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Utilization of Assay Performance Characteristics to Estimate Hemoglobin A_{1c} Result Reliability

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BACKGROUND: Allowable total error (TE_a) goals for hemoglobin (Hb) A_{1c} require minimal assay imprecision and bias and implementation of a robust QC monitoring program. Here, we compare the combined influence on the risk of reporting unreliable results of TE_a goals, a routine QC practice, and assay performance characteristics of 6 Hb A_{1c} instruments across 4 academic medical centers.

METHODS: The CLSI protocols EP-5 and EP-9 were applied to investigate Hb A_{1c} result imprecision and bias on the Variant II Turbo and Variant II (Bio-Rad), G8 (Tosoh), Capillarys 2 Flex Piercing (Sebia), COBAS Integra 800 (Roche), and DCA Vantage (Siemens). Patient-weighted σ values and the risk of reporting unreliable Hb A_{1c} results were determined for each assay at TE_a specifications of 5%, 6%, and 7%.

RESULTS: A large range of patient-weighted σ values spanning 0.5 orders of magnitude at a 6% TE_a was observed. Although imprecision for all instruments was <3%, bias impacted the majority of the σ changes observed. Estimates for reporting unreliable results varied almost 500-fold based on analytical performance alone.

CONCLUSIONS: Considerable differences in the probability of reporting unreliable Hb A_{1c} results between different NGSP (formerly the National Glycohemoglobin Standardization Program)-certified platforms were observed. At a 6% TE_a, our study indicates all but the Capillarys 2 Flex Piercing requires that the maximum affordable QC be run. Risk estimates for individual laboratories' Hb A_{1c} methods can be used to assess QC practices and residual risk of an unreliable Hb A_{1c} result.

Laboratory QC procedures are implemented to detect, reduce, and correct deficiencies in the testing process, with the goal of quickly identifying important errors before patient results are released *(1)*. Historically, several options have been available for meeting CLIA QC requirements for nonwaived testing. The traditional approach requires that 2 levels of external QC be run each day of testing. As manufacturers, large reference laboratories, and hospital laboratories began collecting QC data, they noted that some test systems rarely failed QC and questioned the frequency at which external QC was required. In response, CLIA developed the Equivalent QC option, which reduced the number of external QC tests required for eligible methods. This Equivalent QC option will be discontinued in 2016. Recently, the Centers for Medicare and Medicaid Services announced a new type of QC plan, the Individualized QC Plan (IQCP),[7] beginning January 2014, that allows laboratories to utilize risk management strategies to design a QC program. Laboratories will be able to choose either the traditional approach of testing 2 levels of QC per assay, per day of patient testing, or they may elect to develop the newly introduced IQCP, which determines analytical QC frequency by utilizing risk management principles.

A risk assessment can be performed to determine if the current QC practice is adequate or requires revision *(2)*. Currently there is minimal guidance available regarding how laboratories may quantitatively estimate risk to optimize analytical QC criteria appropriate for an IQCP *(2)*. For the laboratory, risk is related to the chance of producing and reporting unreliable patient results, which are defined as results containing measurement errors that exceed an allowable total error (TE_a) specification. Evaluation of analytical performance characteristics, assay requirements, σ metrics,

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[7] Nonstandard abbreviations: IQCP, Individualized QC Plan; TE_a, allowable total error; Hb, hemoglobin; POC, point-of-care; CAP, College of American Pathologists; SRL, secondary reference laboratory; $E(N_{uf})$, expected number of unreliable final patient results; Max $E(N_{uf})$, maximum $E(N_{uf})$; DPMO, defects per million opportunities.

and statistical QC plans is one way to estimate risk during the analytical phase of testing.

The expected number of unreliable patient results reported when an assay is out of control is a useful metric for characterizing a laboratory's QC strategy in relation to its analytical performance capabilities. When an out-of-control condition occurs in the laboratory, the percentage of unreliable patient results produced while the out-of-control condition exists will differ from the in-control percentage of unreliable results. The number of unreliable patient results produced because of an out-of-control condition will depend on the change in percentage of unreliable results due to the out-of-control condition and the number of patient samples examined before the laboratory's QC procedures detect the out-of-control condition.

Hemoglobin (Hb) A_{1c} is an ideal assay to pilot risk assessment of reporting unreliable patient results because (*a*) the majority of manufactured Hb A_{1c} assays in the US are certified by the NGSP (formerly the National Glycohemoglobin Standardization Program) with stringent analytical performance requirements, (*b*) multiple testing methods and technologies are available and used in laboratory and/or point-of-care (POC) settings, and (*c*) there is considerable knowledge about the clinical impact of test results. Further, the prevalence of diabetes mellitus and prediabetes is increasing around the world and may climb to 50% of the population in the US by 2020 *(3)*. Given that current guidelines recommend the use of Hb A_{1c} for the diagnosis and monitoring of diabetes *(4)*, laboratories may see substantial increases in the volume of Hb A_{1c} orders.

Currently all Hb A_{1c} assay manufacturers standardize to the NGSP Reference Method (or technically NGSP Designated Comparison Method) *(5)*. In 2013, the College of American Pathologists (CAP) proficiency testing acceptance limit decreased to $\pm 6\%$, leading laboratories to closely scrutinize their Hb A_{1c} assay performance characteristics and QC practices. There is, however, limited information available regarding the risk of reporting erroneous Hb A_{1c} results when using NGSP-certified methods. Although the CAP GH2 proficiency testing survey highlights the accuracy and variation within and between Hb A_{1c} assays, less is known about how commonly recommended routine QC practices and assay performance affect the reliability of an Hb A_{1c} result even when these assays pass proficiency testing.

The aim of this study was to evaluate the risk of reporting unreliable Hb A_{1c} results when using currently available NGSP-certified Hb A_{1c} methods. Six different Hb A_{1c} assays across 4 academic medical centers were evaluated using assay performance characteristics according to CLSI protocols. In the new era of risk-based QC plans, this provides one example of quantitative risk estimates that can guide QC strategies appropriate for an IQCP.

Materials and Methods

Hb A_{1C} ASSAYS

Hb A_{1c} was measured on 6 different analyzers across 4 academic medical centers. These included the Variant II Turbo (Bio-Rad), Variant II (Bio-Rad), and Tosoh G8 (Tosoh Bioscience), which are based on ion-exchange HPLC; the Capillarys 2 Flex Piercing (Sebia), which is based on capillary electrophoresis; the COBAS Integra 800 (Roche Diagnostics), which is based on agglutination immunoassay; and DCA Vantage (Siemens), which is based on immunoassay. Two different DCA Vantage instruments using 2 different lots of calibrator were evaluated. The Dimension ExL (Siemens) was also evaluated in this study. However, while this manuscript was in the review process, the manufacturer withdrew from the market the reagent lot that was evaluated. Therefore, these data have been excluded from the study.

All assays tested were NGSP certified as of September 2012.

NGSP SAMPLES

Forty NGSP secondary reference laboratory (SRL) target value–assigned samples (Dr. Randie Little, University of Missouri, performed testing and provided samples for this study for a fee; NGSP SRL) were sent to each laboratory and stored at −80 °C until analysis.

PRECISION AND BIAS STUDIES

Precision for each assay was determined using the CLSI EP5-A2 protocol. Respective laboratory Hb A_{1c} QC materials (both low QC and high QC) were assayed in duplicate twice per day (morning and afternoon) for a total of 20 days. Linear regression and bias were determined according to the CLSI EP9-A2 protocol. Eight of 40 NGSP SRL samples were thawed each day and tested in duplicate over a period of 5 days.

STATISTICAL ANALYSES

A representative patient distribution of Hb A_{1c} values was obtained from 1 facility over a 2-week period. Sigma values $[(TE_a - \%Bias)/CV]$ for each instrument were calculated at each Hb A_{1c} concentration and averaged over the observed Hb A_{1c} patient distribution to obtain patient-weighted σ values. Sigma values directly relate to the predicted probability of producing an unreliable patient result. Given a TE_a specification and a procedure's %Bias and CV, the percentage of patient results predicted to be unreliable during stable operation is computed as:

$$\text{In-control \% unreliable} = 100\{1 - [F(TE_a - \%Bias/CV) - F(-TE_a - \%Bias/CV)]\},$$

where F denotes the standard normal cumulative distribution function.

The expected number of unreliable final patient results [$E(N_{uf})$] owing to an out-of-control condition is defined as the predicted number of unreliable results produced from the inception of an out-of-control condition up to the last acceptable QC evaluation before the out-of-control condition's detection. These results are considered final because they were produced and reported before an acceptable QC evaluation. $E(N_{uf})$ depends on TE_a, the procedure's %Bias and CV, the laboratory's QC rules and frequency of QC evaluations, and the magnitude of the out-of-control condition. The method for computing the expected number of unreliable patient results has been described previously *(6)*.

$E(N_{uf})$ was evaluated over a range of possible out-of-control conditions. Systematic error out-of-control conditions that cause a persistent systematic shift in results proportional to concentration were assessed over a range of negative and positive shifts spanning 2 multiples of TE_a. The maximum predicted value of $E(N_{uf})$ over the range of out-of-control conditions was used to assess and compare performance of the different procedures in response to an out-of-control condition.

For these analyses, TE_a was set to 5%, 6%, and 7% (to encompass the current state of Hb A_{1c} testing acceptability in terms of current and previous manufacturer NGSP certification and proficiency testing through the CAP), QC rules were set to the 1:2s rule (with control limits set at mean ± 2 SD) with 2 QC levels, and the mean number of Hb A_{1c} examinations between QC events was set to 100. Computations were performed using the MATLAB programming language (The Mathworks, Inc.).

Results

The comparisons of measured Hb A_{1c} values to target NGSP SRL results across the 6 Hb A_{1c} assays are shown in Fig. 1 and summarized in Table 1. Based on data evaluated at 2 QC levels, the Variant II Turbo and Capillarys 2 Flex Piercing showed the smallest overall bias, and the Tosoh G8 and Integra 800 had the largest bias (Table 1). The squared correlation for all assays ranged from 0.989 [DCA Vantage-lot 1] to 0.999 (Variant II Turbo, Tosoh G8, Capillarys 2 Flex Piercing) (Table 1). Percentage bias was calculated from the linear regression relationships over the range of NGSP target value–assigned Hb A_{1c} levels and found to differ significantly across assay platforms (Fig. 2). The Integra 800 and Bio-Rad Variant II showed the highest variability in percentage bias across the Hb A_{1c} values tested.

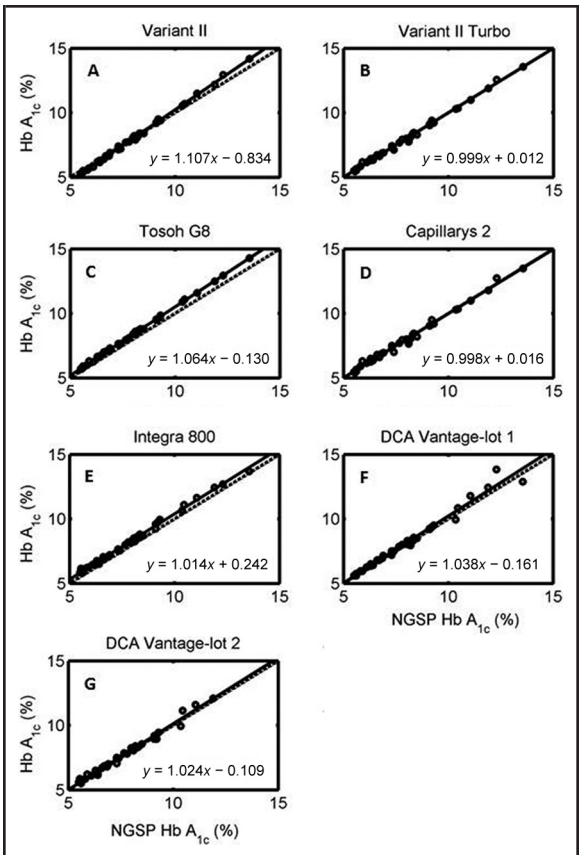

Fig. 1. Hb A_{1c} comparisons to target-assigned NGSP SRL results.

Within-laboratory imprecision (CV) ranged from 1.28% for the Tosoh G8 to 2.97% for the Variant II Turbo when using low Hb A_{1c} QCs (Table 1). At the high QC level, imprecision ranged from 0.8% for the Tosoh G8 to 2.65% for the DCA Vantage-lot 1.

A representative distribution of approximately 1500 Hb A_{1c} patient results for 2 weeks was combined with the analytical performance characteristics of each assay shown in Table 1. Together they were used to generate patient-weighted σ metrics and predicted probabilities of producing unreliable patient results (measurement errors exceeding TE_a) during stable in-control operation for each Hb A_{1c} assay at TE_a specifications of 7%, 6% (the current CAP proficiency testing acceptance limit), and 5% (Table 2).

Assuming a 1:2s QC rule with 2 QCs and a mean of 100 Hb A_{1c} examinations between QC events, the predicted number of unreliable final patient results ex-

Table 1. Assay performance characteristics across platforms/sites: imprecision and bias across 2 QC levels.

	Low QC			High QC				
Assay platform	Mean	% Bias[a]	% CV[b]	Mean	% Bias	% CV	Linear regression[c]	r^2
Variant II	5.09	−4.99	1.43	9.74	2.00	1.33	$1.107x - 0.834$	0.991
Variant II Turbo	5.18	−0.08	2.97	10.07	0.10	1.81	$0.999x + 0.012$	0.999
Tosoh G8	5.75	3.99	1.28	9.60	4.98	0.80	$1.064x - 0.130$	0.999
Capillarys 2	5.24	−0.33	1.66	7.93	−0.01	1.33	$0.998x + 0.016$	0.999
Integra 800	5.61	5.76	2.40	9.90	4.07	1.18	$1.014x + 0.242$	0.997
DCA Vantage-lot 1	5.31	−0.34	1.88	10.31	2.72	2.65	$1.038x - 0.161$	0.989
DCA Vantage-lot 2	5.23	−0.37	1.93	10.49	1.73	1.81	$1.024x - 0.109$	0.991

[a] % Bias = 100 × (observed mean − assigned value)/assigned value.
[b] Precision calculations follow CLSI EP-5A.
[c] Linear regression of assay results compared to NGSP results measured on a Tosoh HPLC.

pected due to the existence of an out-of-control condition was computed over a wide range of possible magnitudes of systematic error out-of-control conditions (Fig. 3). The scales of the *y* axes in Fig. 3 were set the same for the $E(N_{uf})$ graphs shown to provide a head-to-head evaluation of each assay's systematic out-of-control conditions. The lines of the Capillarys 2 Flex Piercing (Fig. 3D) and the DCA Vantage-lot 2 (Fig. 3G) graphs are nearly flat due to these assays' negligible predicted number of unreliable final patient results, $E(N_{uf})$, over the wide range of possible magnitudes of systematic error out-of-control conditions. The maximum expected number of unreliable final patient results [Max $E(N_{uf})$] out of 100 events over the range of out-of-control conditions was determined for each assay and each TE_a (Table 2).

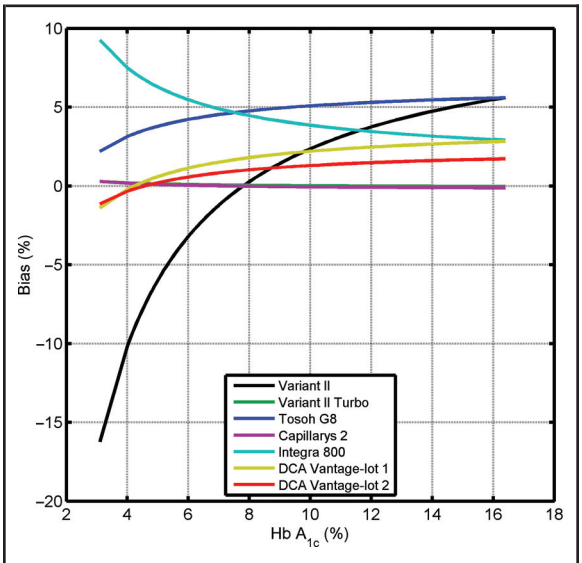

Fig. 2. Percentage bias compared to NGSP results across a range of Hb A_{1c} concentrations.

The 6 assays evaluated in this study reflect a wide range of performance characteristics. The Integra 800 showed the poorest predicted performance. Using a TE_a specification of 6%, its bias and imprecision were associated with a patient-weighted σ value of only 0.36. If 100 patient samples were tested between QC events, 39.35% of results would be unreliable while in-control, and in the worst case, as many as 71 unreliable patient results (out of 100 results total) could be expected when an out-of-control event occurs (Table 2). In contrast, the Capillarys 2 Flex Piercing assay had imprecision and bias profiles that gave the highest patient-weighted σ at each TE_a tested. Only 0.02% of results are predicted to be unreliable while in-control, and <1 unreliable patient result (out of 100 results total) would be expected even for the worst case out-of-control condition (Table 2). As the TE_a specification is decreased, the patient-weighted σ metrics decrease, with a corresponding increase in the risk of reporting unreliable patient results.

Discussion

QC plans are commonly generated to monitor stability of laboratory instruments and methods. More recently, improvements in instrumentation and assay technology have led to a transition from using QC to monitor instrument failure to using QC to minimize risk and/or mitigate residual risk of reporting an inaccurate result. Risk management strategies, popularized years ago in industry *(7)*, have recently been touted as an alternative to a "one-size-fits-all" QC plan that is common in many laboratories *(8, 9)*.

Table 2. Risk analysis for Hb A_{1c} assays at 3 different TE_a limits.

	Patient-weighted sigma			In-control % unreliable			Max E(N_{uf}) out of 100 events		
Assay platform	7% TE_a	6% TE_a	5% TE_a	7% TE_a	6% TE_a	5% TE_a	7% TE_a	6% TE_a	5% TE_a
Variant II	2.30	1.57	0.83	10.03	19.63	32.81	34.27	46.66	51.54
Variant II Turbo	2.67	2.29	1.90	1.23	2.96	6.62	5.94	11.00	18.27
Tosoh G8	2.27	1.43	0.59	1.19	7.80	28.53	13.67	49.92	83.60
Capillarys 2	4.56	3.90	3.25	0.00	0.02	0.19	0.12	0.60	2.58
Integra 800	0.85	0.36	−0.12	25.51	39.35	55.64	60.11	71.48	74.00
DCA Vantage-lot 1	2.84	2.36	1.88	0.69	1.82	4.50	8.85	18.92	36.28
DCA Vantage-lot 2	3.36	2.84	2.32	0.05	0.29	1.32	2.06	6.30	16.55

The goal of this study was to investigate the impact of differences in imprecision and bias for Hb A_{1c} assays on the ability to meet quality goals in terms of patient risk when using currently available NGSP-certified assays. The improvements in Hb A_{1c} instrumentation performance and standardization to the NGSP prompted CAP to reduce the recommended TE_a from 7% to 6% in 2013, with the suggestion that these limits may be further reduced in the future. Thus, a secondary interest of this study was the impact of varying TE_a. A fixed QC rule (1:2s rule with 2 levels of QC) and frequency of QC evaluations (every 100 Hb A_{1c} examinations) was assumed for each Hb A_{1c} assay tested to ensure that differences in risk were a function of only TE_a, %CV, and %Bias. This is not meant to imply an endorsement of a particular QC rule or frequency at which QC should be run.

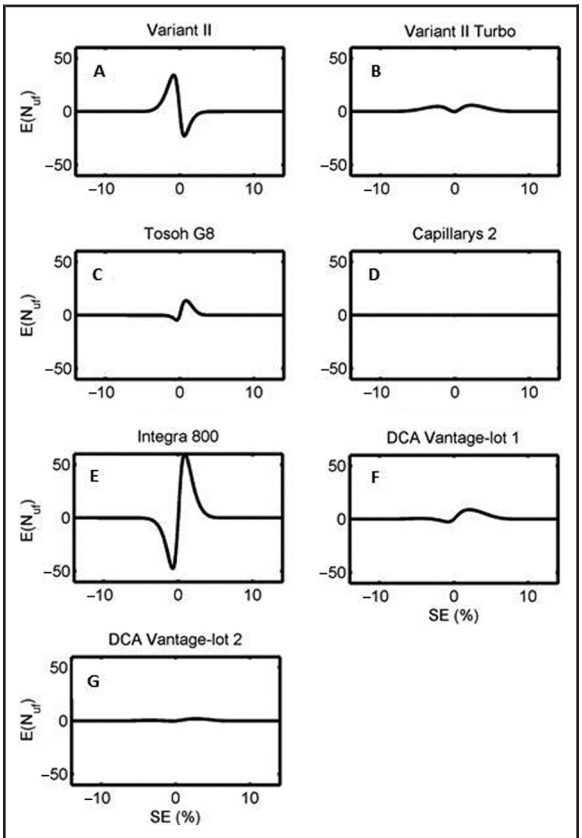

Fig. 3. The predicted change in the expected number of unreliable patient results reported prior to an accepted QC event, E(N_{uf}), represented on the *y* axis computed over a range of possible out-of-control conditions [systematic error (SE)] shown on the *x* axis. TE_a was specified as ±6%.

The overall imprecision and bias are important for interpretation of Hb A_{1c} results. Currently, an intralaboratory imprecision (% CV) of <2% is recommended *(10)*. All assays except the Bio-Rad Variant II Turbo (low QC = 2.97% CV), Roche Integra 800 (low QC = 2.4% CV), and Siemens DCA Vantage-lot 1 (high QC = 2.65% CV) met this goal at the 2 clinically relevant Hb A_{1c} levels (low and high) tested. A %Bias of ≥±3 accounts for one-half the allowable limit (±6%) afforded by the CAP Hb A_{1c} proficiency testing program. Four assays out of 6 in this study displayed a bias of >3%, indicating a potential larger role for bias in the overall assessment of Hb A_{1c} method performance. In this study, bias was sometimes greater at lower or higher Hb A_{1c} concentrations (Fig. 2).

Assessment of bias or poor calibration in a timely fashion is sometimes difficult without instituting additional checks into routine practice. In addition, targets of internal QC may be unreliable, and comparisons that include large numbers of NGSP target value–assigned samples in routine laboratory operations are not easily accomplished. One suggestion is that calibration verification samples (if available through the manufacturer or NGSP) be run alongside QC material after calibration and/or at some predefined time interval of routine testing. Additional analysis of smaller sample sizes of NGSP target value–assigned specimens may

also be performed and compared within-laboratory or across-laboratories. Although each of these suggestions appears valuable, their cost and acceptability would have to be evaluated by each laboratory.

We used both precision and bias to generate several outcome metrics, including patient-weighted σ metrics, in-control percentage unreliable patient results, and maximum expected number of unreliable patient results due to an out-of-control condition [Max $E(N_{uf})$]. Sigma values are directly related to the predicted probability of producing unreliable patient results during stable operation, which may be expressed in terms of defects per million opportunities (DPMO) *(7)*. A 6-σ method is associated with 3.4 DPMO and is classified as "world class quality." Patient-weighted σ values are a weighted average of σ values across a spectrum of patient results. We used these because they are a more accurate reflection of σ metrics for a derived patient population *(11)*. Our results demonstrate that there is not only substantial variability in the metrics across platforms as a result of differing analytical performance, but also a sizeable impact from adjusting the TE_a specification.

At the time of this study, all but 1 Hb A_{1c} assay (Capillarys 2 Flex Piercing) had proficiency testing data available through the CAP, and those assays that were in use for clinical practice at the 4 academic medical centers at the time of this study all successfully passed their CAP GH2 surveys, indicating the observed bias did not affect their ability to pass proficiency testing. However, note the existence of negative $E(N_{uf})$ values for some of the out-of-control conditions shown in Fig. 3. These reflect situations in which the magnitude and direction of the out-of-control condition negates the inherent bias in an assay, thereby reducing the likelihood of measurement errors exceeding TE_a compared to the in-control state.

Interestingly, the 2 different calibrator lots (lot 1 and lot 2) tested for the DCA Vantage point-of-care assay performed better and demonstrated higher patient-weighted σ values than some of the clinical laboratory Hb A_{1c} assays tested. Although the analytical performance of this method has already been shown to be superior to other POC methods *(12)*, this is the first report demonstrating that analytical performance of the DCA assay alone can lead to a reduction in the maximum expected number of unreliable patient results from an out-of-control condition. Although this method performance superiority was evident for both calibrator lots, one caveat to this interpretation is that our assessment did not account for any potential pre-analytical collection variables at the point-of-care level that may have affected the potential quality of point-of-care Hb A_{1c} results.

Westgard QC rules have been available for many years as a guide for monitoring QC. However, laboratories have for the most part failed to optimize their QC procedures *(7)*, opting instead for a one-size-fits-all 2-SD rule. It is important to note that large differences in analytical performance characteristics were observed based on the total volume of patient samples analyzed between QC events, indicating that a one-size-fits-all QC plan is not appropriate. Except for the Capillarys 2 Flex Piercing, the patient-weighted σ metric for all platforms investigated at a TE_a of 6% was <3, indicating that maximum QC (3 levels, 3 times per day) should be performed to achieve the necessary error detection. For this study, the set amount of patient testing between QC events was 100. $E(N_{uf})$ is proportional to the number of patient samples tested between QC events. If the number of patients tested between QC events changes, the risk of reporting unreliable results may also change. For example, if the number of Hb A_{1c} patient samples tested between QC events was set at 10 instead of 100, the max $E(N_{uf})$ when using the Roche Integra 800 would be <1 out of 100 (at a TE_a of 7%). Conversely, if you double the number of patient samples between QC events, $E(N_{uf})$ will also double. Exhaustive QC events are often cost prohibitive and can frequently result in a more complex mechanism of patient testing. The investigation of assay performance and potential approaches for its improvement may yield a better overall solution. A laboratory can alternatively implement different QC designs to reduce cost *(13)*.

Our results show how analytical characteristics can be used to assess the risk of reporting an unreliable result. The model incorporates the 3 types of characteristics that contribute to patient risk: (*a*) the performance characteristics of the testing method (imprecision and bias), (*b*) the QC strategy used by the laboratory [number of QC samples, QC rule(s), and QC frequency], and (*c*) the quality required of the analyte (TE_a). Each of these characteristics must be assessed by the laboratory to claim results are fit for their intended use. Of these, bias and TE_a are characteristics laboratories likely may have the most difficulty with. However, evaluation can be performed first assuming zero bias and again at an alternative bias derived from peer group comparisons to assess the difference in patient risk implications. Likewise, if it is unclear what TE_a to use, different quality specifications can be tested before implementation to assess the impact on patient risk.

This study demonstrates the importance of aligning the risk of reporting unreliable Hb A_{1c} results with the instrumentation, assay, and patient volumes of the individual laboratory. Although currently available NGSP-certified Hb A_{1c} assays can yield satisfactory results with external quality assessment programs, such as proficiency testing, it is important that the limita-

tions of these assays are well understood by laboratory medicine professionals.

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