

## Genetic Testing for Breast, Ovarian, Pancreatic, and Prostate Cancers

Policy Number: AHS – M2003 – Genetic Testing for Breast, Ovarian, Pancreatic, and Prostate Cancers	Policy Revision Date: 02/01/2026 Initial Policy Effective Date: 12/01/2024
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### I. Policy Description

*BRCA1* and *BRCA2* are two distinct tumor suppressor genes involved in a common DNA repair process.<sup>1</sup> Germline mutations of *BRCA* genes are associated with an increased risk of breast and ovarian cancer, as well as other cancer types, including pancreatic and prostate cancer to a lesser extent.<sup>2</sup>

“Prior to 2020, the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian (Breast, Ovarian, and Pancreatic as of 2020) focused largely on testing criteria for *BRCA1/2* and appropriate risk management for carriers of a *BRCA1* or *BRCA2* P/LP variant. Sections on LFS and Cowden syndrome/*PTEN* hamartoma tumor syndrome (PHTS) were also included. Based on strong evidence that genes beyond *BRCA1/2*, *TP53*, and *PTEN* confer markedly increased risk of breast and/or ovarian cancers, these Guidelines have been expanded”<sup>3</sup> to include *BRCA1*, *BRCA2*, *CDH1*, *PALB2*, *PTEN*, and *TP53* as high-penetrance breast cancer susceptibility genes, as well as some moderate-penetrance susceptibility genes. These susceptibility genes are often found on multi-gene panels, in addition to *BRCA1/2*.

### II. Related Policies

Policy Number	Policy Title
AHS-M2004	Lynch Syndrome
AHS-M2020	Molecular Diagnostics for Breast Cancer Prognosis
AHS-M2081	Genetic Testing for Li-Fraumeni Syndrome
AHS-M2087	Genetic Testing for <i>PTEN</i> Hamartoma Tumor Syndrome

### III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the “Applicable State and Federal Regulations” section of this policy document.

The following coverage criteria are designed from National Comprehensive Cancer Network (NCCN) guidelines. “NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. In this [policy], the terms males and females refer to sex assigned at birth.”

*Consideration of both maternal and paternal family histories is necessary in the evaluation of an individual’s risk of carrying a mutation in the *BRCA1* or *BRCA2* gene; each lineage must be considered*

*separately.*

- 1) For individuals without a diagnosis of a *BRCA*-related cancer who are at least 18 years of age, who have received genetic counseling, and who are in a family with a pathogenic familial gene mutation associated with breast cancer, the following testing **MEETS COVERAGE CRITERIA**:
  - a) Testing restricted to the known familial mutation.
  - b) Comprehensive genetic testing, including multi-gene panel testing, when the specific familial mutation is unknown.
- 2) For individuals who have received genetic counseling, multi-gene panel testing (see Note 1, Note 2) for gene mutations associated with breast, ovarian, pancreatic, or prostate cancer **MEETS COVERAGE CRITERIA** when **one** of the following conditions are met:
  - a) The individual has been diagnosed with breast cancer **and** meets at least one of the following conditions:
    - i) Was diagnosed before 51 years of age.
    - ii) Was diagnosed at any age with at least one of the following conditions:
      - (a) High-risk (see Note 3), HER2-negative breast cancer.
      - (b) Lobular breast cancer with a personal or family history of diffuse gastric cancer.
      - (c) Metastatic breast cancer.
      - (d) Triple negative breast cancer.
      - (e) Two or more primary breast cancer diagnoses.
      - (f) Male breast cancer.
      - (g) Has at least one close blood relative (see Note 4) with **any** of the following:
        - (i) Breast cancer before 51 years of age.
        - (ii) Breast cancer at any age in a male.
        - (iii) Ovarian cancer at any age.
        - (iv) Pancreatic cancer at any age.
        - (v) Prostate cancer that is metastatic or a high- or very-high risk group prostate cancer (see Note 5) at any age.
      - (h) Has a combined total of at least three diagnosed cancers (breast or prostate) in a single lineage of close blood relatives (see Note 4) (including the individual).
    - iii) Is of Ashkenazi Jewish ancestry
  - b) The individual has been diagnosed at any age with ovarian cancer (including fallopian tube cancer or peritoneal cancer).
  - c) The individual has been diagnosed at any age with pancreatic cancer.
  - d) The individual has been diagnosed at any age with prostate cancer with at least **one** of the following conditions:

- i) Has metastatic (Stage IVB) or node-positive (Stage IVA) prostate cancer.
  - ii) Has very high-risk or high-risk disease (see Note 5).
  - iii) Has **any** of the following family history:
    - (a) Ashkenazi Jewish ancestry.
    - (b) At least one close blood relative (See Note 4) with **any** of the following:
      - (i) Breast cancer before 51 years of age.
      - (ii) Male breast cancer at any age.
      - (iii) Ovarian cancer at any age.
      - (iv) Pancreatic cancer at any age.
      - (v) Prostate cancer that is metastatic, node positive, or a high- or very-high risk group (see Note 5) at any age.
    - (c) Two or more close blood relatives (See Note 4) with either breast or prostate cancer (any grade) at any age.
  - e) The individual has a gene mutation associated with breast, ovarian, pancreatic, or prostate cancer that was detected by tumor genomic profiling in the absence of germline mutation testing.
  - f) The individual meets testing criteria for Li-Fraumeni syndrome (LFS), Lynch syndrome, or Cowden syndrome/PTEN hamartoma tumor syndrome.
- 3) For individuals with a known family history of *BRCA*-related cancer who have received genetic counseling and are at least 18 years of age, multi-gene panel testing (see Note 1, Note 2) for gene mutations associated with breast, ovarian, pancreatic, or prostate cancer **MEETS COVERAGE CRITERIA** only if the family mutation is unknown (i.e., testing not performed or testing results are unavailable) **and** at least one of the following conditions are met:
- a) The individual has at least one first- or second-degree blood relative (see Note 4) meeting any of the above criteria for an individual with cancer, **except as noted below**:
    - i) Only first-degree relatives of an individual affected with pancreatic cancer should be offered testing.
    - b) The individual has a family member with breast, ovarian, tubal, or peritoneal cancer with positive screening results (5-year probability of 5% or greater) from a tool (see Note 6) designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (*BRCA1* or *BRCA2*).
- 4) For individuals 18 years of age or older who are of Ashkenazi Jewish ancestry and who do not meet any of the above criteria, testing for the three known founder mutations (185delAG and 5385insC in *BRCA1*; 6174delT in *BRCA2*) **MEETS COVERAGE CRITERIA**.
- 5) Testing for gene mutations associated with breast, ovarian, pancreatic, or prostate cancer **DOES NOT MEET COVERAGE CRITERIA** for **any** of the following:
- a) General population screening.

- b) Women diagnosed with breast cancer who are over 65 years of age and who have no close blood relative (see Note 4) with breast, ovarian, pancreatic, or prostate cancer, as there is a low probability that testing will have findings of documented clinical utility.
- c) Individuals diagnosed with localized prostate cancer with Gleason Score <7 and who have no close blood relative (see Note 4) with breast, ovarian, pancreatic, or prostate cancer, as there is a low probability that testing will have findings of documented clinical utility.
- d) In all other situations not specified above.

*The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.*

- 6) Testing family members for a variant of uncertain significance **DOES NOT MEET COVERAGE CRITERIA.**
- 7) For all other purposes, including, but not limited to, testing of the general population, genetic testing for susceptibility to breast, ovarian, pancreatic, or prostate cancer **DOES NOT MEET COVERAGE CRITERIA.**

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**NOTES:**

**Note 1:** For two or more gene tests being run on the same platform, please refer to AHS-R2162 Reimbursement Policy.

**Note 2:** When germline multigene panel testing is performed in individuals with breast, ovarian, pancreatic, or prostate cancer, the panel should at minimum include the following high-penetrance breast, ovarian, pancreatic, and prostate cancer susceptibility genes: *ATM, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, PALB2, PTEN, RAD51C, RAD51D, STK11, and TP53.*

**Note 3:** High-risk disease includes the following:

- The individual has four or more positive lymph nodes.
- The individual has triple negative receptor status cancer.
- The individual has cancer that had an incomplete pathologic response to chemotherapy.

**Note 4:** Close blood relatives include first-degree relatives (i.e., parents, full siblings, and children), second-degree relatives (i.e., grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings), and third-degree relatives (i.e., great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins), all of whom are on the same side of the family.

**Note 5:** Risk groups are defined in NCCN Guidelines for Prostate Cancer [https://www.nccn.org/professionals/physician\\_gls/pdf/prostate.pdf](https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf)

**Note 6:** According to the USPSTF recommendation in 2019, the risk tools evaluated by the USPSTF include the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, 7-Question Family History Screening Tool, International Breast Cancer Intervention Study instrument (Tyrrer-Cuzick), and brief versions of BRCAPro. They do not specifically state the preference of one tool over any of the others listed. According to the USPSTF, “these tools should

be used to guide referrals to genetic counseling.”<sup>4</sup>

#### IV. Table of Terminology

Term	Definition
AA	African American
ACOG	The American College of Obstetricians and Gynecologists
AJ	Ashkenazi Jewish
ALK	<i>Anaplastic lymphoma kinase</i>
ASBS	The American Society of Breast Surgeons
ASCO	American Society of Clinical Oncology
ATM	Ataxia telangiectasia mutated
ATR	<i>Ataxia telangiectasia and rad3-related protein</i>
BRAF	<i>B-raf proto-oncogene</i>
BRCA	<i>Breast cancer gene</i>
BRCA1	<i>Breast cancer gene 1</i>
BRCA2	<i>Breast cancer gene 2</i>
BRIP1	<i>BRCA1 Interacting Protein C-Terminal Helicase 1</i>
BRRS	Bannayan-Riley-Ruvalcaba syndrome
CDH1	<i>Cadherin 1</i>
CDKN2A	<i>Cyclin Dependent Kinase Inhibitor 2A</i>
CDRH	Center for Devices and Radiological Health
CHEK2	<i>Checkpoint kinase 2</i>
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid Services
CRPC	Castrate-resistant prostate cancer
CS	Cowden syndrome
dMMR	Mismatch repair deficiency
DNA	Deoxyribonucleic acid
EDTA	Ethylenediamine tetraacetic acid
EPCAM	<i>Epithelial cell adhesion molecule</i>
ER	Estrogen receptor
ERCC3	<i>Excision repair cross-complementation group 3</i>
FANCC	FA complementation group c
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FGFR2	Fibroblast growth factor receptor 2
FISH	Fluorescence in situ hybridization
GI	Gastrointestinal
GIS	Genomic instability score

HBOC	Hereditary Breast and Ovarian Cancer
<i>HER-2</i>	<i>Human epidermal growth factor 2</i>
<i>HOXB13</i>	<i>Homeobox B13</i>
HRR	Homologous recombination repair
IHC	Immunohistochemistry
<i>KRAS</i>	<i>Kristen rat sarcoma viral oncogene</i>
LDTs	Laboratory-developed tests
LFS	Li-Fraumeni syndrome
<i>MLH1</i>	<i>MutL homolog 1</i>
<i>MSH2</i>	<i>Muts homolog 2</i>
<i>MSH6</i>	<i>Muts homolog 6</i>
MSI	Microsatellite instability
<i>NBN</i>	<i>Nibrin</i>
NCCN	National Comprehensive Cancer Network
NGS	Next-generation sequencing
NICE	National Institute for Health and Care Excellence
<i>NRG1</i>	<i>Neuregulin 1</i>
<i>NTRK</i>	<i>Neurotropic tyrosine receptor kinase</i>
OCCR	Ovarian cancer cluster region
<i>PALB2</i>	<i>Partner and localizer of brca2</i>
<i>PARP</i>	<i>Poly ADP-ribose polymerase</i>
PCR	Polymerase chain reaction
PHTS	PTEN hamartoma tumor syndrome
P/LP	Pathogen/ Likely pathogen
PMS2	Pms1 homolog 2, mismatch repair system component
PR	Progesterone receptor
<i>PTEN</i>	<i>Phosphatase and tensin homolog</i>
PVs	Pathogenic variants
<i>RAD51C</i>	<i>Rad51 paralog c</i>
<i>RAD51D</i>	<i>RAD51 homolog C</i>
<i>RECQL</i>	<i>RecQ Like Helicase</i>
<i>RET</i>	<i>Ret proto-oncogene</i>
RNA	Ribonucleic acid
<i>ROS1</i>	<i>ROS Proto-oncogene 1</i>
<i>SCCOHT</i>	<i>Small cell carcinoma of the ovary (hypercalcemic type)</i>
<i>SCTAT</i>	<i>Sex cord tumor with annular tubules</i>
<i>SMARCA4</i>	<i>Swi/snf related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4</i>
<i>STK11</i>	<i>Serine/threonine kinase 11</i>

TMB	Tumor mutational burden
<i>TP53</i>	<i>Tumor protein p53</i>
USPSTF	The U.S. Preventive Services Task Force
VUS	Variants of uncertain significance

## V. Scientific Background

*BRCA1* and *BRCA2* are critical genes in the process of homologous recombination repair of double-strand DNA breaks.<sup>5</sup> Both genes are very large (occupying about 70 kb) and encode a combined total of 49 exons. They are considered tumor suppressor genes and a loss of function on either gene increases the cancer risk.<sup>6</sup> *BRCA1* is thought to regulate c-Abl kinase activity (as loss of *BRCA1* results in a constitutively activated c-Abl kinase) whereas *BRCA2* is thought to regulate Rad51, which repairs DNA damage such as chromosomal breaks.<sup>7</sup>

Different regions of mutation may confer different types of risk. For example, *BRCA2* has an area called the ovarian cancer cluster region (OCCR) in which mutations predispose the patient for ovarian cancer. Mutations outside the OCCR are more likely to result in breast cancer compared to mutations in the OCCR. On *BRCA1*, mutations closer to the 3' end of the gene may result in higher risk than mutations closer to the 5' end.<sup>8</sup> Other gene defects that affect homologous recombination include hypermethylation of *RAD51C* or *ATR* mutation. However, these are considered to have a phenotype of “BRCAness” and behave like *BRCA*-deficient genes even if the *BRCA* gene itself is normal.<sup>5</sup>

Although the probability of cancer development in carriers is variable, estimates of penetrance in individuals with a pathogenic variant in *BRCA1* or *BRCA2* range from 46% to 87% lifetime risk for breast cancer, and 16.5% to 63% lifetime risk for ovarian cancer.<sup>9</sup> *BRCA1* and *BRCA2* mutations account for about 5 – 10% of breast cancers and 10 – 18% of ovarian cancers.<sup>5</sup> *BRCA* mutations are inherited in an autosomal dominant fashion and are highly penetrant.<sup>10</sup>

It is clinically important to recognize these carriers to guide management of cancer and identify unaffected women with a *BRCA* mutation who will benefit from enhanced surveillance; in addition, recognizing carriers helps physicians tailor care to improve outcomes and more efficiently use health-care resources. Adherence to guidelines for managing cancer risk has the potential to have a significant individual and population health impact on morbidity and mortality.<sup>11</sup> For example, *BRCA* deficient cancers are often targeted for a certain class of drugs called poly(ADP-ribose) polymerase (PARP) inhibitors. These inhibitors target enzymes responsible for the base excision repair pathway. A cell can survive with the loss of either the base excision repair pathway or the homologous recombination mechanism, but not both. Since *BRCA*-deficient cells already have a faulty homologous recombination mechanism, the *BRCA*-deficient cell dies when the PARP inhibitor shuts down the base excision repair pathway. *BRCA*-deficient cells have been shown to be affected 1000 times more by these PARP inhibitors than wild-type cells.<sup>5</sup>

Numerous proprietary tests exist for the assessment of *BRCA* or its related genes such as *RAD51*. For example, gene panels such as Ambry Genetics’ panel include 25 genes such as *BRCA1*, *BRCA2*, *CHEK2*, *ATM*, *RAD51C*, and *BRIP1*. This test is performed by next generation sequencing or Sanger sequencing (except for *EPCAM*) with a turnaround time of two to three weeks. Ambry has several proprietary tests such BRCaPlus and BreastNext.<sup>12</sup> Another gene panel that has been developed to identify genetic mutations associated with inherited breast and ovarian cancers is the AmpliSeq for Illumina *BRCA* Plus,

Extended Hereditary Breast and Ovarian Research Panel. This panel assesses germline variants in 11 genes known to harbor mutations related to breast and ovarian cancer: *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, *NBN*, *CDH1*, *SMARCA4*, and *TP53*. However, though these community panels boasts the convenience of being made-to-order, Illumina warns that they do not have associated performance metrics.<sup>13</sup> myChoice CDx by Myriad Genetics, Inc. is a tumor test that determines homologous recombination deficiency status by detecting *BRCA1* and *BRCA2* (sequencing and large rearrangement) variants. This next generation sequencing-based *in vitro* diagnostic assay focuses on assessing genomic instability by using loss of heterozygosity, telomeric allelic imbalance and large-scale state transitions from tumor tissue specimens. The results can then be used to guide treatment and therapy for ovarian cancer patients with positive homologous recombination deficiency, which is defined by the presence of *BRCA1/2* mutations and/or positive Genomic Instability Score.<sup>14</sup>

### ***Clinical Utility and Validity***

A study performed by Kuchenbaecker, et al. (2017) assessed the cumulative risk of breast and ovarian cancer based on mutation position. A sample of 9856 patients was analyzed, with 6036 patients carrying a *BRCA1* mutation and 3820 with a *BRCA2* mutation. A total of 5046 patients were unaffected by either type of cancer and 4810 had breast cancer, ovarian cancer, or both at baseline. The breast cancer assessment was based on 3886 carriers, and the ovarian cancer assessment was based on 5066 women. The authors evaluated the cumulative risk of breast cancer to 80 years to be 72% for *BRCA1* mutation carriers and 69% for *BRCA2* carriers. Cumulative risk for ovarian cancer to 80 years was found to be 44% for *BRCA1* carriers and 17% for *BRCA2* carriers. *BRCA2* mutations outside the OCCR were found to have a higher risk of breast cancer than mutations inside it (hazard ratio: 1.93 for OCCR ranges 5' to c.2830, c.2831 to c.6401, c.6402 to 3) but no difference in overall ovarian cancer risk. Mutations closer to the 3' or 5' ends of *BRCA1* were found to have a higher risk of breast cancer compared to the middle third of the gene and the third closest to the 3' end had the highest hazard ratio of 1.51 compared to the third closest to the 5' end (1.43).<sup>15</sup>

A meta-analysis of 44 articles was performed to assess the difference in risk factors between *BRCA1* and *BRCA2* carriers. Factors such as breastfeeding, coffee, infertility, and more were examined between both genotypes, and the only risk factor that revealed an association of any kind was age at first live birth for *BRCA1* carriers. Breast cancer risk was found to decrease for *BRCA1* women over 30 compared to women under 30, and the same was found for women from 25-29 compared to women under 25. However, the authors stressed that more research was required.<sup>16</sup>

However, the importance of *BRCA* testing has not only been explored for lifestyle choices or transient states; factors such as ethnicity can also play a role in the predisposition of patients to breast cancer. Palmer, et al. (2020) delved into the risks of breast cancer in African American (AA) women associated with inherited mutations in breast cancer predisposition genes. Using germline DNA samples and drawing from 10 epidemiologic studies encompassing 5054 affected African American women and 4993 unaffected African American women, Palmer, et al. (2020) sequenced mutations in 23 cancer predisposition genes using a QIaseq multiplex amplicon panel and found that pathogenic mutations could be identified in 10.3% of women with estrogen receptor (ER)-negative breast cancer, 5.2% of women with ER-positive breast cancer, and 2.3% of unaffected women. Mutations in *BRCA1*, *BRCA2*, and *PALB2* were associated with an overall increased risk for breast cancer, while *RAD51D* mutations were observed specifically to be linked to higher risk of ER-negative disease. Other mutations the researchers found to be of interest were in *CHEK2*, *ATM*, *ERCC3*, *FANCC*, and *RECQL*. Thus, it was

concluded that the study corroborated the use and “validity of current breast cancer testing panels for use in AA women.”<sup>17</sup>

A study using next generation sequencing (NGS) to identify *BRCA* mutations was performed by Lang, et al. (2017) 4034 patients were screened (2991 breast cancer patients, 1043 healthy controls). *BRCA* mutations were found in 247 of the breast cancer patients or 8.3%. A total of 13.9% (16/115) of the *BRCA1* mutations were of the “c.5470\_5477del” variation, and several clinical characteristics such as high Ki67 index and high tumor grade were related to *BRCA* mutations, *BRCA2* carriers were also found to have poorer disease-free survival among HER2 positive patients.<sup>18</sup>

Tomao, et al. (2019) investigated the ability of *BRCA* mutational status on predicting hematologic toxicity with platinum-based chemotherapy. A total of 176 patients were included, with 58 *BRCA* mutation carriers (40 *BRCA1*, 18 *BRCA2*, 118 controls). The authors identified several differences in hematologic toxicity between the two groups; the *BRCA* positive group was observed to have significantly higher frequency in “thrombocytopenia (24% vs 5%), anemia (21% vs 7%;  $p = 0.006$ ) and neutropenia (62% vs 27%).” The authors also noted that granulocyte-colony stimulating growth factors injection (12% versus 1%,) and dose delay (19% versus 27%) were more likely in the *BRCA* positive group (odds ratio = 2.567 for granulocyte-colony stimulating growth factors injection and 3.860 for dose delay). Overall, the authors concluded that “germline *BRCA* ½ mutations are associated with a higher hematologic toxicity in patients with ovarian cancer who underwent platinum-based chemotherapy.”<sup>19</sup>

Yoo, et al. (2020) conducted *BRCA1/NGS* for 262 hereditary breast and ovarian cancer (HBOC) syndrome patients, and the results were confirmed by using multiplex ligation-dependent probe amplification and direct Sanger sequencing. A multigene panel test was also performed on 120 patients who did not possess *BRCA1/2* pathogenic variants but who met NCCN criteria for testing. The researchers reported that pathogenic variants in *BRCA1/2* were detected in 30 HBOC patients (11.5%), and four out of the 120 patients possessed pathogenic variants of *MSH2*, *PMS2*, *CHEK2* and *PALB2*, which were also detectable by multigene panel testing. The results suggested to the authors that “multi-gene panel testing could be a significant screening tool for HBOC patients, especially for those with a family history of cancer.”<sup>20</sup>

*BRCA* testing has been demonstrated to be potentially beneficial, even when the testing is unselected and is population-based. Manchanda, et al. (2020) examined the North London Ashkenazi-Jewish (AJ) population in a randomized controlled trial consisting of 1034 AJ women and men across two arms—one, a population-screening approach, and a second, a family history/clinical-criteria-based *BRCA* testing—to determine subsequent effects on psychological health and quality of life after providing genetic testing for three Jewish *BRCA* founder-mutations. Based on the results of the study, the researchers drew the conclusion that “Population-based AJ *BRCA* testing does not adversely affect long-term psychological wellbeing or quality-of-life, decreases anxiety and could identify up to 150% additional *BRCA* carriers.”<sup>21</sup> However, these results on the anxiety and health-anxiety of this population may be contested, for validated questionnaires were used to measure the psychological wellbeing of the participants at baseline/one year/two year/three year follow-ups. Moreover, the participants were recruited through self-referral, which may affect the internal validity of the trials.

## VI. Guidelines and Recommendations

### National Comprehensive Cancer Network (NCCN)

The NCCN guidelines titled *Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic*

Version 1.2026 address general hereditary cancer testing. Note that NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. In this guideline, the terms males and females refer to sex assigned at birth. The NCCN list the following scenarios as “clinically indicated” for genetic testing:

1. “Individual with any blood relative with a known pathogenic/likely pathogen variant in a cancer susceptibility gene” [including *BRCA1/2*]
2. “Individuals meeting the criteria below but tested negative with previous limited testing, (eg, single gene and/or absent deletion duplication analysis) and are interested in pursuing multi-gene testing”
3. “A pathogenic/likely pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline”
4. “To aid in systemic therapy and surgical decision-making”
5. “Individual who meets Li-Fraumeni syndrome (LFS) testing criteria or Cowden syndrome/PTEN hamartoma tumor syndrome testing criteria or Lynch syndrome”
6. *For personal or family history of cancer*
  - a. **Testing criteria for high-penetrance breast cancer susceptibility genes** (Specifically *BRCA1*, *BRCA2*, *CDH1*, *PALB2*, *PTEN*, *STK11* and *TP53*):
    - i. Personal history of breast cancer with specific features:
      - a. By Age of diagnosis and family history
        - (a) Diagnosed at age  $\leq 50$ y
        - (b) Diagnosed at any age:
          - Treatment indications:
            - (i) To aid in systematic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting
            - (ii) To aid in adjuvant treatment decisions with Olaparib for high-risk, HER-2 negative breast cancer
          - Pathology/histology:
            - (iii) Triple-negative breast cancer
            - (iv) Multiple primary breast cancers (synchronous or metachronous)
            - (v) Lobular breast cancer with personal or family history of diffuse gastric cancer
          - Family history:
            - (vi)  $\geq 1$  close blood relative with ANY:
              - Breast cancer at age  $\leq 50$ y
              - Male breast cancer
              - Ovarian cancer
              - Pancreatic cancer
              - Prostate cancer with metastatic or high- or very-high-risk group
            - (vii)  $\geq 3$  total diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer.
          - Ancestry:
            - (viii) Ashkenazi Jewish Ancestry
          - Male breast cancer
      - ii. Family history criteria: unaffected; or affected but does not meet above criteria

- a. Individuals with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).
- b. Individuals who have a probability >5% of a BRCA1/2 P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk).
- b. Testing for ovarian cancer susceptibility genes**
  - i. Personal history of epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age
  - ii. Personal history of non-epithelial ovarian cancer (sex-cord tumors with annular tubules [SCTAT], small cell carcinoma of the ovary (hypercalcemic type) (SCCOHT) at any age
  - iii. Family history of cancer only
    - a. An individual unaffected with ovarian cancer with a first- or second-degree blood relative with epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age
    - b. An individual unaffected with ovarian cancer who otherwise does not meet the criteria above but has a probability >5% of a BRCA1/2 pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)
- c. Testing for pancreatic cancer susceptibility genes**
  - i. Exocrine pancreatic cancer
    - a. All individuals diagnosed with exocrine pancreatic cancer including acinar cell carcinoma
    - b. First-degree relatives of individuals diagnosed with exocrine pancreatic cancer
- d. Testing for high-penetrance prostate cancer susceptibility genes**
  - i. Personal history of prostate cancer at any age with:
    - a. Metastatic (Stage IVB) or node-positive (Stage IVA) prostate cancer
    - b. Very high-risk or high-risk disease
    - c. Ancestry: Ashkenazi Jewish
  - d. Family History:
    - (a) ≥1 close blood relative with ANY:
      - (i) breast cancer at age ≤50 y
      - (ii) male breast cancer
      - (iii) ovarian cancer
      - (iv) pancreatic cancer
      - (v) metastatic, node positive, or high- or very-high risk prostate cancer
    - (b) ≥3 close blood relatives with prostate cancer (any grade) and/or breast cancer on the same side of the family including the patient with prostate cancer
  - ii. Family history criteria: unaffected; or affected but does not meet criteria above
    - a. Individual with a first-degree or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making)
- e. Testing for Li-Fraumeni Syndrome**
  - i. Individual from a family with a known TP53 pathogenic/likely pathogenic variant
  - ii. Classic Li-Fraumeni syndrome (LFS) criteria:
    - a. Combination of an individual diagnosed at age <45 years with a sarcoma AND
    - b. A first-degree relative diagnosed at age <45 years with cancer AND

- c. An additional first- or second-degree relative in the same lineage with cancer diagnosed at age <45 years, or a sarcoma at any age
- iii. Chompret criteria:
  - a. Individual with a tumor from LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma), before 46 years of age, AND at least one first- or second-degree relative with any of the aforementioned cancers (other than breast cancer if the proband has breast cancer) before the age of 56 years or with multiple primaries at any age OR
  - b. Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum with the initial cancer occurring before the age of 46 years OR
  - c. Individual with adrenocortical carcinoma, or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset, regardless of family history OR
  - d. Breast cancer before 31 years of age
- iv. Personal or family history of pediatric hypodiploid acute lymphoblastic leukemia
- v. In individuals with cancer with a pathogenic/likely pathogenic *TP53* variant identified on tumor-only genomic testing, germline testing should be considered for:
  - a. Those meeting one or more of the other LFS testing criterion above after reevaluation of personal and family history
  - b. Those diagnosed age <30 years with any cancer  
Those with clinical scenario not meeting these criteria but warranting germline evaluation per clinician discretion.
- vi. Family history criteria: unaffected; or affected but does not meet criteria above
  - a. Individual with a first-degree or second-degree untested, deceased blood relative meeting any of the criteria listed above
- f. **Testing for Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS):**
  - i. Individual from a family with a known PTEN pathogenic/likely pathogenic variant
  - ii. Individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)
  - iii. Individual meeting clinical diagnostic criteria for CS/PHTS
  - iv. Individual not meeting clinical diagnostic criteria for CS/PHTS with a personal history of:
    - a. Adult Lhermitte-Duclos disease (cerebellar tumors); or
    - b. Autism spectrum disorder and macrocephaly; or
    - c. Two or more biopsy-proven trichilemmomas; or
    - d. Two or more major criteria (one must be macrocephaly); or
    - e. Three major criteria, without macrocephaly; or
    - f. One major and  $\geq 3$  minor criteria; or
    - g.  $\geq 4$  minor criteria
  - v. Individual with a relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed
    - a. The individual must have the following:
      - (a) Any one major criterion or
        - (i) Breast cancer
        - (ii) Endometrial cancer
        - (iii) Follicular thyroid cancer

- (iv)  $\geq 3$  GI hamartomas or ganglioneuromas
- (v) Lhermitte-Duclos disease (adult)
- (vi) Macrocephaly (megalcephaly) (ie,  $\geq 97\%$ , 58 cm in adult female, 60 cm in adult male)
- (vii) Macular pigmentation of glans penis
- (viii) Mucocutaneous lesions
  - 1) Trichilemmoma ( $\geq 3$ , at least 1 biopsy-proven)
  - 2)  $\geq 3$  palmo-plantar keratotic pits and/or acral hyperkeratotic papules)
  - 3)  $\geq 3$  mucocutaneous neuromas
  - 4) Oral papillomas (particularly on tongue and gingiva) ( $\geq 3$  or 1 biopsy-proven or dermatologist diagnosed)
- (b) Two minor criteria
  - (i) Autism spectrum disorder
  - (ii) Colon cancer
  - (iii)  $\geq 3$  esophageal glycogenic acanthoses
  - (iv)  $\geq 3$  lipomas
  - (v) Intellectual disability (ie, IQ  $\leq 75$ )
  - (vi) Papillary or follicular variant of papillary thyroid cancer
  - (vii) Thyroid structural lesions (eg, adenoma, nodule[s], goiter)
  - (viii) Renal cell carcinoma
  - (ix) Single GI hamartoma or ganglioneuroma
  - (x) Testicular lipomatosis
  - (xi) Vascular anomalies (including multiple intracranial developmental venous anomalies)
- vi. PTEN pathogenic/likely pathogenic variant detected by tumor genomic testing on any tumor type in the absence of germline analysis
- vii. Family history criteria: unaffected; or affected but does not meet criteria above
  - a. Individual with a first-degree or second-degree untested, deceased blood relative meeting any of
  - b. the criteria listed above

The NCCN states that general hereditary cancer testing may be considered in the following scenario (with appropriate pre-test education and access to post-test management):

- An individual of Ashkenazi Jewish ancestry without additional risk factors.
- Personal history of serious endometrial cancer.

The NCCN states that testing for high-penetrance breast cancer susceptibility genes “may be considered in the following scenarios (with appropriate pre-test education and access to post-test management):

1. Personal history of breast cancer  $\leq 65$  y not meeting any of the above criteria. It is cautioned that the majority of those PVs will be in moderate penetrance genes, which are over-represented in older affected individuals. Access to an experienced genetic counseling team to discuss management options is particularly important in this setting.
2. Personal history of breast cancer diagnosed at any age with  $\geq 1$  close blood relative with

intermediate-risk prostate cancer with intraductal/cribriform histology.

3. Individuals (unaffected; or affected but does not meet above criteria) with a 2.5% - 5% probability of BRCA1/2 P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk).
4. Personal history of malignant phyllodes tumors."<sup>3</sup>

The NCCN states that when testing for high-penetrance breast cancer susceptibility genes, there is “a low probability (<2.5%) that testing will have findings of documented high-penetrance genes in the following scenarios:

1. Female diagnosed with breast cancer at age >65 y, with no close relative with breast, ovarian, pancreatic, or prostate cancer.
2. Diagnosed with localized prostate cancer with Gleason Score <7 and no close relative with breast, ovarian, pancreatic, or prostate cancer."<sup>3</sup>

The NCCN suggests that prior to genetic testing, the following should be taken into consideration:

- “The probability of P/LP variant detection associated with these criteria will vary based on family structure, which includes size of the family, age of the family members, early death, adoption, and number of male and female relatives. Individuals with unknown or limited family history/structure, such as fewer than 2 female first- or second-degree relatives having lived beyond age 45 in either lineage, may have an underestimated probability of familial P/LP variant detection. The estimated likelihood of P/LP variant detection may be low in families with a large number of unaffected and/or male relatives.
- Patients who have received an allogeneic bone marrow transplant or with active or recent hematologic malignancies should not have molecular genetic testing via blood, saliva, or buccal samples (due to unreliable test results from contamination or due to somatic pathogenic variants [PVs] associated with the hematologic malignancy) until other technologies are available. If available, DNA should be extracted from a fibroblast culture. If this source of DNA is not possible, buccal samples can be considered, subject to the risk of donor DNA contamination or malignant cells from the hematologic malignancy.
- If more than one family member is affected with cancers highly associated with a particular inherited cancer susceptibility syndrome, consider initial testing of a family member with youngest age at diagnosis, bilateral disease, multiple primary cancers, or other cancers associated with the syndrome, or most closely related to the proband/patient. If there are no available family members with cancer that is a cardinal feature of the syndrome in question, consider testing first- or second-degree family members affected with other cancers thought to be related to the gene in question (eg, prostate or pancreas with BRCA1/2).
- While testing an affected family member is most informative, it is also appropriate to test unaffected family members who meet testing criteria. Limitations of interpreting negative test results in unaffected individuals should be discussed.
- In children <18 years, genetic testing is generally not recommended when results would not impact medical management.
- LP variants are usually clinically managed similarly to PVs, while patients with variants of uncertain significance (VUS) and likely benign variants should be cared for based on the cancers present in

the family.

- Choice of multi-gene testing.”<sup>3</sup>

Furthermore, in the situation where the presence of a pathogenic or likely pathogenic variant is unknown, the NCCN recommends that “the testing of the unaffected individual (or of unaffected family members) is reasonable when no affected family member is available for testing. In such cases, it is most informative to test the unaffected individual or unaffected close relative with the highest likelihood of testing positive for the P/LP variant,” though “a negative test result in such cases, however, is considered indeterminate and does not provide the same level of information as when there is a known P/LP variant in the family.” The NCCN also remarks that “testing multiple family members may be indicated” when testing unaffected individuals “(in the absence of having tested affected family members)” to aid in interpreting results.<sup>3</sup>

The NCCN also recommends assessing *BRCA1/2* in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy.<sup>22</sup>

Regarding *BRCA* in ovarian cancer, the NCCN recommends testing for *BRCA1/2* mutations prior to initiating treatment for persistent/recurrent ovarian cancer since “germline and/or somatic *BRCA1/2* status informs maintenance therapy.” The NCCN notes that *BRCA* testing may be done prior to this stage.<sup>23</sup>

*BRCA* testing was also mentioned in guidelines for pancreatic adenocarcinoma. The NCCN recommends tumor/somatic gene profiling for those with “locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify clinically actionable and/or emerging alterations. These alterations include, but are not limited to: fusions (*ALK*, *NRG1*, *NTRK*, *ROS1*, *FGFR2*, and *RET*), mutations (*BRAF*, *BRCA1/2*, *KRAS*, and *PALB2*), amplifications (*HER2*), microsatellite instability (*MSI*), mismatch repair deficiency (*dMMR*), or tumor mutational burden (*TMB*) using comprehensive genomic profiling via an FDA-approved and/or validated NGS-based assay, and *HER2* overexpression via *IHC ± FISH*. RNA sequencing assays are preferred for detecting RNA fusions because gene fusions are better detected by RNA-based NGS. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible.”<sup>24</sup>

The NCCN also published guidelines regarding *BRCA* in prostate cancer. Germline genetic testing, which should include *BRCA1/2* among other genes, such as *ATM*, *PALB2*, and *CHEK2* was recommended for initial patients with prostate cancer and any of the following: “a positive family history; high-risk, very-high-risk, regional, or metastatic prostate cancer, regardless of family history; Ashkenazi Jewish ancestry; [and] a personal history of breast cancer.” The NCCN also notes that “germline genetic testing should be considered in patients with a personal history of prostate cancer and 1) intermediate-risk prostate cancer and intraductal/cribriform histology or 2) a personal history of exocrine pancreatic cancer, breast cancer, colorectal, gastric, melanoma, pancreatic cancer, upper tract urothelial cancer, glioblastoma, biliary tract cancer, and small intestinal cancer.” Moreover, the NCCN asserts that germline testing should include “*MLH1*, *MSH2*, *MSH6*, and *PMS2* (for Lynch syndrome) and homologous recombination genes *BRCA1*, *BRCA2*, *ATM*, *PALB2*, and *CHEK2*,” urging that cancer predisposition next-generation sequencing be considered.<sup>25</sup>

Regarding somatic tumor testing in risk groups,

- “Tumor testing for somatic homologous recombination gene mutations (eg, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*, *CDK12*) can be considered in patients with regional (N1) prostate cancer and is recommended for those with metastatic disease.
- Tumor testing for MSI or dMMR can be considered in patients with regional or metastatic castration-naïve prostate cancer and is recommended in the metastatic castrate-resistant prostate cancer (CRPC) setting.
- Tumor mutational burden (TMB) testing may be considered in patients with metastatic CRPC.
- Multigene molecular testing can be considered for patients with low-, intermediate-, and high-risk prostate cancer and life expectancy  $\geq 10$  years.
- The Decipher molecular assay is recommended to inform adjuvant treatment if adverse features are found post-radical prostatectomy and can be considered as part of counseling for risk stratification in patients with PSA resistance/recurrence after radical prostatectomy (category 2B).”<sup>25</sup>

The NCCN published information on *TP53* as a pathogenic/likely pathogenic variant, noting that testing for Li-Fraumeni syndrome should occur when the individual is from a family with a known *TP53* pathogenic/likely pathogenic variant. They specifically note that when this gene is “included as part of a multi-gene panel, an individual does not need to meet these testing criteria [for Li-Fraumeni syndrome]- if “testing criteria on other testing criteria pages are met.”<sup>3</sup>

### **The U.S. Preventive Services Task Force (USPSTF)**

In 2019, the USPSTF published updated recommendations. In it, they state that “the USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with breast cancer susceptibility 1 and 2 (*BRCA1/2*) gene mutations with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing.” This recommendation is intended for women with a “personal or family history of breast, ovarian, tubal, or peritoneal cancer or an ancestry associated with *BRCA1/2* gene mutation.”<sup>26</sup>

Moreover, they do not recommend (i.e. issue a D recommendation) routine screening, genetic testing, or genetic counseling for women who have no family or personal history of breast cancer or whose ancestry or ethnicity is not associated with a higher risk for potentially pathogenic *BRCA1* or *BRCA2* gene mutations.<sup>26</sup>

### **The American College of Obstetricians and Gynecologists (ACOG)**

The ACOG released guidelines in 2019 for Hereditary Cancer Syndromes and Risk Assessments. The ACOG recommends:

- Evaluating a patient’s risk of hereditary breast and ovarian cancer syndrome should be a routine part of obstetric and gynecologic practice. Initial risk evaluation should include a personal medical history and family history.
- Genetic testing is recommended when the results of a detailed risk assessment that is performed as part of genetic counseling suggest the presence of an inherited cancer syndrome for which specific genes have been identified and when the results of testing are likely to influence medical management.

- The two main genetic testing options for hereditary breast and ovarian cancer syndrome are *BRCA* mutation testing and multigene panel testing that includes both *BRCA* and other genetic mutations. Multigene panel testing may be useful when more than one gene may be associated with an inherited cancer syndrome or when a patient has a personal or family history that is consistent with an inherited cancer susceptibility, but single-gene testing has not identified a pathogenic variant.<sup>27</sup>

### **The American Society of Breast Surgeons (ASBS)**

The American Society of Breast Surgeons have released guidelines on genetic testing for hereditary breast cancer. They are as follows:

1. “Breast surgeons, genetic counselors, and other medical professionals knowledgeable in genetic testing can provide patient education and counseling and make recommendations to their patients regarding genetic testing and arrange testing”
2. “Genetic testing should be made available to all patients with a personal history of breast cancer. Recent data support that genetic testing should be offered to each patient with breast cancer (newly diagnosed or with a personal history). If genetic testing is performed, such testing should include *BRCA1/BRCA2* and *PALB2*, with other genes as appropriate for the clinical scenario and family history. For patients with newly diagnosed breast cancer, identification of a mutation may impact local treatment”
3. “Patients who had genetic testing previously may benefit from updated testing. Every patient being seen by a breast surgeon, who had genetic testing in the past and no pathogenic variant was identified, should be re-evaluated and updated testing considered. In particular, a patient who had negative germline *BRCA1* and 2 testing, who is from a family with no pathogenic variants, should be considered for additional testing.<sup>1</sup> Genetic testing performed prior to 2014 most likely would not have had *PALB2* or other potentially relevant genes included and may not have included testing for large genomic rearrangements in *BRCA1* or *BRCA2*”
4. “Genetic testing should be made available to patients without a history of breast cancer who meet NCCN guidelines. Unaffected patients should be informed that testing an affected relative first, whenever possible, is more informative than undergoing testing themselves. When it is not feasible to test the affected relative first, then the unaffected family member should be considered for testing if they are interested, with careful pre-test counseling to explain the limited value of “uninformative negative” results. It is also reasonable to order a multi-gene panel if the family history is incomplete (i.e., a case of adoption, patient is uncertain of exact type of cancer affecting family members, among others) or other cancers are found in the family history, as described above.”<sup>28</sup>

### **American Society of Clinical Oncology (ASCO)**

The ASCO recommends germline genetic testing for *BRCA1/2* for all women diagnosed with epithelial ovarian cancer. Somatic tumor testing for *BRCA1/2* should be performed in women that do not carry a germline pathogenic or likely pathogenic variant.<sup>29</sup>

ASCO also published a guideline regarding PARP inhibitors for ovarian cancer. In recommendation 2.2,

they recommend the use of “Myriad myChoice CDx” to determine *BRCA1/2* status for therapy decisions.<sup>30</sup>

In 2024, ASCO published “Germline Testing in Patients With Breast Cancer: ASCO-Society of Surgical Oncology Guideline” with the following recommendations:

- “*BRCA1/2* mutation testing should be offered to all newly diagnosed patients with breast cancer  $\leq 65$  years and select patients  $>65$  years based on personal history, family history, ancestry, or eligibility for poly(ADP-ribose) polymerase (PARP) inhibitor therapy.”
- “All patients with recurrent breast cancer who are candidates for PARP inhibitor therapy should be offered *BRCA1/2* testing, regardless of family history. *BRCA1/2* testing should be offered to women who develop a second primary cancer in the ipsilateral or contralateral breast.”
- “For patients with prior history of breast cancer and without active disease, testing should be offered to patients diagnosed  $\leq 65$  years and selectively in patients diagnosed after 65 years, if it will inform personal and family risk.”
- “Testing for high-penetrance cancer susceptibility genes beyond *BRCA1/2* should be offered to those with supportive family histories; testing for moderate-penetrance genes may be offered if necessary to inform personal and family cancer risk.”
- “Patients should be provided enough pretest information for informed consent; those with pathogenic variants should receive individualized post-test counseling. Variants of uncertain significance should not impact management, and patients with such variants should be followed for reclassification.”
- “Referral to providers experienced in clinical cancer genetics may help facilitate patient selection and interpretation of expanded testing, and provide counseling of individuals without pathogenic germline variants but with significant family history.”<sup>31</sup>

### **National Institute for Health and Care Excellence (NICE)**

The NICE updated their guidelines on familial breast cancer in 2023. In it, they maintain their *BRCA*-related recommendations from 2013, which are as follows:

“Offer genetic testing in specialist genetic clinics to a relative with a personal history of breast and/or ovarian cancer if that relative has a combined *BRCA1* and *BRCA2* mutation carrier probability of 10% or more.”

“Offer genetic testing in specialist genetic clinics to a person with no personal history of breast or ovarian cancer if their combined *BRCA1* and *BRCA2* mutation carrier probability is 10% or more and an affected relative is unavailable for testing.”

“Offer genetic testing in specialist genetic clinics to a person with breast or ovarian cancer if their combined *BRCA1* and *BRCA2* mutation carrier probability is 10% or more.”<sup>32</sup>

### **European Expert Group**

A group of 19 experts in *BRCA* testing were convened to publish this set of guidelines. These experts

came from across Europe and Israel, and participants included clinical or medical geneticists (32%), oncologists (37%), and gynaecologists (26%).

The guidelines state that with the rise of next-generation sequencing, hotspot testing instead of complete sequencing is “not acceptable,” albeit noting a possible exception of founder mutations representing >99% of pathogenic variants in a specific area.

A majority of experts (60%) voted that *BRCA* testing should be offered to all patients with metastatic breast cancer.<sup>33</sup>

In 2021, the group published guidance on *BRCA* and HRR deficiency testing for recently diagnosed patients with ovarian cancer. Consensus statements pertaining to *BRCA1/2* include (not an all-inclusive list):

1. “Tumour *BRCA1/2* testing should be carried out at primary diagnosis.
2. Tumour *BRCA1/2* testing should be carried out at disease recurrence (if not carried out earlier)
3. Germline and/or tumour *BRCA* testing should be used (in either order) to determine *BRCA* status at primary diagnosis.”<sup>34</sup>

## VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

### Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

The Center for Devices and Radiological Health of the Food and Drug Administration granted premarket approval on January 12, 2018 to BRCAAnalysis CDx<sup>®</sup>, an in vitro diagnostic device intended for the qualitative detection and classification of variants in the protein coding regions and intron/exon boundaries of the *BRCA1* and *BRCA2* genes using genomic DNA obtained from whole blood specimens collected in EDTA.<sup>35</sup> Single nucleotide variants and small insertions and deletions (indels) are identified by polymerase chain reaction (PCR) and Sanger sequencing. Large deletions and duplications in *BRCA1* and *BRCA2* are detected using multiplex PCR. Another FDA-approved device is the “FoundationFocus CDxBRCA,” which is a “next generation sequencing based in vitro diagnostic device for qualitative detection of *BRCA1* and *BRCA2* alterations in formalin-fixed paraffin-embedded (FFPE) ovarian tumor tissue.” This test is intended to be used “as an aid in identifying ovarian cancer patients for whom treatment with Rubraca (rucaparib) is being considered.”<sup>36</sup> A more recent FDA-approved device comes out of Myriad Genetics, Inc., the myChoice HRD CDx, which was approved on October 23, 2019. This test

is a “next generation sequencing-based in vitro diagnostic test that assesses the qualitative detection and classification of single nucleotide variants, insertions and deletions, and large rearrangement variants in protein coding regions and intron/exon boundaries of the BRCA1 and BRCA2 genes and the determination of Genomic Instability Score (GIS)” based off tumor tissue specimens.

#### VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81165	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81166	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81167	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81215	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
81432	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer, hereditary pancreatic cancer, hereditary prostate cancer), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants
81479	Unlisted molecular pathology procedure
0102U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (17 genes [sequencing and deletion/duplication]) Proprietary test: BreastNext® Lab/Manufacturer: Ambry Genetics®
0103U	Hereditary ovarian cancer (e.g., hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (24 genes [sequencing and deletion/duplication], EPCAM [deletion/duplication])

CPT	Code Description
	only]) Proprietary test: OvaNext® Lab/Manufacturer: Ambry Genetics®
0129U	Hereditary breast cancer–related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53) Proprietary test: BRCAplus Lab/Manufacturer: Ambry Genetics
0172U	Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score Proprietary test: myChoice® CDx Lab/Manufacturer: Myriad Genetics Laboratories, Inc
0474U	Hereditary pan-cancer (e.g., hereditary sarcomas, hereditary endocrine tumors, hereditary neuroendocrine tumors, hereditary cutaneous melanoma), genomic sequence analysis panel of 88 genes with 20 duplications/deletions using next-generation sequencing (NGS), Sanger sequencing, blood or saliva, reported as positive or negative for germline variants, each gene Proprietary test: GeneticsNow® Comprehensive Germline Panel Lab/Manufacturer: GoPath Diagnostics, Inc
0475U	Hereditary prostate cancer-related disorders, genomic sequence analysis panel using next-generation sequencing (NGS), Sanger sequencing, multiplex ligation-dependent probe amplification (MLPA), and array comparative genomic hybridization (CGH), evaluation of 23 genes and duplications/deletions when indicated, pathologic mutations reported with a genetic risk score for prostate cancer Proprietary test: ProstateNow™ Prostate Germline Panel Lab/Manufacturer: GoPath Diagnostics, Inc

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*Procedure codes appearing in policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.*

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## X. Review/Revision History

Effective Date	Summary
02/01/2026	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review necessitated the following changes to coverage criteria: CC2.d.i., broken into two subcriteria and updated to align with NCCN guidelines. Now read: "i) Has metastatic (Stage IVB) or node-positive (Stage IVA) prostate cancer. ii) Has very high-risk or high-risk disease (see Note 5)."

	<p>New CC 2.d.iii.b.ii.: “(ii) Male breast cancer at any age.”</p> <p>CC 2.d.iii.b.v., changed “tumor with intraductal/cribiform histology” to “node positive” to align with NCCN. Now reads: “(v) Prostate cancer that is metastatic, node positive, or a high- or very-high risk group (see Note 5) at any age.”</p> <p>CC3, removed “family member is unavailable for testing” and replaced with “testing not performed” from the i.e. statement. Now reads: “(i.e., testing not performed or testing results are unavailable)”</p> <p>Note 1, changed “2” to “two” for consistency across policies.</p> <p>Note 4, changed “1st”, “2nd”, and “3rd” degree to “first”, “second”, and “third” degree for consistency. Added “full” to “siblings” in “first-degree relatives (e.g., parents, full siblings, and children)” for clarity. Changed “e.g.,” to “i.e.,” as all relations are included and the list is definitive, not an example of relation. Added “i.e.,” to “third-degree relatives (i.e., great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins)” for consistency of formatting.</p> <p>Off-Cycle Coding Modification: Removed CPT code 81433 (deleted code; effective date 1/1/2025).</p> <p>Revised code description for CPT code 81432 (effective date 1/1/2025).</p>
<p>12/01/2024</p>	<p>Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review necessitated the following changes to coverage criteria:</p> <p>CC2b., c., and d. edited for clarity and consistency.</p> <p>CC3 a. edited based on NCCN updates. Close relatives is now first- or second-degree relatives, exception in 3.a.i. is now just for pancreatic cancer, does not include prostate cancer. Now reads: “a) The individual has at least one first- or second-degree blood relative (see Note 4) meeting any of the above criteria for an individual with cancer, except as noted below:</p> <p>i) Only first-degree relatives of an individual affected with pancreatic cancer should be offered testing.”</p> <p>Updated CC3.b. to clarify the 5% probability cut-off, now reads “b) The individual has a family member with breast, ovarian, tubal, or peritoneal cancer with positive screening results (5-year probability of 5% or greater) from a tool (see Note 6). . .”</p> <p>CC4 edited for clarity on which individuals of Ashkenazi Jewish ancestry can get testing. Now reads: “4) For individuals 18 years of age or older who are of Ashkenazi Jewish ancestry and who do not meet any of the above criteria, testing for the three known founder mutations (185delAG and 5385insC in BRCA1; 6174delT in BRCA2) MEETS COVERAGE CRITERIA.”</p> <p>New CC7: “7) For all other purposes, including, but not limited to, testing of the general population, genetic testing for susceptibility to breast, ovarian, pancreatic, or prostate cancer DOES NOT MEET COVERAGE CRITERIA.”</p> <p>New Notes 1-3, shifts all note numbers by 3: “Note 1: For 2 or more gene tests being run on the same platform, please refer to AHS-R2162 Reimbursement Policy.”</p> <p>“Note 2: When germline multigene panel testing is performed in individuals with breast, ovarian, pancreatic, or prostate cancer, the panel should at</p>

	<p>minimum include the following high-penetrance breast, ovarian, pancreatic, and prostate cancer susceptibility genes: ATM, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, PALB2, PTEN, RAD51C, RAD51D, STK11, and TP53.”</p> <p>“Note 3: High-risk disease includes the following:</p> <ul style="list-style-type: none"> <li>• The individual has four or more positive lymph nodes.</li> <li>• The individual has triple negative receptor status cancer. • The individual has cancer that had an incomplete pathologic response to chemotherapy.”</li> </ul> <p>Added CPT code 0474U, 0475U (effective date 7/1/2024)</p>
12/01/2024	Initial Policy Implementation