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Management of individuals with heterozygous germline pathogenic variants in *RAD51C*, *RAD51D*, and *BRIP1*: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG)

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Conflict of Interest

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Additional Information

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Abstract

Purpose: *RAD51C*, *RAD51D* and *BRIP1* germline pathogenic variants (GPV) are associated with increased lifetime risks of tubo-ovarian cancer. Resources for managing *RAD51C*, *RAD51D* and *BRIP1* heterozygotes in clinical practice are limited.

Methods: An international workgroup developed a Clinical Practice Resource to guide management of *RAD51C*, *RAD51D* and *BRIP1* heterozygotes using peer-reviewed publications and expert opinion.

Results: *RAD51C*, *RAD51D* and *BRIP1* are moderate (intermediate) penetrance ovarian cancer predisposition genes. Ovarian cancer risks for individuals with *RAD51C*, *RAD51D* and *BRIP1* GPV may be influenced by family history and other modifiers. *RAD51C* and *RAD51D* GPV are also associated with moderate risk for breast cancer, predominantly triple-negative subtype. *RAD51C*, *RAD51D* and *BRIP1* heterozygotes should be offered risk reducing salpingo-oophorectomy close to the age of menopause based on age-specific risks and shared decision making. For *RAD51C* and *RAD51D* heterozygotes, enhanced breast surveillance may be indicated according to their personalized risk estimate and country-specific guidelines. Generally, risk-reducing mastectomy is not recommended. For *RAD51C*, *RAD51D* and *BRIP1* heterozygotes who develop cancer, there is insufficient evidence to guide any specific targeted treatment.

Conclusion: Systematic prospective data collection is needed to establish the outcomes of *RAD51C*, *RAD51D* and *BRIP1* associated cancers and particularly response to cancer treatment and survival.

Keywords

BRIP1 ; Cancer predisposition; Cancer risk; *RAD51C* ; *RAD51D*

Introduction

RAD51C (HGNC:9820), *RAD51D* (HGNC:9823) and *BRIP1* (HGNC:20473) are involved in the homologous recombination (HR) repair of DNA double-stranded breaks. Homologous recombination is a highly regulated DNA repair mechanism that ensures genomic integrity during cell division. Germline pathogenic and likely pathogenic variants (collectively referred to in this document as “germline pathogenic variants” (GPVs)) in *RAD51C*, *RAD51D* and *BRIP1* can cause genomic instability through loss of the wildtype allele, with potential malignant transformation.¹ Monoallelic GPV in *RAD51C*, *RAD51D* and *BRIP1* are associated with increased lifetime risks of cancer, predominantly epithelial ovarian, fallopian tube and primary peritoneal cancer (henceforth defined as ovarian cancer (OC)) (Table 1). Additionally, biallelic homozygous or compound heterozygous GPVs in *BRIP1* (FA-J/BACH1) and *RAD51C* (FA-O) cause Fanconi anemia.²

Currently, OC is the eighth most common cancer in women worldwide and accounted for 4.7% of cancer deaths in 2020.³ OC is known to be associated with family history. Individuals with a first-degree relative with OC have a 3-fold risk of OC compared to the general population.⁴ Approximately 20% of OC is due to an underlying monogenic cause.⁵ This is predominantly explained by GPVs in high-risk genes, such as *BRCA1* (HGNC:1100) and *BRCA2* (HGNC:1101). GPVs in other genes, such as *RAD51C*, *RAD51D* and *BRIP1* have also been implicated in OC risk, while a smaller proportion (ie, <3%) is explained by GPVs in the mismatch-repair genes associated with Lynch syndrome (*MLH1* (HGNC:7127), *MSH2* (HGNC:7325), *MSH6* (HGNC:7329)).⁶

A meta-analysis of 63 studies in patients with OC showed a prevalence of 149/23,802 (0.6%) for *RAD51C*, 94/22,787 (0.5%) for *RAD51D* and 200/22,494 (0.9%) for *BRIP1*.⁷ Among healthy controls, the BRIDGES study showed a prevalence of 26/50,703 (0.05%) for *RAD51C*, 25/50,703 (0.05%) for *RAD51D* and 75/50,703 (0.15%) for *BRIP1*.⁸ This is in line with data in unaffected Australian women that showed a prevalence of 0.04% for *RAD51C* and *RAD51D* and 0.17% for *BRIP1*.⁹ Though individually small, the sum of these numbers shows that a clinically meaningful number of women in the population harbor a GPV in one of these genes. Although *RAD51C*, *RAD51D* and *BRIP1* are generally considered moderate (also known as intermediate) risk OC-predisposition genes, the data indicate that OC cancer risks for heterozygotes can vary, influenced by the specific variant, family history and modifying genetic and non-genetic risk factors. Furthermore, cancers (other than OC) have been reported in *RAD51C*, *RAD51D* and *BRIP1* heterozygotes, such as breast cancer (BC). Challenges in unraveling the associated risks and making recommendations for clinical practice include: (1) varied estimates of penetrance depending on the study design and the population studied; (2) uncertainties about the tumor spectrum and characteristics; (3) the role of family history and other modifiers in cancer risk estimates; (4) the difficulties of establishing robust genotype/phenotype associations, particularly for those missense variants that may impart lower or higher risks than predicted truncating variants; and (5) the balance of OC risk and potential long term sequelae of an early surgical menopause due to risk-reducing interventions. Disentangling the available data and information and translating this into guidance for clinical practice has been both challenging and nuanced, similar to other moderate risk genes.^{10,11} Currently, there are consensus recommendations in the UK¹² and in Australia¹³ for management of individuals with *RAD51C*, *RAD51D* and *BRIP1* GPV.

Based on international guidelines, germline genetic testing of a panel of OC predisposition genes, including *RAD51C*, *RAD51D* and *BRIP1*, is currently standard practice in many countries in patients with OC due to the potential implications for patient management and cancer risk estimation and management for family members. Furthermore, rapid progress in genetic sequencing technologies has led to the use of germline or tumor multigene panel testing and/or tumor genome/exome sequencing with the possibility to identify *RAD51C*, *RAD51D* and *BRIP1* heterozygotes outside the setting of OC. As a result, there is a clinical need for consistent, evidence-based, pragmatic guidance for the management of these individuals in international clinical practice, specifically considering the clinical utility of personalized (rather than generalized) risk assessment and risk-reducing interventions based on age specific risks.

Methods

After proposal approval and review of potential or actual conflicts as per the relevant American College of Medical Genetics and Genomics (ACMG) policies, an international workgroup was identified, comprising members across North America, Europe, and Asia, including Australia, Singapore, the United States, Canada, the United Kingdom, Germany, and Spain, with expertise in clinical cancer genetics, genetic counseling, breast surgery, gynecologic surgery, and medical oncology. A biomedical librarian used a list of clinical areas in the management of *RAD51C*, *RAD51D* and *BRIP1* heterozygotes developed by

the workgroup to create the search strategy (see Supplemental Methods) and searched PubMed/MEDLINE (US National Library of Medicine) in March and April 2024. All reported disease-causing variants are referred to as GPV. Older (pre-2015) reported disease-associated *RAD51C*, *RAD51D* and *BRIP1* variants were not reclassified according to more modern criteria.

The workgroup met monthly via video conference calls beginning in February 2024 and participated in email discussion and review throughout the process. Section authors critically reviewed the literature search results and synthesized findings narratively. Additional relevant publications were included based on author judgment and expertise. Workgroup members independently drafted sections of the document commensurate with their area of expertise and reviewed the entire manuscript. Clinical management recommendations were derived by consensus from the literature resource and the collective expertise of the authors. Working and final drafts were reviewed and approved by members of the Professional Practice and Guidelines (PP&G) Committee and the ACMG Board of Directors. As per ACMG policy, a mature draft of the manuscript was sent to ACMG membership for review and comment. The workgroup reviewed the comments and revisions were made to the final manuscript, which was then approved by the PP&G Committee and the ACMG Board of Directors.

Germline pathogenic and likely pathogenic variants in *RAD51C*, *RAD51D* and *BRIP1*

GPVs in *RAD51C*, *RAD51D* and *BRIP1* are a rare but consistent finding in patients and families with OC and/or BC. Indeed, the frequency of GPVs have been estimated to be <2% for each gene (0.6–1.2% for *RAD51C*, 0.4–1.8% for *RAD51D* and 0.6–0.9% for *BRIP1*) with slight variations depending on the populations studied including cases with both OC and BC within the family, cases with OC only or BC only, and cases with prior negative testing for other more common hereditary breast and ovarian cancer (HBOC) predisposition genes, such as *BRCA1* and *BRCA2*.^{14–19}

Similar to other cancer predisposition genes where loss of function is a mechanism of disease, most of the GPVs identified in *RAD51C*, *RAD51D* and *BRIP1* are loss of function variants. According to ClinVar data (as of July 2024), frameshifts are the most common molecular consequence with nonsense and splice site variants representing most of the remaining GPVs for each gene.²⁰ This is consistent with findings from a recent meta-analysis by Suszynska et al, which identified the most prevalent GPVs found through multi-gene panels in patients with BC and/or OC largely of White and East Asian ethnicity to be NM_058216.3:c.1026+5_1026+7del and NM_058216.3:c.706–2A>G in *RAD51C*, NM_002878.4:c.694C>T p.(Arg232Ter) and NM_002878.4:c.270_271dup p.(Lys91fs) in *RAD51D* and NM_032043.3:c.2392C>T p.(Arg798Ter) in *BRIP1*.^{7,21} In contrast, only a small number of missense GPVs have been described including seven in *RAD51C*, one in *RAD51D* and three in *BRIP1* representing <1% of reported GPVs for each gene (ClinVar entries with multiple submitters as of July 2024).²⁰

Clinically relevant differences in cancer risk between truncating and missense variants have been reported in genes with intermediate cancer risk, such as *CHEK2*.¹⁰ Although some studies have suggested that truncating and missense variants are associated with different

risks,⁸ due to small numbers, similar genotype-phenotype correlations for *RAD51C*, *RAD51D* and *BRIP1* have not yet been fully characterized. Indeed, most case control studies have not stratified cancer risk analyses by variant type, which is likely due to the overall rarity of GPVs in these genes and, more specifically, the very low frequency of well-established missense GPVs.

Overall, the association with cancer risk has shown a clearer link for truncating variants but there is some evidence suggesting a particularly increased risk of cancer for some missense variants. Illustratively, the French-Canadian founder variant NM_002878.4:c.620C>T p.(Ser207Leu) in *RAD51D* has been associated with a significantly increased risk for ovarian high-grade serous carcinoma (HGSC; 3.8% cases vs 0.2% controls).²² A detailed list of missense GPVs and founder variants can be found in Supplemental Tables 1 and 2. HGNC gene ID and nomenclature for all variants described in the manuscript are listed in Supplemental Tables 3 and 4.

Regarding the location of GPVs within the genes, small clusters of GPVs have been recently mapped to specific genomic regions (eg, the Walker A motif in *RAD51C*).²³ However, germline pathogenic variation in the genes appears to be largely homogenous all along the primary structure of the proteins.

Challenges in variant interpretation

Intermediate penetrance is perhaps the greatest challenge in risk assessment of variants in *RAD51C*, *RAD51D* and *BRIP1*. This is in part due to the widely used ACMG/Association of Molecular Pathology (AMP) framework for classification of sequencing variants, which is better suited for the interpretation of variants in genes associated with early-onset, highly penetrant phenotypes.^{24,25} To address this problem, the ClinGen HBOC Variant Curation Expert Panel has developed specifications for the ACMG/AMP recommendations on classifications of variants in other HBOC genes with intermediate penetrance, such as *PALB2* and *ATM*.²⁶ However, similar recommendations for *RAD51C*, *RAD51D* or *BRIP1* have yet to be released.

Furthermore, proving co-segregation of the variant with the disease can be used to refine risk and to resolve the clinical significance of a variant. However, due to the lower penetrance in these genes, co-segregation of a variant with the disease is harder to establish within families, even with a history of BC or OC and usually requires statistical methods to detect.²⁷

The relative lack of functional data for variants in these genes is another contributing factor complicating variant interpretation (see also section on variants of uncertain significance below). The ACMG/AMP PM1 criterion provides moderate evidence of pathogenicity for variants occurring in well-established mutational hotspots. GPVs in *RAD51C*, *RAD51D* and *BRIP1* are generally dispersed over the entire genes⁷ and there is limited evidence regarding well-established hotspots or critically relevant functional domains without benign variation.^{7,28}

Population databases are useful in obtaining the frequencies of variants in large populations. However, in contrast with other cancer-predisposition genes in which pathogenic variation is more common and penetrant, specific allele frequency cut-offs have not been established for variants in *RAD51C*, *RAD51D* and *BRIP1*. In addition, these databases typically contain overrepresentation of evidence for variants in European populations, which disproportionately complicates the analysis of variants in diverse groups.^{29,30}

Variants of Uncertain Significance

Most hereditary cancer multigene panels used in clinical practice include the *RAD51C*, *RAD51D* and *BRIP1* genes, which has likely contributed to the numerous variants of uncertain significance (VUS) identified by laboratories around the world. This identification of VUS can lead to clinical uncertainty and ethical dilemmas regarding individualized management and genetic counseling. Conflicting interpretations of these variants by different laboratories can further complicate clinical decision-making, as noted by Balmaña et al.³¹ Variants classified as VUS in *RAD51C*, *RAD51D* and *BRIP1* are predominantly missense variants. Indeed, from all variant submissions to ClinVar, a public database that archives information on the relationship between human variations and diseases, VUS represent approximately half of the entries for each of these genes (*RAD51C* 47.2%, *RAD51D* 45.6%, *BRIP1* 51.1% in ClinVar as of September 2024) and even more variants in these genes have conflicting interpretations of pathogenicity.²⁰

Although variants in *BRCA1* and *BRCA2* are more easily characterized due to well-studied structural and functional properties, the impact of variants in *RAD51C*, *RAD51D* and *BRIP1* is usually less well understood.³² Many groups have performed functional assays to determine the pathogenicity of these variants. For example, Kolinjivadi et al demonstrated that certain *RAD51C* missense variants impair critical elements required for genomic stability including replication fork protection and HR while Sanoguera-Miralles et al highlighted the importance of analyzing splice-site variants, as many of these can lead to significant splicing anomalies and protein truncation.^{33,34} Focusing on *RAD51D* variation, Baldock et al identified specific GPVs in this gene that disrupt its interaction with *XRCC2*, which is critical for HR.³⁵ Lastly, Moyer et al highlighted that many missense variants in *BRIP1* render the protein hypomorphic or null, affecting its ability to repair DNA interstrand cross-links, underscoring the need for functional assays to assess the impact of these variants.³⁶ Most recently, saturation genome editing was used to functionally assess 9188 unique *RAD51C* variants, representing nearly all possible coding sequence single-nucleotide alterations. This study allowed functional classification of 3094 variants as disruptive and demonstrated a high degree of concordance with a clinical truthset.³⁷

Variant Reporting

The Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) group established guidelines to standardize the reporting of germline cancer susceptibility variants. These guidelines take into account several factors including pathogenicity, penetrance, and clinical actionability. According to their proposed framework, they recommend reporting variants that carry a two-fold or higher risk, as variants with less than a two-fold relative risk (RR) are deemed to have limited clinical relevance when considered

alone.³⁸ Although these variants can still be reported, some clinical laboratories may opt not to do so if they lack clinical utility. Moreover, recommendations for clinical management should be based on a thorough evaluation of the specific variant, as well as the individual's personal and/or family medical history, alongside other known genetic and environmental risk factors.

Variant Reclassification

Variants in *RAD51C*, *RAD51D* and *BRIP1* may undergo reclassification ("upgraded" or "downgraded") as new evidence or revised classification frameworks emerge over time. In the setting of cancer predisposition genes, in most situations, the reclassification results in a downgrade of the classification of VUS to benign or likely benign.^{39,40} This reclassification, particularly if a VUS is upgraded, could change the clinical implications both for early detection and risk-reducing interventions, as well as advice on cascade testing, underscoring the importance of discussing these potential updates between clinicians and individuals during testing. Various professional societies have issued guidelines regarding the recontacting of individuals, reclassification processes, and updating of reports.^{41–43}

Consistent with standard clinical practice,

- VUS in *RAD51C*, *RAD51D* and *BRIP1* should not be used to guide clinical management or for predictive genetic testing for family members, as is the case for all VUS results.
- Reporting of *RAD51C*, *RAD51D*, and *BRIP1* variants should include clear language on variant pathogenicity and predicted penetrance.
- Clinicians should discuss the potential for reclassification of *RAD51C*, *RAD51D*, and *BRIP1* variants (especially VUS) with individuals.

Cancer risks for *RAD51C*, *RAD51D* and *BRIP1* heterozygotes

Ovarian cancer: In 2010, six GPVs in *RAD51C* were identified in 1100 German families with gynecological malignancies.⁴⁴ The variants were found only within families with the occurrence of both BC and OC (n=480) and not in 620 families with BC only or in 2912 healthy German controls, suggesting that the greater association was for OC. Further studies also reported the detection of *RAD51C* GPVs in studies of BC/OC families.^{45–47}

In 2011, eight GPVs in *RAD51D* were described in 911 BC/OC families, compared with one GPV identified in 1060 controls ($p<0.05$).⁴⁸ Similar to the observation for *RAD51C*, the association was principally for OC, with three variants identified in 59 pedigrees with three or more patients with OC ($p<0.05$).

The largest study of cancer risk in *RAD51C* and *RAD51D* heterozygotes collected information from 28 centers in 12 countries, identifying cases through *RAD51C* or *RAD51D* variant screening of individuals with multiple relatives diagnosed with BC/OC or women diagnosed with BC/OC unselected for cancer family history. This included data from 215 women with *RAD51C* GPVs from 125 families and 92 women with *RAD51D* GPVs from 60 families.⁴⁹ For *RAD51C* heterozygotes, a RR of OC was reported as 7.6 (95% CI:

5.6–10.2) ($p < 0.05$). For *RAD51D* heterozygotes, a similar RR of 7.6 (95% CI: 5.6–10.3) ($p < 0.05$) was observed.⁴⁹ For both genes, most risk was conferred after age 50 years with a cumulative lifetime risk (to age 80 years) of developing OC estimated to be 11% (95% CI: 6–21%) for *RAD51C* heterozygotes and 13% (95% CI: 7–23%) for *RAD51D* heterozygotes. For both genes, lifetime OC risk was shown to be modified by family history with a lifetime risk exceeding 30% for heterozygotes with two first-degree relatives diagnosed with OC.⁴⁹

Unlike *RAD51C* and *RAD51D*, *BRIP1* was initially reported as a BC predisposition gene.⁵⁰ However, GPVs in *BRIP1* are now firmly established to be associated with OC, rather than BC susceptibility.^{51,52} The association appears strongest for the HGSC subtype, although other histological subtypes have been reported. An international study of 3236 cases of OC calculated a RR for all epithelial ovarian cancer of 11.2 (95% CI: 3.2–34.1) and for high-grade epithelial OC of 14.1 (95% CI: 4.0–45.0).¹⁹ The study authors reported an average age of OC diagnosis of 63.8 years ($n=30$) compared to 58 years in non-heterozygotes ($p=0.07$) and calculated a cumulative risk for *BRIP1* heterozygotes of epithelial OC by age 80 years to be 5.8% (95% CI: 3.6%–9.1%). However, this cumulative risk has been suggested to be an underestimate given the reported RR of 11, potentially due to the control group including unaffected high-risk women from a clinical screening trial of ovarian cancer (UKFOCSS) that had to be unaffected with OC to participate.

Data from a meta-analysis that pooled findings of 44 studies published prior to September 2019 including 200 *BRIP1* GPVs (71 distinct variants) identified in 22,494 cases calculated a lower odds ratio (OR) of 4.9 for OC (95% CI: 4.1–6.0; $p < 0.05$).⁷ However, a recent paper from a single UK center demonstrated that GPVs in *BRIP1* are the most commonly detected finding in OC patients after GPV in *BRCA1/2*.⁵³ They also calculate an OR for *BRIP1* heterozygotes of 8.7 (95% CI: 4.6–15.8) and suggest that lifetime OC risk is comparable to *RAD51C* and *RAD51D* heterozygotes at 7–10%.

With respect to age of diagnosis of OC, there is good evidence that most OC risk for *RAD51C*, *RAD51D* and *BRIP1* heterozygotes is conferred after age 50. Replicating the age of onset reported by other studies, a large study of heterozygotes identified through multigene panel testing, showed that in 855 *RAD51C*, 455 *RAD51D* and 222 *BRIP1* heterozygotes, the median age at OC diagnosis was 62, 57 and 65 years, respectively, with the majority (*RAD51C* 82.6% (119/144); *RAD51D* 77.5% (55/71); *BRIP1* 90.1% (200/222)), diagnosed after age 50.⁵⁴

Breast cancer: For many years, *RAD51C* was thought to be mainly an OC-predisposition gene with only small BC series reported.⁵⁵ The RR was first estimated by Yang et al to be 2.0 (95% CI: 1.4–2.9; $p < 0.05$) resulting in a cumulative risk of BC to 80 years of 21% (95% CI: 15%–29%).⁴⁹ Similarly, for *RAD51D*, the RR was estimated to be 1.8 (95% CI: 1.2–2.7; $p < 0.05$), resulting in a cumulative risk of BC to 80 years of 20% (95% CI: 14%–28%).⁴⁹ The authors showed how family history could influence risk; for example, the cumulative BC risk to age 80 for a woman with two affected heterozygous first-degree relatives would be 46% (95% CI: 36%–56%) for *RAD51C* and 44% (95% CI: 33%–55%) for *RAD51D*.

The association with BC was subsequently supported by data from two large case control studies. The Breast Cancer Association Consortium (BCAC) study⁸ included 54 *RAD51C* heterozygotes in the cases (0.11%) and 26 in the controls (0.05%), generating an OR of 1.9 (95% CI: 1.2–3.1; $p < 0.05$). Similarly, 51 *RAD51D* heterozygotes were included in the cases (0.10%) and 25 in the controls (0.05%) generating an OR of 1.8 (95% CI: 1.1–2.9; $p < 0.05$). The CARRIERS consortium study included 41 *RAD51C* heterozygotes in the cases (0.13%) and 35 in the controls (0.11%), generating an OR of 1.2 (95% CI: 0.8–1.9; $p = 0.44$) and 26 *RAD51D* heterozygotes in the cases (0.08%) and 15 in the controls (0.04%), generating an OR of 1.7 (95% CI: 0.9–3.5; $p = 0.12$).⁵⁶

Although there was no evidence of an association with missense variants in either study, the possibility remains that a small number of missense variants may be associated with increased BC risk. There was insufficient data to assess the contralateral BC risk.

A recent meta-analysis of both studies and data from the UK Biobank confirmed the magnitude of association and frequency of heterozygote cases to be low for *RAD51C* (OR=1.5 (95% CI: 1.2–2.0), 1 in 913) and *RAD51D* (OR=1.8 (95% CI: 1.2–2.4), 1 in 1079).⁵⁷

The BCAC study is the largest BC case-control study including *BRIP1* heterozygotes including 86 heterozygotes in the BC cases (0.18%) and 75 in the controls (0.14%) and generating an OR of 1.1 (95% CI: 0.8–1.5; $p = 0.54$) and thus *not* supporting an association with breast cancer.⁸

Contralateral breast cancer: Limited data showed no elevated risk of contralateral breast cancer in women harboring a *RAD51C* or *RAD51D* protein-truncating variant. However, the confidence intervals were wide due to modest case counts and the hazard ratio > 1 for both genes.⁵⁸ The same study examined breast cancer-specific survival and found no evidence of association with *RAD51C* or *RAD51D* protein-truncating variants.⁵⁸

Other cancer risks: RAD51C, RAD51D and BRIP1: Compared to the risks established for OC and BC, the data for other possible cancer associations for *RAD51C*, *RAD51D* and *BRIP1* are currently limited to suggestive early findings. The available information comes mostly from large case-only series in which GPVs in a range of different genes have been found but it is currently not possible to determine if the associations are causative or to estimate the degree of any risk. Given the role that these genes play in the HR pathway, a number of studies have focused on cancers known to be associated with GPVs in other HR genes such as *BRCA1*, *BRCA2*, or *PALB2*. An example is pancreatic cancer, where several case series have documented GPV in each of the three genes.^{59–63} Even in the larger series,⁵⁹ this amounts to a small number of individual variants and without control data is difficult to interpret.

Similar studies have documented GPVs in individuals with prostate cancer^{64,65} and colorectal cancer (CRC).^{66,67} Some studies have also suggested treatment responses in individuals with GPV for both these cancers^{68,69} and rarely other cancers, such as small cell lung cancer, where there is no data suggestive of associated cancer risk.⁷⁰

There are equally data that suggests a need for continuing caution; studies that have examined the Finnish founder variants in *RAD51D* (c.576+1G>A) and *RAD51C* (c.837+1G>A and c.93del) in Finnish cancer cohorts have found these in BC and OC cases but not individuals with CRC or prostate cancer.^{71,72} Given the relative rarity of GPVs in these genes, it is likely that collaborative efforts to bring together information from known families segregating GPV to perform pedigree-based analyses will be needed to address the question of the broader cancer spectrum.

With respect to cancer risks,

- ACMG recognizes a clinically actionable risk association for OC predisposition for *RAD51C*, *RAD51D* and *BRIP1* heterozygotes.
- ACMG recognizes an association for BC predisposition in *RAD51C* and *RAD51D* heterozygotes with specific clinical actionability dependent on additional factors.
- ACMG considers that there is insufficient evidence to support a clear association for other cancers.

Individuals with biallelic pathogenic variants (Fanconi anemia)

GPVs in both the *RAD51C* (FA-O) and the *BRIP1* (FA-J/BACH1) genes in the homozygous or compound heterozygous state are a very rare cause of Fanconi anemia, a childhood-onset condition associated with bone marrow failure, physical abnormalities, organ defects, and an increased risk of certain cancers.⁷³ FA-O/*RAD51C* accounts for <1% of cases, whereas FA-J/*BRIP1* accounts for ~2% of cases.^{2,74} Of note, *RAD51D* is *not* currently known to predispose to any autosomal recessive condition, including but not limited to, Fanconi anemia.

The detection of germline *RAD51C* or *BRIP1* GPVs in a child with Fanconi anemia and/or childhood cancer offers an opportunity for cascade testing to determine whether other adult family members are at risk (discussed further in the counseling section below).

Personalized Risk Estimation

For ‘moderate risk’ genes where the best estimates of the average risks associated with a pathogenic variant fall close to various thresholds of clinical actionability, it is possible for the modifying effect of other personal, genomic, or familial risk factors to make an important difference to the final risk assessment and risk management advice. Although models are available that aim to further personalize OC and BC risk assessments in individuals heterozygous for a GPV in *RAD51C*, *RAD51D* and *BRIP1* by incorporating additional information, in clinical practice this remains a complicated area.

One source of additional variation comes from the background polygenic risk, made up of the cumulative minor effects from large numbers of common genomic variants, measured as a polygenic risk score (PRS). PRS have been developed that describe an important part of the distribution of risk for BC⁷⁵ and OC,⁷⁶ both in the general population and in individuals with a GPV in a cancer predisposition gene.⁷⁷ The clinical utility of cancer

PRS remains a matter of considerable discussion,⁷⁸ not least due to the lack of ancestral diversity present in the genome-wide association studies that underlie the development of the PRS resulting in reduced performance in diverse populations.⁷⁹ For some moderate BC risk genes, such as *CHEK2*, where GPVs are more frequent, it has been possible to generate integrated risk models from data that combine contributions from polygenic risk data, the known epidemiological risk factors and family history, and validate these in large groups of individuals with GPVs;⁸⁰ however, this process remains at an early stage in relation to *RAD51C*, *RAD51D* and *BRIP1* and for OC risk in comparison to BC.

The underlying assumption of integrated risk models, that all contributing risk factors combine in an independent multiplicative manner to determine an individual's risk, is supported by the data that are available: Pearce et al⁸¹ confirmed this as the best fit for a model of OC risk that included known environmental risk factors and an early form of the OC PRS, while Yang et al⁴⁹ observed the expected modification of the OC and BC risks associated with GPV in *RAD51C* and *RAD51D* by family history (as described above). In contrast, there are currently no direct data examining the modifying effect of polygenic risk for individuals with GPVs in these genes. A comprehensive model, BOADICEA (implemented in CanRisk)^{82,83} is available that synthesises all of this information (pathogenic variants, personal risk factors, BC and OC polygenic risk and family history of OC and BC). However, as the authors note, for genes such as *RAD51C* and *RAD51D*, where GPVs are relatively rare, no sufficiently large dataset containing all the model features was available to determine risks directly, and notably, *BRIP1* GPVs are not currently included. The full model has been validated in large prospective cohorts for BC⁸⁴ and OC⁸⁵ but inevitably, despite the scale of these studies, only a very small group of *RAD51C* or *RAD51D* heterozygotes were included. A number of clinical trials are currently examining the use of a full personalized model, including polygenic risk, for risk prediction in individuals undergoing genetic testing for BC and OC predisposition genes,⁸⁶ but outside a research context, the limited data means that, for *RAD51C*, *RAD51D* and *BRIP1*, risk personalization in clinical practice remains restricted to the incorporation of information on family history and personal risk factors.

With respect to risk assessment,

- ACMG encourages the use of personalized cancer risk estimates (eg, consideration of family history and/or use of tools such as CanRisk where available) for OC as this may influence clinical actionability in *RAD51C*, *RAD51D* and *BRIP1* heterozygotes.
- ACMG encourages the use of personalized cancer risk estimates (eg, consideration of family history and/or use of tools such as CanRisk where available) for BC as this may influence clinical actionability in *RAD51C* and *RAD51D* heterozygotes.
- ACMG considers that although PRS can support personalized risk assessment, knowledge of the clinical utility of PRS continues to accumulate, and at this time, use of PRS to influence clinical management should be limited to clinical trials.

Pathology

Ovarian cancer: OC includes several distinct histotypes, each representing a different disease entity with distinct biology and specific clinical management strategies.⁸⁷ Therefore, each histotype should be considered separately when examining associations with predisposing germline variants.

Large population-based studies reporting on OC histotypes have shown that approximately 1.2% of HGSC and endometrioid carcinoma (EC), as well as 0.8% of low-grade serous carcinoma (LGSC) of the ovary harbor GPVs in *BRIP1*.^{5,19,88} In contrast, no such variants were identified in mucinous ovarian carcinoma (MUC) or clear cell carcinoma (CCC) of the ovary, although the number of cases was small in these studies. Based on two large population-based studies, approximately 0.4–0.5% of HGSC, EC, CCC, and 0.35% of LGSC harbor GPVs in *RAD51C*.^{15,88} No such variants were identified in MUC. Data from the same studies showed GPVs in *RAD51D* in 0.5% HGSC and 0.9% EC, while no such variants were identified in CCC, LGS, and MUC cases. Results from tumor-normal sequencing have shown biallelic inactivation and LOH in OC harboring GPVs in *BRIP1*, *RAD51C* and *RAD51D*, with a prominence in HGSC when compared to other histotypes.^{18,89,90} Interestingly, a recent study observed an enrichment in mutational signatures related to homologous repair deficiency (HRD) in tumors associated with GPVs in *RAD51C* and *RAD51D* compared with *BRIP1*.⁸⁹

Given the above, GPVs in *BRIP1*, *RAD51D* and *RAD51C* are more likely to be associated with the development of HGSC, compared to other subtypes of OC.

Breast cancer: BC is a heterogenous disease, with each subtype exhibiting unique biology, prognosis and clinical management strategies. Although it is generally accepted that if very large studies are conducted, *RAD51C* and *RAD51D* emerge as BC susceptibility genes,^{8,56} by contrast, whether or not GPVs in *BRIP1* are associated with BC has been questioned for some years.⁹¹ For *BRIP1*, reported associations have been restricted to high-grade triple-negative BC (TNBC);⁹² however, very large population-based case-control studies found no association with BC risk overall.^{8,56} It is important to note that even in TNBC, GPVs in these genes are rare (0.3–0.5% for all three genes).^{93–95} TNBC with GPVs in *RAD51C* and *RAD51D* typically show a high frequency of biallelic inactivation and functional HRD.⁹⁰ In contrast, estrogen receptor-positive BC shows a higher prevalence of HR proficiency and concomitant retained heterozygosity compared with ER-negative BC in the context of *RAD51D* and *RAD51C* GPVs.⁹⁰ Given the above, GPVs in *RAD51D* and *RAD51C* may not be associated with the tumorigenesis of ER-positive BC and *RAD51C* and *RAD51D* heterozygotes who develop BC are more likely to develop triple-negative BC, compared to other subtypes.

With respect to pathology,

- ACMG recognizes an association of GPVs in *BRIP1*, *RAD51D* and *RAD51C* with high grade serous ovarian cancer, compared to other subtypes of OC
- ACMG recognizes an association of GPVs in *RAD51D* and *RAD51C* with triple-negative BC compared to other subtypes of BC

Clinical Management

Ovarian cancer: As moderate-risk GPs, the strength of the evidence for recommendations for clinical management of *RAD51C*, *RAD51D* and *BRIP1* heterozygotes vary, with most only pertaining to risk-reducing strategies.

There is a paucity of data to support surveillance for OC. Multiple studies have shown that OC surveillance has no proven benefit as it does not detect preclinical lesions or lead to a significant effect on survival rate. Additionally, OC screening can lead to potential harms with over-testing and overtreatment due to false-positive results and associated financial toxicity to the individual and healthcare systems.^{96–99} At present, there is no evidence to recommend any surveillance strategy for OC in *RAD51C*, *RAD51D* and *BRIP1* heterozygotes.¹² Individuals should undergo routine gynecologic care in accordance with recommendations by age and other health risks. At-risk individuals should be advised on symptoms of OC such as bloating, early satiety, pelvic pain or pressure or unexplained weight loss and encouraged to seek prompt clinical advice.

With regards to risk-reducing surgery, many professional groups recommend a risk-reducing salpingo-oophorectomy (RRSO) when the risk of OC is above the range of 3–5%.^{12,100,101} The National Comprehensive Cancer Network (NCCN) estimates a 10–15% absolute risk of OC in *RAD51C* and *RAD51D* heterozygotes and 5–15% in *BRIP1* heterozygotes. As discussed above, the median age of OC in women with GPV in *RAD51C* (age 62), *RAD51D* (age 57) and *BRIP1* (age 65) is comparable to the general population (age 63), supporting the consideration to delay RRSO until age 50.⁵⁴ Oophorectomy prior to menopause results in a hypoestrogenic state leading to symptoms of menopause including hot flushes and sleep disturbances as well as decreased bone density and cardiovascular disease. These effects can be minimized in the premenopausal population with hormone replacement therapy in appropriately selected individuals.¹⁰² However, at the age of 50 and above, this risk is reduced, and individuals should be offered surgery with minimal concern for risks associated with early menopause.¹⁰³ Family history of OC, menopausal symptoms and shared decision-making may influence individualized risk assessment of RRSO in women under the age of 50.¹² Several studies have shown that opportunistic salpingectomy alone can reduce the risk of future development of OC. These studies included women who underwent salpingectomy or tubal ligation for the purpose of sterilization and included all comers in terms of risk for developing OC.¹⁰⁴ Researchers are currently investigating whether risk-reducing salpingectomy with delayed oophorectomy in premenopausal individuals with inherited predisposition to OC, including *RAD51C*, *RAD51D* and *BRIP1* heterozygotes, is safe. Results from these studies will not be available for a decade. The data may indicate an additional management option for premenopausal women wishing to reduce their risk prior to completion of an oophorectomy at age 50.^{105,106}

Surgical risk reduction with RRSO should be performed in conjunction with the Sectioning and Extensively Examining the Fimbria (SEE-FIM) protocol¹⁰⁷ for pathologic analysis of the specimen in accordance with NCCN guidelines to optimize detection of occult serous carcinoma of the adnexa. This more extensive pathologic analysis, coupled with a thorough surgical exploration, can identify even occult cancerous lesions.^{108,109} The risk of occult

cancer at the time of RRSO for women with GPV in *BRCA1* and *BRCA2* is well reported in the literature, however, a small series of women with GPV in *RAD51C*, *RAD51D* and *BRIP1* who underwent RRSO found no occult cancers and one serous tubal intraepithelial carcinoma lesion in a woman with a *BRIP1* GPV to date reflecting the age dependent risk for the moderate compared to high risk genes.¹¹⁰

ACMG advises:

- OC surveillance is not recommended for clinical management of *RAD51C*, *RAD51D* and *BRIP1* heterozygotes.
- Female *RAD51C*, *RAD51D* and *BRIP1* heterozygotes should be offered RRSO around age 50. Consideration of RRSO under 50 years is based on individualized risk assessment, including assessment of medical and family history, menopausal symptoms and shared decision making.

Breast cancer: Recommended BC surveillance for females with GPVs in *RAD51C* and *RAD51D* varies across countries. Most *RAD51C* and *RAD51D* heterozygotes will meet the criteria for enhanced breast surveillance above population-based surveillance and some will meet the criteria for breast MRI, based on country specific guidelines/criteria. Although outcomes of breast surveillance in *RAD51C* and *RAD51D* heterozygotes have not been specifically studied, as noted in the pathology section, *RAD51C* and *RAD51D* heterozygotes who develop BC are more likely to develop TNBC, compared to other subtypes. Given the lower sensitivity and higher frequency of interval cancers with respect to TNBC,^{111–113} breast MRI should be considered where appropriate.

The NCCN guidelines recommend an annual mammogram with consideration for MRI beginning at age 40.⁹⁶ In the United Kingdom, screening and surveillance incorporates family history risk; individuals with lifetime risk less than 40% typically initiate an annual mammography at age 40 and those with a risk assessment suggesting a lifetime risk >40% are eligible for a MRI.¹²

Modifying factors are important for determining BC risk for individuals with *RAD51C* and *RAD51D* GPV. Risk assessment models, such as CanRisk, incorporate several risk factors, including molecular genetic test results including *RAD51C* and *RAD51D* GPV and PRS, personal and family history, hormonal and lifestyle risk factors, and breast density.⁸² Note that CanRisk currently incorporates BC risks associated with truncating variants into the risk assessment,⁸² and thus may overestimate risks for missense variants. The model-calculated based risk, along with country-specific guidelines, may then be used to determine recommendations for BC screening.

Guidelines across multiple countries, including the US and Europe, all indicate insufficient evidence to routinely recommend risk-reducing mastectomy in female *RAD51C* and *RAD51D* heterozygotes unaffected with breast cancer. For those with high risk based on individualized BC estimates, as determined by risk calculation tools such as CanRisk, discussion of risk-reducing mastectomy should be part of a shared decision-making process and include a thorough discussion of surgical options and risks.

Although risks for contralateral BCs are not reported to be increased,^{58,114,115} individuals with GPV in *RAD51C* and *RAD51D* with a personal history of BC and remaining at-risk breast tissue may be offered individualized surveillance. In general, the data on *RAD51C* and *RAD51D*-related BC risk does not support routine consideration of risk-reducing mastectomy; however, the decision for a *RAD51C* and *RAD51D* heterozygote to undergo bilateral mastectomy at the time of diagnosis of unilateral BC should be a shared decision-making process based on individual estimated risk and BC characteristics (ie, age, tumor size, stage, grade, receptor status, laterality, family history) and the competing risks of their current cancer diagnosis.

Given that there are no established data confirming increased BC risk among females with a *BRIP1* GPV, BC surveillance should be based on family history.

For *RAD51C* and *RAD51D* GPV, ACMG advises:

- BC surveillance recommendations should be based on an individualized risk assessment using a model such as CanRisk. Most *RAD51C* and *RAD51D* heterozygotes will meet the criteria for enhanced breast surveillance above population-based surveillance and some will meet the criteria for breast MRI, based on country-specific guidelines/criteria.
- Female *RAD51C* and *RAD51D* heterozygotes do not usually meet the risk threshold to offer bilateral risk-reducing mastectomy; thus, they should not be offered routinely but may be considered based on an individualized risk assessment using a model such as CanRisk and shared medical decision-making.
- For females affected with BC, contralateral risk-reducing mastectomy should not be routinely offered, but may be considered based on an individualized risk assessment using a model such as CanRisk and shared medical decision-making.

For *BRIP1* GPV, ACMG advises:

- BC surveillance recommendations should be based on family and personal risk factors.

Therapeutic implications

Our literature review did not identify any studies directly exploring therapeutic implications in *BRIP1*, *RAD51C* and *RAD51D* heterozygotes. Presently, there are no therapeutic implications for individuals with a *BRIP1*, *RAD51C* or *RAD51D* GPV across all cancer subtypes. Most studies recruited participants based on homologous recombination repair (HRR) genes whereas *BRIP1*, *RAD51C* and *RAD51D* heterozygotes accounted for either single/limited number of cases, making it difficult for any inference on therapeutic benefit to be made.

In the exploratory subgroup analysis of the PAOLA-1 study for OC,¹¹⁶ patients with HRD negative testing on MyChoice HRD plus assay does not appear to derive a progression free survival benefit with maintenance olaparib and bevacizumab. Genes of interest included *BLM*, *BRIP1*, *RAD51C*, *PALB2*, and *RAD51D*, which are either directly or indirectly involved in the HRR pathway. One postulation was that there may be HR mechanisms

not picked up in the current HRD testing assays, such as *RAD51C* hypermethylation that have been reported to be associated with poly (ADP-ribose) polymerase (PARP) inhibitor response.¹¹⁷ In addition, findings may be confounded by small numbers in the context of modest effect size. Such epigenetic changes may be more easily reversed with ongoing PARP inhibitor treatment, resulting in resistance with subsequent treatment due to reversion of hypermethylation.¹¹⁸ Nonetheless, the number of non-*BRCA1/2* genes in the PAOLA-1 analysis was small, which may limit the precise nature of analyzing their sensitivity. Prospective research of genes that include *BRIP1*, *RAD51C* or *RAD51D* with high GIS are needed to evaluate their response to PARP inhibitors.

There is an ongoing European study, the RADIOLA trial, exploring olaparib sensitivity in patients with unresectable locally advanced/metastatic HER2-negative BC with any of *BRCA1*, *BRCA2*, *PALB2*, *RAD51C* or *RAD51D* GPV or functional HRD, defined by RAD51-low score ($\leq 10\%$).¹¹⁹

- ACMG acknowledges that at this time there is insufficient evidence for *RAD51C*, *RAD51D* or *BRIP1* status to guide any specific targeted treatment.

Outcomes

Data on outcomes, survival and mortality are limited since GPVs in *BRIP1*, *RAD51C* and *RAD51D* are included in studies far less frequently than GPVs in *BRCA1*, *BRCA2*, *PALB2*, *CHEK2* and *ATM*.⁶⁸ A number of small studies have suggested potentially poorer overall outcomes for *BRIP1* and *RAD51D* heterozygotes.^{18,58,120,121} However, some studies suggest that *RAD51C* and *RAD51D* heterozygotes may have better outcomes. In general, genes associated with HR repair are associated with more favourable outcomes in individuals with ovarian cancer.^{89,122,123} However, in the studies undertaken to date, individuals with GPV in genes associated with HR were grouped together and comprised very small numbers of individuals with GPV in *BRIP1*, *RAD51C* and *RAD51D*. Therefore, while the findings from these studies are important, there are limitations due to the lack of gene-specific data and small numbers. Larger multi-center studies on outcomes for individuals with *BRIP1*, *RAD51C* and *RAD51D* GPVs are needed to draw any firm conclusions.

Genetic Counseling

At this time, *BRIP1*, *RAD51C* and *RAD51D* are not included on the ACMG Secondary Findings list for reporting following exome or genome sequencing.¹²⁴ Therefore, individuals who have a heterozygous GPV in *BRIP1*, *RAD51C* or *RAD51D* are most typically identified following targeted or multigene panel testing performed because of a personal cancer diagnosis of an associated cancer, personal diagnosis of unrelated cancers, or family history of cancer.

There are challenges in counseling *BRIP1*, *RAD51C* or *RAD51D* heterozygotes including (1) evolving estimates of absolute risk for individuals and (2) minimal evidence on the impact of surveillance and management recommendations for heterozygotes. It is highly recommended that heterozygotes seek consultation with a healthcare professional with

expertise and experience in cancer genetics who is familiar with the above challenges and who will be able to provide guidance should recommendations change in the future.

For genes associated with high-penetrance for cancer risk, such as *TP53* or *BRCA1*, confirmation that an individual has not inherited a familial variant is considered a “true negative” result that reduces cancer risks close to the population level. However, predictive testing is more complex for *BRIP1*, *RAD51C* or *RAD51D* GPV than for high-penetrance genes, as a “negative result” may not return an associated cancer risk to the population level. In this scenario, an individual risk calculation, particularly for BC, should be performed for these individuals with surveillance recommendations based on the remaining residual risk. Genetic counseling is recommended before and after testing for a familial GPV, so that appropriate clinical management can be advised in the absence or presence of a negative result. See Figures 1 to 4 for examples of genetic counseling and management issues in pedigrees that harbor a *RAD51C*, *RAD51D* or *BRIP1* germline variant.

Predictive genetic testing for a familial *BRIP1*, *RAD51C* or *RAD51D* pathogenic variant is not routinely recommended in childhood, as the known risks are adult-onset.

The detection of germline *RAD51C* or *BRIP1* GPVs in a child with Fanconi anemia and/or childhood cancer offers an opportunity for cascade testing to determine whether other adult family members are at risk. Conversely, while genetic counseling of individuals with a *RAD51C* or *BRIP1* GPV may include a discussion of bi-allelic inheritance (and implications to family planning with consideration of partner testing prior to achieving pregnancy), in reality, outside of countries (or populations) with a founder variant, this risk is very small. Specifically, the *RAD51C* carrier frequency is estimated to be 1 in 1600 (0.06%) with the probability of a liveborn offspring with Fanconi anemia of 1 in 6400; while *BRIP1* carrier frequency is estimated to be 1 in 500 (0.2%), with the probability of a liveborn offspring with Fanconi anemia of 1 in 2000.^{56,125} Funding for partner testing varies across countries and healthcare systems, and some healthcare systems do not fund partner testing. For example, the National Health Service in England only funds partner testing when the carrier frequency of the condition is higher than 1 in 70 in the relevant population.¹²⁶ Where partner testing is offered, this could be undertaken as a single-gene test or as part of a cancer panel, particularly if the partner’s family history warrants this. It is important to note that *BRIP1* and *RAD51C* are not a part of typical ‘expanded carrier screening’ panels. The ACMG practice resource about screening for autosomal recessive and X-linked conditions during pregnancy and preconception¹²⁷ proposes a tiered definition of carrier screening, in which *BRIP1* and *RAD51C* would fit into Tier 4, which includes genes that are recommended to not be offered routinely but in specific circumstances such as consanguineous pregnancies and when family history suggests screening would be beneficial.

When both parents carry GPVs in *BRIP1* or *RAD51C*, considerations for family planning including pre-implantation genetic testing and prenatal diagnosis through chorionic villus sampling or amniocentesis for detection of biallelic variants should be discussed. *RAD51D* has not thus far been associated with recessive disease.

Pre-implantation genetic testing or prenatal diagnosis for detection of a single heterozygous GPV in any of these *BRIP1*, *RAD51C* or *RAD51D* genes in the fetus is a complex discussion. Pre-implantation genetic testing or prenatal diagnosis for these genes, in countries where available, requires careful and sensitive genetic counseling regarding reproductive options and lifetime risks. Although the cancer predisposition is adult onset and in general moderate, there can be situations where the risk is higher. It is recommended that discussions around reproductive options for moderate risk cancer susceptibility genes should be provided by an appropriately trained genetic/genomic health care professional with expertise in this area.¹²⁸

Pre-implantation genetic testing or prenatal diagnosis for these genes, in countries where available, requires careful and sensitive genetic counseling regarding reproductive options and lifetime risks.

Consistent with standard clinical practice,

- *BRIP1*, *RAD51C* and *RAD51D* heterozygotes should be referred to a genetics health care professional to discuss cancer risks, surveillance, and reproductive options as well as implications for other family members.
- Pre- and post-test genetic counseling should be undertaken when considering predictive genetic testing for GPV in *BRIP1*, *RAD51C* and *RAD51D*.
- Residual risk estimation (particularly for BC) and breast surveillance guidance should be provided for individuals who test negative for a familial *BRIP1*, *RAD51C* and *RAD51D* variant to guide future surveillance.
- For *BRIP1* and *RAD51C*, genetic counseling should include a discussion of biallelic inheritance and partner testing may be offered for couples who are pregnant or planning a pregnancy according to country-specific guidelines.

Research gaps in clinical areas of need

There remains a paucity of data for cancer risk and clinical outcomes for *BRIP1*, *RAD51C* and *RAD51D* heterozygotes compared with higher risk cancer predisposition genes such as *BRCA1* and *BRCA2*. Furthermore, published data would benefit from a greater understanding of heterozygotes across different populations, geographically matched control populations, and a clearer understanding of risk associated with rare missense variants and the impact of risk modifying factors.

Although data from large case-control analyses have helped refine cancer risks for BC, and these risks are incorporated into the CanRisk model allowing personalized BC risk estimation for truncating variants in *RAD51C* and *RAD51D*, a greater understanding of genotype-phenotype correlation with *RAD51C*, *RAD51D* and *BRIP1*, as well as risk models and calculators validated across diverse populations are needed. With regards to management, a greater understanding of contralateral BC risk for *RAD51C*, *RAD51D* and surveillance outcomes are required to improve current recommendations. Efforts are currently underway to consolidate research efforts globally through international consortiums to ensure best evidence-based management approaches.

Similarly, there are ongoing discussions about the appropriateness and timing of risk-reducing surgery, with the safety of OC risk-reduction following early salpingectomy with delayed oophorectomy still to be established for women at an increased familial risk including *RAD51C*, *RAD51D* and *BRIP1* heterozygotes. Prospective databases will aid in assessing the efficacy of surveillance and risk-reducing surgery.

Efforts can also be directed at histopathological and molecular characterization of *RAD51C*, *RAD51D* and *BRIP1* OC, given the heterogeneous nature of OC and the correlation with clinical outcomes. The role of chemoprevention also needs to be studied, as OC tends to be detected when there is metastatic disease and treated with palliative intent.

ACMG acknowledges research is required to address,

- Need for development of risk models and calculators validated across diverse populations to improve risk assessment tools.
- Need for prospectively collected clinical data from *RAD51C*, *RAD51D* and *BRIP1* heterozygotes to:
 - Refine and improve cancer risk estimates.
 - Establish clear metrics on surveillance and treatment outcomes and survival.
 - Evaluate *RAD51C*, *RAD51D* and *BRIP1*-specific response to established and novel therapies.
 - Collection of information on specific tumor (sub)type from *RAD51C*, *RAD51D* and *BRIP1* heterozygotes affected by OC or BC to establish clear metrics for genotype-phenotype association.

Conclusion

The statements made in this Clinical Practice Resource are based on expert opinion using a comprehensive literature ascertainment approach. As for other moderate risk genes, cancer risks for *RAD51C*, *RAD51D* and *BRIP1* are influenced by other factors including family history, other genetic background, reproductive and lifestyle factors. Personalized rather than generalized advice on appropriate cancer risk management is required to offer the most appropriate medical management.

Further studies are needed to fully define cancer risk in *RAD51C*, *RAD51D* and *BRIP1* heterozygotes, as well as the effectiveness of early detection and risk-reducing interventions and explore targeted treatments.

Given the rarity of GPVs in these genes, healthcare professionals are encouraged to contribute follow-up data to long term studies, thereby facilitating the generation of prospective cancer risk estimates and the evaluation of prevention measures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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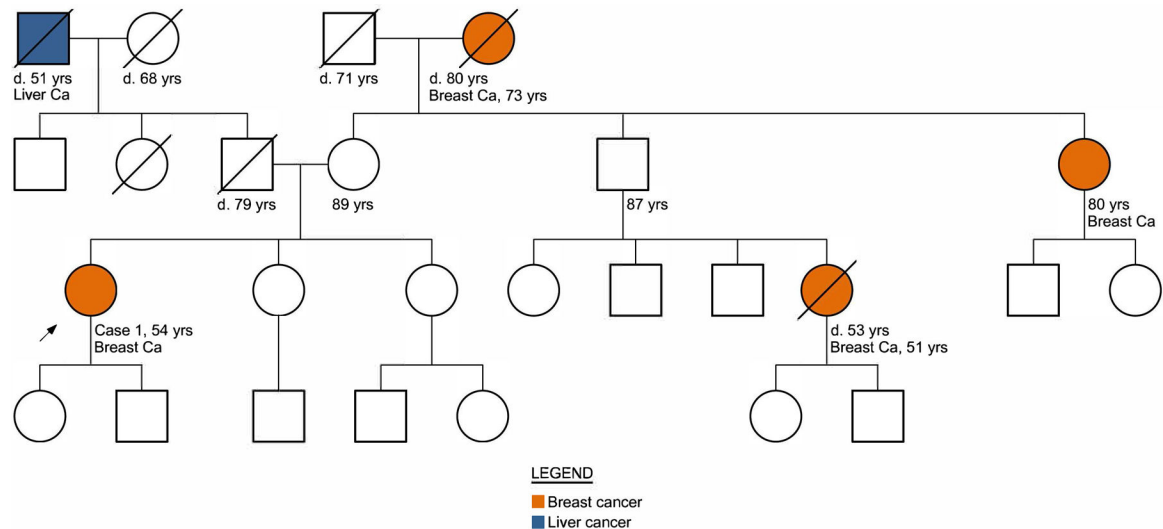
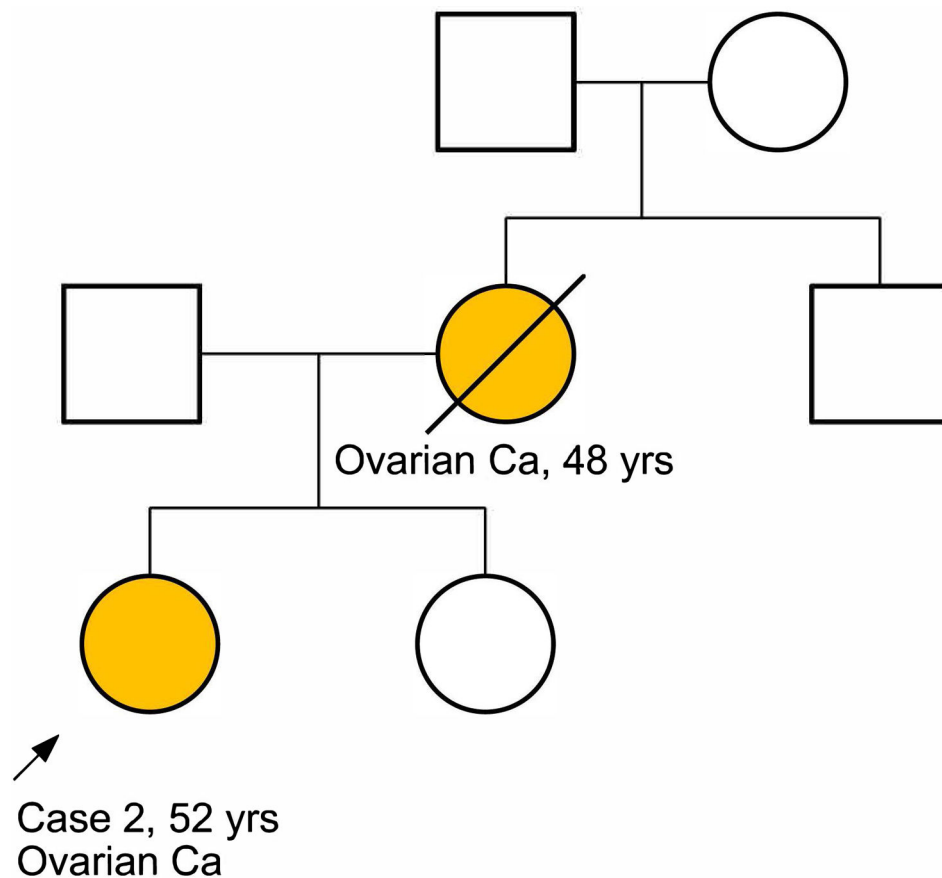


Figure 1. Proband with personal and family history of breast cancer and *RAD51D* germline pathogenic variant.

A 54-year-old woman presented to the clinic with a personal history of triple negative breast cancer and a maternal family history of breast cancer. She was tested through a commercial laboratory who identified a pathogenic variant in *RAD51D*.

Discussion points are as follows:

- *RAD51D* heterozygotes who develop breast cancer are more likely to develop triple-negative breast cancer, compared to other subtypes.
- Although there is no family history of ovarian cancer, with the identification of a *RAD51D* pathogenic variant, an increased future risk of ovarian cancer is recognized. Discussion of risk reducing bilateral salpingo-oophorectomy is recommended.
- Predictive genetic testing can be offered to relatives. To determine breast surveillance recommendations the use of a risk assessment tool, such as CanRisk incorporating genetic test results, family history and personal risk factors will be helpful following the results of both a positive and negative predictive test.



LEGEND

■ Ovarian cancer

Figure 2. Proband with personal and family history of ovarian cancer and *BRIP1* germline pathogenic variant.

A 52-year-old woman was diagnosed with a high grade serous ovarian cancer and had standard of care germline testing of a panel of ovarian cancer predisposition genes which identified a pathogenic variant in *BRIP1*.

Discussion points are as follows:

- Genetic testing in her mother who was diagnosed with high grade serous ovarian cancer at age 48 included only *BRCA1* and *BRCA2* genes at the time of her diagnosis, rather than a wider ovarian cancer predisposition panel. Where genetic testing has previously been undertaken for a personal and family history of ovarian cancer, it is important to understand what the genetic test included, given that the association of *RAD51C*, *RAD51D* and *BRIP1* with ovarian cancer is only more recently described. *BRIP1* is reported to be the most detected finding in patients with ovarian cancer after GPV in *BRCA1* and *BRCA2*.
- The identification of a *BRIP1* GPV will not alter clinical management.

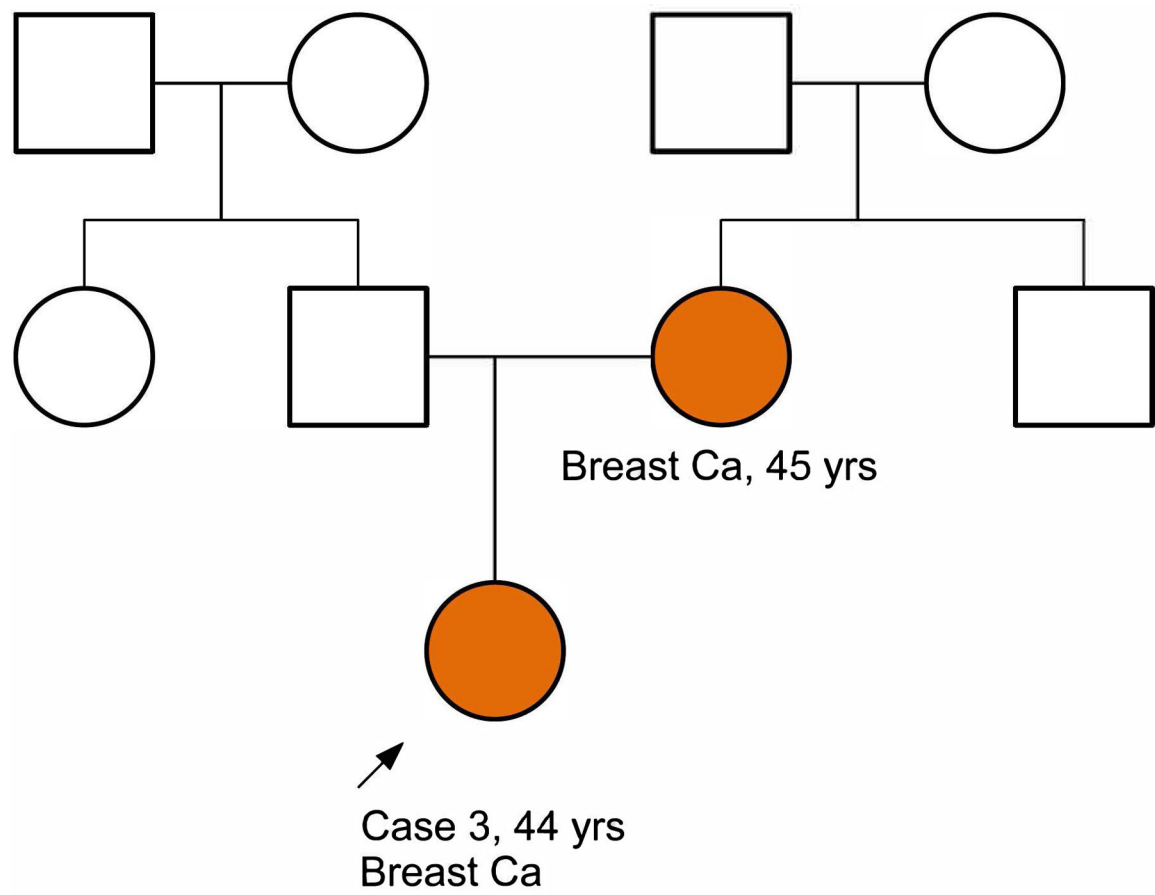
- Predictive genetic testing can be offered to relatives.
- Breast cancer surveillance should be offered according to population screening programs and is not altered by the finding of the *BRIP1* GPV.

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LEGEND

■ Breast cancer

Figure 3. Proband with personal history of breast cancer and likely unrelated *BRIP1* germline pathogenic variant.

A 44-year-old woman diagnosed with ER positive breast cancer and a family history of early onset breast cancer in her mother was tested through a commercial laboratory who identified a pathogenic variant in *BRIP1*. Subsequent cascade testing confirmed that this was paternally inherited, ie, from the side of the family without a history of breast cancer.

Discussion points are as follows:

- *BRIP1* GPV are not strongly associated with breast cancer. It is likely that the breast cancer in this patient is not linked to the presence of *BRIP1*.
- Predictive genetic testing can be offered to other family members, eg, sister, to help determine the management of future ovarian cancer risk, but advice on future breast cancer surveillance should be based on the family history of breast cancer

- Genetic counseling should include discussion of biallelic inheritance and partner testing may be offered for couples who are pregnant or planning a pregnancy according to country specific guidelines.

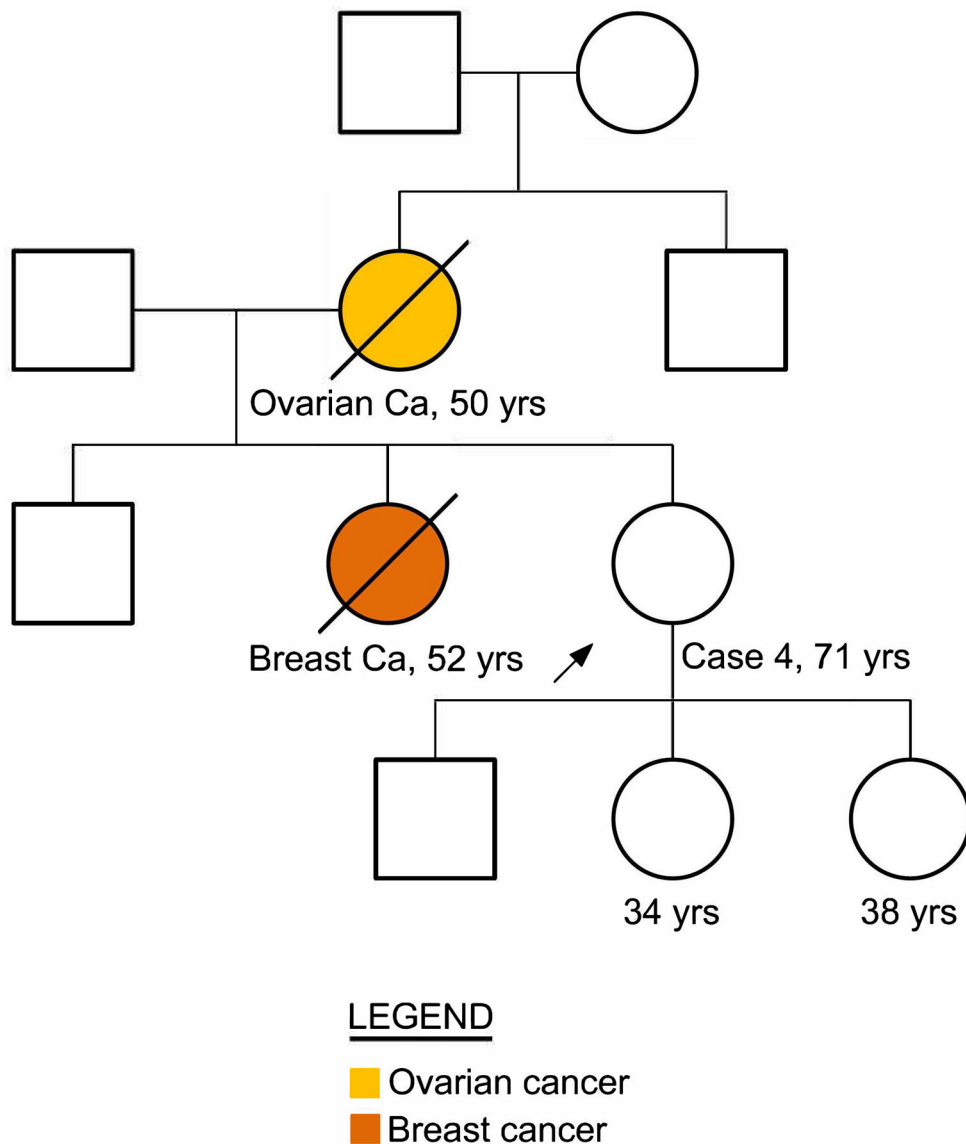


Figure 4. Consideration of risk-reducing salpingo-oophorectomy in a family with a germline pathogenic variant in *RAD51C*.

A 71-year-old woman unaffected with cancer underwent genetic testing due to her family history of breast and ovarian cancer and was identified to have a pathogenic variant in *RAD51C*. Her daughters are seeking predictive genetic testing to manage their future cancer risk.

Discussion points are as follows:

- Predictive genetic testing can be offered to her daughters to evaluate if they have inherited the *RAD51C* pathogenic variant
- If her daughters have inherited *RAD51C*, then risk-reducing salpingo-oophorectomy should be discussed, but as both are in their 40s, this would not typically be offered under the age of 50 years. However, individualized assessment, discussion of menopausal symptoms and competing medical problems should be utilized in a shared decision-making approach if earlier risk-reducing salpingo-oophorectomy is considered.

- Breast cancer surveillance recommendations should be based on an individualized risk assessment using a model such as CanRisk according to country specific guidelines.

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Table 1.Summary of breast and ovarian cancer risk in *RAD51*, *RAD51D* and *BRIP1* heterozygotes

Gene	Breast Cancer Risk	Ovarian Cancer Risk
RAD51C	RR 2.0 (95% CI: 1.4–2.9) Lifetime risk ^a : 21% (95% CI: 15–29%) ⁴⁹	RR 7.6 (95% CI: 5.6–10.2) Lifetime risk ^a : 11% (95% CI: 6–21%) Increased risk after age 50 ⁴⁹
RAD51D	RR 1.8 (95% CI: 1.2–2.7) Lifetime risk ^a : 20% (95% CI: 14–28%) ⁴⁹	RR 7.5 (95% CI: 5.6–10.3) Lifetime risk ^a : 13% (95% CI: 7–23%) Increased risk after age 50 ⁴⁹
BRIP1	Not associated with breast cancer ⁸	RR 11.2 (95% CI: 3.2–34.1) Lifetime risk: 5.8% (95% CI: 3.6%–9.1%) Increased risk after age 50 ¹⁹

RR, relative risk.

^aModified by family history.