Testing for Homologous Recombination Repair or Homologous Recombination Deficiency for Poly (ADP-ribose) Polymerase Inhibitors: A Current Perspective

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Current Perspective

Testing for homologous recombination repair or homologous recombination deficiency for poly (ADP-ribose) polymerase inhibitors: A current perspective

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Poly(ADP-ribose) polymerase inhibitors;
Ovarian neoplasms;
Prostate neoplasms;
Breast neoplasms;

Abstract Poly (ADP-ribose) polymerase inhibitors (PARPis) have demonstrated clinical activity in patients with BRCA1 and/or BRCA2 mutated breast, ovarian, prostate, and pancreatic cancers. Notably, BRCA mutations are associated with defects in the homologous recombination repair (HRR) pathway. This homologous recombination deficiency (HRD) phenotype can also be observed as genomic instability in tumour cells. Accordingly, PARPi sensitivity has been observed in various tumours with HRD, independent of BRCA mutations. Currently, four PARPis are approved by regulatory agencies for the treatment of cancer across multiple tumour types. Most indications are specific to tumours with a confirmed
1. Introduction

Genome stability is essential to life, and the cell has evolved multiple DNA damage response (DDR) pathways to detect and repair DNA damage [1,2]. Defects in these pathways can lead to mutations, genomic instability, cell death and tumorigenesis [1,2]. Poly(ADP-ribose) polymerases (PARPs) play an essential role in DDR pathways and represent a target for anticancer therapy [1,3]. In the past decade, PARP inhibitors (PARPis) have emerged as a new class of anticancer drugs in multiple cancers, including ovarian (niraparib, olaparib and rucaparib), metastatic castration-resistant prostate (mCRPC; olaparib and rucaparib), breast (olaparib and talazoparib) and metastatic pancreatic (olaparib) [4–11]. Predicting benefit from PARPis is critical for optimal clinical use, and several biomarker tests are available to determine patient selection for PARPis across treatment settings, with more tests in development [3]. These tests identify tumours with defects in DNA repair pathways, most specifically the homologous recombination repair (HRR) pathway, which make them vulnerable to PARPis. Choice of the appropriate biomarker test depends on tumour type and may even differ by line of therapy for the same tumour type, thereby presenting challenges for the clinician. This review aims to enhance the understanding of different biomarker tests to assess homologous recombination deficiency (HRD) and their relevance for PARPi treatment selection in different tumour types.

2. HRD in cancer

Numerous genes have been implicated in the HRR pathway, including those encoding sensor proteins involved in DSB detection (i.e. $\gamma$H2AX, ATM and ATR), signal mediator proteins (i.e. BRCA1, BRCA2 and PALB2), and an effector protein (RAD51) that promotes strand invasion and replication fork stabilisation (Fig. 1) [12]. The best-characterised HRR genes in relation to cancer are BRCA1 and BRCA2, which have been associated with breast, ovarian, pancreatic and prostate cancers [13].

HRD is characterised by an inability to repair DNA DSBs through the HRR pathway. Causes of HRD are not always known but include loss-of-function mutations and epigenetic modifications in HRR-related genes, particularly BRCA1 and/or BRCA2 [14]. HRD typically results in accumulation of genomic damage, which may lead to mitotic catastrophe and cell death as well as carcinogenesis [15]. Consequently, cancer cells can demonstrate genomic instability [16,17], which may manifest as loss of heterozygosity (LOH; existence of a single allele resulting from a cross-chromosomal event that leads to the loss of entire genes and the surrounding chromosomal region [17]); telomeric allelic imbalance...
BRCA mutations have been reported to range from 1% to static breast cancer, 12% that harbour BRCA mutations [21]. The prevalence of PARPi sensitivity has been well established for tumours with the drug approvals to facilitate patient selection. Companion diagnostics are approved in conjunction with platinum-sensitive disease relapse [4]. PARPi therapy is also broadly indicated for patients HRD genomic instability (Supplementary Table 1), but most indications are specific to tumours with a known HRD. The first approach is evaluating tumour mutation status by gene sequencing of a panel of specified genes known to cause HRD. BRCA1 and BRCA2 are the most well-characterised HRR genes in terms of their relationship to cancer and should always be evaluated. This approach can be expanded to include multiple other genes related to the HRR pathway, but, in some diseases, such as first-line ovarian cancer, non-BRCA HRR mutations do not predict PARPi response, while HRD genomic instability has been predictive (Fig. 1) [3,22,23,30]. Emerging evidence suggests that other HRR gene alterations may be associated with different PARPi sensitivity.

The second approach investigates whether the consequences of HRD, namely genomic instability, are present by identifying chromosomal aberrations (i.e. genomic scars), which are changes in the genome as a consequence of the dysfunctional HRR pathway (both direct and indirect) including LOH, TAI and LST [3,22,25]. Given the recognition of BRCA mutations as an archetypal cause of HRD, BRCA testing is invariably conducted. As such, some assays combine the measurement of both the HRR mutations (i.e. BRCA) and HRD genomic instability approaches.

The third approach directly evaluates HRR function in tumour cells to determine if there is proficiency. An example of a functional assay is the RAD51 foci assay, which measures the capacity of tumour cells to recruit nuclear RAD51 foci during the S/G2 cell cycle phase in the presence of DSBs using immunofluorescence [31]. Functional assays provide a measure of HRR competency, which may be important when, for example, a reversion mutation results in a tumour switching from HRD status to being HRD proficient [32]. Because of technical complexity, functional assays such as RAD51 foci are not routinely used clinically.

Table 1 [33–39] summarises the HRD diagnostics for various PARPi indications. These assays use a variety of sample types (blood or tumour tissue). Other tests for HRR mutations and HRD genomic instability, including locally developed tests, are being established, validated and commercialised.

5. Clinical validity and utility of HRR mutations and tests for HRD in various cancers

In the first-line maintenance treatment setting of ovarian cancer, the benefit of PARPis in BRCA-mutated tumours was demonstrated in randomised phase 3 trials (Table 2 [28,30,40–49]). HRD positivity (defined as a tumour with a BRCA mutation or a genomic instability score above a specified threshold for the HRD assay used) was also associated with a PFS benefit with PARPis in randomised phase 3 trials in the first-line maintenance treatment setting in advanced ovarian cancer (Table 2 [28,30,40–49]). A recent exploratory analysis evaluating HRR mutations other than BRCA demonstrated that only a small percentage (4%) of patients with HRD-positive tumours without a BRCA mutation harbour other non-BRCA HRR mutations commonly included in the HRR mutation testing panel [30]. A PFS benefit with olaparib plus bevacizumab versus placebo plus bevacizumab was not observed in the subgroup of patients with non-BRCA HRR mutations; however, in a small number...
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<tr>
<th>Diagnostic</th>
<th>Sample used</th>
<th>Biomarkers evaluated</th>
<th>Cancer type (regulatory-approved PARPi)</th>
<th>Test category</th>
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<tr>
<td>FoundationOne® CDx is a comprehensive genomic profiling test that detects substitutions, insertion and deletion alterations and copy number alterations in 324 genes and select gene rearrangements, including a number of HRR genes, as well as genomic signatures including MSI and TMB. LOH is evaluated for patients with ovarian cancer. FoundationOne CDx defines positive HRD status as a BRCA mutation in the tumour and/or LOH-high. On this device, assessment of LOH is designated by the FDA as a complementary, not companion, diagnostic [33]</td>
<td>DNA from FFPE tumour tissue</td>
<td>BRCA1 and/or BRCA2 alterations, HRR genes (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D and RAD54L) alteration</td>
<td>Ovarian cancer (olaparib, rucaparib), Prostate cancer (olaparib)</td>
<td>HRR mutation test</td>
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<tr>
<td>FoundationOne® LiquidCDx evaluates specific HRR gene variants in circulating cell-free DNA [34]</td>
<td>cfDNA isolated from plasma derived from anticoagulated peripheral whole blood</td>
<td>BRCA1 and BRCA2 alterations, BRCA1, BRCA2 and ATM alterations, BRCA1 and BRCA2 alterations</td>
<td>Ovarian cancer (rucaparib), Prostate cancer (olaparib), Prostate cancer (rucaparib)</td>
<td>HRR mutation test</td>
</tr>
<tr>
<td>Myriad BRACAnalysisCDx® evaluates BRCA1 and BRCA2 variants in genomic DNA from blood [35]</td>
<td>Genomic DNA from whole blood specimens</td>
<td>Deleterious or suspected deleterious mutations in BRCA1 and BRCA2 genes, Deleterious or suspected deleterious mutations in BRCA1 and BRCA2 genes, Deleterious or suspected deleterious mutations in BRCA1 and BRCA2 genes, Deleterious or suspected deleterious mutations in BRCA1 and BRCA2 genes</td>
<td>Breast cancer (olaparib, talazoparib), Ovarian cancer (olaparib or rucaparib), Pancreatic cancer (olaparib), Prostate cancer (olaparib)</td>
<td>BRCA (HRR) mutation test</td>
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<tr>
<td>Myriad MyChoice® CDx is a comprehensive genomic profiling test specifically for determining HRD status in ovarian cancer [36]</td>
<td>DNA from FFPE tumour tissue</td>
<td>Myriad HRD (defined as deleterious or suspected deleterious mutations in BRCA1 and BRCA2 genes and/or positive Genomic Instability Score)</td>
<td>Ovarian cancer (olaparib, niraparib)</td>
<td>BRCA (HRR) mutation test and HRD genomic instability test</td>
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<tr>
<td><strong>CE-IVD (European Union)</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
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<td><strong>Sample used</strong></td>
<td><strong>Biomarkers evaluated</strong></td>
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<tr>
<td>Myriad MyChoice&lt;sup&gt;c&lt;/sup&gt;/CDx PLUS is a next-generation sequencing based in vitro diagnostic device that provides sequencing and large rearrangement analyses on a panel of genes and/or detects genomic instability [37]</td>
<td>DNA from FFPE tumour tissue</td>
<td>Tumour genomic instability and/or detect sequence variants and large rearrangements in up to 15 genes (ATM, BARD1, BRCA1, BRCA2, BRI1, CDKL2, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and RAD54L)</td>
<td>Ovarian cancer</td>
<td>HRR mutation test and HRD genomic instability test</td>
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<tr>
<td>SOPHiA DDM&lt;sup&gt;d&lt;/sup&gt;/ Dx Homologous Recombination Deficiency Solution&lt;sup&gt;b&lt;/sup&gt; is a deep learning–powered diagnostic application leveraging low-pass whole genome sequencing in conjunction with a convolutional neural network–based deep-learning algorithm to produce the Genomic Integrity Index. This score measures the extent of genomic scarring across the genome as a result of mutations within genes associated with HRR, yielding HRD impact on tumour samples [38]</td>
<td>DNA from FFPE tumour tissue</td>
<td>BRCA1, BRCA2, ATM, BARD1, BRCA1, BRCA2, BRI1, CCNE1, CDKL2, CHEK1, CHEK2, ESRI, FANCA, FANCD2, FANCL, FGFR1, FGFR2, FGFR3, MRE11, NBN, PALB2, PIK3CA, PPP2R2A, PTEN, RAD51B, RAD51C, RAD51D, RAD54L and TP53</td>
<td>Ovarian cancer</td>
<td>HRR mutation test and HRD genomic instability test</td>
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<tr>
<td>AmoyDx&lt;sup&gt;e&lt;/sup&gt; HRD Focus Panel is a next-generation sequencing-based in vitro diagnostic assay intended for qualitative determination of HRD status via detection and classification of single nucleotide variants and insertions and deletions in protein coding regions and intron/exon boundaries of the BRCA1 and BRCA2 genes and the determination of the Genomic Scar Score, which is an algorithmic measurement of genomic instability status [39]</td>
<td>DNA from FFPE tumour tissue</td>
<td>BRCA1, BRCA2 and Genomic Scar Score</td>
<td>Ovarian cancer</td>
<td>BRCA (HRR) mutation test and HRD genomic instability test</td>
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Abbreviations: CE-IVD, CE-marked in vitro diagnostics; FFPE, formalin-fixed paraffin embedded; HRD, homologous recombination deficiency; HRR, homologous recombination repair; LOH, loss of heterozygosity; LST, large-scale state transitions; MSI, microsatellite instability; NGS, next-generation sequencing; PARPi, poly (ADP-ribose) polymerase inhibitor; TAI, telomeric allelic imbalance; TMB, tumour mutational burden.

<sup>a</sup> A number of BRCA1/BRCA2 tests are also designated CE-IVD.

<sup>b</sup> HRR gene panel analysis of this test is not covered by the CE-IVD claim.

<sup>c</sup> Hotspot coverage only.
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<th>Study</th>
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<td><strong>First-line maintenance therapy</strong></td>
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<tr>
<td>PAOLA-1/ENGOT-ov25 (NCT02477644) [44]</td>
<td>Phase 3, randomised, double-blind, multicenter</td>
<td>Olaparib 300 mg BID + bevacizumab (n = 537) versus placebo + bevacizumab (n = 269)</td>
<td>Newly diagnosed, advanced high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer; complete or partial response after platinum-taxane chemotherapy plus bevacizumab</td>
<td>Deleterious germline BRCA1 or BRCA2 mutation (MyChoice assay)</td>
<td>PFS: Overall: 22.1 versus 16.6 mo (HR 0.59; 95% CI: 0.49–0.72)</td>
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<tr>
<td>SOLO1 (NCT01844986) [45]</td>
<td>Phase 3, randomised, double-blind, multicenter</td>
<td>Olaparib 300 mg BID (n = 260) versus placebo (n = 131)</td>
<td>Newly diagnosed, advanced high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer; complete or partial response after platinum-based chemotherapy</td>
<td>Deleterious or suspected deleterious germline or somatic BRCA1 and/or BRCA2 mutation (BRACAnalysis test)</td>
<td>PFS: NR versus 13.8 mo (HR 0.30; 95% CI: 0.23–0.41)</td>
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<tr>
<td>PRIMA/ENGOT-OV26/GOG-3012 (NCT02655016) [28]</td>
<td>Phase 3, randomised, double-blind, multicenter</td>
<td>Niraparib 300 mg/day (200 mg/day if bodyweight &lt;77 kg; n = 487) versus placebo (n = 246)</td>
<td>Newly diagnosed, advanced high-grade serous or endometrioid ovarian, peritoneal or fallopian tube cancer; complete or partial response after platinum-based chemotherapy</td>
<td>HRD-positive defined as HRD score ≥42</td>
<td>PFS: Overall: 13.8 versus 8.2 mo (HR 0.62; 95% CI: 0.50–0.76)</td>
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<tr>
<td>ATHENA-MONO/GOG-3020/ENGOT-ov45 (NCT03522246) [46]</td>
<td>Phase 3, randomised, double-blind, multicenter</td>
<td>Rucaparib 600 mg BID (n = 427) versus placebo (n = 111)</td>
<td>Newly diagnosed, advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer; complete or partial response after platinum-based chemotherapy</td>
<td>Tumour HRD test status (BRCA mutations and genomic LOH; FoundationOne CDx)</td>
<td>PFS: ITT: 20.2 versus 9.2 mo (HR 0.52; 95% CI: 0.40–0.68)</td>
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<td><strong>Relapsed/recurrent treatment strategies</strong></td>
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<tr>
<td>QUADRA (NCT02354586) [47]</td>
<td>Phase 2, open-label, single-arm, multicenter</td>
<td>Niraparib 300 mg QD (N = 463)</td>
<td>Metastatic, relapsed high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer; ≥3 prior lines of chemotherapy</td>
<td>HRD-positive defined as HRD score ≥42 and/or a deleterious BRCA mutation (MyChoice test)</td>
<td>PFS: Overall: 19.1 versus 5.5 mo (HR 0.30; 95% CI: 0.22–0.41)</td>
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<tr>
<td>Study 19 (NCT00753545) [40]</td>
<td>Phase 2, randomised, double-blind, multicenter</td>
<td>Olaparib 400 mg BID (n = 136) versus placebo (n = 129)</td>
<td>Recurrent high-grade serous ovarian, fallopian tube or primary peritoneal cancer; platinum-sensitive; ≥2 courses of platinum-based chemotherapy</td>
<td>Germline BRCA1 and/or BRCA2 variants and HRD score (MyChoice HRD test)</td>
<td>PFS: ITT: 8.4 versus 4.8 mo (HR 0.35; 95% CI: 0.25–0.49)</td>
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<tr>
<td>SOLO2/ENGOT-Ov21 (NCT01874353) [30]</td>
<td>Phase 3, randomised, double-blind, multicenter</td>
<td>Olaparib 300 mg BID (n = 196) versus placebo (n = 99)</td>
<td>Relapsed, high-grade serous or endometrioid ovarian, fallopian tube or primary peritoneal cancer; platinum-sensitive; ≥2 prior lines of platinum-based chemotherapy; BRCA1 and/or BRCA2 mutation status not required</td>
<td>Deleterious BRCA1 and/or BRCA2 mutation (BRACAnalysis assay)</td>
<td>PFS: 19.1 versus 5.5 mo (HR 0.30; 95% CI: 0.22–0.41)</td>
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<tr>
<td>SOLO3 (NCT02282020)</td>
<td>Phase 3, randomised, open-label, multicenter</td>
<td>Olaparib 300 mg BID (n = 178) versus nonplatinum chemotherapy (n = 88)</td>
<td>Relapsed, high-grade serous or endometrioid ovarian, primary peritoneal and/or fallopian tube cancer; platinum-sensitive; ≥2 prior lines of platinum-based chemotherapy; gBRCA mutation</td>
<td>Deleterious or suspected deleterious germline BRCA1 or BRCA2 mutation (BRACAnalysis assay)</td>
<td>PFS</td>
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<td>13.4 versus 9.2 mo (HR 0.62; 95% CI: 0.43 –0.91)</td>
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<td>NOVA/ENGOT-OV16 (NCT01847274)</td>
<td>Phase 3, randomised, double-blind, multicenter</td>
<td>Niraparib 300 mg (gBRCA mutation cohort, n = 138; non-BRCA cohort, n = 234) versus placebo (gBRCA mutation cohort, n = 65; non-gBRCA mutation cohort, n = 116)</td>
<td>Recurrent, high-grade serous ovarian, fallopian tube or primary peritoneal cancer; platinum-sensitive; ≥2 prior lines of platinum-based chemotherapy</td>
<td>Germline BRCA mutation (BRACAnalysis assay) HRD status also assessed (MyChoice HRD assay)</td>
<td>PFS</td>
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<td>gBRCA-mutated cohort: 21.0 versus 5.5 mo (HR 0.27; 95% CI: 0.17–0.41) Non-gBRCA–mutated HRD-positive cohort: 12.9 versus 3.8 mo (HR 0.38; 95% CI: 0.24–0.59) Overall non-gBRCA–mutated cohort: 9.3 versus 3.9 mo (HR 0.45; 95% CI: 0.34–0.61)</td>
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<td>ARIEL3 (NCT01968213)</td>
<td>Phase 3, randomised, double-blind, multicenter</td>
<td>Rucaparib 600 mg BID (n = 375) versus placebo (n = 189)</td>
<td>Recurrent, high-grade serous or endometrioid ovarian, fallopian tube or primary peritoneal cancer; platinum-sensitive; ≥2 prior lines of platinum-based chemotherapy</td>
<td>BRCA1 or BRCA2 mutation non-BRCA HRR-related gene mutation (T5 next-generation sequencing assay; germline mutations identified with BRACAnalysis CDx test)</td>
<td>Investigator-assessed PFS (primary analysis) Investigator-assessed PFS2 (post-progression)</td>
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<td>Overall: 10.8 versus 5.4 mo (HR 0.36; 95% CI: 0.30–0.45) BRCA mutated cohort: 16.6 versus 5.4 mo (HR 0.23; 95% CI: 0.16–0.34) HRD cohort: 13.6 versus 5.4 mo (HR 0.32; 95% CI: 0.24–0.42) Chemotherapy-free interval (post-progression)</td>
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<td>Overall: 14.3 versus 8.8 mo (HR 0.43; 95% CI: 0.35–0.53) BRCA-mutated cohort: 20.8 versus 8.7 mo (HR 0.28; 95% CI: 0.19–0.41) HRD cohort: 18.0 versus 9.1 mo (HR 0.40; 95% CI: 0.31–0.53) Investigator-assessed PFS2 (post-progression)</td>
</tr>
<tr>
<td>ARIEL4 (NCT02855944)</td>
<td>Phase 3, randomised, open-label, multicenter</td>
<td>Rucaparib 600 mg BID (n = 233) versus chemotherapy (n = 116)</td>
<td>Relapsed, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer; PARPi-naive; ≥2 prior lines of chemotherapy</td>
<td>Deleterious BRCA1 and/or BRCA2 mutation BRCA reversion mutations were also assessed</td>
<td>PFS</td>
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<td>Significantly longer for rucaparib versus chemotherapy BRCA4 reversion mutation subgroup: 2.9 versus 5.5 mo (HR 2.769; 95% CI: 0.989–7.755)</td>
</tr>
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</table>

**Abbreviations:** BID, twice daily; gBRCA germline BRCA mutation; HR, hazard ratio; HRD, homologous recombination deficiency; HRRm, homologous recombination repair gene mutation; ITT, intention-to-treat; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival.
of these patients, HRD-positive status by genomic instability testing was predictive of a PFS benefit [30].

In patients with relapsed platinum-sensitive ovarian cancer, HRR mutation, HRD status and response to immediate platinum chemotherapy are all predictive of a PFS benefit with PARPi, as demonstrated by the findings from four clinical trials (Table 2 [28,30,40–49]).

The European Society for Medical Oncology Translational Research and Precision Medicine Working Group recently assessed evidence of predictive biomarkers in high-grade serous ovarian cancer and recommended the use of germline or somatic BRCA mutation testing and a validated scar-based (genomic instability) test for HRD to select patients for PARPi treatment in the first-line maintenance and in the platinum-sensitive relapsed settings [3]. This group concluded that evidence is currently insufficient to determine the clinical validity of non-BRCA HRR mutation, next-generation sequencing-based mutational signature, BRCA1 or RAD51C promoter methylation and functional assays for predicting a PARPi response [3]. Data on the clinical validity of somatic BRCA mutations, HRR mutations and HRD genomic instability tests in other cancers besides mCRPC are limited.

Olaparib, rucaparib and niraparib have demonstrated antitumour activity in people with BRCA-mutated mCRPC [50,51]. The PROfound and TRITON2 trials explored treatment outcomes in patients with mutations in other HRR genes [52,53]. PROfound was a randomised, open-label phase 3 trial evaluating olaparib versus physician’s choice of hormone therapy (enzalutamide or abiraterone) in mCRPC with a qualifying alteration in any one of 15 HRR genes [52]. In patients with ≥1 alteration in BRCA1, BRCA2 or ATM, PFS was significantly prolonged for the olaparib versus the control group (median, 7.4 versus 3.6 months; hazard ratio [HR] 0.34; 95% CI: 0.25–0.47) and with statistically significant OS benefit (median, 19.1 versus 14.7 months; HR 0.69; 95% CI: 0.50–0.97; p = 0.0175) [54]. A PFS benefit was also observed in the overall population (any HRR mutation) with an HR of 0.49 (95% CI: 0.38–0.63), and a trend toward improved OS was also seen (HR 0.79; 95% CI: 0.61–1.03; nominal p = 0.0515). The HR for PFS in patients with HRD mutations other than BRCA1, BRCA2 or ATM was 0.88. In the phase 2 TRITON2 trial, rucaparib was evaluated in patients with mCRPC and a non-BRCA HRR mutation. The trial found limited radiographic and prostate-specific antigen responses to rucaparib in patients with an alteration in ATM, CDK12 or CHEK2; patients with alterations in other HRR mutations (e.g. PALB2) may benefit from rucaparib, but the patient subgroup sizes were too small to make definitive conclusions; further investigation was deemed warranted [53].

In advanced/metastatic breast cancer, olaparib has demonstrated a PFS benefit versus chemotherapy in patients with a germline BRCA mutation in two randomised, open-label phase 3 clinical trials [55,56]. In OlympiAD, olaparib significantly prolonged median PFS versus chemotherapy (7.0 versus 4.2 months; HR 0.58; 95% CI: 0.43–0.80) in patients with a germline BRCA mutation and human epidural growth factor receptor type 2-negative metastatic breast cancer treated with ≤2 previous chemotherapies. Olaparib has also been associated with a median PFS of 6.3 months (90% CI: 4.4–not available) in 16 patients with metastatic breast cancer and a somatic BRCA2 mutation [57]. In the EMBRACA study, talazoparib significantly prolonged median PFS versus chemotherapy in patients with a germline BRCA2 mutation and advanced breast cancer treated with ≤3 previous chemotherapies (8.6 versus 5.6 months; HR 0.54; 95% CI: 0.41–0.71) [56].

Approval of olaparib maintenance therapy for pancreatic cancer was based on results from the pivotal phase 3 POLO trial in patients with a germline BRCA1 or BRCA2 mutation and metastatic disease that had not progressed during first-line platinum-based chemotherapy. A PFS benefit in favour of olaparib versus placebo was reported (median, 7.4 versus 3.8 months; HR 0.53; 95% CI: 0.35–0.82) [58].

6. Conclusions

Patients with HRD tumours caused by a BRCA mutation represent the subgroup with the best-documented clinical benefit from a PARPi, and whether non-BRCA HRR mutations or HRD genomic instability tests best predict PARPi response by disease site requires further research in many indications. BRCA mutations remain the best-characterised measure of HRD and should always be assessed regardless of other assays that might be used (e.g. assessment of other HRR-related genes or HRD genomic instability). However, patients with HRD tumours without a BRCA mutation can benefit from PARPi in first-line ovarian cancer. HRD is a phenotype that can be measured in different ways, such as by identifying genomic scars or mutational signatures or by measuring HRR function. Further, HRD genomic instability gives a historical rather than a functional view of the genome, hence the interest in functional assays such as that for RAD51 foci. However, varying degrees of evidence exist for the predictive value of these different measures. Inconsistent use of terminology adds to the confusion over these tests. The regulatory-approved companion diagnostics are specific to each PARPi, tumour type, and treatment setting. HRD mutations and HRD genomic instability tests have different predictive power in different clinical settings and are not interchangeable. In newly diagnosed advanced ovarian cancer, HRD positivity by genomic instability tests, but not non-BRCA HRR mutations, are predictive of benefit from PARPi maintenance treatment after response to first-line platinum chemotherapy. In the relapsed setting, selection for benefit
from PARPi is based on platinum sensitivity. HRR mutation tests have been validated in patients with prostate cancer whereas there are few data on the clinical validity of HRD genomic instability testing. Future clinical and translational studies are needed to further elucidate the mechanisms by which PARPis interact with HRD to inform treatment strategies and patient selection.

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**Data sharing**

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymised data and clinical study reports from the company’s clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of clinical trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

**Author contributions**

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Maha Hussain: other — critically reviewing or revising the manuscript for important intellectual content and final approval.

**Conflict of interest statement**

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: TH reports scientific advisory boards for AstraZeneca, Caris, Clovis, Eisai, Episilogen, Genentech, GSK, Immunogen, J&J, Merck, Mersana, and Seagen.

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LGG reports scientific advisory boards for AstraZeneca, Merck, Lantheus and Exelixis.

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Appendix A. Supplementary data

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