Corporate Medical Policy

BRCA AHS - M2003

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Description of Procedure or Service

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).

Related Policies:

Gene Expression Testing for Breast Cancer Prognosis AHS- M2020

General Genetic Testing, Germline Disorders AHS-M2145

General Genetic Testing, Somatic Disorders AHS-M2146

Genetic Cancer Susceptibility Using Next Generation Sequencing AHS-M2066

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for BRCA testing when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When BRCA is covered

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

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 BRCA 2 gene; each lineage must be considered separately.

1. *BRCA 1* and *2* testing should be offered for individuals meeting any of the criteria described in 2 through 4 below if the individual has received genetic counseling.

2. *BRCA 1* and *2* testing in an individual from a family with a known deleterious *BRCA 1/BRCA 2* gene mutation, is considered **medically necessary** and is limited to the known familial mutation. If the specific familial mutation is unknown, testing for large genomic rearrangements of *BRCA1 and/or BRCA2*, is considered **medically necessary.**

3. *BRCA 1* and *2* testing is considered **medically necessary** when an individual with cancer meets any of the following criteria:
    a) Has a history of ovarian carcinoma, fallopian tube, or primary peritoneal cancer at any age (excluding germ cell cancers)
    b) Has a history of male breast cancer at any age
    c) Has a history of metastatic or intraductal prostate cancer with radiographic evidence of or biopsy-proven disease at any age
    d) Has a personal history of high-grade prostate cancer with Gleason score ≥7 at any age AND at least one of the following:
        i. .≥1 close blood relative (See Note 1) with breast cancer at age <50 years, ovarian carcinoma, pancreatic, metastatic or intraductal prostate cancer; OR
        ii. Two close blood relatives (See Note 1) with breast cancer, or prostate cancer of any grade at any age; OR
        iii. Is of Ashkenazi Jewish ancestry (See Note 4).
    e) Has a personal history of exocrine pancreatic cancer at any age
    f) Diagnosed with breast cancer at age ≤ 45 years of age
    g) Diagnosed with breast cancer between ages 46 and 50 years and one of the following:
        i. An additional breast cancer at any age
        ii. At least one close blood relative (See Note 1) with breast, ovarian, pancreatic, or prostate cancer at any age (defined as Gleason Score 8 or
        iii. 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)
    h. Diagnosed with breast cancer at any age and one of the following:
        i. At least one close blood relative (See Note 1) with:
            1. Breast cancer diagnosed by age 50 years: OR
            2. Ovarian carcinoma (including fallopian tube cancer or peritoneal cancer) at any age (excluding germ cell cancers); OR
            3. Male breast cancer at any age; OR
            4. Metastatic or intraductal high or very high risk group (See Note 4) 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); OR
            5. Pancreatic cancer at any age (excluding neuroendocrine pancreatic cancer
        ii. A combined total of at least three diagnoses of breast cancer at any age in patient and/or in combination with any blood relatives (See Note 1).
    i. Diagnosed with breast cancer at age ≤ 60 years **and** triple negative breast cancer (estrogen receptor/ ER negative, progesterone receptor/ PR negative and human epidermal growth factor/HER-2 negative)

j. An individual with ethnicity associated with high mutation frequency (as in Ashkenazi Jewish persons) no additional family history may be required * (See Note 4).
k. Has a BRCA 1 or 2 mutation detected by tumor profiling in the absence of germline mutation testing
l. Patient is being considered for treatment with a PARP (PolyADP-ribose polymerase) inhibitor or for platinum therapy.

4. Testing for individuals without cancer (note the significant limitation interpreting test results in persons unaffected by cancer) is considered **medically necessary** ONLY if 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) Individuals 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*).

When BRCA is not covered

Testing for BRCA 1 and BRCA 2 is considered **not medically necessary** for the following:

a) General population screening
b) Women diagnosed with breast cancer at age > 65 years, with no close 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
c) Men diagnosed with localized prostate cancer with Gleason Score <7 and no close 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) In all other situations not specified above

Testing family members for a variant of unknown significance is considered **investigational.**

*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 NCCN Guidelines for Prostate Cancer
http:// https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

*Note 3: 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 (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).

*Note 5: For multi-gene next generation sequencing panel testing that includes *BRCA1* and *BRCA2* please refer to AHS-M2066-Genetic Cancer Susceptibility Using Next Generation Sequencing.

Policy Guidelines

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, 2020b). 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, tailor care to improve outcomes, and more efficiently use health-care resources. This has the potential to have a significant individual and population health impact on morbidity and mortality if these women adhere to guidelines for managing cancer risk (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 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).

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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.

State and Federal Regulations, as applicable

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.

Guidelines and Recommendations

National Comprehensive Cancer Network (NCCN, 2020a, 2020b, 2020f, 2021a, 2021b)

NCCN guidelines titled *Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Version 2.2021* 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. *Personal history of cancer*
    - Breast cancer with at least one of the following:
        - Diagnosed at age ≤45 years; or
        - Diagnosed at age 46 – 50 years with:
            - Unknown or limited family history; or
            - A second breast cancer diagnosed at any age; or
            - ≥1 close blood relative with breast, ovarian, pancreatic, or prostate cancer
        - Diagnosed at age ≤60 years with triple negative breast cancer;
        - Diagnosed at any age with:
            - Ashkenazi Jewish ancestry; or
            - ≥1 close blood relative with breast cancer diagnosed at age ≤50 years, or ovarian, pancreatic, metastatic, intraductal/cribriform histology, or high- or very-high risk group prostate cancer at any age; or
            - ≥3 additional diagnoses of breast cancer in patient and/or in close blood relatives
        - Diagnosed at any age with male breast cancer
    - 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 ≤50 years, 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

4. *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. Multiple primary breast cancers, first diagnosed between the ages of 50 and 65 years
2. An Ashkenazi Jewish individual
3. An affected or unaffected individual who otherwise does not meet any of the above criteria but with a 2.5%-5% probability of a *BRCA1/2* 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. Women diagnosed with breast cancer at age >65 years, with no close relative with breast, ovarian, pancreatic, or prostate cancer
2. Men diagnosed with localized prostate cancer with Gleason Score <7 and no close relative with breast, ovarian, pancreatic, or prostate cancer (NCCN, 2020d)

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, 2020d)

When there is a known deleterious mutation in a family member, the NCCN recommends that genetic testing in additional family members should be limited to known familial mutations.

In patients with unknown familial *BRCA* mutation and who meet testing criteria, the NCCN suggests starting testing in the affected family member first because this individual has the highest likelihood of a positive result. NCCN recommends that "unless the affected individual is a member of an ethnic group for which particular founder pathogenic or likely pathogenic variants are known, comprehensive genetic testing (i.e. full sequencing of the genes and detection of large gene rearrangements) should be performed by commercial or academic laboratories that are clinically approved or validated." (NCCN, 2020b)

For individuals with family histories consistent with a pattern of hereditary breast and/or ovarian cancer on both the maternal and paternal sides, NCCN states that "the possibility of a second pathogenic or likely pathogenic mutation in the family should be considered, and full sequencing may be indicated, even if a mutation has already been identified in a relative" (NCCN, 2020b,

2020c).

Furthermore, in the situation of an unaffected family member with a significant family history, 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. 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, 2020d)

NCCN also mentions that "certain large genomic rearrangements are not detectable by a primary sequencing assay, thereby necessitating supplementary testing in some cases… Therefore, the NCCN Guidelines Panel emphasizes the need for comprehensive testing, which encompasses full *BRCA1*/2 sequencing and detection of large gene rearrangements" (NCCN, 2020b, 2020c).

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, 2020b).

The NCCN also recommends assessing *BRCA1/2* in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy (NCCN, 2020a).

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, 2020b, 2020e, 2021a).

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, 2020f).

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 patients with prostate cancer and: "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, 2021b).

With regards to somatic tumor testing in risk groups, "Tumor testing for somatic homologous recombination gene mutations (eg, *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2*) can be considered in patients with regional or metastatic cancer." All testing recommendations should also be considered among those with metastatic castrate-resistant prostate cancer (CRPC) (NCCN, 2021b).

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, 2019) recommend:

- 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 (Manahan et al.,2019) 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."

American Society of Clinical Oncology (ASCO) (Konstantinopoulos et al., 2020; Tew et al., 2020)

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, 2019)

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 (Singer et al., 2019)

A group of 19 experts in *BRCA* testing were convened to publish this set of guidelines. These experts came from all across Europe and included occupations such as 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).

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81162, 81163, 81164, 81165, 81166, 81167, 81212, 81215, 81216, 81217, 96040, S0265. 0172U

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Medical Director review 4/2019

Medical Director review 5/2019

Specialty Matched Consultant Advisory Panel 8/2019

Medical Director review 4/2020

Specialty Matched Consultant Advisory Panel 8/2020

Medical Director review 1/2021

Medical Director review 4/2021

Specialty Matched Consultant Advisory Panel 8/2021

Policy Implementation/Update Information

1/1/2019	New policy developed. BCBSNC will provide coverage for BRCA when it is determined to be medically necessary and criteria are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)
4/16/19	Reviewed by Avalon 4th Quarter 2018 CAB. Clarified "When Covered" section bullets 3. & 4, added Note 1. Medical Director review 4/2019. (lpr)

5/3/19 Under "When Covered" section 3.f. revised the statement by deleting the following segment: "at any age with ≥1 first-, second-, or third-degree relative on same side of family with ovarian carcinoma at any age or breast cancer ≤50 y or two relatives with breast, pancreatic, or prostate cancer with Gleason score ≥7 or metastatic at any age." Medical Director review 4/30/2019. (lpr)

5/14/19 Reviewed by Avalon 1st Quarter 2019 CAB. Extensive revisions under When Covered section regarding personal and family history of cancer based on updated NCCN guidelines. Removed wording "Individual has a third-degree relative with breast cancer and/or ovarian carcinoma…" from the criteria on testing for individuals without cancer. Under When Not Covered section, added Notes 1-4. Reordered the notes for clarity, added Note 1 concerning ovarian cancer excluding germline tumors, and added a Note 4 concerning what tools are recommended by the USPSTF for clarity. Medical Director review 5/2019. Notification given 5/14/19 for effective date 7/16/19. (lpr)

10/1/19 Specialty Matched Consultant Advisory Panel review 8/21/2019. No change to policy statement. Coding table deleted from Billing/Coding section. Medical Director review 8/2019. (lpr)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)

3/10/20 Under "When Covered" section 1. age limit of 18 removed. No change to policy intent. (lpr)

5/12/20 Reviewed by Avalon 1st Quarter 2020 CAB. Medical Director review 4/2020. Removed a. age requirement of 18 years in When Not Covered section. Added "at any age" and "intraductal" for specific indications throughout When Covered section. Added related policies in Description section and updated references. (lpr)

9/8/20 Specialty Matched Consultant Advisory Panel review 8/19/2020. No changes to policy statement. (lpr)

2/9/21 Off-cycle review by Avalon. Under "When Covered" section added exocrine to statement 3.e.; reworded statement 3.l.; reworded Note 1 for clarity. Added CPT code 0172U to Billing/Coding section. Extensive updates to Policy Guidelines section. Updated references. Medical Director review 1/2021. (lpr)

5/4/21 Reviewed by Avalon 1st Quarter 2021 CAB. Medical Director review 4/2021. Under "When Not Covered" section added two non-covered indications: c. Women diagnosed with breast cancer at age >65 years, with no close relative 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 relative with breast, ovarian, pancreatic, or prostate cancer as there is a low probability that testing will have findings of documented clinical utility. Clarified items in "When Covered" section with no content changes. Updated Policy Guidelines section as well as References. Under Description section added related policy AHS-M2066 Genetic Cancer Susceptibility Using Next Generation Sequencing. Reordered and clarified *Notes 1-5. **Notification 5/4/21 for effective date 7/13/21.** (lpr)

9/7/21 Specialty Matched Consultant Advisory Panel review 8/18/2021. No change to policy statement. (lpr)