

Corporate Medical Policy

BRCA AHS - M2003

File Name:	brca
Origination:	1/2019
Last CAP Review:	8/2020
Next CAP Review:	8/2021
Last Review:	1/2021

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

*****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.*

BRCA AHS - M2003

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 *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, (See Note 1) fallopian tube, or primary peritoneal cancer at any age
 - 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 2) with breast cancer at age < 50 years, ovarian carcinoma (See Note 1), pancreatic cancer or metastatic or intraductal prostate cancer; OR
 - ii. Two close blood relatives (See Note 2) with breast cancer, or prostate cancer of any grade at any age; OR
 - iii. Is of Ashkenazi Jewish ancestry (See Note 3).
 - 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 2) with breast, ovarian, pancreatic, high-grade (Gleason score > 7) prostate cancer, or intraductal prostate at any age
 - iii. An unknown or limited family history
 - h) Diagnosed with breast cancer at any age and one of the following:
 - i. At least one close blood relative (See Note 2) with:
 1. Breast cancer diagnosed by age 50 years; OR
 2. Ovarian carcinoma (See Note 1) at any age; OR
 3. Male breast cancer at any age; OR
 4. Metastatic or intraductal prostate cancer at any age; OR
 5. Pancreatic cancer at any age
 - 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 2).
 - 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 3).
 - k) Has a *BRCA 1* or 2 mutation detected by tumor profiling in the absence of germline mutation testing

BRCA AHS - M2003

1. Patient is being considered for treatment with a PARP (PolyADP-ribose polymerase) inhibitor.

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 (See Note 1), 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 relative meeting any of the criteria in #3, OR
 - b) Women who have family members with breast, ovarian, tubal, or peritoneal cancer with positive screening results from a tool (See Note 4) 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) In all other situations not specified above

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

*Note 1: Ovarian cancer excluding germ cell tumors

*Note 2: 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 3: 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 testing is negative for founder mutations, comprehensive genetic testing may be considered. Comprehensive genetic testing can also be considered if ancestry also include non-Ashkenazi Jewish relatives or if other *BRCA*-related criteria are met. In addition, before August 2006, testing for large deletions and rearrangements was not performed, thus some patients with familial breast cancer who had negative *BRCA* testing before this time may consider repeat testing for the rearrangements.

*Note 4: According to the USPSTF recommendation in 2013, the risk tools include the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, and FHS-7. They do not specifically state the preference of one tool over any of the others listed; however, the USPSTF specifically states, “To determine which patients would benefit from *BRCA* risk assessment, primary care providers should not use general breast cancer risk assessment models (for example, the National Cancer Institute Breast Cancer Risk Assessment Tool, which is based on the Gail model) because they are not designed to determine which women should receive genetic counseling or *BRCA* testing (USPSTF, 2013).” The USPSTF does not specifically list what constitutes an increased risk within the recommendation.

Policy Guidelines

BRCA1 and *BRCA2* are critical genes in the process of homologous recombination repair of double-strand DNA breaks (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, 2018). Although the probability

BRCA AHS - M2003

of cancer development in carriers is variable, estimates of penetrance in individuals with a pathogenic variant in *BRCA1* or *BRCA2* range from 41% to 90% lifetime risk for breast cancer, and 8% to 62% lifetime risk for ovarian cancer (Petruccioli, Daly, & Pal, 2016).

BRCA1 and *BRCA2* mutations account for about 5 – 10% of breast cancers and 10 – 18% of ovarian cancers (Walsh, 2015). 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).

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 BRCAAnalysis 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, 2020c, 2020d, 2020e)

NCCN guidelines titled *Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Version 1.2021* list the following scenarios as “clinically indicated” for genetic testing:

1. “Individual from a family with a known pathogenic/likely pathogen variant in a cancer susceptibility gene” [including *BRCA1/2*]
2. Individuals meeting the criteria below but 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 ≤45y; or
 - Diagnosed at age 46 – 50y 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 y with triple negative breast cancer;
 - Diagnosed at any age with:
 - Ashkenazi Jewish ancestry; or
 - ≥1 close blood relative with breast cancer diagnosed at age ≤50y, 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

BRCA AHS - M2003

- Any NCCN risk group with the following family history:
 - Ashkenazi Jewish ancestry; or
 - ≥ 1 close relative with breast cancer at age ≤ 50 y, 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 y
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 y, 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, 2020b)

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).

BRCA AHS - M2003

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, 2020b)

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).

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).

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, 2020d).

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.” 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, 2020e).

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

BRCA AHS - M2003

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.”

BRCA AHS - M2003

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

ACOG. (2019). Practice Bulletin No. 182 Summary: Hereditary Breast and Ovarian Cancer Syndrome. *Obstet Gynecol*, 130(3), 657-659. doi:10.1097/aog.0000000000002285

BRCA AHS - M2003

- Ambry. (2020). OvaNext. Retrieved from <https://www.ambrygen.com/clinician/genetic-testing/3/oncology/ovanext>
- Buchanan, A. H., Voils, C. I., Schildkraut, J. M., Fine, C., Horick, N. K., Marcom, P. K., . . . Skinner, C. S. (2017). Adherence to Recommended Risk Management among Unaffected Women with a BRCA Mutation. *J Genet Couns*, 26(1), 79-92. doi:10.1007/s10897-016-9981-6
- FDA. (2018). Premarket Approval (PMA) 	BRCAAnalysis CDx. from Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P140020s012>
- Friebel, T. M., Domchek, S. M., & Rebbeck, T. R. (2014). Modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: systematic review and meta-analysis. *J Natl Cancer Inst*, 106(6), dju091. doi:10.1093/jnci/dju091
- Isaacs, C., & Peshkin, B. N. (2020, September 9). Cancer risks and management of BRCA1/2 carriers without cancer. Retrieved from <https://www.uptodate.com/contents/cancer-risks-and-management-of-brca1-2-carriers-without-cancer>
- Konstantinopoulos, P. A., Norquist, B., Lacchetti, C., Armstrong, D., Grisham, R. N., Goodfellow, P. J., . . . Annunziata, C. M. (2020). Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. *Journal of Clinical Oncology*, JCO.19.02960. doi:10.1200/JCO.19.02960
- Kuchenbaecker, K. B., Hopper, J. L., Barnes, D. R., Phillips, K. A., Mooij, T. M., Roos-Blom, M. J., . . . Olsson, H. (2017). Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *Jama*, 317(23), 2402-2416. doi:10.1001/jama.2017.7112
- Lang, G. T., Shi, J. X., Hu, X., Zhang, C. H., Shan, L., Song, C. G., . . . Shao, Z. M. (2017). The spectrum of BRCA mutations and characteristics of BRCA-associated breast cancers in China: Screening of 2,991 patients and 1,043 controls by next-generation sequencing. *Int J Cancer*, 141(1), 129-142. doi:10.1002/ijc.30692
- Manahan, E. R., Kuerer, H. M., Sebastian, M., Hughes, K. S., Boughey, J. C., Euhus, D. M., . . . Taylor, W. A. (2019). Consensus Guidelines on Genetic Testing for Hereditary Breast Cancer from the American Society of Breast Surgeons. *Ann Surg Oncol*, 26(10), 3025-3031. doi:10.1245/s10434-019-07549-8
- Meric-Bernstam, F., Gutierrez-Barrera, A. M., Litton, J., Mellor-Crummey, L., Ready, K., Gonzalez-Angulo, A. M., . . . Arun, B. K. (2013). Genotype in BRCA-associated breast cancers. *Breast J*, 19(1), 87-91. doi:10.1111/tbj.12056
- Moyer, V. A. (2014). Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*, 160(4), 271-281. doi:10.7326/m13-2747
- NCCN. (2020a, 9/8/20) Breast Cancer, V6 2020. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
- NCCN. (2020b, 9/8/20). Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Version 1.2021. *NCCN Clinical Practice Guidelines in Oncology*. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf
- NCCN. (2020c, 3/11/20). Ovarian Cancer Including Fallopian Tube Cancer and Peritoneal Cancer V1 2020. *NCCN Clinical Practice Guidelines in Oncology*. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

BRCA AHS - M2003

NCCN. (2020d, October 23 2020). Pancreatic adenocarcinoma V1 2021. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

NCCN. (2020e, May 21 2020). Prostate Cancer V2 2020. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

NICE. (2019). Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. Retrieved from <https://www.nice.org.uk/guidance/cg164/chapter/Recommendations#genetic-testing>

Pan, Z., & Xie, X. (2017). BRCA mutations in the manifestation and treatment of ovarian cancer. *Oncotarget*, *8*(57), 97657-97670. doi:10.18632/oncotarget.18280

Paul, A., & Paul, S. (2014). The breast cancer susceptibility genes (BRCA) in breast and ovarian cancers. *Front Biosci (Landmark Ed)*, *19*, 605-618.

Petrucci, N., Daly, M., & Pal, T. (2016). BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer (Text) (Publication no. <https://www.ncbi.nlm.nih.gov/books/NBK1247/>). Retrieved 2016/12/15, from University of Washington, Seattle <https://www.ncbi.nlm.nih.gov/pubmed/>

Roy, R., Chun, J., & Powell, S. N. (2012). BRCA1 and BRCA2: different roles in a common pathway of genome protection. *Nat Rev Cancer*, *12*(1), 68-78. doi:10.1038/nrc3181

Singer, C. F., Balmaña, J., Bürki, N., Delaloge, S., Filieri, M. E., Gerdes, A.-M., . . . Evans, D. G. (2019). Genetic counselling and testing of susceptibility genes for therapeutic decision-making in breast cancer—2014;an European consensus statement and expert recommendations. *European Journal of Cancer*, *106*, 54-60. doi:10.1016/j.ejca.2018.10.007

Tew, W. P., Lacchetti, C., Ellis, A., Maxian, K., Banerjee, S., Bookman, M., . . . Kohn, E. C. (2020). PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline. *J Clin Oncol*, *38*(30), 3468-3493. doi:10.1200/jco.20.01924

Tomao, F., Musacchio, L., Di Mauro, F., Boccia, S. M., Di Donato, V., Giacotti, A., . . . Benedetti Panici, P. (2019). Is BRCA mutational status a predictor of platinum-based chemotherapy related hematologic toxicity in high-grade serous ovarian cancer patients? *Gynecol Oncol*, *154*(1), 138-143. doi:10.1016/j.ygyno.2019.04.009

USPSTF. (2013, 12/2013). Final Recommendation Statement: BRCA-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing. Retrieved from <https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing>

USPSTF. (2019, August 20). BRCA-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing. Retrieved from <https://www.uspreventiveservicestaskforce.org/uspstf/document/RecommendationStatementFinal/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing>

Walsh, C. S. (2015). Two decades beyond BRCA1/2: Homologous recombination, hereditary cancer risk and a target for ovarian cancer therapy. *Gynecol Oncol*, *137*(2), 343-350. doi:10.1016/j.ygyno.2015.02.017

Yoshida, K., & Miki, Y. (2004). Role of BRCA1 and BRCA2 as regulators of DNA repair, transcription, and cell cycle in response to DNA damage. *Cancer Sci*, *95*(11), 866-871.

Medical Director review 4/2019

BRCA AHS - M2003

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

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

BRCA AHS - M2003

Billing/Coding section. Extensive updates to Policy Guidelines section. Updated references. Medical Director review 1/2021. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.