

Genetic Testing for Breast and/or Ovarian Cancer Susceptibility (BRCA1/BRCA2)

Policy MP-033

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Disclaimer:

1. Policies are subject to change in accordance with State and Federal notice requirements.
2. Policies outline coverage determinations for U of U Health Plans Commercial and Healthy U (Medicaid) plans. Refer to the "Policy" section for more information.
3. Services requiring prior-authorization may not be covered, if prior-authorization is not obtained.
4. **This Medical Policy does not guarantee coverage or payment of the service. The service must be a benefit in the member's plan and the member must be eligible for coverage at the time of service. Additional payment guidelines may be applied that are not included in this policy.**

Description:

According to the American Cancer Society, as of 2018, breast cancer is the second most common cause of cancer-related deaths among women, ovarian cancer is the fifth. The inherited tendency to develop breast and ovarian cancer has been termed HBOC (Hereditary Breast and Ovarian Cancer) syndrome. This syndrome describes the familial cancer syndromes that are related to mutations in the BRCA genes (BRCA1 located on chromosome 17q21 and BRCA2 located on chromosome 13q12-13). Normally, the BRCA1 and BRCA2 genes protect you from getting certain cancers by using tumor suppressor genes that encode proteins that play a role in the DNA repair process.

Germline mutations in the BRCA1 and BRCA2 genes are responsible for the cancer susceptibility in the majority of HBOC families, especially if ovarian cancer or male breast cancer are features. However, in site-specific breast cancer, BRCA mutations are responsible for only a proportion of affected families. If inherited, one of these mutations increases the susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer, melanoma, fallopian tube and primary peritoneal cancer as well as other cancers, such as prostate and pancreatic cancers.

BRCA gene mutations are inherited in an autosomal dominant fashion through either the maternal or paternal lineage. BRCA mutation testing can reveal abnormalities in BRCA1 and BRCA2 genes and the specific mutation in cancer cases. Family members with increased cancer

risk can be identified. Preventative measures may then be considered to reduce risk and mortality for family members without existing cancers but in whom the mutation is present. BRCA mutation testing is currently only recommended in individuals at high risk for BRCA mutations.

Policy Statement and Criteria

1. Commercial Plans

U of U Health Plans covers genetic testing for BRCA1 and BRCA2 mutations in adult individuals at high risk for heritable breast and ovarian cancer syndromes when specific clinical coverage criteria are met:

Clinical criteria for coverage (Must meet any A-I):

- A. Individual is from a family with a known BRCA1 or BRCA2 pathogenic/likely pathogenic variant, including such variants found on research testing (irrespective of degree of relatedness)
- B. Personal history of breast cancer (includes invasive and ductal carcinoma in situ breast cancers), plus one or more of the following (i-v):
 - i. Diagnosed with breast cancer \leq age 45 years
 - ii. Diagnosed with breast cancer between ages 46 to 50, with:
 - a) An additional breast cancer primary at any age (two breast cancer primaries include bilateral [contralateral] disease or two or more clearly separate ipsilateral primary tumors diagnosed either synchronously or asynchronously), or
 - b) \geq 1 close blood relative* with breast cancer primary at any age, or
 - c) \geq 1 close blood relative* with high-grade prostate cancer (Gleason score \geq 7), or
 - d) An unknown or limited family history^o.
 - iii. Diagnosed with breast cancer \leq age 60 years, with:
 - a) Triple-negative breast cancer
 - iv. Diagnosed at any age with (a or b):
 - a) \geq 1 close blood relative* with:
 - 1. Breast cancer diagnosed \leq age 50 years, or
 - 2. Ovarian carcinoma (includes fallopian tube and primary peritoneal cancers^A), or

3. Male breast cancer, or
 4. Metastatic prostate cancer (biopsy proven and/or with radiographic evidence, and includes distant metastasis and regional bed or nodes), or
 5. Pancreatic cancer.
- b) ≥ 2 additional diagnoses of breast cancer at any age in patient and/or in close blood relatives* (two breast cancer primaries include bilateral [contralateral] disease or two or more clearly separate ipsilateral primary tumors diagnosed either synchronously or asynchronously).
- v. Ashkenazi Jewish ancestry
- C. Personal history of ovarian carcinoma (includes fallopian tube and primary peritoneal cancers^Δ)
 - D. Personal history of male breast cancer
 - E. Personal history of pancreatic cancer[#]
 - F. Personal history of high-grade prostate cancer (Gleason score ≥ 7) at any age, with:
 - i. ≥ 1 close blood relative* with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer (biopsy proven and/or with radiographic evidence, and includes distant metastasis and regional bed or nodes), or
 - ii. ≥ 2 close blood relatives* with breast, or prostate cancer (any grade) at any age, or
 - iii. Ashkenazi Jewish ancestry[~].
 - G. BRCA1 or BRCA2 pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline pathogenic/likely pathogenic variant analysis
 - H. Regardless of family history, some individuals with a BRCA-related cancer may benefit from genetic testing to determine eligibility for targeted treatment
 - I. An individual who does not meet the above criteria, but with ≥ 1 first- or second degree blood* relative⁺ meeting criteria A thru H.

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

[◊] Refer to applicable NCCN Guidelines (listed in the last paragraph of the rationale).

^Δ BRCA-related ovarian cancers are associated with epithelial, non-mucinous histology. Lynch syndrome can be associated with both non-mucinous and mucinous epithelial tumors. Be attentive for clinical evidence of Lynch syndrome. Specific types of non-epithelial ovarian cancers and tumors can also be associated with other rare syndromes. Examples include an association between sex-chord tumors with annular tubules and Peutz-Jeghers syndrome or Sertoli-Leydig tumors and DICER1-related disorders.

[#] Approximately 2%–5% of unselected cases of pancreatic adenocarcinoma will have a BRCA1 or BRCA2 pathogenic/likely pathogenic variant. However, the disease is highly lethal and the option to test the affected relative may not be available in the future. Thus, there may be significant benefit to family members in testing these patients near the time

of diagnosis. In addition, increasing evidence suggests that identification of a BRCA1 or BRCA2 pathogenic/likely pathogenic variant may direct use of targeted therapies for patients with pancreatic cancer.

+ This may be extended to an affected third-degree relative if related through two male relatives (e.g., paternal grandfather's mother or sister).

~ Testing for Ashkenazi Jewish founder-specific pathogenic/likely pathogenic variant(s), should be performed first. Comprehensive genetic testing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if other BRCA-related criteria are met. Founder pathogenic/likely pathogenic variants exist in other populations.

Gleason Score: Table

GLEASON SCORES IN CATEGORICAL ORDER	
Gleason X	Gleason score cannot be determined
Gleason 6 or less	The tumor tissue is well differentiated, less aggressive and likely to grow more slowly
Gleason 7	The tumor tissue is moderately differentiated, moderately aggressive and likely to grow but may not spread quickly
Gleason 8-10	The tumor tissue is poorly differentiated or undifferentiated, highly aggressive and likely to grow faster and spread

U of U Health Plans does NOT cover BRCA1 and BRCA2 variant testing in minors as it is considered investigational.

U of U Health Plans COVERS BRCA testing in individuals with triple negative breast cancer being considered for PARP therapy as a medical benefit.

U of U Health Plans does not Cover Myriad Genetics *myRISK*[®], Ambry Genetics *BreastNEXT*[™], or similar hereditary breast/ovarian cancer specialty panels as they are considered investigational.

2. Medicaid Plans

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at: <https://medicaid.utah.gov/utah-medicaid-official-publications/> or the [Utah Medicaid code Look-Up tool](#)

CPT/HCPCS codes covered by Utah State Medicaid may still require further evaluation to determine medical necessity for coverage.

Clinical Rationale

According to the National Cancer Institute (NCI) BRCA mutations increase a woman's lifetime risk of developing breast and/or ovarian cancer. Approximately 12% of women in the general population will develop breast cancer and 1.3% will develop ovarian cancer during their lifetime. By way of comparison, an estimated 72% of women who inherit the BRCA1 mutation and 69% who inherit the BRCA2 mutation will develop breast cancer by the age of 80. Then by the first 20 years after the first diagnosis it is estimated that about 40% of those women with BRCA1 and 26% with BRCA2 will develop cancer in the other breast. As far as ovarian cancer, it is estimated that 44% of women that have the BRCA1 mutation and 17% that have the BRCA2 mutation will develop ovarian cancer by the age of 80. The NCI agrees with the USPSTF's recommendations for BRCA testing.

The U.S. Preventative Services Task Force (USPSTF) is currently of updating the 2013 topic of BRCA1 and BRCA2 genetic testing. As for now, their recommendations are to use one of the many screening tools used to identify family history in women who have had family members that have been diagnosed with breast, ovarian, tubal or peritoneal cancer and may be at an increased risk of having a mutation in breast cancer susceptibility genes (i.e. BRCA1 and BRCA2). If the screening comes back positive the woman should have genetic counseling and then determine if BRCA testing is warranted. If the woman does not have a family history of an associated increased risk, the USPSTF does not recommend genetic counseling or BRCA testing. These recommendations do not apply to men, although some male members may be identified during testing.

Looking at cost and health benefits, Kwon et al. used a simulation model in 2010 to evaluate six populations of women younger than 50 with breast cancer. Nearly 10% of women with breast cancer who are younger than age 50 have BRCA mutations. Most of the BRCA-positive women do not have personal or family histories of breast or ovarian cancer and are not of Ashkenazi Jewish ancestry. The results concluded that testing women with triple negative breast cancers who were younger than 50 years for BRCA mutations should be adopted into current guidelines for genetic testing.

In a 2011 cohort study of germline and somatic BRCA1 and BRCA2 mutations in 77 unselected Triple Negative Breast Cancer (TNBC) patients (Gonzalez-Angulo et al), 15 (19.5%) had BRCA mutations. Out of the 15 patients, 12 had BRCA1 (1 of them somatic) and 3 had BRCA2. Median age was 51 years (27-83 years). The authors recommend that genetic testing should be discussed with TNBC patients and it should be noted that TNBC patients with BRCA mutations have a significantly lower risk of relapse.

In a 2018 UpToDate® article on triple negative breast cancer (TNBC), BRCA testing is recommended in the metastatic stage, in that a better strategy for therapy may be determined depending on prior treatment history and the mutation status. If patients have advanced TNBC with germline BRCA mutations and have been previously treated with chemo in the adjuvant, neoadjuvant or metastatic disease setting, UpToDate experts suggest polyadenosine diphosphate-ribose polymerase (PARP)—an oral inhibitor—for treatment. If the patient has advanced TNBC, is chemo naïve and a BRCA carrier, initial treatment should consist of chemo and either a taxane or a platinum agent.

A 2012 clinical database review (Stadler et al) evaluated Breast Cancer (BC) probands in the Ashkenazi Jewish (AJ) population to determine if a BRCA mutation was harbored in those who had a family history of pancreatic cancer. Of the 211 AJ BC probands identified, 30 (14.2%) harbored a mutation, of those, 14 (47%) of the mutations were in BRCA1 and 16 (53%) were in BRCA2. Patients diagnosed with BC at age ≤ 50 years were found to have a higher BRCA1/2 mutation prevalence than probands with BC who were diagnosed at age > 50 years (21.1% vs 6.9%). In patients with first, second, or third degree relatives with pancreatic cancer, mutation prevalence was 15.4%, 15.3% and 8.6%, respectively. In conclusion, it

appears that BRCA1 and BRCA2 mutations are observed with nearly equal distribution in AJ breast-pancreas cancer families, suggesting that both genes are associated with pancreatic cancer risk. However, a family history of pancreatic cancer, at least in this population, was found to have limited effect on mutation prevalence.

Petrucelli et al published a study in 2016 regarding the HBOC syndrome and its association with BRCA1 and BRCA2 mutations. This study characterized the increased risk for female and male breast cancer, ovarian cancer and other cancers such as prostate, pancreatic and melanoma. The study determined the exact cancer risk depends on whether HBOC is caused by BRCA1 or 2. The diagnosis is established in a proband by the identification of a heterozygous germline pathogenic variant in BRCA1 or 2 on molecular genetic testing. Treatment could include bilateral mastectomy because of elevated rate of ipsilateral and contralateral breast cancer for surgical treatment. Ovarian and other cancers are treated similar to that of sporadic cancers. Prevention may include prophylactic bilateral mastectomy, prophylactic oophorectomy, and chemoprevention (e.g., tamoxifen) for breast cancer; however, these have not been assessed in high-risk women by randomized trials. Surveillance for women include a combination of monthly self-breast exams, annual or semiannual clinical breast exams, annual mammograms, and breast MRI's. Annual transvaginal ultrasounds and CA-125 concentration may be used beginning at age 35 for ovarian cancer, although in detecting early-stage ovarian cancer either in high or average risk women, this screening has not been effective. For men with breast cancer risk, screening should begin at age 35 with self-breast exams and annual clinical exams, prostate cancer risk screening should start at age 45.

A 2017 study (Kolor et al) summarized medical claims for BRCA testing among women aged 18-64 with employer-sponsored healthcare and the resulting interventions between 2009 and 2014. During the study period, BRCA testing increased by 2.3 times in metropolitan, and by 3 times in non-metropolitan areas. The percentage of women who were less likely to receive a MRI of the breast in non-metropolitan areas was 8.2% vs. 10.3% in metropolitan area and mammography in non-metro 11.5% vs. 13.8% in metro. Preventive services received within 90 days of testing also varied between these regions. Receiving genetic counseling before or after testing, increased over the study period from 5.3% to 8% in metropolitan areas and from 3.8% to 5.2% in non-metropolitan areas. After the implementation of the USPSTF guidelines and the availability of BRCA counseling and testing under the Affordable Care Act in September of 2010 the differences between the groups declined, the authors indicate that these implementations may have influenced the increase in testing and the reduction in variances between the two groups. Comparable to the estimated prevalence of BRCA mutations in the general U.S. population, the study's highest rate of BRCA testing was 332.5 women per 100,000 women aged 44-54. It should be noted that to minimize potential bias, this study did not include Ashkenazi Jewish women as they have a greater risk of carrying BRCA mutations and are highly populated in metropolitan areas.

Due to the lack of guidelines for genetic counseling and testing in the pediatric population, Druker et al. arranged an expert consensus of recommendations in 2017 for the testing and surveillance of pediatric cancers from the 2016 American Association for Cancer Research (AACR) Childhood Cancer Predisposition Workshop. When to refer patients to pediatric cancer genetics clinics, pretest counseling, informed consent and assent for cancer genetic testing of children, test selection and timing of testing, posttest counseling, and psychosocial aspects of cancer surveillance for children with hereditary cancer syndromes were all included in the consensus. The following recommendations were provided: The child and family should be referred to genetic counseling at the time the tumor is diagnosed or germline genetic testing is being considered; the clinician should consider clinical presentation and family history to determine whether to order a test for a familial variant or a broader panel; if a family pathogenic

variant is known, the test should only be for that variant (if possible use the same lab that identified the mutation in the initial family member); when the patient's presentation clearly fits a specific syndrome, only the gene(s) for that specific syndrome should be tested; if a patient presents with symptoms that may be explained by multiple syndromes, a multi-gene hereditary cancer panel may be considered; however, this also increases the chance of second findings which may cause additional challenges; and finally, for those with multi-system phenotypes, negative multigene panel results and wanting to participate in research, whole exome or genome sequencing should be considered. It should be noted however, that there are inconsistent findings with whole exome or genome sequencing. The authors concluded that, the clinician should confirm the test ordered includes the gene(s) of interest and has been well validated; and understands the lab's reinterpretation practices, costs, turnaround times, and policies regarding data sharing.

In a 2018 UpToDate article on "Genetic Testing", experts found that more than 35% of pediatric medical conditions are due to genetic issues. Most genetic testing is only included when the findings of the test will affect the current management of the child. The testing of children for adult-onset genetic conditions, that would have no current impact on a child's care or prognosis, raises additional issues such as the patient and family being burdened rather than empowered by the results. The American Society of Human Genetics (ASHG) released a position statement in 2015 regarding the testing of children. The UpToDate experts agree with the following ASHG recommendations:

1. Unless there is a clinical intervention appropriate in childhood, parents should be encouraged to defer predictive or pre-dispositional testing for adult-onset conditions until adulthood or at least until the child is an older adolescent who can participate in decision making in a relatively mature manner.
2. Based on clinical presentation, targeted gene panels or single gene testing should be tested initially, then if those tests are not definitive whole exome or whole genome sequencing may be used. The first approach reduces the possibility of secondary findings.
3. Unless there is clear medical benefit that outweighs potential harms, discovery of misattribution of parentage from genetic testing should not be disclosed.
4. Adolescents should have the opportunity to discuss concerns of genetic testing and related disorders. A separate conversation that discusses other aspects of informed consent in adolescent health care should be performed as well.

In 2015, Hayes reported on the BRCAAnalysis® Rearrangement Test™ (BART). BART was introduced to the market as a refinement of the BRCA genetic tests and was used to detect rare, large rearrangements of DNA in the BRCA1 and BRCA2 genes which were previously undetected by standard genetic testing. Myriad now includes BART testing as part of the Comprehensive BRCAAnalysis test. Hayes conducted a search strategy that backdated to 1996 and found only 3 studies that evaluated BART specifically. NCCN guidelines recommend testing for large genomic rearrangements in individuals meeting criteria for HBOC as part of BRCA1/2 comprehensive testing, however, they do not define a specific test or mention BART specifically. Hayes was unable to perform a Genetic Test Evaluation (GTE) health technology assessment based on the insufficient published evidence; and therefore, cannot recommend BART for use until further studies demonstrate its efficacy with analytical validity, clinical validity, and clinical utility.

The U.S. Food and Drug Administration (FDA) approved the first direct-to-consumer (DTC) test to market the Personal Genome Service® Genetic Health Risk (GHR) Report for BRCA1 and BRCA2 (Selected Variants) by 23andMe® on March 6, 2018. The test uses saliva to detect three specific BRCA gene

mutations out of thousands, which are mostly prevalent in people from the Ashkenazi Jewish descent, that are not the most common in the general population. The FDA states that health care professionals or consumers should not make any decisions for treatment using the results of this test. If concerns are raised from test results, individuals should see their physicians, have confirmatory testing, and seek genetic counseling.

With regard to pre- and post-test genetic counseling, the Society of Gynecology Oncology (SGO) and the American College of Obstetricians and Gynecologists (ACOG) published a joint statement in the ACOG Practice Bulletin #182 in September 2017. This document replaced the previous Practice Bulletin #103 published in April 2009. These new guidelines recommend the following: Genetic Counseling for all women who have ovarian epithelial cancer and for individuals who have a personal or family history of breast or ovarian cancer. ACOG and SGO have issued guidance on what risk factors should be included when collecting an individual's family history of cancer assessment. If counseling suggests the presence of an inherited cancer syndrome to which genetic testing will likely influence medical management that option should be offered to the individual. If the individual agrees, the next phase is to see if that individual meets criteria for genetic testing. To give a little background on BRCA genes, the phrase "two-hit hypothesis" describes how an individual may develop cancer. The BRCA genes are actually tumor suppressor genes, which they encode proteins that assist in DNA repair. Hereditary breast and ovarian cancer (HBOC) syndrome are inherited from either the mother or the father with one defective allele from either side; however, they have a second functional allele. If the second allele becomes non-functional because of somatic mutation, cancer may develop. BRCA1 and BRCA2 germline mutations are estimated to cause approximately 4.5% breast cancer cases and 9% to 24% of epithelial cancer cases. According to ACOG, approximately 39-46% of women harboring the BRCA1 mutation have a risk of developing ovarian, primary peritoneal, and/or fallopian tube cancer by the age of 70; 10% to 27% carrying the BRCA2 mutation have the risk of developing ovarian cancer. Ovarian cancer associated with BRCA1/BRCA2 mutations is usually high grade and has a distinct histologic phenotype that is predominantly endometrioid or serous. Mutations in the BRCA genes have also been associated with other types of cancer such as melanoma, prostate, pancreatic, and potentially uterine cancer.

The American Society of Clinical Oncology (ASCO) recommended in 2003 that genetic testing be offered when three factors are at play: (1) the individual has personal or family history features suggestive of a genetic cancer susceptibility condition, (2) the test can be adequately interpreted, and (3) the results will aid in diagnosis or influence the medical or surgical management of the patient or family member at hereditary risk of cancer. A 2010 update of this statement recommended "genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials."

National Comprehensive Cancer Network's (NCCN) 2022 Recommendations:

BRCA1 and BRCA2 Testing Criteria for Hereditary Breast and/or Ovarian Cancer Syndrome:

1. Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene
2. Individuals meeting the criteria below but tested negative with previous limited testing (e.g., single gene and/or absent deletion duplication analysis) interested in pursuing multi-gene testing
3. Personal history of cancer
 - a. Breast cancer with at least one of the following:
 - Diagnosed at age ≤ 45 y; or
 - Diagnosed at age 46–50 y with:

- Unknown or limited family history; or
 - A second breast cancer diagnosed at any age; or
 - ≥ 1 close blood relative with breast, ovarian, pancreatic, or prostate cancer at any age
 - Diagnosed at age ≤ 60 y with triple-negative breast cancer;
 - Diagnosed at any age with:
 - Diagnosed at any age with male breast cancer
 - b. Epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age
 - c. Exocrine pancreatic cancer at any age
 - d. Prostate cancer at any age with:
 - Metastatic, intraductal/cribriform histology, or high- or very-high-risk group
 - Any NCCN risk group (see NCCN Guidelines for Prostate Cancer) with the following family history:
 - Ashkenazi Jewish ancestry; or
 - ≥ 1 close relative with breast cancer at age ≤ 50 y or ovarian, pancreatic, metastatic, or intraductal/cribriform prostate cancer at any age; or
 - ≥ 2 close relatives with either breast or prostate cancer (any grade) at any age
 - e. A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline
 - f. Individual who meets Li-Fraumeni syndrome (LFS) testing criteria or Cowden syndrome/PTEN hamartoma tumor syndrome testing criteria
 - g. To aid in systemic therapy decision making, such as for HER2-negative metastatic breast cancer
4. Family history of cancer
- a. An affected or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except individuals who meet criteria only for systemic therapy decision-making).
 - If the affected relative has pancreatic cancer or prostate cancer (metastatic, intraductal/cribriform, or NCCN Guidelines for Prostate Cancer - High- or Very-High-Risk Group), only first-degree relatives should be offered testing unless indicated for other relatives based on additional family history.
 - b. An affected or unaffected individual who otherwise does not meet the criteria above but has a probability $>5\%$ of a BRCA1/2 pathogenic variant based on prior probability models

Applicable Coding

CPT Codes

Covered as preventive in appropriate population

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)
- 81215** BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
- 81217** BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant

Covered as medical benefit in appropriate population

- 81162** BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis
- 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, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
- 81216** BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis

HCPCS Codes

- G0452** Molecular pathology procedure; physician interpretation and report

References:

1. Achatz MI, Porter CC, Brugières L, et al. Cancer Screening Recommendations and Clinical Management of Inherited Gastrointestinal Cancer Syndromes in Childhood. Clin Cancer Res. 2017 Jul 1;23(13):e107-e114.
2. American Cancer Society® (2018) "Cancer Statistics for Breast Cancer". Available at: <https://cancerstatisticscenter.cancer.org/#!/cancer-site/Breast>
3. American Cancer Society® (2018) "Key Statistics for Ovarian Cancer". Available at: <https://www.cancer.org/cancer/ovarian-cancer/about/key-statistics.html>
4. American College of Obstetricians and Gynecologists (ACOG) and Society of Gynecologic Oncology Practice Bulletin No. 182: Hereditary breast and ovarian cancer syndrome. Obstetrics & Gynecology 2017; 130(3):e110-e126.
5. American Society of Clinical Oncology (ASCO). American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. J Clin Oncol. Jun 15 2003;21(12):2397-2406. PMID 12692171

6. Anders CK, Carey LA et al. Epidemiology, risk factors and the clinical approach to ER/PR negative, HER2-negative (Triple-negative) breast cancer. UpToDate®. Nov 9, 2018. Available at: www.uptodate.com
7. Buys SS, Sandbach JF, Gammon A, et al. A study of over 35,000 women with breast cancer tested with a 25-gene panel of hereditary cancer genes. *Cancer*. May 15 2017;123(10):1721-1730. PMID 28085182
8. Centers for Disease Control and Prevention (CDC). "The BRCA Genes and Hereditary Breast and Ovarian Cancer". Last updated July 29, 2016. Assessed December 7, 2018. Available at: https://www.cdc.gov/genomics/resources/diseases/breast_ovarian_cancer/genes_hboc.htm
9. Couch FJ, Shimelis H, Hu C, et al. Associations between cancer predisposition testing panel genes and breast cancer. *JAMA Oncol*. Sep 01 2017;3(9):1190-1196. PMID 28418444
10. Druker H, Zellek K, McGee RB, et al. Genetic counselor recommendations for cancer predisposition evaluation and surveillance in the pediatric oncology patient. *Clin Cancer Res* 2017;23
11. Ferrone CR, Levine DA, Tang LH, et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. *J Clin Oncol*. 2009 Jan 20;27(3):433-8.
12. Gonzalez-Angulo AM, Timms KM, Liu S, et al. Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative Breast Cancer. *Clin Cancer Res*. 2011 Mar 1;17(5):1082-9.
13. Hampel H, et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Guideline Development Group, American College of Medical Genetics and Genomics Professional Practice and Guidelines Committee and National Society of Genetic Counselors Practice Guidelines Committee. *Genet Med*. 2015 Jan;17(1):70-87.
14. Hayes, Winifred S, Inc. (2015) Hayes, Inc. "BRCAAnalysis Large Rearrangement Test (BART)" GTE Synopsis. Mar 19, 2015. Available at: <https://www.hayesinc.com>
15. Kolor K, Chen Z, Grosse SD, et al. BRCA Genetic Testing and Receipt of Preventive Interventions Among Women Aged 18–64 Years with Employer-Sponsored Health Insurance in Nonmetropolitan and Metropolitan Areas — United States, 2009–2014. *MMWR Surveillance Summaries*. 2017;66(15):1-11.
16. Kwon JS, Gutierrez-Barrera AM, Young D, et al. Expanding the criteria for BRCA mutation testing in Breast Cancer survivors. *J Clin Oncol*. 2010 Sep 20;28(27):4214-20.
17. LaDuca H, Stuenkel AJ, Dolinsky JS, et al. Utilization of multigene panels in hereditary cancer predisposition testing: analysis of more than 2,000 patients. *Genet Med*. 2014; 16(11):830-837.
18. Lancaster JM, Powell CB, Chen LM, et al. Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol*. Jan 2015;136(1):3-7. PMID 25238946
19. Langer LR, McCoy H, Kidd J, et al. A study of patients with ovarian cancer tested with a 25-gene hereditary cancer panel. *J Community Support Oncol*. 2016;14(7):314-319.
20. Lincoln SE, Kobayashi Y, Anderson MJ, et al. A systematic comparison of traditional and multigene panel testing for hereditary breast and ovarian cancer genes in more than 1000 patients. *J Mol Diagn*. 2015; 17(5):533-544.
21. National Cancer Institute (NCI) "BRCA Mutations: Cancer Risk and Genetic Testing" Last reviewed: January 30, 2018. Available at: www.cancer.gov
22. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Breast Cancer (V1.2018). Genetic/familial high-risk assessment: breast and ovarian. (V1.2018). 2018 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org/index.asp>.
23. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology®. NCCN Guidelines Version 2.2019. Genetic/familial high-risk assessment: breast and ovarian. (V2.2019). 2019 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf.
24. National Comprehensive Cancer Network, Inc. (NCCN) (2022). Clinical Practice Guidelines in Oncology®. Version 1.2022-August 11, 2021. Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic. Accessed: January 3, 2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf
25. O'Leary E, Iacoboni D, Holle J, et al. Expanded gene panel use for women with breast cancer: identification and intervention beyond breast cancer risk. *Ann Surg Oncol*. Oct 2017;24(10):3060-3066. PMID 28766213
26. Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. 1998 Sep 4 [Updated 2016 Dec 15]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1247/>. Accessed May 8, 2018.
27. Raby, B, MD, Kohlmann, W, MS, Venne, V, MS. "Genetic counseling: Family history interpretation and risk assessment" UpToDate®. Last update August 17, 2018. Topic 103304 Version 11.0.
28. Raskin L, Schwenter F, Freytsis M, et al. Characterization of two Ashkenazi Jewish Founder mutations in MSH6 gene causing Lynch syndrome. *Clin Genet*. 2011 Jun;79(6):512-22.
29. Robson ME, Storm CD, Weitzel J, et al. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. *J Clin Oncol*. Feb 10 2010;28(5):893- 901. PMID 20065170

30. Robson, ME, Bradbury, AR, Arun, B et al. American Society of Clinical Oncology policy statement update: Genetic and Genomic Testing for Cancer Susceptibility. *J Clin Oncol*. Nov 1 2015;33(31):3660-3667 PMID 26324357
31. Shannon KM, Rodgers LH, Chan-Smutko G, et al. Which individuals undergoing BRAC Analysis need BART testing? *Cancer Genet*. 2011; 204(8):416-422.
32. Stadler ZK, Salo-Mullen E, et al. Prevalence of BRCA 1 and BRCA2 Mutations in Ashkenazi Jewish Families with Breast and Pancreatic Cancer. *Cancer*. 2012 Jan 15; 118(2):493-9. doi:10.1002/cncr.26191. Epub 2011 May 19.
33. Susswein LR, Marshall ML, Nusbaum R, et al. Pathogenic and likely pathogenic variant prevalence among the first 10,000 patients referred for next-generation cancer panel testing. *Genet Med*. 2016; 18(8):823-832.
34. Tung N, Battelli C, Allen B, et al. Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel. *Cancer*. Jan 1 2015;121(1):25-33. PMID 25186627
35. U.S. Food and Drug Administration (FDA). FDA authorizes, with special controls, direct-to-consumer test that reports three mutations in the BRCA breast cancer genes. Silver Spring, MD: FDA; March 6, 2018. Available at: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm599560.htm>.
36. U.S. Preventative Services Task Force (USPSTF). (2013). Final Recommendation Statement "BRCA-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing" Available at: <https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing#Pod1>

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