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Clinical implications of the type and genomic location of pathogenic BRCA1 and BRCA2 variants in hereditary breast and ovarian cancer

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ABSTRACT

Germline pathogenic or likely pathogenic variants (P/LPVs) in *BRCA1* and *BRCA2* are major determinants of hereditary breast and ovarian cancer susceptibility. Although clinical management has traditionally relied on the presence of a *BRCA1/BRCA2* alteration regardless of its specific characteristics, growing evidence suggests that not all *BRCA* P/LPVs are biologically and clinically equivalent. Variant location within *BRCA1* and *BRCA2* influences the relative distribution of breast and ovarian cancer risk. Breast cancer cluster regions (BCCRs) are associated with a higher relative risk of breast versus ovarian cancer, whereas ovarian cancer cluster regions (OCCRs), largely encompassing exon 11, are associated with a relative shift toward ovarian cancer risk. Variant type may also be clinically relevant. Protein-truncating P/LPVs have been associated with higher cancer risks than selected missense variants with residual protein function and lower penetrance. Some studies have also reported poorer outcomes for carriers of protein-truncating P/LPVs and more favorable outcomes for those with missense variants. In this narrative review, we summarize current evidence on the clinical implications of *BRCA1/BRCA2* P/LPV type and genomic location. While associations between variant location and breast or ovarian cancer risk are supported by large international consortia, prognostic and predictive associations remain largely exploratory. A better understanding of variant-specific genotype-phenotype correlations may ultimately refine risk prediction, preventive strategies, and treatment selection in hereditary breast and ovarian cancer.

1. Introduction

Germline pathogenic/likely pathogenic variants (P/LPVs) in either *BRCA1* or *BRCA2* account for approximately 5% of breast cancer (BC) and 10–15% of ovarian cancer (OC) cases (Cancer Genome Atlas Network, 2012; Cancer Genome Atlas Research Network, 2011). Although the overall impact of *BRCA1* and *BRCA2* P/LPVs on lifetime BC and OC risk, prognosis and treatment response is well established, emerging evidence suggests that specific variant types and locations within these genes may be associated with distinct risk profiles and

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clinical outcomes (Cortesi et al., 2017, 2014; Dullens et al., 2020; Grandi et al., 2021, 2019; Mastrodomenico et al., 2023; Piombino et al., 2020; Toss et al., 2019).

Over the past two decades, *BRCA1* and *BRCA2* have become paradigms of precision oncology, guiding not only risk assessment and prophylactic surgical interventions but also therapeutic decision-making. The introduction of poly(ADP-ribose) polymerase inhibitors (PARPi) has revolutionized the management of *BRCA*-associated tumors, providing substantial benefits (Golan et al., 2019; Litton et al., 2018; Moore et al., 2018; Robson et al., 2017). However, resistance to PARPi and platinum-based therapies has emerged as a major clinical challenge. Among the mechanisms of acquired resistance, reversion mutations can restore homologous recombination proficiency and thereby limit PARPi efficacy. Emerging evidence suggests that the occurrence of such reversions may be influenced by the type and location of the germline P/LPVs within *BRCA1* or *BRCA2* (Piombino and Cortesi, 2022). Importantly, recent large international studies, together with exploratory analyses from clinical trials and emerging genotype-phenotype studies, have substantially expanded the evidence on the potential clinical relevance of *BRCA1/BRCA2* P/LPV type and location, providing a timely rationale for a critical reassessment of this field (Akamandisa et al., 2025; Labidi-Galy et al., 2023; Toss et al., 2026).

This narrative review was designed to provide a broad and critical overview of the available evidence regarding the clinical implications of germline P/LPVs in *BRCA1* and *BRCA2* according to variant type and genomic location. The scope of the review encompasses BC and OC risk, age at diagnosis, tumor phenotype, prognosis, and response to systemic therapies, including PARPi. In contrast to previous reviews, which have primarily focused on hereditary cancer risk assessment, surveillance strategies, or the overall management of *BRCA1/BRCA2* carriers, this review specifically examines how the type and location of individual P/LPVs may influence clinical outcomes.

2. Methods

2.1. Review design and literature search

This article was developed as a structured critical narrative review rather than a systematic review or meta-analysis. PubMed/MEDLINE was searched for English-language publications up to July 2026. Search terms included combinations of “BRCA1”, “BRCA2”, “breast cancer”, “ovarian cancer”, “pathogenic variant”, “likely pathogenic variant”, “variant type”, “variant location”, “mutation type”, “mutation location”, “breast cancer cluster region”, “ovarian cancer cluster region”, “functional domain”, “cancer risk”, “age at diagnosis”, “tumor phenotype”, “prognosis”, “survival”, “treatment response”, “platinum salts”, “PARPi”, “cyclin-dependent kinase 4/6 (CDK4/6) inhibitor”. Reference lists of relevant original studies and reviews were also examined to identify additional publications, including earlier landmark studies.

2.2. Evidence appraisal and terminology

Evidence was critically interpreted according to study design, sample size, population characteristics, *BRCA1/BRCA2* variant classification, definition of variant type or genomic region, clinical endpoint, adjustment for relevant confounders, and availability of independent validation. Greater weight was given to large collaborative or consortium-based analyses and to findings replicated across independent populations, while associations derived from small retrospective cohorts or exploratory subgroup analyses were interpreted cautiously.

Throughout the review, the term P/LPV is used in accordance with contemporary variant-classification terminology. Variant type refers to the molecular nature of the alteration, whereas variant location refers to its position within *BRCA1* or *BRCA2* genes, including regions encoding functionally relevant protein domains (see Section 3.1). Because definitions of BCCRs/OCCRs and variant groupings have varied across studies, the terminology and boundaries adopted in each original study were considered when interpreting and comparing results.

3. BRCA1 and BRCA2 functional domains and P/LPV classification

3.1. Structure and functional domains of BRCA1 and BRCA2

The *BRCA1* gene comprises 24 exons, including 22 coding exons. The encoded protein contains multiple functional domains: the N-terminal RING domain, which mediates interactions with BARD1 and possesses E3 ubiquitin ligase activity; two nuclear localization sequences (NLS); a coiled-coil domain, responsible for interaction with PALB2; the *BRCA1* C-terminal (BRCT) domain, which binds ATM-phosphorylated proteins, contributing to BRCA1 recruitment to DNA damage sites and the initiation of the homologous recombination process (Fig. 1) (Fu et al., 2022; Hu et al., 2021; Ismail et al., 2024; Roy et al., 2011). Although the BRCA1 DNA-binding domain (DBD) is not included in the most recent structural models and is therefore not shown in Fig. 1, the term is retained in selected sections of this review because it is still used in several studies evaluating the clinical implications of *BRCA1* variants.

Similarly, current exon numbering is based on the MANE Select transcripts (Morales et al., 2022). However, because most studies included in this review used legacy exon nomenclature, exon numbering is reported according to that used in the original publications when discussing study-specific results. In particular, *BRCA1* exon 11 in the legacy nomenclature corresponds to exon 10 in the current MANE Select transcript. This difference reflects the use of distinct exon-numbering schemes across transcript models and databases, particularly for the 5′ untranslated exons and the small 21-bp exon 4. Most earlier studies used the legacy nomenclature, whereas Toss et al. (2026) adopted the current exon numbering.

The *BRCA2* gene comprises 27 exons and encodes the BRCA2 protein, which contains four main functional regions. Its N-terminal region, encoded by the first few exons, contains a PALB2-interacting domain. The central region, corresponding to exon 11, includes eight BRC repeats that recruit RAD51 to DNA double-strand break (DSB) sites, a key step in homologous recombination. The C-terminal DBD comprises a helical domain, three oligonucleotide/oligosaccharide-binding (OB) folds, and a tower domain (Fig. 2) (Fradet-Turcotte et al., 2016; Roy et al., 2011). The NLS is located at the extreme C-terminal end (Shailani et al., 2018).

3.2. P/LPV types

BRCA1 and *BRCA2* harbor thousands of known sequence variants, but only a subset is classified as P/LPVs. There is considerable variability in the frequency and types of *BRCA1/BRCA2* P/LPVs among different populations (Maxwell et al., 2016), but the description of the distribution by population is beyond the scope of this work. Most known *BRCA1* and *BRCA2* P/LPVs reported in major databases (ENIGMA, https://enigmaconsortium.org/; *BRCA* Exchange, https://brcaexchange.org; ClinVar, https://www.ncbi.nlm.nih.gov/clinvar/ and LOVD, https://www.lovd.nl/) are small deletions or insertions (indels), followed by single-nucleotide variants (SNVs), broadly distributed across both genes. Indels frequently disrupt the reading frame, resulting in frameshift variants that may introduce premature termination codons (PTCs). PTC-containing transcripts may undergo nonsense-mediated mRNA decay (NMD) or escape NMD and be translated into truncated proteins with potentially impaired function (Lejeune, 2017). Conversely, in-frame indels do not necessarily result in loss of protein function, particularly if they do not disrupt known functional domains (Nepomuceno et al., 2022).

SNVs may result in amino acid substitutions (missense variants) or introduce PTCs (nonsense variants) (Fig. 3). Not all missense variants are classified as P/LPVs because the replacement of one amino acid with another may not be deleterious to protein function (Aljarf et al., 2022).

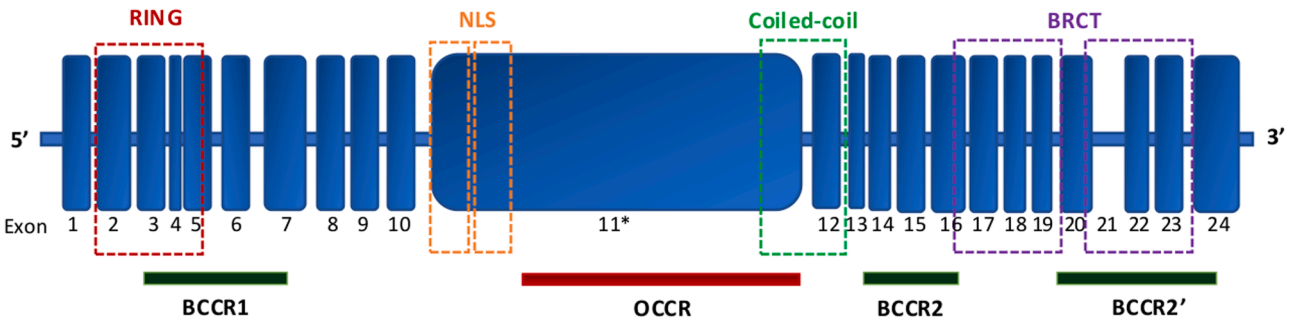


Fig. 1. Schematic representation of *BRCA1* structure and the corresponding protein domain organization. Key protein domains are highlighted, including the RING domain (red), two nuclear localization signal (NLS) domains (orange), the coiled-coil domain (green), and the BRCA1 C-terminal (BRCT) domain (violet). The current MANE Select reference transcript for *BRCA1* is NM_007294.4. Exon numbering in the schematic follows the legacy nomenclature used in the studies defining the BCCR/OCCR regions. Legacy exon 11 corresponds to exon 10 in the current MANE Select transcript. * *Legacy exon numbering.* Abbreviations: BCCR, Breast Cancer Cluster Region; BRCT, BRCA1 C-terminus; NLS, nuclear localization signal; OCCR, Ovarian Cancer Cluster Region.

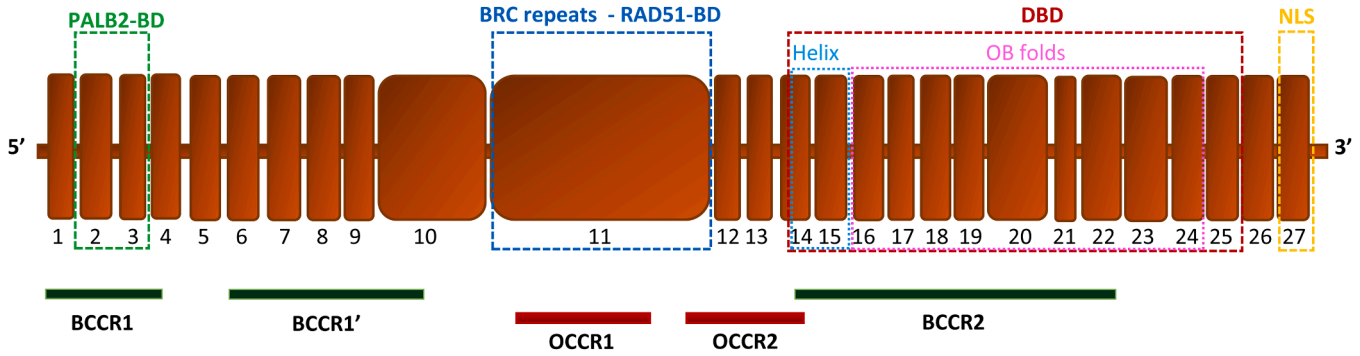


Fig. 2. Schematic representation of *BRCA2* structure and the corresponding protein domain organization. Key protein domains are highlighted, including the PALB2-binding (PALB2-BD) domain (green), the BRC repeats domain (blue), the DNA-binding domain (DBD) (red) with the helical domain(light blue) and the oligonucleotide/oligosaccharide-binding (OB) folds (pink), the nuclear localization signal (NLS) domain (yellow). The MANE Select reference transcript for *BRCA2* is NM_000059.4. Abbreviations: BCCR, Breast Cancer Cluster Region; BD, binding domain; DBD, DNA-binding domain; NLS, nuclear localization signal; OB-folds, oligonucleotide/oligosaccharide-binding folds; OCCR, Ovarian Cancer Cluster Region.

Furthermore, the pathogenic potential of splicing variants depends on their effects on RNA splicing and the resulting transcripts (Mesman et al., 2020).

Structural variants, including large deletions and duplications [copy-number variants (CNVs)], as well as inversions, are rarer, generally accounting for around 5% of all *BRCA1/BRCA2* P/LPVs (Pócza et al., 2021).

Recently, a distinct clinical-genetic category based on cancer penetrance has been proposed. Reduced-penetrance pathogenic variants (RPPVs) represent a heterogeneous group of *BRCA1/BRCA2* P/LPVs, encompassing selected missense, splice-site, and frameshift variants. These variants may retain partial function through different molecular mechanisms, including alternative splicing or escape from NMD, and have been associated with lower cancer risk than conventional high-penetrance *BRCA1/BRCA2* P/LPVs (Pal et al., 2024).

4. Breast cancer

4.1. Risk of developing breast cancer according to cluster regions and P/LPV types

4.1.1. Cluster regions

Among the clinical implications of *BRCA1/BRCA2* P/LPV types and genomic locations investigated to date, associations between variant location and relative BC and OC risk are supported by the strongest available evidence. Although BC risk remains overall higher than OC risk across *BRCA1/BRCA2* variants, specific genomic regions appear to be associated with a relative enrichment of OC versus BC susceptibility. The relationship between the location of P/LPVs and the associated risk of BC or OC has been recognized since the early days of *BRCA* gene research. In 1995, Gayther et al. demonstrated that P/LPVs at the 3′ end of *BRCA1* were linked to a higher risk of BC compared with other regions (Gayther et al., 1995). Years later, in the landmark study of Rebbeck et al., three regions within *BRCA1* were inferred to be BC cluster regions (BCCRs) of P/LPVs, one located in the 5′ (BCCR1) region and the other two in the 3′ (BCCR2 and BCCR2') (Rebbeck et al., 2015) (Fig. 1). In this study, variant-specific cancer risk profiles were expressed using the ratio of hazard ratio estimates (RHR), calculated as the BC hazard ratio (HR) divided by the OC HR for a given genomic region, with RHR $>$ 1 indicating a relative shift toward BC and RHR $<$ 1 indicating a relative shift toward OC. Importantly, these HR estimates operate on different absolute baseline risks, as BC risk remains substantially higher than OC risk overall among *BRCA1/BRCA2* carriers. Therefore, the RHR reflects a relative shift toward greater OC versus BC susceptibility rather than indicating that OC risk exceeds BC risk in absolute terms. The BCCRs were characterized by RHR estimates consistently above 1 across all identified regions (Rebbeck et al., 2015). BCCR1 partially overlaps with the RING domain of the BRCA1 protein, whereas BCCR2 and BCCR2′ overlap to some extent with the BRCT domain (Rebbeck et al., 2015).

Potential biological mechanisms underlying these associations remain largely speculative. The RING domain mediates heterodimerization with BARD1 and confers BRCA1's E3 ubiquitin ligase function. Estrogen receptor alpha (ERα) is a putative substrate of the BRCA1/BARD1 ubiquitin ligase: RING domain-mediated mono-ubiquitination of ERα regulates its transcriptional activity (Eakin et al., 2007). Moreover, the BRCA1/BARD1 complex catalyzes

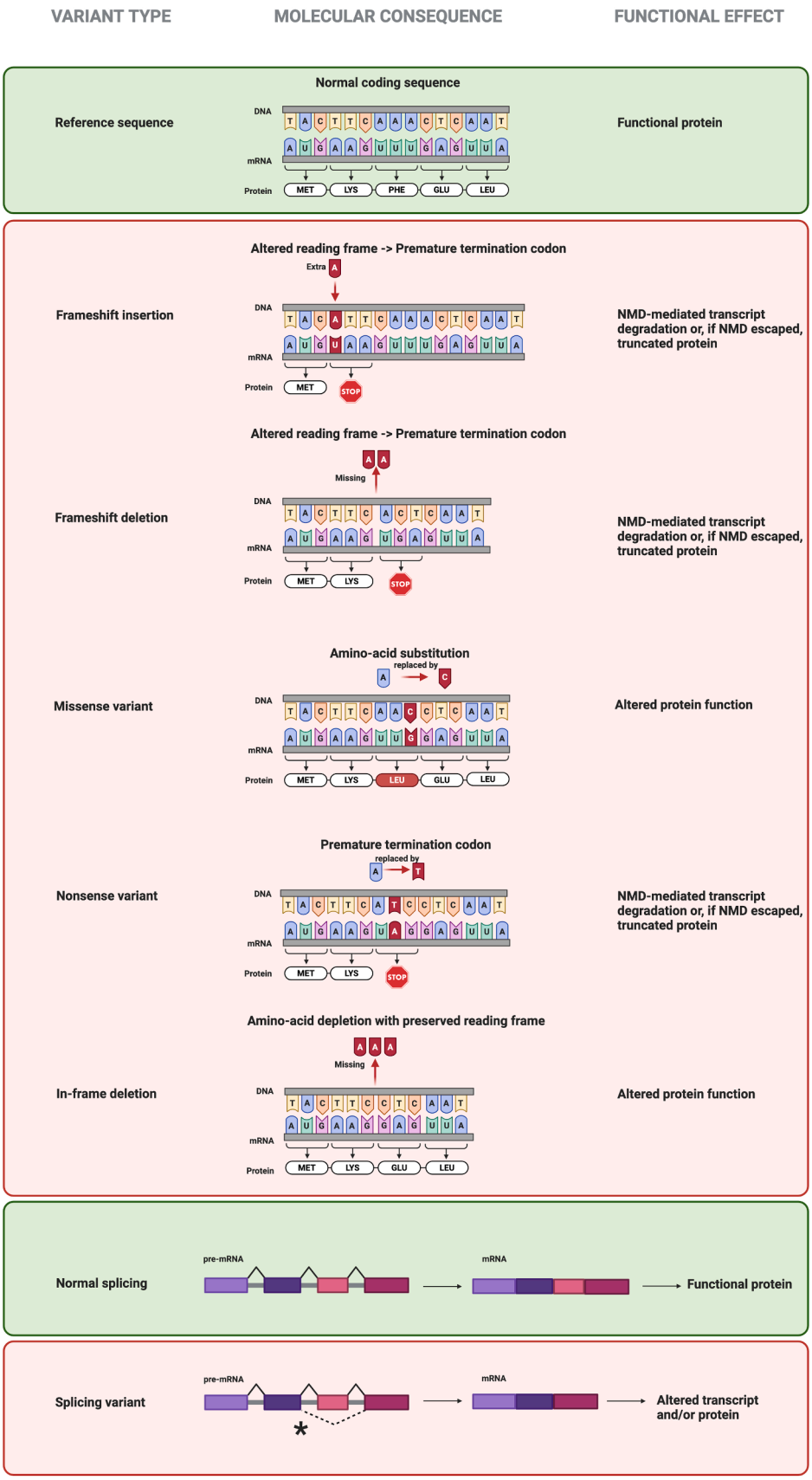


Fig. 3. P/LPV types and their consequences at the transcript/protein level. Large structural variants (large deletions or rearrangements) are not represented. Abbreviations: A, adenine; Ala, alanine; C, cytosine; G, guanine; Glu, glutamic acid; Gly, glycine; Leu, leucine; Lys, lysine; Met, methionine; NMD, nonsense-mediated mRNA decay; Phe, phenylalanine; T, thymine; U, uracil. Created in BioRender. ZATTARIN, E. (2026) https://BioRender.com/x66n961.

monoubiquitination of histone H2A, a critical step in promoting homologous recombination (Densham et al., 2016). Impaired DNA repair and dysregulated estrogen signaling have been proposed as potential mechanisms that could contribute to the particularly elevated BC risk associated with RING domain P/LPVs. On the other hand, given that the BRCT domain mediates BRCA1 recruitment to sites of DNA damage (Ismail et al., 2024), and that estrogens can induce DNA damage, loss of BRCT function could theoretically increase the susceptibility of mammary cells to estrogen-induced genomic instability.

Conversely, P/LPVs located within exon 11 of *BRCA1* have been associated with a relative shift toward OC versus BC susceptibility compared with variants outside exon 11, as reflected by a lower BC-to-OC RHR [0.62, 95% confidence interval (95% CI) 0.56–0.70] (Rebbeck et al., 2015). Furthermore, a smaller study suggested that P/LPVs located in exon 20 of *BRCA1* might be associated with a significantly higher risk of developing combined BC and OC compared with variants in other exons (Bayraktar et al., 2015) (Table 1). However, the available evidence is limited and this finding requires further validation before any definitive conclusions can be drawn.

Variant location has also been associated with differences in relative BC and OC susceptibility among *BRCA2* P/LPV carriers. Several BCCRs, all located outside exon 11, have been identified in *BRCA2*, including BCCR1 and BCCR1' in the 5' region and BCCR2 in the 3' region, the latter involving the OB folds. The P/LPVs in these regions were found to be characterized by a higher BC-to-OC risk compared to variants located in other regions, with RHR estimates consistently above 1 (Gayther et al., 1997; Rebbeck et al., 2015).

The recent analysis from the large CARRIER Consortium also supported a lower BC risk associated with *BRCA2* exon 11 P/LPVs compared with P/LPVs located outside exon 11 (Akamandisa et al., 2025).

4.1.2. P/LPV types

Beyond genomic location, P/LPV types and their functional consequences may also be relevant for BC risk, although the available evidence is less robust than that supporting location-specific associations (Table 1). Some studies have suggested that CNVs/structural variants may be associated with higher BC risk versus non-CNV P/LPVs (i.e.

Table 1
Summary of reported associations according to *BRCA1*/*BRCA2* P/LPV type and location.

	Region	BC risk (relative)[#]	OC risk (relative)[#]	BC prognosis (trend)[°]	OC prognosis (trend)[°]	Additional notes
Location-specific associations (*BRCA1*/*BRCA2*)						
BRCA1 P/LPV						
	BCCRs	↑	↓	NA	NA	Earlier BC onset
	OCCR - exon 11[£]	↓	↑	Worse OS	Greater PARPi treatment effect in exploratory analysis; conflicting OS results	Earlier OC onset
	exon 2[£]	NA	NA	Worse OS	NA	NA
	exon 20[£]	possible combined BC + OC risk	possible combined BC + OC risk	NA	NA	NA
BRCA2 P/LPV						
	BCCRs	↑	↓	NA	NA	Earlier BC onset
	OCCRs - exon 11[£*]	↓	↑	NA	Favorable outcomes reported	Earlier OC onset; later BC onset; "ER-negative BC cluster" (exon 11 PT)
	exon 10[£]	NA	NA	NA	NA	Earlier BC onset (< 30)
	exons 12–26[£]	NA	NA	Worse OS	NA	NA
	DBD	NA	NA	NA	NA	Greater PARPi treatment effect in exploratory analysis; lower frequency of BRCA reversion mutations reported
Variant type-specific associations (across *BRCA1*/*BRCA2*)						
	PT	↑[§]	↑[§]	NA	NA	Possible higher PARPi sensitivity in OC
	Missense	↓[§]	↓[§]	Favorable outcomes reported	Favorable outcomes reported	NA
	CNV/ structural	↑[§]	NA	NA	NA	Possible prolonged PARPi benefit in OC
	RPPV[&]	↓[§]	↓[§]	NA	NA	NA

Arrows indicate the direction of reported associations and should not be interpreted as indicating established clinical utility. Evidence strength varies substantially across associations, and prognostic and treatment-related findings are largely exploratory.
[#]Relative risk refers to the distribution of BC versus OC risk and does not reflect absolute cancer risk.
[°]Prognostic associations remain preliminary.
[£]We have retained the exon classification that was in use at the time each publication was released.
[§]Arrows for variant type refer to relative comparisons across variant classes.
*The *BRCA2* OCCR1 is located within exon 11.
[&]RPPVs include selected missense, splice-site, and frameshift variants that escape nonsense-mediated decay.
Abbreviations: BC, breast cancer; BCCR, breast cancer cluster region; BRCA1, breast cancer gene 1; BRCA2, breast cancer gene 2; CNV, copy number variation; DBD, DNA-binding domain; ER, estrogen receptor; NA, not available; OC, ovarian cancer; OCCR, ovarian cancer cluster region; OS, overall survival; PARPi, poly(ADP-ribose) polymerase inhibitor; PT, protein-truncating; RPPV, reduced-penetrance pathogenic variant.

indels or SNVs) (*BRCA1* CNVs: HR = 1.21, 95% CI 1.09–1.35) (Hakkaart et al., 2022). Conversely, *BRCA1/BRCA2* missense P/LPVs might be associated with a lower BC risk versus protein-truncating variants: in the study of Li et al. this difference was statistically significant only for *BRCA1* (for *BRCA1* missense P/LPVs: HR = 3.9, 95% CI 2.4–6.2; for *BRCA1* protein-truncating variants: HR = 12.8, 95% CI 5.7–28.7; P = 0.01) (Li et al., 2022). These findings remain preliminary and should not be interpreted as evidence of uniformly lower penetrance across missense variants.

With regard to RPPVs, available evidence suggests that the BC risk associated with some variants may approximate that observed for moderate-penetrance genes such as *ATM* or *CHEK2*. However, penetrance appears to be variant-specific, and current evidence is insufficient to generalize these risk estimates across all RPPVs (Pal et al., 2024).

4.2. Age at breast cancer onset

Genomic regions associated with greater relative BC susceptibility also appear to be associated with a younger age at BC diagnosis. Evidence from large studies suggests that, for both *BRCA1* and *BRCA2*, the mean age at BC diagnosis is lower among carriers of P/LPVs located in BCCRs than among those with variants in other regions (Akamandisa et al., 2025; Rebbeck et al., 2015). Moreover, some founder variants, i.e. variants observed with high frequency in a specific population due to a common ancestor, have been associated with an earlier age at BC diagnosis (Rebbeck et al., 2015). In the analysis of the *BRCA* BCY Collaboration, involving 3294 *BRCA1/BRCA2* carriers diagnosed with stage I-III BC at age $\leq$ 40, *BRCA2* exon 10 P/LPVs were associated with earlier BC onset (< 30 years) compared with variants in other exons (Toss et al., 2026).

4.3. Prevalence of BRCA1/BRCA2 P/LPV types in patients with breast cancer

The prevalence of specific *BRCA1/BRCA2* P/LPVs in BC patients is population-dependent, as their distribution varies across ethnic and geographic groups, in part due to founder effects. Nevertheless, available studies have reported broadly similar distributions of variant types across different study populations. In the phase III OlympiAD trial, the majority of enrolled patients carried a germline *BRCA1/BRCA2* frameshift P/LPV (185, 62.3%), followed by nonsense variants (60, 20.2%), missense (23, 7.7%), splice-site variants (15, 5.1%), and large rearrangements (13, 4.4%) (Toss et al., 2026).

In the large population-based CARRIER study, as well as in other smaller observational studies, broadly similar patterns were reported, with frameshift variants representing approximately 60%, followed by nonsense (about 20%), missense (around 10%), splicing variants (less than 10%), and a smaller proportion of large genomic rearrangements and in-frame deletions (Akamandisa et al., 2025; Corso et al., 2023; Toss et al., 2026).

4.4. Breast cancer phenotype

It is well established that more than 70% of BCs in *BRCA1* P/LPV carriers are triple-negative (TNBC), whereas around 75% of BCs in *BRCA2* P/LPV carriers are estrogen receptor (ER)-positive, more often Luminal B-like (Breast Cancer Association Consortium et al., 2022; Lambertini et al., 2025; Zattarin et al., 2023). In contrast, whether specific P/LPV types or genomic locations are associated with distinct BC phenotypes remains uncertain. To date, most studies have not identified significant associations between specific P/LPV characteristics and the occurrence of TNBC or ER-positive BC (Bayraktar et al., 2015; Incorvaia et al., 2020; Li et al., 2022; Toss et al., 2026). However, an analysis from the large CARRIER Consortium reported an association between protein-truncating variants located in exon 11 of *BRCA2* and a higher relative risk of ER-negative BC, leading the authors to propose a potential "ER-negative cluster region" (Akamandisa et al., 2025). This finding requires independent validation before a robust genotype-phenotype association can be established.

4.5. Breast cancer prognosis and treatment response

An increasing number of studies are exploring the relationship between the type or genomic location of *BRCA1/BRCA2* P/LPVs and BC prognosis; however, the available evidence remains preliminary, heterogeneous, and largely derived from retrospective analyses.

As for variant type and coding consequence, some studies have suggested a potential association between missense P/LPVs and more favorable BC outcomes, although findings have not been consistent across endpoints. Corso et al. (2023) found that missense/splicing P/LPVs were independently associated with a lower incidence of locoregional recurrence after primary surgery with curative intent, compared with other variants. However, overall survival (OS) did not vary according to variant subtypes.

In the analysis of the *BRCA* BCY Collaboration, missense *BRCA1/BRCA2* P/LPVs were associated with improved OS versus frameshift variants for *BRCA1* and splicing variants for *BRCA2* (Toss et al., 2026). Moreover, in the same study, protein-truncating P/LPVs in both *BRCA1* and *BRCA2* were associated with worse OS compared to non-truncating variants (statistically significant only for *BRCA1* carriers). In *BRCA2* carriers, a trend toward shorter disease-free survival (DFS) was also observed, and this appeared to be driven by a higher rate of locoregional and distant relapses, which might have contributed to a numerically poorer OS. Conversely, in *BRCA1* carriers the significant difference in OS was not paralleled by DFS. The reasons underlying this discordance remain unclear, and a potential contribution of factors unrelated to BC recurrence, including comorbidities, can only be hypothesized (Toss et al., 2026).

Regarding genomic location, *BRCA1* exon 2 and exon 10 (former exon 11) P/LPVs have been associated with worse BC OS compared to other exons in the *BRCA* BCY study (Toss et al., 2026). Another retrospective study found no significant differences in OS in relation to *BRCA1* variant location (Bayraktar et al., 2015). These two studies also showed that P/LPVs located in the later exons of *BRCA2* were associated with worse outcomes (for Toss et al.: exons 15–26 versus exon 10; for Bayraktar et al.: exons 12–25 versus other exons) (Bayraktar et al., 2015; Toss et al., 2026). In another small cohort, a specific *BRCA1* CNV (BRCA1 ex9–12del), a founder mutation in the Mexican population, was associated with improved outcomes in stage I-III TNBC patients aged $\leq$ 50 (Villarreal-Garza et al., 2021).

As previously stated, the type and location of *BRCA1/BRCA2* P/LPVs may result in different degrees of functional protein impairment and have also been associated with differences in allele-specific loss of heterozygosity (LOH) patterns (Santana Dos Santos et al., 2022). LOH has been investigated as a potential biomarker of functional BRCA deficiency and sensitivity to DNA-damaging agents; however, its ability to predict treatment benefit or clinical outcomes according to specific germline P/LPVs remains uncertain (Maxwell et al., 2017).

Evidence supporting differential benefit from systemic BC treatments according to the specific type or location of germline *BRCA1/BRCA2* P/LPVs is currently lacking. In a small exploratory analysis based on a retrospective study, no significant associations were found between *BRCA2* P/LPV type or location and progression-free survival (PFS) with CDK4/6 inhibitors plus endocrine therapy or with PARPi in a small cohort of 57 *BRCA2* carriers (Zattarin et al., 2025). Given the small sample size, these findings should be regarded as hypothesis-generating and do not exclude the possibility of variant-specific differences in treatment response.

5. Ovarian cancer

5.1. Risk of developing ovarian cancer according to cluster regions and P/LPV types

5.1.1. Cluster regions

BRCA1/BRCA2 P/LPVs are known to be associated with a lifetime OC risk of around 40% for *BRCA1* carriers and around 20% for *BRCA2* carriers (Kuchenbaecker et al., 2017). Among the various genotype-phenotype associations described in *BRCA* carriers, the relationship between variant location and the relative risks of BC and OC is supported by the most consistent available evidence. The location of P/LPVs within *BRCA1 or BRCA2* appears to influence the relative likelihood of developing OC versus BC (Gayther et al., 1997, 1995; Rebbeck et al., 2015). Carriers of P/LPVs located in exon 11 of either *BRCA1* or *BRCA2* appear to have a relative shift toward OC rather than BC susceptibility (Rebbeck et al., 2015). In *BRCA1*, the OCCR identified by Rebbeck et al. is entirely enclosed within legacy exon 11 (corresponding to exon 10 in the current MANE transcript). P/LPVs located in the OCCR are associated with a relatively lower risk of BC versus OC (RHR = 0.62, 95% CI 0.56–0.70) (Table 1) (Rebbeck et al., 2015). In *BRCA2,* the OCCR1 colocalizes with the BRC repeats within exon 11, while the OCCR2 involves the downstream exons. P/LPVs occurring in either OCCR1 or OCCR2 are associated with a relative decrease in BC versus OC risk (for OCCR1, RHR = 0.51, 95% CI 0.44–0.60; for OCCR2, RHR = 0.57, 95% CI 0.41–0.80) (Table 1) (Rebbeck et al., 2015). The BRCA2 BRC repeats mediate direct RAD51 binding and are essential for homologous recombination (Fradet-Turcotte et al., 2016). Impaired RAD51 binding capacity has been hypothesized to have greater biological relevance in tissues with high proliferative activity, such as the fallopian tube secretory epithelium (Galhenage et al., 2023). Consistent with this, germline P/LPVs in *RAD51C* and *RAD51D* also confer OC risk (Daly et al., 2021). This remains a hypothesis-generating interpretation and requires mechanistic validation.

5.1.2. P/LPV types

As mentioned above for BC, some observational data suggest that OC risk may differ according to variant type, with lower risk estimates reported for carriers of missense *BRCA1/BRCA2* P/LPVs compared with protein-truncating variants (missense variants: HR = 3.9, 95% CI 2.0–7.2; protein-truncating variants: HR = 7.0, 95% CI 3.3–14.7) (Li et al., 2022). In the same retrospective study, the *BRCA2* (NM_000059.4):c.7878 G>C, p.(Trp2626Cys) missense variant was associated with a lower estimated penetrance for OC compared with other *BRCA2* missense or protein-truncating P/LPVs (Li et al., 2022). Given the retrospective nature of these findings and the limited evidence available for individual variants, these observations should be considered hypothesis-generating and require validation in independent cohorts.

5.2. Age at ovarian cancer onset

Understanding whether the age at OC onset varies according to the type or location of germline P/LPVs could potentially support more personalized counseling regarding the timing of risk-reducing salpingo-oophorectomy (RRSO). Several studies have reported that *BRCA1* carriers develop OC at a younger age than *BRCA2* carriers, with a median age at diagnosis of approximately 53 years, around 5 years earlier than that reported for *BRCA2* carriers (Marchetti et al., 2023).

Beyond gene-specific differences, some studies have suggested that variant type or location may also influence age at OC onset, although the available evidence remains limited and not entirely consistent. For example, P/LPVs located within the *BRCA1* OCCR have been associated with an earlier onset of OC compared with variants located outside exon 11 (Rebbeck et al., 2015). In a recent multicenter European study including 474 OC patients carrying germline *BRCA1/BRCA2* P/LPVs, nonsense variants were associated with the youngest median age at diagnosis (52.2 years), whereas frameshift variants were associated with the oldest (55.9 years) (Marchetti et al., 2023). However, a Japanese cohort study of nearly 500 OC patients found no significant differences in age at OC onset across P/LPV types, although an earlier onset was observed among *BRCA1* compared with *BRCA2* carriers (Sekine et al., 2022).

5.3. Prevalence of BRCA1/BRCA2 P/LPV types in patients with ovarian cancer

In OC studies, approximately half of the *BRCA1/BRCA2* P/LPVs are located in exon 11 of the respective genes (Labidi-Galy et al., 2023; Marchetti et al., 2025). When considering variant types, over half of *BRCA1/BRCA2* P/LPVs are frameshift, followed by nonsense variants in about 20–30% of cases. Missense variants comprise roughly 10%, whereas large rearrangements and splicing mutations each account for around 5% (Labidi-Galy et al., 2023; Marchetti et al., 2025; Ray-Coquard et al., 2019).

According to historical functional domain classifications (see Section 3.1), the BRCA1 regions in which variants were most frequently observed were the DBD and BRCT domains, followed by the RING domain (Liu et al., 2026). In BRCA2, approximately half of the variants are located within the BRC repeats/RAD51-binding domain, followed by the DBD (Labidi-Galy et al., 2023; Marchetti et al., 2025). While these data describe the distribution of *BRCA1/BRCA2* P/LPVs across variant types and functional regions in OC cohorts, the relative frequency of variants within specific domains should not, by itself, be interpreted as evidence of differential biological or clinical relevance.

5.4. Ovarian cancer prognosis and treatment response

The majority of reports in OC have examined *BRCA1/BRCA2* P/LPVs without differentiating germline (constitutional) from somatic (acquired) variants. Since somatic *BRCA1/BRCA2* P/LPVs often occur early during tumorigenesis and are frequently associated with biallelic inactivation, several studies have suggested substantial biological and clinical similarities between germline and somatic *BRCA* alterations in OC patients (Dougherty et al., 2017).

Several studies have reported more favorable OC outcomes among *BRCA2* P/LPV carriers compared with *BRCA1* carriers, including greater sensitivity to platinum-based chemotherapy and PARPi, as well as longer survival (Bolton et al., 2012; Škof et al., 2024; Yang et al., 2011). However, whether prognosis and treatment response are further influenced by the specific type or genomic location of *BRCA1/BRCA2* P/LPVs remains an area of ongoing investigation, with the available evidence still preliminary, heterogeneous, and sometimes conflicting.

Given its biological relevance, including its overlap with the OCCR, exon 11 has received particular attention in studies exploring the prognostic and predictive implications of *BRCA1* P/LPV location. In a post hoc subgroup analysis of the large phase III PAOLA-1/ENGOT-ov25 trial, all patients with *BRCA1/BRCA2* P/LPVs derived benefit from maintenance olaparib plus bevacizumab, but the magnitude of benefit tended to be higher for patients with P/LPVs located in exon 11 (Labidi-Galy et al., 2023). However, in an Italian retrospective study, the greatest benefit from PARPi was observed among carriers of variants located outside exon 11 (Marchetti et al., 2025), and a small South Korean observational study reported improved PFS, but not OS, among carriers of variants located outside the OCCR region/exon 11 (Ha et al., 2022).

Conflicting results have also emerged regarding the clinical relevance of other specific BRCA1 regions. Although the BRCA1 DBD is a historically defined region within legacy exon 11 that is no longer recognized as a distinct structural domain, and was therefore not included as a separate region in Table 1 (see Section 3.1), it continues to be considered in clinical studies. Notably, several studies have reported

favorable clinical outcomes associated with P/LPVs located within the BRCA1 DBD, including exploratory evidence of greater PARPi benefit. In the PAOLA-1 study, the magnitude of benefit from olaparib plus bevacizumab was particularly high among patients carrying *BRCA1* P/LPVs located within the DBD (Labidi-Galy et al., 2023). Similar observations have emerged from other recent PARPi-treated cohorts (Kim et al., 2025a; Liu et al., 2026; Momi et al., 2026). In addition, Zwimpfer et al. reported improved PFS and OS among carriers of *BRCA1* P/LPVs affecting the DBD, compared with noncarriers (Zwimpfer et al., 2026).

In the PAOLA-1/ENGOT-ov25 trial, P/LPVs affecting the RING domain were associated with a relatively reduced magnitude of benefit from olaparib plus bevacizumab therapy (Labidi-Galy et al., 2023). Consistent with this observation, two single-center studies reported reduced OC survival among carriers of RING domain variants (Momi et al., 2026; Škof et al., 2024). Preclinical studies have proposed a biological explanation for these observations, suggesting that RING-less BRCA1 isoforms may retain partial homologous recombination function and subsequently reduced sensitivity to PARPi through RAD51 activation (Drost et al., 2016). Conversely, Marchetti et al. reported greater benefit from PARPi among carriers of variants located within the RING and BRCT domains compared with those affecting the BRCA1 DBD (Marchetti et al., 2025), underscoring the heterogeneity of findings across studies.

Data regarding *BRCA1* variant type are similarly limited and conflicting. In post hoc analyses from Study 10 and ARIEL2, structural variants were associated with prolonged duration of response to PARPi (Swisher et al., 2021), while the study by Marchetti et al. suggested improved outcomes among carriers of missense variants, potentially driven by the enrichment of a specific NM_007294.4(BRCA1): c.5123 C>A (p.Ala1708Glu) variant (Marchetti et al., 2025).

Among *BRCA2* carriers, several retrospective studies and a meta-analysis have reported favorable outcomes for patients harboring variants located within exon 11, including improved PFS and, in some studies, OS and greater benefit from PARPi (Gallardo-Rincón et al., 2020; Ha et al., 2022; Kim et al., 2025b; Labidi-Galy et al., 2018). Similar observations have been described for variants affecting the BRC repeats (RAD51-binding domain) (Labidi-Galy et al., 2018; Marchetti et al., 2025; Momi et al., 2026). These findings are biologically plausible, as disruption of this central region may result in profound impairment of homologous recombination function, potentially enhancing sensitivity to platinum agents and PARPi and, consequently, contributing to improved survival outcomes (Ware et al., 2006).

Additional evidence derives from subgroup analyses of PARPi-treated cohorts. In PAOLA-1/ENGOT-ov25, the largest treatment effect was observed among carriers of *BRCA2* P/LPVs located within the DBD (Labidi-Galy et al., 2023). One hypothesis is that the relatively low frequency of reversion mutations reported in the 3′ portion of *BRCA2*, which encodes the DBD, might contribute to a lower likelihood of acquired resistance; however, this potential mechanism remains speculative (Tobalina et al., 2021). Consistent with this hypothesis, *BRCA2* structural variants, which appear less prone to reversion events (Piombino and Cortesi, 2022), were associated with prolonged benefit from rucaparib in post hoc analyses of responders from Study 10 and ARIEL2 (Swisher et al., 2021). However, these findings should be interpreted with caution. Most available data derive from retrospective cohorts, post hoc subgroup analyses, or relatively small patient populations, and several studies have failed to confirm a prognostic or predictive role for *BRCA2* exon 11 variants or specific variant classes (Alsop et al., 2012; Dougherty et al., 2017).

Overall, current evidence suggests that *BRCA1/BRCA2* P/LPV type and location may influence treatment response and clinical outcomes in OC, but these associations remain conflicting and insufficiently validated for routine clinical application, and should currently be regarded as hypothesis-generating.

6. Conclusions and future perspectives

Accumulating evidence indicates that *BRCA1* and *BRCA2* P/LPVs are not biologically equivalent and that variant type and genomic location may contribute to the clinical heterogeneity observed among *BRCA*-associated cancers. The most robust data support an association between specific genomic regions and the relative risks of BC and OC, particularly within the framework of BCCRs and OCCRs. By contrast, evidence regarding age at onset, tumor phenotype, prognosis, and treatment response remains less mature and, in some cases, conflicting. Interpretation of these associations is limited by the retrospective design and relatively small sample size of many available studies, heterogeneous approaches to grouping variants by type or genomic location, and the limited number of carriers within specific variant subgroups. Beyond genotype-phenotype correlations for established P/LPVs, a related challenge in *BRCA1/BRCA2* variant interpretation is the classification of variants of uncertain significance (VUS) (Parsons et al., 2024).

Future research should integrate clinical and epidemiological data with emerging functional approaches to address these unresolved questions. High-throughput functional approaches, including saturation genome editing, may enable systematic characterization of individual variants and provide experimentally derived evidence that, when integrated with other lines of evidence, can refine variant classification and help resolve VUS (Huang et al., 2025). Beyond their role in variant pathogenicity classification, these approaches may also help characterize differences in functional impairment among established P/LPVs. Integration of functional evidence with large-scale epidemiological and clinical datasets will therefore be essential to determine whether these differences translate into clinically meaningful differences in cancer risk and penetrance and whether they are associated with specific variant types or genomic regions.

With further validation, the genotype-based management of *BRCA1/BRCA2* P/LPVs might be relevant to several aspects of daily practice. Firstly, robust variant-specific penetrance estimates could refine risk assessment within families and help contextualize cascade testing results by providing relatives carrying the same P/LPV with more precise estimates of their individual cancer risk. Such information could also enable more personalized genetic counseling and primary prevention strategies. While current National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend RRSO with different cut-off ages depending on *BRCA1* or *BRCA2* and the earliest case of OC in the family, in the future the optimal age at which RRSO should be performed could potentially vary according to the specific type or location of the P/LPV (Daly et al., 2021; Sessa et al., 2023). Similarly, the indication for risk-reducing bilateral mastectomy (RRBM) could be evaluated based on the specific risk associated with the individual P/LPV.

Variant-specific risk estimates might also inform the intensity, timing, and modality of surveillance, potentially allowing secondary prevention strategies to be tailored to the magnitude and age-specific pattern of cancer risk associated with individual P/LPVs. For example, more intensive or earlier surveillance could potentially be considered for variants associated with higher or earlier cancer risk, whereas lower-penetrance variants might warrant less intensive approaches. The choice of the most appropriate treatment might also eventually be informed by specific germline or somatic P/LPVs associated with greater or lower treatment benefit, particularly from targeted therapies such as PARPi.

However, the current body of evidence remains insufficient to support the clinical use of variant type or genomic location as predictive biomarkers, and substantially stronger, consistent, and prospectively validated data will be required before such information can inform treatment selection.

Similar studies should also be extended to other cancers for which PARPi have been approved, such as prostate and pancreatic cancer, to better define genotype-phenotype correlations across the full spectrum

of *BRCA*-associated tumors.

7. Critical View

This review highlights the heterogeneous spectrum of *BRCA1* and *BRCA2* P/LPVs, their functional consequences, and the available evidence regarding their associations with BC and OC risk, prognosis, and treatment benefit. A deeper understanding of the distinctive features of individual P/LPVs may ultimately help refine risk assessment and treatment strategies. However, translating these emerging genotype-phenotype associations into clinically actionable information remains challenging. Most available data derive from retrospective studies, exploratory subgroup analyses, post hoc analyses of clinical trials, or relatively small cohorts. Consequently, many of the reported associations between specific *BRCA1/BRCA2* P/LPVs and prognostic outcomes or therapeutic sensitivity should currently be regarded as hypothesis-generating rather than practice-changing. The principal contribution of this review is the critical synthesis of both established and emerging evidence regarding variant-specific clinical implications. Future international collaborations, large real-world datasets, and integrated genomic-clinical analyses will be essential to determine whether variant-specific information can ultimately be incorporated into personalized risk assessment, genetic counseling, preventive strategies, and treatment selection for individuals carrying *BRCA1/BRCA2* P/LPVs.

CRediT authorship contributions statement

Emma Zattarin: Conceptualization, Methodology, Writing - original draft, Project administration. Claudia Piombino: Conceptualization, Methodology, Writing - original draft. Elena Tenedini: Writing - original draft. Flavia Siciliano: Writing - review & editing. Isabella Galasso: Writing - review & editing. Elena Barbieri: Writing - review & editing. Mina Grippa: Writing - review & editing. Silvia Zaniboni: Writing - review & editing. Ornella Ponzoni: Writing - review & editing. Pablo Mando: Writing - review & editing. Matteo Lambertini: Validation, Writing - review & editing. Eva Blondeaux: Writing - review & editing. Enrico Tagliafico: Writing - review & editing. Federico Piacentini: Validation, Writing - review & editing. Siddhartha Yadav: Validation, Writing - review & editing. Giovanni Grandi: Writing - review & editing. Massimo Dominici: Supervision. Laura Cortesi: Validation, Writing - review & editing. Angela Toss: Conceptualization, Methodology, Validation, Writing - review & editing, Supervision, Project administration, Funding acquisition. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

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