MEDICAL POLICY

POLICY TITLE	**MOLECULAR TESTING FOR GERMLINE VARIANTS ASSOCIATED WITH OVARIAN CANCER (BRIP1, RAD51C, RAD51D, NBN)**
POLICY NUMBER	**MP 2.377**

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**7/1/2024**

I. POLICY

Testing for germline *BRIP1*, *RAD51C*, and *RAD51D* variants for ovarian cancer risk assessment in adults may be considered **medically necessary** when the following criteria are met:

- The individual has a diagnosis of epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer; AND
    - The individual has not previously been tested for these gene variants; AND
    - The individual is thought to be the most informative member of a family (proband) to have genetic testing (see Policy Guidelines); AND
    - The individual has closely related (1st- or 2nd-degree*) relatives who are considering genetic testing for these gene variants to inform prophylactic decision-making or who have test results that cannot be fully interpreted without testing an affected relative; OR
- The individual has not been diagnosed with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer; AND
    - The individual has any blood relative with a known pathogenic/likely pathogenic *BRIP1*, *RAD51C*, or *RAD51D* variant; OR
    - The individual has a 1st- or 2nd-degree relative* diagnosed with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.

Testing for germline *NBN* variants for ovarian cancer risk assessment in adults is considered **investigational** as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Testing for germline *BRIP1, RAD51C, RAD51D, and NBN* variants in individuals diagnosed with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer to guide treatment of the diagnosed individual is considered **investigational** as there is insufficient evidence to

support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Testing for germline *BRIP1*, *RAD51C*, and *RAD51D* variants in adults who do not meet the criteria above is considered **investigational** as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat, and manage patients with cancer. Guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital Blue Cross when determining medical necessity according to this policy.

POLICY GUIDELINES

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

- 1st-degree relatives: parents, siblings, and children
- 2nd-degree relatives: grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings

Note: If the individual has a diagnosis of epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, the provider's request for testing must indicate that the individual is the proband.

Recommended Genetic Testing Strategies

Individuals who meet criteria for germline (not somatic) genetic testing as outlined in the policy statements should be tested for variants in *BRIP1*, *RAD51C*, and *RAD51D*. Recommended strategies are listed below.

- In individuals with a known familial germline *BRIP1, RAD51C, or RAD51D* variant, targeted testing for the specific variant is recommended.
- In individuals with an unknown familial germline *BRIP1, RAD51C, or RAD51D* variant:
    - To identify clinically significant variants, the National Comprehensive Cancer Network (NCCN) advises testing a relative who has early-onset disease, bilateral disease, or multiple primaries, because that individual has the highest likelihood of obtaining an informative, positive test result. This individual, the first-affected individual in a family who brings a genetic disorder to the attention of the medical community, is commonly referred to as the proband.
    - Testing undiagnosed, at-risk family members when a diagnosed relative is unavailable for testing, is unwilling to undergo testing, or is unwilling to share genetic testing results, should still be considered. However, indeterminate genetic testing results may be poorly understood by family members. Therefore, significant limitations of interpreting test results, including uninformative negative

results or non-actionable variants of unknown significance (VUS), should be discussed.

This policy applies to testing for ovarian cancer risk assessment and does not address testing for autosomal recessive conditions associated with *BRIP1, RAD51C, or NBN*.

Germline genetic testing for *BRCA1, BRCA2, and PALB2* is addressed separately in MP 2.211.

Germline testing for Fanconi Anemia is addressed separately in MP 2.362.

Mismatch repair genes associated with Lynch syndrome are addressed in MP 5.013.

Testing Undiagnosed, At-Risk Individuals

In unaffected (i.e., undiagnosed), at-risk family members of potential *BRIP1, RAD51C, or RAD51D* variant families, most test results will be negative and uninformative. Therefore, it is strongly recommended that an *affected* (i.e., diagnosed) family member be tested first whenever possible to adequately interpret the test. Should a causative variant be found in an affected family member(s), DNA from an *unaffected* family member can be tested specifically for the same variant of the affected family member without having to sequence the entire gene. Interpreting test results for an *unaffected* family member without knowing the genetic status of the family may be possible in the case of a positive result for an established disease-associated variant but leads to difficulties in interpreting uninformative negative test results or VUS because the possibility of a causative variant is not ruled out. Non-actionable VUS are highly prevalent with multi-gene testing, which may be avoided with targeted testing for a known familial variant.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology - "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" - to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition

Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Likely pathogenic	**Definition**
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Change in DNA sequence with uncertain effects on disease
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Cross-reference:

MP 2.211 Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and other High-Risk Cancers (BRCA1, BRCA2, PALB2)
MP 2.279 Germline Genetic Testing for Gene Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk (CHEK2, ATM, and BARD1)
MP 2.325 Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
MP 2.362 Genetic Testing for Fanconi Anemia

II. PRODUCT VARIATIONS

TOP

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO: Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

TOP

Ovarian Cancer and Genetics

In 2022, it is estimated that there will be 19,880 new diagnosed cases of ovarian cancer (OC) and that an estimated 12,810 women will die from their disease. Over 95% of OC are derived from epithelial cells. High-grade serous epithelial ovarian carcinoma, fallopian tube carcinoma, and primary peritoneal carcinomas are thus considered a single clinical entity (i.e., epithelial OC [EOC]) due to their shared pathologic behavior and treatment. Based upon data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program, approximately 1.2% of women in the United States will be diagnosed with OC in their lifetime.

Due to the limited benefit of presymptomatic screening for OC, identifying women at high risk of the disease who may benefit from prophylactic risk-reducing surgery is critically important. Approximately 70% of women are diagnosed with late-stage disease, resulting in a 5-year relative survival rate of 29% compared to 92% for early-stage disease. It is estimated that greater than 20% of women diagnosed with OC have a hereditary predisposition to the disease, harboring loss-of-function (LoF) mutations in cancer-related genes. Most of the identified germline mutations in OC occur in the highly penetrant *BRCA1* and *BRCA2* genes which regulate DNA repair. It is estimated that high penetrance variants in *BRCA1* and *BRCA2* genes account for ~27% of familial OC cases. Mutations in these genes results in homologous recombination deficiency (HRD), which has been targeted with platinum-based chemotherapy and poly (ADP-ribose) polymerase (PARP) inhibitors. Other mechanisms of HRD lead to a phenotype known as BRCAness and include germline and somatic mutations in genes related to homologous recombination, epigenetic modifications, and *EMSY* amplification or overexpression. Homologous recombination-related genes with a documented association with OC risk include *BRIP1, RAD51C,* and *RAD51D,* and may represent the most important OC predisposition genes after *BRCA1/2.* Hereditary OC risk may also be influenced by mismatch repair genes and variants in *PALB2*. *BRIP1*, *RAD51C*, and *RAD51D,* and the mismatch repair genes are estimated to contribute to 10% of hereditary OC cases. Approximately 60% of the

familial relative risk in OC is unexplained. Risk estimates may be higher in patients with a family history of OC or a family history of a specific gene variant.

Penetrance of Pathogenic Variants

Penetrance is the risk conferred by a pathogenic variant or the proportion of individuals with the variant expected to develop cancer. For example, a woman's lifetime risk for developing OC is roughly 36% to 63% for *BRCA1* carriers and 10% to 27% for *BRCA2* carriers. Penetrance can be modified by environmental factors and by family history, which is an important modifier for low and moderate penetrance genes. Moreover, specific pathogenic variants within a gene may confer somewhat different risks.

There is no consensus on how to calculate lifetime risk. Cumulative lifetime risk (CLTR) may be calculated as a multiple of the US SEER Program estimates of 'ever' developing cancer combined with the average relative risk for the gene variant in question. Other experts may calculate risk of cancer development by a defined age, which is often described as lifetime penetrance. Others describe remaining lifetime risk (LTR) as the CLTR remaining after an individual reaches a particular age. The lack of a consensus for defining LTR may confound guidelines based on this measurement. It is also important to note that the risk threshold separating moderate-penetrance from high-penetrance genes is defined arbitrarily. Average relative risks may not account for individual risk modifications due to genetic and non-genetic factors.

Determining Variant Pathogenicity

Determining the pathogenicity of variants in a more commonly detected cancer susceptibility gene (e.g., founder sequence mutations) is generally straightforward because associations are repeatedly observed. For uncommonly identified variants, such as those found in a few individuals or families, defining pathogenicity can be more difficult. For example, predicting the pathogenicity of previously unidentified variants typically requires in silico (computational) analysis predicting protein structure/function, evolutionary conservation, and splice site prediction. The approach to defining pathogenicity is clearly outlined in standards and reporting guidelines. Still, distinctions between a VUS and a pathogenic one from different laboratories may not always be identical.[9,]

Genes Associated With a Moderate-to-High Penetrance of Ovarian Cancer

***BRIP1* Gene**

The *BRIP1* (*BRCA1* interaction protein C-terminal helicase 1) gene, also known as *FANCJ*, is located at 17q23.2 and encodes a protein which binds to BRCT repeats in BRCA1 via a nuclear localization signal in its helicase domain to facilitate DNA repair. Biallelic germline mutations result in Fanconi anemia, which is also seen in *BRCA2* germline mutations. *BRIP1*-inactivating truncating and frameshift mutations have been associated with an increased risk of OC. Ovarian tumors from heterozygous carriers of the c.1702_1703del mutation showed loss of the wildtype allele, suggesting behavior typical of a classical tumor suppressor gene.

The RAD51 paralogs, *RAD51C* and *RAD51D*, are involved in the FA-*BRCA1/2* homologous recombination pathway. Biallelic missense mutations in the *RAD51C* gene are associated with a Fanconi anemia-like phenotype. These mutations are rare and are associated with an increased risk of OC as well as a potential increased risk of triple-negative breast cancer.

NBN Gene

The NBN gene encodes the nibrin protein, which is mapped within a critical region for Nijmegen breakage syndrome (NBS) on chromosome 8q21. The encoded protein, also known as p95, is a member of the MRE11/RAD50 double-strand break repair complex and is implicated in cell cycle checkpoint functions and cellular responses to ionizing radiation.

Identifying Women at Risk of an Inherited Susceptibility to Ovarian Cancer

Risk factors for OC include older age, early menarche or late menopause, family history of disease, genetic factors, nulliparity, endometriosis, and exposure to asbestos. Risk assessed through family history is dependent on the number and closeness of affected relatives, the age at which cancer developed, and if other cancers occurred (e.g., breast). For a woman without OC, the probability of detecting a pathogenic variant can be estimated from a detailed multigenerational pedigree (e.g., Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm), screening tools (e.g., BRCAPRO), or by referring to guidelines that define specific family history criteria (see Supplemental Information Section on Practice Guidelines and Position Statements). For women with OC, family history also affects the likelihood of carrying a pathogenic variant.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. *BRIP1, RAD51C, RAD51D,* and *NBN* testing are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories offering to test and voluntarily list are available through the National Center for Biotechnology Genetic Testing Registry. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

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

Myriad Genetic Laboratories offers the myRisk® Hereditary Cancer multi-gene panel test which includes 35 genes. Testing for OC risk includes analysis of *BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, EPCAM, TP53, STK11, PALB2*, *BRIP1*, *RAD51C*, and *RAD51D* genes.

Ambry Genetics offers the BRCANext-Expanded® panel which includes 23 genes associated with risk of gynecologic cancer, including *BRIP1*, *RAD51C*, and *RAD51D.* Testing for *NBN* is also included in this panel.

IV. RATIONALE

TOP

SUMMARY OF EVIDENCE

For individuals without diagnosed epithelial ovarian cancer (EOC) and in a family at risk of developing EOC who receive germline genetic testing for genes associated with hereditary OC (i.e., *BRIP1*, *RAD51C*, and *RAD51D*), the evidence includes studies of clinical validity and studies of OC risk, including meta-analyses. Relevant outcomes are overall survival (OS), disease-specific survival, and test validity. Evidence supporting clinical validity was obtained from numerous studies reporting relative risk (RR) or odds ratio (OR) and 4 studies provided penetrance estimates. Study designs included family-based case-control and population- or multicenter-based case-control. The number of P/LP variants identified in association studies ranged from 10 to 36, 11 to 44, and 8 to 13 for *BRIP1*, *RAD51C*, and *RAD51D*, respectively. The RR for OC associated with *BRIP1* ranged from 3 to 19, with population-based studied reporting the 2 highest and lowest values. The RR for OC associated with *RAD51C* ranged from 3 to 6, with a family-based study reporting the highest value. The RR for OC associated with *RAD51D* ranged from 5 to 12, with family- and population-based studies reporting the highest values. Evidence of preventative interventions in women with *BRIP1*, *RAD51C*, and *RAD51D* variants is indirect, relying on studies of high-risk women and *BRCA* carriers. These interventions include chemoprevention with oral contraceptives and risk-reducing oophorectomy and RRSO. Given the penetrance of *BRIP1*, *RAD51C*, and *RAD51D* variants, the outcomes following risk-reducing oophorectomy and RRSO examined in women with a family history consistent with hereditary OC (including *BRCA1* and *BRCA2* carriers) can be applied to women with *BRIP1*, *RAD51C*, and *RAD51D* variants, with the benefit-to-risk balance affected by penetrance. In women at high-risk of hereditary OC who would consider risk-reducing interventions, identifying a *BRIP1*, *RAD51C*, or *RAD51D* variant provides a more precise estimated risk of developing OC compared to family history alone and can offer women a more accurate understanding of benefits and potential harms of any intervention. Additionally, RRSO may provide an opportunity for occult gynecologic cancer detection in high-risk *BRCA*-negative women. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals without diagnosed EOC and in a family at risk of developing EOC who receive germline genetic testing for *NBN* gene variants, the evidence includes studies of clinical validity and studies of OC risk, including a meta-analysis. Relevant outcomes are OS, disease-specific survival, and test validity. *NBN* variants have been associated with a 2- to 3.5-fold increased risk of OC across studies. However, a significantly increased frequency of *NBN* mutations has not been consistently observed in cases versus controls and penetrance estimates have not been reported. Accordingly, national guidelines have not recommended risk-reducing interventions for *NBN* carriers at this time due to insufficient data to define risk and recommend managing these individuals based on family history alone. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals without diagnosed EOC and in a family at risk of developing EOC who are considering prophylactic surgery who receive germline genetic testing of first- and/or second-

degree relative(s) with a personal history of EOC for genes associated with hereditary OC (i.e., *BRIP1*, *RAD51C*, and *RAD51D*) to guide prophylactic decision-making or interpretation of test results in the undiagnosed, at-risk family member, the evidence on the use of preventative interventions is indirect, relying on studies of at-risk women and *BRCA* carriers. Relevant outcomes are OS, disease-specific survival, and test validity. Evidence of preventative interventions in women with *BRIP1*, *RAD51C*, and *RAD51D* variants is indirect, relying on studies of high-risk women and *BRCA* carriers. Preventative interventions include chemoprevention with oral contraceptives and risk-reducing oophorectomy and RRSO. Given the penetrance of *BRIP1*, *RAD51C*, and *RAD51D* variants, the outcomes following risk-reducing oophorectomy and RRSO examined in women with a family history consistent with hereditary OC (including *BRCA1* and *BRCA2* carriers) can be applied to women with *BRIP1*, *RAD51C*, and *RAD51D* variants, with the benefit-to-risk balance affected by penetrance. In women at risk of hereditary OC who are considering prophylactic surgery, genetic testing of first- and/or second-degree relative(s) with a personal history of EOC to identify a familial *BRIP1*, *RAD51C*, or *RAD51D* germline variant provides a more precise estimated risk of developing OC compared to family history alone and reduces the incidence of uninformative negative test results or non-actionable variants of unknown significance. Identification of and targeted testing for a known familial variant can offer women a more accurate understanding of benefits and potential harms of prophylactic surgery and is a testing strategy supported by national guidelines. Testing a relative with early-onset disease, bilateral disease, or multiple primaries is recommended, as that individual has the highest likelihood of obtaining an informative, positive test result. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals without diagnosed EOC and in a family at risk of developing EOC who are considering prophylactic surgery who receive germline genetic testing of first- and/or second-degree relative(s) with a personal history of EOC for *NBN* gene variants to guide prophylactic decision-making or interpretation of test results in the undiagnosed, at-risk family member, direct evidence is lacking. Relevant outcomes are OS, disease-specific survival, and test validity. National guidelines have not recommended prophylactic surgery due to insufficient data to establish absolute risk estimates. Given that the clinical validity of *NBN* germline variant testing has not been established, a chain of evidence cannot be constructed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with diagnosed OC who receive germline genetic testing for genes associated with hereditary OC (i.e., *BRIP1*, *RAD51C*, *RAD51D*, and *NBN*) to guide treatment decisions in the individual with diagnosed EOC, the evidence includes studies of variant prevalence and studies of OC risk. Relevant outcomes are OS, disease-specific survival, and test validity. Direct evidence for the clinical utility of genetic testing for *BRIP1*, *RAD51C*, *RAD51D*, and *NBN* variants in individuals with OC was not identified. Due to the standard surgical management of OC patients, the clinical utility of *BRIP1*, *RAD51C*, *RAD51D*, and *NBN* variant testing to inform therapy was reviewed. In studies evaluating HRD assays in *BRCA* wild-type patients, an overlapping therapeutic benefit was found between deficient/high loss-of-

heterozygosity and proficient/low loss-of-heterozygosity tumors and results were not stratified by non-*BRCA* HRD genes. The use of *BRIP1*, *RAD51C*, *RAD51D*, and *NBN* variant status to guide maintenance and recurrence therapy continues to be elucidated in the clinical trial setting. In contrast to undiagnosed women at high familial risk of OC, women diagnosed with OC who undergo testing for *BRIP1*, *RAD51C*, *RAD51D*, and *NBN* variants do not yield clinically actionable results. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

V. DEFINITIONS

TOP

N/A

VI. BENEFIT VARIATIONS

TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

TOP

Capital Blue Cross' medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

TOP

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational when used for testing *BRIP1*, *RAD51C*, and *RAD51D* variants:

Procedure Codes							
0102U	0103U	0131U	0132U	0134U	0135U	0475U	81432
81433							

Covered when medically necessary when used for testing *BRIP1*, *RAD51C*, and *RAD51D* variants:

Procedure Codes							
81479							

ICD-10-CM Diagnosis Code	Description
C48.0	Malignant neoplasm of retroperitoneum
C48.1	Malignant neoplasm of specified parts of peritoneum
C48.2	Malignant neoplasm of peritoneum, unspecified
C48.8	Malignant neoplasm of overlapping sites of retroperitoneum
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C56.3	Malignant neoplasm of bilateral ovaries
C56.9	Malignant neoplasm of unspecified ovary
C57.00	Malignant neoplasm of unspecified fallopian tube
C57.01	Malignant neoplasm of right fallopian tube
C57.02	Malignant neoplasm of left fallopian tube
C57.8	Malignant neoplasm of overlapping sites of female genital organs
Z80.41	Family history of malignant neoplasm of ovary
Z80.49	Family history of malignant neoplasm of other genital organs
Z80.8	Family history of malignant neoplasm of other organs or systems

IX. REFERENCES

TOP

1. *American Cancer Society. Key Statistics for Ovarian Cancer. 2022*
2. *National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Stat Facts: Ovarian Cancer. 2022*
3. *Suszynska M, Klonowska K, Jasinska AJ, et al. Large-scale meta-analysis of mutations identified in panels of breast/ovarian cancer-related genes - Providing evidence of cancer predisposition genes. Gynecol Oncol. May 2019; 153(2): 452-462. PMID 30733081*
4. *Suszynska M, Ratajska M, Kozlowski P. BRIP1, RAD51C, and RAD51D mutations are associated with high susceptibility to ovarian cancer: mutation prevalence and precise*

risk estimates based on a pooled analysis of ~30,000 cases. J Ovarian Res. May 02 2020; 13(1): 50. PMID 32359370

5. *Jervis S, Song H, Lee A, et al. A risk prediction algorithm for ovarian cancer incorporating BRCA1, BRCA2, common alleles and other familial effects. J Med Genet. Jul 2015; 52(7): 465-75. PMID 26025000*
6. *Domchek SM, Rebbeck TR. Preventive surgery is associated with reduced cancer risk and mortality in women with BRCA1 and BRCA2 mutations. LDI Issue Brief. Oct-Nov 2010; 16(2): 1-4. PMID 21545057*
7. *Tung N, Domchek SM, Stadler Z, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. Nat Rev Clin Oncol. Sep 2016; 13(9): 581-8. PMID 27296296*
8. *Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. May 2015; 17(5): 405-24. PMID 25741868*
9. *Kurian AW, Antoniou AC, Domchek SM. Refining Breast Cancer Risk Stratification: Additional Genes, Additional Information. Am Soc Clin Oncol Educ Book. 2016; 35: 44-56. PMID 27249685*
10. *Online Mendelian Inheritance in Man (OMIM). Johns Hopkins University, Baltimore, MD. MIM Number: 605882. April 19, 2019*
11. *Online Mendelian Inheritance in Man (OMIM). Johns Hopkins University, Baltimore, MD. MIM Number: 167000. December 20, 2019*
12. *Online Mendelian Inheritance in Man (OMIM). Johns Hopkins University, Baltimore, MD. MIM Number: 602774. August 21, 2019; https://www.omim.org/entry/602774. Accessed July 23, 2022.*
13. *Online Mendelian Inheritance in Man (OMIM). Johns Hopkins University, Baltimore, MD. MIM Number: 602954. August 21, 2019; https://www.omim.org/entry/602954. Accessed July 24, 2022.*
14. *Apostolou P, Fostira F. Hereditary breast cancer: the era of new susceptibility genes. Biomed Res Int. 2013; 2013: 747318. PMID 23586058*
15. *National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (v.2.2022). March 9, 2022*
16. *Online Mendelian Inheritance in Man (OMIM). Johns Hopkins University, Baltimore, MD. MIM Number: 602667. October 11, 2016*
17. *Antoniou AC, Pharoah PP, Smith P, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancer. Br J Cancer. Oct 18 2004; 91(8): 1580-90. PMID 15381934*
18. *Ramus SJ, Song H, Dicks E, et al. Germline Mutations in the BRIP1, BARD1, PALB2, and NBN Genes in Women With Ovarian Cancer. J Natl Cancer Inst. Nov 2015; 107(11). PMID 26315354*

19. *Song H, Dicks E, Ramus SJ, et al. Contribution of Germline Mutations in the RAD51B, RAD51C, and RAD51D Genes to Ovarian Cancer in the Population. J Clin Oncol. Sep 10 2015; 33(26): 2901-7. PMID 26261251*
20. *Loveday C, Turnbull C, Ruark E, et al. Germline RAD51C mutations confer susceptibility to ovarian cancer. Nat Genet. Apr 26 2012; 44(5): 475-6; author reply 476. PMID 22538716*
21. *Loveday C, Turnbull C, Ramsay E, et al. Germline mutations in RAD51D confer susceptibility to ovarian cancer. Nat Genet. Aug 07 2011; 43(9): 879-882. PMID 21822267*
22. *Lhotova K, Stolarova L, Zemankova P, et al. Multigene Panel Germline Testing of 1333 Czech Patients with Ovarian Cancer. Cancers (Basel). Apr 13 2020; 12(4). PMID 32295079*
23. *Weber-Lassalle N, Hauke J, Ramser J, et al. BRIP1 loss-of-function mutations confer high risk for familial ovarian cancer, but not familial breast cancer. Breast Cancer Res. Jan 24 2018; 20(1): 7. PMID 29368626*
24. *Norquist BM, Harrell MI, Brady MF, et al. Inherited Mutations in Women With Ovarian Carcinoma. JAMA Oncol. Apr 2016; 2(4): 482-90. PMID 26720728*
25. *Lilyquist J, LaDuca H, Polley E, et al. Frequency of mutations in a large series of clinically ascertained ovarian cancer cases tested on multi-gene panels compared to reference controls. Gynecol Oncol. Nov 2017; 147(2): 375-380. PMID 28888541*
26. *Kurian AW, Hughes E, Handorf EA, et al. Breast and Ovarian Cancer Penetrance Estimates Derived From Germline Multiple-Gene Sequencing Results in Women. JCO Precision Oncology 2017;1: 1-12.*
27. *Yang X, Song H, Leslie G, et al. Ovarian and Breast Cancer Risks Associated With Pathogenic Variants in RAD51C and RAD51D. J Natl Cancer Inst. Dec 14 2020; 112(12): 1242-1250. PMID 32107557*
28. *Flaum N, van Veen EM, Smith O, et al. Dominant-negative pathogenic variant BRIP1 c.1045G C is a high-risk allele for non-mucinous epithelial ovarian cancer: A case-control study. Clin Genet. Jan 2022; 101(1): 48-54. PMID 34585738*
29. *Rafnar T, Gudbjartsson DF, Sulem P, et al. Mutations in BRIP1 confer high risk of ovarian cancer. Nat Genet. Oct 02 2011; 43(11): 1104-7. PMID 21964575*
30. *Kushnir A, Laitman Y, Shimon SP, et al. Germline mutations in RAD51C in Jewish high cancer risk families. Breast Cancer Res Treat. Dec 2012; 136(3): 869-74. PMID 23117857*
31. *Catucci I, Milgrom R, Kushnir A, et al. Germline mutations in BRIP1 and PALB2 in Jewish high cancer risk families. Fam Cancer. Sep 2012; 11(3): 483-91. PMID 22692731*
32. *Balmana J, Digiovanni L, Gaddam P, et al. Conflicting Interpretation of Genetic Variants and Cancer Risk by Commercial Laboratories as Assessed by the Prospective Registry of Multiplex Testing. J Clin Oncol. Dec 2016; 34(34): 4071-4078. PMID 27621404*
33. *Nelson HD, Pappas M, Cantor A, et al. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. Aug 20 2019; 322(7): 666-685. PMID 31429902*

34. *Schrag D, Kuntz KM, Garber JE, et al. Decision analysis--effects of prophylactic mastectomy and oophorectomy on life expectancy among women with BRCA1 or BRCA2 mutations. N Engl J Med. May 15 1997; 336(20): 1465-71. PMID 9148160*
35. *University of Cambridge. CanRisk Tool v1.0.4 (BOADICEA V). January 14, 2020*
36. *Lee A, Mavaddat N, Wilcox AN, et al. BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors. Genet Med. Aug 2019; 21(8): 1708-1718. PMID 30643217*
37. *Himes DO, Gibbons DK, Birmingham WC, et al. Female family members lack understanding of indeterminate negative BRCA1/2 test results shared by probands. J Genet Couns. Oct 2019; 28(5): 950-961. PMID 31199558*
38. *Sherman ME, Piedmonte M, Mai PL, et al. Pathologic findings at risk-reducing salpingo-oophorectomy: primary results from Gynecologic Oncology Group Trial GOG-0199. J Clin Oncol. Oct 10 2014; 32(29): 3275-83. PMID 25199754*
39. *Gornjec A, Merlo S, Novakovic S, et al. The prevalence of occult ovarian cancer in the series of 155 consequently operated high risk asymptomatic patients - Slovenian population based study. Radiol Oncol. May 28 2020; 54(2): 180-186. PMID 32463390*
40. *National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Ovarian Cancer (v.3.2022). July 25, 2022*
41. *Konstantinopoulos PA, Norquist B, Lacchetti C, et al. Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. J Clin Oncol. Apr 10 2020; 38(11): 1222-1245. PMID 31986064*
42. *Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. Dec 19 2019; 381(25): 2391-2402. PMID 31562799*
43. *Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. Oct 28 2017; 390(10106): 1949-1961. PMID 28916367*
44. *Swisher EM, Kristeleit RS, Oza AM, et al. Characterization of patients with long-term responses to rucaparib treatment in recurrent ovarian cancer. Gynecol Oncol. Dec 2021; 163(3): 490-497. PMID 34602290*
45. *Swisher EM, Kwan TT, Oza AM, et al. Molecular and clinical determinants of response and resistance to rucaparib for recurrent ovarian cancer treatment in ARIEL2 (Parts 1 and 2). Nat Commun. May 03 2021; 12(1): 2487. PMID 33941784*
46. *Kondrashova O, Nguyen M, Shield-Artin K, et al. Secondary Somatic Mutations Restoring RAD51C and RAD51D Associated with Acquired Resistance to the PARP Inhibitor Rucaparib in High-Grade Ovarian Carcinoma. Cancer Discov. Sep 2017; 7(9): 984-998. PMID 28588062*
47. *Norquist BM, Brady MF, Harrell MI, et al. Mutations in Homologous Recombination Genes and Outcomes in Ovarian Carcinoma Patients in GOG 218: An NRG Oncology/Gynecologic Oncology Group Study. Clin Cancer Res. Feb 15 2018; 24(4): 777-783. PMID 29191972*

48. Society of Gynecologic Oncology (SGO). SGO Clinical Practice Statement: Salpingectomy for Ovarian Cancer Prevention. November 2013
49. Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.149. Molecular Testing for Germline BRIP1, RAD51C, and RAD51D Variants Associated with Ovarian Cancer. September 2022.

X. POLICY HISTORY

TOP

MP 2.377	**New Policy.** Adopting BCBSA policy. Medically necessary criteria for *BRIP1*, *RAD51C*, and *RAD51D* variants. Effective 5/1/2021
	11/19/2021 Minor Review. Updated criteria per BCBSA that individual can have a diagnosis of epithelial ovarian and related cancers. Testing to guide treatment for diagnosed individual is INV. Added NCCN statement. Updated policy guidelines, FEP, and background. Added CPT and ICD-10 codes to policy.
	12/30/2022 Minor Review. Added NBN investigational statement. Title change. Updated cross-references, background, rationale, coding table and references.
	06/07/2024 Administrative Update. Added 0475U. Effective date 7/1/24

Top