U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Idos G, Valle L. Lynch Syndrome. 2004 Feb 5 [Updated 2021 Feb 4]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Lynch Syndrome

Gregory Idos, MD, MS[1] and Laura Valle, PhD[2,3,4]

Created: February 5, 2004; Updated: February 4, 2021.

Summary

Clinical characteristics

Lynch syndrome is characterized by an increased risk for colorectal cancer (CRC) and cancers of the endometrium, ovary, stomach, small bowel, urinary tract, biliary tract, brain (usually glioblastoma), skin (sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas), pancreas, and prostate. Cancer risks and age of onset vary depending on the associated gene. Several other cancer types have been reported to occur in individuals with Lynch syndrome (e.g., breast, sarcomas, adrenocortical carcinoma). However, the data are not sufficient to demonstrate that the risk of developing these cancers is increased in individuals with Lynch syndrome.

Diagnosis/testing

The diagnosis of Lynch syndrome is established in a proband by identification on molecular genetic testing of a germline heterozygous pathogenic variant in *MLH1*, *MSH2*, *MSH6*, or *PMS2* or of an *EPCAM* deletion.

Management

Treatment of manifestations: Adenomas of colon: complete endoscopic polypectomy with follow-up colonoscopy every one to two years. For colon cancer, segmental or extended colonic resection is indicated depending on clinical scenario and factors such as age. For individuals with rectal adenocarcinoma, proctectomy or total proctocolectomy is indicated. Other tumors are managed as in the general population.

Prevention of primary manifestations: Prophylactic hysterectomy and bilateral salpingo-oophorectomy can be considered after childbearing is completed. Prophylactic colectomy prior to the development of colon cancer is generally not recommended for individuals known to have Lynch syndrome because screening colonoscopy with

Author Affiliations: 1 Associate Professor of Clinical Medicine, Division of Gastroenterology, Division of Clinical Cancer Genomics, Center for Precision Medicine, City of Hope National Medical Center, Duarte, California; Email: gidos@coh.org. 2 Hereditary Cancer Program, Catalan Institute of Oncology, Barcelona, Spain; Email: lvalle@idibell.cat. 3 Institut d'Investigació Biomédica de Bellvitge (IDIBELL), Barcelona, Spain; Email: lvalle@idibell.cat. 4 Centro de Investigación Biomédica en Red Cáncer (CIBERONC) Madrid, Spain; Email: lvalle@idibell.cat.

Copyright © 1993-2024, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.

polypectomy is an effective preventive measure. Aspirin therapy has been shown to decrease the risk for CRC in individuals with Lynch syndrome.

Surveillance: Colonoscopy with removal of precancerous polyps every one to two years beginning between ages 20 and 25 years or two to five years before the earliest CRC diagnosis in the family, whichever is earlier. Annual education for females regarding the symptoms of endometrial and ovarian cancers. Consider transvaginal ultrasound examination and endometrial biopsy every one to two years. Consider upper endoscopy examination every three to five years beginning between ages 30 and 35 years particularly for individuals with a family history of gastric cancer and those of Asian ancestry. Biopsies should be evaluated for *H pylori* infections so that appropriate treatment can be given as needed. Consider capsule endoscopy and small bowel enterography for distal small bowel cancers. Consider urine analysis with urine cytology to identify microscopic hematuria in those with a family history of urothelial cancer. Consider pancreatic cancer screening in individuals with a family history of pancreatic cancer with alternating endoscopic ultrasound and/or MRI/magnetic resonance cholangiopancreatography.

Agents/circumstances to avoid: High body mass, cigarette smoking, type 2 diabetes, and high cholesterol.

Evaluation of relatives at risk: When a diagnosis of Lynch syndrome has been confirmed in a proband, molecular genetic testing for the Lynch syndrome-related pathogenic variant should be offered to first-degree relatives to identify those who would benefit from early surveillance and intervention. Although molecular genetic testing for Lynch syndrome is generally not recommended for at-risk individuals younger than age 18 years, a history of early cancers in the family may warrant predictive testing prior to age 18.

Genetic counseling

Lynch syndrome caused by a heterozygous germline pathogenic variant in *MLH1*, *MSH2*, *MSH6*, or *PMS2* or by an *EPCAM* deletion is inherited in an autosomal dominant manner. Individuals with Lynch syndrome caused by constitutional inactivation of *MLH1* by methylation typically represent simplex cases but families with non-mendelian inheritance of hypermethylation have been reported. The majority of individuals with Lynch syndrome inherited a pathogenic variant from a parent; however, because of incomplete penetrance, variable age of cancer development, cancer risk reduction as a result of screening or prophylactic surgery, or early death, not all individuals with a pathogenic variant in one of the genes associated with Lynch syndrome have a parent who had cancer. Each child of an individual with Lynch syndrome has a 50% chance of inheriting the pathogenic variant. Prenatal testing for a pregnancy at increased risk is possible if the pathogenic variant in the family is known.

Diagnosis

No consensus clinical diagnostic criteria for Lynch syndrome have been published.

Suggestive Findings

A diagnosis of Lynch syndrome **should be suspected** in a proband with:

- A diagnosis of a tumor of the Lynch syndrome spectrum (e.g., colorectal, endometrial, ovarian, stomach, small bowel, urinary tract [urothelial], biliary tract, prostate, brain [usually glioblastoma], skin [sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas], and pancreas) with one of the following on **tumor tissue testing**:
    - Microsatellite instability (MSI) testing showing that tumor tissue is MSI high. (For information on MSI testing, including advantages and disadvantages, click here.)

  - Immunohistochemistry (IHC) demonstrating loss of expression of one or more of the mismatch repair (MMR) gene products: MLH1, MSH2, MSH6, and/or PMS2. (For information on advantages and disadvantages of IHC testing, click here.)
  - Next-generation sequencing in tumor tissue revealing MSI
  - Identification of a pathogenic variant in tumor tissue in an MMR gene

- A diagnosis of colorectal cancer (CRC) or endometrial cancer and **one or more** of the following:*
  - Colorectal or endometrial cancer diagnosed before age 50 years
  - Synchronous or metachronous Lynch syndrome-related cancers (e.g., colorectal, endometrial, ovarian, stomach, small bowel, urinary tract, biliary tract, prostate, brain, sebaceous adenomas, sebaceous carcinomas, keratoacanthomas, pancreatic)
  - Colorectal tumor tissue with MSI-high histology (e.g., poor differentiation, tumor-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation, medullary growth pattern)
  - At least one first-degree relative with any Lynch syndrome-related cancer diagnosed before age 50 years
  - At least two first-degree relatives with any Lynch syndrome-related cancers regardless of age of cancer diagnosis

- A family member with colorectal or endometrial cancer who meets one of the above criteria

  Note: Molecular genetic testing ideally begins with a person who has had a Lynch syndrome-related cancer. However, in some families there may be no affected individual who is alive or willing to be tested.

- A family member with a confirmed diagnosis of Lynch syndrome (pathogenic variant in one of the genes listed in Table 1)

- A ≥5% probability of having a pathogenic variant in one of the genes listed in Table 1 based on risk assessment models

  Note: Several risk assessment models including PREMM5 [Kastrinos et al 2017], MMRPredict [Barnetson et al 2006], and MMRPro [Chen et al 2006] predict the likelihood of identifying a germline pathogenic variant in one of the genes listed in Table 1. Some data suggest utilizing a lower threshold of ≥2.5% for the PREMM5 predictive model.

* Adapted from revised Bethesda Guidelines and National Comprehensive Cancer Network Guidelines; click here (no-fee registration and login required).

Population screening strategies for Lynch syndrome. Lynch syndrome screening guidelines for individuals have been developed by the NCCN; click here (no-fee registration and login required).

Screening approaches include:

- Screen all CRC and endometrial cancers with MSI or IHC testing. This was shown to be a cost-effective approach for identifying individuals who should be offered germline molecular genetic testing for Lynch syndrome [EGAPP 2009, Ladabaum et al 2011, Moreira et al 2012, Mange et al 2015]. (For information on universal tumor testing, including advantages and disadvantages of IHC and MSI testing, see Hampel et al [2018].)
- Use age of onset, familial cancer history, and pathologic features to predict which individuals are more likely to have a germline MMR pathogenic variant [Rabban et al 2014].
- Tumor tissue sequence analysis for a pathogenic variant in one of the genes listed in Table 1 can simplify the screening and provide additional prognostic and/or treatment information [Hampel et al 2018, Salvador et al 2019]. Note: Simultaneous tumor tissue and germline testing that includes analysis of the

genes listed in Table 1 may become the preferred approach because it will (1) simplify the screening protocol, (2) reduce the need for reflex testing, and (3) provide additional prognostic or treatment information [Hampel et al 2018, Salvador et al 2019].

Targeted molecular genetic testing on tumor tissue. Approximately 15% of sporadic CRCs have evidence of MMR deficiency. Determining which CRCs are not due to a Lynch-associated germline pathogenic variant is possible with additional tumor tissue testing on either all CRCs with MSI or on tumors with absence of MLH1/PMS2 on IHC. Targeted tumor tissue testing includes the following:

- ***MLH1* promoter methylation analysis.** 10%-15% of CRCs are MSI high or MMR deficient due to somatic methylation of the *MLH1* promoter silencing gene expression in the tumor tissue.

  Note: Lynch syndrome-related cancers do not have hypermethylation of the *MLH1* promoter (see Differential Diagnosis, Sporadic Colorectal Cancer) unless there is constitutional inactivation of *MLH1* by promoter methylation.

- **Targeted analysis of *BRAF* pathogenic variant p.Val600Glu (p.V600E)**

  Note: (1) Somatic *BRAF* pathogenic variant c.1799T>A (p.Val600Glu; NM_004333.4) rarely occurs in colorectal tumor tissue in individuals with Lynch syndrome, while it is present in approximately 15% of all CRCs (see Differential Diagnosis, Sporadic Colorectal Cancer). (2) *BRAF* pathogenic variants are not common in sporadic endometrial cancers; thus, *BRAF* testing is not helpful in distinguishing endometrial cancers that are sporadic from those that are Lynch syndrome related. (3) Tumor tissue *MLH1* promoter methylation testing is currently considered a more effective screening test for Lynch syndrome than somatic targeted sequence analysis for *BRAF* p.Val600Glu [Newton et al 2014].

Establishing the Diagnosis

The diagnosis of Lynch syndrome can be **established** in a proband by identification of a heterozygous germline pathogenic (or likely pathogenic) variant in one of the genes listed in Table 1 using molecular genetic testing.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous variant of uncertain significance in one of the genes listed in Table 1 does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a **multigene panel** or **DNA methylation studies** (see Option 1), and **serial single-gene testing** (see Option 2). **Comprehensive genomic testing** (see Option 3) may also be considered.

Option 1 (recommended)

A multigene panel that includes *MLH1*, *MSH2*, *MSH6*, and *PMS2* as well as *EPCAM* deletion analysis (see Table 1) and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype [Idos et al 2019, Heald et al 2020]. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

DNA methylation studies of *MLH1* promoter. Lynch syndrome can be due to constitutional inactivation of *MLH1* by methylation of its promoter. This epimutation is usually present in all tissues and is most often simplex (i.e., a single occurrence in a family), but a few families with inherited *MLH1* promoter methylation have been reported [Hitchins 2015].

Option 2 (not often recommended)

Serial single-gene testing. IHC results on tumor tissue testing may show loss of expression of one or more of the MMR genes indicating that loss of function of a particular MMR gene is most likely (see Table 2). However, this correlation is not 100% and testing of more than one gene, including other MMR and non-MMR genes, may be necessary. Therefore, molecular genetic testing using a multigene panel is often more cost effective than serial single-gene testing.

Option 3

Comprehensive genomic testing (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., a pathogenic variant in a different gene or genes that results in a similar clinical presentation). If this option is chosen, it is important that the genes of interest be well covered and the analysis driven by phenotype.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Lynch Syndrome

Gene [1]	Proportion of Lynch Syndrome Attributed to Pathogenic Variants in Gene [2]	Proportion of Probands w/a Pathogenic Variant [3] Detectable by Method	
		Sequence analysis [4, 5, 6]	Gene-targeted deletion/ duplication analysis [5, 6, 7]
MLH1 [8]	15%-40%	80%-90%	10%-20%
MSH2	20%-40%	60%-80%	20%-40%
MSH6	12%-35%	90%-100%	0%-10%
PMS2 [9, 10]	5%-25%	45%-80% [9]	20%-55% [9]

Table 1. continued from previous page.

Gene [1]	Proportion of Lynch Syndrome Attributed to Pathogenic Variants in Gene [2]	Proportion of Probands w/a Pathogenic Variant [3] Detectable by Method	
		Sequence analysis [4, 5, 6]	Gene-targeted deletion/duplication analysis [5, 6, 7]
EPCAM [11]	<10%	None reported	100% [12]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. Data obtained from universal Lynch syndrome screening for colorectal and endometrial cancers
3. See Molecular Genetics for information on variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants. Detection of exon or whole-gene deletions/duplications require specific sequencing data analysis or use of alternative molecular methods (see footnote 7). For issues to consider in interpretation of sequence analysis results, click here.
5. Smith et al [2016], van der Klift et al [2016], Yurgelun et al [2017]
6. Alteration of the proportions may occur in populations with over-representation of specific founder variants.
7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include specific data analysis of gene panels, quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
8. Constitutional inactivation of *MLH1* by methylation, along with somatic loss of heterozygosity of the functional allele, has been reported to be a rare cause of Lynch syndrome. Such cases are not detectable by either sequence analysis or deletion/duplication analysis of *MLH1* (see Molecular Genetics).
9. Due to the high level of homology between *PMS2* and pseudogenes, testing and interpretation of findings in this gene are difficult. A laboratory that adheres to ACMG guidelines for analysis of *PMS2* and that has expertise in testing this gene should be selected when a *PMS2* pathogenic variant is suspected in a family [Hegde et al 2014]. Long-range PCR, cDNA sequence analysis, and other strategies have been devised to analyze *PMS2* [Li et al 2015a, Jansen et al 2020].
10. Methods to sequence and identify large rearrangements in *PMS2* have been developed and improved over time, making it difficult to determine the proportion of pathogenic variants detected by each method in an affected population. Variants detectable by sequence analysis appear to be more common; however, large rearrangements may comprise 20%-50% of pathogenic variants in this gene [van der Klift et al 2010, Vaughn et al 2010, Smith et al 2016, van der Klift et al 2016].
11. Although *EPCAM* is not a mismatch repair gene, recurrent germline deletions of the 3' region result in silencing of the adjacent downstream *MSH2* by hypermethylation [Niessen et al 2009, Goel et al 2011, Kuiper et al 2011].
12. Germline deletions of *EPCAM* result in silencing of the adjacent *MSH2* allele by hypermethylation. The adjacent *MSH2* allele itself is not mutated (see Molecular Pathogenesis). Sequence analysis of *EPCAM* without deletion analysis is not appropriate for diagnosis of Lynch syndrome; methods for the detection of large rearrangements should be used (see footnote 7).

Table 2. Tumor Tissue Test Results, Interpretation, and Additional Testing Options

Tumor Testing [1]							Plausible Etiologies	Additional Testing Options for Lynch Syndrome [3, 4, 5]
Immunohistochemistry				MSI	*BRAF* V600E [2]	*MLH1* Promoter Methylation		
MLH1	*MSH2*	*MSH6*	*PMS2*					
+	+	+	+	MSS			• Sporadic cancer • Cancer due to other hereditary cancer syndrome	None [6]
+	+	+	+	MSI high			• Sporadic cancer • Germline MMR gene pathogenic variant	• Germline MMR gene testing or paired germline/tumor tissue MMR gene testing • If germline testing negative & paired germline/tumor tissue not done, consider tumor tissue MMR gene testing.

Table 2. continued from previous page.

Tumor Testing [1]							Plausible Etiologies	Additional Testing Options for Lynch Syndrome [3, 4, 5]
Immunohistochemistry				MSI	*BRAF* V600E [2]	*MLH1* Promoter Methylation		
MLH1	*MSH2*	*MSH6*	*PMS2*					
				MSI high			• Sporadic cancer • Germline MMR gene pathogenic variant	• IHC • If IHC not available, consider germline MMR gene testing or paired germline/tumor tissue MMR gene testing. • If germline testing negative & paired germline/tumor tissue not done, consider tumor tissue MMR gene testing.
–	+	+	–				• Sporadic cancer • Germline *MLH1* pathogenic variant • Germline *PMS2* pathogenic variant (rare)	• Targeted *BRAF* &/or *MLH1* promoter methylation testing on tumor tissue • If *BRAF*/*MLH1* methylation normal, germline MMR gene testing or paired germline/tumor tissue MMR gene testing • If germline testing negative & paired germline/tumor tissue not done, consider tumor tissue MMR gene testing.
–	+	+	–		Pos		• Sporadic cancer • Germline *MLH1* path var (rare) • Constitutional *MLH1* epimutation	• If early-onset cancer (< age 50 yrs) or significant family history of cancer: germline MMR gene testing • If not: no additional testing • For early onset only: constitutional *MLH1* epimutation testing [7]
–	+	+	–		Neg	Pos	• Sporadic cancer • Germline *MLH1* path var (rare) • Constitutional *MLH1* epimutation	

Table 2. continued from previous page.

Tumor Testing [1]							Plausible Etiologies	Additional Testing Options for Lynch Syndrome [3, 4, 5]
Immunohistochemistry				MSI	*BRAF* V600E [2]	*MLH1* Promoter Methylation		
MLH1	*MSH2*	*MSH6*	*PMS2*					
–	+	+	–		Neg	Neg	• Germline *MLH1* path var • Germline *PMS2* path var (rare) • Sporadic cancer	• Germline MMR testing or paired germline/tumor tissue MMR gene testing • If germline testing negative & paired germline/tumor tissue not done: consider tumor tissue MMR gene testing.
+	–	–	+				• Germline *MSH2/EPCAM* path var • Germline *MSH6* path var (rare) • Sporadic cancer	
+	+	+	–				• Germline *PMS2* path var • Germline *MLH1* path var • Sporadic cancer	
+	–	+	+				• Germline *MSH2/EPCAM* path var • Sporadic cancer	
+	+	–	+				• Germline *MSH6* path var • Germline *MSH2/EPCAM* path var • Sporadic cancer w/ treatment effect [8]	• Germline MMR gene testing or germline/tumor tissue MMR gene testing • If germline testing negative & paired germline/tumor tissue not done: consider tumor tissue MMR gene testing. • If applicable, consider MSI analysis or repeat IHC on nontreated tumor.
–	+	+	+				• Sporadic cancer: MLH1 promoter methylation or somatic *MLH1* or *PMS2* path var • Germline *MLH1* path var • Germline *PMS2* path var	• Targeted *BRAF* &/or *MLH1* promoter methylation testing on tumor tissue • If *BRAF* & *MLH1* methylation normal: germline MMR gene testing or paired germline/tumor tissue MMR gene testing • If germline testing negative & paired germline/tumor tissue not done: consider tumor tissue MMR gene testing.

Table 2. continued from previous page.

Tumor Testing [1]							Plausible Etiologies	Additional Testing Options for Lynch Syndrome [3, 4, 5]
Immunohistochemistry				MSI	*BRAF* V600E [2]	*MLH1* Promoter Methylation		
MLH1	*MSH2*	*MSH6*	*PMS2*					
–	–	–	–				• Germline MMR gene path var • Sporadic cancer	• Targeted *BRAF* &/or *MLH1* promoter methylation testing AND germline MMR gene testing or paired germline/tumor tissue MMR gene testing (often incl *MLH1* methylation testing) • If germline testing negative & paired germline/tumor tissue not done, consider tumor tissue MMR gene testing

Adapted from Gupta et al [2019].
Empty cells indicate either that testing was not done or that results may not influence testing strategy.
– = absent staining of protein; + = normal staining of protein; IHC = immunohistochemistry; MMR = mismatch repair; MSI = microsatellite instability; MSS = microsatellite stability; Neg = negative; path var = pathogenic variant; Pos = positive
1. Tumor testing strategies apply to colorectal and endometrial cancers. Limited data exist regarding the efficacy of tumor testing in other types of Lynch syndrome tumors.
2. BRAF testing is not appropriate for tumors other than colorectal cancer.
3. 45%-68% of tumors with evidence of MMR deficiency have biallelic somatic pathogenic variants. If biallelic somatic pathogenic variants are identified, the affected individual and their relatives should be managed based on the family cancer history and NOT as if they had Lynch syndrome.
4. Prior to germline genetic testing, proper pre-test counseling should be done.
5. For information on testing for germline pathogenic variants, see Table 1. A multigene panel that includes *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* is recommended. Other colorectal cancer-predisposing genes (e.g., *MUTYH*, *POLE*, *POLD1*, *NTHL1)* should also be considered (see Differential Diagnosis).
6. In the presence of a strong family history (e.g., Amsterdam criteria are met), or if additional features of a hereditary cancer syndrome are present, additional testing may be warranted in the proband or tumor testing in another affected family member because of the possibility that the original tumor selected for testing was a sporadic colorectal cancer (phenocopy).
7. Constitutional *MLH1* epimutation testing involves *MLH1* promoter hypermethylation analysis on blood or other sources of normal tissue.
8. Absent MSH6 IHC staining in rectal tumors may be due to treatment effect (neoadjuvant chemoradiotherapy).

Clinical Characteristics

Clinical Description

Individuals with Lynch syndrome are at increased risk for colorectal cancer (CRC) and other cancers including those of the endometrium, ovary, stomach, small bowel, urinary tract, biliary tract, brain (usually glioblastoma), skin (sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas), pancreas, and prostate (Table 3).

Table 3. Cancer Risks by Gene in Individuals with Lynch Syndrome by Age 70 Years Compared to the General Population

Cancer Location	General Population Risk by Age 74 [1]	Cancer Risk by Age 70 [2, 3]							
		MLH1		*MSH2*		*MSH6*		*PMS2*	*EPCAM*
		F	M	F	M	F	M	F&M	F&M
Any	20%	78%	64%	77%	71%	62%	28%	22%	
Colorectum	2% [4]	44%	53%	42%	46%	20%	12%	3%	75% [5]
Endometrium	1% [4]	35%		46%		41%		13%	12% [5]
Ovary	0.7%	11%		17%		11%		3%	
Stomach	1%	8%	16%	10%	16%	2%	4%	4%	
Small bowel	<1%								
Ureter, kidney	<1%	3%	4%	13%	16%	6%	2%		
Urinary bladder	<1%	3%	5%	7%	9%	1%	4%		
Prostate	4%		7%		16%		5%	5%	
Brain	<1%	2%	1%	2%	4%	1%	2%		
Breast	5% [4]	11%		13%		11%		8%	

F = female; M = male

1. Cumulative risk (age: 0-74) for both sexes estimated from worldwide data [Bray et al 2018, Ferlay et al 2018]; see gco.iarc.fr/today/fact-sheets-cancers for region-specific cancer risks.

2. Organ-specific cancer risks calculated based on an international multicenter prospective observational study (Prospective Lynch Syndrome Database) using independent test and validation cohorts including 6,350 individuals with class 4 (likely pathogenic) or class 5 (pathogenic) variants and 51,646 follow-up years [Dominguez-Valentin et al 2020]

3. Data on cancer risks for those with an *EPCAM* deletion are limited (see Phenotype Correlations by Gene).

4. Lifetime (birth to death) cumulative cancer risks for colorectal, endometrial, and breast cancers have been estimated to be 4%, 3%, and 13%, respectively, for the US population [Siegel et al 2020].

5. As of December 2020 there are no data from the Prospective Lynch Syndrome Database for EPCAM. The information included in the table has been obtained from Kempers et al [2011]. The authors observed that risk for CRC is similar to that of *MLH1* or *MSH2* heterozygotes.

Dowty et al [2013], using sophisticated statistical methodology, revealed that the average risk of cancer (represented in Table 3) does not accurately represent the distribution of cancer risk in individuals with Lynch syndrome. For example, while the average risk of CRC could be 30%-40%, a significant proportion of people with Lynch syndrome have a low risk for CRC (<10%) and a significant proportion have a high risk of developing CRC (>80%). The distribution of cancer risks is due to genetic and/or environmental modifiers.

Colorectal cancer (CRC). The risk of developing CRC associated with *MLH1* and *MHS2* pathogenic variants is significantly higher than the risk associated with *MSH6* or *PMS2* pathogenic variants. Of note, risk estimations based on cohort studies compared to the Prospective Lynch Syndrome Database are higher, particularly for *PMS2* (9%-20% vs 3%). The mean ages at onset for CRC in individuals with *MSH6* and *PMS2* pathogenic variants are older than for CRC associated with *MLH1* and *MSH2* pathogenic variants: 42-69 years for *MSH6* and 61-66 years for *PMS2*, compared with 44 years for *MLH1* and *MSH2* [Gupta et al 2019, NCCN 2020]. These data explain why CRC screening in individuals with an *MLH1* or *MSH2* pathogenic variant should start earlier than in individuals with an *MSH6* or *PMS2* pathogenic variant unless family history suggests otherwise.

CRCs with MSI tend to have a better prognosis in a stage-wise comparison than MSS tumors, potentially reflecting active anti-tumor immune responses. Moreover, treatments supporting the anti-tumoral immune response, such as the immune checkpoint blockade therapy, showed great success in MSI-high tumors [Le et al 2017].

The risk of recurrent CRC is increased in individuals with Lynch syndrome. A meta-analysis of six studies including a total of 871 individuals found that based on an average of 91 months' follow up, the rate of metachronous cancers was 23% among those individuals who had a segmental colectomy, compared to 6% among individuals who had a colectomy (colectomy defined as subtotal or colectomy with ileosigmoid anastomosis) [Anele et al 2017]. The risk of metachronous CRC may be as high as 43% for individuals with an *MLH1* or *MSH2* pathogenic variant who have segmental resection. Available data indicate that risks of metachronous CRC may be lower for individuals with an *MSH6* pathogenic variant, and negligible or absent for those with a *PMS2* pathogenic variant.

Endometrial cancer. According to the Prospective Lynch Syndrome Database, the highest risks for endometrial cancer occur in those with *MSH2* and *MSH6* pathogenic variants (46% and 41% by age 70, respectively), followed by *MLH1* (35%), also agreeing with cohort studies [Gupta et al 2019]. In individuals with a *PMS2* pathogenic variant, the risk of endometrial cancer is 12%-26%, depending on the study type.

The mean age at endometrial cancer diagnosis is between 47 and 50 years for *MLH1*, *MSH2* and *PMS2*, and between 53 and 55 years for *MSH6*. The risk for subsequent endometrial cancer in females with Lynch syndrome presenting first with CRC has been estimated at 26% within ten years of the initial CRC diagnosis [Obermair et al 2010]. As occurs for CRC, endometrial cancers with MSI show better prognosis [Ramchander et al 2020].

Ovarian cancer risk in females with a germline *MLH1*, *MSH2*, or *MSH6* pathogenic variant has been found to be 11%-17% by age 70. Risk estimates obtained from cohort studies show high variability. Females with a germline *PMS2* pathogenic variant have a relatively low increased risk for ovarian cancer. The mean age of diagnosis of Lynch syndrome-associated ovarian cancer has been reported between age 43 and 46 years. Most Lynch syndrome-associated ovarian cancers are of endometrioid histologic subtype [Crosbie et al 2021]. Borderline ovarian tumors do not appear to be associated with Lynch syndrome [Watson et al 2001].

Gastric and small bowel cancers. The risk of gastric and small bowel cancers in individuals with an *MLH1* or *MSH2* pathogenic variant is 8%-16%. The risk is relatively low for individuals with an *MSH6* or *PMS2* pathogenic variant. Intestinal-type adenocarcinoma, the most commonly reported pathology of Lynch syndrome-related gastric cancers [Aarnio et al 1997], differs histologically from the diffuse gastric cancer that is most commonly seen in hereditary diffuse gastric cancer, caused by pathogenic variants in *CDH1* [Guilford et al 1999]. However, Capelle et al [2010] reported that up to 20% of Lynch syndrome-related gastric cancers may be the diffuse type.

The duodenum and jejunum are the most common sites for cancer of the small bowel, with approximately 50% in reach of upper endoscopy [Schulmann et al 2005]. The majority of small bowel cancers are adenocarcinomas [Rodriguez-Bigas et al 1998, Schulmann et al 2005].

Urinary tract cancers. The urinary tract cancers most commonly associated with Lynch syndrome are transitional carcinomas of the ureter, renal pelvis, and kidney. Bladder cancer risk is also increased in individuals with Lynch syndrome [Dominguez-Valentin et al 2020]. Risk estimates for urinary tract cancers vary significantly based on the individual's sex and the gene involved (see Table 3). Individuals with Lynch syndrome and a prior diagnosis of CRC are also at increased risk for subsequent bladder cancer (7%) and other urinary tract cancers (kidney, renal pelvis, and ureter) (13%) [Win et al 2013].

Prostate cancer. A pathogenic variant in a mismatch repair (MMR) gene was identified in four of 692 men (0.5%) with metastatic prostate cancer [Pritchard et al 2016], and in 26 of 1,501 men (1.7%) with prostate cancer and no prior genetic testing [Pritzlaff et al 2020]. The Prospective Lynch Syndrome Database estimates the risk of prostate cancer for men with an *MSH2* pathogenic variant at 16%, and 5%-7% for men with a pathogenic variant in one of the other MMR genes. The mean age at prostate cancer diagnosis was 59-63 years [Gupta et al 2019].

Brain tumors. Data from the National Danish Hereditary Nonpolyposis Colorectal Cancer Register indicated that primary brain tumors were identified in 41 of 288 (14%) Lynch syndrome families, mainly in those with an *MSH2* pathogenic variant. Glioblastoma was the most frequent histologic subtype (56%), followed by astrocytoma (22%) and oligodendroglioma (9%) [Therkildsen et al 2015].

Sebaceous neoplasms described in individuals with Lynch syndrome include sebaceous adenomas, sebaceous epitheliomas, sebaceous carcinomas, and keratoacanthomas. Sebaceous neoplasms associated with Lynch syndrome are typically MSI high [Entius et al 2000, Machin et al 2002]. Sebaceous tumors are detected in 1%-9% of individuals with Lynch syndrome, although the available data are limited [Ponti et al 2006, South et al 2008, Ferreira et al 2020].

Pancreatic cancer. Numerous pancreatic cancer cohort studies have identified individuals with a pathogenic variant in an MMR gene [Grant et al 2015, Salo-Mullen et al 2015, Takeuchi et al 2018, Yurgelun et al 2019].

Other Cancers

Breast cancer. The data from the Prospective Lynch Syndrome Database point to a 8%-13% risk by age 70, similar to what is observed in cohort studies [Gupta et al 2019], and representing a marginal increase compared with the general population. To date there is not enough evidence to support additional screening beyond population-based breast cancer screening recommendations or those based on personal/family history of breast cancer.

Additional cancer risks. Several other cancer types have been reported to occur in individuals with Lynch syndrome. In some instances, MSI and/or IHC testing of tumor tissue demonstrated concordance between the extracolonic cancer and the germline pathogenic variant identified in the affected individual. While such findings suggest that the underlying presence of a pathogenic variant in an MMR gene contributed to the development of the cancer, data are not sufficient to demonstrate that the risk of developing these cancers is increased in individuals with Lynch syndrome.

- Several types of sarcomas have been reported in individuals with an MMR pathogenic variant, including fibrous histiocytomas, rhabdomyosarcomas, leiomyosarcoma, and liposarcoma [Sijmons et al 2000, den Bakker et al 2003, Nilbert et al 2009]. Nilbert et al [2009] determined that six of eight sarcomas in individuals with Lynch syndrome exhibited defective MMR, suggesting that sarcomas may also be part of the spectrum of Lynch syndrome tumors. Due to the rarity of sarcomas it has been difficult to determine the risk associated with Lynch syndrome.
- Adrenocortical carcinoma (ACC) has also been reported in families with Lynch syndrome. The most extensive study of this association, performed through a hereditary cancer clinic at the University of Michigan, found that two (1.7%) of 114 individuals presenting with ACC had a family history consistent with Lynch syndrome and had a pathogenic variant in an MMR gene identified. This association was further evaluated by case review of 135 individuals with pathogenic variants in an MMR gene, which identified two (1.4%) individuals who also had ACC [Raymond et al 2013].

Lynch Syndrome Variants

Muir-Torre syndrome is an uncommon variant of Lynch syndrome that describes individuals presenting with the combination of sebaceous neoplasms of the skin and one or more visceral malignancies, commonly those seen in Lynch syndrome. The types of sebaceous skin neoplasms described include sebaceous adenomas, sebaceous epitheliomas, sebaceous carcinomas, and keratoacanthomas [John & Schwartz 2016].

Turcot syndrome is a historical term used to describe individuals presenting with CRC or one or more colorectal adenomas in addition to tumors of the central nervous system. Turcot syndrome is usually caused by either a pathogenic variant in one of the MMR genes or an *APC* pathogenic variant (see *APC*-Associated Polyposis Conditions). The pathology of the CNS tumor can help distinguish between the underlying genetic

causes: *APC* pathogenic variants are more commonly associated with medulloblastoma; pathogenic variants in MMR genes are more commonly associated with glioblastoma.

Constitutional MMR deficiency (CMMRD) is a rare childhood cancer predisposition syndrome caused by biallelic pathogenic variants in *MLH1*, *MSH2*, *MSH6*, or *PMS2*. Affected individuals often have CRC or cancer of the small intestine prior to the second decade of life. In a review of 146 individuals with CMMRD, colonic adenomas were the most frequent finding [Wimmer et al 2014]. The cutaneous phenotype in affected individuals may be remarkably similar to that seen in neurofibromatosis type I, as nearly all will have café au lait macules [Wimmer 2012, Bakry et al 2014]. Hematologic cancers and brain tumors have also been reported [Wimmer & Etzler 2008, Durno et al 2010, Bakry et al 2014].

Features in the family history that increase suspicion of CMMRD include a family history of Lynch syndrome, consanguineous parents, and/or at least one parent with clinical findings of Lynch syndrome. However, this diagnosis should not be excluded if the family history is negative, as a significant number of children with CMMRD will not have a family history consistent with Lynch syndrome [Bakry et al 2014]. A European consortium developed clinical criteria indicating when to test for CMMRD [Wimmer et al 2014, Suerink et al 2021].

Phenotype Correlations by Gene

Cancer risks vary among the genes associated with Lynch syndrome (see Table 3).

Germline pathogenic variants in *MSH6* and *PMS2* are estimated to have lower disease penetrance and older ages at CRC diagnosis [Goodenberger et al 2016, Haraldsdottir et al 2017].

MLH1. Heterozygosity for an *MLH1* pathogenic variant is associated with the highest risk for CRC, while the risk for extracolonic cancers is smaller than for *MSH2* heterozygotes. *MLH1* may also be silenced by constitutional epimutation (*MLH1* promoter methylation). In this case, available evidence suggests that constitutional *MLH1* epimutations cause a severe Lynch syndrome phenotype, including young age of cancer onset and high risk for multiple primary tumors [Pinto et al 2018].

MSH2. Heterozygosity for an *MSH2* pathogenic variant is associated with the greatest risk for extracolonic cancers. *MSH2* pathogenic variants have been reported more commonly than a pathogenic variant in the other three MMR genes in individuals with the Muir-Torre variant of Lynch syndrome [Everett et al 2014, Lamba et al 2015, Jessup et al 2016].

MSH6. CRC in individuals with an *MSH6* pathogenic variant may be later in onset and more distally located than CRC in individuals with a pathogenic variant in *MLH1* or *MSH2*. Slightly lower risks for CRC and risks for endometrial cancer similar to those of *MSH2* heterozygotes have been reported in individuals with an *MSH6* pathogenic variant. *MSH6*-associated cancers may be missed on MSI testing because *MSH6* is preferentially involved in the repair of mononucleotide repeats and mononucleotide markers are not included in all MSI panels.

PMS2. Heterozygosity for a *PMS2* pathogenic variant is associated with the lowest risk (22%) for any Lynch syndrome-related cancer [Dominguez-Valentin et al 2020]. However, while the overall risk for CRC is lower, age of onset may still be early. A review of 234 individuals with a *PMS2* pathogenic variant found that 8% were diagnosed before age 30 [Goodenberger et al 2016].

EPCAM. Deletions of *EPCAM* that result in epigenetic silencing of *MSH2* are associated with a significantly increased risk for CRC. Individuals with an *EPCAM* deletion typically have early-onset CRC and a CRC cumulative risk up to 75%. Compared to individuals with an *MSH2* pathogenic variant, individuals with an *EPCAM* deletion rarely develop extra-gastrointestinal tumors, including endometrial cancer [Kempers et al 2011].

Genotype-Phenotype Correlations

EPCAM. The risk for extracolonic cancers is dependent on the size of the deletion. 3' *EPCAM* deletions have been shown to confer a lower risk for extracolonic cancers, whereas deletions that extend into *MSH2* confer extracolonic cancer risks similar to intragenic *MSH2* pathogenic variants [Tutlewska et al 2013].

Penetrance

Penetrance of CRCs and extracolonic cancers associated with pathogenic variants in an MMR gene or *EPCAM* is less than 100% (see Table 3). Therefore, some individuals with a cancer-predisposing pathogenic variant in an MMR gene or *EPCAM* may never develop cancer.

Nomenclature

Lynch syndrome may also be referred to as hereditary non-polyposis colorectal cancer (HNPCC). However, HNPCC currently encompasses Lynch syndrome and all other forms of MMR-deficient and MMR-proficient hereditary nonpolyposis colorectal cancer (even those where a genetic cause has not been identified), whereas the diagnosis of Lynch syndrome requires identification of a pathogenic variant in an MMR gene or *EPCAM*, or a constitutional *MLH1* epimutation.

Prevalence

The population prevalence of Lynch syndrome has been estimated at 1:279 (1 in 1,946 for *MLH1*, 1 in 2,841 for *MSH2*, 1 in 758 for *MSH6*, and 1 in 714 for *PMS2*) [Win et al 2017]. With the exception of a few founder deletions (see Molecular Genetics), alterations in *EPCAM* are rare.

Lynch syndrome accounts for approximately 3% of CRCs and 3% of endometrial cancers [Moreira et al 2012, Jiang et al 2019, Kahn et al 2019, Dong et al 2020].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *MLH1*, *MSH2*, *MSH6*, and *PMS2*.

Pathogenic variants in *EPCAM* cause the autosomal recessive disorder diarrhea 5 with congenital tufting enteropathy (OMIM 613217).

Sporadic tumors (including colorectal and endometrial cancers) found to have mismatch repair (MMR) deficiency (based on MSI and/or IHC analysis) may be due to methylation or biallelic somatic pathogenic variants in *MLH1*, *MSH2*, *MSH6*, or *PMS2* that are **not** present in the germline; predisposition to these tumors is not heritable [Haraldsdottir et al 2014].

Differential Diagnosis

Hereditary Cancer Syndromes

Table 4. Hereditary Cancer Syndromes with Increased Risk of Colorectal Cancer in the Differential Diagnosis of Lynch Syndrome

Gene(s)	Disorder	MOI	Polyps	Colorectal Cancer		Other Associated Cancers / Clinical Manifestations
				Risk	Mean Age of Onset (Years)	
RPS20	*RPS20*-assoc hereditary nonpolyposis CRC [1]	AD	No	High (MMR proficient tumors)	Adult	No other assoc cancers / clinical manifestations
APC	Familial adenomatous polyposis (FAP) (See *APC*-Assoc Polyposis Conditions.)	AD	Colonic, gastric & duodenal adenomas (>100 cumulative polyps)	~100% if untreated	• 39 (range: 34-43) • Polyp diagnosis: 16 (range: 7-36)	• CHRPE • Osteomas, supernumerary teeth, odontomas • Desmoids, epidermoid cysts • ↑ risk of medulloblastoma, thyroid papillary carcinoma, hepatoblastoma, & pancreatic, gastric & duodenal cancers
	Attenuated familial adenomatous polyposis (AFAP) (See *APC*-Assoc Polyposis Conditions.)	AD	Colonic, gastric & duodenal adenomas (10-100 cumulative polyps)	70% by age 80 yrs	50	• Upper GI findings & thyroid & duodenal cancer risks are similar to FAP. • Other extraintestinal manifestations are unusual. • Desmoid tumors assoc w/3' APC variants
POLE	Polymerase proofreading-assoc polyposis (PPAP) (See OMIM 615083.)	AD	Colonic adenomas (0-100 cumulative polyps)	• 30%-40% by age 70 yrs [2] • CRC may develop in absence of polyposis. • Note: Most CRCs are MSS; some are MSI high.	50 [2]	• ↑ risk of cancers of endometrium, ovary, brain, breast, & other tumor types • Adenomas in upper GI tract

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Polyps	Colorectal Cancer		Other Associated Cancers / Clinical Manifestations
				Risk	Mean Age of Onset (Years)	
POLD1	Polymerase proofreading-assoc polyposis (PPAP) (See OMIM 612591.)	AD	Colonic adenomas (0-100 cumulative polyps)	• 50%-60% by age 70 yrs [2] • CRC may develop in absence of polyposis. • Note: Most CRCs are MSS; some are MSI high.	35-40 [2]	• ↑ risk of cancers of endometrium, ovary, brain, breast, & other tumor types • Adenomas in upper GI tract
MUTYH	*MUTYH* polyposis	AR	• Colonic adenomas (10->100 cumulative polyps) • Hyperplastic &/or serrated polyps may occur. • Duodenal adenomas	• 43%-63% by age 60 yrs • 80%-90% lifetime risk if untreated • CRC may develop in absence of polyposis • Note: Most CRCs are MSS; a minority are MSI high.	48	• Duodenal adenomas are common w/↑ risk of duodenal cancer. • ↑ risk of ovarian & bladder malignancies • Additional features: thyroid nodules, benign adrenal lesions, jawbone cysts, & CHRPE
NTHL1	*NTHL1* tumor syndrome	AR	• Colonic adenomas (1-100 cumulative polyps) • Hyperplastic &/or serrated polyps may occur. • Duodenal adenomas	High lifetime risk	61 [3]	• High risk of multiple primary tumors • ~35%-78% risk of extracolonic cancer by age 60 yrs • ↑ risk of breast & endometrial cancers & other tumors types: cervical, urothelial carcinoma of the bladder, meningiomas, unspecified brain tumors, basal cell carcinomas, head & neck squamous cell carcinomas, & hematologic malignancies

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Polyps	Colorectal Cancer		Other Associated Cancers / Clinical Manifestations
				Risk	Mean Age of Onset (Years)	
MSH3	*MSH3*-assoc polyposis (OMIM 617100)	AR	• Colonic adenomas (10-100 cumulative polyps) • Duodenal adenomas	Unknown	Adult [4]	↑ risk of benign & malignant neoplasia; thyroid adenomas, mammary intraductal papillomas & cysts, gastric cancer, astrocytoma
MLH3	*MLH3*-assoc polyposis [5]	AR	Colonic adenomas (10->100 cumulative polyps)	Unknown	48-52	↑ risk of breast cancer
BMPR1A *SMAD4*	Juvenile polyposis syndrome (JPS)	AD	Hamartomatous polyps in GI tract (stomach, small intestine, colon & rectum)	~68% by age 60 yrs	42	• ↑ risk of cancers of upper GI tract & pancreas • Some *SMAD4* pathogenic variants can result in a combined syndrome of JPS & hereditary hemorrhagic telangiectasia.
STK11	Peutz-Jeghers syndrome	AD	Peutz-Jeghers-type hamartomatous polyps in GI tract (esp in small intestine, but also in stomach, colon, & rectum)	39%	42-46	• Peutz-Jeghers-type hamartomatous polyps can occur in extraintestinal sites incl renal pelvis, bronchus, gall bladder, nasal passages, urinary bladder, & ureters. • Mucocutaneous pigmentation (melanocytic macules) • Gonadal tumors • ↑ risk of GI cancers, & cancers of the breast, ovary, cervix, endometrium, pancreas, & testis
Duplication upstream of *GREM1*	Hereditary mixed polyposis syndrome (OMIM 601228)	AD	Multiple polyps of more than 1 histologic type (adenomas, hyperplastic/serrated, & juvenile), &/or individual polyps w/ overlapping histologic features (atypical juvenile w/ admixed histologic features)	↑ CRC risk (unknown estimate)	• 40s [6] • Polyp diagnosis: late 20s or later (also reported in adolescence)	Unknown

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Polyps	Colorectal Cancer		Other Associated Cancers / Clinical Manifestations
				Risk	Mean Age of Onset (Years)	
RNF43	*RNF43*-assoc serrated polyposis (OMIM 617108)	AD	Colonic serrated polyposis (0->100 cumulative polyps)	↑ CRC risk (unknown estimate)	Adult	No extracolonic clinical manifestations reported

AD = autosomal dominant; AR = autosomal recessive; CHRPE = congenital hypertrophy of the retinal pigment epithelium; CRC = colorectal cancer; FAP = familial adenomatous polyposis; GI = gastrointestinal; MOI = mode of inheritance; MSI = microsatellite instability; MSS = microstatellite stable

1. Nieminen et al [2014]

2. Buchanan et al [2018]. Data should be taken with caution due to the limited number of heterozygotes considered for the estimation of risks.

3. Grolleman et al [2019]; data obtained from 33 individuals with biallelic *NTHL1* pathogenic variants

4. Adam et al [2016]. Data obtained from four individuals with biallelic *MSH3* pathogenic variants. One individual developed CRC at age 55.

5. Olkinuora et al [2019] identified *MLH3* c.3563C>G (p.Ser1188Ter) in three Finnish individuals and one Swedish individual. Experimental data supports founder origin.

6. Lieberman et al [2017]

Moderate-Risk Colorectal Cancer (CRC) Predisposition

Multigene panels may include testing for genes and/or variants associated with moderate risk of CRC. For many of these variants there are no clear guidelines for the clinical management of heterozygotes. In many cases, the information from testing for variants associated with moderate penetrance does not change the risk management based on family history alone. Variants associated with moderate risk can confer a roughly twofold increased CRC risk – similar to that associated with having a first-degree relative with CRC [Powers et al 2019].

The most prevalent known variants associated with moderate risk for CRC are listed in Table 5 [Yurgelun et al 2017]. Katona et al [2018] defined a counseling framework for these moderate-penetrance variants based on the estimated CRC risk associated with each variant [Ma et al 2014] and the estimated CRC risk for average-risk individuals.

Table 5. Most Prevalent Known Variants Associated with Moderate Risk for CRC

Gene	Pathogenic Variant	CRC Risk [1]
APC	p.Ile1307Lys [2]	4%
CHEK2	c.1100del	3.8%
CHEK2	p.Ile157Thr	3.2%
MUTYH [3]	All germline *MUTYH* pathogenic variants	2.4% [4]

1. Katona et al [2018]; cumulative risk by age 70

2. Present in ~7% of individuals with Ashkenazi Jewish ancestry. Individuals with this variant do not have polyposis.

3. Germline heterozygous *MUTYH* variants are present in ~2% of the general population [Yurgelun et al 2017]; see also *MUTYH* Polyposis, Individuals Heterozygous for a Germline *MUTYH* Pathogenic Variant.

4. The CRC risk estimates for monoallelic *MUTYH* pathogenic variants are conflicting, and there is no consensus about whether these individuals have increased CRC risk compared to the general population [Ma et al 2014, Katona et al 2018]. The NCCN Panel recommends screening for CRC mainly based on family history. For specific recommendations, see www.nccn.org (no-fee registration and login required).

Sporadic Colorectal Cancer

Sporadic MMR-deficient tumors commonly occur in older individuals (predominantly in females). These tumors show lack of MLH1 protein expression due to *MLH1* promoter methylation and are strongly associated with the CpG island methylator phenotype (CIMP) and the serrated route of carcinogenesis related to somatic activating hotspot oncogenic variants in *BRAF*.

- ***BRAF*-related.** Somatic *BRAF* pathogenic variants, the most common being p.Val600Glu (p.V600E) NM_004333.4, occur in 15% of all CRC and, in rare instances, may be identified in tumor tissue from individuals with Lynch syndrome. In a meta-analysis Bläker et al [2020] showed the frequency of *BRAF* somatic pathogenic variants in Lynch syndrome-associated tumor tissue was 1.6%. The prevalence of *BRAF* pathogenic variants in MSI-high CRCs also increased with age. Although effective for screening for Lynch syndrome in older age groups, *BRAF* testing is cost-inefficient for screening in those with MSI-high CRCs diagnosed before age 50 [Bläker et al 2020].
- **Somatic *MLH1* promoter methylation.** Between 10% and 15% of CRCs are MSI high or MMR deficient due to somatic methylation of the promoter region of *MLH1* that silences gene expression in the tumor tissue, rather than due to Lynch syndrome. Sporadic endometrial cancers may also be found to be MSI high or show MMR deficiency due to somatic *MLH1* promoter methylation. Tumor *MLH1* promoter methylation testing is currently considered a more effective screening test for Lynch syndrome than *BRAF* p.V600E testing [Newton et al 2014].

  Despite its rarity, analysis for constitutional *MLH1* epimutation when *MLH1* promoter methylation is identified in a tumor is recommended.

  Individuals in whom a Lynch syndrome-associated germline pathogenic variant is not identified and who have somatic *MLH1* promoter methylation are likely to have sporadic cancer. Management and additional surveillance for these individuals should be based on their family history of cancer.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Lynch syndrome, the evaluations summarized in Table 6 are recommended.

Table 6. Recommended Evaluations Following Initial Diagnosis in Individuals with Lynch Syndrome

System/Concern	Evaluation	Comment
Colorectal cancer	Colonoscopy w/removal of precancerous polyps [1]	Beginning between ages 20 & 25 yrs or 2-5 yrs before earliest CRC diagnosis in family, whichever is earlier
Endometrial cancer	Educate females re symptoms of endometrial cancers (e.g., abnormal uterine bleeding, postmenopausal bleeding).	Eval of symptoms should incl endometrial biopsy every 1-2 yrs [2]
	Screening by endometrial biopsy [2]	Beginning between ages 30 & 35 yrs
Ovarian cancer	Educate females re symptoms assoc w/ovarian cancer (e.g., pelvic or abdominal pain, bloating, ↑ abdominal girth, difficulty eating, early satiety, urinary frequency or urgency).	Symptoms that persist for several wks & are a change from baseline should prompt eval by physician.

Table 6. continued from previous page.

System/Concern	Evaluation	Comment
Gastric & duodenal cancers	• Consider upper endoscopy exam esp for those w/family history of gastric cancer & those of Asian ancestry. • Biopsies should be evaluated for *H pylori* infections so that appropriate treatment can be given as needed. [3]	Beginning at age 40 yrs
Distal small bowel	Consider capsule endoscopy & small bowel enterography.	In symptomatic persons
Urinary tract cancers (renal pelvis, ureter, &/or bladder)	Consider analysis w/urine cytology to identify microscopic hematuria in those w/family history of urothelial cancer. [4]	Beginning between ages 30 & 35 yrs
Pancreatic cancer	Consider pancreatic cancer screening in carriers w/family history of pancreatic cancer w/alternating EUS &/or MRI/MRCP.	Beginning at age 50 yrs [5]
Genetic counseling	By genetics professionals [6]	To inform affected persons & their families re nature, MOI, & implications of Lynch syndrome to facilitate medical & personal decision making

CRC = colorectal cancer; EUS = endoscopic ultrasound; MOI = mode of inheritance; MRCP = magnetic resonance cholangiopancreatography

1. Colonoscopy is recommended rather than flexible sigmoidoscopy because of the predominance of proximal colon cancers in Lynch syndrome.

2. Studies on the effectiveness of transvaginal ultrasound and endometrial biopsy have not shown them to reduce endometrial cancer mortality. In a systematic review of cost effectiveness of early detection and prevention strategies for endometrial cancer, prophylactic surgery was more effective and less costly than screening with transvaginal ultrasound, CA-125, or endometrial biopsy [Sroczynski et al 2020]. However, in individuals that forgo prophylactic surgery, endometrial cancer surveillance can be performed via endometrial biopsy every 1-2 years [Bercow & Eisenhauer 2019, Gupta et al 2019, NCCN 2020]

3. Studies have not supported that surveillance for gastric and duodenal cancers improve early detection or outcomes of these cancers, but because the stomach and duodenum are the most common extracolonic non-gynecologic cancer in Lynch syndrome, periodic upper endoscopy exams have been included in guidelines.

4. There is no clear evidence to support surveillance of urothelial cancers in Lynch syndrome. Surveillance may be considered in selected individuals with a family history of urothelial cancer.

5. Begin surveillance at 50 years old (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family) for individuals with pancreatic cancer in first- or second-degree relatives from the same side of the family as the identified pathogenic germline variant.

6. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Table 7. Treatment of Manifestations in Individuals with Lynch Syndrome

Manifestation/Concern	Treatment
Adenomas of the colon	Complete endoscopic polypectomy w/follow up colonoscopy every 1-2 yrs
Colorectal cancer	Segmental or extended colonic resection is indicated depending on clinical scenario & factors such as age. For those w/rectal adenocarcinoma, proctectomy or total proctocolectomy is indicated.
Other tumors	Management as in general population

Prevention of Primary Manifestations

Prophylactic hysterectomy and bilateral salpingo-oophorectomy can be considered after childbearing is completed.

Because screening colonoscopy with polypectomy is an effective preventive measure for colorectal cancer, prophylactic colectomy (removal of the colon prior to the development of cancer) is generally not recommended for individuals with Lynch syndrome.

Aspirin therapy has been shown to decrease the risk for CRC in individuals with Lynch syndrome. Based on combined experience, several consensus statements and expert reviews including the NCCN, the Mallorca guidelines, and the US Multi-Society Task Force on CRC suggest that aspirin can be considered, taking into account an individual's personal health and comorbidities, in the management of individuals with Lynch syndrome [Vasen et al 2013, Giardiello et al 2014, Gupta et al 2019]. The CAPP2 study used a dose of 600 mg/day, which is much higher than the dose of 75 mg/day found to be effective for reducing the risk for sporadic CRC. The investigators found that taking 600 mg of aspirin daily for 25 months substantially reduces the risk of CRC (HR=0.42, 95% CI 0.19-0.86; p=0.02) after 55.7 months [Burn et al 2011]. Recently, the investigators reported ten-year follow-up data of the CAPP2 trial. They demonstrated that those taking aspirin had a significantly reduced risk of CRC (HR=0.65, 95% CI 0.43-0.97; p=0.035) as compared to the placebo group [Burn et al 2020]. The CAPP3 study is currently under way with the goal of identifying the minimum dose of aspirin for reducing CRC risk in individuals.

Surveillance

Table 8. Recommended Surveillance for Individuals with Lynch Syndrome

System/Concern	Evaluation	Frequency
Colorectal cancer	Colonoscopy w/removal of precancerous polyps [1]	Every 1-2 yrs beginning between ages 20 & 25 yrs or 2-5 yrs before earliest CRC diagnosis in the family, whichever is earlier
Endometrial cancer	Educate females re symptoms of endometrial cancers (e.g., abnormal uterine bleeding, postmenopausal bleeding).	Annually
	Consider transvaginal ultrasound exam & endometrial biopsy [2]	Every 1-2 yrs
Ovarian cancer	Educate females re symptoms assoc w/ovarian cancer (e.g., pelvic or abdominal pain, bloating, ↑ abdominal girth, difficulty eating, early satiety, urinary frequency or urgency).	Annually
Gastric & duodenal cancers	• Consider upper endoscopy exam esp for those w/family history of gastric cancer & those of Asian ancestry. [3] • Biopsies should be evaluated for *H pylori* infections so that appropriate treatment can be given as needed.	Every 3-5 yrs beginning between ages 30 & 35 yrs
Distal small bowel	Consider capsule endoscopy & small bowel enterography.	In symptomatic persons
Urinary tract cancers (renal pelvis, ureter, &/or bladder)	Consider urine analysis w/urine cytology to identify microscopic hematuria in those w/family history of urothelial cancer. [4]	Annually beginning between ages 30 & 35 yrs
Pancreatic cancer	Consider pancreatic cancer screening in those w/family history of pancreatic cancer w/alternating EUS &/or MRI/MRCP	Annually

Table 8. continued from previous page.

System/Concern	Evaluation	Frequency
Other cancers	• No additional specific screening recommendations for other Lynch syndrome-assoc cancers • Follow general population screening guidelines & seek prompt medical attention for changes in health or persistent symptoms.	If there is family history of early onset of other cancer types, cancer screening recommendations should be adjusted to begin screening at an earlier age.

CRC = colorectal cancer; EUS = endoscopic ultrasound; MRCP = magnetic resonance cholangiopancreatography
1. Colonoscopy is recommended rather than flexible sigmoidoscopy because of the predominance of proximal colon cancers in Lynch syndrome.
2. Studies on the effectiveness of transvaginal ultrasound and endometrial biopsy have not shown them to reduce endometrial cancer mortality. In a systematic review of cost effectiveness of early detection and prevention strategies for endometrial cancer, prophylactic surgery was more effective and less costly than screening with transvaginal ultrasound, CA-125, or endometrial biopsy [Sroczynski et al 2020]. However, in individuals that forgo prophylactic surgery, endometrial cancer surveillance can be performed via endometrial biopsy every 1-2 years [Bercow & Eisenhauer 2019, Gupta et al 2019].
3. Upper gastrointestinal endoscopy has recently been recommended for surveillance in individuals with Lynch syndrome [Kumar et al 2020, Ladigan-Badura et al 2021]. However, this has not yet been included in surveillance guidelines for all individuals with Lynch syndrome, rather only in individuals with specific risk factors [see Gupta et al 2019], probably due to the limitations of the published studies, and previous data arguing against the benefit of endoscopic surveillance in Lynch syndrome [Renkonen-Sinisalo et al 2002, Haanstra et al 2015].
4. Limited data exist to advocate for surveillance for urothelial cancers in Lynch syndrome. Surveillance may be considered in individuals with a family history of urothelial cancer.

Agents/Circumstances to Avoid

There is accumulating evidence that a high body mass, cigarette smoking, type 2 diabetes, and high cholesterol increase the risk of CRC in Lynch syndrome. The direction and strength of observed associations are similar to those for the general population [Win & Scott 2016, Dashti et al 2019].

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of all first-degree relatives (parents, sibs, and children) of an affected individual by molecular genetic testing for the Lynch syndrome-related pathogenic variant in the family in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures.

Early recognition of cancers associated with Lynch syndrome may allow for timely intervention and improved final outcome.

- Sibs should be considered at risk even if the parents have not had cancer because most Lynch syndrome results from an inherited (not *de novo*) pathogenic variant.
- If clinical history and family history cannot identify the parent from whom the proband inherited the Lynch syndrome-related pathogenic variant, molecular genetic testing should be offered to both parents to determine which has the pathogenic variant.

In general, molecular genetic testing for Lynch syndrome is not recommended for at-risk individuals younger than age 18 years. However, predictive testing should be considered if there is a history of early-onset cancer in the family. For unaffected individuals with a Lynch syndrome-related pathogenic variant, screening should begin between ages 20 and 25 years, or two to five years earlier than the earliest diagnosis in the family [Gupta et al 2019]. Therefore, a history of early cancers in the family may also warrant testing prior to age 18.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Ideally cancer screening exams would be planned around a pregnancy. An affected female would be encouraged to be current on her cancer screening before attempting to become pregnant. If an affected female is diagnosed with cancer during pregnancy, she should be counseled about cancer treatment options and their potential implications for the fetus.

Therapies Under Investigation

Chromoendoscopy vs narrow band imaging (NBI) vs high-definition white-light colonoscopy for Lynch syndrome surveillance. Two studies compared different colonoscopy imaging modalities against chromoendoscopy. In a study of 138 individuals with Lynch syndrome undergoing back-to-back colonoscopies (first with NBI followed by indigo carmine chromoendoscopy), the adenoma detection rate (ADR) for NBI alone was 20.3% while the ADR for both was 30.4%. A 10.1% difference in detection failed to reach the prespecified noninferiority assumption margin of 5% [Cellier et al 2019]. In another study of 256 individuals with Lynch syndrome randomized to indigo carmine chromoendoscopy versus high-definition white-light colonoscopy, no significant difference in ADR was detected by pancolonic chromoendoscpy (34.4%; 95% CI 26.4%-43.4%) as compared to white-light endoscopy (28.1%; 95% CI 21.1%-36.4%; p=0.28) [Rivero-Sánchez et al 2020]. In both studies, chromoendoscopy better identified flat or diminutive adenomas, but also reported significantly longer withdrawal time with chromoendoscopy.

Oral contraceptives and endometrial cancer risk. Epidemiologic studies have found that use of oral contraceptives for more than one year is associated with significant reduction in endometrial cancer risk (HR 0.39, 95% CI 0.23-0.64) [Dashti et al 2015]. To date there are no prospective trials evaluating the impact of oral contraceptives on endometrial cancer risk. One study has demonstrated reduced endometrial proliferation in women with Lynch syndrome after a three-month course of oral contraceptives [Lu et al 2013]. At this time oral contraceptives are not included in recommendations for women with Lynch syndrome, but they are commonly used for managing routine gynecologic issues and for family planning. Data support that oral contraceptives will likely confer benefits to women with Lynch syndrome similar to those in the general population.

Immunotherapy for Lynch syndrome associated cancers. The development of antibodies to immune checkpoint proteins (anti-PD-1 and anti-CTLA4) demonstrate prolonged T-cell response against cancer cells. The emergence of immune checkpoint inhibitors that manipulate and leverage the immune system represent a breakthrough in treatment of Lynch syndrome-associated (and other MSI-high/MMR-deficient) cancers. Recent studies of the treatment of metastatic MSI-high Lynch associated cancer, not limited to colon cancer, with anti-PD-1 monoclonal antibodies have demonstrated 70% or greater disease control rates [Le et al 2015, Le et al 2017, Overman et al 2017].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

In most individuals, Lynch syndrome is caused by a heterozygous germline pathogenic variant in *MLH1*, *MSH2*, *MSH6, PMS2*, or *EPCAM*, and is inherited in an autosomal dominant manner.

Individuals with Lynch syndrome caused by constitutional inactivation of *MLH1* by methylation typically represent simplex cases (i.e., a single occurrence in a family) but families with non-mendelian inheritance of hypermethylation have been reported [Hitchins et al 2011, Hitchins 2015].

Note: Several factors (in addition to the possibility of a constitutional *MLH1* epimutation) can hinder the diagnosis of Lynch syndrome based on family history. Screening and removal of precancerous polyps and prophylactic surgery may prevent colon or endometrial cancer in some at-risk relatives; some who died young from other causes may never have developed cancer.

Risk to Family Members

Parents of a proband

- The majority of individuals diagnosed with Lynch syndrome inherited a pathogenic variant from a parent who may or may not have had cancer.
- If clinical and family history cannot identify the parent from whom the proband inherited the pathogenic variant, molecular genetic testing should be offered to both parents to determine which parent is heterozygous for the pathogenic variant identified in the proband.
- In the rare event that the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent (and parental identity testing has confirmed biological maternity and paternity), possible explanations include the following:
  - A *de novo* pathogenic variant in the proband (The precise *de novo* pathogenic variant rate for Lynch syndrome is unknown but estimated to be extremely low [Win et al 2011].)
  - Germline mosaicism in a parent (Though theoretically possible, no instances of a proband inheriting a Lynch syndrome-related pathogenic variant from a parent with germline mosaicism have been reported to date.)
- A parent who is heterozygous for a Lynch syndrome-related pathogenic variant may not have had cancer because of incomplete penetrance, variable age of cancer development, cancer risk reduction resulting from screening or prophylactic surgery, or early death. Therefore, an apparently negative family history cannot be confirmed without appropriate molecular genetic testing to establish that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband has the pathogenic variant identified in the proband, the risk to the sibs is 50%. Note: Molecular genetic testing for the familial Lynch syndrome-related variant should be offered to all sibs (see Evaluation of Relatives at Risk).
- If the proband has a known Lynch syndrome-related pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the genetic status of the parents is unknown, sibs should be considered at risk for cancers associated with Lynch syndrome (regardless of whether parents have had cancer) and offered molecular genetic testing.

Offspring of a proband. Each child of an individual with Lynch syndrome has a 50% chance of inheriting the Lynch syndrome-related pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the pathogenic variant (as is the case in most families), the parent's family members are at risk (family history or molecular genetic testing can help determine whether maternal or paternal relatives are at risk).

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Genetic cancer risk assessment and counseling. For a comprehensive description of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see Cancer Genetics Risk Assessment and Counseling – for health professionals (part of PDQ®, National Cancer Institute).

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the Lynch syndrome-related pathogenic variant has been identified in an affected family member.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals age <18 years)

- In general, genetic testing for Lynch syndrome is not recommended for at-risk individuals younger than age 18 years. However, predictive testing should be considered if there is a history of early-onset cancer in the family. In unaffected individuals with a Lynch syndrome-related pathogenic variant, screening is recommended beginning at age 20 to 25 years, or two to five years prior to the earliest diagnosis in the family [Gupta et al 2019, NCCN 2020]. Therefore, a history of early cancers in the family may also warrant testing prior to age 18.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of Lynch syndrome, it is appropriate to consider testing of symptomatic individuals regardless of age.

Prenatal Testing and Preimplantation Genetic Testing

Once a germline heterozygous Lynch syndrome-related pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Collaborative Group of the Americas on Inherited Gastrointestinal Cancer (CGA-IGC)**
  www.cgaigc.com
- **Lynch Syndrome International**
  P.O. Box 5456
  Vacaville CA 95688
  Phone: 707-689-5089
  Email: info@lynchcancers.com
  Lynch Syndrome International
- **National Cancer Institute (NCI)**
  6116 Executive Boulevard
  Suite 300
  Bethesda MD 20892-8322
  Phone: 800-422-6237 (toll-free)
  Email: cancergovstaff@mail.nih.gov
  Genetics of Colorectal Cancer (PDQ®)
- **American Cancer Society**
  Phone: 800-227-2345
  cancer.org
- **Colorectal Cancer Alliance**
  1025 Vermont Avenue Northwest
  Suite 1066
  Washington DC 20005
  Phone: 877-422-2030
  www.ccalliance.org
- **Fight Colorectal Cancer**
  Phone: 877-427-2111
  Email: info@fightcolorectalcancer.org
  www.fightcolorectalcancer.org
- **International Society for Gastrointestinal Hereditary Tumours (InSiGHT)**
  insight-group.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Lynch Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
EPCAM	2p21	Epithelial cell adhesion molecule	EPCAM homepage - Colon cancer gene variant databases	EPCAM	EPCAM
MLH1	3p22.2	DNA mismatch repair protein Mlh1	MLH1 homepage - Colon cancer gene variant databases MLH1 @ ZAC-GGM	MLH1	MLH1
MSH2	2p21-p16.3	DNA mismatch repair protein Msh2	MSH2 homepage - Colon cancer gene variant databases MSH2 @ ZAC-GGM	MSH2	MSH2
MSH6	2p16.3	DNA mismatch repair protein Msh6	MSH6 homepage - Colon cancer gene variant databases MSH6 @ ZAC-GGM	MSH6	MSH6
PMS2	7p22.1	Mismatch repair endonuclease PMS2	PMS2 @ LOVD PMS2 @ ZAC-GGM	PMS2	PMS2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Lynch Syndrome (View All in OMIM)

114500	COLORECTAL CANCER; CRC
120435	LYNCH SYNDROME 1; LYNCH1
120436	DNA MISMATCH REPAIR PROTEIN MLH1; MLH1
158320	MUIR-TORRE SYNDROME; MRTES
185535	EPITHELIAL CELLULAR ADHESION MOLECULE; EPCAM
276300	MISMATCH REPAIR CANCER SYNDROME 1; MMRCS1
600259	PMS1 HOMOLOG 2, MISMATCH REPAIR SYSTEM COMPONENT; PMS2
600678	MutS HOMOLOG 6; MSH6
609309	MutS HOMOLOG 2; MSH2
609310	LYNCH SYNDROME 2; LYNCH2
613244	LYNCH SYNDROME 8; LYNCH8

Molecular Pathogenesis

Lynch syndrome is caused by pathogenic variants in genes involved with the mismatch repair (MMR) pathway. This pathway functions to identify and remove single-nucleotide mismatches or insertions and deletion loops. Pathogenic variants in four of the MMR genes can cause Lynch syndrome [Peltomäki 2003]. The functions of the MMR genes can be disrupted by missense variants, truncating variants, splice site variants, large deletions, or genomic rearrangements. In addition, germline deletions within *EPCAM*, which is not an MMR gene, can disrupt the MMR pathway by inactivating the adjacent MMR gene *MSH2*, even though *MSH2* itself has not been mutated.

Mechanism of disease causation. Loss of function

Table 9. Lynch Syndrome: Gene-Specific Laboratory Considerations

Gene [1]	Special Consideration
EPCAM	Only large deletions that incl the last exon of *EPCAM* are causative of Lynch syndrome; other *EPCAM* variants are not assoc w/Lynch syndrome [Arnold et al 2020].
MLH1	Constitutional inactivation of the *MLH1* promoter by methylation, along w/somatic loss of heterozygosity of the functional allele, has been reported as a rare cause of Lynch syndrome. Most instances of *MLH1* promoter methylation are simplex (i.e., a single occurrence in a family), but a few families w/inherited hypermethylation have been reported [Hitchins 2015]. *MLH1* promoter methylation is not detectable by either sequence analysis or duplication/deletion analysis of *MLH1*.
PMS2	Molecular analysis of *PMS2* is more complex due to the presence of multiple *PMS2* pseudogenes. The presence of genomic regions w/high sequence homology to *PMS2* hampers conventional analysis. Long-range PCR, cDNA sequencing, or specific solutions to NGS testing can help distinguish between *PMS2* pathogenic variants & pseudogene variants [Li et al 2015a, Lee et al 2021].

1. Genes in alphabetic order

Notable variants by gene. Table 10 includes founder and common pathogenic variants in different populations.

Table 10. Lynch Syndrome: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment / Population [2]
EPCAM	NM_002354.2	c.859-1462_*1999del4909 (del exons 8-9)	--	Netherlands
		c.858+2478_*4507del8674 (del exons 8-9)	--	
		c.858+2568_*4596del8673 (del exons 8-9)	--	Spain
		c.858+2488_*7469del11626 (del exons 8-9)	--	
		c.859-1860_*25547del (*EPCAM* del exons 8-9 & *MSH2* del exons 1-3)	--	
		c.859–1430_*2033del (del exons 8-9)	--	Italy
MLH1	NM_000249.3 NP_000240.1	c.1731+2247_1897-402del (del exon 16)	p.Pro579_Glu633del	Finland
	NM_000249.3	c.454-1G>A	--	
	NM_000249.3 NP_000240.1	c.112A>C	p.Asn38His	Netherlands
	NM_000249.3	c.306+5G>A	--	Spain; variants are assoc w/ moderate penetrance.
	NM_000249.3 NP_000240.1	c.1865T>A	p.Leu622His	

Table 10. continued from previous page.

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment / Population [2]
		c.1896+280_*8935del11626 (*MLH1* del exons 17-19 & *LRRFIP2* del exons 26-29)	--	Portugal
	NM_000249.3	c.545+3A>G	--	Italy, Canada-Quebec (persons of Italian ancestry) & Brazil
		c.589-2A>G	--	United States & Italy
	NM_000249.3 NP_000240.1	c.731G>A	p.Gly244Asp	Italy
	NM_000249.3	c.1558+1G>T	--	
	NM_000249.3 NP_000240.1	c.2252_2253delAA	p.Lys751SerfsTer3	
		c.2269dupT	p.(*757LeuextTer33)	
		c.1731G>A	p.Ser556ArgfsTer14	
		c.1489dupC	p.Arg497ProfsTer6	Germany
	NM_000249.3	c.1667+2_1667+8delTAAATCAinsATTT	–	Denmark
	NM_000249.3 NP_000240.1	c.2142G>A	p.Trp714Ter	Switzerland
		c.2195_2198dupAACA	p.His733GlnfsTer14	Canada-Quebec
		c.1831_1832delAT	p.Ile611CysfsTer2	
		c.1039-2329_1409+827del3527	p.Thr347LysfsTer8	
		c.1381A>T	p.Lys461Ter	United States
		c.2044_2045delAT	p.Met682ValfsTer11	Puerto Rico
		c.392C>G	p.Ser131Ter	Republic of Macedonia
	NM_000249.3	1.8-kb deletion of exon 11	--	China
	NM_000249.3 NP_000240.1	c.793C>T	p.Arg265Cys	Taiwan
		c.1758dupC	p.Met587HisfsTer6	Korea
MSH2	NM_000251.2	c.942+3A>T	--	Common worldwide

Table 10. continued from previous page.

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment / Population [2]
	NM_000251.2 NP_000242.1	c.388_389delCA	p.Gln130ValfsTer2	Portugal, South America
		c.2152C>T	p.Gln718Ter	Portugal
		c.2063T>G	p.Met688Arg	Spain
	NM_000251.2	c.[2635-3C>T; 2635-5T>C]	--	
		c.-3568_*28336del36681 (del exons 4-8)	--	
		c.*4136_*13502del9366 (del exon 7)	--	
		c.-11844_1077-6021delins(155) (del exons 1-6)	--	Italy
		c.1277−1180_1386+2226del3516insCATTCTCTTTGAAAA) (del exon 8)	--	
		c.1276+198_1386+3761del19280 (del exon 8)	--	
	NM_000251.2 NP_000242.1	c.1786_1788delAAT	p.Asn596del	Denmark
	NM_000251.2	c.-823_1076+5984del (del exons 1-6)	–	United States
	NM_000251.2 NP_000242.1	c.1906G>C	p.Ala636Pro	Ashkenazi Jews
		c.1165C>T	p.Arg389Ter	Canada-Quebec
		c.2185_2192delATGTTGGAinsCCCT	p.Met729ProfsTer2	Chile
		c.1457_1460delATGA	p.Asn486fsTer10	China (Guangdong)
MSH6	NM_000179.2 NP_000170.1	c.467C>G	p.Ser156Ter	Netherlands
		c.651dupT	p.Lys218Ter	
		c.1614_1615delTCinsAG	p.Tyr538Ter	
		c.2983G>T	p.Glu995Ter	Finland
		c.1346T>C	p.Leu449Pro	Sweden
		c.2931C>G	p.Tyr977Ter	
		c.3959_3962delCAAG	p.Ala1320GlufsTer6	Ashkenazi Jews
		c.3984_3987dupGTCA	p.Leu1330ValfsTer12	

Table 10. continued from previous page.

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment / Population [2]
PMS2	NM_000535.6	c.989-1G>T	--	Norway
	NM_000535.6 NP_000526.2	c.736_741delCCCCCTins11	p.Pro246CysfsTer3	United States
		c.137G>T	p.Ser46Ile	United States
		c.1A>G	p.Met1?	
		c.903G>T	p.Lys301Asn	
		c.989-296_1144+706del1158 (del exon 10)	p.Glu330_Glu381del	Australia
		c.2002A>G	p.Ile668Val	Inuit

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Genes from Table 1 in alphabetic order
2. Information obtained from Kuiper et al [2011], Pérez-Carbonell et al [2012], Tomsic et al [2013], Mur et al [2014], Li et al [2015b], Ponti et al [2015], Dymerska et al [2017], Rossi et al [2017], Cini et al [2019], Pinheiro et al [2019]

Chapter Notes

Author History

Stephen B Gruber, MD, PhD; USC Norris Comprehensive Cancer Center (2004-2021)
Gregory Idos, MD, MS (2021-present)
Wendy Kohlmann, MS; University of Utah Huntsman Cancer Institute (2004-2021)
Laura Valle, PhD (2021-present)

Revision History

- 4 February 2021 (sw) Comprehensive update posted live
- 12 April 2018 (sw) Revision: Tumor testing table added (Table 2)
- 1 February 2018 (sw) Comprehensive update posted live
- 22 May 2014 (me) Comprehensive update posted live
- 20 September 2012 (cd) Revision: Multigene panels for Lynch syndrome (hereditary non-polyposis colon cancer) available clinically
- 11 August 2011 (me) Comprehensive update posted live
- 29 November 2006 (me) Comprehensive update posted live
- 5 February 2004 (me) Review posted live
- 18 April 2003 (sg) Original submission

References

Published Guidelines / Consensus Statements

American College of Medical Genetics technical standards and guidelines for genetic testing for inherited colorectal cancer (Lynch syndrome, familial adenomatous polyposis, and MYH-associated polyposis). Available online. 2014. Accessed 5-11-23.

American College of Medical Genetics/American Society of Human Genetics. Joint statement on genetic testing for colon cancer (pdf). Available online. 2000. Accessed 5-11-23.

American Gastroenterological Association. Medical position statement: hereditary colorectal cancer and genetic testing (pdf). Available online. 2001. Accessed 5-11-23.

American Society of Clinical Oncology. Policy statement update: genetic testing for cancer susceptibility. Available online. 2010. Accessed 5-11-23.

American Society of Colon and Rectal Surgeons. Practice parameters for the treatment of patients with dominantly inherited colorectal cancer (FAP and HNPCC). Available online. 2003. Accessed 5-11-23.

Committee on Bioethics, Committee on Genetics, and American College of Medical Genetics and Genomics Social, Ethical, Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Available online. 2013. Accessed 5-11-23.

Giardiello FM, Brensinger JD, Petersen GM. American Gastroenterological Association technical review on hereditary colorectal cancer and genetic testing. Gastroenterology. 2001;121:198-213. [PubMed]

Lu KH, Wood ME, Daniels M, Burke C, Ford J, Kauff ND, Kohlmann W, Lindor NM, Mulvey TM, Robinson L, Rubinstein WS, Stoffel EM, Snyder C, Syngal S, Merrill JK, Wollins DS, Hughes KS, et al. American Society of Clinical Oncology Expert Statement: collection and use of a cancer family history for oncology providers. J Clin Oncol. 2014;32:833-40. [PubMed]

National Comprehensive Cancer Network. Genetic/familial high-risk assessment: colorectal cancer. 2020.

National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available online. 2018. Accessed 5-11-23.

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;21:484-93. [PubMed]

Literature Cited

Aarnio M, Salovaara R, Aaltonen LA, Mecklin JP, Jarvinen HJ. Features of gastric cancer in hereditary non-polyposis colorectal cancer syndrome. Int J Cancer. 1997;74:551–5. PubMed PMID: 9355980.

Adam R, Spier I, Zhao B, Kloth M, Marquez J, Hinrichsen I, Kirfel J, Tafazzoli A, Horpaopan S, Uhlhaas S, Stienen D, Friedrichs N, Altmüller J, Laner A, Holzapfel S, Peters S, Kayser K, Thiele H, Holinski-Feder E, Marra G, Kristiansen G, Nöthen MM, Büttner R, Möslein G, Betz RC, Brieger A, Lifton RP, Aretz S. Exome sequencing identifies biallelic MSH3 germline mutations as a recessive subtype of colorectal adenomatous polyposis. Am J Hum Genet. 2016;99:337–51. PubMed PMID: 27476653.

Anele CC, Adegbola SO, Askari A, Rajendran A, Clark SK, Latchford A, Faiz OD. Risk of metachronous colorectal cancer following colectomy in Lynch syndrome: a systematic review and meta-analysis. Colorectal Dis. 2017;19:528–36. PubMed PMID: 28407411.

Arnold AM, Morak M, Benet-Pagès A, Laner A, Frishman D, Holinski-Feder E. Targeted deep-intronic sequencing in a cohort of unexplained cases of suspected Lynch syndrome. Eur J Hum Genet. 2020;28:597–608. PubMed PMID: 31822864.

Bakry D, Aronson M, Durno C, Rimawi H, Farah R, Alharbi QK, Alharbi M, Shamvil A, Ben-Shachar S, Mistry M, Constantini S, Dvir R, Qaddoumi I, Gallinger S, Lerner-Ellis J, Pollett A, Stephens D, Kelies S, Chao E,

Malkin D, Bouffet E, Hawkins C, Tabori U. Genetic and clinical determinants of constitutional mismatch repair deficiency syndrome: report from the constitutional mismatch repair deficiency consortium. Eur J Cancer. 2014;50:987–96. PubMed PMID: 24440087.

Barnetson RA, Tenesa A, Farrington SM, Nicholl ID, Cetnarskyj R, Porteous ME, Campbell H, Dunlop MG. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. N Engl J Med. 2006;354:2751–63. PubMed PMID: 16807412.

Bercow AS, Eisenhauer EL. Screening and surgical prophylaxis for hereditary cancer syndromes with high risk of endometrial and ovarian cancer. J Surg Oncol. 2019;120:864–72. PubMed PMID: 31355450.

Bläker H, Haupt S, Morak M, Holinski-Feder E, Arnold A, Horst D, Sieber-Frank J, Seidler F, von Winterfeld M, Alwers E, Chang-Claude J, Brenner H, Roth W, Engel C, Löffler M, Möslein G, Schackert HK, Weitz J, Perne C, Aretz S, Hüneburg R, Schmiegel W, Vangala D, Rahner N, Steinke-Lange V, Heuveline V, von Knebel Doeberitz M, Ahadova A, Hoffmeister M, Kloor M, et al. Age-dependent performance of BRAF mutation testing in Lynch syndrome diagnostics. Int J Cancer. 2020;147:2801–10. PubMed PMID: 32875553.

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424. PubMed PMID: 30207593.

Buchanan DD, Stewart JR, Clendenning M, Rosty C, Mahmood K, Pope BJ, Jenkins MA, Hopper JL, Southey MC, Macrae FA, Winship IM, Win AK. Risk of colorectal cancer for carriers of a germ-line mutation in POLE or POLD1. Genet Med. 2018;20:890–5. PubMed PMID: 29120461.

Burn J, Gerdes AM, Macrae F, Mecklin JP, Moeslein G, Olschwang S, Eccles D, Evans DG, Maher ER, Bertario L, Bisgaard ML, Dunlop MG, Ho JW, Hodgson SV, Lindblom A, Lubinski J, Morrison PJ, Murday V, Ramesar R, Side L, Scott RJ, Thomas HJ, Vasen HF, Barker G, Crawford G, Elliott F, Movahedi M, Pylvanainen K, Wijnen JT, Fodde R, Lynch HT, Mathers JC, Bishop DT, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet. 2011;378:2081–7. PubMed PMID: 22036019.

Burn J, Sheth H, Elliott F, Reed L, Macrae F, Mecklin JP, Möslein G, McRonald FE, Bertario L, Evans DG, Gerdes AM, Ho JWC, Lindblom A, Morrison PJ, Rashbass J, Ramesar R, Seppälä T, Thomas HJW, Pylvänäinen K, Borthwick GM, Mathers JC, Bishop DT, et al. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. Lancet. 2020;395:1855–63. PubMed PMID: 32534647.

Capelle LG, Van Grieken NC, Lingsma HF, Steyerberg EW, Klokman WJ, Bruno MJ, Vasen HF, Kuipers EJ. Risk and epidemiological time trends of gastric cancer in Lynch syndrome carriers in the Netherlands. Gastroenterology. 2010;138:487–92. PubMed PMID: 19900449.

Cellier C, Perrod G, Colas C, Dhooge M, Saurin JC, Lecomte T, Coron E, Rahmi G, Savale C, Chaussade S, Bellanger J, Dray X, Benech N, Le Rhun M, Barbieux JP, Pereira H, Chatellier G, Samaha E. Back-to-back comparison of colonoscopy with virtual chromoendoscopy using a third-generation narrow-band imaging system to chromoendoscopy with indigo carmine in patients with Lynch syndrome. Am J Gastroenterol. 2019;114:1665–70. PubMed PMID: 31498154.

Chen S, Wang W, Lee S, Nafa K, Lee J, Romans K, Watson P, Gruber SB, Euhus D, Kinzler KW, Jass J, Gallinger S, Lindor NM, Casey G, Ellis N, Giardiello FM, Offit K, Parmigiani G, et al. Prediction of germline mutations and cancer risk in the Lynch syndrome. JAMA. 2006;296:1479–87. PubMed PMID: 17003396.

Cini G, Quaia M, Canzonieri V, Fornasarig M, Maestro R, Morabito A, D'Elia AV, Urso ED, Mammi I, Viel A. Toward a better definition of EPCAM deletions in Lynch syndrome: report of new variants in Italy and the associated molecular phenotype. Mol Genet Genomic Med. 2019;7:e587. PubMed PMID: 30916491.

Crosbie EJ, Ryan NAJ, McVey RJ, Lalloo F, Bowers N, Green K, Woodward ER, Clancy T, Bolton J, Wallace AJ, McMahon RF, Evans DG. Assessment of mismatch repair deficiency in ovarian cancer. J Med Genet. 2021;58:687–91. PubMed PMID: 32917768.

Dashti SG, Chau R, Ouakrim DA, Buchanan DD, Clendenning M, Young JP, Winship IM, Arnold J, Ahnen DJ, Haile RW, Casey G, Gallinger S, Thibodeau SN, Lindor NM, Le Marchand L, Newcomb PA, Potter JD, Baron JA, Hopper JL, Jenkins MA, Win AK. Female hormonal factors and the risk of endometrial cancer in Lynch syndrome. JAMA. 2015;314:61–71. PubMed PMID: 26151267.

Dashti SG, Li WY, Buchanan DD, Clendenning M, Rosty C, Winship IM, Macrae FA, Giles GG, Hardikar S, Hua X, Thibodeau SN, Figueiredo JC, Casey G, Haile RW, Gallinger S, Le Marchand L, Newcomb PA, Potter JD, Lindor NM, Hopper JL, Jenkins MA, Win AK. Type 2 diabetes mellitus, blood cholesterol, triglyceride and colorectal cancer risk in Lynch syndrome. Br J Cancer. 2019;121:869–76. PubMed PMID: 31551580.

den Bakker MA, Seynaeve C, Kliffen M, Dinjens WN. Microsatellite instability in a pleomorphic rhabdomyosarcoma in a patient with hereditary non-polyposis colorectal cancer. Histopathology. 2003;43:297–9. PubMed PMID: 12940783.

Dominguez-Valentin M, Sampson JR, Seppälä 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-Köstner F, Gluck N, Katz LH, Heinimann K, Vaccaro CA, Büttner R, Görgens H, Holinski-Feder E, Morak M, Holzapfel S, Hüneburg R, Knebel Doeberitz MV, Loeffler M, Rahner N, Schackert HK, Steinke-Lange V, Schmiegel W, Vangala D, Pylvänäinen K, Renkonen-Sinisalo L, Hopper JL, Win AK, Haile RW, Lindor NM, Gallinger S, Le Marchand L, Newcomb PA, Figueiredo JC, Thibodeau SN, Wadt K, Therkildsen C, Okkels H, Ketabi Z, Moreira L, Sánchez A, Serra-Burriel M, Pineda M, Navarro M, Blanco I, Green K, Lalloo F, Crosbie EJ, Hill J, Denton OG, Frayling IM, Rødland 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, Möslein G, Mecklin JP, Nielsen M, Møller 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;22:15–25. PubMed PMID: 31337882.

Dong L, Jin X, Wang W, et al. Distinct clinical phenotype and genetic testing strategy for Lynch syndrome in China based on a large colorectal cancer cohort. Int J Cancer. 2020;146:3077–86. PubMed PMID: 32030746.

Dowty JG, Win AK, Buchanan DD, Lindor NM, Macrae FA, Clendenning M, Antill YC, Thibodeau SN, Casey G, Gallinger S, Marchand LL, Newcomb PA, Haile RW, Young GP, James PA, Giles GG, Gunawardena SR, Leggett BA, Gattas M, Boussioutas A, Ahnen DJ, Baron JA, Parry S, Goldblatt J, Young JP, Hopper JL, Jenkins MA. Cancer risks for MLH1 and MSH2 mutation carriers. Hum Mutat. 2013;34:490–7. PubMed PMID: 23255516.

Durno CA, Holter S, Sherman PM, Gallinger S. The gastrointestinal phenotype of germline biallelic mismatch repair gene mutations. Am J Gastroenterol. 2010;105:2449–56. PubMed PMID: 20531397.

Dymerska D, Gołębiewska K, Kuświk M, Rudnicka H, Scott RJ, Billings R, Pławski A, Boruń P, Siołek M, Kozak-Klonowska B, Szwiec M, Kilar E, Huzarski T, Byrski T, Lubiński J, Kurzawski G. New EPCAM founder deletion in Polish population. Clin Genet. 2017;92:649–53. PubMed PMID: 28369810.

EGAPP; Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Genet Med. 2009;11:35–41. PubMed PMID: 19125126.

Entius MM, Keller JJ, Drillenburg P, Kuypers KC, Giardiello FM, Offerhaus GJ. Microsatellite instability and expression of hMLH-1 and hMSH-2 in sebaceous gland carcinomas as markers for Muir-Torre syndrome. Clin Cancer Res. 2000;6:1784–9. PubMed PMID: 10815898.

Everett JN, Raymond VM, Dandapani M, Marvin M, Kohlmann W, Chittenden A, Koeppe E, Gustafson SL, Else T, Fullen DR, Johnson TM, Syngal S, Gruber SB, Stoffel EM. Screening for germline mismatch repair mutations following diagnosis of sebaceous neoplasm. JAMA Dermatol. 2014;150:1315–21. PubMed PMID: 25006859.

Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available online. Accessed 12-1-20.

Ferreira I, Wiedemeyer K, Demetter P, Adams DJ, Arends MJ, Brenn T. Update on the pathology, genetics and somatic landscape of sebaceous tumours. Histopathology. 2020;76:640–9. PubMed PMID: 31821583.

Giardiello FM, Allen JI, Axilbund JE, Boland CR, Burke CA, Burt RW, Church JM, Dominitz JA, Johnson DA, Kaltenbach T, Levin TR, Lieberman DA, Robertson DJ, Syngal S, Rex DK. 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;109:1159–79. PubMed PMID: 25070057.

Goel A, Nguyen TP, Leung HC, Nagasaka T, Rhees J, Hotchkiss E, Arnold M, Banerji P, Koi M, Kwok CT, Packham D, Lipton L, Boland CR, Ward RL, Hitchins MP. De novo constitutional MLH1 epimutations confer early-onset colorectal cancer in two new sporadic Lynch syndrome cases, with derivation of the epimutation on the paternal allele in one. Int J Cancer. 2011;128:869–78. PubMed PMID: 20473912.

Goodenberger ML, Thomas BC, Riegert-Johnson D, Boland CR, Plon SE, Clendenning M, Win AK, Senter L, Lipkin SM, Stadler ZK, Macrae FA, Lynch HT, Weitzel JN, de la Chapelle A, Syngal S, Lynch P, Parry S, Jenkins MA, Gallinger S, Holter S, Aronson M, Newcomb PA, Burnett T. Le Marchan d L, Pichurin P, Hampel H, Terdiman JP, Lu KH, Thibodeau S, Lindor NM. PMS2 monoallelic mutation carriers: the known unknown. Genet Med. 2016;18:13–9. PubMed PMID: 25856668.

Grant RC, Selander I, Connor AA, Selvarajah S, Borgida A, Briollais L, Petersen GM, Lerner-Ellis J, Holter S, Gallinger S. Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. Gastroenterology. 2015;148:556–64. PubMed PMID: 25479140.

Grolleman JE, de Voer RM, Elsayed FA, Nielsen M, Weren RDA, Palles C, Ligtenberg MJL, Vos JR, Ten Broeke SW, de Miranda NFCC, Kuiper RA, Kamping EJ, Jansen EAM, Vink-Börger ME, Popp I, Lang A, Spier I, Hüneburg R, James PA, Li N, Staninova M, Lindsay H, Cockburn D, Spasic-Boskovic O, Clendenning M, Sweet K, Capellá G, Sjursen W, Høberg-Vetti H, Jongmans MC, Neveling K, Geurts van Kessel A, Morreau H, Hes FJ, Sijmons RH, Schackert HK, Ruiz-Ponte C, Dymerska D, Lubinski J, Rivera B, Foulkes WD, Tomlinson IP, Valle L, Buchanan DD, Kenwrick S, Adlard J, Dimovski AJ, Campbell IG, Aretz S, Schindler D, van Wezel T, Hoogerbrugge N, Kuiper RP. Mutational signature analysis reveals NTHL1 deficiency to cause a multi-tumor phenotype. Cancer Cell. 2019;35:256–66.e5. PubMed PMID: 30753826.

Guilford PJ, Hopkins JB, Grady WM, Markowitz SD, Willis J, Lynch H, Rajput A, Wiesner GL, Lindor NM, Burgart LJ, Toro TT, Lee D, Limacher JM, Shaw DW, Findlay MP, Reeve AE. E-cadherin germline mutations define an inherited cancer syndrome dominated by diffuse gastric cancer. Hum Mutat. 1999;14:249–55. PubMed PMID: 10477433.

Gupta S, Provenzale D, Llor X, Halverson AL, Grady W, Chung DC, Haraldsdottir S, Markowitz AJ, Slavin TP Jr, Hampel H. CGC, Ness RM, Weiss JM, Ahnen DJ, Chen LM, Cooper G, Early DS, Giardiello FM, Hall MJ, Hamilton SR, Kanth P, Klapman JB, Lazenby AJ, Lynch PM, Mayer RJ, Mikkelson J; CGC, Peter S, Regenbogen SE, Dwyer MA; CGC, Ogba N. NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Colorectal, Version 2.2019. J Natl Compr Canc Netw. 2019;17:1032–41. PubMed PMID: 31487681.

Haanstra JF, Al-Toma A, Dekker E, Vanhoutvin SA, Nagengast FM, Mathus-Vliegen EM, van Leerdam ME. de Vos tot Nederveen Cappel WH, Sanduleanu S, Veenendaal RA, Cats A, Vasen HF, Kleibeuker JH, Koornstra

JJ. Prevalence of small-bowel neoplasia in Lynch syndrome assessed by video capsule endoscopy. Gut. 2015;64:1578–83. PubMed PMID: 25209657.

Hampel H, Pearlman R, Cragun D. Universal tumor screening for Lynch syndrome. In: Valle L, Gruber S, Capellá G, eds. *Hereditary Colorectal Cancer*. Cham, Switzerland: Springer; 2018:233-55.

Haraldsdottir S, Hampel H, Wei L, Wu C, Frankel W, Bekaii-Saab T, de la Chapelle A, Goldberg RM. Prostate cancer incidence in males with Lynch syndrome. Genet Med. 2014;16:553–7. PubMed PMID: 24434690.

Haraldsdottir S, Rafnar T, Frankel WL, et al. Comprehensive population-wide analysis of Lynch syndrome in Iceland reveals founder mutations in MSH6 and PMS2. Nat Commun. 2017;8:14755. PubMed PMID: 28466842.

Heald B, Hampel H, Church J, Dudley B, Hall MJ, Mork ME, Singh A, Stoffel E, Stoll J, You YN, Yurgelun MB, Kupfer SS, et al. Collaborative Group of the Americas on Inherited Gastrointestinal Cancer Position statement on multigene panel testing for patients with colorectal cancer and/or polyposis. Fam Cancer. 2020;19:223–39. PubMed PMID: 32172433.

Hegde M, Ferber M, Mao R, Samowitz W, Ganguly A, et al. ACMG technical standards and guidelines for genetic testing for inherited colorectal cancer (Lynch syndrome, familial adenomatous polyposis, and MYH-associated polyposis). Genet Med. 2014;16:101–16. PubMed PMID: 24310308.

Hitchins MP, Rapkins RW, Kwok CT, Srivastava S, Wong JJ, Khachigian LM, Polly P, Goldblatt J, Ward RL. Dominantly inherited constitutional epigenetic silencing of MLH1 in a cancer-affected family is linked to a single nucleotide variant within the 5'UTR. Cancer Cell. 2011;20:200–13. PubMed PMID: 21840485.

Hitchins MP. Constitutional epimutation as a mechanism for cancer causality and heritability? Nat Rev Cancer. 2015;15:625–34. PubMed PMID: 26383139.

Idos GE, Kurian AW, Ricker C, Sturgeon D, Culver JO, Kingham KE, Koff R, Chun NM, Rowe-Teeter C, Lebensohn AP, Levonian P. Multicenter prospective cohort study of the diagnostic yield and patient experience of multiplex gene panel testing for hereditary cancer risk. JCO Precision Oncology. 2019;3:1–2. Available. Accessed 2-2-21.

Jansen AML, Tops CMJ, Ruano D, van Eijk R, Wijnen JT, Ten Broeke S, Nielsen M, Hes FJ, van Wezel T, Morreau H. The complexity of screening PMS2 in DNA isolated from formalin-fixed paraffin-embedded material. Eur J Hum Genet. 2020;28:333–8. PubMed PMID: 31616036.

Jessup CJ, Redston M, Tilton E, Reimann JD. Importance of universal mismatch repair protein immunohistochemistry in patients with sebaceous neoplasia as an initial screening tool for Muir-Torre syndrome. Hum Pathol. 2016;49:1–9. PubMed PMID: 26826402.

John AM, Schwartz RA. Muir-Torre syndrome (MTS): an update and approach to diagnosis and management. J Am Acad Dermatol. 2016;74:558–66. PubMed PMID: 26892655.

Jiang W, Cai MY, Li SY, Bei JX, Wang F, Hampel H, Ling YH, Frayling IM, Sinicrope FA, Rodriguez-Bigas MA, Dignam JJ, Kerr DJ, Rosell R, Mao M, Li JB, Guo YM, Wu XY, Kong LH, Tang JH, Wu XD, Li CF, Chen JR, Ou QJ, Ye MZ, Guo FM, Han P, Wang QW, Wan DS, Li L, Xu RH, Pan ZZ, Ding PR, et al. Universal screening for Lynch syndrome in a large consecutive cohort of Chinese colorectal cancer patients: high prevalence and unique molecular features. Int J Cancer. 2019;144:2161–8. PubMed PMID: 30521064.

Kahn RM, Gordhandas S, Maddy BP, Baltich Nelson B, Askin G, Christos PJ, Caputo TA, Chapman-Davis E, Holcomb K, Frey MK. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population? Cancer. 2019;125:3172–83. PubMed PMID: 31150123.

Kastrinos F, Uno H, Ukaegbu C, Alvero C, McFarland A, Yurgelun MB, Kulke MH, Schrag D, Meyerhardt JA, Fuchs CS, Mayer RJ, Ng K, Steyerberg EW, Syngal S. Development and validation of the PREMM5 model for

comprehensive risk assessment of Lynch syndrome. J Clin Oncol. 2017;35:2165–72. PubMed PMID: 28489507.

Katona BW, Yurgelun MB, Garber JE, Offit K, Domchek SM, Robson ME, Stadler ZK. A counseling framework for moderate-penetrance colorectal cancer susceptibility genes. Genet Med. 2018;20:1324–7. PubMed PMID: 29493579.

Kempers MJ, Kuiper RP, Ockeloen CW, Chappuis PO, Hutter P, Rahner N, Schackert HK, Steinke V, Holinski-Feder E, Morak M, Kloor M, Büttner R, Verwiel ET, van Krieken JH, Nagtegaal ID, Goossens M, van der Post RS, Niessen RC, Sijmons RH, Kluijt I, Hogervorst FB, Leter EM, Gille JJ, Aalfs CM, Redeker EJ, Hes FJ, Tops CM, van Nesselrooij BP, van Gijn ME, Gómez García EB, Eccles DM, Bunyan DJ, Syngal S, Stoffel EM, Culver JO, Palomares MR, Graham T, Velsher L, Papp J, Oláh E, Chan TL, Leung SY, van Kessel AG, Kiemeney LA, Hoogerbrugge N, Ligtenberg MJ. Risk of colorectal and endometrial cancers in EPCAM deletion-positive Lynch syndrome: a cohort study. Lancet Oncol. 2011;12:49–55. PubMed PMID: 21145788.

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;32:407–14. PubMed PMID: 21309036.

Kumar S, Dudzik CM, Reed M, Long JM, Wangensteen KJ, Katona BW. Upper endoscopy surveillance in Lynch syndrome detects gastric and duodenal adenocarcinomas. Cancer Prev Res (Phila). 2020;13:1047–54. PubMed PMID: 32859614.

Ladabaum U, Wang G, Terdiman J, Blanco A, Kuppermann M, Boland CR, Ford J, Elkin E, Phillips KA. Strategies to identify Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis. Ann Intern Med. 2011;155:69–79. PubMed PMID: 21768580.

Ladigan-Badura S, Vangala DB, Engel C, Bucksch K, Hueneburg R, Perne C, Nattermann J, Steinke-Lange V, Rahner N, Schackert HK, Weitz J, Kloor M, Kuhlkamp J, Nguyen HP, Moeslein G, Strassburg C, Morak M, Holinski-Feder E, Buettner R, Aretz S, Loeffler M, Schmiegel W, Pox C, Schulmann K, et al. Value of upper GI endoscopy for gastric cancer surveillance in patients with Lynch syndrome. Int J Cancer. 2021;148:106–14. PubMed PMID: 32930401.

Lamba AR, Moore AY, Moore T, Rhees J, Arnold MA, Boland CR. Defective DNA mismatch repair activity is common in sebaceous neoplasms, and may be an ineffective approach to screen for Lynch syndrome. Fam Cancer. 2015;14:259–64. PubMed PMID: 25637498.

Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Duffy SM, Goldberg RM, de la Chapelle A, Koshiji M, Bhaijee F, Huebner T, Hruban RH, Wood LD, Cuka N, Pardoll DM, Papadopoulos N, Kinzler KW, Zhou S, Cornish TC, Taube JM, Anders RA, Eshleman JR, Vogelstein B, Diaz LA Jr. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372:2509–20. PubMed PMID: 26028255.

Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA, Diaz LA Jr. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357:409–13. PubMed PMID: 28596308.

Lee CY, Yen HY, Zhong AW, Gao H. Resolving misalignment interference for NGS-based clinical diagnostics. Hum Genet. 2021;140:477–92. PubMed PMID: 32915251.

Li J, Dai H, Feng Y, Tang J, Chen S, Tian X, Gorman E, Schmitt ES, Hansen TA, Wang J, Plon SE, Zhang VW, Wong LJ. A comprehensive strategy for accurate mutation detection of the highly homologous PMS2. J Mol Diagn. 2015a;17:545–53. PubMed PMID: 26320870.

Li L, Hamel N, Baker K, McGuffin MJ, Couillard M, Gologan A, Marcus VA, Chodirker B, Chudley A, Stefanovici C, Durandy A, Hegele RA, Feng BJ, Goldgar DE, Zhu J, De Rosa M, Gruber SB, Wimmer K, Young B, Chong G, Tischkowitz MD, Foulkes WD. A homozygous PMS2 founder mutation with an attenuated constitutional mismatch repair deficiency phenotype. J Med Genet. 2015b;52:348–52. PubMed PMID: 25691505.

Lieberman S, Walsh T, Schechter M, Adar T, Goldin E, Beeri R, Sharon N, Baris H, Ben Avi L, Half E, Lerer I, Shirts BH, Pritchard CC, Tomlinson I, King MC, Levy-Lahad E, Peretz T, Goldberg Y. Features of patients with hereditary mixed polyposis syndrome caused by duplication of GREM1 and implications for screening and surveillance. Gastroenterology. 2017;152:1876–80.e1. PubMed PMID: 28242209.

Lu KH, Loose DS, Yates MS, Nogueras-Gonzalez GM, Munsell MF, Chen LM, Lynch H, Cornelison T, Boyd-Rogers S, Rubin M, Daniels MS, Conrad P, Milbourne A, Gershenson DM, Broaddus RR. Prospective multicenter randomized intermediate biomarker study of oral contraceptive versus depo-provera for prevention of endometrial cancer in women with Lynch syndrome. Cancer Prev Res (Phila). 2013;6:774–81. PubMed PMID: 23639481.

Ma X, Zhang B, Zheng W. Genetic variants associated with colorectal cancer risk: comprehensive research synopsis, meta-analysis, and epidemiological evidence. Gut. 2014;63:326–36. PubMed PMID: 23946381.

Machin P, Catasus L, Pons C, Munoz J, Conde-Zurita JM, Balmana J, Barnadas M, Marti RM, Prat J, Matias-Guiu X. Microsatellite instability and immunostaining for MSH-2 and MLH-1 in cutaneous and internal tumors from patients with the Muir-Torre syndrome. J Cutan Pathol. 2002;29:415–20. PubMed PMID: 12139636.

Mange S, Bellcross C, Cragun D, Duquette D, Gorman L, Hampel H, Jasperson J. Creation of a network to promote universal screening for Lynch syndrome: the Lynch syndrome screening network. J Genet Couns. 2015;24:421–7. PubMed PMID: 25220566.

Moreira L, Balaguer F, Lindor N, de la Chapelle A, Hampel H, Aaltonen LA, Hopper JL, Le Marchand L, Gallinger S, Newcomb PA, Haile R, Thibodeau SN, Gunawardena S, Jenkins MA, Buchanan DD, Potter JD, Baron JA, Ahnen DJ, Moreno V, Andreu M, Ponz de Leon M, Rustgi AK, Castells A, et al. Identification of Lynch syndrome among patients with colorectal cancer. JAMA. 2012;308:1555–65. PubMed PMID: 23073952.

Mur P, Pineda M, Romero A, Del Valle J, Borràs E, Canal A, Navarro M, Brunet J, Rueda D, Ramón Y, Cajal T, Lázaro C, Caldés T, Blanco I, Soto JL, Capellá G. Identification of a founder EPCAM deletion in Spanish Lynch syndrome families. Clin Genet. 2014;85:260–6. PubMed PMID: 23530899.

NCCN. Genetic/Familial High-Risk Assessment: Colorectal, Version 1.2020. 2020.

Newton K, Jorgensen NM, Wallace AJ, Buchanan DD, Lalloo F, McMahon RF, Hill J, Evans DG. Tumour MLH1 promoter region methylation testing is an effective prescreen for Lynch Syndrome (HNPCC). J Med Genet. 2014;51:789–96. PubMed PMID: 25280751.

Niessen RC, Hofstra RM, Westers H, Ligtenberg MJ, Kooi K, Jager PO, de Groote ML, Dijkhuizen T, Olderode-Berends MJ, Hollema H, Kleibeuker JH, Sijmons RH. Germline hypermethylation of MLH1 and EPCAM deletions are a frequent cause of Lynch syndrome. Genes Chromosomes Cancer. 2009;48:737–44. PubMed PMID: 19455606.

Nieminen TT, O'Donohue MF, Wu Y, Lohi H, Scherer SW, Paterson AD, Ellonen P, Abdel-Rahman WM, Valo S, Mecklin JP, Järvinen HJ, Gleizes PE, Peltomäki P. Germline mutation of RPS20, encoding a ribosomal

protein, causes predisposition to hereditary nonpolyposis colorectal carcinoma without DNA mismatch repair deficiency. Gastroenterology. 2014;147:595–598.e5. PubMed PMID: 24941021.

Nilbert M, Therkildsen C, Nissen A, Akerman M, Bernstein I. Sarcomas associated with hereditary nonpolyposis colorectal cancer: broad anatomical and morphological spectrum. Fam Cancer. 2009;8:209–13. PubMed PMID: 19130300.

Obermair A, Youlden DR, Young JP, Lindor NM, Baron JA, Newcomb P, Parry S, Hopper JL, Haile R, Jenkins MA. Risk of endometrial cancer for women diagnosed with HNPCC-related colorectal carcinoma. Int J Cancer. 2010;127:2678–84. PubMed PMID: 20533284.

Olkinuora A, Nieminen TT, Mårtensson E, Rohlin A, Ristimäki A, Koskenvuo L, Lepistö A; Swedish Extended Genetic Analysis of Colorectal Neoplasia (SWEN) Study Group. Gebre-Medhin S, Nordling M, Peltomäki P. Biallelic germline nonsense variant of MLH3 underlies polyposis predisposition. Genet Med. 2019;21:1868–73. PubMed PMID: 30573798.

Overman MJ, McDermott R, Leach JL, Lonardi S, Lenz HJ, Morse MA, Desai J, Hill A, Axelson M, Moss RA, Goldberg MV, Cao ZA, Ledeine JM, Maglinte GA, Kopetz S, André T. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol. 2017;18:1182–91. PubMed PMID: 28734759.

Peltomäki P. Role of DNA mismatch repair defects in the pathogenesis of human cancer. J Clin Oncol. 2003;21:1174–9. PubMed PMID: 12637487.

Pérez-Carbonell L, Ruiz-Ponte C, Guarinos C, Alenda C, Payá A, Brea A, Egoavil CM, Castillejo A, Barberá VM, Bessa X, Xicola RM, Rodríguez-Soler M, Sánchez-Fortún C, Acame N, Castellví-Bel S, Piñol V, Balaguer F, Bujanda L, De-Castro ML, Llor X, Andreu M, Carracedo A, Soto JL, Castells A, Jover R. Comparison between universal molecular screening for Lynch syndrome and revised Bethesda guidelines in a large population-based cohort of patients with colorectal cancer. Gut. 2012;61:865–72. PubMed PMID: 21868491.

Pinheiro M, Francisco I, Pinto C, Peixoto A, Veiga I, Filipe B, Santos C, Maia S, Silva J, Pinto P, Santos R, Claro I, Lage P, Lopes P, Ferreira S, Rosa I, Fonseca R, Rodrigues P, Henrique R, Chaves P, Pereira AD, Brandão C, Albuquerque C, Teixeira MR. The nonsense mutation MSH2 c.2152C>T shows a founder effect in Portuguese Lynch syndrome families. Genes Chromosomes Cancer. 2019;58:657–64. PubMed PMID: 30968502.

Pinto D, Pinto C, Guerra J, Pinheiro M, Santos R, Vedeld HM, Yohannes Z, Peixoto A, Santos C, Pinto P, Lopes P, Lothe R, Lind GE, Henrique R, Teixeira MR. Contribution of MLH1 constitutional methylation for Lynch syndrome diagnosis in patients with tumor MLH1 downregulation. Cancer Med. 2018;7:433–44. PubMed PMID: 29341452.

Ponti G, Castellsagué E, Ruini C, Percesepe A, Tomasi A. Mismatch repair genes founder mutations and cancer susceptibility in Lynch syndrome. Clin Genet. 2015;87:507–16. PubMed PMID: 25345868.

Ponti G, Losi L, Pedroni M, Lucci-Cordisco E, Di Gregorio C, Pellancani G, Seidenari S. Value of MLH1 and MSH2 mutations in the appearance of Muir-Torre syndrome phenotype in HNPCC patients presenting sebaceous gland tumors or keratoacanthomas. J Invest Dermatol. 2006;126:2302–7. PubMed PMID: 16826164.

Powers JM, Ebrahimzadeh JE, Katona BW. Genetic testing for hereditary gastrointestinal cancer syndromes: Interpreting results in today's practice. Curr Treat Options Gastroenterol. 2019;17:636–49. PubMed PMID: 31761969.

Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, Garofalo A, Gulati R, Carreira S, Eeles R, Elemento O, Rubin MA, Robinson D, Lonigro R, Hussain M, Chinnaiyan A, Vinson J, Filipenko J, Garraway L, Taplin ME, AlDubayan S, Han GC, Beightol M, Morrissey C, Nghiem B, Cheng HH, Montgomery B, Walsh T, Casadei S, Berger M, Zhang L, Zehir A, Vijai J, Scher HI, Sawyers C, Schultz N, Kantoff PW, Solit D,

Robson M, Van Allen EM, Offit K, de Bono J, Nelson PS. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med. 2016;375:443–53. PubMed PMID: 27433846.

Pritzlaff M, Tian Y, Reineke P, Stuenkel AJ, Allen K, Gutierrez S, Jackson M, Dolinsky JS, LaDuca H, Xu J, Black MH, Helfand BT. Diagnosing hereditary cancer predisposition in men with prostate cancer. Genet Med. 2020;22:1517–23. PubMed PMID: 32439974.

Rabban JT, Calkins SM, Karnezis AN, Grenert JP, Blanco A, Crawford B, Chen LM. Association of tumor morphology with mismatch-repair protein status in older endometrial cancer patients: implications for universal versus selective screening strategies for Lynch syndrome. Am J Surg Pathol. 2014;38:793–800. PubMed PMID: 24503759.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Ramchander NC, Ryan NAJ, Walker TDJ, Harries L, Bolton J, Bosse T, Evans DG, Crosbie EJ. Distinct immunological landscapes characterize inherited and sporadic mismatch repair deficient endometrial cancer. Front Immunol. 2020;10:3023. PubMed PMID: 31998307.

Raymond VM, Everett JN, Furtado LV, Gustafson SL, Jungbluth CR, Gruber SB, Hammer GD, Stoffel EM, Greenson JK, Giordano TJ, Else T. Adrenocortical carcinoma is a lynch syndrome-associated cancer. J Clin Oncol. 2013;31:3012–8. PubMed PMID: 23752102.

Renkonen-Sinisalo L, Sipponen P, Aarnio M, Julkunen R, Aaltonen LA, Sarna S, Jarvinen HJ, Mecklin JP. No support for endoscopic surveillance for gastric cancer in hereditary non-polyposis colorectal cancer. Scand J Gastroenterol. 2002;37:574–7. PubMed PMID: 12059060.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Rivero-Sánchez L, Arnau-Collell C, Herrero J, Remedios D, Cubiella J, García-Cougil M, Alvarez V, Albéniz E, Calvo P, Gordillo J, Puig I, López-Vicente J, Huerta A, López-Cerón M, Salces I, Peñas B, Parejo S, Rodriguez de Santiago E, Herraiz M, Carretero C, Gimeno-Garcia AZ, Saperas E, Alvarez-Urturi C, Moreira R, Rodriguez de Miguel C, Ocaña T, Moreira L, Carballal S, Sánchez A, Jung G, Castells A, Llach J, Balaguer F, Pellisé M, et al. White-light endoscopy is adequate for Lynch syndrome surveillance in a randomized and noninferiority study. Gastroenterology. 2020;158:895–904.e1. PubMed PMID: 31520613.

Rodriguez-Bigas MA, Vasen HF, Lynch HT, Watson P, Myrhoj T, Jarvinen HJ, Mecklin JP, Macrae F, St John DJ, Bertario L, Fidalgo P, Madlensky L, Rozen P. Characteristics of small bowel carcinoma in hereditary nonpolyposis colorectal carcinoma. International Collaborative Group on HNPCC. Cancer. 1998;83:240–4. PubMed PMID: 9669805.

Rossi BM, Palmero EI, López-Kostner F, Sarroca C, Vaccaro CA, Spirandelli F, Ashton-Prolla P, Rodriguez Y, de Campos Reis Galvão H, Reis RM, Escremim de Paula A, Capochin Romagnolo LG, Alvarez K, Della Valle A, Neffa F, Kalfayan PG, Spirandelli E, Chialina S, Gutiérrez Angulo M, Castro-Mujica MDC, Sanchez de Monte J, Quispe R, da Silva SD, Rossi NT, Barletta-Carrillo C, Revollo S, Taborga X, Morillas LL, Tubeuf H, Monteiro-Santos EM, Piñero TA, Dominguez-Barrera C, Wernhoff P, Martins A, Hovig E, Møller P, Dominguez-Valentin M. A survey of the clinicopathological and molecular characteristics of patients with suspected Lynch syndrome in Latin America. BMC Cancer. 2017;17:623. PubMed PMID: 28874130.

Salo-Mullen EE, O'Reilly EM, Kelsen DP, Ashraf AM, Lowery MA, Yu KH, Reidy DL, Epstein AS, Lincoln A, Saldia A, Jacobs LM, Rau-Murthy R, Zhang L, Kurtz RC, Saltz L, Offit K, Robson ME, Stadler ZK. Identification of germline genetic mutations in patients with pancreatic cancer. Cancer. 2015;121:4382–8. PubMed PMID: 26440929.

Salvador MU, Truelson MRF, Mason C, Souders B, LaDuca H, Dougall B, Black MH, Fulk K, Profato J, Gutierrez S, Jasperson K, Tippin-Davis B, Lu HM, Gray P, Shah S, Chao EC, Ghahramani N, Landsverk M, Gau CL, Chen D, Pronold M. Comprehensive paired tumor/germline testing for Lynch syndrome: bringing resolution to the diagnostic process. J Clin Oncol. 2019;37:647–57. PubMed PMID: 30702970.

Schulmann K, Brasch FE, Kunstmann E, Engel C, Pagenstecher C, Vogelsang H, Kruger S, Vogel T, Knaebel HP, Ruschoff J, Hahn SA, Knebel-Doeberitz MV, Moeslein G, Meltzer SJ, Schackert HK, Tympner C, Mangold E, Schmiegel W. HNPCC-associated small bowel cancer: clinical and molecular characteristics. Gastroenterology. 2005;128:590–9. PubMed PMID: 15765394.

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7–30. PubMed PMID: 31912902.

Sijmons R, Hofstra R, Hollema H, Mensink R, van der Hout A, Hoekstra H, Kleibeuker J, Molenaar W, Wijnen J, Fodde R, Vasen H, Buys C. Inclusion of malignant fibrous histiocytoma in the tumour spectrum associated with hereditary non-polyposis colorectal cancer. Genes Chromosomes Cancer. 2000;29:353–5. PubMed PMID: 11066081.

Smith MJ, Urquhart JE, Harkness EF, Miles EK, Bowers NL, Byers HJ, Bulman M, Gokhale C, Wallace AJ, Newman WG, Evans DG. The contribution of whole gene deletions and large rearrangements to the mutation spectrum in inherited tumor predisposing syndromes. Hum Mutat. 2016;37:250–6. PubMed PMID: 26615784.

South CD, Hampel H, Comeras I, Westman JA, Frankel WL, de la Chapelle A. The frequency of Muir-Torre syndrome among Lynch syndrome families. J Natl Cancer Inst. 2008;100:277–81. PubMed PMID: 18270343.

Sroczynski G, Gogollari A, Conrads-Frank A, Hallsson LR, Pashayan N, Widschwendter M, Siebert U. Cost-effectiveness of early detection and prevention strategies for endometrial cancer-a systematic review. Cancers (Basel). 2020;12:1874. PubMed PMID: 32664613.

Suerink M, Wimmer K, Brugieres L, Colas C, Gallon R, Ripperger T, Benusiglio PR, Bleiker EMA, Ghorbanoghli Z, Goldberg Y, Hardwick JCH, Kloor M, le Mentec M, Muleris M, Pineda M, Ruiz-Ponte C, Vasen HFA. Report of the fifth meeting of the European Consortium 'Care for CMMRD' (C4CMMRD), Leiden, The Netherlands, July 6th 2019. Fam Cancer. 2021;20:67–73. PubMed PMID: 32613597.

Takeuchi S, Doi M, Ikari N, Yamamoto M, Furukawa T. Mutations in BRCA1, BRCA2, and PALB2, and a panel of 50 cancer-associated genes in pancreatic ductal adenocarcinoma. Sci Rep. 2018;8:8105. PubMed PMID: 29802286.

Therkildsen C, Ladelund S, Rambech E, Persson A, Petersen A, Nilbert M. Glioblastomas, astrocytomas and oligodendrogliomas linked to Lynch syndrome. Eur J Neurol. 2015;22:717–24. PubMed PMID: 25648859.

Tomsic J, Senter L, Liyanarachchi S, Clendenning M, Vaughn CP, Jenkins MA, Hopper JL, Young J, Samowitz W, de la Chapelle A. Recurrent and founder mutations in the PMS2 gene. Clin Genet. 2013;83:238–43. PubMed PMID: 22577899.

Tutlewska K, Lubinski J, Kurzawski G. Germlie deletions in the EPCAM gene as a cause of Lynch syndrome. Hered Cancer Clin Pract. 2013;11:9. PubMed PMID: 23938213.

van der Klift HM, Tops CM, Bik EC, Boogaard MW, Borgstein AM, Hansson KB, Ausems MG, Gomez Garcia E, Green A, Hes FJ, Izatt L, van Hest LP, Alonso AM, Vriends AH, Wagner A, van Zelst-Stams WA, Vasen HF, Morreau H, Devilee P, Wijnen JT. Quantification of sequence exchange events between PMS2 and PMS2CL provides a basis for improved mutation scanning of Lynch syndrome patients. Hum Mutat. 2010;31:578–87. PubMed PMID: 20186688.

van der Klift HM, Mensenkamp AR, Drost M, Bik EC, Vos YJ, Gille HJ, Redeker BE, Tiersma Y, Zonneveld JB, García EG, Letteboer TG, Olderode-Berends MJ, van Hest LP, van Os TA, Verhoef S, Wagner A, van Asperen CJ, Ten Broeke SW, Hes FJ, de Wind N, Nielsen M, Devilee P, Ligtenberg MJ, Wijnen JT, Tops CM. Comprehensive mutation analysis of PMS2 in a large cohort of probands suspected of Lynch syndrome or

constitutional mismatch repair deficiency syndrome. Hum Mutat. 2016;37:1162–79. PubMed PMID: 27435373.

Vasen HF, Blanco I, Aktan-Collan K, Gopie JP, Alonso A, Aretz S, Bernstein I, Bertario L, Burn J, Capella G, Colas C, Engel C, Frayling IM, Genuardi M, Heinimann K, Hes FJ, Hodgson SV, Karagiannis JA, Lalloo F, Lindblom A, Mecklin JP, Møller P, Myrhoj T, Nagengast FM, Parc Y, Ponz de Leon M, Renkonen-Sinisalo L, Sampson JR, Stormorken A, Sijmons RH, Tejpar S, Thomas HJ, Rahner N, Wijnen JT, Järvinen HJ, Möslein G, et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. Gut. 2013;62:812–23. PubMed PMID: 23408351.

Vaughn CP, Robles J, Swensen JJ, Miller CE, Lyon E, Mao R, Bayrak-Toydemir P, Samowitz WS. Clinical analysis of PMS2: mutation detection and avoidance of pseudogenes. Hum Mutat. 2010;31:588–93. PubMed PMID: 20205264.

Watson P, Butzow R, Lynch HT, Mecklin JP, Jarvinen HJ, Vasen HF, Madlensky L, Fidalgo P, Bernstein I. The clinical features of ovarian cancer in hereditary nonpolyposis colorectal cancer. Gynecol Oncol. 2001;82:223–8. PubMed PMID: 11531271.

Wimmer K. Relationship between NF1 and constitutive mismatch repair deficiency. In: Upadhyaya M, Cooper DN, eds. *Neurofibromatosis Type 1*. Berlin, Germany: Springer-Verlag; 2012:235-51.

Wimmer K, Etzler J. Constitutional mismatch repair-deficiency syndrome: have we so far seen only the tip of an iceberg? Hum Genet. 2008;124:105–22. PubMed PMID: 18709565.

Wimmer K, Kratz CP, Vasen HF, Caron O, Colas C, Entz-Werle N, Gerdes AM, Goldberg Y, Ilencikova D, Muleris M, Duval A, Lavoine N, Ruiz-Ponte C, Slavc I, Burkhardt B, Brugieres L, et al. Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). J Med Genet. 2014;51:355–65. PubMed PMID: 24737826.

Win AK, Jenkins MA, Buchanan DD, Clendenning M, Young JP, Giles GG, Goldblatt J, Leggett BA, Hopper JL, Thibodeau SN, Lindor NM. Determining the frequency of de novo germline mutations in DNA mismatch repair genes. J Med Genet. 2011;48:530–4. PubMed PMID: 21636617.

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;26:404–12. PubMed PMID: 27799157.

Win AK, Lindor NM, Jenkins MA. Risk of breast cancer in Lynch syndrome: a systematic review. Breast Cancer Research. 2013;15:R27. PubMed PMID: 23510156.

Win AK, Scott RJ. Genetic and environmental modifiers of cancer risk in Lynch syndrome. In: Valle L, Gruber S, Capellá G, eds. *Hereditary Colorectal Cancer*. Cham, Switzerland: Springer; 2016:67-89.

Yurgelun MB, Chittenden AB, Morales-Oyarvide V, Rubinson DA, Dunne RF, Kozak MM, Qian ZR, Welch MW, Brais LK, Da Silva A, Bui JL, Yuan C, Li T, Li W, Masuda A, Gu M, Bullock AJ, Chang DT, Clancy TE, Linehan DC, Findeis-Hosey JJ, Doyle LA, Thorner AR, Ducar MD, Wollison BM, Khalaf N, Perez K, Syngal S, Aguirre AJ, Hahn WC, Meyerson ML, Fuchs CS, Ogino S, Hornick JL, Hezel AF, Koong AC, Nowak JA, Wolpin BM. Germline cancer susceptibility gene variants, somatic second hits, and survival outcomes in patients with resected pancreatic cancer. Genet Med. 2019;21:213–23. PubMed PMID: 29961768.

Yurgelun MB, Kulke MH, Fuchs CS, Allen BA, Uno H, Hornick JL, Ukaegbu CI, Brais LK, McNamara PG, Mayer RJ, Schrag D, Meyerhardt JA, Ng K, Kidd J, Singh N, Hartman AR, Wenstrup RJ, Syngal S. Cancer susceptibility gene mutations in individuals with colorectal cancer. J Clin Oncol. 2017;35:1086–95. PubMed PMID: 28135145.

License

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (http://www.genereviews.org/) and copyright (© 1993-2024 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii) reproducers, distributors, and/or translators comply with the GeneReviews® Copyright Notice and Usage Disclaimer. No further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the GeneReviews® Copyright Notice and Usage Disclaimer.

For questions regarding permissions or whether a specified use is allowed, contact: admasst@uw.edu.