Familial adenomatous polyposis (FAP) Attenuated FAP (AFAP) Associated cancer(s)/tumor(s): colon, duodenal, thyroid, pancreas, stomach, medulloblastoma, hepatoblastoma	AD
AXIN2	604025	Oligodontia-colorectal cancer syndrome (OSCRCS) Associated cancer(s): colon[a]	AD
BMPR1A	601299	Juvenile polyposis syndrome (JPS) Associated cancer(s)/tumor(s): colon, stomach, small intestine, pancreas	AD
CDH1	192090	Hereditary diffuse gastric cancer (HDGC) Associated cancer(s)/tumor(s): diffuse gastric, lobular breast	AD
CHEK2	604373	Associated cancer(s)/tumor(s): breast, colorectal,[a] prostate,[a] thyroid[a]	AD
EPCAM	185535	Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others	AD
MLH1	120436	Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others	AD
		Constitutional mismatch repair deficiency (CMMRD)	AR
MSH2	609309	Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others	AD
		Constitutional mismatch repair deficiency (CMMRD)	AR
MSH3	600887	Associated cancer(s)/tumor(s): polyposis[a]	AR
MSH6	600678	Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others	AD
		Constitutional mismatch repair deficiency (CMMRD)	AR
MUTYH	604933	Associated cancer(s)/tumor(s): breast[a]	AD
		MUTYH-associated polyposis (MAP) Associated cancer(s)/tumor(s): colon, duodenal	AR
NTHL1	602656	Associated cancer(s)/tumor(s): polyposis[a]	AR
PMS2	600259	Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, and others	AD
		Constitutional mismatch repair deficiency (CMMRD)	AR
POLD1	174761	Polymerase proofreading-associated polyposis (PPAP) Associated cancer(s)/tumor(s): polyposis,[a] colorectal[a]	AD
POLE	174762	Associated cancer(s)/tumor(s): polyposis,[a] colorectal[a]	AD
PTEN	601728	Cowden syndrome/*PTEN* hamartoma tumor syndrome Associated cancer(s)/tumor(s): breast, endometrial, thyroid, colon, 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	Juvenile polyposis syndrome (JPS); hereditary hemorrhagic telangiectasia (HHT) syndrome Associated cancer(s)/tumor(s): colon, stomach, small intestine, pancreas	AD

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
STK11	602216	Peutz-Jeghers syndrome (PJS) Associated cancer(s)/tumor(s): breast, colon, stomach, small intestine, pancreas, ovary, testes, lung	AD
TP53	191170	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	AD

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

[b]Paternal parent-of-origin effect

AD, autosomal dominant; AR, autosomal recessive

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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

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