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# Homologous recombination deficiency in ovarian cancer: Global expert consensus on testing and a comparison of companion diagnostics

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ABSTRACT

*Background:* Poly (ADP ribose) polymerase inhibitors (PARPis) are a treatment option for patients with advanced high-grade serous or endometrioid ovarian carcinoma (OC). Recent guidelines have clarified how homologous recombination deficiency (HRD) may influence treatment decision-making in this setting. As a result, numerous companion diagnostic assays (CDx) have been developed to identify HRD. However, the optimal HRD testing strategy is an area of debate. Moreover, recently published clinical and translational data may impact how HRD status may be used to identify patients likely to benefit from PARPi use. We aimed to extensively compare available HRD CDx and establish a worldwide expert consensus on HRD testing in primary and recurrent OC.
*Methods:* A group of 99 global experts from 31 different countries was formed. Using a modified Delphi process, the experts aimed to establish consensus statements based on a systematic literature search and CDx information sought from investigators, companies and/or publications.
*Results:* Technical information, including analytical and clinical validation, were obtained from 14 of 15 available HRD CDx (7 academic; 7 commercial). Consensus was reached on 36 statements encompassing the following topics: 1) the predictive impact of HRD status on PARPi use in primary and recurrent OC; 2) analytical and clinical validation requirements of HRD CDx; 3) resource-stratified HRD testing; and 4) how future CDx may include additional approaches to help address unmet testing needs.
*Conclusion:* This manuscript provides detailed information on currently available HRD CDx and up-to-date guidance from global experts on HRD testing in patients with primary and recurrent OC.

## 1. Introduction

Precision medicine aims to adapt medical treatments to the individual tumour characteristics of each patient, necessitating accurate and validated companion diagnostic assays (CDx). Indeed, CDx are essential tools as they help identify patients who are most likely to benefit from specific therapies by detecting biomarkers that predict response to treatments. In the context of advanced high-grade serous or endometrioid ovarian carcinoma (OC; including fallopian tube and primary peritoneal carcinoma), the use of poly (adenosine diphosphate [ADP] ribose) polymerase inhibitors (PARPis) has exemplified this concept. Starting with precise molecular alterations, namely pathogenic or likely pathogenic variants of *BRCA1* or *BRCA2* (*BRCA*m), clinical implementation of PARPis in some settings/regions has been extended to include patients with tumours demonstrating homologous recombination deficiency (HRD) [1–10], as summarised in Supplementary Table S1.

Some recent guidelines clarify how an HRD phenotype may influence treatment decision-making for patients with OC [11–13]. Consequently, there has been significant interest in developing various CDx to identify HRD status in recent years, both in academic and commercial settings. Numerous HRD CDx now exist, including academic (e.g., ShallowHRDv2) and approved commercial (e.g., Myriad MyChoice® HRD Plus assay) tests [14–27]; of note, the SOPHiA DDM™ Dx HRD CDx has been developed through commercial and academic (Centre Léon Bérard, France) collaboration [26]. The number of available CDx has raised questions as to the relevance, performance, cost and access of individual CDx and their equivalence to others. Current CDx also exhibit specific limitations, notably the fact that their results do not necessarily reflect the current HRD status of the tumour, as they mainly rely on measurement of genetic defects. Moreover, there are currently no guidelines as to how HRD should be measured. The optimal HRD testing strategy is therefore under debate (including the most appropriate sequence of germline and tumour *BRCAm* testing), making it challenging for clinicians to choose the most appropriate CDx. Recently published additional clinical and translational data [28–40] have also illustrated how HRD status may be used to identify patients likely to benefit from PARPi treatment.

Here, we compare currently available CDx and provide a worldwide expert consensus pertaining to the predictive impact of HRD status on PARPi use in primary and recurrent settings (taking into account new and emerging data from randomised clinical trials and recent approval restrictions), analytical/clinical validation requirements of HRD CDx, resource-stratified HRD testing, and how future CDx may include additional approaches (such as deep-learning algorithms or functional assays assessing RAD51 foci) to help address unmet testing needs.

## 2. Overview of the consensus methodology

A group of global experts was convened under the auspices of the European Society of Pathology (ESP), the French Society of Predictive and Personalized Medicine (SFMPP), Groupe d'Investigateurs Nationaux pour l'Etude des cancers de l'ovaire et du sein (GINECO) and Cours St Paul. The group consisted of a chair, co-chair, steering committee (n = 14), author contributors (n = 5) and other contributors (n = 78); their roles and responsibilities are provided in Supplementary Table S2. Participants were from 31 countries and various specialties, including medical oncology (n = 29), gynaecological oncology (n = 27), molecular biology (n = 20), clinical genetics (n = 9), pathology (n = 7), patient advocacy (n = 6) and clinical bioinformatics (n = 1). The chair, co-chair and steering committee members selected contributors based on their expertise.

A modified Delphi process was used (Supplementary Fig. S1). A systematic literature review was conducted to identify articles and abstracts relating to PARPi use and HRD testing in ovarian cancer using PubMed (01 Jan 2021 to 31 May 2023), Web of Science (01 Jan 2021 to 31 May 2023) and congresses (held 01 Jan 2022 to 31 May 2023) (Supplementary methods). All identified articles/abstracts were graded by the steering committee according to their level of evidence. Articles/abstracts reporting the efficacy and safety of PARPis in clinical studies were graded using the Infectious Diseases Society of America (IDSA) public health grading system, while articles reporting on genomic tests (analytical or clinical validation) were assessed using the IDSA public health grading system and Evaluation of Genomic Applications in Practice and Prevention grading system (Supplementary methods). Detailed information for CDx was obtained from lead investigators (for academic CDx), companies (for commercial CDx) and/or relevant publications.

The literature search and CDx information was to aid the development of consensus statements on the following: 1) maintenance treatment in primary and recurrent OC; 2) HRD assay validity; 3) resource-stratified guidelines for HRD testing in OC; and 4) future CDx development. Consensus statements were agreed upon by the chair, co-chair and steering committee. Statements were circulated to participants (via a survey), who then voted on each statement using a five-point Likert scale (strongly agree, agree, undecided, disagree and strongly disagree); an open comment box was provided for additional feedback or questions. The survey results were analysed and statements that had not reached consensus (< 75 % agreement [strongly agree/agree]) were discussed during a virtual meeting (Jan 2024) to which all participants were

invited. Discussed consensus statements were either revised or discarded during this meeting, with live voting used to determine if the revised statements reached consensus (> 75% agreement [strongly agree/agree]). An overview of this process, including the number of survey respondents and meeting attendees, is outlined in Supplementary Fig. S2.

## 3. Literature search results

The literature search results are summarised in Supplementary Fig. S3. A total of 82 articles and 32 congress abstracts were selected from the search results. A further 58 articles (including evidence-graded articles used in the previously published European-wide consensus [12], articles published after 31 May 2023, guidelines and prescribing information) were selected during manuscript development. All articles and congress abstracts identified in the literature search, along with their level of evidence, are listed in Supplementary Table S3. The technical specifications and analytical/clinical validation of currently available HRD CDx are summarised in Tables 1 and 2, respectively. Full details of these tests (technical specification; performance; analytical/clinical validation; economic, regulatory and access considerations; data availability and handling) are provided in Supplementary Tables S4–S10.

Selected articles, congress abstracts, and collated genomic test information were used by the steering committee to generate the consensus statements. A total of 38 statements were prepared and included in the survey, of which 28 achieved consensus (>75% agreement [strongly agree/agree]), seven were close to consensus (65–75% agreement), and three did not reach consensus (<65% agreement). The 10 statements that were close to/did not reach consensus were discussed and revised in the consensus meeting: eight revised statements were voted on and achieved consensus and two revised statements were discarded (due to redundancy/relevance) without voting. The final 36 statements are discussed by category below.

## 4. Maintenance treatment in primary and recurrent OC

Consensus statements are shown in Table 3. Our literature review captured final overall survival (OS) and updated progression-free

**Table 1**
Technical information on academic and commercial CDx.

| Test | Principle (s) of test | Items Assessed | | GI definition | HRD definition |
|---|---|---|---|---|---|
| | | t*BRCA* alterations | Alterations other than *BRCA* and GIS | | |
| **Academic CDx** | | | | | |
| Geneva HRD Test [14] | CNVs with GW-SNP | CNVs | CNVs (pan-genomic) | N° of LST normalised by n° of whole genome doubling events | GIS ≥ 15 |
| NOGGO GIS Assay [15] | Targeted NGS (57 cancer-related genes + GW-SNP) | SNVs, indels, CNVs | 55 HRR and other cancer-related genes | Combined score (reflects n° of large-scale CNVs) | NOGGO GIS ≥ 83 |
| GIScar [16] | Targeted NGS (127 genes, including HRR genes) | SNVs, indels, CNVs | NA[a] | Combined score (integrates n° of LGA, SIS and AI) | GIScar score ≥ 0.48 |
| Leuven HRD test [17] | Targeted NGS (9 HRR genes) + GW-SNP (GI) | SNVs, indels | 6 other HRR genes + *TP53* | Combined score (LOH + LST + TAI) | *BRCA*m and/or GIS ≥ 56 |
| Shallow HRDv2 [18] | sWGS | NA | NA | Number of LGAs (i.e., CN breaks between genomic segments >9 Mb) | > 20 LGAs |
| *BRCA*-Like Classifier [19] | Targeted NGS (34 HRR genes) + sWGS | SNVs, indels, CNVs | 32 other HRR genes | Posterior probability (i.e., tumour CN profile similar to HRD reference set) | Posterior probability > 0.5 |
| **Approved Commercial CDx** | | | | | |
| MyChoice® CDx Plus | Targeted sequencing (15 HRR genes) + GW-SNP (GI) | SNVs, indels, CNVs | 13 other HRR genes (scientific purpose only) | Combined score (LOH + TAI + LST) | *BRCA*m and/or GIS ≥ 42 |
| OncoDEEP® [20] | A targeted NGS (638 genes + RNA-based 20-gene panel for gene fusions and splicing RNA) | SNVs, indels, CNVs, splicing alterations, intronic mutations | 14 other HRR genes | Proprietary algorithm | GIS > 39 |
| SeqONE HRD [21] | Targeted NGS + sWGS (GI) | SNVs, indels | Amplifications of *CCNE1* and *RAD51B* (for HRD determination) | Composite score (LGA + LOH) | *BRCA*m and/or HRD status (probability ≥ 50%; based on composite score and gene amplification at two locations) |
| SOPHiA DDM™ Dx HRD CE-IVD [26] | Targeted NGS (28 HRR genes) + sWGS (GI) | SNVs, indels | 26 other HRR genes | Proprietary algorithm (determined through deep-learning algorithm) | GII > 0 |
| FoundationOne® CDx [23] | Targeted NGS (324 genes) + GW-SNP (GI, MSI and TMB) | SNVs, indels, CNVs, splicing alterations | 12 other HRR genes | gLOH score (% of LOH) | *BRCA*m and/or gLOH score ≥ 16% |
| HRD Focus [24] | Targeted NGS (of *BRCA*) + GW-SNP (GI) | SNVs, indels | NA | GSS ≥ 50, proprietary algorithm (determined through deep-learning algorithm) | *BRCA*m and/or a GSS ≥ 50 |
| Caris HRD Status | *BRCA*m + GSS (comprising gLOH + LST) | SNVs, indels, CNVs | - | - | *BRCA*m or high GSS |

Data were sourced directly from each supplier via questionnaire, except for the Caris HRD test (data sourced from the company website).
AI, allelic imbalance; *BRCA*m, *BRCA* mutation; CDx, companion diagnostic; CN, copy number; CNV, copy number variation; GI, genome instability; GII, genome instability index; GIS, genome instability score; gLOH, genomic loss of heterozygosity; GSS, genome scar score; GW-SNP, genome-wide SNP-based assay; HRD, homologous recombination deficiency; HRR, homologous recombination repair; indel, insertion or deletion; LGA, large genomic alterations; LOH, loss of heterozygosity; LST, large-scale state transitions; MSI, microsatellite instability; NA, not applicable; NGS, next-generation sequencing; SIS, structural instability score; SNP, single nucleotide polymorphism; SNV, single nucleotide variant; sWGS, shallow whole genome sequencing; TAI, telomeric-allelic imbalance; t*BRCA*, tumour BRCA; TMB, tumour mutational burden.
[a] HRR genes are sequenced but not analysed.

**Table 2**
Analytical and clinical validation of academic and commercial CDx.

| Test | Analytical validation | | Clinical validation | | |
|---|---|---|---|---|---|
| | Cohort (n)[a] | % of agreement NPA; PPA; OPA | Cohort (n)[a] | Median PFS for patients with HRD Mo (HR; 95%CI) | Median PFS for patients with HRP Mo (HR; 95%CI) IDEM form HRD |
| **Academic CDx** | | | | | |
| Geneva HRD test [14] | PAOLA−1 (469) | 81; 98; 90 | PAOLA−1 (469) | OLA + BEV: 51<br>PL + BEV: 20<br>(0.41; 0.30–0.57) | OLA + BEV: 16<br>PL + BEV: 16<br>(1.20; 0.86–1.70) |
| NOGGO GIS Assay [15] | PAOLA−1 (469) | 92; 86; 88 | PAOLA−1 (469) | NA<br>(0.31; 0.21–0.46) | NA<br>(1.02; 0.73–1.44) |
| GIScar [16] | Prospective collection (250) | 90; 88; 89 | PAOLA−1 (469) | OLA: 43<br>PL: 20<br>(0.45; 0.33–0.62) | OLA: 17<br>PL: 17<br>(1.02; 0.74 −1.40) |
| Leuven HRD test [17] | PAOLA−1 (468) | 86; 95; 91 | PAOLA−1 (468) | OLA + BEV: 49%[b]<br>PL + BEV: 20%[b]<br>(0.43; 0.31–0.59) | OLA + BEV: 14%[b]<br>PL + BEV: 12%[b]<br>(0.88; 0.61–1.28) |
| Shallow HRDv2 [18] | PAOLA−1 (449) | 92; 95; 94 | PAOLA−1 (449) | OLA + BEV: 66<br>PL + BEV: 20<br>(0.36;0.24–0.53) | OLA + BEV: 17<br>PL + BEV: 16<br>(0.96; 0.70–1.33) |
| *BRCA*-Like Classifier [27] | PAOLA−1 (469)[c] | 61[d]; 90[e]; 78[f] | PAOLA−1 (469) | OLA + BEV: 36<br>PL + BEV: 19<br>(0.49; 0.37–0.65) | OLA + BEV: 18<br>PL + BEV: 17<br>(1.02; 0.68–1.51) |
| **Approved Commercial CDx** | | | | | |
| MyChoice® CDx Plus | Fixed non-clinical and clinical specimens (209)[g] | 99; 99; 99 | PAOLA−1 (806)<br>PRIMA (733)[h] | OLA + BEV: 37 PL + BEV: 18<br>(0.33; 0.25–0.45)<br>NIR: 22 PL: 10<br>(0.43; 0.31–0.59) | OLA + BEV: 17, PL + BEV: 16<br>(1.00; 0.75–1.35)<br>NIR: 8, PL: 5<br>(0.68; 0.49–0.94) |
| OncoDEEP® [20] | Clinical samples with known Myriad score (66) or German QUIP proficiency testing (10) | 98; 96; 96 | Upcoming (PAOLA−1) | NA | NA |
| SeqONE HRD [21] | One centre (95) | 98; 91; 93 | PAOLA−1 (368) | OLA + BEV: 46<br>PL + BEV: 19<br>(0.38; 0.26–0.54) | OLA + BEV: 17<br>PL + BEV: 16<br>(0.98; 0.68–1.41) |
| SOPHiA DDM™ Dx HRD CE-IVD [26] | Ovarian cancer with DQN ≥ 3 (238) | 96; 93; 94 | PAOLA−1 (359) | OLA + BEV: 56<br>PL + BEV: 19<br>(0.32; 0.22–0.45) | OLA + BEV: 17<br>PL + BEV: 16<br>(1.04; 0.71–1.52) |
| FoundationOne® CDx (F1CDx) [32,56] | ARIEL3 (489)[i] | 95; 98; 97[g] | ARIEL2/ARIEL3 (NA)<br>ATHENA (111) | RUC: 14<br>PL: 5<br>(0.32; 0.24–0.42)<br>RUC: 28.7<br>PL: 11.3<br>(0.47; 0.31–0.72) | RUC: 7<br>PL: 5<br>(0.58; 0.40–0.85)<br>RUC: 12.1<br>PL: 9.1<br>(0.65; 0.45–0.95) |
| HRD Focus [24] | SNV/indel: 47 clinical samples (35 OC, 7 BC, 5 other cancers). HRD: 154 clinical samples (122 OC, 25 BC, 7 other cancers)[j] | > 95; > 95; > 95 | NA | NA | NA |
| Caris HRD Status | NA | > 99; > 95; - | NA | NA | NA |

Data were sourced directly from each supplier via questionnaire or from the cited references, except for the Caris HRD test (data sourced from the company website). BC, breast cancer; BEV, bevacizumab; CI, 95% confidence interval; CDx, companion diagnostic; DQN, deep Q-network; GIS, genome instability score; HR, hazard ratio; HRD, homologous recombination deficiency; HRP, homologous recombination proficient; indel, insertion or deletion; LOH, loss of heterozygosity; mo, months; NA, not available; NIR, niraparib; NPA, negative percent agreement; OC, ovarian cancer; OLA, olaparib; OPA, overall percent agreement; PFS, progression-free survival; PL, placebo; PPA, positive percent agreement; QUIP, quality in pathology; RUC, rucaparib; SNV, single nucleotide variant.

[a] Comparator is the Myriad MyChoice® CDx, unless otherwise stated.
[b] 5-year PFS values are shown.
[c] Earlier stage validations in TCGA and OVHIPC trial.
[d] Among 405 samples successfully analysed with both assays (test and comparator), 34% (107/314) were negative in both assays.
[e] 66% (207/314) were successfully analysed with both assays (test and comparator).
[f] 77% (314/405) were successfully analysed with both assays (test and comparator).
[g] Validated integrated DNA technologies HRD comparator assay.
[h] No comparator (first in class).
[i] FoundationFocus CDx BRCA LOH was used as the comparator.
[j] AmoyDx LDT NGS assay was used as the comparator.

survival (PFS) data from the placebo-controlled PAOLA-1/ENGOT-OV25 phase 3 trial, which assessed olaparib in combination with bevacizumab in patients with OC who had responded to platinum-based chemotherapy plus bevacizumab [28]. In this trial (which used the Myriad MyChoice® HRD Plus assay to determine tumour HRD status), olaparib plus bevacizumab was associated with a reduction in the risk of death compared with placebo plus bevacizumab in patients with HRD test positive tumours (regardless of tumour *BRCA*m [t*BRCA*m] status), whereas no such benefit was seen in patients with HRD test negative tumours [28]. Updated PFS analyses were consistent with these findings [28]. Although no statistical comparisons were made between groups, the greatest OS and PFS benefits with olaparib plus bevacizumab were in patients with t*BRCA*m or t*BRCA* wild-type (t*BRCA*wt) HRD test positive tumours [28]. Maintenance olaparib plus bevacizumab continued to provide clinical benefit after first progression, significantly prolonging the time from randomisation to second progression or death (PFS2) relative to placebo plus bevacizumab [29].

Our searches also captured mature data for olaparib monotherapy

**Table 3**
Maintenance treatment in primary and recurrent OC.

| Consensus statements relating to primary maintenance treatment | Level of contributor agreement (%)[a] |
|---|---|
| HRD status, using the Myriad MyChoice® HRD test, is predictive of olaparib + bevacizumab efficacy as frontline maintenance, based on both PFS and OS data | 91 |
| HRD status is predictive of niraparib (with Myriad MyChoice® HRD test) or rucaparib (with FoundationOne® LOH test) efficacy as frontline maintenance, based on PFS data | 80 |
| An HRD negative status, assessed using the Myriad MyChoice® HRD test, is predictive of modest PFS benefit with niraparib as frontline maintenance | 92 |
| A negative HRD status, assessed using the FoundationOne® LOH test, may be associated with modest PFS benefit with rucaparib as frontline maintenance | 84 |
| Alteration of t*BRCA1/2* is the best predictive factor of PARPi efficacy as frontline maintenance, based on both PFS and OS data | 85 |
| PARPi-based maintenance should be considered for all patients with t*BRCA*m or HRD test positive tumours with complete or partial response after a platinum-based regimen | 93 |
| Currently, non-*BRCA1/2* HRR gene panels cannot substitute for HRD evaluation to predict PARPi sensitivity | 98 |
| *RAD51C* and *PALB2* pathogenic or likely pathogenic variants are associated with genomic instability | 88 |
| *BRCA1* promoter methylation may be associated with tumour genomic instability | 95 |
| **Consensus statements relating to recurrent disease maintenance treatment** | **Level of contributor agreement (%)[a]** |
| Alteration of t*BRCA1/2* is the best predictive biomarker of PARPi efficacy as second-line maintenance in patients without prior PARPi treatment, based on both PFS and OS data | 80 |
| In the context of t*BRCA*wt, platinum-free interval and response to last platinum challenge may be used as surrogates of PARPi sensitivity | 92 |

HRD, homologous recombination deficiency; HRR, homologous recombination repair; LOH, loss of heterozygosity; OC, advanced high-grade serous or endometrioid ovarian carcinoma (including fallopian tube and primary peritoneal carcinoma); OS, overall survival; PARPi, poly (ADP ribose) polymerase inhibitor; PFS, progression-free survival; t*BRCA*, tumour *BRCA*; t*BRCA*m, tumour *BRCA* mutation; t*BRCA*wt, tumour *BRCA* wild-type.

[a] Proportion of contributors agreeing (agree/strongly agree) with a survey statement.

from SOLO1/GOG 3004, a placebo-controlled phase 3 trial in patients with OC with a response to platinum-based chemotherapy and a deleterious or suspected deleterious *BRCA* mutation, assessed using the Myriad BRACAnalysis® CDx [30,31]. In a 5-year follow-up of SOLO1/GOG 3004, olaparib monotherapy significantly improved PFS and PFS2 versus placebo [30]. Furthermore, in an interim analysis at 7 years of follow-up, patients who received olaparib had an OS benefit relative to those who received placebo, although the magnitude of benefit was not statistically significant according to a prespecified threshold [31].

Olaparib is approved in numerous markets, including the EU [2], US [1] and China [3], as a maintenance treatment following response to primary platinum-based chemotherapy in patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer; it is approved as monotherapy in patients with germline/tumour *BRCA*m (g/t*BRCA*m; t*BRCA*m encompasses both germline and somatic mutations) [1–3] (deleterious or suspected deleterious [1]), and in combination with bevacizumab in patients whose cancer is HRD test positive (*BRCA*m and/or genomic instability) [1–3]. In this primary maintenance setting, current American Society of Clinical Oncology (ASCO) guidelines recommend olaparib monotherapy for patients with pathogenic or likely pathogenic g/t*BRCA*m [41], while European Society of Medical Oncology (ESMO) guidelines recommend olaparib, alone or in combination with bevacizumab, for patients with *BRCA*m tumours, and olaparib plus bevacizumab for patients with *BRCA*wt/HRD test positive tumours [42]. Somewhat different guidance is provided in the European Society of Gynaecological Oncology-ESMO-ESP (ESGO-ESMO-ESP) consensus recommendations, with a PARPi (with or without bevacizumab) recommended for *BRCA*m or genomic instability score (GIS)-positive tumours [13].

In patients with OC who have responded to platinum-based chemotherapy, rucaparib and niraparib have each demonstrated a PFS benefit relative to placebo when used as primary maintenance therapy in phase 3 trials (ATHENA-MONO/GOG-3020/ENGOT-OV45 [32], PRIMA/ENGOT-OV26/GOG-3012 [33] and PRIME [43]). For each of these PARPis, improvements in PFS versus placebo were seen across HRD status subgroups, confirmed by the FoundationOne® CDx (i.e., *BRCA*m, *BRCA*wt/loss of heterozygosity [LOH] high or *BRCA*wt/LOH low tumours) [32], Myriad MyChoice® CDx (i.e., *BRCA*m, *BRCA*wt/HRD test positive or HRD test negative tumours) [33] or BGI Genomics CDx (i.e., g*BRCA*m status and tumour HRD status) [43]. These improvements were most notable in patients with *BRCA*m tumours, and less pronounced in other subgroups in the ATHENA-MONO/GOG-3020/ENGOT-OV45 and PRIMA/ENGOT-OV26/GOG-3012 trials [32,33], although this trend was not seen in the PRIME study [43]. Recently, updated data from the PRIMA/ENGOT-OV26/GOG-3012 trial found long-term PFS benefit with niraparib versus placebo in most HRD/*BRCA* status subgroups; nevertheless, no significant difference in OS was observed between treatment arms, either in the overall population or the HRD/*BRCA* status subgroups [44]. Based on these findings, rucaparib (EU [8]) and niraparib (EU [5]/US [4]/China [6]) are approved as maintenance therapies following response to primary platinum-based chemotherapy in patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer. The ASCO [41], ESGO-ESMO-ESP [13] and ESMO [42] guidelines currently include niraparib [13,41,42] and rucaparib [13,41] among the recommended options in this setting, irrespective of tumour HRD test status.

Whether non-*BRCA* homologous recombination repair (HRR) gene mutations (non-*BRCA* HRRm) may be biomarkers of PARPi sensitivity was explored in a post-hoc analysis of PAOLA-1/ENGOT-OV25, using six panels of non-*BRCA* genes with roles in HRR to identify patients with non-BRCA HRRm-positive tumours; however, none of the panels were predictive of PFS benefit with olaparib plus bevacizumab versus placebo plus bevacizumab [34]. Notably, mutations in six HRR genes, including *RAD51C/D* and *PALB2*, were identified in non-*BRCA* HRRm-positive tumours with a median GIS of $\geq$ 42 [34]. Furthermore, mutations in *RAD51C/D* and *PALB2* have been associated with clinical benefit in patients receiving niraparib [45], and mutations in *RAD51C/D* have been associated with exceptional benefit in patients receiving rucaparib [46] (drug activity confirmed by *RAD51C* reversion mechanisms have been described in patients receiving rucaparib [47]). ESMO guidelines acknowledge that the clinical relevance of individual or panels of non-*BRCA* HRR genes in predicting PARPi response is currently difficult to interpret [11], and ESGO-ESMO-ESP guidelines state that tumour testing for HRRm is not required, but should be encouraged for research purposes [13]. However, ASCO recommend that, when testing for g*BRCA*m, a multi-gene panel that includes HRR genes alongside *BRCA* should be considered, as the costs may be comparable to testing for *BRCA* alone [48]. Future clinical trials are thus needed to determine how such testing approaches could impact treatment decisions.

Epigenetic alterations, such as methylation of *BRCA1* or *RAD51C* promoters, may also impact tumour genomic instability. In a PAOLA-1 ancillary study, 12.9% and 4.8% of samples had *BRCA1* or *RAD51C* promoter methylation, respectively; most methylation-positive tumours were GIS positive [35]. Patients with *RAD51C* or *BRCA1* promoter methylation experienced a similar clinical benefit on olaparib plus bevacizumab to patients with non-methylated, *BRCA*wt HRD test positive tumours [35]. However, measuring *BRCA1* promoter methylation to

predict PARPi response can be technically challenging, as the zygosity of *BRCA1* promoter methylation could have an impact [49]. ESMO guidelines state that the evidence supporting the clinical validity of *BRCA1* promoter methylation in predicting PARPi benefit is currently insufficient [11].

Three PARPis (olaparib, [1,2] niraparib [4–6] and rucaparib [7,8]) are widely approved (as monotherapy) for the maintenance treatment of patients with recurrent/relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer in complete or partial response to platinum-based chemotherapy. Another PARPi (fuzuloparib) is approved for a similar indication only in China [50,51] and, as such, is not discussed further here. Pivotal clinical trials (SOLO2/ENGOT-OV21, [52] Study 19 [53], NOVA/ENGOT-OV16 [54,55], ARIEL3 [56] and NORA [57]) have demonstrated improvements in PFS with these agents versus placebo, with an open-label non-comparative study (L-MOCA [58]) of olaparib supporting these findings. A meta-analysis of several of these trials indicated a similar magnitude of PFS benefit with PARPi therapy in patients with g*BRCA*m or t*BRCA*m [59]. Our consensus is that t*BRCA*m is the best predictor of PARPi efficacy when used as second-line maintenance treatment (80% contributor agreement).

In an exploratory analysis of ARIEL3, exceptional benefit from rucaparib was associated with clinical factors related to platinum sensitivity, including a penultimate platinum-free interval > 12 months and no measurable disease at baseline [46]. Furthermore, in NOVA/ENGOT-OV16, PFS benefit was seen with niraparib versus placebo in patients with a complete or partial response to their last platinum therapy, regardless of the presence or absence of g*BRCA*m [55]. In the context of t*BRCA*wt, platinum-free interval and response to the last platinum challenge may thus be used as potential markers of PARPi sensitivity, rather than GIS (92% contributor agreement).

In the EU summary of product characteristics [2,5,8] and Chinese prescribing information [3,6] for olaparib [2,3], niraparib [5,6] and rucaparib [8], indications for the recurrent setting do not include *BRCA* or HRD status restrictions; however, in the US, the indications have recently been narrowed to include only patients with deleterious [1,4,7] or suspected deleterious [1,4] g*BRCA*m [1,4,7] and/or t*BRCA*m [1,7]. These indication changes were based on data suggesting PARPi use may be detrimental to OS, particularly in patients without g*BRCA*m [36,37]. An OS benefit was seen in patients with *BRCA*m in SOLO2/ENGOT-OV21 at final analysis, although it was not statistically significant [38].

Although olaparib, niraparib and rucaparib have each previously been approved for the treatment of heavily pretreated (≥2 or ≥3 prior lines of chemotherapy) *BRCA*m/HRD test positive recurrent epithelial OC, the approvals have been withdrawn following post-hoc analyses of the phase 3 ARIEL4 and SOLO3 trials. These analyses suggested a potential detrimental effect of PARPis on survival relative to chemotherapy [39,40].

## 5. HRD assay validity

Consensus statements are shown in Table 4. The majority of available CDx assess HRD via composite evaluation of t*BRCA* plus GIS (Table 1). The suitability of a CDx for HRD evaluation requires consideration of both its analytical validity (i.e., its sensitivity, specificity and accuracy in correctly identifying the relevant biomarker[s]) and its clinical validity (i.e., its ability to select patients for treatment or predict response to treatment) [60]. Most academic (6/6) [14,15,17–19,61] and commercial (4/7) [20,22] CDx have undergone analytical and clinical validation (Table 2).

The Myriad MyChoice® CDx has typically been used as the comparator when assessing the analytical validity of most other HRD CDx (Table 2). For analytical validation to be considered optimal, we recommend that the positive and negative percent agreement with the standard HRD assay comparator should each be > 90%, the overall percent agreement should be > 95%, and < 10% of the results should be non-contributive based on good quality samples (80% contributor agreement). The percent agreement (positive, negative, overall) is typically lower for academic CDx than for approved commercial CDx (Table 2). However, the steering committee recognises that sample deterioration over time may impact validation, when archived samples (which may have deteriorated to a lesser quality) are used for testing the study CDx compared with the initial tests performed with fresh samples using a standard CDx. Furthermore, achieving agreement thresholds may be easier for tests that assess a specific mutation than those assessing more complex genetic signatures.

**Table 4**
HRD assay validity.

| Consensus statements | Level of contributor agreement (%)[a] |
|---|---|
| Composite evaluation (t*BRCA1/2* + GIS) currently represents the gold standard for HRD evaluation in newly diagnosed OC | 94 |
| Assays require both analytical and clinical validation prior to their use in routine clinical practice | 90 |
| Optimal analytical validation, as compared to standard HRD assays, requires positive percent agreement to be > 90%, negative percent agreement to be > 90% and overall percent agreement to be > 95% | 80 |
| Optimal analytical validation, based on good quality samples, as compared to standard HRD assays, requires < 10% of results to be non-contributive | 80 |
| Clinical validation requires at least non-inferior performance with a gold standard CDx relating to survival (both for HRD test positive and GIS positive/ t*BRCA1/2*wt populations) | 83 |

CDx, companion diagnostic assays; GIS, genomic instability score; HRD, homologous recombination deficiency; OC, advanced high-grade serous or endometrioid ovarian carcinoma (including fallopian tube and primary peritoneal carcinoma); t*BRCA*, tumour *BRCA*; t*BRCA*wt, tumour *BRCA* wild-type.
[a] Proportion of contributors agreeing (agree/strongly agree) with a survey statement.

For clinical validation of HRD CDx, PFS has been used as the metric of treatment response and the Myriad MyChoice® CDx has typically been used as the comparator (Table 2). The steering committee agreed that the performance of a CDx in predicting survival should be at least non-inferior to (i.e., no worse than) that of a gold standard CDx (83% contributor agreement), with non-inferiority established if the between-test difference does not cross a predefined inferiority margin [62]. Notably, none of the CDx comparisons reported to date have formally assessed non-inferiority. Analyses of particular interest may include comparisons of CDx assessing HRD through LOH, large-scale state transitions and telomeric-allelic imbalance versus those that assess LOH alone, as the former may yield more precise information.

## 6. Resource-stratified guidelines for OC

Consensus statements are shown in Table 5. Recommendations for implementing genetic testing in OC have been published by several organisations and societies [11,13,42,48,63–67]. Current guidelines recognise the importance of *BRCA* testing upon OC diagnosis but differ with regard to whether they prioritise g*BRCA* and/or t*BRCA* testing. A working group representing several Italian societies recommends that t*BRCA* testing is performed first whenever possible [64]. ASCO [48] and Society of Gynecologic Oncology (SGO) [63] recommend all patients undergo g*BRCA* testing upon diagnosis, with t*BRCA* testing recommended in parallel [63] or when g*BRCA* testing is negative [48,63]. By contrast, ESMO [42], ESGO-ESMO-ESP [13], National Comprehensive Cancer Network (NCCN) [65], and SFMPP [67] guidelines do not favour g*BRCA* testing over t*BRCA* testing, or vice versa.

In support of g*BRCA* testing, a study of 21,333 cancer patients demonstrated that tumour testing is unable to detect all pathogenic/likely pathogenic germline variants detected by germline testing (6.2%

**Table 5**
Resource-stratified guidelines for HRD testing in OC.

| Consensus statements relating to HRD testing prior to frontline treatment | Level of contributor agreement (%)[a] |
|---|---|
| As part of routine clinical practice, t*BRCA1/2* testing should be performed upon diagnosis of all OC | 97 |
| When obtaining samples from a patient with clinically suspected OC, care should be taken to ensure they are of sufficient quality to be used for detecting t*BRCA*m and GIS | 99 |
| Due to technical limitations regarding tumour analysis of *BRCA1/2* CNV and because of the prophylactic importance of identifying a germline predisposition, g*BRCA1/2* testing should be performed in all cases of OC upon diagnosis | 78 |
| Upon t*BRCA1/2* testing, physicians should inform patients of the possible discovery of a germline alteration | 87 |
| Following discovery of a t*BRCA1/2* alteration, g*BRCA1/2* testing should be proposed to the patient | 97 |
| Results of g*BRCA1/2*, t*BRCA1/2* and GIS assessment should be available for the optimal management of patients with OC | 90 |
| In time-restricted cases, concomitant t*BRCA1/2* and GIS assessment should be performed initially | 88 |
| In economic-restricted cases, t*BRCA1/2* testing should initially be prioritised, owing to its prognostic and predictive value regarding PARPi efficiency, followed by GIS evaluation in cases found to be t*BRCA1/2*wt | 77 |
| In economic-restricted cases, reflex targeted g*BRCA1/2* testing should be proposed following t*BRCA*m discovery | 88 |
| **Consensus statements relating to HRD testing prior to recurrence treatment** | **Level of contributor agreement (%)[a]** |
| In patients who have not previously received a PARPi, if previously unassessed, t*BRCA1/2* status remains of prime importance and testing should be performed in all recurrent OC cases | 92 |
| In the context of recurrent OC, GIS evaluation is not essential for PARPi decision-making | 83 |

CNV, copy number variation; g*BRCA*, germline *BRCA*; GIS, genomic instability score; HRD, homologous recombination deficiency; OC, advanced high-grade serous or endometrioid ovarian carcinoma (including fallopian tube and primary peritoneal carcinoma); PARPi, poly (ADP ribose) polymerase inhibitor; t*BRCA*m, tumour *BRCA* mutation; t*BRCA*wt, tumour *BRCA* wild-type.

[a] Proportion of contributors agreeing (agree/strongly agree) with a survey statement.

and 2.1% of all *BRCA1* and *BRCA2* variants, respectively, were not detected), possibly for reasons such as the tumour sample quality and genetic heterogeneity within the tumour (which may impact the ability to detect germline copy number variation [deletions/duplications]) [68]. By contrast, other studies in patients with advanced OC have shown that, overall, tumour testing detects more *BRCA*m than germline testing [69,70], highlighting its potential to detect both somatic and germline mutations. However, analytical modelling using real-world data from patients with OC in the Netherlands has suggested that the cost per patient of genetic testing is lower when t*BRCA* testing is performed prior to g*BRCA* testing, than when g*BRCA* testing is performed first [71].

Some guidelines include recommendations as to the quality of the tumour samples used for genetic testing [11,13,66], such as the minimum tumour cellularity requirements (≥30% neoplastic cells [11,13], although this may differ depending on the specific assay used [66]) and appropriate sample handling (e.g., fixation times) [11,66]. The importance of the pathologist in selecting appropriate areas of the tumour for sampling and assessing sample adequacy is also highlighted [11,66]. In cases where t*BRCA* testing has been conducted first, guidelines recommend informing the patient of possible germline alterations and discussing [66] or offering [67] g*BRCA* testing if a t*BRCA*m has been detected. For optimal management of patients with OC, we recommend assessment of g*BRCA*, t*BRCA* and GIS status. In economic-restricted cases, we recommend that t*BRCA* testing is initially prioritised, followed by GIS evaluation in t*BRCA*wt cases (77% contributor agreement) and reflex targeted g*BRCA* testing in t*BRCA*m cases (88% contributor agreement). Reflex g*BRCA* testing would be recommended in GIS-positive cases, as well as those with t*BRCA*m, to screen/search for the low proportion of cases with large *BRCA* deletions that can be missed by tumour testing, as well as to address all clinical implications that may affect the patient or their family members.

For recurrent disease, SGO and NCCN guidelines recommend extensive tumour molecular analysis (including *BRCA*, HRD status, microsatellite instability and tumour mutational burden) [63,65], if not performed previously [65], whereas ESMO recommend *BRCA* testing only [42]. Although genomic instability in *BRCA*wt patients with recurrent disease may be a marker of PARPi sensitivity [45,54,56], its predictive impact in this setting remains limited. Furthermore, genomic instability evaluation is not mandatory prior to PARPi prescription in the recurrent setting [1,2,4,5,7,8] (as all patients with platinum-sensitive relapse might benefit from PARPi therapy [53,54,56,57]), and we therefore do not consider GIS evaluation (initial or updated) essential for PARPi decision making in the context of recurrent OC (83% contributor agreement). However, we do recommend t*BRCA* testing for all patients with recurrent disease who have not received a PARPi previously, if previously unassessed, to predict the magnitude of PARPi benefit and manage hereditary issues (92% contributor agreement).

## 7. Future CDx

Consensus statements are shown in Table 6. Current CDx have their limitations. For some patient populations, additional tests and approaches may be required to further understand their likelihood of responding to therapy. For instance, current CDx are not functional

**Table 6**
Future companion diagnostics.

| Consensus statements | Level of contributor agreement (%)[a] |
|---|---|
| Current CDx exhibit limited information for two distinct populations: patients with an HRD test positive tumour that progresses during PARPi treatment and patients with an HRD test negative tumour that is sensitive to PARPis | 86 |
| t*BRCA1/2*-altered tumours without genomic instability (assessed by GIS) represent a distinct subpopulation that should be better characterised | 85 |
| Currently, there is no impact on treatment decision or follow-up based on the types of alterations of t*BRCA1/2*; however, in the future there may be | 96 |
| For recurrent disease (both for challenge and re-challenge with PARPis), the development of dynamic assays (e.g., functional assays and reversion mutation analysis) is of prime importance | 89 |
| Development of liquid biopsy-based solutions is encouraged, as they may help to understand mechanisms of resistance to PARPis | 94 |
| Future CDx for PARPi sensitivity should be integrated with multimodal clinico-biological parameters for more accurate and individualised medicine | 92 |
| Alternative, open-source, delocalised assays are a prime necessity for a more accessible, personalised medicine approach | 79 |
| Alternative tests should integrate accessibility, feasibility, quality-control considerations and cost within their parameters | 94 |
| Open access algorithms are encouraged for data access and sharing purposes | 91 |

CDx, companion diagnostic assays; GIS, genomic instability score; HRD, homologous recombination deficiency; PARPi, poly (ADP ribose) polymerase inhibitor; t*BRCA*, tumour *BRCA*.

[a] Proportion of contributors agreeing (agree/strongly agree) with a survey statement.

assays of homologous recombination (HR) compliance and are not benchmarked against PARPi sensitivity, but rather HR score distribution relative to that observed in *BRCAm* tumours. In addition, these scores do not change with HR compliance changes, such as functional tumour alterations (e.g., reversion mutations). As such, they do not provide sufficient information to understand why some patients with a positive HRD test progress during PARPi treatment, or why some patients with a negative HRD test are sensitive to PARPis. Moreover, the location of mutations within *BRCA* may impact the magnitude of benefit that patients experience with PARPis, as suggested by an exploratory analysis of PAOLA-1/ENGOT-OV25 [72]. However, current CDx do not provide the type of *BRCA*m alteration, although future tests providing this information may help to inform treatment decisions. Notably, an academic CDx (Leuven PARPi benefit test) has recently been developed based on the same technical next-generation sequencing (NGS) backbone as the Leuven HRD test but that detects *BRCA* variants by domain (along with copy number features of certain genes and specific LOH regions) [73].

Tumour samples for CDx are typically obtained at diagnosis prior to pharmacological treatment. However, real-time monitoring of the disease over the course of therapy, including challenge and re-challenge with PARPis, would be beneficial to identify the emergence of reversion mutations (which can confer resistance to PARPis and platinum agents [74]) or changes in HR compliance. Investigation is underway into several alternative approaches to approved CDx, including functional assays to measure HR activity (e.g., *RAD51* foci [75–77]; direct repeat-green fluorescent protein based [78]), liquid biopsies [79–85] and prediction models (including deep/machine-learning models [86–90] and nomograms [91,92]).

While *RAD51* functional assays are still carried out using tumour specimens, they can be performed on samples containing a low percentage of tumour cells [75], which may make them more suitable for monitoring HR status in patients with a recent treatment response. Liquid biopsies represent a less invasive approach that involves sampling of biological fluids, including blood to measure circulating tumour DNA (ctDNA) [79–84], and peritoneal fluid to isolate tumour cells and cell-free tumour DNA [85], for screening and monitoring tumour genetic profiles over time. Most recent studies have focused on ctDNA monitoring and have demonstrated the feasibility of this approach for mutation analyses in patients with OC [79–84], including for the detection of reversion/resistance mutations [80,83,84]. Liquid biopsies may capture tumour heterogeneity better than conventional tumour biopsies, as DNA/cells from the entire primary tumour, as well as metastases, can be analysed [93]. This benefit was evident in an analysis of samples from the ARIEL2 study, with more *BRCA* reversion mutations detected by liquid biopsy (ctDNA) than by conventional biopsy, both within and across patient samples [80]. ESMO recommends ctDNA analysis to test for pathogenic or likely pathogenic t*BRCA*m in women with *gBRCA*wt ovarian cancer for whom tissue is unavailable [94].

Various machine-learning approaches have been used to analyse histopathological images to predict genetic features in patients with OC, including *BRCA*m and HRD test score [86–90]. As histopathological samples (in the form of haematoxylin and eosin-stained tissue sections) are readily available for patients with cancer, using such samples to predict genetic features may be a potential option for characterising patients for screening or treatment, although further validation is needed. Future work with machine learning and generative artificial intelligence will likely increase the precision of testing by evaluating multi-dimensional data sets incorporating biological, molecular and clinical parameters, along with functional assays of HR compliance. Other prediction models, such as nomograms, could be developed to incorporate a variety of clinico-biological parameters (e.g., g/t*BRCA*m status, including reversion mutations; mutations in other HRR pathway genes; GIS/LOH; *BRCA1/RAD51C* promoter methylation; *RAD51* foci; response to platinum-based chemotherapy; and CA125 levels), which may allow for more accurate and individualised treatment.

Given the current and future roles of HRD test status in selecting patients for PARPi treatment, it is important to consider ways to reduce the cost and turnaround times for HRD tests while maintaining accuracy/reliability. Studies have shown the feasibility of conducting commercial tests (Myriad MyChoice® [95–97], HRD focus [22,24,98] and SOPHiA DDM™ [22]) in academic laboratories, which could potentially lower costs/turnaround times. The various CDx currently being developed in academic centres (Table 1; Supplementary Tables S4–S10) may also help in this regard, providing they meet the standards required to be certified as an in vitro diagnostic.

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## Appendix A. Supporting information

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