Physician Reference - Inherited Risk for Colorectal Cancer

About 5 to 10 percent of all colorectal cancers are caused by an inherited mutation

Colorectal cancer is the third leading cause of death due to cancer among men and women in the US.

Estimated New Cases In 2017	135,430
% Of All New Cancer Cases	8.0%
Estimated Deaths in 2017	50,260
% Of All Cancer Deaths	8.4%

Number of New Cases and Deaths per 100,000: The number of new cases of colon and rectum cancer was 40.1 per 100,000 men and women per year. The number of deaths was 14.8 per 100,000 men and women per year. These rates are age-adjusted and based on 2010-2014 cases and deaths.

Lifetime Risk of Developing Cancer: Approximately 4.3 percent of men and women will be diagnosed with colon and rectum cancer at some point during their lifetime, based on 2012-2014 data.

Prevalence of This Cancer: In 2014, there were an estimated 1,317,247 people living with colon and rectum cancer in the United States.

Survival Rate five years after being diagnosed is 64.9% (2007-2013).

Lifestyle influences along with genetic risk factors are known to play a significant role in the development of colon cancer. Individuals with a family history of colorectal cancer in two or more first-degree relatives have two to three fold increased risk for developing this disease.

Otogenetics Genetic Testing for Colorectal Cancer

The **Colorectal Cancer Gene Panel** allows for the identification of gene variants with known risk association for colorectal cancer and screens for the following types colorectal cancers:

- Lynch Syndrome (LS) also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC)
- Familial Adenomatous Polyposis (FAP)
- Attenuated Familial Adenomatous Polyposis (AFAP)
- MYH-Associated Polyposis (MAP)
- Juvenile Polyposis Syndrome (JPS)
- Micro-Satellite Instability (MSI)
- Peutz-Jeghers Syndrome (PJS)

- **Colorectal Cancer Panel – 12 genes** APC, BMPR1A, CDH1, EPCAM, MLH1, MSH2 MSH6, MUTYH, PMS2, PTEN, SMAD4, STK11
- **Lynch Syndrome - 5 genes** EPCAM, MLH1, MSH2, MSH6, PMS2
- **Inherited Cancer Comprehensive Panel – 39 genes** linked to breast, ovarian, colon, pancreatic, and other major cancers. APC, ATM, BARD1,BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKn2A, CHEK2, ELAC2, EPCAM, FANCC,HRAS1, MEN1, METMLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, NTRK1, PALB2, PALLD, PMS2, PTCH, PTEN, RAD50,RAD51, RAD51C, RAD51D, RET, SMAD4, STK11, TP53, VHL
- **Comprehensive Cancer Panel ~578 genes (FOR RESEARCH ONLY)**

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The Test Panels Provide

- High depth coverage to detect both common and rare mutations
- Somatic point mutations, indels, and gene fusions are detected
- Copy Number Variants are reported
- Identification of individual mutations that determine specific tumor or cancer type

Methodology

Analyses is performed using Next Generation Sequencing with custom oligonucleotide-based target capture followed by Illumina HiSeq sequencing of the coding regions of the genes included in each panel, affording >100 fold average coverage.

Principles Of IHC And MSI Testing For Lynch Syndrome

- IHC and MSI (microsatellite instability-high) analyses are screening tests that are done on colon cancer tissue to identify individuals at risk for Lynch Syndrome.
- >90% of LS tumors are MSI-H and/or lack expression of at least one of the MMR (mismatch repair) proteins by IHC.
- 10-15% of sporadic colon cancers exhibit abnormal IHC and are MSI-H due to abnormal methylation of the MLH1 gene promoter rather than due to LS.
- The Bethesda criteria states that CRC patients tumors should be tested for MMR defects by MSI and/or IHC analysis as a way to help identify patients with a greater chance of having LS.
- However, although Bethesda criteria are more sensitive than the Amsterdam criteria, up to 50% of patients with LS fail to meet even the Bethesda criteria.
- IHC refers to staining tumor tissue for protein expression of the 4 MMR (mismatch pair) genes known to be mutated in Lynch Syndrome: MLH1, MSH2, MSH6, and PMS2.
- A normal IHC test implies that all 4 MMR proteins are normally expressed and therefore it is unlikely that an underlying MMR gene mutation is present.
- An abnormal IHC test means that at least one of the proteins is not expressed and an inherited mutation may be present in the related gene.
- Loss of protein expression by IHC in any of the MMR genes guides genetic testing of the gene(s) where protein expression is not observed.
- MSI-H in tumors refers to the tumor having a proportion of alterations in panel of microsatellite repeat markers that indicates loss of MMR activity. MSI is used in a similar way to IHC.
- There is a 5-10% false positive rate with IHC and MSI testing.

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Colorectal Cancer Gene List					
Gene	**NCBI Reference**	**OMIM**	**Description**	**CDA bps**	**Number of Exons**
APC	NM_000038.5	611731	Adenomatous polyposis coli	8697	16
MLH1	NM_000249.3	120436	MutL homolog 1	2271	19
MSH2	NM_000251.2	609309	MutS homolog 2	2805	16
MSH6	NM_000179.2	600678	MutS homolog 6	4083	10
TP53	NM_000546.5	191170	Tumor protein p53	2591	11
P16(CDKN2A)	NM_058195.3	600160	Cyclin-dependent kinase inhibitor 2A	1050	5
PTEN	NM_000314.4	601728	Phosphate and tensin homolog	5572	9
MUTYH	NM_001128425.1	604933	MutY homolog	1765	17
BMPRIA	NM_004329.2	601299	Bone morphogenetic protein receptor type IA	1599	11
SMAD4	NM_005359.5	600993	SMAD family member 4	1659	11
STK11	NM_000455.4	602216	Serine/threonine kinase 11	1302	9

Screening Guidelines

A patient, who is age 50 and older, is at **average** risk if they have the following:

- No symptoms
- No personal or family history of colorectal cancer or precancerous polyps (benign growths in the inside surface of the colon or rectum)
- No personal history of inflammatory bowel disease (ulcerative colitis or Crohn's colitis)
- No family history of colorectal cancer precancerous polyps
- People with an increased risk for colorectal cancer may benefit from earlier, more frequent screenings.

A patient is at **increased** risk if they have one of the following:

- Personal history of colorectal cancer or precancerous polyps
- Family history of a first-degree relative (such as a parent or sibling) who had cancer or a precancerous polyp in the colon or rectum before the age of 50, or multiple family members with colorectal cancer or polyps
- Personal history of long-standing (more than eight years) inflammatory bowel disease (ulcerative colitis or Crohn's colitis)
- Family history of familial adenomatous polyposis (FAP). A rare form of hereditary colon cancer, FAP is a condition that can lead to the development of hundreds or thousands of polyps in the colon at a very early age. If left untreated, these individuals will almost always go on to develop colon cancer by age 40.
- family history of Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer), a condition caused by mutations in specific genes that accounts for approximately 2 to 3 percent of all colorectal cancer diagnoses
- A patient may also have an increased risk for colorectal cancer if they've had therapy for another type of cancer. In that case, more frequent screenings may be recommended.

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National Comprehensive Cancer Network, NCCN Guidelines

Meeting one or more of the below criteria warrants further personalized risk assessment, genetic counseling, testing and management.

- Revised Bethesda Guidelines
  - CRC diagnosed in a patient who is younger than 50 years of age
  - Presence of synchronous or metasynchronous, colorectal, or other LS related tumors, regardless of age
  - CRC with MSI-H histology diagnosed in a patient who is younger than 60 years of age
  - CRC diagnosed in a patient with one or more first-degree relatives with an LS related cancer, with one of the cancers being diagnosed before 50 years
  - CRC diagnosed in a patient with two or more first- or second-degree relatives with LS related cancers regardless of age
- Amsterdam III Criteria
  - At least three relatives must have cancer associated with LS (colorectal, endometrial, small bowel, ureter or renal-pelvis)
  - All of the following present:
  - One must be a first-degree relative of the other two
  - At least two successive generations must be affected
  - At least one relative with cancer associated LS should be diagnosed before age 50 years
  - FAP should be verified whenever possible
- Endometrial cancer at age <50 years
- Known LS in the family
- Consider testing individuals with ≥5% risk of LS on mutation prediction models. Testing affected individuals in the family with LS related cancer is preferred

Test Results

Pathogenic Variant(s) Identified or Variants(s) Likely to be Pathogenic, VLP

The result means that a mutation, or a genetic change, was identified in a specific gene that increases the lifetime chance of developing certain cancers. The final Report contains detailed risk information specific to the mutation identified in the genes. This result does not mean that the patient has cancer or will definitely develop cancer in their lifetime.

No Known Pathogenic Variant(s) Identified

The result means that no variant or genetic change known to be associated with or predicted to be associated with, based on current knowledge and test methods, disease(s) is identified.

Variant(s) of Unknown Significance

Sometimes, variant(s) of unknown significance (**VUS)** is included in the report. VUS are variants that do not fit into pathogenic, likely pathogenic or benign classifications according to ACMG and/or other relevant Professional standards, or the criteria for pathogenic or likely pathogenic and benign are contradictory for the variant.

Frequently Used ICD-10 Codes	
Z80.0	Family history of malignant neoplasm of digestive organs
Z83.71	Family history of colonic polyp
Z86.010	Personal history of colonic polyps