# Clinical relevance evaluation of a novel homologous recombination deficiency CE-IVD decentralized solution that identifies ovarian cancer patients that could potentially benefit from treatment with PARP inhibitors

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Poster #**PA-065**

## 1 Highlights

- The novel **deep learning-based, decentralized SOPHiA DDM™ Dx HRD Solution (SOPHiA GENETICS SA)** determines homologous recombination deficiency (HRD) status in ovarian cancer samples.
- The PFS clinical relevance* metric was **non-inferior** when HRD status was determined with the SOPHiA DDM™ Dx HRD Solution compared to Myriad myChoice® CDx.
- The SOPHiA DDM™ Dx HRD Solution **was highly concordant (overall percentage of agreement** [OPA] = **93.03%)** with the reference method, Myriad myChoice® CDx.
- This multicenter validation study demonstrates the **clinical utility of the CE-IVD-certified, decentralized SOPHiA DDM™ Dx HRD Solution** for the accurate identification of HRD-positive ovarian cancer patients that could potentially benefit from first-line maintenance treatment with PARP inhibitors (Clinical Decision Support Only).

## 2 Background

- **Homologous recombination deficiency (HRD)** is a complex biomarker with predictive value in **ovarian cancer**. A positive HRD status has been shown to be predictive of response to poly (ADP-ribose) polymerase inhibitors (**PARPi**) in the context of first-line maintenance therapy for advanced ovarian cancer (PAOLA-1 clinical trial).[1]
- HRD assays can assess the causes of HRD (e.g., pathogenic alterations in homologous recombination repair [HRR] genes) and/or the consequences (e.g., genomic instability).
- Here, we present analytical performance and clinical relevance* results using Genomic Integrity Index to define HRD status (CE-IVD) with the **SOPHiA DDM™ Dx HRD Solution**, a decentralized NGS assay that evaluates the causes and consequences of HRD in a single workflow.

## 3 Methods

**The SOPHiA DDM™ Dx HRD Solution combines a hybridization-based capture panel and low-pass Whole Genome Sequencing (lpWGS)**

- **Capture panel:** Detects SNVs and Indels in 28 genes involved in the HRR pathway, including *BRCA1* and *BRCA2* (Clinical Decision Support Only).
- **lpWGS:** Leverages a proprietary deep-learning algorithm to recognize patterns of genomic instability in lpWGS profiles (CE-IVD).

**Study design**

- Multicenter performance and clinical relevance* studies of the SOPHiA DDM™ Dx HRD Solution used samples collected through partnerships during the SOPHiA GENETICS early-access program and during the randomized, double-blind, Phase III PAOLA-1 clinical trial[1].†
- PAOLA-1/ENGOT-ov25 was a randomized, first-line, phase 3 trial for patients with advanced ovarian cancer that compared maintenance treatment with olaparib + bevacizumab to placebo + bevacizumab. The primary objective was to evaluate progression-free survival (PFS). The study was sponsored by ARCAGY research with GINECO as ENGOT group leader.
- lpWGS libraries (x1 coverage, ~10 million reads, Illumina) were generated from formalin-fixed paraffin-embedded (FFPE) ovarian cancer samples (**Table 1**).

**Analytical performance**

- Assay concordance was determined based on a comparison of GI status with Myriad myChoice® CDx (Myriad Genetic Laboratories, Inc.; US FDA-approved).
- Samples were required to have DNA quality number (DQN)-300bp ≥3, tumor content >30%, ≥50 ng input DNA, and an NGS library yield ≥250 ng.

| Sample | Processed across 4 independent laboratories | Processed at SOPHiA GENETICS laboratory | Total |
|---|---|---|---|
| **Analytical performance study** | | | |
| Overall | 84 | 235 | **319** |
| Myriad GI status available | 77 | 210 | 287[a] |
| Myriad GI score available | 75 | 41 | 116[a] |
| **Clinical relevance* study** | | | |
| PAOLA-1 clinical trial | NA | 195 | **195[a]** |

**Table 1.** Details of samples used to test the analytical and clinical relevance* of SOPHiA DDM™ Dx HRD Solution.
[a] Samples had GI conclusive results with both assays. GI, genomic instability; Myriad, Myriad MyChoice® CDx.

**Clinical relevance***

- PFS for patients taking olaparib + bevacizumab or placebo + bevacizumab was assessed and analyzed for patients stratified according to GI status using the SOPHiA DDM™ Dx HRD Solution and according to GI+BRCA status using Myriad myChoice® CDx.
- Samples were required to have DQN-300bp ≥3.

## 4 Results

**Analytical concordance of the SOPHiA DDM™ Dx HRD Solution with a validated reference method**

- GI status **overall percent agreement was high (93.03%)** (**Table 2, Figure 1**).
- The overall rejection rate was low (4.09%).

| Performance metric | Percent (95% CI) |
|---|---|
| **Overall percent agreement (OPA)** | **93.03% (89.48 - 95.44)** |
| Negative percent agreement (NPA) | 96.55% (92.18 - 98.52) |
| Positive percent agreement (PPA) | 89.44% (83.30 - 93.49) |
| Overall rejection rate[a] | 4.09% |

**Table 2.** Concordance of GI status between SOPHiA DDM™ Dx HRD Solution and Myriad MyChoice® CDx (n = 287). [a] n = 318 (all samples tested with both assays). GI, genomic instability.

**Decentralized analysis**

- **No significant difference** in GI status OPA was observed between samples processed by SOPHiA GENETICS (n = 210, OPA = 92.38% [95% CI: 87.98% - 95.26%]) or by 4 independent clinical laboratories (n = 77, OPA = 94.81% [87.39% - 97.96%]), **supporting a decentralized approach to HRD analysis.**

**Clinical relevance* of the SOPHiA DDM™ Dx HRD Solution using PAOLA-1 samples**

- The PFS validation metric was **non-inferior** with the SOPHiA DDM™ Dx HRD Solution compared to Myriad myChoice® CDx on the subset of 195 PAOLA-1 samples with clinical response data (**Table 3, Figure 2**).

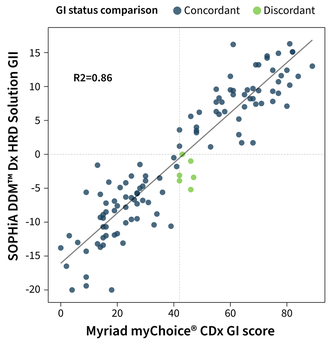


**Figure 1.** Concordance of GI index/score between SOPHiA DDM™ Dx HRD Solution and Myriad MyChoice® CDx (n = 116). GI, genomic instability; GII, genomic integrity index.

| | GI status according to SOPHiA DDM™ Dx HRD Solution | GI+BRCA status according to Myriad MyChoice® CDx |
|---|---|---|
| **Progression-free survival in patients with a GI positive status** | | |
| Number of samples | 88 | 95 |
| Hazard ratio (95% CI) | **0.49** (0.28 - 0.85) | **0.58** (0.35 - 0.98) |
| Median survival time, months (95% CI) | | |
| Placebo + bevacizumab | 15.9 (13.4 – 38.6) | 15.4 (13.0 - 38.6) |
| Olaparib + bevacizumab | 33.3 (21.9 - NA) | 29.8 (21.0 - NA) |
| **Progression-free survival in patients with a GI non-positive status** | | |
| Number of samples | 107 | 100 |
| Hazard ratio (95% CI) | **0.88** (0.55 - 1.38) | **0.74** (0.46 - 1.19) |
| Median survival time, months (95% CI) | | |
| Placebo + bevacizumab | 15.1 (10.4 - 22.0) | 15.8 (12.3 - 19.3) |
| Olaparib + bevacizumab | 16.8 (14.9 - 22.1) | 17.6 (15.5 - 22.1) |

**Table 3.** Progression-free survival in PAOLA-1 patients stratified according to SOPHiA DDM™ Dx HRD Solution GI status and Myriad MyChoice® CDx GI+BRCA status (n = 195). GI, genomic instability.

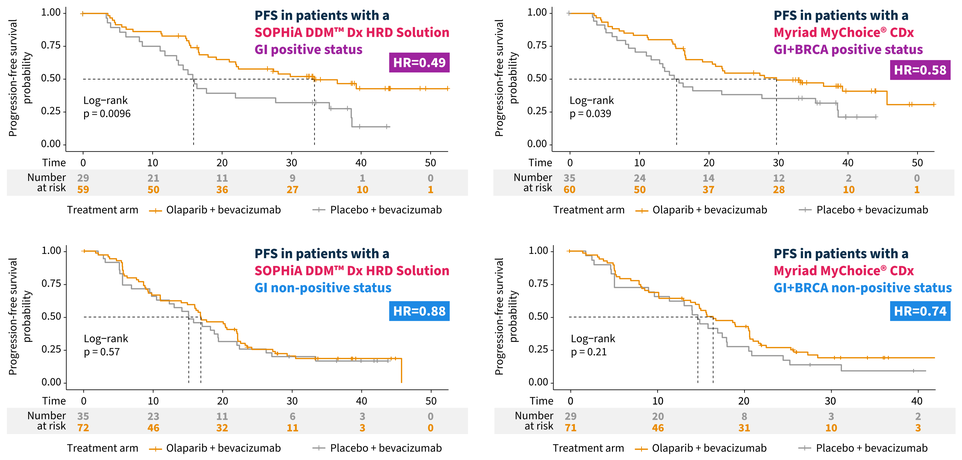


**Figure 2.** Progression-free survival in a PAOLA-1 sub-cohort of patients stratified according to SOPHiA DDM™ Dx HRD Solution GI status or Myriad MyChoice® CDx GI+BRCA status (n = 195). GI, genomic instability; PFS, progression-free survival.

*Preliminary results only based on retrospective correlation findings outside the context of a clinical trial. †Research center committees individually provided ethical approval for research on biological samples and/or clinical information according to the clinical research regulations in each country, and patient consent was obtained.

**References:** 1. PAOLA-1 ClinicalTrials.gov number, NCT02477644. Ray-Coquard I, Pautier P, Pignata S, et al. N Engl J Med. 2019;381(25):2416-2428.

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