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

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.

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

When Services Are Eligible for Coverage
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 variants is negative, to be eligible for coverage.

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 variants in cancer-affected individuals to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility for genetic testing for BRCA1 and BRCA2 variants in cancer-affected individuals will be considered when ANY of the following criteria are met:
- Individual from a family with a known BRCA1/BRCA2 variant; or
- Personal history of breast cancer and ≥1 of the following:
  - Diagnosed age ≤45 years; or
  - 2 primary breast cancers when 1st breast cancer diagnosis occurred age ≤50 years; or
  - 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; or
  - Diagnosed any age AND ≥1 1st-, 2nd-, or 3rd-degree relative with breast cancer diagnosed ≤50 years; or
  - Diagnosed any age AND ≥2 1st-, 2nd-, or 3rd-degree relatives with breast cancer at any age; or
  - Diagnosed any age AND ≥1 1st-, 2nd-, or 3rd-degree relative with epithelial ovarian/fallopian tube/primary peritoneal CA; or
Genetic Testing for Hereditary Breast and/or Ovarian Cancer Syndrome (BRCA1 or BRCA2)

Policy # 00047
Original Effective Date: 05/13/2003
Current Effective Date: 06/20/2018

- Diagnosed any age AND ≥2 1st-, 2nd-, or 3rd-degree relatives with pancreatic cancer or prostate cancer at any age; or
- 1st-, 2nd-, or 3rd-degree male relative with breast cancer; or
- Ethnicity associated with deleterious founder variants, e.g., Ashkenazi Jewish descent;
- Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer; or
- Personal history of male breast cancer; or
- Personal history of pancreatic cancer or prostate cancer at any age AND ≥1 1st-, 2nd-, or 3rd-degree relatives with either of the following.
  - Breast cancer ≤50; or
  - Ovarian/fallopian tube/primary peritoneal cancer at any age;
- Personal history of pancreatic cancer or prostate cancer at any age AND ≥2 1st-, 2nd-, or 3rd-degree relatives with breast, pancreatic or prostate cancer at any age.; or
- For pancreatic cancer, if Ashkenazi Jewish ancestry no additional affected relative is needed.

Patients without Cancer
Based on review of available data, the Company may consider genetic testing for BRCA1 and BRCA2 variants in unaffected individuals to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility for genetic testing for BRCA1 and BRCA2 variants in unaffected individuals will be considered when ANY of the following criteria are met:
- Individual from a family with a known BRCA1/BRCA2 variant; 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 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.)

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

- For familial assessment, prostate cancer is defined as Gleason score ≥7.
Genetic Testing for Hereditary Breast and/or Ovarian Cancer Syndrome (BRCA1 or BRCA2)

Policy # 00047
Original Effective Date: 05/13/2003
Current Effective Date: 06/20/2018

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

Testing for Ashkenazi Jewish or other founder mutation(s) should be performed first (see Policy Guidelines section):

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 variants 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.

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

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

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

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

- In patients with a known familial BRCA variant, targeted testing for the specific variant is recommended.
- In patients with unknown familial BRCA variant:
Genetic Testing for Hereditary Breast and/or Ovarian Cancer Syndrome (BRCA1 or BRCA2)

Policy # 00047
Original Effective Date: 05/13/2003
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Page 4 of 18
testing before this time may consider repeat testing for the rearrangements (see When Services May Be Eligible for Coverage section for criteria).

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

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

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

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

GENETIC COUNSELING
Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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

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**Background/Overview**

Several genetic syndromes with an autosomal dominant pattern of inheritance that feature breast cancer have been identified. Of these, hereditary breast and ovarian cancer (HBOC) and some cases of hereditary site-specific breast cancer have in common causative variants 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 evidence review, we refer collectively to both as *hereditary breast and/or ovarian cancer*.

Germline variants 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 cancer, *BRCA* variants are responsible only for a proportion of affected families. *BRCA* gene variants are inherited in an autosomal dominant fashion through maternal or paternal lineage. It is possible to test for abnormalities in *BRCA1* and *BRCA2* genes to identify the specific variant in cancer cases and to identify family members at increased cancer risk. Family members without existing cancer who are found to have *BRCA* variants can consider preventive interventions for reducing risk and mortality.

**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 Amendments (CLIA). Per the GeneTests website (www.genetests.org), there are currently 6 CLIA-certified U.S. laboratories that offer sequence analysis of the entire gene coding; and 4 CLIA-certified U.S. laboratories offer deletion, duplication, and copy number analysis. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

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

Policy # 00047
Original Effective Date: 05/13/2003
Current Effective Date: 06/20/2018

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

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

Centers for Medicare and Medicaid Services (CMS)
There are no national coverage determinations. There is a local coverage determination by Palmetto MolDX Program, which 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 met Medicare criteria for a covered service.

Rationale/Source
This review was informed by a 1997 Technology Evaluation Center (TEC) Assessment.

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

TESTING FOR BRCA1 AND BRCA2 VARIANTS IN HIGH-RISK INDIVIDUALS
Clinical Context and Test Purpose
The purpose of testing for BRCA1 and BRCA2 variants in high-risk individuals is to evaluate whether HBOC syndrome is present and, if it is, to determine the appropriate surveillance and treatment to decrease the risk of mortality from breast and/or ovarian cancer.

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

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

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

Intervention
The intervention of interest is BRCA1 and BRCA2 variant testing.
Comparator
The comparator of interest is standard of care without genetic testing for HBOC syndrome.

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

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

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

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

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

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

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

Policy # 00047
Original Effective Date: 05/13/2003
Current Effective Date: 06/20/2018

19.8% for BRCA1 or BRCA2; in unselected Ashkenazi Jewish women, 2.1%; and in Ashkenazi Jewish women from high-risk families, 10.2%.

Estimates of lifetime risk of cancer for BRCA variant carriers (penetrance), based on studies of families with extensive history of disease, have been as high as 85%. For example, Kuchenbaecher et al (2017) found that the cumulative risk of breast cancer up to age 80 was 72% in BRCA1 carriers and 69% in BRCA2 carriers. Because other factors that influence risk may be present in families with extensive breast and ovarian cancer histories, early penetrance estimates may have been biased upward. Studies of founder mutations in ethnic populations (eg, Ashkenazi Jewish, Polish, Icelandic populations) unselected for family history indicated lower penetrance estimates, in the range of 40% to 60% for BRCA1 and 25% to 40% for BRCA2. However, a genotyping study of Ashkenazi Jewish women with incident invasive breast cancer, selected regardless of family history of cancer and their family members, resulted in an 82% lifetime risk of breast cancer for carriers of any of 3 BRCA founder mutations (185delAG, 5382insC, 6174delT). Importantly, the risk of cancer in variant carriers from families with little history of cancer (~50% of all carriers) did not differ significantly. Lifetime risks of ovarian cancer were 54% for BRCA1, and 23% for BRCA2 variant carriers.

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

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

Clinical Features Suggestive of BRCA Variant

Young age of onset of breast cancer, even in the absence of family history, is a risk factor for BRCA1 variants. Winchester (1996) estimated that hereditary breast cancers account for 36% to 85% of patients diagnosed before age 30. In several studies, BRCA variants are independently predicted by early age at onset, being present in 6% to 10% of breast cancer cases diagnosed at ages younger than various premenopausal age cutoffs (age range, 35-50 years). In cancer-prone families, the mean age of breast cancer diagnosis among women carrying BRCA1 or BRCA2 variants is in the 40s. In the Ashkenazi Jewish population, Frank et al (2002) reported that 13% of 248 cases with no known family history and diagnosed before 50 years of age had BRCA variants. In a similar study (2000), 31% of Ashkenazi Jewish women, unselected for family history, diagnosed with breast cancer at younger than 42 years of age had BRCA variants. Other studies have indicated that early age of breast cancer diagnosis is a significant predictor of BRCA variants in the absence of family history in this population.
As in the general population, family history of breast or ovarian cancer, particularly of early age onset, is a significant risk factor for a BRCA variant in ethnic populations characterized by founder mutations. For example, in unaffected individuals of Ashkenazi Jewish descent, 12% to 31% will have a BRCA variant depending on the extent and nature of the family history. Several other studies have documented the significant influence of family history.

In patients with “triple-negative” breast cancer (i.e., negative for expression of estrogen and progesterone receptors; and negative for overexpression of human epidermal growth factor receptor 2 receptors), there is an increased prevalence of BRCA variants. Pathophysiologic research has suggested that the physiologic pathway for development of triple-negative breast cancer is similar to that for BRCA-associated breast cancer. In 200 randomly selected patients with triple-negative breast cancer from a tertiary care center, there was a greater than 3-fold increase in the expected rate of BRCA variants. BRCA1 variants were found in 39.1% of patients and BRCA2 variants in 8.7%. Young et al (2009) studied 54 women with high-grade, triple-negative breast cancer with no family history of breast or ovarian cancer, representing a group that previously was not recommended for BRCA testing. Six BRCA variants (5 BRCA1, 1 BRCA2) were found, for a variant rate of 11%. Finally, in a 2011 study of 77 patients with triple-negative breast cancer, 15 patients (19.5%) had BRCA variants (12 in BRCA1, 3 in BRCA2).

**BRCA Variant Rates Associated With Pancreatic Cancer**

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

**BRCA Variant Rates Associated With Ovarian Cancer**

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

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

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

Testing for Large BRCA Rearrangements

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

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

Clinical Utility

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

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

Prophylactic mastectomy reduces the risk of breast cancer in high-risk women (based on family history) by 90%. Prophylactic oophorectomy significantly reduces the risk of ovarian cancer by 80% or more and

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

Policy # 00047
Original Effective Date: 05/13/2003
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reduces the risk of breast cancer by approximately 50%. In women who have already had breast cancer, prophylactic oophorectomy reduces the risk of cancer relapse. Prophylactic oophorectomy or salpingo-oophorectomy in women with BRCA1 or BRCA2 reduced the risk of all-cause mortality by 77% in a 2014 study and by 60% in a 2010 study.

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

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

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

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

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

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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.

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

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

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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
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

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Page 15 of 18
Genetic Testing for Hereditary Breast and/or Ovarian Cancer Syndrome (BRCA1 or BRCA2)

Policy # 00047
Original Effective Date: 05/13/2003
Current Effective Date: 06/20/2018

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 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.
06/04/2015 Medical Policy Committee review.
06/17/2015 Medical Policy Committee approval. Title changed to match BCBSA. No change to coverage eligibility.
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.
06/07/2018 Medical Policy Committee review.
06/20/2018 Medical Policy Implementation Committee approval. Replaced “mutation(s)” with “variant(s)” throughout the policy. Created a “When Services Are Eligible for Coverage” section for the first coverage statement, since it stands alone with no criteria. Changed the last three criteria bullets in the “Patients with Cancer” section to as follows:
- Personal history of pancreatic cancer or prostate cancer≥ at any age AND ≥1 1st-, 2nd-, or 3rd-degree relatives with either of the following.
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- Breast cancer ≤ 50; or
- Ovarian/fallopian tube/primary peritoneal cancer at any age.
- Personal history of pancreatic cancer or prostate cancer at any age AND ≥ 2 1st-, 2nd-, or 3rd-degree relatives with breast, pancreatic or prostate cancer at any age.
- For pancreatic cancer, if Ashkenazi Jewish ancestry no additional affected relative is needed.

Added footnotes (a-d) from BCBSA’s policy to the end of the “When Services May Be Eligible for Coverage” section.

Next Scheduled Review Date: 06/2019

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:

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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

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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