Hereditary Gastric Cancer Panel, Sequencing and Deletion/Duplication

Last Literature Review: December 2022 Last Update: September 2023

Pathogenic germline variants in multiple genes have been implicated in hereditary gastric cancer. Hereditary gastric cancer syndromes are often characterized by an early age of disease onset (typically before age 50) and multiple, multifocal, and/or similar cancers in a single individual or one or more closely related family members.

Genetics

Genes

Refer to the Genes Tested table for genes included in the panel.

Etiology

Approximately 5-10% of gastric cancers are associated with a hereditary cause.

Inheritance

- Typically autosomal dominant (AD)
- Some genes are also associated with autosomal recessive (AR) childhood cancer predisposition or other syndromes.

Test Interpretation

Contraindications for Ordering

- For individuals with a suspected diagnosis of Lynch syndrome, consider testing specific to Lynch syndrome as some relevant variants are not included on this panel. Refer to Lynch Syndrome - Hereditary Nonpolyposis Colorectal Cancer (HNPCC) for more information.
- This test should not be ordered to detect somatic variants associated with malignancy because sensitivity for mosaic variants is low with the methodology used for germline assays.
- Individuals with hematological malignancy and/or a previous allogeneic bone marrow transplant should not undergo molecular genetic testing on a peripheral blood specimen.
  - Testing cultured fibroblasts is required for the accurate interpretation of test results.

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 the 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 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 polymerase chain reaction (PCR) testing 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

Featured ARUP Testing

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

Hereditary Gastric Cancer Panel, Sequencing and Deletion/Duplication 3005963

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

- Recommended test to confirm a hereditary cause of gastric cancer in individuals with a personal or family history of gastric cancer
- 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.

- Multiplex ligation-dependent probe amplification (MLPA) testing is performed on the following genes to call exon-level deletions and duplications:
  - *PMS2* (NM_000535)

Sensitivity/Specificity

Clinical Sensitivity

Variable; dependent on phenotype

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 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 gastric cancer or another cancer.
- Diagnostic errors can occur due to rare sequence variations.
- The interpretation of this test result may be impacted if this patient 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 gene(s)
  - Regulatory region and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Sequence variants in *EPCAM*
  - The following exons are not sequenced due to the technical limitations of the assay:
    - *APC* (NM_001354896) 12
    - *APC* (NM_001354898, NM_001354904) 2
    - *APC* (NM_001354900) 11
- 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.
  - Low-level somatic variants
  - Certain other variants due to technical limitations in the presence of pseudogenes and/or repetitive/homologous regions
  - Deletions/duplications in the following exons:
    - *APC* (NM_001354896) 12
    - *APC* (NM_001354898, NM_001354904) 2
    - *APC* (NM_001354900) 11
    - *BMPR1A* (NM_004329) 12-13

- *CDH1* (NM_001317185) 10
- *CTNNA1* (NM_001290307) 19
- *CTNNA1* (NM_001324002, NM_001324004) 13
- *CTNNA1* (NM_001324003) 15
- *CTNNA1* (NM_001324005) 16

Genes Tested

To compare directly to other hereditary cancer panels offered by ARUP Laboratories, refer to 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, pancreatic, thyroid, and others	AD
BMPR1A	601299	JPS Colorectal, juvenile polyps, small intestine, stomach	AD
CDH1	192090	HDGC Diffuse gastric, lobular breast	AD
CTNNA1	116805	Breast,[a] stomach	AD
EPCAM (exon 9 deletion/duplications only)	185535	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreatic, prostate, renal pelvis and/or ureter, stomach, and others	AD
MLH1	120436	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR
MSH2	609309	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR
MSH6	600678	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR
PMS2	600259	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD

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

AFAP, attenuated familial adenomatous polyposis; 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; PJS, Peutz-Jeghers syndrome

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
		CMMRD	AR
SMAD4	600993	JPS, HHT syndrome Colorectal, juvenile polyps, small intestine, and 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

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