STATE OF IOWA DEPARTMENT OF
Health AND Human
SERVICES

Genetic Testing for Lynch Syndrome
LAB-005

Iowa Medicaid Program:	Prior Authorization	**Effective Date:**	7/16/2021
Revision Number:	3	**Last Rev Date:**	7/21/2023
Reviewed By:	Medicaid Medical Director	**Next Rev Date:**	7/19/2024
Approved By:	Medicaid Clinical Advisory Committee	**Approved Date:**	7/16/2021

Descriptive Narrative

Lynch syndrome (LS) is an inherited, autosomal dominant disorder characterized by a predisposition to developing colorectal, endometrial, and other cancers. The diagnosis is based on germline mutations in one of the mismatch repair (MMR) genes - MLH1, MSH2, MSH6, and PMS2, or deletions in the EPCAM gene that silences MSH2. The function of MMR genes is to find sections of DNA that are not matched together properly and to repair that match. When a mutation occurs in one of the MMR genes, the individual's DNA becomes abnormal and predisposes certain cell types to malignant transformation.

Colorectal cancer (CRC) is the most common LS-associated cancer. Up to 4 percent of all CRC cases are associated with LS. For women who have LS, the most common extra-colonic malignancy is endometrial cancer. LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, prostate, and small intestinal cancers, as well as skin cancers including sebaceous adenomas, sebaceous carcinomas, and keratocanthomas.

The Amsterdam II criteria were developed to help identify families affected with LS. These criteria take into account family history as well as the age of the individual at the time of the diagnosis of CRC. In order to meet the Amsterdam II criteria, all of the following must be met:

1. Three or more family members with histologically confirmed LS-associated cancer, one of whom is a first-degree relative of the other two.
2. Two or more successive affected generations.
3. At least one relative with LS-associated cancer diagnosed before 50 years of age.
4. The diagnosis of familial adenomatous polyposis (FAP) has been excluded.

The Amsterdam II criteria have high specificity; however, they still miss a substantial percentage LS cases.

The Bethesda guidelines were created to help to determine if colorectal tumors should be tested and are only useful for individuals already diagnosed with cancer. The guidelines were

modified in 2005 to increase sensitivity and to include patients with endometrial cancer. Testing is considered appropriate if the individual demonstrates one or more of the following:

1. CRC or endometrial cancer in an individual younger than 50 years of age.
2. Synchronous or metachronous LS-related tumors, regardless of age.
3. CRC in an individual younger than 60 years of age with MSI-high histology (tumor-infiltrating lymphocytes, a Crohn's-like lymphocytic reaction, mucinous or signet ring differentiation, or a medullary growth pattern).
4. CRC or endometrial cancer, and an LS-related tumor in one or more first-degree relatives younger than 50 years of age.
5. CRC or endometrial cancer, and two or more first- or second-degree relatives with LS-related cancers, regardless of age

Combined use of the modified Bethesda and Amsterdam II criteria still fails to detect 22 to 28 percent of LS cases. Subsequently, computer-based screening tools were developed to improve detection. These screening tools include MMRpredict, MMRpro, and PREMM5. The models take into consideration multiple factors, including personal and family history, sex, age, and tumor information to calculate the risk of having LS. Although the positive predictive values of these tools vary greatly across studies due to differing samples, each appears to be more sensitive than the Amsterdam II and Bethesda criteria.

Definitions

MMR: mismatch repair.

PCR: polymerase chain reaction.

NGS: next generation sequencing.

IHC: immunohistochemistry.

MSI: microsatellite instability.

First-degree relative – parent, sibling, children.

Second-degree relative – grandparent, aunt, uncle, niece, nephew, grandchild, half-sibling.

Third-degree relative – great grandparent, great aunt, great uncle, great grandchild, first cousin, half-aunt, half-uncle.

Criteria

ALL requests for testing must be accompanied by genetic counseling performed by a qualified professional, such as a certified genetic counselor or oncologist. This must include the following:

1. Taking a personal and family history to assess risk of disease, **AND**
2. Education about inheritance and resources, **AND**
3. Counseling to promote informed choices and the psychological implications of undergoing testing.

Genetic testing for LS is considered medically necessary when **ONE** of the following is met:

1. Presence of a known LS pathogenic variant in the family; **OR**
2. Personal history of a tumor with MMR deficiency determined by PCR, NGS, or IHC diagnosed at any age; **OR**
3. An individual with colorectal or endometrial cancer and **ONE** the following:
   a. Diagnosed younger than 50 years of age; **OR**
   b. A synchronous or metachronous LS-related cancer; **OR**
   c. One first- or second-degree relative with an LS-related cancer diagnosed younger than 50 years of age; **OR**
   d. Two or more first- or second-degree relatives with an LS-related cancer regardless of age; **OR**
4. Family history (same side of family) with **ONE** of the following:
   a. One or more first-degree relative with a colorectal or endometrial cancer diagnosed younger than 50 years of age; **OR**
   b. One or more first-degree relative with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer; **OR**
   c. Two or more first- or second-degree relatives with LS-related cancers, including one or more diagnosed younger than 50 years of age; **OR**
   d. Three or more first- or second-degree relatives with LS-related cancers, regardless of age; **OR**
5. An individual with a 5 percent or greater risk of having an MMR gene pathogenic variant based on predictive models (e.g., PREMM5, MMRpro, MMRpredict).

All criteria are Level of Evidence Category 2A per NCCN.

Coding

The following list of codes are provided for reference purposes only and may not be all inclusive. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment, nor does the exclusion of a code imply that its association to the HCPCS/CPT code is inappropriate.

HCPCS	Description
81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis.
81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis.

HCPCS	Description
81293	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants.
81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants.
81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis.
81296	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants.
81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants.
81298	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis.
81299	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants.
81300	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants.
81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis.
81318	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants.
81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants.
81403	Molecular Pathology Procedure Level 4 (includes EPCAM (epithelial cell adhesion molecule) (e.g., Lynch syndrome), duplication/deletion analysis).

Compliance

1. Should conflict exist between this policy and applicable statute, the applicable statute shall supersede.
2. Federal and State law, as well as contract language, including definitions and specific contract provisions or exclusions, take precedence over medical policy and must be considered first in determining eligibility for coverage.
3. Medical technology is constantly evolving, and Iowa Medicaid reserves the right to review and update medical policy on an annual and as-needed basis.

Medical necessity guidelines have been developed for determining coverage for member benefits and are published to provide a better understanding of the basis upon which coverage decisions are made. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in the service area who are medical experts in the particular field, FDA and other government agency policies, and standards adopted by national accreditation organizations. Criteria are revised and updated annually, or more frequently if new evidence becomes available that suggests needed revisions.

References

Win AK. Hall MJ. Neumann CC. Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis. UpToDate. Last updated: Nov 20, 2020.

Chung DC. Rodgers LH. Gene test interpretation: Lynch syndrome genes (MLH1, MSH2, MSH6, PMS2, EPCAM). UpToDate. Last updated: Jan 08, 2021.

Lynch Syndrome - EPCAM, MLH1, MSH2, MSH6, and PMS2 Genes and Gene Panel. MCG Health Ambulatory Care Guidelines. ACG: A-0533 (AC) 24th Edition.

MolDX: Genetic Testing for Lynch Syndrome (L36793) Local Coverage Determination (LCD): Wisconsin Physicians Services. Effective date 12/26/2019.
EncoderPro Optum 360.

Genetic/Familial High-Risk Assessment: Colorectal. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology Version1.2020 - July 21, 2020.

Development of utilization management criteria may also involve research into other state Medicaid programs, other payer policies, consultation with experts and review by the Medicaid Clinical Advisory Committee (CAC). These sources may not be referenced individually unless they are specifically published and are otherwise applicable to the criteria at issue.

Criteria Change History

Change Date	Changed By	Description of Change	Version

Signature

Change Date	Changed By	Description of Change	Version

Signature

Change Date	Changed By	Description of Change	Version
7/21/2023	CAC	Annual review.	3

Signature
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Change Date	Changed By	Description of Change	Version
7/15/2022	CAC	Annual review.	2

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Change Date	Changed By	Description of Change	Version
7/16/2021	CAC	Criteria implementation.	1

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