Developing EQA for HRD testing in ovarian cancer

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Introduction

Testing for homologous recombination repair (HRR) deficiency (HRD) is now recognised as part of the standard practice for ovarian cancer. This testing is required to determine the likelihood of response to PARP inhibitors with patients with being HRR deficient showing better response to the drugs than those who are homologous repair proficient.[1]

A large percentage of tumours which have HRD have been demonstrated to have pathogenic variants in either *BRCA1* or *BRCA2*. However, there is a cohort of patients which exhibit HRD in the absence of *BRCA1* or *BRCA2* pathogenic variants.[2] Some of these patients have been identified using techniques which investigate genomic scarring looking for signs of different repair defects in the genome.[3] A number of different algorithms to examine this are being developed.

Previously testing for HRD was performed centrally in one reference laboratory but is increasingly being performed within individual centres and there is a need for external quality assessment (EQA).

GenQA delivered a pilot ring trial to participants performing HRD testing in their own laboratories and compared these results to those originally obtained using central laboratory testing.

Methods

- The samples were supplied in the format of DNA extracted from formalin fixed paraffin embedded (FFPE) tumour tissue and were sourced from the participating laboratories according to GenQA instructions.
- Ten samples were selected. These samples were anonymised and given mock patient details by GenQA prior to distribution.
- 10µl of each DNA sample at a concentration of 10µg/µl was sent to each participating laboratory for testing.
- Laboratories were requested to perform genomic instability testing on the samples. Testing for *BRCA1* and *BRCA2* was not requested.
- These samples had been previously tested for HRD/genomic instability at Myriad. These results along with the consensus results obtained by the participating laboratories were used to assess the results
- Details of the samples distributed and the original results obtained from Myriad along with the ring trial consensus result are shown in Table 1.

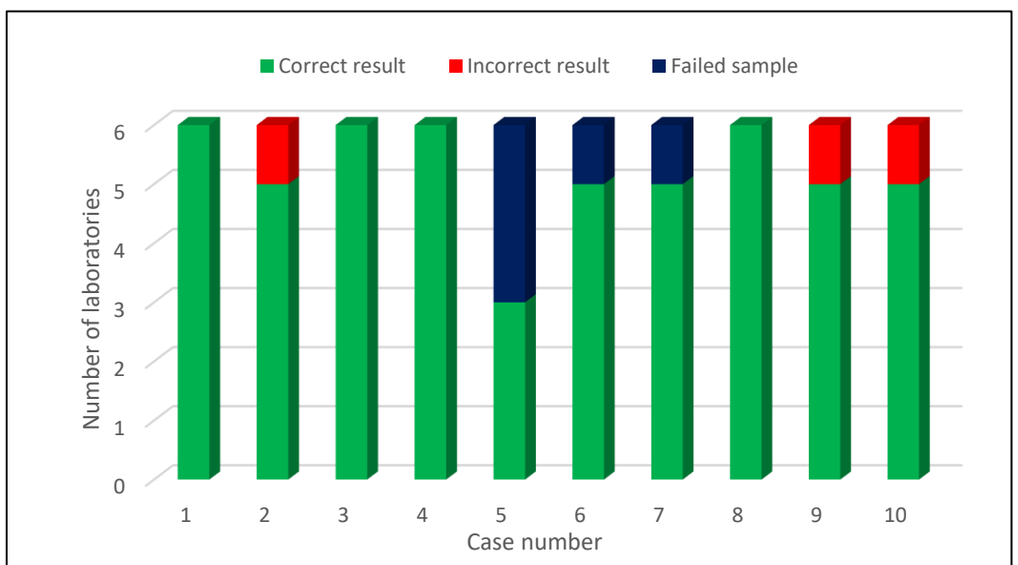
Table 1: Samples provided for testing for the ring trial.

Ring Trial Patient name/ Date of birth	Sample ID	Supplied result from Myriad		Ring trial consensus result (HRR proficient or deficient)	Ring trail result concordant with expected result
		Genomic instability score (GIS) and overall result (HRD)	*BRCA1/BRCA2* results		
Sylvia HUGHES 23/04/1965	HRDRT1	Positive GIS 59	No results provided	Deficient	Yes
Sian DAVIES 21/12/1958	HRDRT2	Negative GIS 13	No results provided	Proficient	Yes
Patsy WILSON 13/04/1959	HRDRT3	Inconclusive No GIS provided	No clinically relevant *BRCA1* or *BRCA2* variant detected	Proficient	No
Celine DUBOIS 15/02/1960	HRDRT4	Negative GIS 13	No results provided	Proficient	Yes
Felicity SMITH 27/08/1968	HRDRT5	Negative No GIS provided	No results provided	Proficient	Yes
Olivia MANNING 23/08/1970	HRDRT6	Positive GIS 82	No results provided	Deficient	Yes
Janet PINDER 29/10/1954	HRDRT7	Positive (no GIS provided)	No results provided	Deficient	Yes
Shazia HUSSEIN 19/07/1969	HRDRT8	Positive GIS 67	*BRCA1* pathogenic c.5503C>T p.(Arg1835Ter) detected No clinically relevant *BRCA2* variant detected	Deficient	Yes
Carmen LOPEZ 20/06/1966	HRDRT9	Positive GIS 21	No clinically relevant *BRCA1* or *BRCA2* variant detected	Proficient	Yes
Michelle HARRIS 17/11/1974	HRDRT10	Borderline GIS 41	No results provided	Deficient	No

Table 2: Methodology used by participating laboratories for HRD testing.

Method	Number of laboratories
Oncomine Comprehensive Assay Plus	1
SOPHiA Genomics GINGER	2
SomaHRD pipeline version 1.2 (SeqOne)	1
In-house SNP based assay	1
TSO500 CGP & HRD	1

Figure 1: Case results for the ring trial.



Results

- Six laboratories participated in the ring trial.
- Laboratories used a selection of different testing methodologies shown in Table 2.
- The overall concordance rate for the samples was 86% (52/60, concordant results). Figure 1 shows the results obtained for each case.
- One participating laboratory reported correct results for all 6 samples.
- Three laboratories reported correct results for five samples and a failed result for one sample (case 3). This sample was originally reported as inconclusive by Myriad although the three other laboratories participating in this trial reported it as HRD positive.
- One laboratory reported failed results for two cases (cases 4 and 5).
- One laboratory incorrectly reported two samples as HRD positive compared to the consensus result of HRD negative (cases 2 and 9).
- One laboratory incorrectly reported case 10 as HRD negative, all other participating laboratories reported this as HRD positive although it was originally identified as a borderline case.
- Three laboratories supplied results for *BRCA1* and *BRCA2* gene testing for the samples. This ring trial was designed to assess genomic scarring and *BRCA1* and *BRCA2* gene testing was not requested, however there were no errors reported for *BRCA1* and *BRCA2* testing.
- The participant submitted reports were reviewed and there was variation in the format and wording of reports.
- Different terminology was used to describe HRD with many laboratories using the terms ‘positive’ and ‘negative’. This is not recommended for other types of genomic testing and in this instance, the use of terms ‘proficient’ and ‘deficient’ is encouraged.

Conclusion

The introduction of laboratory based HRD testing requires a measure of external assessment. The returns from this ring trial for HRD testing demonstrate that there are discrepancies in the results and reporting. In order for laboratories to deliver consistent high quality results there is a need for further harmonisation and education which EQA can facilitate.

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Conflicts of interest: The authors have no conflicts of interest to declare.

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