riscover®
HEREDITARY CANCER

Result Navigator

⊕ Positive Test Result: *MSH2*

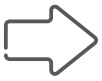
Positive test results identify a change, or "misspelling," of DNA that is known or predicted to cause an increased risk for cancer. DNA is the blueprint of life—it carries all of the genetic information needed for our bodies to function. A section of DNA with a specific job is called a gene. A pathogenic variant is a change in a gene that is known to cause increased risk for cancer. A likely pathogenic variant is a change in a gene that is very likely to cause increased risk for cancer.

After a positive test result, there can be many questions about what to do next.

This guide is a supplement to Riscover® Hereditary Cancer test results, helping patients and healthcare providers understand the results and together determine the best path forward.

Navigate Your Results

Learn | *page 2*
Review the test results along with this guide, and discuss the meaning of these results with your healthcare provider.



Plan | *page 3*
Develop a healthcare plan for early detection and prevention of specific cancers.

Share | *page 4*
Understand the risks for other family members, and consider how to inform relatives of their risks.

Connect | *page 5*
Reach out to medical experts and find local and national groups that can provide more information and support.

Glossary of Terms

CA-125: A substance that can indicate the development of ovarian cancer. Testing for CA-125 is performed on a sample of blood.

Colonoscopy: An imaging test that uses a scope to take images of the inner lining of the large intestine.

Gene: A section of DNA with a specific job.

EGD (Esophagogastroduodenoscopy): Also called upper endoscopy, this is an imaging test that uses a scope to take images of the esophagus (part of the gastrointestinal tract that connects the throat to the stomach), stomach, and first part of the small intestine (called the duodenum).

H. pylori: A type of bacteria found in the stomach that can cause ulcers and also increases the risk of stomach cancer.

Hepatobiliary tract: Includes the liver, gall bladder, and bile ducts.

Hysterectomy: Surgical removal of the uterus.

Pathogenic: Causing or capable of causing disease.

Risk: The chance, or possibility, of developing a disease.

Salpingo-oophorectomy: Surgical removal of the ovaries and fallopian tubes.

Transvaginal ultrasound: An imaging test performed by inserting an ultrasound probe into the vagina to take detailed images of the ovaries, fallopian tubes, and uterus.

Urinalysis: A test that measures different substances in the urine that may indicate a wide range of disorders such as kidney disease or the development of cancer.

Urinary tract: The system in the body that is in charge of eliminating waste through urine. The urinary tract contains the kidneys, ureters (part of the body that takes the waste from the kidneys and transports it to the bladder), bladder, and urethra (part of the body that moves urine outside of the body).

Variant: A change, or "misspelling," in the DNA sequence. Variants can be benign (not associated with disease), pathogenic (associated with disease), or of uncertain significance.

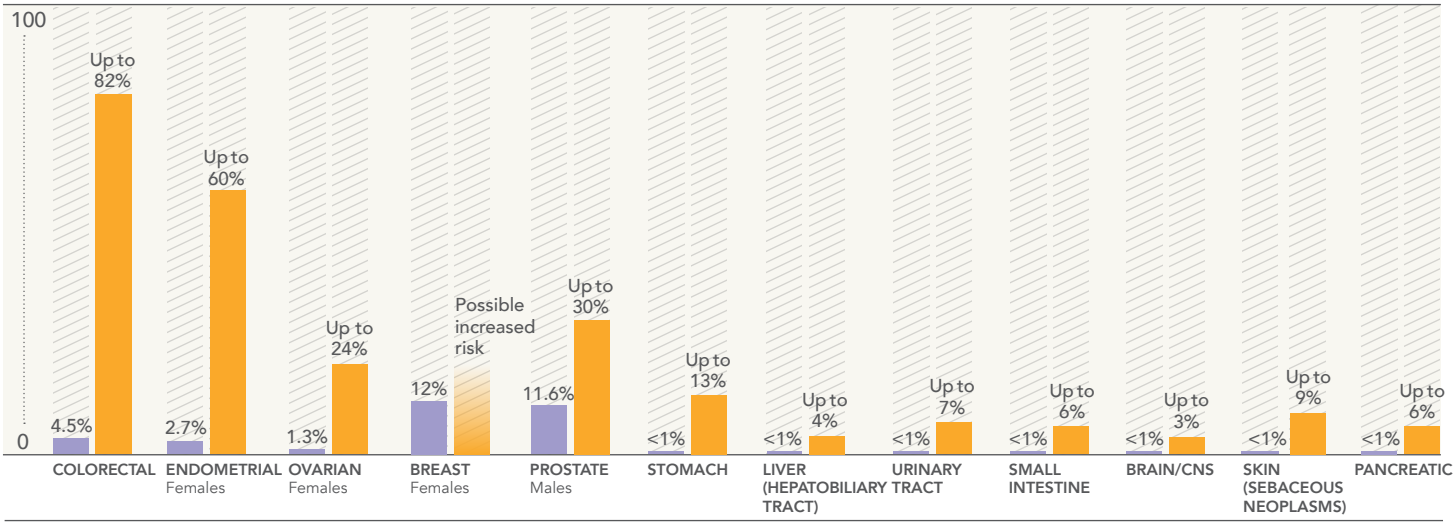
Your Diagnosis: Lynch Syndrome

Lynch syndrome is an inherited disorder caused by a pathogenic/likely pathogenic variant in one of the following mismatch repair genes: *MLH1, MSH2, MSH6,* or *PMS2*. Certain pathogenic variants in a fifth gene, *EPCAM*, can also cause Lynch syndrome by "turning off" *MSH2*. The normal job of a mismatch repair gene is to check DNA for errors. When these genes have pathogenic/likely pathogenic variants, new errors in DNA can go unchecked, which can lead to the development of cancer. Lynch syndrome caused by pathogenic/likely pathogenic variants in *MSH2* is associated with an increased risk for the following cancers: brain/central nervous system (CNS), breast (in females), colorectal, endometrial (in females), liver (hepatobiliary tract), ovarian (in females), pancreatic, prostate (in males), skin (sebaceous neoplasms), small intestine, stomach, and urinary tract.

Lynch syndrome accounts for approximately 3 – 5% of all colorectal cancers. About 1 in 400 people in the general population have Lynch syndrome. People who have two pathogenic variants (one inherited from each parent) in the same gene are affected with a condition called constitutional mismatch repair deficiency (CMMRD). The risks described below are for people with one pathogenic variant.

Your Risk

Not all people with positive test results will develop cancer, but the chance for cancer is higher than the general population risk. The graphs below show how much the risk for cancer increases when a pathogenic variant is found. The cancer risks are presented in ranges based on multiple studies of families who have a pathogenic variant. There is not enough evidence available to give a specific risk to a person or family.



Your Screening and Management Options

Listed below are the intervention options that are recommended by medical experts for individuals who carry this cancer gene variant. Your healthcare provider can explain these options in more detail, and together you can make a plan for cancer prevention and/or early detection.

COLORECTAL CANCER	
Colonoscopy	A colonoscopy every 1 – 2 years is recommended starting at age 20 – 25 (or 2 – 5 years before the earliest diagnosis in the family if under age 25).
Aspirin	Your healthcare provider may prescribe aspirin to help prevent colorectal cancer, based on your personal and family history.
ENDOMETRIAL/OVARIAN CANCERS (FEMALES)	
Dysfunctional uterine bleeding warrants evaluation	Seek evaluation with your healthcare provider when present.
Endometrial biopsy	Consider an endometrial biopsy every 1 – 2 years.
Transvaginal ultrasound and CA-125 (at clinician discretion)	Your healthcare provider may consider a transvaginal ultrasound and/or a blood test for cancer antigen 125 (CA-125) to screen for endometrial and ovarian cancers.
Total hysterectomy and bilateral salpingo-oophorectomy	Removal of the uterus, ovaries and fallopian tubes can be considered after a woman has had her last child and based on her personal and family history.
BREAST CANCER (FEMALES)	
No specific guidelines	Your healthcare provider can recommend screening options based on your personal and family history of breast cancer.
PROSTATE CANCER (MALES)	
No specific guidelines	Your healthcare provider can recommend screening options based on your personal and family history of prostate cancer.
STOMACH/SMALL INTESTINE CANCERS	
EGD with extended duodenoscopy	Consider an upper endoscopy with visualization of the duodenum at the time of colonoscopy every 3 – 5 years beginning at age 40, based on your personal and family history of stomach or small intestine cancer and your ethnicity. (Stomach cancer in Lynch syndrome is more common in people of Asian descent.)
Testing for and treating *H. pylori*	Consider testing for *H. pylori* as recommended by your healthcare provider.
HEPATOBILIARY TRACT CANCER	
No specific guidelines	Your healthcare provider can recommend screening options based on your personal and family history of hepatobiliary tract cancer.
URINARY TRACT CANCER	
Urinalysis	Consider an annual urinalysis beginning at age 30 – 35 based on your personal and/or family history of urinary tract cancers.
BRAIN/CNS CANCER	
Physical and neurological exam	Consider an annual physical and neurological exam beginning at age 25 – 30.
PANCREATIC CANCER	
No specific guidelines	Your healthcare provider can recommend screening options based on your personal and family history of pancreatic cancer.
SEBACEOUS NEOPLASMS	
No specific guidelines	Your healthcare provider can recommend screening options based on your personal and family history.

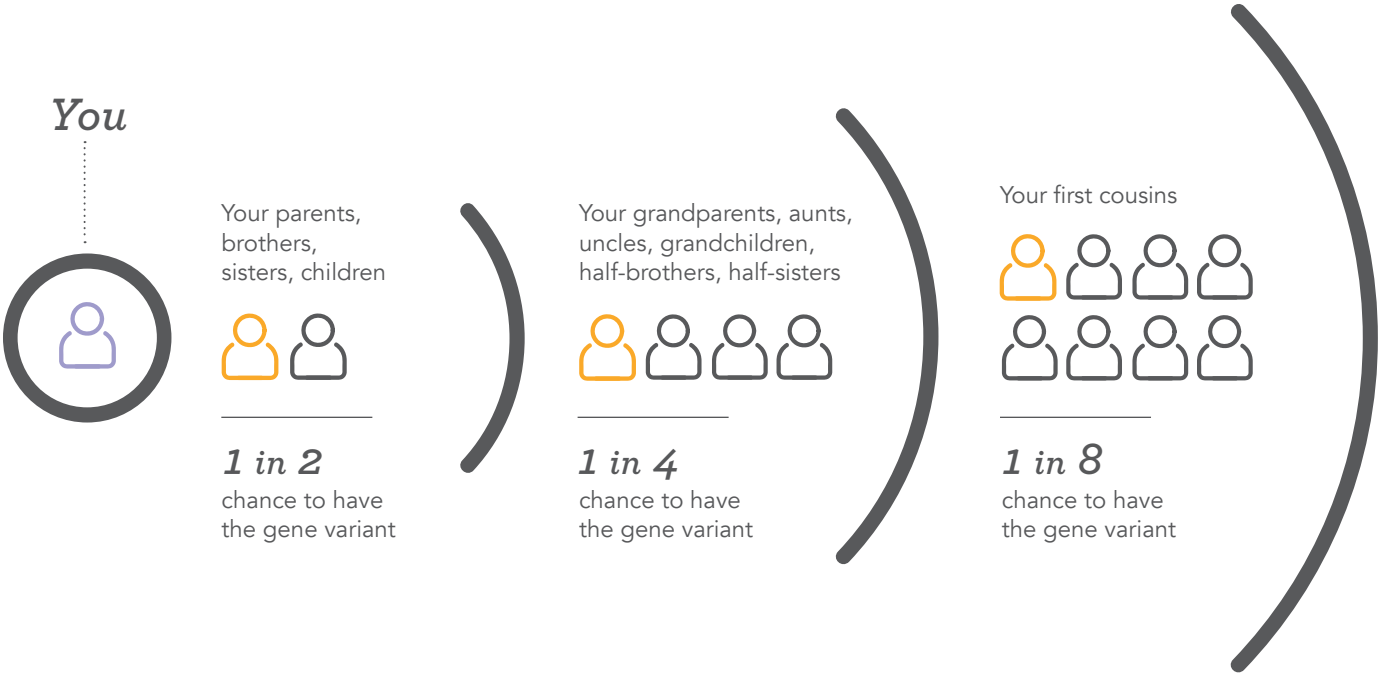
Your Family Matters

Cancer gene variants are inherited in an autosomal dominant manner. This means that when a parent tests positive, each child has a 1 in 2 chance to inherit the variant. Some people who inherit the variant will develop cancer, and some will not, but the risks are significantly increased compared to the average person. People in the same family may develop different types of cancers at varying ages, and the pattern of cancer and age of onset can differ from family to family.

Gene variants can be passed through families for many generations. When a gene variant is identified in one person in the family, relatives can be tested for just that variant. Sharing information about test results with family members is important, because it allows them to make informed choices about their healthcare and to decide whether they want genetic testing.

Some people who have pathogenic and likely pathogenic variants are interested in learning how to avoid passing these variants on to their children. If you are planning to have a child, you may wish to consult with a reproductive medicine specialist to discuss all of your reproductive options, including use of an egg or sperm donor, preimplantation genetic diagnosis, and prenatal genetic testing.

The likelihood for family members to carry the same gene variant depends on how closely related they are to the person with a known gene variant.



Your Expert Team

As you take your next steps, it can help to have a team of experts on your side. This team may include your primary care provider and a number of specialists who will help along the way.

If you haven't already done so, you may wish to speak with a genetic counselor. Genetic counselors are healthcare professionals with specialized training in medical genetics and counseling. They can help you understand your test results, discuss your healthcare plan, and connect to other resources in your area. Your healthcare provider may be able to provide a referral to a local genetic counselor. You can also find a genetic counselor through the National Society of Genetic Counselors at www.nsgc.org.

For questions about your test results, our genetic counseling team is available to help.
To reach a genetic counselor, call +1 855-293-2639 and select option 3.

Helpful Resources

GeneReviews
ncbi.nlm.nih.gov/books/NBK1211
A detailed clinical summary of Lynch syndrome written for healthcare providers.

Hereditary Colon Cancer Takes Guts
www.hcctakesguts.org/about
A support group whose mission is to serve the hereditary colon cancer community by connecting individuals to resources and promoting research and health care initiatives.

Lynch Syndrome International
lynchcancers.com
A support group whose mission is to provide support to those with Lynch syndrome and to promote public awareness, education, and research.

Lynch Syndrome Screening Network
lynchscreening.net
A support group for medical providers whose mission is to promote universal Lynch syndrome screening on colorectal and endometrial cancers and provide resources for appropriate management guidelines.

National Comprehensive Cancer Network (NCCN)
nccn.org
Expert guidelines for cancer screening and treatment. Information available for both healthcare providers and patients.

REFERENCES

Kohlmann W, Gruber SB. Lynch Syndrome. 2004 Feb 5 [Updated 2018 Apr 12]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1211/

National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal (Version 1.2018). Available from: http://www.nccn.org/