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Assessing quality from an accuracy-based HbA1c proficiency survey

Randie R. Little¹ and Curt L. Rohlfing¹

¹Departments of Pathology & Anatomical Sciences and Child Health, University of Missouri School of Medicine, Columbia, MO

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To the Editor

Westgard, et al [1] recently described an assessment scheme for proficiency testing using Six Sigma metrics and using HbA1c as an example. The authors used the accuracy based College of American Pathologists (CAP) survey data for HbA1c in which values were assigned by the NGSP network. Sigma proficiency assessment charts were developed for each sample by graphing the %bias vs. %CV and including lines representing the sigma quality. Sigma was calculated from the allowable total analytical error ($\pm 6\%$) used for the CAP survey and each method group's bias and CV.

According to this article, "Six Sigma is the goal for world class quality. Three-Sigma is commonly set as the minimum quality acceptable for a production process". But is this reasonable for the clinical laboratory? What does it take to achieve this for HbA1c measurement? The CAP and NGSP agree that results between 5 and 10% (31 and 86 mmol/mol) HbA1c should be within $\pm 6\%$ of an accurately assigned value. Overall, based on recent surveys, approximately 95% of laboratories report results within 6% of the assigned values. Of course, some method groups have relatively low pass rates while for others, all the laboratories using that method report results within $\pm 6\%$ (100% pass rate). Is a Six Sigma goal reasonable? Or, would a 100% pass rate be more reasonable and appropriate for a goal? Pass rates and corresponding Sigma values for a recent survey sample is shown in figure 1 (CAP GH5 2015B, sample 10, target value 7.38% (57mmol/mol) HbA1c). Clearly, a method

Corresponding author: Randie R. Little, Diabetes Diagnostic Laboratory, M766, Departments of Pathology & Anatomical Sciences, University of Missouri School of Medicine, 1 Hospital Dr., Columbia, MO 65212, phone: 573-882-1257, FAX: 573-884-4748, Littler@health.missouri.edu; Curt L. Rohlfing, Diabetes Diagnostic Laboratory, M767, Department of Pathology & Anatomical Sciences, University of Missouri School of Medicine, 1 Hospital Dr., Columbia, MO 65212, phone: 573-884-2385, FAX: 573-884-4748, Rohlfingc@health.missouri.edu.

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can have a 100% pass rate and still only have a sigma value of 2 or less; eight method groups actually did have 100% pass rates for this sample and 19 methods had a pass rate of 95–100%. Indeed, Westgard et al report that the weighted average sigma (weighting based on number of laboratories in the method group) was only 1.46 for the diagnostic level (6.5% or 48mmol/mol HbA1c) sample in the 2014A CAP survey while the cumulative pass rate reported by the CAP for this sample was close to 90%. Pass rates for the more recent sample from the 2015 survey (figure 1) ranged from 70.8% to 100% and the cumulative pass rate was reported by the CAP to be 94.9%. For this survey sample the weighted sigma was still only 1.78.

While it is true that there are still methods that demonstrate suboptimal performance, mainly due to imprecision, these methods are used by few laboratories. The methods with pass rates below 90% for the sample shown in figure 1 represent only approximately 10% of the total number of participating laboratories.

Considering HbA1c for diagnosis, according to Westgard, et al, too many people would be misclassified even with a bias of 0.1% HbA1c. However, the International Expert Committee Report on the Role of HbA1c in the Diagnosis of Diabetes clearly stated that the 6.5% cutoff “should not be construed as an absolute dividing line between normal glycaemia and diabetes” [2]. Instead, 6.5% (48mmol/mol) was considered sufficiently sensitive and specific to identify individuals who are at risk for developing retinopathy and who should be diagnosed as having diabetes. In addition, the committee chose to emphasize specificity rather than sensitivity and to include a prediabetes group defined by a HbA1c between 6.0 and 6.5% (42 and 48 mmol/mol) (subsequently revised to 5.7–6.5% (39–48 mmol/mol) by the American Diabetes Association) which included those at highest risk of developing diabetes. It should also be noted that testing for diabetes is done more than once, and over years, in an individual that is at risk for diabetes. Therefore, if an individual’s HbA1c is just below the diagnostic cutoff, they will likely be diagnosed at future testing. If HbA1c in a particular laboratory shows a positive bias, and an individual is therefore mistakenly diagnosed with diabetes when they are really at the upper end of the pre-diabetic range, the treatment they would receive is very likely to be appropriate for prediabetes as well and would lower the risk of diabetes complications [3]. The committee also considered the performance of current assays (as of 2009 when the report was released) as well as assay interferences when they made the decision to include HbA1c for use in diagnosis. Since the time of that report in 2009, the assays have actually improved further [4].

So again, what is a reasonable goal for HbA1c and how can laboratories be made aware of their performance related to this goal? I would suggest that the goal of all laboratories reporting HbA1c should be to consistently pass the CAP survey for all samples. Beginning in 2015, if a laboratory participates in the GH5 survey they will have 15 opportunities per year (3 surveys with 5 samples each) to assess their performance. As far as evaluating the performance of each method, looking at each method’s pass rate (along with the %CV and bias provided in the CAP report) for each survey/sample would be most useful.

According to Westgard et al, information about quality on the Sigma scale would help laboratories understand the capabilities and limitations of current test systems and that the

Sigma Proficiency Assessment Chart may be helpful in this regard. But does that mean that their performance is inadequate if their Sigma value is <3 even if they pass all survey challenges? Should we say that standardization is far from adequate because most methods are not up to 3 sigma? Weykamp et al [5] also used Sigma-Metrics for evaluating quality targets and suggested that a target of 2 Sigma is sufficient for routine laboratories. Can we take a more pragmatic approach by assessing overall performance in proficiency testing based on the overall pass rate since the pass/fail cutoff has been established based on clinical need? We would recommend the latter. And for method assessment, the pass rate for each method group would provide needed information for laboratories interested in performance of their method or for those considering changing methods.

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Abbreviations

NGSP	National Glycohemoglobin Standardization Program
HbA1c	hemoglobin A1c

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Figure 1. Relationship between survey pass rate and Sigma for each method using sample #10 of the CAP GH5B 2015 survey. Best fit line is estimated using a 3rd order polynomial equation ($y = 0.3466x^3 - 7.1594x^2 + 27.342x + 69.963$, $R^2 = 0.8713$)