

# Lynch Syndrome: Information for families with a pathogenic variant in the *PMS2* gene

The purpose of this handout is to give you detailed information about your genetic test result which you may read and discuss with your medical providers. Researchers will continue to study the *PMS2* gene, so please check in with your medical providers once a year to learn of any new information that may be important for you and your family members. (Please see the last page for a glossary of medical terms which are underlined in this document.)

**You have a pathogenic variant in the *PMS2* gene. This means you have Lynch syndrome (also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC) syndrome).**

## What is hereditary cancer?

- Cancer is a common disease. One out of every 3 people in the United States will develop some type of cancer in their lifetime.
- About 5-10% of cancers (up to 1 in 10) are hereditary. A hereditary cancer occurs when a person is born with a pathogenic variant (also known as a mutation) in a gene that increases the chance to develop certain types of cancer. A pathogenic variant can be passed on from one generation to the next.
- Typically, families with a *PMS2* pathogenic variant have one or more of the following features:
  - Colon cancer and/or pre-cancerous colon polyps (often occurring before age 50)
  - Endometrial (uterine) cancer
  - Other cancers (stomach, ovarian, small bowel, urinary tract, brain) may be present
  - Individuals with more than one of the cancers listed above
  - Multiple family members with colon or other Lynch syndrome-related cancers
  - Lynch syndrome-related cancers in several generations of a family

## What is a pathogenic variant?

- DNA is our genetic material which is passed on from parent to child. It contains the instructions for how our bodies develop, grow, and function. A gene is a small piece of DNA which has a specific job to do in the body. Some genes determine features like eye color or height, while other genes are involved with our health.
- We all have variations in our genes that make us different from one another. Most of these variations do not change the way our genes work. However, some variations do prevent a gene from working correctly. This type of variation is called a pathogenic variant or mutation.

## Why does having this pathogenic variant cause an increased risk for cancer?

- The job of the *PMS2* gene is to prevent cancer. It is called a tumor suppressor gene. *PMS2* is a type of tumor suppressor gene known as a DNA mismatch repair gene. When working correctly, tumor suppressor genes help to prevent cancer by controlling the growth and division of cells.

- People born with a *PMS2* pathogenic variant have only one working copy of the *PMS2* gene, so their risk for cancer is higher than average.

### What are the cancer risks linked to this pathogenic variant?

- People born with a *PMS2* pathogenic variant (who have Lynch syndrome) have higher risks for certain types of cancer which are outlined in the table below.

Table: **Lifetime Cancer Risk (chance to get cancer at any time during life)**

	People who do not have a genetic pathogenic variant	People who have a <i>PMS2</i> gene pathogenic variant
Colon cancer	4.2%	8.7-20%*
Endometrial (uterine) cancer	3.1%	13-26%*

National Comprehensive Cancer Network Genetic/Familial High-Risk Assessment: Colorectal Guideline, Version 1.2023

\*These risks are based on people who did not have regular screening and/or other treatments such as risk-reducing surgery.

- The numbers above are shown as a range. This is because not all families/individuals have the exact same degree of risk. Risks may be affected by the environmental factors, lifestyle, personal medical history, family cancer history, and other genetic or unknown factors.
- In some families with Lynch syndrome, there may also be an increased risk for other cancers, including gastric, ovarian, biliary tract, urinary tract, small bowel, pancreas, brain, and prostate cancers. Some families may also have higher risks for certain types of skin tumors, such as sebaceous neoplasms.
- People born with a *PMS2* pathogenic variant also have a higher risk for pre-cancerous polyps in the colon, called adenomas. An adenoma is a pre-cancerous growth, and if it is not removed it can grow into a colon cancer.

### Is it possible to fix the pathogenic variant?

Unfortunately, it is not yet possible to fix a pathogenic variant in the *PMS2* gene. However, it is possible to change your medical care and certain things in your lifestyle. Your provider(s) will work with you to discuss these options and create a medical care plan that is right for you.

### What are the medical care recommendations?

The medical care recommendations for people with a *PMS2* pathogenic variant are divided into three categories: **surveillance, surgery, and medications.**

#### Surveillance:

The purpose of surveillance (also referred to as 'screening') is to diagnose cancer at as early a stage as possible. Although scientists and physicians can't prevent a cancer from developing, early detection is important. When a cancer is detected early, it is more likely to be treated successfully. There are very good surveillance methods for some, but not for all types of cancer.



The table below outlines surveillance recommendations for individuals with a *PMS2* pathogenic variant (adapted from the National Comprehensive Cancer Network Genetic/Familial High-Risk Assessment: Colorectal Guideline, Version 1.2023). Please note that these are general guidelines. Specific guidelines for individual patients and families may differ.

Cancer type	Surveillance recommendations
Colon cancer	Colonoscopy beginning at age 30-35 (or earlier based on family history); repeat every 1-3 years.
Endometrial (uterine) cancer	No proven benefit to screening. Consider endometrial biopsy every 1-2 years starting at age 30-35. Prompt response to symptoms (e.g. abnormal bleeding)
Gastric and upper GI (small bowel) cancers	Based on family history, consider upper endoscopy every 2-4 years, beginning at age 30-40.
Ovarian cancer	No proven benefit to screening. Close follow-up with a gynecologist. Prompt response to symptoms (e.g. bloating).
Urothelial cancer	No proven benefit to screening. Based on family history, consider yearly urinalysis beginning at age 30-35.
Central nervous system cancer	Education regarding signs and symptoms of neurologic cancer with prompt response to symptoms.
Pancreatic cancer	Those with a family history of pancreatic cancer should discuss personalized pancreas screening recommendations with their health care providers.
Prostate cancer	Based on family history, begin shared decision making about prostate cancer screening at age 40 and consider screening at annual intervals rather than every other year.
Skin Tumors	Consider skin exam every 1–2 years with a health care provider skilled in identifying Lynch-associated skin manifestations. Age to start surveillance is uncertain and can be individualized.

### Risk-reducing surgery options:

The goal of risk-reducing surgery is to reduce the risk of cancer by removing healthy tissue before cancer develops. This is also called prophylactic surgery. Risk-reducing surgery does not eliminate the chance to get cancer, but it does greatly lower the chance.

- **Hysterectomy:** This surgery removes the uterus to lower the risk of endometrial cancer (cancer of the lining of the uterus). Hysterectomy should be discussed with all patients who carry a *PMS2* pathogenic variant. Those who are planning to have children may consider this surgery when they are done having children.
- **Risk-reducing bilateral salpingo-oophorectomy (RRBSO):** This surgery removes the ovaries and fallopian tubes to lower the risk of ovarian cancer. The timing of RRBSO should be individualized based on whether childbearing is complete, personal medical history, and family history. Even after RRBSO, there is still a small (1%-5%) risk of a rare cancer called primary peritoneal cancer (cancer of the abdominal lining which behaves like ovarian cancer).
- **Colectomy:** This surgery removes all or part of the colon (large intestine) to lower the risk of colon cancer. Colectomy is usually necessary once a person develops a large number of polyps that cannot be managed through colonoscopy alone. The timing of a colectomy depends upon age, number of polyps, and other factors.



This surgery may also be recommended in patients that have developed colon cancer and have Lynch syndrome. There are different types of procedures for removal of the colon and/or rectum which should be discussed with a gastroenterologist and specially trained surgeon. Most colectomy operations do not require a permanent external bag.

### Medications (Chemoprevention):

In some cases, medication may be prescribed to lower the chance of developing cancer.

- **Aspirin:** Research shows that aspirin may lower the chance for colon cancer in people with Lynch syndrome. However, there is still much to be learned about the use of aspirin in people with Lynch syndrome, and it may or may not be right for you. **The use of aspirin is not appropriate for everyone and should not be taken without talking to your healthcare providers first.**

### Who should I see for my medical care?

It is important to find health care providers you trust for long-term follow-up care. Your primary care providers may be able to provide some of this care. In some cases, you may need to see specially trained medical providers. We are happy to provide you with referrals to specialists at Mass General as needed.

### How can I live a healthy lifestyle to lower my risk of developing cancer?

Everyone should follow a healthy lifestyle, but this may be even more important for someone with an increased risk of cancer. According to the American Cancer Society, a healthy lifestyle includes:

- Avoiding tobacco.
- Maintaining a healthy weight.
- Participating in regular physical activity.
- Keeping a healthy diet with plenty of fruits and vegetables.
- Limiting yourself to no more than 1-2 alcoholic drinks per day.
- Protecting your skin and eyes from the sun.
- Knowing your own body and medical history, your family history, and your risks.
- Having regular check-ups and cancer screening tests.

### What are the chances that my family members also have the pathogenic variant?

- **Your children:** Each of your children has a 50% chance to inherit the normal (working) copy of the *PMS2* gene and a 50% chance to inherit the *PMS2* pathogenic variant (the non-working copy). *PMS2* pathogenic variants are not linked to childhood cancers and will not change a person's medical care plan until the age of 20-25. Therefore, testing children (minors, under the age of 18) for *PMS2* pathogenic variants is not recommended.
  - In very rare circumstances, when both parents carry a *PMS2* pathogenic variant, a child may inherit a disease called Constitutional Mismatch Repair Deficiency (CMMRD). Please contact your genetic counselor if you have questions or concerns about CMMRD.
- **Your siblings and other relatives:** In most cases, siblings of a person with a *PMS2* pathogenic variant have a 50% chance to have the same pathogenic variant. Additionally, other family members (such as parents, cousins, aunts, uncles) may also be at risk to have the pathogenic variant.
- **Family planning:** People with *PMS2* pathogenic variants may have concerns about passing a *PMS2* pathogenic variant to a child. There are reproductive options that can be used to lower the chance of passing a *PMS2* pathogenic variant to a child. If you are interested in learning more about these options, please contact your genetic counselor for a referral.

The letter you received from your genetic counselor will give more specific recommendations about which relatives are candidates for genetic testing. However, please feel free to contact us with any further questions.



## Where can I find additional information?

Feel free to contact us if you have any questions or would like additional resources. Some people find it useful to speak with other people with *PMS2* pathogenic variants who have similar concerns. We would be happy to arrange this for you if you are interested.

The following is a list of additional sources of information:

Center for Cancer Risk Assessment  
Mass General Cancer Center  
[www.massgeneral.org/ccra](http://www.massgeneral.org/ccra)  
(617) 724-1971

American Cancer Society  
[www.cancer.org](http://www.cancer.org)  
(800) 227-2345

AliveAndKickn  
Haworth, NJ 07641  
[aliveandkickn.org](http://aliveandkickn.org)

Lynch Syndrome International

<https://rarediseases.org/non-member-patient/lynch-syndrome-international/>

## Glossary of cancer genetics terms:

- **Cell:** The basic structural and functional unit of any living thing. Each cell is a small container of chemicals and water wrapped in a membrane. The human body is made up of 100 trillion cells forming all parts of the body such as the organs, bones, and blood.
- **DNA:** Deoxyribonucleic acid, or DNA, is the genetic material that is passed on from parent to child, which gives the instructions for how our bodies develop, grow, and function on a daily basis.
- **Early detection:** The process of finding cancer when it is just starting to develop.
- **Gene:** A gene is a small piece of DNA that gives instructions for a specific trait.
- **Inherited trait:** A character or feature that is passed on from a parent to a child.
- **Lifetime cancer risk:** The chance that a person will develop cancer in his or her life. This is sometimes defined as the chance of developing cancer by the age of 75 or 80.
- **Pathogenic variant:** A change in a gene that prevents it from working correctly. Also called mutation.
- **Risk-reducing surgery:** Surgery to remove healthy tissue or organs before cancer develops. Also called prophylactic surgery.
- **Surveillance:** Screening tests or procedures to look for early signs of cancer development or cancer returning (recurrence).
- **Syndrome:** A set of signs and symptoms that appear together and characterize a disease or medical condition.
- **Tumor suppressor gene:** When working correctly, tumor suppressor genes prevent cancers from developing by controlling the growth of cells.
  - Mismatch repair (MMR) genes: There are many types of tumor suppressor genes and MMR genes are just one type. As new DNA is being made in a cell, the MMR genes help proofread the new DNA strands to detect and correct mistakes.

