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, RAD51D, and NBN variants for ovarian cancer risk 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: Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2); 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, first- and second-degree relatives are blood relatives on the same side of the family (maternal or paternal):
- First-degree relatives: parents, siblings, and children
• Second-degree relatives: grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.

**Recommended Genetic Testing Strategies**

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

- In individuals with a known familial germline *BRIP1*, *RAD51C*, or *RAD51D* variant, targeted testing for the specific variant is recommended.
- In individuals with an unknown familial germline *BRIP1*, *RAD51C*, or *RAD51D* variant:
  - To identify clinically significant variants, the National Comprehensive Cancer Network (NCCN) advises testing a relative who has early-onset disease, bilateral disease, or multiple primaries, because that individual has the highest likelihood of obtaining an informative, positive test result. This individual, the first-affected individual in a family who brings a genetic disorder to the attention of the medical community, is commonly referred to as the proband.
  - Testing undiagnosed, at-risk family members when a diagnosed relative is unavailable for testing, is unwilling to undergo testing, or is unwilling to share genetic testing results, should still be considered. However, indeterminate genetic testing results may be poorly understood by family members (Himes et al [2019]; PMID 31199558). 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 Blue Shield of California Medical Policy: Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (*BRCA1*, *BRCA2*, *PALB2*)

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 for *ATM* in the context of hereditary breast cancer is addressed separately in Blue Shield of California Medical Policy: Germline Genetic Testing for Gene Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk (CHEK2, ATM, and BARD1). NCCN recommends that *ATM* carriers at risk for epithelial ovarian cancer should be managed based on family history alone.

**Testing Undiagnosed, At-Risk Individuals**

In unaffected (i.e., undiagnosed), at-risk family members of potential *BRIP1*, *RAD51C*, or *RAD51D* variant families, most test results will be negative and uninformative. Therefore, it is strongly recommended that an affected (i.e., diagnosed) family member be tested first whenever possible to adequately interpret the test. Should a causative variant be found in an affected family member(s), DNA from an unaffected family member can be tested specifically for the same variant of the affected family member without having to sequence the entire gene. Interpreting test results for an unaffected family member without knowing the genetic status of the family may be possible in the case of a positive result for an established disease-associated variant but leads to difficulties in interpreting uninformative negative test results or VUS because the possibility of a causative variant is not ruled out (Himes et al [2019]; PMID 31199558). Non-actionable VUS are highly prevalent with multi-gene testing, which may be avoided with targeted testing for a known familial variant (Tung et al [2016]; PMID: 27296296).

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**

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>
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, RAD51D, NBN, 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, RAD51D, and NBN carriers is increased approximately 3- to 19-fold, 3- to 6-fold, 5- to 12-fold, and 2- to 3.5-fold respectively. Risk estimates may be higher in patients with a family history of OC or a family history of a specific gene variant.

Related Policies

- Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing
- Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
- Germline Genetic Testing for Gene Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk (CHEK2, ATM, and BARD1)
- Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

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, RAD51D, and NBN testing are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories offering to test and voluntarily list are available through the National Center for Biotechnology Genetic Testing Registry. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

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

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

\section*{Rationale}

\subsection*{Background}

\subsubsection*{Ovarian Cancer and Genetics}

In 2023, it is estimated that there will be 19,710 new diagnosed cases of ovarian cancer (OC) and that an estimated 13,270 women will die from their disease.\textsuperscript{1} 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 1.1\% of women in the United States will be diagnosed with OC in their lifetime.\textsuperscript{2}

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.\textsuperscript{3,4} 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 more 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 \textit{BRCA1} and \textit{BRCA2} genes which regulate DNA repair. It is estimated that high penetrance variants in \textit{BRCA1} and \textit{BRCA2} genes account for \textasciitilde27\% of familial OC cases.\textsuperscript{5}

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.\textsuperscript{3,4} Other mechanisms of HRD lead to a phenotype known as \textit{BRCA}ness, and include germline and somatic mutations in genes related to homologous recombination, epigenetic modifications, and \textit{EMSY} amplification or overexpression. Homologous recombination-related genes with a documented association with OC risk include \textit{BRIP1}, \textit{RAD51C}, and \textit{RAD51D}, and may represent the most important OC predisposition genes after \textit{BRCA1/2}. Hereditary OC risk may also be influenced by mismatch repair genes and variants in \textit{PALB2}, \textit{BRIP1}, \textit{RAD51C}, and \textit{RAD51D}, and the mismatch repair genes are estimated to contribute to 10\% of hereditary OC cases.\textsuperscript{5} 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 \textit{BRCA1}/\textit{BRCA2} and \textit{PALB2} is addressed separately in Blue Shield of California Medical Policy: Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (\textit{BRCA1}, \textit{BRCA2}, \textit{PALB2}).

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.

Penetrance of Pathogenic Variants

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

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

Determining Variant Pathogenicity

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

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

**BRIP1 Gene**

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

**RAD51 Genes**

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

**NBN Gene**

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

Identifying Women at Risk of an Inherited Susceptibility to Ovarian Cancer

Risk factors for OC include older age, early menarche or late menopause, family history of disease, genetic factors, nulliparity, endometriosis, and exposure to asbestos. Risk assessed through family history is dependent on the number and closeness of affected relatives, the age at which cancer
developed, and if other cancers occurred (e.g., breast). For a 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), 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.

**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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA [Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual]; Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

**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 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. 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. 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
Germline Genetic Testing for Ovarian Cancer Risk (BRIP1, RAD51C, RAD51D, NBN)

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. Study designs included family-based case-control and population-based or multicenter case-control. 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. 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 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. 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. 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. 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). 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. 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=0.01). 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=0.0005). 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. The study identified 215 women with pathogenic RAD51C variants from 125 families (n=1784) 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=5×10^-40) for RAD51C and 7.60 (95% CI, 5.61 to 10.30; p=5×10^-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 to 69 years and decreased thereafter. A similar trend was observed for RAD51D pathogenic variant carriers, with relative risk peaking at 50 to
59 years. In a model assuming a residual familial polygenic 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. Overall, 91.4% of OC cases were unselected for family history. Additionally, 2000 unaffected (i.e., 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). RAD51C 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. An additional 2167 unaffected women who had previously tested negative 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 x 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. 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 LoF counterparts.

Rafnar et al (2011) identified approximately 16 million sequence variants through whole-genome sequencing of 457 Icelanders. 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 x 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 x 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. 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.\(^3\) Cases were negative for BRCA1/2 mutations. One novel missense mutation (p.Ala745Thr) and 2 previously described missense mutations (p.Val193Ile 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.\(^3\)

**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.\(^3\) 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**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>N</th>
<th>Families</th>
<th>Variants</th>
<th>Totals</th>
<th>P/LP Variants Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lhotova et al</td>
<td>2020</td>
<td>Czech Republic</td>
<td>Population-based CC</td>
<td>3611</td>
<td>10</td>
<td>5</td>
<td>1333</td>
<td>2278</td>
</tr>
<tr>
<td>Weber-Lasalle et al</td>
<td>2018</td>
<td>Germany</td>
<td>Population-based CC</td>
<td>9236</td>
<td>18;</td>
<td>17</td>
<td>2189</td>
<td>706; 611</td>
</tr>
<tr>
<td>Lilyquist et al</td>
<td>2017</td>
<td>U.S.</td>
<td>CC</td>
<td>7768</td>
<td>58</td>
<td>NR</td>
<td>7768</td>
<td>NR</td>
</tr>
<tr>
<td>Kuria et al</td>
<td>2017</td>
<td>U.S.</td>
<td>CC</td>
<td>95,561</td>
<td>36</td>
<td>NR</td>
<td>5020</td>
<td>51,200</td>
</tr>
<tr>
<td>Norquist et al</td>
<td>2016</td>
<td>U.S.</td>
<td>Multicenter CC</td>
<td>42,491</td>
<td>26</td>
<td>60</td>
<td>1915</td>
<td>36,276</td>
</tr>
<tr>
<td>Ramus et al</td>
<td>2015</td>
<td>Multinational CC</td>
<td>Multicenter CC</td>
<td>6861</td>
<td>30</td>
<td>3</td>
<td>3277</td>
<td>3444</td>
</tr>
</tbody>
</table>

CC: case-control; NR: not reported; OC: ovarian cancer; 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 the Exome Aggregation Consortium.
### Table 2. Measures of Association and Penetrance for Ovarian Cancer and *BRIP1*

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Analysis</th>
<th>RR or OR (95% CI)</th>
<th>Age; Penetrance, % (95% CI)</th>
<th>Mean (Median) Age at Onset, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lhotova et al (2020)²²</td>
<td>2020</td>
<td>Standard CC</td>
<td>3.5 (1.1 to 13)</td>
<td>NR</td>
<td>58.0 (Range: 30-71)</td>
</tr>
<tr>
<td>Weber-Lasalle et al (2018)²³</td>
<td>2018</td>
<td>Standard CC</td>
<td>19.17 (11.13 to 33.03); 20.97 (12.02 to 36.57)</td>
<td>NR</td>
<td>54 (Range: 20-93); 54 (Range: 20-93)</td>
</tr>
<tr>
<td>Kurian et al (2017)²⁶</td>
<td>2017</td>
<td>Standard CC</td>
<td>2.62 (1.72 to 3.98)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ramus et al (2015)²⁸</td>
<td>2015</td>
<td>Standard CC &amp; SEG</td>
<td>11.22 (3.22 to 34.10) (CC); 3.41 (2.12 to 5.54) (SEG)</td>
<td>80; 5.8 (3.6 to 9.1)²²²³</td>
<td>58 (Range: 18-91)</td>
</tr>
</tbody>
</table>

CC: case-control; CI: confidence interval; EOC: endothelial ovarian cancer; NR: not reported; OC: ovarian cancer; OR: odds ratio; RR: relative risk; SEG: segregation analysis.

⁴ 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.

⁵ Reflects cases compared to controls from the Exome Aggregation Consortium.

⁶ 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>N</th>
<th>Families</th>
<th>Variants</th>
<th>Totals</th>
<th>P/LP Variants Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al (2020)²²</td>
<td>2020</td>
<td>Multinational</td>
<td>Multicenter, family-based CC</td>
<td>NR</td>
<td>6178</td>
<td>125b</td>
<td>6178b</td>
<td>125b 2.02²²</td>
</tr>
<tr>
<td>Lhotova et al (2020)²²</td>
<td>2020</td>
<td>Czech Republic</td>
<td>Population-based CC</td>
<td>3611</td>
<td>13</td>
<td>4</td>
<td>1333</td>
<td>13 0.98</td>
</tr>
<tr>
<td>Lilyquist et al (2017)²⁵</td>
<td>2017</td>
<td>U.S. CC</td>
<td></td>
<td>7768</td>
<td>44</td>
<td>NR</td>
<td>6294</td>
<td>44 0.79</td>
</tr>
<tr>
<td>Kurian et al (2017)²⁶</td>
<td>2017</td>
<td>U.S. CC</td>
<td></td>
<td>95561</td>
<td>32</td>
<td>NR</td>
<td>5020 51,200</td>
<td>32 0.64</td>
</tr>
<tr>
<td>Song et al (2015)²³</td>
<td>2015</td>
<td>Multinational</td>
<td>Multicenter CC</td>
<td>6201</td>
<td>14</td>
<td>2</td>
<td>3429 2772</td>
<td>14 0.41</td>
</tr>
</tbody>
</table>

CC: case-control; NR: not reported; P/LP: pathogenic/likely-pathogenic.

⁴ Reflects cases compared to controls from the Exome Aggregation Consortium.

⁵ Reflects number of affected families with ovarian or breast cancer.
### Table 4. Measures of Association and Penetrance for Ovarian Cancer and RAD51C

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Analysis</th>
<th>RR or OR (95% CI)</th>
<th>Age: Penetrance, % (95% CI)</th>
<th>Mean (Median) Age at Onset, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al (2020)</td>
<td>2020</td>
<td>SEG</td>
<td>7.55 (5.60 to 10.19)</td>
<td>30; 0.02 (0.02 to 0.02)</td>
<td>NR</td>
</tr>
<tr>
<td>Lhotova et al (2020)</td>
<td>2020</td>
<td>Standard CC</td>
<td>5.7 (1.7 to 23.8)</td>
<td>NR</td>
<td>52.2 (Range: 25-69)</td>
</tr>
<tr>
<td>Kurian et al (2017)</td>
<td>2017</td>
<td>Standard CC</td>
<td>4.98 (3.09 to 8.04)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Norquist et al (2016)</td>
<td>2016</td>
<td>Standard CC</td>
<td>3.4 (1.5 to 7.6)</td>
<td>NR</td>
<td>64 (Range: 47-70)</td>
</tr>
<tr>
<td>Song et al (2015)</td>
<td>2015</td>
<td>Standard CC</td>
<td>5.2 (1.1 to 24)</td>
<td>50; 1.3 (0.3 to 6.0)</td>
<td>58.7</td>
</tr>
<tr>
<td>Loveday et al (2012)</td>
<td>2012</td>
<td>SEG</td>
<td>5.88 (2.91 to 11.88)</td>
<td>80; &gt;9 (NR)</td>
<td>NR</td>
</tr>
</tbody>
</table>

CC: case-control; CI: confidence interval; NR: not reported; OR: odds ratio; RR: relative risk; SEG: segregation analysis.

* Reflects cases compared to controls from the Exome Aggregation Consortium.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>N</th>
<th>Families Variants</th>
<th>Totals</th>
<th>P/LP Variants Identified</th>
<th>Cases</th>
<th>Controls</th>
<th>Cases</th>
<th>Controls</th>
<th>N</th>
<th>Prevalence Cases, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al (2020)</td>
<td>2020</td>
<td>Multinational</td>
<td>Multicenter, family-based CC</td>
<td>NR</td>
<td>6690</td>
<td>60b</td>
<td>6690b</td>
<td>NR</td>
<td>60b</td>
<td>0.89b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lhotova et al (2020)</td>
<td>2020</td>
<td>Czech Republic</td>
<td>Population-based CC</td>
<td>3611</td>
<td>13</td>
<td>2</td>
<td>1333</td>
<td>2278</td>
<td>0.98</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lilyquist et al (2017)</td>
<td>2017</td>
<td>U.S.</td>
<td>CC</td>
<td>7768</td>
<td>11</td>
<td>NR</td>
<td>6294</td>
<td>NR</td>
<td>0.31</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kurian et al (2017)</td>
<td>2017</td>
<td>U.S.</td>
<td>CC</td>
<td>95561</td>
<td>9</td>
<td>NR</td>
<td>5020</td>
<td>51,200</td>
<td>0.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norquist et al (2016)</td>
<td>2016</td>
<td>U.S.</td>
<td>Multicenter CC</td>
<td>42491</td>
<td>11</td>
<td>14</td>
<td>1915</td>
<td>36,276</td>
<td>0.57</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Song et al (2015)</td>
<td>2015</td>
<td>Multinational</td>
<td>Multicenter CC</td>
<td>6201</td>
<td>12</td>
<td>1</td>
<td>3429</td>
<td>2772</td>
<td>0.35</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CC: case-control; NR: not reported; P/LP: pathogenic/likely-pathogenic.

* Reflects cases compared to controls from the Exome Aggregation Consortium.

b Reflects number of affected families with ovarian or breast cancer.
## Table 6. Measures of Association and Penetrance for Ovarian Cancer and RAD51D

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Analysis</th>
<th>RR or OR (95% CI)</th>
<th>Age: Penetrance, % (95% CI)</th>
<th>Mean (Median) Age at Onset, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al (2020)27</td>
<td>2020</td>
<td>SEG</td>
<td>7.60 (5.61 to 10.30)</td>
<td>30; 0.02 (0.02 to 0.02)</td>
<td>NR</td>
</tr>
<tr>
<td>Lhotova et al (2020)22</td>
<td>2020</td>
<td>Standard CC</td>
<td>11.3 (2.6 to 103.4)</td>
<td>NR</td>
<td>56.0 (Range: 36-69)</td>
</tr>
<tr>
<td>Kurian et al (2017)26</td>
<td>2017</td>
<td>Standard CC</td>
<td>4.78 (2.13 to 10.7)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Norquist et al (2016)24</td>
<td>2016</td>
<td>Standard CC</td>
<td>10.9 (4.6 to 26.0)</td>
<td>NR</td>
<td>54 (Range: 35-75)</td>
</tr>
<tr>
<td>Song et al (2015)19</td>
<td>2015</td>
<td>Standard CC</td>
<td>12 (1.5 to 90)</td>
<td>50; 3.0 (0.4 to 21) 70; 12 (1.5 to 60)</td>
<td>58.7</td>
</tr>
<tr>
<td>Loveday et al (2011)21</td>
<td>2011</td>
<td>SEG</td>
<td>6.30 (2.86 to 13.85)</td>
<td>80; -10 (NR)</td>
<td>NR</td>
</tr>
</tbody>
</table>

CC: case-control; CI: confidence interval; NR: not reported; OR: odds ratio; RR: relative risk; SEG: segregation analysis.

*Reflects cases compared to controls from the Exome Aggregation Consortium.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>N Families</th>
<th>Variants</th>
<th>Totals</th>
<th>P/LP Variants Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lhotova et al (2020)22</td>
<td>2020</td>
<td>Czech Republic</td>
<td>Population-based CC</td>
<td>3611</td>
<td>14 7</td>
<td>1333 2278</td>
<td>14 1.06</td>
</tr>
<tr>
<td>Lilyquist et al (2017)25</td>
<td>2017</td>
<td>U.S.</td>
<td>CC</td>
<td>7768</td>
<td>22 NR</td>
<td>6294 NR</td>
<td>22 0.38</td>
</tr>
<tr>
<td>Kurian et al (2016)26</td>
<td>2017</td>
<td>U.S.</td>
<td>CC</td>
<td>95561</td>
<td>17 NR</td>
<td>5020 51,200</td>
<td>17 0.34</td>
</tr>
<tr>
<td>Norquist et al (2016)24</td>
<td>2016</td>
<td>U.S.</td>
<td>Multicenter CC</td>
<td>42491</td>
<td>9 49</td>
<td>1915 36,276</td>
<td>9 0.47</td>
</tr>
<tr>
<td>Ramus et al (2015)18</td>
<td>2015</td>
<td>Multinational</td>
<td>Multicenter CC</td>
<td>6861</td>
<td>9 8</td>
<td>3248 3439</td>
<td>9 0.28</td>
</tr>
</tbody>
</table>

CC: case-control; NR: not reported; P/LP: pathogenic/likely-pathogenic.

*Reflects cases compared to controls from the Exome Aggregation Consortium.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Analysis</th>
<th>RR or OR (95% CI)</th>
<th>Age: Penetrance, % (95% CI)</th>
<th>Mean (Median) Age at Onset, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lhotova et al (2020)22</td>
<td>2020</td>
<td>Standard CC</td>
<td>3.5 (1.3 to 10.2)</td>
<td>NR</td>
<td>54.5 (Range: 18-76)</td>
</tr>
<tr>
<td>Lilyquist et al (2017)25</td>
<td>2017</td>
<td>Standard CC</td>
<td>2.03 (1.27 to 3.08)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
Study | Year | Analysis | RR or OR (95% CI) | Age: Penetrance, % (95% CI) | Mean (Median) Age at Onset, y
---|---|---|---|---|---
Kurian et al (2016) | 2017 | Standard CC | 1.85 (1.05 to 3.24) | NR | NR
Norquist et al (2016) | 2016 | Standard CC | 2.3 (0.99 to 5.4)* | NR | NR

CC: case-control; CI: confidence interval; NR: not reported; OR: odds ratio; RR: relative risk; SEG: segregation analysis.

* Reflects cases compared to controls from the Exome Aggregation Consortium.

### Table 9. Study Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Duration of Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al (2020)</td>
<td>4. Family-based case-control population of OC and breast cancer cases in breast-ovarian pedigrees (and controls); likely overestimated risk</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lhotova et al (2020)</td>
<td>4. Case-control population of Czech OC patients (and controls), likely overestimated risk</td>
<td>1. Not clear which variants were included</td>
<td>2. Noncancer and unselected controls included individuals with known (negative) or unknown family histories and male subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weber-Lasalle et al (2018)</td>
<td>4. Case-control population of German OC and breast cancer patients (and controls), likely overestimated risk; above average prevalence rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lilyquist et al (2017)</td>
<td>4. Case-control population of Caucasian OC patients referred for hereditary multi-gene panel testing (and controls); likely overestimated risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kurian et al (2017)</td>
<td>4. Case-control population of OC and breast cancer</td>
<td>1. Not clear which variants were included</td>
<td>1. Control chosen from patients being</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Population</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Outcomes</td>
<td>Duration of Follow-Up</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>------------</td>
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<td>-----------------------</td>
</tr>
<tr>
<td>Norquist et al (2016)</td>
<td>patients referred for hereditary multi-gene panel testing (and controls); likely overestimated risk</td>
<td>4. Case-control population of OC patients unselected for age or family history (and controls); likely overestimated risk</td>
<td></td>
<td>tested for hereditary cancer; unclear how many developed cancer</td>
<td></td>
</tr>
<tr>
<td>Ramus et al (2015)</td>
<td>4. Multicenter case-control population of OC patients (and controls); likely overestimated risk</td>
<td></td>
<td>1. Unclear how many women in UKFOCSS cohort developed cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Song et al (2015)</td>
<td>4. Multicenter case-control population of OC patients (and controls); likely overestimated risk</td>
<td></td>
<td>1. Unclear how many women in UKFOCSS cohort developed cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loveday et al (2012)</td>
<td>4. Family-based case-control population of OC cases in breast-ovarian pedigrees (and controls); likely overestimated risk</td>
<td>4. Family-based case-control population of OC cases in breast-ovarian pedigrees (and controls); likely overestimated risk</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Loveday et al (2011)</td>
<td>4. Family-based case-control population of OC cases in breast-ovarian pedigrees (and controls); likely overestimated risk</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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.

* 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.
* 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.
* 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).

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection*</th>
<th>Blinding*</th>
<th>Delivery of Test*</th>
<th>Selective Reporting*</th>
<th>Data Completeness*</th>
<th>Statistical†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al (2020)²⁷</td>
<td>1. Selection not fully described</td>
<td></td>
<td>1. Registration not reported</td>
<td>1. Incomplete description of disposition of eligible patients/samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lhotova et al (2020)²²</td>
<td>1. Selection of population-matched controls not fully described</td>
<td></td>
<td>1. Registration not reported</td>
<td>1. Incomplete description of family history subgroups and eligible dispositions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weber-Lasalle et al (2018)²³</td>
<td>1. Selection of geographically-matched controls not fully described</td>
<td></td>
<td>1. Registration not reported</td>
<td>1. Incomplete description of disposition of eligible patients/samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lilyquist et al (2017)²⁵</td>
<td>1. Selection of controls not fully described</td>
<td></td>
<td>1. Registration not reported; number of controls unknown</td>
<td>1. No description of disposition of eligible patients for multi-gene panel testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kurian et al (2017)²⁶</td>
<td></td>
<td></td>
<td>1. Registration not reported</td>
<td>1. No description of disposition of eligible patients/samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norquist et al (2016)²⁴</td>
<td>1. Selection not fully described</td>
<td></td>
<td>1. Registration not reported</td>
<td>1. No description of disposition of eligible patients/samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramus et al (2015)¹⁸</td>
<td>1. Selection not fully described</td>
<td></td>
<td>1. Registration not reported</td>
<td>1. Incomplete description of disposition of eligible patients/samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Song et al (2015)¹⁹</td>
<td>1. Selection not fully described</td>
<td></td>
<td>1. Registration not reported</td>
<td>1. Incomplete description of disposition of eligible patients/samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loveday et al (2012)²⁰</td>
<td>1. Selection not fully described</td>
<td></td>
<td>1. Registration not reported</td>
<td>1. Incomplete description of disposition of eligible patients/samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loveday et al (2011)²¹</td>
<td>1. Selection not fully described</td>
<td></td>
<td>1. Registration not reported</td>
<td>1. Incomplete description of disposition of eligible patients/samples</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

*Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
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 OC 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. Combined surveillance methods have been associated with an unneeded rate of diagnostic surgery of 55% and significantly higher cancer-related distress. OC screening has not been shown to reduce mortality among women at risk of hereditary disease. 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.

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 years would gain an expected 0.3 years with a prophylactic oophorectomy. 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), 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

<table>
<thead>
<tr>
<th>Risk Level and Strategy</th>
<th>Age of Carrier, y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30</td>
</tr>
<tr>
<td>5% Risk of Ovarian Cancer</td>
<td></td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>0.3</td>
</tr>
<tr>
<td>Oophorectomy delayed 10 years</td>
<td>0.2</td>
</tr>
<tr>
<td>20% Risk of Ovarian Cancer</td>
<td></td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>1.0</td>
</tr>
<tr>
<td>Oophorectomy delayed 10 years</td>
<td>0.8</td>
</tr>
<tr>
<td>40% Risk of Ovarian Cancer</td>
<td></td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>1.7</td>
</tr>
<tr>
<td>Oophorectomy delayed 10 years</td>
<td>1.2</td>
</tr>
</tbody>
</table>

1 Adapted from Schrag et al (1997).

Tung et al (2016) developed a counseling framework for moderate-penetrance cancer-susceptibility mutations associated with OC risk, including BRIPI, RAD51C, and RAD51D genes. Cumulative lifetime risk (CLTR) (i.e., 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) and Song et al (2015). 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 versus 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 BRIPI, 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 BRIPI, RAD51C, and RAD51D mutation carriers that warrants consideration of RRSO. However, since 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 to 55 years for BRIPI, 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 to 50 years of age or earlier based on specific family history of an earlier onset of OC.

Table 12. Estimated Ovarian Cancer Cumulative Risks According to BRIPI, RAD51C, and RAD51D Mutations

<table>
<thead>
<tr>
<th>Patient Age, y</th>
<th>Cumulative Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>US Population</td>
</tr>
</tbody>
</table>

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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, 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. 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 years and died at 52 years has an estimated 10.4% risk of OC by age 80 years 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 years; this risk increases to 18% if both mother and daughter test positive for a RAD51D variant.

Therefore, it is strongly recommended that an affected (i.e., diagnosed) family member be tested first whenever possible to adequately interpret genetic testing of the unaffected (i.e., undiagnosed) at-risk individual and to provide a more accurate risk assessment. 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. Non-actionable VUS are highly prevalent with multi-gene testing, which may be avoided with targeted testing for a known familial variant.

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. 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.\textsuperscript{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 \textit{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.\textsuperscript{15} Although tubal intraepithelial carcinoma (TIC), hypothesized to serve as an early precursor lesion for serous OC, appears to be more prevalent in \textit{BRCA} carriers, TIC has also been documented in patients with serous carcinomas unselected for family history or \textit{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 \textit{BRCA1} carriers, 3.5\% of \textit{BRCA2} carriers, and 0.5\% of non-carriers; \(p<.001\)).\textsuperscript{38} In a study of asymptomatic Slovenian women with P/LP \textit{BRCA4} variants (\(n=145\)) and \textit{BRCA4}-negative high-risk status (\(n=10\)) (i.e., 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 \textit{BRCA1}-positive women and 1 in a high-risk \textit{BRCA}-negative woman.\textsuperscript{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 \textit{BRIP1}, \textit{RAD51C}, and \textit{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 \textit{NBN} variants and OC risk was not consistently significant across studies and penetrance estimates are not available.

Pathogenic and likely pathogenic germline variants in \textit{BRIP1}, \textit{RAD51C}, and \textit{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 \textit{BRIP1}, \textit{RAD51C}, and \textit{RAD51D} germline variants is indirect, relying on studies of high-risk women and \textit{BRCA} carriers. In women at increased risk of hereditary OC who would consider preventive interventions, identifying a \textit{BRIP1}, \textit{RAD51C}, and \textit{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 \textit{NBN} germline variant testing since 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 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 to 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. 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. 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). 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). In 2022, O’Malley et al reported that out of 10 EOC patients with *RAD51C* and *RAD51D* alterations enrolled in ARIEL3, 60% derived exceptional benefit compared to patients harboring mutations in other non-*BRCA* homologous recombination repair genes. However, the relevance of these findings is unclear since only 3 of these patients had confirmed germline mutations. 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. 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 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.

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 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, since companion diagnostics for approved therapies do not directly

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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.

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.3.2023) review single-gene tests for BRIP1, RAD51C, and RAD51D.15, However, the inclusion of these genes 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. It is also recommended that RAD51C and RAD51D germline variant carriers receive annual mammograms and to consider breast magnetic resonance imaging (MRI) with contrast starting at age 40 years. Regarding NBN, the guideline states that there is insufficient evidence to make any recommendations for breast MRI, RRSO, or risk-reducing mastectomy.

The NCCN guidelines on EOC (v.2.2023) 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 provide information on the magnitude of benefit of 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. 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

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02489006</td>
<td>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)</td>
<td>71</td>
<td>Dec 2024 (ongoing)</td>
</tr>
<tr>
<td>NCT04009148</td>
<td>Cascade Testing in Families With Newly Diagnosed Hereditary Breast and Ovarian Cancer Syndrome</td>
<td>300</td>
<td>Mar 2025 (recruiting)</td>
</tr>
<tr>
<td>NCT03294343</td>
<td>Risk-Reducing Surgeries of Salpingo-oophorectomy With/Without Hysterectomy for Carriers With Mutation Genes of Hereditary Ovarian Cancer</td>
<td>600</td>
<td>Sep 2023 (recruiting)</td>
</tr>
<tr>
<td>NCT03246841</td>
<td>Investigation of Tumour Spectrum, Penetrance and Clinical Utility of Germline Mutations in New Breast and Ovarian Cancer Susceptibility Genes (TUMOSPEC)</td>
<td>500</td>
<td>Dec 2024 (recruiting)</td>
</tr>
<tr>
<td>NCT04294927</td>
<td>TUBectomy With Delayed Oophorectomy as Alternative for Risk-reducing Salpingo-oophorectomy in High Risk Women to Assess the Safety of Prevention (TUBA-WISP II)</td>
<td>3000</td>
<td>Feb 2040 (recruiting)</td>
</tr>
<tr>
<td>NCT02760849</td>
<td>Women Choosing Surgical Prevention (WISP)</td>
<td>374</td>
<td>May 2042 (ongoing)</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT04171700*</td>
<td>A Phase 2 Multicenter, Open-label Study of Rucaparib as Treatment for Solid Tumors Associated With Deleterious Mutations in Homologous Recombination Repair Genes (LODESTAR)</td>
<td>83/220</td>
<td>Jul 2022 (terminated due to change in development priorities)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
* Denotes industry-sponsored or cosponsored trial.
References


4. Suszynska M, Ratajska M, Kozlowski P. BRIP1, RAD51C, and RAD51D mutations are associated with high susceptibility to ovarian cancer: mutation prevalence and precise risk estimates based on a pooled analysis of ~30,000 cases. J Ovarian Res. May 02 2020; 13(1): 50. PMID 32359370


6. Domchek SM, Rebbeck TR. Preventive surgery is associated with reduced cancer risk and mortality in women with BRCA1 and BRCA2 mutations. LDI Issue Brief. 2010; 16(2): 1-4. PMID 21545057


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.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT*</td>
<td>0102U</td>
<td>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])</td>
</tr>
<tr>
<td></td>
<td>0103U</td>
<td>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])</td>
</tr>
<tr>
<td></td>
<td>0131U</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>0132U</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>0134U</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>0135U</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>81432</td>
<td>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</td>
</tr>
</tbody>
</table>

**HCPCS** None
Policy History

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/01/2020</td>
<td>New policy.</td>
</tr>
<tr>
<td>03/01/2021</td>
<td>Administrative update.</td>
</tr>
<tr>
<td>10/01/2022</td>
<td>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.</td>
</tr>
<tr>
<td>10/01/2023</td>
<td>Annual review. No change to policy statement. Literature review updated.</td>
</tr>
</tbody>
</table>

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](http://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.
## POLICY STATEMENT

<table>
<thead>
<tr>
<th>BEFORE</th>
<th>AFTER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Germline Genetic Testing for Ovarian Cancer Risk (BRIP1, RAD51C, RAD51D, NBN) 2.04.149</strong></td>
<td><strong>Germline Genetic Testing for Ovarian Cancer Risk (BRIP1, RAD51C, RAD51D, NBN) 2.04.149</strong></td>
</tr>
<tr>
<td><strong>Policy Statement:</strong></td>
<td><strong>Policy Statement:</strong></td>
</tr>
<tr>
<td>I. Testing for germline (not somatic) <em>BRIP1, RAD51C,</em> and <em>RAD51D</em> variants for ovarian cancer risk assessment in adults may be considered <strong>medically necessary</strong> when <strong>either</strong> of the following criteria are met:</td>
<td>I. Testing for germline (not somatic) <em>BRIP1, RAD51C,</em> and <em>RAD51D</em> variants for ovarian cancer risk assessment in adults may be considered <strong>medically necessary</strong> when <strong>either</strong> of the following criteria are met:</td>
</tr>
<tr>
<td>A. The individual has a diagnosis of epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer and have both of the following:</td>
<td>A. The individual has a diagnosis of epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer and have both of the following:</td>
</tr>
<tr>
<td>1. The individual has not previously been tested for these gene variants</td>
<td>1. The individual has not previously been tested for these gene variants</td>
</tr>
<tr>
<td>2. The individual has closely related (first- and/or second-degree) relatives who may be at increased risk of developing hereditary ovarian cancer</td>
<td>2. The individual has closely related (first- and/or second-degree) relatives who may be at increased risk of developing hereditary ovarian cancer</td>
</tr>
<tr>
<td>B. The individual has not been diagnosed with epithelial ovarian cancer and has <strong>either</strong> of the following:</td>
<td>B. The individual has not been diagnosed with epithelial ovarian cancer and has <strong>either</strong> of the following:</td>
</tr>
<tr>
<td>1. The individual has any blood relative with a known pathogenic or likely pathogenic germline <em>BRIP1, RAD51C,</em> or <em>RAD51D</em> variant</td>
<td>1. The individual has any blood relative with a known pathogenic or likely pathogenic germline <em>BRIP1, RAD51C,</em> or <em>RAD51D</em> variant</td>
</tr>
<tr>
<td>2. The individual has a <strong>first- or second-degree</strong> relative diagnosed with ovarian cancer</td>
<td>2. The individual has a <strong>first- or second-degree</strong> relative diagnosed with ovarian cancer</td>
</tr>
<tr>
<td>II. Individual testing for germline NBN variants for ovarian cancer risk assessment in adults is considered <strong>investigational</strong>, but can be allowed when part of an otherwise approved small panel.</td>
<td>II. Individual testing for germline <em>NBN</em> variants for ovarian cancer risk assessment in adults is considered <strong>investigational</strong>, but can be allowed when part of an otherwise approved small panel.</td>
</tr>
<tr>
<td>III. Testing for germline <em>BRIP1, RAD51C,</em> and <em>RAD51D</em> variants in individuals diagnosed with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer to guide treatment of the diagnosed individual is considered <strong>investigational</strong> (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</td>
<td>III. Testing for germline <em>BRIP1, RAD51C,</em> and <em>RAD51D</em> variants in individuals diagnosed with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer to guide treatment of the diagnosed individual is considered <strong>investigational</strong> (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</td>
</tr>
</tbody>
</table>
IV. Testing for germline BRIP1, RAD51C, 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.