

Hereditary Colorectal Cancer Risk Panel (15 genes)

<i>APC</i>	<i>ATM</i>	<i>BMPR1A</i>	<i>CDH1</i>	<i>CHEK2</i>	<i>EPCAM</i>	<i>MLH1</i>	<i>MSH2</i>	<i>MSH6</i>	<i>MUTYH</i>
<i>PMS2</i>	<i>PTEN</i>	<i>SMAD4</i>	<i>STK11</i>	<i>TP53</i>					

Indication

Hereditary Colorectal Cancer Risk Panel is a comprehensive screen of 15 genes linked to increased risk of inherited forms of colorectal cancer. Genetic susceptibility to polyposis or non-polyposis colorectal cancer can be caused by several inherited genetic syndromes. Lynch syndrome accounts for approximately 2-5% of colorectal cancers and is caused by germline mutations in mismatch repair genes: *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*. This syndrome is characterized by a substantially increased risk for hereditary non-polyposis colorectal cancer (HNPCC) and several types of extra-colonic tumors. Colonic polyposis syndromes include classical and attenuated Familial Adenomatous Polyposis syndromes (FAP and AFAP) caused by mutations in *APC*, *MUTYH*-associated polyposis (MAP) syndrome caused by biallelic mutations in *MUTYH*, and Juvenile Polyposis Syndrome primarily caused by mutations in *SMAD4* or *BMPR1A*. This panel also includes genes associated with moderately increased risk for hereditary colorectal cancer (*ATM*, *CHEK2*) as well as genes responsible for rare hereditary cancer syndromes, such as Li-Fraumeni (*TP53*), Peutz-Jeghers (*STK11*), Cowden (*PTEN*), and hereditary diffuse gastric cancer (*CDH1*) syndrome. These syndromes are associated with increased lifetime risk for multiple cancer types including colorectal cancer and are also characterized by other clinical features specific for each syndrome. Identifying individuals with genetic predisposition to colorectal cancer can allow earlier detection of cancer through increased frequency and younger age of initiating colonoscopy and other cancer screening; consideration of prophylactic colectomy or other risk-reducing measures; availability of targeted therapy options for cancer treatment (e.g., Pembrolizumab for mismatch repair deficient and microsatellite instability (MSI)-high tumors in individuals with Lynch syndrome); and identification of at-risk family members.

Hereditary cancer syndrome is a genetic predisposition to develop certain types of cancers, often at an early age. Hereditary cancer risk assessment is performed to identify patients and families who may be at risk. Clues that a hereditary cancer syndrome may be present include the following:

- Cancer diagnosed at an unusually young age (<50 years of age for colorectal cancer)
- Multiple primary tumors or several different types of cancer in the same person
- Several close blood relatives with colorectal, uterine, ovarian, and/or stomach cancer, especially when on the same side of the family
- Unusual presentation of a specific type of cancer (tumors with MSI-high phenotype or DNA mismatch repair deficiency suggestive of an inherited Lynch syndrome)
- 10 or more GI polyps during one's lifetime (adenomatous, hyperplastic, hamartomatous, and/or other types of polyps)
- The presence of birth defects that are known to be associated with inherited cancer syndromes
- Occurrence of certain types of adult cancer in which the probability of harboring a hereditary cancer syndrome is high

Testing method

Next Generation Sequencing (NGS) provides coverage of all coding exons and noncoding DNA in exon-flanking regions (on average 50 bp) enriched using hybrid capture Illumina TruSight Cancer Sequencing Panel. Single base pair (point) mutations, small insertions/deletions (1-25 bp), complex insertions and deletions, or larger deletions and duplication (<100 bp) are detected using a combination of clinically validated computational data analysis methods for sequence variant calling, filtering, and annotation. Gross deletions and duplications at each targeted gene and exon are evaluated through comparative depth of coverage analysis of NGS targeted sequencing data using clinically-validated analysis algorithm. All reportable copy number variants are confirmed by independent methodology using gene-specific Multiplex Ligation-dependent Probe Amplification (MLPA) or genome-wide SNP microarray assay. If a pathogenic mutation or deletion is detected in exons 13, 14 or 15 of *PMS2*, confirmatory send out testing will be performed to determine if this variant is located in the *PMS2* gene or pseudogene, *PMS2CL*.

Turnaround time

5-10 business days

Sample requirements

3 ml peripheral blood in EDTA (lavender) top tube

Specimen stability: Ambient - 72 hours; Refrigerated - 1 week

CPT codes

81435, 81436, G0452

References

Lu KH, Wood ME, Daniels M, Burke C, et al. American Society of Clinical Oncology Expert Statement: collection and use of a cancer family history for oncology providers. *J Clin Oncol* 2014;32:833-840.

Lynch syndrome. Practice Bulletin No. 147. American College of Obstetricians and Gynecologists. *Obst Gynecol* 2014;124:1042-1054

Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Evaluation of Genomic Applications in Practice and Prevention (EGAP) Working Group. *Genet Med* 2009;11:35-41

Hampel H, Bennett RL, Buchanan A, Pearlman R, Wiesner GL. A practice guideline from the American College of Medical Genetics and genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. *Genet Med* 2015;17:70-87.

Ship Specimens to:

Henry Ford Center for Precision Diagnostics
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