Clinical Biochemistry 57 (2018) 3–6

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Review

Measurement uncertainty: Friend or foe?

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ARTICLE INFO

Keywords:
Measurement uncertainty
Reference materials
Analytical performance specifications

ABSTRACT

The definition and enforcement of a reference measurement system, based on the implementation of metrological traceability of patients' results to higher order reference methods and materials, together with a clinically acceptable level of measurement uncertainty, are fundamental requirements to produce accurate and equivalent laboratory results. The uncertainty associated with each step of the traceability chain should be governed to obtain a final combined uncertainty on clinical samples fulfilling the requested performance specifications. It is important that end-users (i.e., clinical laboratory) may know and verify how in vitro diagnostics (IVD) manufacturers have implemented the traceability of their calibrators and estimated the corresponding uncertainty. However, full information about traceability and combined uncertainty of calibrators is currently very difficult to obtain. Laboratory professionals should investigate the need to reduce the uncertainty of the higher order metrological references and/or to increase the precision of commercial measuring systems. Accordingly, the measurement uncertainty should not be considered a parameter to be calculated by clinical laboratories just to fulfil the accreditation standards, but it must become a key quality indicator to describe both the performance of an IVD measuring system and the laboratory itself.

1. Introduction

Today, the concept of measurement uncertainty (MU) in clinical laboratories has definitely achieved a scientific role, witnessed by the continuous increase in the number of papers published on this topic in the last years if compared with early 1990s, when uncertainty was introduced due to the lack of consensus on how to express the quality of measurement results (Fig. 1) [1]. However, in clinical laboratory daily life MU is often interpreted as a 'foe', its calculation being mandatory to comply accreditation requirements, but without any practical value. The aim of this contribution is to show that this opinion is shallow and dictated by ignorance, demonstrating the role of MU as key quality indicator in laboratory medicine. In doing this, we will primarily avoid discussion about the approaches that are useful to estimate MU (i.e., the so-called 'bottom-up' and 'top-down' approaches [2–4]) nor about the MU estimate as a specific requirement for the accreditation of medical laboratories according to ISO 15189:2012 [5].

2. Is MU a foe for clinical laboratories?

In 2015, more than 550 laboratories from over 85 countries around the world participated to the Global Measurement Uncertainty Survey organized by Westgard QC, Inc. [6]. The main results, related to countries other than United States, were that most laboratories (64%) assessed and calculated MU for the performed tests, but the majority of them did not include it in test results and laboratory reports. These outcomes, as interpreted by the survey organizers, were translated as the following 'certainties about MU': one must calculate MU (because this is mandatory for obtaining the accreditation according to ISO 15189:2012), and many laboratories do, but most laboratories do nothing with MU after that.

To address these conclusions, we should first turn the concept of MU upside-down. Although, in the common belief, the word 'uncertainty' relates to the general concept of doubt, MU does not actually imply doubt about the validity of a measurement; on the contrary, knowledge of the uncertainty implies increased confidence in the validity of a measurement result [3]. If I am able to estimate MU it is no longer an uncertainty, but it is now the defined confidence limit within which the result will fall. More importantly, as note 3 of the ISO 15189:2012 standard reports, the knowledge of MU may give to laboratory users the confirmation (or not) that patients' results meet performance specifications (PS) [5].

3. Why MU matters

There is now a global consensus that the definition and implementation of a reference measurement system, based on an unbroken metrological traceability chain linking patients' results to higher

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hiips://doi.org/10.1016/j.clinbiochem.2018.01.025
Received 2 January 2018; Received in revised form 31 January 2018; Accepted 31 January 2018
Available online 02 February 2018

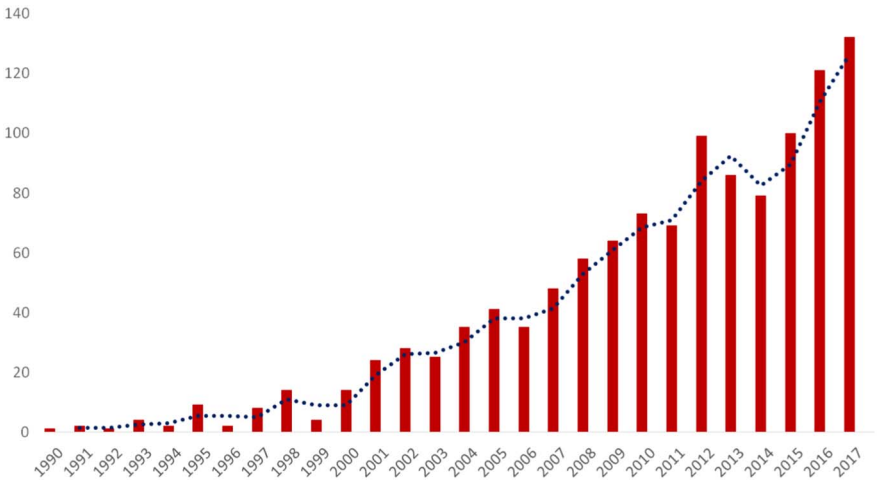

Fig. 1. Number of hits retrieved from PubMed using the key word 'Measurement Uncertainty' [www.ncbi.nlm.nih.gov/pubmed (Accessed December 2017)].

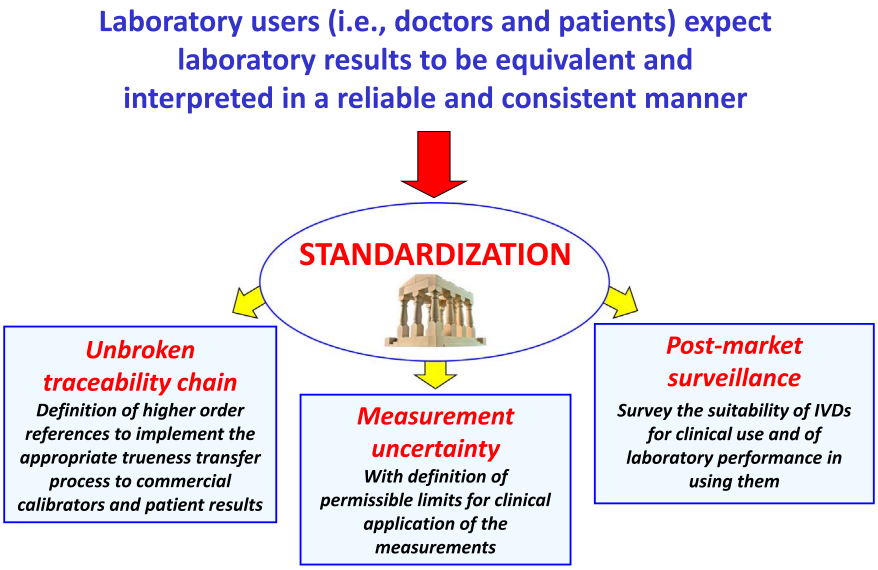

Fig. 2. Scheme describing the main components needed to produce standardized laboratory results.
IVDs, in vitro diagnostics.

order references (materials and methods), together with a clinically acceptable MU, coupled with a proper post-market surveillance, are the fundamental pillars to produce standardized laboratory results (Fig. 2) [7–9]. A MU that fits for purpose must be defined across the entire traceability chain, starting with the providers of reference materials (RM), extending through the in vitro diagnostics (IVD) manufacturers and their processes for assignment of calibrator values, and ultimately to the result reported to clinicians by clinical laboratories [8,10]. Results produced by commercial measuring systems in laboratories on clinical samples have an associated MU that derives both from uncertainties accumulated along the steps of the metrological chain and from random effects in laboratory measurements. This challenges the common conception that the reproducibility of a measurement result per se equals its overall MU.

Considering these premises, each of the three main sources of MU, once estimated, may become useful in defining the suitability of the measuring system and the performance of the laboratory using it (Table 1).

Table 1
Why measurement uncertainty matters in laboratory medicine.

- Uncertainty of higher order references → to define their suitability
- Uncertainty of commercial calibrators → to verify quality of in vitro diagnostics products
- Uncertainty of clinical results → to provide evidence of unpredictable bias and to demonstrate their clinical suitability

3.1. Uncertainty of references matters to define their suitability

The higher order references represent the first contribution to the overall MU budget. Due to error propagation in the calibration hierarchy, it is intuitive that MU of the RM certified value should be markedly lower than the analytical PS for MU on clinical samples [10]. Accordingly, we recommended to turning the approach upside down by focusing first on the established PS of the field measurement results and then to define by intended use the goal for MU of RM (Fig. 3) [10]. Unfortunately, none of the 293 RM entries available on March 2017 in the database of the Joint Committee on Traceability in Laboratory Medicine (JCTLM) have been evaluated from this point of view, even if one could argue that these RM are as good as they can be, i.e., they represent the state of the art, and improvement, when needed, could not be easily feasible [11].

Serum albumin is a representative measurand for which the currently available RM (i.e., ERM-DA470k/IFCC), because of its too large

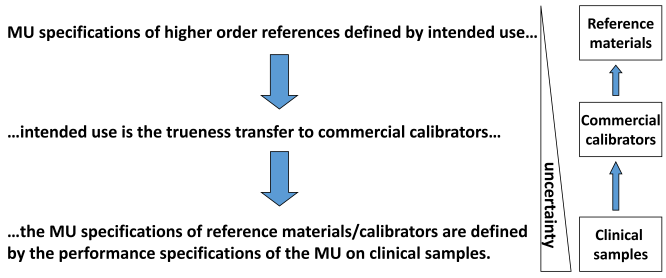

Fig. 3. Defining the suitability of the measurement uncertainty (MU) of higher order references by turning the approach upside down, focusing first on the established performance specifications for MU of clinical samples.

associated MU, is probably not enough to guarantee the performance needed for the clinical usefulness of the test [8–10]. Considering that the MU associated with the ERM-DA470k/IFCC is consuming a too large portion of the total MU budget established to fulfil the analytical goal of albumin measurement, RM providers were therefore asked to concentrate their efforts in reducing RM uncertainties by considering alternative ways of characterization [12].

3.2. Uncertainty of commercial calibrators matters to verify the quality of IVD products

To comply with EU Directive demand, diagnostic manufacturers are required to ensure the metrological traceability of their measuring systems to the available higher order references [7–9]. In doing this, only the association of traceability implementation by IVD manufacturers with the demonstration that the commercial system meets the PS established for its clinical use guarantees to achieve the effectiveness of laboratory measurements. IVD manufacturers should define a calibration hierarchy to assign traceable values to their system calibrators and to fulfil during this process MU limits, which represent a proportion of the MU budget allowed for clinical laboratory results [9,10]. However, this does not guarantee that manufacturers had transferred trueness successfully as currently no normative verification of the manufacturers' statement by a third party is provided [13]. And, even when the traceability of calibration is correctly implemented, this does not mean that MU of calibrators meets clinical needs [10].

We previously highlighted that IVD manufacturers may spend different amounts of the total MU budget in implementing traceability of their measuring systems just by selecting different available traceability chains [9,10,14]. Using the examples of glucose and creatinine, four different types of chains, all metrologically sound [i.e., traceable to the International System of Measurement (SI)] and listed in the JCTLM database, are available to manufacturers for assigning traceable values and corresponding MU to commercial calibrators. The quality of glucose or creatinine measurements in terms of MU may be therefore strongly dependent on the type of traceability chain selected for trueness transferring, sometimes making it difficult (or even impossible) to achieve the suitable limits for MU on clinical samples. Moreover, the creatinine example shows that the same commercial calibrators may display different MU also depending on which analytical method is employed, with alkaline picrate-based assays displaying markedly higher calibrator MU than enzymatic assays [10]. As the traceability implementation is unable to correct for analytical non-selectivity issues [15], the manufacturers' approach trying to mitigate this problem by introduction of some negative offsets inevitably leads to higher MU of commercial calibrators when used for alkaline picrate methods. But even when the commercial measuring system in their design perfectly fulfil PS for combined MU of serum creatinine measurements on clinical samples, an inadequacy of the manufacturer's calibrator value-assignment protocol may markedly impair the quality of laboratory measurements [16].

Lacking external verification of the manufacturers' statements in terms of traceability and calibrator MU, it is up to our profession to improve the post-market surveillance of IVD medical devices through the retrieving of the correct information about IVD metrological traceability and MU and a careful inspection of characteristics of commercial products [9]. A main tasks of laboratory profession are the definition of the clinically acceptable MU for relevant tests and the knowledge and verification of how IVD manufacturers have implemented the traceability of their calibrators and estimated the corresponding MU [9,10]. Accordingly, the value of combined MU of commercial calibrators and which, if any, acceptability limits were applied in the validation of the measuring systems should be available.

3.3. Assessment of uncertainty of patient results helps to demonstrate their clinical suitability

As discussed above, to allow that diagnostic laboratories provide clinically reliable results fulfilling PS it is necessary that uncertainties accumulated at the levels of RM and IVD manufacturers' calibrators be sufficiently confined. Therefore, through the analysis of MU associated with clinical results, it is possible to demonstrate the clinical suitability of the entire measurement system. Furthermore, as basics to the measurement standardization and traceability is that a possible systematic measurement error, i.e., bias, is appropriately corrected by adjusting the value assigned to the calibrator [17], it is possible, by verifying the alignment of the employed IVD measuring system and by participating in appropriately structured external quality assessment schemes (EQAS), to demonstrate the presence of an unpredictable bias that may significantly affect the clinical use of patient's results [18].

Some years ago, we showed that serum albumin results obtained using the Tina-quant Albumin Gen. 2 immunoturbidimetric assay (Roche Diagnostics) were significantly biased when compared with the higher order RM ERM-DA470k/IFCC, concluding that the performance of this assay was probably not suitable for clinical application of the test [19]. The manufacturer took positively control of the problem and, as recently reported in a study conducted to assess the status of harmonization of serum albumin measurements, the Roche Tina-quant assay gives now values well within the uncertainty of the RM target value [20].

In 2013, by analysing the combined MU of the traceability chain for glycated hemoglobin (HbA_{1c}), we showed the need of improvement in the quality of HbA_{1c} MU [21]. Stimulated by these considerations, Abbott Diagnostics has improved the analytical performance of their enzymatic HbA_{1c} assay, by providing, on one hand, virtually unbiased HbA_{1c} results on patient samples and, on the other hand, an enough low imprecision that significantly contributes to keep the MU within the desirable PS when their measuring system is employed [22].

4. Concluding remarks

MU in laboratory medicine is useful for a number of reasons. Firstly, it gives objective information about the quality of laboratory performance and serves as management tool for clinical laboratories and IVD manufacturers, forcing them to investigate and eventually fix the identified problems. Secondly, the MU information helps those manufacturers that produce superior products and measuring systems to demonstrate the superiority of those products. Finally, the MU estimate permits to identify analytes that need analytical improvement for their clinical use and to induce IVD manufacturers to work for improving the quality of assay performance, when needed, obliging them (and consequently the end users) to abandon assays with demonstrated insufficient quality.

But to estimate MU is not enough! MU is not a finding to be calculated only to fulfil accreditation parameters and then immediately forgotten, like the interpretation of Westgard's survey tries to make us believe [6]. Together with the MU, the laboratory must define the PS to

validate it and, if needed, all attempts must be made to improve on the MU value if PS are not achieved. Overall, MU must become a key quality indicator in clinical laboratories because it can be used to describe both the performance of an IVD measuring system and the laboratory itself. Quoting the Anand's ode, “once we learn how to calculate MU half the battle is won, but only if we ascertain if it affects the interpretation of our results, our job is almost done.” [23].

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