# Evaluation of UK NEQAS (H) Hb $A_2$ and related performance data

*This report was commissioned by UK NEQAS (H) from Sheffield Teaching Hospitals Foundation NHS Trust on behalf of the NHS Sickle and Thalassaemia Screening Programme. The full text of the report is available to download from www.ukneqash.org. This summary is distributed for information to all UK participants in the UK NEQAS Abnormal Haemoglobins Scheme.*

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## UK NEQAS (H) Commentary on the Sheffield report

### Scope

This overview encompasses the take-home messages that UK NEQAS (H) has identified from the evaluation of UK NEQAS (H) Hb $A_2$ data, undertaken by Mrs Hannah Batterbee from Sheffield Teaching Hospitals NHS Trust, on behalf of UK NEQAS (H), in the period July 2008 to December 2009. The report examines data from surveys of the UK NEQAS Abnormal Haemoglobins (AH) scheme during the period 2000 – 2008 for changes in methodology and evaluates participant Hb $A_2$ data submitted in the period 2006 – 2008.

### Acknowledgement

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UK NEQAS (H) thanks Mrs Hannah Batterbee for her excellent work on this project and the Sheffield Teaching Hospitals NHS Trust for allowing her secondment to UK NEQAS (H).

### Contact

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### Methodology used

During the period of the study, laboratories enrolled in the UK NEQAS (H) Abnormal Haemoglobins (AH) scheme largely changed from ion exchange column chromatography to high performance liquid chromatography (HPLC), with less than 10% of participants using column chromatography at the end of the study period (2008). Following completion of this report, a re-examination of current data has shown that just one UK clinical laboratory continues to use ion exchange column chromatography; this is a children's hospital that does not undertake antenatal screening. The most frequently used HPLC manufacturer is BioRad, followed by Tosoh, then Menarini.

### Performance trends

Standard deviation (SD) and coefficient of variation (CV%) have decreased for both UK and non-UK participants indicating improvement in accuracy, however the improvement is best for UK laboratories. Since the study demonstrated a slight overall difference in performance improvement between UK and non-UK laboratories, performance analysis has focused on UK participants.

### Instrument bias

Different instrument groups demonstrate bias compared to the all laboratories (or all methods) trimmed mean (ALTM). The ALTM is influenced in favour of the instrument group with the greatest numbers (in this study the BioRad group) and hence this observation should not be interpreted to indicate that any instrument is more correct than another.

In this study however the following general observations can be made concerning instrument bias:

1. Bias remains whether looking at all participants (UK and non-UK) or UK only.
2. Compared to the ALTM the Tosoh G7 instrument showed a strong positive bias; the BioRad D10, BioRad Variant Classic and BioRad V2 instruments showed a weaker positive bias.
3. Compared to the ALTM, the Menarini HA8160 instrument group shows a strong negative bias; the BioRad V2 using the Dual Kit reagent pack shows a weaker negative bias.

**Reference ranges and cut off points**

UK laboratories are still using widely differing reference ranges, even when using the same instrument. The source of reference ranges used is not clear.

Some UK laboratories are clearly not using the defined cut off Hb $A_2$ value of greater than or equal to 3.5% for the diagnosis of beta thalassaemia carrier status. This may reflect the fact that participants include laboratories from UK home countries that have not implemented the Screening Programme algorithm (Scotland, Wales, Northern Ireland), or are laboratories that do not undertake antenatal screening.

**Performance assessment**

There is little difference in performance assessment if this is undertaken against the ALTM (as currently used by UK NEQAS (H)) or the all laboratories (methods) median. However, if participants' results are examined by sub-method (i.e. the analyser group) a difference is seen: a greater proportion of participants show results outside the ± 2 standard deviation range and, when performance scores are calculated, more BioRad and Tosoh users have unsatisfactory performance scores.

Some proof of concept work has been done on altering the scoring algorithm. The current multiplier and truncation limits were originally chosen to give 5% of participants an unsatisfactory performance score of equal to or greater than 100: this may no longer be applicable in the light of the documented improved performance. The possibility of changing the multiplier will need to be tested using the UK NEQAS (H) scoring module and a larger amount of data, to assess the true impact on participant performance assessment. The use of alternative cut off values for performance assessment (e.g. 90 or 110 instead of 100) will also require fuller evaluation but this approach is generally undesirable as this would provide a further complication to the scoring system and the risk of confusion for participants who are enrolled in other UK NEQAS (H) schemes.

Out of consensus participant assessment of their Hb $A_2$ results is mostly due to the use of an 'aberrant' reference range. Transcription was the least most likely cause of an incorrect assessment. Instrument bias also has an effect.

**Evaluation of interpretive comments – clinical significance**

Between 2006 and 2008, 30 participants (37% in UK) failed to identify beta thalassaemia in the interpretive comment codes used for specimens with an Hb $A_2$ greater than 3.5%. The evaluation of free text comments where applicable is included in the UK NEQAS (H) supplementary report that accompanies each survey report; in general, approximately half of the UK laboratories that fail to identify beta thalassaemia in any form of comment in a borderline Hb $A_2$ specimen have returned a result below the 3.5% cut-off; the remainder have a result above the cut-off but have failed to return a correct interpretation. Although any screening programme will not be expected to identify 100% of affected individuals, especially at borderline levels, instrument bias will result in an unequal distribution of these 'misses' dependent upon the analyser used. Conversely, 42 participants (43% in UK) incorrectly identified beta thalassaemia in specimens where this did not exist: again there are issues around the generation of an incorrect Hb $A_2$ result or the interpretation of data from sickle cell carriers with possible co-existent alpha thalassaemia or iron deficiency. In this scenario, instrument bias against a fixed cut-off could result in over diagnosis and unnecessary partner testing, with the associated distress for the patient that this entails.

**Manufacturers' feedback**

This report has been reviewed by the equipment manufacturers prior to publication and comments from Tosoh Bioscience, Helena Biosciences, BioRad Laboratories and Menarini Diagnostics are included in full in appendices to the report.

**Further work and discussion**

UK NEQAS (H) has found this evaluation of data extremely helpful in confirming and summarising performance trends. Inevitably, this report has highlighted the need for additional work, which UK NEQAS (H) will submit to the NHS Sickle and Thalassaemia Screening Programme for consideration.

This report will provoke discussion between the developers of policy in haemoglobinopathy and thalassaemia screening and those responsible for service delivery, quality monitoring and equipment manufacture. This is welcome and should result in further improvement in the quality of laboratory services provided to patients.

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