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Review

Measurement uncertainty: Friend or foe?

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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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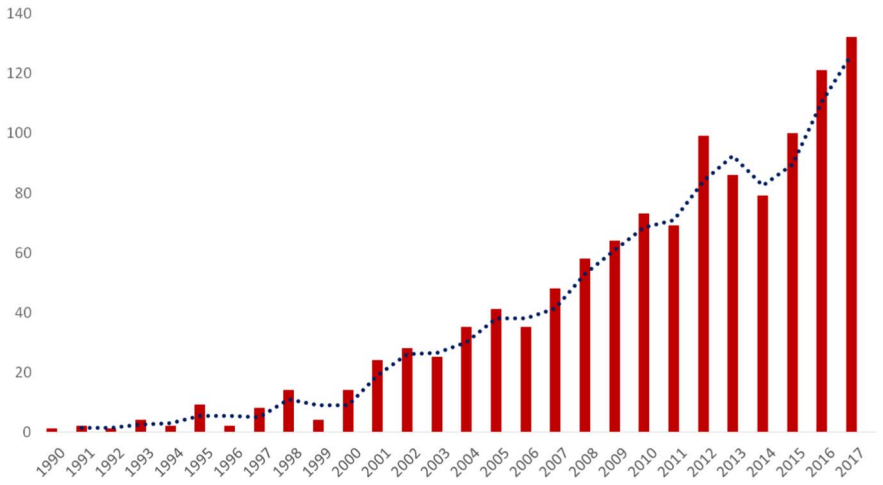

Fig. 1. Number of hits retrieved from PubMed using the key word 'Measurement Uncertainty' [www.ncbi.nlm.nih.gov/pubmed (Accessed December 2017)].

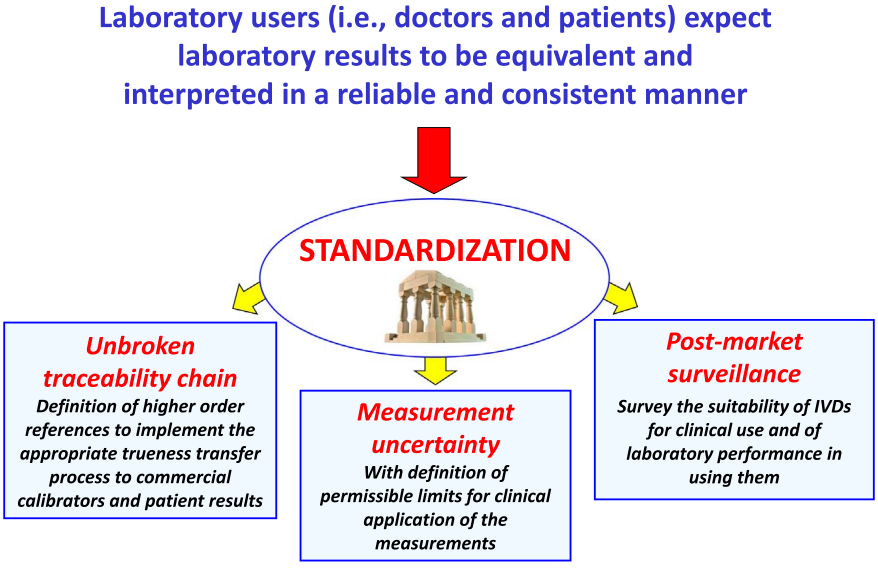

Fig. 2. Scheme describing the main components needed to produce standardized laboratory results.
IVDs, in vitro diagnostics.

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