**BRCA Testing, Prophylactic Mastectomy, and Prophylactic Oophorectomy**

**Policy**

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

**Prophylactic Mastectomy**

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; or
11. Women with atypical hyperplasia of lobular or ductal origin
    and/or lobular carcinoma in situ (LCIS) confirmed on biopsy
    with dense, fibronodular breasts that are mammographically
    or clinically difficult to evaluate.

Aetna considers prophylactic mastectomy experimental and
investigational for all other indications (e.g., atypical ductal
hyperplasia, fibrocystic breast disease, pseudo-angiomatous
stromal hyperplasia (PASH)) because its effectiveness for
indications other than the ones listed above has not been
established.

*Note: Prophylactic removal of contralateral breast tissue is
considered medically necessary in men with breast cancer.
Prophylactic mastectomy is considered experimental and
investigational for men with BRCA mutations or family history
of breast cancer because there is no clinical data on the clinical
value of this approach and there are no guidelines on this
situation.

A skin-sparing mastectomy is considered an acceptable
alternative method of performing a medically necessary
prophylactic mastectomy where there is no cancer involving the
skin. A nipple-sparing mastectomy is considered an acceptable
alternative of performing a medically necessary prophylactic mastectomy where there is no cancer involving the nipple-areola complex.

**Prophylactic Bilateral Oophorectomy**

Aetna considers prophylactic bilateral oophorectomy or salpingo-oophorectomy medically necessary in selected women with risk factors for epithelial ovarian carcinoma -- including nulliparity, low parity, infertility, early menarche, late menopause, and late first pregnancy -- if they meet any of the following criteria:

1. Women who are beyond child-bearing age (40 years of age or older) who have been diagnosed with an hereditary epithelial ovarian cancer syndrome based on a family pedigree constructed by a genetic counselor or physician competent in determining the presence of an autosomal dominant inheritance pattern; or
2. Women who have 2 1st-degree relatives (e.g., mother, sister, daughter) with a history of epithelial ovarian cancer; or
3. Women with a personal history of breast cancer and at least 1 1st-degree relative (e.g., mother, sister, daughter) with history of epithelial ovarian cancer; or
4. Women with BRCA1 or BRCA2 mutations confirmed by molecular susceptibility testing; or
5. Women with 1 1st-degree relative (e.g., mother, sister, daughter) and 1 or more 2nd-degree relatives (e.g., maternal or paternal aunt, grandmother, niece) with epithelial ovarian cancer.

Aetna considers prophylactic bilateral oophorectomy or salpingo-oophorectomy experimental and investigational for all other indications (e.g., post-menopausal women with breast cancer who do not meet criteria above, regardless of whether they are on tamoxifen or aromatase inhibitors) because its effectiveness for indications other than the ones listed above has not been established.
Hysterectomy with Prophylactic Oophorectomy

The medical literature suggests that a prophylactic hysterectomy should be performed in conjunction with oophorectomy in women from families with Lynch syndrome I. However, for women from families with breast-ovarian cancer syndrome, site-specific ovarian cancer syndrome, or a family history of epithelial ovarian cancer who choose to have prophylactic oophorectomy, the choice to 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\(^1\) 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\(^1\).

II. Women with personal history of breast cancer\(^2\) 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\(^3\) with breast cancer at age 50 years or younger; or
2. at least 1 close blood relative\(^3\) with epithelial ovarian cancer\(^1\), pancreatic cancer, or prostate 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,\(^4\) or no family history available because member is adopted.

C. Breast cancer is diagnosed at age 60 years or younger, and is triple negative.\(^8\)

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

1. at least 2 close blood relatives\(^3\) on the same side of the family with breast cancer and/or epithelial ovarian cancer\(^1\) at any age; or
2. the member has 2 breast primaries\(^5\) 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\(^5\) and also has at least 1 close blood relative\(^3\) with epithelial ovarian cancer; or
4. at least 1 close male blood relative\(^3\) with breast cancer; or
5. at least 1 1st-, 2nd-, or 3rd-degree blood relative with a known BRCA1 or BRCA2 mutation\(^9\); or
6. 2 close relatives\(^1\) 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.\(^6\)

III. Women with a personal history of pancreatic adenocarcinoma at any age with 2 close relatives\(^3\) on the
side 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); 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.

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. For purposes of BRCA testing criteria, half-siblings would be considered first-degree relatives.
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).

10. As an exception to this rule, repeat BRCA testing with BRACAnalysis CDx (Myriad Genetics) is considered medically necessary for women with ovarian cancer who had another brand of BRCA test and who are being considered for treatment with olaparib (Lynparaza) after three or more previous lines of chemotherapy. Repeat BRCA testing with FoundationFocus CDxBRCA (Foundation Medicine) is considered medically necessary for women with ovarian cancer who had another brand of BRCA test and who are being considered for treatment with rucaparib (Rubraca) after two or more previous lines of chemotherapy.

See CPB 715 - Pharmacogenetic and Pharmacodynamic Testing (../700_799/0715.html).

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.

**Elective Salpingectomy for Ovarian Cancer Prevention in Low Hereditary Risk Women:**

Aetna considers elective salpingectomy for ovarian cancer prevention in low hereditary risk women experimental and investigational because of insufficient evidence of its effectiveness.
Aetna considers multigene hereditary cancer panels that accompany BRCA testing (e.g., MyRisk (Myriad Genetics), BRCAPlus (Ambry Genetics), BRCAvantage Plus (Quest Diagnostics), High Risk Hereditary Breast Cancer (Invitae), OncoGeneDx Comprehensive Cancer Panel (GeneDx), and OncoGeneDx High/Moderate Risk Panel) experimental and investigational because there is insufficient published evidence of their clinical validity and utility. However, the BRCA testing portion of these panels are considered medically necessary if the above outlined criteria are met.

Aetna members may NOT be eligible under the Plan for genetic testing for breast and/or ovarian cancer susceptibility for indications or tests other than those listed above including, but may not be limited to, the following:

- Any of the following genes, alone or as part of a panel:
  ATM, BARD1, BRIP1, CHEK2, Mre11 (MRN) complex, NBN, PALB2, RAD50 or RAD51 paralogs (ie, RAD51C or RAD51D), and STK11.
- Any of the following genes as part of a breast or ovarian cancer panel: CDH1, MUTYH (but see CPB 140 - Genetic Testing, for medical necessity criteria for CDH1 and MUTYH).
- Multigene panels (including next-generation sequencing [NGS]) for breast and/or ovarian cancer susceptibility including, but may not be limited to, the following:
  - BRCAPlus
  - BRCAvantage Plus
  - BRCAvantage with Reflex to Breast Plus Panel
  - Breast Plus Panel without BRCA
  - BreastNext
  - BreastTrue High Risk Panel
  - Color Test
  - GYNplus
  - Invitae Breast and Gyn Cancers Panel Invitae
  - Breast Cancer Guidelines-Based Panel
• Invitae Breast Cancer High-Risk Panel
• Invitae Breast Cancer Panel
• OncoGeneDx Breast Cancer High/Moderate Risk Panel
• OncoGeneDx Breast Cancer High Risk Panel
• OncoGeneDx Breast Cancer High Risk Panel and PALB2
• OncoGeneDx Breast/Ovarian Cancer Panel
• OvaNext; OR
• Single nucleotide polymorphism (SNP) genotyping tests (eg, BREVAGen, OncoVue)

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:

- 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.
- 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).

- 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).

- 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 Services Task Force (2005).

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 and BRCA2 (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 rearrangements 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 Mastectomy**

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 ductal 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 (2015) 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 (odds ratios [OR]
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 failures 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 states 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.”

Wong and colleagues (2016) updated and examined national temporal trends in contralateral prophylactic mastectomy (CPM) and examined if survival differed for invasive breast cancer patients based on hormone receptor status and age. These investigators identified women diagnosed with unilateral stage I to III breast cancer between 1998 and 2012 within the Surveillance, Epidemiology, and End Results registry. They compared characteristics and temporal trends between patients undergoing breast-conserving surgery, unilateral mastectomy, and CPM. These researchers then performed Cox proportional-hazards regression to examine breast cancer-specific survival (BCSS) and overall survival (OS) in women diagnosed between 1998 and 2007, who underwent breast-conserving surgery with radiation (breast-conserving therapy), unilateral mastectomy, or CPM, with subsequent subgroup
analysis stratifying by age and hormone receptor status. Of 496,488 women diagnosed with unilateral invasive breast cancer, 59.6 % underwent breast-conserving surgery, 33.4 % underwent unilateral mastectomy, and 7.0 % underwent CPM. Overall, the proportion of women undergoing CPM increased from 3.9 % in 2002 to 12.7 % in 2012 (p < 0.001).

Reconstructive surgery was performed in 48.3 % of CPM patients compared with only 16.0 % of unilateral mastectomy patients, with rates of reconstruction with CPM rising from 35.3 % in 2002 to 55.4 % in 2012 (p < 0.001). When compared with breast-conserving therapy, these researchers found no significant improvement in BCSS or OS for women undergoing CPM (BCSS: HR 1.08, 95 % CI: 1.01 to 1.16; OS: HR 1.08, 95 % CI: 1.03 to 1.14), regardless of hormone receptor status or age. The authors concluded that the use of CPM more than tripled during the study period despite evidence suggesting no survival benefit over breast conservation. They stated that further examination on how to optimally counsel women about surgical options is needed.

Atypical Ductal Hyperplasia:

Prpic et al (1992) stated that the majority of benign breast disorders may be classified as developmental and involutive. Mastalgia and breast nodularity represent the greatest groups of these disorders, while epithelial hyperplasia is a complex benign disorder that is most difficult to be evaluated. A total of 60 women with diagnosis of cyclic mastalgia and 30 with non-cyclic breast pain were followed-up. Patients were administered bromocryptine, danazol or a local progestogel. Better treatment results were achieved in cyclic mastalgia than in women with non-cyclic mastalgia; 145 biopsies of the benign breast tissue were examined histologically. Non-proliferative forms were found in 66.9 % of the women, proliferative without atypia in 29.65 %, and proliferative with atypia in 3.45 % of the patients. The authors concluded that atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) increased 4- to 5-fold the risk for breast cancer. However, they stated that prophylactic subcutaneous or total mastectomy is
not as a rule indicated in atypical epithelial hyperplasia, only regular follow-up is required.

Hartmann et al (2015) noted that “NCCN guidelines state that bilateral prophylactic mastectomy should generally be considered only for women who have a genetic predisposition to breast cancer or possibly those who have been treated with thoracic radiation before 30 years of age or who have a history of lobular carcinoma in situ. The Society of Surgical Oncology recognizes atypical hyperplasia as a possible but not routine indication for bilateral prophylactic mastectomy. In one small, retrospective study, atypical hyperplasia was the indication for the procedure in 11 of 46 patients (24 %) who had not undergone BRCA testing and were undergoing risk-reduction surgery. In current practice, with minimal data available on this topic and with chemopreventive agents for risk reduction available, atypical hyperplasia is generally not an indication for prophylactic mastectomy”.

Furthermore, an UpToDate review on “Atypia and lobular carcinoma in situ: High risk lesions of the breast” (Sable and Collins, 2016) states that “Atypical hyperplasia (AH) includes both atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH). ADH is usually found as the target lesion on biopsy of mammographic microcalcifications whereas ALH is usually an incidental finding on breast biopsies performed for other reasons (e.g., abnormal mammogram, breast mass) …. If AH is diagnosed on an excisional biopsy, no additional surgery is indicated. Even if the atypical hyperplasia extends to the margins, as long as the area was adequately sampled, re-excision is not recommended. Instead, attention should be directed towards risk reduction …. Breast cancer surveillance is performed for all women known to be at an increased risk of breast cancer (e.g., positive family history of breast cancer, atypical hyperplasia, LCIS) as well as those at population risk …. Most experts consider prophylactic bilateral mastectomy too drastic for the moderate level of risk associated with LCIS in the absence of other contributory risk factors (e.g., family history premenopausal breast cancer)”.

The review does not mention
prophylactic mastectomy for atypical ductal hyperplasia.

**Pseudo-Angiomatous Stromal Hyperplasia (PASH):**

An UpToDate review on “Overview of benign breast disease” (Sable, 2016) states that “Pseudoangiomatous stromal hyperplasia -- Pseudoangiomatous stromal hyperplasia (PASH) is a benign stromal proliferation that simulates a vascular lesion. PASH may present as a mass or thickening on physical examination. The most common appearance on mammography and ultrasound is a solid, well-defined, non-calcified mass. The characteristic histologic appearance is a pattern of slit-like spaces in the stroma between glandular units. PASH can be confused with mammary angiosarcoma. If there are any suspicious features on imaging, the diagnosis of PASH on a core biopsy should not be accepted as a final diagnosis, and excisional biopsy should be performed. However, in the absence of suspicious imaging characteristics, a diagnosis of PASH at core biopsy is considered sufficient, and surgical excision is not always necessary. There is no increased risk of subsequent breast cancer associated with PASH”. The review does not mention prophylactic mastectomy as a management option.

**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 occurs 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 organs. 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”.

Elective Salpingectomy for Ovarian Cancer Prevention in Low Hereditary Risk Women:

Walker et al (2015) stated that mortality from ovarian cancer may be dramatically reduced with the implementation of attainable prevention strategies. The new understanding of the cells of origin and the molecular etiology of ovarian cancer
warrants a strong recommendation to the public and health care providers. These researchers discussed potential prevention strategies, which include (i) oral contraceptive use, (ii) tubal sterilization, (iii) risk-reducing salpingo-oophorectomy in women at high hereditary risk of breast and ovarian cancer, (iv) genetic counseling and testing for women with ovarian cancer and other high-risk families, and (v) salpingectomy after child-bearing is complete (at the time of elective pelvic surgeries, at the time of hysterectomy, and as an alternative to tubal ligation). The authors stated that the Society of Gynecologic Oncology has determined that recent scientific breakthroughs warranted a new summary of the progress toward the prevention of ovarian cancer. This review was intended to emphasize the importance of the fallopian tubes as a potential source of high-grade serous cancer in women with and without known genetic mutations in addition to the use of oral contraceptive pills to reduce the risk of ovarian cancer.

Furthermore, based on the current understanding of ovarian carcinogenesis and the safety of salpingectomy, the ACOG (2015) supports the following recommendations and conclusions:

- The surgeon and patient should discuss the potential benefits of the removal of the fallopian tubes during a hysterectomy in women at population risk of ovarian cancer who are not having an oophorectomy.
- When counseling women about laparoscopic sterilization methods, clinicians can communicate that bilateral salpingectomy can be considered a method that provides effective contraception.
- Prophylactic salpingectomy may offer clinicians the opportunity to prevent ovarian cancer in their patients.
- Randomized controlled trials are needed to support the validity of this approach to reduce the incidence of ovarian cancer.

An UpToDate review on “Management of patients with hereditary and/or familial breast and ovarian cancer” (Isaacs
and Peshkin, 2016) states that “The only proven risk-reducing procedure for ovarian cancer in BRCA mutation carriers is bilateral salpingo-oophorectomy [BSO]. However, there is controversy about whether it is appropriate to perform a salpingectomy alone for BRCA mutation carriers who wish to defer oophorectomy, based upon a possible fallopian tube origin for some ovarian cancers. The Society of Gynecology Oncology (SGO) Clinical Practice Statement opens with the statement: "Salpingectomy may be appropriate and feasible as a strategy for ovarian risk reduction". However, the statement and a lengthier explication make clear that this procedure does not eliminate the risk of ovarian cancer, and it does not reduce the risk of breast cancer. Guidelines from the National Comprehensive Cancer Network thus indicate that "salpingectomy alone is not the standard of care and is discouraged outside a clinical trial". Until there are sufficient data from randomized control trials or prospective studies to support salpingectomy as an effective risk-reducing procedure for BRCA mutation carriers, we recommend against salpingectomy without an oophorectomy for these women”.

Kapurubandara et al (2015) stated that recent evidence supports the fallopian tube as the site of origin for many pelvic serous cancers (PSC) including epithelial ovarian cancers (EOC). As a result, a change in practice with opportunistic bilateral salpingectomy (OBS) at the time of hysterectomy has been advocated as a preventative strategy for PSC in a low-risk population. These investigators evaluated current clinical practice in Australia with respect to OBS during gynecological surgery for benign indications. An anonymous online survey was sent to all active Royal Australian and New Zealand College of Obstetrics and Gynecology (RANZCOG) Fellows in Australia. Data regarding clinician demographics and the proportion of clinicians offering OBS were collected. Reasons for and against offering or discussing OBS were sought. A descriptive analysis was performed. The response rate was 26 % (280/1,490) with 70 % of respondents offering or discussing OBS to women undergoing gynecological surgery for benign indications, usually at the time of abdominal (96 %) or laparoscopic (76 %)
hysterectomy. The main reason for offering or discussing OBS was current evidence to suggest the fallopian tubes as the site of origin for most EOC. Main reasons for not offering OBS were insufficient evidence to benefit the woman (36%) or being unaware of recent evidence (33%). The authors concluded that the survey responses indicated that OBS is frequently discussed or offered in Australia, usually at the time of hysterectomy. They stated that given the lack of robust evidence to suggest a benefit at a population-based level, a national registry is recommended to monitor outcomes.

Chene and colleagues (2016) noted that since the recent evidence of a tubal origin of most ovarian cancers, opportunistic salpingectomy could be discussed as a prophylactic strategy in the general population and with hereditary predisposition. These researchers surveyed French gynecological surgeons about their current surgical practice of prophylactic salpingectomy. An anonymous online survey was sent to French obstetrician-gynecologists and gynecological surgeons. There were 13 questions about their current clinical practice and techniques of salpingectomy during a benign hysterectomy or as a tubal sterilization method, salpingectomy versus salpingo-oophorectomy in the population with genetic risk, salpingectomy in relationship with endometriosis and questions including histopathological considerations. Among the 569 respondents, opportunistic salpingectomy was always performed between 42.48% and 43.44% during laparoscopic, laparoscopic-assisted vaginal or laparotomic hysterectomy and only 12.26% in case of vaginal route. In the genetic population, salpingo-oophorectomy was mainly performed. Tubal sterilization was often practiced by the hysteroscopic route. More than 90% of respondents didn't perform salpingectomy in case of endometriosis. There was not any specific tubal histopathological protocol in 71.54% of cases. The authors concluded that salpingectomy may be a preventing strategy in the low- and high-risk population. The survey's responses showed that salpingectomy appeared to be a current practice during benign hysterectomy for more than 40% doctors. However, there was not any change with no more
salpingectomy in the population with genetic risk, or in case of endometriosis or tubal sterilization.

Furthermore, National Comprehensive Cancer Network’s clinical practice guideline on “Ovarian cancer” (Version 1.2016) stated that “The prevention benefit of salpingectomy alone are not yet proven”.

Multigene Breast and Ovarian Cancer Panels:

Cancer predisposing genes can be categorized according to their relative risk of a particular type of cancer. High-penetrant genes are associated with a cancer relative risk higher than 5. Low-penetrant genes are presented with relative risk around 1.5, whereas moderate-penetrant genes confer relative cancer risks from 1.5 to 5. Rare moderate-penetrant genes are CHEK2, ATM, BRIP1, and PALB2 (KCE, 2015). Recent data suggest that the penetrance of PALB2 may be higher than reported before and that BRIP may be associated with increased risk of ovarian cancer only. The clinical implications of moderate-risk genes remain unclear. This has been attributed to the fact that moderate risk breast cancer susceptibility genes typically are encountered in a polygenic setting, meaning that several common low-risk breast cancer susceptibility alleles together confer increased breast cancer risks. When they do operate in a monogenic setting, their functional or clinical impact could be low (KCE, 2015).

Aloraifi and colleagues (2015) noted that several "moderate-risk breast cancer susceptibility genes" have been conclusively identified. Pathogenic mutations in these genes are thought to cause a 2- to 5-fold increased risk of breast cancer. In light of the current development and use of multi-gene panel testing, these researchers estimated the cancer risk associated with loss-of-function mutations within these genes. An electronic search was conducted to identify studies that sequenced the full coding regions of ATM, CHEK2, BRIP1, PALB2, NBS1, and RAD50 in a general and gene-targeted approach. Inclusion was restricted to studies that sequenced the germline DNA in both
high-risk cases and geographically matched controls. A meta-analysis was then performed on protein-truncating variants (PTVs) identified in the studies for an association with breast cancer risk. A total of 10,209 publications were identified, of which 64 studies comprising a total of 25,418 cases and 52,322 controls in the 6 interrogated genes were eligible under the study's selection criteria. The pooled ORs for PTVs in the susceptibility genes were at least greater than 2.6. Furthermore, mutations in these genes have shown geographic and ethnic variation. The authors concluded that the finding of this comprehensive study emphasized the fact that caution should be taken when identifying certain genes as moderate susceptibility with the lack of sufficient data, especially with regard to the NBS1, RAD50, and BRIP1 genes. They stated that further data from case-control sequencing studies, and especially family studies, are needed.

Winship and Southey (2016) noted that inherited predisposition to breast cancer is explained only in part by mutations in the BRCA1 and BRCA2 genes. Most families with an apparent familial clustering of breast cancer who are investigated through Australia's network of genetic services and familial cancer centers do not have mutations in either of these genes. More recently, additional breast cancer predisposition genes, such as PALB2, have been identified. New genetic technology allows a panel of multiple genes to be tested for mutations in a single test. This enables more women and their families to have risk assessment and risk management, in a preventive approach to predictable breast cancer. Predictive testing for a known family-specific mutation in a breast cancer predisposition gene provides personalized risk assessment and evidence-based risk management. Breast cancer predisposition gene panel tests have a greater diagnostic yield than conventional testing of only the BRCA1 and BRCA2 genes. However, the clinical validity and utility of some of the putative breast cancer predisposition genes is not yet clear. The authors stated that ethical issues warrant consideration, as multiple gene panel testing has the potential to identify secondary findings not originally sought by the test requested; multiple
gene panel tests may provide an affordable and effective way to investigate the heritability of breast cancer.

Thompson and colleagues (2016) stated that gene panel sequencing is revolutionizing germline risk assessment for hereditary breast cancer. Despite scant evidence supporting the role of many of these genes in breast cancer predisposition, results are often reported to families as the definitive explanation for their family history. These investigators evaluated the frequency of mutations in 18 genes included in hereditary breast cancer panels among index cases from families with breast cancer and matched population controls. Cases (n = 2,000) were predominantly breast cancer-affected women referred to specialized Familial Cancer Centers on the basis of a strong family history of breast cancer and BRCA1 and BRCA2 wild type. Controls (n = 1,997) were cancer-free women from the LifePool study. Sequencing data were filtered for known pathogenic or novel loss-of-function mutations. Excluding 19 mutations identified in BRCA1 and BRCA2 among the cases and controls, a total of 78 cases (3.9 %) and 33 controls (1.6 %) were found to carry potentially actionable mutations. A significant excess of mutations was only observed for PALB2 (26 cases, 4 controls) and TP53 (5 cases, 0 controls), whereas no mutations were identified in STK11. Among the remaining genes, loss-of-function mutations were rare, with similar frequency between cases and controls. The authors concluded that the frequency of mutations in most breast cancer panel genes among individuals selected for possible hereditary breast cancer is low and, in many cases, similar or even lower than that observed among cancer-free population controls. They noted that although multigene panels can significantly aid in cancer risk management and expedite clinical translation of new genes, they equally have the potential to provide clinical misinformation and harm at the individual level if the data are not interpreted cautiously.

Young and associates (2016) noted that moderate-risk genes have not been extensively studied, and missense substitutions in them are generally returned to patients as variants of
uncertain significance lacking clearly defined risk estimates. The fraction of early-onset breast cancer cases carrying moderate-risk genotypes and quantitative methods for flagging variants for further analysis have not been established. These researchers evaluated rare missense substitutions (rMS) identified from a mutation screen of ATM, CHEK2, MRE11A, RAD50, NBN, RAD51, RINT1, XRCC2 and BARD1 in 1,297 cases of early-onset breast cancer and 1,121 controls via scores from Align-Grantham Variation Grantham Deviation (GVGD), combined annotation dependent depletion (CADD), multivariate analysis of protein polymorphism (MAPP) and PolyPhen-2. They also evaluated subjects by polygenotype from 18 breast cancer risk SNPs. From these analyses, these investigators estimated the fraction of cases and controls that reach a breast cancer OR of greater than or equal to 2.5 threshold. Analysis of mutation screening data from the 9 genes revealed that 7.5 % of cases and 2.4 % of controls were carriers of at least 1 rare variant with an average OR of greater than or equal to 2.5. 2.1 % of cases and 1.2 % of controls had a polygenotype with an average OR of greater than or equal to 2.5. The authors concluded that among early-onset breast cancer cases, 9.6 % had a genotype associated with an increased risk sufficient to affect clinical management recommendations. Over 2/3 of variants conferring this level of risk were rMS in moderate-risk genes. Placement in the estimated OR of greater than or equal to 2.5 group by at least 2 of these missense analysis programs should be used to prioritize variants for further study; panel testing often creates more heat than light; quantitative approaches to variant prioritization and classification may facilitate more efficient clinical classification of variants.

The authors also stated that “Our analysis raised additional questions regarding standard clinical genetic testing practices using panel tests. For the established moderate-risk genes ATM, CHEK2 and NBN, the majority of the pathogenic variants that the test can actually detect are rMS, likely to be reported to patients as variants of uncertain significance (VUS), and likely to be normalized during counselling. In this circumstance, how
does one answer the clinical validity question, “Are the variants the test is intended to identify associated with disease risk, and are these risks well quantified?” What is the impact on studies intended to explore the penetrance and tumor spectrum of pathogenic variants in these genes if the studies focus on T+SJVs even though these may represent a minority of the pathogenic variants? One path forward lies in a more nuanced use of the IARC 5-class system for variant classification and reporting to incorporate more data from ongoing research on missense substitution evaluation. From work that defined the sequence analysis-based prior probabilities of pathogenicity for rMS in BRCA1, BRCA2 and the mismatch repair genes, one can clearly define subsets of rMS that have relatively high probabilities of pathogenicity. A straightforward approach for clinicians could be to make systematic efforts to enroll carriers of high probability of pathogenicity rMS in research studies, such as those coordinated through the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) consortium, while still describing these findings to patients as VUS. For BRCA1, BRCA2 and the mismatch repair genes, these could be defined as rMS with prior probabilities of pathogenicity of ≥ 0.66 as defined at the calibrated prior probability of pathogenicity websites (priors.hci.utah.edu/PRIORS/index.php and hci-lovd.hci.utah.edu/home.php, respectively). rMS from the nine genes examined here that are placed in an OR ≥ 2.5 grouping by two or more of the missense analysis programs similarly fall into a relatively high probability of pathogenicity subset. VUS with lower probabilities of pathogenicity could reasonably be normalized since future reclassification to a clearly pathogenic variant is rather unlikely. Such an approach would better prioritize those missense substitutions with high probabilities of pathogenicity, leading to better understanding of these VUS by clinicians and patients. This approach should empower research towards gene validation, penetrance and tumor spectrum and thereby address the question of clinical validity in the future”.

Lynce and Isaacs (2016) stated that the traditional model by
which an individual was identified as harboring a hereditary susceptibility to cancer was to test for a mutation in a single gene or a finite number of genes associated with a particular syndrome (e.g., BRCA1 and BRCA2 for hereditary breast and ovarian cancer or mismatch repair genes for Lynch syndrome).

The decision regarding which gene or genes to test for was based on a review of the patient’s personal medical history and their family history. With advances in next-generation DNA sequencing technology, offering simultaneous testing for multiple genes associated with a hereditary susceptibility to cancer is now possible. These panels typically include high-penetrance genes, but they also often include moderate- and low-penetrance genes. A number of the genes included in these panels have not been fully characterized either in terms of their cancer risks or their management options. Another way some patients are unexpectedly identified as carrying a germline mutation in a cancer susceptibility gene is at the time they undergo molecular profiling of their tumor, which typically has been carried out to guide treatment choices for their cancer. The authors focused on the issues that need to be considered when deciding between recommending more targeted testing of a single or a small number of genes associated with a particular syndrome (single/limited gene testing) versus performing a multigene panel. They also reviewed the issues regarding germline risk that occur within the setting of ordering molecular profiling of tumors.

The authors stated that “Although multigene panel testing provides a more comprehensive and efficient approach to testing an individual for a hereditary susceptibility to cancer, the information obtained can be challenging to interpret. Furthermore, many of the genes included in multigene panels have not been fully characterized either in terms of their cancer risks or management strategies. In many cases, single/limited gene testing remains a very appropriate testing option. Presently, we live in an era in which our technical capabilities have outstripped our medical knowledge. A strong and continuous partnership among clinicians, individuals with genetics expertise, and laboratory geneticists is critical to bridge
this gap. As to the detection of incidental findings on tumor sequencing, more research is clearly necessary to better clarify how to approach this complex area. Until such time, as stated by ASCO, it is critical that individuals undergoing tumor sequencing be fully apprised of the possibility, benefits, risks, and limitations that such testing could uncover unanticipated mutations in cancer susceptibility genes”.

An INESSS assessment (2016) concluded that hereditary cancer panels raises questions about surveillance for carriers of deleterious mutations, the risks of invasive interventions following the incidental discovery of mutations, the lack of recommendations for mutations in certain genes, and an increase in the detection of variants of unknown significance (VUS). The assessment noted that several questions remain regarding the management of patients with certain mutations in genes where the mutation is associated with a moderate or uncertain risk of cancer.

Individuals with a PALB2 mutation have an increased lifetime risk for breast, pancreas, and possibly other cancers. PALB2 mutations are rare intermediate-penetrance genes; women with a PALB2 mutation have a 2-4 fold increased lifetime risk of breast cancer compared to the general population risk of 12% (KCE, 2015). However, risks associated with a PALB2 mutation may be higher in persons with a family history of breast cancer. The PALB2 mutation works in conjunction with other cancer susceptibility genes to modify risk; the exact lifetime cancer risks for individuals with one mutation in this gene are not fully understood. There is a lack of adequate evidence on the clinical utility of testing for PALB2 mutations; it is not known whether enhanced surveillance or preventative measures in persons with PALB2 mutations will lead to improved health outcomes.

Testing for BARD 1 and RAD51D Mutations for Ovarian Cancer:

Loveday et al (2011) stated that recently, RAD51C mutations were identified in families with breast and ovarian cancer. This
observation prompted us to investigate the role of RAD51D in cancer susceptibility. These researchers identified 8 inactivating RAD51D mutations in unrelated individuals from 911 breast-ovarian cancer families compared with one inactivating mutation identified in 1,060 controls (p = 0.01). The association found here was principally with ovarian cancer, with 3 mutations identified in the 59 pedigrees with 3 or more individuals with ovarian cancer (p = 0.0005). The relative risk of ovarian cancer for RAD51D mutation carriers was estimated to be 6.30 (95% confidence interval [CI]: 2.86 to 13.85, p = 4.8 × 10(-6)). By contrast, these investigators estimated the relative risk of breast cancer to be 1.32 (95% CI: 0.59 to 2.96, p = 0.50). The authors concluded that these data indicated that RAD51D mutation testing may have clinical utility in individuals with ovarian cancer and their families. Moreover, they showed that cells deficient in RAD51D are sensitive to treatment with a PARP inhibitor, suggesting a possible therapeutic approach for cancers arising in RAD51D mutation carriers.

Ratajska et al (2012) stated that the breast cancer susceptibility gene BARD1 (BRCA1-associated RING domain protein, MIM# 601593) acts with BRCA1 in DNA double-strand break (DSB) repair and also in apoptosis initiation. These researchers screened 109 BRCA1/2 negative high-risk breast and/or ovarian cancer patients from North-Eastern Poland for BARD1 germline mutations using a combination of denaturing high-performance liquid chromatography and direct sequencing. They identified 16 different BARD1 sequence variants, 5 of which are novel. Three of them were suspected to be pathogenic, including a protein truncating nonsense mutation (c.1690C>T, p.Gln564X), a splice mutation (c.1315-2A>G) resulting in exon 5 skipping, and a silent change (c.1977A>G) which alters several exonic splicing enhancer motifs in exon 10 and resulted in a transcript lacking exons 2-9. The authors concluded that these findings suggested that BARD1 mutations may be regarded as cancer risk alleles and warrant further investigation to determine their actual contribution to non-BRCA1/2 breast and ovarian cancer families.
Thompson et al (2013) stated that mutations in RAD51D have been associated with an increased risk of hereditary ovarian cancer and although they have been observed in the context of breast and ovarian cancer families, the association with breast cancer is unclear. These researchers attempted to validate the reported association of RAD51D with ovarian cancer and assessed for an association with breast cancer. They screened for RAD51D mutations in BRCA1/2 mutation-negative index cases from 1,060 familial breast and/or ovarian cancer families (including 741 affected by breast cancer only) and in 245 unselected ovarian cancer cases. Exons containing novel non-synonymous variants were screened in 466 controls. Two overtly deleterious RAD51D mutations were identified among the unselected ovarian cancer cases (0.82 %) but none was detected among the 1,060 families. The authors concluded that these data provided additional evidence that RAD51D mutations are enriched among ovarian cancer patients, but are extremely rare among familial breast cancer patients.

Huang et al (2013) noted that homologous recombination mediates error-free repair of DNA double-strand breaks (DSB). RAD51 is an essential protein for catalyzing homologous recombination and its recruitment to DSBs is mediated by many factors including RAD51, its paralogs, and breast/ovarian cancer susceptibility gene products BRCA1/2. Deregulation of these factors leads to impaired DNA repair, genomic instability, and cellular sensitivity to chemotherapeutics such as cisplatin and PARP inhibitors. MicroRNAs (miRNA) are short, non-coding RNAs that post-transcriptionally regulate gene expression; however, the contribution of miRNAs in the regulation of homologous recombination is not well understood. To address this, a library of human miRNA mimics was systematically screened to pinpoint several miRNAs that significantly reduce RAD51 foci formation in response to ionizing radiation in human osteosarcoma cells. Subsequent study focused on 2 of the strongest candidates, miR-103 and miR-107, as they are frequently deregulated in cancer. Consistent with the inhibition of RAD51 foci formation, miR-103 and miR-107 reduced homology-directed repair and sensitized cells to various
DNA-damaging agents, including cisplatin and a PARP inhibitor. Mechanistic analyses revealed that both miR-103 and miR-107 directly target and regulate RAD51 and RAD51D, which is critical for miR-103/107-mediated chemo-sensitization. Furthermore, endogenous regulation of RAD51D by miR-103/107 was observed in several tumor subtypes. The authors concluded that taken together, these data showed that miR-103 and miR-107 over-expression promoted genomic instability and may be used therapeutically to chemo-sensitize tumors.

UpToDate reviews on “Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Clinical features and diagnosis” (Chen and Berek, 2016), “Neoadjuvant chemotherapy for newly diagnosed advanced ovarian cancer” (Konstantinopoulos and Bristow, 2016) do not mention the use of BARD1 and RAD51D mutation testing.

The National Comprehensive Cancer Network’s clinical practice guideline on “Ovarian cancer” (Version 2.2015) does not mention the use of BARD1 and RAD51D mutation testing.

**CHEK2 Mutation Testing:**

Myszka and associates (2011) noted that CHEK2 gene encodes cell cycle checkpoint kinase 2 that participates in the DNA repair pathway, cell cycle regulation and apoptosis. Mutations in CHEK2 gene may result in kinase inactivation or reduce both catalytic activity and capability of binding other proteins. Some studies indicated that alterations in CHEK2 gene confers increase the risk of breast cancer and some other malignancies, while the results of other studies are inconclusive. Thus, the significance of CHEK2 mutations in etiology of breast cancer is still debatable. These researchers evaluated the relationship between the breast/ovarian cancer and CHEK2 variants by: (i) the analysis of the frequency of selected CHEK2 variants in breast and ovarian cancer patients compared to the controls; and (ii) evaluation of relationships between the certain CHEK2 variants and clinico-histopathological and pedigree data. The
study was performed on 284 breast cancer patients, 113 ovarian cancer patients, and 287 healthy women. These investigators revealed the presence of 430T > C, del5395 and IVS2 + 1G > A variants; but not 1100delC in individuals from both study and control groups. The authors did not observe significant differences between cancer patients and controls neither in regard to the frequency nor to the type of CHEK2 variants.

Liu and colleagues (2012) stated that CHEK2 gene I157T variant may be associated with an increased risk of breast cancer, but it is unclear if the evidence is sufficient to recommend testing for the mutation in clinical practice. In a systematic review, these investigators systematically searched PubMed, Embase, Elsevier and Springer for relevant articles published before November 2011. Summary OR and 95 % CI incidence rates were calculated using a random-effects model with STATA (version 10.0) software. A total of 15 case-control studies, including 19,621 cases and 27,001 controls based on the search criteria, were included for analysis. A significant association was found between carrying the CHEK2 I157T variant and increased risk of unselected breast cancer (OR = 1.48, 95 % CI: 1.31 to 1.66, p < 0.0001), familial breast cancer (OR = 1.48, 95 % CI: 1.16 to 1.89, p < 0.0001), and early-onset breast cancer (OR = 1.47, 95 % CI: 1.29 to 1.66, p < 0.0001). These researchers found an even stronger significant association between the CHEK2 I157T C variant and increased risk of lobular type breast tumors (OR = 4.17, 95 % CI: 2.89 to 6.03, p < 0.0001). The authors concluded that their research indicated that the CHEK2 I157T variant may be another important genetic mutation which increases risk of breast cancer, especially the lobular type. The methodological quality of this systematic review/meta-analysis was limited; the evidence was not quality appraised for risk of bias.

Young and co-workers (2012) noted that links between the CHEK2 1100delC heterozygote and breast cancer risk have been extensively explored. However, both positive and negative associations with this variant have been reported in individual studies. For a detailed assessment of the CHEK2 1100delC
heterozygote and breast cancer risk, relevant studies published as recently as May 2012 were identified using PubMed and Embase and selected using a priori defined criteria. The strength of the relationship between the CHEK2 1100delC variant and breast cancer risks was assessed by ORs under the fixed effects model. A total of 29,154 cases and 37,064 controls from 25 case-control studies were identified in this meta-analysis. The CHEK2 1100delC heterozygote was more frequently detected in cases than in controls (1.34 % versus 0.44 %). A significant association was found between CHEK2 1100delC heterozygote and breast cancer risk (OR = 2.75, 95 % CI: 2.25 to 3.36). The ORs and CIs were 2.33 (95 % CI: 1.79 to 3.05), 3.72 (95 % CI: 2.61 to 5.31)) and 2.78 (95 % CI: 2.28 to 3.39), respectively in unselected, family, early-onset breast cancer subgroups. The authors concluded that the CHEK2 1100delC variant could be a potential factor for increased breast cancer risk in Caucasians. However, more consideration is needed in order to apply it to allele screening or other clinical work.

Huzarski et al (2014) estimated the 10-year survival rates for patients with early onset breast cancer, with and without a CHEK2 mutation and identified prognostic factors among CHEK2-positive breast cancer patients. A total of 3,592 women with stage I to stage III breast cancer, diagnosed at or below age 50, were tested for 4 founder mutations in the CHEK2 gene. Information on tumor characteristics and on treatments received was retrieved from medical records. Dates of death were obtained from the Poland Vital Statistics Registry. Survival curves were generated for the mutation-positive and -negative sub-cohorts. Predictors of survival were determined among CHEK2 carriers using the Cox proportional hazards model. Of the 3,592 patients eligible for the study, 140 (3.9 %) carried a CHEK2-truncating mutation and 347 (9.7 %) carried a missense mutation. The mean follow-up was 8.9 years. The 10-year survival for all CHEK2 mutation carriers was 78.8 % (95 % CI: 74.6 to 83.2 %) and for non-carriers was 80.1 % (95 % CI: 78.5 to 81.8 %). Among women with a CHEK2-positive breast cancer, the adjusted HR associated with ER-positive status was
Among women with an ER-positive breast cancer, the adjusted HR associated with a CHEK2 mutation was 1.31 (95% CI: 0.97 to 1.77). The survival of women with breast cancer and a CHEK2 mutation is similar to that of patients without a CHEK2 mutation.

In a cross-sectional study, Tung and colleagues (2015) evaluated the frequency of deleterious germline mutations among individuals with breast cancer who were referred for BRCA1/2 gene testing using a panel of 25 genes associated with inherited cancer predisposition. This study utilized next-generation sequencing (NGS) in 2,158 individuals, including 1,781 who were referred for commercial BRCA1/2 gene testing (cohort 1) and 377 who had detailed personal and family history and had previously tested negative for BRCA1/2 mutations (cohort 2). Mutations were identified in 16 genes, most frequently in BRCA1, BRCA2, CHEK2, ATM, and PALB2. Among the participants in cohort 1, 9.3% carried a BRCA1/2 mutation, 3.9% carried a mutation in another breast/ovarian cancer susceptibility gene, and 0.3% carried an incidental mutation in another cancer susceptibility gene unrelated to breast or ovarian cancer. In cohort 2, the frequency of mutations in breast/ovarian-associated genes other than BRCA1/2 was 2.9%, and an additional 0.8% had an incidental mutation (i.e., mutations were identified in additional genes in 14 women, of which CHEK2 was the most frequent (n = 5), comprising approximately 33% of mutations identified in mutation-positive, BRCA-negative patients). In cohort 1, Lynch syndrome-related mutations were identified in 7 individuals. In contrast to BRCA1/2 mutations, neither age at breast cancer diagnosis nor family history of ovarian or young breast cancer predicted for other mutations. The frequency of mutations in genes other than BRCA1/2 was lower in Ashkenazi Jews compared with non-Ashkenazi individuals (p = 0.026). The authors concluded that using an NGS 25-gene panel, the frequency of mutations in genes other than BRCA1/2 was 4.3%, and most mutations (3.9%) were identified in genes associated with breast/ovarian cancer.
Easton and associates (2015) reported that the magnitude of relative risk of breast cancer associated with CHEK2 truncating mutations is likely to be moderate and unlikely to be high. On the basis of 2 large case-control analyses, these researchers calculated an estimated relative risk of breast cancer associated with CHEK2 mutations of 3.0 (90% CI: 2.6 to 3.5), and an absolute risk of 29% by age 80 years.

Adank et al (2015) stated that in the majority of breast cancer families, DNA testing does not show BRCA1 or BRCA2 mutations and the genetic cause of breast cancer remains unexplained. Routine testing for the CHEK2*1100delC mutation has recently been introduced in breast cancer families in the Netherlands. The 1100delC mutation in the CHEK2-gene may explain the occurrence of breast cancer in about 5% of non-BRCA1/2 families in the Netherlands. In the general population the CHEK2*1100delC mutation confers a slightly increased breast cancer risk, but in a familial breast cancer setting this risk is between 35 to 55% for 1st degree female carriers. Female breast cancer patients with the CHEK2*1100delC mutation are at increased risk of contralateral breast cancer and may have a less favorable prognosis. Female heterozygous CHEK2*1100delC mutation carriers are offered annual mammography and specialist breast surveillance between the ages of 35 to 60 years. The authors concluded that prospective research in CHEK2-positive families is essential in order to develop more specific treatment and screening strategies.

Palmero et al (2016) stated that in Brazil, breast cancer is a public health care problem due to its high incidence and mortality rates. In this study, these researchers investigated the prevalence of hereditary breast cancer syndromes (HBCS) in a population-based cohort in Brazil's southernmost capital, Porto Alegre. All participants answered a questionnaire about family history (FH) of breast, ovarian and colorectal cancer and those with a positive FH were invited for genetic cancer risk assessment (GCRA). If pedigree analysis was suggestive of HBCS, genetic testing of the BRCA1, BRCA2, TP53, and CHEK2 genes was offered. Of 902 women submitted to GCRA, 214 had
pedigrees suggestive of HBCS; 50 of them underwent genetic testing: 18 and 40 for BRCA1/BRCA2 and TP53 mutation screening, respectively, and 7 for CHEK2 1100delC testing. A deleterious BRCA2 mutation was identified in 1 of the HBOC probands and the CHEK2 1100delC mutation occurred in 1 of the HBCC families. No deleterious germline alterations were identified in BRCA1 or TP53. The authors concluded that although strict inclusion criteria and a comprehensive testing approach were used, the suspected genetic risk in these families remains unexplained. They stated that further studies in a larger cohort are needed to better understand the genetic component of hereditary breast cancer in Southern Brazil.

Furthermore, it has been reported that CHEK2 mutations do not contribute substantially to hereditary breast cancer in various ethnic populations such as Greeks (Apostolou et al, 2015), Malaysians (Mohamad et al, 2015), and Moroccans (Marouf et al, 2015).

Available evidence has demonstrated that a CHEK2 mutation is of moderate-penetrance and confers a risk of breast cancer of 2 to 5 times that of the general population. This risk seems to be higher in individuals who also have a family history of breast and/or ovarian cancer; however, accurate risk estimates are subject to bias and over-estimation. Well-designed studies are needed to examine if some patients with a CHEK2 mutation have a risk that is similar to the risk with a high-penetrance mutation and who would be best managed according to established guidelines for high-risk patients. Clinical management recommendations for inherited conditions associated with moderate-penetrance mutations (e.g., BRIP, CHEK2, NBS1, and RAD50) are not standardized, nor is it known if testing for CHEK2 mutations will result in alterations in the management of patient or improved health outcomes. Thus, the available evidence is insufficient to determine the effects of CHEK2 mutation testing on health outcomes.
### CPT Codes / HCPCS Codes / ICD-10 Codes

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":*

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

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>19301</td>
<td>Mastectomy, partial (e.g., lumpectomy, tylectomy, quadrantectomy, segmentectomy)</td>
</tr>
<tr>
<td>19303</td>
<td>Mastectomy, simple, complete</td>
</tr>
<tr>
<td>19304</td>
<td>Mastectomy, subcutaneous</td>
</tr>
<tr>
<td>58150 - 58294</td>
<td>Hysterectomy procedures</td>
</tr>
<tr>
<td>58541 - 58554</td>
<td>Laparoscopy, surgical, with hysterectomy</td>
</tr>
<tr>
<td>58661</td>
<td>Laparoscopy surgical; with removal of adnexal structures (partial or total oophorectomy and / or salpingectomy)</td>
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<td>58700</td>
<td>Salpingectomy, complete or partial, unilateral or bilateral (separate procedure) [not covered for ovarian cancer prevention in low hereditary risk women]</td>
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<td>58720</td>
<td>Salpingo-oophorectomy, complete or partial, unilateral or bilateral (separate procedure)</td>
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<td>58940</td>
<td>Oophorectomy, partial or total, unilateral or bilateral</td>
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<td>Code</td>
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<td>BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)</td>
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<td>BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
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<td>81216</td>
<td>BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis</td>
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<td>BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
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<td>88271</td>
<td>Molecular cytogenetics</td>
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<td>88272</td>
<td>CPT codes not covered for indications listed in the CPB:</td>
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<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence [not covered for multigene hereditary cancer panels that accompany BRCA testing]</td>
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<td>81203</td>
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<td>CPT Code</td>
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<tr>
<td>81432</td>
<td>Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 14 genes, including ATM, BRCA1, BRCA2, BRIP1, CDH1, MLH1, MSH2, MSH6, NBN, PALB2, PTEN, RAD51C, STK11, and TP53</td>
</tr>
<tr>
<td>81433</td>
<td>Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11</td>
</tr>
<tr>
<td>81435</td>
<td>Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11</td>
</tr>
</tbody>
</table>

**Other CPT codes related to the CPB:**

- 58570 - 58573: Laparoscopy, surgical, with total hysterectomy

**ICD-10 codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C25.0 - C25.9</td>
<td>Malignant neoplasm of pancreas</td>
</tr>
<tr>
<td>C48.0 - C48.8</td>
<td>Malignant neoplasm of retroperitoneum and peritoneum</td>
</tr>
<tr>
<td>C50.011 - C50.929</td>
<td>Malignant neoplasm of breast [male/female]</td>
</tr>
<tr>
<td>C56.1 - C56.9</td>
<td>Malignant neoplasm of the ovary [epithelial]</td>
</tr>
<tr>
<td>C57.00 - C57.02</td>
<td>Malignant neoplasm of fallopian tube</td>
</tr>
<tr>
<td>D05.00 - D05.92</td>
<td>Carcinoma in situ, breast [invasive and ductal carcinoma in situ (DCIS) is not included]</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>D24.1 -</td>
<td></td>
</tr>
<tr>
<td>D24.9</td>
<td>Benign neoplasm of breast [pseudo-angiomatous stromal hyperplasia (PASH) –</td>
</tr>
<tr>
<td></td>
<td>not covered for prophylactic mastectomy] [atypical hyperplasia of lobular</td>
</tr>
<tr>
<td></td>
<td>or ductal origin]</td>
</tr>
<tr>
<td>N60.91 -</td>
<td></td>
</tr>
<tr>
<td>N60.99</td>
<td>Unspecified benign mammary dysplasia [atypical hyperplasia of lobular or</td>
</tr>
<tr>
<td></td>
<td>ductal origin]</td>
</tr>
<tr>
<td>Z15.01</td>
<td>Genetic susceptibility to malignant neoplasm of breast [BRCA1 or BRCA2</td>
</tr>
<tr>
<td></td>
<td>mutations confirmed by molecular susceptibility testing for breast cancer]</td>
</tr>
<tr>
<td></td>
<td>[genetic mutation in the TP53 or PTEN genes (Li-Fraumeni syndrome, Cowden</td>
</tr>
<tr>
<td></td>
<td>syndrome, and Bannayan-Riley-Ruvalcaba syndrome)]</td>
</tr>
<tr>
<td>Z15.02</td>
<td>Genetic susceptibility to malignant neoplasm of ovary [BRCA1 or BRCA2</td>
</tr>
<tr>
<td></td>
<td>mutations confirmed by molecular susceptibility testing for ovarian cancer]</td>
</tr>
<tr>
<td>Z40.01</td>
<td>Encounter for prophylactic removal of breast</td>
</tr>
<tr>
<td>Z40.02</td>
<td>Encounter of prophylactic removal of ovary</td>
</tr>
<tr>
<td>Z80.0</td>
<td>Family history of malignant neoplasm of digestive organs [pancreas]</td>
</tr>
<tr>
<td>Z80.3</td>
<td>Family history of malignant neoplasm of breast</td>
</tr>
<tr>
<td>Z80.41</td>
<td>Family history of malignant neoplasm of ovary [epithelial]</td>
</tr>
<tr>
<td>Z85.07</td>
<td>Personal history of malignant neoplasm of pancreas</td>
</tr>
</tbody>
</table>

**ICD-10 codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C00.1 -</td>
<td></td>
</tr>
<tr>
<td>C24.9,</td>
<td></td>
</tr>
<tr>
<td>C26.0 -</td>
<td></td>
</tr>
<tr>
<td>C47.9,</td>
<td></td>
</tr>
<tr>
<td>C49.0 -</td>
<td></td>
</tr>
<tr>
<td>C49.9,</td>
<td></td>
</tr>
<tr>
<td>C51.0 -</td>
<td></td>
</tr>
<tr>
<td>C55,</td>
<td></td>
</tr>
<tr>
<td>C57.10 -</td>
<td></td>
</tr>
<tr>
<td>D09.9</td>
<td>Malignant neoplasms [other than breast, ovary, pancreas, retroperitoneum</td>
</tr>
<tr>
<td></td>
<td>and peritoneum, breast, ovary, fallopian tube, and carcinoma in situ of</td>
</tr>
<tr>
<td></td>
<td>breast]</td>
</tr>
<tr>
<td>N60.11 -</td>
<td></td>
</tr>
<tr>
<td>N60.19</td>
<td>Diffuse cystic mastopathy [fibrocystic breast disease - not covered for</td>
</tr>
<tr>
<td></td>
<td>prophylactic mastectomy]</td>
</tr>
</tbody>
</table>
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).


20. American College of Medical Genetics Foundation. Genetic susceptibility to breast and ovarian cancer: assessment, counseling, and testing guidelines. Albany,


32. Drucker L, Stackievitz R, Shpitz B, Yarkoni S. Incidence of


60. Brozek I, Ochman K, Deblniak J, et al. High frequency of


69. U.S. Food and Drug Administration (FDA). FoundationFocus CDxBRCA next generation sequencing oncology panel, somatic or germline variant detection system. PMA No. P160018. Silver Spring, MD: FDA; December 19, 2016.


47. Sabel MS. Overview of benign breast disease. UpToDate Inc., Waltham, MA. Last reviewed January 2016.


23. Eisen A, Rebbeck TR, Wood WC, Weber BL. Prophylactic surgery in women with a hereditary predisposition to


33. Agencia de Evaluacion de Tecnologias Sanitarias de Andalucia (AETSA). Preventive mastectomy and oophorectomy in women who carry mutations in BRCA


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


Elective Salpingectomy for Ovarian Cancer Prevention in Low Hereditary Risk Women

3. Isaacs C, Peshkin BN. Management of patients with hereditary and/or familial breast and ovarian cancer. UpToDate Inc., Waltham, MA. Last reviewed January 2016.


Testing for BARD 1 and RAD51D Mutations for Ovarian Cancer


CHEK2 Mutation Testing

11. Palmero EI, Alemar B, Schüler-Faccini L, et al. Screening for germline BRCA1, BRCA2, TP53 and CHEK2 mutations in families at-risk for hereditary breast cancer identified

Multigene Breast and Ovarian Cancer Panels


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Amendment to
Aetna Clinical Policy Bulletin Number: CPB 0227
BRCA Testing, Prophylactic Mastectomy, and Prophylactic Oophorectomy

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania
Updated 05/2017