Protocol

Genetic Testing for Hereditary Breast and Ovarian Cancer Syndrome

(20402, 204126)

Medical Benefit		**Effective Date**: 01/01/18	**Next Review Date**: 09/18
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	

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.

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: • No genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Morbid events • Quality of life • Treatment-related morbidity
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	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • 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	Relevant outcomes include: • Overall survival • Disease specific survival • Test accuracy • 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	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity

Description

Hereditary breast and ovarian cancer (HBOC) syndrome describes the familial cancer syndromes that are related to mutations in the *BRCA* genes (*BRCA1* located on chromosome 17q21, *BRCA2* located on chromosome 13q12-13). Families with HBOC syndrome have an increased susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer at any age, cancer of the fallopian tube, and primary

peritoneal cancer as well as other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer.

About 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, rather than having one of the well described familial breast/ ovarian cancer syndromes (e.g., BRCA1, BRCA2). PALB2, CHEK2, and ATM variants are considered to be of moderate penetrance and carriers have an approximately two to four fold increased risk of developing breast cancer compared with the general population. Risk estimates may be higher in patients with a family history of breast cancer or for a specific variant.

Summary of Evidence

For individuals who have cancer or a personal or family cancer history and meeting criteria suggesting a risk of hereditary breast and ovarian cancer (HBOC) syndrome who receive genetic testing for a BRCA1 or BRCA2 mutation, the evidence includes a TEC Assessment and studies of mutation prevalence and cancer risk. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, quality of life, and treatment-related morbidity. The accuracy of mutation testing has been shown to be high. Studies of lifetime risk of cancer for carriers of a BRCA mutation have shown a risk as high as 85%. Knowledge of BRCA mutation status in individuals at risk of a BRCA mutation may impact health care decisions to reduce risk, including intensive surveillance, chemoprevention, and/or prophylactic 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 PALB2 variant, the evidence include studies of analytic validity, variant prevalence, and multiple studies of breast cancer risk, including one meta-analysis. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. The reported evidence supporting analytic validity is not substantial, but given current next-generation sequencing techniques with variant confirmation by conventional methods, high analytic sensitivity such as reported by Judkins et al (2015) is expected in a laboratory certified by the Clinical Laboratory Improvement Amendments meeting standards for high-complexity molecular diagnostics. Evidence supporting clinical validity was obtained from nine studies reporting relative risks 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 variants) to 48. Relative risks 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 on preventive interventions in women with PALB2 variants is indirect, relying on studies of high-risk women and BRCA carriers. Compared with other screening modalities, magnetic resonance imaging (MRI) has a higher sensitivity, but increased false positives when high-risk women are screened. Screening recommendations for high-risk asymptomatic women include beginning at an earlier age and addition of MRI to mammography. However, there is no direct evidence and limited observational data suggesting improved outcomes. There is limited observational evidence that chemoprevention can decrease the risk of invasive cancers in high-risk women; the U.S. Preventive Services Task Force (USPSTF) report and National Comprehensive Cancer Network (NCCN) support a chemoprevention option. In high-risk women, prophylactic mastectomy (bilateral or contralateral) reduces the risk of breast cancer and breast cancer mortality and decision analytic models project increased life-expectancy. Prophylactic mastectomy can be accompanied by a significant risk of adverse effects and studies have found a minority of asymptomatic BRCA carriers choose to undergo a bilateral prophylactic mastectomy. Given the penetrance of PALB2 variants, the outcomes following bilateral and contralateral prophylactic 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 preventive 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 tradeoffs involved for 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 of for a CHEK2 variant or an ATM variant, the evidence includes studies of analytic validity, variant prevalence, and studies of breast cancer risk. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. The available studies on clinical validity have demonstrated that both CHEK2 and ATM2 variants are of moderate penetrance, with lower relative risks for breast cancer than PALB2, and 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 CHEK2 or ATM variants in individuals with risk of hereditary breast/ovarian cancer was not identified. For women with high-risk hereditary cancer syndromes, interventions to decrease breast cancer risk in high-risk women include screening (e.g., starting at an early age, addition of MRI to mammography, and annually), chemoprevention, prophylactic mastectomy, and prophylactic oophorectomy. Following the logic applied in the case of PALB2, there is limited evidence that chemoprevention can decrease the risk of invasive cancers in high-risk women; the USPSTF report and NCCN support a chemoprevention option. 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 women with a CHEK2 variant making a decision about a prophylactic mastectomy. It is unclear that the relative risk associated with the moderate penetrance variants would increase risk enough beyond that already conferred by familial risk to change screening behavior. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

For individuals from a family with a known deleterious BRCA1 or BRCA2 mutation, genetic testing for a BRCA1 or BRCA2 mutation may be considered **medically necessary**.

Genetic testing for a *BRCA1* and *BRCA2* mutations may be considered **medically necessary** for testing an individual with cancer or history of cancer AND for testing an unaffected individual with a strong family history of cancer when ANY of the following criteria are met:

- Diagnosed with breast cancer prior to 45 years of age; OR
- Diagnosed with two breast cancers prior to 50 years of age; OR
- Diagnosed at any age and at least one first-, second- or third-degree relative with breast cancer diagnosed at 50 years of age or younger; OR
- Multiple primary breast cancers or bilateral breast cancer; OR
- Male with breast cancer; OR
- Triple negative breast cancer diagnosed at 60 years of age or younger;
- Breast cancer and at least one first-, second- or third-degree male relative with breast cancer; OR
- Breast cancer AND two or more 1st-, 2nd-, or 3rd-degree relatives on the same side of the family with breast, ovarian, fallopian tube, primary peritoneal or pancreatic cancer; OR
- Ovarian, fallopian tube or primary peritoneal CA; OR

- Pancreatic cancer and two or more 1st-, 2nd-, or 3rd-degree relatives on the same side of the family with breast, ovarian, fallopian tube, primary peritoneal or pancreatic cancer; OR
- Ashkenazi Jewish descent and has a history of pancreatic cancer and a first-, second-, or third-degree relative on the same side of the family with breast, ovarian, fallopian tube, primary peritoneal or pancreatic cancer; OR
- 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).
- Family history of three or more first-, second- or third-degree relatives with breast (at least one of which has breast cancer prior to age 50), ovarian, fallopian tube or primary peritoneal cancer.
- Large genomic rearrangement testing (BART) when testing for mutations is negative in individuals who meet criteria for genetic testing.
- Personal history of epithelial ovarian cancer

Testing for PALB2 is considered **medically necessary** when all of the following criteria are met:

- Age 18 years or older
- Individual tested negative for BRCA1 and/or BRCA2
- Individual is at risk for hereditary breast cancer, as indicated by any ONE of the following:
    - Personal history of male breast cancer diagnosed at any age
    - Personal history of breast cancer
    - Family history of two or more first, second or third degree blood relatives with breast cancer diagnosed age 45 or younger
    - Family history of two or more first, second or third degree blood relatives with ovarian cancer diagnosed at any age

Unless criteria above are met, genetic testing either for those affected by breast, ovarian, fallopian tube, or primary peritoneal cancer or for unaffected individuals, including those with a family history of pancreatic cancer, is considered **investigational**.

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

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

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

Genetic testing using multi-gene panels is **investigational**.

NGS (Next Generation Sequencing), when used for genetic testing for BRCA1, BRCA2, PALB2 and CHEK2 mutations, is **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 interpretation 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 mutations 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)

<u>A Recommended Testing Strategy</u>

- In patients with known familial BRCA mutation:
  - Targeted testing for the specific, known mutation only.
- In patients with unknown familial BRCA mutation:
  - If more than one family member is affected with cancers highly associated with a particular inherited cancer susceptibility syndrome, consider testing first a family member most likely to carry a mutation, such as the youngest age at diagnosis, bilateral disease, multiple primary cancers, or other cancers associated with the syndrome, or most closely related to the proband/patient.
  - If no living family member with breast or ovarian cancer exists, NCCN suggests testing first- or second-degree family members affected with a different cancer type that is thought to be related to deleterious BRCA1 or BRCA2 mutations (e.g., prostate cancer, pancreatic cancer, and melanoma).
- 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; see Comprehensive Mutation Analysis, below) may be performed as is recommended by NCCN.
  - If following full sequencing and testing for common large genomic rearrangements is negative, testing for uncommon large genomic rearrangements (e.g., Myriad's BART) may be done.

- If of Ashkenazi Jewish descent:
  - In Ashkenazi Jewish patients, testing for founder-specific mutation(s) should be performed first. Comprehensive genetic testing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if other HBOC criteria are met.
  - In members 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, below).

Comprehensive Variant Analysis

Comprehensive variant analysis currently includes sequencing the coding regions and intron and exon splice sites, as well as tests 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 sequence variants should begin with tests specifically for these mutations. For example, founder mutations account for approximately three quarters of the *BRCA* sequence variants found in Ashkenazi Jewish populations. When testing for founder mutations is negative, comprehensive mutation analysis should then be performed.

Testing Unaffected Individuals

In unaffected family members of potential *BRCA* sequence 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* mutation 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* mutation is not ruled out.

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.

Background

Breast Cancer and Genetics

In 2016, researchers anticipate breast cancer will be diagnosed in 246,660 women and 40,450 will die from the disease[1]; a woman's lifetime risk is 12.3% (seer.cancer.gov/statfacts/html/breast.html). Breast cancers can be classified as sporadic, familial, or hereditary.[2] Most are sporadic (70% to 75%), occurring in women without a family history of 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[a,] while small proportions are attributed to pathogenic variants in other highly penetrant genes (e.g., *TP53*, *CDH1*, *PTEN*, *STK11*).

[a] http://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet

Hereditary breast and ovarian cancer

Several genetic syndromes with an autosomal dominant pattern of inheritance that feature breast cancer have been identified. Of these, HBOC and some cases of hereditary site-specific breast cancer have in common causative mutations 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, we refer collectively to both as hereditary breast and/or ovarian cancer.

Germline mutations 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 breast cancer, *BRCA* mutations are responsible only for a proportion of affected families. *BRCA* gene mutations are inherited in an autosomal dominant fashion through either the maternal or paternal lineage. 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.

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[3]). 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.[4]

Penetrance can be modified by environmental factors and by family history, which is a particularly important modifier for low- and moderate-penetrance genes. In addition, specific pathogenic variants within a gene may confer somewhat different risks.

In contrast, about 3% to 5% of women presenting for hereditary breast/ovarian cancer risk assessment have sequence variants in a moderate penetrance gene.

Determining Variant Pathogenicity

Determining the pathogenicity of variants in a cancer-susceptibility gene most commonly detected (e.g., founder sequence variants) 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.[5] The approach to defining pathogenicity is clearly outlined in standards and reporting guidelines.[5] Still, distinctions between a variant of uncertain significance and a pathogenic one from different laboratories may not always be identical.[6]

Genes Associated With a Moderate Penetrance of Breast Cancer

PALB2

The PALB2 gene (partner and localizer of BRCA2) encodes for a protein first described in 2006.[7] The gene is located at 16p12.2[a] and has 13 exons (www.omim.org/entry/610355). 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[b]. 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.[8] Variants are more prevalent in ethnic populations where founder variants have persisted (e.g., Finns, French Canadians, Poles), while infrequently found in others (e.g., in Ashkenazi Jews[9, 10]). In women with a family history of breast cancer, the prevalence of pathogenic PALB2 variants ranges between 0.9% and 3.9%,[8] 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[8]; and in populations with founder variants cause 0.5% to 1% of all breast cancers.[11]

Protein-truncating PALB2 variants appear responsible for some cases of familial pancreatic cancers, but the proportion is unclear. Whether screening asymptomatic high-risk patients for pancreatic cancer can improve health outcomes is uncertain.

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 mutation 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 variant, three other founder variants of CHEK2 (IVS2+1G>A, del5395, I157T) have been associated with breast cancer in Eastern Europe. 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.[12]

ATM Gene

ATM (ataxia-telangiectasia [AT] mutated), located on chromosome 11q22.3, is associated with the autosomal recessive condition AT. 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, but 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. 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.[13] A family history of breast cancer confers between a two and a four fold increased risk varying according to the number and close-

ness of affected relatives, age at which cancers developed, whether breast cancers were bilateral, and if other cancers occurred (e.g., ovarian).[14] 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),[15] screening tools (e.g., BRCAPRO,[16] Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, Family History Screen[17, 18]), or by referring to guidelines that define specific family history criteria (see Table 1). For women with breast cancer, family history also affects the likelihood of carrying a pathogenic variant, although somewhat different criteria are applied (see Table 2) as is risk assessment from a pedigree.[15]

Table 1. NCCN Criteria for Genetic Risk Evaluation of an Individual Without a History of Breast Cancer[2]

Individual Without a History of Breast Cancer
"A close relative with any of the following:
A known mutation in a cancer susceptibility gene within the family
≥ 2 breast cancer primaries in a single individual
≥ 2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤ 50 years
Ovarian cancer
Male breast cancer
First- or second-degree relative with breast cancer ≤ 45 years
Family history of three or more of the following (especially if early onset and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥ 7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations, and/or macrocephaly, hamartomatous polyps of GI tract"

GI: gastrointestinal; NCCN: National Comprehensive Cancer Network.

Table 2. NCCN Criteria for Genetic Risk Evaluation of an Individual With Breast Cancer[2]

Individual With Breast Cancer
"A known sequence variant in a cancer susceptibility gene within the family:
Early-age-onset breast cancer
Triple negative (ER-, PR-, HER2-) breast cancer diagnosed ≤ 60 years
Two breast cancer primaries in a single individual
Breast cancer at any age, and
≥ 1 close blood relative with breast cancer ≤ 50 years, or
≥ 1 close blood relative with invasive ovarian cancer at any age, or
≥ 2 close blood relatives with breast cancer and/or pancreatic cancer at any age, or
From a population at increased risk
Male breast cancer
An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age
An individual with a personal and/or family history of three or more of the following (especially if early onset and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥ 7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations, and/or macrocephaly, hamartomatous polyps of gastrointestinal (GI) tract."
An individual with an ovarian cancer

ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; NCCN: National Comprehensive Cancer Network; PR: progesterone receptor.

Patient Populations

Genetic testing can be considered for women at increased risk of developing hereditary breast cancer based on their family history, or in women with breast cancer whose family history or cancer characteristics (e.g., triple-negative disease, young age) increase the likelihood that the breast cancer is hereditary. Testing may also be considered for women from families with known variants. Potential benefit derives from interventions (screen-

ing, chemoprevention, risk reducing surgery) that can prevent a first breast cancer, a contralateral breast cancer, or cancer in a different organ caused by the same variant. Whether benefit outweighs harms depends on the risk of developing breast cancer (a first cancer or a contralateral one), the effectiveness and the harms of interventions. Assessing the net health outcome requires:

1. that a test accurately identifies variants and pathogenicity can be determined;
2. that a variant alters (increasing or decreasing) a woman's risk of developing breast cancer (including contralateral disease in women already diagnosed) sufficient to change decision making, and of a magnitude that
3. management changes informed by testing can lead to improved health outcomes.

Additionally, if a familial pathogenic variant is identified, asymptomatic at-risk family members may benefit from cascade testing for the known variant. If that variant is identified in an at-risk relative, then risk-reducing management options could be offered; if the familial variant is not identified, then the relative may be considered near population risk and could avoid increased surveillance for breast cancer and risk reducing options would not be considered.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). PALB2, CHEK2, and ATM testing are available under the auspices of CLIA (a list of laboratories offering testing is available at NCBI's Genetic Testing Registry https://www.ncbi.nlm.nih.gov/gtr/). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

Myriad Genetic Laboratories (Salt Lake City, UT) offers: (1) Comprehensive BRACAnalysis® that includes complete sequencing of *BRCA1* and *BRCA2* and gap polymerase chain reaction for five common rearrangements (deletions/duplications) in *BRCA1*; (2) BRACAnalysis® Large Rearrangement Test (BART™), which may be ordered as a reflex test for patients who test negative for Comprehensive BRACAnalysis® to detect uncommon large rearrangements in *BRCA1* and *BRCA2*; and (3) Integrated BRACAnalysis®, which includes BART as part of *BRCA1* or *BRCA2* analysis.

Per the www.genetests.org website there are currently six CLIA-certified U.S. laboratories that offer sequence analysis of the entire gene coding and four that offer deletion.

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

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

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

Related Protocol

Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing

Genetic Testing for Li-Fraumeni Syndrome

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

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