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Review

What information on measurement uncertainty should be communicated to clinicians, and how?

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ABSTRACT

The communication of laboratory results to physicians and the quality of reports represent fundamental requirements of the post-analytical phase in order to assure the right interpretation and utilization of laboratory information. Accordingly, the International Standard for clinical laboratories accreditation (ISO 15189) requires that "laboratory reports shall include the information necessary for the interpretation of the examination results". Measurement uncertainty (MU) is an inherent property of any quantitative measurement result which express the lack of knowledge of the true value and quantify the uncertainty of a result, incorporating the factors known to influence it. Even if the MU is not included in the report attributes of ISO 15189 and cannot be considered a post-analytical requirement, it is suggested as an information which should facilitate an appropriate interpretation of quantitative results (quantity values). Therefore, MU has two intended uses: for laboratory professionals, it gives information about the quality of measurements, providing evidence of the compliance with analytical performance characteristics; for physicians (and patients) it may help in interpretation of measurement results, especially when values are compared with reference intervals or clinical decision limits, providing objective information. Here we describe the way that MU should be added to laboratory reports in order to facilitate the interpretation of laboratory results and connecting efforts performed within laboratory to provide more accurate and reliable results with a more objective tool for their interpretation by physicians.

1. Introduction

Uncertainty is ubiquitous in medicine, as well emphasized by the Osler's maxim "medicine is a science of uncertainty and an art of probability" [1]. However, uncertainty is often ignored as a subject in medicine, its importance underappreciated and its consequences suppressed [2]. In particular, despite significant advances in diagnostic testing, physicians still face uncertainty in interpretation, particularly in laboratory testing, and an evidence collected in the last few decades clearly demonstrates the high rates of errors in interpreting laboratory results [3]. As highlighted more than 40 years ago, the "brain-to-brain loop" in laboratory testing was conceptualized as a continuum from several steps until a right interpretation and utilization of the laboratory information is achieved to provide improved clinical and economical outcomes [4]. However, the need for systematic feedback to improve the value of laboratory services has been poorly understood and, even more risky, poorly applied in daily laboratory practice, mainly due to the focus on analytical quality while overlooking the importance of extra-analytical phases [5]. This in turn, lead to view the "brain-to-brain loop" as an open-loop system, sometimes called a "non-feedback controlled system", and more recently, it was emphasized the need to close the loop by evaluating the appropriateness of all steps of the total testing process, including clinical and economical outcomes [6].

2. Laboratory reports

The notification of laboratory results to physicians and the quality of reports represent fundamental requirements of the post-analytical phase in order to assure the right interpretation and utilization of laboratory information. Diagnostic uncertainty may derive from incomplete information in laboratory reports, leading to an increased risk of inappropriate interpretation of laboratory data. According to the ISO 15189 (subclause 5.8.1), laboratory "reports shall include the information necessary for the interpretation of the examination results" [7]. This in turn, means that, at least, in addition to "examination results reported in SI units, units traceable to SI units, or other applicable units, biological reference intervals, clinical decision values, or diagrams/nomograms supporting clinical decision values, where applicable", the following report attributes are needed "to effectively

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communicate laboratory results and meet the users' needs":

a) comments on sample quality that might compromise examination results;
b) comments regarding sample suitability with respect to acceptance/rejection criteria;
c) critical results, where applicable;
d) interpretive comments on results, where applicable, which may include the verification of the interpretation of automatically selected and reported results (see 5.8.2) in the final report. [7]

Regarding the measurement uncertainty (MU), in the clause 5.5 "Examination processes", it is included the subclause 5.5.1.4 "Measurement uncertainty of measured quantity values" that cites: "The laboratory shall consider measurement uncertainty when interpreting measured quantity values. Upon request, the laboratory shall make its estimates of measurement uncertainty available to laboratory users" [7]. Therefore, even if the MU is not included in the report attributes and cannot be considered a post-analytical requirement, it is suggested as an information which should facilitate an appropriate interpretation of quantitative results (quantity values). In fact, for many laboratory tests, particularly those with a strong impact in the clinical decision-making, the presence in the report of the simple numerical value does not immediately provide clinicians with an interpretation. For many laboratory tests, the analytical quality (based on established performance specifications) and the biological content are strictly related and interconnected. Therefore, a correct interpretation is possible only knowing the uncertainty of laboratory results, which derives from both analytical (e.g. bias and imprecision) and biological variability, as well as from other possible sources [8]. The knowledge of biological variation, namely the within-subject biological variation (CV_I) of requested measurands, represents a fundamental issue for a correct interpretation of laboratory results, particularly when serial measurements are requested for disease/therapy monitoring. In these situations, the use of the reference change value (RCV) has been advocated as a most appropriate tool for monitoring individuals [9]. When the result is compared with a reference interval (RI) or a decision limit, the need that clinicians should take into account the biological variation is clearly acknowledged in some clinical guidelines, such as for medical care in diabetes [10], and in providing evidence-base recommendations on retesting times [11]. However, the combination of the biological variation with MU in a laboratory report when data are compared to the reference interval (RI) or a decision limit seems a more complex matter.

3. Measurement uncertainty

MU is a inherent property of any quantitative measurement result which expresses the lack of knowledge of the true value of the result and incorporate the factors known to influence it. As variability of laboratory results is unavoidable, "the result of any measurement represents an approximation or estimate of the value of a measurand and thus is complete only when accompanied by a statement of the uncertainty of that estimate" [12]. MU is not only a quantification of the doubt about the measurement result and an essential indicator of the result quality, but essential information without which measurement results should not be meaningfully interpreted. Fig. 1 shows the main goals of MU.

For laboratory professionals, it gives information about the quality of measurements, providing evidence of the compliance with analytical performance characteristics (as expression of imprecision and bias of the analytical system) and monitoring these performances over time. Moreover, it should be used for comparing the metrological quality either of different clinical laboratories or of different analytical methods as well as different platforms/systems.

For physicians (and patients) it helps in interpretation of measurement results, providing objective information.

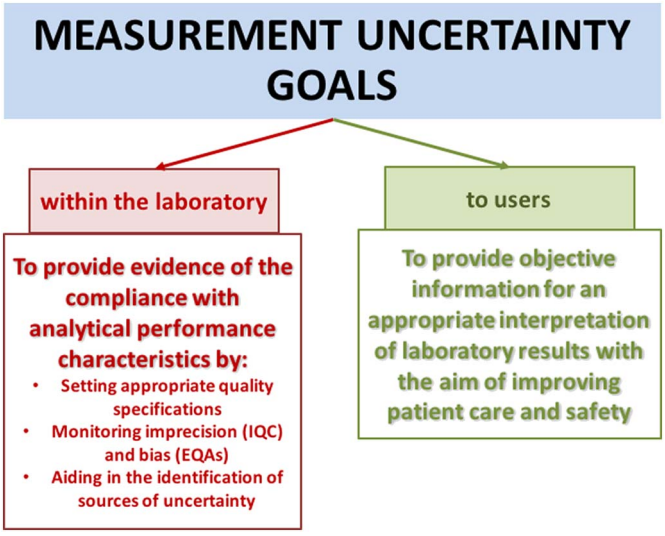

Fig. 1. Summary of the main goals of measurement uncertainty.

For the purpose of quality assurance, in fact, the standard uncertainty and bias should be obligatory and regularly assessed [13] and compared with other from other clinical laboratories as a benchmark and for continuous improvement programs.

For the purpose of allowing a better interpretation of laboratory data, it should be emphasized that a laboratory result per se has no informative value as it has always to be interpreted by comparison. The comparator should be the reference interval (RI), a decision limit and/or a previously obtained result on the same measurand, depending on the fit-for-purpose of test results. RIs are typically statistical confidence limits for the typical spread of results to be found in a healthy reference population. There are some special forms of reference limits for substances not normally found in healthy people such as therapeutic ranges for drug levels, detection limits for toxins (or drugs of abuse), legal limits such as for alcohol. In contrast to *reference intervals*, which are designed to confirm health (*absence* of *any* disease) with high specificity (typically 95%), *clinical decision limits* are more clinically focused and generally aim to confirm the *presence* of *a particular* disease or clinical risk with appropriately high sensitivity [14]. Particularly when a result falls close to the upper or lower limits of the RI, or near to the clinical decision limit, MU can give a clear information and avoid any misclassification that should change the diagnosis and treatment of the patient. When laboratory tests are prevalently used for monitoring a disease (e.g. disease progression and recurrence) or when the individuality index (II) of a measurand is below 0.6 because patients vary much more from one to another than they do individually from day to day ($CV_I < < CV_G$), the comparison of a result with the RI is of scarce usefulness. In these situations, the comparison of the result of the measurand with a previously obtained one, and the reference change value (RCV) represent valuable information. The RCV basically evaluates whether the difference in numerical results is greater than the combined variation (analytical and biological) inherent in the two results. However, recently some important considerations have developed regarding the adoption of RCV then more than two serial results are considered in the calculation [15].

4. Communication of measurement uncertainty to clinician: the past

In 2004, we have formulated a proposal on the communication of MU to clinicians, which should be summarized as follows [16]:

1) "For tests with a uni-modal distribution, the adoption of a decision limit should replace the report the traditional reference value that,