2.04.149	Germline Genetic Testing for Ovarian Cancer Risk (BRIP1, RAD51C, RAD51D, NBN)		
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Section:	2.0 Medicine	**Page:**	Page 1 of 34

Policy Statement

I. Testing for germline (not somatic) *BRIP1*, *RAD51C*, and *RAD51D* variants for ovarian cancer risk assessment in adults may be considered **medically necessary** when **either** of the following criteria are met:
   A. The individual has a diagnosis of epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer and have **both** of the following:
      1. The individual has not previously been tested for these gene variants
      2. The individual has closely related (first- and/or second-degree) relatives who may be at increased risk of developing hereditary ovarian cancer
   B. The individual has not been diagnosed with epithelial ovarian cancer and has **either** of the following:
      1. The individual has any blood relative with a known pathogenic or likely pathogenic germline *BRIP1*, *RAD51C*, or *RAD51D* variant
      2. The individual has a first- or second-degree relative diagnosed with ovarian cancer

II. Individual testing for germline NBN variants for ovarian cancer risk assessment in adults is considered **investigational**. but can be allowed when part of an otherwise approved small panel.

III. Testing for germline *BRIP1*, *RAD51C*, and *RAD51D* 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** (unless part of a limited panel that meets criteria for medical necessity for germline testing under another policy (e.g., Blue Shield of California Medical Policy: Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers, or Blue Shield of California Medical Policy: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes).

IV. Testing for germline *BRIP1*, *RAD51C*, and *RAD51D* and NBN variants in adults who do not meet the criteria above is considered **investigational** unless included in a panel test that is approved for another reason.

NOTE: This policy does not address BRCA 1&2 testing. Germline genetic testing for BRCA1 and BRCA2 is addressed separately in Blue Shield of California Medical Policy: Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers; genes associated with Lynch syndrome (see Blue Shield of California Medical Policy: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes) or other genes with a possible association with ovarian cancer.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

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

Recommended Genetic Testing Strategies

Patients 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 patients with a known familial germline *BRIP1, RAD51C, or RAD51D* variant, targeted testing for the specific variant is recommended.
- In patients 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.[1] 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.[2]
  - 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.[3] Therefore, significant limitations of interpreting test results, including uninformative negative results or non-actionable variants of unknown significance (VUS), should be discussed.

Germline genetic testing for *BRCA1, BRCA2*, and *PALB2* is addressed separately in evidence review Germline Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers

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.*

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.[1] 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.[3] Non-actionable VUS are highly prevalent with multi-gene testing, which may be avoided with targeted testing for a known familial variant.[4]

When criteria are met, small panel testing using CPT code 81432 that includes BRIP1, RAD51C and RAD51D, is preferred as the broadest testing for breast and ovarian cancer risk allowed.

Testing related to hereditary Breast/Ovarian cancer related to BRCA1 and BRCA2, see Blue Shield of California Medical Policy: Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers.

Testing related to hereditary colorectal cancer, see Blue Shield of California Medical Policy: Blue Shield of California Medical Policy: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes.

Panel testing related to cancers other than breast, ovarian, colorectal, and non-small-cell lung cancer, see Blue Shield of California Medical Policy: Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing.

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

Variant Classification	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	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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

Genetic Counseling

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

Coding

The following CPT code may be used for this genomic sequence analysis:

- **81432**: Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53

Description

It is estimated that approximately 20% of women presenting for assessment for hereditary ovarian cancer (OC) risk have a variant in a gene that increases the risk of cancer. *BRIP1*, *RAD51C*, and *RAD51D*, and 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 for *BRIP1*, *RAD51C*, and *RAD51D* carriers is increased approximately 3- to 19-fold, 3- to 6-fold, and 5- to 12-fold, respectively. Risk estimates may be higher in patients with a family history of OC or a family history of a specific gene variant.

Germline genetic testing for *BRCA1* and *BRCA2* is addressed separately in Blue Shield of California Medical Policy: Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers.

Related Policies

- Gene Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk
- Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing
- Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers
- Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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,* and *RAD51D* 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.*

Rationale

Background

Ovarian Cancer and Genetics

In 2020, it is estimated that there will be 21,750 new diagnosed cases of ovarian cancer (OC) and that an estimated 13,940 women will die from their disease.[5] 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.[6]

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. [7,8] 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.[9] 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.[7,8] 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.[9] 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.

Testing for germline pathogenic variants in *BRCA1/BRCA2* is addressed separately in Blue Shield of California Medical Policy: Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers.

Mismatch repair genes associated with Lynch syndrome are addressed in Blue Shield of California Medical Policy: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes.

Pathogenic variants in *PALB2* are addressed in Blue Shield of California Medical Policy: Gene Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk.

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.[10] 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.[4] 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.[11] 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.[12]

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.[13] 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.[14]

RAD51C and *RAD51D* Genes

The RAD51 paralogs, *RAD51C* and *RAD51D*, are involved in the FA-*BRCA1/2* homologous recombination pathway.[15,16] Biallelic missense mutations in the *RAD51C* gene are associated with a Fanconi anemia-like phenotype.[17] 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.[1]

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 women 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),[18] 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.[18]

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Molecular Testing for Variants Associated With Hereditary Ovarian Cancer in Undiagnosed Individuals in a Family at Risk of Epithelial Ovarian Cancer

Clinical Context and Test Purpose

The purpose of germline testing for *BRIP1*, *RAD51C*, *RAD51D,* and *NBN* variants in individuals who are not diagnosed with ovarian cancer (OC) and are in a family at risk of epithelial OC (EOC) is to evaluate whether variants are present, and if so, to determine the appropriate surveillance and treatment to decrease the risk of mortality from OC.

The question addressed in this evidence review is: Does germline testing for BRIP1, RAD51C, RAD51D, and NBN variants improve the net health outcome in individuals who are undiagnosed with EOC and in a family at risk of EOC?

The following PICO was used to select literature to inform this review.

Populations

Genetic testing can be considered for women at increased risk of developing hereditary OC based on their family history. Testing may also be considered for women from families with known variants. The relevant population of interest are patients without a personal history of EOC who are in a family at increased risk of EOC. EOC includes epithelial ovarian carcinoma, fallopian tube carcinoma, and primary peritoneal carcinoma. Invasive EOC histologies commonly include high-grade serous, mucinous, endometrioid, and clear cell tumors.

Interventions

The interventions of interest are germline *BRIP1, RAD51C, RAD51D,* and *NBN* variant testing in at-risk individuals without diagnosed EOC and in their first- and/or second-degree relative(s) diagnosed with EOC to identify a known familial variant to facilitate full test interpretation when prophylactic risk-reducing surgery is being considered by the undiagnosed, at-risk individual.

For patients without an OC diagnosis, results may also guide decisions concerning surveillance and chemoprevention.

Testing for *BRIP1, RAD51C, RAD51D,* and *NBN* germline variants is conducted in individuals when appropriate treatment and/or prophylactic treatment options are available.

Comparators

The alternative would be to manage undiagnosed women who are in a family at risk without genetic testing for *BRIP1, RAD51C, RAD51D*, and *NBN* germline variants. Undiagnosed women may also choose to undergo genetic testing for these variants despite unknown familial variant status.

Outcomes

The outcomes of interest are overall survival (OS), disease-specific survival, and test validity.
For women who undergo genetic testing despite an unknown familial variant, negative test results may be uninformative or yield non-actionable variants of unknown significance (VUS).

Study Selection Criteria

For the evaluation of clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from development cohort

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews

Suszynska et al (2019) reported a systematic review of variants identified in panels of breast and OC-related genes.[3,]The role of 37 genes was evaluated, and results were reported for *BRIP1, RAD51C, RAD51D*, and *NBN.* The systematic review included studies published through July 2017 reporting on genetic test results of breast and OC patients who were referred for evaluation by a multi-gene panel. The studies of panel results were used to calculate mutation frequencies by gene. As a control, population mutation frequencies were extracted from the Genome Aggregation Database. Fifteen studies included panels in OC patients. In the OC studies, 7099 patients were included in the analysis of *BRIP1,* 3791 patients were included in the analysis of *RAD51C,* 3258 patients were included in the analysis of *RAD51D*, and 7050 patients were included in the analysis of *NBN. BRIP1, RAD51C, RAD51D*, and *NBN* variants were identified in 1.06%, 0.55%, 0.58%, and 0.28% of OC patients, respectively. The meta-analytic estimate odds ratio (OR) of the association between *BRIP1, RAD51C*, *RAD51D*, and *NBN* variants and risk of OC was OR = 4.9 (95% confidence interval [CI], 3.7 to 6.4), OR = 4.2 (95% CI, 2.6 to 7.0), OR = 7.3 (95% CI, 4.0 to 13.1), and OR = 2.2 (95% CI, 1.3 to 3.5), respectively. These mutations were not associated with breast cancer risk in this study.

In 2020, Suszynska and coworkers conducted a meta-analysis to more precisely estimate the OC risk associated with *BRIP1*, *RAD51C*, and *RAD51D* mutations.[4,] A total of ~29,400 OC patients from 63 studies were included in the analysis of 443 variants through September 2019. Cases were compared to ~116,000 controls from the Genome Aggregation Database. Family history of OC was variable in OC cases and unknown in the control population. Analyses of *BRIP1*, *RAD51C*, and *RAD51D* included 22,494, 23,802, and 22,787 cases, respectively. *BRIP1, RAD51C,* and *RAD51D* variants were identified in 0.89%, 0.63%, and 0.41% of OC patients, respectively. The meta-analytic OR of the association between *BRIP1, RAD51C*, and *RAD51D* variants and risk of OC was OR = 4.94 (95% CI, 4.07 to 6.00), OR = 5.59 (95% CI, 4.42 to 7.07), and OR = 6.94 (95% CI, 5.10 to 9.44). Cumulatively, 1.93% of OC patients had a mutation in 1 of the 3 genes compared with 0.35% in population controls. The study authors estimate that these genes may contribute to 10% of hereditary OC cases.

Observational Studies

A number of studies reporting relative risks (RR) or ORs for the association between *BRIP1, RAD51C, RAD51D*, and *NBN* and OC were identified (see Tables 1 through 8). Studies from single-country samples are described first followed by multinational collaborative efforts. Four studies reported penetrance estimates.[18,19,20,21,] Study designs included family-based case-control[20,21,] and population-based or multicenter case-control.[22,23,24,18,]Study relevance, design, and conduct limitations are summarized in Tables 9 and 10.

Single-Country Samples

Lhotova et al (2020) evaluated the genetic predisposition for OC with multi-gene panel testing for 219 genes in 1333 Czech patients with OC and 2278 population-matched controls, which included testing for *BRIP1*, *RAD51C*, *RAD51D*, and *NBN*.[22,] From 1333 analyzed OC patients, 1045 (78.4%) women were diagnosed with OC only and 288 (21.6%) women were diagnosed with double primary tumors, including breast cancer (210 patients; 15.8%) or other tumors (78 patients; 5.9%). Approximately half of patients (47.6%) had a negative family cancer history. Germline mutations for breast cancer and OC predisposition genes were detected in 32.0% of patients compared to 2.5% of controls. Mutations

in *RAD51C* and *RAD51D* conferred high OC risk (OR > 5) and mutations in *BRIP1* were associated with moderate risk (OR = 3.5) in this study. Mutations in *BRIP1*, *RAD51C*, and *RAD51D* prevailed in patients diagnosed with OC only. In contrast to prior studies, *NBN* variants were associated with potentially increased risk of OC (OR = 3.5).

Weber-Lasalle et al (2018) assessed the role of deleterious, truncating loss-of-function (LoF) *BRIP1* variants in breast and OC predisposition.[23,] Well-characterized index patients with breast cancer (N=6341), OC (N=706), and geographically matched controls of German descent were analyzed via next-generation sequencing according to German Consortium for Hereditary Breast and Ovarian Cancer inclusion criteria for germline testing and tested negative for BRCA1/2 mutations. Of 706 index OC patients, 523 patients affected by OC only demonstrated a higher risk of OC (OR, 23.12; 95% CI, 13.08 to 40.88) compared to 183 patients affected by both OC and breast cancer (OR, 8.10; 95% CI, 1.96 to 33.53). OC index cases with a family history of OC (N=190) demonstrated a higher risk of OC (OR, 32.21; 95% CI, 15.06 to 68.90) compared to 421 OC index cases with a family history of breast cancer only (OR, 16.01; 95% CI, 7.82 to 23.76). A significant association was also noted in the subgroup of patients with late-onset OC. Breast cancer index patients with a family history of OC only (N=1027) demonstrated a significantly increased risk of OC (OR, 3.59; 95% CI, 1.43 to 9.01; p=.0168) whereas breast cancer index patients with a family history of breast cancer only did not (OR, 1.42; 95% CI, 0.70 to 2.90; p =.3030). The authors conclude that an elevated BRIP1 mutation prevalence in the breast cancer subgroup was driven by the occurrence of OC within families.

Lilyquist et al (2017) included an analysis of 7768 Caucasian adult OC cases of European ancestry who were referred to a single clinical testing laboratory for hereditary multi-gene panel testing.[25,] Testing for 19 genes including *BRIP1*, *RAD51C*, *RAD51D*, and *NBN* was conducted. A family history of breast or OC was reported in 44.9% and 15.1% of study subjects, respectively. OC cases were compared to non-Finnish European controls from the Exome Aggregation Consortium dataset. A 5-fold or greater increased risk of OC was found for *BRIP1*, *RAD51C*, and *RAD51D*. A significantly higher rate of pathogenic/likely pathogenic (P/LP) variants was detected for *BRIP1* and *RAD51D* in cases diagnosed at age 60 or later. In a subset of 3830 cases without a personal or family history of breast cancer, the association between *BRIP1*, *RAD51C*, and *RAD51D* and increased risk of OC was RR = 4.08 (95% CI, 2.59 to 6.13), RR = 4.80 (95% CI, 2.93 to 7.42), and RR = 7.02 (95% CI, 2.58 to 15.27). While the investigators found an elevated frequency of pathogenic alterations in *NBN* among OC cases, this outcome was only marginally significant after Bonferroni correction for the number of genes tested (RR = 2.03; 95% CI, 1.27 to 3.08; p =.004).

Kurian et al (2017) reported the association between pathogenic variants and breast or OC using a commercial laboratory database of 95,561 women tested clinically for hereditary cancer risk using a multi-gene panel that included *BRIP1, RAD51C,RAD51D*, and *NBN*.[26,] Although the country is not stated, the patients underwent testing between 2013 and 2015 performed at a Clinical Laboratory Improvement Amendments laboratory and thus will be assumed to include patients from the U.S. Cases were women with a single diagnosis of breast or OC. Controls were women from the same database (i.e., being tested for hereditary cancer) with no cancer history at the time of genetic testing. No family history of breast or OC was reported in 72% of OC cases. The multivariable models for OC risk are reported here. Among 5020 OC cases, 36 (0.72%), 32 (0.64%) 9 (0.18%), and 17 (0.34%) variants were found in *BRIP1, RAD51C,RAD51D*, and *NBN* genes, respectively. The association between these genes and OC were adjusted for age, ancestry, personal and family cancer histories, and Lynch and adenomatous polyposis colon cancer syndromes. No significant association was found between these genes and an increased risk of breast cancer.

Norquist et al (2016) evaluated 1915 women diagnosed with OC from the University of Washington gynecologic tissue bank (n=570) and from the Gynecologic Oncology Group (GOG) phase III clinical trials 218 (n=788) and 262 (n=557).[24,] Participants were not selected for age or family history. Mutation frequencies in cases were compared to population controls from the National Heart, Lung, and Blood

Institute GO Exome Sequencing Project (ESP; n=4300) and the Exome Aggregation Consortium (ExAC; n=36,276). Overall, 18% of OC patients carried pathogenic germline mutations in genes associated with OC risk of which 3.3% occurred in a BRCA-Fanconi anemia OC-associated gene (e.g., *BRIP1*, *PALB2*, *RAD51C*, *RAD51D*, or *BARD1*). The *NBN* gene was not more frequently mutated in women with OC.

Loveday et al (2012) sequenced the full coding region and intron-exon boundaries of *RAD51C* in 1102 probands from breast-ovarian pedigrees and 30 unrelated index cases from ovarian only pedigrees.[20,] Index cases were screened and negative for *BRCA1/2* germline mutations. At least 97% of families were of European ancestry. A total of 449 index cases had a personal history of OC, of which 149 also had breast cancer and 683 index cases had breast cancer only. The study also included 272 unrelated individuals with OC from the Royal Marsden Hospital with unknown BRCA1/2 status and family histories. Index cases were compared to 1156 population-based controls from the 1958 Birth Cohort Collection in Great Britain. A total of 12 mutations were identified among 1132 familial cases compared to 1 mutation in the control population (p =.009). Among unselected OC cases, 3 mutations were identified. In this study, no evidence for an association with breast cancer was found (RR, 0.91; 95% CI, 0.45 to 1.86; p =.8).

Loveday et al (2011) identified 8 inactivating *RAD51D* mutations in 911 unrelated probands from 1648 breast-OC families compared with 1 inactivating mutation in 1060 controls from the 1958 Birth Cohort Collection (p =.01).[21,] Breast cancer-only pedigrees were associated with 737/911 index cases. Three mutations were identified in 59 pedigrees with 3 or more cases of OC (p =.0005). While a significant association between *RAD51D* and OC was found, no significant association with breast cancer was determined in this study (RR, 1.32; 95% CI, 0.59 to 2.96).

Multinational Samples

Yang et al (2020) conducted a penetrance analysis of *RAD51C* and *RAD51D* in 6178 and 6690 families, respectively, enrolled through 28 study centers from 12 countries in Europe and North America.[27,]The study identified 215 women with pathogenic *RAD51C* variants from 125 families (n=1794) with 65 OC and 73 breast cancer, and 92 women with *RAD51D* pathogenic variants from 60 families (n=935) with 36 OC and 30 breast cancer cases. The majority of patients were identified through individuals with multiple relatives diagnosed with OC or breast cancer. The estimated OC RRs were 7.55 (95% CI, 5.60 to 10.19; $p = 5 \times 10^{-40}$) for *RAD51C* and 7.60 (95% CI, 5.61 to 10.30; $p = 5 \times 10^{-39}$) for *RAD51D* pathogenic variant carriers when RRs were assumed to be constant with age. For relative risk estimates by age-decade, *RAD51C* relative risks increased with age until 60-69 years and decreased thereafter. A similar trend was observed for *RAD51D* pathogenic variant carriers, with relative risk peaking at 50-59 years. In a model assuming a residual familial polygenetic component, the predicted risk of developing OC to age 80 years differed by cancer family history, varying from 11% (95% CI, 6% to 21%) for *RAD51C* and 13% (95% CI, 7% to 23%) for *RAD51D* pathogenic variant carriers with no family history of OC in first- and second-degree relatives to 32% (95% CI, 20% to 50%) for *RAD51C* and 36% (95% CI, 23% to 53%) for *RAD51D* pathogenic variant carriers whose mother and sister developed OC at age 50 years.

Song et al (2015) sequenced and analyzed germline DNA for *RAD51C* and *RAD51D* variants from 3429 women with invasive EOC and 2772 controls from 4 population-based case-control studies, 1 clinic-based case-control study, 1 familial OC series of cases and matched controls, and 2 familial OC registries.[19,] Overall, 91.4% of OC cases were unselected for family history. Additionally, 2000 unaffected (ie, undiagnosed) women with *BRCA1/2*-negative status from the UK Familial Ovarian Cancer Screening Study (UKFOCSS) were also analyzed. Eligible participants were women age 35 or older with an estimated lifetime risk of OC ≥ 10% on the basis of a family history of ovarian and/or breast cancer and/or the presence of known predisposing germline gene mutations (e.g., *BRCA1*, *BRCA2*, and MMR genes) in the family. A significantly greater rate of unaffected UKFOCSS participants were found to carry *RAD51C* (n=7) and *RAD51D* (n=5) deleterious variants

compared to controls (p <.001). *RAD51* mutation carriers were significantly more likely than non-carriers to have a family history of OC (p <.001).
Ramus et al (2015) analyzed 3374 case patients and 3487 control patients from 8 OC case-controls studies, 1 familial OC registry in the U.S., and 1 case series to establish whether rare protein-truncating variants in *BRIP1* are associated with an increased risk of OC in populations of European origin.[18,] An additional 2167 unaffected women who had previously tested negative for BRCA1 and BRCA2 for *BRCA1* and *BRCA2* for *BRCA1* and *BRCA2* variants that participated in the UKFOCSS between June 2002 and September 2010 were also studied. Sequencing results were available for 3236 EOC cases and 3431 control patients and 2000 women from the UKFOCSS. UKFOCSS subjects demonstrated a prevalence rate of 0.60% (12/2000; $p = 8 \times 10^{-4}$). A family history of breast, ovarian, or both cancers was reported in 6.7%, 10% and 13.3% of *BRIP1* carriers and 8.4%, 13.1%, and 18.8% of non-carriers. No significant difference in *NBN* mutations was detected between cases and controls (p =.61).

Specific Variants

Flaum et al (2022) conducted a case-control study of 3767 cases and 2043 controls to investigate the frequency of the *BRIP1* c.1045G>C missense variant.[28,] This variant was associated with a significantly increased risk of familial epithelial OC (OR = 140.8; 95% CI, 23.5 to 1723.0; p <.0001). This missense variant was considered of particular interest as its dominant-negative effect may confer higher risks than loss-of-function counterparts.

Rafnar et al (2011) identified approximately 16 million sequence variants through whole-genome sequencing of 457 Icelanders.[29,] Results were imputed to 41,675 Icelanders and their families through chips identifying single nucleotide polymorphisms. A rare (0.41% allelic frequency) frameshift mutation in the *BRIP1* gene, c.2040_2041insTT, was detected in 656 individuals and found to confer an increase in OC risk (OR, 7.95; $p = 5.65 \times 10^{-13}$). A cohort of 11,741 Icelandic subjects with cancer and 3913 controls was assessed for this variant which was found to significantly increase risk of OC (OR, 8.13; 95% CI, 4.74 to 13.95; $P = 2.8 \times 10^{-14}$) and increase risk of cancer in general, reducing lifespan by 3.6 years (95% CI, 1.5 to 5.7).

Kushnir et al (2012) sequenced 206 high risk Jewish women with breast and/or OC (breast cancer=190; OC=14; breast cancer+OC=2) for *RAD51C* mutations.[30,] Thirty-eight percent of women were of Ashkenazi origin (n=78). No truncating mutations were detected. Two missense mutations were found, p.Ile144Thr and p.Thr287Ala, previously described in Iraqi and mixed ethnicity Balkan-North African cases, respectively. Although some prediction algorithms suggest these variants may be possibly pathogenic, neither of these sequence variants leads to a variant with an unequivocal deleterious effect. The 2 missense variants were not identified in individuals with Ashkenazi origin.
Catucci et al (2012) genotyped 149 high-risk women with breast cancer (n=127) and OC (n=22) from cancer prone families of Ashkenazi origin for *BRIP1* mutations.[31,] Cases were negative for BRCA1/2 mutations. One novel missense mutation (p.Ala745Thr) and 2 previously described missense mutations (p.Val193Iso and p.Ser919Pro) were detected. No truncating mutations were identified. These variants were not detected in any of 93 healthy Ashkenazi cancer-free controls. A subgroup analysis for cases with OC was not reported. The relationship between missense variants in *BRIP1* and OC risk is unclear.[32,]

Variant Classification

Valid variant classification is required to assess penetrance and is of particular concern for low prevalence variants. Due to heterogeneous application of variant classification tools and/or in silico algorithms and widespread use of next generation sequencing, the frequency of specific variants in the clinical validity studies is likely low and difficult to assess. While there are guidelines for variant classification, the consistency of interpretation among laboratories is of interest. Balmaña et al (2016) examined the agreement in variant classification by different laboratories from tests for inherited cancer susceptibility from individuals undergoing panel testing.[32,] The Prospective Registry of Multiplex Testing registry is a volunteer sample of patients invited to participate when test results

were provided to patients from participating laboratories. From 518 participants, 603 variants were interpreted by multiple laboratories and/or found in ClinVar. Discrepancies for *BRIP1* and *RAD51C* were reported. Of 33 *BRIP1* results with multiple interpretations, 3 (9%) had at least 1 conflicting interpretation, 2 (6%) had a conflicting interpretation as P/LP variants and VUS, and all conflicting classifications were missense mutations. Of 26 *RAD51C* results with multiple interpretations, 1 deletion mutation (4%) had a conflicting interpretation as a P/LP variant and a VUS and 12 (46%) missense mutations had a conflicting interpretation as benign/likely benign variants and VUS. Given the nature of the sample, there was a significant potential for biased selection of women with either reported VUS or other uncertainty in interpretation. In addition, the majority of discrepancies were confined to missense variants. It is therefore difficult to draw conclusions concerning the frequency of discrepant conclusions among all tested women.

Table 1. Included Association Studies of Pathogenic *BRIP1* Variants

Study	Year	Country	Design	N	Families	Variants		Totals		P/LP Variants Identified	
						Cases	Controls	Cases	Controls	N	Prevalence Cases, %
Lhotova (2020)[22,]	2020	Czech Republic	Population-based CC	3611		10	5	1333	2278	10	0.98
Weber-Lasalle (2018)[a23,]	2018	Germany	Population-based CC	9236		18; 17	2189	706; 611	3	18; 17	2.55; 2.78
Lilyquist (2017)[25,]	2017	U.S.	CC	7768		58	NR	7768	NR	58	0.99
Kurian (2017)[26,]	2017	U.S.	CC	95,561		36	NR	5020	51,200	36	0.72
Norquist (2016)[b24,]	2016	U.S.	Multicenter CC	42,491		26	60	1915	36,276	26	1.36
Ramus (2015)[18,]	2015	Multinational	Multicenter CC	6861		30	3	3277	3444	30	0.92

CC: case-control; NR: not reported; P/LP: pathogenic/likely pathogenic.
[a] Case numbers and prevalence rates report: 1) all OC index cases; 2) familial OC index cases with a family history of ovarian or breast cancer.
[b] Reflects cases compared to controls from ExAC.

Table 2. Measures of Association and Penetrance for Ovarian Cancer and *BRIP1*

Study	Year	Analysis	RR or OR (95% CI)	Age; Penetrance, % (95% CI)	Mean (Median) Age at Onset, y
Lhotova (2020)[22,]	2020	Standard CC	3.5 (1.1 to 13)	NR	58.0 (Range: 30-71)
Weber-Lasalle (2018)[a23,]	2018	Standard CC	19.17 (11.13 to 33.03); 20.97 (12.02 to 36.57)	NR	54 (Range: 20-93); 54 (Range: 20-93)
Lilyquist (2017)[25,]	2017	Standard CC	4.99 (3.79 to 6.45)	NR	NR
Kurian (2017)[26,]	2017	Standard CC	2.62 (1.72 to 3.98)	NR	NR
Norquist (2016)[b24,]	2016	Standard CC	6.4 (3.8 to 10.6)	NR	65.5 (Range: 43-79)
Ramus (2015)[18,]	2015	Standard CC & SEG	11.22 (3.22 to 34.10) (CC) 3.41 (2.12 to 5.54) (SEG)	80; 5.8 (3.6 to 9.1)[c]	58 (Range: 18-91)

CC: case-control; CI: confidence interval; NR: not reported; OR: odds ratio; RR: relative risk; SEG: segregation analysis.
[a] OR and age at onset are reported for:1) all OC index cases; 2) familial OC index cases with a family history of ovarian or breast cancer.
[b] Reflects cases compared to controls from ExAC.
[c] The lifetime risk at the 80th percentile of the risk distribution is increased at 8.20% (80% CI, 6.02% to 11.34%)

when other EOC risk factors are taken into consideration, including oral contraceptive use, tubal ligation, parity, history of endometriosis, and family history.

Table 3. Included Association Studies of Pathogenic *RAD51C* Variants

Study	Year	Country	Design	N	Families	Variants		Totals		P/LP Variants Identified	
						Cases	Controls	Cases	Controls	N	Prevalence Cases, %
Yang (2020)[27,]	2020	Multinational	Multicenter, family-based CC	NR	6178	125[b]	NR	6178[b]	NR	125[b]	2.02[b]
Lhotova (2020)[22,]	2020	Czech Republic	Population-based CC	3611		13	4	1333	2278	13	0.98
Lilyquist (2017)[25,]	2017	U.S.	CC	7768		44	NR	6294	NR	44	0.79
Kurian (2017)[26,]	2017	U.S.	CC	95561		32	NR	5020	51,200	32	0.64
Norquist (2016)[a24,]	2016	U.S.	Multicenter CC	42491		11	39	1915	36,276	11	0.57
Song (2015)[19,]	2015	Multinational	Multicenter CC	6201		14	2	3429	2772	14	0.41
Loveday (2012)[20,]	2012	U.K.	Family-based CC	2560	Unclear	12	1	1132	1156	12	Unclear

CC: case-control; NR: not reported; P/LP: pathogenic/likely-pathogenic.
[a] Reflects cases compared to controls from ExAC.
[b] Reflects number of affected families with ovarian or breast cancer.

Table 4. Measures of Association and Penetrance for Ovarian Cancer and *RAD51C*

Study	Year	Analysis	RR or OR (95% CI)	Age: Penetrance, % (95% CI)	Mean (Median) Age at Onset, y
Yang (2020)[27,]	2020	SEG	7.55 (5.60 to 10.19)	30; 0.02 (0.02 to 0.02) 40; 0.2 (0.08 to 0.4) 50; 1 (0.6 to 2) 60; 4 (3 to 7) 70; 9 (6 to 14) 80; 11 (6 to 21)	NR
Lhotova (2020)[22,]	2020	Standard CC	5.7 (1.7 to 23.8)	NR	52.2 (Range: 25-69)
Lilyquist (2017)[25,]	2017	Standard CC	5.12 (3.72 to 6.88)	NR	NR
Kurian (2017)[26,]	2017	Standard CC	4.98 (3.09 to 8.04)	NR	NR
Norquist (2016)[a24,]	2016	Standard CC	3.4 (1.5 to 7.6)	NR	64 (Range: 47-70)
Song (2015)[19,]	2015	Standard CC	5.2 (1.1 to 24)	50; 1.3 (0.3 to 6.0) 70; 5.2 (1.1 to 22)	58.7
Loveday (2012)[20,]	2012	SEG	5.88 (2.91 to 11.88)	80; >9 (NR)	NR

CC: case-control; CI: confidence interval; NR: not reported; OR: odds ratio; RR: relative risk; SEG: segregation analysis.
[a] Reflects cases compared to controls from ExAC.

Table 5. Included Association Studies of Pathogenic *RAD51D* Variants

Study	Year	Country	Design	N	Families	Variants		Totals		P/LP Variants Identified	
						Cases	Controls	Cases	Controls	N	Prevalence Cases, %

Study	Year	Country	Design	N	Families	Variants		Totals		P/LP Variants Identified	
Yang (2020)[27,]	2020	Multinational	Multicenter, family-based CC	NR	6690	60[b]	NR	6690[b]	NR	60[b]	0.89[b]
Lhotova (2020)[22,]	2020	Czech Republic	Population-based CC	3611		13	2	1333	2278	13	0.98
Lilyquist (2017)[25,]	2017	U.S.	CC	7768		11	NR	6294	NR	11	0.31
Kurian (2017)[26,]	2017	U.S.	CC	95561		9	NR	5020	51,200	9	0.18
Norquist (2016)[a24,]	2016	U.S.	Multicenter CC	42491		11	14	1915	36,276	11	0.57
Song (2015)[19,]	2015	Multinational	Multicenter CC	6201		12	1	3429	2772	12	0.35
Loveday (2011)[21,]	2011	U.K.	Family-based CC	1971	1648	8	1	911	1060	8	Unclear

CC: case-control; NR: not reported; P/LP: pathogenic/likely-pathogenic.
[a] Reflects cases compared to controls from ExAC.
[b] Reflects number of affected families with ovarian or breast cancer.

Table 6. Measures of Association and Penetrance for Ovarian Cancer and *RAD51D*

Study	Year	Analysis	RR or OR (95% CI)	Age: Penetrance, % (95% CI)	Mean (Median) Age at Onset, y
Yang (2020)[27,]	2020	SEG	7.60 (5.61 to 10.30)	30; 0.02 (0.02 to 0.02) 40; 0.1 (0.06 to 0.3) 50; 0.8 (0.5 to 2) 60; 4 (3 to 7) 70; 9 (6 to 14) 80; 13 (7 to 23)	NR
Lhotova (2020)[22,]	2020	Standard CC	11.3 (2.6 to 103.4)	NR	56.0 (Range: 36-69)
Lilyquist (2017)[25,]	2017	Standard CC	6.34 (3.16 to 11.34)	NR	NR
Kurian (2017)[26,]	2017	Standard CC	4.78 (2.13 to 10.7)	NR	NR
Norquist (2016)[a24,]	2016	Standard CC	10.9 (4.6 to 26.0)	NR	54 (Range: 35-75)
Song (2015)[19,]	2015	Standard CC	12 (1.5 to 90)	50; 3.0 (0.4 to 21) 70; 12 (1.5 to 60)	58.7
Loveday (2011)[21,]	2011	SEG	6.30 (2.86 to 13.85)	80; ~10 (NR)	NR

CC: case-control; CI: confidence interval; NR: not reported; OR: odds ratio; RR: relative risk; SEG: segregation analysis.
[a] Reflects cases compared to controls from ExAC.

Table 7. Included Association Studies of Pathogenic *NBN* Variants

Study	Year	Country	Design	N	Families	Variants		Totals		P/LP Variants Identified	
						Cases	Controls	Cases	Controls	N	Prevalence Cases, %
Lhotova (2020)[22,]	2020	Czech Republic	Population-based CC	3611		14	7	1333	2278	14	1.06
Lilyquist (2017)[25,]	2017	U.S.	CC	7768		22	NR	6294	NR	22	0.38
Kurian (2016)[26,]	2017	U.S.	CC	95561		17	NR	5020	51,200	17	0.34
Norquist (2016)[a24,]	2016	U.S.	Multicenter CC	42491		9	49	1915	36,276	9	0.47
Ramus (2015)[18,]	2015	Multinational	Multicenter CC	6861		9	8	3248	3439	9	0.28

CC: case-control; NR: not reported; P/LP: pathogenic/likely-pathogenic.
[a] Reflects cases compared to controls from ExAC

Table 8. Measures of Association and Penetrance for Ovarian Cancer and *NBN*

Study	Year	Analysis	RR or OR (95% CI)	Age: Penetrance, % (95% CI)	Mean (Median) Age at Onset, y
Lhotova (2020)[22,]	2020	Standard CC	3.5 (1.3 to 10.2)	NR	54.5 (Range: 18-76)
Lilyquist (2017)[25,]	2017	Standard CC	2.03 (1.27 to 3.08)	NR	NR
Kurian (2016)[26,]	2017	Standard CC	1.85 (1.05 to 3.24)	NR	NR
Norquist (2016)[a24,]	2016	Standard CC	2.3 (0.99 to 5.4)[a]	NR	NR
Ramus (2015)[18,]	2015	Standard CC & SEG	NR	NR	58 (Range: 18-91)

CC: case-control; CI: confidence interval; NR: not reported; OR: odds ratio; RR: relative risk; SEG: segregation analysis.
[a] Reflects cases compared to controls from ExAC.

Table 9. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Yang (2020)[27,]	4. Family-based case-control population of OC and breast cancer cases in breast-ovarian pedigrees (and controls); likely overestimated risk				
Lhotova (2020)[22,]	4. Case-control population of Czech OC patients (and controls), likely overestimated risk	1. Not clear which variants were included	2. Noncancer and unselected controls included individuals with known (negative) or unknown family histories and male subjects		
Weber-Lasalle (2018)[23,]	4. Case-control population of German OC and breast cancer patients (and controls), likely overestimated risk; above average prevalence rates				

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Lilyquist (2017)[25],	4. Case-control population of Caucasian OC patients referred for hereditary multi-gene panel testing (and controls); likely overestimated risk				
Kurian (2017)[26],	4. Case-control population of OC and breast cancer patients referred for hereditary multi-gene panel testing (and controls); likely overestimated risk	1. Not clear which variants were included			1. Control chosen from patients being tested for hereditary cancer; unclear how many developed cancer
Norquist (2016)[24],	4. Case-control population of OC patients unselected for age or family history (and controls); likely overestimated risk				
Ramus (2015)[18],	4. Multicenter case-control population of OC patients (and controls); likely overestimated risk				1. Unclear how many women in UKFOCSS cohort developed cancer
Song (2015)[19],	4. Multicenter case-control population of OC patients (and controls); likely overestimated risk				1. Unclear how many women in UKFOCSS cohort developed cancer
Loveday (2012)[20],	4. Family-based case-control population of OC cases in breast-ovarian pedigrees (and controls); likely overestimated risk				
Loveday (2011)[21],	4. Family-based case-control population of OC cases in breast-ovarian pedigrees (and controls); likely overestimated risk				

OC: ovarian cancer; UKFOCSS: UK Familial Ovarian Cancer Screening Study.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 10. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Yang (2020)[27]	1. Selection not fully described			1. Registration not reported	1. Incomplete description of disposition of eligible patients/samples	
Lhotova (2020)[22]	1. Selection of population-matched controls not fully described			1. Registration not reported	1. Incomplete description of family history subgroups and eligible dispositions	
Weber-Lasalle (2018)[23]	1. Selection of geographically-matched controls not fully described			1. Registration not reported	1. Incomplete description of disposition of eligible patients/samples	
Lilyquist (2017)[25]	1. Selection of controls not fully described			1. Registration not reported; number of controls unknown	1. No description of disposition of eligible patients for multi-gene panel testing	
Kurian (2017)[26]				1. Registration not reported	1. No description of disposition of eligible patients/samples	
Norquist (2016)[24]	1. Selection not fully described			1. Registration not reported	1. No description of disposition of eligible patients/samples	
Ramus (2015)[18]	1. Selection not fully described			1. Registration not reported	1. Incomplete description of disposition of eligible patients/samples	
Song (2015)[19]	1. Selection not fully described			1. Registration not reported	1. Incomplete description of disposition of eligible patients/samples	
Loveday (2012)[20]	1. Selection not fully described			1. Registration not reported	1. Incomplete description of	

			disposition of eligible patients/samples
Loveday (2011)[21,]	1. Selection not fully described	1. Registration not reported	1. Incomplete description of disposition of eligible patients/samples

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Review of Evidence

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Direct evidence of clinical utility in undiagnosed, at-risk women with *BRIP1*, *RAD51C*, *RAD51D*, or *NBN* germline variants was not identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The following section describes a chain of evidence for the clinical utility of *BRIP1*, *RAD51C*, and *RAD51D* germline variant testing. The association between *NBN* variants and ovarian cancer does not have established clinical validity and is not discussed further in this section.

Modeling Studies

Studies of women at increased risk for EOC based on family history alone or in those with BRCA1 and *BRCA2* variants are relevant to the clinical utility of *BRIP1, RAD51C, and RAD51D* testing given the penetrance estimates for these genes and their related molecular phenotype ("BRCAness"). Interventions to decrease OC risk in asymptomatic high-risk women include chemoprevention (e.g., oral contraceptives) and prophylactic risk-reducing surgery (e.g., bilateral risk-reducing salpingo-oophorectomy [RRSO]). Screening interventions for OC (e.g., transvaginal ultrasound [TVUS], serum cancer antigen-125 [CA-125] testing) have shown to have limited clinical benefit on health outcomes.[6,33,7,] Combined surveillance methods have been associated with an unneeded rate of diagnostic surgery of 55% and significantly higher cancer-related distress.[33,] OC screening has not been shown to reduce mortality among women at risk of hereditary disease.[7,] Case -control studies have demonstrated that oral contraceptive use reduces the risk of OC by 45% to 50% in *BRCA1* mutation carriers and by 60% in *BRCA2* mutation carriers, with decreasing risk with longer duration of oral contraceptive use.[15,]

In women at increased risk of hereditary OC, including *BRCA1* and *BRCA2* carriers, evidence supports a reduction in subsequent OC after risk-reducing oophorectomy. Decision analyses have modeled the impact of risk-reducing surgery on age-specific gains in life expectancy. Schrag et al (1997) examined penetrance magnitudes in the range of those estimated for *BRIP1*, *RAD51C*, and *RAD51D* variants and found that a 30-year old *BRCA* carrier with an expected 5% cumulative risk of OC by age 70 would gain an expected 0.3 years with a prophylactic oophorectomy.[34,] The age-specific gain in life expectancy increases to 1 year for a 30-year old with 20% risk. Furthermore, among 30-year old women, oophorectomy may be delayed by 10 years with little loss of life expectancy (see Table 11). The Markov model assumed that women receiving prophylactic oophorectomy received hormone replacement therapy until the natural age of menopause and that prophylactic oophorectomy did not have an effect on the probability of breast cancer. In an updated evidence report and systematic review for the US Preventive Services Task Force (2019),[33,] Nelson and coworkers determined that RRSO decreased OC incidence by 69% to 100% and all-cause mortality by 55% to 100% among high-risk women and *BRCA* mutation carriers.

Table 11. Model Results of the Effects of Oophorectomy on Age-Specific Gains in Life Expectancy in *BRCA* Carriers According to Penetrance[1]

Risk Level and Strategy	Age of Carrier, y			
	30	40	50	60
5% Risk of Ovarian Cancer[a]				
Oophorectomy	0.3	0.3	0.1	0
Oophorectomy delayed 10 years	0.2	0.1	0	0
20% Risk of Ovarian Cancer[a]				
Oophorectomy	1.0	1.0	0.4	0.1
Oophorectomy delayed 10 years	0.8	0.3	0.1	0
40% Risk of Ovarian Cancer[a]				
Oophorectomy	1.7	1.7	0.8	0.3
Oophorectomy delayed 10 years	1.2	0.3	0.1	0

[1] Adapted from Schrag et al (1997).[34,]
[a] Cumulative risk of ovarian cancer through age 70.

Tung et al (2016) developed a counseling framework for moderate-penetrance cancer-susceptibility mutations associated with OC risk, including *BRIP1*, *RAD51C*, and *RAD51D* genes.[7,] Cumulative lifetime risk (CLTR) (ie, penetrance) was modeled as the risk of cancer experienced by an individual between birth and the age of 80 years, utilizing average relative-risk multipliers from the population-based case-control studies of Ramus et al (2015)[18,] and Song et al (2015).[19,] Population age-specific incidence rates were obtained from the 2008-2012 SEER cancer statistics for all races. This model is limited by assuming a constant relative risk over the lifetime, utilizing average relative risks despite higher or lower risks seen with truncating vs missense mutations, lack of generalizability to non-US populations, and failure to capture individual modifications in risk from genetic and non-genetic factors. The estimated CLTR associated with mutations in *BRIP1*, *RAD51C*, and *RAD51D* were found to approximate to the lower end of ovarian-cancer risk estimates for *BRCA2* mutation carriers (see Table 12). Due to the limited benefits of OC screening, Tung and coworkers propose a counseling framework for *BRIP1*, *RAD51C*, and *RAD51D* mutation carriers that warrants consideration of RRSO. However, as RRSO is not routinely recommended for women whose only OC risk factor is an affected first-degree relative, it is argued that a woman's cumulative risk of OC should therefore approach or exceed the LTR of a woman with an affected *BRCA*-negative first degree relative (approximately

2.64%) before they are offered RRSO. The model indicates the risk threshold is crossed between the ages of 50-55 years for *BRIP1*, *RAD51C*, and *RAD51D* carriers, thus deferring RRSO until a woman is perimenopausal or postmenopausal may be reasonable. However, women with mutations in these genes who also have a family history of OC in a first-degree relative may cross the risk threshold earlier. Current society guidelines recommend discussing RRSO around 45-50 years of age or earlier based on specific family history of an earlier onset of OC.[15,]

Table 12. Estimated Ovarian Cancer Cumulative Risks According to *BRIP1*, *RAD51C*, and *RAD51D* Mutations[1]

Patient Age, y	Cumulative Risk (%)				
	US Population	*BRIP1* (CC)	*BRIP1* (SEG)	*RAD51C*	*RAD51D*
25-29	0.02	0.22	0.11	0.10	0.23
30-34	0.03	0.36	0.17	0.17	0.38
35-39	0.05	0.54	0.25	0.25	0.58
40-44	0.07	0.81	0.40	0.38	0.87
45-49	0.12	1.32[a]	0.65	0.61	1.41[a]
50-54	0.19	2.12[a]	0.99	0.99	2.27[a]
55-59	0.29	3.20[b]	1.40[a]	1.50[a]	3.43[b]
60-64	0.41	4.53[b]	1.91[a]	2.13[a]	4.85[b]
65-69	0.59	6.14[b]	2.54[b]	2.90[b]	6.57[b]
70-75	0.75	8.10[b]	3.27[b]	3.85[b]	8.66[b]
CLTR (80)	1.2	12.7	4.06	6.12	13.56

CC: case-control study; CLTR: cumulative lifetime risk; SEG: segregation analysis.
[1] Adapted from Tung et al (2016).[7,]
[a] Ages at which cumulative risk reaches ~1.2%, the population CLTR.
[b] Ages at which cumulative risk approaches or exceeds 2.6%, or the approximate average risk of a woman with a *BRCA1/2*-negative relative affected with OC.

Identification of Familial Variants

How variant detection affects penetrance estimates compared with family history alone is of interest. As with *BRCA* variants, model-based estimates allow estimating risks for individual patient and family characteristics. The CanRisk tool,[35,] a web interface to BOADICEA v5, the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm, has been enhanced with a separate prediction model based on the BOADICEA methodology to include the effects of rare pathogenic *BRCA1, BRCA2, BRIP1, RAD51C,* and *RAD51D* variants on OC risk.[5,36,]This enhanced CanRisk tool which integrates the effects of rare variants in moderate and high penetrance genes has not been validated and is intended for research use only. Validated risk-prediction models for familial OC (e.g., BOADICEA v3, BRCAPRO) currently assume that all familial aggregation to OC is due to *BRCA1* and *BRCA2* mutations.

To illustrate OC risk as determined by BOADICEA v5, a 30-year old woman whose *BRCA1/2*-negative mother was diagnosed with OC at age 50 and died at 52 has an estimated 10.4% risk of OC by age 80 compared to the average population risk of 1.3% in the United States; the risk increases to 12.6%, 16.7%, and 18.1% if the daughter carries a *BRIP1*, *RAD51C*, or *RAD51D* variant, respectively. If the mother carries a *RAD51D* variant and the daughter's variant status is unknown, she has an estimated risk of 14.1% by age 80; this risk increases to 18% if both mother and daughter test positive for a *RAD51D* variant.

Therefore, it is strongly recommended that an *affected* (ie, diagnosed) family member be tested first whenever possible to adequately interpret genetic testing of the unaffected (ie, undiagnosed) at-risk individual and to provide a more accurate risk assessment.[15,] In unaffected family members of potential *BRIP1, RAD51C, or RAD51D* variant families, most test results will be negative and uninformative when no known familial variant has been identified. 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.[37,] Non-actionable VUS are highly prevalent with multi-gene testing, which may be avoided with targeted testing for a known familial variant.[7,]

To identify clinically significant familial 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.[15,] Testing unaffected family members when an affected member is not available for testing, unwilling to undergo testing, or unwilling to share genetic testing results should still be considered. However, evidence suggests that indeterminate genetic testing results may be poorly understood by family members.[37,] Therefore, significant limitations of interpreting test results, including uninformative negative results or non-actionable VUS, should be discussed.

Other Benefits of Risk-Reducing Salpingo-Oophorectomy

In studies of women with a *BRCA1/2* mutation who underwent RRSO, occult gynecologic carcinomas were identified in 4.5% to 9% of cases based on careful pathologic examination of the ovaries and fallopian tubes.[15,] Although tubal intraepithelial carcinoma (TIC), hypothesized to serve as an early precursor lesion for serous OC, appears to be more prevalent in *BRCA* carriers, TIC has also been documented in patients with serous carcinomas unselected for family history or *BRCA* status. Among high-risk women, RRSO may provide an opportunity for occult gynecologic cancer detection. An analysis of 966 RRSO procedures detected invasive or intraepithelial ovarian, tubal, or peritoneal neoplasms in 25 (2.6%) of patients (4.6% of *BRCA1* carriers, 3.5% of *BRCA2* carriers, and 0.5% of non-carriers; p <.001).[38,] In a study of asymptomatic Slovenian women with P/LP *BRCA* variants (n=145) and *BRCA*-negative high-risk status (n=10) (ie, at least 2 first- or second-degree relatives with OC) who underwent RRSO from January 2009 to December 2015, 9 (5.8%) occult cancers were identified; 8 in *BRCA1*-positive women and 1 in a high-risk *BRCA*-negative woman.[39,]

Section Summary: Undiagnosed Individuals in a Family at Risk of Developing Epithelial Ovarian Cancer

Clinically Valid

Identified studies differed by populations, designs, sample sizes, analyses, and reported variants. While estimates of the magnitude of the association between *BRIP1*, *RAD51C*, and *RAD51D* and OC risk varied across studies, their magnitudes are at least moderate and approach the range for a highly penetrant variant. The association between *NBN* variants and OC risk was not consistently significant across studies and penetrance estimates are not available.

Pathogenic and likely pathogenic germline variants in *BRIP1*, *RAD51C*, and *RAD51D* predominantly consist of truncating LoF mutations. The pathogenicity of missense variants has been evaluated via in silico (computational) analyses predicting protein structure/function, and the role of these variants in OC risk is uncertain. Errors in variant classification have been reported, particularly for missense variants. False-negatives would result in risk determined by family history alone or may offer incorrect reassurance; the consequences of false-positives may have adverse consequences due to incorrect management decisions. Most studies acknowledged that the role of missense variants in OC risk is controversial, and reported risk estimates typically reflect analyses of truncating LoF variants only.

Clinically Useful

Evidence concerning preventive interventions in women with *BRIP1, RAD51C,* and *RAD51D* germline variants is indirect, relying on studies of high-risk women and *BRCA* carriers. In women at increased risk of hereditary OC who would consider preventive interventions, identifying a *BRIP1, RAD51C, and RAD51D* variant may provide a more accurate estimated risk of developing OC compared with family

history alone and can offer a better understanding of the benefits and potential harms of interventions. The accuracy of this risk assessment increases when a causative familial variant is identified in an affected relative, decreasing the yield of uninformative negative test results. Targeted testing for an identified familial variant may also avoid identification of VUS, as is common with multi-gene testing. Therefore, testing of affected blood relatives for a causative familial variant facilitates more informative interpretation of test results in undiagnosed, at risk family members and supports informed prophylactic decision-making. A chain of evidence cannot be constructed for *NBN* germline variant testing as its clinical validity has not been established.

Molecular Testing for Variants Associated With Hereditary Ovarian Cancer in Individuals Diagnosed With Epithelial Ovarian Cancer

Clinical Context and Test Purpose

The purpose of testing for germline *BRIP1*, *RAD51C*, *RAD51D*, and *NBN* variants in individuals diagnosed with EOC is to evaluate whether variants are present, and if so, to determine the appropriate surveillance and treatment to decrease the risk of mortality from OC.

The question addressed in this evidence review is: Does testing for germline *BRIP1*, *RAD51C*, *RAD51D*, and *NBN* variants improve the net health outcome in individuals with diagnosed OC?
The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are patients with diagnosed EOC, which includes epithelial ovarian carcinoma, fallopian tube carcinoma, and primary peritoneal carcinoma. Invasive EOC histologies commonly include high-grade serous, mucinous, endometrioid, and clear cell tumors.

Interventions

The intervention of interest is germline *BRIP1, RAD51C, RAD51D*, and *NBN* variant testing to guide treatment decisions for the individual diagnosed with EOC.

Testing for *BRIP1, RAD51C, RAD51D*, and *NBN* variants is conducted in adults when appropriate treatment options are available.

Comparators

The alternative would be to manage women diagnosed with OC without genetic testing for germline *BRIP1, RAD51C, RAD51D*, and *NBN* variants.

Outcomes

The outcomes of interest are overall survival (OS), disease-specific survival, and test validity.

Study Selection Criteria

For the evaluation of clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from development cohort

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

The association studies detailed previously (see Tables 1-10) are also relevant to individuals diagnosed with EOC. No studies comparing overall or disease-specific survival outcomes in OC patients with and without germline *BRIP1*, *RAD51C*, *RAD51D*, or *NBN* variants were identified.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Review of Evidence

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Direct evidence of clinical utility limited to women diagnosed with EOC with *BRIP1, RAD51C, RAD51D*, and *NBN* germline variants was not identified.

Chain of Evidence

Primary treatment of EOC involves unilateral or bilateral RRSO and comprehensive staging in patients desiring fertility. In surgical candidates where optimal cytoreduction is likely and fertility is not desired, hysterectomy and RRSO, comprehensive surgical staging, and debulking surgery as needed is recommended. For poor surgical candidates or in individuals with a low likelihood of optimal cytoreduction, neoadjuvant therapy is recommended prior to interval debulking surgery with completion hysterectomy/RRSO and cytoreduction.[40,] Therefore, testing of *BRIP1*, *RAD51C*, *RAD51D*, and *NBN* germline variants may potentially inform therapy.

BRCA mutation status and/or genomic instability-based homologous recombination deficiency (HRD) inform the clinical utility of poly(ADP-ribose) polymerase (PARP) inhibitors (e.g., olaparib, rucaparib, and niraparib) in women diagnosed with OC, and U.S. Food and Drug Administration-approved companion diagnostics that assess HRD for PARP inhibitors calculate genomic instability by measuring loss of heterozygosity, telomeric allelic imbalance, and/or large-scale state transitions using DNA isolated from tumor tissue specimens and do not presently test for gene variants other than *BRCA1* and *BRCA2*. Beyond *BRCA*-mutated tumors, current HRD assays have not provided sufficient differentiation of patient response to PARP inhibitors.[41,] In a phase 3 trial of niraparib, PRIMA investigators stratified results for HRD/*BRCA* wild-type tumors and homologous recombination proficient (HRP) tumors and found an overlapping therapeutic benefit in both groups (HRD - hazard ratio, 0.5; 95% CI, 0.31 to 0.83; HRP - hazard ratio, 0.68; 95% CI, 0.49 to 0.94).[42,] In a phase 3 trial of rucaparib, ARIEL3 investigators reported results for *BRCA* wild-type tumors with low or high loss-of-heterozygosity and found an overlapping therapeutic benefit in both groups (loss-of-heterozygosity low - hazard ratio, 0.58; 95% CI, 0.40 to 0.85; loss-of-heterozygosity high - hazard ratio, 0.44; 95% CI, 0.29 to 0.66).[43,] Results in these studies were not stratified by non-*BRCA* HRD gene. A post hoc exploratory analysis by ARIEL2 investigators found that alterations in RAD51C and RAD51D correlated with meaningful clinical activity of rucaparib similar to that of BRCA-positive high-grade OC.[44,45,]Clinical trials of patients with non-*BRCA* HRD mutations including RAD51C and *RAD51D* have suggested mechanisms that confer sensitivity and acquired resistance to PARP inhibitors[46,] and reported that platinum-based chemotherapy in combination with bevacizumab is effective and does not yield a significant difference in progression-free survival and OS compared to patients with *BRCA* mutations.[47,] Additional details regarding PARP inhibitor therapy are available in evidence review 2.04.02.

While these initial reports are encouraging, the use of germline *BRIP1*, *RAD51C*, *RAD51D*, and *NBN* variant status to guide maintenance and therapy continues to be elucidated in the clinical trial setting (e.g., NCT04171700; see Table 13). In contrast to undiagnosed women at increased familial risk of OC, women diagnosed with OC who undergo testing for *BRIP1*, *RAD51C*, *RAD51D*, and *NBN* germline variants do not yield clinically actionable results.

Section Summary: Individuals Diagnosed With Epithelial Ovarian Cancer

Despite some studies showing improved outcomes for OC patients with non-*BRCA* HRD gene variants such as *BRIP1*, *RAD51C*, and *RAD51D*, it is unclear how this knowledge would be used to alter the treatment of such patients, as companion diagnostics for approved therapies do not directly assess these genes and somatic testing is outside the scope of this evidence review. No direct evidence is available to support the clinical utility of genetic testing for *BRIP1*, *RAD51C*, *RAD51D*, and *NBN* germline variants in OC patients to guide their treatment management and no chain of evidence can be constructed at this time.

Summary of Evidence

For individuals without diagnosed EOC and in a family at risk of developing EOC who receive germline genetic testing for genes associated with hereditary OC (ie, *BRIP1*, *RAD51C*, and *RAD51D*), the evidence includes studies of clinical validity and studies of OC risk, including meta-analyses. Relevant outcomes are OS, disease-specific survival, and test validity. Evidence supporting clinical validity was obtained from numerous studies reporting RR or 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 (ie, *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 VUS. 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 , ie, BRIP1, RAD51C, RAD51D, and NBN gene variants 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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society for Clinical Oncology

In 2020 , the American Society for Clinical Oncology (ASCO) issued guidelines regarding germline and somatic tumor testing for women with epithelial ovarian cancer (EOC).[41,] A systematic review evaluating 19 systematic reviews of observational data, consensus guidelines, and randomized controlled trials informed the guideline recommendations. The ASCO Expert Panel recommends that germline sequencing of *BRCA1* and *BRCA2* be performed in the context of a multi-gene panel. This multi-gene panel should, at minimum, additionally include *RAD51C, RAD51D, BRIP1, MLH1, MSH2, MSH6, PMS2*, and *PALB2*. For women who do not carry a germline pathogenic/likely-pathogenic *BRCA1/2* mutation, somatic tumor testing for *BRCA1/2* is recommended. The guideline recommendations state that women with EOC should be offered testing at the time of diagnosis as this has implications for therapeutic decision-making.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines on genetic/familial high-risk assessment for breast, ovarian, and pancreatic cancer (v.2.2022) review single-gene tests for *BRIP1*, *RAD51C*, *RAD51D*, and *NBN*.[15,] However, the inclusion of thesegenes in the guidelines does not imply endorsement for or against multi-gene testing for moderate-penetrance genes. Based on estimates of lifetime risk of ovarian cancer (OC) in carriers of pathogenic/likely pathogenic variants in *BRIP1*, *RAD51C*, or *RAD51D* from available studies, there appears to be sufficient evidence to justify consideration of risk-reducing salpingo-oophorectomy (RRSO). However, while the current evidence is insufficient to firmly recommend an optimal age for risk-reducing surgery, based on the limited evidence base, the guidelines recommend that a discussion regarding RRSO should be held around 45 to 50 years of age or earlier based on specific family history of an earlier onset of OC. While the guidelines state that these genes may be associated with a potential increase in triple-negative breast cancer, there is currently insufficient evidence for breast cancer risk management. For *NBN*, the guidelines state that there is insufficient data to define absolute risk of epithelial ovarian cancer and recommend that patients with these variants be managed based on family history. Counseling regarding risk of autosomal recessive transmission of Nijmegen breakage syndrome to offspring is also recommended.

The NCCN guidelines on on EOC (v.3.2022) provide primary treatment recommendations for patients with stage IA-IV disease.[40,] For those desiring fertility with stage IA or IB disease, unilateral and bilateral salpingo-oophorectomy with comprehensive surgical staging are recommended, respectively. For stage IA-IV patients not desiring fertility where optimal cytoreduction is likely, hysterectomy and bilateral salpingo-oophorectomy are recommended in combination with debulking as needed. For surgical candidates, germline and somatic testing is recommended following surgery. For poor surgical candidates or those with a low likelihood of optimal cytoreduction, neoadjuvant therapy is recommended with genetic risk evaluation. The guidelines note that *BRCA1/2* status may inform maintenance therapy. In the absence of a *BRCA1/2* mutation, homologous recombination deficiency status may guide therapy with poly(ADP-ribose) polymerase (PARP) inhibitors.

Society of Gynecologic Oncology

In 2013, the Society of Gynecologic Oncology (SGO) issued a clinical practice statement with recommendations concerning salpingectomy for OC prevention.[48,] For women who have *BRCA1* or *BRCA2* germline mutations, counseling regarding bilateral RRSO after completion of

childbearing is recommended. For women who choose to delay or forego RRSO, counseling regarding risk-reducing salpingectomy when childbearing is complete is recommended, followed by oophorectomy at a future date, although data on the safety of this approach are limited. For women who are at average, population risk of OC, risk-reducing salpingectomy should be considered with patients at the time of abdominal or pelvic surgery, hysterectomy, or in place of tubal ligation.

U.S. Preventive Services Task Force Recommendation

No U.S. Preventive Services Task Force recommendations for *BRIP1*, *RAD51C, RAD51D*, or *NBN* variant testing have been identified.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 13.

Table 13. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02489006	A Phase II, Open-Label, Randomized, Multi-Centre Study, of Neoadjuvant Olaparib in Patients With Platinum Sensitive Recurrent High Grade Serous Ovarian/Primary Peritoneal or Fallopian Tube Cancer (NEO)	71	Dec 2024 (recruiting)
NCT04009148	Cascade Testing in Families With Newly Diagnosed Hereditary Breast and Ovarian Cancer Syndrome	300	Mar 2024 (recruiting)
NCT04171700[a]	A Phase 2 Multicenter, Open-label Study of Rucaparib as Treatment for Solid Tumors Associated With Deleterious Mutations in Homologous Recombination Repair Genes (LODESTAR)	220	Jun 2022 (ongoing)
NCT03294343	Risk-Reducing Surgeries of Salpingo-oophorectomy With/Without Hysterectomy for Carriers With Mutation Genes of Hereditary Ovarian Cancer	600	Sep 2023 (recruiting)
NCT03246841	Investigation of Tumour Spectrum, Penetrance and Clinical Utility of Germline Mutations in New Breast and Ovarian Cancer Susceptibility Genes (TUMOSPEC)	500	Dec 2023 (recruiting)
NCT04294927	TUBectomy With Delayed Oophorectomy as Alternative for Risk-reducing Salpingo-oophorectomy in High Risk Women to Assess the Safety of Prevention (TUBA-WISP II)	3000	Feb 2040 (recruiting)
NCT02760849	Women Choosing Surgical Prevention (WISP)	374	May 2042 (ongoing)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration), including cancer history (or lack of cancer)
  - Family history, if applicable, including untested close family relatives who may be at increased genetic risk of ovarian cancer, or who have already been tested (including results)
  - Family relationship(s): (maternal or paternal), (family member [e.g., sibling, aunt, grandparent]), (living or deceased) ((if applicable)
  - Site(s) of cancer if applicable
  - Age at diagnosis (including family members)
  - Reason for test
  - Pertinent past procedural and surgical history
  - Past and present genetic test results if applicable

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0102U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (17 genes [sequencing and deletion/duplication])
	0103U	Hereditary ovarian cancer (e.g., hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (24 genes [sequencing and deletion/duplication], EPCAM [deletion/duplication only])
	0131U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure)
	0132U	Hereditary ovarian cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes) (List separately in addition to code for primary procedure)
	0134U	Hereditary pan cancer (e.g., hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (18 genes) (List separately in addition to code for primary procedure)
	0135U	Hereditary gynecological cancer (e.g., hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (12 genes) (List separately in addition to code for primary procedure)
	81432	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
11/01/2020	New policy.
03/01/2021	Administrative update.
10/01/2021	Annual review. Policy statement, guidelines and literature updated. Policy title changed from Molecular Testing for Variants Associated with Hereditary Ovarian Cancer to current one.
10/01/2022	Annual review. Policy statement, guidelines and literature updated. Policy title changed from Molecular Testing for Germline *BRIP1*, *RAD51C*, and *RAD51D* Variants Associated with Ovarian Cancer to current one.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.
Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
Molecular Testing for Germline *BRIP1*, *RAD51C*, and *RAD51D* Variants Associated with Ovarian Cancer 2.04.149 **Policy Statement:** Testing for **germline** (not somatic) *BRIP1*, *RAD51C*, and *RAD51D* variants for ovarian cancer risk assessment in adults may be considered **medically necessary** when **either** of the following criteria are met: I. The individual has a diagnosis of epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer and have **both** of the following: A. The individual has not previously been tested for these gene variants B. The individual has closely related (first- and/or second-degree) relatives who may be at increased risk of developing hereditary ovarian cancer II. The individual has not been diagnosed with epithelial ovarian cancer and has **either** of the following: A. The individual has any blood relative with a known pathogenic or likely pathogenic germline *BRIP1*, *RAD51C*, or *RAD51D* variant B. The individual has a first- or second-degree relative diagnosed with ovarian cancer Testing for germline *BRIP1*, *RAD51C*, and *RAD51D* 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** (unless part of a limited panel that meets	Germline Genetic Testing for Ovarian Cancer Risk (BRIP1, RAD51C, RAD51D, NBN) 2.04.149 **Policy Statement:** I. Testing for **germline** (not somatic) *BRIP1*, *RAD51C*, and *RAD51D* variants for ovarian cancer risk assessment in adults may be considered **medically necessary** when **either** of the following criteria are met: II. The individual has a diagnosis of epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer and have **both** of the following: A. The individual has not previously been tested for these gene variants B. The individual has closely related (first- and/or second-degree) relatives who may be at increased risk of developing hereditary ovarian cancer III. The individual has not been diagnosed with epithelial ovarian cancer and has **either** of the following: A. The individual has any blood relative with a known pathogenic or likely pathogenic germline *BRIP1*, *RAD51C*, or *RAD51D* variant B. The individual has a first- or second-degree relative diagnosed with ovarian cancer IV. Individual testing for germline NBN variants for ovarian cancer risk assessment in adults is considered investigational. but can be allowed when part of an otherwise approved small panel. Testing for germline *BRIP1*, *RAD51C*, and *RAD51D* 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** (unless part of a limited panel that meets

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
criteria for medical necessity for germline testing under another policy (e.g., Blue Shield of California Medical Policy: Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers, or Blue Shield of California Medical Policy: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes). Testing for germline *BRIP1*, *RAD51C*, and *RAD51D* variants in adults who do not meet the criteria above is considered **investigational** unless included in a panel test that is approved for another reason. **NOTE**: This policy does not address BRCA 1&2 testing. Germline genetic testing for BRCA1 and BRCA2 is addressed separately in Blue Shield of California Medical Policy: Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers; genes associated with Lynch syndrome (see Blue Shield of California Medical Policy: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes) or other genes with a possible association with ovarian cancer.	criteria for medical necessity for germline testing under another policy (e.g., Blue Shield of California Medical Policy: Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers, or Blue Shield of California Medical Policy: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes). Testing for germline *BRIP1*, *RAD51C*, and *RAD51D* and NBN variants in adults who do not meet the criteria above is considered **investigational** unless included in a panel test that is approved for another reason. **NOTE**: This policy does not address BRCA 1&2 testing. Germline genetic testing for BRCA1 and BRCA2 is addressed separately in Blue Shield of California Medical Policy: Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers; genes associated with Lynch syndrome (see Blue Shield of California Medical Policy: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes) or other genes with a possible association with ovarian cancer.