Ambry Genetics®

Clinician Management Resource for *MSH2* (Lynch syndrome)

This overview of clinical management guidelines is based on this patient's positive test result for a pathogenic or likely pathogenic variant in the *MSH2* gene. 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 Cancer		
Encourage prompt response to symptoms (e.g. abnormal uterine bleeding, postmenopausal bleeding)	Individualized	Individualized
Consider the option of risk-reducing hysterectomy. For patients requiring a colorectal surgery such as for colorectal cancer resection, coordination with risk-reducing gynecologic surgery should be considered.	Hysterectomy with bilateral salpingo-oophorectomy: starting at 40 years old	N/A
Consider screening via endometrial biopsy. Routine endometrial cancer screening does not have proven benefit.	30-35 years old	Every 1-2 years
Transvaginal ultrasound may be considered in post menopausal patients.^^	Individualized	Individualized
Consider risk-reduction agents, including oral contraceptive pills and progestin intrauterine systems.	Individualized	Individualized
Ovarian Cancer		
Bilateral salpingo-oophorectomy may reduce the incidence of ovarian cancer. For patients requiring a colorectal surgery such as for colorectal cancer resection, coordination with risk-reducing gynecologic surgery should be considered. As premature menopause due to oophorectomy can cause detriments to bone health, cardiovascular health, and generalized quality of life, estrogen replacement therapy should be considered. Salpingectomy is also an option for premenopausal patients who are not yet ready for oophorectomy.	Hysterectomy with bilateral salpingo-oophorectomy: starting at 40 years old	N/A
Salpingectomy has been shown to reduce the risk of ovarian cancer in the general population and is an option for premenopausal patients who are not yet ready for oophorectomy.	Individualized	Individualized
CA-125 and pelvic ultrasound are recommended for preoperative planning. Data do not support routine ovarian screening.	Individualized	Individualized
Consider risk-reduction agents, including oral contraceptive pills and progestin intrauterine systems.	Individualized	Individualized
Urothelial Cancer		
Selected individuals such as with a family history of urothelial cancer or individuals with *MSH2* mutations (especially males) may consider urinalysis. There is insufficient evidence to recommend a particular surveillance strategy.	30-35 years old	Every 12 months

SCREENING/SURGICAL CONSIDERATIONS[1]	AGE TO START	FREQUENCY
Gastric and Small Bowel Cancer		
Upper GI surveillance with high-quality endoscopic gastroduodenoscopy, 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
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.	Individualized	Individualized
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 *MSH2*, 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, *MSH2* 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, Endometrial, and Gastric. v3.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed October 31, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

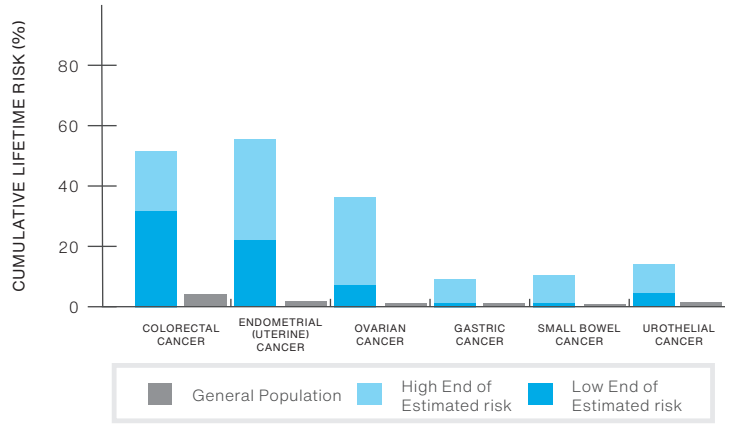
Understanding Your Positive *MSH2* Genetic Test Result

INFORMATION FOR PATIENTS WITH A PATHOGENIC OR LIKELY PATHOGENIC VARIANT

6 Things To Know

1	Result	Your testing shows that you have a pathogenic or likely pathogenic variant in the *MSH2* gene.
2	Lynch syndrome	People with pathogenic or likely pathogenic *MSH2* variants 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 healthcare provider and decide on a plan that works for you.
5	Other Medical Concerns	Individuals with pathogenic or likely pathogenic *MSH2* variants may have an increased risk to have a child with constitutional mismatch repair deficiency (CMMRD), but only if their partner also carries a pathogenic or likely pathogenic variant in the *MSH2* 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 pathogenic or likely pathogenic *MSH2* variant 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.

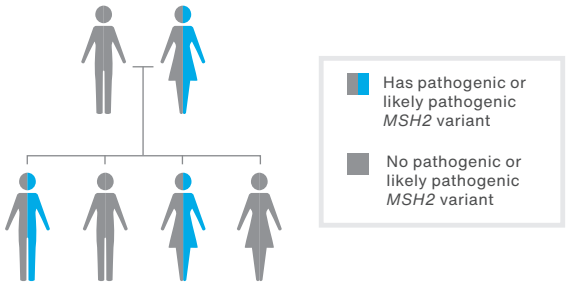
MSH2 Lifetime Cancer Risks*



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

MSH2 in the Family

There is a 50/50 random chance to pass on the pathogenic or likely pathogenic *MSH2* variant to each of your children.



RESOURCES

- AliveAndKickn (Patient Advocacy Group) aliveandkickn.org
- Lynch Syndrome International lynchcancers.com
- National Society of Genetic Counselors nsgc.org
- Canadian Association of Genetic Counsellors cagc-accg.ca

Please discuss this information with your healthcare provider. The cancer genetics field is continuously evolving, so updates related to your *MSH2* 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.

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