

Review

Preanalytical variability: the dark side of the moon in laboratory testing

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Abstract

Remarkable advances in instrument technology, automation and computer science have greatly simplified many aspects of previously tedious tasks in laboratory diagnostics, creating a greater volume of routine work, and significantly improving the quality of results of laboratory testing. Following the development and successful implementation of high-quality analytical standards, analytical errors are no longer the main factor influencing the reliability and clinical utilization of laboratory diagnostics. Therefore, additional sources of variation in the entire laboratory testing process should become the focus for further and necessary quality improvements. Errors occurring within the extra-analytical phases are still the prevailing source of concern. Accordingly, lack of standardized procedures for sample collection, including patient preparation, specimen acquisition, handling and storage, account for up to 93% of the errors currently encountered within the entire diagnostic process. The profound awareness that complete elimination of laboratory testing errors is unrealistic, especially those relating to extra-analytical phases that are harder to control, highlights the importance of good laboratory practice and compliance with the new accreditation standards, which encompass the adoption of suitable strategies for error prevention, tracking and reduction, including process redesign, the use of extra-analytical specifications and improved communication among caregivers.

Keywords: error; laboratory instrumentation; laboratory testing; preanalytical variability.

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The medical error

Systems of medical and healthcare practices have existed among human societies since at least the dawn of recorded history. When medicine was basically characterized by the doctor's intellect, the nurse's empathy, simple surgical procedures and a limited number of drugs, there was little price to be paid for poor safety systems or disorganization, and adverse events were generally attributed to providence, fate, misfortune, or "God's will" (1). As medicine became more powerful and technologically sophisticated, highly specialized teams for care delivery emerged (2). In common with all other human activities, accidents go hand in hand with medicine and represent an unfavorable but inevitable circumstance. There is a long history of errors in medicine and the last century has seen a growing openness on the part of the medical profession regarding the part played by human error in patient mishaps. An evocative body of research describing this problem began to emerge in the early 1990s, supported by the Agency for Health Care Policy and Research, now the Agency for Healthcare Research and Quality (AHRQ), when medical errors were identified as one of the four major challenges facing the USA in improving healthcare quality (3). In its report, "To Err Is Human: Building a Safer Health System", the United States Institute of Medicine (IOM) estimated that 44,000–98,000 Americans die each year not from the medical conditions they checked in with, but from preventable medical errors (4). IOM statistical analysis identifies medical errors as the eighth leading cause of death among Americans, with error-caused deaths each year in hospitals alone exceeding those from car, plane and other traumatic accidents and far ahead of those related to breast cancer or acquired immunodeficiency syndrome (AIDS). In practice, a US patient should be currently much more worried when falling within the net of the healthcare provider rather than deciding to take a plane. Nevertheless, such a significant figure, which is apparently attributable to professional malpractice or to lax compliance with quality requirements, should take into account some peculiar aspects of the care provided in the United States, such as the presence of highly specialized centers where complex procedures are performed (5). Therefore, comparison of error rates among different countries is hampered by substantial differences in design and development of national health systems, incidence of diseases and many other factors. For instance, analysis of the available data suggests that the United States performs the greatest or nearly the

greatest number of medical procedures per capita in several areas, including, for example, coronary bypass, dialysis and magnetic resonance imaging (6).

A medical error, according to the IOM definition, could mean "a health-care provider chose an inappropriate method of care, or it could also mean the health provider chose the right course of care but carried it out incorrectly". Alternatively, a medical error is "the failure to complete a planned action as intended or the use of a wrong plan to achieve an aim". An adverse event is defined as "an injury caused by medical management rather than by the underlying disease or condition of the patient" (4). The key point of the report is that "whether a person is sick or just trying to stay healthy, he or she should not have to worry about being harmed by the health system itself". Following the IOM declaration, the medical community has considerably increased awareness of this topic and several regulatory bodies and specialty organizations have incorporated the provision of increased patient safety as a core principle for accreditation. However, although great emphasis has been placed on medical errors alleged to have resulted in increased patient morbidity and mortality, less attention was paid to the tracking and prevention of diagnostic errors. In general, diagnostic errors are commonly multifactorial in origin and can be clustered within three categories: "system errors" typically play a role when diagnosis is delayed or missed because of latent imperfections in the healthcare system; "no-fault errors" occur when the disease is silent, presents atypically, or mimics something more common; and "cognitive errors" reflect misdiagnosis from faulty data collection or interpretation, flawed reasoning, or incomplete knowledge (7).

Types and frequency of errors in laboratory medicine

Most people, especially those less involved in the healthcare system, tend to believe that medical errors usually occur from misuse of drugs or mishandled surgery. Nevertheless, there are many other types of medical errors, including misinterpretation of medical orders and prescriptions, nosocomial and post-surgical wound infections, equipment failure and, last but not least, diagnostic errors, such as misdiagnosis leading to an incorrect choice of therapy, failure to use an indicated diagnostic test, misinterpretation of test results, and failure to act on abnormal results. Although there are several and heterogeneous characterizations for "laboratory error", a reasonable definition, recently acknowledged by the International Organization for Standardization, could be "any defect from ordering tests to reporting results and appropriately interpreting and reacting on these" (8, 9). Although there is extensive literature dealing with the prevalence and types of mistakes, there is varying information on the total (preanalytical, analytical and postanalytical) error rates for laboratory testing, the relative burden of which traditionally spans a wide range (0.1–9.3%). The main reasons for such a broad

difference are underreporting and impaired error detection techniques, the lack of a definite and universally accepted definition of laboratory testing error before 2002, different study designs and heterogeneous methodological approaches (10). Using data from the current literature, the error probability spans from 1 in 8300 laboratory results (or 2000 patients) (11) to 1 in 33–50 laboratory results (12). As these two limits probably do not reflect the real situation, a more probable error rate might range from 1 in 164 to 1 in 330 events or laboratory results (13–16). However, even very low rates, because of the large number of laboratory tests available, may reflect significant patient numbers (17).

Whatever the type (random or systematic), there are several occasions for laboratory testing errors. Substantial advancements in automation and computer applications, particularly during the last two decades, have raised the awareness that analytical errors are no longer the main factor influencing the quality of laboratory testing, allowing a major sense of security regarding the analytical phase and focusing attention on alternative sources of errors, such as preanalytical and postanalytical factors. The process of laboratory medicine is typically divided into three main phases (preanalytical, analytical and postanalytical), with each of them variably affected by uncertainties and errors (18). Despite heterogeneity in study design, methodology of process analysis and error tracking or classification, the error distribution across the different phases of the entire testing process appears similar. In particular, it has been demonstrated that most laboratory errors occur in the preanalytical phase, primarily because of a lack of standardized protocols. The main reason for the high prevalence of errors in this crucial step of the testing process is that it is currently difficult to monitor all preanalytical variables and to implement any improvement processes necessary, particularly when most of the variables (such as phlebotomy) are not under direct laboratory control or supervision (19). The relative percentage of errors in this phase, suggested to be as high as 84.5% (8, 20), is frightening. There is a considerable difference between in- and outpatients, as reflected by the rather different error rates (0.60% vs. 0.039% for the two categories, respectively), which has been attributed to human factors related to skill in drawing blood and the sheer volume of laboratory tests carried out for inpatients (8, 10). Therefore, patient care involving non-laboratory personnel seems to account for the majority of errors, representing 95.2% of these mistakes (21). The typology of preanalytical errors encountered in laboratory practice is rather heterogeneous (Figure 1). Data from the most representative studies on this topic show that problems directly related to specimen collection are the main cause of preanalytical errors or variability, including hemolyzed (54%), insufficient (21%), incorrect (13%) and clotted (5%) samples (8). In vitro hemolysis, reflecting a more generalized process of blood and vascular cell damage that occurs during phlebotomy, is the most frequent reason for

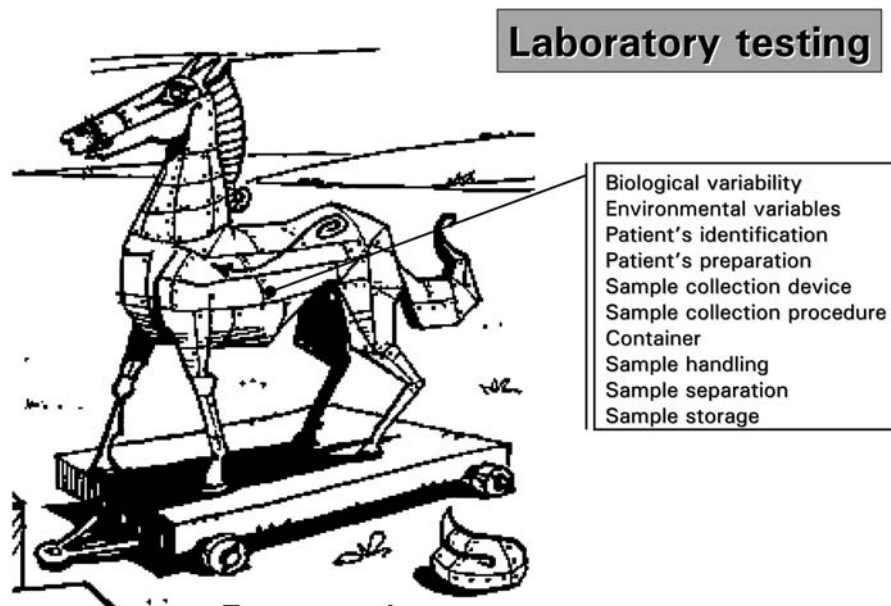


Figure 1 Preanalytical variables and laboratory testing.

specimen rejection, five-fold more frequent than the next reason (insufficient specimen quantity), as indicated by the College of American Pathologists (CAP) Chemistry Specimen Acceptance Q-Probes study (22). In hematology, a clotted specimen is the most frequent reason for rejection and the container type with the highest frequency of rejection is a pediatric tube (17). Overall, inappropriate specimen quality and quantity account for over 60% of preanalytical errors. Additional problems, such as incorrect sample identification or handling, might occur beyond the blood drawing process, although their prevalence is reportedly much lower (22).

Lesser identifiable errors in laboratory medicine

Besides the circumstances previously described, there are some further and less controllable sources of preanalytical errors that can seriously influence the reliability of laboratory testing, but which are barely identifiable by laboratory staff. These primarily include patient-related physical variables (physical exercise, diet, stress, positional effects), mild or visually undetectable hemolysis, hemolyzed specimens for analyses that do not require sample separation, and prolonged tourniquet stasis during blood drawing. Owing to regular training-induced variations of plasma volume and metabolites, regular physical exercise has a strong influence on several biochemical and hematological variables (23–27). Therefore, interpretation of some laboratory data in physically active individuals may require caution, as results falling outside the conventional reference ranges are more likely to reflect a physiological adaptation to regular training rather than underlying pathologies. Thus, individual lifestyle and biological rhythms should be always taken into consideration before sample collection.

Visible hemolysis, usually defined as extracellular hemoglobin concentrations above 0.3 g/L (4.65 mol/L), confers a detectable pink to red hue to serum or plasma and is clearly visible in specimens containing as low as 0.5% hemolysate (28). In vitro hemolysis traditionally reflects a more generalized process of vascular and blood cell damage that can occur during phlebotomy, which causes cell membrane disruption and leakage of hemoglobin and other cellular components into the surrounding fluid. Hemolysis has always plagued clinical laboratories and is a growing concern, as hemolyzed specimens are a rather frequent occurrence, with prevalence as high as 3.3% of all samples submitted to a clinical laboratory (29). Leakage of intracellular analytes in plasma might produce falsely elevated measurable concentrations or dilutional effects, increase the optical absorbance or change the blank value, producing method- and analyte concentration-dependent spectrophotometric interference in common laboratory assays. Unfortunately, clinically meaningful variations of some biochemical and coagulation tests can be observed in specimens displaying hemolysis that is mild or almost undetectable by visual inspection (serum hemoglobin <0.3 g/L) (30, 31). The tentative solution to reporting laboratory test results for hemolyzed specimens by including messages or flags is rather questionable, irrespective of the application of correction formulas calculated from linear regression of absolute error vs. hemoglobin concentration. In fact, the heterogeneous and unpredictable response to lysis observed for several parameters prevents the adoption of reliable statistical corrective measures on the basis of the degree of hemolysis. Therefore, if hemolysis results from an in vitro cause, the most convenient corrective solution might be warning the clinician and collection of a new sample.

Before venipuncture, a tourniquet is frequently used to assist the phlebotomist in locating a suitable

vein. Ideally, the tourniquet should be applied if necessary and quickly removed when the needle is safely in the vein. In clinical practice, however, the tourniquet is rarely released before the blood drawing process is completed. Although blood collection is supposed to be as fast as possible, several circumstances might contribute to increase the time of venous stasis up to minutes, influencing the concentration of several analytes in plasma. In particular, hemoconcentration is recognized as a major factor contributing to increased concentrations of large molecules, such as proteins and protein-bound substances, cells and coagulation factors. We have recently demonstrated that analytically and clinically significant changes from the standard venipuncture are likely to occur for several biochemical, hematological and coagulation tests, even after a traditional time (from 1 to 3 min) for tourniquet placement (32–34). These effects were mostly dependent upon stasis time and biochemical characteristics of the analyte. Therefore, tourniquet-induced variations in laboratory testing can be anticipated, highlighting the need to adopt the most appropriate preventive measures to minimize the influence of venous stasis.

The influence of these lesser or non-identifiable sources of variability (Table 1) represents another challenge that is even greater than that represented by the prevention and solution of other and more typical extra-analytical errors. In fact, because they can scarcely be identified by current strategies based on continuous laboratory monitoring and longitudinal tracking, they can be hard to resolve.

Consequences of laboratory errors

Procedures to measure the quality of laboratory testing have long been a challenging problem for laboratory managers and accreditation agencies. It is now widely accepted that spurious changes in laboratory testing arising from inappropriate or inaccurate application of rigid preanalytical protocols might be harmful and misleading, consuming valuable healthcare resources and leading to potential errors or delays in patient care (35). As laboratory testing errors mainly occur outside the analytical process, they are likely to span the current branches or subspecialties of laboratory medicine, including clinical biochemistry, hematology, coagulation, immunometry and molecular biology. Methods such as sequence analysis of whole

genomes, DNA microarray technology and mass spectrometry have been or are being developed as high-throughput approaches for additional types of genomic analyses, such as determining the parameters of gene expression or the location of gene products, using thousands of samples at a time instead of individually. Thus, as genomic and proteomic technologies progress towards higher throughput, upstream sample preparation becomes a potential bottleneck, and specimen collection, transport, storage and handling appear to be as critical as extraction and purification procedures. In particular, genotypic errors, whether due to mutation or laboratory error, can lead to identification of the genotypes of parents and their offspring as being inconsistent with Mendelian inheritance, with rather unfavorable medical and legal consequences (36). As a prerequisite to the use of molecular biology techniques in the clinical laboratory, there must thus be awareness of the additional preanalytical pitfalls associated with these emerging techniques, such as the type of detergent used in cell lysis, the anticoagulants used for blood collection, residual erythrocytes, and the type and duration of tissue fixation (37).

Although clinicians are increasingly used to a high degree of quality for laboratory results, most recipients of laboratory test results take the probability of errors into account in their clinical practice (35); indeed, in a less desirable scenario, some of them occasionally perceive results of laboratory testing as a “Trojan horse” (Figure 1). Over recent years, laboratory information has been reported and provided to clinicians in an attractive graphical style, associated with appropriate reference ranges for both age and sex. However, this may hide a wide variety of pre-analytical errors that reduce the quality of the whole testing process. Inappropriate laboratory utilization ultimately increases healthcare costs, harms patients and perpetuates the vision of laboratory testing as a commodity. Laboratory expenditure as a proportion of total hospital care accounts for 4% in the United Kingdom, 5.2% in Australia, 7–10% in Canada and 5% in the United States (38). Improvements in specimen quality and result utilization are hence essential for quality improvement initiatives and health cost reductions. The error budget that clinicians might spend on testing errors for the 31 most frequent laboratory tests, based upon critical differences, is 26.9%, when, for the same 31 tests and production conditions, the overall biological variation is 7.9% (18).

Table 1 Synopsis of the interference of some lesser identifiable preanalytical variables on laboratory testing.

Variable	Major effects	References
Physical activity	Plasma volume expansion Increased basal metabolism	(23–25) (26, 27)
Venous stasis	Hemoconcentration (increased plasma concentration of large analytes and protein-bound molecules, decreased plasma concentration of small analytes)	(30, 31)
In vitro hemolysis	Leakage of intracellular analytes Dilutional effects of extracellular analytes Analytical interference	(32, 33) (34)

Preventive and reparative solutions

The IOM emphasizes that most medical errors are likely system-related and less attributable to individual negligence or malpractice. Accordingly, the key to reducing medical errors is to focus on improving the systems of delivering care and not to blame individuals. At this point, the crucial question is: how can we handle this problem in order to minimize the effect of preanalytical variables, while ensuring greater accuracy and confidence in laboratory testing and improving the reliability and quality of our results? Traditionally, laboratory quality has been assessed by direct inspection, proficiency testing, and monitoring of staff credentials. However, none of these approaches was demonstrated to be fully satisfactory in addressing the pivotal problem of providing technically accurate and clinically meaningful information (39). CAP has focused major attention on errors in pathology and laboratory medicine since its inception in 1946, contributing efforts and resources to organized strategies to reduce or eliminate these errors (17).

The evidence that most laboratory testing errors occur for inpatients and are often outside the direct control of the laboratory staff suggests a solution that is apparently the most obvious, though not necessarily the simplest for reducing the complexity of the entire preanalytical phase. Some technologies have improved in a linear fashion or incrementally over time, whereas others have truly led to a paradigm shift. Beyond the rapid spread of point-of-care devices, there are emerging scenarios in biochemical testing that may soon revolutionize the current diagnostic approach *in vitro*. Progress has been made in improving process robustness, and in manufacturing rugged and miniaturized electroanalytical devices. The development of new sensing technologies, such as near-infrared and fluorescence spectroscopy, optical biosensors, *in situ* microscopes, surface plasmon resonance and reflectometric interference spectroscopy, offers considerable promise for improved electrochemical sensing, leading to complete analytical systems capable of monitoring a broad spectrum of analytes *in vivo* (40–42). Optical sensors, which encompass all analytical methods based on interactions of light with matter, can offer the advantages of non-invasive, non-destructive, continuous, and simultaneous multianalyte monitoring, meeting the special demands of several diagnostic processes. Recently, advances were made in the development of implantable chemical sensors capable of real-time monitoring of clinically important species such as PO₂, PCO₂, pH, glucose and lactate (43). Although no commercial optical detection system has been fully developed so far, glucose sensors using the transdermal, microdialysis or open tissue microperfusion technique are currently under clinical development and may also become available in the near future (44). Although iontophoresis, a technique based on the application of a small electric current to enhance the transport of several compounds across the skin, has mainly been

used for transdermal drug delivery, “reverse iontophoresis” has recently been the subject of considerable technological efforts and has been proposed for alternative applications, including general blood chemistry testing, glucose monitoring, detection of diagnostic markers and therapeutic drug monitoring (45). Unfortunately, some of these promising techniques currently do not work for molecules with particular physicochemical properties, such as extremely lipophilic compounds or large proteins, as they either display extremely low aqueous solubility or are simply too large to be extracted in quantifiable amounts. However, a potential use of these revolutionary techniques for clinical chemistry testing without blood sampling exists and represents a futuristic and attractive perspective that may eliminate a wide series of preanalytical procedures directly related to specimen collection, handling, storage and processing.

More realistically, a standard process for detecting, tracking, classifying and reporting laboratory testing errors should be developed and successfully applied. Compliance with new accreditation standards, such as the Clinical Pathology Accreditation or ISO/IEC 15189:2002 requirements, encompasses strict procedures for the extra-analytical phase, such as collection and handling of primary samples, traceability of sample portions and sample storage (38). Besides programs for improving analytical performance by establishing daily quality control (Quality Assurance Service) and proficiency programs (Surveys), CAP has supported protocols to define the frequency of errors throughout all facets of laboratory testing (Q-Probes and Q-Tracks) (17). Accordingly, each error encountered throughout the entire laboratory work-up should be rated and possibly associated with perceived or tangible effects on patient outcome. The use of extra-analytical indicators and specifications for the preanalytical phase constitutes a potentially useful tool and a further preliminary basis for comparison of individual laboratory performance, with the purpose of continuous improvement of laboratory quality (46). These proposed indicators are thus intended as reliable, though not always universally applicable, measures for assessing the outcome of a specific clinical reasoning process, and can be considered a functional aid for the quantitative measurement of quality. Unfortunately, the availability of reliable outcome indicators that can be used to compare diagnostic performances is still sparse.

From a practical viewpoint, total quality management calls for an integrated approach, and error reduction can be achieved through process redesign by, for example, applying the Hazard Analysis and Critical Control Points approach (18). This innovative strategy requires preliminary identification of the most error-prone steps in the whole laboratory work-up, followed by the adoption of control procedures at these critical steps. Error rate measurements and correction systems can be used for parts of the entire process and the overall laboratory procedure might be redesigned more efficiently. Intelligent and automated capabilities for preanalytical process control

could represent an attractive perspective, as they could favorably influence the error rate without negatively impacting the process throughput (47).

Decentralized phlebotomy has been blamed for a litany of quality problems. As most laboratory errors arise from disorganization or lack of standardization, and involve sampling phases outside the laboratory, an effective measure is likely to result from improved communication among caregivers and interdepartmental cooperation to achieve improved specimen quality and data dissemination (48). This process highlights the usefulness of clinical audits. Indeed, there is much better compliance with specimen collection policies and procedures when phlebotomists and specimen collectors clearly understand why things are done according to a standardized and accurate procedure. Although restrictive policies for specimen acceptance and very strict criteria for rejection of inappropriate specimens may represent useful approaches, proactive efforts to intervene further upstream might yield major benefits, especially in the long term. In this context, knowledge dissemination, training and education are key points. Certification of phlebotomists, including training curricula for all collection staff, preferably developed by the laboratory, is another essential part of this crucial process of standardization.

A final approach is based on laboratory quality control procedures for patient data. The wider availability of computers in today's laboratories allows the application of innovative statistical quality control procedures, such as those based on Bull's algorithm and delta checking (49). "Downstream event monitoring" (DEM), based on monitoring of events in laboratory patients within a critical window of time after they have been tested, is a potentially effective instrument. This applies the principles of quality management to determine if the laboratory product has satisfactorily met patient needs (39). In clinical practice, if a laboratory's patients have an unusually high rate of adverse events that happen within a window of time when the laboratory test would have played a critical role, the laboratory should be further examined to see if it is the cause of the problem.

Conclusions

Radical changes have occurred in the organization, number and type of tests and in the role of medical laboratories in healthcare over recent years. The affirmation of a new role for laboratory professionals calls for greater analytical accuracy, and more stringent test selection and interpretation of results (50). The question remains, however, as to where the greatest needs for improvement to achieve these goals are. Laboratory data are an integral, often pivotal, part of the complex decision-making process, influencing up to 70% of medical diagnoses (51). The increasing awareness of issues involving medical errors within healthcare has cast a spotlight on the factors that contribute to the resulting adverse events and has also

made clinical laboratories the subject of scrutiny as essential parts of the overall healthcare system. As preanalytical sources of variation can produce unpredictable and unfavorable impacts on the wellbeing of patients (18), a reduction in laboratory testing errors and quality improvements both play a significant role in programs for assessing and improving quality in healthcare. By definition, technology is dynamic, and in many ways it dictates advances in laboratory diagnostics. Automation, databases and computers have greatly simplified many aspects of previously tedious tasks, creating a greater volume of routine work, as well as significantly improving the analytical error rate over time. Therefore, mistakes outside the analytical phase of testing seem more likely to affect the usefulness of laboratory results in patient care. The attention of laboratory professionals should now be focused on alternative and prevailing sources of errors, such as those occurring within the preanalytical and postanalytical phases. Competent knowledge of these possible sources of variability is a critical precondition for their avoidance, although there is nearly universal agreement that laboratory tests are over-utilized and one of the biggest sources of preanalytical variability might be differences in the test-ordering patterns of care providers (52). Attempts to reduce unnecessary testing have often been difficult to implement or sustain. Interventions with the greatest impact use multiple approaches, are repeated regularly, and include multifaceted education, peer assessment and effective feedback strategies (53). Besides direct policies aimed at improving the appropriateness of test requests and utilization, additional preanalytical factors are common causes of inaccurate test results. Moreover, most complaints about unreliable laboratory testing are frequently a direct outcome of incorrect techniques immediately associated with the sampling procedure, such as phlebotomy and specimen collection. In this respect, consistent quality specimens, resulting from proper training and knowledge of the factors that can influence laboratory results, are essential for minimizing errors and optimizing resource utilization and quality, and finally improving the whole patient management process.

The pursuit of safety is a multidisciplinary enterprise. This is as true for patient safety, hitherto an exclusively medical domain, as for any other safety issue. Each treatment or diagnostic maneuver presents a dark side of the moon, represented by the opportunity for errors. It is thus clear that human error in medicine does exist and is a profound challenge. As is necessary when seeking to solve any problem, the problem must first be described and the factors contributing to it identified. Given the nature of humans to err, we are aware that the complete elimination of errors in clinical and laboratory medicine is probably unattainable. However, emerging tools are available to successfully reduce them or, at least, to limit their potential adverse consequences on the patient's health. In his most eminent dissertation, Marcus Tullius Cicero concluded that "Cujusvis homi-

nis est errare; nullius, nisi insipiens, in errore perseverare" (to err is human, but to persevere in error is only the act of a fool). This is also reasonably true when dealing with laboratory errors, unless such errors can actually be identified.

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