Hereditary Gastrointestinal/Colorectal Cancer Susceptibility Panels

I. Genetic testing using a hereditary gastrointestinal/colorectal cancer susceptibility panel is considered **medically necessary** when:

   A. The member meets at least one of the following:

      1. The member has a personal history of, or at least one blood relative with any of the following:

         a) At least 10 adenomatous polyps, **OR**

         b) At least 2 hamartomatous polyps, **OR**

         c) At least 5 serrated polyps/lesions proximal to the rectum, **OR**

      2. The member meets testing criteria for Lynch syndrome/HNPCC *MLH1, MSH2, MSH6, PMS2,* or *EPCAM* Sequencing and/or Deletion/Duplication Analysis, **AND**

   B. The panel includes, at a minimum, sequencing of the following genes: *APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, BMPR1A, SMAD4, PTEN, STK11,* and *TP53.*

II. Genetic testing using a hereditary gastrointestinal/colorectal cancer susceptibility panel is considered **investigational** for all other indications.

III. Hereditary gastrointestinal/colorectal cancer susceptibility panel targeted 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.

NOTE: If a multigene cancer panel is performed, the appropriate panel code should be used.

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, urothelial, 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- or second-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.

RATIONALE AND REFERENCES

Hereditary Gastrointestinal/Colorectal Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN): Colorectal, Endometrial, and Gastric (1.2025)

This guideline outlines criteria for assessment for hereditary colorectal syndromes as follows:

- Polyposis: Patient with a personal history of, or a single family member with, at least 10 adenomatous polyps, at least 2 hamartomatous polyps, or at least 5 serrated polyps/lesions proximal to the rectum (p. HRS-1)
- Individuals meeting LS testing criteria (p. HRS-1, HRS-3, LS-1) (see *MLH1, MSH2, MSH6, PMS2, EPCAM* Sequencing and/or Deletion/Duplication Analysis).

NCCN also states that the CRC-risk associated genes to include in germline multigene panel testing are as follows: *APC, BMPR1A, EPCAM, MUTYH, MLH1, MSH2, MSH6, PMS2, PTEN, SMAD4, STK11,* and *TP53* (p. HRS-A 2 of 3).

Some individuals will have variants of uncertain significance (VUS); post-test counseling should include considering referral to research studies for the purpose of learning the functional impact of VUSs such as variant reclassification programs through clinical labs or registries (p. EVAL-A 8 of 9).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

DEFINITIONS

1. **Adenomatous polyposis** are conditions that cause multiple adenomas (i.e., benign polyps) in the gastrointestinal tract.
2. **Breast cancer** is a term that applies to patients with invasive cancer or ductal carcinoma in situ (DCIS).
3. **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
4. **Adjuvant treatment with olaparib therapy** may be indicated for cancer defined as
    a. Triple-negative breast cancer treated with either:
        i. Adjuvant chemotherapy with axillary node-positive disease or an invasive primary tumor greater than or equal to 2 cm on pathology analysis, **OR**
        ii. Neoadjuvant chemotherapy with residual invasive breast cancer in the breast or resected lymph nodes, **OR**
    b. Hormone receptor positive disease treated with either:

i. Adjuvant chemotherapy with four or more positive pathologically confirmed lymph nodes, **OR**

ii. Neoadjuvant chemotherapy which did not have a complete pathologic response, with a CPS+CG score [pre-treatment clinical (CS) and post-treatment pathological stage (PS), estrogen-receptor status (E) and grade (G)] of 3 or higher.

5. **High-risk prostate cancer** is defined by NCCN as an individual who has one or more of the following high-risk features, but does not meet criteria for very-high-risk features:
    a. cT3-cT4
    b. Grade Group 4 or 5
    a. PSA > 20ng/ml

6. **Juvenile polyps** are associated with Juvenile Polyposis Syndrome. These polyps are exophytic and eroded. They typically contain the following: marked edema and inflammation within the lamina propria, cystic glands filled with thick mucin, and some degree of smooth muscle proliferation.

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

8. **Maori ancestry** describes individuals who are of indigenous New Zealand ethnic background.

9. **Very-high-risk prostate cancer** is defined by NCCN as an individual who has at least two of the following:
    a. cT3-cT4
    b. PSA >40 ng/mL
    a. Grade Group 4 or 5