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 mutations in the BRCA genes (BRCA1 and BRCA2). Identification of patients with BRCA mutations 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 mutations and therefore, each lineage must be considered separately.

BRCA1/BRCA2 TESTING

1. Family with a Known BRCA1/BRCA2 Mutation

   Genetic testing for BRCA1 and BRCA2 mutations (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 mutation and there is documentation of a signed provider order^ for BRCA testing.
II. **Individuals with Active Cancer or a Personal History of Cancer**

Genetic testing for *BRCA1* and *BRCA2* mutations (including large genomic rearrangement testing i.e., BART) in cancer-affected individuals when the *BRCA* mutation status is unknown may be considered **medically necessary** when there is documentation of a signed provider order for *BRCA* testing and any of the following criteria (A.-D.) are met:

A. Personal history of breast cancer including male breast cancer

B. Personal history of ovarian*, fallopian tube, and/or peritoneal cancer

C. Personal history of pancreatic cancer or prostate cancer (Gleason score ≥ 7) diagnosed at any age and one or more close blood relatives* with any of the following (for pancreatic cancer and of Ashkenazi Jewish ancestry, no additional affected relative is needed):
   1. breast cancer
   2. ovarian*, fallopian tube, and/or peritoneal cancer
   3. pancreatic or prostate cancer (Gleason score ≥ 7)

D. The treating provider has documented genetic counseling and a determination that the patient is high-risk for a *BRCA* mutation, and the US Preventive Services Task Force (USPSTF) *BRCA-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing* recommendation applies.

III. **Individuals without Active Cancer and Without History of Cancer**

Individuals with no personal history of the following: breast cancer, ovarian* cancer, pancreatic cancer, or prostate cancer (Gleason score ≥ 7).

Genetic testing for *BRCA1* and *BRCA2* mutations (including large genomic rearrangement testing i.e., BART) of cancer-unaffected individuals with unknown mutation status, may be considered **medically necessary** when there is documentation of a signed provider order for *BRCA* testing and any of the following criteria (A. or B.) are met:

A. Individual is at increased risk for a *BRCA* mutation as determined by any of the 5 risk stratification tools endorsed by the USPSTF listed below (See Policy Guidelines):
   - Ontario Family History Assessment Tool
   - Manchester Scoring System
   - Referral Screening Tool
   - Pedigree Assessment Tool
   - Family History Screen 7 (FHS-7)

B. The treating provider has documented genetic counseling and a determination that the patient is high-risk for a *BRCA* mutation and the USPSTF *BRCA-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing* recommendation applies.
Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing

IV. Genetic testing for BRCA1 and BRCA2 mutations, 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.

OTHER GENETIC RISK EVALUATION**

V. Genetic testing for one or a combination of the following: PALB2, PTEN, TP53, STK11 and/or CDH1, with or without BRCA testing, may be considered medically necessary when any one or more of the following criteria are met (See Policy Guidelines):

A. BRCA criteria are met (any of the above Criteria I., II. or III.); or
B. From a family with a known PALB2, PTEN, TP53, STK11 or CDH1 mutation; or
C. Personal history of or close blood relative or relatives* with a total of three or more occurrences of any of the following:
   1. pancreatic cancer
   2. prostate cancer (Gleason score ≥ 7)
   3. sarcoma
   4. adrenocortical carcinoma
   5. brain tumor
   6. endometrial cancer
   7. thyroid cancer
   8. kidney cancer
   9. dermatologic manifestations (see Policy Guidelines) and/or macrocephaly
   10. hamartomatous polyps of the gastrointestinal tract
   11. diffuse gastric cancer.

VI. Genetic testing for one or a combination of the following: PALB2, PTEN, TP53, STK11 and/or CDH1, with or without BRCA testing, is considered not medically necessary when Criterion V. is not met.

VII. Testing for any genes other than BRCA1, BRCA2, PALB2, PTEN, TP53, STK11 or CDH1, including CHEK2 genetic abnormalities (mutations, deletions, etc.), is considered investigational, including but not limited to in breast cancer-affected and unaffected patients, regardless of family history.

PANEL TESTING**

VIII. Panel genetic testing for BRCA1, BRCA2, PALB2, PTEN, TP53, STK11 and/or CDH1 with any other genes for the evaluation of hereditary breast and ovarian cancer is considered investigational.

SEE POLICY GUIDELINES BELOW FOR:
^Submission of \textit{BRCA} Testing Documentation

*Policy Definitions

**List of genetic panels that may be considered medically necessary when the relevant policy criteria above are met for all genes and/or gene mutations requested. Please note that the list does not include genetic panels that only test for \textit{BRCA1} and/or \textit{BRCA2} mutations (including large genomic rearrangement testing i.e., BART) which may be considered medically necessary when the \textit{BRCA} criteria (Criteria I., II., or III.) are met.

\textbf{NOTE:} A summary of the supporting rationale for the policy criteria is at the end of the policy.

\textbf{POLICY GUIDELINES}

\textbf{SUBMISSION OF BRCA TESTING DOCUMENTATION}

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

1. Provider’s signed order for \textit{BRCA} testing with the exact gene(s) and/or mutations being tested
2. \textit{BRCA} order form or preauthorization form (please note that Regence does not have a specific \textit{BRCA} order form). If the order form contains the information below, separate submission of that information is not necessary.
3. Name of genetic test(s) and/or panel test
4. Name of performing laboratory and/or genetic testing organization (more than one may be listed)
5. Relevant billing codes
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)

\textbf{DEFINITIONS}

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

- \textit{1st-degree relatives} are parents, siblings, and children of an individual;
- \textit{2nd-degree relatives} are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings (siblings with one shared biological parent) of an individual; and
- \textit{3rd-degree relatives} are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first-cousins.

\textit{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 ductal carcinoma in situ are considered breast cancer for the purposes of this policy.

RISK STRATIFICATION TOOLS FOR IDENTIFYING AN INCREASED RISK OF BRCA MUTATIONS

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 mutation be found in the affected family member(s), unaffected family member DNA can be tested specifically for the same mutation without having to sequence the entire gene.

BRCA TESTING FOR TREATMENT WITH LYNPARZA™ (OLAPARIB)

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

BRCA TESTING FOR TREATMENT WITH RUBRACA™ (RUCAPARIB)

For women who have had a previous BRCA test other than FoundationFocus CDxBRCA (Foundation Medicine), repeat BRCA mutation 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/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]

**GENETIC PANELS THAT MAY BE CONSIDERED MEDICALLY NECESSARY**
The panels listed below may be considered medically necessary when the criteria above are met for every gene and/or gene mutation included in the genetic panel. Other genetic panels may be considered medically necessary when all genes and/or gene mutations meet the medical necessity criteria in the policy.

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer High Risk Panel</td>
<td>GeneDx</td>
</tr>
<tr>
<td>Hereditary Breast and Ovarian Cancer Syndrome Panel</td>
<td>Invitae</td>
</tr>
<tr>
<td>BRCAplus</td>
<td>Ambry</td>
</tr>
</tbody>
</table>

**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 PTEN Hamartoma Tumor Syndrome, Genetic Testing, Policy No. 63
4. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64

**BACKGROUND**

**BRCA1 AND BRCA2 SEQUENCING**

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 mutations 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 with or without male cases, but without ovarian cancer. For this policy, both will be referred to collectively as hereditary breast and/or ovarian cancer.

Germline mutations in the BRCA1 and BRCA2 genes are responsible for cancer susceptibility in the majority of HBOC families, especially if ovarian cancer or male breast cancer are features. However, in site-specific breast cancer, BRCA mutations are responsible for only a proportion of affected families, and research to date has not yet identified other moderate or high-penetrance gene mutations that account for disease in these families. BRCA gene mutations 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 mutation in cancer cases, and to identify family members with increased cancer risk. Family members without existing cancer who are found to have BRCA mutations 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* mutation have a 14% lifetime risk of breast cancer by age 50, which increases to 35% by age 70.[3]

**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.[4] *PTEN* mutations are inherited in an autosomal dominant manner. There is a spectrum of disorders that result from germline mutations 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]

**TP53**

*TP53* (tumor protein 53) encodes a tumor suppressor that is located in the cell nucleus and binds directly to DNA. It is known as the “guardian of the genome” and has important roles in cell cycle arrest, apoptosis, senescence, DNA repair, and cellular metabolism. *TP53* mutations are associated with hereditary cancers such as Li-Fraumeni syndrome, and are inherited in an autosomal dominant manner. Women with LFS are at greatly increased risk of developing early-onset breast cancer, with the median age of diagnosis being 33 years of age.[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* mutations 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* mutations cause hereditary diffuse gastric cancer, which is associated with increased risk of lobular breast cancer, colorectal, thyroid and ovarian cancer.[2] Mutations in the gene are inherited in an autosomal dominant manner.
**CHEK2**

*CHEK2* (cell cycle checkpoint kinase2) 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* mutation, 1100delC in exon 10 has been associated with familial breast cancers.

### EVIDENCE SUMMARY

The clinical utility of testing for mutations 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*, *TP53*, *STK11* and *CDH1*; 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, mutations in these genes are thought to account for at least 5–10% 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 mutations 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.

*PTEN* is the only gene that causes *PTEN* Hamartoma Tumor Syndrome (PHTS), which is diagnosed by a germline mutation 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.[6] Annual breast screening is recommended beginning at 30 years of age.[6]

*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.[7] 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, bi-annual breast screening is recommended, beginning at 20 years of age.[2]

*STK11* is the only gene that causes Peutz-Jeghers syndrome (PJS), which can be diagnosed based on the presence of a germline mutation 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.[6] 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.[6] Up to 70% of LFS-related breast cancers are predominantly positive for HER2/neu, thereby impacting prognosis and treatment decisions.

*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.[6] 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 HDGGC 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.

Mutations 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%,[3] 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;[3] and in populations with founder variants cause 0.5% to 1% of all breast cancers.[8]

**Table 1. Mutations Associated with Increased risk of Hereditary Breast Cancer**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Disease</th>
<th>Penetrancea</th>
<th>Incr. risk of Hereditary Breast Cancera, b</th>
<th>Prevalencea,b</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>Hereditary BrCa</td>
<td>Intermediate- high</td>
<td>Up to 83%</td>
<td>1/300a</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Hereditary BrCa</td>
<td>Intermediate- high</td>
<td>Up to 62%</td>
<td>1/800 a</td>
</tr>
<tr>
<td>PTEN</td>
<td>Cowden syndrome, PTEN hamartoma tumor syndrome</td>
<td>High</td>
<td>Up to 85%</td>
<td>1/200,000 b</td>
</tr>
<tr>
<td>TP53</td>
<td>Li-Fraumeni syndrome</td>
<td>High</td>
<td>4-8% of BRCA1/2 negative; 100% are early onset and up to 83% are HER2+; current recommendations are: prophylactic mastectomy, bi-annual breast exams starting at age 20 or earlier.</td>
<td>1/5000 – 1/20,000 b</td>
</tr>
<tr>
<td>STK11</td>
<td>Peutz-Jeghers syndrome</td>
<td>High</td>
<td>Up to 57%</td>
<td>1/25,000 – 1/280,000 b</td>
</tr>
<tr>
<td>CDH1</td>
<td>Hereditary diffuse gastric cancer</td>
<td>High</td>
<td>Up to 52%</td>
<td>1/2500 – 1/10,000 b</td>
</tr>
</tbody>
</table>
The focus of the scientific evidence review below is on the investigational indications only, such as CHEK2 testing. The evidence review 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) mutations 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 mutations are much less common than BRCA mutations and BRCA rearrangements. For example, in the study by Walsh\[9\] 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 mutations.

A 2015 article in the New England Journal of Medicine by Easton et al.\[10\] reported that the magnitude of relative risk of breast cancer associated with CHEK2 truncating mutations is likely to be moderate and unlikely to be high. On the basis of two large case-control analyses, the authors calculated an estimated relative risk of breast cancer associated with CHEK2 mutations of 3.0 (90% confidence interval [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.\[11\] 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 2011, Cybulski et al. reported on the risk of breast cancer in women with a CHEK2 mutation with and without a family history of breast cancer.\[12\] A total of 7,494 BRCA1-negative breast cancer patients and 4,346 controls were genotyped for the 4 CHEK2 founder mutations. A truncating mutation was present in 227 patients (3.0%) and in 37 controls (0.8%; odds ratio [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 mutations to be 20% for a woman with no affected relative, 28% for a woman with one second-degree relative affected, 34% for a
A woman with one first-degree relative affected, and 44% for a woman with both a first- and second-degree relative affected.

In 2008 Weischer et al. 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. 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 mutation-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 mutation 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 2014 study by Huzarski et al. estimated the 10-year survival rate for patients with early-onset breast cancer, with and without CHEK2 mutations. 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 mutations 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 mutation (140 with truncating mutations, 347 with missense mutations). Mean follow-up was 8.9 years. Ten-year survival for CHEK2 mutation 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 mutation and noncarriers was similar, as for carriers of a truncating mutation and noncarriers.

In 2012, Weischer et al. 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 mutation carriers and noncarriers. 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 mutation carriers were observed. Corresponding numbers among noncarriers were 4864 (19%), 2732 (11%), and 607 (2%), respectively. At the time of
diagnosis, CHEK2 mutation 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.[16] Authors reported a significant association found between the CHEK2 I157T 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 I157T C variant and increased risk of lobular type breast tumors. Authors concluded the CHEK2 I157T variant may be another important genetic mutation which increases risk of breast cancer, especially the lobular type. The methodological quality of this review was limited; the evidence was not quality appraised for risk of bias.

A meta-analysis by Han et al. investigated the relationship of the CHEK2 I157T variant and the incidence of cancer.[17] 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 I157T variant was an important cancer gene, which increases cancer risk, especially for breast and colorectal cancer.

Myszka et al. 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 mutations.[18]

Zhang et al. 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.[19]

In their review, Peng et al. 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 odds ratios (OR) 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).[20]

**CHEK2 Evidence Summary**

The evidence for testing for CHEK2 mutations 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 mutation 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, accurate 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 mutation have a risk that is similar to the risk with a high-penetrance mutation 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 mutations, such as CHEK2, are not standardized, nor is it known if testing for CHEK2 mutations 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. 2.2017) recommend BRCA testing in select individuals.
- According to NCCN guidelines, patients who meet criteria for genetic testing should be tested for mutations in BRCA1 and BRCA2.
- In patients with a known familial BRCA mutation, targeted testing for the specific mutation is recommended.
- In patients with no known familial BRCA mutation, 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 mutations (185delAG and 5182insC in BRCA1; 6174delT in BRCA2) should be completed first.

**CHEK2**

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

**PALB2**

NCCN includes PALB2 with BRCA1/2, TP53, PTEN, STK11, and CDH1 in a list of highly penetrant genes that could potentially be included in a multi-gene test.

**US PREVENTIVE SERVICES TASK FORCE (USPSTF)**

The 2013 USPSTF guideline 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[21] 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[22] (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 mutations 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 mutation 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 genetic testing for one or more of the following genes: PALB2, PTEN, TP53, 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, TP53, STK11 and/or CDH1 mutation testing may be considered medically necessary in patients suspected of hereditary breast cancer, when criteria are met.
There is not enough research to show that testing for CHEK2 mutations 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 mutations in people with any conditions. Therefore, testing for CHEK2 mutations is considered investigational.

There is not enough research to show that testing for genes other than BRCA1, BRCA2, PALB2, PTEN, TP53, STK11 and/or CDH1 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, TP53, STK11 and/or CDH1 done in combination with other genes, is considered investigational.

REFERENCES


### CODES

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| HCPCS | None |

**Appendix 1 Recommended Testing Strategy**

- Individuals meeting the criteria above should be tested for **BRCA1** and **BRCA2** mutations
- Individuals with a **known** familial BRCA mutation
  - Targeted testing for the specific mutation is recommended
- Individuals with **unknown** familial BRCA mutation
  - Non-Ashkenazi Jewish descent
Appendix 1 Recommended Testing Strategy

- If no familial mutation 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 mutation (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 mutations first (i.e., 185delAG and 5182insC in BRCA1; 6174delT in BRCA2).
    - If testing is negative for the founder mutations, comprehensive genetic testing may be considered.

Comprehensive Mutation Analysis

Comprehensive mutation 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