Editorial

Mario Plebani

Analytical quality: an unfinished journey

https://doi.org/10.1515/cclm-2017-0717

In laboratory medicine, a great forward step has been taken toward the pathway to a better understanding of quality, errors and risks to patient safety. An innovative approach for identifying all possible analytical errors, and systematically evaluating errors in individual patient results, is described in the paper by Michael Vogeser and Christoph Seger "Irregular analytical errors in diagnostic testing – a novel concept", in the current issue of the journal [1].

A valuable source of information and a topic for further discussion, the paper (a) focuses on the need for a patient-centered approach for evaluating analytical quality; (b) reinforces the utility of appropriate metrics for measuring and improving upon quality in the analytical phase of laboratory testing; (c) stresses the importance of adequately defining the uncertainty of laboratory results and related "allowable uncertainty"; (d) stresses that a closer clinical-laboratory interface relationship, particularly in the post-post-analytical phase, is needed for adequately identifying the nature of "irregular (individual) analytical errors" – and providing valuable explanations and defining any corrective actions required; (e) is conducive to including the monitoring of "irregular analytical errors" as an additional quality indicator of the IFCC model of the quality indicator (MQI) project [2–4].

The authors state that an "irregular analytical error is given when a test result generated from a sample using a routine method deviates from the reference measurement procedure (RMP) results generated for this sample more than the measurement error estimate of the routine method" [1]. They also state that an irregular analytical error should be generated, particularly in immunoassays, by: a cross-reaction, sometimes with compounds not listed by the manufacturer; anti-reagent antibodies (e.g. heterophilic antibodies); interference in signal-generation (e.g anti-ruthenium antibodies); high levels of compounds (e.g. biotin in streptavidin/biotin binding-based immunoassays); matrix protein interferences (e.g. due to immunocomplexes, rheumatoid factors) and several other matrix effects (e.g. differential impact of matrix factors on target analyte and internal standard in LC-MS assays).

The prevalence of the above types of error (irregular analytical errors) is highly speculative as, currently, no vigilance system is in place for systematically identifying and reporting them, and they are only a source of anecdotal accounts. However, many laboratory-related diagnostic errors described in the literature are linked to this type of error [4–14]. Not only do they exist, but they also incur a risk of adverse events and harm for patients, and faults in diagnostic-therapeutic pathways. The question is "how can we detect this type of error?" An impressive improvement has been achieved in analytical quality, with a 100-fold reduction in analytical errors in the last few decades [15]. This depends, at least in part, on the development and utilization of statistical quality control (SQC) procedures for detecting instabilities in analytical systems (e.g. increase in systematic or random errors), which prevent reported patients results from leading to clinically important errors that could adversely affect clinical decision-making [16, 17]. Although available data do suggest that current QC strategies used in clinical laboratories are effective in detecting systematic errors, they may not reduce residual risk to acceptable levels, in view of the possibility of increases in random errors [18]. Therefore, in addition to the selection of more stringent SQC procedures to limit the number of erroneous patient results reported consequent to an increase in analytical random error, we must develop reliable strategies to identify and, wherever possible, prevent any "irregular (individual) analytical error". While the authors do not answer the key question (how can we detect this type of error?), they do raise awareness of the need to enhance a patient-centered approach, integrating it with current laboratory procedures to identify analytical errors in conventional statistical quality control.

The fundamental issue is, however, that each individual sample potentially presents a specific matrix, sometimes due to an altered ratio between different measurands (e.g. in end-stage renal disease patient samples) or to the presence of cross-reactants, anti-reagent and anti-analyte antibodies. Efforts to improve analytical standardization and use commutable materials for calibration and quality control should be made while taking into consideration the fact that standardization and commutability in human samples are a "relative concept". As standardization and

commutability work for most samples, laboratory professionals should make further efforts to improve upon them in routine practice but, in some groups of patients and individuals, reference measurement procedures may still be affected by interferences thus generating erroneous results [19].

As stressed by Vogeser and Seger, changes in analytical techniques, such as the shift from immunoassays to LC-MS methods, may decrease, but not eliminate, the above type of error risk. In addition, the search for the presence of interferences, anti-reagents or anti-analyte antibodies in all biological samples – before starting the analytical phase – is, so far, a "mission impossible". However, some useful tips for reducing the rates of "irregular analytical errors" can be proposed: (a) in addition to other quality characteristics, clinical laboratories should take into a greater account the risk of interferences when evaluating and selecting the methods to be used in clinical practice (e.g. to avoid the risk of high-dose hook effects in immunoassays) or use assays with reduced interference by heterophilic antibodies; (b) efforts should be made to raise the awareness of laboratory professionals and clinicians of the risk of irregular analytical errors, regardless of the implementation of valuable statistical quality control procedures. This, in turn, should reinforce the need to evaluate and interpret all laboratory results while considering the clinical context and, whenever necessary, make an in-depth investigation into the possible causes of any discrepancy between a laboratory result and the patient's clinical status. This is our approach in cases in which unexpected results may be due to interference from heterophilic antibodies, anti-reagent antibodies or cross-reactions. In other cases, the assay of the measurand using an alternative method should provide information conducive to clarifying the nature of the "irregular error"; (c) laboratory professionals should always be aware that their knowledge on the nature of biological samples is imperfect, as are the tools they use to detect any possible analytical error. The view of clinical laboratories as factories producing an ever-increasing number of standardized results should be counteracted by the evidence that the quest for quality has yet to be completed, and that appropriate test requesting (pre-analytical phase) and interpretation of results (post-analytical phase) are crucial to the value of the diagnostic testing process; (d) the mantra "if you cannot measure it, you cannot improve it" should be adhered to also in this case in order to ensure that the incidence and prevalence of these types of error are evidenced, and appropriate corrective and preventive actions undertaken. Measurement is the first step toward control and, eventually, improvement. If you can't measure something, you cannot understand it. If you cannot understand it, you cannot control it. We must avoid a culture of overconfidence and arrogance concerning the level of quality achieved in laboratory medicine. The paper by Vogeser and Seger represents a lesson to be learned in this context.

The vast body of evidence collected in the last few decades on the greater vulnerability of the extra-analytical phases of the brain-to-brain loop of diagnostic testing should not generate any false assumptions with regard to the assurance of analytical quality. A body of evidence demonstrates that further improvement is required: the overall performances of frequently requested tests do not meet the minimum performance specifications; commercially available and commonly performed immunoassays are still affected by analytical bias that sometimes exceeds desirable quality goals; when evaluated with stringent metrics such as the sigma scale, analytical quality is not yet satisfactory [20, 21]. Available data from external quality assessment schemes (EQAs) highlight the need for further efforts to improve analytical performances. Clinical laboratories using standardized diagnostic systems still provide significantly different results, and appropriate analytical performance specifications for setting and monitoring analytical goals have yet to be homogenously adopted [22]. Analytical quality continues to be the "core business" of laboratory professionals, but only by raising our awareness of the inter-relationship and inter-connection between the different phases of the testing cycle can we hope to improve upon the ultimate value and quality of laboratory information. Pre-analytical variables are often responsible for erroneous test results, despite a reliable analytical phase, and quality bio-specimens are a pre-requisite for analytical accuracy. In addition, accurate results are not enough, as crucially important adjunctive information should be made available in the post-analytical phase to assure the ultimate quality of laboratory information [21].

The issue of irregular analytical errors provides us with an intriguing, albeit challenging, opportunity to rethink the mission of laboratory medicine in order to provide key information for effective clinical decision-making, treatment guidance, and improved patient care. The more essential the laboratory information provided, the more assured its quality will be. Further efforts should therefore be made to improve the tools we use to detect and minimize any possible diagnostic error in both the intra-analytical and extra-analytical phases of the cycle.

Author contributions: The author has accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.

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Corresponding author: Mario Plebani, *CCLM* Editor-in-Chief, Department of Laboratory Medicine, University-Hospital of Padua, Via Giustiniani 2, 35128 Padua, Italy, Phone: +39 0498212792, Fax: +39 049663240, E-mail: mario.plebani@unipd.it.
http://orcid.org/0000-0002-0270-1711