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

I. Lynch syndrome panels, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and/or *EPCAM* sequencing and/or duplication analysis for Lynch syndrome/HNPCC is considered **medically necessary** when:

A. The member has a tumor that shows evidence of mismatch repair (MMR) deficiency (either by microsatellite instability (MSI) or loss of MMR protein expression), **OR**

B. The member has a diagnosis of a Lynch syndrome-related cancer (colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma), **AND** any of the following:

1. Diagnosed before age 50, **OR**
2. Diagnosed at any age with an additional Lynch syndrome-related cancer, **OR**
3. Diagnosed at any age with one or more first- or second-degree relatives diagnosed before age 50 with a Lynch syndrome-related cancer, **OR**
4. Diagnosed at any age with two or more first- or second-degree relatives diagnosed at any age with a Lynch syndrome-related cancer, **OR**

C. The member has a family history of **any** of the following:

1. One or more first-degree relatives diagnosed with colorectal or endometrial cancer before age 50, **OR**
2. One or more first-degree relatives diagnosed with colorectal or endometrial cancer and an additional Lynch syndrome-related cancer, **OR**

3. Two or more first- or second-degree relatives on the same side of the family diagnosed with a Lynch syndrome-related cancer, one of whom was diagnosed before age 50, **OR**

4. Three or more first- or second-degree relatives on the same side of the family diagnosed with a Lynch syndrome-related cancer, **OR**

D. The member has a 5% or greater risk of having Lynch syndrome based on one of the following variant prediction models: MMRpro, PREMM5, MMRpredict, **OR**

E. The member has a personal history of colorectal and/or endometrial cancer with a PREMM5 score of 2.5% or greater.

II. Lynch syndrome panel*, MLH1*, *MSH2*, *MSH6*, *PMS2*, and/or *EPCAM* sequencing and/or duplication analysis for Lynch syndrome/HNPCC is considered **investigational** for all other indications.

III. *MLH1, MSH2, MSH6, PMS2* and *EPCAM* mRNA sequencing analysis for the interpretation of variants of unknown significance is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance, or follow up testing without proven utility.

DEFINITIONS

1. **Close relatives** include first, second, and third degree blood relatives:

   a. **First-degree relatives** are parents, siblings, and children

   b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings

   c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins

2. **Lynch syndrome-related cancer** is defined as any of the following cancer types: colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma.

REFERENCES

1. NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric guidelines (1.2025). https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf.