# PAN-CANCER HEREDITARY CANCER SUSCEPTIBILITY PANELS

A pan-cancer hereditary cancer susceptibility panel includes genes that are associated with inherited susceptibility to several different types of cancer (e.g., breast cancer, colon cancer, stomach cancer, etc.).

I. Genetic testing using a pan-cancer hereditary cancer susceptibility panel (0474U, 81432, 81433) is considered **medically necessary** when:

   A. The member is 18 years or older, **AND**

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

      1. The member meets clinical criteria for *BRCA1* and *BRCA2* sequencing and/or deletion/duplication analysis, **OR**

      2. The member meets clinical criteria for Lynch syndrome/HNPCC *MLH1, MSH2, MSH6, PMS2, or EPCAM* sequencing and/or deletion/duplication analysis, **AND**

   C. The panel includes, at a minimum, sequencing of the following genes: *BRCA1*, *BRCA2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*.

II. Genetic testing using a pan-cancer hereditary cancer susceptibility panel (0474U, 81432, 81433) is considered **investigational** for all other indications.

III. Hereditary cancer susceptibility panel targeted mRNA sequencing analysis for the interpretation of variants of unknown significance (0134U), when billed in addition, 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.

## *BRCA1* and *BRCA2* Sequencing and/or Deletion/Duplication Analysis

I. *BRCA1* and *BRCA2* (81162, 81163, 81164, 81165, 81166, 81167, 81216) sequencing and/or deletion/duplication analysis for hereditary breast and/or ovarian cancer susceptibility is considered **medically necessary** when**:**

A. The member is 18 years or older, **AND**

B. The member has a personal history of any of the following:

1. Male (sex assigned at birth) breast cancer, **OR**
2. Triple-negative breast cancer, **OR**
3. Breast cancer diagnosed at age 65 or younger, **OR**
4. Epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer), **OR**
5. Exocrine pancreatic or ampullary cancer, **OR**
6. Metastatic prostate cancer, **OR**
7. High- or very-high-risk group prostate cancer, **OR**
8. Multiple primary breast cancers (diagnosed synchronously or metachronously), **OR**

C. The member has a personal history of breast cancer **AND** <u>any</u> of the following:

1. Ashkenazi Jewish ancestry, **OR**
2. One or more close relatives with <u>any</u> of the following:

a) Female (sex assigned at birth) breast cancer diagnosed at age 50 years or younger, **OR**

b) Male (sex assigned at birth) breast cancer, **OR**

c) Ovarian cancer, **OR**

d) Pancreatic cancer, **OR**

e) Prostate cancer that is either metastatic, intermediate-risk with intraductal/cribriform histology, or high- or very-high-risk group, **OR**

3. Three or more total diagnoses of breast cancer and/or prostate cancer (any grade) on the same side of the family including the member with breast cancer, **OR**

D. The member has a first- or second-degree relative meeting any of the above criteria, **OR**

E. The member has metastatic breast cancer and is being considered for systemic treatment using PARP inhibitors, **OR**

F. The member has high-risk, HER2-negative breast cancer and is being considered for adjuvant treatment with olaparib, **OR**

G. The member's probability of having a *BRCA1* or *BRCA2* pathogenic variant is greater than 2.5% based on prior probability models (examples: Tyrer-Cuzick, BRCApro, CanRisk).

II. *BRCA1* and *BRCA2* (81162, 81163, 81164, 81165, 81166, 81167, 81216) sequencing and/or deletion/duplication analysis for hereditary breast and/or ovarian cancer susceptibility is considered **investigational** for all other indications.

III. *BRCA1/BRCA2* mRNA sequencing analysis for the interpretation of variants of unknown significance (0138U), when billed in addition, 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.

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

I. *MLH1* (81292, 81294), *MSH2* (81295, 81297), *MSH6* (81298, 81300), *PMS2* (81317, 81319), and/or *EPCAM* (81403) sequencing and/or duplication analysis for Lynch syndrome/HNPCC is considered **medically necessary** when:

A. The member has a Lynch syndrome-related cancer **and** the tumor 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, **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. *MLH1* (81292, 81294), *MSH2* (81295, 81297), *MSH6* (81298, 81300), *PMS2* (81317, 81319), and/or *EPCAM* (81403) 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 (0158U, 0159U, 0160U, 0161U, 0162U), when billed in addition, 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 on the same side of the family:
    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. **Breast cancer**: Term that applies to patients with invasive cancer or ductal carcinoma in situ (DCIS).
3. **High-risk breast cancer** is defined by NCCN as “those with ≥4

positive lymph nodes (confirmed preoperatively and/or at surgery), or 1–3 positive lymph nodes with either grade 3 disease or tumor size ≥5 cm (on pre-operative imaging and/ or at surgery)". (p. BINV-K)

4. **High-risk prostate cancer:** Defined by NCCN as an individual who has no very-high-risk features but has exactly one of the following high-risk features:
    a. cT3a, OR
    b. Grade Group 4 or Grade Group 5, **OR**
    c. PSA > 20ng/ml

5. **Very-high-risk prostate cancer:** Defined by NCCN as an individual who has at least one of the following:
    a. CT3b-cT4
    b. Primary Gleason pattern 5
    c. 2 or 3 high-risk features
    d. >4 cores with Grade Group 4 or 5

6. **Lynch syndrome-related cancer**: 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. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3.2024. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf.
2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal. Version 2.2023. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf.
3. “Use of Multi-Gene Panel Testing.” Position Statement from National Society of Genetic Counselors.

https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/use-of-multi-gene-panel-tests. Released March 14, 2017.
4. Owens DK, Davidson KW, Krist AH, et al. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA -Related Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA - J Am Med Assoc*. 2019;322(7):652-665. doi:10.1001/jama.2019.10987
5. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ampullary Adenocarcinoma. Version 2.2024.
6. Bedrosian I, Somerfield MR, Achatz MI, et al. Germline Testing in Patients With Breast Cancer: ASCO-Society of Surgical Oncology Guideline. J Clin Oncol. 2024;42(5):584-604. doi:10.1200/JCO.23.02225