

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

Professional

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Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> • With cancer or personal or family cancer history and criteria suggesting risk of hereditary breast/ovarian cancer syndrome 	Interventions of interest are: <ul style="list-style-type: none"> • Genetic testing for a <i>BRCA1</i> or <i>BRCA2</i> mutation 	Comparators of interest are: <ul style="list-style-type: none"> • No genetic testing 	Relevant outcomes include: <ul style="list-style-type: none"> • Overall survival • Disease-specific survival • Test accuracy • Test validity • Morbid events • Quality of life • Treatment-related morbidity

DESCRIPTION

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

Objective

The objective of this evidence review is to determine whether genetic testing for BRCA1 or BRCA2 mutations improves outcomes in individuals with cancer or with a personal or family history of cancer suggestive of hereditary breast/ovarian cancer syndrome.

Background

Several genetic syndromes with an autosomal dominant pattern of inheritance that feature breast cancer have been identified. Of these, HBOC and some cases of hereditary site-specific breast cancer have in common causative mutations in *BRCA* (breast cancer susceptibility) genes. Families suspected of having HBOC syndrome are characterized by an increased susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer at any age, as well as cancer of the fallopian tube and primary peritoneal cancer. Other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, laryngeal cancer, occur more frequently in HBOC families. Hereditary site-specific breast cancer families are characterized by early onset breast cancer with or without male cases, but without ovarian cancer. For this policy, both will be referred to collectively as hereditary breast and/or ovarian cancer.

Germline mutations in the *BRCA1* and *BRCA2* genes are responsible for the cancer susceptibility in the majority of HBOC families, especially if ovarian cancer or male breast cancer are features. However, in site-specific breast cancer, *BRCA* mutations are responsible for only a proportion of affected families, and research to date has not yet identified other moderate or high-penetrance gene mutations that account for disease in these families. *BRCA* gene mutations are inherited in an autosomal dominant fashion through either the maternal or paternal lineage. It is possible to test for abnormalities in

BRCA1 and *BRCA2* genes to identify the specific mutation in cancer cases and to identify family members with increased cancer risk. Family members without existing cancer who are found to have *BRCA* mutations can consider preventive interventions for reducing risk and mortality.

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

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

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

LabCorp (Burlington, NC) offers the BRCAssureSM suite of tests which includes: targeted *BRCA1/70BRCA2* analysis for known *BRCA1* or *BRCA2* mutations; a founder mutation panel for Ashkenazi Jewish patients (3 mutations); comprehensive *BRCA1/BRCA2* analysis (full gene sequencing plus analysis of common and uncommon large rearrangements); and deletion/duplication analysis of uncommon large rearrangements only (without sequencing) for use 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 mutation analysis (see Policy Guidelines: Comprehensive Mutation Analysis).

A. Patients With Cancer or With History of Cancer

Genetic testing for *BRCA1* and *BRCA2* mutations 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 age ≤ 45 years
 - b. Two primary breast cancers when 1st breast cancer diagnosis occurred age ≤ 50 years
 - c. Diagnosed age ≤ 50 years AND:
 - i. One or more 1st-, 2nd-, or 3rd-degree relative^a with breast cancer at any age, or
 - ii. Unknown or limited family history^d
 - d. Diagnosed age ≤ 60 years with a triple negative (estrogen receptor–negative, progesterone receptor–negative, human epidermal growth factor receptor 2–negative) breast cancer
 - e. Diagnosed any age AND ≥ 1 1st-, 2nd-, or 3rd-degree relative^a with breast cancer diagnosed ≤ 50 years
 - f. Diagnosed any age AND ≥ 2 1st-, 2nd-, or 3rd-degree relatives^a with breast cancer at any age
 - g. Diagnosed any age AND ≥ 1 1st-, 2nd-, or 3rd-degree relative^a with epithelial ovarian/fallopian tube/primary peritoneal cancer
 - h. Diagnosed any age AND ≥ 2 1st-, 2nd-, or 3rd-degree relatives^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^c
3. Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer
4. Personal history of male breast cancer
5. Personal history of pancreatic cancer or prostate cancer^b at any age AND ≥ 2 1st-, 2nd-, or 3rd-degree relatives^a with any of the following at any age. For pancreatic cancer, if Ashkenazi Jewish ancestry, only 1 additional affected relative is needed.

- a. Breast cancer
 - b. Ovarian/fallopian tube/primary peritoneal cancer
 - c. Pancreatic or prostate cancer^b
- B. **Patients Without Cancer or Without History of Cancer** (see Policy Guidelines: Testing Unaffected Individuals)
Genetic testing for *BRCA1* and *BRCA2* mutations of cancer-unaffected individuals may be considered **medically necessary** under any of the following circumstances:
1. Individual from a family with a known *BRCA1/BRCA2* mutation
 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/primary peritoneal cancer AND two or more 1st-, 2nd-, or 3rd-degree relatives^a with breast cancer (one or more at age ≤50 years) and/or ovarian/fallopian tube/primary peritoneal cancer
- ^a For the purpose of familial assessment, 1st-, 2nd-, and 3rd-degree relatives are blood relatives on the same side of the family (maternal or paternal).
- 1st-degree relatives are parents, siblings, and children.
 - 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.
 - 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.
- ^b For the purpose of familial assessment, prostate cancer is defined as Gleason score ≥7.
- ^c Testing for Ashkenazi Jewish or other founder mutation(s) should be performed first (see Policy Guidelines: High-Risk Ethnic Groups).
- ^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 relatives, the likelihood of mutation detection may be very low.
- 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**.
- D. Genetic testing in minors for *BRCA1* and *BRCA2* mutations is considered **experimental / investigational**.

Policy Guidelines

1. The Policy Statements above are based on current guidelines from the National Comprehensive Cancer Network (NCCN; see Practice Guidelines and Position Statements section).
2. 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)
3. 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-7 (FHS-7)
4. Comprehensive Mutation Analysis: Comprehensive mutation analysis currently includes sequencing the coding regions and intron/exon splice sites, as well as tests to detect common large deletions and rearrangements that can be missed with sequence analysis alone. In addition, before August 2006, testing for large deletions and rearrangements was not performed, thus some patients with familial breast cancer who had negative *BRCA* testing before this time may consider repeat testing for the rearrangements (see policy statements for criteria).
5. High-Risk Ethnic Groups: Testing in eligible individuals who belong to ethnic populations in which there are well-characterized founder mutations should begin with tests specifically for these mutations. For example, founder mutations account for approximately three quarters of the *BRCA* mutations found in Ashkenazi Jewish populations (see Rationale section). When testing for founder mutations is negative, comprehensive mutation analysis should then be performed.
6. Testing Unaffected Individuals: In unaffected family members of potential *BRCA* mutation families, most test results will be negative and uninformative. Therefore, it is strongly recommended that an affected family member be tested first whenever possible to adequately interpret the test. Should a *BRCA* mutation be found in an affected family member(s), DNA from an unaffected family member can be tested specifically for the same mutation of the affected family member without having to sequence the entire gene. Interpreting test results for an unaffected family member without knowing the genetic status of the family may be possible in the case of a positive result for an established disease-associated mutation but leads to difficulties in interpreting negative test results (uninformative negative) or mutations of uncertain significance because the possibility of a causative *BRCA* mutation is not ruled out.
7. Prostate Cancer: Patients with *BRCA* mutations have an increased risk of prostate cancer, and patients with known *BRCA* mutations may therefore consider more aggressive screening approaches for prostate cancer. However, the presence of

prostate cancer in an individual, or in a family, is not itself felt to be sufficient justification for *BRCA* testing.

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. A Recommended Testing Strategy: Patients who meet criteria for genetic testing as outlined in the policy statements above should be tested for mutations in *BRCA1* and *BRCA2*.
 - 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 (eg, 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 (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 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).

RATIONALE

This evidence review was developed following a 1997 TEC Assessment¹ and has been updated on a regular basis with literature searches for articles that contain information regarding professional guidelines for *BRCA* testing, testing of unaffected family members, and testing of high-risk ethnic populations. The most recent update covered the period through October 7, 2016 (see Appendix Table 1 for genetic testing categories).

Testing for *BRCA1* and *BRCA2* Mutations in High-Risk Women

Nelson et al (2013) conducted a systematic review that included meta-analysis estimates of the prevalence and penetrance of *BRCA* mutations, in order to update the U.S. Preventive Services Task Force (USPSTF) recommendation for risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer.² The authors search literature to July 30, 2013, and 72 articles to address 5 key questions were included. *BRCA* prevalence and penetrance were estimated to assess clinical validity of mutation testing. In high-risk women with positive test results, cumulative risks for developing breast cancer by age 70 were 46% for *BRCA1* and 50% for *BRCA2* when a single family member is tested, and 70% for *BRCA1* and 71% for *BRCA2* when multiple family members are tested; cumulative risks for developing ovarian cancer by age 70 were 41% for *BRCA1* and 17% for *BRCA2* when a single family member is tested, and 46% for *BRCA1* and 23% for *BRCA2* when multiple family members are tested. For Ashkenazi Jewish women with positive test results, cumulative risks for developing breast or ovarian cancer by age 75 were 34% and 21%, respectively.

Gabai-Kapara et al (2014) studied breast and ovarian cancer risks among 211 Ashkenazi Jewish female *BRCA1/BRCA2* founder mutation carriers who were identified through an unaffected male carrier relative.³ All study participants underwent *BRCA1/BRCA2* genotyping for 3 founder mutations (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT) that account for 11% of breast cancer and 40% of ovarian cancer in this population. Approximately half of identified carriers were from low-risk families who would not have satisfied criteria for testing. Cumulative risks for developing breast or ovarian cancer were similar to those observed in female *BRCA1/BRCA2* mutation carriers from high-risk families who satisfy criteria for testing. (For example: Cumulative risks for developing breast or ovarian cancer by age 60 and 80 were 60%

and 83%, respectively, for *BRCA1* mutation carriers, and 33% and 76%, respectively, for *BRCA2* mutation carriers; for breast cancer only, cumulative risks were 41% and 60%, respectively, for *BRCA1* mutation carriers, and 26% and 40%, respectively, for *BRCA2* mutation carriers; for ovarian cancer only, cumulative risks were 27% and 53%, respectively, for *BRCA1* mutation carriers, and 7% and 62%, respectively, for *BRCA2* mutation carriers. Among *BRCA2* mutation carriers, higher than expected cumulative risk of ovarian cancer and lower than expected cumulative risk of breast cancer were attributed to reduced prevalence of nongenetic risk factors for breast cancer, eg, late age at first pregnancy, in the study sample and therefore reduced competing risk.) Duration of follow-up was not specified. Based on these findings, several authors of this study advocated universal screening of women for *BRCA1/BRCA2* mutation status.⁴ However, despite the authors' assertion that results of this study are "widely applicable," this is unlikely to be true; as the authors themselves stated, "The Ashkenazi Jewish population is unusual." Others have urged caution in communicating risks associated with radical surgery (prophylactic mastectomy, oophorectomy) in *BRCA1/BRCA2* mutation carriers identified through population screening.⁵

Early estimates of lifetime risk of cancer for *BRCA* mutation carriers (penetrance), based on studies of families with extensive history of disease, have been as high as 85%. Because other factors that influence risk may be present in families with extensive breast and ovarian cancer histories, early penetrance estimates may have been biased upward.⁶ Studies of founder mutations in ethnic populations (eg, Ashkenazi Jewish, Polish, Icelandic populations) unselected for family history indicated lower penetrance estimates, in the range of 40% to 60% for *BRCA1* and 25% to 40% for *BRCA2*.⁷⁻¹⁰ 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).¹¹ Importantly, the risk of cancer in mutation carriers from families with little history of cancer (\approx 50% of all carriers) was not significantly different. Lifetime risks of ovarian cancer were 54% for *BRCA1* and 23% for *BRCA2* mutation carriers.

Women with a history of breast cancer and a *BRCA* mutation have a significant risk of contralateral breast cancer; in 1 prospective study (2004), the risk was 29.5% at 10 years for women with initial stage I or II disease.¹² In a 2013 prospective study (EMBRACE), the cumulative risk of contralateral breast cancer by age 70 years was 83% in *BRCA1* mutation carriers and 62% for *BRCA2* mutation carriers.¹³ These investigators also reported cumulative risks of breast cancer by age 70 years in women without previous cancer of 60% in *BRCA1* carriers and 55% in *BRCA2* carriers. Similarly, the cumulative risks of ovarian cancer by age 70 years in women without previous ovarian cancer were 59% for *BRCA1* carriers and 17% for *BRCA2* carriers. Although there is a significantly increased risk of cancer in *BRCA* carriers, the association between *BRCA* and cancer mortality is not clear. Observational studies have suggested that *BRCA* mutations, in particular *BRCA2*, might be associated with longer overall survival (OS) and progression-free survival in patients with ovarian cancer,^{14,15} at least in the short term.¹⁶ The observed improvement in survival might be due to higher chemotherapy response.¹⁵ *BRCA* mutations are generally associated with poor OS in patients with breast cancer.¹⁷

Thus, the risk of cancer in a *BRCA* mutation carrier is significant, and knowledge of mutation status in individuals at potentially increased risk of a *BRCA* mutation may impact healthcare decisions to reduce risk.¹⁸⁻²⁵ Risk-reducing options include intensive surveillance,

chemoprophylaxis, prophylactic mastectomy, or prophylactic oophorectomy. Prophylactic mastectomy reduces the risk of breast cancer in high-risk women (based on family history) by 90% or more but is invasive and disfiguring.¹⁹ Prophylactic oophorectomy significantly reduces the risk of ovarian cancer to less than 10%^{22,23} and reduces the risk of breast cancer by approximately 50%.¹⁹ In women who have already had breast cancer, prophylactic oophorectomy reduces the risk of cancer relapse.²¹ Systematic reviews of observational studies comparing prophylactic surgeries to observation in women with *BRCA1* and *BRCA2* mutations demonstrate that prophylactic bilateral oophorectomy in women with and without breast cancer and contralateral prophylactic mastectomy in women with breast cancer are associated with significantly lower all-cause mortality while bilateral prophylactic mastectomy was not associated with all-cause mortality.²⁶⁻²⁸ Studies have indicated that genotyping results significantly influence treatment choices.^{20,24,25}

Prevalence of *BRCA* Mutations

Nelson et al included meta-analysis estimates of *BRCA* prevalence in their 2013 systematic review for USPSTF.² In unselected women, *BRCA* mutation prevalence estimates were 0.2% to 0.3%; in women with breast cancer, 1.8% for *BRCA1* and 1.3% for *BRCA2*; in women with breast cancer onset at age 40 years or younger, 6%; in women from high-risk families, 13.6% for *BRCA1*, 7.9% for *BRCA2*, and 19.8% for *BRCA1* or *BRCA2*; in unselected Ashkenazi Jewish women, 2.1%; and in Ashkenazi Jewish women from high-risk families, 10.2%.

The prevalence of *BRCA* mutations is approximately 0.1% to 0.2% in the general population. Prevalence may be much higher for particular ethnic groups with characterized founder mutations (eg, 2.5% [1/40] in the Ashkenazi Jewish population). Family history of breast and ovarian cancer is an important risk factor for *BRCA* mutation. Age and, in some cases, ethnic background can also be independent risk factors. Malone et al (2006) reported on racial and ethnic differences in the prevalence of *BRCA1* and *BRCA2* in American women.²⁹ Among their subjects, 2.4% and 2.3% carried deleterious mutations in *BRCA1* and *BRCA2*, respectively. *BRCA1* mutations were significantly more common in "white" (2.9%) versus "black" (1.4%) cases and in Jewish (10.2%) versus non-Jewish (2.0%) cases; *BRCA2* mutations were slightly more frequent in "black" (2.6%) versus "white" (2.1%) cases.

Clinical Features Suggestive of *BRCA* Mutation

Young age of onset of breast cancer, even in the absence of family history, is a risk factor for *BRCA1* mutations. Winchester estimated that hereditary breast cancers account for 36% to 85% of patients diagnosed before age 30.³⁰ In several studies, *BRCA* mutations are independently predicted by early age at onset, being present in 6% to 10% of breast cancer cases diagnosed at ages younger than various premenopausal age cutoffs (age range, 35-50 years).³⁰⁻³³ In cancer-prone families, the mean age of breast cancer diagnosis among women carrying *BRCA1* or *BRCA2* mutations is in the 40s.³⁴ In the Ashkenazi Jewish population, Frank et al reported that 13% of 248 cases with no known family history and diagnosed before 50 years of age had *BRCA* mutations.³¹ In a similar study, 31% of Ashkenazi Jewish women, unselected for family history, diagnosed with breast cancer at younger than 42 years of age had *BRCA* mutations.³⁵ Additional studies have indicated that early age of breast cancer diagnosis is a significant predictor of *BRCA* mutations in the absence of family history in this population.^{10,36,37}

As in the general population, family history of breast or ovarian cancer, particularly of early age onset, is a significant risk factor for a *BRCA* mutation in ethnic populations characterized by

founder mutations. For example, in unaffected individuals of Ashkenazi Jewish descent, 12% to 31% will have a *BRCA* mutation depending on the extent and nature of the family history.³³ Several other studies have documented the significant influence of family history.^{7,10,35-37}

In patients with “triple-negative” breast cancer (ie, negative for expression of estrogen and progesterone receptors and for overexpression of human epidermal growth factor receptor 2 receptors), there is an increased prevalence of *BRCA* mutations. Pathophysiologic research has suggested that the physiologic pathway for development of triple-negative breast cancer is similar to that for *BRCA*-associated breast cancer.³⁸ In 200 randomly selected patients with triple-negative breast cancer from a tertiary care center, there was a greater than 3-fold increase in the expected rate of *BRCA* mutations.³⁹ *BRCA1* mutations were found in 39.1% of patients and *BRCA2* mutations in 8.7%. Young et al studied 54 women with high-grade, triple-negative breast cancer with no family history of breast or ovarian cancer, representing a group that previously was not recommended for *BRCA* testing.⁴⁰ A total of 6 *BRCA* mutations (5 *BRCA1*, 1 *BRCA2*) were found, for a mutation rate of 11%. Finally, in a study of 77 patients with triple-negative breast cancer, 15 patients (19.5%) had *BRCA* mutations (12 in *BRCA1*, 3 in *BRCA2*).⁴¹

Testing Results

Unaffected individuals with a family history suggestive of hereditary breast and/or ovarian cancer but unknown family mutation may obtain interpretable results in most cases of a positive test. Most *BRCA1* and *BRCA2* mutations reported to date consist of frameshift deletions, insertions, or nonsense mutations leading to premature truncation of protein transcription. These are invariably deleterious and thus are informative in the absence of an established familial mutation.^{31,42} In addition, specific missense mutations and noncoding intervening sequence mutations may be interpreted as deleterious on the basis of accumulated data or from specific functional or biochemical studies. However, some *BRCA* mutations may have uncertain significance in the absence of a family study, and negative results offer no useful information (ie, the patient may still be at increased risk of a disease-associated mutation in an as-yet undiscovered gene).

BRCA Mutation Rates Associated With Pancreatic Cancer

Unaffected individuals also may be at high risk due to other patterns of non-breast-cancer malignancies. A personal history of pancreatic cancer is estimated to raise the risk of a *BRCA* mutation by 3.5- to 10-fold over the general population.⁴³ Couch et al reported on screening for *BRCA2* mutations in 2 cohorts of families at high risk for pancreatic cancer. In the first cohort of high-risk families, there were a total of 5 (3%) *BRCA* mutations in 151 probands; in the second cohort, there were another 5 (17%) *BRCA2* mutations in 29 probands.⁴⁴ The combined *BRCA2* mutation rate for these 2 cohorts was 6% (10/180). Ferrone et al tested 187 Ashkenazi Jewish patients with pancreatic cancer for *BRCA* mutations and found that 5.5% (8/187) had a *BRCA* mutation.⁴⁵

BRCA Mutation Rates Associated With Ovarian Cancer

Women with a personal history of ovarian cancer have an increased rate of *BRCA* mutations. In a 2010 systematic review of 23 studies, Trainer et al estimated the rate of *BRCA* mutations among women with ovarian cancer to be 3% to 15%.⁴⁶ In this review, 3 U.S. studies tested for both *BRCA1* and *BRCA2*; incidences of *BRCA* mutations were 11.3%, 15.3%, and 9.5%. In a 2011 population-based study of 1342 unselected patients with invasive ovarian cancer in Canada, 176 women had *BRCA* mutations, for a rate of 13.3%.⁴⁷ Mutation prevalence was higher for women in their 40s (24%) and for women with serous ovarian cancer (18%). Ethnicity was another risk

factor for *BRCA*, with higher rates seen in women of Italian (43.5%), Jewish (30%), and Indo-Pakistani (29.4%) origin. In the 2013 systematic review for USPSTF by Nelson et al, meta-analytic estimates of *BRCA* prevalence among women with ovarian cancer were 4.4% for *BRCA1* and 5.6% for *BRCA2*.²

BRCA Mutation 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.⁴⁸ 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* mutations. Similarly, 2017 National Comprehensive Cancer Network guidelines for assessing high risk in breast and ovarian cancer include both fallopian tube and primary peritoneal cancer as other malignancies that should be documented when assessing family history for *BRCA1* and *BRCA2* genotyping decisions.⁴⁹

A long-term study (median follow-up, 7 years; range, 3-14 years) followed 32 *BRCA* mutation carriers with occult malignancy (4 ovarian, 23 fallopian tube, 5 ovarian and fallopian tube) diagnosed of prophylactic salpingo-oophorectomy.⁵⁰ Among 15 women with invasive carcinoma (median age, 50 years), 7 (47%) experienced recurrence at a median of 33 months, and OS 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. OS was 100%. The authors concluded that, in *BRCA* mutation carriers, unsuspected invasive carcinoma has a relatively high rate of recurrence, but noninvasive neoplasms rarely recur and may not require adjuvant chemotherapy.

Clinical Outcomes in BRCA Mutation Carriers

A clinical approach to *BRCA* mutation carriers was published in 2007 by Robson and Offit.⁵¹ Phillips et al (2006) reported that although uptake of prophylactic surgery and screening was associated with knowing one's mutation status, in their cohort of 70 unaffected female mutation carriers who had chosen to receive results, a minority had risk-reducing surgery (11% had bilateral mastectomy; 29% bilateral oophorectomy) or chemoprevention.⁵²

In their 2014 systematic review for USPSTF, Nelson et al assessed efficacy of risk-reducing surgery in *BRCA*-positive women.⁵³ For high-risk women and mutation carriers, bilateral mastectomy reduced breast cancer incidence by 85% to 100% and breast cancer mortality by 81% and 100%, respectively; salpingo-oophorectomy reduced breast cancer incidence by 37% to 100%, ovarian cancer incidence by 69% to 100%, and all-cause mortality by 55% to 100%, respectively. Some women experienced reduced anxiety. Although comparison groups varied across studies, results were consistent. Adverse events included physical complications of surgery, postsurgical symptoms, and changes in body image. Limitations of the analysis included the small number of studies (N=7) and small sample sizes. As the authors observed, whether *BRCA* mutation testing reduces cause-specific or all-cause mortality and improves quality of life is currently unknown. Harms associated with false-negative results or variants of uncertain significance also are unknown.

Rennert et al (2007) reported that breast cancer-specific rates of death among Israeli women were similar for carriers of a *BRCA* founder mutation and noncarriers.⁵⁴

Lesnock et al (2013) compared OS in 393 women with *BRCA1*-mutated and *BRCA1*-nonmutated epithelial ovarian cancer who were treated with intraperitoneal or intravenous-only chemotherapy.⁵⁵ All patients had “optimally resected” (<1 cm residual disease) stage III disease. *BRCA1* mutation status was determined by blinded review of immunohistochemistry assays of archived tumor samples. Treatment regimens were intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel (IP therapy) or intravenous paclitaxel and cisplatin (IV therapy). In 204 women with nonmutated *BRCA1*, median OS did not differ statistically between treatment groups (58 months for IP therapy vs 50 months for IV therapy; $p=0.82$). In 189 women with mutated *BRCA1*, median OS was significantly longer in the IP therapy group (84 months vs 47 months, respectively; $p<0.001$).

BRCA Mutation Associated With Prostate Cancer

A number of studies have indicated that *BRCA* mutations are associated with increased risk of prostate cancer in men. In a 2010 study of 832 Ashkenazi Jewish men diagnosed with localized prostate cancer and 454 Ashkenazi Jewish men without prostate cancer, the presence of a *BRCA2* mutation was associated with a more than 3-fold increased risk of prostate cancer (odds ratio [OR], 3.18; 95% confidence interval [CI], 1.52 to 6.66).⁵⁶ In a similar population of 251 Ashkenazi Jewish men with prostate cancer and 1472 volunteers without prostate cancer, the presence of a *BRCA* mutation was associated with a more than a 3-fold increased risk of prostate cancer (OR=3.41; 95% CI, 1.64 to 7.06).⁵⁷ When analyzed by type of *BRCA* mutation, *BRCA2* was associated with an almost 5-fold increased risk (OR=4.82; 95% CI, 1.87 to 12.25), and *BRCA1* mutations were not associated with an increased risk (OR=2.20; 95% CI, 0.72 to 6.70). A 2013 retrospective analysis compared prostate cancer outcomes in 79 *BRCA* mutation carriers (18 *BRCA1*, 61 *BRCA2*) and 2019 noncarriers.⁵⁸ Men with *BRCA* mutations more often had Gleason scores of 8 or higher ($p<0.001$), nodal involvement ($p<0.001$), and metastases at diagnosis ($p=0.005$) than noncarriers. Median OS was 8.1 years in carriers and 12.9 years in noncarriers (hazard ratio [HR], 1.9; 95% CI, 1.1 to 3.3; $p=0.012$). In subgroup analyses, *BRCA2* mutations were independently associated with reduced OS (HR=1.9; 95% CI, 1.1 to 3.1; $p=0.004$), but *BRCA1* mutations were not, possibly due to small sample size and limited follow-up.

Other studies have looked at the results of prostate cancer screening in men with *BRCA* mutations. The IMPACT study (2011) evaluated the results of screening in 205 men 40 to 69 years of age who were *BRCA* mutation carriers and 95 control patients.⁵⁹ 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 normal risk men. Also, the grade of tumor identified was intermediate in 67% of cancers and high in 11%. This differs from the expected distribution of cancer grade in average-risk men, with more than 60% expected to have low-grade cancer.

Candidate Modifier Genes

There has been interest in risk-stratifying patients with known *BRCA* mutations to further assist in clinical decision making. Numerous recent publications have identified a large number of candidate modifier genes,⁶⁰⁻⁶⁶ and nongenetic modifying factors also have been examined. Antoniou et al examined the risk of breast cancer associated with 9 genetic polymorphisms, most which had previously shown an increase cancer risk among *BRCA* carriers.⁶⁰ Seven of the 9 polymorphisms were confirmed to increase breast cancer risk. The magnitude of increased risk

varied by whether the patient was a *BRCA1* versus a *BRCA2* carrier, and the polymorphisms appeared to interact multiplicatively to increase risk.

Kleibl et al reported that the *AIB1* (amplified in breast 1) genotype in general did not influence breast cancer risk in *BRCA* carriers but that the specific *AIB1* genotype consisting of 28 glutamine repeats in both alleles (28/28) conferred a decreased risk of breast cancer (HR=0.64; 95% CI, 0.41 to 0.99; p=0.045).⁶⁴ In 2013, Bianco et al conducted a meta-analysis to examine the effect of *AIB1* polyglutamine repeats on breast cancer risk in *BRCA* mutation carriers.⁶⁷ Seven case-control and cohort studies of 28 of 28, 29 of 29, and 26 or fewer repeats in 1 or both alleles were included. No statistically significant association with breast cancer risk was observed for polyglutamine repeats of any length in *BRCA*, *BRCA1*, or *BRCA2* mutation carriers. Statistical heterogeneity was significant in the analyses of 28 of 28 repeats in *BRCA1* and *BRCA2* mutation carriers.

Zhou et al reported an increased risk of cancer in *BRCA* carriers who also had the *RAD51* 135G>C polymorphism (OR=1.34; 95% CI, 1.01 to 1.78; p=0.04).⁶⁸ Metcalfe et al reported that family history provided additional predictive information in *BRCA* carriers.⁶⁹ For each first-degree relative with breast cancer before age 50 years, the risk of ovarian cancer increased 1.6-fold (HR=1.61; 95% CI, 1.21 to 2.14) in *BRCA1* mutation carriers, and the risk of breast cancer increased 1.7-fold in *BRCA2* mutation carriers (HR=1.67; 95% CI, 1.04 to 2.07).

BRCA Testing in Minors

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

In its updated (2014) statement on risk assessment for inherited gynecologic cancer, the Society of Gynecologic Oncologists (SGO) acknowledged that the risk of developing breast or ovarian cancer in a woman younger than age 21 is very low, "even in families with inherited cancer susceptibility as a result of hereditary breast and ovarian cancer (HBOC) syndrome."⁷⁰ Because detection of an HBOC-associated mutation "would change the management of very few women in this age group," and because testing has potential negative consequences, SGO did "not recommend genetic testing of women younger than age 21 for HBOC in the absence of a family history of extremely early-onset cancer."

Testing for Large BRCA Rearrangements

A number of studies have shown that a significant percentage of women with a strong family history of breast cancer and negative tests for *BRCA* mutations have large genomic rearrangements (including deletions or duplications) in 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*.⁷¹ These patients underwent screening with additional multiple DNA-based and RNA-based methods. Of these 300 patients, 17% carried previously undetected mutations, including 35 (12%) with genomic rearrangement of *BRCA1* or *BRCA2*.

A 2008 study evaluated 251 patients with an estimated *BRCA* mutation prevalence using the Myriad II model of at least 10%.⁷² 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* mutations. No genomic rearrangements were identified in the 115 Ashkenazi Jewish probands, but 47 (40%) had point mutations. The authors indicated that the estimated prevalence of a mutation did not predict the presence of a genomic rearrangement.

Summary of Evidence

For individuals who have cancer or a personal or family cancer history and meeting criteria suggesting a risk of hereditary breast and ovarian cancer (HBOC) syndrome who receive genetic testing for a *BRCA1* or *BRCA2* mutation, the evidence includes a TEC Assessment and studies of mutation prevalence and cancer risk. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, quality of life, and treatment-related morbidity. The accuracy of mutation testing has been shown to be high. Studies of lifetime risk of cancer for carriers of a *BRCA* mutation have shown a risk as high as 85%. Knowledge of *BRCA* mutation status in individuals at risk of a *BRCA* mutation may impact health care decisions to reduce risk, including intensive surveillance, chemoprevention, and/or prophylactic intervention. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

Current National Comprehensive Cancer Network (NCCN) guidelines on genetic and familial high-risk assessment of breast and ovarian cancers (v.1.2017) include criteria for identifying individuals who should be referred for further risk assessment, and separate criteria for genetic testing.⁴⁹ 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."

Table 1. NCCN BRCA1 and BRCA2 Testing Criteria for HBOC Compared to SGO Criteria for Genetic Assessment (Counseling With or Without Testing)

NCCN ⁴⁹	SGO ⁷⁰
1. Individual from a family with a known <i>BRCA1/BRCA2</i> mutation	√
2. Personal history of breast cancer and ≥1 of the following:	
a. Diagnosed age ≤45 years	√
b. 2 primary breast cancers when 1st breast cancer diagnosis occurred age ≤50 years	√ ^f
c. Diagnosed age ≤50 years AND:	
i. One or more 1st-, 2nd-, or 3rd-degree relative ^a with breast cancer at any age, or	
ii. Unknown or limited family history ^b	√
d. Diagnosed age ≤60 years with a triple negative (<i>ER-</i> , <i>PR-</i> , <i>HER2-</i>) breast cancer	√
e. Diagnosed any age AND one or more 1st-, 2nd-, or 3rd-degree relatives ^a with breast cancer diagnosed ≤50 years	√
f. Diagnosed any age AND two or more 1st-, 2nd-, or 3rd-degree relatives ^a with breast cancer at any age	√
g. Diagnosed any age AND one or more 1st-, 2nd-, or 3rd-degree relative ^a with epithelial ovarian/fallopian tube/primary peritoneal CA	√
h. Diagnosed any age AND two or more 1st-, 2nd-, or 3rd-degree relatives ^a with pancreatic cancer or prostate cancer ^c at any age	√
i. 1st-, 2nd-, or 3rd-degree male relative with breast cancer	
j. For individuals of ethnicity associated with increased mutation frequency (eg, Ashkenazi Jewish), no additional family history may be required ^d	√
3. Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer	√
4. Personal history of male breast cancer	
5. Personal history of pancreatic cancer or prostate cancer ^c at any age AND two or more 1st-, 2nd-, or 3rd-degree relatives ^a with any of the following at any age. For pancreatic cancer, if Ashkenazi Jewish ancestry, only 1 additional affected relative is needed:	√ ^g
a. Breast cancer	√
b. Ovarian/fallopian tube/primary peritoneal cancer	√
c. Pancreatic or prostate cancer ^c	√
6. Family history only ^e :	
a. 1st- or 2nd-degree blood relative meeting any of the above criteria	√ ^h
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/fallopian tube/primary peritoneal cancer	√ ^h

NCCN: National Comprehensive Cancer Network; SGO: Society of Gynecologic Oncology.

^a 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 example, fewer than 2 first- or second-degree female relatives having lived beyond age 45 in either lineage.

^c Gleason score ≥7.

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

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

^f SGO does not include age restriction.

^g SGO does not include qualifier for Ashkenazi-Jewish patients.

^h For unaffected women, this SGO criterion states, "A first or several close relatives who meet one of the above criteria." SGO additionally recommends genetic assessment for unaffected women who have a male relative with breast cancer.

American Society of Clinical Oncology

The American Society of Clinical Oncology recommended in 2003 that cancer predisposition testing be offered when (1) there is a personal or family history suggesting genetic cancer susceptibility, (2) the test can be adequately interpreted, and (3) results will influence medical management of the patient or family member at hereditary risk of cancer.⁷³ A 2010 update of this policy statement recommended that "genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials."⁷⁴

Society of Clinical Oncology

In 2014, Society of Clinical Oncology (SGO) updated its 2007 evidence-based consensus statement on risk assessment for inherited gynecologic cancer.⁷⁰ The statement includes 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 align. Differences are: exclusion of women with breast cancer onset at age 50 years or younger who have one 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. SGO additionally recommends genetic assessment for unaffected women who have a male relative with breast cancer. SGO allows 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.

U.S. Preventive Services Task Force

Current U.S. Preventive Services Task Force (USPSTF) recommendations for genetic testing of *BRCA1* and *BRCA2* mutations in women are listed next.⁷⁵

- “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 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00685256	Standard Genetic Counseling With or Without a Decision Guide in Improving Communication Between Mothers Undergoing <i>BRCA1/2</i> Testing and Their Minor-Age Children	400	Dec 2016
NCT00287898	Telephone-Based Genetic Counseling or Standard Genetic Counseling in Women at Risk of Carrying the <i>BRCA1</i> or <i>BRCA2</i> Mutation	600	Dec 2016
NCT02133703	Decision Making Interventions for Women Receiving Uninformative <i>BRCA1/2</i> Test Results or Positive <i>BRCA1/2</i> Test Results	600	Jul 2017
NCT02225015	Cancer Prevention in Women With a <i>BRCA</i> Mutation: A Follow-up Genetic Counseling Intervention	300	Jun 2019
Unpublished			
NCT01851109	Prevention of Ovarian Cancer in Women Participating in Mammography	458	Dec 2015 (completed)

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, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis
81211	BRCA 1, <i>BRCA2</i> (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication / deletion variants in <i>BRCA1</i> (ie, exon 13 del 3.835kb, exon 13 dup 6kp, exon 14-20 del 26kb, exon 22 del 510kb,exon 8-9 del 7.1kb)
81212	BRCA 1, <i>BRCA2</i> (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81213	BRCA 1, <i>BRCA2</i> (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; uncommon duplication / deletion variants
81214	<i>BRCA1</i> (breast cancer1) (eg, 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 26 kb, exon 22 del 510bp, exon 8-9 del 7.1kb)
81215	<i>BRCA1</i> (breast cancer1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	<i>BRCA2</i> (breast cancer) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	<i>BRCA2</i> (breast cancer) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant

ICD-9 Diagnoses

174.0	Malignant neoplasm of female breast, nipple and areola
174.1	Malignant neoplasm of female breast, central portion
174.2	Malignant neoplasm of female breast, upper-inner quadrant
174.3	Malignant neoplasm of female breast, lower-inner quadrant
174.4	Malignant neoplasm of female breast, upper-outer quadrant
174.5	Malignant neoplasm of female breast, lower-outer quadrant
174.6	Malignant neoplasm of female breast, axillary tail
174.8	Malignant neoplasm of female breast, other specified sites of female breast
174.9	Malignant neoplasm of female breast, Breast (female), unspecified
175.0	Malignant neoplasm of male breast, nipple and areola
175.9	Malignant neoplasm of male breast, other and unspecified sites of male breast
183.0	Malignant neoplasm of ovary and other uterine adnexa; ovary
198.6	Secondary malignant neoplasm of other specified sites; ovary
198.81	Secondary malignant neoplasm of other specified sites; breast
233.0	Carcinoma in situ of breast and genitourinary system; breast
233.30	Other and unspecified female genital organs; Unspecified female genital organ
233.39	Other and unspecified female genital organs; Other female genital organ
V10.3	Personal history of malignant neoplasm; breast

- V10.43 Personal history of malignant neoplasm; genital organs; ovary
- V16.3 Family history of malignant neoplasm; breast
- V16.41 Family history of malignant neoplasm genital organs; ovary
- V16.8 Family history of malignant neoplasm of breast, Other specified malignant neoplasm

ICD-10 Diagnoses (*Effective October 1, 2015*)

- 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
Z80.8	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: <ul style="list-style-type: none"> 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 <i>BRCA1</i> and <i>BRCA2</i> genes (BART—BRAC Analysis Rearrangement Test) may be considered medically necessary in patients who meet criteria for <i>BRCA</i> 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 <i>BRCA</i> 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 <i>BRCA</i> 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 <i>BRCA</i> 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: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> Added CPT code: 81406 Removed CPT codes: 83890, 83891, 83892, 83893, 83894, 83896, 83912, 83913

	(Effective 12-31-2012)
02-26-2013	<p>Updated Description section.</p> <p>In the Policy section:</p> <ul style="list-style-type: none"> ▪ 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 <i>BRCA1</i> or <i>BRCA2</i> mutation, but are affected with one of the following: <ul style="list-style-type: none"> ○ 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. ▪ 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 <i>BRCA1</i> and <i>BRCA2</i> 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." <p>Updated Rationale section.</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Removed HCPCS codes: S3818, S3819, S3820, S3822, S3823 <p>Updated Reference section.</p>
07-22-2013	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Maintenance completed on coding section, correcting "V16.4" to read "V16.41".
12-11-2013	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added ICD-10 Diagnosis (<i>Effective October 1, 2014</i>)
08-28-2014	<p>Description section updated.</p> <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ 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. <p>"I. Genetic testing may be considered medically necessary under any one of the following circumstances:</p> <ol style="list-style-type: none"> A. Member of family with a known <i>BRCA1/BRCA2</i> mutation B. Personal history of breast cancer plus one or more of the following: <ol style="list-style-type: none"> 1. Diagnosed at 45 years of age or younger 2. Diagnosed at 50 years of age or younger with: <ol style="list-style-type: none"> 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-)]

	<p>8. Diagnosed age <50 years with a limited family history (see policy guidelines)</p> <p>9. Personal history of breast and / or ovarian cancer at any age with ≥ 2 close blood relatives with pancreatic cancer at any age</p> <p>10. Diagnosed at any age with breast cancer or pancreatic cancer, who are not from families with a high risk of <i>BRCA1</i> or <i>BRCA2</i> mutation, but are affected with one of the following:</p> <ul style="list-style-type: none"> ▪ 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. <p>C. Personal history of epithelial ovarian / fallopian tube / primary peritoneal cancer</p> <p>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</p> <p>E. Personal history of male breast cancer</p> <p>F. Family history only –</p> <ol style="list-style-type: none"> 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. <p>II. Testing for genomic rearrangements of the <i>BRCA1</i> and <i>BRCA2</i> genes (BART—BRAC Analysis Rearrangement Test) may be considered medically necessary in patients who meet criteria for <i>BRCA</i> testing, whose testing for point mutations is negative.</p> <p>III. Genetic testing when policy requirements are not met is experimental / investigational.</p> <p><u>Policy Guidelines</u></p> <ol style="list-style-type: none"> 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 <i>BRCA</i> 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 <i>BRCA</i> 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). <p>Testing eligible individuals who belong to ethnic populations in which there are well characterized founder mutations should begin with tests specifically for these mutations</p>
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	(multi site testing)."
	Rationale section updated
	In Coding section: <ul style="list-style-type: none"> ▪ 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: <ul style="list-style-type: none"> ▪ 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 "dFor 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 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 <i>BRCA1</i> and <i>BRCA2</i> genes may be considered medically necessary in patients who meet criteria for <i>BRCA</i> testing, whose testing for point mutations is negative." ▪ Removed Item E, "Testing for <i>CHEK2</i> 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 <i>BRCA1</i> and <i>BRCA2</i> 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. <u>Comprehensive Mutation Analysis</u>. 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: <ul style="list-style-type: none"> • 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. <u>A Recommended Testing Strategy</u>. Patients who meet criteria for genetic testing as outlined in the Policy Stgements above should be tested for mutations in BRCA1 and BRCA2. <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 1) Non-Ashkenazi Jewish descent <ul style="list-style-type: none"> 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

	<p>suggests testing first- or second-degree family members affected with cancer thought to be related to deleterious <i>BRCA1/BRCA2</i> mutations (e.g., prostate cancer, pancreatic cancer, melanoma).</p> <p>c) If no familial mutation can be identified, two possible testing strategies are:</p> <p>i. Full sequencing followed by testing for common large genomic rearrangements (deletions/duplications) only if sequencing detects no mutation (negative result).</p> <ul style="list-style-type: none"> • More than 90% of BRCA mutations will be detected by full sequencing.(4) <p>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.</p> <ul style="list-style-type: none"> • Comprehensive testing can detect 92.5% of <i>BRCA1/BRCA2</i> mutations.(4) <p>d) If comprehensive BRCA testing is negative, testing for uncommon large genomic rearrangements (e.g., BART™) may be done.</p> <p>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.</p> <ul style="list-style-type: none"> • Among patients with negative comprehensive testing, BART™ identified a deleterious mutation (positive result) in less than 1%.(4) <p>C. Ashkenazi Jewish descent</p> <ul style="list-style-type: none"> • In patients of known Ashkenazi Jewish descent, NCCN recommends testing for the 3 known founder mutations (185delAG and 5182insC in <i>BRCA1</i>; 6174delT in <i>BRCA2</i>) 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.

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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.
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.

APPENDIX

Appendix Table 1. Categories of Genetic Testing Addressed in Policy

Category	Addressed
1. Testing of an affected individual's germline to benefit the individual	
1a. Diagnostic	X
1b. Prognostic	
1c. Therapeutic	
2. Testing cancer cells from an affected individual to benefit the individual	
2a. Diagnostic	
2b. Prognostic	
2c. Therapeutic	

Category	Addressed
3. Testing an asymptomatic individual to determine future risk of disease	X
4. Testing of an affected individual's germline to benefit family members	X
5. Reproductive testing	
5a. Carrier testing: preconception	
5b. Carrier testing: prenatal	
5c. In utero testing: aneuploidy	
5d. In utero testing: mutations	
5e. In utero testing: other	
5f. Preimplantation testing with in vitro fertilization	