Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis

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INTRODUCTION

Lynch syndrome is the most common cause of inherited colorectal cancer (CRC). It is characterized by a significantly increased risk for CRC and endometrial cancer as well as a risk of several other malignancies. This topic will review the genetic basis, clinical manifestations, and diagnosis of Lynch syndrome. Surveillance strategies for individuals with Lynch syndrome are discussed separately. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management".)

TERMINOLOGY

- Hereditary nonpolyposis colorectal cancer refers to patients and/or families who fulfill the Amsterdam criteria (table 1). A portion of these patients will have Lynch syndrome on germline molecular testing. (See 'Family history-based criteria' below.)

- Lynch syndrome refers to patients and families with a germline mutation in one of the DNA mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*) or the *EPCAM* gene.

EPIDEMIOLOGY

Approximately 20 percent of patients with colorectal (CRC) have a family history of CRC in at least one first-degree relative. Lynch syndrome is the most common inherited CRC susceptibility syndrome and accounts for approximately 3 percent of newly diagnosed cases of CRC and 2 to 3 percent of endometrial cancer [1]. It is estimated that 1 in 279 of the population carry mutations in DNA mismatch repair genes [2]. Lynch syndrome is the cause of approximately 8 percent of incident CRC diagnosed under the age of 50.

GENETICS

Germline mutation — Lynch syndrome is an autosomal dominant disorder that is caused by a germline mutation in one of several DNA mismatch repair (MMR) genes or loss of expression of *MSH2* due to deletion in the *EPCAM* gene (previously called *TACSTD1*). The MMR genes that are associated with Lynch syndrome include:

- *MLH1* (MutL homolog 1), which is located on chromosome 3p22.2
- *MSH2* (MutS homolog 2), which is located on chromosome 2p21-16
- *MSH6* (MutS homolog 6), which is located on chromosome 2p16.3
- *PMS2* (postmeiotic segregation 2), which is located on chromosome 7p22.1

Mutations in *PMS2* are estimated to be the most prevalent in the population overall, followed by *MSH6, MLH1*, and *MSH2* [2], but *MLH1* and *MSH2* mutations confer the highest risks of CRC. In a population-based sample of 450 CRCs diagnosed under age 50 years, germline *MSH2* mutations were present in 3.8 percent and germline *MLH1* mutations were present in 2.9 percent. Germline *MSH6* and *PMS2* mutations were in 0.4 and 1.1 percent, respectively, with a total prevalence of Lynch syndrome of 8.2 percent [1,3]. A clinic-based sample of 1058 patients with CRC unselected for age or family history found *MLH1* mutations in 1.2 percent of patients, *MSH2* mutations in 0.7 percent, *MSH6* mutations in 0.6 percent, and *PMS2* mutations in 0.7 percent of patients for a total prevalence of Lynch syndrome of 3.1 percent [4].

The role of the DNA MMR system is to maintain genomic integrity by correcting base substitution mismatches and small insertion-deletion mismatches that are generated by errors in base pairing during DNA replication. Normal MMR requires the coordinated function of several different gene products. The MMR system recognizes base-pair mismatches by two heterodimeric protein complexes termed MutS-alpha and MutS-beta. MutS-alpha is a heterodimer of MSH2 and MSH6 proteins and MutS-beta is an MSH2/MSH3 heterodimer. Either the MSH2/6 or the MSH2/3 pair can recognize insertion/deletion loops that contain more than two bases, but the MSH2/6 pair preferentially recognizes single base mispairs and small (one to two base) insertion-deletion loops [5]. The repair components of the MMR system consist of

three other heterodimer pairs termed MutL-alpha, MutL-beta, and MutL-gamma. MutL-alpha is a heterodimer of MLH1 and PMS2, MutL-beta is a MLH1/PMS1 heterodimer, and MutL-gamma is a MLH1/MLH3 heterodimer.

Although germline MMR mutations are inherited in an autosomal dominant inheritance pattern (ie, via a single mutated allele), inactivation of both alleles needs to occur for MMR function to become defective. As a general rule, patients with Lynch syndrome have a germline mutation in one allele of an MMR gene and the second allele is inactivated somatically by mutation, loss of heterozygosity, or epigenetic silencing by promoter hypermethylation. Biallelic inactivation of MMR genes in a cell then causes an increased mutation rate (genomic instability) due to failure to repair the DNA mismatches that occur during normal DNA synthesis (about one in every 10^6 bases). DNA mismatches commonly occur in regions of repetitive nucleotide sequences called microsatellites. Thus, a characteristic feature of loss of MMR in tumors is the expansion or contraction of these microsatellite regions in the tumor compared with normal tissue. This genetic alteration is termed microsatellite instability (MSI) and is characteristic of Lynch-associated cancers. MSI may affect genes that control cell growth (transforming growth factor [TGF] beta and insulin-like growth factor [sIGF] receptors), regulate apoptotic cell death (Caspase 5, Bax), and some of the DNA MMR genes themselves (*hMSH3, hMSH6*) [6]. Accumulation of mutations in these cancer-related genes is thought to drive the process of carcinogenesis in Lynch syndrome.

Large deletions in the 3' end of the *EPCAM* gene leads to transcriptional read-through into and subsequent epigenetic silencing of the neighboring *MSH2* gene [7]. In *EPCAM* 3' end deletion carriers, *MSH2* inactivation is cell type-specific. *MSH2* is only inactivated in cells in which the *EPCAM* locus is active, therefore showing a mosaic pattern of *MSH2* inactivation. This may lead to a tumor spectrum that is different from individuals with a germline *MSH2* mutation or a deletion that encompasses *EPCAM* as well as *MSH2* or extending close to the *MSH2* promoter [7]. (See 'Genotype phenotype correlation' below.)

Genotype phenotype correlation — The CRC and endometrial cancer risks are similar in individuals with *MLH1* and *MSH2* mutations, but the risks for urothelial cancers and Lynch syndrome skin manifestations are higher in *MSH2* mutation carriers (table 2) [8-14]. Individuals with an *EPCAM* mutation appear to have a comparable risk of CRC as *MSH2* mutation carriers, but the risk for endometrial cancer is lower unless the deletion extends close to the promoter of *MSH2* [15,16]. For some cancers, families with *MSH6* and *PMS2* mutations appear to have an attenuated cancer phenotype with a later age of cancer diagnosis and a lower penetrance as compared with *MLH1* and *MSH2* families except for endometrial cancer in *MSH6* carriers [7,8,17]. However, penetrance is variable, and high penetrance families with *MSH6* mutations have been reported [8,14,17-20].

Pathogenic mutations in *PMS2* have a lower penetrance than mutations in the other three genes (table 2). *PMS2* mutation carriers have a comparatively smaller increased risk of CRC and endometrial cancer and do not appear to be at increased risk of other cancers associated with Lynch syndrome [14,17,18,20]. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management", section on 'Management'.)

CLINICAL FEATURES

Individuals with Lynch syndrome are at an increased risk of colorectal cancer (CRC), endometrial cancer, and several other malignancies.

Colonic manifestations — The majority of patients are asymptomatic until they present with symptoms of CRC such as gastrointestinal bleeding, abdominal pain, or a change in bowel habits. The lifetime risk of CRC in Lynch syndrome varies from 12 percent to as high as 90 percent depending on the sex, the mismatch repair (MMR) gene mutated, and the penetrance of the mutation in the patient and family, with male carriers of *MLH1* mutations having the highest risk estimates (table 2) [8,9,18,21-23]. Although the age of onset varies by genotype, CRC in Lynch syndrome frequently occurs at a younger age as compared with sporadic CRC. However, it should also be noted that many CRCs in patients with Lynch syndrome will occur over the age of 50 [8-10,12-14,17-19,22,24-32]. (See "Clinical presentation, diagnosis, and staging of colorectal cancer", section on 'Clinical presentation'.)

Individuals with Lynch syndrome are at increased risk for synchronous and metachronous CRCs. Approximately 7 percent of individuals with Lynch syndrome have more than one cancer by the time of diagnosis [33]. In individuals with Lynch syndrome who had only undergone a segmental resection for the first colon cancer, 16 percent developed a metachronous CRC at 10 years, 41 percent at 20 years, and 62 percent at 30 years [34]. Similarly, in individuals with Lynch syndrome who had undergone surgery for the first rectal cancer, 19 percent developed a metachronous CRC at 10 years, 47 percent at 20 years, and 69 percent at 30 years [35]. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management".)

CRCs in Lynch syndrome differ from sporadic CRCs in that they are predominantly right-sided in location. Although most Lynch-associated CRCs are thought to evolve from adenomas, the adenomas tend to be larger, flatter, are more often proximal, and are more likely to have high-grade dysplasia and/or villous histology as compared with sporadic adenomas. The adenoma-carcinoma sequence may also progress more rapidly in Lynch syndrome as compared with sporadic CRC (35 months versus 10 to 15 years). Adenoma development may also be bypassed

altogether, with cancers developing directly from microscopic colonic mucosal crypts [36]. However, the overall 10-year survival from CRC in Lynch syndrome is high (88 percent for colon cancer and 70 percent for recto-sigmoid cancers) [14,37].

Extracolonic manifestations — The most common extracolonic tumor in Lynch syndrome is endometrial cancer. The risk of endometrial cancer varies depending on the MMR gene mutated [8-10,12-14,17-20,22,24-32]. Individuals with Lynch syndrome are also at increased risk of cancer of the ovary, stomach, small bowel, pancreatobiliary system, genitourinary system (renal pelvis, ureter, bladder), brain (glioma), as well as various skin pathologies (sebaceous neoplasms, keratoacanthomas, possibly others). (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Screening and prevention of endometrial and ovarian cancer", section on 'Risk for endometrial cancer'.)

A growing body of evidence suggests men with Lynch syndrome are at increased risk of prostate cancer [14,38-41], which may be as high as a 30 percent lifetime risk. An increased risk of female breast cancer has also been reported in several studies among women with Lynch syndrome [14,42-45], however, others have not detected an increased risk [46]. Cancers of the lower uterine segment and the adrenal gland (adrenocortical carcinomas) appear to be rare manifestations of Lynch syndrome [9,39-41,44,47-53]. Several other cancers including laryngeal cancer, hematologic malignancies, and sarcomas have been reported in individuals with Lynch syndrome, but it is unclear if the incidence of these cancers is increased in individuals with Lynch syndrome above the general population [54-56].

Muir-Torre syndrome is an outdated term that describes patients with Lynch syndrome who also develop characteristic skin manifestations, including sebaceous tumors and cutaneous keratoacanthomas, in addition to cancers associated with Lynch syndrome [32,57]. Sebaceous tumors have been reported in carriers of all four MMR genes, but individuals with *MSH2* mutations seem to be particularly predisposed. (See "Muir-Torre syndrome".)

Turcot syndrome is also an outdated term that originally described the association of familial CRC with brain tumors (primarily medulloblastomas and gliomas). As the genetics of the familial CRCs were defined, it became clear that brain tumors were associated with both familial adenomatous polyposis (FAP) and Lynch syndrome. The majority of FAP-associated brain tumors are medulloblastomas, whereas in Lynch syndrome gliomas are more common.

IDENTIFICATION OF INDIVIDUALS AT RISK FOR LYNCH SYNDROME

Lynch syndrome is largely under-recognized [58]. Traditionally, a family history of colorectal cancer (CRC) and other cancers was the primary tool to identify Lynch syndrome. Once it was

recognized that Lynch-associated CRCs were microsatellite unstable, tumor testing became an additional tool for identification of Lynch syndrome. Universal screening of CRC and endometrial cancers for microsatellite instability (MSI) has improved identification of Lynch syndrome among cancer patients [59]. Studies also suggest Lynch syndrome mutations, primarily *MSH6* and *PMS2*, are also present in a small percentage of patients with microsatellite stable (MSS) tumors [55]. (See 'Genetics' above and 'Tumor MSI/IHC testing' below.)

Tumor characteristics — Tumors in Lynch syndrome demonstrate evidence of high MSI (MSI-H) and loss of expression of a mismatch repair (MMR) protein on immunohistochemistry. CRCs in Lynch syndrome also have distinct histologic features. They are more often mucinous, signet ring cell or medullary histologic type, poorly differentiated, and have a brisk lymphocytic infiltrate or are rimmed by a Crohn-like, germinal center-producing lymphoid reaction [60,61]. (See 'Tumor MSI/IHC testing' below and "Pathology and prognostic determinants of colorectal cancer", section on 'Mismatch repair deficiency'.)

Family history-based criteria — Several family history-based criteria have been used to identify individuals at risk for Lynch syndrome. They have limited sensitivity for identification of patients with Lynch syndrome but are useful in guiding the approach to genetic evaluation. (See 'Approach' below.)

- **Amsterdam criteria** — The Amsterdam I criteria were originally proposed to identify individuals who were likely to be mutation carriers for Lynch syndrome [62,63]. These criteria require the presence of young-onset CRC in addition to a family history of three CRCs involving two successive generations. The Amsterdam I criteria were subsequently modified to include other Lynch-associated malignancies. According to the Amsterdam II criteria [63], Lynch syndrome should be suspected in kindreds that meet all of the following criteria:

  - **Three** or more relatives on the same side of the family with histologically verified Lynch-associated cancers (CRC, cancer of the endometrium or small bowel, transitional cell carcinoma of the ureter or renal pelvis), one of whom is a first-degree relative of the other two and in whom familial adenomatous polyposis (FAP) has been excluded.

  - Lynch-associated cancers involving at least **two** generations.

  - **One** or more cancers diagnosed before the age of 50 years.

  The Amsterdam criteria can be remembered by the "3-2-1 rule" (3 affected members, 2 generations, 1 under age 50) (table 1). The sensitivity and specificity of Amsterdam II criteria for a diagnosis of Lynch syndrome are 22 and 98 percent, respectively. While the

clinical utility of the Amsterdam criteria has declined, they remain useful in distinguishing families who have Lynch syndrome from those who have strong hereditary CRC risk but do not have Lynch syndrome (Familial Colorectal Cancer Type X [FCCTX]). (See 'Differential diagnosis' below.)

- **Revised Bethesda criteria** — The Bethesda and revised Bethesda criteria have largely been replaced by universal Lynch syndrome screening for MMR deficiency by immunohistochemistry and/or MSI testing in CRCs and endometrial cancers. The Bethesda and the revised Bethesda criteria were originally developed to identify individuals with CRC who should undergo tumor testing for MSI (table 3). The sensitivity and specificity of any one of the revised Bethesda guidelines for a diagnosis of Lynch syndrome are 82 and 77 percent, respectively [64-66]. (See 'Tumor MSI/IHC testing' below.)

Clinical prediction models — Prediction models have been developed to provide quantitative estimates of the likelihood of an MMR mutation [67-70]. As these models use different data, they can provide a range of mutation-likelihood estimates in the same patient, thereby assisting patients in their decision to undergo genetic testing. Although the performance characteristics of these models improve on clinical criteria in identifying patients with Lynch syndrome, the models still depend on clinicians to suspect the possibility of a hereditary syndrome and elicit an accurate family history.

- **MMRpredict model** – The MMRpredict model includes sex, age at diagnosis of CRC, location of the tumor (proximal versus distal), multiple CRCs (synchronous or metachronous), occurrence of endometrial cancer in any first-degree relatives, and age at diagnosis of CRC in first-degree relatives to calculate the risk of a patient having a Lynch syndrome gene mutation in *MLH1*, *MSH2*, or *MSH6* [67]. In a validation study involving 725 consecutive patients with CRC whose DNA MMR status was available, the sensitivity and specificity of the MMRpredict model were 94 and 91 percent, respectively [71]. A calculator for this model is available online.

- **MMRpro model** – The MMRpro model uses the personal history and family history of CRC and endometrial cancer, age of diagnosis (or current age in unaffected family members), and the results of tumor testing for MMR and previous germline testing results (when it is available) to determine the probability of a person having a deleterious germline mutation in the *MLH1, MSH2*, or *MSH6* genes. The model also provides an estimate of future cancer risk in unaffected persons, including mutation carriers, untested persons, and those in whom no mutation is found. It takes into account CRC, endometrial cancer, and MSI status, but it does not include other Lynch-associated cancers. A validation study reported a better discriminatory ability compared with the Bethesda guidelines [72].

- **PREMM5 model** – The PREMM5 model provides risk estimates of the likelihood of an MMR mutation and the probability of finding a mutation in *MLH1, MSH2/EPCAM, MSH6*, and *PMS2* genes [73]. Variables included in the model include proband sex, and personal and/or family history (including age at diagnosis) of CRC, endometrial cancer, or other Lynch-associated cancers. Genetic evaluation is recommended for individuals with a score of 2.5 percent or higher [73]. The PREMM5 model is available online.

Few studies have directly compared the prediction models [67,71,74,75]. In a study of 736 individuals that compared the performance of PREMM5 with the MMRpredict model in distinguishing 83 carriers of Lynch syndrome mutations from noncarriers, both models identified *MLH1* and *MSH2* carriers with a high degree of accuracy and were fairly accurate for *MSH6* mutation carriers (PREMM5 area under the curve [AUC] 0.69 and MMRpredict 0.66) [76]. This study found that the AUC for *PMS2* carriers was somewhat better for MMRpredict (AUC 0.72) versus PREMM5 (AUC 0.51) at a 5 percent or greater risk-testing threshold [76]. (See 'Indications for germline testing' below.)

DIAGNOSTIC APPROACH

When to suspect Lynch syndrome — Lynch syndrome should be suspected in patients with synchronous or metachronous colorectal cancer (CRC), CRC or endometrial cancer prior to 50 years of age, multiple Lynch-associated cancers (eg, CRC and endometrial, ovarian, stomach, small intestine, or renal pelvis/ureter), and in cases of familial clustering of Lynch-associated cancers. Lynch syndrome should also be suspected in any tumor found to have deficient mismatch repair (MMR) on microsatellite instability (MSI) or immunohistochemistry (IHC) testing. (See "Pathology and prognostic determinants of colorectal cancer", section on 'Mismatch repair deficiency' and "Clinical presentation, diagnosis, and staging of colorectal cancer", section on 'Tumor markers'.)

Evaluation

Approach — The approach to evaluation for Lynch syndrome varies based on the individual's personal or family history of Lynch-associated cancer, including the types of cancer and ages of onset. Ideally, genetic evaluation for Lynch syndrome should begin with a patient affected with a Lynch syndrome cancer.

We begin with germline genetic evaluation for Lynch syndrome in individuals with one of the following (see 'Germline testing' below):

- CRC or endometrial cancer prior to age 50 years

- CRC or endometrial cancer diagnosed at age >50 years with additional personal and family history suggestive of Lynch syndrome
- Identification of a pathogenic MMR variant on somatic tumor testing in any tumor type
- Unaffected (no cancer) individuals with one of the following:
  - >2.5 percent chance of an MMR gene mutation by prediction models (see 'Clinical prediction models' above)
  - Family cancer history meeting Amsterdam I or II criteria or revised Bethesda guidelines (see 'Family history-based criteria' above)
  - First-degree or second-degree relative of those with known MMR/*EPCAM* gene mutation

Tumor-based genetic screening for Lynch syndrome with MSI or IHC testing should be performed in individuals with one of the following (see 'Tumor characteristics' above):

- CRC at age 50 years or older
- Endometrial cancer at any age

Individuals with MSI-high (MSI-H) tumors or loss of expression of an MMR protein on IHC require additional testing based on the pattern of loss of expression of an MMR protein (algorithm 1). (See 'Tumor MSI/IHC testing' below and 'Additional evaluation based on tumor MSI/IHC results' below.)

If tumor testing is not feasible and the clinical suspicion of a hereditary cancer risk due to family history is strong or unavailable (eg, due to adoption, sperm donation, etc) patients should be offered germline testing. (See 'Germline testing' below.)

Germline testing — Prior to germline testing, the standard of care is that the patient or a guardian undergoing germline genetic testing for Lynch syndrome has received appropriate counseling that includes the limitations of genetic testing and has provided written informed consent. The provision of professional genetic counseling accompanying genetic testing is supported by most professional medical societies and medical guidelines that include genetic risk assessment. Important practical issues related to genetic testing, including counseling, psychosocial, and ethical issues, are discussed in detail separately. (See "Genetic testing", section on 'Practical issues' and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management".)

Indications for germline testing — Germline testing for a deleterious mutation in the MMR (*MLH1, MSH2, MSH6*, and *PMS2*) or *EPCAM* gene should be offered to:

- Patients diagnosed with CRC or endometrial cancer prior to 50 years of age
- Individuals with a CRC or endometrial cancer diagnosed at age >50 years with additional personal and family history suggestive of Lynch syndrome
- Identification of a pathogenic MMR variant on somatic tumor testing in any tumor type
- If tumor testing is not feasible (unaffected individual) and the clinical suspicion of a hereditary cancer risk due to family history is strong or totally unavailable (eg, due to adoption, sperm donation, etc) (see 'Approach' above)

Choice of germline analysis — We perform genetic evaluation of patients with a suspected hereditary CRC syndrome with multigene panel testing to evaluate all potential or suspected high-risk genes simultaneously. This approach evaluates approximately 10 to 15 high-risk CRC genes (including the MMR genes of Lynch syndrome) simultaneously, although this varies between clinical laboratories. The costs associated with genetic risk assessment and germline genetic testing have fallen dramatically, increasing access to testing for Lynch syndrome and other hereditary syndromes and high-risk genes. In addition, there has also been a dramatic increase in the number of genes that are known to be associated with a risk of hereditary CRC and other cancers. While mutations in many of these newer genes are considerably rarer than Lynch syndrome, the overlapping phenotypes of many genes and the availability of multigene-panel-based genetic testing has changed the way genetic risk assessment is approached in CRC and other cancers (algorithm 1).

Multigene panel testing is the most time- and cost-efficient means to evaluate a patient with early-onset CRC for high- and moderate-penetrance genes that may be identified in patients with early-onset CRC. Studies have demonstrated that while a substantial number of patients with early-onset CRC (prior to age 50 years) will have Lynch syndrome (approximately 8 percent), many others will carry mutations in other CRC-associated and non-CRC-associated due to other clinically actionable genes [3,4].

In patients 50 or older with an MMR deficient CRC by MSI or IHC screening, a targeted approach to testing for Lynch syndrome can also be performed if universal tumor screening has detected deficient MMR and has raised suspicion for Lynch syndrome. However, if there is a personal or family history of other cancers (not associated with Lynch syndrome), multigene panel testing should be performed [4].

Single-site genetic analysis remains an option in a family with a known mutation in an MMR gene. However, multigene panel testing can still be considered as an option even in families with

known mutations, particularly if the familial mutation does not fully explain all the cancers in the family.

Interpretation of germline testing

- A disease-causing variant (pathogenic or likely pathogenic) in an MMR gene or in *EPCAM* in an affected individual establishes the diagnosis of Lynch syndrome (algorithm 1). (See 'Diagnosis' below.)
- If a disease variant has been identified in a family, and the tested individual does not have that variant, this rules out a diagnosis of Lynch syndrome (algorithm 2).
- A variant of unknown significance (VUS) in an at-risk individual is an inconclusive finding and does not establish the presence or absence of risk in the individual tested. However, normal DNA sequencing (no VUS) does offer some degree of reassurance that the hereditary risk genes tested appear to have normal (nonmutated) sequences when compared with the reference sequences used by the laboratory performing testing. In individuals with VUS, updated interpretation of pathogenicity should be obtained periodically (eg, annually) and should not be used in clinical management decision-making until proven to be pathogenic (algorithm 2).

Tumor MSI/IHC testing — Testing tumors for evidence of deficient DNA MMR has been used to identify individuals at risk for Lynch syndrome.

Indications for tumor testing — We perform tumor-based genetic screening for Lynch syndrome with MSI or IHC testing in individuals with one of the following (see 'Tumor characteristics' above):

- CRC at age 50 years or older
- Endometrial cancer at age 50 years or older

Universal tumor-based genetic screening for Lynch syndrome, with MSI or IHC testing of all CRCs regardless of age, has slightly greater sensitivity for identification of Lynch syndrome as compared with other strategies and has been shown to be cost-effective [1,77,78].

Microsatellite instability testing — Patients with Lynch syndrome develop tumors in the Lynch syndrome tumor spectrum that characteristically demonstrate MSI due to deficient DNA MMR. MSI testing is performed using polymerase chain reaction (PCR) to amplify a standard panel of DNA sequences containing nucleotide repeats. In the most commonly used panel, if 30 percent or more of the markers show expansion or contraction of the repetitive sequences in the tumor compared with the normal mucosa from the same patient, the tumor is reported to

have a high level of MSI (MSI-H). MSI testing can also be performed with next-generation sequencing panels. As there are thousands of microsatellites through the genome, readily captured with next-generation sequencing methods, laboratories have developed different methods of gauging the level of relevant genomic instability. In general, these results have a high level of concordance with traditional MSI testing [79-81].

The presence of an MSI-H tumor phenotype is associated with Lynch syndrome in solid tumors other than CRC and endometrial cancer and warrants germline testing for Lynch syndrome. In a study of 15,045 individuals with solid tumors, the prevalence of Lynch syndrome in patients with MSI-H, indeterminate (MSI-I), and stable (MSS) tumors was 16, 2, and 0.3 percent, respectively [55]. Among 66 patients with Lynch syndrome with MSI-H/I tumors, 33 (50 percent) had non-CRC/endometrial cancer tumors, including melanoma, mesothelioma, urothelial, prostate, pancreas, adrenocortical, small bowel, sarcoma, gastric, and germ cell tumors. Of the 33 patients with Lynch syndrome with MSI-H/I non-CRC/endometrial cancer tumors, only 18 (55 percent) met criteria for genetic evaluation for Lynch syndrome based on their personal or family cancer history. (See 'Additional evaluation based on tumor MSI/IHC results' below.)

The sensitivity and specificity of MSI testing for Lynch syndrome are approximately 85 and 90 percent, respectively. MSI is not specific for Lynch syndrome, and approximately 15 percent of all sporadic CRCs and 5 to 10 percent of metastatic CRCs demonstrate MSI due to hypermethylation of *MLH1* [60,82]. Sporadic MSI-H CRCs typically develop through a methylation pathway called CpG island methylator phenotype (CIMP), which is characterized by aberrant patterns of DNA methylation and frequently by mutations in the *BRAF* gene. These cancers develop somatic promoter methylation of *MLH1*, leading to loss of MLH1 function and resultant MSI. The prevalence of loss of MLH1 expression in CRC increases markedly with aging and this trend is particularly evident in women [83]. Another cause of MSI is bi-allelic somatic mutation or inactivation of one of the MMR proteins [38,84,85]. Bi-allelic somatic mutations are found in approximately 80 percent of the MSI-H CRCs that are neither caused by a germline MMR gene mutation nor MLH1 promoter hypermethylation. In addition, *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. Inclusion of mononucleotide markers can compensate for this difference adequately [15]. (See 'Genetics' above and 'Germline mutation' above and "Molecular genetics of colorectal cancer", section on 'Hypermethylation phenotype (CIMP+) pathway' and 'Additional evaluation based on tumor MSI/IHC results' below and 'Tumor MSI/IHC testing' above and "Molecular genetics of colorectal cancer", section on 'Mismatch repair genes'.)

Immunohistochemistry — The mutations in the MMR genes that cause Lynch syndrome typically result in a truncated or lost MMR protein that can be detected as **loss of staining of the**

protein on tumor IHC testing [86,87]. The likelihood of finding a germline mutation in one of the MMR genes based on IHC results varies depending on the protein that is absent (table 4) [59].

IHC testing of tumor tissue for lack of expression of MMR proteins has sensitivity and specificity of 83 and 89 percent, respectively. IHC is generally more available in the community hospital setting than MSI, can be performed on small biopsies, is inexpensive, and has the added value of helping identify which of the MMR genes may be causing an MMR-deficient tumor (table 4). The sensitivity of IHC for Lynch syndrome may be decreased in rectal tumor tissue that has been previously radiated [88]. Therefore, performing IHC on a pretreatment biopsy is optimal.

IHC in other Lynch syndrome tumors has been studied less rigorously and, while abnormal tumor studies may be indicative of Lynch syndrome, normal tumor studies do not necessarily rule out Lynch syndrome. IHC results in these tumors should be evaluated in light of the family and personal history of tumors [86].

Additional evaluation based on tumor MSI/IHC results

- **Absence of MSI and intact expression of all four MMR proteins** – The absence of MSI and intact expression of all four MMR proteins on IHC rules out most cases of Lynch syndrome. However, it is possible to have a sporadic cancer develop through the more common pathways, even in someone with Lynch syndrome; this is called a phenocopy. (See 'Immunohistochemistry' above.)

- **MSI-H or loss of expression of an MMR protein** – In individuals with tumors that demonstrate evidence of MSI-H or loss of expression of an MMR protein, the decision can then be made to move forward with multigene panel-based testing or more selective testing for Lynch syndrome based on the pattern of IHC loss (algorithm 1).

  - **Loss of MLH1/PMS2** – CRCs that show loss of MLH1/PMS2 by IHC may be tested for the common *BRAF* V600E mutation to help determine whether the loss of MLH1/PMS2 expression by IHC is due to Lynch syndrome or hypermethylation of the *MLH1* promoter [89,90]. *BRAF* V600E mutations are found in 40 to 87 percent of sporadic MSI-H CRCs but are rare in Lynch syndrome CRCs:

    - *BRAF* V600E mutation present – The presence of *BRAF* V600E mutation strongly suggests that a germline Lynch syndrome mutation is not present [91].

    - If the *BRAF* V600E mutation is not present, additional testing to identify hypermethylation of the MLH1 promoter may be conducted and will identify another approximately 25 percent of those tumors with MLH1/PMS2 loss on IHC as being due to *MLH1* promoter hypermethylation. It is also acceptable to skip the

BRAF V600E testing step and go right to *MLH1* promoter hypermethylation testing, although many health systems have continued to do *BRAF* V600E testing as it is more readily available in many hospital laboratories and is less costly than MLH1 promoter hypermethylation testing. Endometrial tumors are not eligible f*or BRAF* V600E testing, so those with loss of MLH1/PMS2 on IHC should have *MLH1* promoter hypermethylation testing. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Screening and prevention of endometrial and ovarian cancer".)

In the absence of *MLH1* promoter methylation, germline testing for Lynch syndrome should be performed (algorithm 1) (see 'Germline testing' above). Approximately 25 percent of tumors showing loss of MLH1/PMS2 (approximately 3 percent of all CRCs total) will show evidence of MMR by IHC or MSI, will not show evidence of *MLH1* promoter hypermethylation, but will also not have a germline mutation identified on germline testing. The majority of this group of tumors (approximately 80 percent) will be found, on tumor DNA testing, to have bi-allelic inactivation (by mutation and/or loss of heterozygosity) of *MLH1* or *PMS2*. While rarer, bi-allelic inactivation is also seen in the *MSH2* and *MSH6* genes and can lead to a germline testing negative MMR-deficient tumor [38,84,85]. (See 'Differential diagnosis' below.)

The minority (approximately 20 percent) of patients will be found to have an MSI-H tumor but will not have a germline Lynch syndrome mutation, will not have *MLH1* promoter hypermethylation, and will not have evidence of bi-allelic somatic inactivation of one of the Lynch syndrome genes. We prefer to label these individuals "clinical Lynch syndrome," as we remain suspicious until proven otherwise that their MSI-H tumors may be caused by an occult Lynch syndrome mutation or another genetic cause that produces an MSI-H tumor. If an explanation for the MSI-H tumor cannot be determined, these patients are usually clinically managed (eg, screening) as having Lynch syndrome until proven otherwise. However, management of family members is challenging without a clear genetic risk factor and, therefore, is generally individualized based on family history, patient preference, and clinician presentation. (See 'Differential diagnosis' below.)

- **Loss of expression of MSH2/MSH6** – In individuals with loss of expression of MSH2/MSH6, the decision to pursue multigene panel testing versus testing focused on diagnosing Lynch syndrome only should be based on a comprehensive family history and consideration of other diverse genetic cancer risks in the family, such as additional family history of non-Lynch syndrome related cancers or cancer risk mutations or being

a member of a particular ethnic group associated with high prevalence of hereditary cancer risk mutations , ethnicity, the prevalence of particular genetic founder mutations in some populations, and patient preference.

Diagnosis — A pathogenic germline mutation in the MMR or *EPCAM* gene is required for a definitive diagnosis of Lynch syndrome.

Differential diagnosis

- **Bi-allelic somatic mutations in suspected Lynch syndrome** – This describes individuals with CRC or endometrial cancer in which molecular testing shows the presence of MSI-H and/or abnormalities in the expression of MMR gene proteins on IHC testing of tumor tissue expression, but no pathogenic germline mutation in DNA MMR genes can be found in the individual, and the phenotype is not explained by acquired *MLH1* promoter hypermethylation or *BRAF* mutations [38,84,85]. As genetic testing in tumors has become clinically available, this should be offered to those individuals that fit this profile, as proving somatic causation will prevent them from being erroneously labeled as Lynch syndrome, with all the attendant screening and risks. The term "Lynch –like" has been previously used to describe this population, but we believe this term should not be used; these individuals do not have Lynch syndrome.

- **Constitutional mismatch repair deficiency (CMMR-D) syndrome** – Refers to patients and/or families with germline bi-allelic mutations of a DNA MMR gene. In contrast with Lynch syndrome, in which cancers occur in the fifth or sixth decade of life, homozygous or compound heterozygous mutation carriers of *MLH1, MSH2, MSH6,* or *PMS2* mutations often develop Lynch-associated malignancies, hematologic and brain malignancies, and sarcomas during childhood, often in the first decades of life [92-102]. Some of these individuals have a family history of Lynch syndrome on both the maternal and paternal sides of their families. *PMS2* is implicated in 60 percent of CMMR-D cases [103,104]. Given the low penetrance for cancer in individuals with heterozygote *PMS2* mutations [14], often the family history is not greatly suggestive of Lynch syndrome. In addition to the cancer risk in the first two decades of life, individuals with CMMR-D may have a neurofibromatosis type-1-like phenotype, presenting with café au lait spots, neurofibromas, Lisch nodules, and axillary freckling.

- **Familial Colorectal Cancer Type X (FCCTX)** – Refers to patients and/or families that meet Amsterdam I criteria but when tumors are tested, lack MSI that is characteristic of Lynch syndrome. Patients with FCCTX also do not appear to have an increased risk of endometrial or other Lynch-associated cancers [105]. These individuals should undergo multigene

panel testing to rule out rare genetic causes of familial CRC. (See 'Family history-based criteria' above and "Molecular genetics of colorectal cancer", section on 'Mismatch repair genes'.)

- **Clinical Lynch syndrome** – Clinical Lynch syndrome describes rare individuals with no clear explanation for their MMR-deficient tumor. The individuals have an MSI-H tumor but will not have a germline Lynch syndrome mutation, will not have *MLH1* promoter hypermethylation, and will not have evidence of bi-allelic somatic inactivation of one of the Lynch syndrome genes. These individuals and families are clinically managed as Lynch syndrome and/or have management strongly guided by personal/family history.

- **Attenuated familial adenomatous polyposis (AFAP) and *MUTYH*-associated polyposis (MAP)** – Individuals with AFAP and MAP and a few colorectal adenomas may be difficult to distinguish clinically from Lynch syndrome [106]. Only genetic testing can definitively distinguish between AFAP, MAP, and Lynch syndrome, although an autosomal dominant pattern of CRC inheritance makes MAP unlikely. AFAP is characterized by germline mutations in the *APC* gene and individuals with MAP have bi-allelic mutations in the *MUTYH* genes. (See 'Genetics' above and "*MUTYH*-associated polyposis" and "Clinical manifestations and diagnosis of familial adenomatous polyposis", section on 'Clinical manifestations'.)

GENETIC EVALUATION FOR FAMILY MEMBERS

At-risk relatives should be referred for genetic counseling and testing for the familial mutation that causes Lynch syndrome in the pedigree and additional genetic testing if warranted due to personal and family history. Testing in children should be offered 10 years before the earliest age of cancer onset in the family or by age 20 to 30 years when CRC screening is recommended for individuals with Lynch syndrome. The presence of the same mutation establishes a diagnosis of Lynch syndrome, and a negative test result for the familial mutation indicates that the individual does not have Lynch syndrome (algorithm 2).

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hereditary colorectal cancer syndromes".)

SUMMARY AND RECOMMENDATIONS

- **Epidemiology and genetics** – Lynch syndrome is an autosomal dominant disorder that is caused by a germline mutation in one of several DNA mismatch repair (MMR) genes (*MLH1, MSH2, MSH6, PMS2*) or loss of expression of *MSH2* due to deletion in the *EPCAM* gene. Lynch syndrome is the most common inherited colorectal cancer (CRC) susceptibility syndrome and accounts for approximately 3 percent of newly diagnosed cases of CRCs and 2 to 3 percent of endometrial cancers. (See 'Epidemiology' above and 'Genetics' above.)

- **Clinical features and cancer risk** – The lifetime risk of CRC to age 70 years in Lynch syndrome is anywhere from 10 to 90 percent, depending on the patient's sex, the MMR gene mutated, and the penetrance of the gene in the family (table 2). Individuals with Lynch syndrome are also at an increased risk for endometrial cancer and several other malignancies, including cancers of the ovary, stomach, and genitourinary system, and more rarely, small bowel, bile duct, pancreas, skin (sebaceous neoplasms), and brain tumors (gliomas). *PMS2* carriers in particular have a lower lifetime cancer risk than the other Lynch syndrome genes. (See 'Clinical features' above.)

- **Colorectal manifestations** – CRCs in Lynch syndrome differ from sporadic CRCs in that they are predominantly right-sided in location. Although the CRCs appear to evolve from adenomas, the adenomas tend to be larger, flatter, are more often proximal, and more commonly have high-grade dysplasia and/or villous histology as compared with sporadic adenomas. The adenoma-carcinoma sequence also progresses much more rapidly in Lynch syndrome as compared with sporadic CRC. Individuals with Lynch syndrome are at increased risk for both synchronous and metachronous CRCs. (See 'Colonic manifestations' above.)

- **Molecular characteristics of Lynch syndrome associated tumors** – Tumors in Lynch syndrome typically show microsatellite instability (MSI) and loss of staining of MMR proteins on immunohistochemistry (IHC) testing. As compared with sporadic CRCs, they are more often mucinous, signet ring cell or medullary histologic type, poorly differentiated, and have a brisk lymphocytic infiltrate or are rimmed by a Crohn-like, germinal center-producing lymphoid reaction. (See 'Tumor characteristics' above.)

- **When to suspect Lynch syndrome** – Lynch syndrome should be suspected in patients with synchronous or metachronous CRC, CRC or endometrial cancer prior to 50 years of age, multiple Lynch-associated cancers (eg, CRC and endometrial, ovarian, stomach, small intestine, or renal pelvis/ureter), and in cases of familial clustering of Lynch-associated cancers. Lynch syndrome should also be suspected in any tumor found to have deficient MMR on MSI or IHC testing. (See 'Diagnostic approach' above.)

- **Diagnostic evaluation** – The approach to evaluation for Lynch syndrome varies based on the individual's personal or family history of Lynch-associated cancer, the type of cancer and age of onset. Ideally, genetic evaluation for Lynch syndrome should begin with a patient affected with a Lynch syndrome cancer.

  - Germline genetic evaluation – We begin with germline genetic evaluation for Lynch syndrome in individuals with one of the following (algorithm 1 and algorithm 2) (see 'Germline testing' above):

    - CRC or endometrial cancer prior to age 50 years
    - CRC or endometrial cancer diagnosed at age >50 years with additional personal and family history suggestive of Lynch syndrome
    - Unaffected (no cancer) individuals with one of the following:
    - ≥2.5 percent chance of an MMR gene mutation by prediction models (see 'Clinical prediction models' above)
    - Family cancer history meeting Amsterdam I or II criteria or revised Bethesda guidelines (see 'Family history-based criteria' above)
    - First-degree or second-degree relative of those with known MMR/*EPCAM* gene mutation

  - Tumor-based genetic screening – Tumor-based genetic screening for Lynch syndrome with MSI or IHC testing in individuals with one of the following (see 'Tumor characteristics' above):

    - CRC at age 50 years or older
    - Endometrial cancer at age 50 years or older

    Individuals with MSI-high tumors or loss of expression of an MMR protein on IHC require additional testing based on the pattern of loss of expression of an MMR protein.

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Topic 2605 Version 46.0

GRAPHICS

Amsterdam II criteria for Lynch syndrome

There should be at least three relatives with any Lynch syndrome-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis)
One should be a first-degree relative of the other two
At least two successive generations should be affected
At least one should be diagnosed before age 50
Familial adenomatous polyposis should be excluded in the colorectal cancer case(s), if any
Tumors should be verified by pathological examination

Adapted from Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology 1999; 116:1453.

Graphic 59832 Version 7.0

Lifetime cancer risk related to Lynch genotypes

Cancer site	MLH1			MSH2[Δ]			MSH6			
	Female	Male	Both	Female	Male	Both	Female	Male	Both	Fem
Any Lynch cancer	**71 to 81%**	**71 to 72%**	**71 to 90%**	**61 to 84%**	**52 to 75%**	**52 to 84%**	**62 to 65%**	**41 to 47%**	**58 to 73%**	
Colorectal	35 to 57%	39 to 78%	35 to 90%	26 to 68%	31 to 63%	52 to 84%	20 to 30%	12 to 69%	18 to 58%	12 15
Endometrial	20 to 57%	–	–	21 to 71%	–	–	17 to 71%	–	–	13 15
Gastric	3 to 15%	6 to 37%	Up to 37%	13 to 19%	5 to 20%	Up to 20%	1 to 4%	1 to 8%	Up to 8%	
Ovarian	8 to 20%	–	–	12 to 38%	–	–	1 to 11%	–	–	3 to
Ureter/kidney	2 to 5%	4 to 5%	Up to 5%	6 to 19%	6 to 18%	Up to 19%	1 to 5%	1 to 2%	Up to 5%	
Bladder	1 to 5%	4 to 11%	Up to 11%	3 to 8%	4 to 13%	Up to 13%	1 to 2%	1 to 8%	Up to 8%	
Prostate	9 to 14%			24 to 30%			9 to 30%			
Breast[¶]	Up to 19%			Up to 16%			Up to 14%			
Brain	Up to 2%			Up to 8%			Up to 4%			
Small bowel	Up to 4%			Up to 8%			Up to 4%			
Pancreatobiliary	Up to 5%			Up to 5%			Unknown*			
Skin	Up to 4%			Up to 10%			Up to 4%			

* Data are insufficient to make a determination.

¶ There is ongoing debate as to whether breast cancer is a Lynch syndrome associated cancer.

Δ Cancer risks in individuals with a pathogenic *EPCAM* variant are similar to those with a pathogenic *MSH2* variant.

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Graphic 52285 Version 11.0

The revised Bethesda guidelines for testing colorectal tumors for microsatellite instability (MSI)

Tumors from individuals should be tested for MSI in the following situations:
1. Colorectal cancer diagnosed in a patient who is less than 50 years of age.
2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors*, regardless of age.
3. Colorectal cancer with the MSI-H¶-like histologyΔ diagnosed in a patient who is less than 60 years of age◇.
4. Colorectal cancer diagnosed in a patient with one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years.
5. Colorectal cancer diagnosed in a patient with two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

HNPCC: hereditary nonpolyposis colorectal cancer; MSI-H: microsatellite instability-high.

* HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratocanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

¶ MSI-H in tumors refers to changes in two or more of the five National Cancer Institute-recommended panels of microsatellite markers.

Δ Presence of tumor infiltrating lymphocytes. Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

◇ There was no consensus among the Workshop participants on whether to include the age criteria in guideline 3 above; participants voted to keep less than 60 years of age in the guidelines.

Graphic 72965 Version 5.0

Approach to screening for Lynch syndrome in individuals with colorectal and/or

CRC: colorectal cancer; IHC: immunohistochemistry; MSI: microsatellite instability; MMR: mismatch repair.

* Germline genetic evaluation may be appropriate in individuals with any one of the following: 1) Family canc
Bethesda guidelines; 2) >2.5% chance of an MMR gene mutation by prediction models; 3) First-degree relativ

¶ Normal IHC is only approximately 85% sensitive for Lynch syndrome. Consider MSI testing to confirm or ru

Δ The presence of MLH1 promoter methylation or BRAF V600E mutation is suggestive of sporadic CRC.

◇ Endometrial tumors are not eligible for BRAF V600E testing, so those with loss of MLH1/PMS2 on IHC shou

§ Lynch syndrome should be suspected in individuals with synchronous or metachronous CRC, CRC prior to 5
CRC and endometrial, ovarian, stomach, small intestine, or renal pelvis/ureter), and in cases of familial cluste

¥ Other important considerations include ethnicity, the prevalence of particular genetic founder mutations ir

‡ Refer to UpToDate content on genetic evaluation for Lynch syndrome.

† Individuals with bi-allelic somatic inactivation (by mutation and/or loss of heterozygosity) of MMR genes do

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Graphic 130015 Version 1.0

Approach to evaluation for Lynch syndrome in individuals with a known family

* Lynch syndrome should be suspected in individuals with synchronous or metachronous colorectal cancer, c
cancer prior to 50 years of age, multiple Lynch-associated cancers (eg, colorectal and endometrial, ovarian, s
small intestine, or renal pelvis/ureter), and in cases of familial clustering of Lynch-associated cancers.

Graphic 130023 Version 1.0

Interpretation of immunohistochemistry results for mismatch repair genes

Result	Possible interpretation	Explanation/comments	Next steps to consider
Loss of MLH1 only (rare)	1. *MLH1* germline mutation. 2. *MLH1* promoter hypermethylation. 3. Bi-allelic (double) somatic *MLH1* or *PMS2* inactivation.	▪ Epigenetic silencing of the *MLH1* gene can occur through *MLH1* promoter hypermethylation. ▪ Bi-allelic (double) inactivation of *MLH1* can rarely cause isolated MLH1 loss.	1. *BRAF* V600E mutation testing (if negative, proceed to #2). 2. Tumor testing for *MLH1* promoter hypermethylation testing.¶ 3. Germline panel testing for at least the MMR genes if family history is suggestive of Lynch syndrome.* 4. Tumor sequencing to evaluate for bi-allelic (double) somatic *MLH1* inactivation due to mutation and/or LOH.
Loss of MLH1 and PMS2 (common)	1. *MLH1* germline mutation. 2. *PMS2* germline mutation. 3. *MLH1* promoter hypermethylation. 4. Bi-allelic (double) somatic *MLH1* inactivation through mutation and/or LOH. 5. Bi-allelic (double) somatic *PMS2* inactivation through mutation and/or LOH.	▪ Because the MLH1 and PMS2 proteins form a heterodimer, altered expression of either the MLH1 or PMS2 protein due to germline mutations frequently leads to loss of both MLH1 and PMS2 expression. ▪ Altered expression of either *MLH1* or *PMS2* due to bi-allelic (double) somatic mutation or LOH of the *MLH1* or *PMS2* gene can also lead to this pattern.	1. *BRAF* V600E mutation testing (if negative, proceed to #2). 2. Tumor testing for *MLH1* promoter hypermethylation.¶ 3. Tumor testing for bi-allelic (double) somatic *MLH1* or *PMS2* inactivation due to mutation and/or LOH. 4. Germline panel testing for at least the MMR genes if family history is suggestive of Lynch syndrome.*

Loss of PMS2 only (less common)	1. *PMS2* germline mutation. 2. Bi-allelic (double) somatic PMS2 inactivation through mutation and/or LOH. 3. *MLH1* germline mutation. 4. Bi-allelic (double) somatic *MLH1* inactivation through mutation and/or LOH.	▪ Because the MLH1 protein has heterodimer partner proteins other than the PMS2 protein, germline *PMS2* mutations may not cause loss of *MLH1* expression by IHC. ▪ PMS2 protein expression by IHC can be interpreted as equivocal—not clearly positive or negative. ▪ *MLH1* germline mutations have rarely been identified when tumors show loss of staining of PMS2 only; bi-allelic double somatic *MLH1* mutation or LOH could also mimic this.	1. Germline MMR panel testing.* 2. If panel testing is negative consider tumor testing for the MMR genes to identify bi-allelic (double) somatic *PMS2* or *MLH1* inactivation due to mutation and/or LOH. 3. If PMS2 expression by IHC is equivocal consider secondary MSI testing to confirm or rule out presence of dMMR.
Loss of MSH2 only (rare)	1. *MSH2* germline mutation. 2. *EPCAM* germline mutation. 3. Bi-allelic (double) somatic inactivation of *MSH2* through mutation and/or LOH.	▪ Strong likelihood of germline *MSH2* or *EPCAM.* ▪ Bi-allelic (double) somatic inactivation of *MSH2* is rare but has been reported.	1. Germline MMR panel testing.* 2. If panel testing is negative consider tumor testing for the MMR genes to identify bi-allelic (double) somatic *MSH2* inactivation due to mutation and/or LOH.
Loss of MSH2 and MSH6 (common)	1. *MSH6* germline mutation. 2. *MSH2* germline mutation. 3. *EPCAM* germline mutation. 4. Bi-allelic (double) somatic inactivation of *MSH2* through mutation and/or LOH.	▪ Because the MSH2 and MSH6 proteins form a heterodimer, alterations of expression of either the MSH2 or MSH6 protein due to germline or bi-allelic (double) somatic mutations in either the *MSH2* or *MSH6* genes could cause this pattern on IHC.	1. Germline MMR panel testing.* 2. If panel testing is negative consider tumor testing for the MMR genes to identify bi-allelic (double) somatic *MSH2* or *MSH6* inactivation due to mutation and/or LOH.

	5. Bi-allelic (double) somatic inactivation of *MSH6* through mutation and/or LOH.		
Loss of MSH6 (common)	1. *MSH6* germline mutation. 2. Bi-allelic (double) somatic inactivation of *MSH6* through mutation and/or LOH. 3. *MSH2* germline mutation. 4. Bi-allelic (double) somatic inactivation of *MSH2* through mutation and/or LOH.	▪ Because MSH2 has heterodimer partners other than MSH6, germline *MSH6* mutations may not cause loss of MSH2 expression by IHC and frequently cause loss of staining of MSH6 only; similar reasoning holds for bi-allelic (double) somatic *MSH6* inactivation through mutation and/or LOH.	1. Germline MMR panel testing.* 2. If panel testing is negative consider tumor testing for the MMR genes to identify bi-allelic (double) somatic *MSH6* inactivation due to mutation and/or LOH.
Loss of all 4 MMR proteins	1. Likely an artifact of tissue fixation and IHC staining procedures. 2. Germline mutation in any one of the Lynch syndrome genes		1. Consider MSI testing to confirm or rule out dMMR. 2. Germline MMR panel testing if family history warrants testing.*
All proteins expressed	1. Likely not Lynch syndrome if MSS. 2. If MSI-H, rare missense germline mutations in *MLH1, MSH2, MSH6,* and *PMS2* can demonstrate normal IHC. 3. If MSI-H, rare patients with bi-allelic (double) somatic alterations due to mutation and/or LOH.	Normal IHC is only approximately 85% sensitive for Lynch syndrome.	1. Consider MSI testing to confirm or rule out dMMR. 2. If MSI-H, germline MMR panel testing if family history warrants testing.* 3. If MSI-H and germline panel testing are negative consider tumor testing for the MMR genes to identify bi-allelic (double) somatic inactivation

			due to mutation and/or LOH.

LOH: loss of heterozygosity; MMR: mismatch repair; dMMR: deficient mismatch repair; IHC: immunohistochemistry; MSI: microsatellite instability; MSI-H: high microsatellite instability.

* A multi-syndrome gene panel is an option if there is a personal or family history of other cancers (not associated with Lynch syndrome).

¶ Rarely, MLH1 methylated or BRAF V600E+ tumors can harbor germline MLH1 mutations. MLH1 methylation may also rarely be caused by constitutional MLH1 epimutation

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Graphic 63906 Version 12.0

Contributor Disclosures

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