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Commutability and traceability in EQA programs

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ABSTRACT

Objectives: The concept of commutability of samples has focused laboratories on the importance of traceability. However, the critical role of External Quality Assurance (EQA) in achieving the primary role of traceability (i.e. facilitating comparable patient results in different laboratories) has largely been lost. The aim of this paper is to review the role of EQA in achieving traceable/commutable results.

Design and methods: The role of commutability and traceability in EQA and Internal Quality Control (IQC) are discussed. Examples of commutable EQA samples are given to highlight the problem of assuming EQA material does not behave like patient samples.

Results: We provide the conventional traceability chain (top down) and the role of EQA in a "bottom up" model using conventional EQA samples.

Conclusions: The quest for commutable samples has compromised the value of EQA without an understanding that some EQA materials are commutable for some measurands.

EQA plays a key role in performance improvement, but laboratories need to understand the importance of using a range of values appropriate to the assay to identify areas of quality need. Traceability and EQA using conventional samples are not mutually exclusive concepts.

1. Introduction

In this paper the intertwined concepts of traceability and External Quality Assurance (EQA) will be explored and the current focus on commutability critically discussed. Metrological traceability is defined as the "property of a measurement result whereby the result can be related to a stated reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty" [1]. Establishing traceability requires a reference measurement system consisting of: Measurand definition; stated reference procedure and/or reference material; knowledge of the measurement uncertainties, and unbroken chain of calibrations and value assignments.

Traceability is an essential goal in laboratory medicine. As Vesper and Thienpont state [2] "The goal for traceability is to assure that results used for care of patients are accurate and comparable over time and location. Establishing metrological traceability satisfies the basic requirements of evidence-based laboratory medicine. Thus, it improves patient care, disease control and prevention, and saves money by allowing the pooling of clinical trial data rather than repeating studies". To achieve metrological traceability (Top down), Reference Methods, Reference Materials and Reference Laboratories are required (see Fig. 1C). However, in reality, the goal of traceability for many assays is years away. There are currently about 250 reference materials listed for 141 analytes, 157 reference methods for 80 analytes and 63 reference laboratory services for 32 analytes [3], so there are many measurands for which full traceability is not currently available.

This does not mean that a more limited, but just as useful, form of traceability is not available. EQA provides traceability to a method, method group and/or instrument group (see Fig. 1B). This allows a laboratory to ensure that they are achieving the same result on a given patient sample as other laboratories using the same method/instrument, and for many measurands it is the only form of traceability available.

2. EQA and traceability

The important role that EQA provides in traceability has been largely ignored to date and it is worthwhile recalling the primary purposes of an EQA scheme [4].

- Characterise test bias and imprecision across multiple methods
- Correlate specific method variables with bias and imprecision
- Identify interfering substances and quantify their effects across multiple methods
- Provide clinical laboratories with reliable information for replacing unsatisfactory methods

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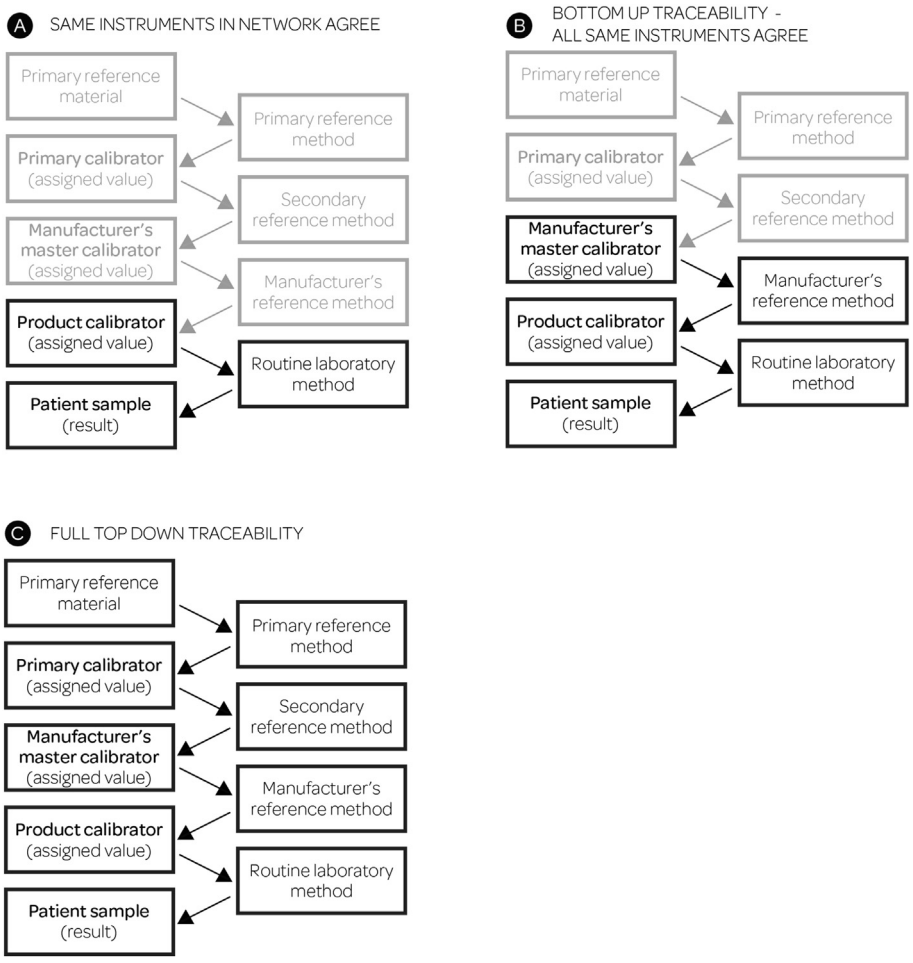

Fig. 1. A, B and C Traceability hierarchies [(20).]

- Identify clinical laboratories that are at risk for poor performance
- Satisfy accreditation and regulatory requirements
- Assessment of method robustness to clinically relevant interference
- Assessment of individual laboratory performance
- Communication with participating laboratories
- Audit of wider aspects of analytical performance and educational activities.

The roles of EQA are compared and contrasted with IQC in Table 1 [5]. IQC should stop the release of results if the inherent bias of the method changes. IQC and EQA are complementary and mutually dependent Quality Improvement activities.

Table 1
A comparison of EQA and IIQC.

Comparison	IQC	EQA
Results	Known	Unknown
Results Available	Immediately	Later
Decision purpose	Release or repeat analysis	Quality Improvement
Frequency	Minimum daily, per batch, per shift	Periodically eg 1 / 4 weeks 2 / 4 weeks 5 × 3 / year
Concentrations[a]	Normal, abnormal	Multiple concentrations, eg 6–8
Assesses	Bias	Accuracy & imprecision
Comparison[a]	Your lab only	Your lab to all labs & other labs using your method

[a] Note the additional information that EQA provides (compared to IQC) in terms of the greater range of concentrations and comparison against other users of the same method.

3. Commutable samples

Commutability is a property of reference materials and is defined as those materials having the same inter-assay relationships to those of clinical samples [6–9]. However, commutability only implies that results for a reference material had the same mathematical relationship between methods that was observed for native clinical samples measured by those methods [10]. The ideal reference material would be commutable across all platforms however non-commutability has been demonstrated in many situations [11] including IQC [12,13] and EQA/Proficiency Testing material [9,14]. Possible causes of non-commutability can be differentiated into the following categories: 1) use of non-human additives (e.g. preservatives, animal proteins) 2) artefacts resulting from the processing of the material (e.g. charcoal stripping, dialysing, freeze/thaw cycles, lyophilisation) 3) pooling of material from multiple serum donors (resulting in the dilution of sample specific effects) and 4) manipulating the levels of constituents to obtain abnormal results (e.g. use of non-human biomarkers, different isoenzymes, varying proportions of bound and free components). However, when high levels of enzymes or hormones are added to produce an abnormal IQC or EQA sample, this situation may not in fact result in a matrix effect, but is often reflective of real patient (abnormal) sample.

Patient samples are, by definition, commutable. However, the criteria for the assessment of non-commutability has recently been questioned [18] and reassessed [21], and while it is still preferred, the application of commutability criteria based on clinical requirements

appears unnecessarily stringent. Miller et al. [19] also reported on discordant LDL and HDL measurements for their diseased vs non-diseased study participants across different methods. They noted six of 8 HDL-C and 5 of 8 LDL-C direct methods met their National Cholesterol Education Program total error goals for non-diseased individuals, but all methods failed to meet the same goals for diseased individuals due to a lack of specificity toward abnormal lipoproteins. Both Miller and Delatour have questioned the criteria used to assess performance in diseased patients, but there are broader issues raised by these papers.

In practice, the EQA sample very often is a compromise between ideal behaviour in accordance with native samples and stability of the material.

4. Top down and bottom up traceability

Ideally, clinical specimens used in a commutability assessment should consist of fresh materials. If not possible (and acknowledging it is often difficult to obtain a large number of fresh clinical specimens in sufficient amounts to cover a broad concentration range), frozen single donations could be used, but in this case, effect of freezing should be evaluated in a preliminary experiment.

Jones has identified a traceability hierarchy which is pertinent to the discussion of commutability [20]. If the purpose of traceability is to assist with interpretation of results, it is also necessary to consider how numerical laboratory results are used for decisions on patient care. All such results are interpreted by comparison to Reference Intervals which should have been derived from the same or other (ideally traceable) equivalent measurements. Commutability can likewise be applied to the conventional traceability chain (see Fig. 1 A, B and C). Fig. 1A is the lowest level of traceability and applies to a network of laboratories using the same instrument and perhaps a model of IQC commutability applies in this situation. Fig. 1B is consistent with traceability to a method/method group/instrument group which is a key role of EQA programs when the full chain is not available. This is reinforced by Miller et al.: “traceability of the measurement procedure's calibration to the highest order reference system is provided by the manufacturer. Consequently, verification that the PT/EQA results meet the manufacturer's specifications indirectly verifies the accuracy of patient results if it is assumed that the manufacturer has correctly calibrated an assay” [8]. Fig. 1C is the accepted full (top down) traceability approach, which can only be assessed using commutable samples.

The use of an artificial sample can still show traceability to a method or method group, and other studies have shown that in some cases PT material is commutable. For example, the RCPAQAP material for 2017 has 29 out of 36 measurands in the General Serum Chemistry (lyophilised) program which could be considered as being commutable when compared to the same measurands in the RCPAQAP (commutable) Liquid Serum Chemistry Program. Specifically, the measurands which were not commutable were Cholesterol, GGT, LDH, Lipase, Triglycerides, Urate and HDL-Cholesterol. So, in fact there are likely to be far fewer issues with non-commutable samples in EQA programs than has been widely suggested. These findings have been replicated in other studies demonstrating that in many cases PT material is commutable [15–17]. These commutable PT/EQA samples are useful in identifying poor selectivity for a measurand across different methods [21].

5. Conclusion

The major role of EQA is to improve laboratory performance, but this cannot be achieved with only a small number of challenges a year, nor can it be achieved with samples that are ‘normal’. The quest for commutable samples has compromised the value of EQA without an understanding that some EQA materials are commutable for some measurands. In an ideal world, all EQA material would be commutable, but this is not an ideal world and quality improvement cannot stop while we wait.

References

[1] International Organization for Standardization, International vocabulary of basic and general terms in metrology (VIM), ISO/IEC Guide 99, 2007 Geneva.
[2] H.W. Vesper, L.M. Thienpont, Traceability in laboratory medicine, Clin. Chem. 55 (6) (2009) 1067–1075.
[3] Bureau Internationale des Poids et Mesures, https://www.bipm.org/jctlm/home.do , Accessed date: 2 January 2018.
[4] M. Plebani, M.C. Sanzari, L. Zardo, Quality control in coagulation testing, Semin. Thromb. Hemost. 34 (2008) 642–646.
[5] International Federation of Clinical Chemistry and Laboratory Medicine, http://www.ifcc.org/ifccfiles/docs/Fundamentals-for-EQA.pdf , Accessed date: 3 January 2018.
[6] W.G. Miller, G.L. Myers, R. Rej, Why commutability matters, Clin. Chem. 52 (2006) 553–554.
[7] W.G. Miller, G.L. Myers, Commutability still matters, Clin. Chem. 59 (9) (2013) 1291–1293.
[8] W.G. Miller, G.R. Jones, G.L. Horowitz, C. Weykamp, Proficiency testing/external quality assessment: current challenges and future directions, Clin. Chem. 57 (2011) 1670–1680.
[9] W.G. Miller, Specimen materials, target values and commutability for external quality assessment (proficiency testing) schemes, Clin. Chim. Acta 327 (2003) 25–37.
[10] Clinical and Laboratory Standards Institute (CLSI), Evaluation of commutability of processed samples; approved guideline. Document EP14-A3, (2014) (Wayne, PA, USA).
[11] I. Zegers, R. Beetham, T. Keller, J. Sheldon, D. Bullock, F. MacKenzie, S. Trapmann, H. Emons, G. Merlini, H. Schimmel, The importance of commutability of reference materials used as calibrators: the example of ceruloplasmin, Clin. Chem. 59 (9) (2013) 1322–1329.
[12] W.G. Miller, A. Erek, T.D. Cunningham, O. Oladipo, M.G. Scott, R.E. Johnson, Commutability limitations influence quality control results with different reagent lots, Clin. Chem. 57 (2011) 76–83.
[13] F. Ceriotti, Prerequisites for use of common reference intervals, Clin. Biochem. Rev. 28 (2007) 15–21.
[14] A. Stavelin, P.H. Petersen, U.O. Sølvik, S. Sandberg, External quality assessment of point-of-care methods: model for combined assessment of method bias and single-participant performance by the use of native patient samples and noncommutable control materials, Clin. Chem. 59 (2) (2013) 363–371.
[15] C.A. Ferrero, A. Carobene, F. Ceriotti, A. Modenese, C. Arcelloni, Behavior of frozen serum pools and lyophilized sera in an external quality-assessment scheme, Clin. Chem. 41 (4) (1995) 575–580.
[16] W.E. Schreiber, D.B. Endres, G.A. McDowell, G.E. Palomaki, R.J. Elin, G.G. Klee, et al., Comparison of fresh frozen serum to proficiency testing material in College of American Pathologists surveys: alpha-fetoprotein, carcinoembryonic antigen, human chorionic gonadotropin, and prostate-specific antigen, Arch. Pathol. Lab. Med. 129 (2005) 331–337.
[17] J.L. Bock, D.B. Endres, R.J. Elin, E. Wang, et al., Comparison of fresh frozen serum to traditional proficiency testing material in a College of American Pathologists survey for ferritin, folate, and vitamin B12, Arch. Pathol. Lab. Med. 129 (3) (2005) 323–327.
[18] V. Delatour, Q. Liu, H.W. Vesper, Commutability assessment of external quality assessment materials with the difference in Bias approach: are acceptance criteria based on medical requirements too strict? Clin. Chem. 62 (12) (2016) 1670–1671.
[19] W.G. Miller, G.L. Myers, I. Sakurabayashi, L.M. Bachmann, S.P. Caudill, P. Dziekonski, S. Edwards, M.M. Kimberly, W.J. Korzun, E.T. Leary, K. Nakajima, M. Nakamura, G. Nilsson, R.D. Shamburek, G.W. Vetrovec, G.R. Warnick, A.T. Remaley, Seven direct methods for measuring HDL and LDL cholesterol compared with ultracentrifugation reference measurement procedures, Clin. Chem. 56 (6) (2010) 977–986.
[20] G.R.D. Jones, Measurement uncertainty for clinical laboratories - a revision of the concept, Clin. Chem. Lab. Med. 54 (8) (2016) 1303–1307.
[21] W.G. Miller, Heinz Schimmel, Robert Rej, et al., IFCC working group recommendations for assessing commutability part 1: general experimental design, Clin. Chem. 64 (3) (2018) 447–454.