

## Result Navigator

### ⊕ Positive Test Result: *POLD1*

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

**Colonoscopy:** Visual exam of the inside of the colon with a flexible, lighted tube inserted through the rectum.

**Gene:** A section of DNA with a specific job.

**Pathogenic:** Causing or capable of causing disease.

**Polyp:** An abnormal growth of cells that can become a cancer tumor.

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

**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.



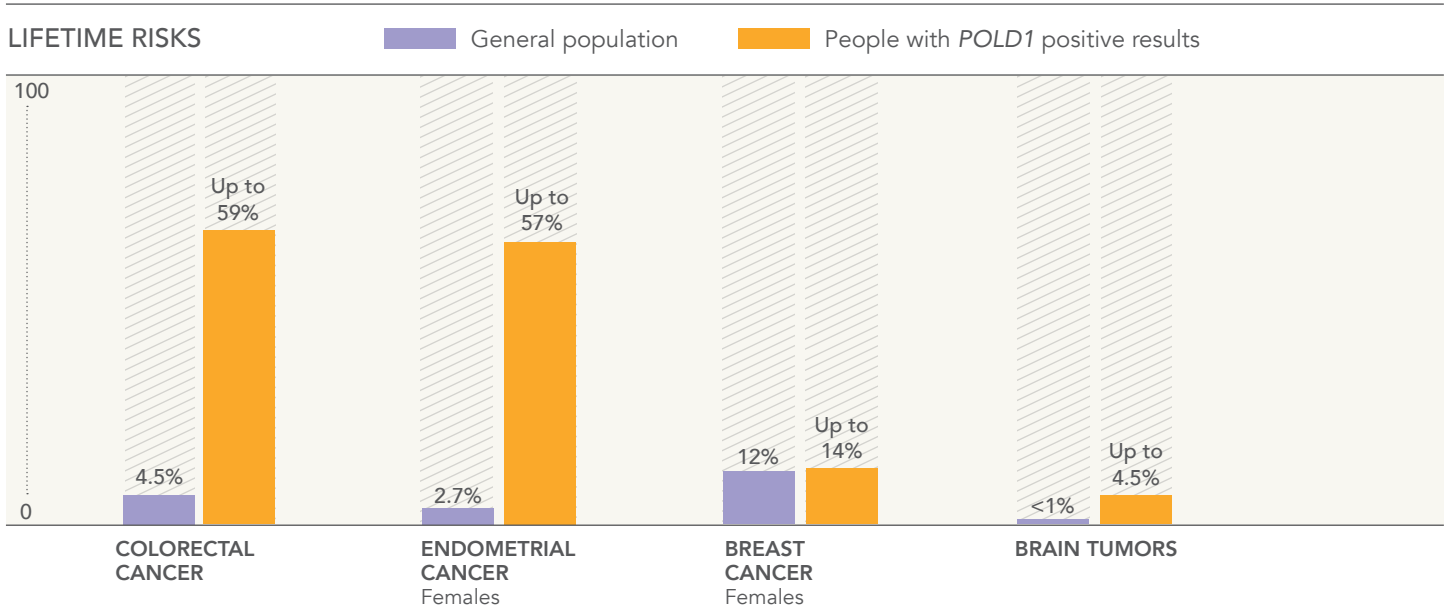
## Your Diagnosis: Polymerase Proofreading-Associated Polyposis

Polymerase Proofreading-Associated Polyposis (PPAP) is an inherited cancer syndrome caused by pathogenic/likely pathogenic variants in the *POLD1* and *POLE* genes. People with PPAP related to *POLD1* have an increased lifetime risk of colorectal, endometrial, and breast cancers. PPAP is also associated with an increased risk for brain tumors.

PPAP is a relatively newly discovered cancer predisposition syndrome, and the frequency of individuals with pathogenic variants in the *POLD1* gene is unknown. Management guidelines and information regarding associated cancers may change with the identification of more individuals with this syndrome.

## 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 is recommended every 2 – 3 years, beginning between 25 – 30 years of age. If polyps are identified, more frequent screening (every 1 – 2 years) may be recommended.
Surgical evaluation	Surgery may be recommended by your healthcare provider, depending on the number of polyps present.

### ENDOMETRIAL CANCER (FEMALES)

Dysfunctional uterine bleeding warrants evaluation	Seek evaluation with your healthcare provider when present.
--	---

### BREAST CANCER (FEMALES)

No specific guidelines	Your healthcare provider can recommend screening options based on your personal and family history of breast cancer.
------------------------	--

### BRAIN TUMORS

No specific guidelines	Your healthcare provider can recommend screening options based on your personal and family history.
------------------------	---

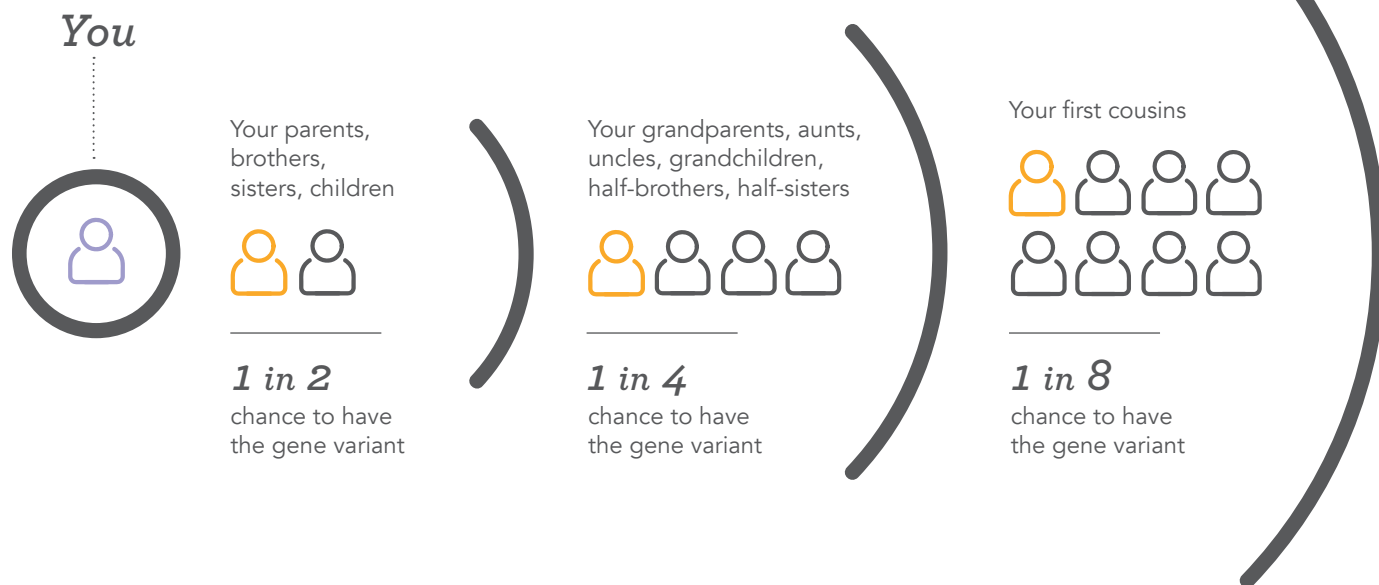
## Your Family Matters

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](http://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

### National Comprehensive Cancer Network (NCCN)

[nccn.org](http://nccn.org)

Expert guidelines for cancer screening and treatment. Versions available for both providers and patients.

### REFERENCES

Bellido F, Pineda M, Aiza G, et al. POLE and POLD1 mutations in 529 kindred with familial colorectal cancer and/or polyposis: review of reported cases and recommendations for genetic testing and surveillance. *Genet Med*; 2016 Apr;18(4):325-32.

National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal (Version 1.2018)

Palles C, Cazier JB, Howarth KM, et al.; CORGI Consortium; WGS500 Consortium. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas; *Nat Genet* 2013;45:136-144.

Spier I, Holzapfel S, Altmüller J, et al. Frequency and phenotypic spectrum of germline mutations in POLE and seven other polymerase genes in 266 patients with colorectal adenomas and carcinomas. *Int J Cancer*; 2015;15;137(2):320-31.