Genetic Testing for Hereditary Breast and/or Ovarian Cancer

Policy # 00047
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Patients with Cancer
Based on review of available data, the Company may consider genetic testing for BRCA1 and BRCA2 mutations in cancer-affected individuals to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility for genetic testing for BRCA1 and BRCA2 mutations in cancer-affected individuals will be considered when ANY of the following criteria are met:

- Individual from a family with a known BRCA1/BRCA2 mutation
- Personal history of breast cancer and ≥1 of the following:
  - Diagnosed age ≤45 years
  - 2 primary breast cancers when 1st breast cancer diagnosis occurred age ≤50 years
  - Diagnosed age ≤50 years AND:
    - ≥1 1st-, 2nd-, or 3rd-degree relative with breast cancer at any age, or
    - Unknown or limited family history
  - Diagnosed age ≤60 years with a triple negative (ER−, PR−, HER2−) breast cancer
  - Diagnosed any age AND ≥1 1st-, 2nd-, or 3rd-degree relative with breast cancer diagnosed ≤50 years
  - Diagnosed any age AND ≥2 1st-, 2nd-, or 3rd-degree relatives with breast cancer at any age
  - Diagnosed any age AND ≥1 1st-, 2nd-, or 3rd-degree relative with epithelial ovarian/fallopian tube/primary peritoneal CA
  - Diagnosed any age AND ≥2 1st-, 2nd-, or 3rd-degree relatives with pancreatic cancer or prostate cancer at any age
  - 1st-, 2nd-, or 3rd-degree male relative with breast cancer
  - Ethnicity associated with deleterious founder mutations, eg, Ashkenazi Jewish descent
- Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer
- Personal history of male breast cancer
- Personal history of pancreatic cancer or prostate cancer at any age AND ≥2 1st-, 2nd-, or 3rd-degree relatives with any of the following at any age. For pancreatic cancer, if Ashkenazi Jewish ancestry, only 1 additional affected relative is needed.
  - Breast cancer
  - Ovarian/fallopian tube/primary peritoneal cancer
  - Pancreatic or prostate cancer
Patients without Cancer

Based on review of available data, the Company may consider genetic testing for BRCA1 and BRCA2 mutations in unaffected individuals to be eligible for coverage.

Patient Selection Criteria

Coverage eligibility for genetic testing for BRCA1 and BRCA2 mutations in unaffected individuals will be considered when ANY of the following criteria are met:

- Individual from a family with a known BRCA1/BRCA2 mutation; or
- 1st- or 2nd-degree blood relative meeting any criterion listed above for Patients with Cancer; or
- 3rd-degree blood relative with breast cancer and/or ovarian/fallopian tube/primary peritoneal cancer AND ≥2 1st-, 2nd-, or 3rd-degree relatives\(^a\) with breast cancer (≥1 at age ≤50 years) and/or ovarian/fallopian tube/primary peritoneal cancer; or
- Individual with a positive screening result from a familial risk stratification tool that has received an in-depth genetic counseling session from a cancer genetics professional that results in a recommendation for BRCA testing. (Records may be requested that document genetic counseling session notes with a 3 generation pedigree.)

Based on review of available data, the Company may consider testing for genomic rearrangements of the BRCA1 and BRCA2 genes in patients who meet criteria for BRCA testing, whose testing for point mutations is negative, to be eligible for coverage.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

The use of genetic testing either for those affected by breast, ovarian, fallopian tube, or primary peritoneal cancer or for unaffected individuals, including those with a family history of pancreatic cancer, when patient selection criteria are not met is considered to be investigational.*

Based on review of available data, the Company considers testing for CHEK2 (cell cycle checkpoint kinase 2) abnormality (mutations, deletions, etc.) in affected and unaffected patients with breast cancer, irrespective of family history, to be investigational.*

Based on review of available data, the Company considers genetic testing in minors for BRCA1 and BRCA2 mutations to be investigational.*

When Services Are Not Covered

The Company does not consider BRCA gene testing to be eligible for coverage if testing is performed primarily for the medical management of persons not covered by Blue Cross and Blue Shield of Louisiana or HMO Louisiana, Inc.
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Background/Overview

Hereditary breast and ovarian cancer (HBOC) syndrome describes the familial cancer syndromes that are related to mutations in the BRCA genes (BRCA1 located on chromosome 17q21 and BRCA2 located on chromosome 13q12-13). Identification of patients with BRCA mutations may lead to enhanced screening and/or surveillance that could lead to improved outcomes.

Several genetic syndromes with an autosomal dominant pattern of inheritance that feature breast cancer have been identified. Of these, HBOC and some cases of hereditary site-specific breast cancer have in common causative mutations in BRCA (breast cancer susceptibility) 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, and 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 most HBOC families, especially if ovarian cancer or male breast cancer are features. However, in site-specific breast cancer, BRCA mutations are responsible only for 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.

Cell cycle checkpoint kinase 2 is also involved with deoxyribonucleic acid (DNA) repair and human cancer predisposition, like BRCA1 and BRCA2. Cell cycle checkpoint kinase 2 is normally activated in response to DNA double-stranded breaks. Cell cycle checkpoint kinase 2 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.

a For the purpose of 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 the purpose of familial assessment, prostate cancer is defined as Gleason score ≥7.

c Testing for Ashkenazi Jewish or other founder mutation(s) should be performed first.
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Current U.S. Preventive Services Task Force (USPSTF) 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 mutations in \textit{BRCA1} or \textit{BRCA2} are:

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

Comprehensive mutation analysis

Comprehensive \textit{BRCA} mutation analysis should be performed in patients with breast cancer, ovarian cancer, cancer of the fallopian tube, or primary peritoneal cancer who are:

- Eligible for testing, and
- From families without a known deleterious \textit{BRCA1} or \textit{BRCA2} mutation, and
- Not from ethnic groups with known founder mutations.

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, before August 2006, testing for large deletions and rearrangements was not performed, thus some patients with familial breast cancer who had negative \textit{BRCA} testing before this time may consider repeat testing for the rearrangements.

High-risk ethnic groups:

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 \textit{BRCA} mutations found in Ashkenazi Jewish populations. When testing for founder mutations is negative, comprehensive mutation analysis should then be performed.

Testing unaffected individuals

In unaffected family members of potential \textit{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 \textit{BRCA} mutation be found in an affected family member(s), DNA from an unaffected family member can be tested specifically for the same mutation 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 mutation but leads to difficulties in interpreting negative test results (uninformative negative) or mutations of uncertain significance because the possibility of a causative \textit{BRCA} mutation is not ruled out.
Prostate cancer

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.

Rationale/Source

This policy was developed based on a 1997 Technology Evaluation Assessment (TEC) Assessment and has been updated on a regular basis with literature searches for articles that contained information regarding professional guidelines for BRCA testing, testing of unaffected family members, and testing of high-risk ethnic populations. In addition, relevant professional organizations were consulted for clinical guidelines.

Testing for BRCA1 and BRCA2 Mutations in High-Risk Women

Early estimates of lifetime risk of cancer for BRCA mutation carriers (penetrance), based on studies of families with extensive history of disease, have been as high as 85%. 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 (e.g., 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 mutation carriers from families with little history of cancer (~50% of all carriers) was not significantly different. Lifetime risks of ovarian cancer were 54% for BRCA1 and 23% for BRCA2 mutation carriers.

Women with a history of breast cancer and a BRCA mutation have a significant risk of contralateral breast cancer; in 1 prospective study (2004), the risk was 29.5% at 10 years 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 mutation carriers and 62% for BRCA2 mutation carriers. These investigators also reported cumulative risks of breast cancer by age 70 years in women without previous cancer of 60% in BRCA1 carriers and 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.

Thus, the risk of cancer in a BRCA mutation carrier is significant, and knowledge of mutation status in individuals at potentially increased risk of a BRCA mutation may impact healthcare decisions to reduce risk. Risk-reducing options include intensive surveillance, chemoprophylaxis, prophylactic mastectomy, or prophylactic oophorectomy. Prophylactic mastectomy reduces the risk of breast cancer in high-risk women (based on family history) by 90% or more but is invasive and disfiguring. Prophylactic oophorectomy significantly reduces the risk of ovarian cancer to less than 10% 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. Studies indicate that genotyping results significantly influence treatment choices.
Prevalence of BRCA Mutations

The prevalence of BRCA mutations is approximately 0.1% to 0.2% in the general population. Prevalence may be much higher for particular ethnic groups with characterized founder mutations (eg, 2.5% [1/40] in the Ashkenazi Jewish population). Family history of breast and ovarian cancer is an important risk factor for BRCA mutation. Age and, in some cases, ethnic background can also be independent risk factors. Malone et al reported on racial and ethnic differences in the prevalence of BRCA1 and BRCA2 in American women. Among their cases, 2.4% and 2.3% carried deleterious mutations in BRCA1 and BRCA2, respectively. BRCA1 mutations were significantly more common in “white” (2.9%) versus “black” (1.4%) cases and in Jewish (10.2%) versus non-Jewish (2.0%) cases; BRCA2 mutations were slightly more frequent in “black” (2.6%) versus “white” (2.1%) cases. Rennert et al reported that breast cancer-specific rates of death among Israeli women were similar for carriers of a BRCA founder mutation and noncarriers.

Clinical Features Suggestive of BRCA Mutation

Young age of onset of breast cancer, even in the absence of family history, has been demonstrated to be a risk factor for BRCA1 mutations. Winchester estimated that hereditary breast cancers account for 36% to 85% of patients diagnosed before age 30. In several studies, BRCA mutations 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 mutations is in the 40s. In the Ashkenazi Jewish population, Frank et al reported that 13% of 248 cases with no known family history and diagnosed before 50 years of age had BRCA mutations. In a similar study, 31% of Ashkenazi Jewish women, unselected for family history, diagnosed with breast cancer at younger than 42 years of age had BRCA mutations. Additional studies indicate that early age of breast cancer diagnosis is a significant predictor of BRCA mutations 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 mutation in ethnic populations characterized by founder mutations. For example, in unaffected individuals of Ashkenazi Jewish descent, 12% to 31% will have a BRCA mutation depending on the extent and nature of the family history. Several other studies document the significant influence of family history.

In patients with breast cancer that is “triple-negative”, ie, negative for expression of estrogen and progesterone receptors and for overexpression of HER2 receptors, there is an increased incidence of BRCA mutations. 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 mutations. BRCA1 mutations were found in 39.1% of patients and BRCA2 mutations in 8.7%. Young et al 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. A total of 6 BRCA mutations, 5 BRCA1, and 1 BRCA2, were found for a mutation rate of 11%. Finally, in a study of 77 patients with triple-negative breast cancer, 15 patients (19.5%) had BRCA mutations: 12 in BRCA1 and 3 in BRCA2.
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Testing Results
Unaffected individuals with a family history suggestive of hereditary breast and/or ovarian cancer but unknown family mutation may obtain interpretable results in most cases of a positive test. Most BRCA1 and BRCA2 mutations reported to date consist of frameshift deletions, insertions, or nonsense mutations leading to premature truncation of protein transcription. These are invariably deleterious and thus are informative in the absence of an established familial mutation. In addition, specific missense mutations and noncoding intervening sequence mutations may be interpreted as deleterious on the basis of accumulated data or from specific functional or biochemical studies. However, some BRCA mutations may have uncertain significance in the absence of a family study, and negative results offer no useful information, ie, the patient may still be at increased risk of a disease-associated mutation in an as yet undiscovered gene.

BRCA Mutation 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 mutation by 3.5- to 10-fold over the general population. Couch et al reported on screening for BRCA2 mutations in 2 cohorts of families at high risk for pancreatic cancer. In the first cohort of high-risk families, there were a total of 5 BRCA mutations in 151 probands (3%), and in the second cohort, there were another 5 BRCA2 mutations in 29 probands (17%). The combined BRCA2 mutation rate for these 2 cohorts was 6% (10/180). Ferrone et al tested 187 Ashkenazi Jewish patients with pancreatic cancer for BRCA mutations and found that 5.5% (8/187) had a BRCA mutation.

BRCA Mutation Associated With Ovarian Cancer
Women with a personal history of ovarian cancer also have an increased rate of BRCA mutations. In a systematic review of 23 studies, Trainer et al estimated the rate of BRCA mutations for women with ovarian cancer to be in the range of 3% to 15%. In this review, there were 3 studies that were performed in the United States and tested for both BRCA1 and BRCA2. The incidence of BRCA mutations in these studies was 11.3%, 15.3%, and 9.5%. In a population-based study of 1342 unselected patients with invasive ovarian cancer performed in Canada, there were 176 women with BRCA mutations, for a rate of 13.3%. The prevalence of mutations was higher for women in their 40s (24.0%) and in women with serous ovarian cancer (18.0%). Ethnicity was also an additional risk factor for BRCA, with higher rates seen in women of Italian (43.5%), Jewish (30.0%), and Indo-Pakistani origin (29.4%).

BRCA Mutation Associated With Fallopian Tube Cancer
A 2009 publication described the high rate of occult fallopian tube cancers in at-risk women having prophylactic bilateral salpingo-oophorectomy. In this prospective series of 45 women, 4 (9%) were found to have fallopian tube malignancies. The authors noted that this supports other studies that have demonstrated the fimbrial end of the fallopian tube as an important site of cancer in those with BRCA1 or BRCA2 mutations. Similarly, current National Comprehensive Cancer Network (NCCN) guidelines for assessing high risk in breast and ovarian cancer include both fallopian tube and primary peritoneal cancer as other malignancies that should be documented when assessing family history for BRCA1 and BRCA2 genotyping decisions.
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A long-term study (median follow-up, 7 years [range, 3-14 years]) followed 32 BRCA mutation carriers with occult malignancy (4 ovarian, 23 fallopian tube, and 5 ovarian and fallopian tube) diagnosed at 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 (OS) was 73%. Among 17 women with noninvasive neoplasia (median age, 53 years), 4 (24%) received chemotherapy, none of whom experienced recurrence. One patient (6%) who did not receive chemotherapy experienced recurrence at 43 months. Overall survival was 100%. The authors concluded that, in BRCA mutation carriers, unsuspected invasive carcinoma has a relatively high rate of recurrence, but noninvasive neoplasms rarely recur and may not require adjuvant chemotherapy.

Clinical Outcomes in BRCA Mutation Carriers

A clinical approach to these patients was published in 2007 by Robson and Offit Phillips et al (2006) reported that although uptake of prophylactic surgery and screening was associated with knowing one’s mutation status, in their cohort of 70 unaffected female mutation carriers who had chosen to receive results, a minority utilized risk-reducing surgery (11% had bilateral mastectomy and 29% bilateral oophorectomy) or chemoprevention.

In 2013, Lesnock et al compared OS in 393 women with BRCA1-mutated and BRCA1-nonmutated epithelial ovarian cancer who were treated with intraperitoneal (IP) or intravenous (IV) only chemotherapy. All patients had “optimally resected” (<1 cm residual disease) stage III disease. BRCA1 mutation status was determined by blinded review of immunohistochemistry assays of archived tumor samples. Treatment regimens were IV paclitaxel plus intraperitoneal cisplatin and paclitaxel (IP therapy) or IV paclitaxel and cisplatin (IV therapy). In 204 women with nonmutated BRCA1, median OS was not statistically different between treatment groups (58 months vs 50 months in the IP therapy and IV therapy groups, respectively; p=0.82). In 189 women with mutated BRCA1, median OS was significantly longer in the IP therapy group (84 months vs 47 months, respectively; p<0.001).

BRCA Mutation Associated With Prostate Cancer

A number of studies have indicated that BRCA mutations are associated with increased risk of prostate cancer in men. In a 2010 study of 832 Ashkenazi Jewish men diagnosed with localized prostate cancer, and 454 Ashkenazi Jewish men without prostate cancer, the presence of a BRCA2 mutation was associated with a more than 3-fold increased risk of prostate cancer (odds ratio [OR], 3.18; 95% confidence interval [CI], 1.52 to 6.66). In a similar population of 251 Ashkenazi Jewish men with prostate cancer and 1472 volunteers without prostate cancer, the presence of a BRCA mutation was associated with a more than 3-fold increased risk of prostate cancer (OR=3.41; 95% CI, 1.64 to 7.06). When analyzed by type of BRCA mutation, BRCA2 was associated with an almost 5-fold increased risk (OR=4.82; 95% CI, 1.87 to 12.25), and BRCA1 mutations were not associated with an increased risk (OR=2.20; 95% CI, 0.72 to 6.70). A 2013 retrospective analysis compared prostate cancer outcomes in 79 BRCA mutation carriers (18 BRCA1, 61 BRCA2) and 2019 noncarriers. Men with BRCA mutations more often had Gleason scores of 8 or higher (p<0.001), nodal involvement (p<0.001) and metastases at diagnosis (p=0.005) than noncarriers. Median OS was 8.1 years in carriers and 12.9 years in noncarriers (hazard ratio [HR], 1.9; 95% CI, 1.1 to 3.3; p=0.012). In subgroup analyses, BRCA2 mutations were independently associated with reduced OS
(HR=1.9; 95% CI, 1.1 to 3.1; p=0.004), but BRCA1 mutations were not, possibly due to small sample size and limited follow-up.

Other studies have looked at the results of prostate cancer screening in men with BRCA mutations. The IMPACT study (2011) evaluated the results of screening in 205 men 40 to 69 years of age who were BRCA mutation carriers and 95 control patients. At the baseline screen, biopsies were performed in 7.0% of patients with a prostate specific antigen (PSA) 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 normal risk men. Also, 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.

Candidate Modifier Genes
There has been interest in further risk-stratifying patients with known BRCA mutations to further assist in clinical decision making. Numerous recent publications have identified a large number of candidate modifier genes, and nongenetic modifying factors also have been examined. Antoniou et al examined the risk of breast cancer associated with 9 genetic polymorphisms, most which had previously shown an increase cancer risk among BRCA carriers. Seven of the 9 polymorphisms were confirmed to increase breast cancer risk. The magnitude of increased risk varied by whether the patient was a BRCA1 versus a BRCA2 carrier, and the polymorphisms appeared to interact multiplicatively to increase risk.

Kleibl et al reported that the AIB1 (amplified in breast 1) genotype in general did not influence breast cancer risk in BRCA carriers but that the specific AIB1 genotype consisting of 28 glutamine repeats in both alleles (28/28) conferred a decreased risk of breast cancer (HR=0.64; 95% CI, 0.41 to 0.99; p=0.045). In 2013, Bianco et al conducted a meta-analysis to examine the effect of AIB1 polyglutamine repeats on breast cancer risk in BRCA mutation carriers. Seven case-control and cohort studies of 28 of 28, 29 of 29, and ≤26 repeats in 1 or both alleles were included. No statistically significant association with breast cancer risk was observed for polyglutamine repeats of any length in BRCA, BRCA1, or BRCA2 mutation carriers. Statistical heterogeneity was significant in the analyses of 28/28 repeats in BRCA1 and BRCA2 mutation carriers.

Zhou et al reported an increased risk of cancer in BRCA carriers who also had the RAD51 135G>C polymorphism (OR=1.34; 95% CI, 1.01 to 1.78; p=0.04). Metcalfe et al reported that family history provided additional predictive information in BRCA carriers. For each first-degree relative with breast cancer before age 50 years, the risk of ovarian cancer increased 1.6-fold (HR=1.61; 95% CI, 1.21 to 2.14) in BRCA1 mutation carriers, and the risk of breast cancer increased 1.7-fold in BRCA2 mutation carriers (HR=1.67; 95% CI, 1.04 to 2.07).

BRCA Testing in Minors
The use of genetic testing for BRCA mutations 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 mutation. In addition, there are potential harms related to stigmatization and discrimination.
Testing for Large BRCA Rearrangements

Over the past few years, 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 mutations have large genomic rearrangements (including deletions or duplications) in 1 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 ribonucleic acid (RNA)-based methods. Of these 300 patients, 17% carried previously undetected mutations, including 35 (12%) with genomic rearrangement of BRCA1 or BRCA2.

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

Based on these published studies, a substantial minority of clinically significant BRCA mutations will be large genomic rearrangements that are not detected by sequence analysis. These mutations will be missed if BART testing (BRACAnalysis® Rearrangement Test) is not performed. Commercial laboratories began to offer expanded testing in August 2006; BRCA testing done before this date did not include analysis for genomic rearrangement. After August 2006, based on information available from the laboratory, this additional testing is conducted on a subset of patients, and additional information on breast cancer risk may be requested in some cases. Clinical guidelines, such as those from NCCN, consider BART testing as part of comprehensive BRCA testing and do not require additional criteria other than a negative sequence result. Therefore, testing for genomic rearrangements of BRCA1 and BRCA2 with BART may be considered medically necessary as part of comprehensive BRCA analysis, when testing for standard mutations on sequence analysis is negative.

CHEK2 Mutations

A number of publications also have described the association of CHEK2 mutations with hereditary breast cancer. The prevalence of this finding varies greatly by geographic region, being most common in northern and Eastern Europe. It has been detected in 4% of early breast cancer patients in the Netherlands and in 2.3% of such patients in Germany, but has been noted to be rare in patients in Spain or Australia. In the U.S., this mutation is much less common than BRCA mutations and BRCA rearrangements. For example, in the study by Walsh et al cited earlier, 14 (4.7%) of the 300 patients with a positive family history of breast cancer (4 affected relatives) who were negative by standard BRCA testing, were positive for CHEK2 mutations. The low frequency makes evaluation of risk and treatment implications less precise. In general, the risk of breast cancer associated with this mutation is less that that associated with either BRCA1 or BRCA2.

A 2008 meta-analysis by Weischer et al concluded that for familial breast cancer, the cumulative risk at age 70 years for the CHEK2*1100delC mutation was 37% (95% CI, 28% to 56%). This risk is lower than...
cumulative risk at age 70 of 57% for \textit{BRCA1} and 49% for \textit{BRCA2}. In an accompanying editorial, Offit and Garber raised a number of questions about potential use of this assay. In particular, they questioned the breast cancer risk estimates presented in the Weischer study and the variable methods of ascertainment used in the studies in the meta-analysis. They also noted the varying frequencies of the mutation across populations, eg, 0.5% to 1.0% in Northern and Eastern Europe and 0.2% to 0.3% in the U.S. In other populations, other mutations, such as \textit{CHEK2}\textsuperscript{S428F}, may be more common, eg, in Ashkenazi Jews. Finally, they raised concerns about the implications of the low penetrance of this mutation. They concluded that on the basis of data available at this time, there is no compelling evidence to justify routine clinical testing for \textit{CHEK2} to guide the management of families affected with breast cancer. Thus, based on a number of concerns, testing for \textit{CHEK2} mutations is considered investigational because the impact on net health outcome is uncertain.

Since the meta-analysis by Weischer, there have been additional studies evaluating the risk of breast cancer associated with the \textit{CHEK2} mutation. In 2011, Myszka et al examined 284 breast cancer patients, 113 ovarian cancer patients, and 287 healthy women from a cohort of Polish individuals. The \textit{CHEK2} mutation rate was not higher among patients with breast or ovarian cancer compared to healthy women.

In 2011, Zhang et al performed a systematic review of candidate-gene association studies, identifying more than 1000 published articles. Meta-analysis was performed for a total of 279 genetic variants in 128 genes that were identified by at least 3 different researchers. Significant associations with the risk of breast cancer were found for 29 variants in 20 genes. The association was strong for 10 variants in 6 genes, 4 of which were located in the \textit{CHEK2} gene; for 2 variants of the \textit{ATM} gene and an additional 4 genes that had a single variant with a strong association (\textit{CASP8, CTLA4, NBN, TP53}). In 2011, Peng et al performed an overview of systematic reviews and pooled analyses on the association of genetic variants with breast cancer. A total of 87 analyses were identified, which examined 145 candidate gene variants and found that 46 variants were significantly associated with breast cancer. The ORs for these associations ranged from 0.66 to 3.13. Using the method of false-positive report probability, there were 10 associations in 7 genes that were noteworthy: \textit{CASP8, CHEK2, CTLA4, FGFR2, ILIB, LSP1, and MAP3K1}.

Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received through 3 Physician Specialty Societies (5 reviews) and 3 Academic Medical Centers (5 reviews) while this policy was under review for January 2010. Although 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. Those providing input were in general agreement with the Policy Statements considering testing for genomic rearrangements of \textit{BRCA1} and \textit{BRCA2} as medically necessary, with the statement considering \textit{CHEK2} testing as investigational, and with adding fallopian tube and primary peritoneal cancer as additional \textit{BRCA}-associated malignancies to assess when obtaining the family history.
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Summary
The presence of a BRCA1 or BRCA2 mutation confers a high lifetime risk for breast and ovarian cancer among affected women. These mutations may be gene sequence variations or large rearrangements/deletions. Knowledge of mutation status in individuals at risk of a BRCA mutation may impact healthcare decisions to reduce risk. Risk-reducing options include intensive surveillance, chemoprophylaxis, prophylactic mastectomy, or prophylactic oophorectomy. Criteria for testing high-risk women have been developed by NCCN, the USPSTF and other review bodies. Definitions of high-risk vary somewhat, and there is not widespread agreement on the optimal criteria that should be used for defining high-risk. When testing high-risk women, health outcomes are improved; therefore, testing high-risk women for BRCA1 and BRCA2 mutations may be considered medically necessary.

Mutations other than BRCA1 and BRCA2 have been reported to be associated with an increased risk of breast cancer. Although a number of these, for example the CHEK2 mutation, have been confirmed to be associated with increased risk, clinical utility of testing for these non-BRCA mutations has not been demonstrated. Therefore, genetic testing for mutations other than BRCA1 and BRCA2 to determine risk of breast and/or ovarian cancer is considered investigational.

Practice Guidelines and Position Statements
National Comprehensive Cancer Network
The NCCN guideline, Genetic/Familial High-Risk Assessment: Breast and Ovarian cancer, was updated in 2014. The guideline contains 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 are 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.”

Table 1. NCCN Hereditary Breast and/or Ovarian Cancer Syndrome Testing Criteria

<table>
<thead>
<tr>
<th>Testing Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Individual from a family with a known BRCA1/BRCA2 mutation</td>
</tr>
<tr>
<td>2. Personal history of breast cancer and ≥1 of the following:</td>
</tr>
<tr>
<td>a. Diagnosed age ≤45 years</td>
</tr>
<tr>
<td>b. 2 primary breast cancers when 1st breast cancer diagnosis occurred age ≤50 years</td>
</tr>
<tr>
<td>c. Diagnosed age ≤50 years AND:</td>
</tr>
<tr>
<td>i. ≥1 1st-, 2nd-, or 3rd-degree relativea with breast cancer at any age, or</td>
</tr>
<tr>
<td>ii. Unknown or limited family history</td>
</tr>
<tr>
<td>d. Diagnosed age ≤60 years with a triple negative (ER−, PR−, HER2−) breast cancer</td>
</tr>
</tbody>
</table>
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- Diagnosed any age AND ≥1 1st-, 2nd-, or 3rd-degree relativea with breast cancer diagnosed ≤50 years
- Diagnosed any age AND ≥2 1st-, 2nd-, or 3rd-degree relativesa with breast cancer at any age
- Diagnosed any age AND ≥1 1st-, 2nd-, or 3rd-degree relativea with epithelial ovarian/fallopian tube/primary peritoneal CA
- Diagnosed any age AND ≥2 1st-, 2nd-, or 3rd-degree relativesa with pancreatic cancer or prostate cancerb at any age
- 1st-, 2nd-, or 3rd-degree male relative with breast cancer

For individuals of ethnicity associated with increased mutation frequency (eg, Ashkenazi 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 pancreatic cancer or prostate cancerb at any age AND ≥2 1st-, 2nd-, or 3rd-degree relativesa with any of the following at any age. For pancreatic cancer, if Ashkenazi Jewish ancestry, only 1 additional affected relative is needed:
   a. Breast cancer
   b. Ovarian/fallopian tube/primary peritoneal cancer
   c. Pancreatic or prostate cancerb
6. Family history onlyd:
   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-, 3rd-degree relatives with breast cancer (≥1 at age ≤50 years) and/or ovarian/fallopian tube/primary peritoneal cancer.

a Blood relatives on the same side of the family (maternal or paternal).
   1. 1st-degree relatives are parents, siblings, and children.
   2. 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.
   3. 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.

b Gleason score ≥7.

c Testing for Ashkenazi Jewish or other founder mutation(s) should be performed first.

d Significant limitations of interpreting test results for an unaffected individual should be discussed.

According to NCCN guidelines, patients who meet criteria for genetic testing should be tested for mutations in BRCA1 and BRCA2. In patients with a known familial BRCA mutation, targeted testing for the specific mutation is recommended. In patients with no known familial BRCA mutation, comprehensive testing, including full sequencing and testing for large genomic rearrangements, is recommended; if the affected individual is of Ashkenazi Jewish descent, testing for the 3 known founder mutations (185delAG and 5182insC in BRCA1; 6174delT in BRCA2) should be done first. The guidelines do not include recommendations for genotyping low or moderate penetrance susceptibility genes, such as CHEK2.
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U.S. Preventive Services Task Force
Current USPSTF recommendations for genetic testing of BRCA1/BRCA2 mutations in women are listed next. Screening tools recommended for assessment of genetic risk are: the Ontario FHAT; Manchester scoring system; RST; PAT; and FHS-7.

- The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with one 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. (Grade B recommendation; Recommended)
- 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. (Grade D recommendation; Not recommended)

American Society of Clinical Oncology
The American Society of Clinical Oncology (ASCO) recommended in 2003 that cancer predisposition testing be offered when (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 policy statement recommended that “genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials.” The CHEK2*1100delC variant was cited as a mutation with unproven clinical utility.

American College of Medical Genetics
In 1999, the American College of Medical Genetics (ACMG) published guidelines for BRCA testing under the auspices of a grant from the New York State Department of Health to the ACMG Foundation. This guideline was retired in 2013.

References
4. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). BRCA1 and BRCA2 testing to determine the risk of breast and ovarian cancer. TEC Assessments 1997; volume 12, tab 4.


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60. Walsh T, Casadei S, Goats KH et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. JAMA 2006; 295(12):1379-88.
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<th>Code Type</th>
<th>Code</th>
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<tr>
<td>CPT</td>
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<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-9 Diagnosis</td>
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</tr>
<tr>
<td>ICD-9 Procedure</td>
<td>No codes</td>
</tr>
</tbody>
</table>

Policy History
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04/25/2003 Medical Policy Committee review
05/12/2003 Managed Care Advisory Council approval
05/07/2004 Medical Director review
05/18/2004 Medical Policy Committee review. Format revision. No substance changes to policy.
06/28/2004 Managed Care Advisory Council approval
04/05/2005 Medical Director review

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04/19/2005 Medical Policy Committee review. Investigational statements added to address: BRCA testing for unaffected individuals without family history or early age diagnosis as well as the use of BRCA testing in minors.
05/23/2005 Managed Care Advisory Council approval
06/07/2006 Medical Director review
05/02/2007 Medical Director review
05/23/2007 Medical Policy Committee approval
05/07/2008 Medical Director review
05/21/2008 Medical Policy Committee approval. Title changed to match BCBSA. No change to coverage eligibility.
07/02/2009 Medical Director review
07/22/2009 Medical Policy Committee approval. No change to coverage eligibility.
07/01/2010 Medical Policy Committee approval
07/21/2010 Medical Policy Implementation Committee approval. Two statements were added to the coverage section: one to indicate testing for genomic rearrangements may be considered to be eligible with criteria and a second that testing for CHEK2 mutations is investigational. Fallopian tube cancer and primary peritoneal cancer added to the coverage statements as additional cancers to be assessed in determining family history to assess risk.
07/07/2011 Medical Policy Committee review
04/12/2012 Medical Policy Committee review
04/25/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/06/2012 Medical Policy Committee review
09/19/2012 Medical Policy Implementation Committee approval. Replaced the Patient Selection Criteria for both Cancer-affected Individuals and Unaffected Adults with criteria from the 2012 NCCN Guidelines. Added a Note following the Patient Selection Criteria for clarification.
11/01/2012 Medical Policy Committee review
11/28/2012 Medical Policy Implementation Committee approval. Removed “and either (1) there are 3 or more family members (1 lineage) affected with breast or ovarian or fallopian tube or primary peritoneal cancer or (2) who have a risk of a BRCA mutation of at least 10%” from that last eligible for coverage statement on testing for genomic rearrangements of the BRCA1 and BRCA 2 genes.
03/04/2013 Coding updated
04/04/2013 Medical Policy Committee review
04/24/2013 Medical Policy Implementation Committee approval. Criteria revised to track BCBSA.
06/05/2014 Medical Policy Committee review
06/18/2014 Medical Policy Implementation Committee approval. Policy coverage statement rewritten for clarity and policy was updated with current NCCN guidelines. Added a 4th criteria bullet for patients without cancer regarding BRCA testing. “Including those with a family history of pancreatic cancer” added to investigational statement.

Next Scheduled Review Date: 06/2015

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
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B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
   2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:
   A. in accordance with nationally accepted standards of medical practice;
   B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
   C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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