Lynch Syndrome Genetic Testing

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Introduction

Lynch syndrome genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
EPCAM deletion/duplication analysis	81403
Genomic Unity Lynch Syndrome Analysis	0238U
Known familial variant not otherwise specified	81403
MLH1 deletion/duplication analysis	81294
MLH1 known familial mutation analysis	81293
MLH1 sequencing	81292
MSH2 deletion/duplication analysis	81297
MSH2 known familial mutation analysis	81296
MSH2 sequencing	81295
MSH6 deletion/duplication analysis	81300
MSH6 known familial mutation analysis	81299
MSH6 sequencing	81298
PMS2 deletion/duplication analysis	81319
PMS2 known familial mutation analysis	81318
PMS2 sequencing	81317

Criteria

Introduction

Requests for Lynch syndrome genetic testing are reviewed using the following criteria.

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Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing that would detect the familial mutation, AND
- Family History:
  - Known MLH1, MSH2, MSH6, PMS2, or EPCAM mutation in a close blood relative (1st, 2nd, or 3rd degree), AND
- Age- 18 years and older, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Gene Sequencing and/or Deletion/Duplication Analysis of MLH1, MSH2, MSH6, PMS2, or EPCAM

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - Gene requested has not been tested previously by the same methodology (i.e., sequencing or deletion/duplication analysis), AND
- Age- 18 years or older, AND
- Familial adenomatous polyposis (FAP) has been ruled out, AND
- Diagnostic Testing for Symptomatic Individuals
  - Personal history of colorectal cancer (CRC) (or other Lynch syndrome-related tumor[***]), and
    - Colorectal or endometrial cancer diagnosed before 50 years of age, or
    - Colorectal or endometrial cancer diagnosed at any age with abnormal tumor testing indicative of a mutation in a mismatch repair gene (see Figure A), or
    - Presence of synchronous or metachronous Lynch syndrome-associated tumors, regardless of age, or
    - Amsterdam II criteria are met:
      - ≥ 3 close blood relatives (1st, 2nd, or 3rd degree) with Lynch syndrome-associated tumor (symptomatic member can be one of the three), and
      - One should be a first-degree relative of the other two, and

        - ≥ 2 successive generations affected, and
        - ≥ 1 diagnosed before age 50, or

    - 5% or greater risk of Lynch syndrome based on one of the following mutations prediction models (MMRPro or MMRPredict), or
    - 2.5% or greater risk of Lynch syndrome based on PREMM[5], OR

- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
    - Immunohistochemistry (IHC) and/or Lynch syndrome genetic testing results from affected family member are unavailable, AND
        - Colorectal or endometrial cancer diagnosed before age 50 in a first-degree relative, or
        - Colorectal or endometrial cancer and another synchronous or metachronous Lynch syndrome-associated tumor in a first-degree relative, or
        - ≥ 3 close blood relatives (1st, 2nd, or 3rd degree) with Lynch syndrome-associated tumor, where Amsterdam II criteria are met:
            - One should be a first-degree relative of the other two, and
            - ≥ 2 successive generations affected, and
            - ≥ 1 diagnosed before age 50, OR
    - 5% or greater risk of Lynch syndrome based on one of the following mutations prediction models (MMRPro or MMRPredict), OR
    - 2.5% or greater risk of Lynch syndrome based on PREMM[5], AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

***Lynch syndrome-associated tumors include colorectal, endometrial, small bowel, stomach, ovarian, pancreatic, ureteral and renal pelvis, biliary tract, brain/CNS tumors (usually glioblastomas), sebaceous adenomas, and keratoacanthomas.

Other Considerations

- Lynch syndrome testing may be performed as part of a multigene, multisyndrome panel. For information on multigene, multisyndrome panel testing, please refer to the guideline *Hereditary Cancer Syndrome Multigene Panels*, as this testing is not addressed here.
- NCCN recommends universal screening for Lynch syndrome for all colorectal and endometrial cancers by MSI (microsatellite instability) and/or IHC regardless of the individual's age. Most people affected with colorectal or endometrial cancer who are appropriate candidates for Lynch syndrome testing should have access to MSI and/

or IHC. Lynch syndrome genetic testing without MSI and/or IHC results will only be considered necessary in extenuating circumstances and will require medical necessity review.

Billing and Reimbursement

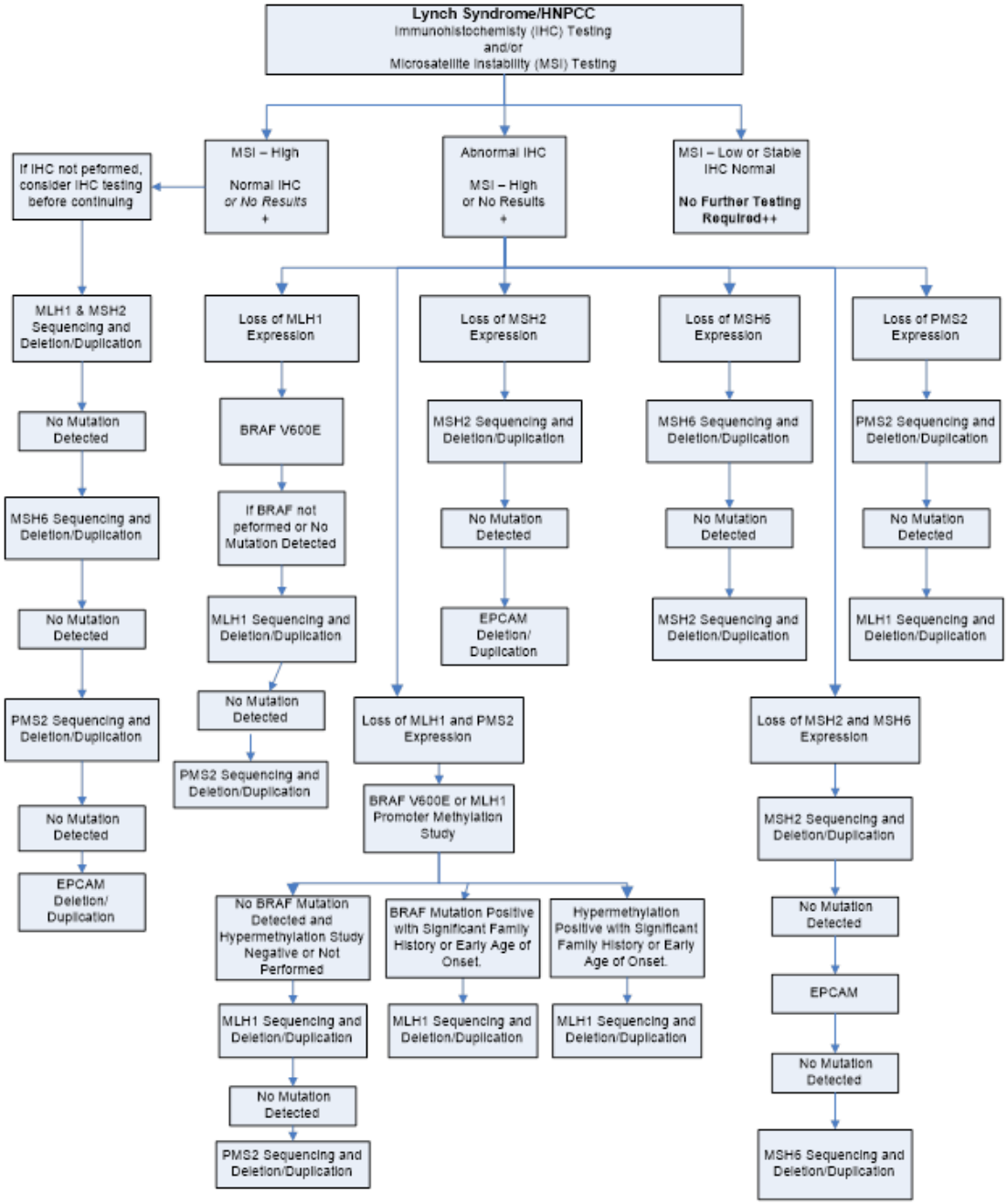
Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- For individuals that have had previous tumor testing (MSI and/or IHC), the testing algorithm as outlined in Figure A must be followed for payment of claim.

Figure A [9, 11]

Diagnostic Testing for Individuals with Previous Tumor Testing (MSI and/or IHC)



+ “Studies have shown that 45%–68% of cases with unexplained defective MMR (MSI-H and/or abnormal IHC with no evidence of MLH1 promoter hypermethylation when indicated) have biallelic somatic MMR gene inactivation (sometimes referred to as double somatic MMR mutations). Biallelic somatic MMR gene inactivation is defined by having either two pathogenic sequence variants or one pathogenic sequence variant and loss of heterozygosity [LOH] in the MMR genes. ... tumor sequencing may be

helpful for individuals with tumor testing showing dMMR and no germline pathogenic variant detected. If biallelic somatic MMR gene inactivation is identified, LS is ruled out but there may still be some increased familial risk. If only one somatic pathogenic variant is found, the unidentified pathogenic variant could either be germline or somatic. If no somatic pathogenic variants are found, it is possible that the IHC results were incorrect (especially if the tumor was found to be MSS on tumor sequencing) or that none of the pathogenic variants (germline or somatic) are identifiable. In any of these cases, the individual and their close relatives still need to receive care based on their personal and/or family history." [1]

++"If strong family history (i.e. Amsterdam criteria) or additional features of hereditary cancer syndromes (multiple colon polyps) are present, additional testing may be warranted in the proband, or consider tumor testing in another affected family member due to the possibility of a phenocopy." [1]

+++ Per NCCN guidelines, MLH1 promoter mutation analysis, not BRAF testing, is recommended for endometrial tumors when IHC testing has indicated a loss of MLH1 protein.[1]

What is Lynch syndrome?

Definition

Lynch syndrome (LS), also called hereditary non-polyposis colorectal cancer (HNPCC), is a hereditary cancer syndrome that is the most common cause of inherited colon and endometrial cancer.[1-3]

Prevalence

Lynch syndrome affects approximately 1 in 35 individuals with colorectal and endometrial cancer and around 1 in 370 individuals in the general population. Lynch syndrome accounts for 3% of all colorectal and endometrial cancer cases.[1-4]

Symptoms

Lynch syndrome is associated with up to a 61% lifetime risk for colorectal cancer and up to a 57% risk for endometrial cancer.[1] The risk is also increased for the development of the following cancers: small bowel, stomach, ovarian, pancreatic, ureteral and renal pelvis, biliary tract, brain, bladder and prostate.[1,5] The average age of diagnosis for these cancers varies based on the gene that harbors the mutation.[1] Individuals may also develop skin lesions such as sebaceous adenomas and keratoacanthomas.[1,5]

Lynch syndrome should be suspected when the personal and family cancer history meets the *Revised Bethesda Guidelines* or the *Amsterdam II Criteria* (see below).[6,7] Risk prediction models, such as PREMM5, MMRpro, and MMRpredict, can be used to gauge the likelihood an individual has a mutation in a Lynch syndrome causative gene.[8]

Cause

Lynch syndrome is caused by mutations in any one of the following five genes: MLH1, MSH2, MSH6, PMS2, or EPCAM.[4,9]

Inheritance

Lynch syndrome is an autosomal dominant disorder.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Lynch syndrome mutations inherited in an autosomal recessive manner cause constitutional MMR deficiency syndrome (CMMR-D). Testing for CMMR-D is not addressed in this summary.[4,5]

Diagnosis

Lynch syndrome is diagnosed with the identification of a constitutional (germline) pathogenic variant in MLH1, MSH2, MSH6, PMS2, or EPCAM.[4]

Management

Management for individuals with Lynch syndrome include more frequent cancer screenings and the option for risk reducing surgeries. The recommended management is dependent on which gene has the mutation. The recommended management guidelines include:[1,10]

- Colonoscopy: begin at 20-25 years for individuals with mutations in MLH1, MSH2, or EPCAM. Begin at 30-35 years in individuals with mutations in MSH6 or PMS2. Colonoscopy screening may begin earlier, 2-5 years earlier than the youngest diagnosis of colon cancer in the family, but not later than the aforementioned ages. Repeat colonoscopy is recommended every 1-2 years in individuals with mutations in MLH1, MSH2, or EPCAM, and every 1-3 years in individuals with mutations in MSH6 or PMS2.
- "[T]he panel suggests that aspirin may be used to reduce the future risk of CRC in patients with LS, but it is emphasized that the optimal dose and duration of therapy should be determined on an individual basis… Discussion of individual risks, benefits, adverse effects, and childbearing plans should also be included. The panel also recommends that providers carefully review patient-specific factors that may increase the risk of aspirin therapy, as well as factors that indicate a low future cumulative risk of CRC, as some individuals may be less likely to experience significant benefit."

- Hysterectomy and bilateral salpingo-oophorectomy (BSO) are available risk-reducing surgeries. "...timing of BSO should be individualized based on whether childbearing is complete, menopause status, comorbidities, family history, and LS gene, as risks for ovarian cancer vary by pathogenic variant." For women who decline this risk-reducing surgery, endometrial cancer screening may be an option, although a proven benefit of such screenings has not been documented. Insufficient evidence exists in order to make a specific recommendation for prophylactic bilateral salpingo-oophorectomy for individuals with mutations in MSH6 and PMS2. Individuals with a PMS2 mutation "appear to be at no greater than average risk for ovarian cancer and may consider deferring surveillance and may reasonably elect not to have oophorectomy."
- Annual urinalysis at 30-35 years may be considered to screen for urothelial cancers. This screening may be considered in select individuals (e.g. those with a family history of urothelial cancer or in individuals with a mutation in MSH2).
- "Upper GI surveillance with EGD starting at age 30–40 years and repeat every 2–4 years, preferably performed in conjunction with colonoscopy... Age of initiation prior to 30 years and/or surveillance interval less than 2 years may be considered based on family history of upper GI cancers or high-risk endoscopic findings (such as incomplete or extensive gastric intestinal metaplasia, gastric or duodenal adenomas, or Barrett esophagus with dysplasia). Random biopsy of the proximal and distal stomach should at minimum be performed on the initial procedure to assess for H. pylori (with treatment indicated if H. pylori is detected), autoimmune gastritis, and intestinal metaplasia... Individuals not undergoing upper endoscopic surveillance should have one-time noninvasive testing for H. pylori at the time of LS diagnosis, with treatment indicated if H. pylori is detected. The value of eradication for the prevention of gastric cancer in LS is unknown."
- Screening for pancreatic cancer can be considered at 50 years or 10 years younger than the earliest case of pancreatic cancer diagnosis in the family but not later than 50 years. This screening can be considered in individuals with at least one first- or second-degree relative with exocrine pancreatic cancer and on the same side of the family (or presumed same side) with the mutation in the Lynch syndrome causative gene. Notably, PMS2 mutations have not shown to increase the risk for pancreatic cancer.
- "Patients with LS should consider their risk based on the LS gene and family history of prostate cancer. The NCCN Guidelines for Prostate Cancer Early Detection recommend that it is reasonable for patients with LS to consider beginning shared decision-making about prostate cancer screening at age 40 years and to consider screening at annual intervals rather than every other year."
- "The panel recommends consideration of a skin exam every 1 to 2 years with a health care provider skilled in identifying LS- associated skin manifestations. The age at which to begin surveillance cannot be recommended with certainty, and therefore can be individualized."
- "Patients should be educated regarding signs and symptoms of neurologic cancer and the importance of prompt reporting of abnormal symptoms to their physicians."

- Annual physical examination starting at 20-25 years is recommended.

Special Considerations

Historically, Lynch syndrome has included the variants Muir-Torre syndrome (one or more Lynch syndrome-associated cancers and sebaceous neoplasms of the skin) and Turcot syndrome (Lynch syndrome with glioblastoma).[4] These variant designations are considered outdated.

Test information

Introduction

Testing for Lynch syndrome may include tumor testing, known familial mutation testing, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Test Strategy

When the family Lynch syndrome mutation is known, at-risk relatives should be tested for that specific mutation only. Otherwise, genetic testing usually starts either with

sequencing and deletion/duplication analysis of the gene identified from tumor IHC results or multigene panel testing. The National Comprehensive Cancer Network has outlined a comprehensive strategy for molecular testing of Lynch syndrome.[1] The first person tested should be the relative most likely to have Lynch syndrome in the family.

Testing those with a suspected Lynch syndrome-related cancer should typically begin with microsatellite instability or immunohistochemistry testing10325 on tumor tissue. The following table lists and describes the various testing scenarios.

When ...	Then ...
tumor tests suggest Lynch syndrome	that individual should be offered genetic testing to look for a mutation that causes Lynch syndrome. IHC studies may suggest which mismatch repair gene is likely to harbor a mutation.[1,9-11]
tumor tests are normal, and there is a young age of diagnosis or a strong family history of Lynch syndrome-associated cancers is present	genetic testing may still be warranted, or tumor testing in another family member with the most suspicious cancer history may be considered.[9]
tumor screening is not possible, and the individual meets the guideline criteria	direct genetic testing may be reasonable.

Guidelines and evidence

Multiple Society Recommendations

The US Multi-Society Task Force (MSTF, 2014), the National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer (NSGC/CGA-ICC, jointly published, 2022), the National Comprehensive Cancer Network (NCCN, 2023), and the American College of Gastroenterology (ACG, 2015) have practice guidelines that addressed Lynch syndrome genetic testing. Generally, these recommendations agreed:[1,9,10,12]

- Test colorectal or endometrial tumors by microsatellite instability and/or immunohistochemistry first when tissue is available.
- Individuals with abnormal microsatellite instability and/or immunohistochemistry results (and no demonstrated BRAF mutation or hypermethylation of MLH1) should be offered genetic testing to identify a Lynch syndrome disease-causing mutation. Results from tumor testing should guide the genetic testing cascade. When tumor testing is not possible or results are inconclusive, genetic testing for an inherited mutation is indicated if an individual with a suspected Lynch syndrome-related cancer is at increased risk for Lynch syndrome based on tumor type, age at diagnosis, and/or family history. If no affected family member is available for testing, at-risk relatives can consider genetic testing if the family meets certain criteria.

However, only a mutation positive result can be clearly interpreted. Mutation-negative results must be interpreted with caution; the chance of inconclusive results is high because the family mutation may not be detectable. Once a Lynch syndrome disease-causing mutation has been identified, at-risk relatives should be offered genetic testing for that specific mutation.

Manchester International Consensus Group

The Manchester International Consensus Group (2019) stated the following regarding germline testing for Lynch syndrome in women with gynecological cancer:[13]

- "The Consensus Group strongly recommends that tumor MMR or MSI status is used to identify women for germline MMR testing. There is no evidence to advocate MSI over MMR immunohistochemistry or vice versa (grade B)."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2023) guideline for genetic/familial high-risk assessment of colorectal cancer recommended the following:[1]

- "universal screening of all CRCs and endometrial cancers to maximize sensitivity for identifying individuals with LS and to simplify care processes."
- "considering tumor screening for MMR deficiency for sebaceous neoplasms as well as the following adenocarcinomas: small bowel, ovarian, gastric, pancreatic, biliary tract, brain, bladder/urothelial, and adrenocortical cancers regardless of age at diagnosis"

Germline multigene panel testing was recommended as an alternate or additional option for Lynch syndrome screening for the following:

- "An individual with a LS-related cancer and any of the following:
  - Diagnosed <50 y
  - A synchronous or metachronous LS-related cancer regardless of age
  - 1 first-degree or second-degree relative with a LS-related cancer diagnosed <50 y
  - ≥2 first-degree or second-degree relatives with a LS-related cancer regardless of age
- Family history of any of the following:
  - ≥1 first-degree relative with a colorectal or endometrial cancer diagnosed <50 y
  - ≥1 first-degree relative with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer regardless of age
  - ≥2 first-degree or second-degree relatives with LS-related cancers, including ≥1 diagnosed <50 y

  - ≥3 first-degree or second-degree relatives with LS-related cancers regardless of age

- Increased model-predicted risk for LS"
- "Personal history of a tumor with MMR deficiency determined by PCR, NGS, or IHC diagnosed at any age"

NCCN recommended genetic testing start with the most informative person in a family. Other close family members may consider testing if a person affected with a related cancer is not available.

Society of Gynecologic Oncology

The Society of Gynecologic Oncology (SGO, 2023) recommended that all individuals diagnosed with endometrial cancer undergo molecular testing that includes assessment of mismatch repair deficiency status.[14]

Revised Bethesda Guidelines

According to the *Revised Bethesda Guidelines*, consider Lynch syndrome tumor screening when any one of the following criteria are met:[6,15]

- colorectal cancer is diagnosed before the age of 50
- presence of synchronous or metachronous colorectal cancer, or other Lynch syndrome-associated tumor***, regardless of age
- microsatellite unstable (MSI-H) tumor pathology before the age of 60, examples include
  - tumor-infiltrating lymphocytes
  - Crohn's-like lymphocytic reaction
  - mucinous or signet-ring differentiation
  - medullary growth pattern, or
  - other reported features
- colorectal cancer diagnosed in an individual with at least one first-degree relative, including parent, sibling, or child with a Lynch syndrome-related tumor***, one of whom was diagnosed before the age of 50, or
- colorectal cancer diagnosed in an individual with at least two first- or second-degree relatives with Lynch syndrome-related tumors*** at any age.

Amsterdam II Criteria

According to *Amsterdam II Criteria*, Lynch syndrome is likely when all of the following criteria are met:[7]

- there are at least three relatives with Lynch syndrome associated tumors***
- one affected relative is a first-degree relative (parent, sibling, child) of the other two
- affected relatives are in two or more successive generations
- at least one Lynch syndrome-related tumor was diagnosed before age 50, and
- FAP has been excluded on the basis of no polyposis.

Tumors must be verified by pathology.

***Lynch syndrome-associated tumors include

- colorectal
- endometrial
- small bowel
- stomach
- ovarian
- pancreatic
- ureteral and renal pelvis
- biliary tract
- brain tumors, usually glioblastomas associated with Turcot syndrome variant
- sebaceous adenomas, and
- keratoacanthomas, associated with a Muir-Torre syndrome variant.

Note This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Lynch syndrome genetic testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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