



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Genetic Testing for Susceptibility to Breast and Ovarian Cancer (e.g., BRCA1 & BRCA2)

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- Tumor Markers for Diagnosis and Management of Cancer

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Coverage Policy

CIGNA covers BRCA1 and BRCA2 genetic testing for susceptibility to breast or ovarian cancer in adults as medically necessary for ANY of the following:

- biologically-related individual from a family with a known BRCA1 or BRCA2 mutation
- personal history of breast cancer and ANY of the following:
 - diagnosed at age 45 or younger
 - diagnosed at age 50 or younger with EITHER of the following:
 - at least one close blood relative* with breast cancer at age 50 or younger
 - at least one close blood relative* with epithelial ovarian, fallopian tube, or primary peritoneal cancer
 - diagnosed with two breast primaries (includes bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors) when the first breast cancer diagnosis occurred prior to age 50
 - diagnosed at age 60 or younger with a triple negative breast cancer

- diagnosed at age 50 or younger with a limited family history (e.g., fewer than two first- or second-degree female relatives or female relatives surviving beyond 45 years in either lineage)
- diagnosed at any age and there are at least two close blood relatives* with breast cancer or epithelial ovarian, fallopian tube, or primary peritoneal cancer at any age
- close male blood relative* with breast cancer
- personal history of epithelial ovarian, fallopian tube, or primary peritoneal cancer
- an individual of ethnicity associated with higher mutation frequency (e.g., founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian or Dutch)
- personal history of epithelial ovarian, fallopian tube, or primary peritoneal cancer
- personal history of male breast cancer
- personal history of breast, ovarian or pancreatic cancer at any age with two or more close blood relatives* with breast, ovarian, or pancreatic cancer at any age
- family history only with EITHER of the following:
 - first or second degree blood relative meeting any of the above criteria
 - third-degree blood relative with two or more close blood relatives* with breast and/or ovarian cancer (with at least one close blood relative with breast cancer prior to age 50)

*A close blood relative/close family member includes first-, second-, and third-degree relatives.

A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children.

A second-degree relative is defined as a blood relative with whom an individual shares approximately 25% of his/her genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings.

A third-degree relative is defined as a blood relative with whom an individual shares approximately 12.5% of his/her genes, including the individual's great-grandparents and first-cousins.

CIGNA covers BRCAAnalysis[®] Rearrangement Test (BART) (Myriad Genetic Laboratories, Inc., Salt Lake City, UT) as medically necessary for ANY of the following:

- breast cancer diagnosed before age 50 and a family history** of EITHER of the following:
 - two or more diagnoses of breast cancer before age 50 (male breast cancer at any age)
 - ovarian cancer at any age
- ovarian cancer diagnosed at any age and a family history** of EITHER of the following:
 - two or more diagnoses of breast cancer before age 50 (male breast cancer at any age)
 - ovarian cancer at any age
- male breast cancer diagnosed at any age and a family history** of EITHER of the following:
 - two or more diagnoses of breast cancer before age 50 (male breast cancer at any age)
 - ovarian cancer at any age
- breast cancer diagnosed at or after age 50 and ovarian cancer at any age and a family history** of EITHER of the following:
 - one or more diagnosis of breast cancer before age 50 (male breast cancer any age)
 - ovarian cancer at any age
- diagnosed with both breast cancer before age 50 and ovarian cancer at any age

**at least one relative must be a first- or second-degree relative and qualifying cancers must be on the same side of the family

CIGNA does not cover BRCA1/BRCA2 genetic testing for susceptibility to breast or ovarian cancer for the following because it is considered not medically necessary or of unproven benefit for these indications (this list may not be all-inclusive):

- genetic screening in the general population
- testing of individuals with no personal history of breast or ovarian cancer, except as noted above
- testing of individuals under 18 years of age

CIGNA does not cover other genetic tests for susceptibility to breast and ovarian cancer (e.g., candidate breast cancer susceptibility genes and single nucleotide polymorphisms [SNPs] testing) because they are considered experimental, investigational or unproven.

All individuals undergoing genetic testing for any reason should have both pre- and post-test genetic counseling with a physician or a licensed or certified genetic counselor.

General Background

Among women, breast cancer is the most commonly diagnosed cancer after non-melanoma skin cancer and is the second leading cause of cancer death after lung cancer. Ovarian cancer is the ninth most common cancer and is noted to be the fifth most deadly (National Cancer Institute [NCI], 2011a). Epithelial ovarian cancer, which is cancer that begins in the cells on the surface of the ovary, comprises the majority of malignant ovarian neoplasm. Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States and its fifth most common cause of cancer mortality in women (National Comprehensive Cancer Network[®] [NCCN[®]], 2011c).

While the vast majority of breast cancer cases do not demonstrate strong familial tendencies, it has been reported that 5–10% are due to inherited forms of the disease, with similar rates reported for ovarian cancer (NCI, 2011a). Several genes associated with the predisposition to breast and ovarian cancers have been identified. Specific genetic mutations found in two autosomal dominant cancer predisposition genes, BRCA1 (BRCA1 Breast Cancer Susceptibility 1) and BRCA2 (BRCA2 Breast Cancer Susceptibility 2), are thought to account for the majority of inherited forms of breast and ovarian cancers. The autosomal dominant inheritance of breast/ovarian cancer is characterized by transmission of the cancer predisposition through either the mother's or father's side of the family. When the parent carries an autosomal dominant genetic predisposition, the child has a 50% chance of inheriting the predisposition. Although the risk of inheriting the predisposition is 50%, not everyone with this predisposition will develop cancer. The risk of developing cancer depends on numerous variables, including the penetrance of the mutation, the gender of the individual and the age of the individual. It is also noted that both males and females can inherit and transmit an autosomal dominant cancer predisposition. The family characteristics that suggest hereditary breast and ovarian cancer predisposition include the following (NCI, 2011a):

- multiple cancers within a family.
- cancers typically occur at an earlier age than in sporadic cases (i.e., cancers not associated with genetic risk)
- two or more primary cancers in a single individual. This could be multiple primary cancers of the same type (e.g., bilateral breast cancer) or primary cancers of different types (e.g., breast and ovarian)
- cases of male breast cancer

Studies indicate that a woman with mutations in either BRCA1 or BRCA2 carries a lifetime breast cancer risk of 45–84%, and an 11–62% cumulative lifetime risk of invasive epithelial ovarian cancer, depending on the population studied (NCCN, 2011b). It is unclear whether the disease expression in mutation carriers is related to the specific mutation identified in a family or whether additional factors, either genetic or environmental, affect the disease expression (NCCN, 2011b). Male carriers of mutations in these genes also have a greater risk of cancer susceptibility.

As the result of cultural and historical factors (e.g., population isolation), certain mutations have been found at higher frequencies in the founder populations of certain ethnic groups. A founder population is created when a small number of individuals from a larger population, carrying only a small fraction of the genetic variation of the original population, establish a new population through their descendents. As a result, the new population may be distinctively different genetically from the original larger population. Three characteristically recurrent BRCA1 and BRCA2 mutations have been identified in Ashkenazi Jewish individuals (i.e., a genetically distinct population of Jewish people of eastern and central European ancestry). Certain founder mutations have also been recognized in other populations (NCCN, 2011b).

The goal of BRCA1 and BRCA2 testing is to provide patients and their physicians with information that will allow them to make informed decisions regarding cancer prevention, screening, surveillance, and treatment options

(e.g., prophylactic surgery). A significant benefit of genetic testing is the ability to quantify cancer risk estimates more precisely, thereby improving the process of determining the most appropriate management strategies in patients who test positive. For patients who test negative, unnecessary treatment (e.g., prophylactic surgery) may be avoided.

There are some histopathologic features that have been noted to occur more frequently in breast cancers that associated with BRCA1 or BRCA2 mutation. Several studies have demonstrated that BRCA1 breast cancer is more likely to be characterized as estrogen receptor (ER) negative, progesterone receptor (PR) negative, and human epidermal growth factor receptor 2 (HER2) negative, also referred to as triple negative breast cancer (NCCN, 2011b; NCI, 2011a). Studies have indicated BRCA1 mutations in 11% to 28% of patients with triple-negative breast cancer. It has also been noted that in patients with triple-negative disease, the BRCA mutation carriers were diagnosed at a younger age compared to non-carriers (NCCN, 2011b).

There is evidence in the published, peer-reviewed scientific literature to demonstrate that testing methods used to identify BRCA mutations are accurate in detecting specific mutations. If a BRCA1 or BRCA2 mutation is identified within a family, unaffected family members can also be tested for the presence of a mutation, and those testing negative can be provided with the reassurance that their risk of developing breast or ovarian cancer is more similar to that of the general population. Sensitivity of BRCA testing has been reported to be up to 98% of all mutations, and sequencing should detect almost 100% of all nucleotide differences. The specificity of BRCA testing has not been well studied.

Evidence in the published, peer-reviewed scientific literature indicates that BRCA1 and BRCA2 genetic testing is appropriate for a specific subset of adult individuals who have been identified to be at high risk for hereditary breast and ovarian cancers. Furthermore, several specialty organizations, including the NCCN, American College of Medical Genetics (ACMG), and American Society of Clinical Oncology (ASCO), have issued statements recognizing the role of BRCA testing in the management of at-risk patients. The U.S. Preventive Services Task Force (USPSTF) has published recommendations regarding genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility. Studies have demonstrated that patients with BRCA mutations are at increased risk for developing breast and ovarian cancer.

There is insufficient evidence in the published, peer-reviewed scientific literature to support the use of genetic testing for susceptibility to breast and ovarian cancer for the following:

- testing in the general population
- testing of unaffected individuals, in the absence of a known mutation or family history as noted in NCCN guidelines
- patients under 18 years of age, as this population has not been well-studied

Testing Strategy

According to the NCCN Guidelines™ for genetic/familial high-risk assessment of breast and ovarian cancer for the majority of families with an unknown mutation status, it is best to consider testing an affected family member first, especially a family member with disease, bilateral diseases, or multiple primaries, because that individual is most likely to test positive (NCCN, 2011b). In cases where there are no affected individuals available or willing to undergo testing, then research and individualized recommendations for management are based on the personal and family history. In general, the first person to be tested in a family would undergo complete sequence analysis of both the BRCA1 and BRCA2 genes. If a mutation is identified, relatives may be tested only for that specific mutation. For patients of Ashkenazi Jewish descent, initial testing will generally be done only for the three specific mutations that account for most hereditary breast and ovarian cancer in that population. The most common variants found in these women are 185delAG and 5382insC in the BRCA1 gene and 6174delT in the BRCA2 gene. If the test results are negative, full analysis of the BRCA1 and BRCA2 genes may or may not be done, according to the patient's personal and family history.

BRACAnalysis® (Myriad Genetics, Inc., Salt Lake City, UT) is a patented genetic test for BRCA1 and BRCA2. According to the Myriad website the test includes:

- Single Site BRACAnalysis®: This test includes the DNA sequence analysis for a specified variant in BRCA1 and/or BRCA2, also known as mutation specific. It is a test for a specified mutation in BRCA1 and BRCA2. This is used when there are known familial mutations.

- Comprehensive BRACAnalysis[®] examines the full gene sequence of BRCA1 and BRCA2 genes. This test also includes detection of five specific large genomic rearrangements of BRCA1 gene. These are thought to account for nearly half of all such rearrangements. A rearrangement is a structural alteration in a chromosome that usually involves breakage and reattachment of a segment of chromosome material, resulting in an abnormal configuration (Petrucci, et al., 2007).
- Multisite 3 BRACAnalysis[®]: this test is a DNA sequence analysis for specified sequence portions of BRCA1 and BRCA 2. This testing is for individuals of Ashkenazi ancestry. It tests for the three most common abnormalities found in people of this heritage.

BRACAnalysis Rearrangement Test (BART)[®] (Myriad Genetic Laboratories, Inc., Salt Lake City, UT):

BART was introduced in 2006 for use on patient samples that meet defined clinical criteria. All coding exons of BRCA1/BRCA2 and their respective promoters are examined for evidence of deletions and duplications by quantitative endpoint PCR analysis.

This test is utilized to detect rare, large rearrangements of DNA in the BRCA1 and BRCA2 genes. It is intended for use only in individuals at an exceptionally high risk for breast cancer who have previously tested negative for sequence mutations and common large rearrangements on Myriad Genetics standard BRACAnalysis test.

Indications for BART test include the following (Myriad Genetic Laboratories, Inc.):

- breast cancer diagnosed before age 50 and a family history* that includes EITHER of the following:
 - two or more diagnoses of breast cancer before age 50 (male breast cancer at any age)
 - ovarian cancer at any age
- ovarian cancer diagnosed at any age and a family history* and EITHER of the following:
 - two or more diagnoses of breast cancer before age 50 (male breast cancer at any age)
 - ovarian cancer at any age
- male breast cancer diagnosed at any age and a family history* and EITHER of the following:
 - two or more diagnoses of breast cancer before age 50 (male breast cancer at any age)
 - ovarian cancer at any age
- breast cancer diagnosed at or after age 50 and ovarian cancer at any age and a family history* that include EITHER of the following:
 - of one or more diagnosis of breast cancer before age 50 (male breast cancer at any age)
 - ovarian cancer at any age
- diagnosed with both breast cancer before age 50 and ovarian cancer at any age

*at least one relative must be a first- or second-degree relative and qualifying cancers must be on the same side of the family

Rearrangements, such as large genomic alterations including translocations, inversions, or large deletions or insertions are believed to be responsible for 12% to 18% of BRCA1 inactivating mutations but are less common in BRCA2 and in individuals of Ashkenazi Jewish descent (NCI, 2010a; Unger, et al., 2000; Walsh, et al., 2006; Palma, et al., 2008). The NCCN guidelines note, "it is important to mention that certain large genomic rearrangements are not detectable by a primary sequencing assay thereby necessitating supplementary testing, in some cases. For example, there are tests that detect rare, large cancer-associated rearrangements of DNA in the BRCA1 and BRCA2 genes that not detected by sequencing the BRCA 1/2 genes." (NCCN, 2011b).

Palma et al. (2008) conducted a study to define the prevalence and spectrum of point mutations and genomic rearrangements in BRCA genes in a large U.S. high-risk clinic population of both non-Ashkenazi and Ashkenazi Jewish descent, using a sample set representative of the U.S. genetic testing population. The study included 251 probands with commercial testing for BRCA1 and BRCA2, with an estimated prevalence of BRCA mutation ≥10% using the Myriad II model and a DNA sample available. Individuals without deleterious point mutations were screened for genomic rearrangements in BRCA1 and BRCA2. The study found that in the 136 non-Ashkenazi Jewish probands, 36 (26%) BRCA point mutations and 8 (6%) genomic rearrangements (7 in BRCA1 and 1 in BRCA2) were identified. Forty-seven of the 115 (40%) Ashkenazi Jewish probands no genomic rearrangements were identified in the group without mutations. In the non-Ashkenazi Jewish probands, genomic rearrangements constituted 18% of all identified BRCA mutations.

Walsh et al. (2006) studied the frequency and type of undetected cancer-predisposing mutations in BRCA 1, BRCA2 and other genes associated with breast cancer (CHEK2, TP53, and PTEN) among patients with breast

cancer from high-risk families with negative (wild-type) genetic test results for BRCA1 and BRCA2. The study included probands from 300 families with 4 or more cases of breast or ovarian cancer but with negative (wild-type) commercial genetic test results for BRCA1 and BRCA2. The study found that of the 300 probands, 52 (17%) carried previously undetected mutations, including 35 (12%) with genomic rearrangements of BRCA1 or BRCA2. With the BRCA1 and BRCA2, 22 different genomic rearrangements were found, of sizes less than 1 kb to greater than 170 kb—of these, 14 were not previously described and all were individually rare.

Unger et al. (2000) examined the frequency of genomic rearrangements in BRCA1 in 42 families with breast and ovarian cancer who were seeking genetic testing and were subsequently found to be negative for BRCA1 and BRCA2 coding-region mutations. The exon 13 duplication was detected in one family, and four families were found to have other genomic rearrangements. Four of five families with BRCA1 genomic rearrangements included at least one individual with both breast and ovarian cancer—four (30.8%) of 13 families with a case of multiple primary breast and ovarian cancer had a genomic rearrangement in BRCA1. The families found to have genomic rearrangements had prior probabilities of having a BRCA1 mutation that ranged from 33% to 97% (mean 70%). The families without rearrangements the prior probabilities of having a BRCA1 mutation ranged from 7% to 92% (mean 37%).

Testing Results

A positive test reveals the presence of a mutation in either the BRCA1 or BRCA2 gene that prevents the translation of the full-sized protein or that is known to interfere with protein function in other ways. A true positive result is the patient who is a carrier of an alteration in the known cancer-predisposing gene. A woman who carries a mutation with such a deleterious effect has a lifetime breast cancer risk of 60–85% and a significantly increased risk of ovarian cancer.

A negative test result is interpreted within the context of a patient's individual and family cancer history, notably regarding whether a family member has previously been identified as possessing a mutation. The affected individual may still have an inherited predisposing mutation in one of the BRCA genes or in another gene that predisposes to breast or ovarian cancer. An individual identified as at-risk who does not carry a BRCA1 or BRCA2 mutation that has been positively identified in another family member is considered to have a true negative result.

A person is considered to have an indeterminate result if that person is not a carrier of a known cancer-predisposing gene and the carrier status of other family members is either also negative or unknown (NCCN, 2010b). In some situations, especially where a single base pair change or missense mutation is identified, interpretation of results is more difficult. Single base pair changes do not always result in a nonfunctional gene product. Missense mutations are typically reported as indeterminate results.

Results are considered inconclusive if the individual is a carrier of an alteration in a gene that currently has no known significance.

Other Genetic Testing for Susceptibility to Breast Cancer

While the syndromes most strongly associated with breast cancers are BRCA1 or BRCA2 mutation syndromes, there has been recent research in other genetic variants that may have a role in familial breast cancer. There is a suggestion that the remaining breast cancer susceptibility is polygenic in nature, meaning that a relatively large number of low-penetrance genes are involved, with each locus expected to have a relatively small effect on breast cancer risk and not produce dramatic familial aggregation or influence patient management (NCI, 2011a).

There are two research strategies that have been undertaken to identify low-penetrance polymorphisms leading to breast cancer susceptibility: candidate gene and genome-wide searches. The candidate gene approach involves selecting genes based on their known or presumed biological function, relevance to carcinogenesis or organ physiology, and searching for or testing known genetic variants for an association with cancer risk. This strategy relies on imperfect and incomplete biological knowledge, and has been relatively disappointing (NCI, 2011a). Confirmed candidate breast cancer susceptibility genes include, but are not limited to the following:

- CHEK2
- Ataxia telangiectasia (AT or ATM)
- BRIP1 (also known as BACH1)

- PALB2
- CASP8 and TGFB1
- RAD51C

The genome-wide association studies have largely replaced the candidate gene research. This involves a very large number of single nucleotide polymorphisms (SNPs) (potentially 1,000,000 or more) that are chosen within the genome and tested largely without regard to their possible biological function, but instead to capture more uniformly all genetic variation throughout the genome. Genome-wide searches are demonstrating promise in identifying common, low-penetrance susceptibility alleles for many complex diseases including breast cancer (NCI, 2011a). However, further research is needed regarding the genetic and functional characterization. Until their individual and collective influences on cancer risk are evaluated prospectively, they are not considered clinically relevant (NCI, 2011a). An example of SNP testing is the deCode BreastCancer[®] test (deCode Diagnostic Laboratory, Reykjavik, Iceland). It tests genotypes for seven known SNPs that have been linked to breast cancer.

Unlike guidelines and criteria that have been established for BRCA testing, criteria have yet to be defined for requirements for when genetic testing of candidate genes or SNPs should be implemented in routine diagnostics (Ripperger, et al., 2008). Specialty professional organizations, in their statements regarding breast cancer susceptibility testing, have not included these methods of testing.

Management/Treatment Strategies for Patients with Known Mutations and At-Risk Relatives

Several strategies have been proposed for achieving the goal of reducing cancer risk for individuals with known BRCA mutations. The NCCN guidelines include the following strategies for at-risk patients (NCCN, 2010b):

- Women:
 - breast self-exam (BSE) training and starting at age 18
 - clinical breast exam, every 6–12 months, starting at age 25
 - annual mammogram and breast magnetic resonance imaging (MRI) screening starting at age 25, or individualized based on earliest age of onset in family
 - discuss option of risk-reducing mastectomy on case-by-case basis and counsel regarding degree of protection, reconstruction options, and risks
 - discuss option of risk-reducing salpingo-oophorectomy ideally between ages 35–40 or upon completion of child-bearing or individualized based on earliest age of onset of ovarian cancer in the family, after discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, and management of menopausal symptoms, and possible short-term hormone replacement therapy (HRT) to a recommended maximum age of natural menopause, and related medical issues
 - for those patients who have not elected risk-reducing surgery, consider concurrent transvaginal ultrasound (preferably day 1–10 of menstrual cycle in premenopausal women) along with CA125 (preferably after day five of menstrual cycle in premenopausal women) every six months starting at age 35 or 5–10 years earlier than the earliest age of first diagnosis of ovarian cancer in the family
 - consider chemoprevention options for breast and ovarian cancer, including discussion of risks and benefits
 - consider investigational imaging and screening studies, when available (e.g., novel imaging technologies and more frequent screening intervals)
- Men:
 - BSE training
 - clinical breast exam every 6–12 months, starting at age 35
 - consider baseline mammogram at age 40, annual mammogram if gynecomastia or parenchymal/glandular breast density on baseline study
 - adhere to screening guidelines for prostate cancer
- Men and women:
 - education regarding signs and symptoms of cancer(s), especially those associated with BRCA gene mutations
 - refer to other NCCN guidelines for other cancer screening
- Risk to relatives:

- advise about possible inherited cancer risks to relatives, options for risk assessment, and management
- recommend genetic counseling and consideration of genetic testing for at-risk relatives
- Reproductive options:
 - for couples expressing the desire that their offspring not carry a familial BRCA mutation advise about options for prenatal diagnosis and assisted reproduction, including pre-implantation genetic diagnosis—discussion should include known risks and benefits of these technologies
 - for reproductive age carriers of BRCA2 mutations, discussion of risk of the rare (recessive) Fanconi anemia/brain tumor phenotype in offspring if both partners carry a BRCA2 mutation

Literature Review

Sivell et al. (2007) conducted a Cochrane review to evaluate the impact of cancer genetic risk assessment services on patients at risk of familial breast cancer. Trials selected for inclusion included studies looking at interventions for cancer genetic risk assessment delivery for familial breast cancer. Three studies with 1,251 participants were included in the review. The review suggested that cancer genetic risk assessment services help to reduce psychological distress and worry about breast cancer and improve the accuracy of perceived risk about breast cancer, while assisting to increase knowledge of breast cancer and genetics. The review also found that further longitudinal research is needed to assess long-term effects, particularly since cancer genetics can involve many genetic counseling sessions and a protracted period of waiting for results of genetic testing.

A systematic evidence review was performed to determine the impact of genomic tests that are used to guide treatment for ovarian cancer on health outcomes in asymptomatic women (Myers, et al., 2006). The report was issued by the Agency for Healthcare Research and Quality (AHRQ) and the Centers for Disease Control and Prevention's (CDC) Division of Cancer Prevention and Control and the CDC's National Office of Public Health Genomics. In the near future, the EGAPP working group will be evaluating the evidence presented in the report and making recommendations about the use of these tests for screening, diagnosis and treatment of ovarian cancer. The review sought evidence regarding: the analytic performance of tests in clinical laboratories; the sensitivity and specificity of tests in different patient populations; the clinical impact of testing in asymptomatic women, women with suspected ovarian cancer, and women with diagnosed ovarian cancer; the harms of genomic testing; and the impact of direct-to-consumer and direct-to-physician advertising on appropriate use of tests. The reviewers constructed a computer simulation model to test the impact of different assumptions about the natural history of ovarian cancer on the relative effectiveness of different strategies. The review noted that genomic test sensitivity/specificity estimates are limited by small sample size, spectrum bias, and unrealistically large prevalence of ovarian cancer. The reviewers found no evidence relevant to the question of the impact of these tests on health outcomes in asymptomatic women. It was noted in the review that there was no evidence found that genomic tests for ovarian cancer have unique harms beyond those common to other tests for genetic susceptibility or other tests used in screening, diagnosis, and management of ovarian cancer. The reviewers noted that limitations of the review were that there was no attempt to perform meta-analysis of specific tests due to the heterogeneity in design and patient populations; and many of the key parameters used in modeling ovarian cancer incidence and mortality are unknown and, in some cases, unknowable. The authors concluded that, although the research remains promising, adaptation of genomic tests into clinical practice must await appropriately designed and powered studies in relevant clinical settings.

A systematic evidence review was performed by Nelson et al. (2005) regarding the genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility. This review was performed as part the development of the USPSTF recommendations for genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility. The objective of the review was to determine the benefits and harms of screening for inherited breast and ovarian cancer susceptibility in the general population of women without cancer. The findings included (Nelson, et al., 2005):

- Tools assessing risks for mutations and referral guidelines have been developed; however, their accuracy, effectiveness, and adverse effects in primary care settings are unknown.
- Risk assessment, genetic counseling, and mutation testing did not cause adverse psychological outcomes.
- Counseling improved distress and risk perception in the highly selected populations studied.
- Intensive cancer screening studies are inconclusive.
- Chemoprevention trials indicate risk reduction for breast cancer in women with varying levels of risk, as well as increased adverse effects.

- Observational studies of prophylactic surgeries report reduced risks for breast and ovarian cancer in mutation carriers.

The reviewers concluded that, “A primary care approach to screening for inherited breast and ovarian cancer susceptibility has not been evaluated, and evidence is lacking to determine benefits and harms for the general population.”

Professional Societies/Organizations

American College of Obstetricians and Gynecologists (ACOG): ACOG published clinical management guidelines regarding hereditary breast and ovarian cancer syndrome. Included in the guidelines are criteria for genetic risk assessment, which include the following (ACOG, 2009/2011):

- Patients with greater than an approximate 20–25% chance of having an inherited predisposition to breast cancer and ovarian cancer and for whom genetic risk assessment is recommended:
 - women with a personal history of both breast cancer and ovarian cancer¹
 - women with ovarian cancer¹ and a close relative² with ovarian cancer or premenopausal breast cancer or both
 - women with ovarian cancer¹ who are of Ashkenazi Jewish ancestry
 - women with breast cancer at age 50 years or younger and a close relative² with ovarian cancer¹ or male breast cancer at any age
 - women of Ashkenazi Jewish ancestry in whom breast cancer was diagnosed at age 40 years or younger
 - women with a close relative² with a known BRCA1 or BRCA2 mutation
- Patients with greater than an approximate 5–10% chance of having an inherited predisposition to breast cancer and ovarian cancer and for whom genetic risk assessment may be helpful:
 - women with breast cancer at age 40 years or younger
 - women with ovarian cancer, primary peritoneal cancer, or fallopian tube cancer of high grade, serous histology at any age
 - women with bilateral breast cancer (particularly if the first case of breast cancer was diagnosed at age 50 years or younger)
 - women with breast cancer at age 50 years or younger and a close relative² with breast cancer at age 50 years or younger
 - women of Ashkenazi Jewish ancestry with breast cancer at age 50 years or younger
 - women with breast cancer at any age and two or more close relatives² with breast cancer at any age (particularly if at least one case of breast cancer was diagnosed at age 50 years or younger)
 - unaffected women with a close relative² that meets one of the previous criteria

¹Cancer of the peritoneum and fallopian tubes should be considered a part of the spectrum of the hereditary breast and ovarian cancer syndrome.

²Close relative is defined as a first-degree relative (mother, sister, daughter) or second-degree relative (grandmother, granddaughter, aunt, niece).

American College of Medical Genetics (ACMG): The ACMG published guidelines regarding the assessment, counseling and testing guidelines for genetic susceptibility to breast and ovarian cancer. The guidelines note that the likelihood of having a mutation in a known cancer susceptibility gene should be assessed on the basis of factors that include, but are not limited to (ACMG, 1999):

- the number of family members with breast or ovarian cancer
- the relationship to the patient
- the age(s) of family members at diagnosis
- whether or not patient is a member of an ethnic group at higher risk for specific mutations

The ACMG guidelines note, that except in unusual circumstances, it is not generally recommended that individuals under 18 be tested, since there is no recommended intervention in childhood. The guidelines note that increased risk for a mutation in a known cancer susceptibility gene is evident in the following circumstances (ACMG, 1999):

- There are three or more affected first- or second-degree relatives on the same side of the family, regardless of age at diagnosis
- There are fewer than three affected relatives, but one of the following factors is present:

- The patient was diagnosed at 45 years of age or less.
- A family member has been identified with a detectable mutation.
- There are one or more cases of ovarian cancer at any age and one or more members on the same side of the family with breast cancer at any age.
- There are multiple primary or bilateral breast cancers in the patient or one family member.
- There is breast cancer in a male patient or in a male relative.
- The patient is at increased risk for specific mutation(s) due to ethnic background (e.g., Ashkenazi Jewish descent) and has one or more relatives with breast cancer or ovarian cancer at any age.

American Society of Clinical Oncology (ASCO): The ASCO published a policy statement regarding genetic testing for cancer susceptibility. The ASCO statement includes recommendations that genetic counseling and testing be offered when (ASCO, 2003; Robson, et al., 2010):

- The individual has personal or family history and the features suggestive of a genetic cancer susceptibility condition.
- The genetic test can be adequately interpreted.
- The test results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer.

In addition, the ASCO recommends that genetic testing only be done in the setting of pre- and post-test counseling, which should include discussion of possible risks and benefits of cancer early detection and prevention modalities. It is also noted by the ASCO that none of the cancer susceptibility tests currently available is as yet appropriate for screening of asymptomatic individuals in the general population. However, in the setting of clinically-defined cancer susceptibility syndromes or suggestive individual cancer histories with or without family history information, the identification of a mutation in an affected member of the family may influence medical management and can be used as a critical baseline in the testing of other family members (ASCO, 2003; Robson, et al., 2010).

National Comprehensive Cancer Network (NCCN): The National Comprehensive Cancer Network Guidelines™ (NCCN Guidelines™) published clinical practice guidelines for genetic/familial high-risk assessment of breast and ovarian cancer. These guidelines include criteria for further professional evaluation. The guidelines note that in situations where Individuals have limited family history, such as fewer than two first- or second- degree female relatives or female relatives surviving beyond 45 years in either lineage may have an underestimated probability of familial mutation. When investigating family histories, the maternal and paternal sides should be considered independently. Close relatives are considered to include first-, second-, and third-degree relatives. Other malignancies reported in some families with hereditary breast and ovarian cancer includes prostate and melanoma. Patients who have received an allogeneic bone marrow transplant should not have molecular genetic testing via blood or buccal samples due to contamination by donor DNA. DNA should be extracted from a fibroblast culture. The early onset of breast or epithelial ovarian/fallopian tube/primary peritoneal cancers also increases suspicion. The guidelines include the following hereditary breast and/or ovarian cancer syndrome testing criteria (NCCN, 2011b):

- individual from a family with a known BRCA1/BRCA2 mutation
- personal history of breast cancer¹ plus one or more of the following:
 - diagnosed at age ≤45 years
 - diagnosed at age ≤50 years, with one or more close blood relative with breast cancer at ≤50 years and/or one or more close blood relative with epithelial ovarian/fallopian tube/primary peritoneal cancer
 - two breast primaries² when first breast cancer diagnosis occurred prior to age 50
 - diagnosed at age 60 or younger with a triple negative breast cancer
 - diagnosed at age 50 or younger with a limited family history(e.g., fewer than two first- or second degree female relatives or female relatives surviving beyond 45 years in either lineage)
 - diagnosed at any age, with two or more close blood relatives with breast and/or epithelial ovarian/ fallopian tube/primary peritoneal cancer at any age
 - close male blood relative with breast cancer
 - personal history of epithelial ovarian³ /fallopian tube/primary peritoneal cancers

- for an individual of ethnicity associated with higher mutation frequency (e.g., founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian or Dutch), no additional family history may be required⁴
- personal history of epithelial ovarian/fallopian tube/primary peritoneal cancers
- personal history of male breast cancer
- personal history of breast or ovarian cancer at any age with two or more close blood relatives* with breast, ovarian, or pancreatic cancer at any age
- personal history of pancreatic cancer at any age with two or more close blood relatives* with breast, ovarian or pancreatic cancer at any age
- family history only with one of the following:
 - First- or second-degree blood relative meeting any of the above criteria
 - Third-degree blood relative with ≥ 2 close relatives with breast and/or ovarian cancer (at least one close blood relative with breast cancer ≤ 50 years)

¹for purposes of the guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

²two breast primaries including bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors

³ovarian cancer is a component tumor of hereditary non-polyposis colorectal cancer (HNPCC)/Lynch syndrome, be attentive for clinical evidence of this syndrome.

⁴testing for founder-specific mutation(s), if available, should be performed first. Full sequencing may be considered if other hereditary breast and/or ovarian cancer criteria met.

U.S. Preventive Services Task Force (USPSTF): The USPSTF published evidenced-based recommendations regarding the genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility. The USPSTF guidelines refer to women who have not received a diagnosis of breast or ovarian cancer. They do not apply to women with a family history of breast or ovarian cancer that includes a relative with a known deleterious mutation in BRCA1 or BRCA2 genes; these women should be referred for genetic counseling. These recommendations do not apply to men. The USPSTF recommendations note the following (USPSTF, 2005):

- They recommend against routine referral for genetic counseling or routine breast cancer susceptibility gene (BRCA) testing for women whose family history is not associated with an increased risk for deleterious mutations in breast cancer susceptibility gene 1 (BRCA1) or breast cancer susceptibility gene 2 (BRCA2).
- They recommend that women whose family history is associated with an increased risk for deleterious mutations in BRCA1 or BRCA2 genes be referred for genetic counseling and evaluation for BRCA testing.
- Women who are NOT of Ashkenazi (Eastern European) Jewish heritage should be referred for genetic evaluation if they have:
 - two first-degree relatives with breast cancer, one of whom was diagnosed when they were younger than age 50
 - three or more first- or second-degree relatives diagnosed with breast cancer at any age
 - a first-degree relative diagnosed with cancer in both breasts
 - two or more first- or second-degree relatives diagnosed at any age
 - a male relative with breast cancer
- Women of Ashkenazi (Eastern European) Jewish heritage should be referred for genetic evaluation if they have:
 - a first-degree relative with breast or ovarian cancer at any age
 - two second-degree relatives on the same side of the family with breast or ovarian cancer at any age

Summary

Genetic testing for cancer susceptibility provides patients and their physicians with information that will allow them to make informed decisions regarding disease prevention, screening and surveillance, and treatment options. There is a consensus in the medical literature that indicates BRCA testing is appropriate for a specific subset of adult individuals who have been identified to be at high risk for hereditary breast and ovarian cancers. Several specialty professional organizations have issued statements recognizing the role of BRCA testing in the management of at-risk patients. In particular, the National Comprehensive Cancer Network (NCCN) publishes

clinical practice guidelines regarding assessment for hereditary breast and ovarian cancer that includes specific criteria for referral to risk assessment and counseling and consideration of genetic testing.

There is insufficient evidence in the published peer-reviewed medical literature to support the clinical utility of genetic tests for susceptibility to breast and ovarian cancer other than BRCA testing (e.g., candidate breast cancer susceptibility genes and single nucleotide polymorphisms [SNPs] testing). Impact of this testing on health outcomes has not been demonstrated. Specialty professional organizations that have issued statements regarding susceptibility to breast and ovarian cancer testing have not recognized testing other than BRCA testing.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT [®] * Codes	Description
83891 [†]	Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie, DNA or RNA)
83898 [†]	Molecular diagnostics; amplification, target, each nucleic acid sequence
83909 [†]	Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis), each nucleic acid preparation
83912 [†]	Molecular diagnostics; interpretation and report

[†]**Note:** Covered when medically necessary when used to report BRCAAnalysis[®] Rearrangement Test (BART).

HCPCS Codes	Description
S3818	Complete gene sequence analysis; BRCA1 gene
S3819	Complete gene sequence analysis; BRCA2 gene
S3820	Complete BRCA1 and BRCA2 gene sequence analysis for susceptibility to breast and ovarian cancer
S3822	Single mutation analysis (in individuals with a known BRCA1 and BRCA2 mutation in the family) for susceptibility to breast and ovarian cancer
S3823	Three-mutation BRCA1 and BRCA2 analysis for susceptibility to breast and ovarian cancer in Ashkenazi individuals

ICD-9-CM Diagnosis Codes	Description
158.8	Malignant neoplasm of specified parts of peritoneum
158.9	Malignant neoplasm of peritoneum, unspecified
174.0 – 174.9	Malignant neoplasm of female breast
175.0 – 175.9	Malignant neoplasm of male breast
183.0	Malignant neoplasm of ovary
198.6	Secondary malignant neoplasm of ovary
198.81	Secondary malignant neoplasm of breast
233.0	Carcinoma in situ of breast
238.3	Neoplasm of uncertain behavior of breast
V10.3	Personal history of malignant neoplasm of breast
V10.41	Personal history of malignant neoplasm of cervix uteri
V10.43	Personal history of malignant neoplasm of ovary
V10.44	Personal history of malignant neoplasm of other female genital organs

V10.88	Personal history of malignant neoplasm of other endocrine glands and related structures
V16.0	Family history of malignant neoplasm of gastrointestinal tract
V16.3	Family history of malignant neoplasm, breast
V16.41	Family history of malignant neoplasm, ovary

***Current Procedural Terminology (CPT®) ©2010 American Medical Association: Chicago, IL.**

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	7/15/2008	0001	Genetic Testing for Susceptibility to Breast and Ovarian Cancer (BRCA1 & BRCA2)
Great-West Healthcare	4/23/2007	05.274.02	Genetic Testing for Susceptibility to Breast and Ovarian Cancer, BRCA1 and BRCA2

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