DRAFT

BlueCross BlueShield of Alabama

Name of Policy:

Genetic Testing for Hereditary Breast/Ovarian Cancer (BRCA1 or BRCA2)

Policy #: 513
Category: Laboratory

Latest Review Date: October 2018
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Hereditary breast and ovarian cancer (HBOC) syndrome describes the familial cancer syndromes that are related to variants in the *BRCA* genes (*BRCA1* located on chromosome 17q21 and *BRCA2* located on chromosome 13q12-13). Families with hereditary breast and ovarian cancer syndrome have an increased susceptibility to the following types of cancer: breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer (at any age), cancer of the fallopian tube, primary peritoneal cancer, prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer.

Several genetic syndromes with an autosomal dominant pattern of inheritance that features 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, ovarian cancer at any age, as well as cancer of the fallopian tube and primary peritoneal cancer. 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 variants 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* variants 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 variants 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* variants can consider preventive interventions for reducing risk and mortality.

Policy:

Effective for dates of service on or after November 1, 2018:

I. Patients With Cancer or With Personal History of Cancer:

Genetic testing for *BRCA1* and *BRCA2* variants in cancer-affected individuals **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage for any of the following circumstances:

- Individual from a family with a known *BRCA1* or *BRCA2* variant
- Personal history of breast cancer **AND** one or more of the following:
    - o Diagnosed at age ≤45 years
    - o Two primary breast cancers when 1st breast cancer diagnosis occurred age at ≤50 years
    - o Diagnosed at age ≤50 years **AND**:
        - One or more 1st-, 2nd-, or 3rd-degree relative(s)[a] with breast cancer at any age, pancreatic cancer or prostate cancer[b] , **or**

        - Unknown or limited family history[c]
    - o Diagnosed at age ≤60 years with a triple-negative (estrogen receptor–negative, progesterone receptor–negative, human epidermal growth factor receptor 2–negative) breast cancer
    - o Diagnosed at any age **AND** 1 or more 1st-, 2nd-, or 3rd-degree relative[a] with breast cancer diagnosed at ≤50 years
    - o Diagnosed at any age **AND** 2 or more 1st-, 2nd-, or 3rd-degree relatives[a] with breast cancer at any age
    - o Diagnosed at any age **AND** 1 or more 1st-, 2nd-, or 3rd-degree relative[a] with epithelial ovarian, fallopian tube, or primary peritoneal cancer
    - o Diagnosed at any age **AND** 2 or more 1st-, 2nd-, or 3rd-degree relatives[a] with pancreatic cancer or prostate cancer[b] at any age
    - o 1st-, 2nd-, or 3rd-degree male relative with breast cancer
    - o Ethnicity associated with deleterious founder mutations (e.g., Ashkenazi Jewish descent[d])
- Personal history of epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Personal history of male breast cancer
- Personal history of pancreatic cancer or prostate cancer[c] at any age **AND** 1 or more 1st-, 2nd-, or 3rd-degree relatives[a] with **either** of the following:
    - o Breast cancer ≤50
    - o Ovarian, fallopian tube, or primary peritoneal cancer at any age
- Personal history of pancreatic cancer or prostate cancer[b] at any age **AND** 2 or more 1st-, 2nd-, or 3rd-degree relatives[a] with breast, pancreatic or prostate cancer[b] at any age.
- For pancreatic cancer, if Ashkenazi Jewish ancestry (no additional affected relative is needed).

II. Patients Without Cancer or Without History of Cancer:

Genetic testing for *BRCA1* and *BRCA2* variants of cancer-unaffected individuals **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage for any of the following circumstances:

- Individual from a family with a known *BRCA1* or *BRCA2* variant
- 1st- or 2nd-degree blood relative meeting any criterion listed above for Patients With Cancer
- 3rd-degree blood relative with breast cancer and/or ovarian, fallopian tube, or primary peritoneal cancer **AND** 2 or more 1st-, 2nd-, or 3rd-degree relatives[a] with breast cancer (≥1 at age ≤50 years) and/or ovarian, fallopian tube, or primary peritoneal cancer.

[a]For familial assessment, 1st-, 2nd-, and 3rd-degree relatives are blood relatives on the same side of the family (maternal or paternal).

- 1st-degree relatives are parents, siblings, and children.
- 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.
- 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.

[b]For familial assessment, prostate cancer is defined as Gleason score ≥7.

[c]For example, fewer than 2 first- or second-degree female relatives having lived beyond age 45 in either lineage. In families with a large number of unaffected female relatives, the likelihood of variant detection may be very low.

[d]Testing for Ashkenazi Jewish or other founder mutation(s) should be performed first

Genetic testing for *BRCA1* and *BRCA2* variants in cancer-affected individuals or of cancer-unaffected individuals with a family history of cancer when criteria above are not met **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Genetic testing in **minors** for *BRCA1* and *BRCA2* variants **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Policy Guidelines

Current U.S. Preventive Services Task Force guidelines recommend screening women with any family history of breast, ovarian, tubal, or peritoneal cancer. Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing (grade B recommendation)

Recommended screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful variants in BRCA1 or BRCA2 are:

- Ontario Family History Assessment Tool (FHAT)
- Manchester Scoring System
- Referral Screening Tool (RST)
- Pedigree Assessment Tool (PAT)
- Family History Screen (FHS-7)

Recommended Testing Strategies

Patients who meet criteria for genetic testing as outlined in the policy statements above should be tested for variants in BRCA1 and BRCA2.

- In patients with a known familial BRCA variant, targeted testing for the specific variant is recommended.
- In patients with unknown familial BRCA variant:
    - Non-Ashkenazi Jewish descent
        - To identify clinically significant variants, NCCN advises testing a relative who has breast or ovarian cancer—especially with early-onset disease, bilateral disease, multiple primaries, or ovarian cancer—because that individual has the highest likelihood of obtaining a positive test result.
        - If no living family member with breast or ovarian cancer exists, NCCN suggests testing first- or second-degree family members affected with cancer thought to be related to deleterious BRCA1 or BRCA2 variants (e.g., prostate cancer, pancreatic cancer, melanoma).
        - If no familial variant can be identified, 2 possible testing strategies are:
            - ✓ Full sequencing followed by testing for common large genomic rearrangements (deletions, duplications) only if sequencing detects no variant (negative result).
                - ➢ More than 90% of BRCA variants will be detected by full sequencing.
            - ✓ Alternatively, simultaneous full sequencing and testing for common large genomic rearrangements (also known as

comprehensive BRCA testing; see Comprehensive Variant Analysis below) may be performed as is recommended by NCCN.
    - ➢ Comprehensive testing can detect 92.5% of BRCA1 or BRCA2 variants.
- If comprehensive BRCA testing is negative, testing for uncommon large genomic rearrangements (e.g., BART™) may be done.
    - ✓ Testing for uncommon large rearrangements should not be done unless both sequencing and testing for common large rearrangements have been performed and are negative.
        - ➢ Among patients with negative comprehensive testing, BART™ identified a deleterious variant (positive result) in less than 1%.

- Ashkenazi Jewish descent
    - In patients of known Ashkenazi Jewish descent, NCCN recommends testing for the 3 known founder mutations (185delAG and 5182insC in BRCA1; 6174delT in BRCA2) first.
    - If testing is negative for founder mutations, comprehensive genetic testing may be considered (see Comprehensive Variant Analysis).

Comprehensive Variant Analysis
Comprehensive variant analysis currently includes sequencing the coding regions and intron and exon splice sites, as well as testing to detect common large deletions and rearrangements that can be missed with sequence analysis alone. 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 (see Policy section for criteria).

High-Risk Ethnic Groups
Testing of eligible individuals who belong to ethnic populations in which there are well-characterized founder mutations should begin with tests specifically for these variants. For example, founder mutations account for approximately three-quarters of the BRCA variants found in Ashkenazi Jewish populations (see Rationale section). When testing for founder mutations is negative, comprehensive variant analysis should then be performed.

Testing Unaffected Individuals
In unaffected family members of potential BRCA mutation families, most test results will be negative and uninformative. Therefore, it is strongly recommended that an affected family member be tested first whenever possible to adequately interpret the test. Should a BRCA variant be found in an affected family member(s), DNA from an unaffected family member can be tested specifically for the same variant of the affected family member without having to sequence the entire gene. Interpreting 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 variant but leads to difficulties in interpreting negative test results (uninformative negative) or variants of uncertain significance because the possibility of a causative BRCA variant is not ruled out.

Testing Minors
The use of genetic testing for BRCA variants has limited or no clinical utility in minors. This is because there is no change in management for minors as a result of knowledge of the presence or absence of a deleterious variant. In addition, there are potential harms related to stigmatization and discrimination.

Prostate Cancer
Patients with BRCA variants have an increased risk of prostate cancer, and patients with known BRCA variants may, therefore, consider more aggressive screening approaches for prostate cancer. However, the presence of prostate cancer in an individual, or in a family, is not itself considered sufficient justification for BRCA testing.

Effective for the dates of service January 1, 2014 through October 31, 2018
Genetic testing for BRCA1 and BRCA2 mutations in cancer-affected individuals meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for any of the following circumstances:

- 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**;
- Women who are affected with breast cancer or pancreatic cancer, who are not from families with a high risk of BRCA1 or BRCA2 mutation as defined in Policy Guidelines, but are affected with any one of the following:
    - early onset breast cancer (diagnosed at or before age 45)
    - 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 over-express HER2) diagnosed at younger than age 60
    - two or more close blood relatives with pancreatic cancer at any age, **OR**;
- Women affected with 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

Genetic testing for BRCA1 and BRCA2 mutations of unaffected adults meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for 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 (see Policy Guidelines), 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.

Further, the genetic testing should be performed in a setting that has suitably trained healthcare providers who can give appropriate pre- and post-test counseling and that has access to a CLIA-licensed laboratory that offers comprehensive mutation analysis (see Policy Guidelines).

Testing for genomic rearrangements of the BRCA1 and BRCA2 genes (BART—BRCA analysis rearrangement testing) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in patients who meet criteria for BRCA testing and whose testing for point mutations is negative.

Unless they meet the criteria above, genetic testing either for those affected with breast, ovarian, fallopian tube, or primary peritoneal cancer or for unaffected individuals, including those with a family history of pancreatic cancer, **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Genetic testing in minors for BRCA1 and BRCA2 mutations does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Policy Guidelines:

In identifying families with a high risk of mutation in the *BRCA1* or *BRCA2* 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 including the affected person is considered. **The following criteria for non-Ashkenazi Jewish women unaffected with cancer** were derived by the U.S. Preventive Services Task Force (USPSTF) in 2005 after extensive literature review:

- 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 2013 revised recommendations from National Comprehensive Cancer Network (NCCN). The following high-risk criteria largely represent NCCN hereditary breast and/or ovarian cancer syndrome testing criteria with some modifications based on additional guidelines and evidence review.

The presence of one or more of the following criteria suggests hereditary breast/ovarian cancer syndrome (HBOC):

- Individual from a family with a known deleterious BRCA1/BRCA2 mutation
- Personal history of breast cancer plus one or more of the following:
    - Diagnosed at an early age (diagnosed at or before age 45)
    - Diagnosed at age ≤50 years with at least one close blood relative (see definition, following) with breast cancer at any age or with a limited family history
    - 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 at any age with at least 1 close blood relative with:
        - Breast cancer diagnosed at age ≤50 years, **or**
        - Epithelial ovarian/fallopian tube/primary cancer
    - Diagnosed at any age, with ≥2 close blood relatives with:
        - Breast cancer at any age, **or**
        - Pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age
    - Close male relative with breast 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 pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age with ≥2 close blood relatives with breast and/or ovarian/fallopian tube/primary peritoneal cancer and/or pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age
- Family history only:
    - Close blood relative meeting any of the above criteria

Definition: Early age at diagnosis refers generally to diagnosis before age 40 to 45 years; an exact cutoff for testing affected individuals without known family history but with cancer diagnosis at an early age has not been established, although National Comprehensive Cancer Network (NCCN) guidelines 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.

Definition: 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 (uninformative negative) 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.

Patients with *BRCA* mutations have an increased risk of prostate cancer, and patients with known *BRCA* mutations may therefore consider more aggressive screening approaches for prostate cancer. However, the presence of prostate cancer in an individual, or in a family, is not itself felt to be sufficient justification for *BRCA* testing.

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. 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 (see Policy Statements for criteria).

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.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature update was performed through September 11, 2017.

This review was informed by a 1997 TEC Assessment.

Assessment of a diagnostic technology typically focuses on three categories of evidence: (1) analytic validity (including test-retest reliability or interrater reliability); (2) clinical validity (sensitivity, specificity, positive and negative predictive values) in relevant populations of patients; and (3) clinical utility (i.e., demonstration that the diagnostic information can be used to improve patient outcomes).

Testing for BRCA1 and BRCA2 Variants in High-Risk Individuals

Clinical Context and Test Purpose

The purpose of testing for *BRCA1* and *BRCA2* variants in high-risk individuals is to evaluate whether hereditary breast and ovarian cancer (HBOC) syndrome is present and, if it is, to determine the appropriate surveillance and treatment to decrease the risk of mortality from breast and/or ovarian cancer.

The question addressed in this evidence review is: Does testing for HBOC syndrome improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients with cancer (i.e., breast cancer, epithelial ovarian, fallopian tube, primary peritoneal cancer), or patients with a personal or family history of cancer and criteria that might suggest they are at risk of HBOC syndrome.

Intervention

The intervention of interest is BRCA1 and BRCA2 variant testing.

Comparator

The comparator of interest is standard of care without genetic testing for HBOC syndrome.

Outcomes

The outcomes of interest are overall survival, disease-specific (breast and ovarian cancer) survival, test accuracy and validity, and quality of life (e.g. anxiety).

Time

The time is testing as an adult, when appropriate treatment and/or prophylactic treatment options are available.

Setting

These tests are offered in a primary care setting (eg, for people without cancer) or the speciality setting (e.g., multidisciplinary oncology care) commercially through various manufacturers and institutions.

Analytic Validity
The analytic validity of variant testing for BRCA1 and BRCA2 is generally accepted.

Clinical Validity
Studies have focused on identifying the population that is appropriate for testing (ie, those with a personal or family history of cancer who meet certain criteria that increases the likelihood of having HBOC syndrome).

Prevalence of BRCA Variants and Risks of Cancer and Survival
The prevalence of *BRCA* variants is approximately 0.1% to 0.2% in the general population. Prevalence may be much higher for particular ethnic groups with characterized founder mutations (e.g., 2.5% [1/40] in the Ashkenazi Jewish population). Family history of breast and ovarian cancer is an important risk factor for *BRCA* variant; additionally, age and ethnicity could be independent risk factors.

Nelson et al (2013) conducted a systematic review that included meta-analytic estimates of the prevalence and penetrance of *BRCA* variants, in order to update the U.S. Preventive Services Task Force (USPSTF) recommendation for risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer. In high-risk women with positive test results, cumulative risks for developing breast cancer by age 70 were 46% for *BRCA1* and 50% for *BRCA2* when a single family member was tested, and 70% for *BRCA1* and 71% for *BRCA2* when multiple family members were tested; cumulative risks for developing ovarian cancer by age 70 were 41% for *BRCA1* and 17% for *BRCA2* when a single family member was tested; and 46% for *BRCA1* and 23% for *BRCA2* when multiple family members were tested. For Ashkenazi Jewish women with positive test results, cumulative risks for developing breast or ovarian cancer by age 75 were 34% and 21%, respectively. Nelson et al included meta-analytic estimates of *BRCA* prevalence in their 2013 systematic review for USPSTF. In unselected women, *BRCA* variant prevalence estimates were 0.2% to 0.3%; in women with breast cancer, 1.8% for *BRCA1* and 1.3% for *BRCA2*; in women with breast cancer onset at age 40 years or younger, 6%; in women from high-risk families, 13.6% for *BRCA1*, 7.9% for *BRCA2*, and 19.8% for *BRCA1* or *BRCA2*; in unselected Ashkenazi Jewish women, 2.1%; and in Ashkenazi Jewish women from high-risk families, 10.2%.

Estimates of lifetime risk of cancer for *BRCA* variant carriers (penetrance), based on studies of families with extensive history of disease, have been as high as 85%. For example, Kuchenbaecher et al (2017) found that the cumulative risk of breast cancer up to age 80 was 72% in *BRCA1* carriers and 69% in *BRCA2* carriers. Because other factors that influence risk may be present in families with extensive breast and ovarian cancer histories, early penetrance estimates may have been biased upward. Studies of founder mutations in ethnic populations (eg, Ashkenazi Jewish, Polish, Icelandic populations) unselected for family history indicated lower penetrance estimates, in the range of 40% to 60% for *BRCA1* and 25% to 40% for *BRCA2*. However, a genotyping study of Ashkenazi Jewish women with incident invasive breast cancer, selected regardless of family history of cancer and their family members, resulted in an 82% lifetime risk of breast cancer for carriers of any of 3 *BRCA* founder mutations (185delAG, 5382insC, 6174delT). Importantly, the risk of cancer in variant carriers from families with little

history of cancer (~50% of all carriers) did not differ significantly. Lifetime risks of ovarian cancer were 54% for *BRCA1*, and 23% for *BRCA2* variant carriers.

Women with a history of breast cancer and a *BRCA* variant have a significant risk of contralateral breast cancer; in 1 prospective study (2004), the 10-year risk was 29.5% for women with initial stage I or II disease. In a 2013 prospective study (EMBRACE), the cumulative risk of contralateral breast cancer by age 70 years was 83% in *BRCA1* variant carriers, and 62% for *BRCA2* variant carriers. These investigators also reported cumulative risks of breast cancer by age 70 in women without previous cancer (60% in *BRCA1* carriers, 55% in *BRCA2* carriers). Similarly, the cumulative risks of ovarian cancer by age 70 years in women without previous ovarian cancer were 59% for *BRCA1* carriers and 17% for *BRCA2* carriers.

A systematic review published by Zhu et al in 2016 found a significantly lower risk of overall survival in breast cancer patients with *BRCA1* (pooled hazard ratio [HR], 1.69; 95% confidence interval [CI], 1.35 to 2.12) and with *BRCA2* (pooled HR=1.50; 95% CI, 1.02 to 2.09; p=0.034).12 However, in patients with breast cancer, *BRCA1* and *BRCA2* were not associated with a lower breast cancer-specific survival.

Clinical Features Suggestive of *BRCA* Variant

Young age of onset of breast cancer, even in the absence of family history, is a risk factor for *BRCA1* variants. Winchester (1996) estimated that hereditary breast cancers account for 36% to 85% of patients diagnosed before age 30. In several studies, *BRCA* variants are independently predicted by early age at onset, being present in 6% to 10% of breast cancer cases diagnosed at ages younger than various premenopausal age cutoffs (age range, 35-50 years). In cancer-prone families, the mean age of breast cancer diagnosis among women carrying *BRCA1* or *BRCA2* variants is in the 40s. In the Ashkenazi Jewish population, Frank et al (2002) reported that 13% of 248 cases with no known family history and diagnosed before 50 years of age had *BRCA* variants. In a similar study (2000), 31% of Ashkenazi Jewish women, unselected for family history, diagnosed with breast cancer at younger than 42 years of age had *BRCA* variants. Other studies have indicated that early age of breast cancer diagnosis is a significant predictor of *BRCA* variants in the absence of family history in this population.

As in the general population, family history of breast or ovarian cancer, particularly of early age onset, is a significant risk factor for a *BRCA* variant in ethnic populations characterized by founder mutations. For example, in unaffected individuals of Ashkenazi Jewish descent, 12–31% will have a *BRCA* variant depending on the extent and nature of the family history. Several other studies document the significant influence of family history.

In patients with "triple-negative" breast cancer (i.e., negative for expression of estrogen and progesterone receptors; and negative for overexpression of human epidermal growth factor receptor 2 receptors), there is an increased prevalence of *BRCA* variants. Pathophysiologic research has suggested that the physiologic pathway for development of triple-negative breast cancer is similar to that for *BRCA*-associated breast cancer. In 200 randomly selected patients with triple-negative breast cancer from a tertiary care center, there was a greater than 3-fold increase in the expected rate of *BRCA* variants. *BRCA1* variants were found in 39.1% of patients and *BRCA2* variants in 8.7%. Young et al (2009) studied 54 women with high-grade, triple-

negative breast cancer with no family history of breast or ovarian cancer, representing a group that previously was not recommended for *BRCA* testing. Six *BRCA* variants (5 *BRCA1*, 1 *BRCA2*) were found, for a variant rate of 11%. Finally, in a 2011 study of 77 patients with triple-negative breast cancer, 15 patients (19.5%) had *BRCA* variants (12 in *BRCA1*, 3 in *BRCA2*).

BRCA Variant Rates Associated With Pancreatic Cancer
Unaffected individuals also may be at high risk due to other patterns of non-breast-cancer malignancies. A personal history of pancreatic cancer is estimated to raise the risk of a BRCA variant by 3.5- to 10-fold over the general population. Couch et al (2007) reported on screening for BRCA2 variants in two cohorts of families at high risk for pancreatic cancer. In the first cohort of high-risk families, there were a total of 5 (3%) BRCA variants in 151 probands; in the second cohort, there were another 5 (17%) BRCA2 variants in 29 probands. The combined BRCA2 variant rate for these 2 cohorts was 6% (10/180). Ferrone et al (2009) tested 187 Ashkenazi Jewish patients with pancreatic cancer for BRCA variants and found that 5.5% (8/187) had a BRCA variant.

***BRCA* Variant Rates Associated with Ovarian Cancer**
Women with a personal history of ovarian cancer have an increased rate of *BRCA* variants. In a 2010 systematic review of 23 studies, Trainer et al estimated the rate of *BRCA* variants among women with ovarian cancer to be 3% to 15%. In this review, 3 U.S. studies tested for both *BRCA1* and *BRCA2*; incidences of *BRCA* variants were 11.3%, 15.3%, and 9.5%. In a 2011 population-based study of 1342 unselected patients with invasive ovarian cancer in Canada, 176 women had *BRCA* variants, for a rate of 13.3%. Variant prevalence was higher for women in their 40s (24%) and for women with serous ovarian cancer (18%). Ethnicity was another risk factor for *BRCA*, with higher rates seen in women of Italian (43.5%), Jewish (30%), and Indo-Pakistani (29.4%) origin. In the 2013 systematic review for USPSTF by Nelson et al, meta-analytic estimates of *BRCA* prevalence among women with ovarian cancer were 4.4% for *BRCA1* and 5.6% for *BRCA2*.

BRCA Variant Associated with Fallopian Tube Cancer
A 2009 study described the high rate of occult fallopian tube cancers in at-risk women having prophylactic bilateral salpingo-oophorectomy.30 In this prospective series of 45 women, 4 (9%) had fallopian tube malignancies. Reviewers noted that these findings supported other studies that have demonstrated the fimbrial end of the fallopian tube as an important site of cancer in those with *BRCA1* or *BRCA2* variants.

A 2013 long-term study (median follow-up, 7 years; range, 3-14 years) followed 32 *BRCA* variant carriers with occult malignancy (4 ovarian, 23 fallopian tube, 5 ovarian and fallopian tube) diagnosed of prophylactic salpingo-oophorectomy. Among 15 women with invasive carcinoma (median age, 50 years), 7 (47%) experienced recurrence at a median of 33 months, and overall survival was 73%. Among 17 women with noninvasive neoplasia (median age, 53 years), 4 (24%) received chemotherapy, none of whom experienced recurrence. One (6%) patient who did not receive chemotherapy experienced recurrence at 43 months. Overall survival was 100%. The authors concluded that, in *BRCA* variant carriers, unsuspected invasive carcinoma has a relatively high rate of recurrence, but noninvasive neoplasms rarely recur and may not require adjuvant chemotherapy.

Testing for Large *BRCA* Rearrangements

A number of studies have shown that a significant percentage of women with a strong family history of breast cancer and negative tests for *BRCA* variants have large genomic rearrangements (including deletions or duplications) in one of these genes. For example, in 2006 Walsh et al reported on probands from 300 U.S. families with 4 or more cases of breast or ovarian cancer but with negative (wild-type) commercial genetic tests for *BRCA1* and *BRCA2*. These patients underwent screening with additional multiple DNA-based and RNA-based methods. Of these 300 patients, 17% carried previously undetected variants, including 35 (12%) with genomic rearrangement of *BRCA1* or *BRCA2*.

A 2008 study evaluated 251 patients with an estimated *BRCA* variant prevalence using the Myriad II model of at least 10%. In 136 non-Ashkenazi Jewish probands, 36 (26%) had *BRCA* point variants and 8 (6%) had genomic rearrangements (7 in *BRCA1*, 1 in *BRCA2*). Genomic rearrangements comprised 18% of all identified *BRCA* variants. No genomic rearrangements were identified in the 115 Ashkenazi Jewish probands, but 47 (40%) had point variants. The authors indicated that the estimated prevalence of a variant did not predict the presence of a genomic rearrangement.

Clinical Utility

Clinical utility is how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

As discussed above, the risk of cancer in a *BRCA* variant carrier is significant. Thus, knowledge of variant status in individuals at potentially increased risk of a *BRCA* variant may impact health care decisions to reduce risk. Risk-reducing options include intensive surveillance, chemoprevention, prophylactic mastectomy, or prophylactic oophorectomy.

Prophylactic mastectomy reduces the risk of breast cancer in high-risk women (based on family history) by 90%. Prophylactic oophorectomy significantly reduces the risk of ovarian cancer by 80% or more and reduces the risk of breast cancer by approximately 50%. In women who have already had breast cancer, prophylactic oophorectomy reduces the risk of cancer relapse. Prophylactic oophorectomy or salpingo-oophorectomy in women with *BRCA1* or *BRCA2* reduced the risk of all-cause mortality by 77% in a 2014 study and by 60% in a 2010 study.

Systematic reviews of observational studies comparing prophylactic surgeries to observation in women with *BRCA1* and *BRCA2* variants demonstrate contralateral prophylactic mastectomy in women with breast cancer are associated with significantly lower all-cause mortality while bilateral prophylactic mastectomy was not associated with all-cause mortality. Studies have indicated that the results of genotyping have a significant influence on treatment choices.

Phillips et al (2006) reported that although uptake of prophylactic surgery and screening was associated with knowing one's variant status, in their cohort of 70 unaffected female variant carriers who had chosen to receive results, a minority had risk-reducing surgery (11% had bilateral mastectomy; 29% had bilateral oophorectomy) or chemoprevention.

In their 2014 systematic review for USPSTF, Nelson et al assessed efficacy of risk-reducing surgery in *BRCA*-positive women. For high-risk women and variant carriers, bilateral mastectomy reduced breast cancer incidence by 85% to 100% and breast cancer mortality by 81% and 100%, respectively; salpingo-oophorectomy reduced breast cancer incidence by 37% to 100%, ovarian cancer incidence by 69% to 100%, and all-cause mortality by 55% to 100%, respectively. Some women experienced reduced anxiety. Although comparison groups varied across studies, results were consistent. Adverse events included physical complications of surgery, postsurgical symptoms, and changes in body image. Limitations of the analysis included the small number of studies (N=7) and small sample sizes. As the authors observed, it is still currently unknown whether *BRCA* variant testing reduces cause-specific or all-cause mortality, or if it improves the quality of life. Harms associated with false-negative results or variants of uncertain significance also are unknown.

Other studies have looked at the results of prostate cancer screening in men with *BRCA* variants. The IMPACT study (2011) evaluated the results of screening in 205 men 40 to 69 years of age who were *BRCA* variant carriers and 95 control patients. At the baseline screen, biopsies were performed in 7.0% of men with a prostate-specific antigen level greater than 3.0, and prostate cancer was identified in 3.3%. This resulted in a positive predictive value of 47.6%, which is considerably higher than that estimated for men at normal risk. Moreover, the grade of tumor identified was intermediate in 67% of cancers and high in 11%. This differs from the expected distribution of cancer grade in average-risk men, with more than 60% expected to have low-grade cancer.

Summary of Evidence

For individuals who have cancer or a personal or family cancer history and meet criteria suggesting a risk of hereditary breast and ovarian cancer syndrome who receive genetic testing for a *BRCA1* or *BRCA2* variant, the evidence includes a TEC Assessment and studies of variant prevalence and cancer risk. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and quality of life. The accuracy of variant testing has been shown to be high. Studies of lifetime risk of cancer for carriers of a *BRCA* variant have shown a risk as high as 85%. Knowledge of *BRCA* variant status in individuals at risk of a *BRCA* variant may impact health care decisions to reduce risk, including intensive surveillance, chemoprevention, and/or prophylactic intervention. In individuals with *BRCA1* or *BRCA2* variants, prophylactic mastectomy and oophorectomy have been found to significantly increase disease-specific survival and overall survival. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received through 3 physician specialty societies (5 reviewers) and 3 academic medical centers (5 reviewers) while this policy was under review in 2010. Those

providing input were in general agreement with the Policy statements considering testing for genomic rearrangements of *BRCA1* and *BRCA2* as medically necessary and with adding fallopian tube and primary peritoneal cancer as *BRCA*-associated malignancies to assess when obtaining the family history.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network guidelines on genetic and familial high-risk assessment of breast and ovarian cancers (v.1.2018) include criteria for identifying individuals who should be referred for further risk assessment, and separate criteria for genetic testing. Patients who satisfy any of the testing criteria listed in Table 1 should undergo "further personalized risk assessment, genetic counseling, and often genetic testing and management." For these criteria, both invasive and in situ breast cancers were included. Maternal and paternal sides of the family should be considered independently for familial patterns of cancer. Testing of unaffected individuals should be considered "only when an appropriate affected family member is unavailable for testing."

BRCA1 and *BRCA2* somatic variants are not common. The National Comprehensive Cancer Network recommends if a somatic variant is identified through tumor profiling, then *BRCA1* and *BRCA2* germline testing is recommended.

Table 1. BRCA1 and BRCA2 Testing Criteria for Hereditary Breast and Ovarian Cancer Syndrome

Recommendations
1. Individual from a family with a known BRCA1/BRCA2 mutation
2. Personal history of breast cancer and ≥1 of the following:
a. Diagnosed age ≤45 years
b. Diagnosed age ≤50 years AND:
An additional breast cancer primary
≥1 close blood relative with breast cancer at any age
≥1 close relative with pancreatic cancer
≥1 close relative with prostate cancer (Gleason score ≥7), or
Unknown or limited family history
c. Diagnosed age ≤60 years with a triple-negative (ER–, PR–, HER2–) breast cancer
d. Diagnosed any age AND
≥2 close blood relatives with breast, pancreatic or prostate cancer (Gleason score ≥7) at any age
≥1 close blood relative with breast cancer diagnosed at age 50 or younger
≥1 close blood relative with ovarian cancer or
A close male blood relative with breast cancer
For an individual of ethnicity associated with higher mutation frequency (e.g. Ashkenazi Jewish), no additional family history may be required
3. Personal history of ovarian cancer
4. Personal history of male breast cancer
5. Personal history of prostate cancer (Gleason score ≥7) at any age AND ≥1 close blood relative with ovarian cancer at cancer at any age or breast cancer at or before age 50 or 2 relatives with breast, pancreatic or prostate cancer (Gleason score ≥7) at any age.
6. Personal history of pancreatic cancer at any age AND ≥1 blood relative with ovarian cancer at any age or breast cancer at or before age 50 or 2 relatives with breast, pancreatic or prostate cancer (Gleason score ≥7 or metastatic) at any age For an individual of ethnicity associated with higher mutation frequency (e.g. Ashkenazi Jewish), no additional family history may be required
7. BRCA1/2 mutation detected by tumor profiling in the absence of germline mutation analysis

8. Family history only
    a. 1st- or 2nd-degree blood relative meeting any of the above criteria
    b. 3rd-degree blood relative with breast cancer and/or ovarian/fallopian tube/primary peritoneal cancer AND ≥2 1st-, 2nd-, or 3rd-degree relatives with breast cancer (≥1 at age ≤50 years) and/or ovarian cancer

ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; PR: progesterone receptor.

American Society of Clinical Oncology

The American Society of Clinical Oncology recommended in 2003 that cancer predisposition testing be offered when 3 factors are at play: (1) there is a personal or family history suggesting genetic cancer susceptibility, (2) the test can be adequately interpreted, and (3) results will influence medical management of the patient or family member at hereditary risk of cancer. A 2010 update of this statement recommended that "genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials."

Society of Gynecologic Oncology

In 2014, the Society of Gynecologic Oncology (SGO) published an evidence-based consensus statement on risk assessment for inherited gynecologic cancer. The statement included criteria for recommending genetic assessment (counseling with or without testing) to patients who may be genetically predisposed to breast or ovarian cancer. Overall, SGO and the National Comprehensive Cancer Network recommendations are very similar; the main differences being the exlusion of: women with breast cancer onset at age 50 years or younger who have 1 or more first-, second-, or third-degree relatives with breast cancer at any age; women with breast cancer or history of breast cancer who have a first-, second-, or third-degree male relative with breast cancer; and men with a personal history of breast cancer. Additionally, SGO recommended genetic assessment for unaffected women who have a male relative with breast cancer. Moreover, SGO indicated that some patients who do not satisfy criteria may still benefit from genetic assessment (eg, few female relatives, hysterectomy, or oophorectomy at a young age in multiple family members, or adoption in the lineage).

U.S. Preventive Services Task Force

Current U.S. Preventive Services Task Force (USPSTF) recommendations for genetic testing of *BRCA1* and *BRCA2* variants in women are listed next.

> "The USPSTF 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* gene. (D recommendation)"

Recommended screening tools include the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, and Family History Screen-7.

Key Words:

BRCA1, BRCA2, ~~CHEK2~~, genetic testing for inherited BRCA1 or BRCA2 mutations, genetic testing for inherited BRCA1 or BRCA2 variants, BART, BRCA Analysis Rearrangement Test, breast cancer, ovarian cancer, ovarian cancer syndrome, cancer of the fallopian tube, primary peritoneal cancer, prostate cancer, pancreatic cancer, gastrointestinal cancer, melanoma, laryngeal cancer, hereditary breast and ovarian cancer, HBOC, epithelial ovarian cancer, male breast cancer, Ashkenazi Jewish ancestry, germline variants, Comprehensive BRACAnalysis® test, BRCAvantage™, BRCAssureSM, founder mutation panel

Approved by Governing Bodies:

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Per the GeneTests website (www.genetests.org), there are currently 6 CLIA-certified U.S. laboratories that offer sequence analysis of the entire gene coding; and 4 CLIA-certified U.S. laboratories offer deletion, duplication, and copy number analysis. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Myriad Genetic Laboratories (Salt Lake City, UT) offers (1) the Comprehensive BRACAnalysis® test, which includes complete sequencing of *BRCA1* and *BRCA2* and gap polymerase chain reaction for 5 common rearrangements (deletions, duplications) in *BRCA1*; (2) the BRACAnalysis® Large Rearrangement Test (BART™), which may be ordered as a reflex test for patients who test negative for Comprehensive BRACAnalysis® to detect uncommon large rearrangements in *BRCA1* and *BRCA2*; (3) the Integrated BRACAnalysis® test, which includes BART™ as part of *BRCA1* or *BRCA2* analysis and (4) the BRACAnalysi CDxs®, which is intended to detect germline *BRCA1* and *BRCA2* variants to aid in identifying ovarian cancer patients who may be considered for treatment with olaparib.

Quest Diagnostics (Madison, NJ) offers BRCAvantage™, which includes sequencing of *BRCA1* and *BRCA2* and a multiplex ligation-dependent probe amplification assay to detect both common and uncommon gene rearrangements.

LabCorp (Burlington, NC) offers the BRCAssureSM suite of tests, which includes: targeted *BRCA1* and *BRCA2* variant analysis; a founder mutation panel for Ashkenazi Jewish patients (3 variants); comprehensive *BRCA1* and *BRCA2* analysis (full gene sequencing plus analysis of common and uncommon large rearrangements); and deletion and duplication analysis of uncommon large rearrangements only (without sequencing) when comprehensive analysis is negative.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.

FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved. Will be reviewed for medical necessity.

Current Coding:

CPT Codes:

81211	BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (i.e., exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)
81162	; full sequence analysis and full duplication/deletion analysis
81212	; 185delAG, 5385insC, 6174delT variants
81213	; uncommon duplication/deletion variants
81214	BRCA1 (breast cancer 1) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (i.e., exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)
81215	; known familial variant
81216	BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	; known familial variant

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Policy History:

Medical Policy Group, August 2003 **(1)**
Medical Policy Administration Committee, August 2003
Available for comment October 20-December 3, 2003
Medical Policy Group, November 2004 **(1):** Update to Key Points and References related to MPP update; no change in policy statement
Medical Policy Group, September 2005 **(1):** Update to Key Points and References related to MPP update; no change in policy statement
Medical Policy Group, March 2008 **(1):** Update to Policy, Key Points and References related to MPP update.
Medical Policy Administration Committee, April 2008
Available for comment April 4-May 18, 2008
Medical Policy Group, April 2010 **(1):** Changed coverage for genomic rearrangements (BART) testing, non-coverage for CHEK2 testing
Medical Policy Committee, April 2010
Available for comment April 7-May 21, 2010
Medical Policy Group, June 2011 **(1):** Clarification on BRCA1 and BRCA2 criteria for individuals with early-onset breast or ovarian cancer
Medical Policy Group, December 2011 **(1):** 2012 Coding Update – added, deleted, changed codes for 2012
Medical Policy Group, February 2012 **(3):** 2012 Coding Update – deleted 'S' codes effective 4/1/12
Medical Policy Group, October 2012 **(1):** Update to Policy, Policy Guidelines, Key Points and References related to MPP update; Genetic Testing for Hereditary Breast and/or Ovarian Cancer created in this new and separate policy, all aspects removed from policy 133 and replaced with a statement to refer to this policy; Policy statement edited for clarity and redundancy around epithelial ovarian/fallopian tube/primary peritoneal cancer; addition to policy criteria under affected women , not from high risk family—two or more close blood relatives with pancreatic cancer at any age—;removed additional criteria required for BART testing; defined early onset breast cancer as diagnosed at or before age 45; defined limited family history in policy guidelines
Medical Policy Administration Committee, October 2012

Available for comment October 24 through December 10, 2012
Medical Policy Group, December 2012 **(3):** 2013 Coding Update – Deleted code range 83890 through 83906 and 83912 effective 01/01/2013.
Medical Policy Panel, November 2013
Medical Policy Group, January 2014 **(1):** Update to Policy, Policy Guidelines, Key Points and References related to addition of personal or family history of prostate cancer and removing certain age limits on some criteria points, all effective 01/01/2014
Medical Policy Administration Committee, January 2014
Available for comment January 15 through February 28, 2014
Medical Policy Group, August 2015 **(3)**: added to current applicable Policy Statement the following cross-reference: "Refer to Medical Policy #605, *Genetic Testing for CHEK2 Mutations for Breast Cancer Policy* for additional information." No other changes at this time.
Medical Policy Group, November 2015: 2016 Annual Coding Update: Added new CPT code 81162 to Current Coding.
Medical Policy Group, April 2017 (**5**): Changed refer to MP 605 to refer to MP 609, *Moderate Penetrance Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk.* Medical Policy 605 has been retired and information combined with medical policy 609.
Medical Policy Group, October 2018 **(9):** Removed information related to CHEK2 testing from medical policy 513 and placed into medical policy 609; Added new key words: ovarian cancer syndrome, cancer of the fallopian tube, primary peritoneal cancer, prostate cancer, pancreatic cancer, gastrointestinal cancer, melanoma, laryngeal cancer, hereditary breast and ovarian cancer, HBOC, epithelial ovarian cancer, male breast cancer, Ashkenazi Jewish ancestry, germline variants, Comprehensive BRACAnalysis® test, BRCAvantage™, BRCAssureSM, founder mutation panel; removed key word: CHEK2; 2018 Updates to Title (Changed from *Genetic Testing for Hereditary Breast and/or Ovarian Cancer* to *Genetic Testing for Hereditary Breast/Ovarian Cancer (BRCA1 or BRCA2)*, Key Points, Description, References, verbiage updated (mutation replaced with variant); Policy statement updated to reflect current NCCN recommendations, no change to intent.
Available for comment October 29, 2018 through December 13, 2018.
Medical Policy Administration Committee, November 2018.
