COLORECTAL CANCER

Genetics

A Guide to Understanding Hereditary Colorectal Cancer Syndromes

FIGHT COLORECTAL CANCER

What is Genetic Testing?

All colorectal cancer (CRC) begins with changes (also known as mutations or variants) in genes. Genes are segments of DNA that perform important functions in the body. Some of these genes fix errors or mistakes in DNA that happen as we age. If too many DNA errors build up in a cell, or if the genes responsible for repairing those errors malfunction, those cells can grow out of control and cause cancer.

There are two types of genetic mutations to be aware of:

- **Somatic mutations:** acquired after birth during your lifetime.
- **Germline mutations:** inherited from a family member, and you are born with them.

Sporadic cancer is when DNA mistakes build up over time, primarily due to age and environmental factors. Most cancers are sporadic in nature. Sporadic cancer normally occurs after age 50.

Familial cancer is when there are clusters of cancer within a family, but there is no known genetic cause. This often occurs due to shared risk factors, such as diet and environment. Familial cancer also tends to occur later in life, after age 50.

Hereditary cancer is cancer caused by specific, identifiable gene mutations which can be passed down from one family member to another. Hereditary cancer can affect many generations of a family, and tends to occur earlier in life, before age 50.

TOTAL CRC DIAGNOSES (%)

5–10%	**Hereditary** (inherited mutation)
20–30%	**Familial** (runs in families without a single known mutation)
60–70%	**Sporadic** (no family pattern identified)

3 Questions to Ask

1. Do I need an inherited (germline) test, and what happens to the results?
2. If my genetic test was positive, which family members should be tested, and when?
3. Was my tumor tested for MMR/MSI?

Genetic testing can determine whether your cancer is hereditary (germline mutation) and who in your family might also be at risk of developing similar cancers.

"As a three-time cancer survivor who was diagnosed with Lynch Syndrome, genetic testing played a crucial role in shaping my treatment, future surveillance plan, and understanding my health risks. Genetic testing gave me answers and options that I wouldn't have had otherwise, and that's why I advocate for others to consider it as part of their cancer journey."

Wenora J.
STAGE 3B SURVIVOR WITH LYNCH SYNDROME

Ready to tell your story and offer your advice? ***fightcrc.org/story***

Learn more & find support — Fight CRC empowers patients & families with evidence-based resources, advocacy, and community.
fightcrc.org/genetics

ADDITIONAL RESOURCES

Your rights (GINA) Protects against genetic discrimination in employment and health insurance. ***Note: Life, disability, and long-term care may not be covered (check timing and state rules).***

ChatCRC Get patient-friendly answers about genetic testing or text ChatCRC to (318) 242-8272. chatbot.fightcrc.org

A Resource for Patients by Patients

Who Should Consider Genetic Testing?

- Anyone diagnosed with colorectal cancer before the age of 50, or with a Lynch-related cancer (uterine, ovarian, gastric, urinary, among others).
- If you have multiple close relatives with colorectal cancer, uterine, endometrial, or other Lynch-related cancers.
- If there is a suggestive history of a hereditary cancer syndrome.

Anyone, at any age, who has been diagnosed with colorectal cancer can consider germline (genetic) testing. It is important to work with a genetic counselor to understand your options, benefits of testing, and the impact of your test results on your biological family.

TIP Bring your family's cancer history (including their ages). If you have prior reports, bring copies or upload to your portal.

How Testing is Performed

CRC Diagnosis

MMR/MSI Testing

If DMMR/MSI-H Or Suggestive Family History

Consider Genetic Testing

Results, positive or negative, help guide care & family next steps

Inherited (germline) testing is performed on blood or saliva. Next generation sequencing (NGS) panels are able to check many genes at once. Results often take two to three weeks, and testing is often covered by insurance with an appropriate physician referral.

Tumor (somatic) testing is performed on tumor tissue, often obtained during a tumor biopsy or surgery. Specific results, such as MSI-H vs MSS, can influence your treatment options. Additionally, an MSI-H/dMMR result can raise suspicion for Lynch Syndrome, a hereditary cancer syndrome.

If your tumor shows loss of the MLH1 gene, your team may check for a BRAF mutation or for signs that MLH1 has been "switched off" in the tumor to help determine sporadic from hereditary genetic issues.

Genetic Test Results

POSITIVE

A harmful (pathogenic) mutation was found. You should expect a tailored treatment plan detailing your future screening intervals, surgical options, and medications. Some MSI-H/dMMR tumors are eligible for immunotherapy options in advanced/metastatic changes. If positive, you should discuss with your genetic counselor the need for your first-degree (parents, siblings, children) family members to be tested.

NEGATIVE

No harmful mutations were found. Your care plan will follow your personal/family history and risk.

VARIANT OF UNCERTAIN SIGNIFICANCE (VUS)

A mutation was found, but its impact on your health is currently unknown.

> **IMPORTANT**
> A VUS result may be reclassified in the future. Make sure your genetic counselor has your current contact information.

If You Test Positive

If you have colorectal cancer your positive result will guide your treatment plan, surgery and medication options, as well as surveillance now and into the future.

If you don't have cancer you might be labeled a "previvor". Your risk is higher, but not 100% certain. You should start earlier and more frequent screening as advised.

Your treatment plan, if you have cancer, will consider your gene mutation/syndrome, your age, prior treatment history, and your family history (including the ages when your family members were diagnosed).

PATIENT TIPS — WHEN VISITING A GENETIC COUNSELOR

Following these simple steps can make an appointment more productive and easier to understand. As always, you can bring a family member to help you remember to ask questions and request clarification when needed.

BRING YOUR HISTORY Your own personal medical history, as well as your family history. In particular, note any family history of cancer, and the age they were diagnosed.

TAKE NOTES OR RECORD YOUR APPOINTMENT (WITH PERMISSION) Genetic counseling sessions are complex and there will be a lot to remember. Notes or a recording will help you remember the important parts.

ASK FOR CLARITY If you don't understand your test results, your treatment plan moving forward, or what your results mean for your family, ask for an explanation that makes sense.

KNOW WHAT'S NEXT Leave with your next steps, referrals, and a clear understanding of what to expect.

SHARE YOUR GENETIC TESTING WITH FAMILY So they can understand their risk and get the right care before a diagnosis. Ask your counselor for a letter to share with family members. Remember, just because you have an inherited genetic condition does not mean your family members necessarily will.

TIP Need help finding a genetic counselor? Ask for a referral from your physician, visit findageneticcounselor.com, or cgaigc.com.

TIP Before you leave your genetic counseling session, repeat your results and treatment plan back to ensure you understand it.

Hereditary Cancer Syndromes

GENETIC SYNDROMES	FEATURES	GENES IMPACTED
Lynch Syndrome	Most commonly inherited colon cancer condition, impacting 1 in 279 individuals. (Around 3 out of 100, or 3%, of people with colorectal cancer have Lynch Syndrome.) Patients have a higher risk of developing multiple cancer types.	MLH1, MSH2, MSH6, PMS2, EPCAM
Familial Adenomatous Polyposis (FAP)	The second-most common hereditary colorectal cancer condition impacting 1 in 8,000 to 10,000 people. Causes the growth of hundreds to thousands of polyps (adenomas) in the colon, often at an early age (teens). The risk of developing colorectal cancer with a FAP diagnosis is nearly 100% if left untreated. The risk for other cancers and growths, like desmoids, also increases.	Adenomatous polyposis coli (APC)
Peutz-Jeghers Syndrome (PJS)	A rare hereditary disorder that leads to polyp growth, dark spots on the lips/mouth and hands/feet, and an increased risk of certain cancers.	STK11/LKB1
MUTYH-Associated Polyposis (MAP)	A rare hereditary cancer disorder that increases the risk for colon polyps and colon cancer. Because MUTYH is recessive, generally there is not a family history of CRC. Reproductive partners of someone with MAP should consider testing to determine if there is a risk to their children. Tell your doctor if you have a family member with MAP, as it could increase your risk for colon cancer.	MUTYH

Common Acronym Definitions

MMR (mismatch repair) Fixes DNA mistakes

MSI (microsatellite instability) Lab sign of many DNA repeat errors; MSI-H = "MSI-High"

Germline test Blood/saliva test for genetic changes you were born with (can be passed to family)

FAP (Familial Adenomatous Polyposis), MAP (MUTYH-Associated Polyposis), PJS (Peutz-Jeghers Syndrome) Hereditary syndromes that increase CRC risk

dMMR When mismatch repair isn't working well

IHC (immunohistochemistry) Lab technique used to detect MMR proteins in a sample

VUS (Variant of Uncertain Significance) Change we don't yet understand; most later found to be OK

GINA (Genetic Information Nondiscrimination Act) U.S. law protecting genetic information in employment & health insurance

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