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

Policy # 00047  
Original Effective Date: 05/13/2003  
Current Effective Date: 06/21/2017

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.

Note: Testing for CHEK2, PALB and ATM variants in assessment of breast cancer risk is addressed separately in medical policy 00504.

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
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- Personal history of pancreatic cancer or prostate cancer\(^b\) at any age AND ≥2 1st-, 2nd-, or 3rd-degree relatives\(^a\) 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\(^b\)

**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 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.
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.

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

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

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 BRCA1 or BRCA2 are:

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

A Recommended Testing Strategy

Patients who meet criteria for genetic testing as outlined in the Policy Statements above 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 unknown familial BRCA mutation:
  - Non-Ashkenazi Jewish descent
    - To identify clinically significant mutations, 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 for 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/BRCA2 mutations (eg. Prostate cancer, pancreatic cancer, melanoma).
    - If no familial mutation can be identified, two possible testing strategies are:
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Full sequencing followed by testing for common large genomic rearrangements (deletions/duplications) only if sequencing detects no mutation (negative result).
  - More than 90% of BRCA mutations 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 Mutation analysis below) may be performed as is recommended by NCCN.
    - Comprehensive testing can detect 92.5% of BRCA1/BRCA2 mutations.
  - If comprehensive BRCA testing is negative, testing for uncommon large genomic rearrangements (eg BART™) may be done.
    - Among patients with negative comprehensive testing, BART identified a deleterious mutation (positive result) in less than 1%.

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 the testing is negative for founder mutations comprehensive genetic testing may be considered (see Comprehensive Mutation Analysis, below).

COMPREHENSIVE MUTATION ANALYSIS

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 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 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 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 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
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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 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.

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. 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.
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FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
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 Act (CLIA). Per the www.genetests.org website, there are currently 6 CLIA-certified U.S. laboratories that offer sequence analysis of the entire coding and 4 that offer deletion/duplication/copy number analysis. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Myriad Genetic Laboratories (Salt Lake City, UT) offers (1) Comprehensive BRACAnalysis™† that includes complete sequencing of BRCA1/BRCA2 and gap polymerase chain reaction for 5 common rearrangements (deletions/duplications) in BRCA1; (2) BRACAnalysis Large Rearrangement Test (BART), which may be ordered as a reflex for patients who test negative for Comprehensive BRACAnalysis to detect uncommon large rearrangements in BRCA1 and BRCA2; and (3) Integrated BRACAnalysis, which includes BART as part of BRCA1/BRCA2 analysis.

Quest Diagnostics (Madison, NJ) offers BRCAvantage™‡ that 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 BRCAssure™ suite of tests which includes: targeted BRCA1 and BRCA2 analysis for known BRCA1 or BRCA2 mutations; a founder mutation panel for Ashkenazi Jewish patients (3 mutations); comprehensive BRCA1/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) for use when comprehensive analysis is negative.

Centers for Medicare and Medicaid Services (CMS)
Palmetto’s MolDx Program has determined that BRCA1- and BRCA2-targeted mutation analysis (familial or founder mutation), sequencing with common deletion and duplication analysis, and uncommon deletion and duplication analysis meets Medicare criteria for a covered service.

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 contain information regarding professional guidelines for BRCA testing, testing of unaffected family members, and testing of high-risk ethnic populations. The most recent update covered the period through October 7, 2016.

Testing for BRCA1 and BRCA2 Mutations in High-Risk Women
Nelson et al (2013) conducted a systematic review that included meta-analysis estimates of the prevalence and penetrance of BRCA mutations, 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. Based on a literature search through December 31, 2012, the authors selected 70 articles to address 5 key questions. BRCA prevalence and penetrance were estimated to assess clinical validity of mutation testing.
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 is tested, and 70% for BRCA1 and 71% for BRCA2 when multiple family members are tested; cumulative risks for developing ovarian cancer by age 70 were 41% for BRCA1 and 17% for BRCA2 when a single family member is tested, and 46% for BRCA1 and 23% for BRCA2 when multiple family members are 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.

Gabai-Kapara et al (2014) studied breast and ovarian cancer risks among 211 Ashkenazi Jewish female BRCA1/BRCA2 founder mutation carriers who were identified through an unaffected male carrier relative. All study participants underwent BRCA1/BRCA2 genotyping for 3 founder mutations (BRCA1 185delAG, BRCA1 5382insC, and BRCA2 6174delT) that account for 11% of breast cancer and 40% of ovarian cancer in this population. Approximately half of identified carriers were from low-risk families who would not have satisfied criteria for testing. Cumulative risks for developing breast or ovarian cancer were similar to those observed in female BRCA1/BRCA2 mutation carriers from high-risk families who satisfy criteria for testing. For example: Cumulative risks for developing breast or ovarian cancer by age 60 and 80 were 60% and 83%, respectively, for BRCA1 mutation carriers, and 33% and 76%, respectively, for BRCA2 mutation carriers; for breast cancer only, cumulative risks were 41% and 60%, respectively, for BRCA1 mutation carriers, and 26% and 40%, respectively, for BRCA2 mutation carriers; for ovarian cancer only, cumulative risks were 27% and 53%, respectively, for BRCA1 mutation carriers, and 7% and 62%, respectively, for BRCA2 mutation carriers. Among BRCA2 mutation carriers, higher than expected cumulative risk of ovarian cancer and lower than expected cumulative risk of breast cancer were attributed to reduced prevalence of nongenetic risk factors for breast cancer, eg, late age at first pregnancy, in the study sample and therefore reduced competing risk.) Duration of follow-up was not specified. Based on these findings, several authors of this study advocated universal screening of women for BRCA1 and BRCA2 mutation status. However, despite the authors’ assertion that results of this study are “widely applicable,” this is unlikely to be true; as the authors themselves stated, “The Ashkenazi Jewish population is unusual.” Others have urged caution in communicating risks associated with radical surgery (prophylactic mastectomy, oophorectomy) in BRCA1 and BRCA2 mutation carriers identified through population screening.

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 (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 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.
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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 were 59% for BRCA1 carriers and 17% for BRCA2 carriers. Although there is a significantly increased risk of cancer in BRCA carriers, the association between BRCA and cancer mortality is not clear. Observational studies have suggested that BRCA mutations, in particular BRCA2, might be associated with longer overall survival (OS) and progression-free survival in patients with ovarian cancer, at least in the short term. The observed improvement in survival might be due to higher chemotherapy response. BRCA mutations are generally associated with poorer OS in patients with breast cancer.

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, chemoprevention, 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. Systematic reviews of observational studies comparing prophylactic surgeries to observation in women with BRCA1 and BRCA2 mutations demonstrate that prophylactic bilateral oophorectomy in women with and without breast cancer and 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 genotyping results significantly influence treatment choices.

Prevalence of BRCA Mutations

Nelson et al included meta-analysis estimates of BRCA prevalence in their 2013 systematic review for USPSTF. In unselected women, BRCA mutation 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%.

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.

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 “triple-negative” breast cancer (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.

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
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... uncertain significance in the absence of a family study, and negative results offer no useful information, i.e., the patient may still be at increased risk of a disease-associated mutation in an as yet undiscovered gene.

**BRCA Mutation 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 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 Rates Associated With Ovarian Cancer**
Women with a personal history of ovarian cancer also have an increased rate of BRCA mutations. In a 2010 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 U.S. studies that tested for both BRCA1 and BRCA2; incidences of BRCA mutations were 11.3%, 15.3%, and 9.5%. In a 2011 population-based study of 1342 unselected patients with invasive ovarian cancer performed in Canada, 176 women had BRCA mutations, for a rate of 13.3%. Mutation 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 Mutation Rates 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. Reviewers 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, 2017 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.

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
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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 their 2014 systematic review for USPSTF, Nelson et al assessed efficacy of risk-reducing surgery in BRCA-positive women. For high-risk women and mutation 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, whether BRCA mutation testing reduces cause-specific or all-cause mortality and improves quality of life is currently unknown. Harms associated with false-negative results or variants of uncertain significance also are unknown.

Rennert et al (2007) reported that breast cancer-specific rates of death among Israeli women were similar for carriers of a BRCA founder mutation and noncarriers.

Lesnock et al (2013) compared OS in 393 women with BRCA1-mutated and BRCA1-nonmutated epithelial ovarian cancer who were treated with intraperitoneal or intravenous-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 intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel (IP therapy) or intravenous 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 Rates 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).
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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.

In its updated (2014) statement on risk assessment for inherited gynecologic cancer, the Society of Gynecologic Oncologists (SGO) acknowledged that the risk of developing breast or ovarian cancer in a woman younger than age 21 is very low, "even in families with inherited cancer susceptibility as a result of HBOC syndrome." Because detection of an HBOC-associated mutation "would change the management of very few women in this age group," and because of potential negative consequences of testing, SGO "does not recommend genetic testing of women younger than age 21 for HBOC in the absence of a family history of extremely early-onset cancer."

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.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this policy are listed in Table 1.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
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<th>Completion Date</th>
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<td>Ongoing NCT00685256</td>
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<td>NCT02133703</td>
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Uninformative BRCA1/2 Test Results or Positive BRCA1/2 Test Results

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<td>NCT02225015</td>
<td>Cancer Prevention in Women With a BRCA Mutation: A Follow-up Genetic Counselling Intervention</td>
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Unpublished

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<tr>
<td>NCT01851109</td>
<td>Prevention of Ovarian Cancer in Women Participating in Mammography</td>
<td>458</td>
<td>Dec 2015 (completed)</td>
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NCT: national clinical trial.

Clinical Input Received From 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.

2010 Input

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 for January 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 additional BRCA-associated malignancies to assess when obtaining the family history.

Summary

For individuals who have cancer or a personal or family cancer history and meeting criteria suggesting a risk of HBOC syndrome who receive genetic testing for a BRCA1 or BRAC2 mutation, the evidence includes a TEC Assessment and studies of mutation prevalence and cancer risk. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, quality of life, and treatment-related morbidity. The accuracy of mutation testing has been shown to be high. Studies of lifetime risk of cancer for carriers of a BRCA1 mutation have shown a risk as high as 85%. Knowledge of BRCA mutation status in individuals at risk of a BRCA mutation may impact health care decisions to reduce risk, including intensive surveillance, chemoprevention, and/or prophylactic intervention. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

References

2. 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. PMID

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Current Effective Date: 06/21/2017
04/25/2003 Medical Policy Committee review
05/12/2003 Managed Care Advisory Council approval

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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
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 BRCA2 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.
06/04/2015 Medical Policy Committee review
06/17/2015 Medical Policy Committee approval. Title changed to match BCBSA. No change to coverage eligibility.
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08/03/2015  Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
01/01/2016  Coding update
06/02/2016  Medical Policy Committee review
06/20/2016  Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017  Coding update: Removing ICD-9 Diagnosis Codes
06/01/2017  Medical Policy Committee review
06/21/2017  Medical Policy Implementation Committee approval. Removed CHEK2 statement and added reference to 00504 which addresses CHEK2, PALB and ATM testing.

Next Scheduled Review Date: 06/2018

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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*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. 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 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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