Policy Statement

Genetic testing should be performed in a setting that has suitably trained health care providers who can give appropriate pre- and posttest counseling and that has access to a Clinical Laboratory Improvement Amendments-licensed laboratory that offers comprehensive variant analysis (see Policy Guidelines section: Comprehensive Variant Analysis).

Patients with Cancer or With Personal History of Cancer

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

- Individual from a family with a known BRCA1 or BRCA2 variant
- Personal history of breast cancer (including invasive and ductal carcinoma in situ) and one or more of the following:
  - Diagnosed at age 45 or younger
  - Two primary breast cancers when first breast cancer diagnosis occurred on or before 50 years of age (includes bilateral [contralateral] disease or cases where there are two or more clearly separate [ipsilateral] primary tumors either synchronously or asynchronously)
  - Diagnosed on or before 50 years of age and:
    - One or more 1st-, 2nd-, or 3rd-degree relative(s) with breast cancer at any age, pancreatic cancer or prostate cancer
    - Unknown or limited family history
  - Diagnosed on or before 60 years of age with a triple-negative (estrogen receptor-negative, progesterone receptor-negative, human epidermal growth factor receptor 2-negative) breast cancer
  - Diagnosed at any age AND one or more 1st-, 2nd-, or 3rd-degree relative(s) with breast cancer diagnosed on or before 50 years of age
  - Diagnosed at any age AND two or more 1st-, 2nd-, or 3rd-degree relatives with breast cancer at any age
  - Diagnosed at any age AND one or more 1st-, 2nd-, or 3rd-degree relatives with epithelial ovarian, fallopian tube, or primary peritoneal cancer
  - Diagnosed at any age AND two or more 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 (e.g., Ashkenazi Jewish descent)
- Personal history of epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Personal history of male breast cancer
- Personal history of pancreatic cancer and Ashkenazi Jewish ancestry
- Personal history of high-grade pancreatic cancer or prostate cancer at any age AND one or more 1st-, 2nd-, or 3rd-degree relatives with any of the following:
  - Breast cancer at age 50 or younger
  - Ovarian, fallopian tube, or primary peritoneal cancer at any age
  - Pancreatic or prostate cancer
- Personal history of metastatic prostate cancer (radiographic evidence of or biopsy-proven disease)
- Personal history of pancreatic cancer or prostate cancer at any age AND 2 or more 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)
• BRCA1 or BRCA2 pathogenic mutation detected by tumor profiling on any tumor type in the absence of germline mutation analysis

Patients without Cancer or Without History of Cancer
(See Policy Guidelines section: Testing Unaffected Individuals.)

Genetic testing for BRCA1 and BRCA2 variants of cancer-affected individuals may be considered medically necessary under any of the following circumstances:
- Individual from a family with a known BRCA1 or BRCA2 variant
- First- or second-degree blood relative meeting any criterion listed above for Patients With Cancer
- Third-degree blood relative with both of the following:
  - Breast cancer (including invasive and ductal carcinoma in situ) and/or ovarian, fallopian tube, or primary peritoneal cancer
  - Two or more 1st-, 2nd-, or 3rd-degree relatives with breast cancer (at least one with breast cancer at age 50 or younger) and/or ovarian, fallopian tube, or primary peritoneal cancer

Genetic testing for BRCA1 and BRCA2 variants in cancer-affected individuals or of cancer-affected individuals with a family history of cancer when criteria above are not met is considered investigational.

Genetic testing in minors for BRCA1 and BRCA2 variants is considered investigational.

BRCA Analysis Rearrangement Test (BART)
Testing for large genomic rearrangements of the BRCA1 or BRCA2 genes (BART) to identify adult patients at risk for BRCA1 or BRCA2 related cancers may be considered medically necessary when both of the following are met:
- Criteria for BRCA1 and BRCA2 testing (as above)
- Testing for point mutations (BRCA1 and BRCA2) is negative

Genetic testing for BRCA1 and BRCA2 mutations and/or large genomic rearrangements (BART) is considered investigational in any of the following situations:
- Adults not meeting the indications/criteria for BRCA1 and BRCA2, and/or BART testing described above
- Individuals under the age of 18
- Genetic screening in the general population

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

- In patients with a known familial BRCA variant, targeted testing for the specific variant is recommended.
- In patients with unknown familial BRCA variant:
  - Non-Ashkenazi Jewish descent
    - To identify clinically significant variants, NCCN advises testing a relative who has breast or ovarian cancer—especially with early-onset disease, bilateral disease, multiple primaries, or ovarian cancer—because that individual has the highest likelihood of obtaining a positive test result.
    - If no living family member with breast or ovarian cancer exists, NCCN suggests testing first- or second-degree family members affected with cancer thought to be related to deleterious BRCA1 or BRCA2 variants (e.g., prostate cancer, pancreatic cancer, melanoma).
  - If no familial variant can be identified, 2 possible testing strategies are:
    - Full sequencing followed by testing for common large genomic rearrangements (deletions, duplications) only if sequencing detects no variant (negative result).
    - More than 90% of BRCA variants will be detected by full sequencing.
    - Alternatively, simultaneous full sequencing and testing for common large genomic rearrangements (also known as comprehensive BRCA testing; see Comprehensive Variant Analysis below) may be performed as is recommended by NCCN.
  - Comprehensive testing can detect 92.5% of BRCA1 or BRCA2 variants.
  - If comprehensive BRCA testing is negative, testing for uncommon large genomic rearrangements (e.g., BART™) may be done.
    - Testing for uncommon large rearrangements should not be done unless both sequencing and testing for common large rearrangements have been performed and are negative.
    - Among patients with negative comprehensive testing, BART™ identified a deleterious variant (positive result) in less than 1%.
  - Ashkenazi Jewish descent
    - In patients of known Ashkenazi Jewish descent, NCCN recommends testing for the 3 known founder mutations (185delAG and 5182insC in BRCA1; 6174delT in BRCA2) first.
    - If testing is negative for founder mutations, comprehensive genetic testing may be considered (see Comprehensive Variant Analysis).

Comprehensive Variant Analysis
Comprehensive variant analysis currently includes sequencing the coding regions and intron and exon splice sites, as well as testing to detect common large deletions and rearrangements that can be missed with sequence analysis alone. In addition, before August 2006, testing for large deletions and rearrangements was not performed, thus some patients with familial breast cancer who had negative BRCA testing before this time may consider repeat testing for the rearrangements (see Policy section for criteria).

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

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

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

**Familial Assessment Descriptions**

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

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

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

*d* Testing for Ashkenazi Jewish or other founder mutation(s) should be performed first (see Policy Guidelines section: High-Risk Ethnic Groups).

**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.

**Description**

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

- Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing
- Moderate Penetrance Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk
- Prophylactic Mastectomy

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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

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

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

LabCorp (Burlington, NC) offers the BRCAssure™ 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.
Rationale

Background
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.

Literature Review
See Appendix Table 1 for genetic testing categories.

This review was informed by a 1997 Blue Cross Blue Shield Association 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 (ie, demonstration that the diagnostic information can be used to improve patient outcomes).

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

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

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

 Patients
The relevant population of interest is patients with cancer (ie, 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.
2.04.02 Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome (BRCA1 or BRCA2)

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 speciality setting (e.g., multidisciplinary oncology care) commercially through various manufacturers and institutions.

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

Clinical Validity
Studies have focused on identifying the population that is appropriate for testing (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 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 (e.g., Ashkenazi Jewish, Polish, Icelandic populations) unselected for family history indicated lower penetrance estimates, in the range of 40% to 60% for BRCA1 and 25% to 40% for BRCA2.
However, a genotyping study of Ashkenazi Jewish women with incident invasive breast cancer, selected regardless of family history of cancer and their family members, resulted in an 82% lifetime risk of breast cancer for carriers of any of 3 BRCA founder mutations (185delAG, 5382insC, 6174delT). Importantly, the risk of cancer in 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 one 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 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 in is 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 (ie, 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 RNA-based methods. Of these 300 patients, 17% carried previously undetected variants, including 35 (12%) with genomic rearrangement of BRCA1 or BRCA2.

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

**Clinical Utility**

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

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

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

Systematic reviews of observational studies comparing prophylactic surgeries to observation in women with BRCA1 and BRCA2 variants demonstrate contralateral prophylactic mastectomy in women with breast cancer are associated with significantly lower all-cause mortality while bilateral prophylactic mastectomy was not associated with all-cause mortality. Studies have indicated that the results of genotyping have a significant influence on treatment choices. Phillips et al (2006) reported that although uptake of prophylactic surgery and screening was associated with knowing one’s variant status, in their cohort of 70 unaffected female variant carriers who had chosen to receive results, a minority had risk-reducing surgery (11% had bilateral mastectomy; 29% had bilateral oophorectomy) or chemoprevention.

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

Other studies have looked at the results of prostate cancer screening in men with BRCA variants. The IMPACT study (2011) evaluated the results of screening in 205 men 40 to 69 years of age who were BRCA variant carriers and 95 control patients. At the baseline screen, biopsies were performed in 7.0% of men with a prostate-specific antigen level greater than 3.0, and prostate cancer was identified in 3.3%. This resulted in a positive predictive value of 47.6%, which is considerably higher than that estimated for men at normal risk. Moreover, the grade of tumor identified was intermediate in 67% of cancers and high in 11%. This differs from the expected distribution of cancer grade in average-risk men, with more than 60% expected to have low-grade cancer.
Summary of Evidence
For individuals who have cancer or a personal or family cancer history and meet criteria suggesting a risk of hereditary breast and ovarian cancer syndrome who receive genetic testing for a BRCA1 or BRCA2 variant, the evidence includes a TEC Assessment and studies of variant prevalence and cancer risk. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and quality of life. The accuracy of variant testing has been shown to be high. Studies of lifetime risk of cancer for carriers of a BRCA variant have shown a risk as high as 85%. Knowledge of BRCA variant status in individuals at risk of a BRCA variant may impact health care decisions to reduce risk, including intensive surveillance, chemoprevention, and/or prophylactic intervention. In individuals with BRCA1 or BRCA2 variants, prophylactic mastectomy and oophorectomy have been found to significantly increase disease-specific survival and overall survival. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information
Clinical Input 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.

In response to requests from Blue Cross Blue Shield Association, input was received through 3 physician specialty societies (5 reviewers) and 3 academic medical centers (5 reviewers) in 2010. Those providing input were in general agreement with the Policy statements considering testing for genomic rearrangements of BRCA1 and BRCA2 as medically necessary and with adding fallopian tube and primary peritoneal cancer as BRCA-associated malignancies to assess when obtaining the family history.

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

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

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

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</thead>
<tbody>
<tr>
<td>1. Individual from a family with a known BRCA1/BRCA2 mutation</td>
</tr>
<tr>
<td>2. Personal history of breast cancer and ( \geq 1 ) of the following:</td>
</tr>
<tr>
<td>a. Diagnosed age ( \leq 45 ) years</td>
</tr>
<tr>
<td>b. Diagnosed age ( \leq 50 ) years AND:</td>
</tr>
<tr>
<td>An additional breast cancer primary</td>
</tr>
<tr>
<td>( \geq 1 ) close blood relative with breast cancer at any age</td>
</tr>
<tr>
<td>( \geq 1 ) close relative with pancreatic cancer</td>
</tr>
<tr>
<td>( \geq 1 ) close relative with prostate cancer (Gleason score ( \geq 7 )), or</td>
</tr>
<tr>
<td>Unknown or limited family history</td>
</tr>
<tr>
<td>c. Diagnosed age ( \leq 60 ) years with a triple-negative (ER-, PR-, HER2-) breast cancer</td>
</tr>
<tr>
<td>d. Diagnosed any age AND</td>
</tr>
</tbody>
</table>

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### Recommendations

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 close blood relatives with breast, pancreatic or prostate cancer</td>
<td>(Gleason score ≥7) at any age</td>
</tr>
<tr>
<td>≥1 close blood relative with breast cancer diagnosed at age 50 or younger</td>
<td></td>
</tr>
<tr>
<td>≥1 close blood relative with ovarian cancer or</td>
<td></td>
</tr>
<tr>
<td>A close male blood relative with breast cancer</td>
<td></td>
</tr>
<tr>
<td>For an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish), no additional family history may be required</td>
<td></td>
</tr>
</tbody>
</table>

3. Personal history of ovarian cancer
4. Personal history of male breast cancer
5. Personal history of prostate cancer (Gleason score ≥7) at any age AND ≥1 close blood relative with ovarian cancer at cancer at any age or breast cancer at or before age 50 or 2 relatives with breast, pancreatic or prostate cancer (Gleason score ≥7) at any age.
6. Personal history of pancreatic cancer at any age AND ≥1 blood relative with ovarian cancer at any age or breast cancer at or before age 50 or 2 relatives with breast, pancreatic or prostate cancer (Gleason score ≥7 or metastatic) at any age For an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish), no additional family history may be required.
7. BRCA1/2 mutation detected by tumor profiling in the absence of germline mutation analysis
8. Family history only
   a. 1st- or 2nd-degree blood relative meeting any of the above criteria
   b. 3rd-degree blood relative with breast cancer and/or ovarian/fallopian tube/primary peritoneal cancer AND ≥2 1st-, 2nd-, or 3rd-degree relatives with breast cancer (≥1 at age ≤50 years) and/or ovarian cancer

ER: Estrogen Receptor; HER2: Human Epidermal Growth Factor Receptor 2; PR: Progesterone Receptor.

### American Society of Clinical Oncology

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

### Society of Gynecologic Oncology

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

### U.S. Preventive Services Task Force

Current U.S. Preventive Services Task Force (USPSTF) recommendations for genetic testing of BRCA1 and BRCA2 variants in women are listed next. The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with 1 of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (BRCA1 or BRCA2). Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing. (B recommendation)
The USPSTF recommends against routine genetic counseling or BRCA testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the BRCA1 or BRCA2 gene. (D recommendation)"

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

**Medicare National Coverage**

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.55

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 2.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02154672</td>
<td>Prostate Cancer Screening in Men With Germline BRCA2 Mutations</td>
<td>100</td>
<td>May 2018</td>
</tr>
<tr>
<td>NCT02225015</td>
<td>Cancer Prevention in Women With a BRCA Mutation</td>
<td>300</td>
<td>Jun 2019</td>
</tr>
<tr>
<td>NCT02321228</td>
<td>Early Salpingectomy (Tubectomy) With Delayed Oophorectomy in BRCA1/2 Gene Mutation Carriers (TUBA)</td>
<td>510</td>
<td>Jan 2035</td>
</tr>
</tbody>
</table>

NCT: National Clinical Trial.

**Appendix**

**Appendix Table 1. Categories of Genetic Testing Addressed in 2.04.02**

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
<td>X</td>
</tr>
<tr>
<td>1a. Diagnostic</td>
<td>X</td>
</tr>
<tr>
<td>1b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>1c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td>X</td>
</tr>
<tr>
<td>2a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>2b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>2c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td>X</td>
</tr>
<tr>
<td>4. Testing of an affected individual’s germline to benefit family members</td>
<td>X</td>
</tr>
<tr>
<td>5. Reproductive testing</td>
<td></td>
</tr>
<tr>
<td>5a. Carrier testing: preconception</td>
<td></td>
</tr>
<tr>
<td>5b. Carrier testing: prenatal</td>
<td></td>
</tr>
<tr>
<td>5c. In utero testing: aneuploidy</td>
<td></td>
</tr>
<tr>
<td>5d. In utero testing: familial variants</td>
<td></td>
</tr>
<tr>
<td>5e. In utero testing: other</td>
<td></td>
</tr>
<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
<td></td>
</tr>
</tbody>
</table>

**References**

1. 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.
2.04.02 Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome (BRCA1 or BRCA2) 

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**Documentation for Clinical Review**

**Please provide the following documentation (if when requested):**
- History and physical and/or consultation notes including:
  - Ethnicity/Ancestry
  - Personal and/or family history of cancer (if applicable) including:
    - Family relationship(s): (maternal or paternal), (family member [e.g., sibling, aunt, grandparent]), (living or deceased) (if applicable)
    - Site(s) of cancer
2.04.02  Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome (BRCA1 or BRCA2)

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- Age at diagnosis (including family members)
- If breast cancer, indicate if bilateral, premenopausal, or triple negative cancer
  - BRCA1/BRCA2 mutation history (if applicable)
- Genetic counseling/professional results (if applicable)
- Laboratory or Pathology reports (e.g., BRCA results for BART testing requests, or hormone receptor assay. If founder mutation (81212) testing is requested, a negative 81212 result is required before 81211, with reflex to 81213, is allowable.) (if applicable)

Post service
- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE
The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>81162</td>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis</td>
</tr>
<tr>
<td></td>
<td>81211</td>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)</td>
</tr>
<tr>
<td></td>
<td>81212</td>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis</td>
</tr>
<tr>
<td></td>
<td>81213</td>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants</td>
</tr>
<tr>
<td></td>
<td>81214</td>
<td>BRCA1 (breast cancer 1) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)</td>
</tr>
<tr>
<td></td>
<td>81215</td>
<td>BRCA1 (breast cancer 1) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
</tr>
<tr>
<td></td>
<td>81216</td>
<td>BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td></td>
<td>81217</td>
<td>BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
</tr>
<tr>
<td></td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
</tbody>
</table>

HCPCS | None
ICD-10 Procedure | None
### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.
Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.