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Opinion Paper

Closing the brain-to-brain loop in laboratory testing

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Abstract

The delivery of laboratory services has been described 40 years ago and defined with the foremost concept of ''*brain-to-brain turnaround time loop*''. This concept consists of several processes, including the final step which is the action undertaken on the patient based on laboratory information. Unfortunately, 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. Currently, major problems arise from the unavailability of consensually accepted quality specifications for the extra-analytical phase of laboratory testing. This, in turn, does not allow clinical laboratories to calculate a budget for the ''patient-related total error''. The definition and use of the term ''total error'' refers only to the analytical phase, and should be better defined as ''total analytical error'' to avoid any confusion and misinterpretation. According to the hierarchical approach to classify strategies to set analytical quality specifications, the ''*assessment of the effect of analytical performance on specific clinical decision-making*'' is comprehensively at the top and therefore should be applied as much as possible to address analytical efforts towards effective goals. In addition, an increasing number of laboratories worldwide are adopting risk management strategies such as FMEA, FRACAS, LEAN and Six Sigma since these techniques allow the identification of the most critical steps in the total testing process, and to reduce the patient-related risk of error. As a matter of fact, an increasing number of laboratory professionals recognize the importance of understanding and monitoring any step in the total testing process, including the appropriateness of the test request as well as the appropriate interpretation and utilization of test results.

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An open-loop system, sometimes called a ''non-feedback controlled'' system is one that makes decisions based solely on pre-programmed criteria and pre-existing models (1). This approach does not use feedback to calibrate its output or to determine if desired goals are achieved. Open-loop systems are hence unable to correct any error they make or compensate for any disturbance to the process. Laboratory tests, along with clinical symptoms, signs and other diagnostic investigations are the means to achieve a diagnosis, so that further action can be undertaken in the form of a diagnostic or therapeutic intervention. The delivery of laboratory services was described 40 years ago and defined with the foremost concept of the ''*brain-to-brain turnaround time loop*'' (2). According to this theory, any laboratory test consists of nine steps which include ordering, collection, identification (at several stages), transportation, separation (or preparation), analysis, reporting, interpretation and action. At that point, the system should be still viewed as an open-loop. However, 20 years later, George D. Lundberg, the former inventor of the concept, emphasized in a seminal editorial that even the final step, that is the action undertaken on the patient and based on laboratory information, is not far enough. Lundberg emphasized that ''*clinicians and laboratorians should all be concerned about the effects of that laboratory test and whether the performance of it was useful for the patient or for the public's health*'' (3), which necessarily paves the way for an outcomes research agenda.

Unfortunately, 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. The article published in this issue of *Clinical Chemistry and Laboratory Medicine* by Krouwer and Cembrowski should be welcomed since it debates some open issues regarding the current limitations of ''common performance specifications for quantitative assays'', total error estimation and risk management techniques (4). However, it deserves some editorial comment and criticism.

First and foremost, major problems arise from the current unavailability of consensually accepted quality specifications for the extra-analytical phase of laboratory testing. According to recent evidence, most errors within the brain-to-brain loop do not arise from the analytical phase. An exploration of beginning and end of the loop reveals that the pre-pre-analytical steps (initial procedures performed neither in the

clinical laboratory nor, at least partially, under the control of laboratory personnel), and the post-post-analytical steps (final procedures performed outside the laboratory, consisting of receiving, reading, interpreting and using laboratory information for patient management) are more prone to errors (5). Data from different clinical settings such as primary care, internal medicine and emergency departments attest that the rates of errors in test request and result interpretation is still unacceptably high, and translate into missed, delayed or inappropriate diagnoses (6). The current concept of ''total error'' (or ''total allowable error'' as depicted by James Westgard) (7) is simply misleading. In fact, it only refers to the analytical performance of laboratory testing, thus missing the final goal that is the improvement of patient outcomes because it overlooks all the remaining processes involved in the brain-to-brain loop. If more than 50% of urgent laboratory tests were never consulted in the hospital setting (8), and if the extent of failure to follow-up diagnostic tests in ED ranged from 1.0% to 75% (9), would clinical laboratories really need to perform costly and time-consuming techniques for setting and monitoring highly stringent analytical quality specifications? In other words, analytical quality specifications, when not appropriately defined and established, may reflect internal laboratory efforts to pursue surrogate goals that are unrelated to the final scopes. Therefore, from the modern patient-centered viewpoint, as well as in the context of clinical risk management, the concept of ''total analytical error'' or ''total analytical allowable error'' is and remains an essential feature, but it does not refer to the ''patient-related total laboratory error'' which instead really matters and results from any possible failure in the so-called ''testing loop''. Current projects aimed to define quality indicators and related quality specifications for the extra-analytical phases of the loop will assure more valuable information on ''patient-related total laboratory error''. In their article, Krouwer and Cembrowski classify specifications as either clinical or regulatory. This classification seems to be equivocal and potentially dangerous. In the hierarchical approach to classify strategies to set analytical quality specifications as established in the 1999 Stockholm Conference (10), the ''*assessment of the effect of analytical performance on specific clinical decision-making*'' is comprehensively at the top. Therefore, it is essential to comply as much as possible with this requirement and any dissociation between clinical and regulatory specifications is not advisable. According to this approach, even if we agree with the concept that quality specifications have to be the same in different analytical settings (point-of-care testing and near-patient testing vs. clinical laboratory testing) (11), it should be clearly established that a different clinical utilization of the same test may require and justify the adoption of different quality specifications. This is the case, for example, of glucose measurements. When this test is used to diagnose diabetes, quality specifications must be much more stringent than those required when the test is used for patient monitoring and home testing. The problem is that regulatory bodies have to clearly understand this foremost concept, since they should eventually approve and/or release a specific assay with the appropriate clinical indications, avoiding doubts, confusions and misunderstandings.

Even the example of the cardiac troponin – cited by the authors – may be misleading. The analytical performance specifications recommended by joint cardiology and laboratory scientific organizations were of foremost value to stimulate manufacturers to produce better and higher sensitive assays for both diagnosis and risk stratification of myocardial infarction, and not for endorsing the analytical performance of existing assays. Improved pathophysiological knowledge, revised clinical needs, as well as the availability of high-sensitivity assays may allow for the setting of newer and better analytical quality specifications. This is a clear example of the dynamics of the process to define and improve analytical quality specifications based on clinical needs. In the error grid presented by the authors, a fundamental issue is to define the zone(s) where an error more frequently may translate into patient risk. This requires the adoption of quality control and assessment strategies for setting and monitoring analytical performances at those values which are more probabilistically associated with patient harm. However, the use of ''analytical goals'' for setting limits that demarcate no harm from minor harm arising from certain common laboratory measurements, such as blood glucose (i.e., imprecision below 2.9%), might be simply unsuitable since they are nearly two-times lower than the within-subject biologic variation (i.e., 5.7%). As such, a diagram based on the former source of (analytical) data would be unsuitable to estimate the overall ''budget'' of laboratory testing that we are allowing for preventing major harm. Therefore, the error grid is of value to establish more valuable targets for analytical errors but, as presented by the authors, does not allow really alarming clinical laboratories on all potential errors (both analytical and extra-analytical) that might translate into harm for the patient, because the error budget needs information on other pre- and post-analytic quality specifications.

Also, the authors recommend discontinuation of the use of the term ''clinically acceptable'' when referring to current specifications. This is because only 95% of the results are required to fall within the limit (range). We basically agree with the author that new metrics have to be established to manage and reduce patient risk, but the problem is not the term (clinically acceptable) but its use within the wrong context. The decision to accept or reject an analytical run, and therefore an individual result, is based on a compromise between the need to avoid false rejection and to accept wrong results. However, the risk is much more limited when quality specifications are based on reliable criteria, and control procedures are appropriate. A more appropriate reduction of the clinical risk arises from the correct interpretation and utilization of laboratory information within the clinical context and according to the Bayesian probability. Inherent to this concept is the biggest limitation of this paper which is the approach used to settle error grids which should help establish – once analytical limits are exceed – the probability of major harm to the patient. From a strictly theoretical point of view, the article has thereby little practical implications so far. The solution suggested by the author is to define

errors grids on the basis of ''clinician opinion''. However, this is arbitrary and does not necessarily reflect an evidence based (laboratory) medicine approach. As such, this seems a rather unsuitable prospective strategy. Error grids should be defined retrospectively, after having accumulated, analyzed and troubleshot a large number of clinical adverse events strictly related to laboratory errors which have arisen throughout the total testing process, and thereby established which is the analytical and extra-analytical ''budget'' that we can rely on before imprecision and uncertainty translate into major harm.

We finally disagree with the comment regarding difficulties by clinical laboratories in adopting risk management techniques. In fact, the International Standard for laboratory accreditation (ISO 15189:2007) (12) is a valuable tool for implementing a quality system that minimizes the risk of errors in daily practice and, even more importantly, a specific ISO Technical Specification has been released for error reduction through risk management and continual improvement in laboratory medicine (13). Moreover, an increasing number of laboratories worldwide are adopting risk management strategies such as FMEA, FRACAS, LEAN and Six Sigma. These techniques allow for the identification of the most critical steps in the total testing process, compare them with other risky but non-clinical activities, and allow reduction of patient-related risk of error. The evidence is that an increasing number of laboratory professionals recognize the importance of understanding and monitoring any step of the total testing process, including appropriateness in the test request as well as the appropriate interpretation and utilization of test results. However, two major issues still require further efforts: the identification of suitable quality indicators and quality specifications for the extra-analytical phases of the testing process (14), and close cooperation with stakeholders (i.e., clinicians and other healthcare operators). What we still really need is a systematic approach, one that comprehensively involves laboratory and healthcare professionals and encompasses an infrastructure able to capture and – particularly – learn from adverse patient outcomes. Teamwork and feedback are key factors in efforts to improve overall laboratory performances in a patient-centered scenario. Such a way we will assure that the brain-to-brain will not be an open-loop anymore.

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