Poster ID: AS-ECP-2025-02138

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External Quality Assessment (EQA) for Homologous Recombination Deficiency (HRD) testing in ovarian cancer: Findings of a new international Quality Network for Pathology (IQN Path) pilot scheme

Arfa Maqsood,[1] Victoria Williams,[1] Francesca Fenizia,[2] Jennifer A Fairley,[3] Tracy Stockley,[4] Sze Chai,[5] Etienne Rouleau,[6] Simon J Patton[1]

1. European Molecular Quality Network (EMQN CIC), United Kingdom, 2. Associazione Italiana di Oncologia Medica (AIOM), 3. Genomics Quality Assessment (GenQA), 4. Canadian Biomarker Quality Assurance (CBQA), 5. The Royal College of Pathologists of Australasia Quality Assurance Programs (RCPAQAP), 6. GFCO, Service de Genetique des Tumeurs (Gen&Tiss)

Background & Objective

HRD occurs when cells lose their ability to repair double-stranded DNA breaks via the high-fidelity, homologous recombination repair (HRR) mechanism. Multiple genes mediate the HRR pathway with *BRCA1/BRCA2* being the most well characterized. However, HRD can also be a consequence of defects in other HRR genes and may lead to genomic structural alterations known as “genomic scars”.

HRD is a hallmark of approximately 50% of ovarian cancers and is a predictive marker for response to poly (ADP-ribose) polymerase (PARP) inhibitor treatment.

Introduction of new diagnostic tests in clinical practice presents certain challenges. EQA is an essential tool to monitor quality and benchmark results to help improve quality of testing.

This HRD testing in ovarian cancer pilot scheme was facilitated by IQN Path with the aims to:

- Develop a model for the on-going provision of this EQA scheme.
- Promote high quality HRD testing through harmonisation of practice and publication of EQA results.

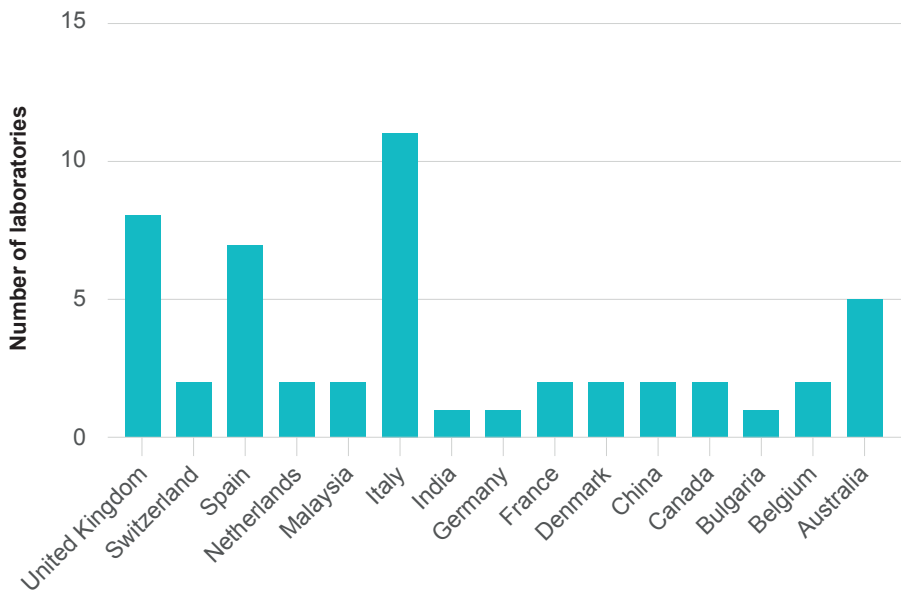
Methods

Five EQA providers (AIOM, CBQA, EMQN, GenQA, Gen&Tiss and RCPAQAP) under the umbrella of IQN Path, collaborated to develop a new EQA for HRD testing.

A total of 84 laboratories from 28 countries expressed interest in participating using an online survey.

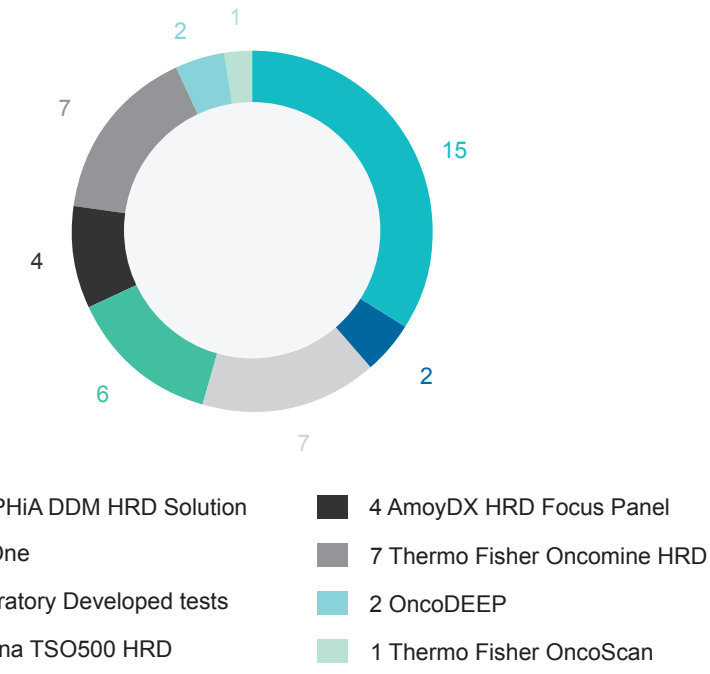
A total of 50 laboratories from 15 countries were selected.

Geolocation of participating laboratories



Three formalin fixed paraffin embedded (FFPE) reference materials were provided to participants to test for HRD using their routine diagnostic procedures. Participants were required to submit a clinical report for each sample.

Assays used by participating laboratories



Results

Forty-four laboratories submitted results. Accuracy was high overall, but ther were 3 instances where incorrect GI status was reported in case 1, the over overall HRD status incorrect in 2 of these reports. One laboratory missed the *BRCA1* variant in case 3. Clinical interpretation was also generally of a high standard with 88% of reports interpreting the results in relation to PARP inhibitor therapy.

Validated GIS and HRD status of the samples and participant results

		Case 1 *GIS 31±2, HRD negative)	Case 2 *GIS 72±3, HRD positive)	Case 3 *GIS 54±2, HRD positive, *BRCA1* c.5266dup p.(Gln1756ProfsTer74)
Genotyping category	Correct HRD status	39	42	40
	Incorrect HRD status (including *BRCA*m)	2	0	1
	Correct GI status	38	42	39
	Incorrect GI status	3	0	0
	Test failures	3	2	3
Clinical interpretation category	Overall correct interpretation	36	37	6
	Critical interpretation errors	0	0	0

*GIS Genomic Instability Status

Good reproducibility of the HRD status was noted. However, the following observations were raised by the EQA assessment team that may inform future HRD EQA design and guidance for reporting standardization and harmonization:

- Laboratories used a range of terminology which included HR proficient and HR deficient, HRD positive and HRD negative, and in some instances, GI score was described as HRD score.
- Many laboratories failed to include the cut-offs for the GI scores for their assays in the report.
- Laboratories using extended HRR panels did not consistently report the HRR variants despite testing for the non BRCA HRR genes.

Conclusions

- There is high interest in HRD EQA participation.
- Overall high inter-laboratory reproducibility was good, but errors were identified. Critical genotyping errors (incorrect HRD status, including *BRCA*m) were reported by 3/42 (7.1%) of laboratories with an overall error rate of 4/125 results (3.2%).
- The pilot EQA provided a snapshot of current HRD testing strategies and reporting formats.
- There is need for standardisation of reporting and terminology for HRD.

Future perspectives

The continued provision of EQA based on the pilot model will improve reporting standards whilst facilitating the development of best practice guidelines.

Sponsorship

This pilot EQA was supported by AstraZeneca and MSD.