
Revised April 2014

Aetna considers prophylactic mastectomy medically necessary for reduction of risk of breast cancer in any of the following categories of high-risk women:

1. Women diagnosed with breast cancer at 45 years of age or younger; or
2. Women who are at increased risk for specific mutation(s) due to ethnic background (for instance: Ashkenazi Jewish descent) and who have 1 or more relatives with breast cancer or epithelial ovarian cancer at any age; or
3. Women who carry a genetic mutation in the TP53 or PTEN genes (Li-Fraumeni syndrome and Cowden and Bannayan-Riley-Ruvalcaba syndromes); or
4. Women who possess BRCA1 or BRCA2 mutations confirmed by molecular susceptibility testing for breast and/or epithelial ovarian cancer; or
5. Women who received radiation treatment to the chest between ages of 10 and 30 years, such as for Hodgkin disease; or
6. Women with a 1st- or 2nd-degree male relative with breast cancer*; or
7. Women with multiple primary or bilateral breast cancers in a 1st- or 2nd-degree blood relative; or
8. Women with multiple primary or bilateral breast cancers; or
9. Women with 1 or more cases of epithelial ovarian cancer AND 1 or more 1st- or 2nd-degree blood relatives on the same side of the family with breast cancer; or
10. Women with 3 or more affected 1st- or 2nd-degree blood relatives on the same side of the family, irrespective of age at diagnosis.
have prophylactic hysterectomy in conjunction with oophorectomy depends on the women's attitudes regarding hormone replacement and the potential morbidity from the hysterectomy, either abdominally or vaginally.

An unilateral oophorectomy at the time of hysterectomy when both ovaries are in place is considered not medically necessary because this is considered inappropriate under current, generally accepted guidelines.

**BRCA Testing**

Aetna considers molecular susceptibility testing for breast and/or epithelial ovarian cancer ("BRCA testing") medically necessary once per lifetime in any of the following categories of high-risk adults with breast or epithelial ovarian cancer (adapted from guidelines from the U.S. Preventive Services Task Force (for screening indications) and from the American College of Obstetricians and Gynecologists and the American College of Medical Genetics (for testing persons with cancer)):

I. Women with a history of epithelial ovarian cancer.

II. Women with personal history of breast cancer and any of the following:

A. Breast cancer is diagnosed at age 45 years or younger, with or without family history; or

B. Breast cancer is diagnosed at age 50 years or younger, with any of the following:

1. at least 1 close blood relative with breast cancer at age 50 years or younger; or
2. at least 1 close blood relative with epithelial ovarian cancer; or
3. bilateral breast cancer, or 2 primary breast cancers with 1st primary diagnosed at age 50 years or younger; or
4. limited family structure, or no family history available because member is adopted.

C. Breast cancer is diagnosed at age 60 years or younger, and is triple negative.

D. Breast cancer is diagnosed at any age, with any of the following:

1. at least 2 close blood relatives on the same side of the family with breast cancer and/or epithelial ovarian cancer at any age; or
2. the member has 2 breast primaries and also has at least 1 close blood relative with breast cancer diagnosed at age 50 years or younger; or
3. the member has 2 breast primaries and also has at least 1 close blood relative with epithelial ovarian cancer; or
4. at least 1 close male blood relative with breast cancer; or
5. at least 1 1st-, 2nd-, or 3rd-degree blood relative with a known BRCA1 or BRCA2 mutation; or
6. 2 close relatives on the same side of the family with pancreatic adenocarcinoma at any age; or
7. if ethnicity is associated with higher mutation frequency (Ashkenazi Jewish), no additional family history is required.

III. Women with a personal history of pancreatic adenocarcinoma at any age with 2 close relatives on the same side of the family with breast cancer, epithelial ovarian cancer, and/or pancreatic adenocarcinoma at any age.

IV. Women without a personal history of breast cancer, epithelial ovarian cancer, or pancreatic adenocarcinoma, and any of the following:

A. Women with 3 or more close blood relatives on the same side of the family with breast cancer, irrespective of age at diagnosis; or
B. Women with 1 or more close blood relatives on the same side of the family with breast cancer and 1 or more close blood relatives on the same side of the family with epithelial ovarian cancer; or
C. Women with 2 or more close blood relatives on the same side of the family with epithelial ovarian cancer; or
D. Women with 1 or more male close blood relatives with breast cancer; or
E. Women with 2 or more close blood relatives on the same side of the family with breast cancer, 1 of whom was diagnosed at age 50 years and younger; or
F. Women with 1 or more 1st-degree relatives with bilateral breast cancer; or
G. Women with 1 or more close blood relatives with both breast and epithelial ovarian cancer; or
H. Women of Ashkenazi Jewish descent with 1 or more 1st-degree relatives or two or more 2nd-degree relatives on the same side of the family with breast or epithelial ovarian cancer; or
I. Women with 1 or more 1st-, 2nd-, or 3rd-degree blood relatives with a known BRCA1 or BRCA2 mutation.

V. Women who do not meet any of the above criteria but are determined through both independent formal genetic counseling and validated quantitative risk assessment tool to have at least a 10% pre-test probability of carrying a BRCA1 or BRCA2 mutation. Note: In this category only, a 3-generation pedigree and quantitative risk assessment results must be provided to Aetna.
VI. Men with any of the following:

A. A 1st-, 2nd-, or 3rd-degree blood relative who has a known BRCA1 or BRCA2 mutation, where the results will influence clinical utility (e.g., reproductive decision-making)\textsuperscript{9}; or

B. A personal history of breast cancer.

Aetna considers BRCA testing experimental and investigational for all other indications including testing in men for surveillance, screening of breast or epithelial ovarian cancers as well as assessment of risk of other cancers such as pancreatic cancer, prostate cancer, and colon cancer because its effectiveness for these indications has not been established.

Aetna considers multigene hereditary breast cancer panels that accompany BRCA testing (e.g., MyRisk (Myriad Genetics), BRCAPlus (Ambry Genetics), BRCAvantage (Quest Diagnostics), High Risk Hereditary Breast Cancer (Invitae)) experimental and investigational because there is insufficient published evidence of their clinical validity and utility.

Footnotes on BRCA testing:

1. For the purposes of this policy, fallopian tube and primary peritoneal carcinoma should be included.

2. For purposes of this policy on BRCA testing, the term "breast cancer" includes both invasive and ductal carcinoma in situ (DCIS) breast cancers. Lobular carcinoma in situ (LCIS) is not included.

3. Close blood relatives include 1st-degree relatives (e.g., mother, sister, daughter) and 2nd-degree relatives (e.g., aunt, grandmother, niece), all of whom are on the same side of the family.

4. A limited family history is defined as a member who has fewer than 2 1st- or 2nd-degree female relatives in the same lineage that lived to age 45. The "limited family history" can occur on either the maternal or paternal side of family. A 3-generation pedigree is needed to assess whether family history is limited.

5. Two breast primaries in a single individual includes bilateral disease or cases where there are 2 or more clearly separate ipsilateral primary tumors.

6. For screening of Ashkenazi Jewish women, a screening panel for the founder mutations common in the Ashkenazi Jewish population (multisite testing) is considered medically necessary. If founder mutation testing is negative, full gene sequencing (reflex testing) is considered medically necessary only if the member meets any one of the criteria described above for comprehensive testing.

7. Validated quantitative risk assessment tools include BRCAPRO, Yale, University of Pennsylvania (UPenn I or UPenn II), BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm) and Tyrer-Cuzick (IBIS Breast Cancer Risk Evaluation Tool).

8. Triple negative breast cancer is when the individual's breast cancer cells test negative for estrogen receptors (ER negative), progesterone receptors (PR negative) and human epidermal growth factor receptors (HER2 negative).
9. Testing in this scenario is for the specific identified mutation (single site testing).

**Notes on BRCA testing:**

BRCA testing is not considered medically necessary for individuals less than 18 years of age.

Aetna does not cover BRCA testing of Aetna members if testing is performed primarily for the medical management of other family members that are not covered under an Aetna benefit plan. In these circumstances, the benefit plan for the family members who are not covered by Aetna should be contacted regarding coverage of BRCA mutation analysis and sequencing.

Occasionally, tissue samples from other family members who are not covered by Aetna are required to provide the medical information necessary for the proper medical care of an Aetna member. Aetna considers molecular-based testing for BRCA and other specific heritable disorders in non-Aetna members medically necessary in relation to Aetna members when all of the following conditions are met:

- The information is needed to adequately assess risk in the Aetna member; *and*
- The information will be used in the immediate care plan of the Aetna member; *and*
- The non-Aetna member's benefit plan (if any) will not cover the test.

A copy of the denial letter from the non-Aetna member's benefit plan must be provided.

Aetna may also request a copy of the certificate of coverage from the non-member's health insurance plan if:

- The denial letter from the non-member's insurance carrier fails to specify the basis for non-coverage; *or*
- The denial is based on a specific plan exclusion; *or*
- The genetic test is denied by the non-member's insurance carrier as not medically necessary and the medical information provided to Aetna does not make clear why testing would not be of significant medical benefit to the non-member.

Generally, in cases where BRCA testing is indicated due to family history of breast cancer and a specific BRCA mutation has been detected in the family member affected by breast cancer (the index case), then a mutation-specific assay for that single mutation, rather than full gene sequencing, is considered medically necessary for testing unaffected family members at high risk for breast cancer. However, full gene sequencing may be considered medically necessary if the member requesting approval for BRCA testing is the child of an individual with a known BRCA mutation, and the member would also qualify for BRCA testing solely due to risks from the other parent's family and the other parent has not been tested for a BRCA mutation.
BRCA testing of men with breast cancer is considered medically necessary to assess the man's risk of recurrent breast cancer and/or to assess the breast cancer risk of a female member where the affected male is a 1st- or 2nd-degree blood relative of that member. BRCA testing to assess the risk of breast or prostate cancer in men without breast cancer or for surveillance is considered experimental and investigational.

**Large Genomic Re-Arrangements**

There is inadequate information regarding the frequency of large genomic re-arrangements (BART testing) in the United States populations to indicate that use of this technique or re-testing for these specific mutations is established and medically necessary for members with a personal or family history of breast, epithelial ovarian cancer, or pancreatic cancer (e.g., the BRACAnalysis® Rearrangement Test or BRCAvantage™ Rearrangements). Thus, Aetna considers the use of BART or re-testing previously tested high-risk members for large genomic re-arrangements experimental and investigational.

**Background**

**BRCA Testing**

*BRCA Testing Documentation Requirements:* An “Aetna BRCA Prior Authorization Form” for BRCA Molecular Testing is to be sent along with the Laboratory's Test Requisition Form to Aetna for precertification. Documentation of specific cancer diagnosis in the proband(s) and pertinent medical records may be required prior to authorization. A summary indicating how this testing will change the immediate medical care of the member must also be included with the Prior Authorization request.

*Note on BRCA Test Authorization Workflow:* In order to facilitate proper administrative support for coverage of BRCA laboratory testing, the following workflow should be complied with for all BRCA testing requests:

When a member's physician believes that BRCA testing is an integral component for their medical care:

1. The member's provider (primary care physician [PCP] -- medical internist, family practitioner, or gynecologist) documents the family history with special attention to breast and ovarian cancer. Generally, information such as prior pathology reports, physicians' notes, and a formal 3-generation pedigree are required to confirm the family history.
2. Genetic counseling as to the appropriateness of the testing may be performed by the PCP or the PCP can authorize counseling by an appropriate participating specialist (e.g., medical geneticist).
3. When testing is medically indicated, the Aetna BRCA Prior Authorization Form is completed by the provider, confirming the basis for high-risk status (-the form can be obtained from Aetna by calling 877-794-8720).
4. A copy of the BRCA Prior Authorization Form is then submitted to the requesting Laboratory along with the Laboratory's test requisition form. The
blood specimen should not be tested by the Laboratory until confirmation of
coverage is received and the test is precertified.
Both the Laboratory and Aetna will confirm member eligibility and then
perform the appropriate testing requested once eligibility is determined.
If the member does not meet the pre-determined criteria, the member's
physician will be contacted with a review of the clinical information provided
by the physician.

Post-test results counseling can be authorized by the PCP when appropriate.

Aetna's policy on BRCA testing of women with breast cancer is based on the
guidelines from the American College of Obstetricians and Gynecologists (2009),
the American College of Medical Genetics (1999) and the U.S. Preventive

Hereditary breast cancer is characterized by multiple family members with a history
of pre-menopausal breast cancer. In some families, hereditary breast cancer can
be additionally associated with an increased risk for ovarian cancer. Mutations in 2
highly penetrant autosomal dominant genes, BRCA1 and BRCA2 (BRCA stands
for BReast CAncer), have been identified; these mutations are thought to be
responsible for an estimated 5 to 7 % of all breast and ovarian cancers. A woman
from a high-risk family who inherits a BRCA1 mutation has a greater than 80 %
lifetime risk of developing breast cancer and an estimated 45 % risk of developing
ovarian cancer by the age of 70. It is estimated that as many as
1 in 200 women may harbor a BRCA mutation.

Approximately 80 % of families with multiple cases of early-onset female breast
cancer have the BRCA1 gene mutation. The presence of a BRCA1 mutation is
associated with an increased risk of ovarian cancer.

Patients are assigned to categories based upon their pre-test probability of having
a BRCA mutation, with a less than 10 % probability considered as low-risk, a 10 to
25 % probability considered as moderate risk, and a greater than 25 % probability
being considered as high-risk (USPSTF, 2005). American Society of Clinical
Oncology guidelines (2006) state that a woman with greater than 10 % likelihood
of carrying a deleterious BRCA mutation (based on family history and ethnic
background) should be offered genetic testing. BRCA1 and BRCA2 mutation
analysis (and, if necessary, gene sequencing) is primarily indicated in women who
are at high-risk of hereditary breast or ovarian cancer, including women with a
family history of breast or ovarian cancer and women with 1 or more relatives who
are known to have a mutation in the BRCA1 or BRCA2 genes.

There is some evidence to suggest that men with BRCA2 mutations are at
increased risk of developing cancers of the breast and prostate. It has been
estimated that approximately 6 % of men who are positive for BRCA2 will develop
breast cancer by the age of 70 (Wolpert et al, 2000). In addition, there is some
evidence that suggests that men who are BRCA-positive are at moderately
increased risk for prostate cancer. However, it is not known how these findings
would affect a man's clinical management, as there are no prospective outcome
studies of BRCA testing of men. In addition, current evidence-based guidelines
from the American College of Medical Genetics do not include recommendations
for BRCA testing of men. Note, however, that BRCA testing of a man with breast
cancer may be necessary to assess the breast cancer risk of a female blood relative.

Before a physician orders BRCA analysis, it is essential that the patient undergo adequate education and counseling because molecular susceptibility testing raises important medical, psychological, and social issues for patients and their families. The educational process, “genetic counseling”, which is a covered benefit in all Aetna products and is often accomplished using trained genetic counselors or medical geneticists, should include the following:

- Alternatives to molecular susceptibility testing;
- Clarification of the patient's increased risk status;
- Counseling regarding therapeutic options; including discussions which address the limitations of these options;
- Explanation of how genetics affects cancer susceptibility;
- Limited data regarding efficacy of methods for early detection and prevention;
- Possible outcomes of testing (e.g., positive, negative, or uncertain test results);
- Possible psychological and social impact of testing;
- Potential benefits, risks, alternatives, and limitations of testing.

Performing BRCA screening on an unaffected member in a high-risk family, without knowing the genetic status of the mutation(s) in the family, may sometimes lead to difficulties in interpreting the BRCA screening results. Although a positive test in a high-risk family is usually consistent with increased risk in the individual being screened, a negative test might not necessarily be reassuring. A negative test could be due to lack of inheritance of a BRCA1 or BRCA2 abnormality (true negative), due to testing an inappropriate gene (false negative). In some cases, false-positive results can arise due to the presence of a clinically insignificant polymorphism in one of the BRCA genes.

The 3 types of clinical testing for BRCA1/2 are full gene sequencing, a panel for the founder mutations common in the Ashkenazi Jewish population, and a mutation-specific assay. For persons of Ashkenazi Jewish descent, available guidelines state that the most efficient strategy is to first screen for the 3 common founder mutations, which are present in approximately 3% of the general Ashkenazi Jewish population and account for about 90% of all identified BRCA mutations among Jewish women.

According to established guidelines, if the woman is found to be negative for the founder mutations, then further testing is not considered necessary unless she has other characteristics that place her in a high risk category. If the woman has other characteristics placing her into the high-risk category, she may still carry a rare BRCA mutation that is not detected, so that full gene sequencing is considered necessary to detect a rare BRCA1/2 mutation. By sequencing the entire BRCA1/2 genes, the test is potentially able to identify mutations along the entire length of the gene.

If a specific BRCA mutation is detected in the family member affected by breast cancer (the index case), established guidelines indicate that unaffected family
members can be tested for this single mutation using a mutation-specific assay, a highly specific test that only looks for a specific mutation unique to their family.

The U.S. Preventive Services Task Force (2005) released a recommendation that primary care physicians should not routinely refer all women for genetic counseling and DNA testing to detect the presence of specific BRCA1 and BRCA2 gene mutations that may be associated with breast or ovarian cancers. However, if a woman has certain specific family history patterns that put her at risk for these gene mutations, her PCP should suggest counseling and possible DNA testing.

Three tools have been developed to guide PCPs in assessing risk and guiding referral: the Family History Risk Assessment Tool (FHAT), the Manchester scoring system, and the Risk Assessment in Genetics (RAGs) tool (USPSTF, 2005; Nelson et al, 2005). The sensitivity and specificity of FHAT for a clinically important BRCA1 or BRCA2 mutation were 94 % and 51 %, respectively. The Manchester scoring system was developed in the United Kingdom to predict deleterious BRCA1 or BRCA2 mutations at the 10 % likelihood level and had an 87 % sensitivity and a 66 % specificity (Evans et al, 2004). The RAGs tool (Emery et al, 1999; Emery et al, 2000), a computer program designed to support assessment and management of family breast and ovarian cancer in primary care settings, is used to assign patients to categories of low-risk (less than 10 %), moderate-risk (10 % to 25 %), and high-risk (greater than 25 %). Primary care clinicians can then manage recommendations of re-assurance, referral to a breast clinic, or referral to a geneticist on the basis of the patient's respective risk categories (USPSTF, 2005).

Guidelines from the U.S. Preventive Services Task Force (2005) state that several quantitative tools to predict risk for deleterious BRCA mutations have been developed from data on previously tested women. These risk tools include the Myriad Genetic Laboratories model, the Couch model, BRCAPRO, the Penn Model, the Yale Model, and the Tyrer model (Nelson et al., 2005; Marroni et al, 2004). The USPSTF (2005) noted that much of the data used to develop the models are from women with existing cancer, and their applicability to asymptomatic, cancer-free women in the general population is unknown.

Available evidence suggests that current models for predicting BRCA mutation may tend to over-estimate risk when family history is adequate and under-estimate risk when family history is limited. Researchers have speculated that, in young women with limited family structures (e.g., fewer than 2 women who survived past age 45 in either parental lineage), the genetic models that are used to predict carrier status would under-estimate the prevalence of BRCA mutations. Weitzel et al (2007) sought to determine if BRCA gene mutations are more prevalent among single cases of early onset breast cancer in families with limited versus adequate family structure than would be predicted by 3 currently available probability models, the Couch, Myriad, and BRCAPRO models. The investigators studied 306 women who had breast cancer before age 50 years and no 1st- or 2nd-degree relatives with breast or ovarian cancers. The investigators found that about 50 % of these women had limited family structure, defined as fewer than 2 1st- or 2nd-degree female relatives surviving beyond age 45 years in either lineage. The mean probability of identifying a BRCA mutation in the study cohort was 20.4 % based on the Couch model, 8.0 % based on the Myriad model, and 7.3 % based
on the BRCAPRO model. These probabilities were not dependent on whether participants had limited or adequate family structures. However, when BRCA gene sequences were determined, deleterious mutations were identified in 13% of women with limited family structures versus only 5.2% of women with adequate family structure (p = 0.02). Participants with limited family history were 2.8 times more likely to be carriers of BRCA gene mutations than women with adequate family history (p = 0.02). These investigators concluded that family structure can affect the accuracy of mutation probability models. These investigators recommended making genetic testing guidelines more inclusive for single cases of breast cancer when the family structure is limited. They stated that probability models need to be created using limited family history as an actual variable.

Although there is some preliminary evidence to suggest that the presence of a BRCA mutation may increase the risk of cancers at sites other than the breast, including prostate cancer, pancreatic cancer and colon cancer, there is insufficient evidence to indicate BRCA testing for assessment of risk of non-breast cancers. Current evidence-based guidelines from leading medical professional organizations have not recommended BRCA testing for assessment of risk of prostate cancer, pancreatic cancer, colon cancer or other non-breast cancers.

**Large Genomic Re-Arrangements**

A clinical study has demonstrated a low overall prevalence of BRCA1/2 large genomic rearrangements in a cohort of patients referred for BRCA testing. Judkins, et al. (2012) reported on the prevalence of BRCA1/2 large genomic rearrangements in 48,456 patients referred for clinical molecular testing for suspicion of hereditary breast and ovarian cancer. Prevalence data were analyzed for patients from different risk and ethnic groups. Patients were designated as "high-risk" if their clinical history predicted a high prior probability, wherein large genomic rearrangement testing was performed automatically in conjunction with sequencing. "Elective" patients did not meet the high-risk criteria, but underwent large genomic rearrangement testing as ordered by the referring health care provider. Among the 25,535 high-risk patients, the prevalence of a full sequence BRCA1/2 mutation was 21.5 percent, and the prevalence of BRCA1/2 large genomic rearrangements was 2.4 percent. Among the 22,921 elective patients, the prevalence of a full sequence BRCA1/2 mutation was 7.8 percent, and the overall prevalence of BRCA1/2 large genomic rearrangements was only 0.48 percent. The greatest prevalence of BRCA1/2 large genomic rearrangements was in the the high risk group of Latin American/Caribbean ethnicity, with an overall rate of BRCA1/2 large genomic rearrangements of 6.7 percent. The prevalence of a large genomic rearrangements in the the elective group of Latin American/Caribbean ethnicity was 1.8 percent. All other ethnicities in the "elective" group had prevalence rates of large genomic rearrangements ranging from 0.0 percent to 0.8 percent.

Sharifah et al (2010) noted that the incidence of breast cancer has been on the rise in Malaysia. It is suggested that a subset of breast cancer cases were associated with germline mutation in BRCA genes. Most of the BRCA mutations reported in Malaysia were point mutations, small deletions and insertions. These researchers reported the first study of BRCA large genomic re-arrangements (LGRs) in Malaysia. They aimed to detect the presence of LGRs in the BRCA
genes of Malaysian patients with breast cancer. Multiplex ligation-dependent probe amplification (MLPA) for BRCA LGRs was carried out on 100 patients (60 were high-risk breast cancer patients previously tested negative/positive for BRCA1 and BRCA2 mutations, and 40 were sporadic breast cancer patients), recruited from 3 major referral centers. Two novel BRCA1 re-arrangements were detected in patients with sporadic breast cancer; both results were confirmed by quantitative PCR. No LGRs were found in patients with high-risk breast cancer. The 2 LGRs detected were genomic amplifications of exon 3 and exon 10. No BRCA2 genomic re-arrangement was found in both high-risk and sporadic breast cancer patients. The authors concluded that these findings will be helpful to understand the mutation spectrum of BRCA1 and BRCA2 genes in Malaysian patients with breast cancer. They stated that further studies involving larger samples are needed to establish a genetic screening strategy for both high-risk and sporadic breast cancer patients.

Ticha and colleagues (2010) noted that LGR represent substantial proportion of pathogenic mutations in the BRCA1 gene, whereas the frequency of re-arrangements in the BRCA2 gene is low in many populations. These investigators screened for LGRs in BRCA1 and BRCA2 genes by MLPA in 521 unrelated patients negative for BRCA1/2 point mutations selected from 655 Czech high-risk breast and/or ovarian cancer patients. Besides long range PCR, a chromosome 17-specific oligonucleotide-based array comparative genomic hybridization (aCGH) was used for accurate location of deletions. They identified 14 patients carrying 8 different LGRs in BRCA1 that accounted for 12.3 % of all pathogenic BRCA1 mutations. No LGRs were detected in the BRCA2 gene. In a subgroup of 239 patients from high-risk families, these researchers found 12 LGRs (5.0 %), whereas 2 LGRs were revealed in a subgroup of 282 non-familial cancer cases (0.7 %). Five LGRs (deletion of exons 1 to 17, 5 to 10, 13 to 19, 18 to 22 and 21 to 24) were novel; 2 LGRs (deletion of exons 5 to 14 and 21 to 22) belong to the already described Czech-specific mutations; 1 LGR (deletion of exons 1 to 2) was reported from several countries. The deletions of exons 1 to 17 and 5 to 14, identified each in 4 families, represented Czech founder mutations. The present study indicates that screening for LGRs in BRCA1 should include patients from breast or ovarian cancer families as well as high-risk patients with non-familial cancer, in particular cases with early-onset breast or ovarian cancer. On the contrary, these analyses do not support the need to screen for LGRs in the BRCA2 gene. Implementation of chromosome-specific aCGH could markedly facilitate the design of primers for amplification and sequence analysis of junction fragments, especially in deletions over-lapping gene boundaries.

Manguoglu and associates (2011) performed the MLPA assay for detection of large re-arrangements of BRCA1 and BRCA2 genes in 16 familial, 29 early onset, 3 male breast cancer, and 2 bilateral breast/ovarian cancer high-risk Turkish index cases. The MLPA assay for all exons of both genes and for 1100delC variant of CHEK2 gene were performed. Analyses, revealed no large genomic re-arrangements in both genes, and, no 1100del variant in CHEK2 gene. The authors concluded that these data, which represents the first results for Turkish patients, suggest that, the frequency of BRCA1 and BRCA2 genes' large re-arrangements is very low.
Prophylactic total or simple mastectomy, not subcutaneous mastectomy, for patients at high-risk of breast cancer is a difficult issue in that it involves the determination of risk in an individual patient, a separate determination of what level of risk is high enough to justify the extreme choice of prophylactic mastectomy, and assurance from scientific studies in the medical literature that this procedure does result in a reduction of breast cancer occurrence. Even if the risk can be estimated, the decision to proceed with a prophylactic mastectomy will be largely patient driven, dependent on whether the patient feels comfortable living with the estimated risk and how she values the psychosexual function of the breast. Although the definition of “high-risk” is somewhat arbitrary, the consensus of opinion is that prophylactic mastectomy may be considered only in patients at high-risk of breast cancer with a demonstrated BRCA gene mutation or a life-long risk level in excess of 25 to 30%. The patients described in the above criteria fall into this range.

BRCA1 and BRCA2 may be responsible for only 5% to 10% of all breast cancers and about 20% of breast cancers diagnosed in women under age 45. About 50% to 60% of women with inherited BRCA1 or BRCA2 mutations will develop breast cancer by the age of 70. Provisional recommendations by the Cancer Genetics Studies Consortium for follow-up of individuals with BRCA1 or BRCA2 mutations involve counseling and early breast cancer screening, including annual mammography and clinical breast examination beginning at age 25 to 35 years, and monthly breast self-examination beginning at age 18 to 21 years. A few recent studies have shown that among women who test positive for a BRCA1 or BRCA2 gene mutation, prophylactic surgery at a young age substantially improves survival.

Even among women with breast cancer in their families, the tests for BRCA1 and BRCA2 may be negative 90% of the time, unless a mutation has been previously identified in the family. A negative BRCA1 and BRCA2 test result would mean that a woman still faces the same risk as the general population of developing sporadic, non-inherited breast cancer. However, in such BRCA negative patients, other significant risk factors come into play. A personal history of invasive breast cancer or lobular carcinoma in situ increases the risk of developing a new breast cancer in any remaining breast tissue in either breast by 0.5% to 1.0% per year.

The degree of reduction of risk of breast cancer with prophylactic mastectomy is not well documented in the literature (ACMG, 1999). It is clear that no surgical technique for prophylactic mastectomy removes all breast epithelium. The 2 techniques used are “subcutaneous mastectomy” and “total mastectomy”. Subcutaneous mastectomy removes the breast tissue leaving the nipple/areolar complex intact in order to preserve appearance and nipple sensation. Approximately 10 to 20% of the breast epithelium remains under the areola after subcutaneous mastectomy. Because a significant proportion of breast tissue is left with the nipple by subcutaneous mastectomy, the American College of Medical Genetics has concluded that this operation is generally not indicated if mastectomy is to be done for breast cancer prevention (ACMG, 1999). Total mastectomy including nipple removal is necessary to remove the maximum amount of breast tissue (Lopez and Porter, 1996; ACMG, 1999).
Carcinoma of the male breast has many similarities to breast cancer in women, but the diseases have different genetic and pathologic features. Both BRCA1 and BRCA2 mutations can cause breast cancer in women, but only BRCA2 mutations confer a significant risk to men (Giordano et al, 2002). Although older articles have reported that men with breast cancer have poorer survival rates than women, most recent series show that men and women have equivalent prognoses when matched for age and stage of disease (Giordano et al, 2002). Prophylactic mastectomy of the contralateral breast may be indicated in a man with breast cancer (LeBlond, 1993; Jaiyesimi et al, 1993). However, there is no published clinical data or evidence-based guidelines on prophylactic mastectomy for men with a BRCA2 mutation or a family history of breast cancer. It has been estimated that approximately 6% of men who are positive for BRCA2 will develop breast cancer by the age of 70 (Wolpert et al, 2000). This is about equal to the risk of breast cancer in average-risk women without BRCA mutations. This difference in risk of breast cancer between BRCA-positive women and men may be due to the fact that men have much less breast tissue and serum estrogen than women.

In a skin-sparing mastectomy, the breast tissue is removed through a conservative incision made around the areola. The increased amount of skin preserved as compared to traditional mastectomy resections serves to facilitate breast reconstruction procedures. Patients with cancers that involve the skin, such as inflammatory cancer, are not candidates for skin-sparing mastectomy. Guidelines on surgery for breast cancer by the British Association for Surgical Oncology and the Royal College of Surgeons (2007) state that skin sparing mastectomy is associated with better cosmetic results. A review article in the New England Journal of Medicine (Cordiero, 2008) also notes that a skin sparing mastectomy provided a good cosmetic result.

Nipple-sparing mastectomy is performed in the setting of immediate reconstruction and can achieve good cosmetic results. A Canadian guideline (Alberta Health Services, 2014) concluded that: “Despite these and other studies reporting promising results with nipple-sparing mastectomy, there is currently no published data from a randomized controlled trial, on the oncologic safety of nipple-sparing, as compared to conventional skin-sparing mastectomy. Therefore, nipple-sparing mastectomy is generally not recommended for patients with malignancy but could be considered for carefully selected patients, and in patients undergoing prophylactic mastectomy, when done in conjunction with a separate biopsy of the ducetal tissue directly underlying the nipple-areola complex. The decision as to whether to pursue a nipple-sparing procedure requires multidisciplinary input and careful discussion with the patient about potential additional risks associated with this approach.”

Yao, et al. (2014) reported on a case series and a review of the literature on nipple sparing mastectomy in BRCA1/2 mutation carriers. The authors found: “Our study and other series show that NSM in BRCA1/2 carriers is associated with low rates of complications and locoregional recurrence that are comparable to results in non-BRCA1/2 carriers. Rates of nipple involvement, nipple recurrence, or development of new cancers in retained nipples are also low with follow-up to date, and comparable to SSMs performed in BRCA1/2 carriers. Longer follow-up of these patients is needed to determine specific locoregional recurrence rates, but
results suggest that BRCA1/2 patients are eligible for NSM for both prevention and treatment of breast cancer."

An earlier systematic evidence review of observational studies found no significant differences observed when patients who received nipple-sparing mastectomy were compared to those who received non-skin sparing mastectomy (OR 0.83, 95% CI 0.45 to 1.52; two studies, n=401).

European Society for Medical Oncology guidelines on prophylactic mastectomy (Balmana, et al., 2011) state that "The NSM preserves the skin envelope and the nipple areola complex. Although follow-up on this procedure is still short, preliminary reports show similar failure rates with superior cosmetic results compared with the other mastectomy techniques."

Guidelines from the National Comprehensive Cancer Network (NCCN, 2014) on Breast Cancer Risk Reduction state that nipple sparing mastectomy should be considered for breast cancer risk reduction, and recommends that clinicians "[d]iscuss risks and benefits of nipple-areolar sparing surgery." "Multidisciplinary consultations are recommended prior to surgery, and should include a surgeon familiar with the natural history and therapy of benign and malignant breast disease to enable the woman to become well informed regarding treatment alternatives, the risks and benefits of surgery, nipple-sparing mastectomy, and surgical breast reconstruction options."

**Prophylactic Bilateral Oophorectomy**

Prophylactic bilateral oophorectomy has been recommended for women at high-risk of ovarian cancer. The term "hereditary ovarian cancer syndrome" refers to 3 rare cancer syndromes, which occur in approximately 5% of all ovarian cancers. These are: (i) breast-ovarian cancer syndrome, (ii) site-specific cancer syndrome, and (iii) hereditary non-polyposis colorectal cancer syndrome (Lynch syndrome I). Breast-ovarian syndrome occurs in families with clusters of women with ovarian cancer and/or breast cancer. Site-specific ovarian cancer syndrome occurs in families with clusters of ovarian cancer. Lynch syndrome I is a familial cancer syndrome characterized by an inherited predisposition to the development of the early onset (usually ages 40 to 50) of adenocarcinomas of the colon with proximal colonic predominance, ovary, pancreas, breast, bile duct, cervix, endometrium, and of the urologic (most commonly ureter and renal pelvis) and gastrointestinal systems. The lifetime probability of ovarian cancer increases from about 1.6% in a 35-year old woman without a family history of ovarian cancer to about 5% if she has 1 relative and 7% if she has 2 relatives with ovarian cancer. Out of those patients who have a positive family history, 3 to 9% may end up having hereditary cancer syndromes. Epithelial ovarian cancer, the most common histopathologic type, is uncommon in women before the age of 40. The incidence rates then increase steeply until a woman reaches her 70s, then decrease somewhat. About 7% of women with ovarian cancer report a family history of ovarian cancer, and of these women, over 90% have only 1 relative with ovarian cancer.

There is no patient at greater risk of developing ovarian cancer than a woman in direct genetic lineage of a family with hereditary ovarian cancer syndrome. The probability of a hereditary ovarian cancer syndrome in a family pedigree increases with the number of affected relatives, with the number of affected generations, and
with young age of onset of disease. Women suspected of having a hereditary ovarian cancer syndrome should have a family pedigree constructed by a physician or genetic counselor competent in determining the presence of an autosomal dominant inheritance pattern. The number of observed ovarian cancer-affected generations in ovarian cancer syndromes ranges from 2 to 4 per family. The sisters and daughters of a woman from a family with an ovarian cancer syndrome may have a lifetime probability as high as 50% of developing ovarian cancer. The mean age for ovarian cancer onset is 59 years for the general population, while that for various hereditary ovarian cancer syndromes is 52 years for breast-ovary, 49 years for site-specific ovary, and 45 years for Lynch I cases.

Screening for ovarian cancer is notoriously difficult in contrast to the much easier and more proven value of screening for breast cancer. As the lifetime risk of ovarian cancer in patients with hereditary ovarian cancer syndromes is sufficiently high to outweigh any possible morbidity from oophorectomy, early surgical menopause, or hormone replacement therapy, prophylactic (bilateral) oophorectomy is an indicated procedure to all women from these high-risk families after completion of childbearing or the age of 35 to 40 years, at the latest. This recommendation is based also on the reported early disease onset in these patients. It is apparent from the available literature that the younger the age of women undergoing prophylactic oophorectomy, the more beneficial the effects of breast cancer risk reduction.

Observational studies have shown that women who have BRCA1 or BRCA2 mutations have higher risks for both ovarian cancer and breast cancer, and that prophylactic oophorectomy reduces the risk of both types of cancer. In a prospective follow-up study, researchers enrolled 170 eligible women (age of 35 or older) with BRCA mutations who were referred for genetic counseling at Memorial Sloan-Kettering Cancer Center during 6 years. A total of 98 women underwent bilateral prophylactic oophorectomy, and 72 chose surveillance (mean follow-up of 24 months). Among women who selected surveillance, breast cancer was diagnosed in 8, ovarian cancer in 4, and peritoneal cancer in 1. Among women who underwent prophylactic oophorectomy, breast cancer was identified subsequently in 3 and peritoneal cancer in 1; 3 early-stage ovarian cancers were found at surgery. The investigators reported that the hazard ratio (HR) for the development of breast or BRCA-related gynecologic cancer after oophorectomy was 0.25.

In a retrospective multi-center study, 6 of 259 BRCA-positive women were found to have stage I ovarian cancer at the time of prophylactic oophorectomy, and 2 subsequently developed peritoneal carcinomas. Among 292 matched controls who didn't undergo prophylactic surgery, 58 were diagnosed with ovarian cancer during a mean follow-up of 8.8 years. Thus, oophorectomy reduced the subsequent risk for ovarian or peritoneal cancer by 96%. In a subgroup analysis to determine breast-cancer risk, 21 of 99 women who underwent oophorectomy developed breast cancer compared with 60 of 142 controls (risk reduction, 53%).

Prophylactic oophorectomy, as the sole surgical procedure, is not indicated under accepted guidelines for women without a BRCA mutation or a family history of ovarian cancer. However, prophylactic mastectomy may be performed in conjunction with another operative procedure that allows access to the pelvic
The decision on prophylactic oophorectomy as a concurrent procedure remains controversial and should depend on the individual patient and her ability to comply with lifelong estrogen therapy. 

Rebbeck et al (2009) stated that risk-reducing salpingo-oophorectomy (RRSO) is widely used by carriers of BRCA1 or BRCA2 (BRCA1/2) mutations to reduce their risks of breast and ovarian cancer. To guide women and their clinicians in optimizing cancer prevention strategies, these investigators summarized the magnitude of the risk reductions in women with BRCA1/2 mutations who have undergone RRSO compared with those who have not. All reports of RRSO and breast and/or ovarian or fallopian tube cancer in BRCA1/2 mutation carriers published between 1999 and 2007 were obtained from a PubMed search. Hazard ratio estimates were identified directly from the original articles. Pooled results were computed from non-overlapping studies by fixed-effects meta-analysis. A total of 10 studies investigated breast or gynecologic cancer outcomes in BRCA1/2 mutation carriers who had undergone RRSO. Breast cancer outcomes were investigated in 3 non-overlapping studies of BRCA1/2 mutation carriers, 4 of BRCA1 mutation carriers, and 3 of BRCA2 mutation carriers. Gynecologic cancer outcomes were investigated in 3 non-overlapping studies of BRCA1/2 mutation carriers and 1 of BRCA1 mutation carriers. Risk-reducing salpingo-oophorectomy was associated with a statistically significant reduction in risk of breast cancer in BRCA1/2 mutation carriers (HR = 0.49; 95 % confidence interval [CI]: 0.37 to 0.65). Similar risk reductions were observed in BRCA1 mutation carriers (HR = 0.47; 95 % CI: 0.35 to 0.64) and in BRCA2 mutation carriers (HR = 0.47; 95 % CI: 0.26 to 0.84). Risk-reducing salpingo-oophorectomy was also associated with a statistically significant reduction in the risk of BRCA1/2-associated ovarian or fallopian tube cancer (HR = 0.21; 95 % CI: 0.12 to 0.39). Data were insufficient to obtain separate estimates for ovarian or fallopian tube cancer risk reduction with RRSO in BRCA1 or BRCA2 mutation carriers. The authors concluded that the summary estimates presented here indicated that RRSO is strongly associated with reductions in the risk of breast, ovarian, and fallopian tube cancers and should provide guidance to women in planning cancer risk reduction strategies.

Domchek et al (2010) estimated risk and mortality reduction stratified by mutation and prior cancer status. Prospective, multi-center cohort study of 2,482 women with BRCA1 or BRCA2 mutations ascertained between 1974 and 2008 were included in this study, which was conducted at 22 clinical and research genetics centers in Europe and North America to assess the relationship of risk-reducing mastectomy or salpingo-oophorectomy with cancer outcomes. The women were followed-up until the end of 2009. Main outcome measures were breast and ovarian cancer risk, cancer-specific mortality, and overall mortality. No breast cancers were diagnosed in the 247 women with risk-reducing mastectomy compared with 98 women of 1,372 diagnosed with breast cancer who did not have risk-reducing mastectomy. Compared with women who did not undergo RRSO, women who underwent salpingo-oophorectomy had a lower risk of ovarian cancer, including those with prior breast cancer (6 % versus 1 %, respectively; HR, 0.14; 95 % CI: 0.04 to 0.59) and those without prior breast cancer (6 % versus 2 %; HR, 0.28 [95 % CI: 0.12 to 0.69]), and a lower risk of first diagnosis of breast cancer in BRCA1 mutation carriers (20 % versus 14 %; HR, 0.63 [95 % CI: 0.41 to 0.96]) and BRCA2 mutation carriers (23 % versus 7 %; HR, 0.36 [95 % CI: 0.16 to 0.82]). Compared with women who did not undergo RRSO, undergoing salpingo-
oophorectomy was associated with lower all-cause mortality (10% versus 3%; HR, 0.40 [95% CI: 0.26 to 0.61]), breast cancer-specific mortality (6% versus 2%; HR, 0.44 [95% CI: 0.26 to 0.76]), and ovarian cancer-specific mortality (3% versus 0.4%; HR, 0.21 [95% CI: 0.06 to 0.80]). The authors concluded that among a cohort of women with BRCA1 and BRCA2 mutations, the use of risk-reducing mastectomy was associated with a lower risk of breast cancer; RRSO was associated with a lower risk of ovarian cancer, first diagnosis of breast cancer, all-cause mortality, breast cancer-specific mortality, and ovarian cancer-specific mortality.

The American College of Obstetricians and Gynecologists’ guidelines on “Hereditary breast and ovarian cancer syndrome” (ACOG, 2009) stated that “risk-reducing salpingo-oophorectomy should be offered to women with BRCA1 or BRCA2 mutations by age 40 or after the conclusion of child-bearing”.

Also, an UpToDate review on “Risk-reducing bilateral salpingo-oophorectomy in women at high risk of epithelial ovarian and fallopian tubal cancer” (Muto, 2013) states that “For women with BRCA mutations who have completed childbearing, we recommend rrBSO [risk-reducing bilateral salpingo-oophorectomy] rather than ovarian or fallopian tubal cancer screening or chemoprevention. For premenopausal women with Lynch syndrome who have completed childbearing, we suggest rrBSO rather than ovarian cancer screening or chemoprevention. Women who wish to avoid the risks of surgery and premature menopause and who understand the risk of ovarian cancer and the limitations of ovarian cancer screening may reasonable choose ovarian cancer screening. Women with Lynch syndrome should also undergo hysterectomy due to their markedly increased risk of endometrial cancer”.

### CPT Codes / HCPCS Codes / ICD-9 Codes

**CPT codes covered if selection criteria are met:**

19301
19303
19304
58150 - 58294
58541 - 58554
58661
58720
58940
81211
CPT codes not covered for indications listed in the CPB:
81213

Other CPT codes related to the CPB:
58570 -
58573

ICD-9 codes covered if selection criteria are met:
157.0 - 157.9 Malignant neoplasm of pancreas
174.0 - 174.9 Malignant neoplasm of female breast
175.0 - 175.9 Malignant neoplasm of male breast
183.0 Malignant neoplasm of the ovary [epithelial]
233.0 Carcinoma in situ, breast [invasive and ductal carcinoma in situ (DCIS) - lobular carcinoma in situ (LCIS) is not included]
V10.09 Personal history of malignant neoplasm, gastrointestinal tract, other [pancreas]
V16.0 Family history of malignant neoplasm, gastrointestinal tract [pancreas]
V16.3 Family history of malignant neoplasm of breast
V16.41 Family history of malignant neoplasm of ovary [epithelial]
V50.41 Prophylactic breast removal
V50.42 Prophylactic ovary removal
V84.01 Genetic susceptibility to malignant neoplasm of breast [BRCA1 or BRCA2 mutations confirmed by molecular susceptibility testing for breast cancer] [genetic mutation in the TP53 or PTEN genes (Li-Fraumeni syndrome, Cowden syndrome, and Bannayan-Riley-Ruvalcaba syndrome)]
V84.02 Genetic susceptibility to malignant neoplasm of ovary [BRCA1 or BRCA2 mutations confirmed by molecular susceptibility testing for ovarian cancer]

ICD-9 codes not covered for indications listed in the CPB:

140.0 - 156.9, Malignant neoplasms [other than breast, ovary, or pancreatic adenocarcinoma]
158.0 - 173.9,
176.0 - 198.5,
198.7 -
208.91, 230.0
- 232.9, 233.1
- 234.9
610.1 Diffuse cystic mastopathy [fibrocystic breast disease - not covered for prophylactic mastectomy]
V26.39 Other genetic testing of male [not covered without diagnosis of breast or prostate cancer]

Other ICD-9 codes related to the CPB:

759.6 Other hamartoses, not elsewhere classified [Cowden syndrome]
V15.3 Personal history of irradiation [women having received chest irradiation (i.e., for the treatment of Hodgkin's disease)]
V26.32 Other genetic testing of female

The above policy is based on the following references:

BRCA Testing

18. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Genetic testing for inherited BRCA1 or BRCA2 mutations. TEC Assessment Program. Chicago, IL: BCBSA; 1997;12(4).


Prophylactic Mastectomy


Prophylactic Bilateral Oophorectomy


42. Muto MG. Risk-reducing bilateral salpingo-oophorectomy in women at high risk of epithelial ovarian and fallopian tubal cancer. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2013.

Large Genomic Re-Arrangements
