Medical Coverage Policy

Genetic Testing: Inherited BRCA1 or BRCA2 Mutations

☐ Device/Equipment ☐ Drug ☐ Medical ☐ Surgery ☒ Test ☐ Other

Effective Date:	7/1/2001	Policy Last Updated:	2/7/2012

☒ **Prospective review is recommended/required. Please check the member agreement for preauthorization guidelines.**

☐ **Prospective review is not required.**

Definitions:

Brac analysis rearrangement test (BART):

Myriad Genetics Laboratories includes analysis for five common BRCA1 genomic rearrangements (large deletions and duplications) in their full testing. This testing is called BART (BRCAnalysis Rearrangement Test) testing for detectable rearrangements beyond these five, is offered free of charge by Myriad to highest risk women (i.e., an affected proband with breast cancer before age 50, and two close relatives with breast cancer under age 50, or ovarian cancer).

Close Blood Relative:

A 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. In some cases (e.g., limited family history, particularly in tracing hereditary breast and ovarian and related cancers in the paternal lineage, accommodation may be made to include third degree relatives (first cousin, great-grandparent, or great-grandchild).

CHEK2 Testing:

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. At this time **CHEK2 Testing** is **not medically necessary** as there is insufficient peer-reviewed scientific literature that demonstrates that this testing is effective.

Description:

Families suspected of hereditary breast and/or ovarian cancer are characterized by cancer occurring at an early age, in multiple generations, and often bilaterally and in a pattern suggesting an autosomal dominant pattern of inheritance. The susceptibility may be transmitted through the maternal or paternal side of the family. Germline alterations in two genes, BRCA1 and BRCA2, are associated with an increased risk of breast and ovarian cancer. Alterations in BRCA1 and BRCA2 explain much but not all inherited forms of breast and ovarian cancer. With the identification of BRCA1 and BRCA2, it is not possible to test for abnormalities in these genes to provide information on future risk of cancer.

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 or ovarian 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 (see Rationale). When the testing for founder mutations is negative, comprehensive mutation analysis should then be performed.

Comprehensive mutation analysis 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.

This criterion may not adequately cover the possibility of paternal transmission of a BRCA1 or BRCA2 mutation. Men rarely develop breast cancer and thus there may not be an affected first-degree relative, and the size of the family may not permit analysis of possible autosomal dominant inheritance.

Unaffected family members should be tested only after finding a mutation in an affected first- or second-degree relative in order to adequately interpret the test. In this situation, 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. Testing an unaffected family member without knowing the genetic status of the family may lead to difficulties in interpreting the test results.

Testing should be obtained in a setting by trained healthcare providers who can give appropriate pre- and post-test counseling and has access to a CLIA-licensed laboratory offering comprehensive mutation analysis.

Medical Criteria:

Genetic testing for BRCA1 and BRCA2 mutations in cancer-affected individuals may be considered **medically necessary** under any of the following circumstances:

- Women who are affected with breast, ovarian, or pancreatic cancer, and are from families with a high risk of *BRCA1* or *BRCA2* mutation as defined in this policy; OR
- Women who do not have a known family history of breast, epithelial ovarian, Fallopian tube, or primary peritoneal cancer, but are affected with any one of the following:
    - early onset breast cancer;
    - two breast primary cancers with the first cancer diagnosis occurring prior to age 50 years;
    - triple negative breast cancer (neither express estrogen receptor and progesterone receptor, nor overexpress HER2) diagnosed at younger than age 60;
    - epithelial ovarian/Fallopian tube/primary peritoneal cancer at any age; OR
    - diagnosed age <50 years with a limited family history; OR
- Women affected with both breast cancer and either epithelial ovarian cancer, Fallopian tube cancer, or primary peritoneal cancer; OR
- Men affected with breast cancer at any age; OR
- 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; OR
- Personal history of breast and/or ovarian cancer at any age with =2 close blood relatives with pancreatic cancer at any age; OR

- Personal history of pancreatic cancer at any age with =2 close blood relatives with pancreatic cancer at any age.

Genetic testing for *BRCA1* and *BRCA2* mutations of unaffected adults may be considered **medically necessary** under any of the following circumstances:

- Unaffected individuals (male or female) from families with a known *BRCA1* or *BRCA2* mutation, OR;
- Unaffected individuals from families with a high risk of *BRCA1* or *BRCA2* mutation based on a family history where it is not possible to test an affected family member for a mutation.
- Unaffected individuals in populations at risk for specific founder mutations due to ethnic background, e.g., Ashkenazi Jewish descent, and with one or more relatives with breast, epithelial ovarian, Fallopian tube, or primary peritoneal cancer at any age.

If above noted criteria has not been met, genetic testing for those affected with breast, ovarian, pancreatic, Fallopian tube, or primary peritoneal cancer or for unaffected individuals is not covered. Although some preliminary evidence suggests that the presence of a BRCA mutation may increase the risk of cancers at sites other than the breast at this time there is insufficient evidence to indicate BRCA testing for assessment of risk of non-breast cancers.

Early age at diagnosis is referred to as having a 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.

Risk Factors:
Families at high-risk for harboring a BRCA1 or BRCA2 mutation are those in which the incidence of breast or ovarian cancer in first- or second-degree relatives suggests an autosomal dominant inheritance (i.e., about half the family members are affected).

- First degree relatives are the parents, brothers, sisters, or children of an individual.
- Second degree relatives are the people with whom one quarter of an individual's genes is shared (i.e., grandparent, grandchild, uncle, aunt, nephew, niece, half-sibling).
- Third degree relatives are the people with whom one eighth of an individual’s genes is shared (i.e., cousin, great-grandparent, great-aunt, or great-uncle).

In identifying families with a high risk of mutation in the BRCA1 or BRCA 2 gene, both maternal and paternal family histories are important but each lineage must be considered separately. Any of the following scenarios indicates 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. For non-Ashkenazi Jewish women, high-risk includes the following (1):

- 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.

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

- Individual from a family with a known deleterious BRCA2/BRCA2 mutation
- Personal history of breast cancer plus one or more of the following:
  - Diagnosed at an early age (see definition);
  - Diagnosed at age = 50 years with at least one close blood relative (see definition) 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
  - Diagnoses 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 (e.g. Ashkenazi Jewish) no additional family history may be required.
- Personal history of epithelial ovarian/Fallopian tube/primary peritoneal cancer
- Personal history of male breast cancer
- Personal history of breast and/or ovarian cancer at any age with =2 close blood relatives with pancreatic cancer at any age
- Personal history of pancreatic cancer at any age with =2 close blood relatives with pancreatic cancer at any age.
- Family history only:
  - First- or second- degree blood relative meeting any of the above criteria;
  - Third-degree blood relative with breast cancer and/or ovarian/Fallopian tube/primary peritoneal cancer with =2 close blood relatives with breast cancer (at least one with breast cancer =50 years) and/or ovarian cancer.

For the policy statements, meeting one criterion indicates that an individual without cancer is from a family at “high risk for a mutation.” For an individual with cancer, the family is considered “high risk for a mutation” if the overall family history (one lineage) including the affected individual meets one of the above criteria.

Note:
Cancer of the Fallopian tube and primary peritoneal cancer may be added as additional cancers to consider in assessing risk.

BART testing:

Testing for genomic rearrangements of the BRCA1 and BRCA2 genes may be considered **medically necessary** in patients:

- who meet criteria for comprehensive (BRCA1 and BRCA2) testing; **and**
- whose testing for point mutations is **negative**; **and** either
  - there are 3 or more family members (one lineage) affected with breast and/or ovarian cancer; **or**
  - who have a risk of a BRCA mutation of at least 10%.

CHEK2 Testing:

Testing for CHEK2 genetic abnormalities (mutations, deletions, etc.) is considered **not medically necessary** in affected and unaffected patients with breast cancer irrespective of the family history. At this time **CHEK2 Testing** is **not medically necessary** as there is insufficient peer-reviewed scientific literature that demonstrates that this testing is effective.

Genetic testing of minors:

Genetic testing on minors for BRCA1 or BRCA2 mutations is considered **not medically necessary** as there is insufficient peer-reviewed scientific literature to demonstrate the efficacy of this testing.

Unless criteria listed above has been met, genetic testing for either those affected with breast, pancreatic, or ovarian cancer, or for unaffected individuals, is considered **not medically necessary**.

Policy:
Genetic testing for BRCA1 and BRCA2 mutations, and BART testing is considered **medically necessary** when the above listed medical criteria has been met**. Prior authorization is required for BlueCHiP for Medicare and recommended for all other lines of business.**

NOTE: At the present time, Myriad Genetics Laboratory is the only provider of BRCA and BART testing, and as they are non-participating, out of network co-pays can be waived when a request is determined to be medically necessary.

Coverage:
Medicare excludes all screening (not just genetic screening) with certain statutory exceptions. Blue CHiP for Medicare provides no additional benefits for genetic screening. **Only** if the patient exhibits signs or symptoms of the disease, would the test not be considered screening.

Benefits may vary between groups/contracts. Please refer to the appropriate Evidence of Coverage, Subscriber Agreement, or Benefit Booklet for applicable genetic testing benefits/coverage.

Coding:
Prior authorization is required for BlueCHiP for Medicare and recommended for all other lines of business:
S3818 (code deleted effective April 1, 2012)
S3819 (code deleted effective April 1, 2012)
S3820 (code deleted effective April 1, 2012)
S3822 (code deleted effective April 1, 2012)
S3823 (code deleted effective April 1, 2012)

BCBSRI follows Medicare guidelines, and the following codes should be used:
81211
81212
81213
81214
81215
81216
81217

The following codes are not appropriate for use as the S codes (listed above) are more specific:
83890
83891
83892
83893
83894
83896
83897
83898
83900
83902
83903
83906

Brac analysis rearrangement test (BART):

Brac analysis rearrangement test (BART) should be reported using an unlisted code as at this time there is no code specific to the test.

Also known as:
Not applicable

Related Topics:
Genetic Testing

Published:
Policy Update, July 2001
Policy Update, August 2006
Policy Update, January 2008
Provider Update, November 2008
Provider Update, February 2009
Provider Update, November 2009
Provider Update, April 2011
Provider Update, April 2012

Public Policy Description

References:

American Society of Clinical Oncology. Policy Statement Update. Genetic Testing for Cancer Susceptibility (posted online April 11, 2003) Journal of Clinical Oncology:21;12;June 15, 2003.

American College of Medical Genetics, Policy Statement: Statement on Population Screening for BRCA-1 Mutation in Ashkenazi Jewish Women. (http://www.acmg.net/resources/policies/pol-002.asp) accessed 5/4/07**.**

Blue Cross Blue Shield Association Medical Policy Reference. Policy 2.04.02 - Genetic Testing for Hereditary Breast and/or Ovarian Cancer. Reviewed with literature search/February 2009.

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Rennert G, Bisland-Naggan S, Barnett-Griness O. et. al. Clinical Outcomes of Breast Cancer in Carriers of *BRCA1* and *BRCA2* Mutations. New England Journal of Medicine:200;357;2;115-123.

Struewing, JP; Hartge, P; Wacholder, S; Baker, SM; Berlin, M; McAdams, M; Timmerman, MM; Brody, LC; Tucker, MA The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. New England Journal of Medicine:1997;336;20;1401-1408.