Genetic Insights: quick reference guide for healthcare providers

This guide is intended to facilitate a discussion between a provider and their patient.

Genetic Insights test results: **Lynch syndrome**

Key results

A pathogenic or likely pathogenic variant associated with Lynch syndrome was found in the *MLH1* gene.

People with Lynch syndrome have a significantly increased risk of developing certain cancers, especially colon cancer and uterine cancer.

Next steps

Clinical recommendations	Resources
Genetic Insights is a screening test and is not intended for diagnosis. A follow-up genetic test should be performed in a clinical setting before any other action is taken.	**Ready to order?** Check with your institution and/or patient's insurance about the preferred testing laboratory. Blueprint Genetics® offers offers hereditary cancer testing. To confirm this test result, **targeted variant testing** for the variant identified is available. You can order a confirmation test here: Blueprint Genetics/TVT **Have questions?** Call **1.866.GENE.INFO** (1.866.436.3463) to speak to a specialized Quest genetic counselor or geneticist available to healthcare providers to discuss test selection and results.
Refer your patient to a genetic counselor specializing in hereditary cancer.	Your patient can schedule a 1-on-1 remote genetic counseling session through their online Genetic Insights Cancer Risk Report at no additional cost.
Genetic counselors can provide counseling on the implications of this test result and next steps for your patient.	To find a genetic counselor with expertise in hereditary cancer practicing in your patient's area for an in-person session, please visit FindAGeneticCounselor.NSGC.org

Patient conversation starters:

Patient conversation starters summarize the preceding information in plain language to support meaningful conversations between you and your patient.

FindAGeneticCounselor.NSGC.org

Your Genetic Insights test is a screening test. The next step is to have your result confirmed with a second genetic test.

It's also important that you talk with a genetic counselor. Genetic counselors are experts in genetics and can help you understand this result and potential next steps.

You can access a genetic counselor through your Genetic Insights dashboard at no additional cost to you, and we can discuss a referral to a local genetic counselor.

Visit QuestDiagnostics.com/Genetic-Health-Screening for more information about this test.

What is Lynch syndrome?

Lynch syndrome is a hereditary cancer predisposition syndrome characterized by a higher-than-average lifetime risk of certain cancers and typically, an earlier age of onset.[2,3] Colon cancer in men and women and uterine cancer in women are the most common.

Risk for other types of cancer may also be increased.[2,3]

Lynch syndrome is primarily associated with DNA variants in the *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* genes.[2,3]

People with Lynch syndrome are recommended to undergo more frequent cancer screening, typically starting at an earlier age than in the general population.[2,3]

See the Management options section for more detail.

Patient conversation starters:

Lynch syndrome is caused by DNA variants in certain genes.

People with Lynch syndrome have a higher than typical chance of developing certain cancers, especially colon cancer and uterine cancer. Not everyone with Lynch syndrome will develop cancer.

People with Lynch syndrome should have cancer screenings earlier in life and more often than typical. This increases the chance that if cancer develops, it 's detected as early as possible.

What this result means for family members

Family members may have the same DNA variant. The DNA variant was most likely inherited from a parent. Full siblings and children have a 50% chance of having this variant.

In people with a confirmed DNA variant associated with Lynch syndrome, cascade genetic testing for other family members 18 and older may help inform their risks and screening protocols.[2,3]

Children of biological parents who both have a DNA variant in *MLH1* are at risk for having a genetic condition called constitutional mismatch repair deficiency (CMMRD).

A genetic counselor can help determine the most appropriate testing options. Therefore, it is strongly recommended that people share their results with their biological relatives and reproductive partners.

Patient conversation starters:

Lynch syndrome runs in families.

That means the DNA variants that cause Lynch syndrome can be inherited or passed down from parents to their children. Your close relatives, like your parents, full siblings, and children have a 50% (or 1 in 2) chance of having the same DNA variant. Other relatives might also have the same DNA variant.

Sharing these results with your family is important so family members can decide if they want to have genetic testing for Lynch syndrome.

Cancer risk

Select estimated cancer risks in people with a confirmed variant in the *MLH1* gene compared to the general population are included below.[1] Individual cancer risks may be higher or lower depending on the specific variant identified, in addition to personal health history and family health history.

Cancer type	Approximate lifetime risk with *MLH1* variant	Approximate lifetime risk in the general population
Males and females:		
Colon	Up to 57%[1]	4.2%[3]
Assigned female at birth:		
Endometrial	Up to 37%[1]	3.1%[3]
Ovarian	Up to 11%[1]	1.3%[3]

Associated cancers and risks may change over time as medical research advances.

Management options

There are options for cancer prevention and early detection for people with Lynch syndrome. Clinical guidelines from the National Comprehensive Cancer Network© (NCCN©) in people with Lynch syndrome and no personal history of an associated cancer include[3]:

Cancer type	Guidelines for people with the *MLH1* variant detected
Colon	Colonoscopy, starting at age 20-25, or 2-5 years prior to the earliest colon cancer diagnosis in the family Colonoscopy should be repeated every 1-2 years
Endometrial	Consider risk-reducing hysterectomy on an individual basis Consider endometrial biopsy every 1-2 years starting at age 30-35
Ovarian	Consider risk-reducing salpingo-oophorectomy on an individual basis
Gastric and small bowel	Upper GI surveillance with upper endoscopy starting at age 30 or earlier based on family history Repeat every 2-4 years or more frequently based on history
Other	Other cancer screenings or risk-reduction options beyond typical recommendations may be considered based on personal health history and family health history

Patient conversation starters:

It's recommended that people with Lynch syndrome have cancer screenings earlier and more often than typical. This way, cancer is more likely to be caught in the early stages when it's most treatable. In fact, colon cancer can even be prevented if pre-cancerous colon polyps are found and removed during a colonoscopy. If your Lynch syndrome result is confirmed, it's important to work with the right specialists—like a medical oncologist or gastroenterologist—to find cancer screening and risk-reducing options that are right for you.

See NCCN for complete recommendations. Guidelines and recommendations may change over time.

If the test result is confirmed, local centers of excellence in hereditary cancer should be consulted for further clinical management. To locate a genetics center or specialty clinic, please visit the American College of Medical Genetics and Genomics at https://www.acmg.net/ACMG/Directories.aspx

Additional resources

The following patient advocacy groups have additional information and resources about Lynch syndrome:

AliveandKickn: AliveAndKickn.org

Facing Our Risk of Cancer Empowered (FORCE): FacingOurRisk.org

References

1. Dominguez-Valentin M, Sampson JR, Seppälä TT, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. *Genetics in medicine: official journal of the American College of Medical Genetics*. 2020;22(1):15-25. doi:10.1038/s41436-019-0596-9
2. Idos G, Valle L. Lynch Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. *GeneReviews*® [Internet]. University of Washington, Seattle; 1993-2022. www.ncbi.nlm.nih.gov/books/NBK1211/
3. National Comprehensive Cancer Network®. Genetic/Familial High-Risk Assessment: Colorectal (Version 2.2022). NCCN Guidelines®. Accessed December 20, 2022. www.nccn.org