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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.

Types of Hereditary Colon Cancer

The three major types of hereditary colon cancer:

1. Lynch Syndrome, also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC) is the most common hereditary cause of colorectal cancer and accounts for 2-3% of all colorectal cancers
2. Familial Adenomatous Polyposis (FAP) or Attenuated FAP (AFAP) which accounts for <1% of colorectal malignancies.
3. MYH-Associated Polyposis (MAP) is a syndrome that was discovered fairly recently. It is a hereditary condition that causes an increased risk for colorectal cancer and colorectal polyps.

Lynch Syndrome

Lynch syndrome is an autosomal dominant familial cancer syndrome caused by mutations in multiple susceptibility genes. The majority of Lynch syndrome is due to mutations in the MLH1, MSH2, MSH6, PMS2, or EPCAM (also known as TACSTD1) genes and are associated with an increased lifetime risk for colorectal cancer (CRC) and other malignancies within the tumor spectrum including at least endometrial, ovarian, gastric, small bowel, urothelial, hepatobiliary tract, sebaceous and pancreatic cancers. These mutations can be inherited from a person's mother or father.

Current literature suggests Lynch Syndrome affects 28,000 individuals annually. It is estimated that 1 in 35 colorectal carcinomas is associated with Lynch Syndrome. In individuals with Lynch Syndrome, the lifetime risk of colon cancer may be as high as 75% by the age of 70 years, with an average age onset of 45 years in MLH1 and MSH2 mutation carriers. While the incidence of adenomas in individuals with Lynch Syndrome is similar to that in the general population, the high rate of colorectal cancer is due to an acceleration of the adenoma to carcinoma sequence.

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Cancer risks associated with Lynch Syndrome are largely derived from family studies. Mutations in MLH1 and MSH2 account for 70-90% of families with Lynch Syndrome. The risk of colon and endometrial cancer is less in MSH6 and PMS2 mutation carriers, although the cancer risk may not be lower for MSH6 carriers if one takes the data out to age 80. While individuals with a single MLH1, MSH2, MSH6 and PMS2 mutation develop cancers in mid-life, individuals with biallelic MLH1, MSH2, MSH6 and PMS2 mutations have a distinctive phenotype and tumor spectrum, and often develop cancer as early as the first decade of life. First-degree relatives of mutation carriers have a 50% probability of having the same germ-line mutation.

Cancer Risks for Lynch Syndrome Mutation Carriers

Lynch Syndrome	Mutation Carrier Risk	General Population Risk
Colorectal	Up to 82%	2%
Endometrial (uterine)	Up to 71%	1.5%
Stomach	Up to 13%	< 1%
Ovarian	Up to 12%	< 1%
Second cancer within 10 years	30%	3.5%
Second cancer within 15 years	50%	5%

Familial Adenomatous Polyposis

Familial Adenomatous Polyposis (FAP) or Attenuated FAP (AFAP) is an inherited condition that is caused by a mutation in the APC gene. Patients who have a mutation in the APC gene can have:

- Many precancerous polyps or adenomas; possibly hundreds or thousands in the colon and rectum
- A milder form of FAP may present with a smaller number of colorectal polyps or adenomas
- A greatly increased risk of colorectal cancer
- An increased risk for other associated cancers

An APC mutation can be inherited either from a person's mother or father.

Cancer Risks for FAP or AFAP; APC Mutation Carriers

FAP and AFAP	Gene Mutation Carrier Risk	General Population Risk
Colorectal cancer in FAP	Approximately 100%	2%
Colorectal cancer in AFAP	80-100%	2%
Small bowel cancer	5-12%	N/A

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MYH-Associated Polyposis (MAP)

MYH-Associated Polyposis (MAP) is a syndrome that was discovered fairly recently. It is a hereditary condition that causes an increased risk for colorectal cancer and colorectal polyps. Because of the numerous colorectal polyps or adenomas that occur in MAP, the colorectal cancer risk is known to be significantly increased. Additionally, it is possible that risks of other cancers, such as small bowel, may be increased as well. Individuals with MAP often do not have a family history of colon cancer or colon polyps in family members, although siblings may be affected. MAP is caused by mutations in the MYH gene. Individuals with MAP have mutations in both of their MYH genes, one from each parent. MYH-associated polyposis is marked by multiple precancerous polyps in the colon and rectum, similar in number to that seen in the milder form of FAP.

Other Types Of Inherited Cancers

Juvenile Polyposis Syndrome (JPS)

- Juvenile polyposis syndrome is a disorder characterized by multiple benign growths called juvenile polyps. People with juvenile polyposis syndrome typically develop polyps before age 20; however, in the name of this condition "juvenile" refers to the characteristics of the tissues that make up the polyp, not the age of the affected individual.
- These growths occur in the gastrointestinal tract, typically in the colon. Most juvenile polyps are benign, but there is a chance that polyps can become malignant. The most common type of cancer seen in people with juvenile polyposis syndrome is colorectal cancer with a 39% cumulative lifetime risk of colorectal cancer.
- Juvenile Polyposis Syndrome can occur sporadically in families (25% of cases) or be inherited in an autosomal dominant manner (75% of cases).
- Mutations in the BMPR1A and SMAD4 genes cause juvenile polyposis syndrome by disrupting cell signaling and interfere with their roles in regulating gene activity and cell proliferation. This causes cells to grow and divide in an uncontrolled way leading to polyp formation..
- Juvenile polyposis syndrome occurs in approximately 1 in 100,000 individuals worldwide.

Micro-Satellite Instability (MSI)

- Microsatellites are repeated sequences of DNA. Microsatellite instability (MSI) is a hypermutable phenotype caused by the loss of DNA mismatch repair (MMR) activity.
- MSI is most prevalent as the cause of colon cancers. MSI is detected in about 15% of all colorectal cancers; 3% of these are associated with Lynch syndrome and the other 12% are caused by sporadic.
- Lynch syndrome is caused by MSI and increases the risk for colon, endometrium, ovary, stomach, small intestine, hepatobiliary tract, urinary tract, brain, and skin cancers.
- MSI tumors in sporadic colorectal cancer result from the hypermethylation of the MLH 1 gene promoter, whereas MSI tumors in Lynch syndrome are caused by germline mutations in MLH 1, MSH 2, MSH 6, and PMS2.
- MSI is a good marker for determining Lynch syndrome and determining a prognosis for cancer treatments. The NCI has agreed on five microsatellite markers necessary to determine MSI presence: two mononucelotides, BAT25 and BAT26, and three dinucelotide repeats, D2S123, D5S346, and D17S250.

Peutz-Jeghers Syndrome (PJS)

- Peutz-Jeghers syndrome is characterized by the development of noncancerous growths called hamartomatous polyps in the gastrointestinal tract, particularly the stomach and intestines, and a greatly increased risk of developing certain types of cancer.
- It is inherited in an autosomal dominant pattern. Mutations in the STK11 gene, also known as LKB1, cause most cases of Peutz-Jeghers syndrome. The STK11 gene is a tumor suppressor gene, which means that it normally prevents cells from growing and dividing too rapidly or in an uncontrolled way. A mutation in this gene alters the structure or function of the STK11 protein, disrupting its ability to restrain cell division. The resulting uncontrolled cell growth leads to the formation of noncancerous polyps and cancerous tumors. In about half of all cases, an affected person inherits a mutation in the STK11 gene from one affected parent. The remaining cases occur in people with no history of Peutz-Jeghers syndrome in their family. These cases appear to result from de novo mutations in the STK11 (serine/threonine kinase 11) gene.
- The prevalence of this condition is uncertain; estimates range from 1 in 25,000 to 300,000 individuals.
- A small percentage of people with Peutz-Jeghers syndrome do not have mutations in the STK11 gene. In these cases, the cause of the disorder is unknown.

Hyperplastic Polyposis Syndrome

- Hyperplastic polyposis syndrome (HPS) is characterized by the development of multiple hyperplastic polyps in the colon and rectum. Currently, there is no gene mutation known to be associated with HPS.

In some families, there is a strong history of colorectal cancer although no known mutations have been detected. It is not known whether the disease susceptibility of these families occurs randomly or by hereditary mutations that have not yet been identified.

Lynch Syndrome Risk Status And Testing Strategy

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FAP, AFAP, And MAP Risk And Treatment Options	
Risk	**Treatment**
FAP	
Personal History of Classic FAP	Proctocolectomy or Colectomy
Family History of Classic FAP Unaffected, No Symptoms, Findings or Adenomas At-Risk Family Member Known Family Mutation	Genetic Testing of APC Gene For Familial Mutation
AFAP	
Personal History of AFAP	
Age <21 Years With Small Adenoma Burden	▪ Colonoscopy And Polypectomy Every 1-2 Years ▪ Surgical Evaluation And Counseling If Appropriate
Age ≥21 Years With Small Adenoma Burden	▪ Colonoscopy And Polypectomy Every 1-2 Years ▪ Colectomy and IRA may be considered ▪ Surgical Evaluation And Counseling If Appropriate
Adenoma Burden That Can Be Handled Endoscopically	▪ Colectomy with IRA preferred in most cases ▪ Consider Proctocolectomy With IPAA If Dense Rectal Polyposis Not Manageable With Polypectomy
Family History of Classic AFAP Unaffected, No Symptoms, Findings or Adenomas At-Risk Family Member Known Family Mutation	Genetic Testing of APC Gene For Familial Mutation
MAP	
Personal History of MAP	
Age <21 Years With Small Adenoma Burden	▪ Colonoscopy And Polypectomy Every 1-2 Years ▪ Surgical Evaluation And Counseling If Appropriate
Age ≥21 Years With Small Adenoma Burden	▪ Colonoscopy And Polypectomy Every 1-2 Years ▪ Colectomy and IRA may be considered ▪ Surgical Evaluation And Counseling If Appropriate
Adenoma Burden That Can Be Handled Endoscopically	▪ Colectomy with IRA ▪ Consider Proctocolectomy With IPAA If Dense Rectal Polyposis Not Manageable With Polypectomy ▪ If Patient Had Colectomy With IRA, Then Endoscopic Evaluation Of Rectum Every 6-12 Months Depending On Polyp Burden
Family History of MAP Unaffected, No Symptoms, Findings or Adenomas At-Risk Family Member Known Family Mutation	Recommend MUTYH Testing For Familial Mutations

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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
- **Comprehensive Inherited Cancer 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)**

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 (LS): 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.

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

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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.

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

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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

Colorectal Cancer Risk Management

Increased Surveillance: Each type of hereditary colorectal cancer calls for a different management strategy, but frequent monitoring is often the primary approach.

Surgical Management:

- Removal of the colon is often recommended in patients who develop colon cancer. The rectum is usually left in place.
- Preventive removal of the colon and rectum may be recommended depending on the number of polyps.
- FAP–Preventive removal of the colon and rectum is recommended. The timing of surgery is based on the number/size of polyps.
- AFAP–Preventive removal of the colon and rectum may be recommended depending on the number of polyps.
- Preventive removal of the uterus (endometrium) and/or ovaries reduces the risk of uterine and/or ovarian cancer and may be an option when childbearing is complete.
- Unaffected mutation carriers not willing or unable to undergo screening colonoscopies may consider preventive removal of the colon.

Chemoprevention: Medications may be used to reduce the number of polyps that remains after colon surgery, while monitoring for signs of cancer.

Surveillance for MLH1, MSH2, MSH6, PMS2, and EPCAM Mutation Carriers			
Site	**Procedure**	**Age To Begin**	**Repeat Test**
Colon	**Colonoscopy**	**20-25 Years** **(Or 2-5 Years Prior To The Earliest Colorectal Cancer If It Is Diagnosed Under Age 25)**	**1-2 Years**
Endometrium (Uterus/Ovaries)	**Gynecological Exam** **Transvaginal Ultrasound** **Endometrial Tissue Sample** **CA-125**	**20-25 Years**	**1-2 Years**
Screening for other Lynch syndrome-related cancers (stomach, kidney/urinary tract, biliary tract, brain, small bowel, pancreatic) may be considered based on the presence of that cancer in a family member.			

Surveillance Findings	Follow-Up
No Pathological Findings	**Continued Surveillance** **Consider Prophylactic Hysterectomy/BSO If Postmenopausal Or Childbearing Complete**
Adenocarcinomas	**See Appropriate Guidelines For Treatment Of Cancer By Site**
Adenomas	**Endoscopic Polypectomy With Follow-Up Colonoscopy Every 1-2 Years Depending On Location, Surgical Risk, Patient Preference**
Adenomas Not Amenable To Endoscopic Resection Or High-Grade Dysplasia	**Segmented Or Extended Colectomy Depending Upon Clinical Scenario – Lower Endoscopic Examination Every 1-2 Years** **Consider Prophylactic Hysterectomy/BSO At Time Of Colon Surgery If Postmenopausal Or Family Completed**

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FAP and AFAP Risk Management

FAP And AFAP Surveillance			
Site	**Procedure**	**Age To Begin**	**Repeat Test**
Colon-FAP	Sigmoidoscopy or Colonoscopy	10-15 Years	Annually
Colon-AFAP	Colonoscopy	Late Teens (Depending On Age Of Polyp Development In The Family)	1-3 Years
Colon-After Colon Surgery	Endoscopy Of Remaining Rectum, Ileal Pouch, Or Ileostomy	After Colon Surgery	6 Months To 3 Years (Depending On Polyp Number And Type Of Surgery)
Duodenum	Baseline Upper Endoscopy (Including Side-Viewing Examination)	25-30 Years	1-4 Years
Thyroid	Physical Examination And Consideration Of Ultrasound	Late Teens	Annually
Screening for other related cancers (brain, pancreatic, hepatoblastoma, etc.) may be considered.			

Managing Your MAP Cancer Risks			
Site	**Procedure**	**Age To Begin**	**Repeat Test**
Colon-Small Adenoma Burden, Manageable By Colonoscopy	Colonoscopy	25-30 years	1-2 Years
Colon-Large Polyp Burden	Counseling Regarding Surgical Options	Varies Based On Polyp (Adenoma) Burden	N/A
Colon-After Colon Surgery	Endoscopy Of Any Remaining Colon And Rectum	After Colon Surgery	1-2 Years
Duodenum And Stomach	Upper Endoscopy And Side Viewing Duodenoscopy	30-35 Years	3-5 Years

Otogenetics Corporation

4553 Winters Chapel Road, Suite 100, Atlanta, GA 30360 USA

www.otogenetics.com