Opinion Paper

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Towards a new paradigm in laboratory medicine: the five rights

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Abstract: A body of evidence collected in the last few decades demonstrates that the pre- and post-analytical phases of the testing cycle are more error-prone than the analytical phase. However, the paradigm of errors and quality in laboratory medicine has been questioned, analytical mistakes continuing to be a major cause of adverse clinical outcomes and patient harm. Although the brain-to-brain concept is widely recognized in the community of laboratory professionals, there is lack of clarity concerning the inter-relationship between the different phases of the cycle, interdependence between the pre-analytical phase and analytical quality, and the effect of the post-analytical steps on the quality of ultimate laboratory information. Analytical quality remains the "core business" of clinical laboratories, but laboratory professionals and clinicians alike should never lose sight of the fact that pre-analytical variables are often responsible for erroneous test results and that quality biospecimens are pre-requisites for a reliable analytical phase. In addition, the pressure for expert advice on test selection and interpretation of results has increased hand in hand with the ever-increasing complexity of tests and diagnostic fields. Finally, the data on diagnostic errors and inappropriate clinical decisions made due to delay or misinterpretation of laboratory data underscore the current need for greater collaboration at the clinical-laboratory interface.

Keywords: analytical quality; diagnostic errors; laboratory medicine; patient safety; pre-analytical phase; total testing process.

Introduction

Evidence collected in the last few decades demonstrates that the pre- and post-analytical phases of the testing cycle are more error-prone than the analytical phase [1, 2]. A further exploration of the beginning and end of the loop has revealed that the pre-pre-analytic steps (initial procedures not performed in the clinical laboratory and outside the control of laboratory personnel) and the post-post-analytic steps (final procedures performed outside the laboratory, i.e. receiving, interpreting, and using laboratory information for patient management) are more error-prone. Therefore, diagnostic testing has been divided into five phases: pre-pre-analytic, pre-analytic, analytic, post-analytic, and post-post-analytic [3]. In 2015, the paradigm of errors in laboratory medicine was reported in the Institute of Medicine (IOM) document "Improving Diagnosis in Health Care" which stressed that "…errors related to diagnostic testing can occur in any of these (the above) five phases, but the analytic phase is the least susceptible to errors" [4]. However, more recently, Vogeser and Seger questioned this paradigm, stating that "for many clinical pathologists, this very optimistic perception of analytics performed in clinical laboratories is somewhat surprising, especially when considering reports on adverse clinical outcomes, e.g. due to false-positive hCG results caused by heterophilic antibodies" [5]. Further studies in the literature stress the current lack of standardization and harmonization of laboratory assays, as well as the existence of numerous sources of interference and errors in the analytic phase [6–8]. Clearly the time has come to re-evaluate the current paradigm of quality and errors in laboratory medicine.

The testing cycle continuum

In a recent paper, George D Lundberg stated that the "brain-to-brain loop", a seminal concept in laboratory testing that he fathered, was conceived as a continuum from step one (when the physician's brain decides on the need for a laboratory test) through various steps (ordering, collection, identification, transportation, preparation, analysis, reporting, interpretation) to the final step, involving the provision of information that enables appropriate action to be undertaken on the patient's

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behalf (diagnosis/therapy). Anything that interferes with any step in the process is at the least a waste and at the most, a tragedy (an error translating into patient harm) [9]. The understanding of the importance of both pre-analytic (front-end) and post-analytic (back-end) laboratory errors springs from this loop. Although the brain-to-brain concept is widely accepted by laboratory professionals, there is little clarity concerning the inter-relationship between the different phases of the cycle, in particular the interdependence between the pre-analytical phase and analytical quality, and the role of post-analytical steps in affecting the quality of the ultimate laboratory information provided.

Good samples make good assays

The mantra "good samples make good assays" has received increasing recognition thanks to two different lines of evidence. One is that native samples are the cornerstone to developing an in vitro diagnostic (IVD) assay and improving analytical standardization/harmonization. As underlined by Van Houcke and Thienpont "IVD manufacturers consider patient samples of the utmost value in the process of establishing/validating metrological traceability of their assays to a higher order calibrator and measurement. Indeed, it is generally recognized that their use in the calibration hierarchy, more particularly at the level of the calibrator of the manufacturer's selected or standing measurement procedure, is the best practice to circumvent commutability issues potentially encountered with processed or artificial calibrators" [10]. The availability of "good" commutable control materials in external quality assessment (EQA)/proficiency testing (PT) programs is a pre-requisite for the right target value assignment, and for assuring accuracy against a reference measurement procedure or a designated comparison method. The agreement between results from different measurement procedures for commutable samples reflects which would be seen for patients' samples [11]. Moreover, recent pilot studies suggest that EQA/PT schemes for cTnI and thyroid stimulating hormone immunoassay methods, based on both quality control samples with tested commutability and robust statistical analyses, enable an evaluation to be made of between-methods variability, and allow the reliable recalibration and harmonization of results [12, 13]. The other line of evidence concerns the relationship between pre-analytical and analytical quality in any individual patient result. For a test result to truly reflect the concentration of an analyte in the blood circulation, the testing must be performed on a sample with a good pre-analytic status. It is well known that pre-analytical variables in handling affect the integrity of biospecimens and, further down the line, the results of analyses by causing in vitro modifications [14]. When a test result deviates from the expected, the analytical integrity of the data, rather than the pre-analytical integrity of the sample, is often questioned. Therefore, there are numerous reasons for evaluating the quality of biological samples, including the need to prevent analytical errors and related unjustified costs and ensure patient safety.

To allow an accurate and reliable analytical step in the pre-pre-analytical phase, "the five rights" rule should be observed to assure for all specimens "the Right Patient (identification), the Right Time, the Right Test, the Right Sample Collection/Handling, and finally the Right Sample Transportation". In the ensuing pre-analytical phase, the "five rights rule" should assure "the right separation (e.g. centrifugation if the case), the right pre-treatment, the right aliquotting, the right sortation, and the right routing, as shown in Figure 1. Only if these rules are effectively observed is the biological integrity of the sample and its suitability for an accurate analytical phase assured. While great advances have been made in the pre-analytical phase thanks to the introduction of pre-analytical working stations, improvement in the pre-pre-analytical phase is a far more complex issue [15, 16].

The five rights in the pre-pre-analytical phase

The right patient (*patient identification issues*): Identification errors in clinical laboratory testing can cause serious patient harm, and the Joint Commission for Accreditation of Healthcare Organizations and the College of American Pathologists have cited accurate patient identification as a cardinal patient safety goal [17, 18]. Yet the factors underlying the current continued frequency of identification errors are poorly understood [19]. The occurrence of "wrong blood in tube" is a nightmare for any clinical laboratory: not only is it impossible to appropriately attribute the results obtained to the right patient, but it also calls for a search for the 'other patient' involved in the mismatch, root cause analysis to understand the source(s) of misidentification, and gives rise to subsequent related issues [20]. Standard operating procedures should assure the use of multiple identifiers. Automated systems for patient and sample identification (e.g. bar codes) and information technology facilities are effective tools in reducing the risk of errors, but education and active involvement

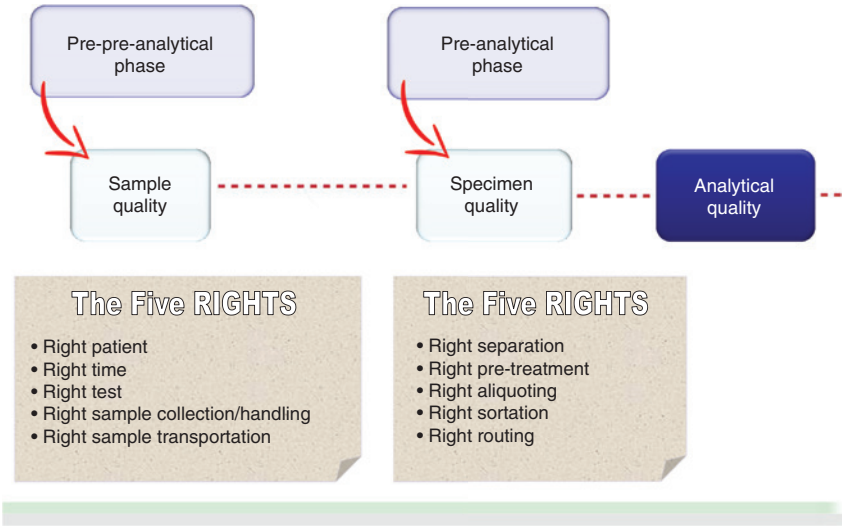

Figure 1: The five rights in the pre-analytical phases.

of the laboratory and non-laboratory (nurses and physicians) are still of crucial importance in reducing the rates of misidentification errors.

Right time: Knowledge of the biological properties and kinetics of a measurand are of utmost importance in requesting a laboratory test. However, current evidence demonstrates the high rates of inappropriate retesting, and points to the need to avoid useless requests. The Association for Clinical Biochemistry and Laboratory Medicine (UK) has promoted a project aiming to improve the appropriateness and timing of laboratory test requests. Minimal re-testing intervals are defined as the minimum time before a test should be repeated based on the properties of the test and the clinical situation in which it is used. The recommendations on re-testing times are based on evidence, if available; if evidence is unavailable, expert opinions are sought [21]. The introduction in clinical practice of minimum retesting times managed by both computer-based and educational interventions, has already been reported as an effective tool in reducing inappropriate retesting [22].

The right test (*appropriateness*): The numerous drivers calling for the management of test demand and improvement in test requesting can be grouped into finance, quality and patient issues. The financial perspective is based on the cost of inappropriate requesting, which includes reagents, consumable and human resources, as well as additional and unnecessary consultations, treatments and investigations. Quality and patient safety issues appear to be even more crucial since inappropriate testing is generally related to bad quality, delayed or missed diagnoses and negative patient experiences [23]. Although concern has been expressed regarding the unnecessary requesting of laboratory tests, evidence of this issue is scarce as most studies fail to meet methodological standards proposed for clinical audit, although a recent 15-year meta-analysis drew the conclusion that in the literature the risk of underutilization is higher than that of over-utilization [24]. As recently suggested, the definition of an inappropriate test demand as a "request that is made outside some form of agreed guidance" should be conducive to improving appropriateness in test requests [25]. The focus on "guidance" aptly reflects one of the major movements that has emerged in medicine in the past decade, its aim being to put medicine on a firm scientific footing, by means of so-called "evidence-based medicine". The type of guidance, in turn, may range from national and international guidelines to locally agreed behaviors, but the "core" of the definition is the need for a reference based on laboratory and clinical consensus [26]. Aligning prescriptions with evidence is universally recognized as an effective measure in improving upon accountability, efficiency and effectiveness in health care [27].

Right sample collection/handling: The evidence available in the literature shows the lack of standardized pre-analytical marker data collection, as well as the existence of a wide variation in the definition, repertoire and collection methods for pre-analytical errors [28]. There are also variations in practices for identifying and rejecting specimens unsuitable for analysis due to, for example, inaccurate or inadequate labeling and defects in sample quality or quantity. The reported rates of specimen rejection vary

widely, ranging from 0.20% [29] to 5.97% [30], clearly reflecting major differences in acceptance/rejection criteria. The causes of specimen rejection also vary: in the majority of studies, haemolyzed samples are the most common reason given [31], but in others, clotted specimens and/or insufficient volume of samples are the more commonly given reasons [32]. Ethnicity has a significant influence on the percentages of rejected specimens, particularly in samples collected in Emergency Departments and inpatient services. This could depend on numerous different factors including disease severity, sample collection practice, and inadequate proficiency of staff (nurses, phlebotomists and doctors) [33]. Specimen rejection has significant clinical consequences: on the one hand, it prevents erroneous results, obviates unjustified analytical costs and enhances patient safety but, on the other, it leads to the need for repeat sample collection, patient discomfort, significant delay in result availability, and a high rate of specimen/test abandonment [29]. Rules for sample rejection should therefore be based on a balance between the need to assure reliable analytical results and the need to minimize waste of resources and patient discomfort. However, not only do the rules for sample acceptance/rejection vary, but also the practices for result reporting, data correction and providing clinicians with information are poorly harmonized [31, 34]. In addition, only a few clinical laboratories document corrective actions undertaken to improve the quality of biological samples and decrease the rejection rates by training non-laboratory personnel to perform blood collection procedures better, and by improving the performance of clinical laboratory and hospital staff, and collaboration between the two. Clinicians' understanding of the significance of hemolysis, lipemia, icterus and other causes of sample rejection is often overestimated, but their poor knowledge often leads to diagnostic errors due to erroneous interpretation of laboratory results. The quality of biospecimens concerns not only blood but also other biological samples such as urine, saliva, feces and cerebrospinal fluid. Moreover, reliable pre-analytical handling of biospecimens is of fundamental importance in assuring quality not only to traditional tests and methods, but also to innovative biomarkers and techniques (genomics, proteomics, miRNA etc.) [14, 35].

Overall, the data available demonstrate that efforts to improve analytical quality should be more closely linked to programs aiming to improve the quality of biological samples; they also demonstrate that good analytical performance on poor quality samples can lead to clinically unreliable results, waste of resources and unjustified costs.

Right sample transportation: The increasing pressure to cut costs in healthcare organizations has affected laboratory activities and workflow, wherein consolidation processes have led to transportation of large numbers of specimens from peripheral collection sites to the core laboratory [36]. This has increased the need for systems that assure quality and safety in biological sample transportation, and for monitoring the risk of errors in this step. Indeed, this part of the pre-analytical process is widely recognized as a major factor contributing to delays in returning high quality clinical laboratory results for both inpatients and ambulatory testing, although little evidence on this issue is available in current literature [37]. Use should be made of integrated systems consisting of secondary and tertiary containers, a device for temperature and time recording, and a system manager that allows the acceptance or rejection of biological samples through the immediate visualization of recorded data, which are compared to accurately defined conditions [37]. However, only the continuous monitoring of the data through the use of valuable quality indicators will allow clinical laboratories to assure quality and safety in this step [38].

Good reports make good laboratory information

Quality in the post-analytical phase: The ISO 15189 standard for medical laboratory quality [39] defines the post-analytical phase as the processes following the examination. In terms of the quality of the clinical laboratory report, the post-analytical phase includes the result validation, formatting, releasing, reporting and retaining test results for future access. To facilitate the interpretation and clinical decision-making process, essential information should be introduced in the laboratory report to convert raw data to information thus making data meaningful. No laboratory result can be interpreted without a means of comparison, the comparator being a reference interval, a decision limit and/or previous result(s). The provision of a system for interpreting numerical data against reference limits or clinical decision values is a mandatory requirement in any laboratory report (ISO 15189; 5.8.5j) [39]. However, particularly for some complex tests, the need for interpretative comments is being recognized increasingly often as important in improving outcomes and safeguarding the patient [40]. In this phase the "five rights" rule to be assured is "the right turnaround time, the right data validation, the right units, the right reference intervals/decision limits and the

right interpretative comment/critical values notification" (Figure 2).

Turnaround time (TAT): Timeliness of results is a quality attribute, as most clinicians judge the adequacy of laboratory services by the speed with which its results are reported [41]. Slow TATs have a number of adverse effects and can lead to duplicate test requests, increased STAT testing and a longer hospital stay [42]. The rapid growth in point-of-care testing (POCT) testifies to the fact that clinicians are seeking faster test results, while sometimes overlooking negative aspects, such as reduced accuracy, a higher risk of interferences and increased costs. Improving TAT is no mean feat, as it involves all aspects of laboratory testing from test ordering to result reporting, but issues of fundamental importance are TAT monitoring on a regular basis, taking into consideration not only the mean TAT, but also results reported within the 90° percentile and beyond the average (outliers). Another issue is TAT benchmark, which allows regular comparison between TATs from different laboratories thus enhancing professionals' understanding of the state-of-the-art in laboratory medicine and to guiding corrective/preventive improvement actions [43].

Data validation: Verification and validation of analytical results is another fundamental step in the post-analytical phase. One of the most serious laboratory errors threatening the patient's safety is still related to the erroneous manual transcription of data [44, 45]; this must be addressed by using reliable procedures. Automated informatics systems for verifying and validating laboratory results enhance the reliability of laboratory reports, not only allowing an enormous number of results to be analyzed, but also allowing a plausibility check between different tests thus adding clinical value to the individual laboratory report [46, 47]. Recently developed decision algorithm models based on the artificial neural network (ANN) approach enable the evaluation and cross-examination of large data sets involving highly nonlinear mathematical calculations [48].

Right units: The evidence of the urgent need to harmonize units used for reporting test results highlights the fact that variations in units incur a risk of clinical interpretation errors. For example, many laboratories are still reporting hemoglobin concentrations in g/dL, although the recommended unit is g/L. Units of measure should have been standardized following the 1971 publication defining SI Units, the mole being the measurement unit proposed. Yet current evidence collected in the UK and in Australia demonstrates significant variation in the units used for some tests and even more widespread variation in the way they are represented on monitors and paper as well as the way they appear in electronic messages. This, in turn, incurs a risk of misinterpretation of laboratory results thus compromising patient safety [49].

Right reference interval/decision limit: Reference intervals, the tools most widely used in laboratory medicine decision-making, underpin many interpretations of laboratory results. As shown in numerous studies, there are wide variations in reference intervals, even when the same platforms and reagents are used, and this contributes to the

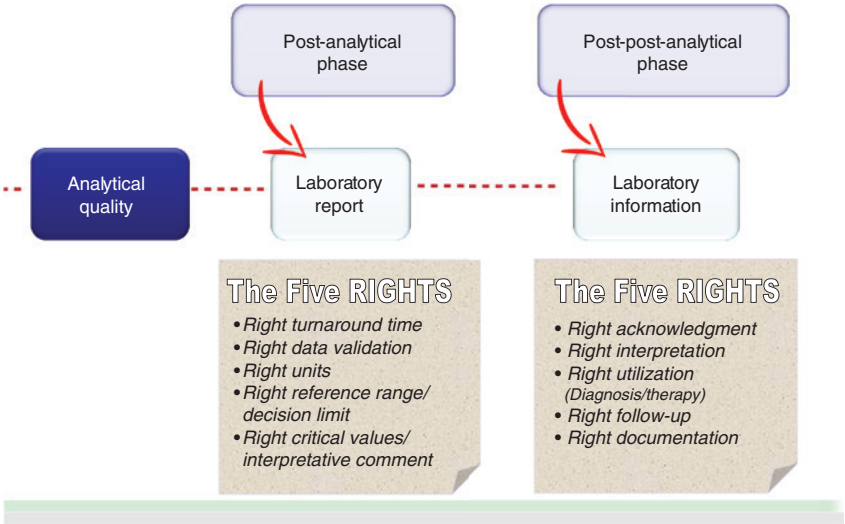

Figure 2: The five rights in the post-analytical phases.

risk of different clinical interpretations, with a consequent risk to patients and unnecessary test repetition [49, 50]. Unlike reference intervals, which are basically designed to confirm health with high specificity (usually 95%), decision limits, which are more clinically focussed and generally aim to confirm the presence of a particular disease or clinical risk with appropriate sensitivity, are used increasingly often in the clinical setting, particularly when recommended in practice guidelines. For some analytes, the variation in reference intervals and decision limits is greater than the analytical inaccuracy in their measurement. In addition, physicians and clinical care providers are unaware of this variation and its implications in the interpretation of laboratory results.

Right interpretative comment/critical values notification: the growing number and complexity of laboratory tests has led to the increased need of, and requests for, clinical advice in results interpretation. Several studies have shown that interpretative comments are an effective tool in enhancing diagnostic accuracy, reducing unnecessary testing and saving time and further tests. The quality of interpretative comments, however, is an open question as data from proficiency testing schemes have found that unacceptable interpretations lead to the conclusion that formal training of laboratory professionals should be provided, and assured [51]. The quality of interpretative comments, however, represents an open issue as data from proficiency testing schemes have found that unacceptable interpretation can be made, and lead to the conclusion that formal training of laboratory professionals should be provided and assured [52]. EQA programs for interpretative comments have been already established and are recognized as a continuing professional development activity [53].

In 1972, George D. Lundberg defined critical values as "a laboratory test representing a pathophysiological state so abnormal that (it) is life-threatening if action is not taken quickly and for which an effective action is possible" [54]. Since then, the recognition, documentation and notification of critical values by clinical laboratories have been promoted as crucial to patient safety and good laboratory practice. A recently published paper shows that in more than 40.0% of cases, critical values were unexpected findings and their notification notification led to a change of treatment in 98.0% of patients admitted to surgical and in 90.6% of those admitted to medical wards [55]. However, in various practices, differences in terminologies and values affect the quality of this post-analytical requirement. Wide variability in critical results practices has been reported, not only in different geographical areas, but also within the same country [56].

While the quality of analysis is undoubtedly important, so too is the quality of the final report including its reference intervals, clinical interpretations and notification. The accurate, construable and timely reporting of laboratory tests is as an important quality requirement as their proper execution.

Quality in the post-post-analytical phase makes good outcomes

During the post-post analytical phase, the ordering clinician, sometimes in consultation with the laboratorian, incorporates the test results into the patient clinical context, considers the probability of a particular diagnosis in the light of the test results and, in the light of the newly acquired information weighs the potential harm of future tests and treatments against their potential benefit. The "five rights" rule in this phase, requires the "Right Acknowledgment, Right Interpretation, Right Utilization (Diagnosis/Therapy), Right Follow-up and Right Documentation" (Figure 2).

Right acknowledgment: evidence in the literature shows that many laboratory reports, sometimes even emergency test results, are acknowledged with great delay. Lack of timely action on test results jeopardizes the patient's safety, and lead to dissatisfaction. Kilpatrick and Holding reported that the results from 1443/3228 (45%) of urgent requests from accident and emergency and 529/1836 (29%) from the admissions ward were not accessed via the ward terminal. Results from 794/3228 (25%) of accident and emergency requests and 413/1836 (22%) of admissions ward requests were seen within 1 h of becoming available, while a further 491/3228 (15%) and 341/1836 (19%), respectively, were accessed after 1 to 3 h [57]. The timely management of test results, an intriguing issue also in the primary care setting, has inspired studies in family medicine offices. Delays in reviewing test results are common, and many physicians are dissatisfied with the way in which test results are managed [58, 59]. Although improvements in information technologies and the introduction of the electronic medical record are of potentially valuable in helping practices improve upon test results management, great progress still needs to be made, especially in the steps calling for thought and input from laboratory staff and clinicians [60].

Right interpretation: Incorrect interpretation of laboratory tests causes a high percentage of errors in the ambulatory,

and in internal medicine and emergency departments [61–63].

Although most contributory factors are mistaken judgment, and lapses in vigilance or memory, an increasing body of evidence highlights the lack of technical competence and knowledge among physicians, particularly where innovative and complex tests are concerned. This, in turn, highlights the need for laboratory professionals to play an increasingly active part in facilitating the right interpretation of laboratory results.

Right utilization (*diagnosis/therapy*): Findings reported in laboratory utilization studies vary markedly due to complexity, different methodologies used, and dialectics between different aspects of diagnostic decision-making. While diagnostic errors have traditionally been dichotomized into so-called cognitive versus system errors [62], the laboratory and clinicians share responsibility for the right/wrong utilization of laboratory information. The laboratory should not be solely responsible for the quality of its reports, the appropriateness of reference intervals/decision limits, as well as the provision of interpretative comments and any further consultations. In fact, in the final part of the loop to assure quality and valuable patient outcomes, the right utilization of laboratory information should begin with the right request, through the right collection/handling of biospecimens and following the right and timely notification of data in an effective laboratory report.

Right follow-up and right documentation: Failure to follow-up on test results, particularly critical abnormal results, contributes greatly to poor quality. A study of closed malpractice claims found that 45% of all cases that included diagnostic errors involved inadequate follow-up of patients with abnormal test results [61]. In a study performed on four high-risk abnormal test results, it was found that in one-third of cases, no appropriate follow-up appeared in the clinical records; in cases with a follow-up, almost half the follow-ups were performed in an untimely manner [64]. Inadequate follow-up emerged as a leading process error also in abnormal imaging studies, highlighting the need to improve upon the final step of diagnostic testing [65]. Current electronic systems enable clinicians to acknowledge that they have viewed test results on-line and to record their follow-up actions. However, for the follow-up of results to occur without error, the information transfer between laboratory staff and clinicians must be re-examined, with a view not only devising technological solutions, but also to working out practice and policy solutions that take this cross-boundary communication process into account [66].

Analytical quality and current paradigm

The current paradigm on errors in the total testing process, and on the greater vulnerability of the extra-analytical phase does not translate into assurance of analytical quality; nor does it mean that efforts to improve it are no longer needed. First, the vulnerability of extra-analytical phase should continue to be predicted in view of the complexity of the processes, the existence of different operators, the lack of a well-identified process owner and the evidence that "the evil is in the boundaries" [67]. Since analytical processes are undertaken in the laboratory by a well-recognized process owner, they are easier to standardize, whereas pre- and post-analytical steps procedures are performed only in part by laboratory staff. Second, data reported in the literature are subject to a "real life" bias, as most laboratory results derive from the more frequently requested and more simple measurands, using more automated and standardized methods, and being verified by widely used quality control measures. Third, there is no discrepancy between the impressive reduction in analytical errors achieved over the last few decades and current evidence that analytical quality is not satisfactory when evaluated on the sigma scale, the Six Sigma being one of the best available approaches for providing objective estimates and metrics in several industries [68]. Despite the impressive improvement made in analytical quality, a body of evidence demonstrates that further improvements are needed. A recently published paper, for example, shows that the overall performance of the measurement of 17 general clinical chemistry analytes in European laboratories met the minimum performance specifications, but for six analytes this was not achieved [69]. In addition to problems related to analytical interference, particularly by heterophilic antibodies, commonly performed immunoassays are still affected by analytical bias which, sometimes, exceeds desirable quality goals [70]. The numerous examples given and evidence reported in the literature highlight the need to further improve the analytical phase. Fourth, the rate of analytical errors detected on analysing only abnormal results is misleading, as laboratory results within the reference interval should represent a significant source of inaccuracy when analysed with more stringent metrics, and evaluated against well-established performance criteria. Fifth, although the test cycle in some subspecialties of laboratory medicine (e.g. surgical pathology, cytology, microbiology) is similar to that in other laboratory tests, in that it consists of pre-analytic, analytic and post-analytic phases, the analytic phase is substantially different in that

it involves the inherent judgment of the professional at the time of the test interpretation [71]. It is therefore more subjective than most clinical chemistry tests, and its subjective nature makes it challenging to define errors in each phase and accurately document their incidence. However, the "magnitudo" of errors in pre-pre- and post-post-analytic phases is much greater than in the analytical phase as errors in patient/sample identification, and poor quality bio-specimens hinder the analytical process and represent an issue for patient safety. This also applies to the post-analytical phase, as transcription errors have been found to cause adverse events and patient harm, and errors in the post-post-analytical phase are closely related to diagnostic errors, delayed and missed diagnoses and therapies. Analytical errors have diminished, thanks to the great improvements made in assay standardization, automation, utilization of informatics, training of laboratory personnel, and the use and monitoring of quality indicators, as shown in Table 1. The setting of appropriate analytical performance specifications (namely bias and imprecision) on the basis of the criteria established in the Consensus Conferences of Stockholm and Milan [72, 73] was the first step in setting out valuable goals. Internal quality control (IQC) and external quality assurance/proficiency testing (EQA/PT) are the tools used by clinical laboratories to verify the achievement of the analytical goals, and the indicators are the intra- and inter-laboratory comparative performances. While these quality indicators have been available for several decades, in the extra-analytical phase the developments and utilization of reliable QIs is till in its infancy, thus making it difficult to control, monitor and improve upon the pre- and post-analytic phases [74–76]. It is time to close the gap between pilot projects on the harmonization of extra-analytical quality indicators and their current limited adoption by clinical laboratories. This phenomenon, currently considered "the quality indicator paradox" must be addressed [77].

Towards a new paradigm in laboratory medicine

The current paradigm on quality and errors in laboratory medicine is of value, and highlights the need to consider the total testing process "a set of interrelated or interacting activities that transform biologic patient sample materials into laboratory results and information to ultimately assure the most appropriate clinical outcome".

Table 1: Major drivers of the analytical quality improvement.

Goals	Analytical performance specifications (bias, imprecision)
Tools	Internal quality control and external quality assessment/proficiency testing
Indicators	Intra- and inter-laboratory comparative performances

Analytical quality continues to be the "core business" of clinical laboratories, but both laboratory professionals and clinicians must never lose sight of the fact that pre-analytical variables are often responsible for erroneous test results and that quality biospecimens are a pre-requisite for a reliable analytical phase. In addition, the pressure for expert advice on test selection and interpretation of results has grown hand in hand with the growth in the complexity of tests and diagnostic fields, thus underscoring the importance of the post-analytical phase. Finally, the data on diagnostic errors and inappropriate clinical decisions due to delay or misinterpretation of laboratory data highlights the need for a more comprehensive interaction at the clinical-laboratory interface. The brain-to-brain loop is experiencing its second youth: the concept of end-to-end service aptly reflects the laboratory process that starts at the point of referral by a doctor or specialist for the appropriate test/panel of tests, sometimes with the support of the laboratory professionals, ending only when action based on the added value of laboratory information is undertaken for the patient, thus enhancing the quality of the laboratory report. The advent of personalized medicine and the understanding of the molecular basis of disease have dramatically changed both the landscape of laboratory medicine and clinical practice, calling for a paradigmatic shift from a focus on analytical quality and volumes of activity to drive major efforts to a focus on assuring total quality and evaluating the outcomes of laboratory testing. Major drivers of this shift are: the need to: (a) offer a patient-centered service; (b) improve appropriateness in test request and interpretation, reducing waste and unjustified costs; (c) provide evidence of the added value of laboratory information; and (d) engage laboratory professionals as full members of the diagnostic team. This approach offers an opportunity for clinical laboratory professionals to greatly expand their mission from a factory model focused almost exclusively on providing accurate, timely test results at the lowest possible cost, to a mission that rapidly and efficiently enables the accurate diagnosis of conditions, the selection of appropriate treatments and the effective monitoring of health status [78]. Health care is shifting focus from the volume of services delivered to the value created for patients, with "value" defined as the outcomes achieved relative to the costs [79]. To survive the new and increasingly challenging landscape of health care, clinical laboratories must effectively demonstrate that laboratory information is of added value

in predicting susceptibility to disease, preventing – and making an early diagnosis of – disease, so as to establish the patient's prognosis and provide personalized treatment. This means that they must clearly play the role of key members in healthcare teams. Laboratory medicine should therefore figure as the "5 R" discipline, the five rights being based on: (1) Appropriateness; (2) Personalized and patient-centered service; (3) Focus on outcomes, (4) Value-added, and (5) Diagnostic partnership.

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