Opinion Paper

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Can current analytical quality performance of UK clinical laboratories support evidence-based guidelines for diabetes and ischaemic heart disease? – A pilot study and a proposal

Abstract

Background: The implementation of national and international guidelines is beginning to standardise clinical practice. However, since many guidelines have decision limits based on laboratory tests, there is an urgent need to ensure that different laboratories obtain the same analytical result on any sample. A scientifically-based quality control process will be a pre-requisite to provide this level of analytical performance which will support evidence-based guidelines and movement of patients across boundaries while maintaining standardised outcomes. We discuss the finding of a pilot study performed to assess UK clinical laboratories readiness to work to a higher grade quality specifications such as biological variation-based quality specifications.

Methods: Internal quality control (IQC) data for HbA_{1c}, glucose, creatinine, cholesterol and high density lipoprotein (HDL)-cholesterol were collected from UK laboratories participating in the Bio-Rad Unity QC programme. The median of the coefficient of variation (CV%) of the participating laboratories was evaluated against the CV% based on biological variation.

Results: Except creatinine, the other four analytes had a variable degree of compliance with the biological variation-based quality specifications. More than 75% of the laboratories met the biological variation-based quality specifications for glucose, cholesterol and HDL-cholesterol. Slightly over 50% of the laboratories met the analytical goal for HBA_{1c}. Only one analyte (cholesterol) had a performance achieving the higher quality specifications consistent with 5σ.

Conclusions: Our data from IQC do not consistently demonstrate that the results from clinical laboratories meet evidence-based quality specifications. Therefore, we propose that a graded scale of quality specifications may be needed at this stage.

Keywords: analytical performance; internal quality control; σ metric.

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Introduction

Many international guidelines include laboratory test values with which diseases are diagnosed or clinical management decisions are made. In general these guidelines have been based on one or more studies for which laboratory support has been provided by one laboratory using a single analytical method, sometimes operating under batch conditions. When these guidelines are translated into clinical practice, patients' blood samples are judged against these target values, yet they are measured with a plethora of methods and platforms using different batches of reagents over long periods of time. All these methods are prone to within- and between-batch variations as well as between-laboratory variation and between-method bias. Laboratory specialists are aware of the between-laboratory variation and -method bias through external quality assurance (EQA) reports, but these only tell half the story. Indeed, the total analytical imprecision may be much more problematic and lead to considerable patient safety issues that are as equally important as prescribing errors.

In the UK, an initiative to set minimum analytical standards has recently started under the auspices of the Royal College of Pathologists (Minimum Analytical Performance Standards [MAPS]). MAPS group has released its first document in a draft form. This document set the minimal performance standards for five analytes; these are HbA_{1c}, glucose, creatinine, cholesterol and HDL-cholesterol. The group followed the Stockholm meeting recommendation and has selected analytical standards based on biological variation, precisely on the desirable level for both precision and bias [1].

In this paper we pose the question, are UK laboratories at this point in time capable of achieving the analytical standards limits proposed by MAPS?

The majority of the UK clinical laboratories services are operating within (National Health Service) NHS hospitals. The Department of Health in England has recommended that clinical laboratories should register with an approved accreditation body. Although accreditation is voluntary, the majority of the UK clinical laboratories and EQA schemes are enrolled for accreditation with Clinical Pathology Accreditation (CPA) [2]. CPA is the national accreditation body in the UK and recognised by the government to assess and declare competence against internationally recognised standards. The accreditation criteria established by CPA standards demand that clinical laboratories have to implement a comprehensive quality management system. The main two components of this quality system is that clinical laboratories should be running an internal quality system and participate in an approved external quality assurance scheme [3].

The principles underlying internal quality monitoring and management in UK clinical laboratories have remained unchanged for decades despite the emergence of globally accepted quality specifications, quality planning and management science and lately the introduction of the concept of 6σ as a tool to measure quality in medical laboratories [4]. Furthermore, UK EQA schemes base their analysis mainly on the state-of-the-art as an analytical goal and comparisons with peer groups using the same analytical platform. The use of commutable material for EQA sample is not a common practice within the UK EQA schemes.

In an attempt to assess the readiness of UK clinical laboratories to meet the proposed MAPS limits and higher grade and probably more demanding but clinically relevant quality specifications such as 6σ, the authors performed two pilot studies to collect data for analytical imprecision and bias from the UK clinical laboratories. However, this paper focuses on the analytical imprecision only.

Pilot study

Analytical imprecision data for five analytes – HbA_{1c}, glucose, creatinine, cholesterol and HDL-cholesterol – were collected from UK laboratories (n=16) that routinely report their internal quality control (IQC) evaluations into the Bio-Rad Unity database (Bio-Rad Laboratories Ltd., Hemel Hempstead, UK). The authors are unaware of the identity of the laboratories included in the study. However, the laboratories were a mix of large networked laboratories, University Hospital laboratories (six out of 16 laboratories) and small district hospital laboratories. Except HbA_{1c}, all other analytes included in this study are measured 24/7.

Monthly means for three QC levels 1, 2 and 3, the number of IQC results and QC lot numbers were collected over a period of 6 months from January to June 2010. It is a customary practice within the clinical laboratories to delete any erroneous IQC data points that does not lead to a recalibration event before closing the statistic for a working day or a reagent lot (e.g., the most common erroneous IQC is switching the place of low QC with high QC on the analyser). Therefore, it has been assumed that all QC data points submitted by participating laboratories to Bio-Rad Unity programme reflect true QC practice, hence no further exclusion criteria has been applied. A 6-month mean, standard deviation (SD) and coefficient of variation (CV) were computed for each laboratory. For statistical reasons, all laboratories with IQC data of <300 points were excluded. The total number of participating laboratories for each analyte is presented in Table 1.

Inter-laboratory statistics were computed by combining the results from laboratories using similar test methods on matching control lot numbers – converting results to a standard unit for comparison. The CV was computed for each individual laboratory and for each analyte. For all the laboratories and for each analyte the median and range of CV has been calculated. Total error (TE) values for the five analytes were determined by the MAPS group as 6.3%, 7%, 8.2%, 8.5% and 11.1% for HbA_{1c}, glucose, creatinine, cholesterol and HDL-cholesterol, respectively. These TE values were selected from the three-levels model, which is based on biological variation [5]. The MAPS panel had allocated all five analytes included in this study to the desirable level [6]. σ Metric was calculated using (TE-Bias)/CV. The bias value was assumed to be zero to aid the illustration of the impact of imprecision only on analytical performance. Calculations of σ driven CV are $CV=TE/\sigma$ [7].

The total error has been calculated for each analyte at a clinical decision-making concentration, i.e., 48

Table 1 Demographics of laboratory methods including mean of internal quality control near clinical decision values, number of analytical platforms and number of laboratories involved in this study.

Analyte	QC mean and range	NPT	Number of platforms	Number of laboratories
HbA_{1c}	38.8 mmol/mol (36.7–39.5) 5.70% (5.51–5.76)	5812	5	9
Glucose	6.63 mmol/L (6.53–6.97)	14,056	5	12
Creatinine	53.97 µmol/L (42.12–71.32)	19,474	6	14
Cholesterol	6.66 mmol/L (6.53–6.19)	15,329	6	12
HDL cholesterol	0.87 mmol/L (0.7–0.98)	13,953	6	12

NPT, number of collective quality control (QC) data points collected for each test over a period of 6 months.

mmol/mol (6.5% DCCT) for HbA_{1c}, 7 mmol/L for glucose, 5 mmol/L for cholesterol, 1.5 mmol/L for HDL-cholesterol and National Kidney Disease Education Program recommended decision limits for creatinine (88 µmol/L) [8].

Analytical CV (CV_a) of the QC mean value closest to clinical decision-making was selected to represent laboratory performance for each analyte, e.g., for HbA_{1c} QC levels 1, 2 and 3 represent means of 39 (5.7% DCCT), 83 (9.7% DCCT) and 133 (14.3% DCCT) mmol/mol, respectively. The CV% at QC level 1 was selected to represent laboratory performance for imprecision because the QC level 1 mean 39 mmol/mol (5.7% DCCT) is the closest to the selected decision limit, which was defined as 48 mmol/mol (6.5% DCCT). The σ status of each CV was calculated by dividing the TE value determined by its corresponding σ value, e.g., 5σ CV for HbA_{1c} is given as 6.3/5=1.26%, where 6.3% is the TE value proposed by MAPS. Data for 5σ CVs are given in Table 2.

The laboratories used analytical instruments from Abbott (Aeroset and Architect; Abbott Laboratories Ltd., Maidenhead, UK), Beckman Coulter (UniCel DxC Series; Beckman Coulter UK Ltd., London, UK), Roche Modular (Roche Diagnostics Ltd, Burgess Hill, UK) and Siemens (ADVIA and Dimension Series; Siemens Healthcare Diagnostics, Camberley, UK).

Data for IQC for HbA_{1c} was collected from seven analytical platforms. However, two laboratories were excluded due to the small number of data points (<300) the remaining five analytical platforms are: Tosoh G7/G8 Series (Tosoh Bioscience Ltd., Redditch, UK), Bio-Rad VARIANT II, Bio-Rad VARIANT II TURBO, Bio-Rad Variant II Single Cartridge Program and Bio-Rad D-10 (Bio-Rad Laboratories Ltd.), All laboratories used the Jaffe method for creatinine and enzymatic methods for cholesterol, HDL-cholesterol and glucose. HbA_{1c} was measured using chromatographic methodology.

Table 1 lists the total number of platforms for each analyte and number of data points collected for each analyte during the 6-month period of study.

The total number of IQC data point collected over period of 6 months was n=74,622. The median CV_a values for HbA_{1c}, glucose, creatinine, cholesterol and HDL-cholesterol were compared to the allowable CV and 5σ-derived CVs. The reason for specifically selecting 5σ was that 5σ is considered the best performance, beyond which little improvement to quality can be achieved [7].

Table 2 Total error proposed by MAPS, corresponding biological variation (CV%) and σ CV compared to the CV collected from UK laboratories using various analytical platforms.

Analyte	%Total error (MAPS)	Allowable[a] CV%	Median and range of the participated laboratories CV	Estimated % of labs achieved Allowable CV	5σ CV	Estimated % of labs achieved 5σ CV
HbA_{1c}	6.3	2.5	1.90 (1.47–3.86)	>50%	1.26	<25%
	7.0[b]	2.3		>50%	1.40	<25%
Glucose	7.0	2.9	1.79 (1.15–3.70)	>75%	1.40	<25%
Creatinine	8.2	2.7	4.60 (2.01–8.96)	<25%	1.64	0%
Cholesterol	8.5	2.7	1.70 (0.81–2.11)	100%	1.70	50%
HDL- cholesterol	11.1	3.6	3.04 (0.86–5.27)	>75%	2.22	<50%

[a]Desirable CV defined as analytical imprecision <0.5 CV_I. [b]HbA_{1c} National Glycated haemoglobin Standardisation Program defined total error based on clinical need. Total error of 7% is equivalent to 4 mmol/mol or ±0.5% of variation, around HbA_{1c} value of 53 mmol/mol (7% DCCT) [1].

Our data (Table 2) shows that more than 75% of laboratories achieved CV_a identical to the allowable CV for glucose and HDL-cholesterol. More than 50% of the laboratories achieved the allowable CV for HbA_{1c}. However, only 25% of the laboratories had the allowable CV for creatinine, while all the laboratories met the allowable limit for cholesterol. Higher quality specifications of 5σ were met by approximately 50% or less of the laboratories for cholesterol and HDL-cholesterol, respectively. Performance of 5σ CV for HbA_{1c}, glucose and creatinine were met by a significantly smaller number of the laboratories.

Our data shows that the majority of the participating laboratories achieved the analytical performance recommended by MAPS for three of the five analytes we included in the study: glucose, cholesterol and HDL-cholesterol. Only cholesterol, however, had CV_a that met the higher quality requirements of 5σ.

The specification of 6σ offers distinct methodology for quantifying and specifying requirements for quality. One role of 6σ which is specific for clinical laboratory is to estimate the likeliness of an analytical process to go beyond defined limits. Performances consistent with 6σ would mean a very stable analytical process that requires only two QCs per run and would be adequately controlled by 3SD control limits. In contrast, 3σ represents an error rate that requires stringent quality control management, since it is highly likely to go out of control, and therefore the laboratories cannot ensure that the defined quality limits are met.

σ Performance for the median CV% for the participant laboratories for the five analytes was 3.3σ for HbA_{1c}, 3.9σ for glucose, 2σ for creatinine, 5σ for cholesterol and 3.8σ for HDL-cholesterol. For example, in the case of HbA_{1c} (TE of 6.3, and the median CV% for analytical variation of the participant laboratories is consistent with a CV% of 1.86%), the performance is consistent with 3.3σ. This performance can ensure only that 97.73% of patients' HbA_{1c} results are meeting the TE of 6.3%. The remaining 2.27% of HbA_{1c} results (equivalent to 22,750 per million results) are exceeding the stated limits. This means that 22,750 patients are at risk of receiving a wrong clinical decision, especially if their HbA_{1c} results were close to the clinical decision limit.

While cholesterol TE has been defined by MAPS as 8.5%, the median CV% of participant laboratories is 1.78%. This performance is consistent with 5σ, hence enabling laboratories to ensure that 99.9767% have patient results that are within the defined limits, so that for 99.9767% there is the possibility of a correct clinical decision being reached.

Evidence from our data shows that analytical quality remains a major issue, and data from IQC do not consistently demonstrate that the results from clinical laboratories meet evidence-based quality specifications. There are two possible reasons for the lack of agreement between the *proposed* limits and the *routinely achieved* analytical variation by laboratories. First, currently used technology is inherently insufficiently robust to allow the achievement of a narrow analytical variation regardless of the effort to control the analytical process (i.e., creatinine Jaffe method). Second, there is sub-optimal control over the IQC process and a lack of defined limits.

However, it is not possible to relate the poor performance to the technology with certainty unless we have a robust and scientifically-based quality monitoring system. The lack of use of a proven commutable EQA sample for the assessment of bias and non-scientific base internal quality process, neither clinical laboratories nor EQA schemes are reflecting on the true technical capabilities of available analytical systems in routine use. A recent study in a UK large network of laboratories showed that the use of an evidence-based scientific approach (involving the use of quality specifications relevant to clinical need and 6σ methodology) to monitor and control variation from current technology was capable of achieving analytical performance of ≥5σ for 70% of methods even when higher-grade quality limits were used [9, 10].

The authors are aware of that the major limitation of this study was the small number of participating laboratories. Therefore, it was not possible to assess the analytical performance of groups using differing methods. Our study represents a snapshot for UK internal quality performance. A larger study would involve a wider range of methodologies, and a larger number of participating laboratories would more truly represent UK analytical quality performance.

The next step

The clinical laboratory professionals must develop a conscious awareness that quality is inherent in the design of a test system and that the most sensitive quality monitoring system cannot change the performance characteristics once an analytical system has been produced. The clinical laboratory professional can only influence the quality if the analytical system has been influenced at the design stage. However, the clinical laboratories can provide important information about the true performance of the technologies in routine use, but they can only do so by

replacing the traditional IQC and EQA systems with one that is modern and scientifically based.

Table 3 presents a proposal for an improved quality monitoring system that involves all stakeholders. This proposal describes a forward-thinking approach to develop a more collaborative attitude that involves interactive dialogue and a systematic feedback mechanism between medical laboratories' representatives and the diagnostic industry.

There are a few examples from European countries where EQA schemes have led to a successful transformation from traditional to higher-grade quality practice [11–13]. We therefore propose an approach where EQA scheme organisers are placed in the lead for this process. Input from EQA schemes is needed to assess the technical capabilities of different methodologies versus two types of limits: one based on state-of-the-art, and the second based on higher-grade specifications (e.g., biological variation or even clinical need). Figure 1 shows two examples from the Dutch quality assurance scheme (Combi) where the two limits are used concurrently to assess the performance of methods. This approach would help to differentiate those assays that are already delivering the optimal performance from those that need further improvement. The Dutch scheme is considered a category 1 scheme according to Miller et al., applying proven commutable samples across the concentration range of interest, targeted with reference methods and using biological variation-based tolerance limits [14].

The role of the scientific and clinical bodies and committees is three-fold. First, these bodies should lead the way through setting up legislations to support the change in implementing a modern culture of scientifically-based quality practice. Second, they should encourage structured teaching and training to emphasise the new practice of quality. Third, they should define the ultimate quality goal in collaboration with EQA schemes that deliver the clinical need. Those limits would then be shared with the diagnostic industry to help focus the development work on those methods that require attention. Meanwhile a

Table 3 Proposal outlining the responsibilities and interaction between all quality improvement programme stakeholders.

EQA schemes organisers: leader of the change	– Establish EQA sample commutability. – Compare performance to a reference method when possible. – Define dual quality limits: limits based on clinical need and technical capabilities.
Clinical laboratories:	– Impalement evidence base quality planning and management. – Implement quality limits defined by EQAS.
Clinical/Scientific bodies and CPA:	– Recommend the use of quality limits that deliver clinical needs. – Promote the science of modern quality.
Diagnostic industry:	– Focus improvement efforts on methods/technologies identified by above schemes.

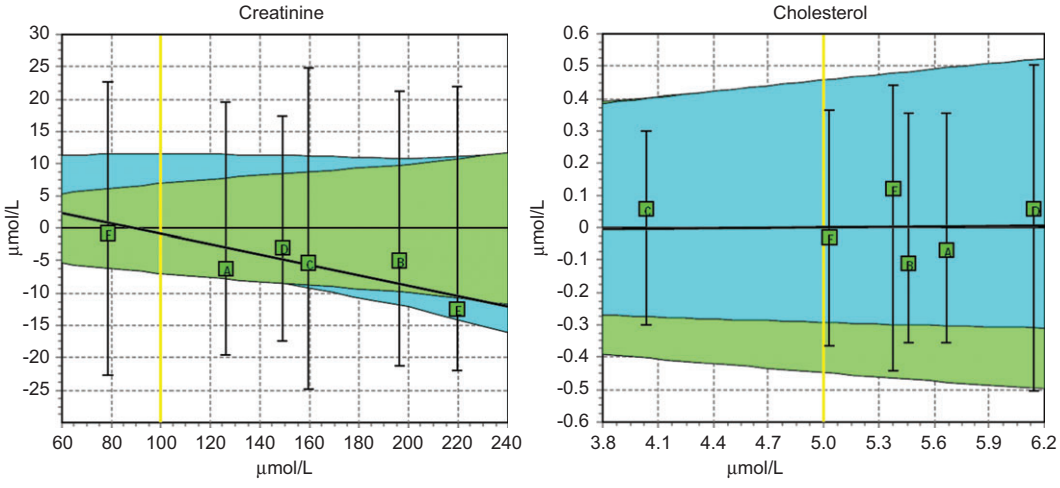

Figure 1 Combi regression graph.
x-Axis=concentration of the consensus mean or, if available, the reference method value. y-axis=bias in relation to the consensus mean or reference value. The blue shaded region gives the state-of-the-art tolerance interval and is based on consensus mean±3×SD. The green shaded region gives the TE_a interval and is based on the biological variation of the respective analyte. The TE_a limits are narrower or wider than the current limits of the state of the art.

wider goal should be adapted initially, with the aim of narrowing the limits until they meet the ultimate goal within the agreed timeframe.

This study shows that comparison of current analytical performance to the recommended performance is necessary to delineate differing approaches to define practical but evidence-based quality specifications. For those analytes whose current analytical performance does not meet the recommended quality specifications, a different approach may be required. Collective and co-operative efforts should be made by the EQA schemes, the diagnostic industry and the MAPS group to set graded quality specifications that are tightened over time and with improvements in technology. However, further and larger scale studies are required to assess the technical capabilities for several method groups and analytical platforms.

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