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Controversies in oncology: are genomic tests quantifying homologous recombination repair deficiency (HRD) useful for treatment decision making?

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Mechanisms that protect DNA are crucial to preserve the genome integrity from injuries produced by environmental agents or those spontaneously generated during DNA metabolism.[1] DNA single-strand breaks (SSBs) are repaired by mismatch repair (MMR), base excision repair (BER) and nucleotide excision repair (NER).[1] Non-homologous end joining (NHEJ) or homologous recombination repair (HRR) processes double-strand breaks (DSBs).[1] While NHEJ solves DSBs in a potentially inaccurate way, HRR is an error-free pathway that restores the genomic sequence of the broken DNA ends by using the sister chromatid as template for repair.[1] Several proteins are involved in the HRR pathway: some of them act as sensors of DSBs such as γH2AX, ATM and ATR, leading to the activation of signal mediator proteins (ie, BRCA1, BRCA2 and PALB2). The final event of the HRR pathway is the loading of a small nuclear protein called RAD51 onto single-stranded DNA, where it promotes strand invasion and replication fork stabilisation (figure 1).[2] Tumours with HRR deficiency (HRD) were described for the first time in cancers that harbour germline mutations of the tumour suppressors *BRCA1* and *BRCA2* (*BRCA1/2*).[3] Nonetheless, genetic and epigenetic events can also result in inactivation of other HRR components, leading to HRD in sporadic cancers.[3]

HRD is harboured by approximately 13% and 15% of ovarian and triple negative breast cancers (TNBC), respectively, and it is attributable to germline *BRCA1/2* (*gBRCA1/2*) mutations.[4 5] Furthermore, 50% and 40% of ovarian and TNBC, respectively, are characterised by harbouring HRD in the absence of *gBRCA1/2* mutations.[4 6] Also, 10%–12% of advanced prostate cancer harbour germline or somatic *BRCA2* inactivation and up to 25% contain a DNA repair defect.[7] As HRR is required for the repair of DSBs generated during DNA interstrand cross-link (ICL) resolution, HRR-deficient tumours are sensitive to ICL-generating platinum chemotherapy.[3 8] Moreover, *BRCA1/2*-mutant cells are sensitive to PARP inhibitors (PARPi), a new class of drugs that block SSB repair, favouring accumulation of DSB that HRR-deficient cells cannot repair.[9] PARPi also trap PARP onto DNA causing replication stress that is toxic in these cells.[9] Several PARPi have been approved for the treatment of ovarian and breast cancers.[10–14] EMA approved olaparib and rucaparib as maintenance treatments for platinum-sensitive ovarian cancer with germline/somatic *BRCA1/2*-mutation; and niraparib was labelled as maintenance treatment for patients who are in response to platinum-based chemotherapy.[10 12 15] Olaparib and talazoparib have been approved for patients with advanced breast cancer and a *gBRCA1/2* mutations who have previously been treated with chemotherapy.[13–15] The current clinical challenge is the identification of *BRCA1/2* wild type (WT) patients who harbour alterations in the HRR pathway and share molecular features of *BRCA1/2*-mutated tumours (the so-called 'BRCAness' phenotype) and who may also benefit from similar therapeutic approaches.[16]

Different approaches are currently being investigated to identify *BRCA1/2* WT tumours that can benefit from DNA-damaging agents and PARPi based on the presence of HRD, that is, (1) scores capturing large genomic aberrations, so-called 'genomic scars', (2) analysis of mutational signatures or (3) point mutations identified in HRR genes using DNA sequencing panels.[9 17–19] In *BRCA1/2*-mutant cells, chromosomal spreads reveal increased gross chromosomal rearrangements. This led to the development of assays to evaluate the 'genomic scars' caused by the loss of HRR

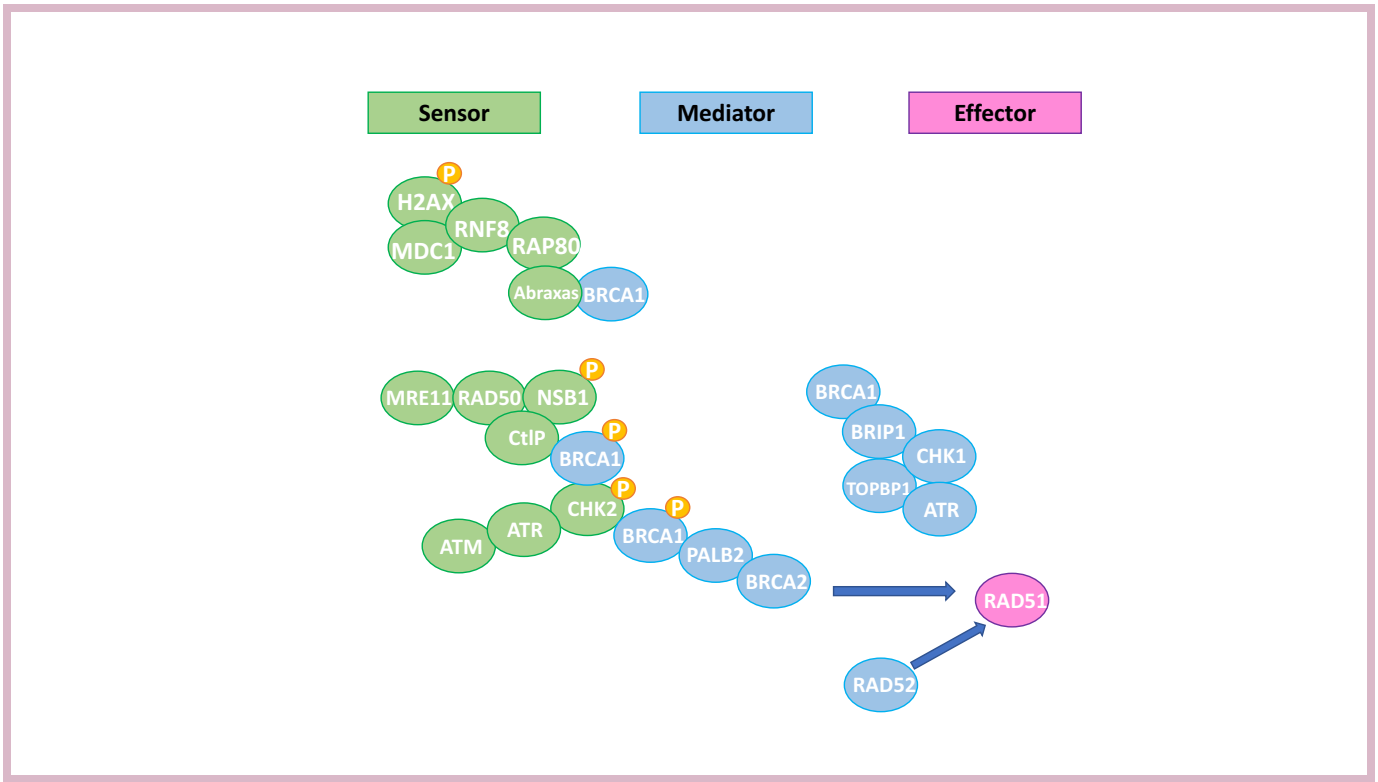

Figure 1 Homologous recombination pathway. Adapted from De Picciotto *et al*.[50]

function using SNP array data.[3] Two commercial genomic scar assays have been tested to identify tumours with HRD in clinical trials. The 'myChoice HRD' assay by Myriad tests for the presence of loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST) across the genome.[17] The readout of this assay is presented as an 'HRD score': a tumour with an HRD score ≥42 is labelled as HRD-positive. The 'FoundationFocus CDx $_{BRCA\ LOH}$' is designed to detect the presence of mutations in the *BRCA1/2* genes and the percentage of the genome affected by LOH in DNA from tumour tissue samples of patients with ovarian cancer.[20] According to the FoundationFocus test, tumours are categorised as LOH-high if score is ≥16. On the other hand, mutational signatures are characteristic patterns left on the cancer genome by each mutational process: for example, HRD has been associated with the 'signature 3' described by Alexandrov *et al*.[21–23] 'Signature 3' is also able to accurately classify missense *BRCA1/2* mutations with known functional implications and it is associated with silencing of *RAD51C* and *BRCA1* by promoter methylation.[24]

So, what is the current clinical evidence around the use of genomics scars to quantify HRD and its impact on treatment decision-making? The main open question is whether genomic scars are predictive biomarkers of response to platinum salts or PARPi, beyond *BRCA1/2* mutation.

In advanced ovarian cancer, the ARIEL2 study demonstrated the efficacy of the PARPi rucaparib as monotherapy in *gBRCA1/2* mutated and/or LOH-high relapsed, platinum-sensitive ovarian cancer, and the ARIEL3 trial demonstrated the benefit of rucaparib as maintenance therapy in platinum-sensitive recurrent patients who responded to platinum, regardless of the LOH status (table 1).[12 20] The NOVA trial investigated the role of the PARPi niraparib as maintenance therapy in platinum-sensitive ovarian cancer and showed that patients with *BRCA1/2* mutations or HRD-positive according to myChoice assay benefited from PARPi.[11] Nevertheless, niraparib also improved PFS in *BRCA1/2* WT patients with an HRD-negative test, although the magnitude of the benefit was smaller compared to *BRCA1/2*-mutated or HRD-positive patients (table 1).[11] From these trials, one may conclude that in the platinum-sensitive population the HRD-genomic scars provide information regarding the magnitude of the clinical benefit, given the high probability of response after platinum sensitivity. Indeed, the magnitude of the benefit is higher among those who are HRD-positive or *BRCA1/2*-mutated. Most importantly, in the ovarian population, further investigations are needed to verify if an HRD test may be useful to select platinum-resistant tumours that may benefit from PARPi or to identify long responders to PARPi and/or platinum salts.

In TNBC, several trials have investigated if HRD-genomic scars predict response to DNA-damaging agents or to the addition of carboplatin to standard chemotherapy beyond *BRCA1/2* mutation (table 2). In the neoadjuvant setting, Telli *et al* retrospectively assessed the predictive value of the 'myChoice HRD' assay in three single-arm trials testing platinum-based therapy.[25] Patients who were HRD-positive had a higher probability to achieve

Table 1 Efficacy of PARPi according to HRD status in ovarian cancer

Clinical trial	Drug	Study population	HRD role
ARIEL-2[12]	Rucaparib, monotherapy	Relapsed, platinum-sensitive ovarian cancer	Higher efficacy in *gBRCA1/2*-mutated and/or LOH-high compared with LOH-low tumours. Not powered to show a difference between LOH-high and LOH-low tumours
ARIEL-3[20]	Rucaparib, maintenance therapy	Relapsed, platinum-sensitive ovarian cancer	Efficacy regardless of LOH-status. Magnitude of the benefit dependent on LOH
NOVA-trial[11]	Niraparib, maintenance therapy	Relapsed, platinum-sensitive ovarian cancer	Efficacy regardless of HRD-status. Magnitude of the benefit dependent on HRD

HRD, homologous recombination repair deficiency; LOH, loss of heterozygosity; PARPi, PARP inhibitors .

a complete pathological response or minimal residual disease (RCB 0-I) after platinum chemotherapy, even among *BRCA1/2* WT tumours.[25] The GeparSixto trial evaluated the benefit of the addition of carboplatin to anthracycline/taxane-based neoadjuvant chemotherapy in TNBC and analysed the predictive and prognostic value of testing for HRD by the composite biomarker including germline/somatic *BRCA1/2* mutations and the 'myChoice' assay.[6] Among all patients with TNBC, addition of carboplatin resulted in a marked increment in pCR rates in HRD-positive tumours (from 33.9 to 63.5%, *P*=0.001), and in HRD-negative tumours (from 20 to 29.6%, *P*=0.399). However, according to the test of interaction, HRD did not predict for carboplatin benefit in this study. Of note, the control arm in this trial lacked cyclophosphamide, which might have overestimated the carboplatin benefit. Other observations regarding the prognostic value of HRD genomic scars will require a powered study to demonstrate the improvement in disease-free survival (DFS) or overall survival (OS). Litton *et al* have recently showed the efficacy of PARPi talazoparib in the neoadjuvant setting in patients with *BRCA1/2* mutations. In this setting, an HRD test could be useful to identify patients with *BRCA1/2* WT who can also benefit from PARPi.[26] Finally, in the adjuvant setting, Sharma *et al* evaluated the predictive role of the 'myChoice HRD' in TNBC to predict outcome of adjuvant anthracycline and cyclophosphamide regimen.[27] The study showed a better DFS in patients with high HRD, even beyond *gBRCA1/2* status.

In metastatic TNBC, Isakoff *et al* conducted a phase II trial aimed to investigate the predictive role of genomic scars to platinum salts. Higher HRD scores were reported in responding patients, independent of *BRCA1/2* mutational status.[28] However, the predictive role of this HRD test was not confirmed in the TNT trial, a randomised phase III trial comparing the efficacy of first-line carboplatin versus docetaxel in patients with advanced TNBC.[29] According to the preplanned biomarker analysis, carboplatin resulted in higher overall response rates (ORR) among patients harbouring a *gBRCA1/2* mutation, but not in subjects with other profiles associated with HRR dysfunction such as high HRD-score, *BRCA1* methylation, or *BRCA1* mRNA-low, mostly evaluated in the primary tumours.[29] These results could be partially explained by the fact that genomic scars tested in the primary tumour may have lower prediction power for response in the advanced setting because metastatic tumours may have restored the HRR function and become resistant to platinum. As in the GeparSixto trial, HRD-positive tumours

Table 2 Efficacy of platinums or DNA-damaging chemotherapy according to HRD status in breast cancer

Clinical trial	Drug	Study population	HRD role
PrECOG 0105 Cisplatin-1 trial Cisplatin-2 trial[51]	Platinum salts	Neoadjuvant TNBC	Patients who were HRD-positive had higher complete pathological response
Gepar-Sixto trial[6]	Carboplatin	Neoadjuvant TNBC	Patients who were HRD-positive had a better prognosis compared with HRD-negative. No robust conclusions regarding the predictive role of HRD for addition of carboplatin
SWOG S9313 trial[27]	Doxorubicin and cyclophosphamide	Adjuvant TNBC	Patients who were HRD-positive had a better DFS, even beyond *gBRCA1/2* status
TBCRC009 trial[28]	Platinum salts	Advanced, first or second line TNBC	Higher HRD scores were reported in responding patients, independent of *BRCA1/2* mutational status.
TNT trial[29]	Carboplatin	Advanced, first line TNBC	ORR did not correlate with HRD-score of the primary tumours.

HRD, homologous recombination repair deficiency; ORR, overall response rate; TNBC, triple negative breast cancers.

were more likely to respond to any chemotherapy regimens compared with the HRD-negative ones. Several open questions may raise from the previous statements: first, that no data are available comparing the HRD status in early and advanced breast cancer, and second, that further studies are required to dissect the role of recovering the HRR function in predicting resistance to PARPi and platinum salts.[30] Furthermore, despite the OlympiAD and EMBRACA trials demonstrated the efficacy of PARPi in *BRCA1/2*-mutated metastatic breast cancer,[13 14] still a relevant proportion of patients did not respond. Further research is needed to investigate if an HRD test would help to refine the subgroup more likely to benefit.

In prostate cancer, the interest in developing DNA damaging and PARPi-based therapeutic strategies arises from the enrichment for DNA damage response gene mutations among cases with advanced disease. The TOPARP-A trial evaluated the antitumor activity of olaparib in advanced prostate cancer, identifying a strong association between the presence of certain DNA repair defects and response to olaparib.[31] Preliminary data from the TRITON2 study, evaluating rucaparib, confirmed the high response rate to PARPi of *BRCA1/2*-deficient prostate cancers.[32] Nevertheless, the predictive value of other defects in DNA repair genes such as *ATM*, *FANCA* or *CHEK2* remains yet to be validated in randomised studies. None of the HRD score tests has been validated yet in prostate cancer clinical trials. Of note, in two recent studies, the prevalence of LOH-high signatures, based on the FoundationOne assay, among *BRCA2*-mutated prostate cancer was lower than for the *BRCA1/2*-mutated ovarian cancer setting.[33 34]

A current limitation of the genomic scar assays is the impossibility to capture tumour evolution processes, such as a restoration of the HRR function in response to therapy-selective pressure. As an alternative, it could be useful to incorporate functional biomarkers based on dynamic assays that assess the activity of a repair pathway. A crucial step of HRR is mediated by the RAD51 protein.[1] In vivo and in vitro studies supported the highly sensitive and specific predictive power of lack of nuclear RAD51 foci to PARPi response.[30 35–37] One limitation is that the RAD51 assay may fail to identify *ATM*-mutated tumours that can benefit from PARPi.[31 38–40] There are several other tests currently used in research to identify tumours with a similar biological behaviour as the *BRCA1/2*-mutated ones. Those tests take into account not only the copy number changes but also methylation or gene expression profiles.[41–43] Even if preclinical and retrospective data suggest that these tests are predictive of high dose alkylating chemotherapy and PARPi response, the lack of prospective validation and concerns regarding their large-scale feasibility seem to be major issues for their clinical application.[43–49]

We can summarise that genomic scars associated with HRR defects in ovarian cancer identify patients who obtain maximum benefit from PARPi maintenance after platinum response. In early breast cancer, HRD-genomic scars have shown a high correlation to DNA-damaging chemotherapy response, and a definitive word to predict the benefit of adding carboplatin is warranted. In prostate cancer, recent data suggest that HRR gene-mutated tumours, including *gBRCA2*, are sensitive to PARPi. Nonetheless, it is of concern that HRD is observed less-frequently than in ovarian cancers.

As future perspectives, research is needed to confirm if clinical implementation of HRD tests might be useful to identify patients with platinum-resistant ovarian cancer who may benefit from PARPi. Likewise, some *BRCA1/2* WT, HRD-positive breast cancers could respond to PARPi. Also, the prognostic role of HRD should be further investigated with *ad hoc* trials in order to recognise patients with early breast cancer candidates for a targeted strategy. Prospective comparison between HRD-genomic scars and functional dynamic tests such as the RAD51 assay is encouraged.

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