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Prognostic and predictive value of HRD in early triple negative breast cancer (TNBC)

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ABSTRACT

This review explores the emerging role of homologous recombination deficiency (HRD) as both a prognostic and predictive biomarker in early-stage triple-negative breast cancer (TNBC). HRD arises from the defective repair of DNA double-strand breaks through homologous recombination, resulting in genomic instability and increased sensitivity to DNA-damaging agents such as platinum compounds. The review outlines the biological basis of HRD, including genomic signatures such as loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions, and highlights its prevalence in TNBC compared with other breast cancer subtypes. Clinical trials have shown that HRD-positive patients often achieve higher pathological complete response rates and improved disease-free survival when treated with chemotherapy. However, conflicting evidence across trials underscores the need for more reliable and standardized methods for HRD assessment. The review also explores the therapeutic potential of poly(ADP-ribose) polymerase inhibitors in TNBC, particularly in *BRCA*-mutated or HRD-positive tumors. Agents such as olaparib, talazoparib, and niraparib have demonstrated promising efficacy in both neoadjuvant and adjuvant settings with some trials suggesting that selected patients may avoid chemotherapy. Furthermore, HRD-positive tumors are characterized by increased genomic instability and a higher neoantigen burden, promoting immune cell infiltration, particularly of tumor-infiltrating lymphocytes, which may enhance responsiveness to immune checkpoint inhibitors. Overall, current evidence supports the role of HRD as a promising biomarker in TNBC. However, further research is required to refine its clinical utility and to integrate HRD testing into personalized treatment strategies, especially in combination with emerging therapies such as immunotherapy.

1. Methods

This review was conducted as a narrative review of the available evidence regarding homologous recombination deficiency (HRD) in triple-negative breast cancer (TNBC), with a particular focus on early-stage disease. Original clinical trials, translational studies, genomic analyses, and landmark biological investigations published in English were considered eligible. Additional studies were identified through manual screening of reference lists from relevant publications. Priority was given to studies evaluating the prognostic and predictive value of HRD, methods for HRD assessment, and the therapeutic implications of HRD in early-stage TNBC. Given the narrative nature of this review, no formal meta-analysis or risk-of-bias assessment was performed.

2. Mechanisms of DNA damage repair and the role of homologous recombination deficiency

DNA is continuously exposed to damage from both environmental and endogenous sources, resulting in a wide spectrum of lesions including single-strand breaks (SSBs), double-strand breaks (DSBs), base modifications, and DNA cross-links. These lesions are repaired by specialized DNA damage-response pathways. SSBs affect only one DNA strand and are primarily repaired through the base excision repair (BER) pathway, which recognizes and removes damaged bases and restores

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DNA integrity. In contrast, nucleotide excision repair (NER) mainly removes bulky DNA adducts and helix-distorting lesions, whereas mismatch repair (MMR) corrects base-pair mismatches and insertion–deletion loops arising during DNA replication. Together, these pathways contribute to the maintenance of genomic stability through the repair of distinct classes of DNA damage. By contrast, DSBs are particularly deleterious because they often lack an intact template for error-free repair and are primarily repaired through homologous recombination (HR) or non-homologous end joining (NHEJ), microhomology-mediated end joining and Polθ-mediated repair. Among these pathways, HR is a high-fidelity repair mechanism essential for genome stability, whereas the others are intrinsically error-prone and promote mutation accumulation and chromosomal rearrangements. The HR system repairs replication coupled DSBs using the sister chromatid as a template, preserving sequence information with minimal mutagenesis (Furlanetto et al., 2021; Hwang et al., 2020; Slavin et al., 2017; Truong et al., 2013; Vogt and He, 2023; Witz et al., 2025).

HR is a multistep process involving several factors, with BRCA1 and BRCA2 as central effectors. DSB recognition by the MRN complex (MRE11–RAD50–NBS1) activates ATM, which coordinates early damage signaling and recruitment of downstream repair proteins. BRCA1, CHEK1, and CHEK2 are subsequently assembled at the break site, promoting DNA end resection and generation of single-stranded DNA (ssDNA) overhangs. These ssDNA regions are coated with replication protein A (RPA), facilitating ATR activation and checkpoint signaling. Subsequent recruitment of PALB2 and BRCA2 enables replacement of RPA with RAD51 on strands, thereby allowing high-fidelity DNA synthesis and completion of repair through additional HR subpathways that restore chromosomal integrity (Stewart et al., 2022).

Loss or dysfunction of key HR components (*BRCA1/2*, *PALB2*, *RAD51* paralogs, Fanconi genes, etc.) decreases HR capacity and shifts DSB repair toward low-fidelity mechanisms. Functionally, this results in both large-scale chromosomal instability and mutational signatures. Repeated replication stress and error-prone repair generate stable genomic alterations that may persist even after HR function is restored. Three classes of large-scale genomic alterations are particularly relevant in HRD. These include loss of heterozygosity (LOH), defined as genomic regions larger than 10–15 Mb characterized by the loss of one parental allele; telomeric allelic imbalance (TAI), consisting of regions typically exceeding 11 Mb that extend to the subtelomeric region and reflects unbalanced rearrangements reaching the chromosome end; and large-scale state transitions (LST), defined as chromosomal breaks between adjacent regions of at least 10 Mb, indicative of clustered chromosomal rearrangements resulting from defective DSB repair. Their combined quantification, referred to as the HRD score or "genomic instability score" (GIS), represents the principal chromosomal-level readout currently used in clinical practice, particularly in ovarian and breast cancers, and correlates with sensitivity to poly (ADP-ribose) polymerase inhibitors (PARPi). Beyond defective DSB repair, impairment of HR also compromises replication fork protection, resulting in fork degradation, collapse, and further accumulation of DNA lesions that exacerbate genomic instability (Birkbak et al., 2012; Ferrer-Torres et al., 2025; Hwang et al., 2020; Popova et al., 2012; Schlacher et al., 2011).

In summary, HRD-positive tumors become dependent on error-prone DSB repair pathways, including NHEJ, which promote structural chromosomal alterations such as large-scale copy number variations (CNVs), chromosomal rearrangements, and micronuclei formation. These irreversible genomic scars reflect prior HR deficiency and represent the biological basis underlying current HRD genomic assays. The growing interest in HRD stems from its ability to confer therapeutic vulnerabilities and remodel the tumor–immune microenvironment (Abkevich et al., 2012; Birkbak et al., 2012; Konstantinopoulos et al., 2015; Maciejowski and Hatch, 2020; Popova et al., 2012; Telli et al., 2016; Witz et al., 2025).

Depending heavily on error-prone DNA repair pathways, HRD–positive tumors become particularly vulnerable to DNA-damaging agents. In high-grade serous ovarian cancers, HRD status correlates with increased initial sensitivity to platinum-based chemotherapy and longer progression-free survival compared with the HRD-negative tumors. Loss of HR function also creates a synthetic lethal dependency on PARP-mediated SSB break repair, which underlies the remarkable efficacy of PARPi in *BRCA1/2*-mutated and HRD-positive cancers. Conversely, restoration of HR proficiency through secondary reversion mutations, replication fork stabilization, or activation of compensatory repair pathways has been identified as a major mechanism of resistance to platinum-based chemotherapy and PARPi (Poveda et al., 2021; Vasconcellos et al., 2025).

Finally, HRD status correlates with a distinct tumor immune microenvironment characterized by concurrent inflammation and immune suppression. HRD-associated genomic instability promotes the accumulation of cytosolic DNA fragments generated by unresolved DNA damage and micronuclei rupture, triggering innate immune signaling pathways such as the cGAS–STING (Stimulator of INterferon Genes) axis. While acute activation of STING can enhance type I interferon production and immune cell recruitment, chronic chromosomal instability may paradoxically drive immune evasion through loss of antigen presentation machinery and sustained immune checkpoint expression. These observations highlight the potential immunological consequences of HRD (Ali et al., 2024; Chopra et al., 2020; Davoli et al., 2017; Eikesdal et al., 2021; Habaka et al., 2025; Harding et al., 2017; Lord and Ashworth, 2013; Pellegrino et al., 2020; Qiu et al., 2024; Silva et al., 2022; Xu et al., 2025).

Although several reviews have addressed HRD in breast cancer, recent advances in genomic HRD testing, PARP inhibitor development, and immunotherapy combinations have substantially expanded the field. Moreover, the clinical significance of HRD in early-stage TNBC remains incompletely defined, particularly in BRCA1/2 wild-type disease. This review aims to provide an updated and clinically focused overview of the biological basis, prognostic significance, predictive value, and therapeutic implications of HRD in early-stage TNBC, while critically discussing current limitations and future directions.

2.1. DNA-based metrics for assessing HRD in tumors

Strategies used to identify HRD can be broadly divided into three categories. The first approach involves detection of genetic or epigenetic alterations that directly impair HR, including mutations, deletions, or promoter methylation involving *BRCA1*, *BRCA2*, or other HR-related genes. The second relies on functional assays that assess the ability of tumor cells to activate HR, most commonly through evaluation of RAD51 foci formation at DSB sites. The third and most widely adopted strategy relies on the genomic consequences of defective DNA repair, commonly referred to as genomic scars. These scars consist of characteristic patterns of genomic instability—such as LOH, LST, and TAI—that reflect the historical activity of error-prone repair mechanisms compensating for HRD. Pathogenic or likely pathogenic somatic or germline variants in *BRCA1* and *BRCA2* remain the most frequent and clinically relevant determinants of HRD, conferring increased susceptibility to breast and ovarian cancers. Nevertheless, mutations in other genes involved in the HR pathway—such as *PALB2, BARD1, RAD50, RAD51, ATM, MRE11, RPA, NBS1, CHEK2, TP53, PTEN*, and *BRIP1*—may also induce HRD, thereby defining the so-called "BRCA-ness" phenotype (Ali et al., 2024; Pellegrino et al., 2020; Stewart et al., 2022).

In addition to sequence variants, epigenetic and transcriptional mechanisms may functionally silence HR genes, such as promoter hypermethylation of *BRCA1* or *RAD51* or dysregulation of epigenetic regulators of HR gene expression. Functional HR capacity can be evaluated using *RAD51* foci–based assays performed on frozen or formalin-fixed paraffin-embedded tissue, or on patient-derived cells or organoids exposed to genotoxic agents. These assays evaluate the current functional status of the HR pathway and may identify tumors in which HR

function has been restored despite persistent genomic scars. However, although several *RAD51*-based assays show promising performance, none has yet been fully standardized for routine clinical use, and their applicability is limited by tissue requirements and tumor proliferation rates. Fig. 1 (Bonnet et al., 2022; Garutti et al., 2019; Kim et al., 2024; Mio et al., 2019; van Biljon et al., 2023).

Most clinically implemented HRD assays rely on detecting genomic alterations arising from defective HR repair, including CNVs, insertions and deletions, point mutations, and structural rearrangements. Advances in sequencing technologies have led to multiple assays targeting different classes of abnormalities, each producing a quantitative score used to infer HRD status. Cutoffs are generally established based on correlations with response to platinum-based chemotherapy and PARPi, particularly in ovarian cancer and increasingly in prostate and breast cancers. Early approaches used single-nucleotide polymorphism (SNP) arrays to detect LOH, TAI, LST, and CNVs, which were integrated through bioinformatic pipelines to infer HRD status. Subsequently, next-generation sequencing (NGS) methods have been introduced. Two FDA-approved companion diagnostic assays based on targeted panels, Myriad myChoice CDx and FoundationOne CDx, are currently used mainly in ovarian carcinoma. MyChoice CDx integrates *BRCA1/2* mutation status with a GIS derived from LOH, TAI, and LST, whereas FoundationOne CDx combines comprehensive genomic profiling with quantification of genomic LOH to classify tumors as HRD-positive or HRD-negative. Fig. 1 (Guffanti et al., 2024; Milbury et al., 2022; Takaya et al., 2020; Telli et al., 2016; Zhao et al., 2024).

Whole-genome sequencing (WGS) enables comprehensive characterization of the somatic mutational landscape. They have proven to be effective in identifying HRD in *BRCA1/2*-wild-type tumors in multiple studies and their applicability has been demonstrated across several tumor types, notably triple-negative breast cancer. Nonetheless, the substantial cost, data burden, and turnaround time associated with WGS currently confine its routine application largely to academic or research settings rather than broad diagnostic use. Low-coverage whole-genome sequencing (sWGS) is increasingly used, in combination with machine-learning classifiers that quantify genomic instability, to infer HRD from broad copy-number profiles at lower cost. In contrast to high-coverage WGS or SNP-array–based approaches, these sWGS methods typically require a tumor cell fraction of about 20–30% to maintain sufficient sensitivity for detecting large-scale CNV patterns and assigning HRD status (Al Assaad et al., 2026; Davies et al., 2017; Eeckhoutte et al., 2020; Pan et al., 2024; Bergstrom et al., 2024; Zhang et al., 2022).

The assays described thus far have been developed and validated using tumor tissue samples. More recently, liquid biopsy approaches have emerged in which HRD is inferred from circulating tumor DNA (ctDNA), including in breast cancer, but these approaches remain investigational and are not yet incorporated into standard-of-care or approved as companion diagnostics. This approach leverages a probabilistic model that integrates genome-wide SNV, indel, and CNV signatures (including LST, genome-wide LOH, and TAI) together with targeted genomic and methylation features in ctDNA to classify tumors as HRD-positive or HRD-negative and to monitor resistance under PARPi or genotoxic therapies (Liang et al., 2025; Panet et al., 2024; Schiavone et al., 2025).

Taken together, current evidence indicates that there is no single universally optimal assay for all clinical contexts. Across tumor types in which HRD testing informs PARPi use, a common strategy in clinical practice and in pivotal studies is to combine comprehensive BRCA1/2 (germline and somatic) testing with a validated genomic-scar assay, using predefined cut-offs correlated with treatment benefit. FDA-approved companion diagnostics such as Myriad myChoice CDx and FoundationOne CDx have provided reference standards for assay design and performance, but their centralized service-based implementation may not be suitable for all health-care settings. In this scenario, analytically and clinically validated in-house NGS or sWGS-based HRD assays that reproduce genomic-scar metrics are increasingly being explored and adopted in local molecular laboratories. Functional RAD51 assays and ctDNA or low-coverage WGS-based approaches are highly promising for capturing the dynamic status of HR proficiency and for extending HRD assessment to additional tumor types, but they remain largely investigational. At present, they are best positioned as complementary tools within prospective studies rather than replacements for validated tissue-based HRD assays in routine practice.

An important limitation of the current literature is the heterogeneity of HRD assessment methods. Clinical studies have used different genomic scar assays, sequencing platforms, and cut-off values to define HRD positivity. Consequently, direct comparisons across trials should be interpreted with caution, as differences in assay design may substantially influence reported treatment outcomes and the estimated predictive value of HRD.

2.2. HRD among breast cancer subtypes

Large retrospective and real-world genomic studies consistently demonstrate that TNBC harbors the highest prevalence of HRD among breast cancer subtypes, with estimates ranging from 50% to more than

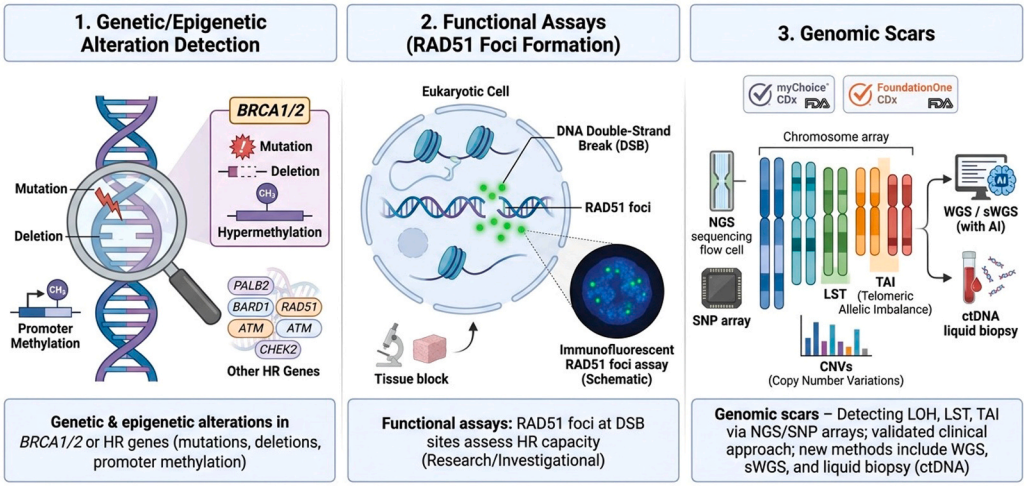

Fig. 1. Strategies for detecting Homologous Recombination Deficiency (HRD). DSB double-strand break, HR Homologous Recombination, LOH loss of heterozygosity, LST large-scale state transitions, NGS/SNP next-generation sequencing/single-nucleotide polymorphism, sWGS low-coverage whole-genome sequencing, TAI telomeric allelic imbalance, WGS whole-genome sequencing.

60%, even after exclusion of germline *BRCA1/2* (g*BRCA1/2*) mutation carriers. In particular, HRD-positive breast cancers are typically hormone receptor-negative and exhibit higher histologic grade, higher T-stage, extensive chromosomal instability and higher Ki−67 levels, reflecting increased cellular proliferation compared with HRD-negative tumors. In fact, HRD is considerably less prevalent in Luminal A and Luminal B tumors. These studies also revealed that HRD-positive patients had a mean age of 41 years, slightly younger than HRD-negative patients. Moreover, HRD positivity has been associated with a higher risk of disease recurrence: 29.4% of HRD-positive patients experienced progression, compared to 13.5% of HRD-negative patients. Huang et al. also demonstrated some differences in disease progression patterns between HRD-positive and HRD-negative tumors. The results revealed that, compared with HRD-negative patients, HRD-positive patients exhibited higher proportions of bone metastasis (46.7% vs. 23.5%), brain metastasis (13.3% vs. 6.3%), breast recurrence or metastasis (20.0% vs. 13.3%), and lymph node metastasis (46.7% vs. 29.4%). However, these differences did not reach statistical significance. Conversely, HRD-negative patients displayed a greater proportion of lung metastasis (52.9% vs. 26.7%), yet the statistical difference remained non-significant (Anon, 2012; Huang et al., 2025).

On the other hand, between 14% and 20% of hormone-sensitive breast cancers also exhibit HRD, with some harboring *BRCA1/2* mutations, indicating potential for HRD-targeted therapies. So, these findings highlight the presence of HRD in a significant proportion of these tumors, which represent the most prevalent breast cancer subtype. However, *BRCA1/2* mutated hormone sensitive breast tumors exhibit lower GIS than *BRCA1/2* mutated ovarian cancer, unlike TNBC tumors showing GIS distributions similar to ovarian cancer which is the tumor with the most validated HRD definition. This suggests that GIS thresholds used for ovarian cancer may not be suitable for hormone sensitive breast cancer, although they may be helpful in predicting response to platinum-based therapies in TNBC. These findings emphasize the need for cancer subtype-specific GIS thresholds to optimize DNA-damaging agent use and refine HRD diagnostics for improved clinical outcomes in precision medicine (Lenz et al., 2023; Moore et al., 2022).

3. HRD predictive value for chemotherapy response in TNBC

Several trials have evaluated the predictive value of HRD for chemotherapy response in early-stage TNBC (Table 1).

The SWOG S9313 trial investigated the effect of adjuvant doxorubicin and cyclophosphamide (AC) in patients with TNBC, stratifying them according to HRD status. HRD-positive patients, defined by the presence of either a deleterious tumor *BRCA1/2* mutation or a predefined HRD score ≥ 42, showed improved disease-free survival (DFS) compared with the HRD-negative group, with a non-significant trend toward better overall survival (OS). Notably, *BRCA* wild-type patients

Table 1
Clinical studies evaluating possible association between HRD status and chemotherapy-based regimens in early-stage TNBC.

CHEMOTHERAPY BASED REGIMEN CLINICAL TRIALS					
Trial name	**Phase**	**Stage and subtype**	**HRD status or condition**	**Treatments and setting**	**Results**
SWOG S9313[60]	III	Early-stage TNBC: high-risk node-negative or low-risk node-positive TNBC breast cancer	HRD-positive defined as HRD score ≥ 42 (Myriad myChoice HRD assay) or presence of *BRCA1/2* mutation.	Doxorubicin and cyclophosphamide chemotherapy in adjuvant setting	HRD-positive status was associated with a better DFS compared with the HRD-negative patients. High HRD score was associated with better DFS and OS. The DFS HR for *BRCA1* mutated patients was similar to that for HRD but did not reach statistical significance.
GeparSixto[44]	II	Stage II-III TNBC	HRD-positive defined as HRD score ≥ 42 (Myriad myChoice HRD assay) or presence of *BRCA1/2* mutation.	Chemotherapy with or without carboplatin neoadjuvant setting	Additional carboplatin improved pCR rates and DFS among TNBC. Addition of carboplatin significantly increased pCR rates in HRD-positive tumors (from 33.9% to 63.5%). Minimal benefit observed in HRD-negative tumors. HR deficiency independently predicted pCR but does not predict carboplatin effect.
NeoCART[80]	II	Stage II-III TNBC	HRD-positive defined as HRD score ≥ 38 (Myriad myChoice HRD assay) or presence of *BRCA1/2* mutation.	Docetaxel plus carboplatin chemotherapy vs. epirubicin/ cyclophosphamide followed by docetaxel chemotherapy in the neoadjuvant setting	pCR was higher in patients with higher HRD scores, especially in docetaxel plus carboplatin group. No significant correlations between HRD scores and pCR or RCB 0/1 were observed in the EC-D group.
Byrski et al.[9]	II	Stage I-III BRCA1-positive TNBC	*BRCA1* mutation carriers	Cisplatin monotherapy in the neoadjuvant setting	Higher pCR rate in TNBC (61%). Evidence of a single platinum agent activity in *gBRCA1* mutation.
NCT01372579[32]	II	Stage I-III TNBC	HRD-positive defined as HRD score ≥ 42 (Myriad myChoice HRD assay) or presence of *BRCA1/2* mutation.	Carboplatin plus eribulin in the neoadjuvant setting	Higher pCR rates in gBRCA1/2 mutation (67%) and in HRD (75%). Not a standard NAC regimen (anthracycline-free), no randomized control.
TBCRC 030[47]	II	Stage I (≥1.5 cm)-III TNBC BRCA wild-type	HRD-positive defined as HRD score ≥ 42 or ≥ 33 (Myriad myChoice HRD assay) or presence of *BRCA1/2* mutation.	Cisplatin vs. paclitaxel in the neoadjuvant setting	HRD-score does not predict pathological response with single chemotherapy (platinum or taxane NAC regimen). Single NAC regimen are not recommended in TNBC *BRCA* WT because of poor response rates.
INFORM[70]	II	Stage I (≥1.5 cm) - III, HER2-negative, BRCA1/ 2 mutation carriers	*BRCA1/2* mutation carriers	Cisplatin vs. doxorubicin plus cyclophosphamide in the neoadjuvant setting	No significant advantage of cisplatin over AC observed: a) pCR rates: 18% with cisplatin, 26% with doxorubicin plus cyclophosphamide b) RCB 0/1: 33% for cisplatin, 46% for AC

DFS Disease Free Survival, HR Hazard Ratio, HRD Homologous Recombination Deficiency, NAC Neoadjuvant Chemotherapy, pCR pathologic Complete Response, RCB Residual Cancer Burden, TNBC Triple Negative Breast Cancer

with a high HRD score had better DFS and OS than their HRD-negative counterparts supporting the prognostic and predictive relevance of HRD beyond *BRCA* mutation status (Sharma et al., 2018).

The GeparSixto trial reinforced these findings. It investigated the impact of adding carboplatin to neoadjuvant chemotherapy (NAC) in patients with HRD-positive TNBC, as defined in the previous study, demonstrating that HRD was independently associated with higher pathological complete response (pCR) rates compared with HRD-negative tumors. In fact, the addition of carboplatin to NAC significantly increased pCR rates in HRD-positive tumors from 33.9% to 63.5% compared with tumors treated without platinum. The improvement was minimal and not statistically significant in HRD-negative tumors (Loibl et al., 2018b).

Similarly, *Wang et al.* highlighted that HRD was significantly associated with higher pCR rates in patients with TNBC treated with NAC, particularly in patients receiving platinum-based regimens and in those with a GIS score ≥ 50 or *BRCA1/2*-mutated tumors. In fact, HRD-positive tumors reached a pCR rate of 41.38% compared with 9.68% in HRD-negative patients among all NAC regimens. HRD significantly correlated with a higher pCR rate in patients treated with carboplatin-containing regimens compared with those treated with other regimens (50% *vs*. 17.65%). After a median follow-up of 50.9 months, HRD-positive patients exhibited significantly better distant metastasis-free survival (DMFS) and a not statistically significant trend toward improved OS (Wang et al., 2024).

These findings support the hypothesis that HRD—regardless of *BRCA* mutation status—confers increased sensitivity to platinum salts in TNBC (Gerratana et al., 2016).

The NeoCART trial evaluated the impact of HRD on treatment outcomes in patients with TNBC receiving carboplatin-based NAC. HRD positivity was defined as the presence of either a high HRD score ($\geq$38) or a deleterious *BRCA1/2* mutation. This study demonstrated that patients achieving pCR exhibited significantly higher HRD scores than non-responders in the docetaxel–carboplatin arm. By contrast, no significant association between HRD scores and pCR was observed in the epirubicin/cyclophosphamide followed by docetaxel regimen. Notably, tumor-infiltrating lymphocytes (TILs) were identified as an independent predictor of pCR in the carboplatin-containing cohort (Zhang et al., 2023).

Byrski et al. investigated the effectiveness of neoadjuvant cisplatin-based chemotherapy in women with *BRCA1*-mutated breast cancer. The results showed particularly high response rates among those with TNBC, where the pCR rate was 61%. The findings suggest that *BRCA1*-related breast cancers, particularly TNBC, are highly sensitive to platinum-based chemotherapy, likely due to their defective DNA repair mechanisms. This supports the role of cisplatin as a potentially effective treatment option in *BRCA1*-associated TNBC and reinforces the evidence that *BRCA1* status is a strong predictor of response to platinum agents (Byrski et al., 2014).

The NCT01372579 phase II neoadjuvant clinical trial evaluated the efficacy and safety of carboplatin and eribulin in women with early-stage TNBC, while also exploring DNA- and protein-based biomarkers as potential predictors of treatment response. Biomarker analysis revealed that both HRD score and HRD status significantly predicted pCR (Kaklamani et al., 2015).

In contrast, the TBCRC030 trial failed to demonstrate a significant association between HRD score and pathological response to either cisplatin or paclitaxel in BRCA1/2 wild-type TNBC. However, interpretation of these findings is limited by the relatively small sample size and the inability to perform HRD assessment in approximately one-quarter of enrolled patients because of insufficient tumor tissue. These limitations may have reduced the statistical power required to detect clinically meaningful associations (Mayer et al., 2020).

Similarly, the INFORM trial did not demonstrate a significant advantage of cisplatin over doxorubicin plus cyclophosphamide in patients with HER2-negative, BRCA1/2-mutated breast cancer. These findings suggest that BRCA-associated tumors may be broadly sensitive to DNA-damaging agents rather than uniquely dependent on platinum compounds. Notably, higher baseline TIL levels were associated with improved pathological response irrespective of treatment assignment, particularly among patients with TNBC (Tung et al., 2020).

4. PARP Inhibitors in the treatment of TNBC: clinical efficacy and therapeutic advances

Poly (ADP-ribose) polymerase (PARP) is a family of enzymes that play a key role in the detection and repair of DNA damage, particularly PARP1. PARP1 collaborates with components of the BER pathway to facilitate DNA repair through the synthesis of poly(ADP-ribose) (PAR) chains on target proteins, including itself, in a process known as poly (ADP-ribosyl)ation (PARylation). PARPis impair this process through two main mechanisms: competitive binding to the catalytic domain of PARP and PARP trapping, whereby PARP enzymes are stabilized on DNA at sites of damage, preventing repair complex assembly and progression. These effects lead to the accumulation of unrepaired SSBs, which are converted into DSBs during DNA replication. In HRD tumors, cells cannot effectively repair DSBs through HRR and therefore become dependent on PARP-mediated repair mechanisms. This dependency makes PARP an attractive therapeutic target, as PARP inhibition leads to accumulation of unrepaired DNA damage and tumor cell death (Habaka et al., 2025).

This therapeutic strategy, known as synthetic lethality, underlies the efficacy of PARPi in the treatment of breast, prostate, pancreatic and ovarian cancers. It represents an effective treatment option which provides significant improvement in PFS and ORR while offering a more favorable safety profile compared with traditional chemotherapy. As explained, a consistent fraction of TNBCs is associated with HRD profiles, particularly *BRCA1/2* mutations. Several clinical trials have established the therapeutic efficacy of PARPi in this breast cancer subgroup, both in the adjuvant and neoadjuvant settings, summarized in Table 2. Fig. 2 (Chambon et al., 1963; Habaka et al., 2025; Liu et al., 2021).

In the adjuvant setting, the OlympiA trial demonstrated the long-term benefit of olaparib in patients with HER2-negative early breast cancer harboring g*BRCA1/2* pathogenic variants who had completed local treatment and (neo)adjuvant chemotherapy. The study showed significant improvements in invasive disease-free survival (IDFS), distant disease-free survival (DDFS), and OS with olaparib compared to placebo. For OS, the HR was 0.72, with 6-year survival rates of 87.5% in the olaparib arm and 83.2% in the placebo arm. Based on these data, olaparib has become a standard-of-care option in the adjuvant treatment of HER2-negative early breast cancer with *gBRCA1/2* pathogenic mutations (Goodman, 2025; Tutt et al., 2021).

Although PARPi are not yet part of the standard neoadjuvant treatment for TNBC, several phase II trials have yielded promising results evaluating PARPi either as monotherapy or in combination with NAC. Notably, *Litton et al.* investigated talazoparib as a single-agent neoadjuvant therapy in patients with operable, HER2-negative breast cancer carrying g*BRCA1/2* mutations, who are traditionally treated with chemotherapy prior to surgery. The study demonstrated encouraging outcomes with 53% of patients achieving a pCR and 63% achieving minimal or no residual disease (RCB−0 or RCB-I). Importantly, this was the first study to show that an oral monotherapy could elicit substantial clinical responses in BRCA-mutated breast cancer in the absence of chemotherapy. Despite its limited sample size and single-institution setting, the study provided a strong rationale for further investigation in larger multicenter studies, such as the PARTNER study (Litton et al., 2019).

Similarly, *Spring et al.* investigated the use of niraparib as a neoadjuvant treatment for patients with HER2-negative, *BRCA*-mutated, resectable breast cancer. After two treatment cycles, more than 90% of participants exhibited a marked reduction in tumor volume, as assessed

Table 2
Clinical studies evaluating possible association between HRD status and PARP inhibitors-based regimens in early-stage TNBC.

PARP INHIBITORS BASED REGIMEN CLINICAL TRIALS					
Trial name	**Phase**	**Stage and subtype**	**HRD status or condition**	**Treatments and setting**	**Results**
OlympiA[25]	III	High-risk, *gBRCA1/2* mutated breast cancer HER2- after definitive local treatment and neoadjuvant or adjuvant chemotherapy	*BRCA1/2* mutation carriers, HRD via *gBRCA1/2* mutation (no assay score)	Oral olaparib vs. placebo in the adjuvant setting	Adjuvant olaparib was associated with significantly longer invasive DFS and distant DFS in *gBRCA1/2* mutation carriers.
PreCOG 0105[67]	II	Stage I - IIIA TNBC or *BRCA1/2* mutation-associated breast cancer	*BRCA1/2* mutated tumor or HRD-LOH $\geq$ 10	Carboplatin plus gemcitabine and iniparib in neoadjuvant setting, before surgery and adjuvant chemotherapy	Higher pCR rates in *BRCA1/2* carriers and in HRD-positive tumors (overall pCR 36%; *BRCA1/2* carriers: 81%; HRD+ 66% vs HRD– 20%)
RIO[12]	II	Treatment-naïve TNBC	*BRCA1/2* mutation carriers, HRD via *gBRCA1/2* mutation (no assay score)	Rucaparib in neoadjuvant setting, before surgery or NAC.	ctDNA significantly decreased in HRD and *BRCA1/2* mutated tumors treated with rucaparib.
NeoTALA[41]	II	Stage I ($\geq$1 cm) - III, *gBRCA1/2* mutation HER2-	*BRCA1/2* mutation carriers, HRD via gBRCA1/2 mutation	Oral talazoparib in neoadjuvant setting, before surgery and adjuvant chemotherapy	Significative RCB−0 rate (~ 50%) with manageable toxicity with talazoparib in gBRCA1/2 mutated tumors
PETREMAC[18]	II	Stage II – III, treatment-naïve TNBC	HRD via somatic/germline *BRCA* and BRCA1 methylation (no assay)	Oral olaparib in neoadjuvant setting, before NAC	Higher clinical response in HRD patients and/or *BRCA1* hypermethylation
Spring et al.[63]	I	Stage I ($\geq$ 1 cm) - III, *gBRCA1/2* mutation	*BRCA1/2* mutation carriers, HRD via *gBRCA1/2* mutation	Oral niraparib in neoadjuvant setting	Evidence of a single PARPi agent activity in *gBRCA1/2* mutation (>90% tumor shrinkage; ~40% pCR)
BrighTNess[43]	III	Stage II-III, TNBC	HRD-positive defined as HRD score $\geq$ 42 or $\geq$ 33 (Myriad myChoice HRD assay) or presence of BRCA1/2 mutation.	Carboplatin plus paclitaxel plus veliparib vs. paclitaxel plus carboplatin plus veliparib placebo vs. paclitaxel plus carboplatin placebo plus veliparib placebo in neoadjuvant setting	Higher pCR rates in carboplatin plus veliparib treatment compared to paclitaxel alone. No statistically significant carboplatin benefit among *gBRCA* mutated patients compared to *BRCA* wild-type subgroup. Higher rates of pCR in HR deficient patients across all treatment arms, especially in platinum regimen group. Patients with higher HRD scores ($\geq$ 33) appeared to have greater sensitivity to the addition of veliparib to platinum.
GeparOLA[19]	II	Stage I-III, HRD-positive, HER2-	*gBRCA1/2* mutation carriers or high HRD score (unspecified assay)	Paclitaxel plus olaparib vs. paclitaxel plus carboplatin, both followed by epirubicin plus cyclophosphamide in neoadjuvant setting	The pCR rate in olaparib group was higher compared to carboplatin. Patients with HRD positive tumors and *gBRCA1/2* carriers had a higher pCR rate with Olaparib compared to carboplatin.
PARTNER[2]	II-III	Early-stage TNBC, *gBRCA* wild-type	*gBRCA* wild-type, no HRD assay	Olaparib plus chemotherapy vs chemotherapy alone in neoadjuvant setting	No significant difference in pCR rates between the two treatment groups (51.1% in the olaparib arm versus 52.4% in the control arm) or improvements in EFS or OS at 36 months. Olaparib did not confer any clinical benefit when added to standard NAC in patients with *gBRCA*wt TNBC.

DFS Disease Free Survival, HRD Homologous Recombination Deficiency, LOH Loss of Heterozygosity, pCR pathologic Complete Response, RCB Residual Cancer Burden, TNBC Triple Negative Breast Cancer

by MRI. Notably, approximately 40% of patients receiving niraparib monotherapy, without additional chemotherapy, achieved a pCR. Treatment duration could be extended up to six cycles based on individual responses, with longer exposure being associated with improved outcomes, supporting a potential benefit of a personalized treatment approach (Spring et al., 2022).

In this context, the phase II PETREMAC trial evaluated olaparib monotherapy prior to chemotherapy in patients with treatment-naïve, unselected early TNBC. The results were encouraging, with more than half of the patients (56.3%) achieving a clinical response, including tumor shrinkage, despite the absence of prior chemotherapy. Among the responders, the majority harbored either somatic or germline alterations affecting HR genes or exhibited *BRCA1* promoter methylation, suggesting a strong association between HRD and sensitivity to olaparib. Notably, patients without HR-related alterations rarely responded, further reinforcing HRD as a predictive biomarker. Additional biomarkers, including low *RAD51* scores, high TILs and PD-L1 expression, were also associated with favorable responses, thereby supporting the rationale for combining PARPi with immunotherapy in this setting (Eikesdal et al., 2021).

Interestingly, *Chopra et al.* investigated the potential of targeting HRD in TNBC using PARPi, with a particular focus on rucaparib. To this end, the RIO trial was designed as a "window of opportunity" study, enrolling treatment-naïve TNBC patients who received rucaparib for two weeks prior to surgery or chemotherapy. Tumor biopsies and blood samples were collected before and after treatment to assess molecular and cellular changes. A significant decrease in ctDNA levels after treatment was observed in HRD-positive cancers, including those harboring *BRCA1/2* mutations. These findings suggest that ctDNA dynamics may represent a more sensitive and non-invasive biomarker of rucaparib activity compared with other tissue-based biomarkers such as Ki67 which was also evaluated in the study but did not show significant changes. Furthermore, gene expression analysis further revealed that in HRD-positive tumors, rucaparib induced the activation of interferon response pathways, likely through the cGAS–cGAMP–STING immune pathway, suggesting that PARPi might not only induce tumor DNA damage but also promote antitumor immune activation (Chopra et al., 2020).

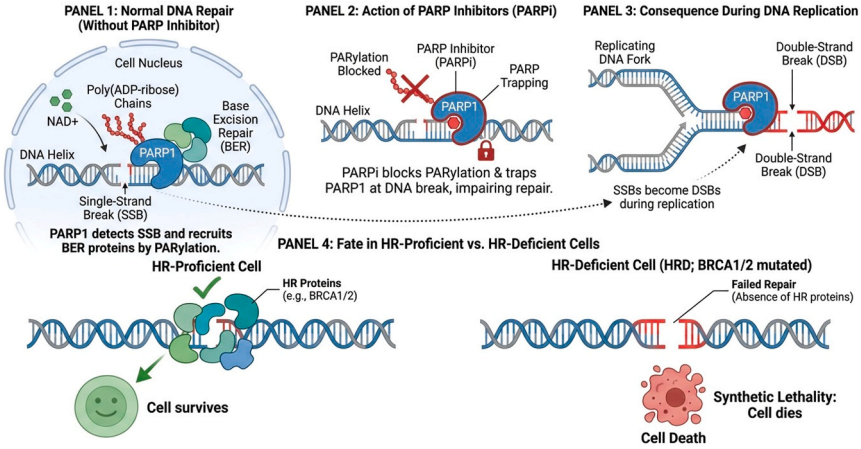

Fig. 2. Mechanism of action of PARP inhibitor in BRCA1/2 mutated tumors. DSB double-strand break, HR Homologous Recombination, HRD Homologous Recombination Deficiency, PARP1 Poly(ADP-ribose) polymerase 1, PARPi PARP Inhibitor, SSB: Single-Strand Break.

In addition, several studies have evaluated the impact of adding a PARPi to chemotherapy in the neoadjuvant setting. In their study, *Telli et al.* investigated the efficacy of a neoadjuvant regimen combining gemcitabine, carboplatin, and iniparib in women with TNBC or *BRCA1/2* mutation-associated early breast cancer. This platinum-based regimen was associated with a pCR rate of 36% among evaluable patients, in line with those reported with third-generation anthracycline/taxane-based regimens but with better tolerability. Notably, a higher pCR rate was observed in *BRCA1/2* carriers compared with non-carriers (81% vs 47%), suggesting increased sensitivity in the presence of *BRCA* mutations. Biomarkers analyses suggested that tumors harboring g*BRCA* mutations or HRD features are more likely to respond better to this regimen with statistically significant evidence. Specifically, HRD-positive tumors (HRD-LOH score $\geq$ 10) achieved a response rate of 66%, while HRD-negative tumors (HRD-LOH score $<$ 10) show a substantially lower response rate of 20% (Telli et al., 2015).

In the BrighTNess trial, *Loibl et al.* compared the efficacy of carboplatin plus paclitaxel plus veliparib versus paclitaxel plus carboplatin and paclitaxel monotherapy in patients with stage II - III TNBC, who were candidates for potentially curative surgery. Patients treated with paclitaxel, carboplatin, and veliparib regimen achieved significantly higher pCR rates compared with those receiving paclitaxel alone, but not compared with those receiving paclitaxel plus carboplatin. Interestingly no statistically significant additional benefit of carboplatin was observed among *gBRCA*-mutated patients compared with *BRCA* wild-type subgroup. Higher pCR rates were observed in HRD-positive tumors across all treatment arms; however, patients receiving platinum-based regimens showed increased pCR rates irrespective of HRD status. Notably, patients with higher HRD scores ($\geq$ 33) appeared to derive greater benefit from the addition of veliparib to platinum-based therapy (Loibl et al., 2018a).

In the GeparOLA trial, patients with stage I-III untreated TNBC and HRD were randomized to receive either paclitaxel plus olaparib or paclitaxel plus carboplatin, both followed by epirubicin plus cyclophosphamide in the neoadjuvant setting. The pCR rate was 55.1% in the olaparib group versus 48.6% in the carboplatin group. It was the only study to assess the efficacy of olaparib instead of carboplatin in breast cancer. Notably, patients with HRD-positive tumors and *gBRCA1/2* mutations treated with olaparib achieved higher pCR rates compared with those receiving carboplatin, suggesting potentially greater efficacy in these subgroups. Regarding carboplatin, both *gBRCA1/2* status and HRD are associated with higher pCR but not with a differential benefit over other regimens in the neoadjuvant setting, in line with findings from the GeparSixto trial (Fasching et al., 2021).

In contrast, the PARTNER trial was designed to evaluate whether the addition of olaparib to standard NAC would improve outcomes in patients with TNBC without g*BRCA1/2* mutations (*gBRCA*wt), based on the hypothesis that TNBC may exhibit HRD features similar to those observed in *BRCA*-mutated tumors. The study concluded that olaparib did not confer a clinical benefit when added to standard NAC in patients with *gBRCA*wt TNBC, in contrast to the clear benefit observed in *BRCA*-mutated populations across multiple PARP inhibitor trials. The authors emphasized the importance of biomarker-driven treatment strategies and highlighted the need for further translational research to identify potential responsive subgroups within the *gBRCAwt* TNBC population (Abraham et al., 2024).

5. Hrd and immunotherapy In Tnbc: an evolving relationship

As previously explained, many studies have shown how cytotoxic chemotherapies or certain target therapies, such as PARPi, may a derive significant benefit in TNBC with HR deficiency. In contrast, the relationship between HRD status and immunotherapy response in TNBC remains poorly understood.

The most compelling evidence linking DNA repair deficiencies to the efficacy of ICIs comes from tumors with mismatch repair deficiency (dMMR). These tumors exhibit high TMB and increased neoantigen production, which are associated with substantial response to ICIs. In contrast, HRD does not consistently predict ICI benefit. Unlike dMMR, HRD is primarily associated with genomic instability characterized by structural alterations, including CNVs, which are inversely correlated with cytotoxic immune signatures. Accordingly, high levels of CNV are often associated with reduced response to ICI, potentially due to impaired antigen presentation and reduced MHC class I expression, leading to limited immune cell infiltration. Moreover, *BRCA1*-deficient tumors tend to exhibit a more immunosuppressive microenvironment, whereas *BRCA2*-deficient tumors appear more immunogenic. Nevertheless, the mechanisms by which HRD influences antitumor immunity remain incompletely understood (Silva et al., 2022).

Emerging evidence suggests that activation of the STING pathway in response to DNA damage may enhance the efficacy of immunotherapy in HRD-positive tumors. STING is activated by cytosolic DNA fragments generated as a consequence of defective DNA repair. Its activation induces type I interferon signaling and chemokines production, including CXCL9 and CXCL10, thereby promoting immune cell recruitment. However, STING signaling may also paradoxically contribute to immune evasion through upregulation of PD-L1 expression on tumor cells. *Gandhi et al.* demonstrated that TNBC exhibits higher expression of CXCL9 and CXCL10 compared to other breast cancer subtypes. These chemokines are associated with improved overall survival after pembrolizumab treatment and correlate with higher PD-L1 expression, TMB, and T-cell infiltration (Ali et al., 2024; Gandhi et al., 2025; Pellegrino

et al., 2020).

Focusing on breast cancer, immunotherapy has become a key treatment component in early-stage TNBC treatment. This subtype is characterized by a high prevalence of HRD; however, several clinical trials have reported inconsistent evidence regarding the utility of HRD status as a standalone biomarker of response to ICIs therapy, suggesting that additional factors may influence treatment outcomes. *Kang et al.* demonstrated that although HRD-positive tumors exhibit greater immune activation compared with HRD-negative tumors, this does not necessarily translate into increased immune infiltration or improved clinical outcomes (Kang et al., 2023).

In this context, TILs play a key role in adaptive immunity and are associated with better prognosis in breast cancer, especially TNBC. In particular, an exploratory analysis in NeoTRIP trial, demonstrated that pretreatment TILs and PD-L1 expression, as well as on-treatment TIL levels—but not on-treatment PD-L1 expression—were associated with higher pCR rates to neoadjuvant therapy in patients with TNBC randomized to nab-paclitaxel plus carboplatin with or without atezolizumab. Furthermore, high on-treatment TIL levels in both groups and PD-L1 positivity, only in ICI arm, were significantly associated with lower risk of recurrence independently of pCR and baseline biomarkers. However, while HR gene mutations can create immunogenic neoantigens that stimulate CD4 and CD8 responses, no clear link between HRD and TIL frequency has been demonstrated. Table 3 (Ali et al., 2024; Bianchini et al., 2025).

Telli et al. confirmed this, finding no correlation between TILs and HRD or *BRCA1/2* status, suggesting these are independent processes (Telli et al., 2020).

This suggests that additional factors such as antigen presentation, may modulate immune cell recruitment in HRD-positive TNBC. For example, HRD-positive tumors exhibit a shift in cancer-associated fibroblast (CAF) subtypes from immunosuppressive to inflammatory phenotypes, thereby promoting immune infiltration. In contrast, HRD-negative tumors are characterized by T cells exhaustion and tolerogenic dendritic cells states, highlighting key immunosuppressive mechanisms within this context. Furthermore, impaired immune cell recruitment in HRD-negative tumors may be driven in part by DPP4 activity. To improve the predictive accuracy of ICI response, *Kang et al.* developed a machine learning model based on DPP4-related gene expression, which outperformed HRD status alone in predicting clinical outcomes in multiple ICI therapy cohorts. The study concluded that HRD alone is insufficient as a predictive biomarker for immunotherapy response and proposed that integrating HRD assessment with measures of immune cell composition, particularly DPP4-associated signature, may improve patient stratification in TNBC. Similarly, *Kaplan et al.* demonstrated that LRRC15, a marker associated with higher immune infiltration and increased CAFs presence, correlates with improved outcomes in TNBC treated with pembrolizumab. Collectively, these findings refine the understanding of HRD-associated immunogenicity in TNBC and support a multi-parametric approach for identifying patients most likely to benefit from immune checkpoint inhibition, ultimately improving therapeutic stratification in this aggressive subtype (Kang et al., 2023; Kaplan, 2025).

Consequently, not all breast cancer patients with HRD respond equally to ICIs, and even current predictive biomarkers, such as PD-L1 expression and TMB, have limitations in accurately identifying responders. For instance, *BRCA1*-mutated tumors often show higher PD-L1 expression than *BRCA2*-mutated tumors but limited responses to ICIs, suggesting that PD-L1 may not be a reliable biomarker when its expression is driven by non-immune mechanisms like HRD. Constitutive PD-L1 expression associated with HRD may impair ICI efficacy through several mechanisms. It may occur in the absence of sufficient TILs, limiting the potential for immune reactivation; however, even in the presence of adequate immune infiltration, persistent PD-L1 expression can saturate PD−1 on effector T cells, thereby promoting immune suppression. Moreover, PD-L1 may also alter tumor metabolism by activating the Akt/mTOR pathway, thereby increasing glycolysis and producing lactic acid, which in turn impairs immune cell function (Ali et al., 2024; Pellegrino et al., 2020; Silva et al., 2022).

Recently, an exploratory biomarker analysis of the KEYNOTE−522 trial evaluated potential predictors of pCR and EFS in patients with TNBC treated with pembrolizumab plus chemotherapy versus chemotherapy alone. Pembrolizumab demonstrated superior efficacy in terms of pCR and EFS across biomarker-defined subgroups, including those stratified by T-cell–inflamed gene expression profile ($Tcell_{inf}GEP$), TMB and HRD status. Notably, higher $Tcell_{inf}GEP$ was associated with a pCR of 73.5% in the pembrolizumab arm compared with 60.2% in the chemotherapy-alone arm. In the immunotherapy treatment arm, the higher $Tcell_{inf}GEP$ was also associated with a higher pCR compared to tumors with a low $Tcell_{inf}GEP$ that had a pCR of 52.1%. $Tcell_{inf}GEP$ demonstrated a positive association with EFS in both treatment groups. Similarly, higher TMB was associated with improved EFS and pCR in the pembrolizumab arm, whereas in the chemotherapy-alone arm it was associated with improved pCR but not with EFS. HRD positivity and PTEN loss were both associated with higher pCR rates in both treatment arms, with pembrolizumab further enhancing responses in HRD-positive patients. Collectively, these findings suggest that while immune activation contributes to response to treatment response, it is unlikely to be the sole determinant of immunotherapy efficacy, underscoring the importance of a multifactorial biomarker approach. In a complementary exploratory analysis from the same study, patients with *gBRCA* mutations achieved higher pCR rates with the ICI-containing regimen, exceeding 70% even in stage III disease, compared with the 45.3% in *BRCA*wt patients with the same stage disease treated with the same regimen. Table 3 (Celeste Tavares et al., 2025; Kaplan, 2025).

Ko et al. confirmed these findings in a study evaluating the

Table 3
Clinical studies evaluating possible association between HRD status and immunotherapy-based regimens in early-stage TNBC.

IMMUNOTHERAPY BASED REGIMEN CLINICAL TRIALS					
Trial name	**Phase**	**Stage and subtype**	**HRD status or condition**	**Treatments and setting**	**Results**
KEYNOTE−522 (exploratory biomarker analysis)[10,34]	III	Early-stage hormone receptors negative and HER2- TNBC	HRD positive status assessed (method unspecified)	Pembrolizumab plus chemotherapy vs chemotherapy alone in the neoadjuvant setting	$Tcell_{inf}GEP$ and high TMB correlate with improved pCR and EFS with pembrolizumab. HRD correlates with higher pCR but not improvement in EFS.
NeoTRIP[6]	III	Early-stage TNBC	HRD not directly reported; focus on TILs and PD-L1	Nab-paclitaxel plus carboplatin plus atezolizumab vs Nab-paclitaxel plus carboplatin in the neoadjuvant setting	Higher pre- and on-treatment TILs predicted pCR. PD-L1 positivity predicted lower recurrence only in immunotherapy arm.

EFS Event Free Survival, HRD Homologous Recombination Deficiency, pCR pathologic Complete Response, TcellinfGEP T-cell–inflamed gene expression profile, TILs Tumor Infiltrating lymphocytes TNBC Triple Negative Breast Cancer

association between genomic instability features and immune response in a real-world breast cancer cohort. A higher proportion of HRD-positive tumors exhibited increased TMB compared with HRD-negative tumors. Authors concluded that breast tumors harboring mutations in the HR genes showed higher TMB and a moderate increase in cellular proliferation index in both tumor and immune compartments, suggesting potential susceptibility to ICI (Ko et al., 2023).

6. Discussion

Despite increasing evidence supporting HRD as a clinically relevant biomarker in TNBC, its biological and predictive value remains incompletely defined. HRD-positive tumors have shown increased sensitivity to DNA-damaging agents, including platinum salts, and to PARPi, with reported improvements in pCR, DFS, and, in selected studies, OS, including in subsets of *BRCA1/2* wild-type tumors. However, these effects are not consistently reproduced across clinical trials.

A key limitation of current HRD assays is their reliance on static genomic scar signatures, including LOH, TAI, and LSTs. Increasing evidence indicates that therapeutic sensitivity is more closely linked to dynamic functional determinants of HR, such as replication fork stability, ATR/CHK1 pathway activity, POLQ-mediated repair, and cell-cycle checkpoint integrity. As a result, tumors with similar HRD scores may display divergent responses depending on their residual capacity to maintain replication fork protection or restore HR. These observations support the concept that HRD represents a biological continuum rather than a binary classification. This framework helps explain why some tumors with intermediate HRD scores remain highly sensitive to platinum compounds, while others with extensive genomic instability are resistant. In several cases, tumors may retain genomic scars of prior HRD while regaining HR proficiency through adaptive mechanisms, including *BRCA* reversion mutations, *RAD51* reactivation, replication fork stabilization, or activation of alternative DNA repair pathways. Consequently, high HRD scores may coexist with resistance to both platinum agents and PARPi, contributing to the variability observed in HRD-guided clinical trials. This complexity is particularly relevant in TNBC, which is characterized by marked genomic plasticity and strong treatment-induced selective pressure. In this setting, static genomic assays may overestimate therapeutic vulnerability, especially in *BRCA1/2* wild-type disease. Interpretation of HRD is further complicated by spatial and temporal heterogeneity involving genomic instability, replication stress responses, stromal interactions, and immune microenvironmental factors. Moreover, GIS thresholds derived from ovarian cancer may not be directly applicable to breast cancer, supporting a tumor-specific interpretation of HRD. Functional assays assessing real-time *RAD51* foci formation may provide a more direct measure of HR competence compared with static genomic scar-based approaches. However, their clinical implementation remains limited by technical challenges and lack of standardization (Drew et al., 2025; Guffanti et al., 2024; Jain et al., 2025; Wang et al., 2025).

An additional critical issue is the relationship between HRD and tumor immunogenicity. HRD-associated genomic instability may enhance neoantigen generation and activate innate immune pathways, including cGAS–STING signaling, thereby promoting type I interferon responses and immune cell recruitment. However, HRD alone has not consistently predicted responsiveness to ICIs. This apparent paradox likely reflects the dual consequences of chronic chromosomal instability. While acute DNA damage may enhance antitumor immunity, sustained genomic instability can promote immune evasion through impaired antigen presentation, persistent PD-L1 expression, T-cell exhaustion, and stromal-mediated immunosuppression. Accordingly, HRD may exert context-dependent immunostimulatory or immunosuppressive effects depending on the evolutionary state of the tumor microenvironment. HRD-positive tumors enriched in TILs, interferon signaling, inflammatory CAF phenotypes, or $Tcell_{inf}GEP$ appear more likely to respond to immunotherapy-based combinations than HRD-positive tumors with immune-desert phenotypes. Conversely, the absence of a consistent association between HRD and TIL abundance suggests that genomic instability alone is insufficient to trigger an effective antitumor immune response. These observations support the development of multidimensional biomarker frameworks that integrate genomic instability, immune activation, stromal composition, and tumor evolutionary dynamics, rather than relying on HRD status alone. In this context, PARPi are of particular interest not only for their synthetic lethal activity in HRD-positive tumors but also for their immunomodulatory effects. PARPi-induced DNA damage may increase cytosolic DNA accumulation, activate cGAS–STING signaling, enhance type I interferon responses, and upregulate PD-L1 expression, thereby potentially improving tumor sensitivity to immunotherapy. Accordingly, several ongoing clinical trials are evaluating PARPi–ICI combinations in TNBC. Preliminary results suggest enhanced immune activation and improved tumor immune recognition, although the current evidence is limited by small sample sizes, heterogeneous patient populations, and the lack of standardized biomarker stratification, underscoring the need for prospective validation (Drew et al., 2025).

Another unresolved issue concerns the biological and clinical significance of HRD in *BRCA1/2* wild-type TNBC. The predictive value of HRD in *BRCA* wild-type disease appears substantially less consistent than in *BRCA*-mutated tumors. Several neoadjuvant studies, including the GeparSixto and NeoCART trials, reported higher pCR rates among HRD-positive/*BRCA* wild-type tumors treated with platinum-containing regimens, whereas other studies, such as TBCRC030, failed to demonstrate a consistent association between HRD scores and chemotherapy response in *BRCA* wild-type populations. One possible explanation is that *BRCA1/2* loss produces a more profound and stable disruption of HRR than many non-*BRCA* alterations, which may instead confer partial or context-dependent HR impairment. Consequently, *BRCA*-mutated tumors may exhibit stronger synthetic lethality following PARP inhibition, whereas non-*BRCA* HRD-positive tumors may retain sufficient residual HR activity to escape therapeutic vulnerability. Moreover, non-*BRCA* HR gene alterations do not appear to confer equivalent levels of genomic instability or sensitivity to PARPi. Increasing evidence indicates that their functional impact depends not only on the specific gene involved but also on zygosity, mutational clonality, epigenetic regulation, and co-occurring genomic alterations. Monoallelic alterations, for example, frequently fail to induce complete HR deficiency, whereas biallelic inactivation appears necessary to generate clinically meaningful therapeutic sensitivity. Similarly, concurrent *TP53* mutations, replication fork stabilization mechanisms, or alterations in 53BP1 signaling may substantially modulate the biological consequences of HR pathway disruption. Interestingly, recent evidence suggests that non-*BRCA* HRD-positive tumors may derive greater benefit from combination strategies rather than PARPi monotherapy. Co-targeting ATR , *CHK1*, *WEE1*, *POLQ*, or immune checkpoint pathways may exploit persistent replication stress dependencies despite partial restoration of homologous recombination function. This may explain why some *BRCA* wild-type HRD-positive tumors display limited sensitivity to single-agent PARPi while remaining susceptible to combinatorial DNA damage response-targeted approaches (Li et al., 2025).

These findings support the concept that HRD represents a dynamic and multidimensional phenotype rather than a static binary biomarker. Emerging translational evidence further suggests that HRD may constitute an adaptive and potentially reversible cellular state. Under therapeutic pressure, TNBC cells may transition between HRD-positive and HR-restored phenotypes through epigenetic reprogramming, replication fork remodeling, and selective clonal evolution. This biological plasticity may contribute to the transient responses frequently observed with platinum-based therapies and PARPi and likely represents a major mechanism underlying acquired resistance. Consequently, longitudinal assessment of HR functionality using serial tumor biopsies or ctDNA-based approaches may become increasingly relevant for treatment selection and disease monitoring.

Artificial intelligence and machine-learning approaches are also emerging as promising tools for HRD assessment. Recent studies have shown that deep-learning algorithms applied to digital histopathology images may predict HRD status and platinum sensitivity with substantial accuracy, potentially capturing phenotypic consequences of genomic instability that are not identified by conventional sequencing-based assays. These technologies may eventually complement molecular testing and expand access to HRD stratification, particularly in resource-limited settings (Bergstrom et al., 2024).

Looking forward, a major challenge for the field will be the transition from static genomic scar-based definitions of HRD toward dynamic models capable of capturing real-time homologous recombination functionality. Future clinical trials should integrate genomic, functional, and immune biomarkers while incorporating longitudinal assessment of HR status through serial tissue sampling or liquid biopsy approaches. Such strategies may improve patient selection for platinum-based therapies, PARP inhibitors, and immunotherapy combinations while overcoming the limitations of current binary HRD classifications.

7. Conclusions and future perspectives

This comprehensive review underscores the critical role of HRD in TNBC as both a biological hallmark and a therapeutic vulnerability. Primarily driven by *BRCA1/2* mutations and other alterations affecting HR repair genes, HRD promotes genomic instability and increases tumor sensitivity to DNA-damaging agents, particularly platinum compounds and PARPi. Accumulating clinical evidence suggest that HRD-positive TNBCs, even in the absence of BRCA mutations, may derive greater benefit from platinum-based chemotherapy and PARPi.

However, the predictive value of HRD has not been uniformly confirmed across clinical trials. Importantly, interpretation of these studies is complicated by substantial heterogeneity in HRD definitions, assay platforms, cut-off values, treatment regimens, and study populations. Furthermore, several available studies are limited by relatively small sample sizes and exploratory biomarker analyses, which may contribute to the inconsistent findings reported across the literature. The relationship between HRD and immunotherapy also remains incompletely defined, although emerging evidence from exploratory analyses suggests potential biological and therapeutic interactions. The integration of immune-related biomarkers, including TILs, ctDNA dynamics, and specific genomic features, may improve predictive accuracy and support the development of combinatorial therapeutic strategies. These findings highlight the need for standardized HRD assessment methods, subtype-specific genomic thresholds, and large prospective clinical studies to validate the clinical utility of HRD in guiding personalized treatment approaches. In the evolving landscape of precision oncology, HRD may represents a promising biomarker for therapeutic decision-making and for expanding treatment opportunities in TNBC beyond conventional chemotherapy.

Future research should therefore focus on integrated biomarker models incorporating genomic, functional, and immunologic determinants of HR biology. Such strategies may improve patient stratification, optimize therapeutic selection, and identify TNBC subgroups—particularly among *BRCA1/2* wild-type tumors—that retain clinically actionable vulnerabilities within DNA damage repair pathways.

During the preparation of this work the authors used “FigureLab” in order to develop Figs. 1 and 2. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Author 1** reports a relationship with Amgen, Astellas, Astra Zeneca, BMS, Daiichi Sankyo, Eli-Lilly, Gilead, Merck Serono, MSD, Novartis, Servier, Takeda. that includes: consulting or advisory. **Author 2** reports a relationship with Astrazeneca, Eisai, Roche that includes: funding grants. **Author 2** reports a relationship with Astrazeneca, Bayer,Daiichi Sankyo, Eli Lilly, Exact Sciences, Gilead, Ipsen, Italfarmaco, Menarini, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Seagen that includes: consulting or advisory. **Author 3** reports a relationship with Novartis, MSD, BMS, Merk, PierreFabre, Gilead, Seagen, Genomic Health, Regeneron, Menarini Stemline that includes: consulting or advisory. **Author 3** reports a relationship with Novartis, MSD, BMS, Merk, Sunpharma, Sanophi Regeneron, PierreFabre, Astra Zeneca, Daiichi Sankio that includes: speaking and lecture fees. **Author 3** reports a relationship with Gilead, Pierre Fabre, Novartis, Lilly, Pfizer that includes: travel reimbursement. **Author 4** reports a relationship with Astrazeneca, Lilly, MSD, Novartis, Pfizer, Seagen that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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