Diaceutics

Better Testing, Better Treatment

The Haematology CDx report programme - Assessment of the current reporting practice for haemato-oncology companion diagnostics (CDx) markers in the UK and Ireland.

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Introduction

In the era of Precision Medicine, CDx (companion diagnostics) has become the basis for optimal patient care. For the purposes of this report, CDx is considered as a test performed that directly influences the use of a specific drug type. Whilst technical aspects of a CDx assay performance are assessed regularly by participation in external quality assessment (EQA) programmes, the reporting of these CDx markers is rarely scrutinised.

Aim

The aim of this CDx Report Programme was to get a detailed picture of haemato-oncology CDx marker reporting in the UK and Ireland.

Methodology

The design of the CDx Report Programme is described in Figure 1. We invited 29 clinical labs in the UK and Ireland to participate in the programme. 10 clinical labs provided information for up to seven biomarkers, which are used to make treatment decisions in haemato-oncology. The seven CDx markers covered in this programme were: ***BCR-ABL1*** in CML (diagnosis), *BCR-ABL1* in CML (MRD), *IDH1* and *IDH2* in AML, *FLT3*-ITD in AML, *FLT3*-TKD in AML, IGHV in CLL, *TP53* in CLL. The information requested included two anonymised reports: one with a mutant result and one with a wild type/negative result. The anonymised reports were reviewed by an expert panel according to standardised review criteria and a score was given for each report from 0 (poor) to 10 (good). The categories evaluated are detailed in table 1.

In addition, labs responded to a short online survey which gathered information about test volumes, turnaround time (TAT), positivity rates, participation in an EQA programme, accreditation status and test reimbursement.

Figure 1. Flow chart of the CDx Report Programme

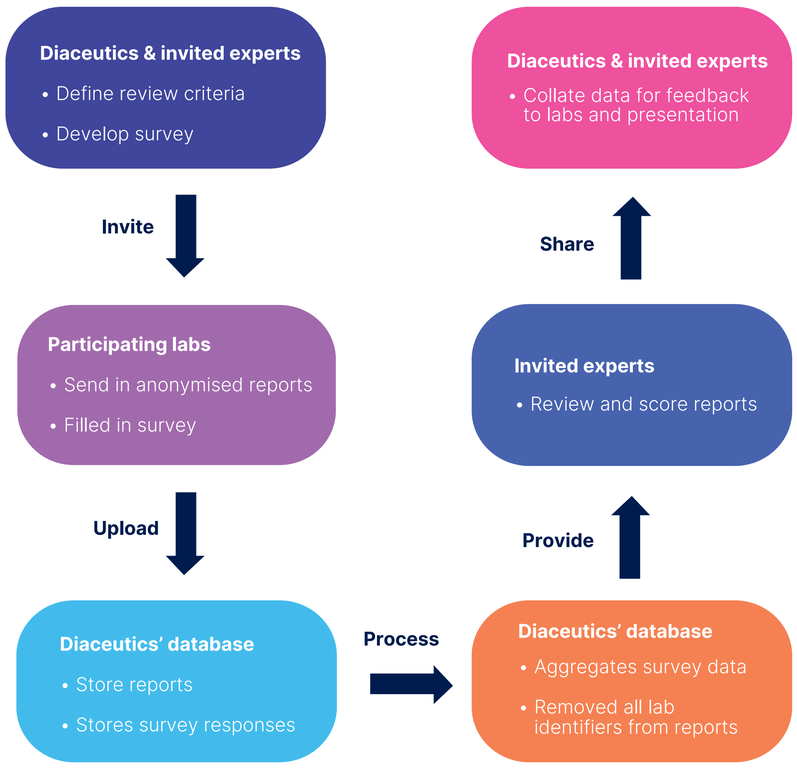


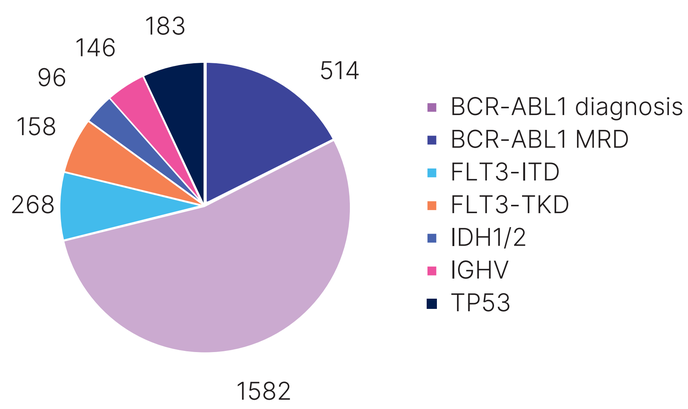
Table 1. Scoring system and criteria used to examine the reports

No.	Criteria	Description	Category	Max. points
1	Demographics	Name, age, gender, referring physician, patient ID, sample ID, suspected diagnosis, date sample taken, date sample obtained at lab, date of reporting	General	10
2	Layout	Report structure, clarity, ease of reading	General	10
3	Performed tests	List with performed tests, pending tests, final or interim report	General	10
4	Final result	Positive, negative or invalid result	CDx result	10
5	Result details	VAF, percentage, signal ratio, exact mutation	CDx result	10
6	Method	Technology, assay type	CDx assay	10
7	Assay limitation	LOD, accession number, analyzed region, covered mutations	CDx assay	10
8	Thresholds	Positivity cut-off, clinical cut-offs	Interpretation	10
9	Guidelines	Relevant guidelines, recommendations and clinical studies	Interpretation	10
10	Clinical relevance	Predictive relevance of the CDx marker mentioned, treatment options	Interpretation	10

Results

We received 49 survey datasets and 46 sets of reports representing approximately 3000 tests per month. The number of datasets per marker ranged from 4 to 10 [number for each in square brackets]: *BCR-ABL1* (diagnosis) [10], *BCR-ABL1* (MRD) [9], *FLT3*-ITD [9], *FLT3*-TKD [6], *IDH1&2* [4], *IGHV* [4], *TP53* [6]. The average TAT across all markers was 9 days (Figure 3). In 46/49 (94%) of the dataset labs participated in EQA programmes. 49/49 (100%), labs were accredited according to ISO15189. Reimbursement was reported as sufficient for 21/49 (43%) of datasets.
The category called 'CDx result' which evaluated the inclusion of result (descriptive and quantitative) was the highest scoring category; the 'CDx assay' category which covered details about the assay used was also generally well reported.
The lowest scoring criteria were those covering thresholds, guidelines and clinical relevance within the 'Interpretation' category, all scoring <5 /10 for all markers, whilst all other categories ranged from 7 to 8.9/10. Relevant clinical guidelines were very rarely mentioned in reports. An overview by CDx marker across all categories showed the highest overall score for *FLT3*-TKD (AML).

Figure 2. Breakdown of the tests/month by CDx marker



The participating labs performed approximately 3000 tests/month for the biomarkers covered in this programme. Most of these tests were BCR-ABL1 (2096 tests/month), followed by AML samples (522 tests/month) and CLL samples (329 tests/month)

Figure 3. Average TAT (in days) per biomarker and across all markers.

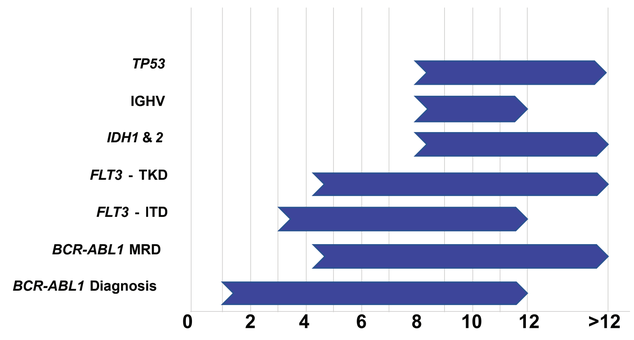


Figure 4a. Evaluation of clinical reports by review category across all markers.

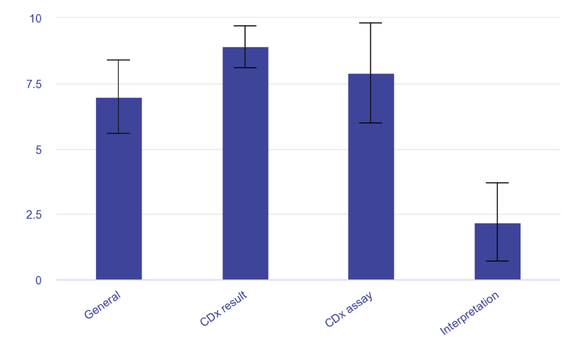
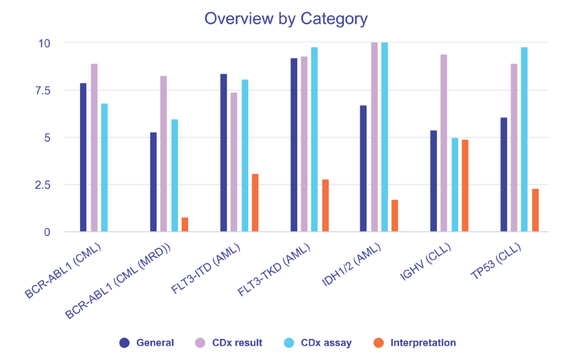


Figure 4b. Evaluation of clinical reports by review category and individual marker.



Clinical reports were rated from 0 (poor) to 10 (good). Of the four evaluated categories, "General," "CDx results," "CDx assay," and "Interpretation," the "Interpretation" category scored lowest with an average rating of only 2.2 points.
The low rating of the "Interpretation" category was consistent across all individual CDx markers and does not reflect bad practice but the lack of need to provide this information in clinical reports

Discussion

This was the first comprehensive national assessment of reporting practices for molecular CDx markers in malignant haematological diseases, and indicates a considerable variation between laboratories. All participants contributing to this programme were accredited and the majority of labs participated in an EQA scheme for all markers surveyed, which implies a high standard of testing from the participating laboratories.

Overall, there was no clear reporting consensus between laboratories even though reporting guidelines are published for the majority of CDx markers studied.
Most laboratories scored highly within the 'General' reporting category although there was marked variation in the layout and presentation of reports, with constraints posed by local LIMS systems clearly evident. Whilst the results themselves were usually clear, sometimes key details were lacking such as the exact mutation type, allelic ratio, etc.
The lowest scoring category was "Interpretation"; however, not all markers require specific interpretation and reference to guidelines; for other markers there may be local policies in place whereby reporting labs are not expected to provide clinical interpretation. The expert panel still felt that some results could be liable to misinterpretation and would benefit from laboratory interpretation where clear guidelines do exist. Such examples are IGHV in CLL[1,2], ELN guidelines for BCR-ABL1 in CML (MRD)[3] and ELN guidelines for FLT3-ITD which depend on the allelic ratio[4]. Where a result indicates a targeted therapy or a change in therapy is recommended based on that result, this should ideally be indicated on the CDx report. Inconsistencies in the way CDx results are represented and interpreted suggest that a programme for more standardised reporting is likely to be beneficial.

Recommendations

Where there are national or international consensus clinical guidelines, laboratories are urged to consider interpreting their results in context. Variation between reporting styles was identified and a general recommendation should be made that laboratories consider the layout and structure of their reports with the end user in mind.
This data provides the basis for further initiatives which could be aimed at guideline updates and for the potential international harmonisation of CDx reporting in haemato-oncology.

Acknowledgements

The authors would like to thank all the participating laboratories for their input.

References

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BSH2020
PO-025-A
Education
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