Hereditary Gastrointestinal Cancer Panels

Pathogenic germline 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 related cancers in a single individual or in closely related family member(s). Pathogenic variants in some genes analyzed by these panels cause variable phenotypes and cancer risks, including non-GI cancers. See the Genes Tested table below for more details regarding the genes and syndromes included on both the Hereditary Colorectal cancer High-Risk Panel and the Hereditary Gastrointestinal Cancer Panel. Genes included on these panels are also included in other ARUP hereditary cancer tests. For more information, refer to the ARUP Hereditary Cancer Panel Comparison table.

Disease Overview

Associated Disorders

APC-Associated Polyposis Conditions

- Familial adenomatous polyposis (FAP), attenuated FAP, and gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)[1]
- Caused by a single pathogenic variant in the *APC* gene[1]
- Classic FAP is characterized by the development of hundreds to thousands of adenomatous colonic polyps with a 100% lifetime risk of colorectal cancer in untreated individuals.[1]

Lynch Syndrome

- Caused by a single pathogenic variant in one of the mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) or *EPCAM* exon 9 deletions
- Individuals are at an increased risk for colorectal (up to approximately 60%), uterine, and other cancers.
- Additional testing is available to assess for genes associated with Lynch syndrome; refer to the Laboratory Test Directory for more information.

MUTYH-Associated Polyposis

- Caused by biallelic pathogenic variants in the *MUTYH* gene[2]
- Colon polyps are less numerous (typically 10-100s) than classic FAP[2]
- Estimated 80-90% lifetime risk of colorectal cancer in untreated individuals[2]

Others

- See the Genes Tested table for more details regarding the additional genes and syndromes included on the Hereditary Gastrointestinal Cancer Panel.

Genetics

Genes

Genes included on these panels are also included in other ARUP hereditary cancer tests. For more information, refer to the ARUP Hereditary Cancer Panel Comparison table.

Featured ARUP Testing

To compare directly to other hereditary cancer panels offered by ARUP Laboratories, see the ARUP Hereditary Cancer Panel Comparison table.

Hereditary Gastrointestinal Cancer High-Risk Panel, Sequencing and Deletion/Duplication 3005697

Method: Massively Parallel Sequencing/Sequencing/Multiplex Ligation-dependent Probe Amplification

- Germline analysis of genes associated with high-risk hereditary colorectal cancer syndromes (including Lynch syndrome, familial adenomatous polyposis [FAP]/other *APC*-associated polyposis condition, or MUTYH-associated polyposis [MAP])
  - Note: For suspected Lynch syndrome, testing specific to Lynch syndrome is recommended. Refer to the Laboratory Test Directory for available test options.

Hereditary Gastrointestinal Cancer Panel, Sequencing and Deletion/Duplication 2013449

Method: Massively Parallel Sequencing/Sequencing/Multiplex Ligation-Dependent Probe Amplification (MLPA)

- Recommended test to confirm a diagnosis of hereditary GI cancer in individuals with a personal or family history of GI cancer and/or polyposis

Testing minors for adult-onset conditions is not recommended; testing will not be performed in minors without prior approval. For additional information, please contact an ARUP genetic counselor at 800-242-2787 ext. 2141.

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Genes Included in ARUP Hereditary GI Cancer Tests		
Gene	Hereditary Gastrointestinal Cancer High-Risk Panel, Sequencing and Deletion/Duplication 3005697	Hereditary Gastrointestinal Cancer Panel, Sequencing and Deletion/Duplication 2013449
EPCAM	✓	✓
MLH1	✓	✓
MSH2	✓	✓
MSH6	✓	✓
PMS2	✓	✓
APC	✓	✓
MUTYH	✓	✓
AXIN2		✓
BMPR1A		✓
CDH1		✓
CHEK2		✓
KIT		✓
MLH3		✓
MSH3		✓
NTHL1		✓
PDGFRA		✓
POLD1		✓
POLE		✓
PTEN		✓
SDHA		✓
SDHB		✓
SDHC		✓
SDHD		✓
SMAD4		✓

STK11	✓
TP53	✓

See the Genes Tested table for detailed information for each gene included on these panels.

Etiology

Greater than 2-4% of colorectal cancers are associated with a hereditary cause.[3]

Prevalence

- The prevalence of Lynch syndrome has been estimated to be 1/279 individuals from the general population.[4]
- The prevalence of FAP has been estimated to be between 1 in 6,850 to 1 in 31,250 live births.[1]
- The prevalence of MAP is estimated to be between 1 in 20,000 to 1 in 60,000 individuals.[2]

Inheritance

- All genes tested on the panels covered by this document are autosomal dominant with the exception of the following:

Gene	Inheritance Pattern
SDHD	Autosomal dominant with paternal parent-of-origin effect
MLH3	Autosomal recessive
MSH3	Autosomal recessive
NTHL1	Autosomal recessive
MUTYH	Autosomal recessive but may also have autosomal dominant risks that are not well defined

- Some genes are associated with autosomal recessive childhood cancer predisposition or other syndromes.
- See the Genes Tested table for additional details.

Test Interpretation

Contraindications for Ordering

- For individuals with a suspected diagnosis of Lynch syndrome, consider testing specific to Lynch syndrome that includes the recurrent *MSH2* inversion and increased detection of single exon deletions/duplications.
- 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 allogeneic 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, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.

- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.
- Long-range PCR followed by nested Sanger sequencing is performed on the following gene and exons:
  - *PMS2* (NM_000535) 11, 12, 13, 14, 15
- Bidirectional Sanger sequencing is performed on the following genes and exons:
  - *MSH2* (NM_000251) 5
  - *PMS2* (NM_000535) 7
  - *PTEN* (NM_000314) 9
- Multiplex ligation-dependent probe amplification (MLPA) is performed on the following gene to call exon-level deletions and duplications:
  - *PMS2* (NM_000535)

Clinical Sensitivity

Variable, dependent on phenotype/condition

Analytic Sensitivity

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) Estimate (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [single exon]	>99.9
Exon-level[c] duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9
Exon-level deletions/duplications (MLPA)	>99	>99

[a]PPA values are derived from larger methods-based MPS and/or Sanger validations. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA) unless otherwise indicated.

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

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*
  - The following exons are not sequenced due to technical limitations of the assay:
    - *APC* (NM_001354896) 12; (NM_001354898, NM_001354904) 2; (NM_001354900) 11

    - *CHEK2* (NM_001005735) 3; (NM_001349956) 4
    - *PDGFRA* (NM_001347827) 17; (NM_001347828) 2; (NM_001347830) 1
    - *SDHA* (NM_004168) 14; (NM_001294332) 13; (NM_001330758) 12
    - *SDHC* (NM_001035511) partial exon 5 (Chr1:161332225-161332330); (NM_001278172) partial exon 4 (Chr1:161332225-161332330)
    - *SDHD* (NM_001276506) 4
- The following may not be detected:
    - Deletions/duplications/insertions of any size by MPS
    - Large duplications less than 3 exons in size
    - Noncoding transcripts
    - Single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement
    - Some variants due to technical limitations in the presence of pseudogenes and/or repetitive/homologous regions
    - Low-level somatic variants
    - Deletions/duplications in the following exons:
        - *APC* (NM_001354896) 12; (NM_001354898, NM_001354904) 2; (NM_001354900) 11
        - *BMPR1A* (NM_004329) 12-13
        - *CDH1* (NM_001317185) 10
        - *CHEK2* (NM_007194) 11-15; (NM_001005735) 3,12-16; (NM_001257387) 12-16; (NM_001349956) 4,10-14; (NM_145862) 10-14
        - *MLH3* (NM_001040108) 7-8; (NM_014381) 7
        - *PDGFRA* (NM_001347827) 17; (NM_001347828) 2; (NM_001347830) 1
        - *PTEN* (NM_000314, NM_001304718) 9; (NM_001304717) 1,10
        - *SDHA* (NM_004168) 1,10-15; (NM_001294332) 1,9-14; (NM_001330758) 1,10-13
        - *SDHD* (NM_001276506) 4

Genes Tested

Refer to the Genes Included in ARUP Hereditary GI Cancer Tests for gene inclusions by panel. To compare directly to other hereditary cancer panels offered by ARUP Laboratories, see the ARUP Hereditary Cancer Panel Comparison table.

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
APC	611731	FAP AFAP GAPPS Colorectal adenomas and cancer, duodenal adenomas and cancer, gastric fundic gland polyps, medulloblastoma, osteomas, pancreas, thyroid, and others	AD
AXIN2	604025	ODCRCS Colorectal,[a] polyposis	AD
BMPR1A	601299	JPS Colorectal, juvenile polyps, small intestine, stomach	AD
CDH1	192090	HDGC Diffuse gastric, lobular breast	AD
CHEK2	604373	Breast, colorectal, prostate, thyroid[a]	AD

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

[b]Paternal parent-of-origin effect.

AD, autosomal dominant; AFAP, attenuated familial adenomatous polyposis; 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; GIST, gastrointestinal stromal tumors; HDGC, hereditary diffuse gastric cancer; HHT, hereditary hemorrhagic telangiectasia; HNPCC, hereditary nonpolyposis colorectal cancer; HPP, hereditary paraganglioma-pheochromocytoma; 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
EPCAM (Exon 9 deletions/duplications only)	185535	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
KIT	164920	GIST	AD
MLH1	120436	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR
MLH3	604395	MLH3-associated polyposis Breast,[a] colorectal,[a] polyposis	AR
MSH2	609309	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR
MSH3	600887	Colorectal,[a] polyposis	AR
MSH6	600678	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR
MUTYH	604933	Breast,[a] colorectal[a]	AD
		MAP Colorectal adenomas and cancer, duodenal adenomas and cancer	AR
NTHL1	602656	Colorectal,[a] polyposis	AR
PDGFRA	173490	GIST, inflammatory fibroid polyp, fibroid tumor	AD
PMS2	600259	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR
POLD1	174761	PPAP Colorectal,[a] polyposis	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
POLE	174762	PPAP Colorectal,[a] polyposis	AD
PTEN	601728	Cowden syndrome/*PTEN* hamartoma tumor syndrome Breast, colorectal, endometrial, Lhermitte-Duclos disease (cerebellar dysplastic gangliocytoma), melanoma, renal cell carcinoma, thyroid, and others	AD
SDHA	600857	HPP syndromes GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, renal clear cell carcinoma	AD
SDHB	185470	HPP syndromes GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, renal clear cell carcinoma	AD
SDHC	602413	HPP syndromes GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, renal clear cell carcinoma	AD
SDHD	602690	HPP syndromes GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, renal clear cell carcinoma	AD[b]
SMAD4	600993	JPS, HHT syndrome Colorectal, juvenile polyps, small intestine, stomach	AD
STK11	602216	PJS Breast, cervix, colorectal, endometrial, lung, ovarian (sex cord with annular tubules), pancreas, Peutz-Jeghers-type hamartomatous polyps, small intestine, stomach, testes	AD
TP53	191170	LFS Adrenocortical carcinoma, breast, choroid plexus carcinoma, CNS, colorectal, melanoma, osteosarcoma, pancreas, prostate, renal, rhabdomyosarcoma, soft tissue sarcoma, stomach, thyroid, and others	AD

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

[b]Paternal parent-of-origin effect.

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References

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4. 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.

Related Information

Colorectal (Colon) Cancer
Gastrointestinal Stromal Tumors (GISTs)
Hereditary Cancer Germline Genetic Testing
Lynch Syndrome - Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

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