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.

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<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
</tr>
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</tbody>
</table>

What is Lynch syndrome

Definition

Lynch syndrome, also called hereditary, non-polyposis colorectal cancer (HNPCC), is a hereditary cancer syndrome that is the most common cause of colon and endometrial cancer.
Prevalence

Lynch syndrome affects approximately 1 in 35 colorectal and endometrial cancer patients and around 1 in 370 individuals in the general population. Lynch syndrome accounts for 2-4% of all colorectal cancer cases.¹⁻³

Cancer risks

Lynch syndrome is associated with an 82% lifetime risk for colorectal cancer and a 15-60% risk of endometrial cancer.⁴⁻⁵ The risk also increases for development of the following cancer types:

- small bowel
- stomach
- ovarian
- pancreatic
- ureteral and renal pelvis
- biliary tract
- brain
- sebaceous adenoma, and
- keratoacanthoma tumors.¹⁻⁵

Onset

The average ages of diagnosis for colorectal, endometrial, and gastric cancers are 44-61, 48-62, and 56 years, respectively.⁴ Ovarian cancer diagnoses are typically earlier, with an average age of diagnosis of 42.5 years, roughly one-third of cases being diagnosed before the age of 40.⁴

Diagnosis

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

Cause

Lynch syndrome is caused by mutations in any one of at least the following five genes: MLH1, MSH2, MSH6, PMS2, and EPCAM.⁴⁻⁸

Inheritance

Lynch syndrome is an autosomal dominant syndrome that is associated with a germline mutation in one of at least five genes: MLH1, MSH2, MSH6, PMS2, and EPCAM. Children of an affected individual have a 50% risk to inherit a mutation.⁴
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

**Associated syndromes**

Lynch syndrome includes 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

**Test information**

**Introduction**

Testing for Lynch syndrome may include tumor testing, gene sequencing, deletion/duplication analysis, known familial mutation testing, or multigene panel testing.

**Testing approaches**

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

<table>
<thead>
<tr>
<th>When ...</th>
<th>Then ...</th>
</tr>
</thead>
<tbody>
<tr>
<td>tumor tests suggest Lynch syndrome</td>
<td>that individual should be offered genetic testing to look for a mutation that causes Lynch syndrome.1,8-10</td>
</tr>
<tr>
<td>immunohistochemistry studies are abnormal</td>
<td>those results may suggest which mismatch repair genes is likely to harbor a mutation.</td>
</tr>
<tr>
<td>tumor tests are normal, and a strong family history of Lynch syndrome-associated cancers is present</td>
<td>genetic testing may still be warranted, or tumor testing in another family member with the most suspicious cancer history may be considered.8</td>
</tr>
<tr>
<td>tumor screening is not possible, and the individual meets the guideline criteria</td>
<td>direct genetic testing may be reasonable.</td>
</tr>
</tbody>
</table>

**Genetic testing**

Genetic testing usually starts either with sequencing and deletion/duplication analysis of the gene identified from tumor IHC results, or with a comprehensive gene panel. The National Comprehensive Cancer Network has outlined a comprehensive strategy for
molecular testing of Lynch Syndrome. The first person tested should be the relative most likely to have Lynch Syndrome in the family.

When the family Lynch syndrome mutation is known, at-risk relatives should be tested for that specific mutation only. This is often called single site mutation analysis. Detection rates approach 100%.

Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to Lynch syndrome genetic testing.

Multiple society recommendations

The US Multi-Society Task Force (2014), the National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer (NSGC/CGA-ICC, jointly published, 2012), the National Comprehensive Cancer Network (NCCN, 2018), and the American College of Gastroenterology (ACG); (2015) have practice guidelines that address Lynch syndrome genetic testing. Generally, these recommendations agree:

- 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 a patient with a suspected Lynch syndrome-related cancer meets one of the first three Bethesda Guidelines or the family meets the Amsterdam Criteria (see tables below). If no affected family member is available for testing, at-risk relatives can consider genetic testing if the family meets the Amsterdam 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.

“The Multi-Society Task Force is composed of gastroenterology specialists with a special interest in CRC, representing the following major gastroenterology professional organizations: American College of Gastroenterology, American Gastroenterological Association Institute, and the American Society for Gastrointestinal Endoscopy. Also, experts on LS from academia and private practice were invited authors of this guideline. Representatives of the Collaborative Group of the Americas on Inherited Colorectal Cancer and the American Society of Colon and Rectal Surgeons also
reviewed this manuscript. In addition to the Task Force and invited experts, the practice committees and Governing Boards of the American Gastroenterological Association Institute, American College of Gastroenterology, American Society for Gastrointestinal Endoscopy reviewed and approved this document.”

**Society of Gynecologic Oncology**

The Society of Gynecologic Oncology recommends “all women who are diagnosed with endometrial cancer should undergo systematic clinical screening for Lynch syndrome (review of personal and family history) and/or molecular screening. Molecular screening of endometrial cancer for Lynch syndrome is the preferred strategy when resources are available.” Universal molecular tumor testing for either all endometrial cancer or cancers diagnosed at age less than 60, regardless of personal or family cancer history, is a sensitive strategy for identifying women with Lynch syndrome.12

**Revised Bethesda Guidelines**

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

- 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
- 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
- at least two first- or second-degree relatives with Lynch syndrome-related tumors*** at any age.

**Amsterdam II Criteria**

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

- 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.

Criteria

Known Familial Mutation Analysis

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
• Previous Testing:
  o No previous testing for inherited Lynch syndrome mutations, AND
• Family History:
  o 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\(^1,13\)
  - Personal history of colorectal cancer (or other Lynch syndrome-related tumor\(^3\)), and
  - If colorectal cancer (see figure A):
    - MSI testing of tumor tissue shows MSI-high, or
    - IHC testing of tumor tissue detects absence of MLH1, MSH2, MSH6, and/or PMS2 encoded protein products, and
    - BRAF mutation analysis and/or MLH1 hypermethylation analysis performed if indicated (according to figure A) and not consistent with sporadic CRC (sporadic CRC is likely when the tumor has MLH1 promoter hypermethylation and/or the BRAF V600E mutation.), or
  - If other Lynch syndrome-associated tumor:
    - Endometrial cancer diagnosed before age 50, or
    - Endometrial cancer diagnosed at any age with abnormal tumor testing indicative of a mutation in a mismatch repair gene, or
    - Presence of synchronous or metachronous Lynch syndrome-associated tumors, regardless of age, or
    - Amsterdam II criteria are met:
      - \(\geq\) 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
      - \(\geq\) 2 successive generations affected, and
      - \(\geq\) 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)\textsuperscript{1,10,11}, or
- 2.5% or greater risk of Lynch syndrome based on PREMM[5],\textsuperscript{14} OR

**Predisposition Testing for Presymptomatic/Asymptomatic Individuals:**\textsuperscript{1}

- $\geq 3$ 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
  - $\geq 2$ successive generations affected, and
  - $\geq 1$ diagnosed before age 50, and

- IHC and/or Lynch syndrome genetic testing results from affected family member are unavailable, OR
- 5% or greater risk of Lynch syndrome based on one of the following mutations prediction models (MMRPro or MMRPredict)\textsuperscript{1,10,11}, OR
- 2.5% or greater risk of Lynch syndrome based on PREMM[5]\textsuperscript{14}, 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 associated with Turcot syndrome variant), sebaceous adenomas, and keratoacanthomas (associated with Muir-Torre syndrome variant).***

**Billing and reimbursement considerations**

- 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.
- Lynch syndrome genetic testing for those with colorectal cancer is generally not indicated in the absence of abnormal MSI and/or IHC results on the colorectal tumor. MSI and/or IHC became part of the standard NCCN recommended evaluation for all people with colorectal cancer under the age of 70 (at a minimum) in May 2013. As a result, most people affected with colorectal 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.
"Individuals with abnormal MSI and/or IHC tumor results and no germline mutation detected in the corresponding gene(s) may still have undetected Lynch syndrome. At this time, no consensus has been reached as to whether these patients should be managed as Lynch syndrome or managed based on personal/family history. Growing evidence suggests that the majority of these individuals with abnormal tumor results and no germline mutation found have double somatic mutations/changes in the MMR protein.
genes. Although the efficacy has not yet been proven, genetic testing of the corresponding gene(s) could be performed on tumor DNA to assess for somatic mutations. Individuals found to have double somatic mutations(changes in the MMR genes likely do not have Lynch syndrome and management should be based on personal/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."¹¹

+++ Per NCCN guidelines, only MLH1 promoter mutation analysis is recommended for endometrial tumors when IHC testing has indicated a loss of MLH1 protein.¹

References

Introduction

The following references are cited throughout the Lynch Syndrome documentation.


