Ambry Genetics®

Clinician Management Resource for *MLH1* (Lynch syndrome)

This overview of clinical management guidelines is based on this patient's positive test result for a *MLH1* gene mutation. Unless otherwise stated, medical management guidelines used here are limited to those issued by the National Comprehensive Cancer Network® (NCCN®)[1] in the U.S. Please consult the referenced guideline for complete details and further information.

Clinical correlation with the patient's past medical history, treatments, surgeries and family history may lead to changes in clinical management decisions; therefore, other management recommendations may be considered. Genetic testing results and medical society guidelines help inform medical management decisions but do not constitute formal recommendations. Discussions of medical management decisions and individualized treatment plans should be made in consultation between each patient and his or her healthcare provider, and may change over time.

SCREENING/SURGICAL CONSIDERATIONS[1]	AGE TO START	FREQUENCY
Colorectal Cancer		
Colonoscopy	20-25 years old (or 2-5 years prior to the earliest colorectal cancer in the family, if it is diagnosed before 25 years)	Every 1-2 years^
Consider daily aspirin to reduce future risk of colorectal cancer, including a discussion of risks and benefits.	Individualized	N/A
Endometrial (Uterine) Cancer		
Consider option of risk-reducing hysterectomy	Individualized	N/A
Consider screening via endometrial biopsy. Routine endometrial cancer screening does not have proven benefit.	30-35 years old	Every 1-2 years
Encourage prompt response to symptoms (e.g. abnormal uterine bleeding, postmenopausal bleeding).	Individualized	Individualized
Transvaginal ultrasound may be considered in post menopausal women.^^	Clinician's discretion	Clinician's discretion
Consider risk reduction agents, including a discussion of risks and benefits.	Individualized	Individualized
Ovarian Cancer		
Bilateral salpingo-oophorectomy (BSO) for women who have completed childbearing	Individualized	N/A
Educate women on the symptoms associated with ovarian cancer (e.g. pelvic/abdominal pain, bloating, difficulty eating, increased abdominal girth, etc.).	Individualized	Individualized
Transvaginal ultrasound and serum CA-125 may be considered. Data do not support routine ovarian screening.	Clinician's discretion	Clinician's discretion
Consider risk reduction agents, including a discussion of risks and benefits.	Individualized	Individualized
Urothelial Cancer		
Selected individuals such as with a family history of urothelial cancer may consider urinalysis. There is insufficient evidence to recommend a particular surveillance strategy.	30-35 years old	Every 12 months
Gastric and Small Bowel Cancer		
Upper GI surveillance with EGD, preferably in conjunction with colonoscopy. Random biopsy of the proximal and distal stomach should at a minimum be performed on the initial procedure to assess for *H. pylori*, autoimmune gastritis, and intestinal metaplasia.	30-40 years old or earlier based on family history or high risk findings	Every 2-4 years or more frequently based on family history or high-risk findings
Individuals not undergoing endoscopic surveillance should have one-time noninvasive testing for *H. pylori* at time of Lynch syndrome diagnosis.	Individualized	N/A
Treatment for *H. pylori* if detected.	Individualized	N/A

SCREENING/SURGICAL CONSIDERATIONS[1]	AGE TO START	FREQUENCY
Pancreatic Cancer*		
For individuals with exocrine pancreatic cancer in >1 first-or second-degree relative on the same side of the family as the identified pathogenic/likely pathogenic germline variant, consider pancreatic cancer screening.*	50 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier)	Every 12 months (with consideration of shorter intervals if worrisome abnormalities seen on screening)
Prostate Cancer		
It is reasonable for men with Lynch syndrome to consider beginning shared decision-making about prostate cancer screening.	40 years old	Consider screening at annual intervals rather than every other year.
Breast Cancer		
Not enough evidence to support increased screening above average-risk screening recommendations or based on personal and/or family history.	Clinician's discretion	Clinician's discretion
Brain Cancer		
Patients should be educated regarding signs and symptoms of neurologic cancer and the importance of prompt reporting of abnormal symptoms to their physicians.	Individualized	Individualized
Skin Manifestations		
Consider skin exam with a health care provider skilled in identifying Lynch syndrome-associated skin manifestations.	Individualized	Every 1-2 years
Reproductive Options		
For patients of reproductive age, counsel about options for prenatal diagnosis and assisted reproduction, including pre-implantation genetic testing.	Individualized	N/A
If both parents are carriers of a pathogenic/likely pathogenic variant in *MLH1*, counsel for risk of a rare autosomal recessive condition called constitutional mismatch repair deficiency (CMMRD).	Individualized	N/A
Risk to Relatives		
Advise patients to tell their relatives about possible inherited cancer risk, options for risk assessment, and management. Recommend genetic counseling and consideration of genetic testing for at-risk relatives.	Individualized	N/A

^ Individuals who may benefit from a shorter screening interval (ie, 1-year vs 2-year) include those with risk factors such as a history of colorectal cancer or adenoma, male sex, *MLH1* pathogenic variant, and age over 40 years.

^^ Transvaginal ultrasound is not highly sensitive or specific for endometrial cancer screening.

* For individuals considering pancreatic cancer screening, the guideline recommends that screening be performed in experienced high-volume centers. The guideline recommends that such screening only take place after an in-depth discussion about the potential limitations to screening, including cost, the high incidence of benign or intermediate pancreatic abnormalities, and uncertainties about the potential benefits of pancreatic cancer screening. The guideline recommends that screening be considered using annual contrast-enhanced MRI/MRCP and/or EUS, with consideration of shorter screening intervals for individuals found to have worrisome abnormalities on screening. The guideline emphasizes that most small cystic lesions found on screening will not warrant biopsy, surgical resection, or any other intervention.

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal. V2.2022. Accessed December 20, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org.

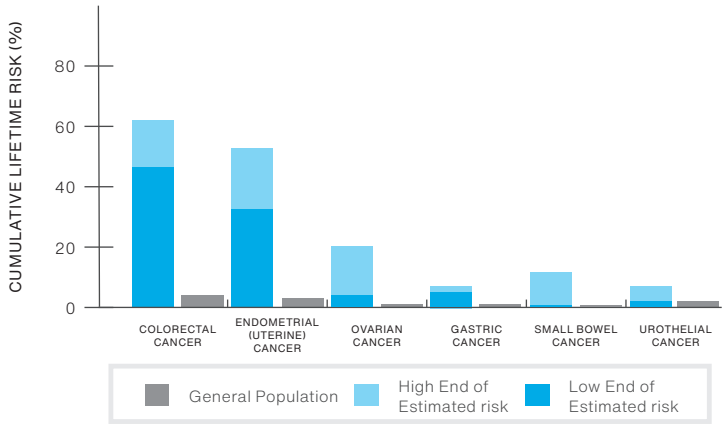
Understanding Your Positive *MLH1* Genetic Test Result

INFORMATION FOR PATIENTS WITH A PATHOGENIC MUTATION OR VARIANT, LIKELY PATHOGENIC

6 Things To Know

1	*MLH1* mutation	Your testing shows that you have a pathogenic mutation or a variant that is likely pathogenic in the *MLH1* gene.
2	Lynch syndrome	People with *MLH1* mutations have Lynch syndrome, previously known as hereditary non-polyposis colorectal cancer (HNPCC).
3	Cancer risks	You have an increased chance to develop colorectal, endometrial/uterine, stomach, ovarian, small bowel, and other types of cancer.
4	What you can do	Risk management decisions are very personal. There are options to detect cancer early or lower the risk to develop cancer. It is important to discuss these options with your doctor and decide on a plan that works for you.
5	Other Medical Concerns	Individuals with *MLH1* mutations may have an increased risk to have a child with constitutional mismatch repair deficiency (CMMRD), but only if their partner also carries a mutation in the *MLH1* gene. CMMRD is a multisystem disorder characterized by specific physical features and an increased risk for hematologic malignancies, brain tumors, and early-onset Lynch syndrome-associated cancers.
6	Family	Family members may also be at risk – they can be tested for the *MLH1* mutation that was identified in you. It is recommended that you share this information with family members so they can learn more and discuss this with their healthcare providers.

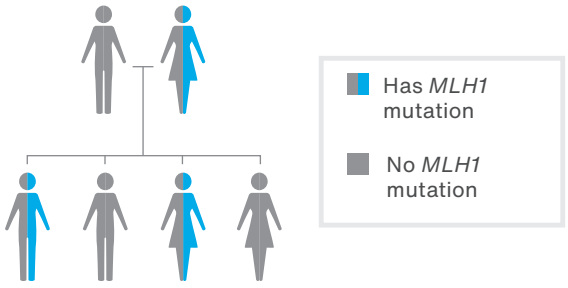
MLH1 Mutation Lifetime Cancer Risks (%)*



* Because risk estimates vary in different studies, only approximate risks are given. Cancer risks will differ based on individual and family history.

MLH1 Mutations in the Family

There is a 50/50 random chance to pass on a *MLH1* mutation to your sons and daughters. The image below shows that both men and women can carry and pass on these mutations.



Reach Out

RESOURCES

- Ambry's hereditary cancer site for families patients.ambrygen.com/cancer
- Hereditary Colon Cancer Foundation hcctakesguts.org
- I Have Lynch Syndrome ihavelynchsyndrome.com
- Lynch Syndrome International lynchcancers.com
- Genetic Information Nondiscrimination Act (GINA) ginahelp.org
- National Society of Genetic Counselors nsgc.org
- Canadian Association of Genetic Counsellors cagc-accg.ca
- AliveAndKickn (Patient Advocacy Group) aliveandkickn.org

Please discuss this information with your healthcare provider. The cancer genetics field is continuously evolving, so updates related to your *MLH1* result, medical recommendations, and/or potential treatments may be available over time. This information is not meant to replace a discussion with a healthcare provider, and should not be considered or interpreted as medical advice.

MKT-ONCO-FLYR-10036-EN v1 | 01.23.23

7 Argonaut, Aliso Viejo, CA 92656 USA Toll Free +1 866.262.7943 Fax +1 949.900.5501 ambrygen.com