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Pilot EQA for HRD testing in ovarian cancer

Contents

11th June 2025

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Dear Colleague,

Thank you for participating in this 2024 pilot external quality assessment (EQA) to assess Homologous Recombination deficiency (HRD) testing in Ovarian Cancer. This EQA has been provided as an IQN Path collaboration between several External Quality Assessment (EQA) providers including: EMQN CIC, GenQA, CBQA, RCPAQAP, SEAP, AIOM and Gen&Tiss. The EQA assessment includes the scoring of genotype, interpretation, and clerical accuracy. This EQA summary report includes combined assessment data using harmonised marking criteria. The collection of results, data analysis and preparation of this report was undertaken by EMQN CIC. The harmonised review of the results has now been completed. This EQA Summary Report is an overarching summary which collates the results from all EQA providers.

Background

Deficiency in the Homologous Recombination Repair (HRR) pathway leads to defects in double stranded DNA repair and genomic instability. HRD is measured by detection of BRCAm and/or genomic scars or signatures of genomic instability including Loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale transitions (LST)[1]. HRD occurs in approximately 50% of patients with high-grade serous ovarian cancer (including those with pathogenic *BRCA1* and *BRCA2* variants (*BRCA*m))[2].

HRD is a predictive biomarker, ovarian cancer patients with HRD have an increased likelihood of response to PARP inhibitors[3]. Consequently, HRD assays have been developed to detect HRD, with the aim to guide therapeutic decision making.

Currently, Myriad myChoice® CDx and FoundationOne®CDx are the only two FDA approved companion diagnostic tests. However other commercial and laboratory developed tests (LDT) are increasingly being utilised in clinical laboratories, especially outside of the USA. These technologies define HRD status using different strategies to assess genomic instability and have different scores and pre-defined cut-offs for HRD status[4]. Harmonisation of HRD testing is needed to ensure reliability and comparability of test results and HRD status for patients[5]. There is also a need for a standardised approached to HRD reporting[6].

Evidence from EQA schemes shows that the introduction of any new test is usually accompanied by a high diagnostic error rate (often up to 25%)[7-10]. Incorrectly genotyping patient samples could result in patient harm, and consequently, the addition of new biomarkers in routine clinical practice, necessitates EQA providers to develop and deliver EQA testing to represent current laboratory practices and clinical testing landscapes to ensure that reliable and accurate test results can be provided by the laboratories.

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

a) Develop a model for the on-going provision of this EQA scheme. After the pilot, each EQA provider will be expected to deliver its own fully costed and financially sustainable independent schemes, based on the model developed by IQN Path.

b) Promote high quality HRD testing through harmonisation of practice and publication of EQA results.

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EQA Design & Purpose

This EQA scheme was designed to test the entire routine diagnostic workflow of a laboratory, from sample processing to data analysis and variant reporting. Three mock clinical referrals and corresponding formalin-fixed paraffin embedded (FFPE) tissue samples were supplied to participants for testing via their routine diagnostic pipeline.

The aim was to assess the ability of participating laboratories to undertake HRD testing in FFPE tissue and to interpret the results in the context of PARP inhibitor therapy.

This included an assessment of testing accuracy and an evaluation of the standard of clinical reporting against three categories: genotyping, interpretation, and clerical accuracy, with the objective of helping laboratories to standardise and improve their reporting. Feedback from the assessment is provided in the form of both individual laboratory reports (ILRs) and this EQA Summary Report.

The EQA design meets these objectives by assessing the ability of the participating laboratories to:

- Genotype sections from artificial FFPE samples accurately to determine the genomic instability (GI) status and identify variants which are relevant to the clinical referral,
- To state the HRD status and interpret the results in response to the clinical referral in a clear and concise format,
- Correctly use internationally accepted standard nomenclature, and
- Provide appropriate and accurate patient and sample information and identifiers.

This scheme report contains information from the cohort of participants including geographical spread, methodologies employed, common errors, learning points and scheme statistics to allow participants to benchmark their results.

Participation

Scheme participants were selected using an online expression of interest survey that was sent by email to each of the EQA membership. Eighty-four laboratories from 28 countries responded.

Fifty laboratories from 15 countries were selected to participate in this pilot (Appendix 1, Figure 1) and registered with EMQN CIC (19), GenQA (10), AIOM (11), RCPAQAP (4), Gen&Tiss (3) and CBQA (2). Inclusion criteria for participating laboratories included accreditation status and level of experience in providing a clinical diagnostic service for HRD testing in FFPE tumour material. Of the 50 laboratories selected to participate in this pilot EQA scheme, 44 returned results by the assessment deadline, equating to a participation rate of 88%. Six laboratories withdrew from participation (Appendix 1, Table 1).

Samples Provided & Testing Required

Scheme participants were provided with three FFPE samples for HRD testing via their routine analytical pipeline(s). The three materials were manufactured by LGC-Seracare, USA, to represent patient samples with high-positive, low-positive and negative HRD. The high-positive and negative materials also contained biosynthetic variants in *BRCA1*, *BRCA2* and HRR-associated genes; *ATM*, *BRIP1*, *RAD51C* and *RAD51D*. Identical samples were distributed for testing to all participating laboratories regardless of which EQA provider they registered with. All laboratories were supplied with samples from the same batch. Each sample was supplied

with a corresponding mock clinical scenario including patient name, date of birth, clinical presentation and test request (Appendix 2, Table 2). Participants were instructed to report results using an online form hosted on the Formdesk app (https://en.formdesk.com) and via direct submission of clinical reports to their respective EQA provider.

Scheme Report on Behalf of the IQN Path HRD testing Working Group

All Cases

Genotyping

Laboratories were assessed on reporting of the GI status, *BRCA1/BRCA2* variants (if within scope of testing)

- Two laboratories each made one critical genotyping error in case 1 (4/44, 3.2%). Each reported a GI score that predicted an incorrect HRD status (Appendix 6, Table 6).
- The use of Human Genome Variation Society (HGVS)[11] nomenclature to describe the variants was high.
- Laboratories were encouraged to adopt the use of MANE Select or MANE Plus Clinical reference sequences in this pilot scheme. The use of MANE Select and MANE Plus Clinical as denoted by the MANE initiative, for the standardization of variant annotation, interpretation, and reporting[12] is recommended as support for Locus Reference Genomic (LRG) reference sequences has been discontinued. RefSeq or Ensembl transcripts specified by MANE are now preferred for sequence nomenclature
- When reporting a continuous score, it is recommended to state the validated threshold for clinical actionability[13]. Many laboratories failed to include the pre-determined assay specific cut off values for the GI scores (no deduction).
- Cases 1 and 2 contained several non-*BRCA* HRR-associated gene variants listed in the validated results (Appendix 2, Table 2). Assessment of these HRR genes was not part of the overall assessment of this EQA as non-*BRCA* HRR variants are not approved biomarkers for PARP inhibitor therapy in ovarian cancer[14]. However, many HRD assays include comprehensive HRR gene panels within the scope of their testing. Many laboratories did not report these HRR variants, despite stating on their reports that they were tested.
- The EQA materials performed well with only 7 test failures reported (5.3%, 7/132).

Interpretation

The interpretation category was assessed using a set of pre-defined comments (Appendix 4, Table 4), as agreed by the working group. Our objective in this regard was to provide educational feedback to the laboratories participating in this first pilot round but also to inform our assessment of the future HRD EQAs.

This EQA was designed to assess the ability of laboratories to perform HRD testing on FFPE samples, to determine the HRD status and interpret the results in the context of ovarian cancer, specifically to guide PARP inhibitor treatment.

- On average across the three cases, 90% of clinical reports linked the genotyping result to PARP inhibitor therapy. This is an important aspect of clinical interpretation and should be reported if local policy allows, preventing missed treatment opportunities due to inadequate reporting.
- Multiple different assays were used to assess HRD with different systems for scoring of GI. However, it was apparent that there is a need to standardise the reporting of HRD results. 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.
- Thirty-seven clinical reports were submitted. Five laboratories stated that they do not offer a clinical interpretation as part of their routine practice. Interpretation was not assessed for the reports with critical genotyping errors or test failures.
- If likely pathogenic/pathogenic *BRCA1/BRCA2* or HRR gene variants are detected, recommendations for confirmatory germline testing and counselling should be provided in the report, if consented and appropriate for the referral.

Patient Identifiers and Clerical Accuracy

During assessment, a series of pre-defined comments agreed by the project team, were applied to the assessment of this category (Appendix 4, Table 4).

The standard of clerical accuracy was generally good across all cases. However, there were some recurrent errors:

- All pages of a report should include correct pagination, in a format which includes the total number of pages (i.e.: 1 of 2; 2 of 2) such that the reader understands how many pages make up the report in its' entirety, and whether any pages are missing. A number of laboratories failed to do this.
- Several participants did not include dates of sample receipt/testing/reporting.

Case 1

Genotyping

- This was a HRD negative case. Laboratories were expected to report a GI score that quantifies the level of genomic instability.
- Case 1 had variants in the *ATM*, *BRIP1*, *RAD51C* and *RAD51D* genes at low VAFs. The pathogenicity of these variants was not confirmed by the manufacturer or by the validating laboratories. Laboratories were not assessed for testing or reporting these variants.
- Forty-one cases were assessed for case 1 and 38 cases (93.0%, 38/41) reported a GI status that was concordant with expected result.
- Three laboratories received a critical error in this category, where they had called this case GI score positive (Appendix 6, Table 6).
- Three laboratories reported a test failure where the GI score could not be determined.

Interpretation

- Laboratories were expected to address the clinical question and comment whether this patient is eligible for PARP inhibitor therapy. Six laboratories did not respond to the clinical question and therefore received a deduction.
- Interpretation was assessed for 36 clinical reports for case 1.

Case 2

Genotyping

- This was a HRD positive case which had biosynthetic variants in the *ATM*, *BRIP1*, *RAD51C* and *RAD51D* genes. The pathogenicity of these variants was not confirmed by the manufacturer or by the validating laboratories. Laboratories were not assessed for testing or reporting these variants, however many laboratories who had stated on their reports that they had tested for these variants did not report them. Seventeen participants reported these variants.
- All laboratories provided a GI status concordant with the validated result.
- Two laboratories reported a test failure where the GI score could not be determined.

Interpretation

- Thirty-seven clinical reports were available for assessment for case 2 and only two reports failed to mention PARP inhibitor therapy in relation to the clinical referral and therefore received a deduction.

Case 3

Genotyping

- This case had a low positive GI score and contained a pathogenic *BRCA1* variant, NM_007294.4: c.5266dup p.(Gln1756ProfsTer74).
- One laboratory reported the correct HRD status from the GI score but received a critical genotyping error for not reporting the *BRCA1* variant (Appendix 6, Table 6).
- Three laboratories reported a test failure where the GI score could not be determined.

Interpretation

- Clinical reports for 36 laboratories were assessed for interpretation for case 3. Three laboratories received deductions for not mentioning PARP inhibitor therapy in relation to the clinical referral.

Professional standards

- Laboratories are assessed against the guidelines, relevant peer reviewed literature and currently available references. Other guidelines against which laboratory reports are assessed may include the international nomenclature HGVS[15], as well as ISO standards (ISO15189)[16].

Organisation

Various aspects of this EQA may be subcontracted, including material preparation by commercial reference material providers and biobanks, assessment by qualified experts and sample distribution. When subcontracting occurs, it is placed with a competent subcontractor and IQN Path is responsible for the work.

Six EQA providers collaborated to supply this pilot scheme on behalf of IQN Path:

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Final comments

- The IQN Path HRD testing EQA Project Group would like to thank all participants for their hard work, prompt return of results and their co-operation during this exercise. We would also like to thank our commercial partners in the pharmaceutical industry for their support and the assessment team for their considerable time and effort to mark the submissions.
- The purpose of the EQA service is to educate and facilitate the raising of standards.

Authorisation

This document has been authorised by:

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Amendments to this summary EQA report

Version	*Page*	*Section*	*Change*	*Published*
1	-	-	*None*	*11th June 2025*
2				
3				

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Appendices

1. Participation

Fifty laboratories from 15 different countries were selected to participate in this pilot EQA scheme for HRD testing:

Figure 1: Participating countries

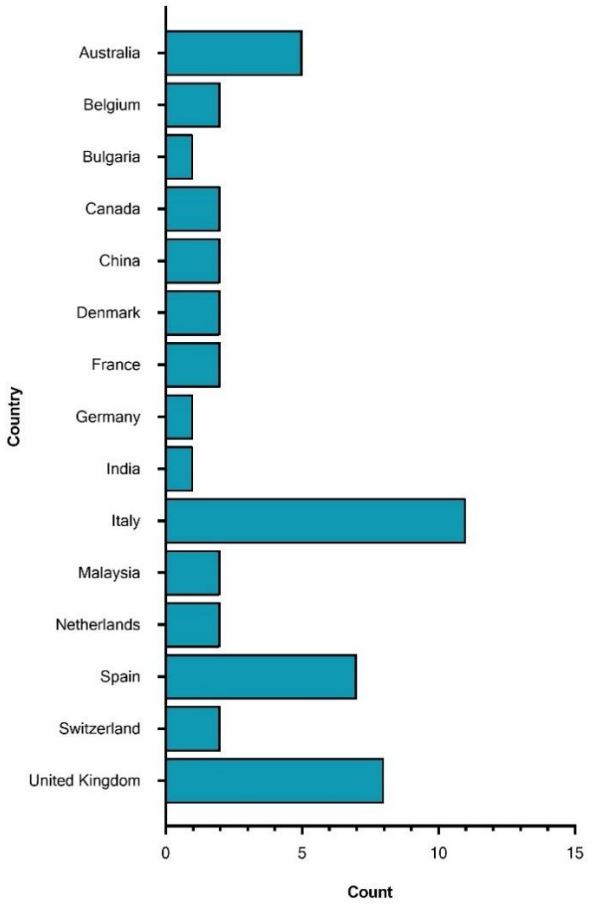

Table 1: Participant numbers by EQA Provider for Pan Fusion Gene Pilot EQA

	No. Registrants	Withdrawn	Did not submit results	Final No. Participants
AIOM	11	0	0	**11**
CBQA	2	2	0	**0**
EMQN	19	4	0	**16**
Gen&Tiss	3	0	0	**3**
GenQA	10	0	0	**10**
RCPQAP	4	0	0	**4**

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2. Samples Provided and Validated Results

Table 2: EQA Sample details and validated results.

Case	Patient Name	Date Of Birth[1]	Batch ID	GI Score[2]	Validated HRD Status[3]	Gene variants[4]	Validated gene variants[5]
1	Vanda NICOLINA	09/12/1955	01.27346	31±2	Negative	*ATM* variant NM_000051.4:c.208A>T p.(Lys70Ter) (VAF 5.9%) *ATM* variant NM_000051.4:c.557del p.(Leu186Ter) (VAF 7.8%) *RAD51D* variant NM_002878.4:c.392dup p.(Asn131LysfsTer23) (VAF 8.1%) *RAD51D* variant NM_002878.4:c.271A>T p.(Lys91Ter) (VAF 8.1%) *RAD51C* variant NM_058216.3:c.242C>A p.(Ser81Ter) (VAF 7.1%) *RAD51C* variant NM_058216.3:c.338dup p.(Gly114TrpfsTer41) (VAF 7.1%) *BRIP1 variant* NM_032043.3:c.157dup p.(Ser53LysfsTer16) (VAF 7.1%) *BRIP1 variant* NM_032043.3:c.107T>G p.(Leu36Ter) (VAF 7.1%)	No pathogenic variants were detected in *BRCA1* and *BRCA2*
2	Amelie MARYSE	10/06/1957	02.39862	72±3	Positive	*ATM* variant NM_000051.4:c.208A>T p.(Lys70Ter) (VAF 35.2%) *ATM* variant NM_000051.4:c.557del p.(Leu186Ter) (VAF 43.7%) *RAD51D* variant NM_002878.4:c.392dup p.(Asn131LysfsTer23) (VAF 42.8%) *RAD51D* variant NM_002878.4:c.271A>T p.(Lys91Ter) (VAF 42.8%) *RAD51C* variant NM_058216.3:c.242C>A p.(Ser81Ter) (VAF 39.3%) *RAD51C* variant NM_058216.3:c.338dup p.(Gly114TrpfsTer41) (VAF 39.3%) *BRIP1* variant NM_032043.3:c.157dup p.(Ser53LysfsTer16) (VAF 42.8%) *BRIP1* variant NM_032043.3:c.107T>G p.(Leu36Ter) (VAF 42.8%)	No pathogenic variants were detected in *BRCA1* and *BRCA2*
3	Yuliana ISKANDER	29/04/1956	03.16429	54±2	Positive	*BRCA1* variant NM_007294.4:c.5266dup p.(Gln1756ProfsTer74)	*BRCA1* variant NM_007294.4: c.5266dup p.(Gln1756ProfsTer74) HGVS short format NM_007294.4: c.5266dup p.(Gln1756fs) (93%)

1. All dates of birth are given in the format dd/mm/yyyy
2. Illumina TruSightTM Oncology 500 HRD RUO Assay that calculates a GIS using an algorithm licenced from Myriad Genetics
3. The HRD status determined by two independent laboratories.
4. The HRR gene variants and variant allelic frequencies (VAF) listed are validated by ddPCR by the manufacturer. The VAF percentages can be found in brackets.
5. The genotype of 3 samples validated by two independent laboratories.
6. HGVS has recently updated guidance (v21.0.4) on preferred sequence references to recommend MANE and MANE Plus Clinical.

3. Sample Validation

Samples used in this pilot EQA scheme were analysed by two, using two different validated testing methodologies and bioinformatics pipelines (Table 3). This analysis was conducted to verify the genotype of each material and to ensure suitability of the samples for testing across a range of testing platforms and analytical pipelines. All validating laboratories reported the same result from testing of each specimen. Expected results for each case are detailed in Table 1 according to HGVS[13] nomenclature.

Validation Laboratory	Source Nucleic Acid	Testing Chemistry/Kit	Sequencing Platform	Analytical Software/Bioinformatics pipeline
1	FFPE	SeqOne	Illumina NovaSeq6000	SomaHRD pipeline V 1.2 (SeqOne)
2	FFPE	SOPHiA DDM HRD Solution	Illumina NextSeq550DX	SOPHiA DDM™ GIInger

Table 3: Details of methodological approaches taken by validating laboratories to verify the genotype of each material used in this scheme.

4. Evaluation Criteria

During this assessment, following marking deductions were applied using a pre-defined set of criteria. For the purpose of this pilot EQA, this assessment assigned marks to genotyping accuracy only. The interpretation of results the laboratory provided in their reports, and patient identifiers and clerical accuracy were assessed, and educational feedback was provided in the form of comments only.

Case	Category	Criterion	Deduction
All Cases	Genotyping	Correct result reported	0
		Critical genotyping error	2
		Major nomenclature error (i.e. Genotype mis-positioned or mis-called)	0.5
		Failure to provide a quantitative GIS score	0
		HGVS nomenclature not provided, or nomenclature provided is incorrect.	0.2
		MANE Select transcript or other RefSeq missing / incorrect / inconsistent	0.0
		MANE Select transcript or other RefSeq version number missing / incorrect / inconsistent	0.2
		Not tested	
		Test Failed	
		Not marked	
		Withdrawn from scheme	
	Interpretation	All essential interpretative elements provided. No deductions.	0.0
		Critical interpretation error	2
		No clinical interpretation (with no explanation provided)	1.5
		Failure to state HRD status (HR deficient/proficient)	0.0
		No mention of PARP inhibitor therapy	1.0
		No statement on referral to clinical genetics	0.0
		No indication of pathogenicity of variant detected / incorrect pathogenicity of variant detected	0.5
		Insufficient detail regarding variant classification system/evidence used to support classification	0.0
		GIS threshold of your assay above which HRD is considered positive should be included in the report.	0.0
		No/insufficient information about the methodology performed	0.5
		No/Insufficient details of the scope of the test	0.0
		No patient specific clinical interpretation given	0.5
		Misleading interpretive comment	1.0

		Interpretation made in the wrong clinical context	0.5
		Clerical error(s) causing potential for patient harm e.g. incorrect or inconsistent use of patient name in the body of the report	1.0
		Comment only	0.0
		Not marked	
		Not marked as failed test reported	
		Not marked (due to critical genotyping error)	
	Clerical Accuracy	All essential patient identifiers present and no significant clerical errors	0.0
		No restatement of the reason for patient referral	0.0
		DOB incorrect or missing	1.0
		Patient name has a spelling error	0.0
		Patient gender is not specified on the report.	0.5
		Failure to provide patient identifiers on each page of the report	0.0
		Failure to provide the dates of sample receipt/testing or reporting	0.0
		Failure to provide the sample type	0.5
		The sample type provided is incorrect	0.5
		No block number provided	0.5
		There is no evidence that the report was authorised i.e. report not signed	0.0
		Pagination should be used on the report e.g. Page 1 of 1, Page 1 of 2 etc.	0.0
		Incorrect/missing pagination	0.0
		Failure to provide a clear presentation of results	0.0
		Failure to anonymise report	0.0
		The essential clinically relevant information is 'lost' in this long report. Consideration should be given to reducing the length of the reports	0.0
		Clear and concise report	0.0
		Not marked	0.0
Case	**Category**	**Criterion**	**Deduction**
1 & 2	**Genotyping**	HRR gene variants present in this sample within the scope and limitations of the test that have not been reported (Educational feedback comment)	0.0

Table 4: EQA Marking Criteria

5. Summary of Concordance for GI Status

A summary of the concordance with the validated result for GI status (Appendix 2, Table 2) for all cases is given below in Table 5. A summary of the number of critical errors per case is provided in Appendix 6, Table 6.

Category		Case 1	Case 2	Case 3
Genotyping	Reported correct GI Status	38	42	40
	Reported Incorrect GI Status	3	0	1
	Test failed	3	2	3

Table 5: Summary of concordance for the GI status.

6. CGE summary

Case	Incorrect GI status reported

	Count	Reported Result	Method
1	3	*Reported deletions in BRCA1 and BRCA2*	ThermoFisher Oncomine
		Reported the GI status as positive	Laboratory developed test
		Reported the GI status as positive	ThermoFisher Oncomine
3	1	*Did not report the BRCA2 variant*	ThermoFisher Oncomine

Table 6: Summary of Critical Genotyping Errors (CGE) made in this EQA scheme

7. Methodologies

Primary methods used for HRD testing by participating laboratories:

Approach Method	**Count**
Microarray	
ThermoFisher OncoScan™ CNV Assay	1
NGS	
AmoyDx® HRD Focus Panel	4
Illumina TruSight Oncology 500 HRD	6
Laboratory Developed Tests	7
OncoDEEP® Kit	2
SeqOne	2
SOPHiA DDM™ HRD Solution	15
ThermoFisher Oncomine Comprehensive Assay	7

Table 7: Approaches to testing and methods used

8. Test scope and limitations parameters which may be included in a clinical report

Current best practice guidelines[15 16,17,18,19] recommend that the following be included:

Item	Description
What material has been tested?	e.g., DNA extracted from FFPE was tested
Minimum neoplastic cell content (NCC) required for the assay	e.g., >20%
What tests were performed?	Define the (horizontal) extent of testing e.g., sequence analysis of all exons and flanking sequences (+/- 20bp) of the genes were analysed.
The method used to perform the tests	e.g., NGS, RT-PCR etc.
Limit of Detection (LOD)	Ideally this should be described as the % of mutant allele that is detectable in a wild-type background. This should be experimentally determined during the assay validation process. If derived from a kit pack insert, then this should be verified in your laboratory.

Analytical scope	A brief summary of the test used and what the laboratory is trying to achieve: What does you test cover e.g., does your test detect all types of variants or are some often missed e.g., indels >15bp, variants in regions of homology or next to homopolymer tracts, large exon rearrangements causing copy number changes (deletions/duplications)?
Clinical yield	What proportion of actionable variants the test detects. The testing strategies provided by the laboratory should be evaluated periodically by authorised personnel to ensure they are clinically appropriate for the test requests received. Any results provided that are considered to be preliminary should be identified in the clinical report.
Analytical sensitivity	Defined by the read depth (vertical coverage)
NGS details	The chemistry/platform used along with details of any kits and the regions/genes covered if appropriate.
NGS sequencing depth	Depth of a genomic position is equal to number of reads aligned to that position, however not every base can be listed on the report so a minimum depth may be provided.
NGS horizontal coverage	Horizontal coverage, given by the percentage of the region of interest (target) meeting the laboratory's minimum read depth, e.g., 99% of the target generated sequence at a minimum read depth of 20x. This must be given for the whole target (panel). It is also recommended to make this information available for individual genes, either in the report or in a separate technical report, or to say that the data is available via a web link, or upon request.