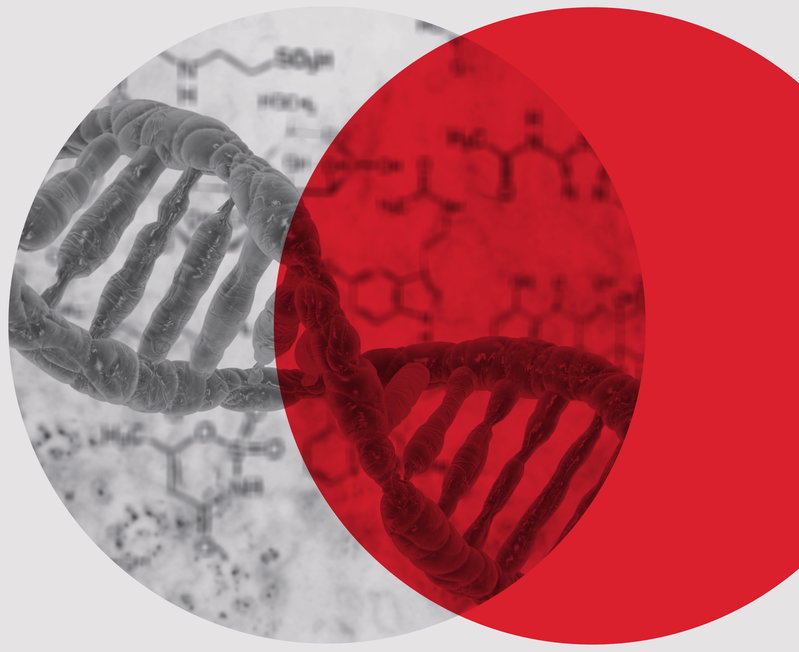
Evaluation of diagnostic testing for *IDH1* and *IDH2* gene variants in acute myeloid leukaemia



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Introduction

Acute myeloid leukaemia (AML) is a heterogeneous disorder with 20% of patients being found to carry an isocitrate dehydrogenase *(IDH)* genetic variation (1). The prognostic significance of *IDH1/IDH2* gene variation remains uncertain, given that *IDH1/IDH2* variants coexist with other gene loci sequence variations (1). However, inhibitors of *IDH1/IDH2* mutant enzymes are currently in clinical trials (2). The identification of genetic variation in these two genes are therefore of therapeutic significance. To assess inter-laboratory performance, an external quality assurance (EQA) pilot was developed in 2017 to monitor laboratories for their ability to detect *IDH1/IDH2* gene variants associated with AML. For this pilot, laboratories were required to test each sample provided for variants in exon 4 of the *IDH1* and *IDH2* genes. Here we report the overall results from 2017 and 2018. Laboratories were assessed according to the consensus values based on a target value obtained from reference and source laboratory results.

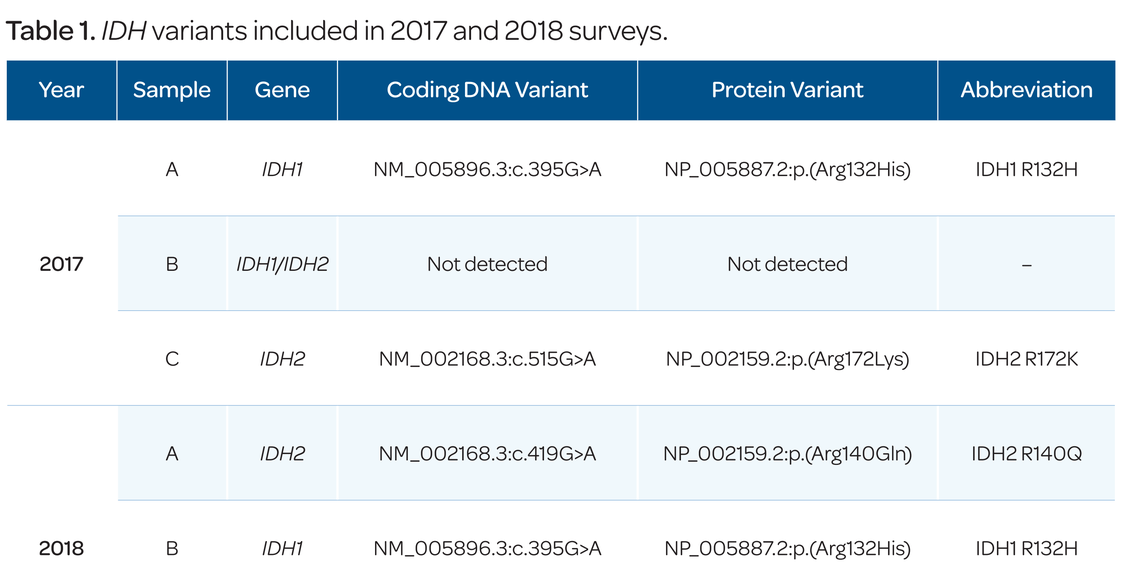
Methods

Three AML patient-derived DNA samples were distributed to twelve laboratories in 2017 and to fifteen laboratories in 2018. Identical sets of samples were sent to each laboratory for testing of *IDH1* and *IDH2* variants. Table 1 lists the expected *IDH* variants in the 2017 and 2018 surveys. In addition to reporting their findings, laboratories were further requested to report on their specific testing platform used. Different types of technology were used for the detection of variants in the *IDH1* and *IDH2* genes. The majority of laboratories used PCR and Sanger sequencing as their method of choice (Figure 1).

Table 1. *IDH* variants included in 2017 and 2018 surveys.

Year	Sample	Gene	Coding DNA Variant	Protein Variant	Abbreviation
2017	A	*IDH1*	NM_005896.3:c.395G>A	NP_005887.2:p.(Arg132His)	IDH1 R132H
	B	*IDH1/IDH2*	Not detected	Not detected	–
	C	*IDH2*	NM_002168.3:c.515G>A	NP_002159.2:p.(Arg172Lys)	IDH2 R172K
2018	A	*IDH2*	NM_002168.3:c.419G>A	NP_002159.2:p.(Arg140Gln)	IDH2 R140Q
	B	*IDH1*	NM_005896.3:c.395G>A	NP_005887.2:p.(Arg132His)	IDH1 R132H
	C	*IDH2*	NM_002168.3:c.515G>A	NP_002159.2:p.(Arg172Lys)	IDH2 R172K

Figure 1. Methods employed by participants for the detection of variants in *IDH1* and *IDH2* genes.



Results

All EQA genotyping data from the two-year survey period are presented here. Laboratory results were assessed as:

- Concordant – if the laboratory's result matched the consensus result.
- Discordant – if the laboratory's result does not match the consensus result or if a laboratory failed to obtain a result where one would be expected and no comparison could be made.
- Not Assessed – if the laboratory did not obtain a result for reasons such as sample issues, assay sensitivity, not a routine test etc.

Following assessment, a comprehensive individual qualitative report on laboratory performance in *IDH1/IDH2* genotyping was generated. Overall performance in *IDH1* and *IDH2* genotyping is presented in Figures 2 and 3. 93% of laboratories correctly identified the common IDH1 R132H variant; one laboratory was unable to detect the IDH1 R132H variant in both 2017 and 2018 surveys. 100% concordance was achieved in the detection of the IDH2 R172K variant; with 93% of laboratories correctly identifying the IDH2 R140Q variant (Figure 3). Laboratories were not assessed for *IDH2* gene in two samples (Sample A in 2017 and Sample B in 2018) as it was noted that only five laboratories were able to identify the IDH2 R140W variant.

Figure 2. Assessment of laboratory results for *IDH1* genotyping over the 2017–2018 period.

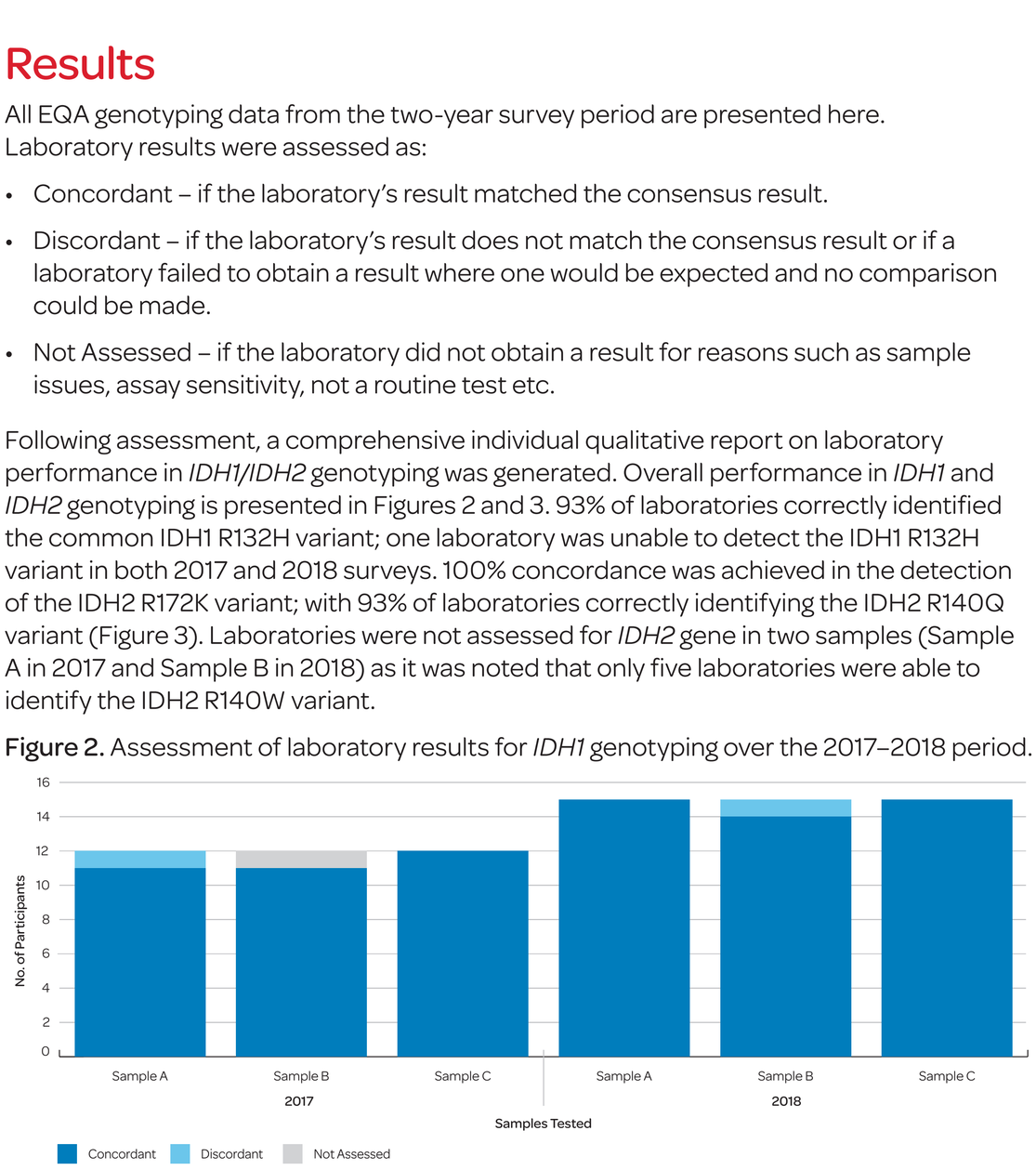
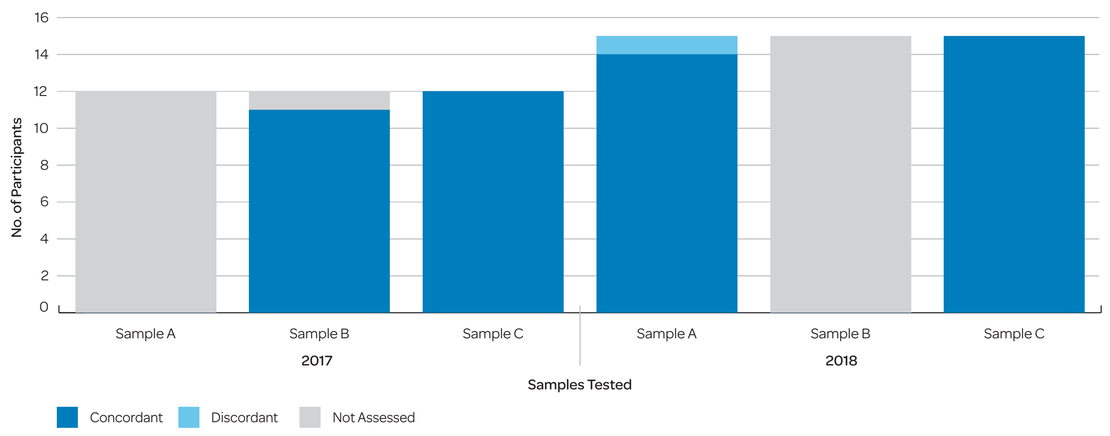


Figure 3. Assessment of laboratory results for *IDH2* genotyping over the 2017–2018 period.



Conclusion

Participation in an EQA is essential to ensure that testing and reporting standards are maintained, which is demonstrated in Figures 2 and 3. Laboratories are encouraged to report gene variants detected using current HGVS nomenclature. Clinical interpretation will be included as part of the assessment from 2019. Overall, laboratories consistently demonstrated good accuracy for genotype characterisation. Throughout the 2017 and 2018 surveys, three discordances due to failure to identify an *IDH* variant were recorded. Given the potential therapeutic implications for false negative findings, it is strongly recommended that laboratories with discordant results review and recalibrate their approach to *IDH1* and *IDH2* mutation screening.

The IDH Variant Analysis in AML (IDH1, IDH2) module is now included in the RCPAQAP scope of accreditation and will become a fully-fledged program from 2019.

References

1. *Isocitrate dehydrogenase mutations in myeloid malignancies.* **Medeiros, BC, et al.** 2, s.l. : Leukemia, 2017, Vol. 31, pp. 272–281.
2. *Biological Role and Therapeutic Potential of IDH Mutations in Cancer.* **Waitkus, MS, Diplas, BH and Yan, H.** 2, 2018, Cancer Cell, Vol. 34, pp. 186–195.

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