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The Need for Accuracy in Hemoglobin A1c Proficiency Testing: Why the Proposed CLIA Rule of 2019 Is a Step Backward

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On February 4, 2019, the Centers for Medicare & Medicaid Services (CMS) and Centers for Disease Control and Prevention (CDC) proposed a rule change to update proficiency testing regulations under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) to address current analytes and newer technologies. One of the analytes specified was hemoglobin A1c (HbA1c). The criterion for acceptable performance of a laboratory measuring this analyte was specified to be ±10%.[1]

Congress enacted CLIA in 1988 to ensure the accuracy and reliability of testing in all laboratories that test human specimens for purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment, or the assessment of health, of human beings. Initial regulations were established for implementing CLIA in 1992 and proficiency-testing regulations became effective for all laboratories in 1994.[1] Recognizing changes in clinical practices, CLIA is now proposing revisions to its existing proficiency testing regulations for target values.

CLIA elected to base its acceptance limits (which it defined as the symmetrical tolerance, plus and minus, around the target value) on estimates of biological variability between patients, which is "the symmetrical tolerance (plus and minus) around the target value."[1] CLIA referenced a publicly available database published in 2014 for some desirable specifications for their allowable limits. The desirable total allowable error for HbA1c in that reference was ±3%.[2] For proficiency testing, the College of American Pathologists (CAP) currently uses an acceptance limit of ±6%, while the limit for certification of methods by the National Glycohemoglobin Standardization Program (NGSP) is ±5%.

We believe that CLIA's proposed rule loosening the acceptance limits for proficiency testing from the current level of ±6% to a proposed level of ±10% would significantly harm the effectiveness of HbA1c testing and threaten patient safety. An acceptance limit as high as ±10% would be a step backward in terms of defining the analytical accuracy of HbA1c assays and, more importantly, would compromise their clinical accuracy and utility in the management and diagnosis of diabetes mellitus.

Analytical Accuracy of Current Hemoglobin A1c Assays

Current HbA1c assays have adequate analytical accuracy for a proficiency testing acceptance limit of 6% and the limit does not need to be relaxed to 10%. Accurate measurement of HbA1c is integral to and essential for the treatment of patients with diabetes. Since the publication in 1993 of the Diabetes

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Control and Complications Trial (DCCT),[3] the NGSP together with the CAP and manufacturers of HbA1c assays have worked toward harmonizing the assays and improving their performance in routine clinical laboratories. The NGSP works with manufacturers of HbA1c assays to standardize their methods to achieve results comparable to the DCCT assay results and provides certification for those methods that meet specified accuracy criteria. Criteria for NGSP certification have tightened over time to encourage the development and use of better methods and better laboratory practices. Currently, 36/40 sample results must be within ±5% of the target. The role of CAP is to provide material for proficiency testing, which laboratories in the USA that report patient results are required to perform. CAP proficiency testing for HbA1c has evolved to accuracy-based surveys with reference values assigned by the NGSP network. HbA1c was not included as a regulated analyte in CLIA 1988, which enabled CAP to contribute to improved assay performance by gradually narrowing the acceptance limits for proficiency testing. Criteria for passing the CAP survey progressively tightened from ±15% in 2007 to ±6% by 2013 and the intent is to reduce this to ±5% in 2020. These coordinated efforts, along with concomitant progress in method performance, have improved HbA1c measurements in patient samples.[4,5] CAP survey results have shown considerable improvement in the comparability of HbA1c results both within and among routine assay methods. The total between laboratory coefficient of variation (CV) for HbA1c results, comprising ~3500 laboratories using over 20 different methods, has improved considerably. All laboratory/method CVs declined from ~5-6% in 2000 to ~3.5% by 2013, and reached <3% by 2018. The CLIA 2019 proposal is the first time that CLIA has mandated an allowable limit for HbA1c proficiency testing.

In addition to monitoring glycemia in patients with diabetes, HbA1c is recommended for diabetes diagnosis. Standardization and improved performance of HbA1c assays were a necessary hurdle, which allowed the acceptance of this metric in 2010 for diagnosis of diabetes.[6] The potential for misdiagnosis of diabetes or missed diagnosis of diabetes will be increased considerably if performance criteria are loosened to comply with less stringent accuracy criteria proposed by CMS.

Importance of Accuracy of Hemoglobin A1c Assays in Treatment and Diagnosis

The HbA1c assay introduced into clinical practice almost 40 years ago with the demonstration of its utility,[7] has become the indispensable measure of chronic glycemia used for the management of diabetes[8] and, more recently, for diagnosis.[9] The role of intensive diabetes therapy as a consistent and effective means of reducing the microvascular complications of diabetes was established for type 1 diabetes in the DCCT[3] and for type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS).[10] Both of these studies determined that a HbA1c concentration of ~7.0% resulted in substantial reductions in all of the microvascular complications. The recommendation of a HbA1c target <7.0% by both the DCCT and UKPDS investigators and subsequently by almost every diabetes and health care organization was predicated on the clinical trial data, since 7.0% was the mean HbA1c achieved in both studies, and by the balance between the benefits and risks of therapy. The importance of achieving target HbA1c levels led to the formation of the NGSP,[11] the major goals of which were to harmonize the myriad assays to the DCCT standard and encourage improvements in assay precision and accuracy.

The great strides that have been made toward these ends are now threatened by the CLIA recommendation to accept results that are within ±10% of the true value. This regressive recommendation from the current requirements that are approaching ±5% will result in less consistent HbA1c results within and between assays. With less reliable HbA1c results, patients will be at greater risk for unacceptably high HbA1c results and increased risk for microvascular complications over time. For every 10% difference in HbA1c (from 7.0 to 7.7%, for example), the risk for retinopathy progression increases by 43%.[12] Conversely, falsely high HbA1c results will place patients at greater risk for hypoglycemia. Inconsistent results between laboratories and more highly variable results over time in a single laboratory will sow confusion in patients and clinicians alike. The concerted efforts by all that have resulted in global improvements in the outlook for people with diabetes will be undermined. An acceptance limit as high as 10% would be a step backward in terms of defining the clinical accuracy of currently available HbA1c assays.

Central Role of Current Hemoglobin A1c Assays in Establishing Glucose Lowering Therapies

The HbA1c assay is used as a measure of future health risk for the purpose of assessing and targeting the use of glucose-lowering therapies. The quantitative relationship of this analyte's concentration to those risks is known, albeit with some imprecision, and is thus used in guiding the development of new medications within this class. The regulatory authorities, as well as health-care professionals in diabetes care, recognize the evidence base focusing the HbA1c value to predict the risk of vascular complications in patients with diabetes.[13] This relationship is derived from major clinical outcome studies in both type 1 and type 2 diabetes, such as the DCCT/EDIC and UKPDS, and other outcome studies in type 2 diabetes. The HbA1c lowering effect regarded as clinically significant and necessary for new drug approval by the US Food and Drug Administration (US FDA) and EU European Medicines Agency (EMA) is 0.3 or 0.4 HbA1c percentage

points.[13,14] In a typical study population with a mean HbA1c of around 8.0% this margin would thus imply an acceptance limit of the HbA1c assay at ±4-5% rather than what is being proposed to become an acceptance limit of ±10%. This 0.3-0.4% absolute difference in HbA1c concentration also represents the US FDA's requirement for noninferiority (upper 95% confidence interval) in comparative trials of glucose-lowering medications as typically and necessarily performed for new insulins. The proposed range of ±10% would generate a reliability range of 0.6-0.8% relative accuracy and result in many noninferior drugs becoming labelled as inferior simply because of the inaccuracy of the study's HbA1c assay. Conversely, relatively ineffective drugs could be proved effective based on poor quality assays. Furthermore, lesser precision, compared to what we have been used to in recent clinical trials, will have disproportionate effects on power requirements for study numbers in phase 2/3 clinical trials, pushing the costs and burdens of medical development in diabetes even higher. An acceptance limit as high as 10% would be a step backward in terms of defining the effectiveness of glucose lowering therapies with HbA1c assays.

Precision of Current Hemoglobin A1c Assays

The newly proposed rule will reduce test precision from the existing ±6% limits to ±10%, if one assumes that an assay has no bias. The proposed rule therefore represents an undesirable step toward imprecision. Individual laboratory results need to be recognized as point estimates within a range of values. Inaccurate assessment due to test imprecision of whether or not an individual patient has met a threshold performance measure, such as HbA1c <7.0% or <8.0%, coupled with the use of performance to drive payment, could lead not only to unnecessary effort and increased costs, but also to adverse short-term outcomes due to inappropriate medication intensification. This is of special concern for patients on insulin, since hypoglycemia is dangerous. Inaccurate or imprecise HbA1c assays can increase its risk of occurring. Conversely, underestimation of the actual HbA1c concentration can result in failure to intensify treatment resulting in increased risk of development of microvascular complications. Precise HbA1c readings are necessary for patient safety. For example, if the imprecision of the HbA1c measurement is allowed to be as high as ±10%, then a true HbA1c value of 6.5% ± 10% means that the measured value can be 5.85-7.15%. The difference in clinical significance between 5.85% and 7.15% spans very different interpretations of either "no diabetes" (5.85%) to "diabetes under control" (6.5%) to "diabetes requiring additional treatment" (7.15%). We need more precision and not less. An allowable error limit as high as 10% would be a step backward in terms of defining the precision of currently available HbA1c assays.

Conclusions

The allowable limit for proficiency testing of HbA1c has been shrinking over the past 27 years since CLIA was founded in 1992. Based on the myriad important roles played by the HbA1c assay, including the diagnosis and management of diabetes and in the approval of new therapies, we believe that CLIA's proposed rule loosening the acceptance limits of proficiency testing from the current level of ±6% to a proposed level of ±10% would reduce the effectiveness of HbA1c assays and compromise the safety of patients.

Abbreviations

CAP, College of American Pathologists; CDC, Centers for Disease Control and Prevention; CLIA, Clinical Laboratory Improvement Amendments; CMS, Centers for Medicare & Medicaid Services; CV, coefficient of variation; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; EMA, EU European Medicines Agency; HbA1c, hemoglobin A1c; NGSP, National Glycohemoglobin Standardization Program; PM, precision medicine; PT, proficiency testing; UKPDS, United Kingdom Prospective Diabetes Study; US FDA, US Food and Drug Administration.

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