

## Lynch Syndrome – *MLH1* Cancer Risks and Management

### Overview

Lynch syndrome is an inherited condition that increases the risk of certain cancers. It is caused by pathogenic variants in one of several genes involved in repairing DNA. One of these genes is *MLH1*.

People with Lynch syndrome have a higher chance of developing certain types of cancer, often at younger ages than the general population. These include colorectal, endometrial, and ovarian cancers, among others.

This page summarizes the cancer risks and management recommendations for individuals with a pathogenic variant in *MLH1*. These may be adjusted depending on a person's personal or family history of cancer.

### Cancer Risks Associated with *MLH1*

Cancer Type	Average Age (years)	<i>MLH1</i> (risk to age 75 years)	General Population Risks
Colorectal (male)	44	57%	6%
Colorectal (female)	44	48%	5.5%
Endometrial (uterine)	49	37%	2.6%
Ovarian	46	11%	1 to 2%
Ureter/renal pelvis	59 to 69	4-5%	Less than 2%
Urinary bladder	59	5-7%	2%

Other cancers may include stomach, hepatobiliary tract, small intestine, pancreas and brain. The risk to age 75 for each of these is less than 10%.

Some families with Lynch syndrome have a small risk of developing certain skin tumors. These include sebaceous adenomas, sebaceous epitheliomas, sebaceous adenocarcinomas, keratoacanthomas, and squamous cell carcinomas. This group of skin conditions was once called Muir-Torre syndrome, but now it is recognized as part of the Lynch syndrome spectrum. Risks specific to the *MLH1* gene are not available.

## **Cancer Screening and Risk Reduction**

### **Colorectal Cancer**

#### **Screening:**

- Colonoscopy every 1–2 years is recommended starting at age 25, or 2–5 years before the youngest colorectal cancer diagnosis in the family if that diagnosis occurred before age 25.

#### **Prevention:**

- Daily low-dose aspirin (81 mg) is recommended, unless contraindicated, to reduce colorectal cancer risk in individuals with Lynch syndrome, with a double dose for those with a BMI of 30 or greater. Aspirin can be initiated five years prior to the start of colonoscopy screening and stop by age 70 (if the sole indication is colorectal cancer prevention). H. pylori testing and eradication as well as blood pressure control reduce the risk of aspirin-related adverse effects.
- Prophylactic colectomy is generally not recommended, except in specific situations outlined below. Surveillance of all remaining colonic mucosa should continue every 1–2 years, even after surgery.
  - Individuals not undergoing regular colonoscopic surveillance may benefit most
  - Segmental or extended colectomy may be considered in cases of adenomas not amenable to endoscopic removal or if high-grade dysplasia is present
  - Colectomy at the time of cancer diagnosis lowers the risk of a second primary colorectal cancer but has not been shown to improve overall survival.

### **Endometrial and Ovarian Cancer**

#### **Screening:**

- Transvaginal ultrasounds (TVUs), annual endometrial biopsies, pelvic exams, and/or CA-125 blood tests are not recommended in British Columbia, as they are either proven ineffective or lack sufficient evidence to support their use for screening purposes.
- Prompt evaluation by a physician is recommended for any unusual uterine bleeding (e.g., bleeding between menstrual periods or any postmenopausal bleeding), or for persistent symptoms such as pelvic or abdominal pain, bloating, increased abdominal girth, early satiety, difficulty eating, or urinary urgency/frequency that are a change from baseline.

#### **Prevention:**

- Recommend consultation with a gynecologic oncologist or gynecologist in community to discuss prevention strategies. Hysterectomy and bilateral salpingo-oophorectomy (BSO) is recommended from age 40 years. Menopausal hormone

therapy is recommended at the time of risk-reducing BSO and should continue until the usual age of menopause.

- There may be a potential benefit to using the oral contraceptive pill (OCP) or Mirena IUD. In the general population, OCP use for at least 5 years reduces the risk of ovarian and endometrial cancer by 50% or more. This protective effect increases with longer duration of use and can persist for at least 20 years after discontinuation. However, it is unclear whether the same level of risk reduction applies to individuals with Lynch syndrome.

The [Gynecologic Cancer Prevention and Survivorship Program](#) provides menopause management, and surgical decision support for individuals considering risk-reducing surgery.

### **Urothelial Cancer (Renal Pelvis, Ureter, Bladder)**

There is no clear data to recommend surveillance for urothelial cancers in Lynch syndrome. Patients are encouraged to report symptoms such as blood in the urine.

Urothelial cancer surveillance may be considered in those with a close relative with urothelial cancer (renal pelvis, ureter, bladder). Surveillance options may include annual urine cytology (urine analysis can also be performed; however, is less sensitive and does not replace urine cytology) and annual upper tract renal ultrasound starting at age 30-35 years.

### **Gastric and Small Bowel Cancer**

There is limited scientific evidence to recommend gastric and small bowel cancer surveillance in Lynch syndrome. The surveillance below can be considered if there is a family history of gastric/small bowel cancer, additional risk factors, or at the discretion of a gastroenterologist.

High-quality esophagogastroduodenoscopy (EGD) every 2-4 years preferably at time of colonoscopy, beginning at age 30-40 years.

Screen for *Helicobacter pylori* and gastritis at the time of EGD, or as one-time noninvasive test if not undergoing endoscopy. Treat *H. pylori* if detected.

### **Pancreatic Cancer**

- To lower the risk, avoid or quit cigarette smoking, exercise regularly, limit alcohol, maintain a weight that supports overall health and choose healthy foods and drinks.
- Begin screening for type 2 diabetes at age 40, repeat every 3 years.
- Investigate new onset of diabetes or unexplained changes in diabetic control carefully, with consideration of pancreatic imaging (CT pancreatic protocol or contrast-enhanced MRI/MRCP); refer to GI specialist if any abnormalities are found.

Surveillance may be recommended for patients with an *MLH1* pathogenic variant AND a close relative with pancreatic cancer, see [this document](#) for more information.

### **Skin Cancer**

A dermatologic examination every 1–2 years is recommended to support early detection of associated skin lesions (e.g. sebaceous neoplasms) and to review risk factor modification strategies, including minimizing sun exposure.

### **Brain Cancer**

Prompt evaluation by a physician is recommended for any new or persistent unexplained neurological symptoms.

### **Breast and Prostate Cancer**

General population screening is sufficient unless there is a strong family history.

## **Family and Reproductive Considerations**

### **Inheritance**

Lynch syndrome follows an autosomal dominant inheritance pattern. Each child of someone with an *MLH1* pathogenic variant has a 50% chance of inheriting the variant.

Family members are encouraged to contact their local genetics clinic to learn more about genetic testing and cancer screening. Family members who live in British Columbia or the Yukon can contact our program directly at [hereditarycancer@bccancer.bc.ca](mailto:hereditarycancer@bccancer.bc.ca) . In BC/Yukon, genetic testing is generally available starting at age 19.

### **CMMRD (Constitutional Mismatch Repair Deficiency)**

CMMRD is a rare condition that happens when a child inherits two pathogenic variants (one from each parent) in the same Lynch gene (e.g. *MLH1*). It causes a high risk of childhood cancers, such as leukemia, brain, and intestinal cancers, usually diagnosed around age 10. If an individual with an *MLH1* pathogenic variant is planning a family, a review of their partner's family history of cancer may be helpful. Genetic counselling may be offered if there is a concern for the risk of CMMRD in children.

*Note: In the information above, male/female refers to sex assigned at birth.*