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Original Citation:

Availability:

This version is available at: 11577/3269887 since: 2019-07-03T15:16:31Z

Publisher:

Elsevier Inc.

Published version:

DOI: 10.1016/j.clinbiochem.2018.01.017

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Contents lists available at ScienceDirect

Clinical Biochemistry

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

Review

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

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ARTICLE INFO

Keywords:

Measurement uncertainty

Total error

Reference change value

Laboratory results interpretation

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”:

- comments on sample quality that might compromise examination results;
- comments regarding sample suitability with respect to acceptance/rejection criteria;
- critical results, where applicable;
- 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 an 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.

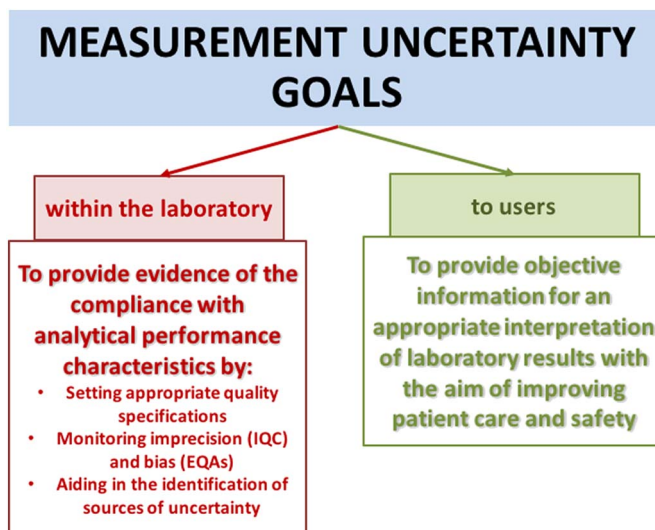


Fig. 1. Summary of the main goals of measurement uncertainty.

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]:

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

in this particular context, can only create confusion. No information on laboratory uncertainty should be added to the report, but the laboratory is responsible for reducing as far as possible imprecision and bias at the decision level. This can be done by creating analytical quality, by selecting methods and diagnostic systems that allow the containment of analytical bias and imprecision, by introducing an internal quality control process specifically designed for monitoring the compliance to quality specifications, and by attending a valuable external quality scheme. Finally, a careful control of pre-analytical variables is mandatory, mainly for analytes such as glucose [16].

- 2) For tests with bi-modal distributions, in addition to traditional reference values, some flags can be added to help clinicians interpret laboratory data. In particular, some flags can indicate data higher or lower than the upper and the lower reference limits, respectively, and likely to be of clinical importance on the basis of analytical and biological variation. Other flags can indicate highly significant changes in serial results, in particular in comparing the present finding with the previous one on the basis of the reference change value [17].
- 3) For tests used in patients monitoring and in evaluating the response to therapy (serial measurements), the reference change value or the most effective threshold of the difference between two consecutive results should be indicated, as recently described for biochemical markers of bone turnover [18–19].
- 4) For tests/test batteries that require interpretive comments, these should be added to the report as well as discussed in multi-disciplinary meetings and interpretive rounds to spread the knowledge on a more objective evaluation of laboratory data”.

Thereafter, we translated the proposal into clinical practice by adding to laboratory reports:

- a) the TE obtained in our laboratory according to the imprecision (data from the internal quality control (IQC) at a concentration near to the decision level) and bias (data from the external quality assurance schemes), as shown in Fig. 2;
- b) the RCV for measurands primarily used in patient monitoring (e.g. tumor and bone markers), based on the imprecision and the biological variation (data from the Westgard database), as shown in Fig. 3.

After an initial concern by some physicians, particularly related to the term “total error” which was interpreted in a negative sense, most users expressed satisfaction for this additional information, particularly regarding the RCV. A huge interest was expressed by students attending the medical degree and post-graduated courses, namely after a series of teaching and educational initiatives on the concept of biological variation, quality specifications and related performance characteristics.

5. Communication of measurement uncertainty to clinician: a new proposal

The debate on the methods for quantifying the quality of laboratory performances, and in particular advantages and disadvantages of the TE theory and the related calculation of allowable TE (ATE), in comparison to the MU is still open with many papers already published [20] and we do not like to further discuss this point. However, answering to the question “when and how” should we have to communicate MU to physicians, we have recently described three different scenarios to add MU in laboratory reports. The different scenarios apply to the type of information usually included in laboratory reports in order to facilitate the interpretation of results, that are: a) the measurand RI, b) diagnostic cut-offs and decision limits, and, finally, c) the RCV [21].

- a) When the test result is compared with the RI, there are three options to include MU in the report, as shown in Fig. 4 MU should be added to the analytical result as a number, as a percentage (%), or as the “confidence interval” with a defined confidence level (e.g. 95%) calculated for the measured value on the basis of the laboratory-specific imprecision; this means that a given result has a probability of 95% of being included in that interval. The most appropriate option seems to be the last one, as the physician has not to calculate the “confidence interval” which is directly provided in the report. This in turn requires a sophisticated Laboratory Information System (LIS) able to calculate for the single measurand the interval of confidence based on the analytical imprecision at the specific concentration level of the measurand, when appropriated [22].
- b) Where a test result is compared with a clinical decision point (e.g. cut-off, decision limit and/or critical value), the MU calculation should include not only the imprecision but also the bias and the uncertainty bias. For example, this should be applied to some measurands such as glucose, HbA1c and cardiac troponin [21].
- c) Finally, when test results are primarily used for monitoring disease and/or therapy, the MU estimation seems of poor clinical value, being the RCV the most appropriate information.

Notably, in all previously reported scenarios, laboratory reports should include the information regarding the confidence levels used to calculate expanded MU (e.g. 95% confidence in case of using a coverage factor $k = 2$).

6. Analytical and total quality

While the quality of analysis is undoubtedly important, so too is the quality of the final report including its RIs, clinical interpretations and notifications. These contain the information and knowledge from laboratory specialists that should support clinical decision-making. Quality in laboratory medicine has been defined “an unfinished journey” as further efforts should be done for better establishing and

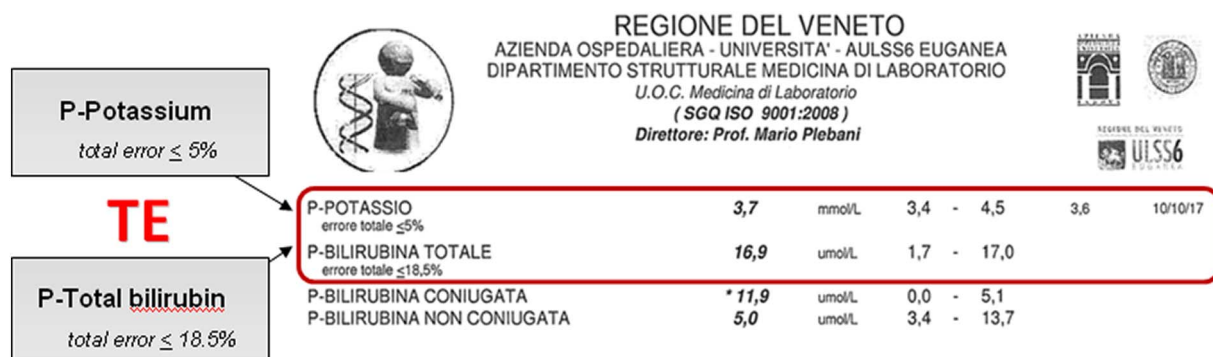


Fig. 2. Example of reporting of Total Error (TE) in medical report.

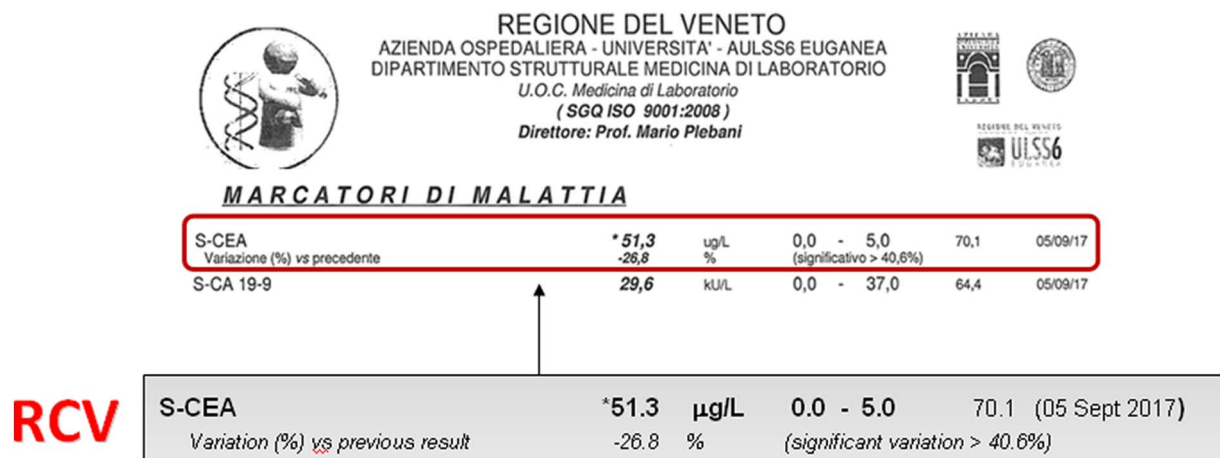


Fig. 3. Example of reporting of reference change value (RCV) in medical report. Significant variation (as %) indicates the RCV.

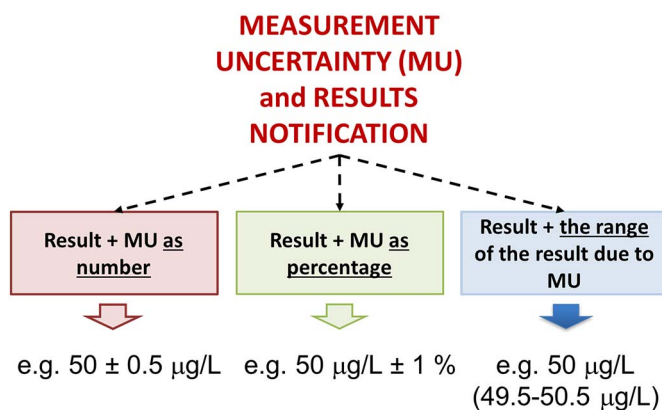


Fig. 4. Possible options to report measurement uncertainty in medical reports.

monitoring analytical characteristics based on the hierarchy of performance specifications [23] and to perform valuable quality control and quality assurance procedures. In addition to a reliable analytical result, however, the evidence collected in the last few years highlights the need for valuable extra-analytical phases, major areas of concerns being inappropriate request of laboratory tests and inappropriate interpretation of laboratory results [24]. Currently, most clinical laboratories offer a repertoire of well over hundreds of tests: some of these are familiar to all physicians, but others are less so. In addition, the improvement in diagnostic systems, and the adoption of more objective quality specifications and more effective quality control rules have allowed clinical laboratories to provide results with a lower degree of analytical uncertainty, consequent to reduced imprecision and bias. The MU in many laboratory tests has been significantly reduced over time, but many clinicians are unaware of these improvements, and this can cause them to under-utilize laboratory information both in diagnosis and in patients management. In addition to the right measurement units, right RIs and/or decision limits, the addition of MU in laboratory reports may allow a more objective interpretation of laboratory data, particularly for quantitative results. However, both for quantitative and qualitative results, the interpretation of laboratory information should always take into consideration the clinical context as well as a wide consensus has been achieved on the evidence that interpretative comments play a fundamental role in improving the interpretation of laboratory data, particularly in some complex diagnostic areas [25]. In addition, the inclusion of the RCV in data used for patient/therapy monitoring is the paradigm of a “personalized” approach to the interpretation of laboratory results, based on the recognition of the importance of the biological variation. The biological variation should be

taken into consideration by clinicians even when laboratory results are compared to RIs or decision limits, particularly when the result is near to the upper/lower limit of the RI or to the decision limit, as suggested in many clinical guidelines.

In conclusion, performance specifications have been defined as “the level of performance required to facilitate clinical decision-making” [17] as they set limits for a test to establish whether it is acceptable for routine use [20]. However, it should be added to this definition, that “they may allow a more objective interpretation of laboratory results” thus connecting efforts done within the laboratory with the due search for total quality and patient safety in laboratory medicine.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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