

Genetic Testing for Hereditary Breast and/or 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

Hereditary breast and ovarian cancer (HBOC) syndrome describes the familial cancer syndromes that are related to variants in the *BRCA* genes (*BRCA1* and *BRCA2*). 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.

- I. **Family with a Known *BRCA1/BRCA2* Variant:** Genetic testing for *BRCA1* and *BRCA2* variants (including large genomic rearrangement testing, i.e., BART) may be considered **medically necessary** when the individual is from a family with a known *BRCA1/BRCA2* variant and there is documentation of a signed provider order (See Policy Guidelines) for *BRCA* testing.

- II. **BRCA1/BRCA2 Variant for Individuals with Active Cancer or a Personal History of Cancer:** Genetic testing for *BRCA1* and *BRCA2* variants (including large genomic rearrangement testing i.e., BART) in cancer-affected individuals when the *BRCA* variant status is unknown may be considered **medically necessary** when there is documentation of a signed provider order (See Policy Guidelines) for *BRCA* testing and any of the following criteria (A.-D.) are met:
- A. Personal history of breast cancer; or
 - B. Personal history of ovarian (See Policy Guidelines), fallopian tube, and/or peritoneal cancer; or
 - C. Personal history of pancreatic cancer or prostate cancer (Gleason score ≥ 7) diagnosed at any age *and* one or more of the following:
 - 1. One or more close blood relatives (See Policy Guidelines) with any of the following:
 - a. Breast cancer
 - b. Ovarian (See Policy Guidelines), fallopian tube, and/or peritoneal cancer
 - c. Pancreatic or prostate cancer (Gleason score ≥ 7)
 - 2. Ashkenazi Jewish ancestry
 - D. The treating provider has documented genetic counseling and a determination that the patient is high-risk for a *BRCA* variant, and the US Preventive Services Task Force (USPSTF) *BRCA-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing* recommendation applies.
- III. **BRCA1/BRCA2 Variant for Individuals without Active Cancer and Without History of Cancer:** Genetic testing for *BRCA1* and *BRCA2* variants (including large genomic rearrangement testing i.e., BART) of 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 there is documentation of a signed provider order (See Policy Guidelines) for *BRCA* testing and any of the following criteria (A. or B.) are met:
- A. Individual is at increased risk for a *BRCA* variant as determined by any of the following five risk stratification tools endorsed by the USPSTF (See Policy Guidelines): Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, Family History Screen 7 (FHS-7); or
 - B. The treating provider has documented genetic counseling and a determination that the patient is high-risk for a *BRCA* variant and the USPSTF *BRCA-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing* recommendation applies.
- IV. Genetic testing for one or a combination of the following, with or without *BRCA* testing, may be considered **medically necessary** when one or more of the following criteria are met (See Policy Guidelines):
- A. *TP53* when the treating provider has documented a determination that the patient is at increased risk for a *TP53* variant, including in the evaluation of

possible Li-Fraumeni syndrome; or

B. *PALB2*, *PTEN*, *STK11* or *CDH1* when any of the following criteria are met:

1. *BRCA* criteria are met (any of the above Criteria I., II. or III.); or
2. From a family with a known *PALB2*, *PTEN*, *STK11* or *CDH1* variant; or
3. Personal history of or close blood relative or relatives (See Policy Guidelines) with a total of three or more occurrences of any of the following:
 - a. Pancreatic cancer
 - b. Prostate cancer (Gleason score ≥ 7)
 - c. Brain tumor
 - d. Endometrial cancer
 - e. Thyroid cancer
 - f. Kidney cancer
 - g. Dermatologic manifestations (see Policy Guidelines) and/or macrocephaly
 - h. Hamartomatous polyps of the gastrointestinal tract
 - i. Diffuse gastric cancer.

V. Genetic testing for *BRCA1* and *BRCA2* variants, including testing for large genomic rearrangements of both *BRCA1* and *BRCA2* (i.e., BART) is considered **not medically necessary** in patients who do not meet Criteria I., II., or III.

VI. Genetic testing for *PALB2*, *PTEN*, *STK11*, *CDH1*, and *TP53* that does not meet medical necessity Criteria IV. above is considered **not medically necessary**.

VII. Single gene or panel testing for any genes other than *BRCA1*, *BRCA2*, *PALB2*, *PTEN*, *STK11*, *CDH1*, or *TP53*, including *CHEK2* genetic abnormalities (variants, deletions, etc.), is considered **investigational**, regardless of family history.

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

POLICY GUIDELINES

SUBMISSION OF GENETIC TESTING DOCUMENTATION

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

1. For *BRCA* requests:
 - a. Provider's signed order for *BRCA* testing with the exact gene(s) and/or variants being tested.
 - b. *BRCA* order form or preauthorization form (please note that Regence does not have a specific *BRCA* order form). If the order form contains the information below, separate submission of that information is not necessary.
2. For all requests:
 - a. Name of genetic test(s) and/or panel test
 - b. Name of performing laboratory and/or genetic testing organization (more than one may be listed)

- c. Relevant billing codes
- d. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence of testing
- e. Clinical documentation by the provider (e.g., primary care physician, family practitioner, gynecologist) of family history and supporting rationale for the requested test(s)

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 positive screens of the five USPSTF-endorsed screening tools are listed below. These tools are accessible in the *Annals of Internal Medicine* article^[1] at: <http://annals.org/article.aspx?articleid=1791499>.

- 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

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 BRCAAnalysis CDx (Myriad Genetics), repeat *BRCA* variant testing with BRCAAnalysis 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.

DERMATOLOGICAL MANIFESTATIONS

A number of dermatological manifestations are indicative of *PTEN* Hamartoma/Cowden syndrome and Peutz-Jeghers syndrome. Examples of these include but are not limited to hyperpigmented macules of the lips and/or oral mucosa, melanoma, trichilemmomas, oral fibromas, palmoplantar keratoses, lipomas. For a more extensive list of dermatological manifestations for Cowden syndrome, please see the NCCN guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.^[2]

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

Human Genome Variation Society (HGVS) nomenclature^[3] 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.

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.

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.^[4]

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.^[5] *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%.^[2]

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.^[2]

CDH1

CDH1 (cadherin 1, type 1, E-cadherin [epithelial]) encodes a tumor suppressor that acts as a calcium dependent cell adhesion molecule. Loss of function is thought to contribute to progression in cancer by increasing proliferation, invasion, and/or metastasis. *CDH1* variants cause hereditary diffuse gastric cancer, which is associated with increased risk of lobular breast cancer, colorectal, thyroid and ovarian cancer.^[2] Variants in the gene are inherited in an autosomal dominant manner.

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).

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

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. Each of these genes, and the hereditary cancers they cause, are summarized below, with additional information in Table 1. 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.

TP53 is the only gene that causes Li-Fraumeni syndrome (LFS), which can be diagnosed based on the presence of a germline mutation in the *TP53* gene. Women with LFS are at increased risk of developing pre-menopausal breast cancer. The median age of breast cancer diagnosis in women with LFS is 33 years of age.^[6] In addition, some women who do not have a diagnosis of LFS but have a *TP53* germline pathogenic variant develop early onset breast cancer. In patients diagnosed with LFS prophylactic mastectomy is recommended in order to reduce the risks of a second primary breast tumor and to avoid radiation therapy. In addition, annual breast screening is recommended, beginning at 20 years of age.^[7]

PTEN is the only gene that causes *PTEN* hamartoma tumor syndrome (PHTS), which is diagnosed by a germline variant in the gene. The lifetime risk of developing breast cancer is up to 85%, with an average age of diagnosis between 38 and 46 years, with 50% penetrance by 50 years of age.^[8] Annual breast screening is recommended beginning at 30 to 35 years of age, or 5 to 10 years before the earliest known breast cancer in the family (whichever is earliest).^[9]

STK11 is the only gene that causes Peutz-Jeghers syndrome (PJS), which can be diagnosed based on the presence of a germline variant in the gene. In women diagnosed with PJS, prophylactic mastectomy to manage high-risk breast cancer and prophylactic hysterectomy and bilateral salpingo-oophorectomy after 35 years of age or after child-bearing has been completed to prevent gynecologic malignancy.^[9] Early-onset breast and ovarian cancers can occur in PJS patients and in relatives. The breast cancer risk in women with PJS approaches that of women who have a pathogenic variant in *BRCA1* or *BRCA2*. Annual breast screening is recommended, beginning at 25 years of age.^[9]

CDH1 is the only gene in which pathogenic variants are known to cause hereditary diffuse

gastric cancer (HDGC). Females with a *CDH1* germline pathogenic variant are at an increased lifetime risk (39%-52%) for lobular breast cancer, with the average age of onset being 53 years of age.^[9] In addition, some women who have a personal and family history of lobular breast cancer but no family history of DGC, have a *CDH1* germline pathogenic variant. In patients diagnosed with HDGC prophylactic mastectomy is recommended.^[2] Because lobular breast cancer is often difficult to diagnose on clinical examination and mammography, it may also be prudent to refer a woman who has a *CDH1* germline pathogenic variant to a high-risk breast cancer screening program, with screening beginning at 35 years of age.

Variants in the *PALB2* gene influencing breast cancer risk are moderately penetrant. The *PALB2* protein 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. Most pathogenic *PALB2* variants are truncating frameshift or stop codons, and are found throughout the gene. Pathogenic *PALB2* variants are uncommon in unselected populations and prevalence varies by ethnicity and family history. In women with a family history of breast cancer, the prevalence of pathogenic *PALB2* variants ranges between 0.9% and 3.9%,^[4] or substantially higher than in an unselected general population. Depending on population prevalence, *PALB2* may be responsible for as much as 2.4% of hereditary breast cancers;^[4] and in populations with founder variants cause 0.5% to 1% of all breast cancers,^[10]

Table 1. Variants Associated with Increased risk of Hereditary Breast Cancer

Gene	Disease	Penetrance ^a	Incr. risk of Hereditary Breast Cancer ^{a, b}	Prevalence ^{a,b}
<i>BRCA1</i>	Hereditary BrCa	Intermediate - high	Up to 83%	1/300 ^a
<i>BRCA2</i>	Hereditary BrCa	Intermediate - high.	Up to 62%	1/800 ^a
<i>PTEN</i>	Cowden syndrome, <i>PTEN</i> hamartoma tumor syndrome	High	Up to 85%	1/200,000 ^b
<i>STK11</i>	Peutz-Jeghers syndrome	High	Up to 57%	1/25,000 – 1/280,000 ^b
<i>CDH1</i>	Hereditary diffuse gastric cancer	High	Up to 52%	1/2500 – 1/10,000 ^b
<i>PALB2</i>	Hereditary BrCa and Fanconi anemia	Intermediate	Up to 35%	Not available

^a As described in the NCCN guidelines^[2]

^b As described in GeneReviews^[9]

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

A number of publications 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^[11] cited above, 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.

An article by Schmidt (2016) evaluated data on *CHEK2* variant status and breast cancer risk from the Breast Cancer Association Consortium.^[12] 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% confidence interval [CI] 1.90 to 3.10). Decker (2017) published a similar analysis from the U.K. of genetic testing results in 13,087 breast cancer cases, and 5,488 controls.^[13] Truncating variants in *CHEK2* were associated with a significantly increased risk of breast cancer (odds ratio [OR] 3.11, 95% CI 2.15 to 4.69).

An article in the New England Journal of Medicine by Easton(2015)^[14] reported that the magnitude of relative risk of breast cancer associated with *CHEK2* truncating variants is likely to be moderate and unlikely to be high. Based on two large case-control analyses, the authors calculated an estimated relative risk of breast cancer associated with *CHEK2* variants of 3.0 (90% CI 2.6 to 3.5), and an absolute risk of 29% by age 80 years.

In a meta-analysis, the link between *CHEK2 1100delC* heterozygote and breast cancer risk was investigated.^[15] 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.

Cybulski (2011) reported on the risk of breast cancer in women with a *CHEK2* variant with and without a family history of breast cancer.^[16] A total of 7,494 *BRCA1*-negative breast cancer patients and 4,346 controls were genotyped for the four *CHEK2* founder variants. A truncating variant was present in 227 patients (3.0%) and in 37 controls (0.8%, OR 3.6, 95% CI 2.6 to 5.1). The OR was higher for women with a first- or second-degree relative with breast cancer (OR 5.0, 95% CI 3.3 to 7.6) than for women with no family history (OR 3.3, 95% CI 2.3 to 4.7), and if both a first- and second-degree relative were affected with breast cancer, the OR was 7.3 (95% CI 3.2 to 16.8). The authors estimated the lifetime risk of breast cancer for carriers of *CHEK2* truncating variants to be 20% for a woman with no affected relative, 28% for a woman with one second-degree relative affected, 34% for a woman with one first-degree relative affected, and 44% for a woman with both a first- and second-degree relative affected.

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 noncarriers, 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 noncarriers 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*.

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 3592 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 *CHEK2* variant carriers was similar to noncarriers, 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 carriers of the missense variant and noncarriers was similar, as for carriers of a truncating variant and noncarriers.

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 *CHEK2* variant carriers and noncarriers.^[19] 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%) were noncarriers. 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 *CHEK2 1100delC* variant carriers were observed. Corresponding numbers among noncarriers were 4864 (19%), 2732 (11%), and 607 (2%), respectively. At the time of diagnosis, *CHEK2* variant carriers versus noncarriers were on average four years younger ($p < 0.001$) and more often had a positive family history ($p < 0.001$).

In a 2012 systematic review and meta-analysis, authors identified fifteen case-control studies with 19,621 cases and 27,001 controls that were included in their analysis.^[20] 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.^[21] 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.

Myszka (2011) conducted a case-control study that compared 284 breast and 113 ovarian cancer patients to 287 healthy Polish women and found that the cancer-affected individuals did not have a higher rate of *CHEK2* variants.^[22]

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.^[23]

In their review, 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).^[24]

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 *CHEK2* carriers 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.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK GUIDELINES (NCCN)

***BRCA1* and *BRCA2* testing**

- The NCCN Guidelines for Genetic/Familial High-Risk Assessment for Breast and Ovarian Cancer (v. 2.2019)^[2] recommend BRCA testing in select individuals.
- According to NCCN guidelines, patients who meet criteria for genetic testing should be tested for variants in *BRCA1* and *BRCA2*.

- In patients with a known familial *BRCA* variant, targeted testing for the specific variant is recommended.
- In patients with no known familial *BRCA* variant, multi-gene testing or comprehensive *BRCA1/BRCA2* testing, including full sequencing and testing for large genomic rearrangements should be considered; if the affected individual is of Ashkenazi Jewish descent, testing for the three known founder variants (185delAG and 5182insC in *BRCA1*; 6174delT in *BRCA2*) should be completed first.

***TP53* testing**

- The NCCN Guidelines for Genetic/Familial High-Risk Assessment for Breast and Ovarian Cancer (v. 2.2019)^[2] recommend *TP53* testing in select individuals.
- In patients with a known familial *TP53* variant, targeted testing for the specific variant is recommended.
- In patients with no known familial *TP53* variant, multi-gene testing or comprehensive *TP53* testing should be considered.

CHEK2

NCCN does not include recommendations for genotyping low or moderate penetrance susceptibility genes, such as *CHEK2*.

US PREVENTIVE SERVICES TASK FORCE (USPSTF)

The 2013 USPSTF guideline^[1] titled *Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility* recommends the following for:

- Women who have family members with breast, ovarian, tubal, or peritoneal cancers
Primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (*BRCA1* or *BRCA2*). Women with positive screening results should receive genetic counseling and, if indicated after counseling, *BRCA* testing (Grade B recommendation).
- Women whose family history is not associated with an increased risk
USPSTF recommends against routine genetic counseling or *BRCA* testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes (Grade D recommendation).

SOCIETY OF GYNECOLOGIC ONCOLOGY (SGO)

In 2014, the SGO^[25] 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 (ASCO)

The ASCO^[26] (2010) policy statement on genetic and genomic testing for cancer susceptibility states that testing for high-penetrance mutations in appropriate populations has clinical utility in that they inform clinical decision making and facilitate the prevention or amelioration of adverse health outcomes but that genetic testing for intermediate-penetrance mutations are of uncertain clinical utility because the cancer risk associated with the mutation is generally too small to form an appropriate basis for clinical decision making. ASCO recommends that genetic tests with uncertain clinical utility (low to moderate penetrance mutations) be administered in the context of clinical trials.

SUMMARY

There is enough research to show that testing for variants in *BRCA1* and *BRCA2* genes can guide treatment decisions and improve health outcomes for people with 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, *BRCA1* and/or *BRCA2* variant testing may be considered medically necessary in patients suspected of hereditary breast or ovarian cancer, when criteria are met.

There is enough research to show that *TP53* genetic testing improves health outcomes for individuals who meet the policy criteria, including those suspected of having Li-Fraumeni syndrome (LFS) or Li-Fraumeni-like syndrome (LFL) and relatives of individuals with *TP53* variants. Clinical guidelines based on research recommend *TP53* genetic testing for individuals that are at increased risk for a *TP53* variant. Therefore, *TP53* genetic testing may be considered medically necessary when policy criteria are met.

There is enough research to show that genetic testing for one or more of the following genes: *PALB2*, *PTEN*, *STK11* and/or *CDH1*, can help guide screening and treatment decisions and improve health outcomes for certain people with hereditary breast cancer. Therefore *PALB2*, *PTEN*, *STK11* and/or *CDH1* variant testing may be considered medically necessary in patients suspected of hereditary breast cancer when criteria are met.

There is enough research to show that *BRCA1* and/or *BRCA2*, *TP53*, *PALB2*, *PTEN*, *STK11* and/or *CDH1* genetic testing does not improve health outcomes for individuals who do not meet the policy criteria. Therefore, *TP53*, *PALB2*, *PTEN*, *STK11* and/or *CDH1* genetic testing is considered not medically necessary when policy criteria are not met.

There is not enough research to show that testing for *CHEK2* variants can improve health outcomes for people suspected of having hereditary breast/ovarian cancer. There are no clinical guidelines based on research that recommend testing for *CHEK2* variants in people with any conditions. Therefore, testing for *CHEK2* variants is considered investigational.

There is not enough research to show that testing for genes other than *BRCA1*, *BRCA2*, *PALB2*, *PTEN*, *STK11*, *CDH1*, and/or *TP53* can improve health outcomes for people with hereditary breast and ovarian cancer. Therefore, testing for any other genes, including panel testing of *BRCA1*, *BRCA2*, *PALB2*, *PTEN*, *STK11*, *CDH1*, and/or *TP53* done in combination with other genes, is considered investigational.

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CODES

Codes	Number	Description
CPT	81162	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis

Codes	Number	Description
	81211	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)
	81212	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
	81213	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants
	81214	BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)
	81215	BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
	81216	BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81217	BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian 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
	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, cytogenomic array analysis for neoplasia)
	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

Appendix 1 Recommended Testing Strategy

- Individuals with unknown familial BRCA variant
 - Non-Ashkenazi Jewish descent
 - If no familial variant can be identified, two possible testing strategies are:
 - 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