THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Hereditary Gastric Cancer Panel

Gastric cancer (GC) is a global public health concern, ranking as the fourth leading cause of cancer mortality, with a 5-year survival of only 20%. Approximately 10% of gastric cancers appear to have a familial predisposition, and about half of these can be attributed to hereditary germline mutations. Germline mutations in the E-cadherin (*CDH1*) gene have been identified in families with an autosomal dominant inherited predisposition to hereditary diffuse gastric cancer (HDGC)[1]. Germline mutations in *KIT* and *PDGFRA* have been reported in familial gastrointestinal stromal tumors (GIST) [2, 3]. GC risk is also elevated in Lynch syndrome, hereditary breast and ovarian cancer syndrome (HBOC), familial adenomatous polyposis (FAP), Li-Fraumeni syndrome (LFS), Peutz-Jeghers syndrome (PJS), and juvenile polyposis syndrome (JPS) [4]. Given the very poor prognosis for most gastric cancer patients once diagnosed, every effort should be made to identify lesions early when they are still curable. Genetic testing for gastric cancer susceptibility allows for identification of families with elevated risk for this and other tumors and development of rational surveillance strategies for early detection.

Our Hereditary Gastric Cancer Panel include sequence and deletion/duplication analysis of all 19 genes listed below.

CDH1	CTNNA1	KIT	PDGFRA	BRCA1	BRCA2	MLH1
MSH2	MSH6	PMS2	EPCAM	APC	SMAD4	BMPR1A
STK11	PTEN	SDHB	SDHC	TP53		

Hereditary Gastric Cancer Panel genes and associated cancer syndromes

Gene	Cancer Syndrome	Frequency of germline mutation in GC	GC Risk	References
CDH1	HDGC	In 30% of families with HDGC.	A lifetime risk for GC is greater than 80%, and up to 60% risk for female carriers developing lobular breast cancer.	[1, 4-6]
CTNNA1	HDGC	Rare	N.A.	[7]
KIT	GIST	Mutations in PDGFRA and KIT together explain almost all familial GIST.	N.A.	[2]
PDGFRA	GIST (AD)		N.A.	[3]
BRCA1	HBOC	Low frequency	Two fold higher than general population.	[4, 8]
BRCA2	HBOC	5.7% of patients with GC in Israel; 20.7% of Polish families with both gastric and breast cancer	1.7-2.6 fold higher than general population.	[4, 8]
MLH1, MSH2, MSH6, PMS2, EPCAM	Lynch syndrome	1.6% in carriers of Lynch syndrome mutations.	4.8% in patients with germline defects of *MLH1* and 9% in those with germline defects of *MSH2*.	[9]
APC	FAP	Low frequency	Adenomas in the upper gastrointestinal tract can progress to malignant disease in 5% of cases.	[9]
SMAD4, BMPR1A	JPS	Low frequency	GC has been found in 21% of JPS patients affected with gastric polyps.	[4, 10, 11]
STK11	PJS	2.1-3% in Peutz-Jeghers syndrome families	29% by age 65 years.	[9, 12]

PTEN	Cowden syndrome	Low frequency	N.A.	[13]
SDHB, SDHC	Carney-Stratakis syndrome	Low frequency	N.A.	[14]
TP53	LFS	Low frequency	2.8%-8.1% of LFS families.	[4, 15, 16]

N.A. Not available.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Deletion/duplication analysis of the panel genes is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

Hereditary Gastric Cancer Panel (sequencing and deletion/duplication analysis of 19 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$3500
CPT codes:	81445, 81406
Turn-around time:	4-6 weeks

Note: We cannot bill insurance for this test.

Results:

Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. One report will be issued for the entire Inherited Bone Marrow Sequencing Panel. All abnormal results are reported by telephone or email.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

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14. Janeway, K.A., et al., *Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations.* Proc Natl Acad Sci U S A, 2011. **108**(1): p. 314-8.
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