Ambry Genetics®
A Konica Minolta Company

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	AGE TO START	FREQUENCY
Colorectal Cancer[1]		
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
Endometrial and Ovarian Cancer[1]		
Consider option of prophylactic hysterectomy	Individualized	N/A
Bilateral salpingo-oophorectomy (BSO) for women who have completed childbearing	Individualized	N/A
Consider screening via endometrial biopsy	30-35 years old	Every 1-2 years
Endometrial: encourage prompt response to symptoms (e.g. abnormal uterine bleeding, postmenopausal bleeding).	Individualized	Individualized
Ovarian: 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	Individualized	Individualized
Gastric and Small Bowel Cancer[1]		
Selected individuals/families at a higher risk^ may consider baseline EGD with random biopsy of the proximal and distal stomach for H. pylori, autoimmune gastritis, and intestinal metaplasia. No clear evidence to support screening for gastric, duodenal, or small bowel cancer. Consider testing and treating *H. pylori*.	Beginning age 40	Every 3-5 years
Brain Cancer[1]		
Consider physical/neurological examination	25-30 years old	Every 12 months
Urothelial Cancer[1]		
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
Breast Cancer[1]		
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
Prostate Cancer[1]		
Insufficient evidence to recommend earlier or more frequent screening	Clinician's discretion	Clinician's discretion

Clinician Management Resource for *MLH1* (Lynch syndrome)

SCREENING/SURGICAL CONSIDERATIONS[1]	AGE TO START	FREQUENCY
Pancreatic Cancer[2]		
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)	Annually (with consideration of shorter intervals if worrisome abnormalities seen on screening)
Other[1]		
Counsel for risk of autosomal recessive condition in offspring If both parents have a *MLH1* mutation, their children are at risk for developing constitutional MMR deficiency (CMMRD) syndrome.	Individualized	N/A

* For individuals considering pancreatic cancer screening, the guideline recommends that screening be performed in experienced high-volume centers, ideally under research conditions. 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 pancreatic abnormalities, and uncertainties about the potential benefits of pancreatic cancer screening.

** There are data demonstrating that the use of 600 mg/daily of aspirin for at least 2 years decreases CRC risk in LS. Ongoing studies are investigating the optimal dose and duration. Decision to use aspirin should be individualized.

ˆ Risk factors for gastric and/or small bowel cancer include male sex, older age, MLH1 or MSH2 pathogenic variants, a first-degree relative with gastric cancer, Asian ethnicity, residing in or immigrant from countries with high background incidence of gastric cancer, chronic autoimmune gastritis, gastric intestinal metaplasia, and gastric adenomas.

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. V1.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed August 20, 2020. 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.
2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. V1.2021. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed September 22, 2020. 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.

One Enterprise, Aliso Viejo, CA 92656 USA Toll Free +1 866 262 7943 Fax +1 949 900 5501 ambrygen.com