Clinical UM Guideline

Subject:	BRCA Genetic Testing		
Guideline #:	CG-GENE-16	**Publish Date:**	04/12/2023
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Description

This document addresses BRCA genetic testing (DNA testing) for individuals who are at higher than average risk for the development of cancer. Genetic tests addressed in this document include BRCA1 and BRCA2 mutations and large genomic rearrangements of DNA in the BRCA1 and BRCA2 genes (BRACAnalysis® Rearrangement Test [BART]).

Note: For additional information on genetic testing for malignant conditions, please refer to:
- CG-GENE-14 Gene Mutation Testing for Cancer Susceptibility and Management
- CG-GENE-15 Genetic Testing for Lynch Syndrome, Familial Adenomatous Polyposis (FAP), Attenuated FAP and MYH-associated Polyposis

This document does not address panel testing. Please refer to:
- GENE.00049 Circulating Tumor DNA Panel Testing (Liquid Biopsy)
- GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling

Clinical Indications

Medically Necessary:

Genetic testing to detect BRCA (BRCA1 and/or BRCA2) mutations and/or large genomic rearrangements is considered **medically necessary** when any one of the criteria A, B, C, or D and **all** of the criteria in E are met:

A. For women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer that suggests an inherited cancer susceptibility as determined by a validated BRCA1 or BRCA2 mutation assessment tool, including any of the following (Ontario Family History Assessment Tool; Manchester Scoring System; Referral Screening Tool; Pedigree Assessment Tool; 7-Question Family History Screening Tool; International Breast Cancer Intervention Study Instrument [Tyrer-Cuzick]; BRCAPRO [brief version]); **or**

B. For individuals who meet one or more BRCA1 or BRCA2 testing criteria established by the National Comprehensive Cancer Network (NCCN); **or**

C. The individual is a candidate for poly (ADP-ribose) polymerase (PARP) inhibitor therapy; **or**

D. For individuals who require confirmatory testing for a BRCA1 or BRCA2 mutation(s) detected by a Food and Drug Administration (FDA)-authorized direct-to-consumer (DTC) test report; **and**

E. Genetic counseling, which encompasses all of the following components, has been performed:
   1. Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; **and**
   2. Education about inheritance, genetic testing, disease management, prevention and resources; **and**
   3. Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; **and**
   4. Counseling for the psychological aspects of genetic testing.

Note: The NCCN testing criteria and BRCA1 or BRCA2 mutation assessment tools are listed below in the Discussion/General Information section.

Not Medically Necessary:

Genetic testing to detect BRCA (BRCA1 and/or BRCA2) mutations and/or large genomic rearrangements is considered **not medically necessary** in individuals not meeting any of the criteria above.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT	
81162	*BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated)* (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)
81163	*BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated)* (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81164	*BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated)* (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81165	*BRCA1 (BRCA1, DNA repair associated)* (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81166	*BRCA1 (BRCA1, DNA repair associated)* (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81167	*BRCA2 (BRCA2, DNA repair associated)* (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)

81212	*BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated* (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81215	*BRCA1 (BRCA1, DNA repair associated)* (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	*BRCA2 (BRCA2, DNA repair associated)* (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	*BRCA2 (BRCA2, DNA repair associated)* (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81479	Unlisted molecular pathology procedure [when specified as common duplication/deletion variant(s) in *BRCA1* (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)]
0172U	Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score myChoice® CDx, Myriad Genetics Laboratories, Inc, Myriad Genetics Laboratories, Inc

ICD-10 Diagnosis

C25.0-C25.9	Malignant neoplasm of pancreas
C48.0-C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C50.011-C50.929	Malignant neoplasm of breast
C56.1-C56.9	Malignant neoplasm of ovary
C57.00-C57.9	Malignant neoplasm of other and unspecified female genital organs
C61	Malignant neoplasm of prostate
R85.89	Other abnormal findings in specimens from digestive organs and abdominal cavity
Z13.71-Z13.79	Encounter for screening for genetic and chromosomal anomalies
Z15.01	Genetic susceptibility to malignant neoplasm of breast
Z15.02	Genetic susceptibility to malignant neoplasm of ovary
Z80.0	Family history of malignant neoplasm of digestive organs [pancreas]
Z80.3	Family history of malignant neoplasm of breast
Z80.41	Family history of malignant neoplasm of ovary
Z80.42	Family history of malignant neoplasm of prostate
Z80.49	Family history of malignant neoplasm of other genital organs
Z80.8	Family history of malignant neoplasm of other organs or systems [peritoneum]
Z85.07	Personal history of malignant neoplasm of pancreas
Z85.3	Personal history of malignant neoplasm of breast
Z85.43	Personal history of malignant neoplasm of ovary
Z85.44	Personal history of malignant neoplasm of other female genital organs
Z85.89	Personal history of malignant neoplasm of other organs and systems [peritoneum]

When services are Not Medically Necessary:
For the procedure codes listed above when criteria are not met or for all other diagnoses not listed.

Discussion/General Information

BRCA1 and BRCA2 Gene Mutations and Cancer Susceptibility
BRCA1 is located on chromosome 17 and BRCA2 is positioned on chromosome 13. Both BRCA genes are tumor suppressor genes that encode proteins that play a role in the DNA repair process (ACOG, 2017).

Between 5% and 10% of women with breast cancer develop the disease due to the inheritance of a mutated copy of BRCA1 or BRCA2 genes. Families suspected of having hereditary breast and/or ovarian cancer are characterized by cancer occurring in premenopause, in multiple generations, often bilaterally and in a pattern suggesting an autosomal dominant pattern of inheritance. A positive test result indicates that a person has inherited a known BRCA1 or BRCA2 gene mutation, and has an increased risk of breast and/or ovarian cancer. Mutations of BRCA1 and BRCA2 are present in 1-2% of individuals of Ashkenazi Jewish ancestry.

Germline mutations in the BRCA1 and BRCA2 (BRCA) genes account for the majority of cases of hereditary breast and ovarian cancer syndrome. It has been estimated that approximately 4.5% of cases of breast cancer and 9–24% of cases of epithelial ovarian cancer are due to germline BRCA1 and BRCA2 mutations. According to the American College of Obstetricians and Gynecologists (ACOG), for a woman harboring the BRCA1 mutation, the risk of ovarian cancer (including primary peritoneal cancer and fallopian tube cancer) by age 70 years is approximately 39-46%. For a woman carrying a BRCA2 mutation, the risk of ovarian cancer is 10-27% by age 70 years. Ovarian cancer associated with BRCA1 and BRCA2 mutations is usually high grade and has a distinct histologic phenotype that is predominantly endometrioid or serous. A woman with high-grade ovarian cancer has a 9-24% probability of carrying a BRCA1 or BRCA2 germline mutation. Mutations in the BRCA genes have also been associated with other types of cancer. Individuals with BRCA mutations are also at increased risk (albeit smaller than their risk of breast and ovarian cancer) for prostate cancer, pancreatic cancer, melanoma, and potentially uterine cancer (ACOG, 2017).

In the general population, it has been estimated that approximately 1 in 300 to 1 in 800 individuals carry a BRCA1 or BRCA2 mutation. However, the prevalence of BRCA1 and BRCA2 mutations is not the same amongst all racial and ethnic populations. In certain populations founded by a small ancestral group, a specific BRCA1 or BRCA2 mutation may occur more often, and is often referred to as a founder mutation. Several ethnic and geographic populations, including but not limited to the Ashkenazi (Central and Eastern European) Jews, French Canadians, and Icelanders have a higher prevalence of specific harmful BRCA1 and BRCA2 mutations. BRCA mutations also have been found in individuals of diverse ethnic backgrounds, including Hispanic, Asian, and African American (ACOG, 2017; Hall, 2009; Nanda, 2005). John and colleagues (2007) reported a BRCA1 mutation frequency of 16.7% amongst black women from California who were diagnosed with breast cancer prior to 35 years of age. Pal and colleagues (2015) analyzed the BRCA mutation frequency and family history of 396 black women residing in

Florida who were diagnosed with invasive breast cancer prior to the age of 50. The researchers determined that 12.4 % of the study participants had either BRCA1 or BRCA2 mutations and for participants 35 years of age or younger, 19.4% had BRCA1 mutations while 4.2% had BRCA2 mutations. Additionally, more than 40% of the individuals with a mutation had no close relatives with breast or ovarian cancer, which suggests that family history alone may not be sufficient to identify those at risk for carrying a BRCA mutation. The researchers noted that amongst the BRCA1 carriers, the rate of prevalence decreased as the age of onset increased whereas amongst the BRCA2 carriers, the overall prevalence of mutations was 4.3% and this finding was similar for women in all age categories. The authors concluded that based on the results of this study, "It is appropriate to recommend BRCA testing in all black women with invasive breast cancer who are diagnosed at age ≤ 50 years, regardless of family history."

The goal of BRCA1 and BRCA2 testing is to provide individuals and their physicians with information that will allow them to make informed decisions regarding cancer prevention, screening, surveillance, and treatment options (for example, prophylactic surgery). A significant benefit of genetic testing is the ability to quantify cancer risk estimates more precisely, thereby improving the process of determining the most appropriate management strategies in individuals who test positive. For individuals who test negative, unnecessary treatment (for example, prophylactic surgery) may be avoided.

There are some histopathologic features that have been noted to occur more frequently in breast cancers that are associated with BRCA1 or BRCA2 mutation. Several studies have demonstrated that BRCA1 breast cancer is more likely to be characterized as estrogen receptor (ER) negative, progesterone receptor (PR) negative, and human epidermal growth factor receptor 2 (HER2) negative, also referred to as triple negative breast cancer. For example, a female with triple negative breast cancer has a 10-39% probability of having a BRCA1 or BRCA2 mutation, with BRCA1 being more probable. In contrast, women with BRCA2 mutations are more likely to be estrogen-receptor and progesterone-receptor positive (ACOG, 2017). It has also been noted that in those with triple-negative disease, the BRCA mutation carriers were diagnosed at a younger age compared to non-carriers.

BRCA1 and BRCA2 testing is currently available individually or as part of multiplex gene panels from a variety of commercial laboratories. There is evidence in the published, peer-reviewed scientific literature to demonstrate that testing methods used to identify BRCA mutations are accurate in detecting specific mutations. If a BRCA1 or BRCA2 mutation is identified within a family, unaffected family members can also be tested for the presence of a mutation, and those testing negative can be provided with the reassurance that their risk of developing breast or ovarian cancer is more similar to that of the general population. Sensitivity of BRCA testing has been reported to be up to 98% of all mutations, and sequencing should detect almost 100% of all nucleotide differences. The specificity of BRCA testing has not been well studied.

Evidence in the published, peer-reviewed scientific literature indicates that BRCA1 and BRCA2 genetic testing is appropriate for a specific subset of adult individuals who have been identified to be at high risk for hereditary breast and ovarian cancers and the testing will impact the medical management of the tested individual or their at-risk family members. Furthermore, several specialty organizations, including the National Comprehensive Cancer Networks (NCCN), American College of Medical Genetics (ACMG), and American Society of Clinical Oncology

(ASCO), have issued statements recognizing the role of BRCA testing in the management of at-risk individuals. The U.S. Preventive Services Task Force (USPSTF) (2019) has published recommendations regarding genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility. Studies have demonstrated that individuals with BRCA mutations are at increased risk for developing breast and ovarian cancer.

The NCCN guidelines on Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Guidelines recommend that mutation testing begin with a relative (male or female) with known BRCA-related cancer to ascertain if a clinically significant mutation is present in the family prior to testing individuals without cancer. If an affected family member is not available for testing, then testing should be conducted on the relative with the highest probability of a BRCA mutation. Ideally, the results of the initial test will be used to guide testing decisions of other family members. Individuals without a personal history of cancer but who may fulfill the NCCN criteria for testing include those from families with known deleterious BRCA1 or BRCA2 mutations or from families with extensive cancer history (NCCN, 2023).

The NCCN guidelines on Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (2022) include the following information with regard to the selection of appropriate candidates to undergo genetic testing:

> The genetic testing strategy is greatly facilitated when a P/LP variant has already been identified in another family member. In that case, the genetic testing laboratory can limit the search for P/LP variants in additional family members to the same location in the gene … For the majority of families in whom presence of a P/LP variant is unknown, it is best to consider testing an affected family member first, especially a family member with early-onset disease, bilateral disease, or multiple primaries, because that individual has the highest likelihood for a positive test result. The testing of the unaffected individual (or of unaffected family members) should only be considered when no affected family member is available for testing. In such cases, the unaffected individual or unaffected close relative with the highest likelihood of testing positive for the P/LP variant should be tested. This may include the relative closest to the family member with the youngest age at diagnosis, bilateral disease, multiple primary tumors, or other cancers associated with a suspected hereditary syndrome. A negative test result in such cases, however, is considered indeterminate and does not provide the same level of information as when there is a known P/LP variant in the family.

The type of gene mutation analysis required is dependent upon family history. Historically, BRCA mutation testing was comprised of single-site testing. However, due to technological advances, option for BRCA mutation testing may now consist of targeted multisite mutation testing, comprehensive gene sequencing, and BRCA rearrangement testing. It may be appropriate for individuals from families with known mutations, or from ethnic groups with common mutations, to be tested for those specific mutations. Individuals without linkages to families or groups with known mutations may undergo direct DNA sequencing (Nelson, 2013).

The NCCN guidelines for prostate cancer (2023) state that individuals with germline BRCA 1/2 mutations have been associated with an increased risk of developing prostate cancer. Those of Ashkenazi Jewish descent can carry germline mutations in BRCA 1/2 and have a 16% chance of developing prostate cancer by 70 years of age.

The NCCN guidelines also point out that the chances of mutation detection may be very low in families with a large number of unaffected female relatives. Genetic counseling is an integral part of the testing process and provides the candidate with opportunity to be made aware of the potential benefits, limitations, and risks of genetic testing.

ACOG states the following regarding BRCA testing:

> If a specific BRCA mutation is identified in an affected individual, a single-site test can be recommended for family members to look for that specific genetic mutation already identified (ie, "predictive testing"). For members of certain ethnic and geographic groups who are at risk of founder mutations, but who do not have a personal or family history of breast or ovarian cancer, targeted multisite testing for common mutations can be performed and is less expensive than full sequence testing. Genetic testing has evolved over the years so patients who underwent BRCA genetic testing before the routine initiation of BRCA Rearrangement Testing, may need repeat testing or evaluation (ACOG, 2017).

A 2021 meta-analysis by Lee and colleagues evaluated studies which looked at the association of BRCA1 or BRCA2 with various cancers (excluding breast and ovarian cancers). There were 12 studies included in the analysis, 5 of which ascertained BRCA mutation carriers, and the remaining studies involved the pedigree to expand the cohort number by adding the pedigree to the calculation of the risk of being a carrier. Cancer types were noted as head and neck cancer. gastrointestinal cancer, biliary and pancreatic cancer, gynecologic cancer, urologic cancer, thyroid cancer, cancer of the bone and connective tissue, hematologic malignancies, melanoma, and others. There were many variations among the studies. One study focused solely on pharyngeal cancer and noted that presence of a BRCA2 variant increased the incidence of this type of cancer. However, other studies looked at general head and neck cancers and did not find the presence of BRCA1 or BRCA2 increased the incidence of head and neck cancers. Another study reported presence of a BRCA2 variant to increase the incidence of uveal melanoma while other studies reported no effect on the incidence of melanoma. One study reported an increase in urological cancer based on the presence of a BRCA1 and BRCA2 variant, however other studies did not report an increase of urological cancers. The incidence of gastric cancer was found by 6 studies to be increased when there was a BRCA2 variant. Presence of BRCA1 or BRCA2 variant can increase the incidence of pancreatic cancer by threefold and uterine cancer marginally. Differences in study designs and outcomes make it difficult to ascertain whether the presence of BRCA1 or BRCA2 variants increase the incidence of certain types of cancer. Additional studies are needed to determine net health outcomes.

BRCA Mutation Status and Treatment for Metastatic Breast Cancer

In January 2018, the United States Food and Drug Administration (FDA) approved olaparib (Lynparza®, AstraZeneca, Wilmington, DE), for use in individuals with deleterious or suspected deleterious germline BRCA-mutated HER2-negative metastatic breast cancer who have been previously treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. In addition to other criteria, the product information indicates that individuals should be selected for therapy based on the FDA-approved companion diagnostic test (BRACAnalysis CDx) from Myriad Genetics. The FDA approval was based on data from the randomized, open-label, Phase III OlympiAD trial (Robson, 2017), which examined olaparib versus physician's choice of chemotherapy (capecitabine, eribulin or vinorelbine).

Large rearrangements of DNA in the BRCA1 and BRCA2 genes
In 2016, the BRACAnalysis® Rearrangement Test™ (BART) was introduced to the market as a refinement of the BRCA genetic tests and was used to detect rare, large rearrangements of deoxyribonucleic acid (DNA) in the BRCA1 and BRCA2 genes which were previously undetected by standard genetic testing. Since then, Myriad has included BART testing as part of the Comprehensive BRACAnalysis test.

Prior to the development of next generation sequencing (also known as massively parallel sequencing), genetic testing was generally carried out using traditional (Sanger) DNA sequencing. Because the traditional DNA sequencing method does not identify large gene rearrangements such as deletions or duplications, a separate technology/test was necessary to detect large genomic rearrangements (Hogervorst 2003). Next generation sequencing accurately detects large genomic alterations such as translocations, inversions, or large deletions or insertions that are overlooked by most genetic testing techniques, including direct DNA sequencing. Such rearrangements are believed to be responsible for approximately 12% to 18% of BRCA1 inactivating variants but are less frequently observed in BRCA2 and in individuals of Ashkenazi Jewish descent. Additionally, studies have indicated that these rearrangements may occur more frequently in Caribbean and Hispanic populations (NCI, 2017; Walsh, 2010).

Walsh and colleagues (2006) reported on probands from 300 families in the United States with 4 or more cases of breast or ovarian cancer but who had tested negative (wild-type) with commercial genetic tests for BRCA1 and BRCA2 mutations. These individuals were screened using additional multiple DNA-based and RNA-based methods to detect genetic mutations including genomic rearrangements in BRCA1 and BRCA2. Of the 300 individuals participating in the study, 35 (12%) carried previously undetected genomic rearrangements of BRCA1 or BRCA2. Palma and colleagues (2008) evaluated 251 individuals with an estimated risk of BRCA mutation of greater than or equal to 10% using the Myriad II model. In the 136 non-Ashkenazi Jewish probands, 36 (26%) had BRCA point mutations and 8 (6%) had genomic rearrangements, (with 7 in BRCA1 and 1 in BRCA2). Point mutations were identified in 47 of the 115 (40%) Jewish probands. There were no genomic rearrangements identified in the group without mutations. In the non-Ashkenazi Jewish probands, large genomic rearrangements accounted for 18% of all identified BRCA mutations. The estimated prevalence of a mutation using the Myriad II model was not predictive of the presence of a genomic rearrangement.

Because certain large genomic rearrangements, such as translocations, inversions, deletions, or insertions, are not detectable by standard DNA sequencing, supplemental testing of large genomic rearrangements (e.g., BART™) has been recommended (NCCN, 2022) for select high-risk individuals. These large genomic rearrangements are estimated to be responsible for 12% to 18% of BRCA1 inactivating mutations, although less is often seen in BRCA2 and, as noted above, in individuals of Ashkenazi Jewish descent. The NCCN emphasizes the need for comprehensive testing, which includes full BRCA1 and BRCA 2 sequencing as well as the detection of large gene rearrangements (NCCN, 2023; Shannon, 2011).

NCCN BRCA 1/2 Testing Criteria (Return to Clinical Indications)

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management.

Note: Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.

General Testing Criteria
Testing is clinically indicated in the following scenarios:

- Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene.
- Individuals meeting the criteria below but tested negative with previous limited testing (eg, single gene and/or absent deletion duplication analysis) interested in pursuing multi-gene testing. A pathogenic/likely pathogenic variant on tumor genomic testing that has clinical implications if also identified in the germline.
- To aid in systemic therapy and surgical decision-making (e.g., PARP inhibitors for ovarian cancer, prostate cancer, pancreatic cancer, and metastatic HER2-negative breast cancer; platinum therapy for prostate cancer and pancreatic cancer; and risk-reducing surgery).

Testing Criteria for High-Penetrance Breast Cancer Susceptibility Genes

- Personal history of breast cancer with specific features:
  - ≤50 y
  - Any age:
    - Treatment indications
      - To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting
      - To aid in adjuvant treatment decisions with olaparib for high-risk, HER-2 negative breast cancer
    - Pathology/histology
      - Triple-negative breast cancer

- Multiple primary breast cancers (synchronous or metachronous)
- Lobular breast cancer with personal or family history of diffuse gastric cancer

▪ Male breast cancer
▪ Ancestry: Ashkenazi Jewish ancestry
▪ Family history
- ≥1 close blood relative with ANY:
  - Breast cancer at age ≤50
  - Male breast cancer
  - Ovarian cancer
  - Pancreatic cancer
  - Prostate cancer with metastatic, or high- or very-high-risk group
- ≥3 total diagnoses of breast cancer in patient and/or close blood relatives
- ≥2 close blood relatives with either breast or prostate cancer (any grade)

- Family history of cancer only
  - An affected individual (not meeting testing criteria listed above) or unaffected individual with a first- or second-degree blood relative not meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).
    ▪ If the affected relative has pancreatic cancer or prostate cancer only first-degree relatives should be offered testing unless indicated based on additional family history.
  - An affected or unaffected individual who otherwise does not meet the criteria above but who has a probability >5% of a BRCA 1/2 pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk).

Testing Criteria for Ovarian Cancer Susceptibility Genes

- Personal history of epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age.
- Family history of cancer only
  - An unaffected individual with a first- or second-degree blood relative with epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age.
  - An unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a BRCA 1/2 pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk).

Testing Criteria for Pancreatic Susceptibility Genes

- Exocrine pancreatic cancers
  - All individuals diagnosed with pancreatic cancer
  - First-degree relatives of individuals diagnosed with exocrine pancreatic cancer
- Neuroendocrine pancreatic tumors

Testing Criteria for High-Penetrance Prostate Cancer Susceptibility Genes

- Personal history of prostate cancer with specific features:
  - By tumor characteristics (any age)
    - Metastatic
    - Histology
      - High- or very-high-risk group
  - By family history and ancestry
    - ≥1 close blood relative with:
      - Breast cancer at age ≤50 y
      - Triple-negative breast cancer at any age
      - Male breast cancer at any age
      - Ovarian cancer any age
      - Pancreatic cancer any age
      - Metastatic, high- or very-high-risk group at any age
    - ≥2 close blood relatives with either breast or prostate cancer (any grade) at any age
    - Ashkenazi Jewish ancestry
- Family history of cancer only
  - An affected (not meeting testing criteria listed above) or unaffected individual with a first-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).

Testing may be considered in the following scenarios (with appropriate pre-test education and access to post-test management):

- Personal history of breast cancer <60y not meeting any of the above criteria may approach a 2.5% probability of having a PV, based on recent data. It is cautioned that the majority of those PVs will be in moderate penetrance genes, which are over-represented in older affected individuals, and for which data on appropriate management are often lacking. Access to an experienced genetic counseling team to discuss management options is particularly important in this setting.
- Personal history of breast cancer diagnosed at any age with ≥1 close blood relative with intermediate-risk prostate cancer with intraductal/cribriform histology.

• An affected or unaffected individual who otherwise does not meet any of the above criteria but with a 2.5%-5% probability of BRCA 1/2 pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)
There is a low probability (<2.5%) that testing will have findings of documented high-penetrance genes in the following scenarios (that is, testing is not recommended): • Female diagnosed with breast cancer at age >60 y, with no close relative with breast, ovarian, pancreatic, or prostate cancer. • Diagnosed with localized prostate cancer with Gleason Score <7 and no close relative with breast, ovarian, pancreatic, or prostate cancer.

*Close blood relatives include first-, second-, and third-degree relatives on the same side of the family

In 2019, the USPSTF published their recommendations for Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer. Their recommendations include the use of validated familial risk assessment tools including: Ontario Family History Assessment Tool; Manchester Scoring System; Referral Screening Tool; Pedigree Assessment Tool; 7-Question Family History Screening Tool; International Breast Cancer Intervention Study Instrument (Tyrer-Cuzick); BRCAPRO (brief version).

In regard to genetic testing, the USPSTF (2019) states:

> Testing for BRCA1/2 mutations should be performed only when an individual has personal or family history that suggests an inherited cancer susceptibility, when an individual is willing to talk with a health professional who is suitably trained to provide genetic counseling and interpret test results, and when test results will aid in decision-making. Clinical practice guidelines recommend that BRCA1/2 mutation testing begin with a relative with known BRCA-related cancer, including male relatives, to determine if a clinically significant mutation is detected in the family before testing individuals without cancer. If an affected family member with a BRCA-related cancer is not available, then the relative with the highest probability of mutation should be tested. The type of mutation analysis required depends on family history. Individuals from families with known mutations or from ancestry groups in which certain mutations are more common (eg, Ashkenazi Jewish founder mutations) can be tested for these specific mutations. Because risk assessment is primarily based on family history, it is unclear how women with a limited or unknown family history should be assessed for BRCA1/2 mutation risk and potential referral to counseling or genetic testing.

Ontario Family History Assessment Tool (Return to Clinical Indications)

Risk Factor	Points
Breast and ovarian cancer	
Mother	10
Sibling	7

Second-/third-degree relative	5
Breast cancer relatives	
Parent	4
Sibling	3
Second-/third-degree relative	2
Male relative (add to above)	2
Breast cancer characteristics	
Onset age, y	
20-29	6
30-39	4
40-49	2
Premenopausal/perimenopausal	2
Bilateral/multifocal	3
Ovarian cancer relatives	
Mother	7
Sibling	4
Second-/third-degree relative	3
Ovarian cancer onset age, y	
<40	6
40-60	4
>60	2
Prostate cancer onset	
Age <50 y	1
Colon cancer onset	
Age <50 y	1
Family total	
Referral	≥10

Manchester Scoring System (Return to Clinical Indications)		
Risk Factor (Age at Onset for Relative in Direct Lineage)	BRCA1 Score	BRCA2 Score
Female breast cancer, y		
<30	6	5
30-39	4	4
40-49	3	3
50-59	2	2
≥60	1	1

Male breast cancer, y		
<60	5	8
≥60	5	5
Ovarian cancer, y		
<60	8	5
≥60	5	5
Pancreatic cancer		
Any age	0	1
Prostate cancer, y		
<60	0	2
≥60	0	1
Total individual genes	10	10
Total for combined = 15		

Referral Screening Tool
(referral if 2 or more checks in table)
(Return to Clinical Indications)

History of Breast or Ovarian Cancer in the Family? If Yes, Complete Checklist

Risk Factor	Breast Cancer at Age ≤50 y	Ovarian Cancer at any Age
Yourself		
Mother		
Sister		
Daughter		
Mother's side		
Grandmother		
Aunt		
Father's side		
Grandmother		
Aunt		
≥2 cases of breast cancer after age 50 y on same side of family		
Male breast cancer at any age in any relative		
Jewish ancestry		

Pedigree Assessment Tool

(score 8 or greater is the optimal referral threshold) (Return to Clinical Indications)	
Risk Factor	Score for Every Family Member with Breast or Ovarian Cancer Diagnosis, Including Second-/Third-Degree Relatives
Breast cancer at age ≥50 y	3
Breast cancer at age <50 y	4
Ovarian cancer at any age	5
Male breast cancer at any age	8
Ashkenazi Jewish heritage	4
Total	

Seven-Question Family History Screening (One positive response initiates referral) (Return to Clinical Indications)
1. Did any of your first-degree relatives have breast or ovarian cancer?
2. Did any of your relatives have bilateral breast cancer?
3. Did any man in your family have breast cancer?
4. Did any woman in your family have breast *and* ovarian cancer?
5. Did any woman in your family have breast cancer before age 50 y?
6. Do you have 2 or more relatives with breast *and/or* ovarian cancer?
7. Do you have 2 or more relatives with breast *and/or* bowel cancer?

International Breast Cancer Intervention Study Model (also known as Tyrer-Cuzick) (Referral for genetic testing if the personal risk level for a mutation in breast cancer susceptibility gene 1 or 2 is 10% or greater) (Return to Clinical Indications)
Risk Factor
1. Personal history: current age, age at menopause, age at menarche, childbirth history, menopausal status, use of menopausal hormone therapy
2. Personal breast history, breast density (optional), prior breast biopsy, history of cancer (breast or ovarian), genetic testing
3. Ashkenazi Jewish inheritance
4. Family history (genetic risk) – relatives with breast or ovarian cancer, age at diagnosis, genetic testing

Poly (ADP-ribose) polymerase (PARP) inhibitor therapy
PARPs are substances that block an enzyme in cells. A PARP helps repair DNA when it becomes damaged. DNA damage can be caused by drugs used to treat cancer. PARPs are known to play a role in

cellular processes such as replication, recombination, and DNA repair. Blocking PARP can help keep cancer cells from repairing the damaged DNA which causes them to die. PARP inhibitors are a type of targeted cancer therapy. Homologous recombination deficiency (HRD) is an attribute characterized by the inability of cells to repair DNA. When genes lose function this can sensitize tumors to PARP inhibitors and platinum-based chemotherapy. Several proprietary tests are available to detect HRD status for potential treatment using a PARP inhibitor, including myChoice® CDx (Myriad Genetics, Salt Lake City, UT)and Tempus HRD (Tempus, Chicago IL).

Pancreatic cancer is known to be found in families with BRCA 1/2 mutations. Individuals with pancreatic cancer who also have Ashkenazi Jewish ancestry may also have a greater likelihood of testing positive for BRCA 1/2 mutations. PARP inhibitors are proposed treatment for cancers associated with BRCA 1/2 mutations. The NCCN guideline for pancreatic adenocarcinoma (2023) considers the use of olaparib as maintenance therapy for individuals with a germline BRCA 1/2 mutation, with no progression of disease after at least 4-6 months of chemotherapy, assuming acceptable tolerance.

In a phase 3 randomized, double-blind, placebo-controlled trial, Golan and colleagues (2019) reported on the efficacy of olaparib as maintenance therapy for individuals with germline BRCA mutation and metastatic pancreatic cancer (without progression during first-line platinum-based chemotherapy). In a 3:2 ratio, participants were randomized to either olaparib (n=92) or placebo (n=62). The primary endpoint was progression-free survival, defined as the time from randomization until disease progression. Secondary endpoints were overall survival, second progression-free survival, or death. Primary endpoint analysis was performed on 104 participants who had disease progression or had died. Median progression-free survival in the olaparib group was 7.4 months compared to 3.8 months in the placebo group. In a planned interim analysis of overall survival that took place at a data maturity level of 46%, the overall survival in the olaparib group was 18.9 months versus 18.1 months in the placebo group. Another analysis with a data maturity level of 46% showed a second progression-free survival showed a median time from randomization to second disease progression or death of 13.2 months in the olaparib group compared to 9.2 months in the placebo group. Adverse events occurred in 24% of the participants receiving olaparib which led to discontinuation of trial agent in 5% of participants. Adverse events occurred in 15% of participants in the placebo group which led to discontinuation of placebo in 2% of participants. The final analysis of overall survival is planned at a data maturity of 69%.

The December 2022 label for niraparib (Zejula®) includes companion diagnostic services for certain individuals receiving therapy (myChoice® CDx. In addition, the December 2022 label for rucaparib (Rubraca®) includes companion diagnostic services for certain individuals receiving therapy (BRACAnalysis CDx [Myriad Genetics, Salt Lake City, UT], FoundationOne CDx and FoundationFocus CDxBRCA Assay [Foundation Medicine, Cambridge, MA]).

Confirmatory Testing for a BRCA1/BRCA2 mutation(s) Detected by a Food and Drug Administration (FDA)-Authorized Direct-to-Consumer (DTC) Test Report

In March 2018, the FDA granted the genetic testing company 23andMe® approval to provide direct-to-consumer genetic testing and to report on selected conditions, including but not limited to three genetic variants of the breast cancer susceptibility genes (BRCA1/BRCA2). The three BRCA variations (founder mutations) represent the most common breast cancer risk genes in individuals of Eastern European (Ashkenazi) Jewish decent (present in approximately 2% of Ashkenazi Jewish women but rarely [0 percent to 0.1 percent] in other ethnic populations). Women with one of these three variants, which account for approximately 90% of BRCA mutations identified in Ashkenazi Jewish women, have a 45-85% probability of developing breast cancer by age 70.

The 23andMe Genetic Health Risk Test examines DNA collected from a saliva sample to report if a woman is at increased risk of developing ovarian or breast cancer, and if a man is at increased risk of developing breast cancer or prostate cancer. The test only identifies 3 out of more than 1000 known BRCA mutations. Therefore, a negative result does not rule out the possibility that an individual carries other BRCA mutations that may put them at increased risk for cancer. The FDA also cautioned that the test results should not be used to determine any treatments, including anti-hormone therapies and prophylactic removal of the breasts or ovaries and that such decisions warrant confirmatory testing and genetic counseling.

The FDA approval obtained by 23andMe was based on the agency's review of data which determined that the company provided sufficient data to demonstrate that the test is accurate (i.e., can correctly identify the three genetic variants in saliva samples), and can provide reproducible results. Of equal importance, the FDA determined that 23andMe will provide consumers with appropriate instructions and a test report which describes what the BRCA test results mean, how the results should be interpreted and where additional information can be accessed. The FDA notes that consumers and health care professionals should not use test results obtained from the 23andMe report to determine treatments, including anti-hormone therapies and prophylactic removal of the breasts or ovaries, and that such decisions require confirmatory testing and genetic counseling.

Genetic Counseling
According to the National Society of Genetic Counselors (NSGC), genetic counseling is the process of assisting individuals to understand and adapt to the medical, psychological, and familial ramifications of a genetic disease. This process typically includes the guidance of a specially trained professional who:

1. Integrates the interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; and
2. Provides education about inheritance, genetic testing, disease management, prevention and resources; and
3. Provides counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; and
4. Provides counseling for the psychological aspects of genetic testing (NSGC, 2006).

Definitions

Ashkenazi Jewish: Persons related to Jewish settlers of the Rhine Valley in Germany and France in the middle ages.

First-degree relative: Any relative who shares approximately 50% of an individual's genetic material, such as an individual's parent (father or mother), full sibling (brother or sister), or offspring.

Founder mutation: A particular mutation occurring among defined ethnic groups or individuals from a specific geographic area that is traceable back to a common ancestor.

Genetic testing: A type of test that is used to determine the presence or absence of a specific gene or set of genes to help diagnose a disease, screen for specific health conditions, and for other purposes.

Germline mutation: Any detectable and heritable change in the lineage of germ cells. Mutations in these cells are transmitted to offspring, while, on the other hand, somatic mutations are not inherited.

Mutation: A change in DNA sequence.

Next-generation sequencing: Any of the technologies that allow rapid sequencing of large numbers of segments of DNA, up to and including entire genomes. This technology includes but is not limited to massively parallel sequencing and microarray analysis.

Panel testing: Involves the analysis of multiple genes for multiple mutations simultaneously.

Poly (ADP-ribose) polymerase (PARP) inhibitors: Any one of a group of enzymes (including PARP1, PARP2 and PARP3) which play a role in DNA damage/repair pathways. PARP inhibitors have also been explored as antitumor agents. The following is a list of FDA-approved PARP inhibitor drugs:

- Niraparib (Zejula®)
- Olaprarib (Lynparza®)
- Rucaparib (Rubraca®)
- Talazoparib (Talzenna®)

Penetrance: The likelihood that a clinical condition will occur when a particular genotype exists.

Second-degree relative: Any relative who shares approximately 25% of an individual's genetic material, such an individual's grandparent, grandchild, uncle, aunt, niece, nephew, or half-sibling.

Third-degree relative: Any relative who shares approximately 12.5% of an individual's genetic material, such an individual's first cousin, great grandparent, great grandchild, great uncle, great aunt, half-uncle, half-aunt, half-niece, or half-nephew.

Triple negative breast cancer: Breast cancer cells which lack estrogen receptors, progesterone receptors and large amounts of HER2/neu protein.

References

Peer Reviewed Publications:

1. Armstrong J, Toscano M, Kotchko N, et al. American BRCA Outcomes and Utilization of Testing (ABOUT) Study: a pragmatic research model that incorporates personalized medicine/patient-centered outcomes in a real world setting. J Genet Couns. 2015; 24(1):18-28.
2. Chong HK, Wang T, Lu HM, et al. The validation and clinical implementation of BRCAplus: a comprehensive high-risk breast cancer diagnostic assay. PLoS One. 2014; 9(5):e97408.
3. de la Hoya M, Gutiérrez-Enríquez S, Velasco E, et al. Genomic rearrangements at the BRCA1 locus in Spanish families with breast/ovarian cancer. Clin Chem. 2006; 52(8):1480-1485.
4. Ferrone CR, Levine DA, Tang LH, et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. J Clin Oncol. 2009; 27(3):433-438.
5. Gad S, Scheuner MT, Pages-Berhouet S, et al. Identification of a large rearrangement of the BRCA1 gene using color bar code on combed DNA in an American breast/ovarian cancer family previously studied by direct sequencing. J Med Genet. 2001; 38(6):388-392.
6. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med. 2019 Jul; 381(4):317-327.
7. Gutiérrez-Enríquez S, de la Hoya M, Martínez-Bouzas C, et al. Screening for large rearrangements of the BRCA2 gene in Spanish families with breast/ovarian cancer. Breast Cancer Res Treat. 2007; 103(1):103-107.
8. Hadar T, Mor P, Amit G, et al. Presymptomatic awareness of germline pathogenic BRCA variants and associated outcomes in women with breast cancer. JAMA Oncol. 2020; 6(9):1460-1463.
9. Hall MJ, Reid JE, Burbidge LA, et al. BRCA1 and BRCA2 mutations in women of different ethnicities undergoing testing for hereditary breast-ovarian cancer. Cancer. 2009; 115(10):2222-2233.
10. Hogervorst FB, Nederlof PM, Gille JJ, et al. Large genomic deletions and duplications in the BRCA1 gene identified by a novel quantitative method. Cancer Res. 2003; 63(7):1449-1453.
11. John EM, Miron A, Gong G, at al. Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic groups. JAMA. 2007; 298(24):2869-2876.
12. Judkins T, Leclair B, Bowles K, et al. Development and analytical validation of a 25-gene next generation sequencing panel that includes the BRCA1 and BRCA2 genes to assess hereditary cancer risk. BMC Cancer. 2015; 15:215.
13. Karami, F, Mehdipour, P. A Comprehensive Focus on Global Spectrum of BRCA1 and BRCA2 Mutations in Breast Cancer. Biomed Res Int. 2013; 2013:928562.
14. Lee YC, Lee YL, Li CY. BRCA genes and related cancers: a meta-analysis from epidemiological cohort studies. Medicina (Kaunas). 2021; 57(9):905.
15. Lucas AL, Frado LE, Hwang C, et al. BRCA1 and BRCA2 germline mutations are frequently demonstrated in both high-risk pancreatic cancer screening and pancreatic cancer cohorts. Cancer. 2014; 120(13):1960-1967.

16. Manchanda R, Loggenberg K, Sanderson S, et al. Population testing for cancer predisposing BRCA1/BRCA2 mutations in the Ashkenazi-Jewish community: a randomized controlled trial. J Natl Cancer Inst. 2014; 30; 107(1):379.
17. Minion LE, Dolinsky JS, Chase DM, et al. Hereditary predisposition to ovarian cancer, looking beyond BRCA1/BRCA2. Gynecol Oncol. 2015; 137(1):86-92.
18. 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. 2011; 107(1):28-39.
19. Murphy KM, Brune KA, Griffin C, et al. Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, and BRCA2 in familial pancreatic cancer: deleterious BRCA2 mutations in 17%. Cancer Res. 2002; 62(13):3789-3793.
20. Nanda R, Schumm LP, Cummings S, et al. Genetic testing in an ethnically diverse cohort of high-risk women: a comparative analysis of BRCA1 and BRCA2 mutations in American families of European and African ancestry. JAMA 2005; 294:1925-1933.
21. Pal T, Bonner D, Cragun D, et al. A high frequency of BRCA mutations in young black women with breast cancer residing in Florida. Cancer. 2015; 121(23):4173-4180.
22. Palma MD, Domchjeck 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. 2008; 68(17):7006-7014.
23. Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. 1998. Updated December 2016. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Updated December 15, 2016. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1247. Accessed on January 20, 2023.
24. Pohl-Rescigno E, Hauke J, Loibl S, et al. Association of germline variant status with therapy response in high-risk early-stage breast cancer: a secondary analysis of the GeparOcto randomized clinical trial. JAMA Oncol. 2020; 6(5):744-748.
25. Robson M; Im SA; Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med. 2017; 377(6):523-533.
26. Shannon KM, Rodgers LH, Chan-Smutko G, et al. Which individuals undergoing BRACAnalysis need BART testing? Cancer Genet. 2011; 204(8):416-422.
27. Smith LD, Tesoriero AA, Wong EM, et al. Contribution of large genomic BRCA1 alterations to early-onset breast cancer selected for family history and tumor morphology: a report from The Breast Cancer Family Registry. Breast Cancer Res. 2011; 13(1):R14.
28. Smith RA, Cokkinides V, Brawley OW. Cancer screening in the United States, 2009: a review of current American Cancer Society guidelines and issues in cancer screening. CA Cancer J Clin. 2009; 59(1):27-41.
29. 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. 2006; 295(12):1379-1388.
30. Walsh T, Casadei S, Lee MK, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci U S A. 2011; 108(44):18032-18037.

31. Walsh T, Lee MK, Casadei S, et al. Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing. Proc Natl Acad Sci U S A. 2010; 107(28):12629-12633.
32. Weinstein LB. Selected genetic disorders affecting Ashkenazi Jewish families. Fam Community Health. 2007; 30(1):50-62.
33. Weitzel JN, Lagos VI, Cullinane CA, et al. Limited family structure and BRCA gene mutation status in single cases of breast cancer. JAMA. 2007; 297(23):2587-2595.
34. Weitzel JN, Lagos VI, Herzog JS, et al. Evidence for common ancestral origin of a recurring BRCA1 genomic rearrangement identified in high-risk Hispanic families. Cancer Epidemiol Biomarkers Prev. 2007; 16(8):1615-1620.
35. Wooster R, Neuhausen SL, Mangion J, et al. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. Science. 1994; 265(5181):2088-2090.
36. Yadav S, Hu C, Hart SN, et al. Evaluation of germline genetic testing criteria in a hospital-based series of women with breast cancer. J Clin Oncol. 2020 Mar 3:JCO1902190. [Epub ahead of print]

Government Agency, Medical Society, and Other Authoritative Publications:

1. American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 182: Hereditary breast and ovarian cancer syndrome. Obstetrics & Gynecology 2017; 130(3):e110-e126.
2. American Society of Breast Surgeons. Consensus guideline on genetic testing for hereditary breast cancer. February 10, 2019. Available at: https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Genetic-Testing-for-Hereditary-Breast-Cancer.pdf. Accessed on January 20, 2023.
3. Lancaster JM1, Powell CB2, Chen LM, et al. Society of Gynecologic Oncology (SGO) Clinical Practice Committee. SGO statement on risk assessment for inherited gynecologic cancer predispositions. Gynecol Oncol. 2015; 136(1):3-7.
4. Lynparza®. [Product Information]. Wilmington, DE. AstraZeneca. Updated October 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208558s024lbl.pdf. Accessed on January 20, 2023.
5. National Cancer Institute (NCI). Genetics of Breast and Ovarian Cancer (PDQ) Updated November 4, 2022. Available at: http://www.cancer.gov/cancertopics/pdq/genetics/breast-and-ovarian/HealthProfessional/page1. Accessed on January 20, 2023.
6. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. © 2023 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website at: http://www.nccn.org/index.asp. Accessed on January 20, 2023.
   - Genetic/familial high-risk assessment: breast, ovarian, and pancreatic. (V2.2023). Revised January 10, 2023.
   - Pancreatic adenocarcinoma. (V2.2022). Revised December 6, 2022.
   - Prostate cancer. (V1.2023). Revised September 16, 2022.
7. National Society of Genetic Counselors. Genetic Counselors' Scope of Practice. Available at: https://www.nsgc.org/Policy-Research-and-Publications/State-Licensure-for-Genetic-Counselors/Model-Legislative-Provisions#scope. Accessed on January 20, 2023.

8. National Society of Genetic Counselors' Definition Task Force, Resta R, Biesecker BB, et al. A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. J Genet Couns. 2006; 5(2):77-83.
9. 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 Syntheses, No. 101. 2013. Available at: http://www.ncbi.nlm.nih.gov/books/NBK179201/. Accessed on January 20, 2023.
10. Randall LM, Pothuri B, Swisher EM, et al. Multi-disciplinary summit on genetics services for women with gynecologic cancers: A Society of Gynecologic Oncology White Paper. Gynecol Oncol. 2017; 146(2):217-224.
11. Rubraca®. [Product Information]. Boulder, CO. Clovis Oncology. Updated December 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf. Accessed on January 20, 2023.
12. Sohal D, Kennedy E, Khorana A, et al. Metastatic pancreatic cancer: ASCO clinical practice guideline update. J Clin Oncol. 2018; 36(24):2545-2556.
13. Talzenna®. [Product Information]. New York, NY. Pfizer. Updated September 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211651s008lbl.pdf. Accessed on January 20, 2023.
14. U.S. Food and Drug Administration (FDA). Office of In Vitro Diagnostics and Radiological Health. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). Available at: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm. Accessed on January 20, 2023.
15. U.S. Food and Drug Administration (FDA). FDA News Release. FDA authorizes, with special controls, direct-to-consumer test that reports three mutations in the BRCA breast cancer genes. Last updated: March 7, 2018. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm599560.htm. Accessed on January 20, 2023.
16. US Preventive Services Task Force, Owens DK, Davidson KW, et al. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2019; 322(7):652-665.
17. Zejula®. [Product Information]. Philadelphia, PA. Glaxo-Smith Kline. Updated December 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208447s025lbl.pdf. Accessed on January 20, 2023.

Websites for Additional Information

1. National Library of Medicine (NLM). Genetics Home Reference. Available at: http://ghr.nlm.nih.gov/. Accessed on January 20, 2023.

Index

BRCA2
BRCAvantage®
BRCAssure®
myChoice® CDx
FoundationOne CDx
FoundationFocus CDxBRCA Assay

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Reviewed	02/16/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Discussion/General Information, Definitions, and References sections.
	09/07/2022	Updated Discussion/General Information and References sections.
Reviewed	02/17/2022	MPTAC review. Updated Discussion/General Information and References sections.
Revised	02/11/2021	MPTAC review. Title changed to BRCA Genetic Testing. Updated Description, Discussion/General Information, Definitions and References sections. Reformatted Coding section.
	11/12/2020	Updated Coding section to add ICD-10-CM diagnosis code C61.
Reviewed	05/14/2020	MPTAC review. Updated Discussion/General Information, References, and Index sections. Updated Coding section with 07/01/2020 CPT changes; added 0172U.
	02/27/2020	Updated Discussion/General Information section.
New	11/07/2019	MPTAC review. Initial document development. Moved content related to gene panel testing from GENE.00029 Genetic Testing for Breast and/or Ovarian Cancer Syndrome to GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling. Moved remaining content of GENE.00029 Genetic Testing for Breast and/or Ovarian Cancer Syndrome to new clinical utilization management guideline document with a new title, BRCA Testing for Breast and/or Ovarian Cancer Syndrome. Revised Clinical Indications to include recommendations from the USPSTF. Added Note to Clinical Indications section to refer to the NCCN testing criteria and BRCA1 or BRCA2 mutation assessment tools listed in the Discussion/General Information section. Updated Coding section; removed 0138U (not applicable).