Pre-Determination of Services IS REQUIRED by the Member’s Contract.

**Professional**
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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). Identification of patients with BRCA mutations may lead to enhanced screening and/or surveillance that could lead to improved outcomes.

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, BRCA4 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.

CHEK2 (cell cycle checkpoint kinase2) is also involved with DNA repair and human cancer predisposition like BRCA1 and BRCA2. CHEK2 is normally activated in response to DNA double-stranded breaks. CHEK2 regulates the function of BRCA1 protein in DNA repair and also exerts critical roles in cell cycle control and apoptosis. The CHEK2 mutation, 1100delC in exon 10 has been associated with familial breast cancers.
**POLICY**

Genetic testing should be performed in a setting that has suitably trained healthcare providers who can give appropriate pre- and posttest 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**

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. 2 primary breast cancers when 1st breast cancer diagnosis occurred age ≤50 years
   c. Diagnosed age ≤50 years AND:
      i. ≥1 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 (ER–, PR–, HER2–) 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 CA
   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** (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 ≥2 1st-, 2nd-, or 3rd-degree relatives\(^a\) with breast cancer (≥1 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).

\(^d\) 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,

C. Testing for genomic rearrangements of the *BRCA1* and *BRCA2* genes may be considered **medically necessary** in patients who meet criteria for *BRCA* testing, whose testing for point mutations is negative.

D. Unless they meet the criteria above, 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**.
E. Testing for CHEK2 abnormality (mutations, deletions, etc.) is considered **experimental / investigational** in affected and unaffected patients with breast cancer, irrespective of family history.

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.

NOTE: Testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing.

**Policy Guidelines**

1. The Policy Statements above are based on current guidelines from the National Comprehensive Cancer Network (NCCN)(1) (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.(2) (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)
   - FHS-7

4. Comprehensive mutation analysis. Comprehensive BRCA mutation analysis should be performed in patients with breast cancer, ovarian cancer, cancer of the fallopian tube, or primary peritoneal cancer who are:
   - Eligible for testing, and
   - From families without a known deleterious BRCA1 or BRCA2 mutation, and
   - Not from ethnic groups with known founder mutations.

5. 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).
6. 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.

7. 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.

8. 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.

RATIONALE
The most recent update covered the period through August 2013. In addition, relevant professional organizations were consulted for clinical guidelines.

Testing for BRCA1 and BRCA2 Mutations in High-Risk Women
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.(4) 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.(5-8) 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).(9) Importantly, the risk of cancer in mutation carriers from families with little history of cancer (~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.(10) 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.(11) 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.

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.(12-19) 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.(13) Prophylactic oophorectomy significantly reduces the risk of ovarian cancer to less than 10%(16,17) and reduces the risk of breast cancer by approximately 50%.(17) In women who have already had breast cancer, prophylactic oophorectomy reduces the risk of cancer relapse.(15) Studies indicate that genotyping results significantly influence treatment choices.(14,18,19)

Prevalence of BRCA Mutations
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 reported on racial and ethnic differences in the prevalence of BRCA1 and BRCA2 in American women.(20) Among their cases, 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. Rennert et al reported that breast cancer-specific rates of death among Israeli women were similar for carriers of a BRCA founder mutation and noncarriers.(21)

Clinical Features Suggestive of BRCA Mutation
Young age of onset of breast cancer, even in the absence of family history, has been demonstrated to be a risk factor for BRCA1 mutations. Winchester(22) estimated that hereditary breast cancers account for 36% to 85% of patients diagnosed before age 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).(22-25) In cancer-prone families, the mean age of breast cancer diagnosis among women carrying BRCA1 or BRCA2 mutations is in the 40s.(26) In the Ashkenazi Jewish population, Frank et al(23) reported that 13% of 248 cases with no known family history and diagnosed before 50 years of age had BRCA4 mutations. 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 BRCA4 mutations.(27) Additional studies indicate that early age of breast cancer diagnosis is a significant predictor of BRCA4 mutations in the absence of family history in this population.(8,28,29)
As in the general population, family history of breast or ovarian cancer, particularly of early age onset, is a significant risk factor for a \textit{BRCA} mutation in ethnic populations characterized by founder mutations. For example, in unaffected individuals of Ashkenazi Jewish descent, 12% to 31% will have a \textit{BRCA} mutation depending on the extent and nature of the family history.(25) Several other studies document the significant influence of family history.(5,8,27-29)

In patients with breast cancer that is “triple-negative”, ie, negative for expression of estrogen and progesterone receptors and for overexpression of HER2 receptors, there is an increased incidence of \textit{BRCA} mutations. Pathophysiologic research has suggested that the physiologic pathway for development of triple-negative breast cancer is similar to that for \textit{BRCA}-associated breast cancer.(30) In 200 randomly selected patients with triple-negative breast cancer from a tertiary care center, (31) there was a greater than 3-fold increase in the expected rate of \textit{BRCA} mutations. \textit{BRCA1} mutations were found in 39.1% of patients and \textit{BRCA2} mutations in 8.7%. Young et al(32) 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 \textit{BRCA} testing. A total of 6 \textit{BRCA} mutations, 5 \textit{BRCA1}, and 1 \textit{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 \textit{BRCA} mutations: 12 in \textit{BRCA1} and 3 in \textit{BRCA2}.(33)

\textbf{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 \textit{BRCA1} and \textit{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.(23,34) 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 \textit{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.

\textbf{\textit{BRCA} Mutation 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 \textit{BRCA} mutation by 3.5- to 10-fold over the general population.(35) Couch et al(36) reported on screening for \textit{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 \textit{BRCA} mutations in 151 probands (3%), and in the second cohort, there were another 5 \textit{BRCA2} mutations in 29 probands (17%). The combined \textit{BRCA2} mutation rate for these 2 cohorts was 6% (10/180). Ferrone et al(37) tested 187 Ashkenazi Jewish patients with pancreatic cancer for \textit{BRCA} mutations and found that 5.5% (8/187) had a \textit{BRCA} mutation.

\textbf{\textit{BRCA} Mutation Associated With Ovarian Cancer}

Women with a personal history of ovarian cancer also have an increased rate of \textit{BRCA} mutations. In a systematic review of 23 studies, Trainer et al(38) estimated the rate of \textit{BRCA} mutations for women with ovarian cancer to be in the range of 3% to 15%. In this review, there were 3 studies that were performed in the United States and tested for both \textit{BRCA1} and
**BRCA2** The incidence of **BRCA** mutations in these studies was 11.3%, 15.3%, and 9.5%. In a population-based study of 1342 unselected patients with invasive ovarian cancer performed in Canada,(39) there were 176 women with **BRCA** mutations, for a rate of 13.3%. The prevalence of mutations was higher for women in their 40s (24.0%) and in women with serous ovarian cancer (18.0%). Ethnicity was also an additional risk factor for **BRCA**, with higher rates seen in women of Italian (43.5%), Jewish (30.0%), and Indo-Pakistani origin (29.4%).

**BRCA2 Mutation Associated With Fallopian Tube Cancer**

A 2009 publication described the high rate of occult fallopian tube cancers in at-risk women having prophylactic bilateral salpingo-oophorectomy.(40) In this prospective series of 45 women, 4 (9%) were found to have fallopian tube malignancies. The authors noted that this supports 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, current NCCN guidelines for assessing high risk in breast and ovarian cancer(1) 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. Thus, these 2 conditions are added to the Policy Statements and Policy Guidelines.

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, and 5 ovarian and fallopian tube) diagnosed at prophylactic salpingo-oophorectomy. (41) Among 15 women with invasive carcinoma (median age, 50 years), 7 (47%) experienced recurrence at a median of 33 months, and overall survival (OS) was 73%. Among 17 women with noninvasive neoplasia (median age, 53 years), 4 (24%) received chemotherapy, none of whom experienced recurrence. One patient (6%) 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 these patients was published in 2007 by Robson and Offit(42) 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 utilized risk-reducing surgery (11% had bilateral mastectomy and 29% bilateral oophorectomy) or chemoprevention.(43)

In 2013, Lesnock et al compared OS in 393 women with **BRCA1**-mutated and **BRCA1**-nonmutated epithelial ovarian cancer who were treated with intraperitoneal or intravenous-only chemotherapy.(44) 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 was not statistically different between treatment groups (58 months vs 50 months in the IP therapy and IV therapy groups, respectively; 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).
**BRCA1** and **BRCA2** Testing

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**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).\(^{(45)}\) 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 3-fold increased risk of prostate cancer (OR=3.41; 95% CI, 1.64 to 7.06).\(^{(46)}\) 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).\(^{(47)}\) 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) then 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.\(^{(48)}\) At the baseline screen, biopsies were performed in 7.0% of patients with a prostate specific antigen (PSA) 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 further 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,\(^{(49-55)}\) and nongenetic modifying factors also have been examined. Antoniou et al\(^{(49)}\) examined the risk of breast cancer associated with 9 genetic polymorphisms, most of which had previously shown an increase cancer risk among **BRCA** carriers. 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\(^{(53)}\) 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). 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.\(^{(56)}\) Seven case-control and cohort studies of 28 of 28, 29 of 29, and ≤26 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 28/28 repeats in BRCA1 and BRCA2 mutation carriers.

Zhou et al(57) reported an increased risk of cancer in BRCA4 carriers who also had the RAD51 135G>C polymorphism (OR=1.34; 95% CI, 1.01 to 1.78; p=0.04). Metcalfe et al(58) reported that family history provided additional predictive information in BRCA carriers. 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.

Testing for Large BRCA Rearrangements
Over the past few years, 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 1 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(59) 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%. (60) In the 136 non-Ashkenazi Jewish probands, 36 (26%) had BRCA point mutations and 8 (6%) had genomic rearrangements, 7 in BRCA1 and 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.

Based on these published studies, a substantial minority of clinically significant BRCA mutations will be large genomic rearrangements that are not detected by sequence analysis. These mutations will be missed if BART testing (BRACAnalysis® Rearrangement Test) is not performed. Commercial laboratories began to offer expanded testing in August 2006(61); BRCA testing done before this date did not include analysis for genomic rearrangement. After August 2006, based on information available from the laboratory, this additional testing is conducted on a subset of patients, and additional information on breast cancer risk may be requested in some cases. Clinical guidelines, such as those from NCCN, consider BART testing as part of comprehensive BRCA testing and do not require additional criteria other than a negative sequence result. Therefore, testing for genomic rearrangements of BRCA1 and BRCA2 with BART may be considered medically necessary as part of comprehensive BRCA analysis, when testing for standard mutations on sequence analysis is negative.
**CHEK2 Mutations**

A number of publications also have described the association of CHEK2 (cell cycle checkpoint kinase 2) mutations with hereditary breast cancer. The prevalence of this finding varies greatly by geographic region, being most common in northern and Eastern Europe. It has been detected in 4% of early breast cancer patients in the Netherlands and in 2.3% of such patients in Germany, but has been noted to be rare in patients in Spain or Australia. In the U.S., this mutation is much less common than BRCA mutations and BRCA rearrangements. For example, in the study by Walsh et al(59) cited earlier, 14 (4.7%) of the 300 patients with a positive family history of breast cancer (4 affected relatives) who were negative by standard BRCA testing, were positive for CHEK2 mutations. The low frequency makes evaluation of risk and treatment implications less precise. In general, the risk of breast cancer associated with this mutation is less that that associated with either BRCA1 or BRCA2.

A 2008 meta-analysis by Weischer et al concluded that for familial breast cancer, the cumulative risk at age 70 years for the CHEK2*1100delC mutation was 37% (95% CI, 26% to 56%).(62) This risk is lower than cumulative risk at age 70 of 57% for BRCA1 and 49% for BRCA2. In an accompanying editorial, Offit and Garber raised a number of questions about potential use of this assay.(63) In particular, they questioned the breast cancer risk estimates presented in the Weischer study and the variable methods of ascertainment used in the studies in the meta-analysis. They also noted the varying frequencies of the mutation across populations, eg, 0.5% to 1.0% in Northern and Eastern Europe and 0.2% to 0.3% in the U.S. In other populations, other mutations, such as CHEK2*S428F, may be more common, eg, in Ashkenazi Jews. Finally, they raised concerns about the implications of the low penetrance of this mutation. They concluded that on the basis of data available at this time, there is no compelling evidence to justify routine clinical testing for CHEK2 to guide the management of families affected with breast cancer. Thus, based on a number of concerns, testing for CHEK2 mutations is considered investigational because the impact on net health outcome is uncertain.

Since the meta-analysis by Weischer, there have been additional studies evaluating the risk of breast cancer associated with the CHEK2 mutation. In 2011, Myszka et al(64) examined 284 breast cancer patients, 113 ovarian cancer patients, and 287 healthy women from a cohort of Polish individuals. The CHEK2 mutation rate was not higher among patients with breast or ovarian cancer compared to healthy women.

In 2011, Zhang et al(65) performed a systematic review of candidate-gene association studies, identifying more than 1000 published articles. Meta-analysis was performed for a total of 279 genetic variants in 128 genes that were identified by at least 3 different researchers. Significant associations with the risk of breast cancer were found for 29 variants in 20 genes. The association was strong for 10 variants in 6 genes, 4 of which were located in the CHEK2 gene; for 2 variants of the ATM gene and an additional 4 genes that had a single variant with a strong association (CASP8, CTLA4, NBN, TP53).

In 2011, Peng et al(66) performed an overview of systematic reviews and pooled analyses on the association of genetic variants with breast cancer. A total of 87 analyses were identified, which examined 145 candidate gene variants and found that 46 variants were significantly associated with breast cancer. The ORs for these associations ranged from 0.66 to 3.13. Using the method of false-positive report probability, there were 10 associations in 7 genes that were noteworthy: CASP8, CHEK2, CTLA4, FGFR2, IL1B, LSP1, and MAP3K1.
Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers
In response to requests, input was received through 3 Physician Specialty Societies (5 reviews) and 3 Academic Medical Centers (5 reviews) while this policy was under review for January 2010. Although 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. Those providing input were in general agreement with the Policy Statements considering testing for genomic rearrangements of BRCA1 and BRCA2 as medically necessary, with the statement considering CHEK2 testing as investigational, and with adding fallopian tube and primary peritoneal cancer as additional BRCA-associated malignancies to assess when obtaining the family history.

Summary
The presence of a BRCA1 or BRCA2 mutation confers a high lifetime risk for breast and ovarian cancer among affected women. These mutations may be gene sequence variations or large rearrangements/deletions. Knowledge of mutation status in individuals at risk of a BRCA mutation may impact healthcare decisions to reduce risk. Risk-reducing options include intensive surveillance, chemoprophylaxis, prophylactic mastectomy, or prophylactic oophorectomy. Criteria for testing high-risk women have been developed by National Comprehensive Cancer Network (NCCN), the U.S. Preventive Services Task Force (USPSTF) and other review bodies. Definitions of high-risk vary somewhat, and there is not widespread agreement on the optimal criteria that should be used for defining high-risk. When testing high-risk women, health outcomes are improved; therefore, testing high-risk women for BRCA1 and BRCA2 mutations may be considered medically necessary.

Mutations other than BRCA1 and BRCA2 have been reported to be associated with an increased risk of breast cancer. Although a number of these, for example the CHEK2 mutation, have been confirmed to be associated with increased risk, clinical utility of testing for these non-BRCA mutations has not been demonstrated. Therefore, genetic testing for mutations other than BRCA1 and BRCA2 to determine risk of breast and/or ovarian cancer is considered investigational.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network
The NCCN guideline, Genetic/Familial High-Risk Assessment: Breast and Ovarian cancer, was updated in 2014.(1) The guideline contains criteria for identifying individuals who should be referred for further risk assessment, and separate criteria for genetic testing. Patients who satisfy any of the testing criteria listed in Table 1 should undergo “further personalized risk assessment, genetic counseling, and often genetic testing and management.”(1) For these criteria, both invasive and in situ breast cancers are 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.”(1)
Table 1. NCCN Hereditary Breast and/ or Ovarian Cancer Syndrome Testing Criteria(1)

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

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 Gleason score ≥7.
c Testing for Ashkenazi Jewish or other founder mutation(s) should be performed first.
d Significant limitations of interpreting test results for an unaffected individual should be discussed.

According to NCCN guidelines, patients who meet criteria for genetic testing should be tested for mutations in BRCA1 and BRCA2. In patients with a known familial BRCA mutation, targeted testing for the specific mutation is recommended. In patients with no known familial BRCA mutation, comprehensive testing, including full sequencing and testing for large genomic rearrangements, is recommended; if the affected individual is of Ashkenazi Jewish descent, testing for the 3 known founder mutations (185delAG and 5182insC in BRCA1; 6174delT in
BRCA2\textsuperscript{1} should be done first. The guidelines do not include recommendations for genotyping low or moderate penetrance susceptibility genes, such as CHEK2.

\textbf{U.S. Preventive Services Task Force}
Current USPSTF recommendations for genetic testing of BRCA1/BRCA2 mutations in women are listed next.\textsuperscript{2} Screening tools recommended for assessment of genetic risk are: the Ontario Family History Assessment Tool (FHAT); Manchester scoring system; Referral Screening Tool (RST); Pedigree Assessment Tool (PAT); and FHS-7.

- The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with one 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. (Grade B recommendation; Recommended)
- 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. (Grade D recommendation; Not recommended)

\textbf{American Society of Clinical Oncology}
The American Society of Clinical Oncology (ASCO) recommended in 2003\textsuperscript{67} 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. 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.”\textsuperscript{68} The CHEK2*1100delC variant was cited as a mutation with unproven clinical utility.

\textbf{American College of Medical Genetics}
In 1999, the American College of Medical Genetics (ACMG)\textsuperscript{69} published guidelines for BRCA testing under the auspices of a grant from the New York State Department of Health to the ACMG Foundation. This guideline was retired in 2013.
## 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

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81211</td>
<td>BRCA 1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication / deletion variants in BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510kb, exon 8-9 del 7.1kb)</td>
</tr>
<tr>
<td>81212</td>
<td>BRCA 1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants</td>
</tr>
<tr>
<td>81213</td>
<td>BRCA 1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; uncommon duplication / deletion variants</td>
</tr>
<tr>
<td>81214</td>
<td>BRCA1 (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 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)</td>
</tr>
<tr>
<td>81215</td>
<td>BRCA1 (breast cancer1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
</tr>
<tr>
<td>81216</td>
<td>BRCA2 (breast cancer) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis</td>
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<tr>
<td>81217</td>
<td>BRCA2 (breast cancer) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
</tr>
<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (eg. Analysis of 11-25 exons by DNA sequence analysis, mutation scanning or publication / deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia): PALB2 (partner and localizer of BRCA2) (eg. Breast and pancreatic cancer), full gene sequence</td>
</tr>
</tbody>
</table>

### ICD-9 Diagnoses

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>174.0</td>
<td>Malignant neoplasm of female breast, nipple and areola</td>
</tr>
<tr>
<td>174.1</td>
<td>Malignant neoplasm of female breast, central portion</td>
</tr>
<tr>
<td>174.2</td>
<td>Malignant neoplasm of female breast, upper-inner quadrant</td>
</tr>
<tr>
<td>174.3</td>
<td>Malignant neoplasm of female breast, lower-inner quadrant</td>
</tr>
<tr>
<td>174.4</td>
<td>Malignant neoplasm of female breast, upper-outer quadrant</td>
</tr>
<tr>
<td>174.5</td>
<td>Malignant neoplasm of female breast, lower-outer quadrant</td>
</tr>
<tr>
<td>174.6</td>
<td>Malignant neoplasm of female breast, axillary tail</td>
</tr>
<tr>
<td>174.8</td>
<td>Malignant neoplasm of female breast, other specified sites of female breast</td>
</tr>
<tr>
<td>174.9</td>
<td>Malignant neoplasm of female breast, Breast (female), unspecified</td>
</tr>
<tr>
<td>175.0</td>
<td>Malignant neoplasm of male breast, nipple and areola</td>
</tr>
<tr>
<td>175.9</td>
<td>Malignant neoplasm of male breast, other and unspecified sites of male breast</td>
</tr>
<tr>
<td>183.0</td>
<td>Malignant neoplasm of ovary and other uterine adnexa; ovary</td>
</tr>
<tr>
<td>198.6</td>
<td>Secondary malignant neoplasm of other specified sites; ovary</td>
</tr>
<tr>
<td>198.81</td>
<td>Secondary malignant neoplasm of other specified sites; breast</td>
</tr>
<tr>
<td>233.0</td>
<td>Carcinoma in situ of breast and genitourinary system; breast</td>
</tr>
<tr>
<td>233.30</td>
<td>Other and unspecified female genital organs; Unspecified female genital organ</td>
</tr>
</tbody>
</table>
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**

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>01-01-2012</td>
<td>In the Policy section: Formatting changes to the policy language.</td>
</tr>
<tr>
<td></td>
<td>In the Coding section: Added new codes: 81211, 81212, 81213, 81214, 81215, 81216, 81217</td>
</tr>
<tr>
<td>10-04-2012</td>
<td>Updated Description section.</td>
</tr>
<tr>
<td></td>
<td>In the Policy section:</td>
</tr>
</tbody>
</table>
|            | - In Item II, removed "Further genetic testing by rearrangement analysis (BART—BRAC Analysis Rearrangement Test) is experimental / investigational (rearrangement analysis includes sequencing the coding regions and intron/extron splice sites as well as tests to detect large dilations and rearrangements that can be missed with sequence analysis only)" and inserted "Testing for genomic rearrangements of the *BRCA1* and *BRCA2* genes (BART—BRAC Analysis Rearrangement Test) may be considered medically necessary in patients who meet criteria for *BRCA* testing, whose testing for point mutations is negative and either (1) there are 3 or more family members (one lineage) affected with breast or ovarian or fallopian tube or primary peritoneal cancer or (2) who have a risk of a *BRCA* mutation of at least 10%."
|            | - In the Policy Guidelines, added "#7 Comprehensive mutation analysis currently includes sequencing the coding regions and intron/exon splice sites, as well as tests to detect common large deletions and rearrangements (BART—BRAC Analysis Rearrangement Test) that can be missed with sequence analysis alone. However, current routine laboratory testing for genomic rearrangement is more limited than the criteria noted in the policy statement; automatic testing is specified for those with a risk of *BRCA* mutation of at least 30%. In addition, prior to August 2006, testing for large deletions and rearrangements was not performed, thus some patients with familial breast cancer who had negative *BRCA* testing prior to this time may consider repeat testing for the rearrangements (see Policy statement for criteria). These rates are calculated using the Myriad II risk model (Available online at: www.myriadtests.com)."
|            |                                                                                                               |
|            | Updated Reference section.                                                                                    |
|            |                                                                                                               |

Contains Public Information*
<table>
<thead>
<tr>
<th>Date</th>
<th>Updates</th>
</tr>
</thead>
</table>
| 10-26-2012 | In the Policy section:  
  - In the Policy Guidelines section, #7, corrected website,  
    "www.myriadtests.com" to "www.myriadpro.com/brca-risk-calculator". |
| 01-15-2013 | In the Coding section:  
  - Added CPT code: 81406  
  - Removed CPT codes: 83890, 83891, 83892, 83893, 83894, 83896, 83912, 83913 (Effective 12-31-2012) |
| 02-26-2013 | Updated Description section.  
  - In the Policy section:  
    - In Item I, B, added "10. Diagnosed at any age with breast cancer or  
      pancreatic cancer, who are not from families with high risk of BRCA1 or  
      BRCA2 mutation, but are affected with one of the following:  
      1. Early onset breast cancer  
      2. Two breast primary cancers with the first cancer diagnosis occurring prior  
         to age 50 years;  
      3. Triple negative breast cancer (neither express estrogen receptor and  
         progesterone receptor, nor overexposure HER2) diagnosed at younger  
         than age 60.  
      4. Two or more close blood relatives with pancreatic cancer at any age.  
   - In Item II, removed "and either (1) there are 3 or more family members (one  
     lineage) affected with breast or ovarian or fallopian tube or primary peritoneal  
     cancer or (2) who have a risk of a BRCA mutation of at least 10%." to read  
     "Testing for genomic rearrangements of the BRCA1 and BRCA2 genes (BART-  
     BRAC Analysis Rearrangement Test) may be considered medically necessary  
     in patients who meet criteria for BRCA testing, whose testing for point  
     mutations is negative." |
| 07-22-2013 | Updated Rationale section.  
  - In Coding section:  
    - Removed HCPCS codes: S3818, S3819, S3820, S3822, S3823  
  - Updated Reference section. |
| 12-11-2013 | In Coding section:  
  - Maintenance completed on coding section, correcting "V16.4" to read  
    "V16.41".                      |
| 08-28-2014 | Description section updated.  
  - In Policy section:  
    - The following medical policy language was removed from the policy and  
      replaced with policy language that mirrors the NCCN criteria (See policy section).  
      This update liberalized the policy and did not restrict any portion of the policy.  
      "I. Genetic testing may be considered medically necessary under any one of the following  
      circumstances:  
      A. Member of family with a known BRCA1/BRCA2 mutation  
      B. Personal history of breast cancer plus one or more of the following:  
         1. Diagnosed at 45 years of age or younger  
         2. Diagnosed at 50 years of age or younger with:  
            a. one or more close blood relatives with breast cancer at 50 years of age or  
               younger; and/or"
b. one or more close blood relatives with epithelial ovarian / fallopian tube / primary peritoneal cancer
3. Two breast primaries when first breast cancer diagnosis occurred prior to age 50
4. Diagnosed at any age with two or more close blood relatives with breast and/or epithelial ovarian / fallopian tube / primary peritoneal cancer at any age
5. Close male blood relative with breast cancer
6. For an individual of ethnicity associated with deleterious mutations (e.g., founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian or other) no additional family history may be required
7. Diagnosed age < 60 years with a triple negative breast cancer [estrogen receptors (ER-), progesterone receptors (PR-), and HER2 (HER2-)]
8. Diagnosed age < 50 years with a limited family history (see policy guidelines)
9. Personal history of breast and/or ovarian cancer at any age with ≥ 2 close blood relatives with pancreatic cancer at any age
10. Diagnosed at any age with breast cancer or pancreatic cancer, who are not from families with a high risk of BRCA1 or BRCA2 mutation, but are affected with one of the following:
   ▪ Early onset breast cancer
   ▪ Two breast primary cancers with the first cancer diagnosis occurring prior to age 50 years;
   ▪ Triple negative breast cancer (neither express estrogen receptor and progesterone receptor, nor overexposure HER2) diagnosed at younger than age 60.
   ▪ Two or more close blood relatives with pancreatic cancer at any age.

C. Personal history of epithelial ovarian / fallopian tube / primary peritoneal cancer
D. Personal history of pancreatic cancer at any age with ≥ 2 close blood relatives with breast and/or ovarian cancer at any age
E. Personal history of male breast cancer
F. Family history only -
   1. Close family member meeting any of the above criteria
   2. Third-degree blood relative with breast cancer and/or ovarian / fallopian tube/ primary peritoneal cancer with ≥ 2 close blood relatives with breast cancer (at least one with breast cancer ≤ 50 years) and/or ovarian cancer.

II. Testing for genomic rearrangements of the BRCA1 and BRCA2 genes (BART—BRAC Analysis Rearrangement Test) may be considered medically necessary in patients who meet criteria for BRCA testing, whose testing for point mutations is negative.

III. Genetic testing when policy requirements are not met is experimental/investigational.

Policy Guidelines
1. Close family member is defined as a first, second, or third degree relative, which includes: Parent, Full Sibling, Half Sibling, Child, Grandparent, Great-Grandparent, Grandchild, Aunt, Great Aunt, Uncle, Great Uncle, Nephew, Niece, and First Cousin.
2. For purposes of this policy, breast cancer includes both invasive and ductal carcinoma in situ (DCIS).
3. For individuals with family history only, an affected family member should be tested first whenever possible to identify specific site mutations.
4. The maternal and paternal sides should be considered independently.
5. Other malignancies reported in some HBOC families include prostate and melanoma.
6. Individuals with limited family history, such as fewer than 2 first- or second-degree female relatives surviving beyond 45 years in either lineage, may have an underestimated probability of a familial mutation.
7. Comprehensive mutation analysis currently includes sequencing the coding regions and intron/exon splice sites, as well as tests to detect common large deletions and rearrangements (BART—BRAC Analysis Rearrangement Test) that can be missed with sequence analysis alone. However, current routine laboratory testing for genomic rearrangement is more limited than the criteria noted in the policy statement; automatic testing is specified for those with a risk of BRCA mutation of at least 30%. In addition, prior to August 2006, testing for large deletions and rearrangements was not performed, thus some patients with familial breast cancer who had negative BRCA testing prior to this time may consider repeat testing for the rearrangements (see Policy statement for criteria). These rates are calculated using the Myriad II risk model (Available online at: www.myriadpro.com/brca-risk-calculator).

Testing eligible individuals who belong to ethnic populations in which there are well characterized founder mutations should begin with tests specifically for these mutations (multi site testing)."

Rationale section updated

In Coding section:
- Updated nomenclature for CPT code:  81215
- Updated nomenclature for ICD-9 codes:  174.8, 174.9, 175.9, 183.0, 198.6, 198.81, 233.0, V10.43, V16.41, V16.8
- Added ICD-9 codes:  233.30, 233.39
- Removed ICD-9 code:  233.3
- Removed ICD-10 codes:  C50.129, C50.229, C50.529, C50.819


References updated

REFERENCES
3. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). BRCA1 and BRCA2 testing to determine the risk of breast and ovarian cancer. TEC Assessments 1997; volume 12, tab 4.


Other References
1. Blue Cross and Blue Shield of Kansas Medical Advisory Committee meeting, November 3, 2005 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report. MAC-03-05).
2. Blue Cross and Blue Shield of Kansas Oncology Liaison Committee CB, February 25, 2009.
5. Blue Cross and Blue Shield of Kansas Internal Medicine Liaison Committee: August 2008, August 2009.
9. Blue Cross and Blue Shield of Kansas Radiology Liaison Committee: February 2012.
10. Blue Cross and Blue Shield of Kansas Oncology Liaison Committee: February 2014.