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Measurement uncertainty in laboratory reports: A tool for improving the interpretation of test results

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ABSTRACT

Background: Measurement uncertainty (MU) estimation has been introduced by ISO 15189 for the accreditation of clinical laboratories. Although MU reporting is not required, its inclusion in medical reports is of potential assistance to physicians in results interpretation.
Methods: MU reporting was evaluated with respect to different test purposes, namely comparison with reference intervals (RI), patient monitoring or comparison with clinical decision limits. Clinical Biochemistry, Hematology, Coagulation and Clinical Immunology measurands were used as examples. Assuming Gaussian RI distribution, the probability of retesting due to MU was determined by simulations. Significant MU variations were compared against the reference change value (RCV) and clinical decision limits.
Results: Three potential scenarios emerged for RI. For 12 measurands, depending on the MU interval, a potential change in results interpretation was found only for Sodium and S-Protein. On considering only the results within RI, simulations confirmed that up to 8.6% of MU intervals encompassed the RI limits, thus potentially leading to retesting. For tests used in patient monitoring, significant MU variations were comparable to those calculated by RCV, with the exception of CEA. For tests results evaluated with respect to clinical decision limits, on including MU, the clinical interpretation may be improved (e.g. for tPSA).
Conclusion: The findings made in the present study, which considers real MU data and hypothetical results obtained for a series of measurands, support the concept that MU may aid the physician's interpretation thus ensuring reliable clinical decision making.

1. Introduction

Medical laboratories should guarantee that laboratory reports contain all the information required for the correct interpretation of tests results. In laboratory medicine the communication of results to physicians, a process included in the post-analytical phase, is of crucial importance, as the interpretation of results is always performed as a comparison. For this purpose, a series of different types of information, usually included in laboratory reports in order to facilitate the interpretation of test results, includes the measurand reference interval (RI), diagnostic cut-offs and decision limits, as well as the reference change value (RCV), where appropriate. However, as stated by the Guide to the expression of Uncertainty in Measurement (JCGM 100:2008) “the result of a measurement is only an approximation or estimate of the value of the measurand and thus is completed only when accompanied by a statement of the uncertainty of that estimate” [1]. In recent years, with the adoption of ISO 15189:2012 for the accreditation of medical laboratories, a requirement made is the estimation of measurement uncertainty (MU) [2]. Nevertheless, the ISO 15189:2012 does not specify methods for estimating MU, and the inclusion or exclusion of MU in laboratory reports is left to the laboratory's discretion, the ISO 15189:2012 only stating that “Upon request, the laboratory shall make its estimates of measurement uncertainty available to laboratory users” [2]. However, the reporting of MU in medical reports does call for considerations to be made and discussed in advance by laboratory medicine experts, in order to guarantee that physicians are provided with the support needed for the correct interpretation of test results. In fact, the reporting of MU may effect a modification of test result interpretation and of clinical reasoning. Moreover, as recently pointed out, when using MU to assist results interpretation (according to ISO 15189:2012), it is also important to choose the most appropriate available model according to the fit-for-purpose of tests [3–5].

In order to ascertain the appropriateness of including the MU in laboratory medical reports, the modality to use, and to focus on how this information could influence the interpretation of test result, the present paper reports on and evaluates a series of different scenarios

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Table 1
Test purposes and uncertainty. Clinically significant components for estimating measurement uncertainty for the different tests purposes.

Test purpose	Examples	Components to include in measurement uncertainty
Primarily for monitoring patients over time	E.g. tumour markers, immunosuppressive drugs	Imprecision only [3,4]
Comparison with reference intervals, either established in the same laboratory or verified in the laboratory using appropriate procedures	E.g. hormones	Imprecision only [3]
Usually compared with a clinical decision point	E.g. glucose, ions	Imprecision, bias and bias uncertainty [3]

regarding the role of MU in test results interpretation, when the attention is focused on RIs, clinical decision points and RCV, respectively, as shown in Table 1. This study requires skills both on essentials and advanced statistical concepts, such as probability distributions, mean and standard deviation, percentiles and the Monte Carlo simulations, and methods for understanding and implementing the proposed approach, but in another paper, a proposal for "what information on measurement uncertainty should be communicated to clinicians, and how" is available as guidance as to how the outcome of this type of study are applicable to clinical laboratories [6].

2. Materials and methods

Two assumptions regarding RI were made in this study: a) the RI distributions are assumed to be Gaussian, b) RI, established by either the laboratory or the manufacturer, are carefully verified by the laboratory. In this context, the total variance of the distribution of reference values consists of: biological (intra-individual, SD_I^2, and inter-individual, SD_G^2, variance) and analytical (SD_A^2) variation and for each individual, both the distribution values around the personal homeostatic set-points, with variance SD_I^2 and the distribution homeostatic set-points of the reference population, with variance SD_G^2, can been considered normal [7–9]. Based on these considerations, and given a measurand, the variance attributable to the distribution of the reference values (SD_T^2), can be calculated by $SD_T^2 = SD_A^2 + SD_I^2 + SD_G^2$, and SD_T^2 can be derived by using RI with the following formula $SD_T^2 = (URL - LRL)/3.92$, where URL and LRL are the upper and the lower RI limits, respectively, and 3.92 derived from the z factor 1.96 multiplied by 2, for a RI covering the 95% interval of the reference values [10,11]. The reference population mean can be derived by mean = (URL + LRL)/2. Therefore, by assuming a) and b), a test result between mean $\pm$ $2 * SD_T$ is within its RI [10]. Imprecision was estimated by using the long-term IQC data (of the latest 6 months), while the expanded MU was estimated by applying the Nordtest approach, with further detailed information available in a previous publication [5,12]. Briefly, MU were estimated by including imprecision or a combination of imprecision, bias and bias uncertainty, depending on the fit-for-purpose of test results (Table 1). The weighted average of IQCs variance were used as imprecision, while bias and bias uncertainty were estimated by External Quality Assessment schemes (EQAs) [5]. The approach used was flexible and feasible, based on the data available for each measurement procedure. Measurement bias was estimated using commutable EQA materials where target values were assigned using high order reference materials and/or reference measurement procedures. If such materials were not available, the consensus value related to the specific diagnostic system was used [5].

The Index of Individuality (II) was calculated using the formula $(CV_A^2 + CV_I^2)^{1/2}/CV_G$ from Petersen et al. [13].

Monte Carlo analyses were performed by simulating random generated normal distribution of n = 200 values. For each measurand considered in the simulation, normally distributed data were generated by using the mean and the total standard deviation, calculated using the above formulas. Finally, for any test result included in the interval between URL and LRL, a total of 1000 iterations were performed to calculate the probability that the corresponding MU interval would include the upper or lower RI (p_{inc}). The Monte Carlo standard error estimate of p_{inc} was also calculated using the standard deviation of p_{inc}. For the same measurands used in the Monte Carlo simulations, data from the Laboratory Information System (LIS) of the Department of Laboratory Medicine of the University-Hospital of Padova where obtained, in a time period of 2 months (from November to December 2017). For the following measurands ALT, Sodium, Potassium, Urea, Cholesterol, Iron, Hemoglobin and MCV results from outpatients (non-hospitalized subjects referring directly to the laboratory for blood testing) were included; for Lactate, S-Protein, C-Protein and D-Dimer, also the inpatients (hospitalized patients) were included, due to the limited number of determinations for these measurands in the group of the outpatients. For test results included in the interval between URL and LRL, the real percentage of MU intervals that would include the upper or lower RI were estimated.

Bidirectional, 95% probability reference change value (RCV) was calculated using the formula $RCV = 2^{1/2} * Z * (CV_A^2 + CV_I^2)^{1/2}$ [14], while the MU critical difference was derived through multiplying the corresponding MU by a factor equal to 2.83, which allows two serial measurements and the two corresponding MU to be taken into account when a test result is used mainly for monitoring patients over time [15].

Data for biological within- and between-subject variations were obtained with the Westgard database on biological variation (https://www.westgard.com/biodatabase1.htm, accessed on May 2017). R for statistical computing v 3.3.1 software, (Statistical Computing, Vienna, Austria) and Microsoft Excel (Microsoft® Corporation, Redmond, Washington, USA) were used for the statistical analyses.

3. Results

3.1. Test results compared with established (or verified) RI

On considering hypothetical test results lying around the upper reference limit (URL) of the distribution of reference values (e.g. at values equal to mean plus 1.5, 2 or 2.5 times SD_T^2), different scenarios may emerge when MU was included in the laboratory report (Fig. 1) and considered for test interpretation. The first, more straightforward Scenario 1 regards the situation in which the test result (x) overlaps to URL ($x = mean + 2 * SD_T$) (Fig. 1, panel A). The MU interval spreads 50% to the left and 50% to the right of test results, irrespective of the MU interval extent and the extent of biological and analytical variations. In this case, if a repeat test is requested on the same sample, the probability of the new result being inside or outside RI should be equal. Other hypothetical scenarios are represented by test results within RI (Scenario 2) or above the URL (Scenario 3). An example of the former case is when a hypothetical test result is at $x = mean + 1.5\ SD_T$; once observed with its MU, the MU interval may include the upper reference interval limit (Fig. 1, panel B). Likewise, also in Scenario 3 the MU interval may include the URL (Fig. 1, panel C). Scenarios 2 and 3 represent the two situations in which the inclusion of MU in the test result might lead to different clinical conclusions. In Scenarios 2 and 3, the contribution of MU to results interpretation became relevant when the ratio of SD_A/SD_T was elevated.

Table 2 shows data that include biological (expressed as CV) and analytical variation, calculated by internal quality control (IQC), and