Laboratory-associated and diagnostic errors: a neglected link

Abstract: Clinical laboratories play a vital role in patient care, but many diagnostic errors are associated with laboratory testing. The past decades have seen sustained improvements in analytical performances but the error rates, particularly in pre- and post-analytical phases is still high. Although the seminal concept of the brain-to-brain laboratory loop has been described more than four decades ago, the awareness about the importance of extra-analytical aspects in laboratory quality is a recent achievement. According to this concept, all phases and activities of the testing cycle should be assessed, monitored and improved in order to decrease the total error rates and thereby improve patient safety. In the interests of patients, any direct or indirect negative consequence related to a laboratory test must be considered, irrespective of which step is involved and whether the error depends on a laboratory professional (e.g., calibration or testing error) or a non-laboratory operator (e.g., inappropriate test request, error in patient identification and/or blood collection). Data collected in various clinical settings demonstrate that many diagnostic errors are associated with laboratory testing. In particular, errors are due to inappropriate test request and/or result interpretation and utilization. Collaborations between laboratory professionals and other care providers, namely clinicians and nurses, are needed to achieve the goal of improved patient safety.

Keywords: brain-to-brain loop; diagnostic errors; laboratory medicine; laboratory-associated errors; patient safety; quality.

Introduction

Laboratory-associated error has a completely different meaning today than it did a half century ago, as shown in Table 1 [1]. At that time the term referred to defects in the analytical performance of the test itself, the so-called analytic phase. One of the first report on errors in laboratory testing, the seminal paper by Belk and Sunderman, which paved the way to the development of external quality assessment programs (EQA), focused solely on analytical errors and identified high rates and serious errors in the measurement of “simple” clinical chemistry analytes [2]. Consequently most of the different terms used in the literature to define errors in laboratory medicine (e.g., mistakes, blunders, defects, outliers, unacceptable results and quality failure) pertained to studies focusing only on the analytical phase or on a limited number of steps in the total testing process (TTP) [3].

A dramatic change in addressing the issue of laboratory-associated errors started at the end of the 1990s, when a body of evidence began to accumulate demonstrating vulnerability in the pre- and post-analytic phases. By that time, the data collected and reported in the literature, including the data published by Witte and coworkers in 1997, showed that analytical error rates had decreased from 162,116 per million laboratory tests (part per million, ppm) to 447 ppm [4–6]. This dramatic and impressive reduction in errors, by about 300-fold, derived from automation, improved laboratory technology, assay standardization, well-defined rules for internal quality control, effective quality assurance schemes and better trained staff. However, with this dramatic improvement in analytic reliability, came the appreciation of errors in the non-analytic phases of the TTP.

The total testing process

In 1975 George D. Lundberg coined the concept of the “brain-to-brain turnaround time” [7], and the related seminal concept of the “brain-to-brain loop” 6 years later. According to these concepts, every laboratory test involves nine steps, including ordering, collection, identification (at several stages), transportation, separation (or preparation), analysis, reporting, interpretation and action [8]. Lundberg highlighted the point that “anything that stands in the way of their (physicians) prompt and perfect receiving of laboratory results for their patients is perceived as a laboratory problem or error” and that the responsibility...
of laboratory professionals cannot be limited to solely performing and monitoring analytical quality. Initially, however, errors in the pre- and post-analytical steps were not widely appreciated, and it was not until the early 1990s that a series of studies focused the attention of the laboratory professionals on the many problems involving pre- and post-analytical error. In particular, two seminal papers articles were published in 1997 and 2007 [9, 10], using a study design that allowed us to investigate the steps of the total testing process within the same clinical context and thereby define the utility and effectiveness of interventions. The results obtained were substantially similar, demonstrating that the distribution of errors was 62%–68.2% pre-analytical, 13.3%–15% analytical, and 18.5%–23.1% post-analytical. The latter study, published ten years after the former one, demonstrated a significant, although not dramatic, decrease in the error rates but a similar distribution of errors. The most frequent problems arose in the pre-analytical phase from mistakes in tube filling, inappropriate containers, and requesting procedures as well as from identification errors.

The main reason for errors in the post-analytic phase was an excessive turnaround time in the latter study, and errors in keyboard entry and missed correction of erroneous findings in the former study. The laboratory community was initially reluctant to accept this evidence, even though the findings might have been predicted given the involvement of healthcare staff other than laboratory professionals in test ordering, data entry, specimen collection and handling. Further studies and publications have more clearly elucidated the nature of errors in laboratory testing through the exploration of the initial and final steps of the testing process that have been grouped and defined “pre-pre-analytical” and “post-post-analytical” phases [11, 12]. In particular, the exploration of the initial steps of the procedures which are usually performed neither in the clinical laboratory, nor, at least in part, under the control of the laboratory personnel [13], has provided a better understanding of the causes and the underlying mechanisms that produce most pre-analytical errors [14]. In the final steps of the loop, delayed acknowledgment of laboratory reports, as well as failures in interpretation, follow-up and documentation of laboratory data were found to be responsible for a high percentage of errors in various clinical settings.

A milestone in reaching the current view of laboratory errors and in achieving more attention to quality of all steps of the TTP was the development by the International Organization for Standardization in 2008 of a Technical Specification (ISO/TS 22367) which defines laboratory error as “failure of planned action to be completed as intended, or use a wrong plan to achieve an aim, occurring at any part of the laboratory cycle, from ordering examinations to reporting results and appropriately interpreting and reacting to them” [15]. This comprehensive definition has several advantages and, in particular, encouraged a patient-centred approach to considering errors in laboratory testing. ISO/TS 22367 stresses that “the promotion of patient-centred care should be translated into the need to investigate any possible defect that occurs in the TTP and that may eventually have a negative impact on the patient”. From this patient-centric viewpoint, any direct or indirect negative consequences related to a laboratory test must be considered, irrespective of whether the source lies in the pre-, intra-, or post-analytic phase. It is, moreover, irrelevant whether an error has been caused by a laboratory professional (e.g., calibration or testing error) or by a non-laboratory operator (e.g., patient/specimen misidentification, inappropriate test request or interpretation) [16, 17]. Therefore, the TTP is the unique and most appropriate framework for considering and identifying laboratory errors, both for testing in “traditional” clinical laboratories and with point-of-care (POC) or alternative testing types (devices for near-patient testing and self-monitoring), as shown in Figure 1.

## Errors in laboratory medicine and patient harm

It seems likely that only a small proportion of laboratory errors results in actual patient harm and adverse events thanks to the several barriers and defensive layers present between the release of laboratory information, the decision-making process and, ultimately, any impact on the patient. There are relatively few studies that have evaluated the link between errors in laboratory medicine and clinical outcomes. Major difficulties in such studies include the numerous steps and the different healthcare staff involved, and the lag time between laboratory testing and any final clinical outcome.
The risk of adverse events and inappropriate care due to laboratory errors ranges from 2.7% to 12%, while in a larger percentage of cases (24.4%–30%), a laboratory error translates into a patient care problem, namely unnecessary laboratory test repetition and further inappropriate investigations. In studies published by our group, for example, errors resulted in inappropriate admissions to critical care units, inappropriate transfusions, and modifications to heparin and digoxin therapies [10–12, 15–18]. In addition, laboratory errors may lead to inappropriate laboratory or imaging examinations, invasive procedures, and unneeded consultations. Although not necessarily harmful, these cascades can create anxiety, discomfort, and higher costs for both patients and the health care system. Therefore, from a risk management viewpoint, the great majority of laboratory errors have little direct impact on patient care but provide important learning opportunities. In fact, any error, regardless of its apparent triviality, might indicate weaknesses in policies and procedures that may not lead to adverse events in their particular context, but might cause patient harm in slightly different circumstances. According to this viewpoint, efforts to improve laboratory performance in all steps of the TTP are of value, even if they are unable to measure the impact on clinical outcomes.

A system for grading laboratory errors according to their clinical impact would help identify priorities for quality improvement and focus corrective/preventive actions. This grading system should be designed to consider not only the real patient harm sustained, but also the potential worst case outcome if such an error were to recur. According to the already cited ISO Technical Specification “Medical laboratories-reduction of error through risk management and continual improvement” [15], clinical laboratories must implement processes for: a) identifying high-risk processes where the potential error could lead to a safety risk for patients; b) identifying actual incidents associated with deviations from standard requirements; c) estimating and evaluating the associated risks to patient safety; d) controlling these risks, and e) monitoring the effectiveness of the control undertaken. A recent proposal suggests that it is possible to assign both an actual (A) and a potential (P) score to describe the seriousness of an individual laboratory error by grading it according to a 5-point severity scoring system based on patient outcome [13]. The lower score identifies “no change in patient management; no adverse clinical outcome” as a result of the individual error, and the higher score, “significant adverse clinical outcome”. A study performed using this score system, over a 30-month period and considering 714,988 requests for laboratory tests received, identified 658 errors. Seventy five percent of errors were given an “A” score of 1 (no adverse event) while 67.9% were allocated on a “P” score of 5 (potential significant adverse clinical outcome), as shown in Table 2 [13]. Once again, these data demonstrate that laboratory errors may play a significant role in affecting the overall quality of patient care, including its safety.

### Table 2 Severity of quality failures-distribution of “A” and “P” scores (data from reference [13]).

<table>
<thead>
<tr>
<th>Severity</th>
<th>“A” score, %</th>
<th>“P” score, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75.1</td>
<td>0.7</td>
</tr>
<tr>
<td>2</td>
<td>6.4</td>
<td>10.8</td>
</tr>
<tr>
<td>3</td>
<td>18.5</td>
<td>16.0</td>
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<tr>
<td>4</td>
<td>0</td>
<td>4.9</td>
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<tr>
<td>5</td>
<td>0</td>
<td>67.9</td>
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Diagnostic errors related to laboratory testing

In recent years, a second research path, which has started from the clinical side, demonstrated that errors in laboratory medicine represent a piece of a much wider puzzle that is commonly known as “diagnostic error”, definitively linking laboratory-associated errors to patient safety problems. Diagnostic error can be defined as “errors in which the diagnosis was unintentionally delayed (while sufficient information was available earlier), wrong (another diagnosis was made before the correct one), or missed (no diagnosis was ever made) as judged from the eventual appreciation of more definitive information (e.g., autopsy studies)” [19].

Recent studies in this area have led to a better understanding of the frequency and nature of diagnostic errors, and their relationship to laboratory testing error. Recent data on errors in the pre-pre analytical phase (initial procedures performed neither in the clinical laboratory nor, at least in part, under the control of laboratory personnel) underline that failures to order appropriate diagnostic tests, including laboratory tests, accounted for 55% of observed breakdowns in missed and delayed diagnosis in the ambulatory setting [20–22] and 58% of errors in the Emergency department [23].

In the final steps of the TTP loop, the incorrect interpretation of diagnostic or laboratory tests was found to be responsible for a high percentage of errors in the ambulatory setting as well as in Emergency departments. A very recent paper underlined that failure to inform patients of clinically significant abnormal test results or to document that the relevant information has been given appear to be relatively common, occurring in one of every 14 tests. Significant examples are patients not being informed of results of total cholesterol as high as 8.2 mmol/L (318 mg/dL), a hematocrit level as low as 28.6% and a potassium level as low as 2.6 mmol/L. The overall rate of failures to inform the patient or record communication of information/document was 71%, ranging among practices from 0% to 26% [24]. A systematic review of the literature demonstrated that failure to follow-up test results is an important safety concern. The rates of abnormal laboratory results not followed-up ranged from 6.8% to 62%. Similarly, for abnormal radiology, lack of follow-up ranged from 1.0% of patient with suspected malignancy to 11%, thus stressing the need of multifaceted interventions and solutions [25]. Further evidence of errors in reacting to laboratory information is given in a study on prescribing potassium despite hyperkalemia [26]; in a further study [14] it was found that more than 2% (2.6% in 2000, 2.1% in 2007) of patients with thyrotropin (TSH) results higher than 20 mU/mL had no follow-up. Finally, in another interesting study, almost half of 1095 discharged patients had pending laboratory and radiology test results and 9% of these results were potentially actionable [27] in another study, approximately one-third of the sub-acute care patients had laboratory tests, particularly microbiology tests, pending at discharge, but few were documented within hospital discharge summaries [28].

Overall, the reported data demonstrate that the initial and final steps of the TTP process, above all test requesting and reaction to laboratory results, not only are more error-prone than all the other steps, but are more important causes of potential adverse outcomes for patients. In addition, these data confirm the existence of a substantial number of failures in the interface between clinician clinics and laboratory sides, and the need for laboratories and front-line physicians to “understand their mutual ownership of this problem and work together to ensure that patients are more safe” [29].

The path towards improved patient safety in laboratory medicine

The available evidence highlights that failures in ordering laboratory tests and interpreting and using laboratory results are major contributors to diagnostic errors, along with residual problems in analytical performance per se. Putting together these findings with the evidence that diagnostic errors are among the most frequent, most severe and most costly type of medical adverse events should lead to the consideration of new strategies for achieving quality in all steps of the TTP to improve patient safety. The evidence that appropriateness in test ordering and result interpretation/utilization are related to diagnostic errors should change the current paradigm which is based primarily on efforts to improve procedures and processes managed or under the control of the laboratory staff. To translate from theory to practice the concept of “patient centered care”, it becomes mandatory to investigate and improve the initial and final steps of the testing cycle.

The search for valuable quality indicators (QIs) for extra-analytical phases of the testing process and for harmonizing all steps, including test ordering and data interpretation, represents a fundamental issue in projects aiming to improve quality and patient safety.
Harmonization projects aiming at improving all steps of the TTP are in progress thanks to the efforts of national and international institutions [34]. Quality indicators should be grouped in two broad classes: a) process and b) outcome measures. The model of quality indicators (MQI) developed by a working group of the IFCC (International Federation of Clinical Chemistry and Laboratory Medicine) is mainly based on measures of the pre-, intra- and analytical procedures and processes. It includes QIs designed to evaluate both the initial (test ordering) and final (result communication) steps of the cycle and therefore is a valuable tool for improving the quality of laboratory services in the TTP [30–33]. However, an outcome-based approach should be added to better highlight the link between laboratory testing and final patient outcomes [35]. Table 3 shows a recently-developed outcomes-based approach to testing-related diagnostic errors (TDE). This approach to reduce testing-related diagnostic errors (TDE) represent a paradigmatic shift for laboratory professionals, clinicians and other healthcare staff [35]. In fact, only coordinated and integrated efforts by laboratory and clinical staff will be able to effectively improve the safety of laboratory testing. The TTP is too complex, the cause of errors too diverse, and the continuing development of new testing modalities and uses is too rapid to allow effective improvements through uncoordinated projects. Reducing the likelihood of harm from diagnostic error can involve technical, cognitive, and system-oriented strategies [36]. The reduction of laboratory-associated error, currently around 5%, may require interventions in each of these domains. Improvement in laboratory and information technologies are needed but, even more important, are efforts to reduce failure at the clinical-laboratory interface. This in turn, requires multidisciplinary work, cooperation and collaboration in identifying critical steps such as patient and sample identification steps, as well as interpretation and utilization of laboratory information. The identification of quality indicators and outcome-based measures are fundamental steps to achieve the goal of improving laboratory testing using a patient-centered approach [37].

Conflict of interest statement: The author declares no conflict of interest.

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References