I. Description

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 mutations in BRCA genes. Families suspected of having HBOC syndrome are characterized by an increased susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer at any age, as well as cancer of the fallopian tube and primary peritoneal cancer. Other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, laryngeal cancer, occur more frequently in HBOC families. Hereditary site-specific breast cancer families are characterized by early onset breast cancer with or without male cases, but without ovarian cancer. For this policy, both will be referred to collectively as hereditary breast and/or ovarian cancer.

Germline mutations in the BRCA1 and BRCA2 genes are responsible for the cancer susceptibility in the majority of HBOC families, especially if ovarian cancer or male breast cancer are features. However, in site-specific breast cancer, BRCA mutations are responsible for only a proportion of affected families, and research to date has not yet identified other moderate or high-penetrance gene mutations that account for disease in these families. BRCA gene mutations are inherited in an autosomal dominant fashion through either the maternal or paternal lineage. It is possible to test for abnormalities in BRCA1 and BRCA2 genes to identify the specific mutation in cancer cases and to identify family members with increased cancer risk. Family members without existing cancer who are found to have BRCA mutations can consider preventive interventions for reducing risk and mortality.

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.
II. Criteria/Guidelines

A. Genetic testing for BRCA1 and BRCA2 mutations is covered (subject to Limitations/Exclusions and Administrative Guidelines) for individuals with a close blood relative* with a known deleterious BRCA1/BRA2 mutation.

B. Genetic testing for BRCA1 and BRCA2 mutations is covered (subject to Limitations/Exclusions and Administrative Guidelines) for individuals with a personal history of breast cancer (includes invasive and ductal carcinoma in situ) and one or more of the following:

1. Early onset breast cancer (diagnosed at age 45 or younger or premenopausal)
2. Two breast primaries including bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously when the first cancer diagnosis occurring at age 50 or younger
3. Diagnosed at age 50 or younger with one or more close blood relative with breast cancer at any age or with limited family history
4. Triple negative breast cancer (neither express estrogen receptor and progesterone receptor, nor overexpress HER2) diagnosed at age 60 or younger
5. Diagnosed at any age with:
   a. One or more close blood relative with breast cancer diagnosed at age 50 or younger
   b. Two or more close blood relatives with breast cancer at any age
   c. One or more close blood relative with epithelial ovarian cancer
   d. Two or more close blood relatives with pancreatic or aggressive prostate cancer (Gleason score >7) at any age
6. Close male blood relative with breast cancer
7. Is from an ethnic background, e.g., Ashkenazi Jewish descent, associated with deleterious founder mutations

C. Genetic testing for BRCA1 and BRCA2 mutations is covered (subject to Limitations/Exclusions and Administrative Guidelines) in any of the following:

1. Women with epithelial ovarian / fallopian tube or primary peritoneal cancer
2. Men with breast cancer
3. Individuals with a history of pancreatic or aggressive prostate cancer (Gleason score > 7) at any age with two or more close blood relatives with breast and/or ovarian and/or pancreatic or aggressive prostate cancer (Gleason score > 7) at any age

* Close blood relatives include first-, second- and third- degree relatives on the same side of the family. The maternal and paternal sides should be considered independently.

D. Genetic testing for BRCA1 and BRCA2 mutations is covered (subject to Limitations/Exclusions and Administrative Guidelines) for unaffected (no personal history of cancer) adults under any of the following circumstances:

1. Individuals from families with a high risk of BRCA1 or BRCA2 mutation based on a family history (see Policy Guidelines), when it is not possible to test an affected family member for a mutation.
2. Individuals in populations at risk for specific founder mutations due to ethnic background, e.g., Ashkenazi Jewish descent; and with one or more relatives with breast, epithelial ovarian, fallopian tube, or primary peritoneal cancer at any age.

E. Testing for genomic rearrangements of the BRCA1 and BRCA2 genes (BART testing) is covered (subject to Limitations/Exclusions and Administrative Guidelines) in patients who meet criteria for BRCA testing, whose testing for point mutations is negative.

Policy Guidelines

A. Certain specific family history patterns are associated with an increased risk for deleterious mutations in the BRCA1 or BRCA2 gene. Both maternal and paternal family histories are important but each lineage must be considered separately. For unaffected non-Ashkenazi Jewish women, high risk includes:

1. Two first-degree relatives** with breast cancer, one of whom received the diagnosis at age 50 years or younger;
2. A combination of three or more first- or second-degree relatives with breast cancer regardless of age at diagnosis;
3. A combination of both breast and ovarian cancer or fallopian tube or primary peritoneal cancer among first- and second-degree relatives;
4. A first-degree relative with bilateral breast cancer;
5. A combination of two or more first- or second-degree relatives with ovarian cancer or fallopian tube or primary peritoneal cancer regardless of age at diagnosis;
6. A first- or second-degree relative with both breast and ovarian cancer or fallopian tube or primary peritoneal cancer at any age; or

B. History of breast cancer in a male relative

C. For women of Ashkenazi Jewish heritage, an increased-risk family history includes any first-degree relative (or 2 second-degree relatives on the same side of the family) with breast or ovarian cancer.

**First-degree relatives refer to parents, full siblings or offspring. Second-degree relatives refer to grandparents, grandchildren, aunts, uncles, nephews, nieces or half-siblings. Third-degree relatives refer to great-grandparents, great-aunts, great-uncles or first cousins.

Genetic Risk Assessments:

A. A genetic risk assessment is covered (subject to Limitations and Administrative Guidelines) in cancer-affected individuals with:

1. Early onset breast cancer (<45 years old or premenopausal).
2. A first or second degree relative with a BRCA-related cancer (breast, ovarian, fallopian tube or primary peritoneal cancer).
3. A first or second degree relative with a BRCA mutation.

B. A genetic risk assessment is covered (subject to Limitations and Administrative Guidelines) in unaffected (no personal history of cancer) individuals with:

1. A first degree relative with early onset breast cancer (<45 years old or premenopausal).
2. Two affected first or second degree relatives with a BRCA-related cancer (breast, ovarian, fallopian tube or primary peritoneal cancer).
3. A first or second degree relative with a BRCA mutation.

III. Limitations/Exclusions

A. An affected family member should be tested first whenever possible. Should a BRCA mutation be found in an affected family member(s), the DNA from the unaffected family member can be tested specifically using a tailored study for the same mutation of the affected family member without having to sequence the entire gene.

B. Genetic testing for unaffected (no personal history of cancer) individuals (of both the general population and of potentially high-risk ethnic populations) without a family history suggesting increased risk of BRCA mutation does not meet payment determination criteria.

C. BRCA1 and BRCA2 genetic testing in minors does not meet payment determination criteria.

D. Genetic testing for BRCA1 and BRCA2 mutations for assessment of risk of other cancers including but not limited to pancreatic, prostate and colon cancer does not meet payment determination criteria.

E. Benefits are provided only for HMSA members; benefits are not provided for family members without current HMSA coverage.

F. Unless they meet the criteria above, genetic testing for either those affected with breast, ovarian, fallopian tube, or primary peritoneal cancer or for unaffected individuals does not meet payment determination criteria.

G. Testing for CHEK2 genetic abnormalities (mutations, deletions, etc.) does not meet payment determination criteria.

H. Laboratories that conduct genetic testing must be CLIA certified.

I. Repeat BRCA1 or BRCA2 mutation testing does not meet payment determination criteria.

J. Testing for one or more single nucleotide polymorphisms (SNPs) to predict an individual's risk of breast cancer does not meet payment determination criteria.

IV. Administrative Guidelines

A. Precertification is required for genetic risk assessments, BRCA1/ BRCA 2 gene mutation testing and BART genetic testing:

1. For unaffected individuals, a genetic risk assessment is considered by HMSA as part of the precertification process to approve genetic testing in unaffected individuals as stated in Criteria/Guidelines - Genetic Risk Assessment

2. For affected individuals, a genetic risk assessment is not required but precertification is required for BRCA1 and BRCA2 gene mutation testing

B. Documentation must specify how the results of genetic testing will impact the clinical management of the patient in terms of improving health outcomes.
C. Services must be conducted in a face-to-face consultation and/or telemedicine consult visit and a subsequent consultation letter or report must be submitted to the treating physician.

D. Services must be conducted by a properly certified/licensed and credentialed genetic specialist (i.e., board-certified medical geneticist (MD), board-certified clinical geneticist (PhD), board-certified genetic counselor (MS and/or CGC), or licensed advanced practice registered nurse in genetics (APRN)).

E. One risk assessment visit after genetic testing is covered for patients who qualified for predictive genetic testing as outlined above.

F. To precertify please complete HMSA’s Precertification Request and fax or mail the form as indicated. The information received should include the member’s family history and a brief summary as to why the genetic test is needed.

G. If precertification is not obtained, the member will not be held responsible for payment of denied services unless an Agreement of Financial Responsibility is completed and signed.

H. **Applicable codes**

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<tr>
<th>CPT Codes</th>
<th>Description</th>
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<td>BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (i.e., 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>
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<td>81214</td>
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<td>BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis</td>
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<tr>
<td>81217</td>
<td>BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
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<tr>
<td>96040</td>
<td>Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family</td>
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</table>

HCPCS  Description
V. Rationale

**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. Studies of founder mutations in ethnic populations (e.g., Ashkenazi Jewish, Polish, and Icelandic populations) unselected for family history indicated lower penetrance estimates, in the range of 40–60% for BRCA1 and 25–40% for BRCA2. However, a genotyping study of Ashkenazi Jewish women with incident, invasive breast cancer, selected regardless of family history of cancer, and their family members resulted in an 82% lifetime risk of breast cancer for carriers of any of 3 BRCA founder mutations. 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 one study the risk was 29.5% at 10 years for women with initially stage I or II disease. In a 2013 prospective study (EMBRACE), the cumulative risk of contralateral breast cancer by age 70 years was 83% in BRCA1 mutation carriers and 62% for BRCA2 mutation carriers. 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. Risk-reducing options include intensive surveillance, 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. Prophylactic oophorectomy significantly reduces the risk of ovarian cancer to less than 10%, and reduces the risk of breast cancer by approximately 50%. In women who have already had breast cancer, prophylactic oophorectomy reduces the risk of cancer relapse. Studies indicate that genotyping results significantly influence treatment choices.

**Prevalence of BRCA Mutations**

The prevalence of BRCA mutations is approximately 0.1–0.2% in the general population. Prevalence may be much higher for particular ethnic groups with characterized founder mutations (e.g., 2.5% (1 in 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 and colleagues reported on racial and ethnic differences in the prevalence of BRCA1 and BRCA2 in American women. 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 and colleagues reported that breast cancer-specific rates of death among Israeli women were similar for carriers of a BRCA founder mutation and noncarriers.

**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 estimated that hereditary breast cancer accounts for 36%–85% of patients diagnosed under age 30. In several studies, BRCA mutations are independently predicted by early age at onset, being present in 6–10% of breast cancer cases diagnosed at ages younger than various premenopausal age cutoffs (ages 35–50 years). In cancer-prone families, the mean age of breast cancer diagnosis among women carrying BRCA1 or BRCA2 mutations is in the 40s. In the Ashkenazi Jewish population, Frank et al. reported that 13% of 248 cases with no known family history and diagnosed before 50 years of age had BRCA mutations. In a similar study, 31% of Ashkenazi Jewish women, unselected for family history, diagnosed with breast cancer at younger than 42 years of age had BRCA mutations. Additional studies indicate that early age of breast cancer diagnosis is a significant predictor of BRCA mutations in the absence of family history in this population.

As in the general population, family history of breast or ovarian cancer, particularly of early age onset, is a significant risk factor for a BRCA mutation in ethnic populations characterized by founder mutations. For example, in unaffected individuals of Ashkenazi Jewish descent, 12–31% will have a BRCA mutation depending on the extent and nature of the family history. Several other studies document the significant influence of family history.

In patients with breast cancer that is “triple-negative”, i.e., negative for expression of estrogen and progesterone receptors and for overexpression of HER2 receptors, there is an increased incidence of BRCA mutations. Pathophysiologic research has suggested that the physiologic pathway for development of triple-negative breast cancer is similar to that for BRCA-associated breast cancer. In 200 randomly selected patients with triple-negative breast cancer from a tertiary care center there was a greater than 3-fold increase in the expected rate of BRCA mutations. BRCA1 mutations were found in 39.1% of patients and BRCA2 mutations in 8.7%. Young et al. studied 54 women with high-grade, triple-negative breast cancer with no family history of breast or ovarian cancer, representing a group that previously was not recommended for BRCA testing. A total of 6 BRCA mutations, 5 BRCA1 and 1 BRCA2, were found for a mutation rate of 11%. Finally, in a study of 77 patients with triple-negative breast cancer, 15 patients (19.5%) had BRCA mutations: 12 in BRCA1 and 3 in BRCA2.

**Testing Results**

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

**BRCA Mutation Associated with Pancreatic Cancer**

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

**BRCA Mutation Associated with Ovarian Cancer**

Women with a personal history of ovarian cancer also have an increased rate of BRCA mutations. In a systematic review of 23 studies, Trainer et al. estimated the rate of BRCA mutations for women with ovarian cancer to be in the range of 3-15%. In this review, there were 3 studies that were performed in the United States and tested for both 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 1,342 unselected patients with invasive ovarian cancer performed in Canada, 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%).

**BRCA 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. 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 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. 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 patient (6%) who did not receive chemotherapy experienced recurrence at 43 months. Overall survival 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 recently published by Robson and Offit. Phillips et al. reported that while 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, the minority utilized risk-reducing surgery (11% had bilateral mastectomy and 29% bilateral oophorectomy) or chemoprevention.

In 2013, Lesnock and colleagues compared overall survival in 393 women with BRCA1-mutated and BRCA1-non-mutated epithelial ovarian cancer who were treated with intraperitoneal or intravenous only chemotherapy. 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 non-mutated BRCA1, median overall survival 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 overall survival was significantly longer in the IP therapy group (84 months vs. 47 months, respectively; p<0.001.

**BRCA Mutation Associated with Prostate Cancer**

A number of studies have indicated that BRCA mutations are associated with increased risk of prostate cancer in men. In a 2010 study of 832 Ashkenazi Jewish men diagnosed with localized prostate cancer, and 454 Ashkenazi Jewish men without prostate cancer, the presence of a BRCA2 mutation was associated with a more than 3-fold increased risk of prostate cancer (odds ratio [OR]: 3.18, 95% confidence interval [CI]: 1.52-6.66). In a similar population of 251 Ashkenazi Jewish men with prostate cancer and 1,472 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: 1.64-7.06). When analyzed by type of BRCA mutation, BRCA2 was associated with an almost 5-fold increased risk (OR: 4.82, 95% CI: 1.87-12.25), and BRCA1 mutations were not associated with an increased risk (OR: 2.20, 95% CI: 0.72–6.70). A 2013 retrospective analysis compared prostate cancer outcomes in 79 BRCA mutation carriers (18 BRCA1, 61 BRCA2) and 2,019 noncarriers. 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 overall survival was 8.1 years in carriers and 12.9 years in noncarriers (hazard ratio 1.9, 95% CI: 1.1-3.3; p=0.012). In subgroup analyses, BRCA2 mutations were independently associated with reduced overall survival (hazard ratio 1.9, 95% CI: 1.1-3.1, 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 40-69 years of age who were BRCA mutation carriers and 95 control patients. 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 in order to further assist in clinical decision making. Numerous recent publications have identified a large number of candidate modifier genes, and there have also been non-genetic modifying factors examined. Antoniou et al. examined the risk of breast cancer associated with nine genetic polymorphisms, the majority of which had previously shown an increase cancer risk among BRCA carriers. Seven of the nine polymorphisms were confirmed to increase breast cancer risk. The magnitude of increased risk varied by whether the patient was a BRCA1 versus a BRCA2 carrier, and the polymorphisms appeared to interact multiplicatively to increase risk.

Kleibl et al. reported that the AIB1 genotype in general did not influence breast cancer risk in BRCA carriers but that the specific genotype AIB1 consisting of 28/28 glutamine repeats conferred a decreased risk of breast cancer (hazard ratio [HR]: 0.64, 95% confidence interval [CI]: 0.41-0.99, p=0.045). In 2013, Bianco and colleagues conducted a meta-analysis to examine the effect of AIB1 polyglutamine repeats on breast cancer risk in BRCA mutation carriers. Seven case-control and cohort studies of 28/28, 29/29, 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.

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Zhou et al. reported an increased risk of cancer in BRCA carriers who also had the RAD51 135G>C polymorphism (odds ratio [OR]: 1.34, 95% CI: 1.01-1.78, p=0.04). Metcalfe et al. 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 (hazard ratio 1.61, 95% CI: 1.21-2.14) in BRCA1 mutation carriers, and the risk of breast cancer increased 1.7-fold in BRCA2 mutation carriers (hazard ratio 1.67, 95% CI: 1.04-2.07).

**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 one of these genes. For example, in 2006 Walsh and colleagues reported on probands from 300 US families with 4 or more cases of breast or ovarian cancer but with negative (wild-type) commercial genetic tests for BRCA1 and
BRCA2. These patients underwent screening with additional multiple DNA-based and RNA-based methods. Of these 300 patients, 17% carried previously undetected mutations, including 35 (12%) with genomic rearrangement of BRCA1 or BRCA2.

A study evaluated 251 patients with an estimated BRCA mutation using the Myriad II model of 10% or greater. 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. No genomic rearrangements were identified in the 115 Ashkenazi Jewish probands, but 47 of the 115 (40%) had point mutations. In this population genomic rearrangements constituted 18% of all identified BRCA mutations. The authors also indicated that the estimated prevalence of a mutation was not predictive of 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; 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 and other Mutations

A number of publications have also described the association of CHEK2 (cell cycle checkpoint kinase 2) mutations with hereditary breast cancer. The prevalence of this finding varies greatly by geographic regions, being most common in northern and eastern Europe. It has been detected in 4% of early breast cancer patients in the Netherlands, in 2.3% of such patients in Germany, but has been noted to be rare in these patients in Spain or Australia. In the US, this mutation is much less common than BRCA mutations and BRCA rearrangements. For example, in the study by Walsh et al cited above, 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 CHECK2 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 meta-analysis by Weischer et al concluded that for familial breast cancer, the cumulative risk at age 70 years for CHEK2*1100delC mutation was 37% (95% CI: 26% to 56%). 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 raise a number of questions about potential use of this assay. In particular, they raise questions about the breast cancer risk estimates presented in the Weischer study; a number of the questions relate to the variable methods of ascertainment used in the studies in this meta-analysis. They also note that other mutations, such as CHEK2*S428F, are observed in other populations. The varying frequency is mentioned, with the mutation noted in 0.5 -1.0% of the population in northern
and eastern Europe compared with 0.2 - 0.3% in the US. Finally, they raise 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 not compelling evidence to justify routine clinical testing for CHECK2 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 looking at the risk of breast cancer associated with the CHEK2 mutation. Myszka et al. 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.

Zhang et al. performed a systematic review of candidate-gene association studies, identifying more than 1,000 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. There was also a strong association found for two variants of the ATM gene and an additional 4 genes that had a single variant with a strong association (CASP8, CTLA4, NBN, and TP53).

Peng et al. 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 odds ratios 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. These genes were CASP8, CHEK2, CTLA4, FGFR2, ILIB, LSP1, and MAP3K1.

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 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. While 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 does not meet payment determination criteria.
Practice Guidelines and Position Statement

The National Comprehensive Cancer Network (NCCN) guideline, Genetic/Familial High-Risk Assessment: Breast and Ovarian cancer, was updated in 2013. The presence of one or more of the following criteria suggests hereditary breast/ovarian cancer syndrome (HBOC):

- Individual from a family with a known deleterious \textit{BRCA1}/\textit{BRCA2} mutation
- Personal history of breast cancer plus at least one of the following:
  - Diagnosed at age \leq 45 years
  - Diagnosed at age \leq 50 years with at least one close blood relative with breast cancer at any age or with a limited family history
  - Two breast primary tumors with the first breast cancer diagnosis at age \leq 50 years
  - Diagnosed age \leq 60 years with a triple negative breast cancer
  - Diagnosed at any age with at least 1 close blood relative with:
    - Breast cancer diagnosed at age \leq 50 years, or
    - Epithelial ovarian/fallopian tube/primary peritoneal cancer
  - Diagnosed at any age with at least 2 close blood relatives with:
    - Breast cancer at any age, or
    - Pancreatic cancer or aggressive prostate cancer (Gleason score \geq 7) at any age
  - Close male relative with breast cancer
  - For an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish) no additional family history may be required.
- Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer
- Personal history of male breast cancer
- Personal history of pancreatic cancer or aggressive prostate cancer (Gleason score \geq 7) at any age with at least 2 close blood relatives with breast and/or ovarian/fallopian tube/primary peritoneal cancer and/or pancreatic cancer or aggressive prostate cancer (Gleason score \geq 7) at any age

The U.S. Preventive Services Task Force (USPSTF) published guidelines for genetic testing of \textit{BRCA1}/\textit{BRCA2} in 2005. Their recommendations were as follows:

- The USPSTF recommends against routine referral for genetic counseling or routine breast cancer susceptibility gene (BRCA) testing for women whose family history is not associated with an increased risk for deleterious mutations in breast cancer susceptibility gene 1 (\textit{BRCA1}) or breast cancer susceptibility gene 2 (\textit{BRCA2}). (Grade D recommendation)
- The USPSTF recommends that women whose family history is associated with an increased risk for deleterious mutations in \textit{BRCA1} or \textit{BRCA2} genes be referred for genetic counseling and evaluation for BRCA testing. (Grade B recommendation)

The American Society of Clinical Oncology (ASCO) recommended in 2003 that cancer predisposition testing be offered when 1) the person has a strong family history of cancer or very early age of onset of disease, 2) the test can be adequately interpreted, and 3) the results will influence the medical management of the patient or family member.
In 1999, the American College of Medical Genetics (ACMG) 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.

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VII. References

4. BCBSA TEC Assessments 1997; Tab 4
24. Langston AA, Malone KE, Thompson JD et al. BRCA1 mutations and breast cancer in the general population: analyses in women before age 35 years and in women before age 45 years with first-degree family history. *JAMA* 1998; 279(12): 922-9


60. Walsh T, Casadei S, Coats KH et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. JAMA 2006; 295(12):1379-88


