

## 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](http://www.bcbsks.com/CustomerService/Forms/pdf/15-17_predeterm_request_frm.pdf)

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Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>• With cancer or personal or family cancer history and criteria suggesting risk of hereditary breast/ovarian cancer syndrome</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Genetic testing for a <i>BRCA1</i> or <i>BRCA2</i> mutation</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Standard of care without genetic testing</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Disease-specific survival</li> <li>• Test accuracy</li> <li>• Test validity</li> <li>• Quality of life</li> </ul>

## **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 history of cancer or have a family history of cancer in their family, which might suggest 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, 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.

### **REGULATORY STATUS**

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

Myriad Genetic Laboratories (Salt Lake City, UT) offers (1) 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 and (4) BRACAnalysis CDxs®, which is intended to detect germline *BRCA1* and *BRCA2* variants to aid in identifying ovarian cancer patients who may be considered for treatment with olaparib.

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 BRCAAssureSM suite of tests which includes: targeted *BRCA1* and *BRCA2* variant analysis; 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) 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 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  $\geq 1$  of the following:
  - a. Diagnosed at age  $\leq 45$  years
  - b. Two primary breast cancers when 1st breast cancer diagnosis occurred at age  $\leq 50$  years
  - c. Diagnosed at age  $\leq 50$  years AND:
    - i. One or more 1st-, 2nd-, or 3rd-degree relative<sup>a</sup> with breast cancer (at any age), pancreatic cancer or prostate cancer<sup>b</sup>, or
    - ii. Unknown or limited family history<sup>c</sup>
  - d. Diagnosed at age  $\leq 60$  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  $\geq 1$  1st-, 2nd-, or 3rd-degree relative<sup>a</sup> with breast cancer diagnosed at  $\leq 50$  years
  - f. Diagnosed at any age AND  $\geq 2$  1st-, 2nd-, or 3rd-degree relative<sup>a</sup> with breast cancer at any age
  - g. Diagnosed at any age AND  $\geq 1$  1st-, 2nd-, or 3rd-degree relative<sup>a</sup> with epithelial ovarian, fallopian tube, or primary peritoneal cancer
  - h. Diagnosed at any age AND  $\geq 2$  1st-, 2nd-, or 3rd-degree relative<sup>a</sup> with pancreatic cancer or prostate cancer<sup>b</sup> 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<sup>d</sup>
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<sup>c</sup> at any age AND  $\geq 1$  1st-, 2nd-, or 3rd-degree relative<sup>a</sup> with any of the following:
  - a. Breast cancer  $\leq 50$
  - b. Ovarian, fallopian tube, or primary peritoneal cancer at any age

6. Personal history of pancreatic or prostate cancer<sup>b</sup> at any age AND  $\geq 2$  or more 1st-, 2nd-, or 3rd-degree relatives<sup>a</sup> with breast, pancreatic, or prostate cancer<sup>b</sup> 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  $\geq 2$  1st-, 2nd-, or 3rd-degree relatives<sup>a</sup> with breast cancer ( $\geq 1$  at age  $\leq 50$  years) and/or ovarian, fallopian tube, or primary peritoneal cancer

<sup>a</sup> 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.

<sup>b</sup> For familial assessment, prostate cancer is defined as Gleason score  $\geq 7$ .

<sup>c</sup> 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.

<sup>d</sup> 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**.**

## 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-7 (FHS-7)
3. Comprehensive Variant Analysis: Comprehensive variant 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 section for criteria).
4. 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 variants. For example, founder mutations account for approximately three quarters of the *BRCA* variants found in Ashkenazi Jewish populations (see Rationale section). When testing for founder mutations is negative, comprehensive mutation analysis should then be performed.
5. Testing Unaffected Individuals: In unaffected family members of potential *BRCA* mutation families, most test results will be negative and uninformative. Therefore, it is strongly recommended that an *affected* family member be tested first whenever possible to adequately interpret the test. Should a *BRCA* variant be found in an affected family member, 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. This is because there is no change in management for minors as a result of knowledge of the presence or absence of a deleterious variant. In addition, there are potential harms related to stigmatization and discrimination.
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 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 variants in *BRCA1* and *BRCA2*.
  - 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, 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* 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* mutations 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/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, above).

## **RATIONALE**

This evidence review was developed following a 1997 TEC Assessment<sup>1</sup> 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 11, 2017 (see Appendix Table 1 for genetic testing categories).

### **Testing for *BRCA1* and *BRCA2* Mutations in High-Risk Individuals**

#### Clinical Context and Test Purpose

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

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

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

#### Patients

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

#### Intervention

The intervention of interest is *BRCA1* and *BRCA2* variant testing.

#### Comparator

The comparator of interest is standard of care without genetic testing for HBOC syndrome.



### Outcomes

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

### Time

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

### Setting

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

### Analytic Validity

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

### Clinical Validity

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

### Prevalence of BRCA Variants and Risks of Cancer and Survival

The prevalence of *BRCA* variants is approximately 0.1% to 0.2% in the general population. Prevalence may be much higher for particular ethnic groups with characterized founder mutations (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.

Nelson et al (2013) conducted a systematic review that included meta-analytic estimates of the prevalence and penetrance of *BRCA* variants, in order to update the U.S. Preventive Services Task Force (USPSTF) recommendation for risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer.<sup>2</sup> In high-risk women with positive test results, cumulative risks for developing breast cancer by age 70 were 46% for *BRCA1* and 50% for *BRCA2* when a single family member was tested, and 70% for *BRCA1* and 71% for *BRCA2* when multiple family members were tested; cumulative risks for developing ovarian cancer by age 70 were 41% for *BRCA1* and 17% for *BRCA2* when a single family member was tested; and 46% for *BRCA1* and 23% for *BRCA2* when multiple family members were tested. For Ashkenazi Jewish women with positive test results, cumulative risks for developing breast or ovarian cancer by age 75 were 34% and 21%, respectively. Nelson et al included meta-analytic estimates of *BRCA* prevalence in their 2013 systematic review for USPSTF. In unselected women, *BRCA* variant prevalence estimates were 0.2% to 0.3%; in women with breast cancer, 1.8% for *BRCA1* and 1.3% for *BRCA2*; in women with breast cancer onset at age 40 years or younger, 6%; in women from high-risk families, 13.6% for *BRCA1*, 7.9% for *BRCA2*, and 19.8% for *BRCA1* or *BRCA2*; in unselected Ashkenazi Jewish women, 2.1%; and in Ashkenazi Jewish women from high-risk families, 10.2%.

Estimates of lifetime risk of cancer for *BRCA* variant carriers (penetrance), based on studies of families with extensive history of disease, have been as high as 85%. For example,

Kuchenbaeher 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.<sup>3</sup> 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.<sup>4</sup> 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*.<sup>5-8</sup> 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).<sup>9</sup> Importantly, the risk of cancer in variant carriers from families with little history of cancer ( $\approx$ 50% of all carriers) did not differ significantly. Lifetime risks of ovarian cancer were 54% for *BRCA1*, and 23% for *BRCA2* variant carriers.

Women with a history of breast cancer and a *BRCA* variant have a significant risk of contralateral breast cancer; in 1 prospective study (2004), the 10-year risk was 29.5% for women with initial stage I or II disease.<sup>10</sup> In a 2013 prospective study (EMBRACE), the cumulative risk of contralateral breast cancer by age 70 years was 83% in *BRCA1* variant carriers, and 62% for *BRCA2* variant carriers.<sup>11</sup> These investigators also reported cumulative risks of breast cancer by age 70 in women without previous cancer (60% in *BRCA1* carriers, 55% in *BRCA2* carriers). Similarly, the cumulative risks of ovarian cancer by age 70 years in women without previous ovarian cancer were 59% for *BRCA1* carriers and 17% for *BRCA2* carriers.

A systematic review published by Zhu et al in 2016 found a significantly lower risk of overall survival in breast cancer patients with *BRCA1* (pooled hazard ratio [HR], 1.69; 95% confidence interval [CI], 1.35 to 2.12) and with *BRCA2* (pooled HR=1.50; 95% CI, 1.02 to 2.09;  $p=0.034$ ).<sup>12</sup> However, in patients with breast cancer, *BRCA1* and *BRCA2* were not associated with a lower breast cancer-specific survival.

#### Clinical Features Suggestive of BRCA Variant

Young age of onset of breast cancer, even in the absence of family history, is a risk factor for *BRCA1* variants. Winchester (1996) estimated that hereditary breast cancers account for 36% to 85% of patients diagnosed before age 30.<sup>13</sup> In several studies, *BRCA* variants are independently predicted by early age at onset, being present in 6% to 10% of breast cancer cases diagnosed at ages younger than various premenopausal age cutoffs (age range, 35-50 years).<sup>13-16</sup> In cancer-prone families, the mean age of breast cancer diagnosis among women carrying *BRCA1* or *BRCA2* variants is in the 40s.<sup>17</sup> 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.<sup>14</sup> In a similar study (2000), 31% of Ashkenazi Jewish women, unselected for family history, diagnosed with breast cancer at younger than 42 years of age had *BRCA* variants.<sup>18</sup> 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.<sup>8,19,20</sup>

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.<sup>16</sup> Several other studies have documented the significant influence of family history.<sup>5,8,18-20</sup>

In patients with “triple-negative” breast cancer (ie, negative for expression of estrogen and progesterone receptors; and negative for overexpression of human epidermal growth factor receptor 2 receptors), there is an increased prevalence of *BRCA* variants. Pathophysiologic research has suggested that the physiologic pathway for development of triple-negative breast cancer is similar to that for *BRCA*-associated breast cancer.<sup>21</sup> In 200 randomly selected patients with triple-negative breast cancer from a tertiary care center, there was a greater than 3-fold increase in the expected rate of *BRCA* variants.<sup>22</sup> *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.<sup>23</sup> Six *BRCA* variants (5 *BRCA1*, 1 *BRCA2*) were found, for a variant rate of 11%. Finally, in a 2011 study of 77 patients with triple-negative breast cancer, 15 patients (19.5%) had *BRCA* variants (12 in *BRCA1*, 3 in *BRCA2*).<sup>24</sup>

#### *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.<sup>25</sup> Couch et al (2007) reported on screening for *BRCA2* variants in two cohorts of families at high risk for pancreatic cancer.<sup>26</sup> In the first cohort of high-risk families, there were a total of 5 (3%) *BRCA* variants in 151 probands; in the second cohort, there were another 5 (17%) *BRCA2* variants in 29 probands. The combined *BRCA2* variant rate for these 2 cohorts was 6% (10/180). Ferrone et al (2009) tested 187 Ashkenazi Jewish patients with pancreatic cancer for *BRCA* variants and found that 5.5% (8/187) had a *BRCA* variant.<sup>27</sup>

#### *BRCA Variant Rates Associated with Ovarian Cancer*

Women with a personal history of ovarian cancer have an increased rate of *BRCA* variants. In a 2010 systematic review of 23 studies, Trainer et al estimated the rate of *BRCA* variants among women with ovarian cancer to be 3% to 15%.<sup>28</sup> In this review, 3 U.S. studies tested for both *BRCA1* and *BRCA2*; incidences of *BRCA* variants were 11.3%, 15.3%, and 9.5%. In a 2011 population-based study of 1342 unselected patients with invasive ovarian cancer in Canada, 176 women had *BRCA* variants, for a rate of 13.3%.<sup>29</sup> Variant prevalence was higher for women in their 40s (24%) and for women with serous ovarian cancer (18%). Ethnicity was another risk factor for *BRCA*, with higher rates seen in women of Italian (43.5%), Jewish (30%), and Indo-Pakistani (29.4%) origin. In the 2013 systematic review for USPSTF by Nelson et al, meta-analytic estimates of *BRCA* prevalence among women with ovarian cancer were 4.4% for *BRCA1* and 5.6% for *BRCA2*.<sup>2</sup>

#### *BRCA Variant Rates Associated with Fallopian Tube Cancer*

A 2009 study described the high rate of occult fallopian tube cancers in at-risk women having prophylactic bilateral salpingo-oophorectomy.<sup>30</sup> In this prospective series of 45 women, 4 (9%) had fallopian tube malignancies. Reviewers noted that these findings supported other studies that have demonstrated the fimbrial end of the fallopian tube as an important site of cancer in those with *BRCA1* or *BRCA2* variants.

A 2013 long-term study (median follow-up, 7 years; range, 3-14 years) followed 32 *BRCA* variant carriers with occult malignancy (4 ovarian, 23 fallopian tube, 5 ovarian and fallopian tube) diagnosed of prophylactic salpingo-oophorectomy.<sup>31</sup> Among 15 women with invasive carcinoma (median age, 50 years), 7 (47%) experienced recurrence at a median of 33 months, and overall

survival was 73%. Among 17 women with noninvasive neoplasia (median age, 53 years), 4 (24%) received chemotherapy, none of whom experienced recurrence. One (6%) patient who did not receive chemotherapy experienced recurrence at 43 months. Overall survival was 100%. The authors concluded that, in *BRCA* variant carriers, unsuspected invasive carcinoma has a relatively high rate of recurrence, but noninvasive neoplasms rarely recur and may not require adjuvant chemotherapy.

#### Testing for Large BRCA Rearrangements

A number of studies have shown that a significant percentage of women with a strong family history of breast cancer and negative tests for *BRCA* variants have large genomic rearrangements (including deletions or duplications) in one of these genes. For example, in 2006 Walsh et al reported on probands from 300 U.S. families with 4 or more cases of breast or ovarian cancer but with negative (wild-type) commercial genetic tests for *BRCA1* and *BRCA2*.<sup>32</sup> These patients underwent screening with additional multiple DNA-based and RNA-based methods. Of these 300 patients, 17% carried previously undetected variants, including 35 (12%) with genomic rearrangement of *BRCA1* or *BRCA2*.

A 2008 study evaluated 251 patients with an estimated *BRCA* variant prevalence using the Myriad II model of at least 10%.<sup>33</sup> In 136 non-Ashkenazi Jewish probands, 36 (26%) had *BRCA* point variants and 8 (6%) had genomic rearrangements (7 in *BRCA1*, 1 in *BRCA2*). Genomic rearrangements comprised 18% of all identified *BRCA* variants. No genomic rearrangements were identified in the 115 Ashkenazi Jewish probands, but 47 (40%) had point variants. The authors indicated that the estimated prevalence of a variant did not predict the presence of a genomic rearrangement.

#### Clinical Utility

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

As discussed above, the risk of cancer in a *BRCA* variant carrier is significant. Thus, knowledge of variant status in individuals at potentially increased risk of a *BRCA* variant may impact health care decisions to reduce risk.<sup>34-41</sup> Risk-reducing options include intensive surveillance, chemoprevention, prophylactic mastectomy, or prophylactic oophorectomy.

Prophylactic mastectomy reduces the risk of breast cancer in high-risk women (based on family history) by 90%.<sup>35</sup> Prophylactic oophorectomy significantly reduces the risk of ovarian cancer by 80% or more<sup>38,39,42</sup> and reduces the risk of breast cancer by approximately 50%.<sup>39</sup> In women who have already had breast cancer, prophylactic oophorectomy reduces the risk of cancer relapse.<sup>37</sup> Prophylactic oophorectomy or salpingo-oophorectomy in women with *BRCA1* or *BRCA2* reduced the risk of all-cause mortality by 77% in a 2014 study<sup>42</sup> and by 60% in a 2010 study.<sup>43</sup>

Systematic reviews of observational studies comparing prophylactic surgeries to observation in women with *BRCA1* and *BRCA2* variants demonstrate contralateral prophylactic mastectomy in women with breast cancer are associated with significantly lower all-cause mortality while bilateral prophylactic mastectomy was not associated with all-cause mortality.<sup>44-46</sup> Studies have indicated that the results of genotyping have a significant influence on treatment choices.<sup>36,40,41</sup>

Phillips et al (2006) reported that although uptake of prophylactic surgery and screening was associated with knowing one's variant status, in their cohort of 70 unaffected female variant carriers who had chosen to receive results, a minority had risk-reducing surgery (11% had bilateral mastectomy; 29% had bilateral oophorectomy) or chemoprevention.<sup>47</sup>

In their 2014 systematic review for USPSTF, Nelson et al assessed efficacy of risk-reducing surgery in *BRCA*-positive women.<sup>48</sup> For high-risk women and variant carriers, bilateral mastectomy reduced breast cancer incidence by 85% to 100% and breast cancer mortality by 81% and 100%, respectively; salpingo-oophorectomy reduced breast cancer incidence by 37% to 100%, ovarian cancer incidence by 69% to 100%, and all-cause mortality by 55% to 100%, respectively. Some women experienced reduced anxiety. Although comparison groups varied across studies, results were consistent. Adverse events included physical complications of surgery, postsurgical symptoms, and changes in body image. Limitations of the analysis included the small number of studies (N=7) and small sample sizes. As the authors observed, it is still currently unknown whether *BRCA* variant testing reduces cause-specific or all-cause mortality, or if it improves the quality of life. Harms associated with false-negative results or variants of uncertain significance also are unknown.

Other studies have looked at the results of prostate cancer screening in men with *BRCA* variants. The IMPACT study (2011) evaluated the results of screening in 205 men 40 to 69 years of age who were *BRCA* variant carriers and 95 control patients.<sup>49</sup> At the baseline screen, biopsies were performed in 7.0% of men with a prostate-specific antigen level greater than 3.0, and prostate cancer was identified in 3.3%. This resulted in a positive predictive value of 47.6%, which is considerably higher than that estimated for men at normal risk. Moreover, the grade of tumor identified was intermediate in 67% of cancers and high in 11%. This differs from the expected distribution of cancer grade in average-risk men, with more than 60% expected to have low-grade cancer.

### **SUMMARY OF EVIDENCE**

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

### **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 guidelines on genetic and familial high-risk assessment of breast and ovarian cancers (v.1.2018) include criteria for identifying individuals who should be referred for further risk assessment, and separate criteria for genetic testing.<sup>50</sup> Patients who satisfy any of the testing criteria listed in Table 1 should undergo “further personalized risk assessment, genetic counseling, and often genetic testing and management.” For these criteria, both invasive and in situ breast cancers were included. Maternal and paternal sides of the family should be considered independently for familial patterns of cancer. Testing of unaffected individuals should be considered “only when an appropriate affected family member is unavailable for testing.”

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

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

Recommendations	
1.	Individual from a family with a known <i>BRCA1/BRCA2</i> mutation
2.	Personal history of breast cancer and ≥1 of the following: <ol style="list-style-type: none"> <li>Diagnosed age ≤45 years</li> <li>Diagnosed age ≤50 years AND:               <ul style="list-style-type: none"> <li>An additional breast cancer primary</li> <li>≥1 close blood relative with breast cancer at any age</li> <li>≥1 close relative with pancreatic cancer</li> <li>≥1 close relative with prostate cancer (Gleason score ≥7), or</li> <li>Unknown or limited family history</li> </ul> </li> <li>Diagnosed age ≤60 years with a triple-negative (<i>ER-</i>, <i>PR-</i>, <i>HER2-</i>) breast cancer</li> <li>Diagnosed any age AND               <ul style="list-style-type: none"> <li>≥2 close blood relatives with breast, pancreatic or prostate cancer (Gleason score ≥7) at any age</li> <li>≥1 close blood relative with breast cancer diagnosed at age 50 or younger</li> <li>≥1 close blood relative with ovarian cancer or</li> <li>A close male blood relative with breast cancer</li> </ul>               For an individual of ethnicity associated with higher mutation frequency (eg Ashkenazi Jewish), no additional family history may be required             </li> </ol>
3.	Personal history of ovarian cancer
4.	Personal history of male breast cancer
5.	Personal history of prostate cancer (Gleason score ≥7) at any age AND ≥1 close blood relative with ovarian cancer at cancer at any age or breast cancer at or before age 50 or 2 relatives with breast, pancreatic or prostate cancer (Gleason score ≥7) at any age.
6.	Personal history of pancreatic cancer at any age AND ≥1 blood relative with ovarian cancer at any age or breast cancer at or before age 50 or 2 relatives with breast, pancreatic or prostate cancer (Gleason score ≥7 or metastatic) at any age For an individual of ethnicity associated with higher mutation frequency (eg Ashkenazi Jewish), no additional family history may be required
7.	<i>BRCA1/2</i> mutation detected by tumor profiling in the absence of germline mutation analysis
8.	Family history only <ol style="list-style-type: none"> <li>1st- or 2nd-degree blood relative meeting any of the above criteria</li> </ol>

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### Recommendations

- b. 3rd-degree blood relative with breast cancer and/or ovarian/fallopian tube/primary peritoneal cancer AND  $\geq 2$  1st-, 2nd-, or 3rd-degree relatives with breast cancer ( $\geq 1$  at age  $\leq 50$  years) and/or ovarian cancer

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

#### American Society of Clinical Oncology

The American Society of Clinical Oncology recommended in 2003 that cancer predisposition testing be offered when 3 factors are at play: (1) there is a personal or family history suggesting genetic cancer susceptibility, (2) the test can be adequately interpreted, and (3) results will influence medical management of the patient or family member at hereditary risk of cancer.<sup>51</sup> 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."<sup>52</sup>

#### Society of Gynecologic Oncology

In 2014, the Society of Gynecologic Oncology (SGO) published an evidence-based consensus statement on risk assessment for inherited gynecologic cancer.<sup>53</sup> The statement included criteria for recommending genetic assessment (counseling with or without testing) to patients who may be genetically predisposed to breast or ovarian cancer. Overall, SGO and the National Comprehensive Cancer Network recommendations are very similar; the main differences being the exclusion of: women with breast cancer onset at age 50 years or younger who have 1 or more first-, second-, or third-degree relatives with breast cancer at any age; women with breast cancer or history of breast cancer who have a first-, second-, or third-degree male relative with breast cancer; and men with a personal history of breast cancer. Additionally, SGO recommended genetic assessment for unaffected women who have a male relative with breast cancer. Moreover, SGO indicated that some patients who do not satisfy criteria may still benefit from genetic assessment (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.<sup>54</sup>

- "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
<b>Ongoing</b>			
NCT02154672	Prostate Cancer Screening in Men With Germline BRCA2 Mutations	100	May 2018
NCT02225015	Cancer Prevention in Women With a BRCA Mutation	300	Jun 2019
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	<p>In the Policy section:          Formatting changes to the policy language.</p> <p>In the Coding section:          Added new codes: 81211, 81212, 81213, 81214, 81215, 81216, 81217</p>
10-04-2012	<p>Updated Description section.</p> <p>In the Policy section:</p> <ul style="list-style-type: none"> <li>▪ 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%."</li> <li>▪ 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: <a href="http://www.myriadtests.com">www.myriadtests.com</a>)."</li> </ul> <p>Updated Reference section.</p> <p>Updated Reference section.</p>
10-26-2012	<p>In the Policy section:</p> <ul style="list-style-type: none"> <li>▪ In the Policy Guidelines section, #7, corrected website, "<a href="http://www.myriadtests.com">www.myriadtests.com</a>" to "<a href="http://www.myriadpro.com/brca-risk-calculator">www.myriadpro.com/brca-risk-calculator</a>".</li> </ul>
01-15-2013	<p>In the Coding section:</p> <ul style="list-style-type: none"> <li>▪ Added CPT code: 81406</li> <li>▪ Removed CPT codes: 83890, 83891, 83892, 83893, 83894, 83896, 83912, 83913 (Effective 12-31-2012)</li> </ul>
02-26-2013	<p>Updated Description section.</p> <p>In the Policy section:</p> <ul style="list-style-type: none"> <li>▪ 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"> <li>○ Early onset breast cancer</li> <li>○ Two breast primary cancers with the first cancer diagnosis occurring prior to age 50 years;</li> </ul> </li> </ul>

	<ul style="list-style-type: none"> <li>○ Triple negative breast cancer (neither express estrogen receptor and progesterone receptor, nor overexpression HER2) diagnosed at younger than age 60.</li> <li>○ Two or more close blood relatives with pancreatic cancer at any age.</li> <li>▪ 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."</li> </ul>
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> <li>▪ Removed HCPCS codes: S3818, S3819, S3820, S3822, S3823</li> </ul>
	Updated Reference section.
07-22-2013	In Coding section: <ul style="list-style-type: none"> <li>▪ Maintenance completed on coding section, correcting "V16.4" to read "V16.41".</li> </ul>
12-11-2013	In Coding section: <ul style="list-style-type: none"> <li>▪ Added ICD-10 Diagnosis (<i>Effective October 1, 2014</i>)</li> </ul>
08-28-2014	Description section updated.
	<p>In Policy section:</p> <ul style="list-style-type: none"> <li>▪ 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.</li> </ul> <p>"I. Genetic testing may be considered medically necessary under any one of the following circumstances:</p> <ol style="list-style-type: none"> <li>A. Member of family with a known <i>BRCA1/BRCA2</i> mutation</li> <li>B. Personal history of breast cancer plus one or more of the following: <ol style="list-style-type: none"> <li>1. Diagnosed at 45 years of age or younger</li> <li>2. Diagnosed at 50 years of age or younger with: <ol style="list-style-type: none"> <li>a. one or more close blood relatives with breast cancer at 50 years of age or younger; and/or</li> <li>b. one or more close blood relatives with epithelial ovarian / fallopian tube / primary peritoneal cancer</li> </ol> </li> <li>3. Two breast primaries when first breast cancer diagnosis occurred prior to age 50</li> <li>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</li> <li>5. Close male blood relative with breast cancer</li> <li>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</li> <li>7. Diagnosed age &lt; 60 years with a triple negative breast cancer [estrogen receptors (ER-), progesterone receptors (PR-), and HER2 (HER2-)]</li> <li>8. Diagnosed age &lt;50 years with a limited family history (see policy guidelines)</li> <li>9. Personal history of breast and / or ovarian cancer at any age with ≥ 2 close blood relatives with pancreatic cancer at any age</li> <li>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: <ul style="list-style-type: none"> <li>▪ Early onset breast cancer</li> <li>▪ Two breast primary cancers with the first cancer diagnosis occurring prior to age 50 years;</li> </ul> </li> </ol> </li> </ol>

	<ul style="list-style-type: none"> <li>▪ Triple negative breast cancer (neither express estrogen receptor and progesterone receptor, nor overexpression HER2) diagnosed at younger than age 60.</li> <li>▪ Two or more close blood relatives with pancreatic cancer at any age.</li> </ul> <p>C. Personal history of epithelial ovarian / fallopian tube / primary peritoneal cancer</p> <p>D. Personal history of pancreatic cancer at any age with <math>\geq 2</math> 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"> <li>1. Close family member meeting any of the above criteria</li> <li>2. Third-degree blood relative with breast cancer and /or ovarian / fallopian tube/ primary peritoneal cancer with <math>\geq 2</math> close blood relatives with breast cancer (at least one with breast cancer <math>\leq 50</math> years) and / or ovarian cancer.</li> </ol> <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"> <li>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.</li> <li>2. For purposes of this policy, breast cancer includes both invasive and ductal carcinoma in situ (DCIS).</li> <li>3. For individuals with family history only, an affected family member should be tested first whenever possible to identify specific site mutations.</li> <li>4. The maternal and paternal sides should be considered independently.</li> <li>5. Other malignancies reported in some HBOC families include prostate and melanoma.</li> <li>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.</li> <li>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: <a href="http://www.myriadpro.com/brca-risk-calculator">www.myriadpro.com/brca-risk-calculator</a> ).</li> </ol> <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 (multi site testing)."</p> <p>Rationale section updated</p> <p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Updated nomenclature for CPT code: 81215</li> <li>▪ 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</li> <li>▪ Added ICD-9 codes: 233.30, 233.39</li> <li>▪ Removed ICD-9 code: 233.3</li> </ul>
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	<ul style="list-style-type: none"> <li>▪ Removed ICD-10 codes: C50.129, C50.229, C50.529, C50.819</li> </ul>
	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	<p>Updated Description section</p> <p>In Policy section:</p> <ul style="list-style-type: none"> <li>▪ In Item A, added "or With History of Cancer," to read, "Patients with Cancer or With History of Cancer"</li> <li>▪ In Item B, added "or Without History of Cancer," to read, "Patients Without Cancer or Without History of Cancer"</li> <li>▪ In Item B, added "dFor example, fewer than 2 1<sup>st</sup>- or 2<sup>nd</sup>-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"</li> <li>▪ 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."</li> <li>▪ 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."</li> <li>▪ Added Item D, "Genetic testing in minors for <i>BRCA1</i> and <i>BRCA2</i> mutations is considered experimental / investigational."</li> <li>▪ 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."</li> <li>▪ 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"> <li>• Eligible for testing, and</li> <li>• From families without a known deleterious BRCA1 or BRCA2 mutation, and</li> <li>• Not from ethnic groups with known founder mutations."</li> </ul> </li> <li>▪ 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"> <li>A. In patients with a known familial BRCA mutation, targeted testing for the specific mutation is recommended.</li> <li>B. In patients with unknown familial BRCA mutation: <ul style="list-style-type: none"> <li>1) Non-Ashkenazi Jewish descent <ul style="list-style-type: none"> <li>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.</li> <li>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 <i>BRCA1/BRCA2</i> mutations (e.g., prostate cancer, pancreatic cancer, melanoma).</li> <li>c) If no familial mutation can be identified, two possible testing strategies are: <ul style="list-style-type: none"> <li>i. Full sequencing followed by testing for common large genomic rearrangements (deletions/duplications) only if sequencing detects no mutation (negative result). <ul style="list-style-type: none"> <li>• More than 90% of BRCA mutations will be detected by full sequencing.(4)</li> </ul> </li> </ul> </li> </ul> </li> </ul> </li> </ul> </li> </ul>

	<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"> <li>• Comprehensive testing can detect 92.5% of <i>BRCA1/BRCA2</i> mutations.(4)</li> </ul> <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"> <li>• Among patients with negative comprehensive testing, BART™ identified a deleterious mutation (positive result) in less than 1%.(4)</li> </ul> <p>C. Ashkenazi Jewish descent</p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• If testing is negative for founder mutations, comprehensive genetic testing may be considered (see Comprehensive Mutation Analysis, above)."</li> </ul>
	In Coding section:
	<ul style="list-style-type: none"> <li>▪ Removed CPT code 81406.</li> </ul>
	Updated Rationale section.
	In Coding section:
	<ul style="list-style-type: none"> <li>▪ Removed CPT code 81406.</li> </ul>
	Updated References section.
01-01-2016	Updated Description section.
	In Policy section:
	<ul style="list-style-type: none"> <li>▪ In Policy Guidelines, added paragraph on Genetic Counseling.</li> </ul>
	Updated Rationale section.
	In Coding section:
	<ul style="list-style-type: none"> <li>▪ Added CPT code: 81162</li> </ul>
	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:
	<ul style="list-style-type: none"> <li>▪ Changed "mutation" to "variant" throughout policy language.</li> <li>▪ In Item A, added "Personal" to read, "Patients With Cancer or With Personal History of Cancer."</li> <li>▪ In Item A 2 c, added "pancreatic cancer or prostate cancer" to read, "One or more 1st-, 2nd, or 3rd-degree relative<sup>a</sup> with breast cancer (at any age), pancreatic cancer or prostate cancer<sup>b</sup>, or".</li> <li>▪ In Item A 6, added "Personal history of" and "at any age AND ≥2 or more 1st-, 2nd-, or 3rd-degree relatives<sup>a</sup> with breast, pancreatic, or prostate cancer<sup>b</sup> at any age" to read, "Personal history of pancreatic or prostate cancer<sup>b</sup> at any age AND ≥2 or more 1st-, 2nd-, or 3rd-degree relatives<sup>a</sup> with breast, pancreatic, or prostate cancer<sup>b</sup> at any age."</li> <li>▪ 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."</li> </ul>

	<ul style="list-style-type: none"> <li>▪ Added new Item C, "Genetic testing for <i>BRCA1</i> and <i>BRCA2</i> variants when criteria above are not met is considered experimental / investigational."</li> <li>▪ Updated Policy Guidelines.</li> </ul>
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> <li>▪ Removed ICD-9 codes.</li> </ul>
	Updated Revisions section.
01-01-2019	In Coding section: <ul style="list-style-type: none"> <li>▪ Added new CPT codes: 81163, 81164, 81165, 81166, 81167.</li> <li>▪ Removed deleted CPT codes: 81211, 81213, 81214.</li> <li>▪ Revised nomenclature to CPT codes: 81162, 81212, 81215, 81216, 81217.</li> <li>▪ Added ICD-10 code: Z80.41.</li> </ul>

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## 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	
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	