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Feasibility and Clinical Utility of Routine HRD Testing in Newly Diagnosed High-Grade Advanced Ovarian Cancer

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ABSTRACT

For patients with high-grade advanced epithelial ovarian cancer (HG-AOC), standard chemotherapy consists of carboplatin and paclitaxel, followed by maintenance treatment with bevacizumab, a PARP inhibitor, or both. The choice of maintenance strategy is influenced by homologous recombination deficiency (HRD) status and BRCA1/2 alterations. This analysis included individuals newly diagnosed with HG-AOC between December 2019 and December 2021. Tumor HRD status was determined using the Myriad myChoice® assay in all patients for whom HRD testing was clinically indicated, and germline BRCA1/2 evaluation was performed for all patients with the TruRisk® panel, according to national recommendations. HRD testing was ordered for 190 patients, and results were successfully obtained for 163 (85.8%). In 27 cases, testing failed due to inadequate tumor material. The median turnaround time for HRD results was 37 days (range 8–97). Among the 163 evaluable samples, HRD was identified in 44.7% (73/163), including 42.9% with a genomic instability score (GIS) ≥ 42 and three cases with tumor BRCA1/2 mutations despite a GIS < 42. Germline results were available for 148 patients, revealing pathogenic variants in 18 individuals (12.2%). Among the 27 patients without adequate tumor for HRD testing, germline BRCA1/2 results were available in 19 cases (70.4%), with two carrying a deleterious germline variant (7.4%). These findings indicate that implementing HRD testing in routine practice is practical, with most results returned within a timeframe compatible with treatment planning. Adequate tumor quantity is essential for the myChoice® assay, and concurrent tumor HRD and germline BRCA1/2 testing is advisable to support timely decisions regarding maintenance therapy and to ensure evaluation of patients whose tumor samples are nonevaluable.

Keywords: Primary high-grade advanced ovarian cancer, Homologous recombination deficiency, BRCA1/2, PARP inhibitor, Tumor testing

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Introduction

Ovarian cancer is the second most frequent malignancy of the female reproductive system and remains the leading cause of gynecologic cancer–related mortality in high-income countries [1, 2]. Standard management involves primary cytoreductive surgery followed by chemotherapy with carboplatin and paclitaxel [3]. Evidence from the GOG 218 and ICON 7 trials demonstrated that adding bevacizumab to this regimen—and continuing it as maintenance therapy for 15 months—significantly extends progression-free survival (PFS) [4, 5].

Poly(ADP-ribose) polymerase inhibitors (PARP inhibitors, PARPis) have been used in recurrent ovarian cancer for nearly a decade, initially in patients with BRCA1/2 mutations and later in broader populations [6–9]. Their success in relapsed disease led to phase III studies evaluating PARPis as first-line maintenance treatment. Across these studies, patients with high-grade tumors were required to have completed platinum-based chemotherapy and achieved at least a partial response before randomization to PARPi therapy or placebo (olaparib for 2 years, niraparib for 3 years, or rucaparib for 2 years).

In the SOLO-1 trial, olaparib maintenance produced a remarkable PFS benefit in BRCA-mutated patients compared with the placebo group [10]. The PRIMA trial, which enrolled both BRCA-mutated and non-mutated patients, also showed a significant PFS improvement with niraparib (8.2 vs 13.8 months; $p < 0.001$) [11]. Similarly, PAOLA-1 evaluated olaparib plus bevacizumab in an unselected population receiving bevacizumab with chemotherapy; the combination prolonged PFS compared with bevacizumab alone (16.6 vs 22.1 months; $p < 0.0001$) [12].

BRCA1/2 mutations impair the homologous recombination DNA repair pathway, one of six key DNA damage response (DDR) mechanisms responsible for maintaining genomic stability [13–15]. Tumors lacking homologous recombination function (HRD) display higher genomic instability and are less capable of repairing DNA double-strand breaks caused by platinum agents or PARP inhibition [16–18]. Although BRCA1/2 are central components of this pathway, multiple other genes also contribute to homologous recombination, and alterations in these genes can likewise result in HRD.

Myriad's HRD assay, used in the PRIMA and PAOLA-1 trials, assesses genomic instability as well as BRCA1/2 status. Subgroup analyses from both trials revealed that patients with HRD or BRCA mutations derive strong benefit from PARPi therapy. PRIMA demonstrated a PFS gain even in HRD-negative patients, whereas PAOLA-1 did not, leading to divergent regulatory approvals: niraparib for all patients regardless of BRCA/HRD status, and olaparib only for BRCA-mutated or HRD-positive patients when combined with bevacizumab.

Given the prognostic and predictive impact of BRCA and HRD status, European expert guidelines recommend BRCA and HRD testing for all newly diagnosed advanced ovarian cancer patients [19]. The purpose of this study was to examine the real-world implementation of the centrally performed Myriad myChoice® HRD test and to evaluate its concordance with germline BRCA1/2 testing.

Materials and Methods

This study included patients treated between December 2019 and December 2021 at the tertiary cancer center of the Department of Gynecology and Gynecologic Oncology, Kliniken Essen-Mitte, who had advanced (FIGO stage ≥ IIIA) high-grade ovarian cancer (HG-AOC). The Myriad myChoice® HRD assay was introduced and analytically validated at the collaborating Institute of Pathology, Philipps-Universität Marburg, Germany, as part of an officially approved partnership with Myriad for decentralized HRD analysis.

Formalin-fixed, paraffin-embedded (FFPE) tumor specimens were requested from external pathology laboratories whenever tissue obtained outside our institution lacked adequate quantity or quality for HRD testing. In addition to the genomic instability score (GIS), the HRD assay reports variants in BRCA1, BRCA2, ATM, PALB2, BARD1, RAD51C, RAD51B, RAD54L, BRIP1, and CDK12.

Indications for germline BRCA1/2 and multigene testing followed the recommendations of the Hereditary Breast and Ovarian Cancer Center (HBOC) at the University of Cologne, Germany. Genetic counseling was provided by gynecologic oncologists according to HBOC standards. Detailed procedures were previously described [20]. Neither tumor nor germline sequencing was performed in our department; we extracted and documented all results in our institutional database.

Germline analysis was carried out using the TruRisk® panel, which includes BRCA1/2 and additional DDR-related genes such as ATM, CDH1, CHEK2, MLH1, MSH2, MSH6, PMS2, PALB2, RAD51C, RAD51D, BARD1, BRIP1, and TP53.

Comparisons of categorical variables were performed using chi-square or Fisher's exact tests, with significance defined as $p < 0.05$. Statistical analyses were conducted using SPSS version 23.0 (IBM Corporation, New York, NY, USA).

Results and Discussion

During the study period, HRD testing was considered for 196 patients. Six of these cases were subsequently withdrawn **(Figure 1)**, leaving 190 patients for whom the HRD assay was ultimately requested. Among these, HRD testing could not be completed in 27 patients because the available tumor material was insufficient.

Germline BRCA1/2 testing results were accessible for 168 patients (88.4%). Of the remaining patients, five declined testing, three did not meet their insurance providers' eligibility criteria because of advanced age, and

eight were denied coverage for other insurance-related reasons. In an additional six patients, germline analysis was not performed because a BRCA1/2 mutation or HRD had already been identified in tumor tissue.

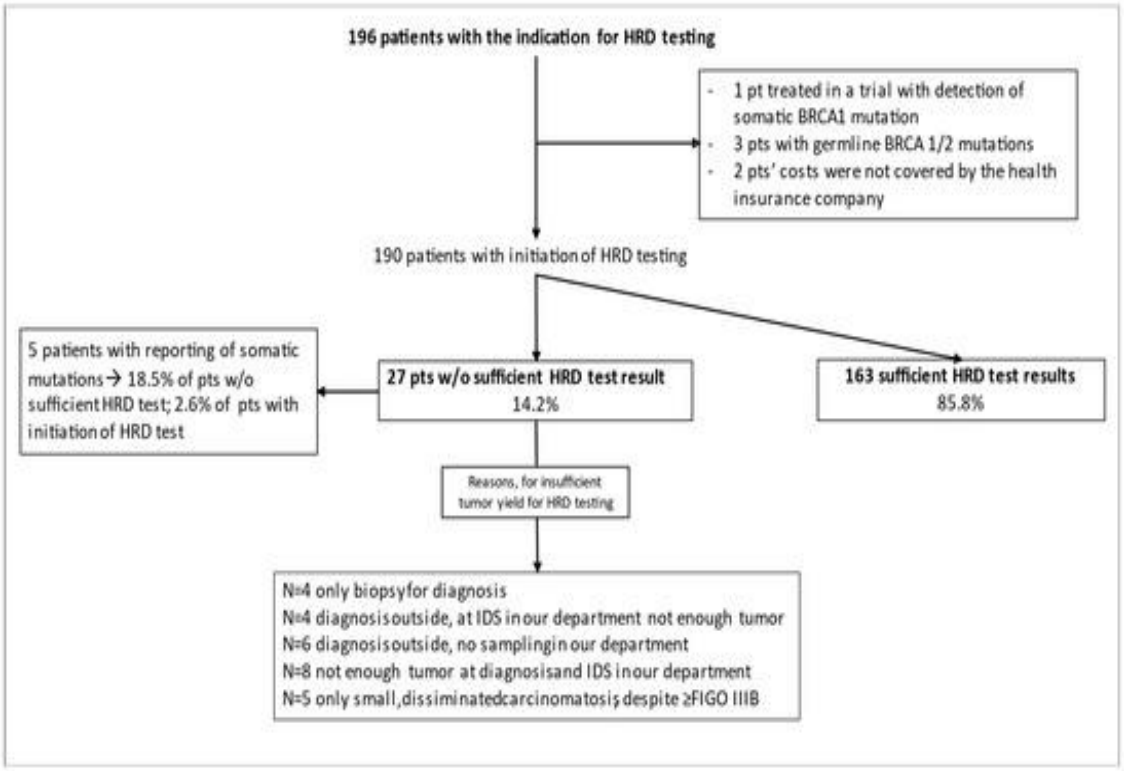


Figure 1. Flow diagram illustrating the pathway from HRD testing indication to final outcomes. HRD indicates homologous recombination deficiency; IDS refers to interval debulking surgery.

The clinical and demographic characteristics of the cohort are summarized in **Table 1**. Most patients presented with advanced disease, with 82.1% classified as FIGO stage IIIC or IV. Primary debulking surgery (PDS) was performed in 71.1% of the cases. High-grade serous carcinoma was the predominant histologic subtype, observed in 95.8% of the patients.

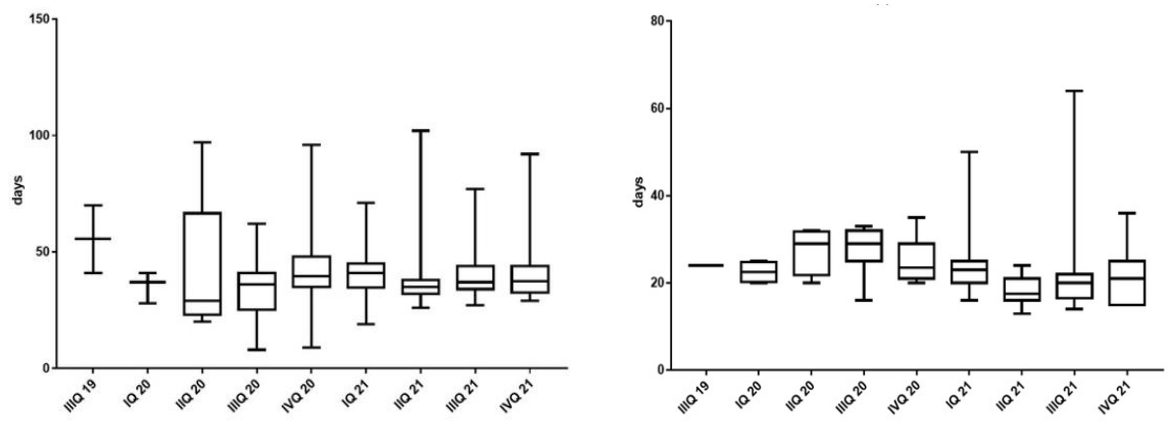
Table 1. Baseline characteristics of the study population. FIGO—International Federation of Gynecology and Obstetrics staging system; ECOG-PS—Eastern Cooperative Oncology Group performance status; HRD—homologous recombination deficiency; §—cases with reported genomic instability score (GIS).

Parameter	**N = 190 (%)**
Age (Median; Min.–Max.)	**62; 23–88**
FIGO	
IIIA	10 (5.3)
IIIB	24 (12.6)
IIIC	64 (33.7)
IV	92 (48.4)
ECOG-PS	
0	171 (90.0)
> 0	19 (10.0)
Surgery	
Primary debulking surgery	135 (71.1)
Interval debulking surgery	40 (21.1)
No surgery	15 (7.8)
Histology	
High-grade serous	182 (95.8)
High-grade endometrioid	2 (1.1)
Clear cell	5 (2.6)

Mucinous destructive/infiltrative	1 (0.5)
BRCA1/2 germline testing	
Yes	168 (88.4)
No	22 (11.6)
Sufficient [§] HRD test result	
Yes	163 (85.8)
No	27 (14.2)

[§] result with reporting of Genomic instability-score (GI-score).

The median time from ordering the HRD test to receiving the results was 37 days. For the first two samples processed in the fourth quarter of 2019, the median turnaround was longer, at 55 days, but no statistically significant differences were observed across the different intervals during the implementation period (p = 0.48) **(Figure 2a).**



a) b)

Figure 2. (a) Interval from ordering to reporting HRD test results across different time periods during implementation. (b) Interval from ordering to reporting germline test results during the HRD test implementation phase.

The median time from genetic counseling and blood collection to receiving germline test results was 23 days. Considerable variation was observed in the median turnaround times for germline testing, ranging from 17.5 to 29 days across the implementation intervals (p < 0.0001), though this did not significantly affect clinical management **(Figure 2b)**. **Figure 1** illustrates the feasibility of HRD testing, including the frequency and reasons for test failures.

Adequate HRD test results, including a reported genomic instability (GI) score, were obtained for 163 patients, whereas 27 patients (14.2%) lacked sufficient HRD results. Among these 27 patients, somatic mutation analysis identified three pathogenic BRCA1 mutations, one CDK12 mutation, and one variant of unknown significance in RAD54L.

The main cause of incomplete HRD results was insufficient tumor material, which was categorized as follows: limited tissue from primary debulking surgery or diagnostic biopsy (N = 5/N = 4), insufficient tissue from an external diagnosis without subsequent interval debulking surgery (IDS) (N = 6), and inadequate tissue from both the external sample and IDS (N = 12). **Figure 3** shows that during the first observational period, 14 of 56 patients (25%) had insufficient tumor material, whereas this decreased to 13 of 113 patients (11.5%) in the second period. Lessons learned during implementation highlighted the importance of adequate tumor sampling, especially before neoadjuvant chemotherapy. As a result, more tissue was collected during primary diagnosis, leading to a relative increase in insufficient tissue from PDS and a decrease in insufficient tissue from initial diagnosis before neoadjuvant therapy over the course of the implementation phase.

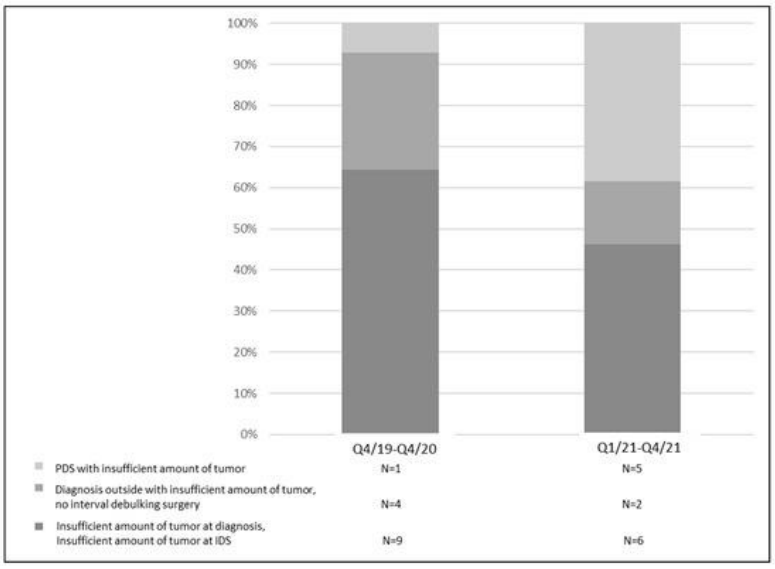


Figure 3. Causes of insufficient tumor tissue resulting in incomplete HRD testing during the implementation phase; Q4/2019–Q4/2020, N = 56; Q1/2021–Q4/2021, N = 113.

Among the 163 patients with a reported GI-score, 70 patients (42.9%) met the HRD cutoff (GIS ≥ 42). An additional three patients (1.8%) were classified as HRD-positive based on the presence of a somatic BRCA1 mutation despite GI-scores of 40, 28, and 26, resulting in an overall HRD positivity rate of 44.7%.

Within the 70 HRD-positive patients with available GI-scores, 24 patients (34.3%) harbored a somatic BRCA1/2 mutation, while 46 patients (65.7%) exhibited HRD in the absence of a BRCA1/2 mutation. Among the 163 patients with sufficient HRD results, germline BRCA1/2 testing was available for 149 patients (91.4%), and 18 patients (12.2%) were found to carry pathogenic germline mutations. For the 27 patients with insufficient HRD testing, germline BRCA1/2 results were available in 19 patients (70.4%), of whom 2 patients (7.4%) had pathogenic germline mutations **(Figure 4).**

Overall, somatic BRCA1/2 mutations were detected in 30 tumors (15.8%) among the 190 patients who underwent HRD testing, with 14 of these also identified through germline testing (62.5%).

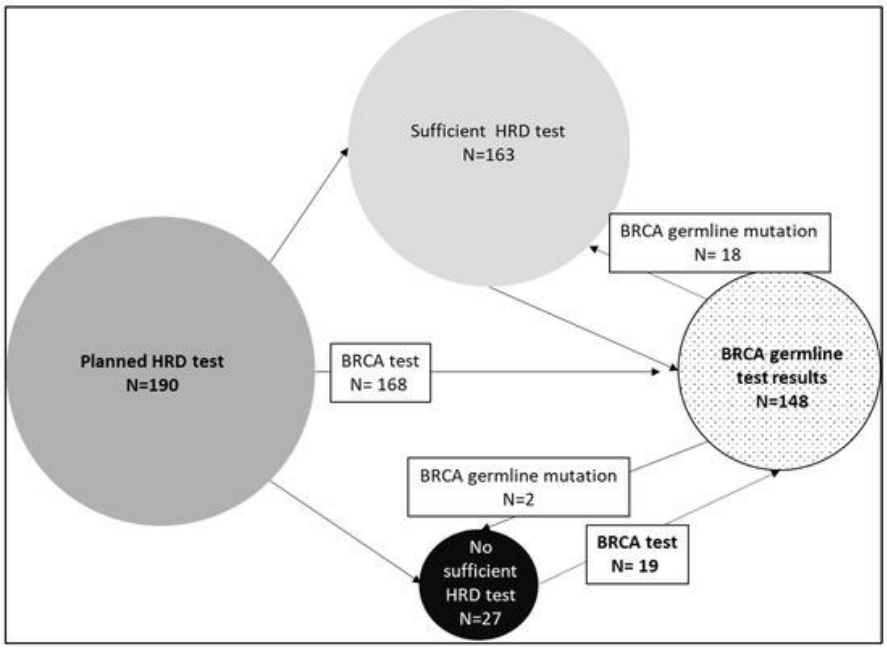


Figure 4. Overview of HRD test results in combination with BRCA1/2 germline test findings. HRD: homologous recombination deficiency; BRCA: breast cancer.

Discussion

This study demonstrated that decentral HRD testing is feasible, even when performed at a central pathology institute in another state. Although the first patients experienced some delays, the overall implementation phase was short, and the median turnaround time for HRD results was generally acceptable for informing treatment decisions. Nevertheless, the availability of sufficient tumor tissue remains the most critical factor for HRD testing. A notable proportion of patients did not receive adequate HRD results due to insufficient tumor material, potentially limiting optimal treatment opportunities. HRD testing is essential for approval-compliant prescription of therapies such as bevacizumab and olaparib in high-grade ovarian cancer. Tumors from eligible patients, particularly those with high-grade histology, should undergo HRD assessment.

Patients with early-stage or low-grade ovarian cancer are not candidates for maintenance therapy with bevacizumab or olaparib. While HRD has clear prognostic significance in ovarian cancer [21, 22], mandatory testing is not required in patients not eligible for bevacizumab maintenance, since HRD alone does not grant access to olaparib maintenance therapy. In the PRIMA trial subgroup analyses, patients with HRD and somatic BRCA1/2 mutations exhibited a strong response to niraparib maintenance therapy (HR: 0.4; 95% CI: 0.27–0.62), as did patients with HRD but without somatic BRCA1/2 mutations (HR: 0.5; 95% CI: 0.31–0.83). Even patients without HRD benefited from niraparib, though to a lesser extent (HR: 0.68; 95% CI: 0.49–0.94) [11]. Accordingly, niraparib maintenance therapy is approved for all patients with advanced high-grade tumors who respond to platinum-based chemotherapy.

In contrast, the PAOLA-1 trial showed that the combination of bevacizumab and olaparib as maintenance therapy significantly prolonged median PFS by 19.5 months in patients with HRD-positive tumors (including somatic BRCA1/2 mutations) compared with placebo, while HRD-positive tumors without BRCA1/2 mutations demonstrated an 11.5-month PFS improvement. HRD-negative patients, however, did not benefit from adding olaparib to bevacizumab [12]. Consequently, olaparib plus bevacizumab is approved only for high-grade carcinoma patients with a BRCA1/2 mutation or HRD who have responded to platinum-based chemotherapy or who have no evidence of disease.

A remaining clinical question is the optimal management of patients with HRD-negative tumors. These patients may receive either bevacizumab during chemotherapy followed by 12 months of maintenance or chemotherapy alone followed by three years of niraparib maintenance. As illustrated in **Figure 5**, treatment decisions could consider tumor burden, tumor-related fluid accumulation (e.g., ascites or pleural effusion), and contraindications to bevacizumab (e.g., bowel perforation, chronic inflammatory bowel disease, uncontrolled hypertension). The ongoing AGO-OVAR 28 phase III trial (NCT05009082) is investigating these strategies, randomizing advanced ovarian cancer patients to carboplatin/paclitaxel with or without bevacizumab while all receive niraparib maintenance, providing further insight into optimal approaches for HRD-negative tumors.

Two important logistical aspects emerged from this analysis. First, HRD testing should be initiated early to ensure results are available for definitive maintenance therapy planning. In this study, the median time to receive HRD results was 37 days, which was adequate for patients undergoing primary debulking surgery followed by six cycles of chemotherapy (~126 days). However, in patients undergoing interval debulking surgery (IDS) with only three additional cycles, delays exceeding 90 days, as occurred in three cases, were suboptimal for planning maintenance therapy. One key factor for delays was the structure of reimbursement in the German medical system, as HRD tests are not included in the DRG framework and can only be ordered at the outpatient level. Inclusion of HRD testing costs in DRGs is strongly recommended. Importantly, the implementation phase saw these delays decrease significantly (**Figure 2a)**.

Second, the rate of nonmeaningful HRD findings was 14.2%, slightly lower than the 18% reported in PAOLA-1 [23], and was entirely due to insufficient tumor tissue. In six of the 27 patients without meaningful HRD results, insufficient tumor tissue was already present at primary surgery. In two-thirds of patients, initial biopsy specimens obtained via laparoscopy or diagnostic biopsy were too small, and the assumption that sufficient tissue could be obtained during IDS was often incorrect, as large portions of the tumor were already in remission. In our cohort, 15 patients lacked adequate tumor tissue during IDS, underscoring the critical importance of obtaining sufficient material during initial sampling.

While establishing a diagnosis is the primary concern—particularly in patients for whom the underlying disease has not yet been confirmed—it is essential that the tumor tissue obtained is of sufficient quantity to allow accurate diagnostic confirmation. Adequate tissue yield is also critical because the efficacy and regulatory approval of subsequent maintenance therapy may depend heavily on the patient's HRD status. Moreover, obtaining sufficient

tissue at the time of diagnosis can help minimize turnaround times for HRD testing. In cases where the initial test fails due to insufficient material, additional FFPE tumor blocks may need to be requested for repeat testing, further delaying the availability of HRD results.

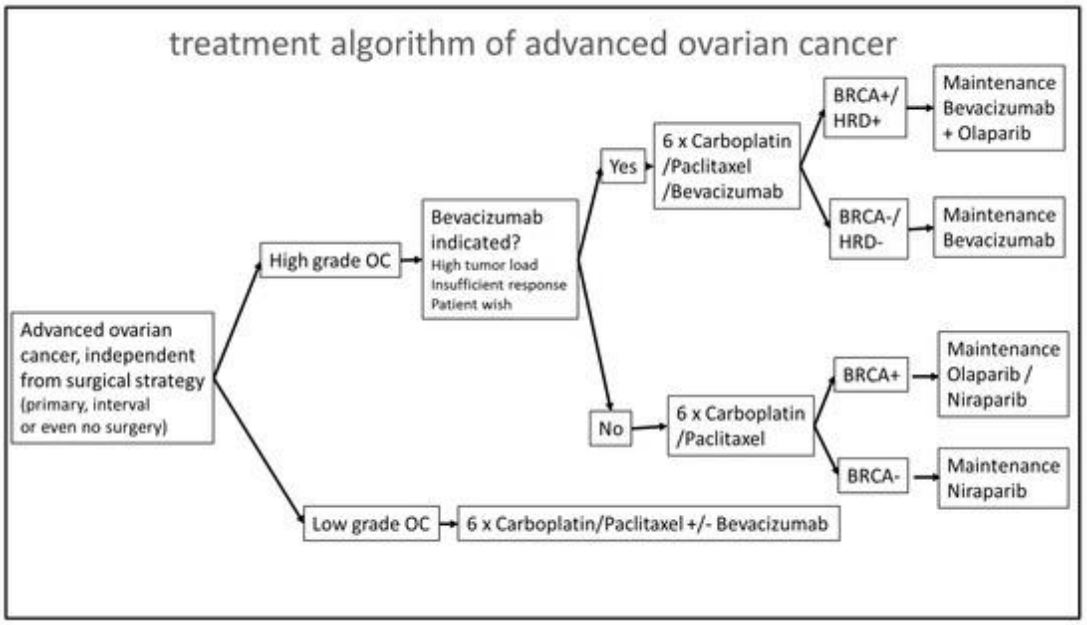


Figure 5. Treatment algorithm for maintenance therapy of patients with advanced ovarian cancer based on clinical and molecular biological parameter.

Another key aspect highlighted in this study was the relationship between HRD/somatic BRCA testing and germline panel testing. Given the relatively high rate of non-evaluable HRD results, germline testing remains essential. Among the 27 patients without sufficient HRD results, two were found to carry deleterious BRCA1/2 germline mutations, who would have otherwise been deprived of potentially effective therapy. Conversely, 37.5% of patients with somatic BRCA1/2 mutations did not have corresponding germline mutations, indicating that relying solely on somatic testing could overestimate hereditary risk and impose unnecessary burdens on patients and their families. Such discordance between tumor and germline BRCA1/2 status has been previously documented: in the PAOLA-1 trial, 29 of 114 patients (25.4%) and in the AGO TR-1 study [23, 24], 31 of 393 patients (7.9%) with a tumor BRCA1/2 mutation did not harbor a germline mutation. Differences in assay methodology between tumor and germline testing in our study may account for the slightly higher discordance rate observed.

Nevertheless, the performance of the Myriad myChoice® test in this decentralized setting was consistent with previously published data. HRD positivity rates and the prevalence of somatic BRCA1/2 mutations closely matched those reported in major trials, with 48.3% of successfully screened tumors classified as HRD-positive in our study, compared to 50.8% in PRIMA and 48% in PAOLA-1[6, 7]. The proportion of somatic BRCA1/2 mutations contributing to HRD positivity was 37% in our cohort, in line with 30.4% in PRIMA and 29% in PAOLA-1. These high concordance rates support the validity and practical applicability of the Myriad myChoice® test in decentralized testing environments [12]. Ongoing academic efforts aim to validate alternative HRD assays that may further decentralize testing and reduce reliance on large tumor samples [25-27].

Conclusion

This study demonstrates that HRD testing can be successfully implemented in a decentralized pathology setting, with results generally available in a timeframe suitable for informing treatment decisions. Adequate tumor tissue obtained at initial diagnosis is critical, as sufficient material may not be available after chemotherapy. Cotesting of HRD and BRCA1/2 germline mutations is recommended to optimize timely treatment planning, particularly for patients in whom HRD testing is unevaluable. Future research should focus on developing HRD testing technologies that require smaller tumor samples to increase accessibility and feasibility.

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Conflict of Interest: The authors disclosed the following conflicts of interest: FH received personal fees/ad boards from NovoCure and PharmaMar; received personal fees/ad boards and nonfinancial support from AstraZeneca, Roche, Tesaro, GSK, Clovis, and amedes; received nonfinancial support from New Oncology; and had a fiduciary role in other boards (unpaid), such as the AGO study group. B.A. had a membership on the advisory boards of Roche, GSK, Amgen, MSD, and Sanofi–Aventis; lectures at Roche, GSK, Celgene, Clovis, AstraZeneca, Novartis, MSD, and Eisai; and other conflicts of interest (congress travel support) with Roche, GSK, AstraZeneca, and PharmaMar. C.S. had no conflicts of interest. C.D. received a research grant given to the institution from Myriad and Roche; received royalties or licenses from VmScope digital pathology software; received consulting fees from MSD Oncology, Daiichi Sankyo, Molecular Health, AstraZeneca, Merck, Roche, and Lilly; received an honorarium from AstraZeneca; received support for attending meetings and/or travel from Roche; had patents WO2015114146A1 and WO2010076322A1 for the therapy response; had the patent application WO2020109570A1 for the cancer immunotherapy; and had other financial or nonfinancial interests in Sividon Diagnostics (cofounder and shareholder until 2016). KR had no conflicts of interest. E.H. had no conflicts of interest. SH had no conflicts of interest. MM had no conflicts of interest. J.W. had no conflicts of interest. TD had no conflicts of interest. VV had no conflicts of interest. M.B. had no conflicts of interest. SS had no conflicts of interest. NC had no conflicts of interest. P.H. received grant support from AstraZeneca, Roche, GSK, Genmab, DFG, the European Union, DKH, Immunogen, and Clovis; received consultancy from AstraZeneca; was on the advisory boards of AstraZeneca, Roche, GSK, Clovis, Immunogen, MSD, and Eisai; received honoraria from AstraZeneca, GSK, Clovis, Immunogen, MSD, Eisai, Amgen, Roche, Sotio, Stryker, and Zai Lab; and had a fiduciary role in other boards, such as the AGO study group.

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Informed consent was obtained from all the subjects involved in the study.

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