Understanding Hereditary Colorectal Cancer and Genetic Testing
GENETICS

This resource is designed to inform you about colorectal cancer (CRC) that is passed down through families (hereditary). It breaks down the basics of inherited genetic syndromes and the importance of genetic testing.

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FIGHT CRC

ABOUT FIGHT COLORECTAL CANCER

We FIGHT to cure colorectal cancer and serve as relentless champions of hope for all affected by this disease through informed patient support, impactful policy change, and breakthrough research endeavors.

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COVER:
Evelyn Keener
Stage I survivor, FAP

• FightCRC.org •
GENES AND CANCER

Inside the center of each of our cells is a full set of our genetic information. This information is found inside the nucleus. Within the nucleus are structures called chromosomes, which are made up of very long strands of DNA. Think of DNA like a library. Within our genomic “library,” each gene is like a book that gives instructions on how to do something specific in the body—making us uniquely who we are. Some genes give instructions to make our eyes a certain color, others determine our height. Your genes that determine whether or not you can wiggle your ears. Some genes give instructions to your body about how to prevent cancer. **All colorectal cancers are due to genetic abnormalities, but not all colorectal cancer is passed down through families.**

As we age, we all acquire genetic mutations—this is natural. But, if we acquire mutations in the genes that work to prevent cancer, or if too many mutations accumulate in a cell and it can no longer control its growth, we can develop cancer.

Cell progression from normal cells to malignant cells

**PEOPLE WITH HEREDITARY CANCER ALREADY HAVE THE FIRST MUTATION**
HOW HEREDITARY (INHERITED) CANCER WORKS

In our bodies there are two copies of every gene – one from each biological parent. If one copy does not work well, we have a second copy that should help us stay well. Like a car, if the front brakes are not working well, the back brakes still function and the car can stop.

When someone has hereditary cancer, this means that when they were born, there was already a mutation in one of their cancer prevention genes, an inherited gene mutation, but the second copy of that gene initially still works to prevent cancer. This is why they were not born with cancer.

If they acquired a mutation in the second copy of the gene (the gene that had previously been working fine), then their cells no longer have a functioning copy of the cancer prevention gene. This is how cancer can begin.

Those born with an inherited gene mutation have a higher likelihood to develop cancer because they are born one step closer to developing a cancer. They already have a mutation in every cell inherited from one of their parents, so one set of brakes is not working. As a result, it doesn’t take as long for the second copy to stop working and they are more likely to develop cancer at an earlier age. In addition, this can happen more than once during their lifetime so they are also more likely to develop more than one cancer. Of course, it is also possible that they will never acquire a second mutation and they may not develop cancer at all.
While most INHERITED cancer mutations are due to family history, some are de novo—MEANING THEY arise new in that individual. Thus, even if family history is negative, cancer at a young age is typically an indication to consider genetic testing.
ON AVERAGE, A PERSON’S LIFETIME RISK OF DEVELOPING SPORADIC COLORECTAL CANCER (CRC) IS 5% (1 IN 20).

SPORADIC CANCER
60%-70% of colorectal cancers
(90% of all cancers)

FAMILIAL CANCER
20%-30% of colorectal cancers

INHERITED / HEREDITARY CANCER
5 - 10% of colorectal cancers

SPORADIC CANCERS TYPICALLY:
✓ Form later in life (after age 50)
✓ Don’t have a clear familial pattern
✓ Don’t have an inherited gene mutation

Most cancer is sporadic, meaning an individual starts out with healthy genes in their cells and genetic mutations accumulate over time (typically due to age and environment).

CRC RISK FACTORS FOR ALL PEOPLE, INCLUDING THOSE AT HIGHER RISK, INCLUDE:
• Getting older
• Smoking
• Excessive alcohol
• Fatty diet
• Obesity
• Precancerous colon polyps (adenomas)

Modifying your lifestyle can lower risk of CRC. So can screening for early detection – this can help you detect cancer early and even prevent it from forming. Talk to your doctor about a screening schedule that’s right for you.

FAMILIAL CANCER
When a family has a “cluster of cancers,” or multiple family members with cancer, it’s considered familial. Family members may exhibit similar behaviors in terms of what they eat, their activity level and their environmental exposures, and these similarities create similar risks for developing CRC. In addition, there may be multiple, less penetrant gene mutations that lead to a slightly increased cancer risk, but these lower-risk gene mutations are currently unknown.
If you have a family member with CRC, your risk for CRC is increased depending on how closely related you are, and how old they were when they were diagnosed.

**FAMILIAL CANCERS TYPICALLY:**
- Have multiple family members with cancer, but no clear pattern
- Occur later in life (over age 50)
- Are a result of:
  - Multiple minor gene variant(s) that increase cancer risk slightly
  - Shared environment (family members tend to have similar diets and other exposures)
  - A combination of the two

If you have close family members diagnosed with CRC, your risk is likely increased. Talk to your doctor about when to start screening and about genetic testing. Current guidelines recommend all individuals with a first degree relative begin colon screening at age 40, or 10 years prior to the youngest diagnosis of colon cancer in the family.

**HEREDITARY CANCER TYPICALLY:**
- Occurs at a younger age (under age 50)
- Affects many generations on one side of the family with the same (or related) cancer(s)
- Can lead to two primary cancers or two related cancers in the same individual

Learning if you have an inherited gene mutation predisposing you to cancer could influence your prevention measures.

This could include:
- Increased screening for CRC and other cancer types (if appropriate)
- Taking certain medications to lower cancer risks
- Preventative surgeries to remove an organ before cancer develops

**HEREDITARY (INHERITED) CANCER**

If you have a hereditary predisposition to CRC, your risk of developing it is increased significantly. This is different than familial cancer because it involves a specific, identifiable gene mutation. Different gene mutations increase the risk for colorectal cancer to varying degrees. Your exact risks will depend upon that gene mutation.

**FAMILY HISTORY MAY CHANGE YOUR SCREENING RECOMMENDATIONS!**

**SPORADIC = AVERAGE RISK**
- General Population/Average Risk CRC Screening (starting at age 45 as recommended by the American Cancer Society).

**FAMILIAL = MODERATE RISK**
- Personalized CRC Screening Recommendations (in general, 10 years before the age of a first-degree relative who was diagnosed with CRC and/or adenomatous polyps).

**INHERITED = HIGH RISK**

- Genetics -
Family history and being diagnosed with cancer under age 50 are typically the greatest indicators of a family’s need to consider genetic testing.

Who is a good candidate for genetic testing?

- Anyone diagnosed with CRC and/or endometrial cancer under the age of 50
- Anyone with 3+ family members with a Lynch syndrome associated cancer (see page 26*)
- Anyone with 2+ Lynch syndrome associated cancers in a single family member
- Anyone who has abnormal IHC for mismatch repair proteins in a tumor (see page 27*)
- Anyone with a tumor that shows MSI (see page 27*)
- Anyone with a family member who has an identified gene mutation
- Anyone who has had 10+ polyps removed over the course of their lifetime, or who has a family member who has had 10+ polyps.

Knowing if the cancer in your family is hereditary is valuable information for you and your family members. If genetic testing identifies an inherited mutation, it can help individuals understand what is causing the cancer in their family.

It can also make individuals aware of other cancer risks that may be increased. This information may help other family members understand whether or not to seek genetic testing.
Talk to your family members to learn about cancers that run in your family, as it could affect your screening recommendations.

**Start the discussion using the following questions:**
(Or use the online family history tools referenced on page 7*)

1. Has anyone in the family been diagnosed with colorectal cancer? At what age?
2. Has anyone in the family had multiple colorectal polyps detected and removed? How many polyps?
3. Have you been screened for CRC? (Anyone over age 50 who has not been screened for CRC yet should be encouraged to get screening as soon as possible.)

**What to do with an incomplete family health history?**

Not everyone has access to their family health history. This could include individuals who were adopted, have estranged family members, and others. If this is the case for you and you cannot access information by asking another family member or through public records, you will likely receive “average risk” screening. Talk to your doctor if you have concerns or signs and symptoms of CRC.

Check out the Taboo-ty Podcast episode about incomplete family histories: [FightColorectalCancer.org/Family-History]
A risk assessment identifies how likely it is that you will develop a certain cancer.

In ideal cases, your doctor will refer you to a genetic counselor if there is suspicion that there could be an inherited cancer mutation. But sometimes, you may need to advocate for yourself. If you have a family history of CRC or numerous polyps, tell your doctor. You can also look for a genetic counselor online or by phone.

Resources for finding a genetic counselor in your area:

- National Society of Genetic Counselors: [http://nsgc.org](http://nsgc.org)
- Call large academic centers in your area as they may have a genetic counselor on staff

Talk to a Genetic Counselor.

“Genetic counselors have advanced training in medical genetics and counseling to guide and support patients seeking more information about how inherited diseases and conditions might affect them or their families, and to interpret test results.” - National Society of Genetic Counselors

During genetic counseling, your genetic counselor will explain in detail how families inherit cancer and how cancer grows.

The goal of genetic counseling is to help you explore whether or not genetic testing is right for you.

“Many individuals think that an appointment with a genetic counselor simply means doing genetic testing; however, testing is only one small piece of the overall session.”

– Michelle Springer, MS, CGC
Certified Genetic Counselor
A genetic counselor will:

• Review and discuss your medical and family history

• Discuss the likelihood that the cancer in your family could be due to an inherited gene mutation

• Explore options for genetic testing

• Explain what a positive test result would mean to you

• Provide you with your personal risk for developing cancer if the testing is positive or negative

• Review what the screening recommendations would be if the testing is positive or negative

• Discuss the pros and cons of genetic testing

• Help you understand if your health insurance will cover the test

• Help you learn ways to manage your cancer risk

• Discuss options to join genetic-related research studies, if appropriate

If you choose to move forward with genetic testing, your relationship with your genetic counselor will continue, even after testing is over. They can help guide you with screening recommendations and keep you up to date on research that may affect you.
It’s your decision whether or not to proceed with genetic testing.

If you’ve been diagnosed with CRC, here are some things to consider and discuss with your genetic counselor:

• Do you have children or do you someday want to have biological children? If you test positive for a gene that increases CRC risk, it may get passed along to your kids. Also, if you test positive, other immediate family members might be at risk.

• Do you have issues with the “unknown?” We currently do not know every gene associated with CRC. Thus, a negative result does not necessarily mean that your cancer or the cancer in your family is not due to an inherited mutation. Some of the newer genes to test for may not be well characterized, so you may not receive exact cancer risks or proven screening recommendations. In addition, you may receive inconclusive test results. More on page 16.

• Do you need to make treatment decisions? Some treatments are more or less effective than others, depending on the presence of a genetic mutation. Genetic testing may help you and your doctor personalize your treatment plan.

If you have NOT been diagnosed with CRC but have a strong family history, here are some things to consider and discuss with your genetic counselor:

• If you test positive, your immediate family could also be at risk.

• If you test positive, you can be proactive about screening and prevention.

• If you test negative, it could relieve anxiety.

• If you test negative, but genetic testing has not yet been done on other family members, the results are not as informative and your risk for cancer would still be increased.
INFORMED CONSENT

If you decide to get tested, you will give written informed consent. This means that you clearly understand:

1. The purpose of the test
2. Why you and your family are candidates
3. The pros and cons of genetic testing
4. The accuracy of the testing
5. That you have the right to change your mind at any time

STEP FOUR: QUESTIONS AND ANSWERS MOVING FORWARD

Who orders the tests?
Genetic testing can be ordered by a doctor, genetic counselor, nurse, physician assistant, or another provider. However, some insurers will only cover genetic testing if it is ordered by a board-certified geneticist or genetic counselor, therefore you may want to check with your insurance policy. Additionally, you can order testing online from certain websites. If you choose to go this route, it’s critical to follow up with a genetic counselor or another health care provider to make sure results are clearly understood and the correct follow-up and screening care are recommended. It is also important to understand that not all genetic tests are created equally. It is important to check with a provider to ensure any genetic test you order online is accurate and comprehensive.

What kind of sample is needed for genetic testing?
For hereditary cancer testing, a nurse at the genetics office will typically collect blood or saliva.
What’s the difference between germline and somatic testing?

Germline testing (genetic alterations): Germline mutations are the gene mutations you were born with, and therefore are found in every cell of your body. They are typically (although not always) inherited from a parent.

There are 3 types of germline tests:

1. Single site: looks at a specific mutation in a specific gene
   - If you already have a family member with a known mutation, you may receive this test since genetic counselors know what gene mutation to look for

2. Single gene: looks at many locations along one or a few specific genes to find a mutation
   - This type of test is done when clinical features (type and number of polyps) suggest a certain gene might hold the mutation

3. Multi-panel gene: used to evaluate many genes in a single test
   - This type of test is done when clinical features (type and number of polyps) could be consistent with multiple different hereditary cancer syndromes

Somatic testing (genomic alterations): Somatic mutations arise spontaneously in a person’s body during their lifetime. They are acquired over time and therefore, they are not passed down in a family. Somatic testing (also referred to as biomarker testing or tumor testing) is done on tumors to see what gene mutations have accumulated in cancer cells. It is often used to make treatment decisions – to find better therapies targeting specific gene mutations found in cancer cells.

What is Next Generation Sequencing (NGS)?

Next Generation Sequencing (NGS) is a method of testing that looks at many genes at the same time. Here are some ways NGS has changed testing for cancer patients:

- Test more genes than ever before
- Lower cost of testing
- May find an answer more quickly than testing one gene at a time
- Most insurers cover testing for patients who meet criteria or have a family history
- Many labs offer patient assistance for out-of-pocket costs
- Medicare covers testing for individuals who meet certain criteria
- Improved mutation (and biomarker) detection
- Give insight to best cancer treatment options
When is the right time for testing?

This is different for everyone. Physicians often discuss genetic testing at the time of cancer diagnosis, as it may guide treatment decisions. However, some patients may be so overwhelmed at this time (processing new and complicated information) that genetic testing may be pursued at a later time. Also, because research is moving rapidly in this field, many doctors may recommend patients receive genetic testing years after their cancer treatment ends. Many individuals who have not had cancer would like to pursue genetic testing to see if they have inherited a genetic mutation. Testing for cancer genes is generally not performed until after age 18 (with the exception of some of the polyposis conditions, such as FAP).

Who should get tested first?

Looking for a gene mutation is like looking through a book for a misspelled word. For the best chances of discovering whether or not a mutation runs in your family, it’s best to test a family member who has already had cancer or multiple colon polyps first. They are the most likely person in your family to have a genetic mutation. In this case, the testing looks through many genes to find a mutation that may be associated with a hereditary cancer predisposition. Once a mutation is identified in a family, testing for other family members is targeted, looking only at the specific genetic change in the family.

Who pays for genetic testing?

Many insurance companies realize the importance and value of testing and provide coverage for individuals who meet certain criteria. Your genetic counselor will discuss this with you to determine if testing is a covered benefit. For individuals who do not qualify or choose to pay out of pocket, costs are often less than $300.

What about discrimination?

State and federal laws are in place to protect your genetic information from being used against you. The Genetic Information Nondiscrimination Act (GINA) was put into law to avoid employer discrimination against people with genetic predispositions to disease. Because of GINA, it is unlawful for employers with more than 15 employees to discriminate based on genetic information. The law also keeps health insurers from dropping, refusing to cover, or charging higher premiums for those with positive genetic test results.

For more information: www.ginahelp.org
Genetic testing is not perfect and we have not yet discovered all of the genes linked to hereditary CRC.

Your genetic counselor will tell you what your results mean for your specific case, and you will work with them and your doctors to decide on screening recommendations. Here is a brief overview of some results you may encounter.

Positive
A positive test result means you have a known, pathogenic (or disease-causing), genetic mutation. This can affect which treatment your doctor recommends if you have a cancer or develop cancer in the future. It may also help guide specific cancer screening recommendations for you.

If you or a family member test positive for a gene mutation, it may affect your blood relatives. Most hereditary cancers are inherited in a dominant pattern, meaning that first-degree relatives (parents, siblings, children) of someone with a mutation have a 50% chance of carrying the mutation and may want to get tested. Work with your genetic counselor to create a plan for telling family members about genetic testing, and suggest they talk with their doctors to see if it is right for them.

Variant of Uncertain Significance / Variant of Unknown Significance (VUS)
A VUS result means there’s an identified change (variation) in the gene that is different than the normal gene, but it’s unknown if it leads to an increased risk for cancer. Up to one third of people who receive multi-gene panel genetic testing get a VUS.

Many variants are likely of no concern and represent normal, unique changes in our genetic code. A VUS does not change clinical management unless proven pathogenic. If researchers later discover that a VUS you have is, in fact, related to cancer risk, it would then be reclassified as a positive/clinically significant inherited gene mutation and you would be contacted by your genetic counselor with your updated result. At that point, your preventive screening schedule and/or treatment plan would change to reflect the new diagnosis. Most labs will contact the clinician who ordered your test if new research shows that a VUS is shown to be cancer-causing. *This is why it’s important to let your genetic counselor know if you move, change phone numbers, or update your email address.
**Negative / No Known Mutation**

Many people test negative for genetic mutations related to hereditary CRC. While this may mean that the cancer is familial or sporadic, the possibility that the cancer is linked to a gene mutation that was not tested for (or has not yet been discovered) cannot be excluded.

When genetic testing is negative, screening and surveillance guidelines are based on your specific personal and family history, and will fall within the recommendations provided by the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network.

If there is a known genetic mutation in your family and you test negative for that specific genetic change, this is considered a “true negative” result. At that point, your cancer risk would likely be that of the general population, also known as “average risk” and you would follow standard screening guidelines.

To learn more about family history, watch the Fight CRC webinar [Genetic Testing and YOU!](https://FightCRC.org) at FightCRC.org
Many different emotions can arise due to genetic testing.

It’s normal to feel emotional when going through genetic counseling and testing. Talk to your genetic counselor about any worries you have and schedule an appointment with a mental health professional (psychologist, social worker, etc.) if you need to. You may even consider inviting your family to join you for an appointment.

- **Waiting for test results** can take up to a month, leaving you feeling vulnerable and uncertain. If you feel stressed during this period, engage in activities that take your mind off of it. Try relaxation techniques like yoga and meditation, go on a hike with friends, or start a new book. Talk to your family about your concerns. Talking to your genetic counselor who is experienced in this topic can be extremely beneficial.

- **Uncertain results.** Receiving a VUS can create distress. You might worry if one day you will find out that it is an inherited gene mutation. If you have a VUS identified and are struggling with worry, talk it through with your genetic counselor.

- **If you have received news that you carry an inherited cancer gene mutation,** it’s common to feel troubled and wonder if you will get cancer, or if you will get cancer again if you’ve already been diagnosed.

  While these are normal concerns, remember that it is not a guarantee that everyone with a gene mutation will develop cancer; rather they are predisposed. Try to focus on things that you do have control over to help lower cancer risk, such as leading a healthy lifestyle and increasing physical activity. Most importantly, follow the increased surveillance recommendations that you were given.

- **If you’re a parent** discovering that you may have passed a genetic mutation to your children, you may experience guilt. It’s a good idea to talk to a mental health professional if feelings of guilt come up for you. Remember that sharing your family and personal health history is extremely important for your children. With this information they can keep up to date on their own screening and prevention measures. With the information, they can keep abreast of their own screening and prevention measures.

There are many individuals who can help you work through your testing and cope. You are not alone!
While approximately 5-10% of cancer is hereditary, not all cancer types have known mutations associated with an increased risk of developing cancer. In addition, there are likely mutations that haven’t been discovered yet. As research evolves in this area, Fight CRC will provide updates on new genetic findings. Remember: we all carry genes that can lead to disease. In many cases, we may not know what these gene mutations are or we may find out after a cancer diagnosis. If you have tested positive for a mutation, your family has powerful information about their genetic code that enables them to be more proactive and potentially prevent cancer or detect it early.

While we can’t change our genes, we can potentially change the outcome!
Wenora Farrell
Stage III survivor
At 45, Wenora was diagnosed with stage IIIb colon cancer. Four years post treatment (and no evidence of disease), her doctor suggested genetic testing. She left the appointment armed with brochures, which quickly landed in the trash – “I’m nearly five years cancer free. What do I have to worry about?” she thought.

At her appointment the following year, Wenora’s oncologist asked if she had considered the genetic testing. With resolve, she answered, “No.” Her oncologist sat her down for a more thorough consultation. She knew that Wenora has a family history of cancer: her mother had a brain tumor at age 42 and her brother had been recently diagnosed with colon cancer. Her maternal grandfather had passed away from colon cancer at age 38.

“After speaking with my doctor, I scheduled an appointment for testing— what did I have to lose?”

As the appointment neared, Wenora began to worry about insurance coverage and potential out-of-pocket expenses. “I didn’t want to pay thousands of dollars out of pocket for something I wasn’t even sure I needed.” Wenora’s genetic counselor made the call to her insurance company, explained her family history and personal history of CRC and confirmed that the testing would be covered.

Genetic testing followed with a simple blood draw. She waited one month to get the results, and when they came back she learned she tested positive for Lynch syndrome.

Wenora was shocked. Her doctor soon explained her options for surveillance and management of Lynch-associated cancers (see page 26). She was told she had a 60% chance of developing uterine cancer, among others.

“After talking with my gynecologist, I decided to be preventive with my care and get a total hysterectomy.”

Her surgery was a success; however, her pathology report revealed a diagnosis of stage 1A endometrial cancer with a grade 3 tumor.

“What surprised me most is how spot on everything was, yet how empowered I felt to take action as a result of my personal and family history. Even if I had selected additional screenings instead of the hysterectomy, the endometrial cancer wouldn’t have been detected. If I didn’t get the genetic testing, who knows what would have happened. As a culture we don’t often discuss the real reason people die or talk about their cancer experiences. Now my daughters, armed with this knowledge, have the opportunity to take their health into their own hands.”

WENORA’S STORY

Photo Credit: Nick Wilkes
“Genetic testing has played a huge role with my family. The history of (mostly) colon cancer in my family is well documented, from my grandfather, my father, my brother, and me.

**Because of the genetic testing and subsequent MLH1 Lynch Syndrome diagnosis, we have been able to stay ahead of the cancers, and treat them at earlier stages when it can be most effective.**

My oldest son had genetic testing when he turned 18, and with the gene being confirmed (it’s a 50/50 chance), he has had three yearly colonoscopies so far and they've all been clear. The younger ones will follow suit when they turn 18 as well. Lynch tumors are all MSI High, and as such, the potential for immunotherapy as a treatment could be in the not-too-distant future. Besides having the AliveAndKickn HEROIC registry for Lynch Syndrome patients, I also work at Mount Sinai Genetic Testing Lab where we screen, counsel, and treat patients all the time, so it's been even more rewarding for me to share my story and encourage testing early.”

- David Dubin
Founder of AliveAndKickn
We are now able to identify individuals who have not yet developed cancer but who may be at a higher risk of developing cancer. These include individuals who have been found to carry a cancer predisposition gene mutation (like Lynch syndrome or FAP) and individuals who have a positive family history of cancer.

Previvor is a term now used to describe these individuals who are at a higher risk of developing cancer but who have not yet developed the disease.

The key is knowing if you are at risk and what you can do differently to minimize that risk.
Hereditary Colorectal Cancer (CRC) occurs when a single gene mutation is passed down (inherited) through the family, leading to a potentially significantly increased cancer risk among family members.

Individuals are suspected of having a hereditary syndrome if they meet certain criteria. For example, a certain number of polyps detected during a screening colonoscopy. As our knowledge of hereditary syndromes has evolved, it is apparent that there can be significant overlap in the features present in the various CRC syndromes. Given this, testing is recommended to confirm which syndrome is actually present.

Most hereditary colorectal cancers are autosomal dominant disorders. This means that the individual carries one normal copy of the gene and one copy of a gene that is mutated, leading to a predisposition (higher risk) for cancer. If you are diagnosed with a dominant condition, your biological parents, children and siblings have a 50% chance of also having it. There are a few exceptions to this rule, including MUTYH-Associated Polyposis (MAP) syndrome and NTHL1-Associated Polyposis (NAP) syndrome, as well as a few others. With recessive disorders, the affected individual has inherited two gene mutations, one from each parent and their children are only at risk for having the condition if their other parent happens to be a carrier of a mutation in the same gene.

The following information is what we know as of October 2019. As our knowledge continues to grow, specific cancer risks and screening recommendations may change. The screening and surveillance recommendations listed here are a general summary and not comprehensive. For the most up-to-date information on hereditary colorectal cancer, visit FightCRC.org.
Autosomal dominant

FAMILY TESTING

DNA → Replication → RNA → Translation → PROTEIN

SNP

Unaffected mother

Affected Father

Unaffected DAUGHTER

Unaffected SON

Affected daughter

Affected SON

Affected DAUGHTER

Affected SON

Unaffected mother

• Genetics •
Lynch Syndrome is **the most common form** of hereditary CRC, with over 1.2 million people in the US currently diagnosed. Up to 3-5% of all CRC is due to Lynch syndrome. Unfortunately, the condition is highly underdiagnosed – it is estimated that 95% of people who have Lynch syndrome don’t know they have it.

**Quick facts about people with Lynch syndrome:**
- 50-80% lifetime risk of CRC
- Diagnosed with CRC at an earlier age (<50)
- Multiple generations on one side of the family (great-grandparent, grandparent, parent, aunt/uncle, child) often have cancer
- ‘Clustering’ of certain cancers in the family (listed below)
- Individuals in the family may have more than one cancer

**The Genetics of Lynch syndrome**

There are four “repair” genes that can be involved with Lynch syndrome, and one gene that can indirectly cause it. These include MSH2, MSH6, MLH1 and PMS2. The gene EPCAM (formerly, TACSTD1) can ‘turn off’ the MSH2 gene, therefore leading to Lynch syndrome.

The genes are in a class called mismatch repair (MMR) genes. MMR genes are like “spell checkers.” Every time your body needs to make a new cell (which happens frequently!), it has to copy all of your genetic material exactly. The MMR genes “spell check” the new copy of DNA to identify if any mistakes were made while it was being copied and then they repair those mistakes. If the MMR genes are not working properly, these mistakes cannot be repaired and the new cell will have an abnormal copy of its genetic material. When any one cell accumulates enough mistakes in its genetic material, it may start to grow out of control and not die when it should. That cell can become a cancer.

**Higher risk of the following cancers:**
- Colorectal
- Endometrial (uterine)
- Stomach
- Ovarian
- Bladder
- Liver
- Kidney
- Brain
- Skin
- Prostate
- Pancreatic
- Breast

Check out the Taboo-ty Podcast episode about incomplete family histories: soundcloud.com/taboo-ty/unknown
Testing for Lynch syndrome

If your family history is suspicious of Lynch syndrome, genetic counseling and testing are recommended. Many institutions now perform a screening test on all CRC and endometrial (uterine) tumors at the time of surgery that can determine whether you are more or less likely to have Lynch syndrome. If you’re not sure this test was done, ask your oncologist. If your surgery was not too long ago, it’s likely the test can still be performed.

The two screening tests that can be performed on tumors to determine if someone is more or less likely to have Lynch syndrome include:

- Microsatellite instability (MSI) is a screening test that looks for changes in the DNA sequence between normal tissue and tumor tissue. Defects in the MMR genes result in an increased accumulation of DNA errors, and stretches of DNA called microsatellites are especially prone to these errors. Interestingly, 77-89% of Lynch-related tumors show MSI, but 10-15% of sporadic tumors also show it. Given that both Lynch and sporadic tumors can show MSI, additional testing is needed to determine if it is truly Lynch syndrome. MSI testing identifies if a tumor is MSI-H.

- Immunohistochemistry (IHC) testing is a screening test for Lynch syndrome which looks for missing proteins in tumor cells. The premise behind the test is that if the MMR genes are working properly, their protein products should be present in the tumor. However, if there is a mutation in one of the Lynch syndrome MMR genes, that gene’s protein will be absent in the tumor. 83-90% of Lynch-related tumors and 20% of sporadic tumors have at least one of these proteins absent. IHC testing looks to see if there are missing proteins, which are made by MMR genes.

Most hospitals perform one of these two screening tests, if not both. If the test is abnormal, you are more likely to have Lynch syndrome. This would need to be determined by doing genetic testing for the Lynch syndrome genes. If the test is normal, you are less likely to have Lynch syndrome, but it cannot be ruled out entirely.
Treatment and surveillance for Lynch Syndrome Colorectal Cancer (CRC) Patients

Recent studies show immunotherapy may be an effective approach to treat patients who have CRC with MSI. Therefore, knowing your MSI status could drastically change your treatment plan! It is generally safe to assume that someone with one of the proteins missing on the IHC test has a tumor with MSI.

If you have Lynch Syndrome, your screening and prevention guidelines are different than the average-risk population, and you may have additional procedures:

- Colonoscopy – every 1-2 years
- Upper Endoscopy – every 1-3 years if you have a family history of stomach cancer or are of Asian ancestry
- Urine cytology
- Transvaginal ultrasound annually to check uterus/ovaries
- Physical Exam – yearly
- Removal of colon (colectomy) at the time of colon cancer diagnosis
- Removal of uterus (hysterectomy) once childbearing is complete (around age 35-40)
- Removal of ovaries (oopherectomy) once childbearing is complete (around age 35-40)
- Medications to reduce polyp risk
FAMILIAL ADENOMATOUS POLYPOSIS (FAP) & ATTENUATED FAMILIAL ADENOMATOUS POLYPOSIS (AFAP)

The **second most common form** of hereditary CRC is familial adenomatous polyposis (FAP). FAP occurs in 1 in 10,000 people and is detected by the growth of hundreds to thousands of polyps (adenomas) in the colon, often at an early age. If not detected, CRC will likely develop. There is a slightly higher risk for other cancers, including stomach, duodenal, thyroid, and brain cancers, desmoid tumors and bony growths, in addition to hepatoblastoma in infants (a specific liver tumor). It’s estimated that a quarter of FAP cases are de novo, meaning the individual has no family history.

7% of individuals with FAP are diagnosed with Colorectal Cancer (CRC) by age 21 and 95% by age 50.

**Attenuated FAP, or AFAP**, is a milder form of FAP, typically with fewer polyps and a slightly lower average risk for developing CRC (close to 70%).

**The Genetics of FAP and AFAP**

FAP and AFAP are caused by mutations in the adenomatous polyposis coli (APC) gene. This gene belongs to a family of genes called tumor suppressors, which play an important role in preventing cancer by making sure cells grow and divide properly – not uncontrollably. When there is an inherited mutation in one of these genes, cells are more susceptible to turn into cancer.

**Testing and surveillance for adenomatous polyposis syndromes**

The clinical criteria to make a diagnosis of FAP is at least 100 adenomatous polyps found during colonoscopy. Individuals with AFAP generally have between 10-100 polyps. Genetic testing to identify mutations in the APC gene is needed to give an accurate diagnosis.

If you have FAP, it is generally recommended to receive a colonoscopy every 1-2 years starting around age 10-12; when polyps begin to form. Removal of the colon (colectomy) is recommended as a preventative measure for all patients with FAP and for many patients with AFAP to prevent colon cancer from developing.

**Additional Surveillance**

- Upper endoscopy at age 20-25 – frequency of follow-up determined by the size and number of polyps in the duodenum
- Annual thyroid exam
- Annual neurologic exam
- Consider Abdominal MRI every one to three years
MUTYH-ASSOCIATED POLYPOSIS (MAP)

Polyps that develop with MAP include adenomas, but can also include hyperplastic and sessile serrated polyps, which can be harder to detect during screening. There may be dozens, hundreds, or thousands of polyps. However, some individuals with MAP may develop CRC without a significant number of polyps.

The Genetics of MAP
The gene associated with MAP is the MUTYH gene.

Parents and children of people with MAP are not generally affected by the disease due to its recessive inheritance pattern. However, tell your doctor if you have a family member known to have MAP. Individuals who carry one abnormal copy of MUTYH do appear to have a somewhat higher risk for colon cancer; earlier, more frequent colonoscopy screenings may be recommended. Siblings of people with MAP have a 25% chance of also having MAP.

Testing and Surveillance for MAP
Genetic testing is appropriate for individuals with more than 10 colorectal adenomas and is usually performed at the same time as APC gene testing as part of a multi-gene panel. This will help determine a personalized screening schedule and what the risks might be to other family members.

Surveillance May Include:
- Colonoscopy between age 25 and 30 and repeated every two to three years if no polyps are found, or every one to two years if polyps are found
- Baseline upper endoscopy at 30-35 – frequency of follow-up determined by the size and number of polyps in the duodenum
- Annual physical exam

POLYMERASE PROOFREADING ASSOCIATED POLYPOSIS (PPAP)

Individuals can have dozens, to hundreds, to thousands of polyps with PPAP. The risk for other cancers may be higher as well. As these genes were recently identified, our knowledge of the condition is growing and screening recommendations will likely change over time.

The Genetics of PPAP
Gene mutations found in the POLE and POLD1 genes.

Surveillance for PPAP
- Colonoscopy between age 25-30 and every 2-3 years (if no polyps are found) or every 1-2 years if polyps are detected
- If polyp burden becomes too great, prophylactic/preventative removal of the colon may be considered
Types of Hereditary Colorectal Cancer

Adenomatous Polyposis Syndromes

Polyposis and Oligodontia

While the detection of polyps is part of the diagnostic criteria, missing teeth is also a characteristic. Individuals with Polyposis and Oligodontia generally have six or more adult teeth that never develop.

The Genetics of Polyposis and Oligodontia

Gene mutation found in the AXIN2 gene.

Other recessive explanations for polyposis

When MAP as a recessive explanation for polyposis has been ruled out, it is important to consider a few other newly described recessive explanations of polyposis, including NTHL1-Associated Polyposis (NAP) and biallelic mutations in MSH3.

Similar to other polyposis predisposition syndromes, individuals with mutations in both copies of their NTHL1 genes (the cause of NAP), or mutations in both copies of their MSH3 genes have an increased risk to develop colorectal adenomas/polyps and colorectal cancer. Although the development of colorectal cancer and attenuated polyposis appears to be the predominant feature of these conditions, other extra colonic cancers have been associated as well. Our knowledge of these conditions is growing and screening recommendations will change as more research becomes available. Until we have more detailed data, the surveillance for these three conditions is the same as follows:

Surveillance for NAP/MSH3:

- Colonoscopy between age 25 and 30 and repeated every two to three years if no polyps are found, or every one to two years if polyps are found
- If the polyp burden becomes too great, prophylactic/preventative removal of the colon may be considered

Hamartomatous Polyposis Conditions

The following conditions are not as common as the syndromes on the previous pages. Researchers are working to learn more about them and how to quickly identify individuals at risk. If you are found to have one of these gene mutations, increased screening and surveillance are likely to begin at an earlier age.
PEUTZ JEGHERS SYNDROME (PJS)

The diagnosis of PJS requires two of the three following criteria:

- 2+ Peutz-Jeghers polyps in the small intestine
- Family history of PJS
- Typical mucocutaneous hyperpigmentation (freckles or spots that develop on the lips and in the mouth, and on other areas including the hands)

The Genetics of PJS

PJS is due to STK11 (also known as LKB1) gene mutations. However, less than half of individuals clinically diagnosed with PJS have inherited the gene mutation from an affected family member. They have the condition as a result of a de novo, or new gene mutation. An individual with PJS has a 50% chance of passing on the condition to their children. In addition to polyps and a higher risk for CRC, gene mutations in STK11 also lead to an increased risk of breast, cervical, uterine, ovarian, testicular, lung, stomach, small intestine, pancreatic, and lung cancers.

Surveillance for PJS

- Colonoscopy and upper endoscopy every two to three years, beginning in later teenage years

Additional Screening

- Breast mammogram and MRI beginning at age 25
- Yearly pelvic exam and Pap smear, with consideration of transvaginal ultrasounds, starting at age 18-20
- Annual testicular exam and observation from age 10
- Pancreatic screening every one to two years, beginning at age 30-35
- Additional screening for other cancers listed above

COWDEN SYNDROME

Individuals with this syndrome often have mixed polyp types in the colon.

They have an increased risk for breast, thyroid, endometrial, kidney, and colorectal cancers. Most individuals will have noncancerous, tumor-like growths (hamartomas) develop on their skin by their 20s, and many have a large head circumference (macrocephaly).

The Genetics of Cowden Syndrome

Cowden syndrome is often due to mutations in the PTEN gene.

Surveillance for Cowden Syndrome

- Annual physical examination with thyroid exam/ultrasound starting in childhood/at the time of diagnosis of Cowden syndrome
- Breast mammogram and MRI yearly, starting at age 30-35
- Endometrial biopsy yearly, starting at age 30-35, with consideration of hysterectomy
**HAMARTOMATOUS POLYPOSISS CONDITIONS**

- Colonoscopy every five years, starting at age 35
- Renal ultrasound every one to two years, starting at age 40
- Consideration of dermatology evaluation

**JUVENILE POLYPOSISS SYNDROME (JPS)**

A clinical diagnosis of JPS is made when a person is found to have any of the following:
- 5+ juvenile polyps
- Any number of juvenile polyps and a family history of juvenile polyps

Although genetic testing only detects mutations in 60% of individuals diagnosed clinically with JPS, it can be extremely important. Individuals who have mutations in the SMAD4 gene can have additional risks, including hereditary hemorrhagic telangiectasia (HHT), a condition involving the blood vessels. About 25% of cases result from a new mutation.

**The Genetics of JPS**

The gene mutations common in JPS are found in the SMAD4 or BMPR1A genes.

**Surveillance for JPS**

- Colonoscopy annually beginning at age 15 and every two to three years if no polyps are detected
- Upper endoscopy every two to three years, from age 15
- Additional screening for vascular/blood vessel lesions in individuals with SMAD4 mutations

**SERRATED POLYPOSISS SYNDROME (SPS*)**

Individuals with Serrated Polyposis Syndrome could have:
- At least five serrated polyps proximal to the sigmoid colon, at least two of them larger than 10mm
- More than 20 serrated polyps of any size, distributed throughout the large intestine
- Any number of serrated polyps proximal to the sigmoid colon in an individual with at least one first-degree relative with SPS

**The Genetics of SPS**

The gene RNF43 has been linked to SPS, but it is thought most SPS is associated with environmental factors.

**HEREDITARY MIXED POLYPOSISS SYNDROME (HMPS)**

Individuals with HMPS have an increased risk for developing polyps in the colon and rectum.

**The Genetics of HMPS**

HPMPS has been linked to duplications in GREM1 genes.

*Previously known as Hyperplastic Polyposis.
I f you have an increased risk of CRC-related family history and not a hereditary syndrome, it’s important to adhere to specific screening guidelines. The following guidelines are recommended by the National Comprehensive Cancer Network-Screening Guidelines for colorectal cancer.

**HIGHER RISK OF COLORECTAL CANCER**

If you have one first-degree relative diagnosed with CRC or confirmed advanced adenomas at any age:
Get screened at age 40, or 10 years younger than the earliest diagnosis in your family, whichever comes first. After that, you will likely have a colonoscopy every five years.

If you have one or more second-degree relatives diagnosed with CRC younger than age 50 (or at any age):
Follow the same screening as those with average risk, starting at age 45-50.

Always talk to your medical providers about your family history of cancer. Learning whether or not you should be screened at an earlier age due to your family history could be life saving!

- Learn more about screening: [FightCRC.org/Screening](http://FightCRC.org/Screening)
- Listen to Fight CRC Podcasts about hereditary CRC: [Soundcloud.com/Taboo-ty](http://Soundcloud.com/Taboo-ty)
- Use the Family History Tool to help you identify your family health history: [FightCRC.org/FamilyHistoryTool](http://FightCRC.org/FamilyHistoryTool)
- Watch webinars on the genetics of CRC: [FightCRC.org/Webinars](http://FightCRC.org/Webinars)
Fight Colorectal Cancer is a trusted, nonprofit advocacy organization dedicated to empowering patients to be their own health advocates.

**RESEARCH**

At Fight CRC, we fight to make breakthrough research a reality. We fund innovative research grants, convene meetings with national and global experts on the biggest issues in CRC, and we train survivors and caregivers to be a part of the scientific discussions. To get involved in research and stay up to date on the latest scientific breakthroughs, follow @FightCRC on Twitter, or visit us at FightCRC.org/research.

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**ADVOCACY**

Are you ready to turn your pain into purpose? By sharing your story and raising awareness, you can help change policy around colorectal cancer. That’s what the Fight CRC Advocacy Program is all about! We advocate on Capitol Hill. We engage and teach grassroots advocates like you to get involved in your communities. To learn more about how to raise your voice for CRC advocacy, visit FightCRC.org/action-center.

**REFERENCES**


**RESOURCES**

To download or request print materials, go to: FightCRC.org/Resources

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