Protocol

Genetic Testing for Hereditary Breast, Ovarian Cancer Syndrome and Other High-Risk Cancers

(20402, 204126)

Medical Benefit		**Effective Date**: 10/01/20	**Next Review Date**: 07/21
Preauthorization	Yes	**Review Dates**: 02/07, 01/08, 11/08, 09/09, 05/10, 05/11, 01/12, 01/13, 01/14, 05/14, 05/15, 05/16, 09/16, 03/17, 09/17, 07/18, 07/19, 01/20, 05/20, 07/20	

Preauthorization is required for services which may be medically necessary under this protocol. For tests that this protocol considers investigational, if the physician feels the service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

RELATED PROTOCOLS

Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing

Genetic Testing for Li-Fraumeni Syndrome

Populations	Interventions	Comparators	Outcomes
Individuals: • With cancer, or a personal or family cancer history and criteria suggesting a risk of hereditary breast/ ovarian cancer syndrome	Interventions of interest are: • Genetic testing for a BRCA1 or BRCA2 mutation	Comparators of interest are: • Standard of care without genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life
Individuals: • With other high-risk cancers (e.g., cancers of the fallopian tube, pancreas, prostate)	Interventions of interest are: • Genetic testing for a BRCA1 or BRCA2 variant	Comparators of interest are: • Standard of care without genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life
Individuals: • With risk of hereditary breast/ovarian cancer	Interventions of interest are: • Genetic testing for a PALB2 variant	Comparators of interest are: • No genetic testing for PALB2 variants	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity
Individuals: • With risk of hereditary breast/ovarian cancer	Interventions of interest are: • Genetic testing for CHEK2 variant	Comparators of interest are: • No genetic testing for CHEK2 variants	Relevant outcomes include: • Overall survival • Disease specific survival • Test validity
Individuals: • With risk of hereditary breast/ovarian cancer	Interventions of interest are: • Genetic testing for an ATM variant	Comparators of interest are: • No genetic testing for an ATM variants	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity

DESCRIPTION

Hereditary breast and ovarian cancer syndrome describe the familial cancer syndromes related to variants in the BRCA genes (BRCA1 located on chromosome 17q21, BRCA2 located on chromosome 13q12-13). Families with hereditary breast and ovarian cancer syndrome have an increased susceptibility to the following types of cancer: breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer (at any age), cancer of the fallopian tube, primary peritoneal cancer, prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer.

It is estimated that 3% to 5% of women presenting for assessment for hereditary breast/ovarian cancer risk have a variant in a gene that moderately increases the risk of cancer. PALB2, CHEK2, and ATM variants are considered to be of moderate penetrance. Carriers of PALB2 have an approximately two- to 13-fold increased risk of developing breast cancer compared with the general population, and risk for CHEK2 and ATM carriers is increased approximately two- to four-fold. Risk estimates may be higher in patients with a family history of breast cancer or a family history of a specific variant.

SUMMARY OF EVIDENCE

For individuals who have cancer or a personal or family cancer history and meet criteria suggesting a risk of hereditary breast and ovarian cancer syndrome who receive genetic testing for a BRCA1 or BRCA2 variant, the evidence includes a TEC Assessment and studies of variant prevalence and cancer risk. The relevant outcomes are overall survival (OS), disease-specific survival, test validity, and quality of life. The accuracy of variant testing has been shown to be high. Studies of lifetime risk of cancer for carriers of a BRCA variant have shown a risk as high as 85%. Knowledge of BRCA variant status in individuals at risk of a BRCA variant may impact health care decisions to reduce risk, including intensive surveillance, chemoprevention, and/or prophylactic intervention. In individuals with BRCA1 or BRCA2 variants, prophylactic mastectomy and oophorectomy have been found to significantly increase disease-specific survival and OS. Knowledge of BRCA variant status in individuals diagnosed with breast cancer may impact treatment decisions. A randomized controlled trial has reported that although patients with human epidermal growth factor receptor 2-negative metastatic breast cancer and a BRCA variant did not experience significantly longer OS, they experienced significantly longer progression-free survival with a targeted therapy vs. standard therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have other high-risk cancers (e.g., cancers of the fallopian tube, pancreas; prostate) who receive genetic testing for a BRCA1 or BRCA2 variant, the evidence includes studies of variant prevalence and cancer risk. The relevant outcomes are OS, disease-specific survival, test validity, and quality of life. The accuracy of variant testing has been shown to be high. Knowledge of BRCA variant status in individuals with other high-risk cancers can inform decisions regarding genetic counseling, chemotherapy, and enrollment in clinical trials. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with a risk of hereditary breast/ovarian cancer who receive genetic testing for a PALB2 variant, the evidence includes studies of clinical validity and studies of breast cancer risk, including a meta-analysis. The relevant outcomes are overall survival, disease-specific survival, and test validity. Evidence supporting clinical validity was obtained from numerous studies reporting relative risks (RR) or odds ratios (two studies estimated penetrance). Study designs included family segregation, kin-cohort, family-based case-control, and population-based case-control. The number of pathogenic variants identified in studies varied from one (founder mutations) to 48. The RR for breast cancer associated with a PALB2 variant ranged from 2.3 to 13.4, with the two family-based studies reporting the lowest values. Evidence of preventive interventions in women with PALB2 variants is

indirect, relying on studies of high-risk women and BRCA carriers. These interventions include screening with magnetic resonance imaging, chemoprevention, and risk-reducing mastectomy. Given the penetrance of PALB2 variants, the outcomes following bilateral and contralateral risk-reducing mastectomy examined in women with a family history consistent with hereditary breast cancer (including BRCA1 and BRCA2 carriers) can be applied to women with PALB2 variants-with the benefit-to-risk balance affected by penetrance. In women at high-risk of hereditary breast cancer who would consider risk-reducing interventions, identifying a PALB2 variant provides a more precise estimated risk of developing breast cancer compared with family history alone and can offer women a more accurate understanding of benefits and potential harms of any intervention. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with risk of hereditary breast/ovarian cancer who receive genetic testing for a CHEK2 variant, the evidence includes studies of variant prevalence and studies of breast cancer risk. The relevant outcomes are overall survival, disease-specific survival, and test validity. The available studies on clinical validity have demonstrated that CHEK2 variants are of moderate penetrance, with lower RR for breast cancer than PALB2, and confer a risk of breast cancer two to three times that of the general population. Direct evidence for the clinical utility of genetic testing for CHEK2 variants in individuals with risk of hereditary breast/ovarian cancer was not identified. It is unclear the RR associated with the moderate penetrance variants other than PALB2 would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to the case of PALB2, where the penetrance approaches that of a BRCA variant, there is unlikely to be a similar benefit-to-risk calculus for risk-reducing mastectomy in women with a CHEK2 variant. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with risk of hereditary breast/ovarian cancer who receive genetic testing for an ATM variant, the evidence includes studies of variant prevalence and studies of breast cancer risk. The relevant outcomes are overall survival, disease-specific survival, and test validity. The available studies on clinical validity have demonstrated that ATM variants are of moderate penetrance, with lower RR for breast cancer than PALB2; 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 hereditary breast/ovarian cancer was not identified. It is unclear that the RR associated with the moderate penetrance variants-other than PALB2-would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to the case of PALB2, where the penetrance approaches that of a BRCA variant, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with an ATM variant. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

Genetic testing should be performed in a setting that has suitably trained health care providers who can give appropriate pre- and posttest counseling and that has access to a Clinical Laboratory Improvement Amendments-licensed laboratory that offers comprehensive variant analysis (see Policy Guidelines section: Comprehensive Variant Analysis).

BRCA1, BRCA2, PALB2

Patients With Cancer or With a Personal History of Cancer

Genetic testing for a BRCA1 and BRCA2 variants (including large genomic rearrangement testing, i.e., BART) and for PALB2 variants in cancer-affected individuals may be considered **medically necessary** under ANY of the following circumstances:

- Individual from a family with a known BRCA1 or BRCA2 variant

- Personal history of breast cancer and one or more of the following:
  - Diagnosed at age ≤45 years
  - Diagnosed 46 to 50 years with:
    - An additional breast cancer primary at any age
    - One or more close relative with breast cancer at any age
    - One or more close relative with high grade (Gleason score ≥7) prostate cancer
    - An unknown or limited family history
  - Diagnosed ≤60 years with:
    - Triple-negative breast cancer
  - Diagnosed at any age with:
    - One or more close blood relative with:
      - Breast cancer diagnosed ≤50 years; or
      - Ovarian carcinoma; or
      - Male breast cancer; or
      - Metastatic prostate cancer; or
      - Pancreatic cancer
    - Two or more additional diagnoses of breast cancer at any age in patient and/or close blood relative
- Ashkenazi Jewish ancestry
- Personal history of ovarian carcinoma
- Personal history of male breast cancer
- Personal history of pancreatic cancer
- Personal history of metastatic prostate cancer
- Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with:
  - One or more close blood relative with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer at any age or breast cancer <50 years; or
  - Two or more close blood relatives with breast or prostate cancer (any grade) at any age; or
  - Ashkenazi Jewish ancestry
- BRCA1 or BRCA2 pathogenic or likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline pathogenic or likely pathogenic variant analysis
- Regardless of family history, some individuals with an BRCA-related cancer may benefit from genetic testing to determine eligibility for targeted treatment
- An individual who does not meet the other criteria but with one or more first- or second-degree blood relatives meeting any of the above criteria

- The member has a history of breast cancer and belongs to a population at risk for specific mutations due to ethnic background (e.g., Ashkenazi Jewish, Icelandic, Swedish, Hungarian or Dutch descent).

PATIENTS WITHOUT CANCER OR WITHOUT HISTORY OF CANCER

(See Policy Guidelines section: Testing Unaffected Individuals.)

Genetic testing for BRCA1 and BRCA2 variants of cancer-unaffected individuals may be considered **medically necessary** under any of the following circumstances:

- Individual from a family with a known BRCA1 or BRCA2 variant
- 1st- or 2nd-degree blood relative meeting any criterion listed above for Patients With Cancer
- 3rd-degree blood relative with breast cancer and/or ovarian, fallopian tube, or primary peritoneal cancer AND two or more 1st-, 2nd-, or 3rd-degree relatives with breast cancer (one or more at age ≤50 years) and/or ovarian, fallopian tube, or primary peritoneal cancer.

*For familial assessment, 1st-, 2nd-, and 3rd-degree relatives are blood relatives on the same side of the family (maternal or paternal).

- 1st-degree relatives are parents, siblings, and children.
- 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.
- 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.

Genetic testing for BRCA1 and BRCA2 variants in cancer-affected individuals or of cancer-unaffected individuals with a family history of cancer when criteria above are not met is considered **investigational**.

Genetic testing in minors for BRCA1 and BRCA2 variants and PALB2 variants is **investigational**.

BRCA and BART testing as a screening test for cancer in women in the general population are **investigational**.

BRCA and BART testing for unaffected members of high-risk populations (e.g., Ashkenazi Jewish descendant) who have no relatives with a history of breast, ovarian, fallopian tube or primary peritoneal cancer at any age is **investigational**.

PALB2, PTEN, STK11, CDH1

For an individual with a personal history of cancer or close blood relative with cancer (other than breast cancer) genetic testing for PALB2, PTEN, STK11, and or CDH1 would be considered **medically necessary** with three or more occurrences of any of the following cancers:

- Pancreatic cancer
- Prostate cancer (Gleason >7)
- Brain tumor
- Kidney cancer
- Endometrial cancer
- Thyroid cancer
- Hamartomatous polyps of the GI tract
- Diffuse gastric cancer

PTEN, STK11, CHD1

For an individual from a family with a known variant in PTEN, STK11, and or CDH1, genetic testing for these genes may be considered **medically necessary**.

CHEK2 and ATM

Testing for CHEK2 and/or ATM genetic abnormalities (mutations, deletions, etc.) is **investigational**.

TESTING FOR ALL VARIANTS

Unless criteria above are met, genetic testing for variants in these genes (BRCA1, BRCA2, PALB2, PTEN, STK11; CDH1) is considered **investigational**.

Genetic testing using multi-gene panels and next generation sequencing (NGS) that tests for more than those genes considered medically necessary in the above policy statements (BRCA1, BRCA2, PALB2, PTEN, STK11, CDH1) is considered **investigational**.

Testing family members for a variant of unknown significance (VUS) is considered **investigational**.

POLICY GUIDELINES

This testing is necessary only once per lifetime.

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The inter-pretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

HEREDITARY BREAST AND OVARIAN CANCER

Current U.S. Preventive Services Task Force (USPSTF) guidelines recommend screening women with any family history of breast, ovarian, tubal, or peritoneal cancer. Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing. (Grade B Recommendation)

Recommended screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful variants in BRCA1 or BRCA2 are:

- Ontario Family History Assessment Tool (FHAT)
- Manchester Scoring System
- Referral Screening Tool (RST)
- Pedigree Assessment Tool (PAT)
- Family History Screen (FHS-7)
- International Breast Cancer Intervention Study instrument (Tyrer-Cuziak)
- Brief versions of the BRCAPRO

Recommended Testing Strategy

Patients who meet criteria for genetic testing as outlined in the policy statements above should be tested for variants in BRCA1 and BRCA2. Recommended strategies are listed below.

- In patients with a known familial BRCA variant, targeted testing for the specific variants recommended.
- In patients with unknown familial BRCA variant:
  - Non-Ashkenazi Jewish descent
- To identify clinically significant variants, National Comprehensive Cancer Network (NCCN) advises testing a relative who has breast or ovarian cancer-especially with early-onset disease, bilateral disease, multiple primaries, or ovarian cancer-because that individual has the highest likelihood of obtaining a positive test result.
- If no living family member with breast or ovarian cancer exists, NCCN suggests testing first- or second-degree family members affected with cancer thought to be related to deleterious BRCA1 or BRCA2 variants (e.g., prostate cancer, pancreatic cancer; melanoma).
- 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).
    - More than 90% of BRCA variants will be detected by full sequencing.
  - Alternatively, simultaneous full sequencing and testing for common large genomic rearrangements (also known as comprehensive BRCA testing; see Comprehensive Variant Analysis below) may be performed as is recommended by NCCN.
  - Comprehensive testing can detect 92.5% of BRCA1 or BRCA2 variants.
- 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.
    - Among patients with negative comprehensive testing, BART identified a deleterious variant (positive result) in less than 1%.
    - Ashkenazi Jewish descent.
- In patients of known Ashkenazi Jewish descent, NCCN recommends testing for the three known founder mutations (185delAG and 5182insC in BRCA1; 6174delT in BRCA2) first.
- If testing is negative for founder mutations, comprehensive genetic testing may be considered (see Comprehensive Variant Analysis).

Comprehensive Variant Analysis

Comprehensive variant analysis currently includes sequencing the coding regions and intron and exon splice sites, as well as testing to detect common large deletions and rearrangements that can be missed with sequence analysis alone. In addition, before 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.

High-Risk Ethnic Groups

Testing in eligible individuals who belong to ethnic populations in which there are well-characterized founder mutations should begin with tests specifically for these variants. For example, founder mutations account for approximately three quarters of the BRCA variants found in Ashkenazi Jewish populations. When testing for founder mutations is negative, comprehensive variant analysis should then be performed.

Testing Unaffected Individuals

In unaffected family members of potential BRCA variant families, most test results will be negative and uninformative. Therefore, it is strongly recommended that an affected family member be tested first whenever possible to adequately interpret the test. Should a BRCA variant be found in an affected family member(s), DNA from an unaffected family member can be tested specifically for the same variant of the affected family member without having to sequence the entire gene. Interpreting test results for an unaffected family member without knowing the genetic status of the family may be possible in the case of a positive result for an established disease-associated variant but leads to difficulties in interpreting negative test results (uninformative negative) or variants of uncertain significance because the possibility of a causative BRCA variant is not ruled out.

Testing Minors

The use of genetic testing for BRCA variants has limited or no clinical utility in minors. This is because there is no change in management for minors as a result of knowledge of the presence or absence of a deleterious variant. In addition, there are potential harms related to stigmatization and discrimination.

Prostate Cancer

Patients with BRCA variants have an increased risk of prostate cancer, and patients with known BRCA variants may therefore consider more aggressive screening approaches for prostate cancer. However, the presence of prostate cancer in an individual, or in a family, is not itself felt to be sufficient justification for BRCA testing.

CRITERIA FOR GENETIC RISK EVALUATION

The National Comprehensive Cancer Network (NCCN) provides criteria for genetic risk evaluation for individuals with no history or breast cancer and for those with a breast cancer. Updated versions of the criteria are available on the NCCN website.

MEDICARE ADVANTAGE

For Medicare Advantage Next Generation Sequencing (NGS) as a diagnostic laboratory test is considered **medically necessary** when performed in a Clinical Laboratory Improvement Amendments CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:

1. The patient has:
    - ovarian or breast cancer; and
    - a clinical indication for germline (inherited) testing for hereditary breast or ovarian cancer; and
    - a risk factor for germline (inherited) breast or ovarian cancer; and
    - not been previously tested with the same germline test using NGS for the same germline genetic content.
2. The diagnostic laboratory test using NGS must have all of the following:
    - Food and Drug Administration (FDA) approval or clearance; and

- results provided to the treating physician for management of the patient using a report template to specify treatment options.

BACKGROUND

HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

Several genetic syndromes with an autosomal dominant pattern of inheritance that features breast cancer have been identified. Of these, HBOC and some cases of hereditary site-specific breast cancer have in common causative variants in BRCA (breast cancer susceptibility) genes. 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, and 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 protocol, BCBSA refers collectively to both as hereditary breast and/or ovarian cancer.

Germline variants in the BRCA1 and BRCA2 genes are responsible for the cancer susceptibility in most HBOC families, especially if ovarian cancer or male breast cancer are features. However, in site-specific cancer, BRCA variants are responsible only for a proportion of affected families. BRCA gene variants are inherited in an autosomal dominant fashion through maternal or paternal lineage. 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 at increased cancer risk. Family members without existing cancer who are found to have BRCA variants can consider preventive interventions for reducing risk and mortality.

Clinical Features Suggestive of BRCA Variant

Young age of onset of breast cancer, even in the absence of family history, is a risk factor for BRCA1 variants. Winchester (1996) estimated that hereditary breast cancers account for 36% to 85% of patients diagnosed before age 30.[1] In several studies, BRCA variants were independently predicted by early age at onset, being present in 6% to 10% of breast cancer cases diagnosed at ages younger than various premenopausal age cutoffs (age range, 35-50 years).[1-4] In cancer-prone families, the mean age of breast cancer diagnosis among women carrying BRCA1 or BRCA2 variants is in the 40s.[5] In the Ashkenazi Jewish population, Frank et al (2002) reported that 13% of 248 cases with no known family history and diagnosed before 50 years of age had BRCA variants.[2] In a similar study by Gershoni-Baruch et al (2000), 31% of Ashkenazi Jewish women, unselected for family history, diagnosed with breast cancer at younger than 42 years of age had BRCA variants.[6] Other studies have indicated that early age of breast cancer diagnosis is a significant predictor of BRCA variants in the absence of family history in this population.[7-9]

As in the general population, a family history of breast or ovarian cancer, particularly of early age onset, is a significant risk factor for a BRCA variant in ethnic populations characterized by founder mutations. For example, in unaffected individuals of Ashkenazi Jewish descent, 12% to 31% will have a BRCA variant depending on the extent and nature of the family history.[4] Several other studies have documented the significant influence of family history.[6-10]

In patients with “triple-negative” breast cancer (i.e., negative for expression of estrogen, progesterone, and overexpression of human epidermal growth factor receptor 2 receptors), there is an increased prevalence of BRCA variants. Pathophysiologic research has suggested that the physiologic pathway for the development of triple-negative breast cancer is similar to that for BRCA-associated breast cancer.[11] In 200 randomly selected patients with triple-negative breast cancer from a tertiary care center, Kandel et al (2006) reported there was a greater than three-fold increase in the expected rate of BRCA variants.[12] BRCA1 variants were found in 39.1% of

patients and BRCA2 variants in 8.7%. Young et al (2009) studied 54 women with high-grade, triple-negative breast cancer with no family history of breast or ovarian cancer, representing a group that previously was not recommended for BRCA testing.[13] Six BRCA variants (five BRCA1, one BRCA2) were found, for a variant rate of 11%. Finally, Gonzalez-Angulo et al (2011) in a study of 77 patients with triple-negative breast cancer, reported that 15 patients (19.5%) had BRCA variants (12 in BRCA1, three in BRCA2).[14]

BREAST CANCER AND GENETICS

In 2016, researchers estimated breast cancer would be diagnosed in 252,710 women and 40,610 would die from the disease[68]; a woman's lifetime risk is 12.4%.69 Breast cancers can be classified as sporadic, familial, or hereditary.[70] Most breast cancers, however, are sporadic (70% to 75%), occurring in women without a family history of the disease. Familial cancers (15% to 25%) aggregate within families but lack clearly discernable patterns of inheritance and are likely polygenic. Hereditary cancers have discernable inheritance patterns, often occur at younger ages, may be bilateral, and comprise between 5% and 10% of breast cancers. Pathogenic BRCA1 and BRCA2 variants appear responsible for 20% to 25% of hereditary breast cancers,[71] while small proportions are attributed to pathogenic variants in other highly penetrant genes (e.g., TP53, CDH1, PTEN, STK11).

PENETRANCE OF PATHOGENIC VARIANTS

Penetrance is the risk conferred by a pathogenic variant or the proportion of individuals with the variant expected to develop cancer. Variant penetrance is considered high, moderate, or low according to lifetime risk: high (>50%), moderate (20% to 50%), and low (<20%) (corresponding relative risks of approximately ≥5, 1.5 to 5, and <1.5)[72]. Variants in only a few breast cancer-susceptibility genes (BRCA1 and BRCA2 [hereditary breast/ovarian cancer syndrome], TP53 [Li-Fraumeni syndrome], PTEN [Cowden syndrome], CDH1 [hereditary diffuse gastric cancer], STK11 [Peutz-Jeghers syndrome]) are considered highly penetrant. For example, a woman with a BRCA1 or BRCA2 variant has roughly a 75% lifetime risk of developing breast cancer and a relative risk of 11 to 12 compared with the general population.[73] Penetrance can be modified by environmental factors and by family history, which is a particularly important modifier for low and moderate penetrance genes. Moreover, specific pathogenic variants within a gene may confer somewhat different risks.

DETERMINING VARIANT PATHOGENICITY

Determining the pathogenicity of variants in a more commonly detected cancer susceptibility gene (e.g., founder sequence mutations) is generally straightforward because associations are repeatedly observed. For uncommonly identified variants, such as those found in a few individuals or families, defining pathogenicity can be more difficult. For example, predicting the pathogenicity of previously unidentified variants typically requires in silico (computational) analysis predicting protein structure/function, evolutionary conservation, and splice site prediction.[74] The approach to defining pathogenicity is clearly outlined in standards and reporting guidelines.[74] Still, distinctions between a variant of uncertain significance and a pathogenic one from different laboratories may not always be identical.[75]

GENES ASSOCIATED WITH A MODERATE PENETRANCE OF BREAST CANCER

PALB2 Gene

The PALB2 gene (partner and localizer of BRCA2) encodes for a protein first described in 2006.[76] The gene is located at 16p12.2[a] and has 13 exons. 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.[b] 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. For example, Antoniou et al (2014) assumed a prevalence of eight per 10,000 in the general population when modeling breast cancer risks.[77] Variants are more prevalent in ethnic populations where founder mutations have persisted (e.g., Finns, French Canadians, Poles), while in-

frequently found in others (e.g., in Ashkenazi Jews[78-79]). In women with a family history of breast cancer, the prevalence of pathogenic PALB2 variants ranges between 0.9% and 3.9%,[79] 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[77]; and in populations with founder mutations cause 0.5% to 1% of all breast cancers.[80]

[a] Short (p) arm of chromosome 16 at position 12.2.

[b] Fanconi anemia is a rare disorder, primarily affecting children, that causes bone marrow failure. Affected individuals also carry a risk of cancers including leukemia.

CHEK2 Gene

The CHEK2 (checkpoint kinase 2) gene is activated in response to DNA double-strand breakage and plays a role in cell-cycle control, DNA repair, and apoptosis.

In 2002, a single recurrent truncating variant in the CHEK2 gene (c.1100delC) was first reported as a cause of breast cancer, and studies have since confirmed this. The incidence of CHEK2 variants varies widely among populations. It is most prevalent in Eastern and Northern Europe, where the population frequency of the c.1100delC allele ranges from 0.5% to 1.4%; the allele is less frequent in North America and virtually absent in Spain and India.

Although most data for truncating CHEK2 variants are limited to the c.1100delC allele, three other founder mutations of CHEK2 (IVS2+1G>A, del5395, I157T) have been associated with breast cancer in Eastern Europe. Both IVS2+1G>A and del5395 are protein-truncating variants, and I157T is a missense variant. The truncating variants are associated with breast cancer in the Slavic populations of Poland, Belarus, Russia, and the Czech Republic. The I157T variant has a wider geographic distribution and has been reported to be associated with breast cancer in Poland, Finland, Germany, and Belarus.[81]

ATM Gene

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 one and four years, telangiectasias of the conjunctivae, oculomotor apraxia, immune defects, and cancer predisposition. Female ATM heterozygotes carriers 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.

IDENTIFYING WOMEN AT RISK OF AN INHERITED SUSCEPTIBILITY TO BREAST CANCER

Breast cancer risk can be affected by genetic and nongenetic factors. The risk is increased in women experiencing an earlier age at menarche, nulliparity, late age of first pregnancy, fewer births, late menopause, proliferative breast disease, menopausal hormone therapy, alcohol, obesity, inactivity, and radiation.[82] A family history of breast cancer confers between a two- and four-fold increased risk varying by several factors: the number and closeness of affected relatives, age at which cancers developed, whether breast cancers were bilateral and if other cancers occurred (e.g., ovarian).[83] For a woman without breast cancer, the probability of detecting a pathogenic variant can be estimated from a detailed multigenerational pedigree (e.g., Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm),[84] screening tools (e.g., BRCAPRO,[85] Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, Family History Screen[86-87]), or by referring to guidelines that define specific family history criteria. For women with breast cancer, family history also affects the likelihood of carrying a pathogenic variant.[86]

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing.

Numerous BRCA tests are available as listed below. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these:

Myriad Genetic Laboratories offers the following tests:

- Comprehensive BRACAnalysis® test includes complete sequencing of BRCA1 and BRCA2 and gap polymerase chain reaction for five common rearrangements (deletions, duplications) in BRCA1
- BRACAnalysis® Large Rearrangement Test (BART™) is a reflex test for patients who test negative on the Comprehensive BRACAnalysis® test to detect uncommon large rearrangements in BRCA1 and BRCA2
- Integrated BRACAnalysis® test includes BART™ as part of BRCA1 or BRCA2 analysis
- BRACAnalysis CDxs® is intended to detect germline BRCA1 and BRCA2 variants to identify patients with breast or ovarian cancer who may be considered for treatment with olaparib, niraparib, or talazoparib.

Quest Diagnostics offers BRCAvantage™, which includes sequencing of BRCA1 and BRCA2 and a multiplex ligation-dependent probe amplification assay to detect both common and uncommon gene rearrangements.

LabCorp offers the BRCAssure^{SM} suite of tests, which includes: targeted BRCA1 and BRCA2 variant analysis; a founder mutation panel for Ashkenazi Jewish patients (three variants); comprehensive BRCA1 and BRCA2 analysis (full gene sequencing plus analysis of common and uncommon large rearrangements); and deletion and duplication analysis of uncommon large rearrangements only (without sequencing) when comprehensive analysis is negative.

In addition to the various individual variant tests which are the focus of this policy, numerous other multigene panel tests exist that include BRCA 1/2 among other genes. Although these multigene panel tests are outside of the scope of this protocol, among them, it is worth noting that FoundationOne CDx™ (F1CDx) is an FDA-approved companion diagnostic for use of Lynparza® (olaparib) and Rubraca® (rucaparib) in accordance with their respective FDA labels in women with ovarian cancer. F1CDx is FDA-approved to assess BRCA 1/2 and other homologous recombination pathway genes (e.g., ATM, BRIP1, CHEK2, FANCA, FANCL, FANCM, NBN, RAD51C, RAD51D, and RAD54L), as well as, MSI and DNA mismatch repair genes (MLH1, MSH2, MSH6, PMS2). FoundationOne CDx is also FDA-approved for determining homologous recombination deficiency based on genomic loss of heterozygosity (LOH) and BRCA mutant status.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. PALB2, CHEK2, and ATM testing are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories offering to test and voluntarily listing are available through the National Center for Biotechnology Genetic Testing Registry. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Customized next-generation sequencing panels provide simultaneous analysis of multiple cancer predisposition genes, and typically include both moderate- and high-penetrant genes.

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. Winchester DP. Breast cancer in young women. Surg Clin North Am. Apr 1996;76(2):279-287. PMID 8610264.
2. Frank TS, Deffenbaugh AM, Reid JE, et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. J Clin Oncol. Mar 15 2002;20(6):1480-1490. PMID 11896095.
3. Langston AA, Malone KE, Thompson JD, et al. BRCA1 mutations in a population-based sample of young women with breast cancer. N Engl J Med. Jan 18 1996;334(3):137-142. PMID 8531967.
4. Malone KE, Daling JR, Thompson JD, et al. BRCA1 mutations and breast cancer in the general population: analyses in women before age 35 years and in women before age 45 years with first-degree family history. JAMA. Mar 25 1998;279(12):922-929. PMID 9544766.
5. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet. Mar 1998; 62(3):676-689. PMID 9497246.
6. Gershoni-Baruch R, Patael Y, Dagan, et al. Association of the I1307K APC mutation with hereditary and sporadic breast/ovarian cancer: more questions than answers. Br J Cancer. Jul 2000;83(2):153-155. PMID 10901363.
7. Warner E, Foulkes W, Goodwin P, et al. Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer. J Natl Cancer Inst. Jul 21 1999;91(14):1241-1247. PMID 10413426.
8. Hartge P, Struewing JP, Wacholder S, et al. The prevalence of common BRCA1 and BRCA2 mutations among Ashkenazi Jews. Am J Hum Genet. Apr 1999;64(4):963-970. PMID 10090881.
9. Hodgson SV, Heap E, Cameron J, et al. Risk factors for detecting germline BRCA1 and BRCA2 founder mutations in Ashkenazi Jewish women with breast or ovarian cancer. J Med Genet. May 1999;36(5):369-373. PMID 10353781.
10. Moslehi R, Chu W, Karlan B, et al. BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer. Am J Hum Genet. Apr 2000;66(4):1259-1272. PM.
11. de Ruijter TC, Veeck J, de Hoon JP, et al. Characteristics of triple-negative breast cancer. J Cancer Res Clin Oncol. Feb 2011;137(2):183-192. PMID 21069385.
12. Kandel MJ, Stadler D, Masciari S, et al. Prevalence of BRCA1 mutations in triple negative breast cancer (BC) [abstract 508]. J Clin Oncol. 2006;24(18S):508.
13. Young SR, Pilarski RT, Donenberg T, et al. The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. BMC Cancer. Mar 19 2009;9:86. PMID 19298662.

14. Gonzalez-Angulo AM, Timms KM, Liu S, et al. Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. Clin Cancer Res. Mar 1 2011;17(5):1082-1089. PMID 21233401.
15. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). BRCA1 and BRCA2 testing to determine the risk of breast and ovarian cancer. TEC Assessments. 1997;Volume 12:Tab 4.
16. Zhu Y, Wu J, Zhang C, et al. BRCA mutations and survival in breast cancer: an updated systematic review and meta-analysis. Oncotarget. Oct 25 2016;7(43):70113-70127. PMID 27659521.
17. Nelson HD, Fu R, Goddard K, et al. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation. Evidence Synthesis No. 101 (AHRQ Publication No. 12-05164-EF-1). Rockville, MD Agency for Healthcare Research and Quality; 2013.
18. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. Jama. Jun 20 2017;317(23):2402-2416. PMID 28632866.
19. Begg CB. On the use of familial aggregation in population-based case probands for calculating penetrance. Journal of the National Cancer Institute. Aug 21 2002;94(16):1221-1226. PMID 12189225.
20. Thorlacius S, Struewing JP, Hartge P, et al. Population-based study of risk of breast cancer in carriers of BRCA2 mutation. Lancet. Oct 24 1998;352(9137):1337-1339. PMID 9802270.
21. King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. Oct 24 2003;302(5645):643-646. PMID 14576434.
22. Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol. Jun 15 2004;22(12):2328-2335. PMID 15197194.
23. Mavaddat N, Peock S, Frost D, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst. Jun 5 2013;105(11):812-822. PMID 23628597.
24. Trainer AH, Meiser B, Watts K, et al. Moving toward personalized medicine: treatment-focused genetic testing of women newly diagnosed with ovarian cancer. Int J Gynecol Cancer. Jul 2010;20(5):704-716. PMID 20973257.
25. Zhang S, Royer R, Li S, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. Gynecol Oncol. May 1 2011;121(2):353-357. PMID 21324516.
26. Kurian AW, Hughes, E., Handorf, E. A., et al. Breast and ovarian cancer penetrance estimates derived from germline multiple-gene sequencing results in women. Precis Oncol. 2017;1:1-12.
27. Langer LR, McCoy H, Kidd J, et al. Hereditary cancer testing in patients with ovarian cancer using a 25-gene panel. J Community Supportive Oncol. 2016;14(7):314-319.
28. Norquist BM, Harrell MI, Brady MF, et al. Inherited mutations in women with ovarian carcinoma. JAMA Oncol. Apr 2016;2(4):482-490. PMID 26720728.
29. Harter P, Hauke J, Heitz F, et al. Prevalence of deleterious germline variants in risk genes including BRCA1/2 in consecutive ovarian cancer patients (AGO-TR-1). PLoS One. Oct 2017;12(10):e0186043. PMID 29053726.
30. Hirst JE, Gard GB, McIllroy K, et al. High rates of occult fallopian tube cancer diagnosed at prophylactic bilateral salpingo-oophorectomy. Int J Gynecol Cancer. Jul 2009;19(5):826-829. PMID 19574767.
31. Powell CB, Swisher EM, Cass I, et al. Long term follow up of BRCA1 and BRCA2 mutation carriers with unsuspected neoplasia identified at risk reducing salpingo-oophorectomy. Gynecol Oncol. May 2013;129(2):364-371. PMID 23391663.
32. Hruban RH, Canto MI, Goggins M, et al. Update on familial pancreatic cancer. Adv Surg. Oct 2010;44:293-311. PMID 20919528.
33. Couch FJ, Johnson MR, Rabe KG, et al. The prevalence of BRCA2 mutations in familial pancreatic cancer. Cancer Epidemiol Biomarkers Prev. Feb 2007;16(2):342-346. PMID 17301269.
34. Ferrone CR, Levine DA, Tang LH, et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. J Clin Oncol. Jan 20 2009;27(3):433-438. PMID 19064968.

35. Holter S, Borgida A, Dodd A, et al. Germline BRCA Mutations in a Large Clinic-Based Cohort of Patients With Pancreatic Adenocarcinoma. J Clin Oncol. Oct 1 2015;33(28):3124-3129. PMID 25940717.
36. Shindo K, Yu J, Suenaga M, et al. Deleterious Germline Mutations in Patients With Apparently Sporadic Pancreatic Adenocarcinoma. J Clin Oncol. Oct 20 2017;35(30):3382-3390. PMID 28767289.
37. Yurgelun MB, Chittenden AB, Morales-Oyarvide V, et al. Germline cancer susceptibility gene variants, somatic second hits, and survival outcomes in patients with resected pancreatic cancer. Genet Med. Jul 2 2018. PMID 29961768.
38. Hu C, Hart SN, Polley EC, et al. Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer. JAMA. Jun 19 2018;319(23):2401-2409. PMID 29922827.
39. Edwards SM, Kote-Jarai Z, Meitz J, et al. Two percent of men with early-onset prostate cancer harbor germline mutations in the BRCA2 gene. Am J Hum Genet. Jan 2003;72(1):1-12. PMID 12474142.
40. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. N Engl J Med. Aug 4 2016;375(5):443-453. PMID 27433846.
41. Abida W, Armenia J, Gopalan A, et al. Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis Oncol. Jul 2017;2017. PMID 28825054.
42. Walsh T, Casadei S, Coats KH, et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. JAMA. Mar 22 2006;295(12):1379-1388. PMID 16551709.
43. Palma MD, Domchek SM, Stopfer J, et al. The relative contribution of point mutations and genomic rearrangements in BRCA1 and BRCA2 in high-risk breast cancer families. Cancer Res. Sep 1 2008;68(17):7006-7014. PMID 18703817.
44. Li X, You R, Wang X, et al. Effectiveness of prophylactic surgeries in BRCA1 or BRCA2 mutation carriers: a meta-analysis and systematic review. Clin Cancer Res. Aug 1 2016;22(15):3971-3981. PMID 26979395.
45. Grann VR, Whang W, Jacobson JS, et al. Benefits and costs of screening Ashkenazi Jewish women for BRCA1 and BRCA2. J Clin Oncol. Feb 1999;17(2):494-500. PMID 10080590.
46. Hartmann LC, Schaid DJ, Woods JE, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med. Jan 14 1999;340(2):77-84. PMID 9887158.
47. Menkiszak J, Rzepka-Gorska I, Gorski B, et al. Attitudes toward preventive oophorectomy among BRCA1 mutation carriers in Poland. Eur J Gynaecol Oncol. Apr 2004;25(1):93-95. PMID 15053071.
48. Moller P, Borg A, Evans DG, et al. Survival in prospectively ascertained familial breast cancer: analysis of a series stratified by tumour characteristics, BRCA mutations and oophorectomy. Int J Cancer. Oct 20 2002; 101(6):555-559. PMID 12237897.
49. Olopade OI, Artioli G. Efficacy of risk-reducing salpingo-oophorectomy in women with BRCA-1 and BRCA-2 mutations. Breast J. Jan-Feb 2004;10 Suppl 1:S5-9. PMID 14984481.
50. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med. May 23 2002;346(21):1616-1622. PMID 12023993.
51. Weitzel JN, McCaffrey SM, Nedelcu R, et al. Effect of genetic cancer risk assessment on surgical decisions at breast cancer diagnosis. Arch Surg. Dec 2003;138(12):1323-1328; discussion 1329. PMID 14662532.
52. Robson M, Goessl C, Domchek S. Olaparib for metastatic germline BRCA-mutated breast cancer. N Engl J Med. Nov 2 2017;377(18):1792-1793. PMID 29091556.
53. Finch AP, Lubinski J, Moller P, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol. May 20 2014;32(15):1547-1553. PMID 24567435.
54. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. Jama. Sep 01 2010;304(9):967-975. PMID 20810374.
55. Elmi M, Azin A, Elnahas A, et al. Concurrent risk-reduction surgery in patients with increased lifetime risk for breast and ovarian cancer: an analysis of the National Surgical Quality Improvement Program (NSQIP) database. Breast Cancer Res Treat. May 14 2018. PMID 29761322.

56. Ludwig KK, Neuner J, Butler A, et al. Risk reduction and survival benefit of prophylactic surgery in BRCA mutation carriers, a systematic review. Am J Surg. Jul 18 2016. PMID 27649974.
57. Marchetti C, De Felice F, Palaia I, et al. Risk-reducing salpingo-oophorectomy: a meta-analysis on impact on ovarian cancer risk and all cause mortality in BRCA 1 and BRCA 2 mutation carriers. BMC Womens Health. Dec 12 2014;14:150. PMID 25494812.
58. Scheuer L, Kauff N, Robson M, et al. Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA mutation carriers. J Clin Oncol. Mar 1 2002;20(5):1260-1268. PMID 11870168.
59. Mitra AV, Bancroft EK, Barbachano Y, et al. Targeted prostate cancer screening in men with mutations in BRCA1 and BRCA2 detects aggressive prostate cancer: preliminary analysis of the results of the IMPACT study. BJU Int. Jan 2011;107(1):28-39. PMID 20840664.
60. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/ Familial High Risk Assessment: Breast and Ovarian. Version 3.2019. https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf Accessed October 6, 2019.
61. Nelson HD, Pappas M, Zakher B, et al. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: a systematic review to update the U.S. Preventive Services Task Force recommendation. Ann Intern Med. Feb 18 2014;160(4):255-266. PMID 24366442.
62. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 4.2019. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf Accessed October 6, 2019.
63. American Society of Clinical Oncology. American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. J Clin Oncol. Jun 15 2003;21(12):2397-2406. PMID 12692171.
64. Robson ME, Storm CD, Weitzel J, et al. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. J Clin Oncol. Feb 10 2010;28(5):893-901. PMID 20065170.
65. Robson ME, Bradbury AR, Arun B, et al. American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. J Clin Oncol. Nov 1 2015;33(31):3660-3667. PMID 26324357.
66. Lancaster JM, Powell CB, Chen LM, et al. Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions. Gynecol Oncol. Jan 2015;136(1):3-7. PMID 25238946.
67. Practice Bulletin No. 182 Summary: hereditary breast and ovarian cancer syndrome. Obstet Gynecol. Sep 2017;130(3):657-659. PMID 28832475.
68. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. Jan-Feb 2016;66(1):7-30. PMID 26742998.
69. National Cancer Institute, Surveillance Epidemiology and End Results Program. Cancer Stat Facts: Female Breast Cancer. n.d.; https://seer.cancer.gov/statfacts/html/breast.html. Accessed June 3, 2019.
70. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/ Familial High-Risk Assessment: Breast and Ovarian. Version 3.2019. https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed June 3, 2019.
71. National Cancer Institute. BRCA Mutations: Cancer Risk and Genetic Testing. 2015; https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet. Accessed June 3, 2019.
72. Apostolou P, Fostira F. Hereditary breast cancer: the era of new susceptibility genes. Biomed Res Int. Apr 2013;2013:747318. PMID 23586058.
73. Easton DF, Pharoah PD, Antoniou AC, et al. Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med. Jun 4 2015;372(23):2243-2257. PMID 26014596.
74. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. May 2015;17(5):405-424. PMID 25741868.

75. Kurian AW, Antoniou AC, Domchek SM. Refining breast cancer risk stratification: additional genes, additional information. Am Soc Clin Oncol Educ Book. 2016;35:44-56. PMID 27249685.
76. Xia B, Sheng Q, Nakanishi K, et al. Control of BRCA2 cellular and clinical functions by a nuclear partner, PALB2. Mol Cell. Jun 23 2006;22(6):719-729. PMID 16793542.
77. Antoniou AC, Casadei S, Heikkinen T, et al. Breast-cancer risk in families with mutations in PALB2. N Engl J Med. Aug 7 2014;371(6):497-506. PMID 25099575.
78. Catucci I, Peterlongo P, Ciceri S, et al. PALB2 sequencing in Italian familial breast cancer cases reveals a high-risk mutation recurrent in the province of Bergamo. Genet Med. Sep 2014;16(9):688-694. PMID 24556926.
79. Casadei S, Norquist BM, Walsh T, et al. Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer. Cancer Res. Mar 15 2011;71(6):2222-2229. PMID 21285249.
80. Cybulski C, Kluzniak W, Huzarski T, et al. Clinical outcomes in women with breast cancer and a PALB2 mutation: a prospective cohort analysis. Lancet Oncol. Jun 2015;16(6):638-644. PMID 25959805.
81. Cybulski C, Wokolorczyk D, Jakubowska A, et al. Risk of breast cancer in women with a CHEK2 mutation with and without a family history of breast cancer. J Clin Oncol. Oct 1 2011;29(28):3747-3752. PMID 21876083.
82. Schottenfeld D, Fraumeni JF. Cancer epidemiology and prevention. 3rd ed. New York: Oxford University Press; 2006.
83. Singletary SE. Rating the risk factors for breast cancer. Ann Surg. Apr 2003;237(4):474-482. PMID 12677142.
84. Antoniou AC, Pharoah PP, Smith P, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancer. Br J Cancer. Oct 18 2004;91(8):1580-1590. PMID 15381934.
85. Berry DA, Iversen ES, Jr., Gudbjartsson DF, et al. BRCAPRO validation, sensitivity of genetic testing of BRCA1/BRCA2, and prevalence of other breast cancer susceptibility genes. J Clin Oncol. Jun 1 2002;20(11):2701-2712. PMID 12039933.
86. Suszynska, MM, Klonowska, KK, Jasinska, AA. Large-scale meta-analysis of mutations identified in panels of breast/ovarian cancer-related genes - Providing evidence of cancer predisposition genes. Gynecol. Oncol., 2019 Feb 9;153(2). PMID 30733081.
87. Erkko H, Dowty JG, Nikkila J, et al. Penetrance analysis of the PALB2 c.1592delT founder mutation. Clin Cancer Res. Jul 15 2008;14(14):4667-4671. PMID 18628482.
88. Heikkinen T, Karkkainen H, Aaltonen K, et al. The breast cancer susceptibility mutation PALB2 1592delT is associated with an aggressive tumor phenotype. Clin Cancer Res. May 1 2009;15(9):3214-3222. PMID 19383810.
89. Rahman N, Seal S, Thompson D, et al. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. Nat Genet. Feb 2007;39(2):165-167. PMID 17200668.
90. Thompson ER, Gorringe KL, Rowley SM, et al. Prevalence of PALB2 mutations in Australian familial breast cancer cases and controls. Breast Cancer Res. Aug 19 2015;17(1):111. PMID 26283626.
91. Southey MC, Goldgar DE, Winqvist R, et al. PALB2, CHEK2 and ATM rare variants and cancer risk: data from COGS. J Med Genet. Sep 5 2016. PMID 27595995.
92. Lu, HH, Li, SS, Black, MM, Lee, SS, Hoiness, RR, Wu, SS, Mu, WW, Huether, RR, Chen, JJ, Sridhar, SS, Tian, YY, McFarland, RR, Dolinsky, JJ, Tippin Davis, BB, Mexal, SS, Dunlop, CC, Elliott, AA. Association of Breast and Ovarian Cancers With Predisposition Genes Identified by Large-Scale Sequencing. JAMA Oncol, 2018 Aug 22. PMID 30128536.
93. Kurian AW, Hughes E, Handorf EA, et al. Breast and Ovarian Cancer Penetrance Estimates Derived From Germline Multiple-Gene Sequencing Results in Women. JCO Precision Oncology 2017 :1, 1-12.
94. Antoniou AC, Foulkes WD, Tischkowitz M, et al. Breast cancer risk in women with PALB2 mutations in different populations. Lancet Oncol. Aug 2015;16(8):e375-376. PMID 26248842.
95. Southey MC, Goldgar DE, Winqvist R, et al. PALB2, CHEK2 and ATM rare variants and cancer risk: data from COGS. J Med Genet. Dec 2016;53(12):800-811. PMID 27595995.

96. Balmaña J, Digiovanni L, Gaddam P, et al. Conflicting Interpretation of genetic variants and cancer risk by commercial laboratories as assessed by the prospective registry of multiplex testing. J Clin Oncol. Dec 2016;34(34):4071-4078. PMID 27621404.
97. Rosenthal, EE, Evans, BB, Kidd, JJ, Brown, KK, Gorringe, HH, van Orman, MM, Manley, SS. Increased Identification of Candidates for High-Risk Breast Cancer Screening Through Expanded Genetic Testing. J Am Coll Radiol, 2016 Dec 25;14(4). PMID 28011157.
98. Phi XA, Saadatmand S, De Bock GH, et al. Contribution of mammography to MRI screening in BRCA mutation carriers by BRCA status and age: individual patient data meta-analysis. Br J Cancer. Mar 15 2016; 114(6):631-637. PMID 26908327.
99. Phillips KA, Milne RL, Rookus MA, et al. Tamoxifen and risk of contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. J Clin Oncol. Sep 1 2013;31(25):3091-3099. PMID 23918944.
100. Hartmann LC, Sellers TA, Schaid DJ, et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. J Natl Cancer Inst. Nov 7 2001;93(21):1633-1637. PMID 11698567.
101. Portschy PR, Kuntz KM, Tuttle TM. Survival outcomes after contralateral prophylactic mastectomy: a decision analysis. J Natl Cancer Inst. Aug 2014;106(8). PMID 25031308.
102. Schrag D, Kuntz KM, Garber JE, et al. Decision analysis--effects of prophylactic mastectomy and oophorectomy on life expectancy among women with BRCA1 or BRCA2 mutations. N Engl J Med. May 15 1997; 336(20):1465-1471. PMID 9148160.
103. Schrag D, Kuntz KM, Garber JE, et al. Life expectancy gains from cancer prevention strategies for women with breast cancer and BRCA1 or BRCA2 mutations. JAMA. Feb 2 2000;283(5):617-624. PMID 10665701.
104. Yang Y, Zhang F, Wang Y, et al. CHEK2 1100delC variant and breast cancer risk in Caucasians: a meta- analysis based on 25 studies with 29,154 cases and 37,064 controls. Asian Pac J Cancer Prev. 2012;13(7):3501-3505. PMID 22994785.
105. Schmidt MK, Hogervorst F, van Hien R, et al. age- and tumor subtype-specific breast cancer risk estimates for CHEK2*1100delC carriers. J Clin Oncol. Aug 10 2016;34(23):2750-2760. PMID 27269948.
106. Weischer M, Bojesen SE, Ellervik C, et al. CHEK2*1100delC genotyping for clinical assessment of breast cancer risk: meta-analyses of 26,000 patient cases and 27,000 controls. J Clin Oncol. Feb 1 2008;26(4):542-548. PMID 18172190.
107. Hauke J, Horvath J, Gross E, et al. Gene panel testing of 5589 BRCA1/2-negative index patients with breast cancer in a routine diagnostic setting: results of the German Consortium for Hereditary Breast and Ovarian Cancer. Cancer Med. Apr 2018;7(4):1349-1358. PMID 29522266.
108. Decker B, Allen J, Luccarini C, et al. Rare, protein-truncating variants in ATM, CHEK2 and PALB2, but not XRCC2, are associated with increased breast cancer risks. J Med Genet. Nov 2017;54(11):732-741. PMID 28779002.
109. Couch FJ, Shimelis H, Hu C, et al. Associations between cancer predisposition testing panel genes and breast cancer. JAMA Oncol. Sep 1 2017;3(9):1190-1196. PMID 28418444.
110. Naslund-Koch C, Nordestgaard BG, Bojesen SE. Increased risk for other cancers in addition to breast cancer for CHEK2*1100delC heterozygotes estimated from the Copenhagen General Population Study. J Clin Oncol. Apr 10 2016;34(11):1208-1216. PMID 26884562.
111. Huzarski T, Cybulski C, Wokolorczyk D, et al. Survival from breast cancer in patients with CHEK2 mutations. Breast Cancer Res Treat. Apr 2014;144(2):397-403. PMID 24557336.
112. Kriege M, Hollestelle A, Jager A, et al. Survival and contralateral breast cancer in CHEK2 1100delC breast cancer patients: impact of adjuvant chemotherapy. Br J Cancer. Aug 26 2014;111(5):1004-1013. PMID 24918820.
113. Weischer M, Nordestgaard BG, Pharoah P, et al. CHEK2*1100delC heterozygosity in women with breast cancer associated with early death, breast cancer-specific death, and increased risk of a second breast cancer. J Clin Oncol. Dec 10 2012;30(35):4308-4316. PMID 23109706.

114. Marabelli M, Cheng SC, Parmigiani G. Penetrance of ATM gene mutations in breast cancer: a meta-analysis of different measures of risk. Genet Epidemiol. Jul 2016;40(5):425-431. PMID 27112364.
115. van Os NJ, Roeleveld N, Weemaes CM, et al. Health risks for ataxia-telangiectasia mutated heterozygotes: a systematic review, meta-analysis and evidence-based guideline. Clin Genet. Aug 2016;90(2):105-117. PMID 26662178.
116. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Screening and Diagnosis. Version 1.2019. https://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf. Accessed June 3, 2019.
117. Centers for Medicare & Medicaid Services. Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450R). 2020; https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=296&DocID=CAG-00450R&bc=gAAAAAgAIAAA&. Accessed April 23, 2020.