To CLIA (Clinical Laboratory Improvement Amendments)

It has come to our attention that Clinical Laboratory Improvement Amendments (CLIA) proposes to change the acceptable criteria for regulated analytes to ± 10% for HbA1c (file code CMS-3355-P). HbA1c has been the cornerstone for targeting the individual treatment of patients with diabetes for decades. The DCCT study proved its value as a biomarker of glycemia by separating the groups by 2% with an HbA1c of 9% in the conventional and 7% in the intensive treatment group, respectively (1). This ~2% difference in HbA1c resulted in a significant reduction in long-term complications in the intensive treatment group. HbA1c has also been used for setting targets for treatment; for example, the 2018 International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines recently lowered the HbA1c target for children and adolescents from 7.5% to 7.0% (2). HbA1c is widely used for national and international benchmarking on a group level, showing considerable differences between high-income countries (3).

There has been a discussion about how large a difference in HbA1c reflects a clinically significant difference in long-term outcome. Lind et al. have shown from analysis of the DCCT data that this is around 0.3% (4). The number needed to treat at this difference was 13; i.e. if 13 persons decrease their HbA1c by 0.3% over 10 years (from 8.3% to 8.0% in the example mentioned), 1 person would be saved from developing retinopathy.

This means that in clinical practice, a healthcare professional can advise the patient with diabetes that a decrease in HbA1c by 0.3% will translate into a meaningful reduction in risk of complications provided this reduction can be sustained for several years. However, this also implies that the results of the HbA1c test are stable. With the current College of American Pathologists (CAP) proficiency testing requirements, the results should be within ± 6%, i.e. a measured value of 7.0% should be within the range 6.58% to 7.42%. This means that the clinically relevant value of 0.3% resides within the currently acceptable error margin. Going down to ± 5%, as CAP has been discussing, provides a narrower interval, i.e. from 6.65% to 7.35%, which is similar to the clinically relevant difference of 0.3%. Therefore, one can inform the patient who has decreased his/her HbA1c by 0.3% that this could be within the margin of error of the measurement. However, this probably reflects a real improvement in glycemia if sustained over subsequent visits. In contrast, the proposed acceptable error margin of ± 10% would yield results within the error margin of 7.0% from 6.3% to 7.7%. In the above example, it would not be possible to state that this person has achieved a clinically meaningful improvement in glycemia when HbA1c has decreased by 0.3%.

The coefficient of variation for all methods of HbA1c evaluated in CAP surveys in the clinically relevant range of 6%-10% (42-86 mmol/mol) has decreased to half (National Glycohemoglobin Standardization Program [NGSP] from ~4% to ~2% and the International Federation of Clinical Chemistry [IFCC] from ~6% to ~3%) from 2009 when the CAP requirement was ± 10% until today when it is ± 6% (5). Raising it again to ± 10% would totally erase the progress in quality improvement in measuring HbA1c that has served the diabetes community so well. ISPAD urges CMS to readdress this matter and change the criteria for acceptable performance of HbA1c to ± 5% in the proposed rule for further quality improvement of HbA1c.
Over half a million children and adolescents around the world depend upon a correct decision in this matter to reduce their risk of long-term complications.

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