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 (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*, **AND**
   D. The panel does not include genes without a known association with cancer by ClinGen.

II. Genetic testing using a pan-cancer hereditary cancer susceptibility panel (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**

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

a) Male breast cancer, **OR**

b) Triple-negative breast cancer, **OR**

c) Epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer), **OR**

d) Pancreatic cancer, **OR**

e) Metastatic prostate cancer, **OR**

f) High- or very-high-risk group prostate cancer, **OR**

g) Multiple primary breast cancers (diagnosed synchronously or metachronously), **OR**

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

a) Female breast cancer diagnosed at age 50 years or younger, **OR**

b) Ashkenazi Jewish ancestry, **OR**

c) One or more close relatives with <u>any</u> of the following:

(1) Female breast cancer diagnosed at age 50 years or younger, **OR**

(2) Male breast cancer, **OR**

(3) Ovarian cancer, **OR**

(4) Pancreatic cancer, **OR**

(5) Metastatic, or high- or very-high-risk group prostate cancer, **OR**

d) Three or more total diagnoses of breast cancer in the member and/or close relatives, **OR**

e) Two or more close relatives with either breast or prostate cancer (of any grade), **OR**

3. The member does not have a personal history of a BRCA1/2-related cancer, but has a first- or second-degree relative meeting any of the above criteria, **OR**

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

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

6. The member's probability of having a *BRCA1* or *BRCA2* pathogenic variant is greater than 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*, 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 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 diagnosed with a Lynch syndrome-related cancer, **OR**

D. The member has a 5% or greater risk of Lynch syndrome 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.

NOTES AND 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**" applies to patients with invasive cancer or ductal carcinoma in situ (DCIS).
3. **High-risk** breast cancer for olaparib therapy is 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. Neoadjustant 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. **ClinGen** is a National Institutes of Health (NIH)-funded resource dedicated to building a central resource that defines the clinical relevance of genes and variants for use in precision medicine and research.

5. **High-risk-prostate cancer** is 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

6. **Very-high-risk prostate cancer** is 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

7. **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

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3. “Use of Multi-Gene Panel Testing.” Position Statement from National Society of Genetic Counselors.

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