Medical Policy

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Title: BRCA1 and BRCA2 Testing

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http://www.bcbsks.com/CustomerService/Forms/pdf/15-17_predeterm_request_frm.pdf

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Populations	Interventions	Comparators	Outcomes
Individuals: • With cancer or personal or family cancer history and criteria suggesting risk of hereditary breast/ovarian cancer syndrome	Interventions of interest are: • Genetic testing for a *BRCA1* or *BRAC2* mutation	Comparators of interest are: • Standard of care without genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Quality of life
Individuals: • With other high-risk cancers (eg, cancers of the fallopian tube, pancreas, prostate)	Interventions of interest are: • Genetic testing for a *BRCA1* or *BRCA2* variant	Comparators of interest are: • Standard of care without genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life

DESCRIPTION

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

OBJECTIVE

The objective of this policy is to determine whether genetic testing for *BRCA1* or *BRCA2* variants improves the net health outcome in individuals with cancer or who have a personal or family history of cancer, which might suggest hereditary breast/ovarian cancer syndrome or other high-risk cancers.

BACKGROUND

Hereditary Breast and Ovarian Cancer Syndrome

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, laryngeal cancer, occur more frequently in HBOC families. Hereditary site-specific breast cancer families are characterized by early onset breast cancer with or without male cases, but without ovarian cancer. For this policy, both will be referred to collectively as *hereditary breast and/or ovarian cancer*.

Germline variants in the *BRCA1* and *BRCA2* genes are responsible for the cancer susceptibility in the majority of HBOC families, especially if ovarian cancer or male breast cancer are features. However, in site-specific breast cancer, *BRCA* variants are responsible for only a proportion of affected families. *BRCA* gene variants are inherited in an autosomal dominant fashion through either the maternal or paternal lineage. It is possible to test for abnormalities in *BRCA1* and *BRCA2* genes to identify the specific variant in cancer cases and to identify family members with increased cancer risk. Family members without existing cancer who are found to have *BRCA* variants can consider preventive interventions for reducing risk and mortality.

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.[1] In several studies, *BRCA* variants were 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).[1-4] In cancer-prone families, the mean age of breast cancer diagnosis among women carrying *BRCA1* or *BRCA2* variants is in the 40s.[5] 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.[2] In a similar study by Gershoni-Baruch et al (2000), 31% of Ashkenazi Jewish women, unselected for family history, diagnosed with breast cancer at younger than 42 years of age had *BRCA* variants.[6] 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.[7-9]

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.[4] Several other studies have documented the significant influence of family history.[6-10]

In patients with "triple-negative" breast cancer (ie, negative for expression of estrogen, progesterone, and 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.[11] In 200 randomly selected patients with triple-negative breast cancer from a tertiary care center, Kandel et al (2006) reported there was a greater than 3-fold increase in the expected rate of *BRCA* variants.[12] *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.[13] Six *BRCA* variants (5 *BRCA1*, 1 *BRCA2*) were

found, for a variant rate of 11%. Finally, Gonzalez-Angulo et al (2011) in a study of 77 patients with triple-negative breast cancer, reported that 15 patients (19.5%) had *BRCA* variants (12 in *BRCA1*, 3 in *BRCA2*).[14]

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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 offers the following tests:

- Comprehensive BRACAnalysis® test includes complete sequencing of *BRCA1* and *BRCA2* and gap polymerase chain reaction for 5 common rearrangements (deletions/duplications) in *BRCA1*
- BRACAnalysis® Large Rearrangement Test (BART™), is a reflex test for patients who test negative for Comprehensive BRACAnalysis® test to detect uncommon large rearrangements in *BRCA1* and *BRCA2*
- Integrated BRACAnalysis® test includes BART as part of *BRCA1* or *BRCA2* analysis
- BRACAnalysis CDxs® is intended to detect germline *BRCA1* and *BRCA2* variants to identify patients with breast or ovarian cancer who may be considered for treatment with olaparib, niraparib, or talazoparib.

Quest Diagnostics 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 offers the BRCAssureSM suite of tests, which includes: targeted *BRCA1* and *BRCA2* variant analysis; a founder mutation panel for Ashkenazi Jewish patients (3 mutations); 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.

POLICY

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

A. **Patients With Cancer or With a 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:

1. Individual from a family with a known *BRCA1* or *BRCA2* variant

2. Personal history of breast cancer and one or more of the following:

   a. Diagnosed at age ≤45 years

   b. Diagnosed 46 to 50 years with:
      i. One or more 1st-, 2nd-, or 3rd-degree blood relative with breast cancer at any age
      ii. An unknown or limited family history[c]
      iii. An additional breast cancer primary at any age
      iv. One or more 1st-, 2nd-, or 3rd-degree blood relative with high grade (Gleason score ≥7) prostate cancer

   c. Diagnosed ≤60 years with:
      i. Triple negative breast cancer

   d. Diagnosed at any age with:
      i. One or more 1st-, 2nd-, or 3rd-degree blood relative with
         - Breast cancer diagnosed at ≤50 years; or
         - Ovarian, fallopian tube, or primary peritoneal cancer; or
         - Male breast cancer; or
         - Metastatic prostate cancer; or
         - Pancreatic cancer
      ii. ≥2 additional diagnoses of breast cancer at any age in patient and/or 1st-, 2nd-, or 3rd-degree blood relative

   e. Ashkenazi Jewish ancestry

3. Personal history of ovarian, fallopian tube, or primary peritoneal cancer

4. Personal history of male breast cancer

5. Personal history of pancreatic cancer

6. Personal history of metastatic prostate cancer

7. Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with:

    a. One or more 1st-, 2nd-, or 3rd-degree blood relative with ovarian, fallopian tube, or primary peritoneal cancer, pancreatic cancer, or metastatic prostate cancer at any age or breast cancer ≤50 years; or
        i. Two or more 1st-, 2nd-, or 3rd-degree blood relatives with breast or prostate cancer (any grade) at any age; or

    b. Ashkenazi Jewish ancestry

8. BRCA1 or BRCA2 pathogenic or likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline pathogenic or likely pathogenic variant analysis

9. Regardless of family history, some individuals with an BRCA-related cancer may benefit from genetic testing to determine eligibility for targeted treatment

10. An individual who does not meet the other criteria but with one or more 1st- or 2nd-degree blood relatives meeting any of the above criteria.

B. **Patients Without Cancer or Without History of Cancer** (see Policy Guidelines: Testing Unaffected Individuals)

1. Genetic testing for *BRCA1* and *BRCA2* variants of cancer-unaffected individuals may be considered **medically necessary** under any of the following circumstances:

    a. Individual from a family with a known *BRCA1* or *BRCA2* variant

    b. 1st- or 2nd-degree blood relative meeting any criterion listed above for Patients With Cancer

    c. 3rd-degree blood relative with breast cancer and/or ovarian, fallopian tube, or primary peritoneal cancer AND two or more 1st-, 2nd-, or 3rd-degree relatives[a] with breast cancer (≥1 at age ≤50 years) and/or ovarian, fallopian tube, or primary peritoneal cancer

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

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

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

3. Genetic testing in minors for *BRCA1* and *BRCA2* variants is considered **experimental / investigational**.

Policy Guidelines

1. Current U.S. Preventive Services Task Force (USPSTF) guidelines recommend screening women with any family history of breast, ovarian, tubal, or peritoneal cancer. Women with positive screening results should receive genetic counseling and, if indicated after counseling, *BRCA* testing (grade B Recommendation).
2. Recommended screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in *BRCA1* or *BRCA2* are:
    - Ontario Family History Assessment Tool (FHAT)
    - Manchester Scoring System
    - Referral Screening Tool (RST)
    - Pedigree Assessment Tool (PAT)
    - Family History Screen (FHS-7)
3. 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).
4. 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 variants is negative, comprehensive variant analysis should then be performed.
5. Testing Unaffected Individuals: In unaffected family members of potential *BRCA* variant 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.

6. Testing Minors: The use of genetic testing for *BRCA* variants has limited or no clinical utility in minors, 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.
7. 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 considered sufficient justification for *BRCA* testing.
8. 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.
9. 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*. Recommended strategies are listed below.
    A. In patients with a known familial *BRCA* variant, targeted testing for the specific variant is recommended.
    B. In patients with unknown familial *BRCA* variant:
        1) Non-Ashkenazi Jewish descent
            a) To identify clinically significant variants, National Comprehensive Cancer Network (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.
            b) 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 (eg, prostate cancer, pancreatic cancer, melanoma).
            c) If no familial variant can be identified, two possible testing strategies are:

i. 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.

ii. Alternatively, simultaneous full sequencing and testing for *common* large genomic rearrangements (also known as comprehensive *BRCA* testing; see Comprehensive Variant Analysis, above) may be performed as is recommended by NCCN.
   - Comprehensive testing can detect 92.5% of *BRCA1* or *BRCA2* variants.

d) If comprehensive *BRCA* testing is negative, testing for *uncommon* large genomic rearrangements (eg, BART) may be done.

i. 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%.

C. 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 Mutation Analysis).

RATIONALE

This evidence review was developed following a 1997 TEC Assessment[15] and has been updated on a regular basis with literature searches for articles that contain information regarding professional guidelines for *BRCA* testing, testing of unaffected family members, and testing of high-risk ethnic populations. The most recent update covered the period through September 4, 2018.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Testing for *BRCA1* and *BRCA2* Variants in Individuals at Risk for Hereditary Breast/Ovarian Cancer Syndrome or Other High-Risk Cancers

Clinical Context and Test Purpose

The purpose of testing for *BRCA1* and *BRCA2* variants in individuals at high-risk for hereditary breast and ovarian cancer (HBOC) syndrome is to evaluate whether variants are present and, if so, 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 *BRCA1* and *BRCA2* variants improve the net health outcome in individuals with or suspected of having HBOC syndrome or other high-risk cancers?

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.

For patients without a cancer diagnosis who are assessing cancer risk, results may guide potential prophylactic measures such as surveillance, chemoprevention, or prophylactic mastectomy, and/or oophorectomy.

For patients with a cancer diagnosis, results may guide treatment decisions.

Comparator

The following practice is currently being used to manage HBOC syndrome or other high-risk cancers: standard of care without genetic testing.

Outcomes

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

Timing

Testing for *BRCA1* and *BRCA2* variants is conducted in adults when appropriate treatment and/or prophylactic treatment options are available.

Setting

Variant testing is offered in a primary care setting (eg, for people without cancer) or the specialty setting (eg, multidisciplinary oncology care) through various test manufacturers and institutions.

Study Selection Criteria

For the evaluation of clinical validity, studies of variant prevalence and cancer risk were included. For the evaluation of clinical utility, studies that represent the intended clinical use of the technology in the intended population were included. The quality and credibility of the evidence

depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings.

Evidence for the 2 indications is presented together because there is overlap in the evidence base for the 2 populations: (1) patients at risk of HBOC syndrome, and (2) patients with other high-risk cancers such as cancers of the fallopian tube, pancreas, and prostate.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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. The prevalence may be much higher for particular ethnic groups with characterized founder mutations (eg, 2.5% [1/40] in the Ashkenazi Jewish population). Family history of breast and ovarian cancer is an important risk factor for *BRCA* variant; additionally, age and ethnicity could be independent risk factors.

Systematic Reviews: A systematic review published by Zhu et al (2016) found a significantly lower risk of overall survival in breast cancer patients with *BRCA1* (pooled hazard ratio, 1.69; 95% confidence interval, 1.35 to 2.12) and with *BRCA2* (pooled hazard ratio, 1.50; 95% confidence interval, 1.02 to 2.09; p=0.034).[16] However, in patients with breast cancer, *BRCA1* and *BRCA2* were not associated with a lower breast cancer–specific survival.

Nelson et al (2013) conducted a systematic review that included meta-analytic estimates of the prevalence and penetrance of *BRCA* variants; this review was used to update the U.S. Preventive Services Task Force (USPSTF) recommendation for risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer.[17] 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 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 an extensive history of the disease, have been as high as 85%. For example, Kuchenbaecker 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.[18] 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.[19] Studies of founder mutations in ethnic populations (eg, Ashkenazi Jewish, Polish, Icelandic populations) unselected for family history have indicated lower penetrance estimates, in the range of 40% to 60% for *BRCA1* and 25% to 40% for *BRCA2.*[7,10,20,21] 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).[22] Importantly, the risk of cancer in variant carriers from families with little history of cancer (≈50% of all carriers) did not differ significantly. Lifetime risk estimates of ovarian cancer were 54% for *BRCA1* and 23% for *BRCA2* variant carriers.

Prospective Studies: Women with a history of breast cancer and a *BRCA* variant have a significant risk of contralateral breast cancer. In a prospective study by Metcalfe et al (2004), the 10-year risk was 29.5% for women with initial stage I or II diseases.[23] In a prospective study, Epidemiological Study of Familial Breast Cancer, Mavaddat et al (2013) reported that the cumulative risk of contralateral breast cancer by age 70 years was 83% in *BRCA1* variant carriers, and 62% for *BRCA2* variant carriers.[24] 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 risk estimates of ovarian cancer by age 70 years in women without previous ovarian cancer were 59% for *BRCA1* carriers and 17% for *BRCA2* carriers.

BRCA Variant Rates Associated with Ovarian Cancer

Women with a personal history of ovarian cancer have an increased rate of *BRCA* variants. In a systematic review of 23 studies, Trainer et al (2010) estimated the rate of *BRCA* variants among women with ovarian cancer to be 3% to 15%.[25] 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 the systematic review for USPSTF by Nelson et al (2013), meta-analytic estimates of *BRCA* prevalence among women with ovarian cancer were 4.4% for *BRCA1* and 5.6% for *BRCA2.*[17] Table 1 lists results from several additional studies measuring the presence of *BRCA* variants among patients with ovarian cancer.[26-30] One study noted that variant prevalence was higher for women in their 40s (24%) and for women with serous ovarian cancer (18%).[26] 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.[26]

Table 1. *BRCA* Variant Rates in Patients with Ovarian Cancer

Study	Population	N	*BRCA* Variant, n (%)	
			BRCA1	*BRCA2*
Harter et al (2017)[30]	Patients with invasive ovarian cancer across 20 medical centers	523	81 (15.5)	29 (5.5)
Kurian et al (2017)[27]	Patients with invasive ovarian cancer tested for hereditary cancer risk from a commercial laboratory database	5020[a]	255 (15.5)	199 (5.5)
Langer et al (2016)[28]	Patients with ovarian cancer tested for hereditary cancer risk from a commercial laboratory database	3088	153 (4.9)	124 (4.0)
Norquist et al (2016)[29]	Patients with invasive ovarian cancer, from 2 phase 3 clinical trials and a gynecologic oncology tissue bank	1915	182 (9.5)	98 (5.1)

Study	Population	N	*BRCA* Variant, n (%)	
			BRCA1	*BRCA2*
Zhang et al (2011)[26]	Patients with invasive ovarian cancer	1342	107 (8.0)	67 (5.0)

[a] Total N was reported as 5020, however, the percentage of *BRCA* variants as reported in article is inconsistent with 5020 as the denominator.

BRCA Variant Rates Associated with Fallopian Tube Cancer

A study by Hirst et al (2009) described the high rate of occult fallopian tube cancers in at-risk women having prophylactic bilateral salpingo-oophorectomy.[31] 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 long-term study by Powell et al (2013; 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.[32] 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.

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.[33] Table 2 lists results from several studies measuring the presence of *BRCA* variants among patients with pancreatic adenocarcinoma.[34-39] Patients with pancreatic adenocarcinoma of Jewish descent appear to have a higher prevalence of *BRCA* variants compared with the general population of patients with pancreatic adenocarcinoma.

Table 2. *BRCA* Variant Rates in Patients with Pancreatic Cancer

Study	Population	N	*BRCA* Variant, n (%)	
			BRCA1	*BRCA2*
Hu et al (2018)[39,a]	Patients with pancreatic adenocarcinoma from a prospective pancreatic cancer registry	3030	18 (0.6)	59 (1.9)
Yurgelun et al (2018)[38]	Patients with pancreatic adenocarcinoma from 3 medical centers	289	3 (1.0)	4 (1.4)
Shindo et al (2017)[37]	Patients with pancreatic adenocarcinoma from 1 medical center	854	3 (0.3)	12 (1.4)
Holter et al (2015)[36]	Patients with pancreatic adenocarcinoma from a large academic health care complex	306	3 (1.0)	11 (3.6)
Ferrone et al (2009)[35]	Jewish patients with pancreatic adenocarcinoma from 1 hospital	145	2 (1.3)	6 (4.1)
Couch et al (2007)[34]	Probands from high-risk families identified through pancreatic cancer clinics and a pancreatic tumor registry	180		10 (5.5)

[a] Case-control study; rates for *BRCA1* and *BRCA2* variants in controls were 0.2 and 0.3, respectively.

BRCA Variant Rates Associated with Prostate Cancer

Table 3 lists the results from several studies measuring the presence of *BRCA* variants among patients with prostate cancer.[40-42]

Table 3. *BRCA* Variant Rates in Patients with Prostate Cancer

Study	Population	N	*BRCA* Variant, n (%)	
			BRCA1	*BRCA2*
Abida et al (2017)[42]	Patients with prostate cancer from 1 clinical practice	221	2 (1)	20 (9)
Pritchard et al (2016)[41]	Patients with metastatic prostate cancer from 7 case series across multiple centers	692	6 (0.9)	37 (5.3)
Edwards et al (2003)[40]	Patients with prostate cancer diagnosed before age 56 from 2 cancer study groups	263		6 (2.3)

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, Walsh et al (2006) 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*.[43] 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 study by Palma et al (2008) evaluated 251 patients with an estimated *BRCA* variant prevalence using the Myriad II model of at least 10%.[44] In 136 non-Ashkenazi Jewish probands, 36 (26%) had *BRCA* point mutations 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 mutations. The authors indicated that the estimated prevalence of a variant did not predict the presence of a genomic rearrangement.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

Knowledge of variant status in individuals at potentially increased risk of a *BRCA* variant may impact health care decisions to reduce risk.[45-52] Risk-reducing options include intensive surveillance, chemoprevention, prophylactic mastectomy, or prophylactic oophorectomy. Among patients already diagnosed with cancer, *BRCA* variant status may guide treatment decisions.[53]

Prophylactic mastectomy reduces the risk of breast cancer in high-risk women (based on family history) by 90%.[46] Prophylactic oophorectomy significantly reduces the risk of ovarian cancer by 80% or more[49,50,54] and reduces the risk of breast cancer by approximately 50%.[50] In women who have already had breast cancer, prophylactic oophorectomy reduces the risk of cancer relapse.[48] Prophylactic oophorectomy or salpingo-oophorectomy in women with *BRCA1* or *BRCA2* reduced the risk of all-cause mortality by 60% to 77%.[54,55] For patients at risk for both breast and ovarian cancer, a study by Elmi et al (2018), drawing on data from the American College of Surgeon's National Surgical Quality Improvement Program dataset, found that prophylactic mastectomy with concurrent salpingo-oophorectomy was not associated with significant additional morbidity compared with prophylactic mastectomy alone.[56]

Systematic reviews of observational studies comparing prophylactic surgeries with observation in women who had *BRCA1* and *BRCA2* variants have demonstrated that contralateral prophylactic mastectomy in women with breast cancer is associated with significantly lower all-cause mortality while bilateral prophylactic mastectomy was not associated with all-cause mortality.[57-59] Studies have indicated that the results of genotyping significantly influenced treatment choices.[47,51,52]

In a systematic review for USPSTF, Nelson et al (2014) assessed the efficacy of risk-reducing surgery in *BRCA*-positive women.[60] The literature search, conducted through December 2012, identified 27 studies for inclusion. For high-risk women and variant carriers, bilateral mastectomy reduced breast cancer incidence by 85% to 100% and breast cancer mortality by 81% to 100%; 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%. 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 reviewers 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.

Robson et al (2017) published a phase 3 RCT in which patients with human epidermal growth factor receptor 2–negative metastatic breast cancer and a germline *BRCA* variant were randomized to olaparib (n=205) or standard therapy (n=97).[53] After a median follow-up of 14.5 months, patients receiving olaparib experienced significantly longer progression-free survival compared with patients receiving standard therapy (hazard ratio, 0.6; 95% confidence interval, 0.4 to 0.8). The rate of grade 3 or higher adverse events was lower in the group receiving olaparib (37%) compared with the group receiving standard therapy (51%).

Other studies have looked at the results of prostate cancer screening in men with *BRCA* variants. The Immunotherapy for Prostate Adenocarcinoma Treatment 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.[61] At the baseline screen, biopsies were performed in 7.0% of men with a prostate-specific antigen level greater than 3.0 ng/mL, 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.

Section Summary: Testing for BRCA1 and BRCA2 Variants in Individuals at Risk for Hereditary Breast/Ovarian Cancer Syndrome or Other High-Risk Cancers
Evidence for the clinical validity of *BRCA1* and *BRCA2* variant testing consists of multiple studies that calculated *BRCA1* and *BRCA2* variant prevalence among samples of patients with HBOC syndrome, fallopian tube cancer, pancreatic cancer, and prostate cancer.

Evidence for the clinical utility of *BRCA1* and *BRCA2* variant testing involves measuring changes in the management of patients with positive results. In terms of prophylactic measures (mastectomy and oophorectomy), RCTs would be difficult to conduct. However, retrospective analyses have shown that prophylactic mastectomy and/or oophorectomy greatly reduced the risk of breast cancer and ovarian cancer (80%-90%). An RCT was conducted on women with breast cancer and a *BRCA* variant in which patients received a targeted therapy or standard chemotherapy. Women treated with the targeted therapy experienced significantly longer progression-free survival and fewer high-level adverse events.

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 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. Knowledge of *BRCA* variant status in individuals diagnosed with breast cancer may impact treatment decisions. A randomized controlled trial has reported that patients with human epidermal growth factor receptor 2–negative metastatic breast cancer and a *BRCA* variant experienced significantly longer progression-free survival with a targeted therapy vs standard therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have other high-risk cancers (eg, cancers of the fallopian tube, pancreas, prostate) who receive genetic testing for a *BRCA1* or *BRCA2* variant, the evidence includes studies of variant prevalence and cancer risk. Relevant outcomes are overall survival, disease-specific survival, test validity, and quality of life. The accuracy of variant testing has been shown to be high. Knowledge of *BRCA* variant status in individuals with other high-risk cancers can inform decisions regarding genetic counseling, chemotherapy, and enrollment in clinical trials. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

CLINICAL INPUT RECEIVED THROUGH PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

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

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

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network

Breast Cancer and Ovarian Cancer

Current National Comprehensive Cancer Network (NCCN) guidelines on genetic and familial high-risk assessment of breast and ovarian cancers (v.2.2019) include criteria for identifying individuals who should be referred for further risk assessment, and separate criteria for genetic testing.[62] Patients who satisfy any of the testing criteria listed in Table 4 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 uncommon. NCCN recommends if a somatic variant is identified through tumor profiling, then *BRCA1* and *BRCA2* germline testing is recommended.

Table 4. *BRCA1* and *BRCA2* Testing Criteria for Hereditary Breast and Ovarian Cancer Syndrome

Recommendations
1. Individual from a family with a known *BRCA1*/*BRCA2* mutation
2. Personal history of breast cancer and ≥1 of the following:
a. Diagnosed age ≤45 years
b. Diagnosed age ≤ 46 to 50 years AND:
An additional breast cancer primary
≥1 close blood relative with breast cancer at any age
≥1 close relative with pancreatic cancer
≥1 close relative with prostate cancer (Gleason score ≥7), or
Unknown or limited family history
c. Diagnosed age ≤60 years with a triple-negative (ER–, PR–, HER2–) breast cancer
d. Diagnosed any age AND
≥2 additional diagnoses of breast cancer at any age in patient and/or in close blood relatives
≥1 close blood relative with breast cancer diagnosed at age 50 or younger or ovarian carcinoma or male breast cancer or metastatic prostate cancer or pancreatic cancer
3. Personal history of ovarian carcinoma
4. Personal history of male breast cancer
5. Personal history of metastatic prostate cancer or high grade prostate cancer (Gleason score ≥7) at any age AND ≥1 close blood relative with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer at any age or breast cancer at or before age 50 or >2 relatives with breast, pancreatic or prostate cancer (any grade) at any age.
6. Personal history of pancreatic cancer
7. BRCA1/2 mutation detected by tumor profiling in the absence of germline mutation analysis
8. An individual who does not meet the other criteria but with ≥1 1st- or 2nd-degree blood relative meeting any of the above criteria
9. Regardless of family history, some individuals with a *BRCA*-related cancer may benefit from genetic testing to determine eligibility for targeted treatment

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

Pancreatic Adenocarcinoma
Current NCCN guidelines for pancreatic adenocarcinoma (v.2.2018) refers to the NCCN guidelines on genetic/familial high-risk assessment of breast and ovarian detailed above, and state: "Consider germline testing for patients with a personal history of cancer, a family history of cancer, or if there is a clinical suspicion of inherited susceptibility."[63]

Prostate Cancer
Current NCCN guidelines (v.4.2018) for prostate cancer state: "Consider testing for mutation in these genes (germline and somatic): BRCA1, BRCA2, ATM, PALB2, FANCA," and that if positive, "this information may be used for genetic counseling, early use of platinum chemotherapy, or eligibility for clinical trials (e.g., PARP inhibitors)."[64]

American Society of Clinical Oncology
The American Society of Clinical Oncology has released statements on genetic and genomic testing for cancer susceptibility since 1996. The Society (2003) recommended 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.[65] 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."[66] A 2015 update affirmed that multigene panel testing "is sufficient for cancer risk assessment to evaluate genes of established clinical utility that are suggested by the patient's personal and/or family history."[67]

Society of Gynecologic Oncology
The Society of Gynecologic Oncology (SGO; 2015) published an evidence-based consensus statement on risk assessment for inherited gynecologic cancer.[68] 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 NCCN recommendations are very similar; the main differences is 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 (eg, few female relatives, hysterectomy, or oophorectomy at a young age in multiple family members, or adoption in the lineage).

American College of Obstetricians and Gynecologists
The American College of Obstetricians and Gynecologists (2017) published a practice bulletin on hereditary breast and ovarian cancer syndrome.[69] The following recommendation was based primarily on consensus and expert opinion (level C): "Genetic testing is recommended when the results of a detailed risk assessment that is performed as part of genetic counseling suggest the presence of an inherited cancer syndrome for which specific genes have been identified and when the results of testing are likely to influence medical management."

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 state[17]:

- "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.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

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

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02154672	Prostate Cancer Screening in Men With Germline BRCA2 Mutations	100	May 2018 (ongoing)
NCT02225015	Cancer Prevention in Women With a BRCA Mutation	300	Jun 2019
NCT03246841	Investigation of Tumour Spectrum, Penetrance and Clinical Utility of Germline Mutations in New Breast and Ovarian Cancer Susceptibility Genes	500	Dec 2023
NCT02321228	Early Salpingectomy (Tubectomy) With Delayed Oophorectomy in BRCA1/2 Gene Mutation Carriers (TUBA)	510	Jan 2035

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

CPT/HCPCS

81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis

81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81165	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81166	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81167	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81212	BRCA 1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81215	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant

ICD-10 Diagnoses

C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.121	Malignant neoplasm of central portion of right male breast
C50.122	Malignant neoplasm of central portion of left male breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.221	Malignant neoplasm of upper-inner quadrant of right male breast
C50.222	Malignant neoplasm of upper-inner quadrant of left male breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.321	Malignant neoplasm of lower-inner quadrant of right male breast
C50.322	Malignant neoplasm of lower-inner quadrant of left male breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.421	Malignant neoplasm of upper-outer quadrant of right male breast
C50.422	Malignant neoplasm of upper-outer quadrant of left male breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.521	Malignant neoplasm of lower-outer quadrant of right male breast
C50.522	Malignant neoplasm of lower-outer quadrant of left male breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast

C50.621	Malignant neoplasm of axillary tail of right male breast
C50.622	Malignant neoplasm of axillary tail of left male breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.821	Malignant neoplasm of overlapping sites of right male breast
C50.822	Malignant neoplasm of overlapping sites of left male breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.921	Malignant neoplasm of unspecified site of right male breast
C50.922	Malignant neoplasm of unspecified site of left male breast
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C79.61	Secondary malignant neoplasm of right ovary
C79.62	Secondary malignant neoplasm of left ovary
C79.81	Secondary malignant neoplasm of breast
D05.01	Lobular carcinoma in situ of right breast
D05.02	Lobular carcinoma in situ of left breast
D05.11	Intraductal carcinoma in situ of right breast
D05.12	Intraductal carcinoma in situ of left breast
D05.81	Other specified type of carcinoma in situ of right breast
D05.82	Other specified type of carcinoma in situ of left breast
D05.91	Unspecified type of carcinoma in situ of right breast
D05.92	Unspecified type of carcinoma in situ of left breast
Z80.3	Family history of malignant neoplasm of breast
Z80.41	Family history of malignant neoplasm of ovary
Z80.8	Family history of malignant neoplasm of other organs or systems
Z85.3	Personal history of malignant neoplasm of breast
Z85.43	Personal history of malignant neoplasm of ovary

REVISIONS

01-01-2012	In the Policy section: Formatting changes to the policy language.
	In the Coding section: Added new codes: 81211, 81212, 81213, 81214, 81215, 81216, 81217
10-04-2012	Updated Description section.
	In the Policy section: ▪ In Item II, removed "Further genetic testing by rearrangement analysis (BART—BRAC Analysis Rearrangement Test) is experimental / investigational (rearrangement analysis includes sequencing the coding regions and intron/extron splice sites as well as tests to detect large dilations and rearrangements that can be missed with sequence analysis only)" and inserted "Testing for genomic rearrangements of the *BRCA1* and *BRCA2* genes (BART—BRAC Analysis Rearrangement Test)may be considered medically necessary in patients who meet criteria for *BRCA* testing, whose testing for point mutations is negative and either (1) there are 3 or more family members (one 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%."

	▪ In the Policy Guidelines, added "#7 Comprehensive mutation analysis currently includes sequencing the coding regions and intron/exon splice sites, as well as tests to detect common large deletions and rearrangements (BART—BRAC Analysis Rearrangement Test) that can be missed with sequence analysis alone. However, current routine laboratory testing for genomic rearrangement is more limited than the criteria noted in the policy statement; automatic testing is specified for those with a risk of *BRCA* mutation of at least 30%. In addition, prior to August 2006, testing for large deletions and rearrangements was not performed, thus some patients with familial breast cancer who had negative *BRCA* testing prior to this time may consider repeat testing for the rearrangements (see Policy statement for criteria). These rates are calculated using the Myriad II risk model (Available online at: www.myriadtests.com)."
	Updated Reference section.
	Updated Reference section.
10-26-2012	In the Policy section: ▪ In the Policy Guidelines section, #7, corrected website, "www.myriadtests.com" to "www.myriadpro.com/brca-risk-calculator".
01-15-2013	In the Coding section: ▪ Added CPT code: 81406 ▪ Removed CPT codes: 83890, 83891, 83892, 83893, 83894, 83896, 83912, 83913 (Effective 12-31-2012)
02-26-2013	Updated Description section.
	In the Policy section: ▪ In Item I, B, added "10. Diagnosed at any age with breast cancer or pancreatic cancer, who are not from families with high risk of *BRCA1* or *BRCA2* mutation, but are affected with one of the following: o Early onset breast cancer o Two breast primary cancers with the first cancer diagnosis occurring prior to age 50 years; o Triple negative breast cancer (neither express estrogen receptor and progesterone receptor, nor overexposure HER2) diagnosed at younger than age 60. o Two or more close blood relatives with pancreatic cancer at any age. ▪ In Item II, removed "and either (1) there are 3 or more family members (one 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%." to read "Testing for genomic rearrangements of the *BRCA1* and *BRCA2* genes (BART-BRAC Analysis Rearrangement Test) may be considered medically necessary in patients who meet criteria for BRCA testing, whose testing for point mutations is negative."
	Updated Rationale section.
	In Coding section: ▪ Removed HCPCS codes: S3818, S3819, S3820, S3822, S3823
	Updated Reference section.
07-22-2013	In Coding section: ▪ Maintenance completed on coding section, correcting "V16.4" to read "V16.41".
12-11-2013	In Coding section: ▪ Added ICD-10 Diagnosis *(Effective October 1, 2014)*
08-28-2014	Description section updated.
	In Policy section: ▪ The following medical policy language was removed from the policy and replaced with policy language that mirrors the NCCN criteria (See policy section). This update liberalized the policy and did not restrict any portion of the policy.

	"I. Genetic testing may be considered medically necessary under any one of the following circumstances: A. Member of family with a known *BRCA1*/*BRCA2* mutation B. Personal history of breast cancer plus one or more of the following: 1. Diagnosed at 45 years of age or younger 2. Diagnosed at 50 years of age or younger with: a. one or more close blood relatives with breast cancer at 50 years of age or younger; and/or b. one or more close blood relatives with epithelial ovarian / fallopian tube / primary peritoneal cancer 3. Two breast primaries when first breast cancer diagnosis occurred prior to age 50 4. Diagnosed at any age with two or more close blood relatives with breast and/or epithelial ovarian / fallopian tube / primary peritoneal cancer at any age 5. Close male blood relative with breast cancer 6. For an individual of ethnicity associated with deleterious mutations (e.g., founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian or other) no additional family history may be required 7. Diagnosed age < 60 years with a triple negative breast cancer [estrogen receptors (ER-), progesterone receptors (PR-), and HER2 (HER2-)] 8. Diagnosed age <50 years with a limited family history (see policy guidelines) 9. Personal history of breast and / or ovarian cancer at any age with ≥ 2 close blood relatives with pancreatic cancer at any age 10. Diagnosed at any age with breast cancer or pancreatic cancer, who are not from families with a high risk of *BRCA1* or *BRCA2* mutation, but are affected with one of the following: ▪ Early onset breast cancer ▪ Two breast primary cancers with the first cancer diagnosis occurring prior to age 50 years; ▪ Triple negative breast cancer (neither express estrogen receptor and progesterone receptor, nor overexposure HER2) diagnosed at younger than age 60. ▪ Two or more close blood relatives with pancreatic cancer at any age. C. Personal history of epithelial ovarian / fallopian tube / primary peritoneal cancer D. Personal history of pancreatic cancer at any age with ≥ 2 close blood relatives with breast and / or pancreatic cancer at any age breast cancer E. Personal history of male breast cancer F. Family history only – 1. Close family member meeting any of the above criteria 2. Third-degree blood relative with breast cancer and /or ovarian / fallopian tube/ primary peritoneal cancer with ≥ 2 close blood relatives with breast cancer (at least one with breast cancer ≤50 years) and / or ovarian cancer. II. Testing for genomic rearrangements of the *BRCA1* and *BRCA2* genes (BART—BRAC Analysis Rearrangement Test) may be considered medically necessary in patients who meet criteria for *BRCA* testing, whose testing for point mutations is negative. III. Genetic testing when policy requirements are not met is experimental / investigational. <u>Policy Guidelines</u> 1. Close family member is defined as a first, second, or third degree relative, which includes: Parent, Full Sibling, Half Sibling, Child, Grandparent, Great-Grandparent, Grandchild, Aunt, Great Aunt, Uncle, Great Uncle, Nephew, Niece, and First Cousin.

	2. For purposes of this policy, breast cancer includes both invasive and ductal carcinoma in situ (DCIS). 3. For individuals with family history only, an affected family member should be tested first whenever possible to identify specific site mutations. 4. The maternal and paternal sides should be considered independently. 5. Other malignancies reported in some HBOC families include prostate and melanoma. 6. Individuals with limited family history, such as fewer than 2 first- or second-degree female relatives surviving beyond 45 years in either lineage, may have an underestimated probability of a familial mutation. 7. Comprehensive mutation analysis currently includes sequencing the coding regions and intron/exon splice sites, as well as tests to detect common large deletions and rearrangements (BART—BRAC Analysis Rearrangement Test) that can be missed with sequence analysis alone. However, current routine laboratory testing for genomic rearrangement is more limited than the criteria noted in the policy statement; automatic testing is specified for those with a risk of *BRCA* mutation of at least 30%. In addition, prior to August 2006, testing for large deletions and rearrangements was not performed, thus some patients with familial breast cancer who had negative *BRCA* testing prior to this time may consider repeat testing for the rearrangements (see Policy statement for criteria). These rates are calculated using the Myriad II risk model (Available online at: www.myriadpro.com/brca-risk-calculator). Testing eligible individuals who belong to ethnic populations in which there are well characterized founder mutations should begin with tests specifically for these mutations (multisite testing)."
	Rationale section updated
	In Coding section: ▪ Updated nomenclature for CPT code: 81215 ▪ Updated nomenclature for ICD-9 codes: 174.8, 174.9, 175.9, 183.0, 198.6, 198.81, 233.0, V10.43, V16.41, V16.8 ▪ Added ICD-9 codes: 233.30, 233.39 ▪ Removed ICD-9 code: 233.3 ▪ Removed ICD-10 codes: C50.129, C50.229, C50.529, C50.819
	Removed Revision dates: 08-29-2006 effective 11-01-2-06, 10-31-2006 effective 01-01-2007, 11-23-2009, 10-08-2010, 09-02-2011.
	References updated
04-02-2015	Updated Description section
	In Policy section: ▪ In Item A, added "or With History of Cancer," to read, "Patients with Cancer or With History of Cancer" ▪ In Item B, added "or Without History of Cancer," to read, "Patients Without Cancer or Without History of Cancer" ▪ In Item B, added "[d]For example, fewer than 2 1st- or 2nd-degree female relatives having lived beyond age 45 in either lineage. In families with a large number of unaffected female relates, the likelihood of mutation detection may be very low.", and removed, "Unknown or limited family history / structure is defined as fewer than 2 first- or second degree female relatives having lived beyond age 45 in either lineage" ▪ Removed Item C, "Testing for genomic rearrangements of the *BRCA1* and *BRCA2* genes may be considered medically necessary in patients who meet criteria for *BRCA* testing, whose testing for point mutations is negative." ▪ Removed Item E, "Testing for *CHEK2* abnormality (mutations, deletions, etc.) is considered experimental / investigational in affected and unaffected patients with breast cancer, irrespective of family history."

	▪ Added Item D, "Genetic testing in minors for *BRCA1* and *BRCA2* mutations is considered experimental / investigational." ▪ Removed "NOTE: Clinical judgment should be used to determine if the patient has reasonable likelihood of a mutation, considering the unaffected patient's current age and the age of female unaffected relatives who link the patient with the affected relatives.", and "NOTE: Testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing." ▪ In Policy Guidelines, removed, "4. Comprehensive Mutation Analysis. Comprehensive BRCA mutation analysis should be performed in patients with breast cancer, ovarian cancer, cancer of the fallopian tube, or primary peritoneal cancer who are: ● Eligible for testing, and ● From families without a known deleterious BRCA1 or BRCA2 mutation, and ● Not from ethnic groups with known founder mutations." ▪ In Policy Guidelines, added "9. A Recommended Testing Strategy. Patients who meet criteria for genetic testing as outlined in the Policy Stagements above should be tested for mutations in BRCA1 and BRCA2. A. In patients with a known familial BRCA mutation, targeted testing for the specific mutation is recommended. B. In patients with unknown familial BRCA mutation: 1) Non-Ashkenazi Jewish descent a) To identify clinically significant mutations, NCCN advises testing a relative who has breast or ovarian cancer, especially with early-onset disease, bilateral disease, multiple primaries, or ovarian cancer, because that individual has the highest likelihood for a positive test result. b) If no living family member with breast or ovarian cancer exists, NCCN suggests testing first- or second-degree family members affected with cancer thought to be related to deleterious *BRCA1*/*BRCA2* mutations (e.g., prostate cancer, pancreatic cancer, melanoma). c) If no familial mutation can be identified, two possible testing strategies are: i. Full sequencing followed by testing for common large genomic rearrangements (deletions/duplications) only if sequencing detects no mutation (negative result). • More than 90% of BRCA mutations will be detected by full sequencing.(4) ii. Alternatively, simultaneous full sequencing and testing for common large genomic rearrangements (also known as comprehensive BRCA testing; see Comprehensive Mutation Analysis, below) may be performed as is recommended by NCCN. • Comprehensive testing can detect 92.5% of *BRCA1*/*BRCA2* mutations.(4) d) If comprehensive BRCA testing is negative, testing for uncommon large genomic rearrangements (e.g., BART™) may be done. i. 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 mutation (positive result) in less than 1%.(4) C. 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 Mutation Analysis, above)."
	In Coding section: ▪ Removed CPT code 81406.
	Updated Rationale section.

	In Coding section: ▪ Removed CPT code 81406.
	Updated References section.
01-01-2016	Updated Description section.
	In Policy section: ▪ In Policy Guidelines, added paragraph on Genetic Counseling.
	Updated Rationale section.
	In Coding section: ▪ Added CPT code: 81162
	Updated References Section.
	Added Appendix section.
01-04-2017	Updated Description section.
	Updated Rationale section.
	Updated References section.
03-17-2018	Updated Description section.
	In Policy section: ▪ Changed "mutation" to "variant" throughout policy language. ▪ In Item A, added "Personal" to read, "Patients With Cancer or With Personal History of Cancer." ▪ In Item A 2 c, added "pancreatic cancer or prostate cancer" to read, "One or more 1st-, 2nd, or 3rd-degree relative[a] with breast cancer (at any age), pancreatic cancer or prostate cancer[b], or". ▪ In Item A 6, added "Personal history of" and "at any age AND ≥2 or more 1st-, 2nd-, or 3rd-degree relatives[a] with breast, pancreatic, or prostate cancer[b] at any age" to read, "Personal history of pancreatic or prostate cancer[b] at any age AND ≥2 or more 1st-, 2nd-, or 3rd-degree relatives[a] with breast, pancreatic, or prostate cancer[b] at any age." ▪ Removed previous Item C, "Unless the criteria above are met, 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, is considered experimental / investigational." ▪ Added new Item C, "Genetic testing for *BRCA1* and *BRCA2* variants when criteria above are not met is considered experimental / investigational." ▪ Updated Policy Guidelines.
	Updated Rationale section.
	In Coding section: ▪ Removed ICD-9 codes.
	Updated Revisions section.
01-01-2019	In Coding section: ▪ Added CPT codes: 81163, 81164, 81165, 81166, 81167. ▪ Deleted CPT codes: 81211, 81213, 81214. ▪ Revised nomenclature to CPT codes: 81162, 81212, 81215, 81216, 81217. ▪ Added ICD-10 code: Z80.41.
04-12-2019	Policy posted to the bcbsks.com website on 03-13-2019; effective 04-12-2019.
	Updated Description section.
	In Policy section: ▪ Removed previous policy language: "A. 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: 1. Individual from a family with a known *BRCA1/BRCA2* mutation 2. Personal history of breast cancer and ≥1 of the following:

	a. Diagnosed at age ≤45 years b. Two primary breast cancers when 1st breast cancer diagnosis occurred at age ≤50 years c. Diagnosed at age ≤50 years AND: i. One or more 1st-, 2nd-, or 3rd-degree relative[a] with breast cancer (at any age), pancreatic cancer or prostate cancer[b], or ii. Unknown or limited family history[c] d. Diagnosed at age ≤60 years with a triple negative (estrogen receptor–negative, progesterone receptor–negative, human epidermal growth factor receptor 2–negative) breast cancer e. Diagnosed at any age AND ≥1 1st-, 2nd-, or 3rd-degree relative[a] with breast cancer diagnosed at ≤50 years f. Diagnosed at any age AND ≥2 1st-, 2nd-, or 3rd-degree relative[a] with breast cancer at any age g. Diagnosed at any age AND ≥1 1st-, 2nd-, or 3rd-degree relative[a] with epithelial ovarian, fallopian tube, or primary peritoneal cancer h. Diagnosed at any age AND ≥2 1st-, 2nd-, or 3rd-degree relative[a] with pancreatic cancer or prostate cancer[b] at any age i. 1st-, 2nd-, or 3rd-degree male relative with breast cancer j. Ethnicity associated with deleterious founder mutations, eg, Ashkenazi Jewish descent[d] 3. Personal history of epithelial ovarian, fallopian tube, or primary peritoneal cancer 4. Personal history of male breast cancer 5. Personal history of pancreatic cancer or prostate cancer[c] at any age AND ≥1 1st-, 2nd-, or 3rd-degree relative[a] with any of the following: a. Breast cancer ≤50 b. Ovarian, fallopian tube, or primary peritoneal cancer at any age 6. Personal history of pancreatic or prostate cancer[b] at any age AND ≥2 or more 1st-, 2nd-, or 3rd-degree relatives[a] with breast, pancreatic, or prostate cancer[b] at any age 7. For pancreatic cancer, if Ashkenazi Jewish ancestry, only 1 additional affected relative is needed. B. Patients Without Cancer or Without History of Cancer (see Policy Guidelines: Testing Unaffected Individuals) Genetic testing for *BRCA1* and *BRCA2* variants of cancer-unaffected individuals may be considered medically necessary under any of the following circumstances: 1. Individual from a family with a known *BRCA1* or *BRCA2* variant 2. 1st- or 2nd-degree blood relative meeting any criterion listed above for Patients with Cancer 3. 3rd-degree blood relative with breast cancer and/or ovarian, fallopian tube, or primary peritoneal cancer AND ≥2 1st-, 2nd-, or 3rd-degree relatives[a] with breast cancer (≥1 at age ≤50 years) and/or ovarian, fallopian tube, or primary peritoneal cancer [a] For familial assessment, 1st-, 2nd-, and 3rd-degree relatives are blood relatives on the same side of the family (maternal or paternal). • 1st-degree relatives are parents, siblings, and children • 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings • 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins. [b] For familial assessment, prostate cancer is defined as Gleason score ≥7.

[c] For example, fewer than 2 1st- or 2nd-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: High-Risk Ethnic Groups).

C. Genetic testing for *BRCA1* and *BRCA2* variants when criteria above are not met is considered experimental / investigational.
D. Genetic testing in minors for *BRCA1* and *BRCA2* variants is considered experimental / investigational."

- Added new policy language: "A. Patients With Cancer or With a 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:

1. Individual from a family with a known *BRCA1* or *BRCA2* variant
2. Personal history of breast cancer and one or more of the following:
   a. Diagnosed at age ≤45 years
   b. Diagnosed 46 to 50 years with:
      i. One or more 1st-, 2nd-, or 3rd-degree blood relative with breast cancer at any age
      ii. An unknown or limited family history[c]
      iii. An additional breast cancer primary at any age
      iv. One or more 1st-, 2nd-, or 3rd-degree blood relative with high grade (Gleason score ≥7) prostate cancer
   c. Diagnosed ≤60 years with:
      i. Triple negative breast cancer
   d. Diagnosed at any age with:
      i. One or more 1st-, 2nd-, or 3rd-degree blood relative with
         - Breast cancer diagnosed at ≤50 years; or
         - Ovarian, fallopian tube, or primary peritoneal cancer; or
         - Male breast cancer; or
         - Metastatic prostate cancer; or
         - Pancreatic cancer
      ii. ≥2 additional diagnoses of breast cancer at any age in patient and/or 1st-, 2nd-, or 3rd-degree blood relative
   e. Ashkenazi Jewish ancestry
3. Personal history of ovarian, fallopian tube, or primary peritoneal cancer
4. Personal history of male breast cancer
5. Personal history of pancreatic cancer
6. Personal history of metastatic prostate cancer
7. Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with:
   a. One or more 1st-, 2nd-, or 3rd-degree blood relative with ovarian, fallopian tube, or primary peritoneal cancer, pancreatic cancer, or metastatic prostate cancer at any age or breast cancer ≤50 years; or
      i. Two or more 1st-, 2nd-, or 3rd-degree blood relatives with breast or prostate cancer (any grade) at any age; or
   b. Ashkenazi Jewish ancestry
8. BRCA1 or BRCA2 pathogenic or likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline pathogenic or likely pathogenic variant analysis
9. Regardless of family history, some individuals with an BRCA-related cancer may benefit from genetic testing to determine eligibility for targeted treatment

	10. An individual who does not meet the other criteria but with one or more 1st- or 2nd-degree blood relatives meeting any of the above criteria. B. Patients Without Cancer or Without History of Cancer (see Policy Guidelines: Testing Unaffected Individuals) 1. Genetic testing for *BRCA1* and *BRCA2* variants of cancer-unaffected individuals may be considered medically necessary under any of the following circumstances: i. Individual from a family with a known *BRCA1* or *BRCA2* variant ii. 1st- or 2nd-degree blood relative meeting any criterion listed above for Patients With Cancer iii. 3rd-degree blood relative with breast cancer and/or ovarian, fallopian tube, or primary peritoneal cancer AND two or more 1st-, 2nd-, or 3rd-degree relatives[a] with breast cancer (≥1 at age ≤50 years) and/or ovarian, fallopian tube, or primary peritoneal cancer [a] For familial assessment, 1st-, 2nd-, and 3rd-degree relatives are blood relatives on the same side of the family (maternal or paternal). • 1st-degree relatives are parents, siblings, and children • 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings • 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins. 2. Genetic testing for *BRCA1* and *BRCA2* variants in cancer-affected indivudals or of cancer-unaffected individuals with a family history of cancer when criteria above are not met is considered experimental / investigational. 3. Genetic testing in minors for *BRCA1* and *BRCA2* variants is considered experimental / investigational.
	Updated Rationale section.
	Updated References section.
	Removed Appendix section.

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6. Blue Cross and Blue Shield of Kansas Family Practice Liaison Committee, July 2009; July 2010; July 2012; July 2014; July 2015.
7. Blue Cross and Blue Shield of Kansas OB/GYN Liaison Committee, July 2009; July 2010; July 2014; July 2015; January 2019.
8. Blue Cross and Blue Shield of Kansas Pathology Liaison Committee, May 2010; May 2011; May 2014.
9. Blue Cross and Blue Shield of Kansas Oncology Liaison Committee, February 2014; February 2015.