

## Lynch syndrome

### Description

Lynch syndrome, often called hereditary nonpolyposis colorectal cancer (HNPCC), is an inherited disorder that increases the risk of many types of cancer, particularly cancers of the colon (large intestine) and rectum, which are collectively referred to as colorectal cancer. People with Lynch syndrome also have an increased risk of cancers of the stomach, small intestine, liver, gallbladder ducts, urinary tract, brain, and skin. Additionally, women with this disorder have a high risk of cancer of the ovaries and lining of the uterus (endometrial cancer). Women with Lynch syndrome have a higher overall risk of developing cancer than men with the condition because of these cancers of the female reproductive system. In individuals with Lynch syndrome who develop cancer, the cancer typically occurs in their forties or fifties.

People with Lynch syndrome may occasionally have noncancerous (benign) growths in the colon, called colon polyps. In individuals with this disorder, colon polyps occur at a younger age but not in greater numbers than they do in the general population.

### Frequency

In the United States, it is estimated that 1 in 279 individuals have a genetic variant (also known as a mutation) associated with Lynch syndrome.

### Causes

Changes in the *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* gene have been found in people with Lynch syndrome.

The *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes are involved in repairing errors that occur when DNA is copied in preparation for cell division (a process called DNA replication). Because these genes work together to fix DNA errors, they are known as mismatch repair (MMR) genes. Variants in any of these genes prevent the proper repair of DNA replication errors. As the abnormal cells continue to divide, the accumulated errors can lead to uncontrolled cell growth and possibly cancer. Variants in the *MLH1* or *MSH2* gene tend to lead to a higher risk (70 to 80 percent) of developing cancer in a person's lifetime, while variants in the *MSH6* or *PMS2* gene have a lower risk (25 to 60 percent) of cancer development.

Variants in the *EPCAM* gene also lead to impaired DNA repair, although the gene is not

itself involved in this process. The *EPCAM* gene lies next to the *MSH2* gene on chromosome 2 and certain *EPCAM* gene variants cause the *MSH2* gene to be turned off (inactivated). As a result, the *MSH2* gene's role in DNA repair is impaired, which can lead to accumulated DNA errors and cancer development.

Although variants in these genes predispose individuals to cancer, not all people with these variants develop cancerous tumors.

#### Learn more about the genes associated with Lynch syndrome

- *EPCAM*
- *MLH1*
- *MSH2*
- *MSH6*
- *PMS2*

### **Inheritance**

Lynch syndrome cancer risk is inherited in an autosomal dominant pattern, which means one inherited copy of the altered gene in each cell is sufficient to increase cancer risk. It is important to note that people with a variant have an increased risk of cancer; not all people who inherit variants in these genes will develop cancer.

### **Other Names for This Condition**

- Cancer family syndrome
- Familial nonpolyposis colon cancer
- Hereditary nonpolyposis colorectal cancer
- Hereditary nonpolyposis colorectal neoplasms
- HNPCC

### **Additional Information & Resources**

#### Genetic Testing Information

- Genetic Testing Registry: Colorectal cancer, hereditary nonpolyposis, type 2 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1333991/>)
- Genetic Testing Registry: Lynch syndrome 1 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C2936783/>)
- Genetic Testing Registry: Lynch syndrome 4 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1838333/>)
- Genetic Testing Registry: Lynch syndrome 5 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1833477/>)

- Genetic Testing Registry: Lynch syndrome 8 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C2750471/>)
- Genetic Testing Registry: Hereditary nonpolyposis colon cancer (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1333990/>)

### Genetic and Rare Diseases Information Center

- Lynch syndrome (<https://rarediseases.info.nih.gov/diseases/9905/index>)

### Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (<https://rarediseases.org/>)

### Clinical Trials

- ClinicalTrials.gov ([https://clinicaltrials.gov/search?cond=%22Lynch syndrome%22](https://clinicaltrials.gov/search?cond=%22Lynch%20syndrome%22))

### Catalog of Genes and Diseases from OMIM

- COLORECTAL CANCER; CRC (<https://omim.org/entry/114500>)
- LYNCH SYNDROME 1; LYNCH1 (<https://omim.org/entry/120435>)

### Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28lynch+syndrome%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+360+days%22%5Bdp%5D>)

## **References**

- Dominguez-Valentin M, Sampson JR, Seppala TT, Ten Broeke SW, Plazzer JP, Nakken S, Engel C, Aretz S, Jenkins MA, Sunde L, Bernstein I, Capella G, Balaguer F, Thomas H, Evans DG, Burn J, Greenblatt M, Hovig E, de Vos Tot Nederveen Cappel WH, Sijmons RH, Bertario L, Tibiletti MG, Cavestro GM, Lindblom A, Della Valle A, Lopez-Kostner F, Gluck N, Katz LH, Heinimann K, Vaccaro CA, Buttner R, Gorgens H, Holinski-Feder E, Morak M, Holzapfel S, Huneburg R, Knebel Doeberitz MV, Loeffler M, Rahner N, Schackert HK, Steinke-Lange V, Schmiegel W, Vangala D, Pylvanainen K, Renkonen-Sinisalo L, Hopper JL, Win AK, Haile RW, Lindor NM, Gallinger S, LeMarchand L, Newcomb PA, Figueiredo JC, Thibodeau SN, Wadt K, Therikildsen C, Okkels H, Ketabi Z, Moreira L, Sanchez A, Serra-Burriel M, Pineda M, Navarro M, Blanco I, Green K, Laloo F, Crosbie EJ, Hill J, Denton OG, Frayling IM, Rodland EA, Vasen H, Mints M, Neffa F, Esperon P, Alvarez K, Kariv R, Rosner G, Pinero TA, Gonzalez ML, Kalfayan P, Tjandra D, Winship IM, Macrae F,

Moslein G, MecklinJP, Nielsen M, Moller P. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. *Genet Med*. 2020 Jan;22(1):15-25. doi:10.1038/s41436-019-0596-9. Epub 2019 Jul 24. Erratum In: *Genet Med*. 2020 Sep;22(9):1569. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/31337882>)

- Hegde M, Ferber M, Mao R, Samowitz W, Ganguly A; Working Group of the American College of Medical Genetics and Genomics (ACMG) Laboratory Quality Assurance Committee. ACMG technical standards and guidelines for genetic testing for inherited colorectal cancer (Lynch syndrome, familial adenomatous polyposis, and MYH-associated polyposis). *Genet Med*. 2014 Jan;16(1):101-16. doi:10.1038/gim.2013.166. Epub 2013 Dec 5. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/24310308>)
- Idos G, Valle L. Lynch Syndrome. 2004 Feb 5 [updated 2021 Feb 4]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. *GeneReviews*(R) [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from <http://www.ncbi.nlm.nih.gov/books/NBK1211/> Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/20301390>)
- Kuiper RP, Vissers LE, Venkatachalam R, Bodmer D, Hoenselaar E, Goossens M, Haufe A, Kamping E, Niessen RC, Hogervorst FB, Gille JJ, Redeker B, Tops CM, van Gijn ME, van den Ouweland AM, Rahner N, Steinke V, Kahl P, Holinski-Feder E, Morak M, Kloor M, Stemmler S, Betz B, Hutter P, Bunyan DJ, Syngal S, Culver JO, Graham T, Chan TL, Nagtegaal ID, van Krieken JH, Schackert HK, Hoogerbrugge N, van Kessel AG, Ligtenberg MJ. Recurrence and variability of germline EPCAM deletions in Lynch syndrome. *Hum Mutat*. 2011 Apr;32(4):407-14. doi:10.1002/humu.21446. Epub 2011 Mar 1. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/21309036>)
- Lagerstedt Robinson K, Liu T, Vandrovcova J, Halvarsson B, Clendenning M, Frebourg T, Papadopoulos N, Kinzler KW, Vogelstein B, Peltomaki P, Kolodner RD, Nilbert M, Lindblom A. Lynch syndrome (hereditary nonpolyposis colorectal cancer) diagnostics. *J Natl Cancer Inst*. 2007 Feb 21;99(4):291-9. doi:10.1093/jnci/djk051. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/17312306>)
- Ligtenberg MJ, Kuiper RP, Chan TL, Goossens M, Hebeda KM, Voorendt M, Lee TY, Bodmer D, Hoenselaar E, Hendriks-Cornelissen SJ, Tsui WY, Kong CK, Brunner HG, van Kessel AG, Yuen ST, van Krieken JH, Leung SY, Hoogerbrugge N. Heritable somatic methylation and inactivation of MSH2 in families with Lynch syndrome due to deletion of the 3' exons of TACSTD1. *Nat Genet*. 2009 Jan;41(1):112-7. doi:10.1038/ng.283. Epub 2008 Dec 21. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/19098912>)
- Lynch HT, de la Chapelle A. Hereditary colorectal cancer. *N Engl J Med*. 2003 Mar 6;348(10):919-32. doi: 10.1056/NEJMra012242. No abstract available. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/12621137>)
- Lynch HT, Lynch JF. What the physician needs to know about Lynch syndrome: an update. *Oncology (Williston Park)*. 2005 Apr;19(4):455-63; discussion 463-4, 466, 469. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/15938070>)
- Martin-Lopez JV, Fishel R. The mechanism of mismatch repair and the

functional analysis of mismatch repair defects in Lynch syndrome. *Fam Cancer*. 2013 Jun;12(2): 159-68. doi: 10.1007/s10689-013-9635-x. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/23572416>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4235668/>)

- Rahner N, Steinke V, Schlegelberger B, Eisinger F, Hutter P, Olschwang S. Clinical utility gene card for: Lynch syndrome (MLH1, MSH2, MSH6, PMS2, EPCAM) - update 2012. *Eur J Hum Genet*. 2013 Jan;21(1). doi: 10.1038/ejhg.2012.164. Epub 2012 Aug 15. No abstract available. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/22892529>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3533316/>)
- Tamura K, Kaneda M, Futagawa M, Takeshita M, Kim S, Nakama M, Kawashita N, Tatsumi-Miyajima J. Genetic and genomic basis of the mismatch repair system involved in Lynch syndrome. *Int J Clin Oncol*. 2019 Sep;24(9):999-1011. doi: 10.1007/s10147-019-01494-y. Epub 2019 Jul 4. Erratum In: *Int J Clin Oncol*. 2019 Jul 31;: Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/31273487>)
- Tanakaya K. Current clinical topics of Lynch syndrome. *Int J Clin Oncol*. 2019 Sep;24(9):1013-1019. doi: 10.1007/s10147-018-1282-7. Epub 2018 May 9. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/29744602>)
- Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Ruschoff J, Fishel R, Lindor NM, Burgart LJ, Hamelin R, Hamilton SR, Hiatt RA, Jass J, Lindblom A, Lynch HT, Peltomäki P, Ramsey SD, Rodriguez-Bigas MA, Vasen HF, Hawk ET, Barrett JC, Freedman AN, Srivastava S. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst*. 2004 Feb 18;96(4):261-8. doi: 10.1093/jnci/djh034. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/14970275>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2933058/>)
- Weissman SM, Burt R, Church J, Erdman S, Hampel H, Holter S, Jasperson K, Kalady MF, Haidle JL, Lynch HT, Palaniappan S, Wise PE, Senter L. Identification of individuals at risk for Lynch syndrome using targeted evaluations and genetic testing: National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer joint practice guideline. *J Genet Couns*. 2012 Aug;21(4):484-93. doi: 10.1007/s10897-011-9465-7. Epub 2011 Dec 14. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/22167527>)
- Win AK, Jenkins MA, Dowty JG, Antoniou AC, Lee A, Giles GG, Buchanan DD, Clendenning M, Rosty C, Ahnen DJ, Thibodeau SN, Casey G, Gallinger S, Le Marchand L, Haile RW, Potter JD, Zheng Y, Lindor NM, Newcomb PA, Hopper JL, MacInnis RJ. Prevalence and Penetrance of Major Genes and Polygenes for Colorectal Cancer. *Cancer Epidemiol Biomarkers Prev*. 2017 Mar;26(3):404-412. doi: 10.1158/1055-9965.EPI-16-0693. Epub 2016 Oct 31. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/27799157>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5336409/>)

**Last updated April 15, 2021**