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BRCA

Policy Number: AHS – M2003 – *BRCA*	Prior Policy Name and Number, as applicable:
Policy Revision Date: 03/09/22	

I. Policy Description

BRCA1 and *BRCA2* are two distinct tumor suppressor genes involved in a common DNA repair process (Roy, Chun, & Powell, 2012). 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 (Paul & Paul, 2014).

II. Related Policies

Policy Number	Policy Title
AHS-M2020	Gene Expression Testing for Breast Cancer Prognosis
AHS-M2066	Genetic Cancer Susceptibility Using Next Generation Sequencing
AHS-M2145	General Genetic Testing, Germline Disorders
AHS-M2146	General Genetic Testing, Somatic Disorders

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 Section VII of this policy document.

Consideration of both maternal and paternal family histories is necessary in the evaluation of individuals for risk of carrying a mutation in the BRCA1 or BRCA2 gene; each lineage must be considered separately.

1) With a known familial mutation, testing for a Breast Cancer Susceptibility Gene (*BRCA) 1* or *2* gene mutation **MEETS COVERAGE CRITERIA** in an individual who has received genetic counseling and is at least 18 years of age, with any of the following conditions:

   a) Testing is limited to the known familial mutation

   b) If the specific familial mutation is unknown, BRCA panel testing is covered in accordance

with Avalon Policy AHS-M2066-Genetic Cancer Susceptibility Using Next Generation Sequencing.

2) With a diagnosis of breast cancer, testing for *BRCA 1* and *BRCA 2* gene mutations **MEETS COVERAGE CRITERIA** in an individual who has received genetic counseling and who meets any of the following criteria:

   a) Diagnosed with breast cancer and at least one of the following:

      i) Diagnosed at age ≤ 45 years of age;

      ii) Diagnosed between ages 46 and 50 years and one of the following:

         (a) An additional breast cancer diagnosed at any age;

         (b) At least one close blood relative (See Note 1) with breast, ovarian, pancreatic, or prostate cancer at any age;

         (c) An unknown or limited family history (e.g., adopted or fewer than 2 first- or second-degree female relatives surviving beyond age 45 years in either lineage)

      iii) Diagnosed with breast cancer at ≥ 51 years with 1 of the following:

         (a) At least one close blood relative (see Note 1) with ANY of the following:

            (i) Breast cancer at age ≤ 50 year or male breast cancer at any age

            (ii) Ovarian cancer at any age

            (iii) Pancreatic cancer at any age

            (iv) Metastatic, intraductal/cribriform histology, or high- over very-high risk group prostate cancer at any age (defined as Gleason score 8 or higher, PSA 20 or higher, intraductal/cribriform histology, or stage III or higher—i.e., extends through prostate capsule)

         (b) A combined total of at least three diagnoses of breast cancer in patient and/or close blood relatives (see Note 1)

         (c) At least two close blood relatives (see Note 1) with either breast or prostate cancer (any grade) at any age

      iv) Diagnosed at any age:

         (a) Of Ashkenazi Jewish ancestry; or

         (b) Lobular breast cancer with personal or family history of diffuse gastric cancer; or

         (c) Diagnosed with triple negative breast cancer; or

         (d) Diagnosed with male breast cancer; or

         (e) Diagnosed with at least one close blood relative with male breast cancer

   b) Has a history of ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age (excluding germ cell cancers)

c) Has a history of pancreatic cancer at any age (excluding neuroendocrine pancreatic cancer)

d) Has a history of prostate cancer at any age with one of the following:

i) Has a history of high- or very-high-risk group (See Note 2) prostate cancer at any age (defined as Gleason score 8 or higher, Prostate Specific Antigen (PSA) 20 or higher, intraductal/cribriform histology, or stage III or higher—i.e., extends through prostate capsule)

ii) Any personal history of prostate cancer (See Note 2) with the following family history:

(a) Is of Ashkenazi Jewish ancestry; or

(b) ≥1 close blood relative (See Note 1) with breast cancer at age ≤50 years or ovarian, pancreatic, metastatic, or intraductal/cribriform prostate cancer at any age; or

(c) Two or more close blood relatives (See Note 1) with either breast or prostate cancer of any grade at any age

e) Has a *BRCA 1 or 2* mutation detected by tumor genomic profiling in the absence of germline mutation testing

f) Patient is being considered for treatment with a PARP (PolyADP-ribose polymerase) inhibitor or for platinum therapy

g) Patient is being considered for adjuvant treatment with Olaparib for high-risk, *HER2* negative breast cancer

h) Patient meets Li-Fraumeni syndrome (LFS) or Lynch syndrome testing criteria. For multi-gene next generation sequencing panel testing, please refer to AHS-M2066-Genetic Cancer Susceptibility Using Next Generation Sequencing

i) Patient meets testing criteria for Cowden syndrome/PTEN hamartoma tumor syndrome

3) With a known family history of BRCA related cancers, testing for *BRCA 1* or *2* gene mutation **MEETS COVERAGE CRITERIA** in an individual who has received genetic counseling ONLY if the family members affected by breast, ovarian, pancreatic, metastatic or intraductal prostate cancer, fallopian tube, or primary peritoneal cancers are not available for testing AND:

a) Individual has a first- or second-degree blood relative meeting any of the above criteria for individual with cancer (if the affected relative has pancreatic or high-risk or very high-risk prostate cancer only first-degree relatives should be offered testing unless indicated for other relatives based on additional family history); or

b) Individual who have family members with breast, ovarian, tubal, or peritoneal cancer with positive screening results (probability of 5% or greater) from a tool (see Note 3) 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*); or

c) An Ashkenazi Jewish individual (see Note 4)

4) Testing for *BRCA* 1 and *BRCA* 2 **DOES NOT MEET COVERAGE CRITERIA** for the following:

a) Genetic testing in minors < 18 years of age

b) General population screening

c) Women diagnosed with breast cancer at age > 65 y, with no close blood relative (see Note 1) with breast, ovarian, pancreatic, or prostate cancer as there is a low probability that testing will have findings of documented clinical utility

d) Men diagnosed with localized prostate cancer with Gleason Score <7 and no close blood relative (see Note 1) with breast, ovarian, pancreatic, or prostate cancer as there is a low probability that testing will have findings of documented clinical utility

e) 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 a patient's illness.

5) Testing family members for a variant of unknown significance **DOES NOT MEET COVERAGE CRITERIA**.

Note 1: Close blood relatives include 1st-degree relatives (e.g., parents, siblings, and children), 2nd-degree relatives (e.g., grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings), and 3rd-degree relatives (great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins), all of whom are on the same side of the family.

Note 2: Risk groups are defined in National Comprehensive Cancer Network (NCCN) Guidelines for Prostate Cancer https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

Note 3: According to the United States Preventive Services Task Force (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 (Tyrer-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" (USPSTF, 2019).

Note 4: Testing of Ashkenazi Jewish individuals without a known familial mutation should be initially limited to the three known founder mutations (185delAG and 518insC in *BRCA1*; 617delT in *BRCA2*) if the patient being tested has no personal or family history of BRCA-related cancers.

(This would allow for members with cancer and strong family history to start with comprehensive testing over founder mutations)

IV. Table of Terminology

Term	Definition
AA	African American
ACOG	The American College of Obstetricians and Gynecologists
AJ	Ashkenazi-Jewish
ASBS	The American Society of Breast Surgeons

ASCO	American Society of Clinical Oncology
ATM	Ataxia telangiectasia mutated
BRCA	*Breast cancer gene*
BRCA1	*Breast cancer gene 1*
BRCA2	*Breast cancer gene 2*
CDH1	*cadherin 1*
CDRH	Center for Devices and Radiological Health
CHEK2	*Checkpoint kinase 2*
CLIA ’88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid
CRPC	Castrate-resistant prostate cancer
DNA	Deoxyribonucleic acid
EDTA	Ethylenediamine tetraacetic acid
ER	Estrogen receptor
FANCC	FA complementation group c
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
GIS	Genomic instability score
HBOC	Hereditary Breast and Ovarian Cancer
HER-2	*Human epidermal growth factor 2*
LDTs	Laboratory-developed tests
LFS	Li-fraumeni syndrome
MMR	Mismatch repair
MSH2	*Muts homolog 2*
NBN	*Nibrin*
NCCN	National Comprehensive Cancer Network
NGS	Next generation sequencing
NICE	National Institute for Health and Care Excellence
OCCR	Ovarian cancer cluster region
PALB2	*Partner and localizer of brca2*
PARP	*Polyadp-ribose polymerase*
PCR	Polymerase chain reaction
PMS2	Pms1 homolog 2, mismatch repair system component
PR	Progesterone receptor
PTEN	*Phosphatase and tensin homolog*
RAD51C	*Rad51 paralog c*
RAD51D	*RAD51 homolog C*
RECQL	*Recq Like Helicase*

SMARCA4	*Swi/snf related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4*
TP53	*Tumor protein p53*
USPSTF	The U.S. Preventive Services Task Force

V. Scientific Background

BRCA1 and *BRCA2* are critical genes in the process of homologous recombination repair of double-strand DNA breaks (Walsh, 2015). 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 (Pan & Xie, 2017). *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 (Yoshida & Miki, 2004).

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 (Meric-Bernstam et al., 2013). 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 (Walsh, 2015).

The overall prevalence of disease related mutations in these genes is estimated to be 1 in 300 for *BRCA1* and 1 in 800 for *BRCA2* (NCCN, 2020). 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 (Petrucelli, Daly, & Pal, 2016). *BRCA1* and *BRCA2* mutations account for about 5 – 10% of breast cancers and 10 – 18% of ovarian cancers (Walsh, 2015). *BRCA* mutations are inherited in an autosomal dominant fashion and are highly penetrant (Isaacs & Peshkin, 2020).

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 (Buchanan et al., 2017). 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 (Walsh, 2015).

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 2-3 weeks. Ambry has several proprietary tests such BRCAplus and BreastNext (Ambry, 2020). 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 (Illumina, 2021). 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 (Myriad Genetics, 2021).

Clinical Validity and Utility

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. 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) (Kuchenbaecker et al., 2017).

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 (Friebel, Domchek, & Rebbeck, 2014).

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" (Palmer et al., 2020).

A study using next generation sequencing (NGS) to identify *BRCA* mutations was performed by Lang et al. 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%. 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 (Lang et al., 2017).

Tomao et al. (2019) investigated the ability of *BRCA* mutational status on predicting hematologic toxicity with platinum-based chemotherapy. 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* 1/2 mutations are associated with a higher hematologic toxicity in patients with ovarian cancer who underwent platinum-based chemotherapy" (Tomao et al., 2019).

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" (Yoo et al., 2020).

BRCA testing has been demonstrated to be potentially beneficial, even when the testing is unselected and 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" (Manchanda et al., 2020). 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/1-year/2-year/3-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 guidelines titled *Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Version 2.2022* 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) that are interested in pursuing multi-gene testing"
3. "A mutation 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. *Personal history of cancer*
    - Breast cancer with at least one of the following:
        - Diagnosed at age ≤45y; or
        - Diagnosed at age 46 – 50y with:
            - Unknown or limited family history; or
            - multiple primary breast cancers (synchronous or metasynchronous); or
            - ≥1 close blood relative with breast, ovarian, pancreatic, or prostate cancer at any age
        - Diagnosed at ≥ 51 y with:
            - ≥1 close blood relative with ANY:
                i. Breast cancer at age ≤ 50 year or male breast cancer at any age
                ii. Ovarian cancer at any age
                iii. Pancreatic cancer at any age
                iv. Metastatic, intraductal/cribriform histology, or high- over very-high risk

group prostate cancer at any age
- ≥3 total diagnoses of breast cancer in patient and/or close blood relatives
- ≥2 close blood relatives with either breast or prostate cancer (any grade) at any age

- At any age:
  - To aid in systematic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting; or
  - To aid in adjuvant treatment decisions with Olaparib for high-risk, HER-2 negative breast cancer; or
  - Triple-negative breast cancer; or
  - Lobular breast cancer with personal or family history of diffuse gastric cancer; or
  - Male breast cancer; or
  - ≥1 close blood relative with male breast cancer

- Ashkenazi Jewish Ancestry
- Epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age
- Exocrine pancreatic cancer at any age
- Prostate cancer at any age with:
  - Metastatic, intraductal/cribriform histology, or high- or very-high-risk group
- Any NCCN risk group with the following family history:
  - Ashkenazi Jewish ancestry; or
  - ≥1 close relative with breast cancer at age ≤50y, or ovarian, pancreatic, metastatic or intraductal/cribriform prostate cancer at any age; or
  - ≥2 close relatives with either breast or prostate cancer (any grade) at any age
- A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline
- Individual who meets Li-Fraumeni Syndrome (LFS) testing criteria or Cowden syndrome/PTEN hamartoma tumor syndrome testing criteria
- To aid in systemic therapy decision-making, such as for *HER2*-negative metastatic breast cancer

7. *Family history of cancer*
   - An affected or unaffected individual with a first- or second- degree blood relative meeting any of the criteria listed above (except for individuals who meet criteria only for systemic therapy decision-making)
     - If the affected relative has pancreatic cancer or prostate cancer (metastatic, intraductal/cribriform, or NCCN Guidelines for Prostate Cancer – High- or Very-High-Risk Group), only first-degree relatives should be offered testing unless indicated for other relatives on additional family history.
   - An affected or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models (e.g. Tyrer-Cuzick, BRCAPro, CanRisk)

Testing may also be considered in the following scenarios (with appropriate pre-test education and access to post-test management):

1. Personal history of breast cancer < 60 y not meeting any of the above criteria may approach a 2.5% probability of having a PV, based on recent data. It is cautioned that many of those PVs will be in moderate penetrance genes, which are over-represented in older affected individuals, and which data on appropriate management are often lacking. Access to an experienced genetic counseling team to discuss management options is particularly important in this setting.
2. An affected or unaffected individual who otherwise does not meet any of the above criteria but with a 2.5%-5% probability of *BRCA 1/2* pathogenic variant based on prior probability models (e.g. Tyrer-Cuzick, BRCAPro, CanRisk).

There is a low probability (<2.5%) that testing will have findings of documented clinical utility in the following scenarios:

1. Female diagnosed with breast cancer at age >60 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 (NCCN, 2022b)

The NCCN suggests that prior to genetic testing,

"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*)" (NCCN, 2022b)

In addition, "Testing for unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed (NCCN, 2022b)"

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) should only be considered when no affected family member is available for testing. In such cases, the unaffected individual or unaffected close relative with the highest likelihood of testing positive for the pathogenic or likely pathogenic variant should be tested," though "A negative test result in such cases, however, is considered indeterminate." 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 (NCCN, 2022b).

The NCCN also writes that "In the case of *BRCA*-related breast/ovarian cancer, if no family member with breast or ovarian cancer is living, consideration can be given testing first- or

second-degree family members affected with cancers thought to be related to the pathogenic or likely pathogenic variant in question (eg prostate or pancreatic cancer)"(NCCN, 2022b).

The NCCN also recommends assessing *BRCA1/2* in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy (NCCN, 2022a).

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 (NCCN, 2020, 2021, 2022c).

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 uncommon mutations," including testing for mutations in *BRAF*, *BRCA1/2*, *HER2*, *KRAS*, and *PALB2* genes, fusions in *ALK*, *NRG1*, *NTRK*, *ROS1* genes, and mismatch repair (MMR) deficiency, detected by "tumor IHC [immunohistochemistry], PCR [polymerase chain reaction], or NGS". NCCN also notes that "Poly (ADP-ribose) polymerase inhibitors provide a promising avenue of treatment for cancers associated with *BRCA1/2* mutations" (NCCN, 2022d).

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] intraductal histology." Moreover, the NCCN asserts that "Family history for known germline variants and genetic testing for germline variants 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. However, in general, the NCCN believes that "Genetic testing in the absence of family history or clinical features (eg, high- or very-high-risk prostate cancer) may be of low yield" (NCCN, 2022e).

With regard to 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." All testing recommendations should also be considered among those with metastatic castrate-resistant prostate cancer (CRPC) (NCCN, 2022e).

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" (NCCN, 2022b).

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

In 2019, the USPSTF updated their 2014 recommendation (Moyer, 2014). 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" (USPSTF, 2019).

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 (USPSTF, 2019).

The American College of Obstetricians and Gynecologists (ACOG)

The ACOG in 2019 recommended:

- 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.

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.1 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" (Manahan et al., 2019).

American Society of Clinical Oncology (ASCO)

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 (Konstantinopoulos et al., 2020).

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 (Tew et al., 2020).

National Institute for Health and Care Excellence

NICE updated their guidelines on familial breast cancer in 2019. 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" (NICE, 2019).

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 (Singer et al., 2019).

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: http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

A. 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 (FDA, 2018) granted premarket approval on 1/12/2018 to BRACAnalysis CDx® is 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. 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 "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" (FDA, 2016). 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.

B. Centers for Medicare & Medicaid Services (CMS)

- L36082 MolDX: BRCA1 and BRCA2 Genetic Testing: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=36082&ver=66&bc=0
- A56854 Billing and Coding: MolDX: BRCA1 and BRCA2 Genetic Testing: https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleId=56854&ver=23
- 90.2 Next Generation Sequencing (NGS): https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=372&ncdver=2&bc=0

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81162	*BRCA1* (*BRCA1*, DNA repair associated), *BRCA2* (*BRCA2*, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)
81163	*BRCA1* (*BRCA1*, DNA repair associated), *BRCA2* (*BRCA2*, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81164	*BRCA1* (*BRCA1*, DNA repair associated), *BRCA2* (*BRCA2*, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81165	*BRCA1* (*BRCA1*, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81166	*BRCA1* (*BRCA1*, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81167	*BRCA2* (*BRCA2*, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81212	*BRCA1* (*BRCA1*, DNA repair associated), *BRCA2* (*BRCA2*, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81215	*BRCA1* (*BRCA1*, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	*BRCA2* (*BRCA2*, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	*BRCA2* (*BRCA2*, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family

CPT	Code Description
S0265	Genetic counseling, under physician supervision, each 15 minutes
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

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

IX. Evidence-based Scientific References

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