Lynch Syndrome Tumor Screening - First-Tier

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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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What is Lynch syndrome tumor screening

Definition

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

- Lynch syndrome is associated with a high lifetime risk for colorectal cancer (up to 82%) and endometrial cancer (15-60%), diagnosed at an earlier than usual age. The risk is also increased for small bowel, stomach, ovarian, pancreatic, ureteral and renal pelvis, biliary tract, brain, sebaceous adenoma, and keratoacanthoma tumors.1,4,5
- Lynch syndrome is caused by mutations in the following mismatch repair genes: MLH1, MSH2, MSH6, and PMS2.4 An additional gene called EPCAM (or TACSTD1) has been found to account for about 1% of Lynch syndrome cases.4
- Lynch syndrome gene mutations are inherited in an autosomal dominant manner (children of an affected individual have a 50% risk to inherit a mutation), but family history alone is unreliable for identifying Lynch syndrome cases.1,4 Lynch syndrome mutations inherited in an autosomal recessive manner cause Constitutional MMR-Deficiency syndrome (CMMR-D).4,5
• Individuals with colorectal or endometrial cancer due to Lynch syndrome often have abnormal immunohistochemistry (IHC) and/or microsatellite instability (MSI) results on their tumors. These tests have good sensitivity and can identify individuals at sufficient risk for Lynch syndrome to warrant follow-up genetic testing.¹

• Tumor screening is generally offered to those with colorectal or endometrial cancer (see guidelines below).¹,⁶,⁷,⁸

• Identifying at-risk individuals is necessary for appropriate surveillance and risk reduction.¹

Test information

• Both immunohistochemistry and microsatellite instability evaluate formalin-fixed, paraffin-embedded tumor tissue for evidence of mismatch repair defects. Lynch syndrome is caused by mutations in mismatch repair genes.

  o **Immunohistochemistry (IHC)** detects the presence or absence of MLH1, MSH2, MSH6, ± PMS2 mismatch repair proteins.¹,⁵ Most Lynch syndrome-causing mutations result in protein truncation or absent protein expression⁷, which leads to abnormal IHC staining. As a result, IHC will detect an estimated 83%-94% of underlying Lynch syndrome mutations in colorectal tumors.²⁹ IHC has the distinct benefit of identifying the gene most likely to have a mutation.⁴,⁹ DNA testing can then be targeted to that specific gene.

  o **Microsatellite Instability (MSI)** compares normal and tumor tissue to detect microsatellite (stretches of repetitive DNA) size changes. Lynch syndrome mutations often cause the size of microsatellites to be unstable.³ When tumor tissue shows high microsatellite instability (MSI-H), it is indirect evidence of an underlying Lynch syndrome gene mutation. Depending on the panel of MSI markers, 80-91% of MLH1 and MSH2 mutations and 55-77% of MSH6 and PMS2 mutations will be detected by MSI testing.²

• No specific tumor screening strategy has been recommended, but studies suggest that both MSI and IHC are cost-effective.¹,²

• MSI and IHC together have better sensitivity for Lynch syndrome than either test alone⁴, and may be used simultaneously or sequentially.

Guidelines and evidence

• The National Comprehensive Cancer Network (NCCN, 2018) has published practice guidelines that address MSI and IHC tumor screening for Lynch syndrome:¹

  o Routine tumor testing for Lynch syndrome is supported either for all CRC patients or CRC patients diagnosed at < 70 years and also those ≥70 years who meet the Bethesda guidelines.
"IHC and/or MSI screening of all colorectal and endometrial cancers (usually from surgical resection but may be performed on biopsies) regardless of age at diagnosis or family history, has been implemented at some centers to identify individuals at risk for Lynch syndrome. This approach was recently endorsed for colorectal cancer by the Evaluation of Genomic Applications in Practice and Prevention Working Group from the CDC and shown to be cost effective."

"An alternative approach is to test all patients with CRC diagnosed prior to age 70 years plus patients diagnosed at older ages who meet the Bethesda guidelines."

This approach gave a sensitivity of 95.1% (95%CI, 89.8-99.0%) and a specificity of 95.5% (95%CI, 94.7-96.1%). This level of sensitivity was better than that of both the revised Bethesda and Jerusalem (testing all patients diagnosed with CRC at age <70) recommendations. While this new selective strategy failed to identify 4.9% of Lynch syndrome cases, it resulted in approximately 35% fewer tumors undergoing MMR testing.

"Endometrial cancer <50 y is not included in the revised Bethesda guidelines; however, recent evidence suggests that these individuals should be evaluated for Lynch syndrome."

Consider Lynch syndrome tumor screening if any one of the following are met:

- Colorectal cancer diagnosed before age 50
- Presence of synchronous or metachronous colorectal cancer, or colorectal cancer with other Lynch syndrome-associated tumors,** regardless of age
- Microsatellite unstable (MSI-H) tumor pathology before age 60 (e.g., tumor-infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet-ring differentiation, medullary growth pattern, or other reported features)
- Colorectal cancer diagnosed in a patient with at least one first-degree relative (parent, sibling, child) with a Lynch syndrome-related tumor*, one of whom was diagnosed before age 50
- Colorectal cancer diagnosed in a patient with at least two first- or second-degree relatives with Lynch syndrome-related tumors * at any age

**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 Muir-Torre syndrome variant).

An evidence-based recommendation from the Centers for Disease Control and Prevention sponsored Evaluation of Genomic Applications in Practice and Prevention Working Group (EGAPP, 2009) found sufficient evidence to recommend Lynch syndrome tumor screening to all individuals with newly diagnosed colorectal cancer since morbidity and mortality can be significantly improved for the patient and at-risk relatives through management changes once Lynch syndrome is
diagnosed. Although not yet standard of care, some centers have instituted screening for all newly diagnosed colorectal and endometrial cancer.

- A National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer (2012) Joint Practice Guideline makes the following recommendations:
  - "Microsatellite instability (MSI) and immunohistochemistry (IHC) tumor analyses should be performed on CRC or endometrial cancers as the first-line testing strategy for any patient being evaluated for Lynch syndrome (this includes individuals with CRC or endometrial cancer who meet Amsterdam I or II criteria or Bethesda guidelines)."
  - "MSI testing should include, at a minimum, the five markers included in the NCI panel."
  - "MSI and IHC should be performed on pretreated specimens."
  - "MSI and IHC can be technically challenging assays and should be performed in laboratories that have experience with these tests to minimize the possibility of false positive or false negative results."
  - "MSI and IHC should be performed, when possible, on an affected relative’s tumor when an unaffected patient is being evaluated for Lynch syndrome."
  - "Direct germline genetic testing (refers to both DNA sequencing and a technology that detects large rearrangements, insertions, deletions and duplications) may be considered on an affected or unaffected patient being evaluated for Lynch syndrome when MSI and IHC testing are not feasible."
  - This guideline also notes that "Approximately 25% of individuals with Lynch syndrome are not going to meet Amsterdam or Bethesda criteria so limiting MSI and IHC to individuals who meet these criteria only is inadequate and will miss a large number of individuals with Lynch syndrome."

- The Multi-Society Task Force (2014) recently published a consensus statement on genetic evaluation for Lynch syndrome and recommended that "Testing for MMR deficiency of newly diagnosed CRC should be performed. This can be done for all CRCs, or CRC diagnosed at age 70 years or younger, and in individuals older than 70 years who have a family history concerning for LS. Analysis can be done by IHC testing for the MLH1 / MSH2 / MSH6 / PMS2 proteins and / or testing for MSI. Tumors that demonstrate loss of MLH1 should undergo BRAF testing or analysis of MLH1 promoter hypermethylation." The Multi-Society Task Force on Colorectal Cancer additional endorsed utilizing The Colorectal Cancer Risk Assessment Tool to aid in identifying individuals with possible Lynch syndrome.
  - 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.

- The American Gastroenterology Association (AGA; 2015) recommends “testing the tumors of all patients with colorectal cancer with either immunohistochemistry (IHC) or for microsatellite instability (MSI) to identify potential cases of Lynch syndrome versus doing no testing for Lynch syndrome.” 6

- The American College of Gastroenterology (ACG; 2015) states that “All newly diagnosed colorectal cancers (CRCs) should be evaluated for mismatch repair deficiency. Analysis may be done by immunohistochemical testing for the MLH1/MSH2/MSH6/PMS2 proteins and/or testing for microsatellite instability (MSI). Tumors that demonstrate loss of MLH1 should undergo BRAF testing or analysis for MLH1 promoter hypermethylation.” 13

- 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.14

- The US Food and Drug Administration (FDA) has approved “Keytruda for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR). This indication covers patients with solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options and patients with colorectal cancer that has progressed following treatment with certain chemotherapy drugs.” 15

**Criteria**

- Testing may be considered for individuals who meet ANY of the following criteria:
  - All colorectal cancers regardless of age, OR
  - All endometrial cancers regardless of age, OR
  - Treatment with Keytruda is being considered, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy
References


15. US Food and Drug Administration. FDA approves first cancer treatment for any solid tumor with a specific genetic feature. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm560167.htm