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corporation

Understanding Colorectal Cancer Screening

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Discovery Diagnosis Better Health Outcomes

About 5 to 10 percent of all colorectal cancers are caused by a heritable mutation

Most cancer occurs by chance. In some families we see more cancer than we would expect by chance alone. In families that carry a genetic change or mutation that is associated with causing cancer, the cancer risk is much higher than that of the general population. Genetic testing helps to determine which of these families have cancer that is related to an inherited gene mutation.

Sporadic Cancer – Cancer which occurs by chance. People with sporadic cancer typically do not have relatives with the same type of cancer.

Familial Cancer – Cancer likely caused by a combination of genetic and environmental risk factors. People with familial cancer may have one or more relatives with the same type of cancer; however, there does not appear to be a specific pattern of inheritance (eg, the cancer risk is not clearly passed from parent to child).

Hereditary Cancer – Cancer occurs when an altered gene (genetic change or mutation) is passed down in the family from parent to child. People with hereditary cancer are more likely to have relatives with the same type or a related type of cancer. They may develop more than one cancer and their cancer often occurs at an earlier than average age.

Types of Common 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. The majority of Lynch syndrome is due to mutations in the MLH1, MSH2, MSH6, PMS2, or EPCAM (also known as TACSTD1) genes.

   These mutations 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.

   Lynch Syndrome affects 28,000 individuals annually. 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.

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 caner within 10 years	30%	3.5%
Second cancer within 15 years	50%	5%

2. Familial Adenomatous Polyposis (FAP) or Attenuated FAP (AFAP) which accounts for <1% of colorectal malignancies.

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

3. **MYH-Associated Polyposis (MAP)** is a syndrome that was discovered fairly recently and is rare. 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 and individuals with MAP have mutations in both of their MYH genes, one from each parent.

Other Types of Inherited Cancer

1. **Hyperplastic Polyposis Syndrome** is very rare and 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.

Screening Guidelines

If you are age 50 and older, you are at **average** risk if you 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.

You are at **increased** risk if you 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

Otogenetics Genetic Testing for Colorectal Cancer

❖ **Colorectal, Endometrial and Ovarian Cancer – 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**

Benefits and Limitations of Testing

BENEFITS	LIMITATIONS
Personalized risk assessment	Testing does not detect all causes of hereditary cancer
Appropriate medical management to help reduce cancer risk. Important information for family members	A negative result is most helpful when there is a known mutation in the family
Reduced anxiety and stress	Some variants are of unknown clinical significance

What Do My Test Results Mean?

Testing does not tell you if you currently have cancer. Your test results tell you about your inherited *risk* of having cancers.

A **negative** test result means that you do not have a gene mutation in the genes that were evaluated.
Although the gene test can detect the majority of mutations:

- You could have a gene mutation that the test wasn't targeted to detect.
- Or if your family carries a high-risk gene mutation that researchers haven't yet identified then the test would not be able to detect this gene mutation and you could be a carrier.

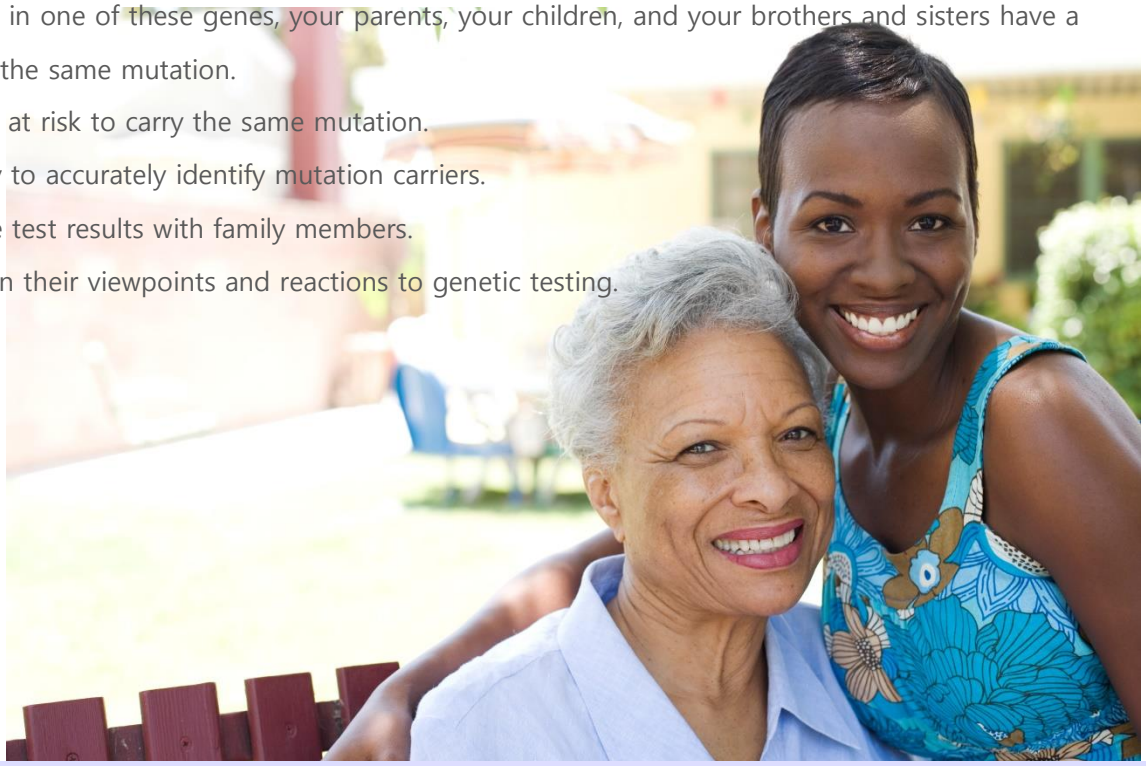
A negative test result does not eliminate the chance of developing non-hereditary cancer. You may still have the same cancer risk as that of the general population.

A **positive** test result means that you have a gene mutation that is associated with colorectal cancer. A positive test result **does not** mean that you have cancer or that you will certainly have cancer. A positive test result tells you that you have a much higher risk of developing CRC cancer compared with someone who does not have the mutation. A positive test result helps you to better understand your personal risk of developing colorectal and associated cancers. You can then make choices on what to do to reduce your risk and about what follow up care is right for you.

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.

Hereditary Colon Cancer Mutations Can Be Passed On In A Family

- If you have a mutation in one of these genes, your parents, your children, and your brothers and sisters have a chance that they have the same mutation.
- Other relatives may be at risk to carry the same mutation.
- Testing is the only way to accurately identify mutation carriers.
- It is important to share test results with family members.
- Individuals may differ in their viewpoints and reactions to genetic testing.



Colorectal Cancer Risk Management

Options for reducing cancer risk are available whether or not you have already had a diagnosis of cancer and/or polyps (adenomas). Your healthcare providers will discuss your testing options and medical management options for reducing risk. Please discuss your options with your medical professionals to determine how you will manage your cancer risks.

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.

Patient Advocacy

Gynecologic Cancers Foundation

www.thegcf.org

Lynch Syndrome International

www.lynchcancers.org

Fight Colorectal Cancer

http://www.globalcoloncancer.com

Please visit our Patient Portal at

www.otogenetics/patientportal.com

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