

## Hereditary Colorectal Cancer Syndromes

Most people develop colorectal cancer due to chance or as a result of multiple risk factors that occur over the course of a lifetime. Risk factors for colon cancer include increasing age, history of colon polyps, cigarette smoking, heavy alcohol use, family history, obesity/being overweight, low physical activity, a diet high in red and processed meats, and a personal history of certain medical conditions, such as inflammatory bowel disease and type 2 diabetes. However, approximately five to 10 percent of people who are diagnosed with colorectal cancer develop it due to a hereditary colorectal cancer syndrome.

A hereditary colorectal cancer syndrome is an inherited increased risk to develop colorectal cancer and possibly other cancers. Inherited conditions can be passed to an individual from one or both of their parents. People who have a hereditary colorectal cancer gene mutation have a higher-than-average risk of developing colorectal and possibly other cancers compared to the general population.

### What Causes Hereditary Colorectal Cancer?

Hereditary colorectal cancer syndromes are caused by an inherited change, called a mutation, in a gene. Genes are the set of instructions that tell all of the cells in our bodies what to do. Genes determine features, such as hair and eye color, the shape of our nose, and blood type. A mutation is a change in a gene that causes it to stop working. In the case of hereditary colorectal cancer, a gene that normally helps to prevent cancer stops working. Therefore, certain types of cancer are more likely to develop and are also more likely to occur at a younger age.

The most common hereditary colorectal cancer syndrome is called Lynch syndrome. Lynch syndrome is sometimes referred to as hereditary non-polyposis colorectal cancer syndrome (HNPCC). Lynch syndrome is caused by a mutation in any one of the following genes: MLH1, MSH2, MSH6, PMS2, or EPCAM. When someone has a mutation in one of these genes, they have an increased chance of developing colorectal, uterine, ovarian, stomach, and some other types of cancer.

There are other genes that can cause hereditary colorectal cancer. Some of these genes also cause a large number of colon polyps to develop, which is called “polyposis”. These colon polyps can become cancerous. The two most common syndromes that cause hereditary colon polyposis are called familial adenomatous polyposis (FAP) syndrome and MUTYH-associated polyposis (MAP) syndrome. These syndromes are caused by mutations in the APC and MUTYH genes and can cause hundreds or thousands of colon polyps, as well as an increased risk for colon and other cancers. Other genes that can increase colorectal cancer risk, including several that also cause colon polyposis, include: ATM, AXIN2, BLM, BMPR1A, CDH1, CHEK2, GALNT12, GREM1, MLH3, MSH3, PTEN, RNF43, RPS20, SMAD4, STK11, and TP53.

### **How Is A Hereditary Colorectal Cancer Syndrome Passed On Through A Family?**

Each person inherits two copies of most genes: one from their mother and one from their father. In most cases, inheriting a mutation in just one copy of a hereditary colorectal cancer gene is enough to increase the risk of developing colorectal cancer and possibly other types of cancer. There is a 50 percent chance that a person with a hereditary colorectal cancer gene mutation will pass it to each of his or her children. However, if a person does not inherit the gene mutation that was identified in his or her family member(s), that person usually has an average chance of developing colorectal cancer.

There are some exceptions to the type of inheritance described above. For example, the hereditary polyposis syndrome MAP is only inherited if a person receives two mutated copies of the MUTYH gene. In other words, a person must inherit a mutated copy of the MUTYH gene from both of their parents in order to have a diagnosis of MAP. Some other hereditary colon cancer syndromes, including those caused by mutations in the NTHL1 and MSH3 genes, are also inherited in this way.

### **Why Is It Important To Diagnose A Hereditary Colorectal Cancer Syndrome In A Family?**

For someone who already has been diagnosed with colorectal cancer, genetic testing may provide information about the chance of developing another cancer and may impact treatment.

Because hereditary colorectal cancer syndromes are inherited, the diagnosis also affects family members. If genetic testing identifies a mutation in a gene that causes a hereditary colorectal cancer syndrome, family members can be tested for that same gene mutation.

It is very important for people with a hereditary colorectal cancer syndrome to consider specialized cancer screening. Cancer screening exams are medical tests performed to help identify cancers at their earlier, more treatable stages. There may also be medical options that can lower the risk of developing cancer. Usually, a team of specialists will tailor a cancer screening and risk reduction plan to each patient and his or her family members. As new information becomes available about a hereditary colorectal cancer syndrome, the screening plan may be updated.

### **How Is A Hereditary Colorectal Cancer Syndrome Diagnosed?**

A genetics evaluation includes a review of a person's medical and family history. This information is used to determine the likelihood that the person has a hereditary colorectal cancer syndrome. A genetic counselor usually conducts this evaluation.

Some signs that suggest hereditary colorectal cancer may run in a family include:

- Multiple close relatives with colon, uterine, and other Lynch syndrome related cancers.
- Colorectal cancer that does not produce certain proteins or that has a feature called "microsatellite instability".
- Colorectal cancer diagnosed at a young age (< 50 years old).
- More than one occurrence of colorectal cancer in a single person.
- Multiple (> 10 to 20) colon polyps.

If you or your family members have any of the above features, you may consider the option of genetic counseling and testing. We encourage you to discuss this with your physician.

## Genetic Testing

A person's blood or saliva sample can be tested to search for a genetic mutation that causes a hereditary colorectal cancer syndrome. This testing may be limited to the Lynch syndrome genes, colon polyposis genes, and/or may include other genes that cause hereditary colorectal cancer. In general, there are three types of results:

- **Positive for a mutation.** If a mutation is found, then the diagnosis of a hereditary colorectal cancer syndrome is confirmed. Next, other family members may have a genetic test to learn whether or not they carry the same mutation and have the same hereditary colorectal cancer syndrome.
- **Negative for a mutation.** If no mutation is found the cancer in the family may not be hereditary. However, a negative genetic test result does not eliminate the possibility of a hereditary colorectal cancer syndrome in the family. This is because current genetic testing technology is not able to identify all mutations that cause hereditary colorectal cancer. It is also possible that the colorectal cancer in the family is being caused by a gene that was not included in the test.
- **Variant of unknown significance.** A variant is a genetic change that does not provide clear information regarding cancer risks. A variant may represent benign genetic differences from one person to the next or may actually represent a true genetic mutation. Until more information regarding the variant is collected by researchers, it remains unknown whether a genetic variant increases cancer risk. A variant result should not be used to make medical decisions.

If you are concerned about the possibility of a hereditary cancer syndrome in your family, you are encouraged to discuss your personal and/or family history with your health care provider. Your physician may refer you to the Cancer Genetics Program of the MD Anderson Cancer at Cooper for genetic evaluation and discussion of your genetic testing options. If genetic testing is warranted and you choose to proceed, a blood or saliva sample will be taken during your visit. Please note that health insurance companies may cover most if not all of the cost of genetic testing.

### Where Can I Find More Information?

Lynch Syndrome Screening Network at [www.lynchscreening.net](http://www.lynchscreening.net).

Alive N' Kickn is a Lynch syndrome advocacy organization. Visit [www.alivenkickn.org](http://www.alivenkickn.org).

Cancer.Net is an oncologist-approved cancer information from the American Society of Clinical Oncology. Visit [www.cancer.net/cancer-types/colorectal-cancer](http://www.cancer.net/cancer-types/colorectal-cancer).

National Cancer Institute has valuable cancer related health information on more than 200 cancer types, clinical trials, cancer statistics, prevention, screening, risk factors, genetics, and support resources. Information is available in Spanish. Visit [www.cancer.gov](http://www.cancer.gov).

American Cancer Society (ACS) is a voluntary national health organization that supports research, provides information about cancer, and offers many programs and services to patients and their families. Information is available in Spanish. Visit [www.cancer.org](http://www.cancer.org).

Genetic Alliance, Inc., supports individuals with genetic conditions and their families, educates the public, and advocates for consumer-informed public policies. This site provides information on genetic policy, research and a helpline for people with genetic questions. Visit [www.geneticalliance.org](http://www.geneticalliance.org).