

Regence

Medical Policy Manual

Genetic Testing, Policy No. 02

Genetic Testing for Hereditary Breast and Ovarian Cancer and Li-Fraumeni Syndrome

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Familial cancer syndromes, including hereditary breast and ovarian cancer (HBOC) syndrome are related to variants in the *BRCA* genes (*BRCA1* and *BRCA2*). Variants in several other genes, including *PALB2* and *STK11*, are also associated with increased risk of breast, ovarian, and other cancers. Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome associated a high lifetime cumulative risk of cancer and a tendency for multiple cancers in affected individuals. LFS is related to variants in the *TP53* gene. Identification of patients with variants in *BRCA1/2*, *TP53*, or other genes may lead to enhanced screening and/or surveillance that could lead to improved outcomes.

MEDICAL POLICY CRITERIA

Note: Both maternal and paternal family histories are important in identifying families with a high risk of genetic variant and therefore, each lineage must be considered separately. For PTEN single-gene testing, see Cross References below.

- I. **Family with a Known Pathogenic Variant:** Genetic testing for a known familial pathogenic variant in *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *PALB2*, *PTEN*, *RAD51C*, *RAD51D*, *STK11* or *TP53* may be considered **medically necessary**.

- II. **Individuals with Active Cancer or a Personal History of Cancer:** Genetic testing (including panel testing) for *BRCA1*, *BRCA2*, *CDH1*, *PALB2*, *PTEN*, *STK11* and/or *TP53* variants in cancer-affected individuals may be considered **medically necessary** when one or more of the following criteria are met:
- A. Personal history of breast, pancreatic, ovarian (See Policy Guidelines), fallopian tube, and/or peritoneal cancer; or
 - B. Personal history of prostate cancer (Gleason score ≥ 7) and one or more of the following:
 - 1. Metastatic prostate cancer; or
 - 2. High-risk prostate cancer, defined as any of the following:
 - a. Gleason score ≥ 8 ; or
 - b. T stage of T3a, T3b, or T4; or
 - c. PSA > 20 ng/mL; or
 - d. Gleason pattern 5 histology
 - 3. Intraductal/ciribriform histology; or
 - 4. Ashkenazi Jewish ancestry; or
 - 5. One or more close blood relatives with any of the following: breast, ovarian, fallopian tube, peritoneal, pancreatic, and/or prostate cancer (Gleason score ≥ 7) (see Policy Guidelines).
 - C. *BRCA1* and *BRCA2* germline (blood-based) testing when tumor genetic testing has been performed and the results indicate that a *BRCA1* or *BRCA2* variant is present in tumor tissue.
 - D. The treating provider has documented that the individual is at increased risk for a *BRCA* variant based on one of the following seven risk-stratification tools endorsed by the USPSTF (See Policy Guidelines) and the documentation indicates which tool was used: the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, Family History Screen 7 (FHS-7), International Breast Cancer Intervention Study instrument (Tyrer-Cuzick), BRCAPro (brief versions).
- III. **Individuals without Active Cancer and Without History of Cancer:** Genetic testing (including panel testing) for *BRCA1*, *BRCA2*, *CDH1*, *PALB2*, *PTEN*, *STK11*, and/or *TP53* variants in cancer-unaffected individuals (no personal history of the following: breast cancer, ovarian cancer, fallopian tube, peritoneal cancer, pancreatic cancer, or prostate cancer [Gleason score ≥ 7]) with unknown variant status, may be considered **medically necessary** when one or more of the following criteria are met:
- A. Individual is at increased risk when one or more of the following family history criteria are met:
 - 1. A first-degree relative has been diagnosed with breast or ovarian cancer; or

2. Two or more close blood relatives (see Policy Guidelines) have been diagnosed with breast cancer, ovarian cancer, pancreatic cancer, prostate cancer, diffuse gastric cancer, and/or colorectal cancer; or
3. A close blood relative (see Policy Guidelines) has been diagnosed with any of the following:
 - a. Bilateral breast cancer; or
 - b. Male breast cancer; or
 - c. Breast cancer before age 50; or
 - d. Both breast and ovarian cancer.
- B. The treating provider has documented that the individual is at increased risk for a *BRCA* variant based on one of the following seven risk-stratification tools endorsed by the USPSTF (See Policy Guidelines) and the documentation indicates which tool was used: the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, Family History Screen 7 (FHS-7), International Breast Cancer Intervention Study instrument (Tyrer-Cuzick), BRCAPro (brief versions); or
- C. Confirmatory *BRCA1* or *BRCA2* testing when the treating provider has documented that direct-to-consumer DNA testing (such as ancestry testing) indicates a pathogenic or likely pathogenic *BRCA1* or *BRCA2* variant.
- IV. Genetic testing for *TP53* may be considered **medically necessary** when the treating provider has documented a concern that the patient is at increased risk for a *TP53* variant, including in the evaluation of possible Li-Fraumeni syndrome.
- V. Genetic testing for *BRIP1*, *RAD51C*, and/or *RAD51D* may be considered **medically necessary** when any of the following criteria are met:
 - A. Personal history of ovarian cancer; or
 - B. A first- or second-degree blood relative with ovarian cancer.
- VI. Genetic testing for *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *PALB2*, *PTEN*, *RAD51C*, *RAD51D*, *STK11* and/or *TP53* variants for hereditary breast/ovarian cancer risk is considered **investigational** in patients who do not meet Criteria I., II., III., IV., or V.
- VII. Single gene or panel testing for any other gene not listed in the criteria above (including but not limited to *ATM*, *BARD1*, and *CHEK2*) is considered **investigational** for hereditary breast and/or ovarian cancer.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

Close blood relatives include 1st-, 2nd-, and 3rd-degree relatives from the same lineage as follows:

- *1st-degree relatives* are parents, siblings, and children of an individual;

- *2nd-degree relatives* are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings (siblings with one shared biological parent) of an individual; and
- *3rd-degree relatives* are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.

Ovarian cancer is a type of cancer that starts in the ovaries and can spread into the pelvis and abdomen. For the purposes of this policy, fallopian tube and peritoneal cancers are also included in the definition of ovarian cancer.

Invasive and stage 0 (including ductal and lobular carcinoma in situ) are considered breast cancer for the purposes of this policy.

RISK STRATIFICATION TOOLS FOR IDENTIFYING AN INCREASED RISK OF *BRCA* VARIANTS

The thresholds for referral for genetic counseling for the USPSTF-endorsed screening tools are listed below. Most of these tools are accessible from the USPSTF website at:

<https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing>

- Ontario Family History Assessment Tool (FHAT): Score of ≥ 10
- Manchester Scoring System: Score of 10 in either column or combined score of 15 for both columns
- Referral Screening Tool (RST): Presence of ≥ 2 items
- Pedigree Assessment Tool (PAT): Score of ≥ 8
- Family History Screen 7 (FHS-7): ≥ 1 positive response
- International Breast Cancer Intervention Study instrument (Tyrer-Cuzick): risk level $\geq 10\%$
- BRCAPro (brief versions): risk level $\geq 10\%$

TESTING AFFECTED FAMILY MEMBERS

Initial testing of an affected family member is strongly recommended whenever possible. Should a *BRCA* variant be found in the affected family member(s), unaffected family member DNA can be tested specifically for the same variant without having to sequence the entire gene.

***BRCA* TESTING FOR TREATMENT WITH LYNPARZA™ (OLAPARIB)**

For individuals who have had a previous *BRCA* test other than BRACAnalysis CDx (Myriad Genetics), repeat *BRCA* variant testing with BRACAnalysis CDx may be necessary when treatment with Lynparza™ (olaparib) is being considered.

***BRCA* TESTING FOR TREATMENT WITH RUBRACA™ (RUCAPARIB)**

For individuals who have had a previous *BRCA* test other than FoundationFocus CDxBRCA (Foundation Medicine), repeat *BRCA* variant testing with FoundationFocus CDxBRCA may be necessary when treatment with Rubraca™ (rucaparib) is being considered.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF GENETIC TESTING DOCUMENTATION

All of the following information must be submitted for review prior to the genetic testing:

1. Name of genetic test(s) and/or panel test
2. The exact gene(s) and/or variants being tested
3. Name of performing laboratory and/or genetic testing organization (more than one may be listed)
4. Relevant billing codes
5. Date of sample collection/blood draw
6. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence of testing
7. Clinical documentation by the provider (e.g., primary care physician, family practitioner, gynecologist) of family history and supporting rationale for the requested test(s)

CROSS REFERENCES

1. [Genetic and Molecular Diagnostic Testing](#), Genetic Testing, Policy No. 20
2. [Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer](#), Genetic Testing, Policy No. 42
3. [Genetic Testing for Myeloid Neoplasms and Leukemia](#), Genetic Testing, Policy No. 59
4. [Genetic Testing for PTEN Hamartoma Tumor Syndrome](#), Genetic Testing, Policy No. 63
5. [Evaluating the Utility of Genetic Panels](#), Genetic Testing, Policy No. 64
6. [Lynparza™ \(olaparib\)](#), Medication Policy Manual, Policy No. dru389

BACKGROUND

BRCA1 AND BRCA2

Several genetic syndromes with an autosomal dominant pattern of inheritance that feature breast cancer have been identified. Of these, hereditary breast and ovarian cancer (HBOC), and some cases of hereditary site-specific breast cancer have causative variants in *BRCA* genes in common. Families suspected of having HBOC syndrome are characterized by an increased susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer at any age, as well as cancer of the fallopian tube and primary peritoneal cancer. Other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, laryngeal cancer, occur more frequently in HBOC families. Hereditary site-specific breast cancer families are characterized by early onset breast cancer, but without ovarian cancer. For this policy, both will be referred to collectively as hereditary breast and/or ovarian cancer.

Germline variants in the *BRCA1* and *BRCA2* genes are responsible for cancer susceptibility in the majority of HBOC families, especially if ovarian cancer is a feature. However, in site-specific breast cancer, *BRCA* variants are responsible for only a proportion of affected families, and research to date has not yet identified other moderate or high-penetrance gene variants that account for disease in these families. *BRCA* gene variants are inherited in an autosomal dominant fashion through either the maternal or paternal lineage (each lineage must be considered separately). It is possible to test for abnormalities in *BRCA1* and *BRCA2* genes to identify the specific variant in cancer cases, and to identify family members with increased cancer risk. Family members without existing cancer who are found to have *BRCA* variants can consider preventive interventions for reducing risk and mortality. Genetic counseling is highly recommended when genetic testing is offered and when the genetic test results are disclosed. Please see Appendix 1 for a recommended testing strategy.

BRIP1

BRIP1 (BRCA1 interacting protein C-terminal helicase 1) encodes a protein that interacts with BRCA1 to function in DNA repair. Heterozygous pathogenic *BRIP1* variants increase the risk of ovarian cancer, while homozygous pathogenic *BRIP1* variants are associated with Fanconi anemia. The prevalence of *BRIP1* variants in women with ovarian cancer appears to be approximately 1% and the lifetime risk associated with a pathogenic variant is estimated to be 5.8%.^[1]

PALB2

PALB2 (partner and localizer of *BRCA2*) encodes a protein that assists BRCA2 in DNA repair and tumor suppression. Heterozygous pathogenic *PALB2* variants increase the risk of developing breast and pancreatic cancers; homozygous variants are found in Fanconi anemia. Pathogenic *PALB2* variants are uncommon in unselected populations and prevalence varies by ethnicity and family history. Women with a pathogenic *PALB2* variant have a 14% lifetime risk of breast cancer by age 50, which increases to 35% by age 70.^[2]

PTEN

PTEN (phosphatase and tensin homolog) encodes a tumor suppressor that antagonizes the PI3K signaling pathway through its lipid phosphatase activity and negatively regulates the MAPK pathway through its protein phosphatase activity.^[3] *PTEN* variants are inherited in an autosomal dominant manner. There is a spectrum of disorders that result from germline variants in *PTEN* referred to as *PTEN* hamartoma tumor syndrome / Cowden syndrome. These syndromes are associated with multiple tumors, including a lifetime risk of breast cancer of up to 50%.^[1]

STK11

STK11 (serine/threonine kinase 11) encodes a tumor suppressor that controls the activity of AMP-activated protein kinase (AMPK) family members, thereby playing a role in cell metabolism, apoptosis and DNA damage response. *STK11* variants are associated with Peutz-Jeghers syndrome, an autosomal dominant syndrome characterized by the gastrointestinal polyps, breast cancer, non-epithelial ovarian cancer, and other neoplasms.^[1]

RAD51C* and *RAD51D

RAD51 genes encode tumor suppressors that are involved in DNA repair. Heterozygous pathogenic variants in these genes are associated with ovarian cancer. The cumulative risk of ovarian cancer for an individual with such a variant approaches 2.6% (the risk for women with a family history of ovarian cancer without a BRCA variant) between the ages of 50 to 54 for *RAD51D* and 60 to 64 for *RAD51C*.^[1]

TP53

The *TP53* gene contains the genetic instructions for the production of tumor protein p53 (or p53). The p53 protein is a tumor suppressor that functions as a cell cycle regulator to prevent cells from uncontrolled growth and division when there is DNA damage. Somatic (acquired) pathogenic variants are one of the most frequent alterations found in human cancers. Germline (inherited) pathogenic variants in *TP53* are associated with Li-Fraumeni syndrome (LFS).

ATM

ATM (ataxia-telangiectasia mutated), located on chromosome 11q22.3, is associated with the autosomal recessive condition ataxia-telangiectasia syndrome. This condition is characterized by progressive cerebellar ataxia with onset between the ages of 1 and 4 years, telangiectasias of the conjunctivae, oculomotor apraxia, immune defects, and cancer predisposition. Females with a heterozygous *ATM* variant have a risk of breast cancer about twice as high as that of the general population; however, they do not appear to have an elevated ovarian cancer risk.

BARD1

The *BARD1* (BRCA1-associated RING domain) gene is located on chromosome 2 (sequence 2q34-q35). *BARD1* encodes a protein which interacts with the N-terminal region of *BRCA1*, and *BARD1* and *BRCA1* can form a heterodimer by their N-terminal RING finger domains which form a stable complex.^[4] *BARD1* variants have been associated with an increased risk of estrogen-receptor (ER) negative breast cancer, triple-negative breast cancer, and with breast cancer at a younger age (under age 50 years) in some studies, but do not appear to increase risk of ovarian cancer.^[5, 6]

CHEK2

CHEK2 (cell cycle checkpoint kinase 2) is involved with DNA repair and human cancer predisposition like *BRCA1* and *BRCA2*. CHEK2 is normally activated in response to DNA double-stranded breaks. CHEK2 regulates the function of *BRCA1* protein in DNA repair and also exerts critical roles in cell cycle control and apoptosis. The *CHEK2* variant, *1100delC* in exon 10 has been associated with familial breast cancers.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature^[7] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

The clinical utility of testing for variants in the *BRCA1* and *BRCA2* genes to inform surveillance, prognosis and treatment of patients with hereditary breast cancer has been unequivocally demonstrated. Therefore, the scientific evidence will no longer be reviewed for the clinical utility of *BRCA1* and *BRCA2* testing, as they may be considered medically necessary.

In addition, there are several genes: *PTEN*, *STK11*, *CDH1*, and *TP53*; which are the causative factors in rare, but highly penetrant cancer syndromes that substantially increase the risk of breast cancer. Although rare, when taken together, variants in these genes are thought to account for at least 5% to 10% of breast cancer diagnoses. Since the clinical utility of testing for variants in these genes to inform surveillance, prognosis and treatment of patients with hereditary breast cancer has been demonstrated, they will not be reviewed extensively in the evidence section below.

The focus of the scientific evidence review below is on the investigational indications only, such as *CHEK2* testing. The evidence review is related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

CHEK2 TESTING

Systematic Reviews on Breast Cancer Association

A number of systematic reviews have described the association of cell cycle checkpoint kinase 2 (*CHEK2*) variants with hereditary breast cancer. The prevalence of this finding varies greatly by geographic region, being most common in Northern and Eastern Europe. In the US, *CHEK2* variants are much less common than *BRCA* variants and *BRCA* rearrangements. For example, in the study by Walsh (2006), 14 (4.7%) of the 300 patients with a positive family history of breast cancer (four affected relatives) who were negative by standard *BRCA* testing, were positive for *CHEK2* variants.^[8]

A systematic review and meta-analysis by Suszynska (2019) included association estimates for *CHEK2* variants.^[9] The systematic review included studies published through July 2017 reporting on genetic test results of breast and ovarian cancer patients who were referred for evaluation by a multi-gene panel. The studies of panel results were used to calculate variant frequencies by the gene. As a control, population variant frequencies were extracted from the Genome Aggregation Database. In the 43 breast cancer studies included in the review, 94,845 patients contributed to the meta-analysis of *CHEK2* in breast cancer patients. The odds ratio (OR) of breast cancer for *CHEK2* variants including variants c.470T>C and c.1283C>T was 0.96 (95% confidence interval [CI] 0.90 to 1.03); after excluding variants c.470T>C and c.1283C>T, the remaining *CHEK2* variants had an OR for breast cancer of 1.73 (95% 1.58 to 1.89).

Liang (2018) conducted a meta-analysis to investigate the link between *CHEK2* and breast cancer.^[10] Two researchers independently searched seven online databases and selected for analysis 26 published studies representing a pooled sample of 118,735 cancer patients and 195,807 controls, all case-control studies conducted in Europe or the Americas. Meta-analysis revealed that *CHEK2* variants are more common in patients with breast cancer (OR 2.89; 95% CI 2.63 to 3.16), with variants 5.9% more likely in female patients with breast cancer than in male patients with breast cancer. Limitations of the study included a study population that might not represent the general population, inaccurate control sampling methods in some original studies, selection biases, and unclear criteria for breast-cancer diagnoses.

A meta-analysis by Schmidt (2016) evaluated data on *CHEK2* variant status and breast cancer risk from the Breast Cancer Association Consortium.^[11] The analysis included 44,777 breast cancer patients and 42,997 controls from 33 studies in which individuals were genotyped for *CHEK2* variants. The estimated odds for invasive breast cancer in patients with and without the *CHEK2* 1100delC variant was 2.26 (95% CI 1.90 to 3.10).

In a meta-analysis by Yang (2012), the link between *CHEK2* 1100delC heterozygote and breast cancer risk was investigated.^[12] A total of 29,154 cases and 37,064 controls from 25 case-control studies were identified in this meta-analysis. A significant association was found between *CHEK2* 1100delC heterozygote and breast cancer risk. Authors concluded that the

CHEK2 1100delC variant could be a potential factor for increased breast cancer risk in Caucasians; however, they suggested that more consideration is needed in order to apply it to allele screening or other clinical work.

In a systematic review and meta-analysis by Liu (2012), authors identified fifteen case-control studies with 19,621 cases and 27,001 controls that were included in their analysis.^[13] Authors reported a significant association found between the *CHEK2 1157T* variant and increased risk of unselected breast cancer, and early-onset breast cancer. In addition, an even stronger significant association was found between the *CHEK2 1157T* variant and increased risk of lobular type breast tumors. Authors concluded the *CHEK2 1157T* variant may be another important genetic variant which increases risk of breast cancer, especially the lobular type. The methodological quality of this review was limited; the evidence was not quality appraised for risk of bias.

A meta-analysis by Han (2013) investigated the relationship of the *CHEK2 1157T* variant and the incidence of cancer.^[14] In total, 26,336 cases and 44,219 controls from 18 case-control studies were used in the meta-analysis. Authors concluded that the *CHEK2 1157T* variant was an important cancer gene, which increases cancer risk, especially for breast and colorectal cancer.

Zhang (2011) performed a systematic review of candidate-gene association studies of breast cancer risk, identifying more than 1,000 published articles. Meta-analysis was performed for a total of 279 genetic variants in 128 genes that were identified by at least three different researchers. Significant associations with the risk of breast cancer were found for 29 variants in 20 genes. The association was strong for ten variants in six genes, four of which were located in the *CHEK2* gene.^[15]

Peng (2011) identified 87 meta-analyses and pooled analyses which examined the association of 145 candidate gene variants and breast cancer. They found significant association for 46 variants, with ORs ranging from 0.66 to 3.13. The further analysis of ORs (using the method of false-positive report probability) identified ten noteworthy associations, including *CHEK2 (*1100delC)*.^[16]

Weischer (2008) performed a meta-analysis of studies on *CHEK2 1100delC* heterozygosity and the risk of breast cancer among patients with unselected (including the general population), early-onset (<51 years of age) and familial breast cancer.^[17] The analysis identified prospective cohort and case-control studies on *CHEK2 1100delC* and the risk of breast cancer published before March 2007. Inclusion criteria were women with unilateral breast cancer who did not have a known multicancer syndrome, Northern or Eastern European descent, availability for *CHEK2* genotyping, *BRCA1* and *BRCA2* variant-negative or unknown status, and breast cancer-free women as controls. The meta-analysis included 16 studies with 26,488 patient cases and 27,402 controls. Using fixed-effect models, for *CHEK2 1100delC* heterozygotes versus those without a variant, the aggregated OR for breast cancer was 2.7 (95% CI 2.1 to 3.4) and 2.4 (95% CI 1.8 to 3.2), respectively, for *CHEK2 1100delC* heterozygotes versus those without a variant in studies of patients with unselected breast cancer, 2.6% (95% CI 1.3 to 5.5) versus 2.7 (95% CI 1.3 to 5.6), respectively, for early-onset breast cancer, and 4.8 (95% CI 3.3 to 7.2) versus 4.6 (95% CI 3.1 to 6.8), respectively, for familial breast cancer. The cumulative risk at age 70 years for *CHEK2*1100delC* variant was 37% (confidence interval 26% to 56%). This risk is lower than cumulative risk at age 70 of 57% for *BRCA1* and 49% for *BRCA2*.

CHEK2 and Breast Cancer Prognosis

A study by Huzarski (2014) estimated the 10-year survival rate for patients with early-onset breast cancer, with and without *CHEK2* variants.^[18] Patients were consecutively identified women with invasive breast cancer diagnosed at or below the age of 50, between 1996 and 2007, in 17 hospitals throughout Poland. Patients were tested for four founder variants in the *CHEK2* gene after diagnosis, and their medical records were used to retrieve tumor characteristics and treatments received. Dates of death were retrieved from a national registry. A total of 3,592 women were eligible for the study, of whom 487 (13.6%) carried a *CHEK2* variant (140 with truncating variants, 347 with missense variants). Mean follow-up was 8.9 years. Ten-year survival for individuals with a *CHEK2* variant was similar to that of individuals without a variant, at 78.8% (95% CI 74.6% to 83.2%) and 80.1% (95% CI 78.5% to 81.8%), respectively. After adjusting for other prognostic features, the hazard ratio comparing those with and without the missense variant was similar, as for those with and without a truncating variant.

A study by Kriege (2014) compared breast cancer outcomes in patients with and without *CHEK2* variants.^[19] Different study cohorts were combined to compare 193 individuals with *CHEK2* variants with 4,529 controls. Distant disease-free survival and breast cancer-specific survival were similar in the first six years after diagnosis. After six years, both distant disease-free survival (multivariate HR 2.65, 95% CI 1.79 to 3.93) and breast cancer-specific survival (multivariate HR 2.05, 95% C, 1.41 to 2.99) were worse in those *CHEK2* variants. No interaction between *CHEK2* status and adjuvant chemotherapy was observed.

Weischer (2012) reported on breast cancer associated with early death, breast cancer–specific death, and the increased risk of a second breast cancer (defined as a contralateral tumor) in patients with and without a *CHEK2* variant.^[20] The study included 25,571 white women of Northern and Eastern European descent who had invasive breast cancer, with data from 22 studies participating in the Breast Cancer Association Consortium conducted in 12 countries. The 22 studies included 30,056 controls. Data were reported on early death in 25,571 women, breast cancer–specific death in 24,345 and a diagnosis of a second breast cancer in 25,094. Of the 25,571 women, 459 (1.8%) were *CHEK2 1100delC* heterozygous and 25,112 (98.2%) did not have a *CHEK2* variant. Median follow-up was 6.6 years, over which time 124 (27%) deaths, 100 (22%) breast cancer–specific deaths, and 40 (9%) second breast cancers among those with a *CHEK2 1100delC* variant were observed. Corresponding numbers among those without this variant were 4,864 (19%), 2,732 (11%), and 607 (2%), respectively. At the time of diagnosis, those with a *CHEK2* variant versus those without were on average four years younger ($p < 0.001$) and more often had a positive family history ($p < 0.001$).

CHEK2 Evidence Summary

The evidence for testing for *CHEK2* variants in individuals who are undergoing risk assessment for breast cancer includes population and family-based case control studies. Relevant outcomes are overall survival, test accuracy, test validity, morbid events, resource utilization, and treatment-related morbidity. Studies have shown that a *CHEK2* variant is of moderate penetrance and confers a risk of breast cancer of two to four times that of the general population; this risk appears to be higher in patients who also have a strong family history of breast cancer, however, risk estimates are subject to bias and overestimation. Several studies have suggested that individuals with *CHEK2* variants with breast cancer may have worse breast cancer-specific survival and distant-recurrence free survival, with about

twice the risk of early death.

Further studies are needed to determine whether some patients with a *CHEK2* variant have a risk that is similar to the risk with a high-penetrance variant and identify those that would be best managed according to the well-established guidelines for high-risk patients. Clinical management recommendations for inherited conditions associated with moderate penetrance variants, such as *CHEK2*, are not standardized, nor is it known if testing for *CHEK2* variants will lead to changes in patient management or improved health outcomes. Therefore, the evidence is insufficient to determine the effects of the technology on health outcomes.

ATM TESTING

Systematic Reviews on Breast Cancer Association

A systematic review conducted by Moslemi (2021) included 24 cross-sectional studies reporting on the prevalence of *ATM* variants in individuals with breast cancer.^[21] The review found a pooled prevalence of 7% (95% CI 6% to 9%) based on 21 studies included in the meta-analysis with high heterogeneity ($I^2=93\%$). In individuals with an *ATM* and *BRCA1* or *BRCA2* variant, prevalence was 11% (95% CI 7% to 11%, $I^2=99\%$), in those with an *ATM* variant but without a *BRCA1/2* variant, the prevalence was 3% (95% CI 2% to 4%, $I^2=85\%$). Meta-regression found age did not have a significant effect on prevalence of *ATM* in individuals with breast cancer, and Egger's test did not reveal evidence of publication bias ($p=0.98$).

The Suszynska (2019) systematic review described previously also included association estimates for *ATM* variants.^[9] In the 43 breast cancer studies included in the review, 94,787 patients contributed to the meta-analysis of *ATM* in breast cancer patients. The OR of breast cancer for *ATM* variants was 2.42 (95% CI 2.16 to 2.71).

Marabelli (2016) reported on a meta-analysis of the penetrance of *ATM* variants in breast cancer, which used a model allowing the integration of different types of cancer risk estimates to generate a single estimate associated with heterozygous *ATM* gene variants.^[22] The meta-analysis included 19 studies, which were heterogeneous in terms of population, study designs, and baseline breast cancer risk. The estimated cumulative absolute risk of breast cancer in those with a heterozygous *ATM* variant was 6.02% by age 50 (95% credible interval 4.58% to 7.42%) and 32.83% by age 80 (95% credible interval 24.55% to 40.43%).

ATM Evidence Summary

For individuals with risk of HBOC who receive genetic testing for an *ATM* variant, the evidence includes studies of variant prevalence and studies of breast cancer risk. Relevant outcomes are OS, disease-specific survival, and test validity. The available studies on clinical validity have demonstrated that *ATM* variants are of moderate penetrance; moreover, *ATM* variants confer a risk of breast cancer two to four times that of the general population. Direct evidence for the clinical utility of genetic testing for *ATM* variants in individuals with risk of HBOC was not identified. It is unclear that the RR associated with the moderate penetrance variants would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to high-penetrance variants, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with a moderate penetrance variant such as *ATM*. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

BARD1 TESTING

Systematic Reviews on Breast Cancer Association

Two systematic reviews conducted by Suszynska (2019)^[9] and (2020)^[23] reported estimates on the association of *BARD1* variants with risk of breast cancer. The prevalence of *BARD1* variants was 0.22% to 0.25% in individuals with breast cancer; prevalence in controls was about 0.09%. The reviews found presence of a *BARD1* variant was associated with approximately a two- to three-fold increased risk of breast cancer. The 2020 review identified 60 distinct pathogenic variants among individuals with breast cancer, 21 of which were present in controls. In individuals with a recurrent pathogenic variant (defined as occurring in three or more cases), risk was elevated among those with the c.334C>T (R112*), c.1652C>G (S551*), c.1690C>T (Q564*) variants, but prevalence was very low ($\leq 0.03\%$ among cases and $\leq 0.004\%$ among controls) and these estimates were imprecise.

BARD1 Evidence Summary

For individuals with risk of HBOC who receive genetic testing for a *BARD1* variant, the evidence includes studies of variant prevalence and studies of breast cancer risk. Relevant outcomes are OS, disease-specific survival, and test validity. The available studies on clinical validity have demonstrated that *BARD1* variants are of low to moderate penetrance; *BARD1* variants confer a risk of breast cancer about two to three times that of the general population. Direct evidence for the clinical utility of genetic testing for *BARD1* variants in individuals with risk of HBOC was not identified. It is unclear that the relative risk associated with the low- to moderate-penetrance variants would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to high-penetrance variants, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with a low- to moderate-penetrance variant such as *BARD1*. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK GUIDELINES (NCCN)

Genetic/Familial High-Risk Assessment for Breast, Ovarian, and Pancreatic Cancer^[1]

High-Penetrance Genes: *BRCA1*, *BRCA2*, *CDH1*, *PALB2*, *PTEN*, and *TP53*

- The NCCN Guidelines for Genetic/Familial High-Risk Assessment for Breast and Ovarian Cancer (v.3.2023) recommend testing for high-penetrance breast and/or ovarian cancer susceptibility genes, including *BRCA1/2*, *CDH1*, *PALB2*, *PTEN*, and *TP53* testing, in select individuals.
- In patients with a known familial pathogenic or likely-pathogenic variant, targeted testing for the specific variant is recommended.
- In patients with no known familial variant, multi-gene testing of the patient or, if the patient is unaffected, testing of the family member with the highest likelihood of a pathogenic/likely pathogenic variant is recommended prior to testing the patient, if possible; if the affected individual is of Ashkenazi Jewish descent, testing for the three known founder variants is recommended.

Additional Genes

The NCCN guidelines include a table listing *BRCA1*, *BRCA2*, *TP53* and a number of other genes associated with increased risks of breast, ovarian, and/or pancreatic cancer, along with cancer risk management for these genes. The authors note that the inclusion of a gene in the table “does not imply the endorsement either for or against multi-gene testing for moderate penetrance genes.

Regarding moderate penetrance genes and multigene testing, the guidelines state:

- Multi-gene testing can include “intermediate” penetrant (moderate-risk) genes. For many of the genes, there are limited data on the degree of cancer risk, and there may currently be no clear guidelines on risk management for carriers of P/LP [pathogenic/likely pathogenic] variants. Not all genes included on available multi-gene tests will change risk management compared to that based on other risk factors such as family history.
- Multi-gene panel testing increases the likelihood of finding P/LP variants in genes; however, some genes do not have clear clinical actionability or have a clear impact on change in medical management.

Prostate Cancer^[24]

The NCCN guidelines for prostate cancer (v.1.2023) include recommendations for germline testing for genes related to hereditary breast and ovarian cancers in patients with prostate cancer, including *BRCA1* and *BRCA2*. Germline testing is recommended for patients with high-risk, very-high-risk, regional, or metastatic prostate cancer patients and those with any of the following:

- Ashkenazi Jewish ancestry
- A family history of a familial cancer risk mutation
- A positive family history of certain types of cancer
- A personal history of breast cancer

US PREVENTIVE SERVICES TASK FORCE (USPSTF)

The 2019 USPSTF guideline titled *Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer* recommends the following:^[25]

- The USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with *BRCA1/2* gene mutations with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing (Grade B recommendation).
- The USPSTF recommends against routine risk assessment, genetic counseling or genetic testing for women whose personal or family history or ancestry is not associated with potentially harmful *BRCA1/2* gene mutations (Grade D recommendation).

SOCIETY OF GYNECOLOGIC ONCOLOGY (SGO)

In 2014, the SGO^[26] published a consensus statement that was evidence informed for inherited gynecologic cancer. SGO recommends genetic assessment (counseling with or without testing) for patients genetically predisposed to breast or ovarian cancer. The SGO and

NCCN guidelines generally align with some slight variations. Specifically, SGO recommends that other individuals may benefit from genetic assessment (e.g., unaffected women with a male relative with breast cancer, few female relatives, hysterectomy or oophorectomy at a young age in multiple family members, or adoption in the lineage).

THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY

The American Society of Clinical Oncology (2015) policy statement update on genetic and genomic testing for cancer susceptibility states that testing for high-penetrance variants in appropriate populations has clinical utility in that the variants inform clinical decision making and facilitate the prevention or amelioration of adverse health outcomes.^[27] Regarding moderate-penetrance genes, the update stated, "Clinical utility remains the fundamental issue with respect to testing for mutations in moderate-penetrance genes. It is not yet clear whether the management of an individual patient or his or her family should change based on the presence or absence of a mutation. There is insufficient evidence at the present time to conclusively demonstrate the clinical utility of testing for moderate penetrance variants, and no guidelines exist to assist oncology providers."

THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY, AMERICAN SOCIETY FOR RADIATION ONCOLOGY, AND SOCIETY OF SURGICAL ONCOLOGY

Consensus guidelines for the management of hereditary breast cancer published in 2020 by the American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology include a number of recommendations related to surgery, radiation, and therapy, including the following:^[28]

- "Germline *BRCA* status should not preclude a patient with newly diagnosed breast cancer otherwise eligible for breast-conserving therapy (BCT) from receiving BCT. (Type: Formal consensus; Evidence quality: Intermediate; Strength of recommendation: Moderate)
- Surgical management of the index malignancy (BCT v ipsilateral therapeutic and contralateral risk-reducing mastectomy [CRRM]) in *BRCA1/2* mutation carriers should be discussed, considering the increased risk of CBC and possible increased risk of an ipsilateral new primary breast cancer compared with noncarriers. (Type: Formal consensus; Evidence quality: Intermediate; Strength of recommendation: Strong)
- The following factors should be considered for assessing risk of CBC and role of risk-reducing mastectomy in *BRCA1/2* mutation carriers: age at diagnosis (the strongest predictor of future CBC; refer to Table 1 in the original guideline), family history of breast cancer, overall prognosis from this or other cancers (e.g., ovarian), ability of patient to undergo appropriate breast surveillance (magnetic resonance imaging [MRI]), comorbidities, and life expectancy. (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)
- *BRCA1/2* mutation carriers who do not have bilateral mastectomy should undergo high-risk breast screening of remaining breast tissue with annual mammogram and MRI. (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)

- For women with newly diagnosed breast cancer who have a mutation in a moderate-penetrance breast cancer susceptibility gene, mutation status alone should not determine local therapy decisions for the index tumor or CRRM. (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)
- In patients with breast cancer with a mutation in a moderate-penetrance breast cancer susceptibility gene, BCT should be offered to those for whom BCT is an appropriate treatment option. There is a lack of data regarding ipsilateral breast cancer events after BCT among patients with moderate-risk mutations. (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)
- The evidence regarding CBC risk is limited for mutations in moderate-penetrance breast cancer genes, aside from some data on *CHEK2* 1100delC. Information about the specific gene and what is known about the risk of CBC should be discussed in the context of shared decision making. (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)
- Patients with mutations in moderate-penetrance genes who do not have bilateral mastectomy should undergo high-risk breast screening of remaining breast tissue with annual mammogram and MRI. (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)”

SUMMARY

BRCA1, BRCA2, TP53, PALB2, PTEN, STK11, and/or CDH1

There is enough research to show that testing for variants in certain genes can guide treatment decisions and improve health outcomes for people suspected of having hereditary breast or ovarian cancer. In addition, clinical guidelines based on research from the National Comprehensive Cancer Network (NCCN) recommend genetic testing of these genes for certain people. Therefore, testing for variants in *BRCA1, BRCA2, TP53, PALB2, PTEN, STK11, and/or CDH1* may be considered medically necessary when criteria are met.

There is not enough research to show that testing for variants in *BRCA1, BRCA2, TP53, PALB2, PTEN, STK11, and/or CDH1* can improve health outcomes for individuals who do not meet the policy criteria. Therefore, this testing is considered investigational.

Other Genes

There is not enough research to show that testing for genes other than *BRCA1, BRCA2, BRIP1, RAD51C, RAD51D, PALB2, PTEN, STK11, CDH1*, and/or *TP53*, including but not limited to *ATM, BARD1*, and *CHEK2* testing, can improve health outcomes for people suspected of having a hereditary breast and ovarian cancer syndrome. While there are a number of genes that are associated with increased risk of breast and/or ovarian cancer, it is not clear that changing patient management based on the results of testing these moderate-penetrance genes will lead to better health outcomes compared to management based on other risk factors such as family history. Therefore, testing for any other genes, including panel testing of *BRCA1, BRCA2, BRIP1, RAD51C, RAD51D, PALB2, PTEN, STK11, CDH1*,

and/or *TP53* done in combination with other genes, is considered investigational for determining risk of hereditary breast or ovarian cancer.

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CODES

Codes	Number	Description
CPT	0102U	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated [17 genes (sequencing and deletion/duplication)]
	0103U	Hereditary ovarian cancer (eg, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated [24 genes (sequencing and deletion/duplication); EPCAM (deletion/duplication only)]
	0129U	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)
	0131U	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure) (Use 0131U in conjunction with 81162, 81432, 0102U)
	0132U	Hereditary ovarian cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes) (List separately in addition to code for primary procedure) (Use 0132U in conjunction with 81162, 81432, 0103U)
	0235U	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
	81162	BRCA1, (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangement)
	81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
	81165	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81166	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
	81167	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
	81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
	81215	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant

Codes	Number	Description
	81216	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81217	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
	81307	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; full gene sequence
	81308	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; known familial variant
	81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
	81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
	81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
	81351	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence
	81352	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)
	81353	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; known familial variant
	81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
	81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
	81432	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 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
	81433	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
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Appendix 1 Recommended Testing Strategy

- Individuals meeting the criteria above should be tested for *BRCA1* and *BRCA2* variants
- Individuals with a known familial BRCA variant
 - Targeted testing for the specific variant is recommended
- Individuals with unknown familial BRCA variant
 - Non-Ashkenazi Jewish descent
 - If no familial variant can be identified, two possible testing strategies are:

Appendix 1 Recommended Testing Strategy

- Full sequencing followed by testing for common large genomic rearrangements (deletions/duplications) only if sequencing detects no variant (negative result).
- Alternatively, simultaneous full sequencing and testing for common large genomic rearrangements (also known as comprehensive BRCA testing) may be performed.
- If comprehensive BRCA testing is negative, testing for uncommon large genomic rearrangements (e.g., BART) may be done.
 - Testing for uncommon large rearrangements should not be done unless both sequencing and testing for common large rearrangements have been performed and are negative.
- Ashkenazi Jewish descent
 - NCCN recommends testing for the three known founder variants first (i.e., 185delAG and 5182insC in *BRCA1*; 6174delT in *BRCA2*).
 - If testing is negative for the founder variants, comprehensive genetic testing may be considered.

Comprehensive Variant Analysis

Comprehensive variant analysis currently includes sequencing the coding regions and intron/exon splice sites, as well as tests to detect common large deletions and rearrangements that can be missed with sequence analysis alone. Prior to August 2006, testing for large deletions and rearrangements was not performed, thus some patients with familial breast cancer who had negative BRCA testing before this time may consider repeat testing for the rearrangements.

Date of Origin: January 2011