MLH1

The *MLH1* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. *MLH1* works together with the *PMS2* gene to remove and repair DNA errors when signaled by the *MSH2* and *MSH6* genes.

Like most genes, each person has two copies of the *MLH1* gene: one inherited from each parent. A mutation in a single *MLH1* gene inherited from one parent causes Lynch syndrome, which is known to increase risks of colorectal, uterine, ovarian, and other cancers over a lifetime.

In very rare cases, a person can inherit two *MLH1* mutations, one from each parent. This causes a condition called Constitutional Mismatch Repair Deficiency (CMMR-D), which is associated with cancers in childhood such as colorectal, small intestine, brain, leukemia/lymphoma, and others.

How common are mutations in the *MLH1* gene?

Mutations that cause Lynch syndrome are rare—found in approximately 1 in 370 individuals.[1] Lynch syndrome accounts for approximately 3% of all colorectal cancers.[2]

How mutations in this gene impact risk

Women

If a woman has a mutation in the *MLH1* gene, her chances of developing ovarian, colorectal, uterine, central nervous system, hepatobiliary tract, pancreatic, sebaceous neoplasms, small bowel, stomach, and urinary tract cancer are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

Cancer by age 70	Average US woman[3]	With *MLH1* mutation
Colorectal	1.6%	36-50%[4,5,6]

[1] Hampel H, De la chapelle A. The search for unaffected individuals with Lynch syndrome: do the ends justify the means?. Cancer Prev Res (Phila). 2011;4(1):1-5.
[2] Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-society Task Force on colorectal cancer. Am J Gastroenterol. 2014;109(8):1159-79.
[3] Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2010-2012. DevCan software (http://surveillance.cancer.gov/devcan) V 6.7.0, Accessed June 2015.
[4] Dowty JG, Win AK, Buchanan DD, et al. Cancer risks for MLH1 and MSH2 mutation carriers. *Hum Mutat.* March 2013; 34(3):490-7.
[5] Barrow E, Robinson L, Alduaij W, et al. Cumulative lifetime incidence of extracolonic cancers in Lynch syndrome: a report of 121 families with proven mutations. *Clin Genet.* February 2009; 75(2):141-9.
[6] Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA.* June 2011; 305(22):2304-10.

Uterine	1.7%	18-54%[4,5,6]
Ovarian	<1%	6-13%[4,5]
Brain	<1%	2%[7]
Hepatobiliary tract	<1%	3%[5]
Pancreatic	<1%	3.7%[8]
Sebaceous neoplasms	<0.1%	Elevated[9]
Small bowel	<1%	3-5%[5,7]
Stomach	<1%	6-11%[4,5,7]
Urinary tract	<1%	1-3%[5,7]

Elevated: Risk is increased, but further research may clarify the exact risk figure.

Men

If a man has a mutation in the *MLH1* gene, his chances of colorectal, brain, hepatobiliary tract, pancreatic, sebaceous neoplasms, small bowel, stomach, and urinary tract cancer are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

Cancer by age 70	Average US man[3]	With *MLH1* mutation
Colorectal	2%	34-41%[4,6]
Brain	<1%	2%[7]
Hepatobiliary tract	<1%	3%[5]
Pancreatic	<1%	3.7%[8]
Sebaceous neoplasms	<0.01%	Elevated[9]
Small bowel	<1%	5-6%[5,7]
Stomach	<1%	6-20%[4,5,7]

[7] Watson P, Vasen HF, Mecklin JP, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. *Int J Cancer*. July 2008; 123(2):444-9.
[8] Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. *JAMA.* October 2009; 302(16):1790-5.
[9] South CD, Hampel H, Comeras I, et al. The frequency of Muir-Torre syndrome among Lynch syndrome families. *JNCI.* February 2008; 100(4):277-81.

Urinary tract	2.2%	3-4%[5,7]

Elevated: Risk is increased, but further research may clarify the exact risk figure.

Additional information

Mutations in five different genes can lead to Lynch syndrome.
Having a mutation in *EPCAM*, *MLH1*, *MSH2*, *MSH6*, or *PMS2* can cause Lynch syndrome. Lynch syndrome used to be referred to as Hereditary Non-Polyposis Colorectal Cancer, or HNPCC. It is an inherited condition that increases the risk of colorectal and other cancers. The associated cancer types and risk levels vary, depending on the gene in which the mutation is found.

Lynch syndrome is sometimes uncovered by testing a cancer or tumor.
Lynch syndrome can sometimes be evaluated by performing certain tests on cancers or tumors. These tests are called immunohistochemistry (IHC) and microsatellite instability (MSI) and are often the first line of screening tests when someone is suspected to have Lynch syndrome.

If a cancer or tumor is missing the protein made by the *MLH1* gene on the IHC test, other tests may be performed on the tumor or cancer. These tests are called *MLH1* promoter methylation testing and *BRAF* V600E mutation testing. The results may help clarify whether the cancer was caused by Lynch syndrome.

Screening guidelines

Below is a summary of screening guidelines from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) established by experts at the National Comprehensive Cancer Network (NCCN).[10] They are specific to individuals who have a mutation in the *MLH1* gene. If you have a mutation in this gene, your healthcare provider may use these NCCN Guidelines® to help create a customized screening plan for you.

Women

Uterine and ovarian cancer[11]

- When you are finished having children: Your healthcare provider may discuss a risk-reducing hysterectomy (the surgical removal of the uterus) and

[10] Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal. V.2.2016. © National Comprehensive Cancer Network, Inc 2016. All rights reserved. Accessed October 26, 2016. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.
[11] National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. NCCN Guidelines Version 2.2016. Available at www.nccn.org. Published September 2016.

salpingo-oophorectomy (the surgical removal of the ovaries and fallopian tubes) with you to lower the risk of developing uterine and ovarian cancer.
- Your healthcare provider may discuss the benefits and limitations of a transvaginal ultrasound along with endometrial biopsies (sampling) every year.
- You should be aware of any uterine cancer symptoms, such as uterine bleeding that is not typical.
- While there may be circumstances where ovarian cancer screening with transvaginal ultrasound and a blood test for a protein called CA-125 are helpful, these techniques have not been shown to be effective in detecting early ovarian cancer.

Colorectal cancer[11]
- Starting at age 20-25 or 2-5 years prior to the earliest colorectal cancer diagnosis in your family if the first diagnosis was before age 25: Colonoscopy every 1-2 years.
- Your provider may discuss the use of medications such as aspirin that might reduce the risk of developing colorectal cancer.

Brain cancer[11]
- Starting at age 25-30: Physical and neurological examination by your provider every year.

Hepatobiliary tract cancer[11]
- Currently, there are no hepatobiliary tract cancer screening guidelines from the NCCN specific to *MLH1* mutation carriers. Your provider may discuss screening or referral to a specialist.

Pancreatic cancer[12]
- Currently, there are no pancreatic cancer screening guidelines from the NCCN specific to *MLH1* mutation carriers. Your provider may discuss screening or referral to a specialist.

Sebaceous neoplasms[11]
- Currently, there are no sebaceous neoplasm screening guidelines from the NCCN specific to *MLH1* mutation carriers. Your provider may discuss screening or referral to a specialist.

Stomach and small bowel cancer[11]
- Starting at age 30-35: Your healthcare provider may discuss an upper endoscopy every 3-5 years, depending on your risk factors such as family history or ancestry.
- Your provider may discuss testing and treatment for a bacteria called H. pylori.

Urinary tract cancer[11]
- Starting at age 30-35: Your healthcare provider may discuss a urinalysis every year.

[12] International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut.* March 2013; 62(3):339-47.

Men

Colorectal cancer[11]

- Starting at age 20-25 or 2-5 years prior to the earliest colorectal cancer diagnosis in your family if the first diagnosis was before age 25: Colonoscopy every 1-2 years.
- Your provider may discuss the use of medications such as aspirin that might reduce the risk of developing colorectal cancer.

Brain cancer[11]

- Starting at age 25-30: Physical and neurological examination by your provider every year.

Hepatobiliary tract cancer[11]

- Currently, there are no hepatobiliary tract cancer screening guidelines from the NCCN specific to *MLH1* mutation carriers. Your provider may discuss screening or referral to a specialist.

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- Your provider may discuss testing and treatment for a bacteria called H. pylori.

Urinary tract cancer[11]

- Starting at age 30-35: Your healthcare provider may discuss a urinalysis every year.

Useful resources

Hereditary Colon Cancer Foundation

A nonprofit organization serving the hereditary colorectal cancer community.

www.hcctakesguts.org

Lynch Syndrome International
Primary mission is to provide support for individuals afflicted with Lynch syndrome.
www.lynchcancers.com

Kintalk
An educational and family communication site for individuals and their families with hereditary cancer conditions
www.kintalk.org

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