BRCA AHS - M2003

**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.
2. *BRCA 1* and *BRCA 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 *BRCA 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 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 *BRCA 2* mutation detected by tumor profiling in the absence of germline mutation testing
Testing for mutations in the \textit{BRCA1} and \textit{BRCA2} genes is limited to once per lifetime unless a patient with ovarian cancer is undergoing treatment with a PARP (PolyADP-ribose polymerase) inhibitor or a patient has HER2-negative recurrent or metastatic breast cancer eligible for single agent therapy with a PARP inhibitor (eg. Olaparib), testing for additional clinically relevant mutations is warranted.

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 (\textit{BRCA1} or \textit{BRCA2}).

\textbf{When BRCA is not covered}

Testing for \textit{BRCA 1} and \textit{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 germline 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 \textit{BRCA1}; 617delT in \textit{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 \textit{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 \textit{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 \textit{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 \textit{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 proteins 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 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 (Petrucelli, 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 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 guidelines (2018) state that “Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. Testing of an individual without cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.” NCCN testing criteria:

- Individual from a family with a known deleterious BRCA1/BRCA2 gene mutation
- Personal history of breast cancer and one or more of the following
  - Diagnosed <45 years
  - Diagnosed <50 years with:
    - An additional breast cancer primary
    - >1 close blood relative with breast cancer at any age
    - >1 close relative with pancreatic cancer
    - >1 relative with prostate cancer
    - An unknown or limited family history
  - Diagnosed <60 years with triple negative breast cancer
  - Diagnosed at any age with
    - >2 close relatives with breast cancer, pancreatic cancer or prostate cancer
    - >1 close blood relative with breast cancer diagnosed <50 years
    - >1 close blood relative with ovarian cancer
    - A close male blood relative with breast cancer
    - An individual of ethnicity associated with higher mutation
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frequency (Ashkenazi Jewish) no additional family history may be required

- Personal history of ovarian cancer
- Personal history of male breast cancer
- Personal history of high grade prostate cancer at any age with >1 close blood relative with ovarian carcinoma at any age or breast cancer <50 years or two relatives with breast, pancreatic or prostate cancer at any age
- Personal history of metastatic prostate cancer
- Personal history of pancreatic cancer at any age with >1 close blood relative with ovarian carcinoma at any age or breast cancer <50 years or two relatives with breast, pancreatic or prostate cancer at any age
- Personal history of pancreatic cancer and Ashkenazi Jewish ancestry
- BRCA ½ pathogenic mutation detected by tumor profiling on any tumor type in the absence of germline mutation analysis
- Family history only:
  - First or second degree blood relative meeting any of the above criteria
  - Third degree blood relative who has breast cancer and/or ovarian cancer and who has >2 close blood relatives with breast cancer and/or ovarian carcinoma

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 to start 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 with known founder gene mutations, comprehensive genetic testing (i.e. full gene sequencing and detection of large gene rearrangements) should be performed”.

For individuals with significant family history on both maternal and paternal sides, NCCN states that “the possibility of a second deleterious mutation should be considered, and full sequencing may be indicated, even if a mutation has already been identified in a relative”. Furthermore, in the situation of an unaffected family member with a significant family history, NCCN recommends that “the testing of the unaffected individual should be considered only when no affected family member is available for testing. A negative test result in such cases, however, is considered indeterminate.”

NCCN also mentions that “certain large genomic rearrangements are not detectable by a primary sequencing assay, there necessitating supplementary testing in some areas. Therefore, the panel emphasizes the need for comprehensive testing, which encompasses full BRCA1 and BRCA 2 sequencing and detection of large gene rearrangements.”

The U.S. Preventive Services Task Force (Moyer, 2014) recommends:

“that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with 1 of several screening tools 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). Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing. (B recommendation) The USPSTF recommends against routine genetic counseling or BRCA testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the BRCA1 or BRCA2 genes.”

The American College of Obstetricians and Gynecologists (ACOG, 2017) 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 (ASBS, 2017) recommends genetic testing

1. Breast surgeons, CGCs and other trained cancer-liaison staff with in-depth knowledge of genetic testing indications, implications, and limitations can provide genetic testing services and recommendations to their patients. Use of specialized risk-assessment services and certified genetic counselors when patient history and test results are more complex is encouraged. Testing qualified patients can include BRCA1 and BRCA2 only, or additional genes (i.e., panel testing) related to hereditary breast cancer, so long as it is within guidelines, and the provider feels comfortable with recommendations.

2. Patients with a personal history of breast cancer: Always obtain information about family history of cancer. Ideally, a three-generation pedigree including maternal and paternal lineage should be obtained. This information can be used to guide the type of testing to be performed and the selection of patients who may benefit from further counseling with a CGC. Patients with a personal history of breast cancer meet criteria for genetic testing with any of the following characteristics:
   a. Age onset of breast cancer ≤50
   b. Triple-negative tumor (ER-PR-HER2-) and age ≤60
   c. Ashkenazi Jewish heritage and breast cancer at any age
   d. Two or more primary breast cancers (cancers can be asynchronous, synchronous, bilateral, or multicentric)
   e. First-degree relative with breast cancer age ≤50
   f. Two relatives on the same side of the family with breast cancer and/or pancreatic cancer
   g. Family or personal history of ovarian cancer, fallopian cancer, or primary peritoneal cancer
   h. Male breast cancer i. Known mutation carrier in the family

3. Patients without a personal history of breast cancer: Patients should be made aware that testing an affected relative first when available can be more informative than testing themselves since a negative result will not give them more insight into their family history. If an affected relative is not available, patients should be reminded of limitations of testing. Ideally, a three-generation pedigree including maternal and paternal lineage should be obtained. This information can be used to guide the type of testing to be performed and the selection of patients who may benefit from further
counseling with a CGC. Patients without a personal history of breast cancer meet criteria for genetic testing for the following family history:

- a. First- or second-degree relative with early age onset of breast cancer ≤45
- b. Ashkenazi Jewish heritage and family history of breast cancer at any age
- c. Two or more primary breast cancers (cancers can be asynchronous, synchronous, bilateral, or multicentric) in a single family member
- d. Two or more relatives on the same side of the family with breast cancer and/or pancreatic cancer
- e. Family or personal history of ovarian cancer, fallopian cancer, or primary peritoneal cancer
- f. Male breast cancer
- g. Known mutation carrier in the family

Referral for cancer genetic consultation is recommended by the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors for individuals with a personal or family history indicative of a hereditary form of cancer.

**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

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**


FDA. (2018). Premarket Approval (PMA) &#x9; BRACAnalysis 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


Medical Director review 4/2019
Medical Director review 5/2019
Specialty Matched Consultant Advisory Panel 8/2019
Medical Director review 4/2020

Policy Implementation/Update Information

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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)

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.