

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** any of the following:
 1. Ashkenazi Jewish ancestry, **OR**
 2. One or more close relatives with any 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/criform 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 for olaparib therapy:** 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
- 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

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https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf.
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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