

Corporate Medical Policy

Genetic Testing for Breast and Ovarian Cancer

File Name: genetic_testing_for_breast_and_ovarian_cancer
Origination: 8/1997
Last CAP Review: 8/2011
Next CAP Review: 8/2012
Last Review: 1/2012

Description of Procedure or Service

Several genetic syndromes with an autosomal dominant pattern of inheritance that feature breast cancer have been identified. Of these, hereditary breast and ovarian cancer (HBOC) and some cases of hereditary site-specific breast cancer have in common causative mutations in BRCA genes. Families suspected of having HBOC syndrome are characterized by an increased susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, and ovarian cancer at any age. Other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, laryngeal cancer, occur more frequently in HBOC families. Hereditary site-specific breast cancer families are characterized by early onset breast cancer with or without male cases, but without ovarian cancer. For this policy, both will be referred to collectively as hereditary breast and/or ovarian cancer.

Germline mutations in the BRCA1 and BRCA2 genes are responsible for the cancer susceptibility in the majority of HBOC families, especially if ovarian cancer or male breast cancer are features. However, in site-specific breast cancer, BRCA mutations are responsible for only a proportion of affected families, and research to date has not yet identified other moderate or high-penetrance gene mutations that account for disease in these families. BRCA gene mutations are inherited in an autosomal dominant fashion through either the maternal or paternal lineage; It is possible to test for abnormalities in BRCA1 and BRCA2 genes to identify the specific mutation in cancer cases, and to identify family members with increased cancer risk. Family members without existing cancer who are found to have BRCA mutations can consider preventive interventions for reducing risk and mortality.

CHEK2 (cell cycle checkpoint kinase2) is also involved with DNA repair and human cancer predisposition like BRCA1 and BRCA2. CHEK2 is normally activated in response to DNA double-stranded breaks. CHEK2 regulates the function of BRCA1 protein in DNA repair and also exerts critical roles in cell cycle control and apoptosis. The CHEK2 mutation, 1100delC in exon 10 has been associated with familial breast cancers.

******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 Genetic Testing for Breast and Ovarian Cancer when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

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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.

Members must have benefits for the anticipated surgery and meet the guidelines for the testing to be covered.

When Genetic Testing for Breast and Ovarian Cancer is covered

- A. Genetic testing of cancer-affected individuals may be medically necessary under any of the following circumstances:
 - 1. Women who are affected with breast cancer or pancreatic cancer, and are from families with a high risk of BRCA1 or BRCA2 mutation as defined in the Policy Guidelines, OR
 - 2. Women who are affected with both breast cancer and either epithelial ovarian cancer, cancer of the fallopian tube, or primary peritoneal cancer, OR;
 - 3. Women who do not have a known family history of breast, epithelial ovarian, fallopian tube, or primary peritoneal cancer, but are affected with the following:
 - a. early onset breast cancer, OR
 - b. two breast primary cancers with the first cancer diagnosis occurring prior to age 50;
 - c. triple negative breast cancer (neither express estrogen receptor and progesterone receptor, nor overexpress HER2) diagnosed at <age 60;
 - d. epithelial ovarian/fallopian tube/primary peritoneal cancer at any age, OR;
 - 4. Men affected with breast cancer at any age, OR;
 - 5. Those affected with breast, epithelial ovarian, fallopian tube, or primary peritoneal cancer and who are from an ethnic background, e.g., Ashkenazi Jewish descent, associated with deleterious founder mutations.
- B. Genetic testing of unaffected adults may be considered medically necessary under any of the following circumstances:
 - 1. Unaffected individuals (male or female) from families with a known BRCA1 or BRCA2 mutation, OR;
 - 2. Unaffected individuals from families with a high risk of BRCA1 or BRCA2 mutation based on a family history (See Policy Guidelines), where it is not possible to test an affected family member for a mutation, OR;
 - 3. Unaffected individuals in populations at risk for specific founder mutations due to ethnic background, e.g., Ashkenazi Jewish descent, with one or more relatives with breast, epithelial ovarian, fallopian tube, or primary peritoneal cancer at any age.
- C. Testing for genomic rearrangements of the BRCA1 and BRCA2 genes may be considered medically necessary when:
 - 1. criteria for BRCA testing are met, and
 - 2. testing for point mutations is negative, and either
 - 3. (a) there are 3 or more family members (one lineage) affected with breast, ovarian, fallopian tube, primary peritoneal cancer, or (b) there is a risk of a BRCA mutation of at least 10%. (See Policy Guidelines)

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When Genetic Testing for Breast and Ovarian Cancer is not covered

- A. Genetic testing for breast and ovarian cancer in affected or unaffected individuals is considered investigational when the criteria listed above are not met.
- B. Genetic testing for BRCA1 and BRCA2 mutations is considered investigational for minors.
- C. Testing for CHEK2 genetic abnormalities (mutations, deletions, etc.) is considered investigational in patients with breast cancer regardless of the family history.

Policy Guidelines

In identifying families with a high risk of mutation in the *BRCA1* or *BRCA2* genes, both maternal and paternal family histories are important but each lineage must be considered separately. Any of the following scenarios indicate a high risk of *BRCA1* or *BRCA2* mutation. In assessing risk of a mutation for those affected with cancer, the overall family history (one lineage) including the affected person is considered. The following criteria for non-Ashkenazi Jewish women unaffected with cancer were derived by the USPTF in 2005 after extensive literature review by the USPTF:

- Three or more first or second degree relatives with breast cancer regardless of age at diagnosis; or
- Two first-degree relatives with breast cancer, one of whom was diagnosed at age 50 years or younger; or
- Combination of both breast and ovarian or fallopian tube or primary peritoneal cancer among first- and second degree relatives; or
- First degree relative with bilateral breast cancer; or
- A combination of two or more first or second degree relatives with ovarian or fallopian tube or primary peritoneal cancer regardless of age at diagnosis; or
- A first or second degree relative with both breast and ovarian or fallopian tube or primary peritoneal cancer at any age; or
- A history of breast cancer in a male relative.

More recent definitions of high-risk have been published, including the 2011 revised recommendations from NCCN. The following high-risk criteria largely represent the National Comprehensive Cancer Network (NCCN) hereditary breast and/or ovarian cancer syndrome testing criteria with some modifications based on additional guidelines and review of evidence.

A personal or family history suggesting genetic cancer susceptibility requires at least one of the following criteria to be present:

1. Individual from a family with a known deleterious BRCA1/BRCA2 mutation
2. Personal history of breast cancer plus one or more of the following:
 - Diagnosed at an early age (see definition, following)
 - Diagnosed at age ≤ 50 years with at least one close blood relative (see definition, following) with breast cancer at age ≤ 50 years and/or at least one close blood relative with epithelial ovarian/fallopian tube/primary peritoneal cancer at any age
 - Two breast primaries when the first breast cancer diagnosis occurred prior to age 50 years
 - Diagnosed age < 60 years with a triple negative breast cancer
 - Diagnosed age < 50 years with a limited family history
 - Diagnosed at any age, with ≥ 2 close blood relatives with breast and/or epithelial ovarian/fallopian tube/primary peritoneal cancer at any age
 - Close male relative with breast cancer
 - Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer
 - For an individual of ethnicity associated with higher mutation frequency (eg Ashkenazi)

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- Jewish) no additional family history may be required
- 3) Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer
 - 4) Personal history of male breast cancer
 - 5) Personal history of breast and/or ovarian cancer at any age with ≥ 2 close blood relatives with pancreatic cancer at any age
 - 6) Personal history of pancreatic cancer at any age with ≥ 2 close blood relatives with breast and/or ovarian cancer and/or pancreatic cancer at any age
 - 7) Family history only:
 - Close blood relative meeting any of the above criteria

Early age at diagnosis refers generally to diagnosis before age 40 to 45; an exact cutoff for testing affected individuals without known family history but with cancer diagnosis at an early age has not been established, although guidelines of the American College of Medical Genetics suggest age 45 or younger. The decision to test an affected individual based on age at diagnosis in the absence of family history will depend on the risk estimate for the individual patient (e.g., from widely available risk assessment computer programs) and the patient tolerance for risk, and the desire to inform the risk of family members.

Close blood relative typically refers to first degree (parent, full sibling, or offspring) and second degree (grandparent, grandchild, uncle, aunt, niece, nephew, or half-sibling) relatives in diseases associated with high penetrance gene mutations such as BRCA1 and BRCA2 mutations. Accommodation may be made to include third degree relatives (first cousin, great grandparent or great grandchild) in some cases, e.g. limited family history, particularly in tracing hereditary breast and ovarian and related cancers in the paternal lineage. Certified genetic counselors or other qualified genetics professionals are best able to assess exceptional cases.

As the majority of test results will be negative and uninformative in unaffected family members of potential BRCA mutation families, it is strongly recommended that an affected family member be tested first whenever possible to adequately interpret the test. Should a BRCA mutation be found in an affected family member(s), the DNA from the unaffected family member can be tested specifically for the same mutation of the affected family member without having to sequence the entire gene. Interpreting the test results for an unaffected family member without knowing the genetic status of the family may be possible in the case of a positive result for an established disease-associated mutation, but leads to difficulties in interpreting negative test results or mutations of uncertain significance because the possibility of a causative BRCA mutation is not ruled out.

In patients with breast cancer, ovarian cancer, cancer of the fallopian tube, or primary peritoneal cancer who are from high-risk families without a known BRCA1 or BRCA2 gene and who are not from ethnic groups with known founder mutations, comprehensive BRCA mutation analysis should be performed.

Testing in eligible individuals who belong to ethnic populations in which there are well-characterized founder mutations should begin with tests specifically for these mutations. For example, founder mutations account for approximately three quarters of the BRCA mutations found in Ashkenazi Jewish populations. When the testing for founder mutations is negative, comprehensive mutation analysis should then be performed.

Comprehensive mutation analysis currently includes sequencing the coding regions and intron/exon splice sites as well as tests to detect common large deletions and rearrangements that can be missed with sequence analysis alone. However, current routine laboratory testing for genomic rearrangement is more limited than the criteria noted in the policy statement; automatic testing is specified for those with a risk of BRCA mutation of at least 30%. In addition, prior to August 2006, testing for large deletions and rearrangements was not performed, thus some patients with familial breast cancer who had negative BRCA testing prior to this time may consider repeat testing for the rearrangements.

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As noted above, cancers of the fallopian tube and primary peritoneal cancer are also considered BRCA-associated malignancies and are to be considered along with breast and ovarian cancer in assessing the family history.

Based on data available at this time, there is no compelling evidence to justify routine clinical testing for CHEK2 to guide the management of families affected with breast 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 codes: 83890, 83891, 81211, 81212, 81213, 81214, 81215, 81216, 81217, 83892, 83893, 83894, 83896, 83897, 83898, 83901, 83902, 83903, 83904, 83905, 83906, 83912

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

MEDLINE database search from 1/97 through 7/97

Consultant Review, August 1997

Plan Medical Director Review, August 1997

BCBSA Medical Policy Reference Manual, 7/31/97

Medical Policy Advisory Group, 5/28/98

Specialty Matched Consultant Advisory Panel 11/1999

Medical Policy Advisory Group 12/2/1999

Hematology/Oncology Clinics of North America. "Breast Cancer Genetics: Implications for Clinical Practice". Volume 14, Number 3, June, 2000. W.B. Saunders Company.

Specialty Matched Consultant Advisory Panel 11/2001

Specialty Matched Consultant Advisory Panel - 10/2003

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.02, 12/17/2003.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.02, 11/9/2004.

Specialty Matched Consultant Advisory Panel - 9/2005

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.02, 9/27/2005.

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Specialty Matched Consultant Advisory Panel - 8/2007

Senior Medical Director Review - 2/2009

American Society of Clinical Oncology. Policy Statement Update: Genetic Testing for Cancer Susceptibility (posted online April 11, 2003). J Clin Oncol 2003; 21(12):1-10.

The US Preventive Services Task Force (USPSTF). 2005. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility. Retrieved 6/3/08 from <http://www.ahrq.gov/clinic/uspstf05/brcagen/brcagenrs.htm>.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.02, 2/14/08.

Specialty Matched Consultant Advisory Panel - 8/28/09

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.02, 2/11/2010

Senior Medical Director – 9/2010

Specialty Matched Consultant Advisory Panel – 8/2011

Genetic/Familial High-Risk Assessment: Breast and Ovarian (V.1.2011). National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: . Retrieved 12/16/2011 from: http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf.

Medical Director 1/2012

Policy Implementation/Update Information

- 8/97 Original policy: Investigational
- 6/98 Reviewed: changed from investigational to medically necessary in cases where the member is considering prophylactic surgery and will be using the results of genetic testing as a decision factor. The member must meet the criteria for genetic testing. Recommended by MPAG.
- 6/99 Reformatted, Description of Procedure or Service changed, Medical Term Definitions added.
- 12/99 Reaffirmed, Medical Policy Advisory Group
- 3/01 Codes 83890-83906, 83912 added to policy.
- 11/01 Specialty Matched Consultant Advisory Panel - 11/2001. Format changes. Criteria revised. Typos corrected.
- 11/03 Specialty Matched Consultant Advisory Panel - 11/2003. Added information in Benefit Application and Billing/Coding sections. Reformatted policy.
- 4/04 Individual CPT codes listed for CPT code ranges 83890-83906 under Billing/Coding section.
- 8/12/04 Added HCPCS codes S3818, S3819, S3820, S3822, S3823 to Billing/Coding section.

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- 9/23/04 Revised Description of Procedure or Service section. Revised When Covered section to include those with early onset breast cancer, members of high-risk populations without an affected family member, and included ovarian cancer in #1. Removed from When Not Covered section, "unaffected individuals from potentially high risk populations (e.g. Ashkenazi Jewish descent)".
- 10/8/05 Specialty Matched Consultant Advisory Panel review 9/19/2005. No changes to criteria. References added.
- 9/24/07 Specialty Matched Consultant Advisory Panel review 8/23/2007. No changes to policy statement. References added. Policy status changed to: "Active policy, no longer scheduled for routine literature review."
- 3/16/09 Reviewed with Senior Medical Director 2/19/09. Reworded the "When Covered" section and added three additional indications. "A. Genetic testing of cancer-affected individuals may be medically necessary under any of the following circumstances: 1.) Women who are affected with breast or ovarian cancer and are from families with a high risk of BRCA1 or BRCA2 mutation as defined in the Policy Guidelines, OR; 2.) Women affected with early onset breast or ovarian cancer, or with breast or ovarian cancer and multiple primary cancers, or with bilateral breast or ovarian cancer, but who do not have a known family history of breast or ovarian cancer, OR; 3.) Women affected with both breast and ovarian cancer, OR; 4.) Men affected with breast cancer at any age, OR; 5.) Those affected with breast or ovarian cancer and who are from an ethnic background, e.g., Ashkenazi Jewish descent, associated with deleterious founder mutations. B. Genetic testing of unaffected adults may be considered medically necessary under any of the following circumstances: 1.) Unaffected individuals (male or female) from families with a known BRCA1 or BRCA2 mutation, OR; 2.) Unaffected individuals from families with a high risk of BRCA1 or BRCA2 mutation based on a family history (See Policy Guidelines), where it is not possible to test an affected family member for a mutation, OR; 3.) Unaffected individuals in populations at risk for specific founder mutations due to ethnic background, e.g., Ashkenazi Jewish descent, with one or more relatives with breast or ovarian cancer at any age." Added to the "Policy Guidelines" section; "The American College of Medical Genetics recommends that "early onset" breast or ovarian cancer be considered cancers that occur in patients age 45 or younger." Policy returned to active review status. References added. (btw)
- 10/12/09 Specialty Matched Consultant Advisory Panel review 8/28/09. Description revised. No change to policy statement. Reformatted wording in the "When Not Covered" section, no change to intent. Added information under "Policy Guidelines" to indicate; "1. The US Preventative Services Task Force (USPSTF) recommends the following in identifying families with a high risk for mutation in the BRCA1 and BRCA2 gene, both the maternal and paternal family histories are important and each lineage must be considered separately. For non-Ashkenazi Jewish women, high risk includes the following: a. Three or more first or second degree relative with breast cancer regardless of age at diagnosis, or b. Two first-degree relatives with breast cancer, one of whom was diagnosed at age 50 years or younger, or c. Combination of both breast and ovarian cancer among first- and second degree relatives, or d. First degree relative with bilateral breast cancer, or e. A combination of two or more first or second degree relatives with ovarian cancer regardless of age at diagnosis, or f. A first or second degree relative with both breast and ovarian cancer at any age, or g. A history of breast cancer in a male relative." and "6. The American Society of Clinical Oncology (ASCO) recommends that cancer predisposition testing be offered when 1) the person has a strong family history of cancer or very early age of onset of disease, 2) the test can be adequately interpreted, and 3) the results will influence the medical management of the patient or family member." References added.

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(btw)

6/22/10 Policy Number(s) removed (amw)

10/26/10 Added the following information to the “Description” section; “CHEK2 (cell cycle checkpoint kinase2) is also involved with DNA repair and human cancer predisposition like BRCA1 and BRCA2. CHEK2 is normally activated in response to DNA double-stranded breaks. CHEK2 regulates the function of BRCA1 protein in DNA repair and also exerts critical roles in cell cycle control and apoptosis. The CHEK2 mutation, 1100delC in exon 10 has been associated with familial breast cancers.” Added “fallopian tube and primary peritoneal cancer” as additional BRCA-associated malignancies to assess when obtaining the family history throughout policy as appropriate. Reformatted the “When Covered” and “When Not Covered” section. Added “C. Testing for genomic rearrangements of the BRCA1 and BRCA2 genes may be considered medically necessary when: criteria for BRCA testing are met, and testing for point mutations is negative, and there are 3 or more family members (one lineage) affected with breast, ovarian, fallopian tube, or primary peritoneal cancer, or there is a risk of a BRCA mutation of at least 10%. (See Policy Guidelines)” to the “When Covered” section. Added “C. Testing for CHEK2 genetic abnormalities (mutations, deletions, etc.) is considered investigational in patients with breast cancer regardless of the family history.” To the “When Not Covered” section. Added the following to the “Policy Guidelines” section; “For the purposes of this policy, an individual with a history of breast, ovarian, fallopian tube, or primary peritoneal cancer is considered to be from a “family with a high risk of BRCA1 or BRCA2 mutation” when one or more of the high risk criteria below are met.” “Please Note: The US Preventative Services Task Force (USPSTF) recommendations for identifying families at high risk for mutation in the BRCA1 and BRCA2 gene applies to women **without** breast, ovarian, fallopian tube, or primary peritoneal cancer. In situations where the woman has breast, ovarian, fallopian tube, or primary peritoneal cancer, the family is considered at high risk for mutation if the overall family history (one lineage) **including** the affected individual meets the criteria below.” “7. Comprehensive mutation analysis currently includes sequencing the coding regions and intron/exonsplice sites as well as tests to detect common large deletions and rearrangements that can be missed with sequence analysis alone. However, current routine laboratory testing for genomic rearrangement is more limited than the criteria noted in the policy statement; automatic testing is specified for those with a risk of BRCA mutation of at least 30%. In addition, prior to August 2006, testing for large deletions and rearrangements was not performed, thus some patients with familial breast cancer who had negative BRCA testing prior to this time may consider repeat testing for the rearrangements.” “8. Based on data available at this time, there is no compelling evidence to justify routine clinical testing for CHECK2 to guide the management of families affected with breast cancer.” Reviewed with Senior Medical Director 9/27/10. References added. (btw)

1/24/12 Specialty Matched Consultant Advisory Panel review August 29, 2011. No change to policy statement. “Policy Guidelines” updated to include NCCN guidelines. Added the following new 2012 CPT codes to the “Billing/Coding” section: 81211, 81212, 81213, 81214, 81215, 81216, and 81217. (btw)

3/30/12 Deleted HCPCS codes S3818, S3819, S3820, S3822, S3823 from Billing/Coding Section. (btw)

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

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medical policies periodically.