The University of Chicago Genetic Services Laboratories

5841 S. Maryland Ave., Rm. G701, MC 0077, Chicago, Illinois 60637
Toll Free: (888) UC GENES □ (888) 824 3637
Local: (773) 834 0555 □ FAX: (773) 702 9130
ucgslabs@genetics.uchicago.edu □ dnatesting.uchicago.edu
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Hereditary Colorectal Cancer Panel Testing

Clinical Features:

Colorectal cancer (CRC) is a major cause of morbidity and mortality around the world, and approximately 5% develop in the context of inherited mutations leading to some form of familial colon cancer syndrome. The features suggestive of a hereditary CRC predisposition include: young age at diagnosis, history of CRC or adenomatous polyps in one or more close relatives, multiple primary cancers in a single individual, and several relatives affected with cancer spanning multiple generations. Of the cases that are suspected of having a hereditary predisposition to CRC, the most common causes are Lynch syndrome, familial adenomatous polyposis (FAP) and attenuated FAP (AFAP) [1, 2]. Individuals with hereditary CRC syndromes often have a high risk of developing gastrointestinal cancers and require increased screening and surveillance to reduce their cancer risk.

Our Comprehensive Hereditary Colorectal Cancer Panel includes mutation analysis of the 21 genes listed below. Other smaller panels are also available, please see below for more details.

APC	AXIN2	BMPR1A	BUB1B	CDH1	CHEK2
ENG	EPCAM	GALNT12	GREM1	MLH1	MSH2
MSH6	MUTYH	PMS2	POLD1	POLE	PTEN
SMAD4	STK11	TP53			

Hereditary Colorectal Cancer Panel genes and associated cancer syndromes

Gene	Associated Syndrome	Cancer Risk	Management Guidelines	References
APC	Familial adenomatous polyposis	Nearly a 100% lifetime risk of CRC in untreated individuals.	NCCN-CRC	[1]
AXIN2	NA	Associated with an apparently milder form of familial polyposis and increased risk of CRC.	N/A	[3]
BMPR1A SMAD4	Juvenile Polyposis Syndrome	The risk of CRC is 40-50%. The risk of stomach cancer is 21% if gastric polyps are present.	NCCN-CRC	[1]
BUB1B	N/A	Homozygosity for BUB1B mutations is associated with an increased susceptibility to gastrointestinal neoplasia.	N/A	[4]
CDH1	N/A	Increased risk for hereditary diffuse gastric cancer, lobular breast cancer, colon cancer, or signet ring cell colon cancer.	NCCN-Gastric	[5]
CHEK2	N/A	The relative risk of breast cancer in in males is 10.3 (95% CI 3.5–30.0); females is 1.70 (95% CI 1.3–2.2). The risk of other types of cancer is also increased including prostate and colon cancer.	NCCN-BR/OV, ACS Breast MRI	[6, 7]
ENG	N/A	Associated with moderate-load colorectal polyps and increased risk of CRC.	N/A	[8]
EPCAM MLH1 MSH2 MSH6 PMS2*	Lynch syndrome, Turcot syndrome, Muir-Torre syndrome	The lifetime risk of colon cancer is 70-80%, endometrial cancer is 20-60%, ovarian cancer is 0.3-20%, gastric cancer is 5-10%, small bowel cancer is 0.4-12%, and urinary tract cancers is 0.2-25%.	NCCN-CRC, CAPS	[9, 10]
GALNT12	N/A	Increased risk for CRC.	N/A	[11]
GREM1**	N/A	Increased risk for CRC.	N/A	[12]
MUTYH	MUTYH-associated polyposis	MUTYH-associated polyposis is associated with a 28-fold increased risk of CRC, with a penetrance of 19% by age 50 years, 43% by 60	NCCN-CRC	[1]

		years, and 80% by 70 years.		
POLD1	polymerase proofreading-associated polyposis	Increased risk for CRC and endometrial cancer.	N/A	[13, 14]
POLE	polymerase proofreading-associated polyposis	Increased risk for CRC.	N/A	[13]
PTEN	Cowden syndrome	Of all of the PTEN mutation carriers, 7% have been diagnosed with CRC. The lifetime risk in PTEN mutation carriers is 85% for breast cancer, 35% for nonmedullary thyroid cancer, and 28% for endometrial cancer.	NCCN-BR/OV	[1]
STK11	Peutz-Jeghers syndrome	The life time risk for breast cancer is 54%, 39% for colon cancer, 11-36% for pancreatic cancer, 29% for stomach cancer, 13% for small bowel cancer, 21% for ovary cancer, 11% for endometrial cancer, 15% for lung cancer.	NCCN-CRC, CAPS#	[1]
TP53	Li-Fraumeni syndrome	Extremely high risk for a multitude of tumor types including breast cancer, sarcoma, brain cancer, hematologic malignancies, adrenocortical, among others.	NCCN-BR/OV	[15]

N/A: Not available.

**Please note variations within exons 1-5, 9 and 11-15 of the PMS2 gene may not be analyzed or reported due to homology issues.*

***Testing of GREM1 includes analysis of the founder duplication in SCG5 intron 2, upstream of the GREM1 gene.*

Testing Options

Lynch Syndrome Panel (mutation analysis of *EPCAM, MLH1, MSH2, MSH6, PMS2*, POLE, POLD1*)

Cost: $3500
CPT codes: 81292, 81295, 81298, 81317, 81403
Turn-around time: 6 weeks

Hereditary Colorectal Cancer High Risk panel (mutaiton analysis of *APC, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2*, POLE, POLD1*)

Cost: $3500
CPT codes: 81201, 81292, 81295, 81298, 81317
Turn-around time: 6 weeks

Colorectal Polyposis Panel (mutation analysis of *APC, AXIN2, BMPR1A, BUB1B, ENG, GREM1, MUTYH, POLE, POLD1, PTEN, SMAD4, STK11*)

Cost: $3500
CPT codes: 81201, 81321, 81404, 81405, 81406
Turn-around time: 6 weeks

Comprehensive Hereditary Colorectal Cancer Panel (mutation analysis of 21 genes*)

Cost: $4000
CPT codes: 81435, 81436
Turn-around time: 6 weeks

**Please note variations within exons 1-5, 9 and 11-15 of the PMS2 gene may not be analyzed or reported due to homology issues.*

Testing 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. Please note variations within exons

1-5, 9 and 11-15 of the *PMS2* gene may not be analyzed or reported due to homology issues. 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.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

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 panel. All abnormal results are reported by telephone or email.

References:

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8. Ngeow, J., et al., *Prevalence of germline PTEN, BMPR1A, SMAD4, STK11, and ENG mutations in patients with moderate-load colorectal polyps.* Gastroenterology, 2013. **144**(7): p. 1402-9, 1409 e1-5.
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11. Guda, K., et al., *Inactivating germ-line and somatic mutations in polypeptide N-acetylgalactosaminyltransferase 12 in human colon cancers.* Proc Natl Acad Sci U S A, 2009. **106**(31): p. 12921-5.
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15. Chun, N. and J.M. Ford, *Genetic testing by cancer site: stomach.* Cancer J, 2012. **18**(4): p. 355-63.

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