Opinion Paper

Preanalytical quality improvement: from dream to reality

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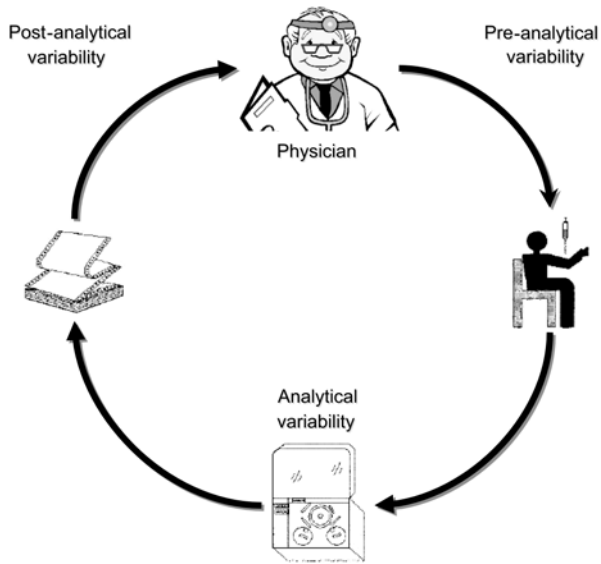
Abstract

Laboratory diagnostics (i.e., the total testing process) develops conventionally through a virtual loop, originally referred to as ''the brain to brain cycle'' by George Lundberg. Throughout this complex cycle, there is an inherent possibility that a mistake might occur. According to reliable data, preanalytical errors still account for nearly 60%–70% of all problems occurring in laboratory diagnostics, most of them attributable to mishandling procedures during collection, handling, preparing or storing the specimens. Although most of these would be ''intercepted'' before inappropriate reactions are taken, in nearly one fifth of the cases they can produce inappropriate investigations and unjustifiable increase in costs, while generating inappropriate clinical decisions and causing some unfortunate circumstances. Several steps have already been undertaken to increase awareness and establish a governance of this frequently overlooked aspect of the total testing process. Standardization and monitoring preanalytical variables is of foremost importance and is associated with the most efficient and well-organized laboratories, resulting in reduced operational costs and increased revenues. As such, this article is aimed at providing readers with significant updates on the total quality management of the preanalytical phase to endeavour further improvement for patient safety throughout this phase of the total testing process.

Keywords: errors; laboratory diagnostics; patient safety; preanalytical phase; quality.

Introduction

Laboratory diagnostics (i.e., the total testing process) develops conventionally through a virtual loop, originally referred to as ''the brain to brain cycle'' by George Lundberg. The eminent scientist pragmatically conjectured that ''… *a laboratory test begins when a person's brain, usually that of a physician, but it could be a patient or some other healthcare professional, decides that it would be a good idea to have a lab test and orders it. After that, a process results in collection of the specimen, identification of the patient and the specimen, and transportation of the specimen to the laboratory, where is received and prepared for analysis. The result is then reported to the stakeholder (i.e., the ''receiver''), who is hopefully the person who placed the original order, and who interprets the result and takes some action on it*''. Throughout this complex cycle, there is an inherent possibility that a mistake might occur (1, 2). The large amount of knowledge gained over the past decades on the

Figure 1 Major sources of pre-analytical variability.

controversial issue of diagnostic errors indicates, however, that most errors do occur in the extra-analytical phases of the total testing process and, especially, in the manually-intensive processes of the preanalytical phase. As such, and according to reliable data, preanalytical errors still account for nearly 60%–70% of all mistakes occurring in laboratory diagnostics, most of them attributable to mishandling during collection, handling and preparing the specimens for testing (Figures 1, 2 and 3) (3, 4). Although most of these errors would be ''intercepted'' by laboratory professional or physicians before inappropriate actions are taken on otherwise unreliable results of laboratory testing, in nearly one-fifth of

the cases these errors might be associated with further inappropriate investigations and unjustifiable increase in costs, and – even more notably – in 6.4% of the cases they might be a cause of inappropriate care or inappropriate modifications to therapy (5).
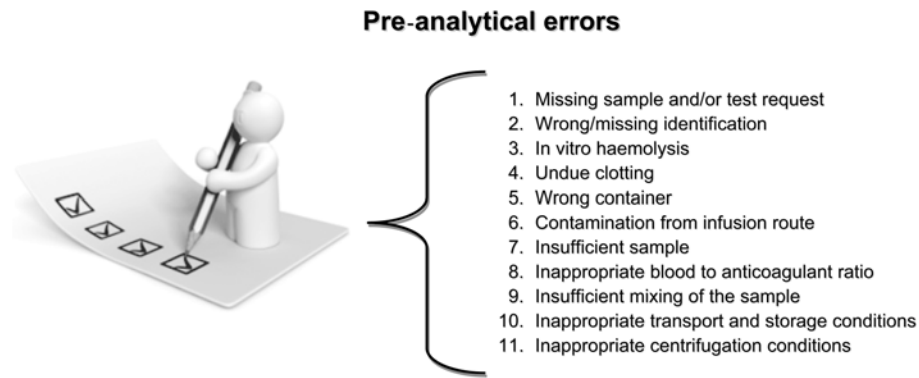
Although several areas of healthcare are still struggling with the concept of patient safety, laboratory diagnostics has been a forerunner in pursuing this issue, and the practice of total quality management (TQM) has now become commonplace throughout most clinical laboratories worldwide (6, 7). While it is clear to everyone working in the field of laboratory medicine that most efforts have been focused on improving the quality in the analytical phase of testing, the high burden of errors still occurring within the preanalytical processes calls for a further broadening of the concept of TQM, to also embrace the processes external to the laboratory, in an enterprise which would enable establishment of a governance of this often mistreated phase of the total testing process (8–10). Several steps have already been undertaken to increase awareness and establish a governance of this frequently overlooked aspect of the total testing process, including: the ''Working Group on Laboratory Errors and Patient Safety (WG-LEPS)'' instituted by the Division of Education and Management (EMD) of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) which has the mission to promote and encourage investigations into every kind of error in laboratory medicine (including the preanalytical phase), collect data available on this issue and recommend strategies and procedures for improving patient safety (11, 12), ''specimencare.com'', is an online resource designed to identify, evaluate and promote the application of best practices in all aspects of the preanalytical phase of laboratory testing in clinical medicine (13). This article, which is aimed at providing readers with significant updates

Major sources of pre-analytical variability

1. **Patient preparation**
   - Biological variability
   - Environmental conditions (e.g., climate, pollution)
   - Postural changes
2. **Sample collection**
   - Patient identification and sample labeling
   - Type of disposal for collecting blood (e.g., straight needle, butterfly, cannula)
   - Caliber (gauge) of the needle
   - Tourniquet time
   - Container (e.g., primary tube)
   - Order of draw
   - Phlebotomy procedure
   - Contamination from ….
   - Tube/s mixing
3. **Sample transportation**
   - Length and environmental conditions
   - Pneumatic tube systems
4. **Sample preparation for analysis**
   - Length, speed and temperature of centrifugation
   - Preparing aliquots
5. **Sample storage**
   - Length
   - Temperature
   - Freezing & thawing

Figure 2 Leading pre-analytical errors.

Pre-analytical errors

1. Missing sample and/or test request
2. Wrong/missing identification
3. In vitro haemolysis
4. Undue clotting
5. Wrong container
6. Contamination from infusion route
7. Insufficient sample
8. Inappropriate blood to anticoagulant ratio
9. Insufficient mixing of the sample
10. Inappropriate transport and storage conditions
11. Inappropriate centrifugation conditions

Figure 3 Pre-analytical errors.

on the TQM of the preanalytical phase to endeavour further improvement for patient safety throughout this crucial phase of the total testing process, represents a synopsis of the lectures of the European Federation of Clinical Chemistry and Laboratory Medicine (EFCC) meeting ''Preanalytical quality improvement: from dream to reality'' (Parma, 1–2 April 2011) (http://www.preanalytical-phase.org/node/1).

Errors in laboratory diagnostics

Errors in laboratory medicine are part of the wider problem concerning diagnostic errors (14). These, in turn, are defined as ''Errors in which 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)''. A body of evidence has been collected to demonstrate both the frequency and relevance of diagnostic errors and their impact on patient safety.

The clinical laboratory is not a completely ''safe'' place as it is traditionally assumed to be and, similarly to other diagnostic areas, something wrong may occur and – incidentally – it does occur (15). At variance with radiological errors, which are mainly dependent on human failures, several surveys over the past decade attest that laboratory errors do follow a rather different pathway. The last few decades have seen a significant decrease in the rates of analytical errors, and available evidence demonstrates that the pre- and post-analytical (PAPA) steps of the total testing process are more error-prone than the analytical phase. In a patient centred approach to the delivery of healthcare services, it is thereby necessary to investigate throughout the total testing process any possible defect that may produce adverse impacts on the patient. In fact, 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) (1, 16). Patient misidentification, which affects the delivery of all diagnostic

services, is widely recognized as the main goal for quality improvement, and some international initiatives aim at improving this aspect. Sample collection and transport of specimens are increasingly recognized as sources of errors in everyday clinical practice. A suitable system for grading laboratory errors on the basis of their seriousness should help identify priorities for quality improvement and encourage a focus on corrective/preventive actions. However, it is important to consider not only the actual patient harm sustained, but also the potential worst case outcome if such an error were to recur. The most important lessons we have learned are that system theory applies also in laboratory testing and that errors and injuries can be prevented by redesigning systems that make it difficult for healthcare professionals to make mistakes. As such, all laboratory professionals are invited to look at the IFCC-WG-''LEPS'' (11) (available at: www3.centroricercabiomedica.it), and to share their experience on some quality indicators, thus allowing benchmarking among medical laboratories at the international level.

The impact of biological variability on laboratory testing

Biological variation comprises between subject and within-subject variation. Between subject variation is the basis for the reference interval, whereas within-subject variation (CVws) permits calculation of the reference change value (RCV) to assess the minimum change from the previous laboratory result that is considered statistically significant. The RCV for interpreting a measured difference is based on the analytical imprecision as well as the CVws estimated from healthy (or diseased) individuals during the steady state, assuming a gaussian distributions and homogeneity. For biological data, inter-individual coefficient of variation (CVi) is often calculated after a log-normal transformation. It is important to emphasize that the RCV provides only a measure for judging the probability that a difference in consecutive results can be explained by the analytical and CVws seen in patients in a stable situation. It does not provide a measure for judging the probability that a true change has occurred. For a thorough evaluation of the difference between two results, it is important that both of these aspects be taken into

account. A model in which one assumes two frequency distributions of differences, one for a stable steady-state situation and one for a certain true change has been suggested. A measured difference will thus represent a ''false change'' for a patient in a stable situation, but a ''true change'' if the patient's condition has actually changed. The ratio between these changes (true change/false change) will be the likelihood ratio (LR) that a change in the test result is caused by the disease, similar to the LR of a diagnostic test (true positive/false positive). The LR for the disease increases with increasing measured differences between the two results. When the LR is combined with the pre-test probability (prevalence of disease), the post-test probability of a true change (i.e., the disease) can be calculated using Bayes theorem (17). Using this model, it can be shown that for a hemoglobin A1c (HbA1c) instrument having an imprecision of 3%, there is a 56% probability of discovering a true change in an HbA1c of 10%, whereas this change will be detected with a probability of 99% using an instrument with an imprecision of 1%. This will be of great importance when deciding what instruments to buy and how to interpret test results. Moreover, combining biases between various HbA1c measurements in different laboratories with the biological CVws, a true change in HbA1c may only be appreciated at much higher values (e.g., 30%).

Governance of the preanalytical variability

Laboratory diagnostics is a highly complex enterprise and it is supposed to be relatively safe, at least as compared with other diagnostic arenas, it is still not as safe as it could, or should be. Laboratory professional have long focused on quality control methods and quality assessment programs dealing with the analytical aspects of the total testing process. However, a large body of evidence demonstrates that quality in laboratory diagnostics cannot be assured by merely focusing on the analytical phase, but rather is should encompass the process at the beginning and at the end of the total testing process. In particular, most errors in laboratory diagnostics occur in the manually intensive preanalytical phase of testing, which spans a wide range of operations which include labeling (i.e., positive identification), collection, handling, transportation, centrifugation, aliquoting, sorting and storage of the specimens. The largest number of unsuitable specimens is attributable to mishandling or inappropriate procedures during collection (i.e., identification errors, in vitro hemolysis, inappropriate clotting, use of wrong containers). Additional problems include inappropriate storage conditions during transportation and inappropriate procedures for sample preparation before analysis (e.g., refrigeration, time delay before analysis, centrifuging conditions). In agreement with the foremost model of human errors of the Swiss cheese model, where defensive layers (slice of cheese) have a number of vulnerabilities (holes) that are continually opening, shutting and shifting their location, leaving the opportunity for a trajectory of accident opportunity that may irreversibly penetrate the barrier, the most reliable and effective approach for limiting the impact of preanalytical variability is the implementation of a multifaceted strategy, encompassing the adoption of a wide series of diversified defensive layers that would limit the eventuality of any adverse event of occurring (8, 10, 18). As such, full implementation of risk management and total quality system is mandatory, through a strategic approach which would include a foremost policy for prediction of accidental events (i.e., process analysis, reassessment and rearrangement of quality requirements, dissemination of operative guidelines and best-practice recommendations for sample collection and management, reduction of complexity in error-prone activities, introduction of error-tracking systems and continuous monitoring of performances), increase and diversification of defences (application of multiple and heterogeneous systems to identify unsuitable specimens), and decrease vulnerability (implementation of reliable and objective detection systems and causal relation charts, education and training). This policy, which requires integration between requirements and design, full commitment and interdepartmental cooperation, would make laboratory activity more compliant to the inalienable paradigm of total quality in the testing process.

Models for analysis of workflows and bottlenecks in the preanalytical phase

The principles of Lean and Six Sigma have been accepted as a means of streamlining operations and improving productivity in the clinical laboratory. Manufacturing sectors have employed these concepts with much success. The primary goal of a Lean initiative is to deliver quality products and services the first time and every time (19). To accomplish this, all activities that do not add value (i.e., waste) must be eliminated or, if this is unfeasible, reduced. These endeavours include methods to decrease preanalytical errors (e.g. hemolysis, a major reason for specimen rejection), which require sample re-collection and re-work, and contribute to delays in test report time.

The demands of today's healthcare environment warrant the integration of quality management systems, such as those employed using Lean and Six Sigma to meet increased workloads, staff shortages, and the demand for rapid turnaround for specimen results. Total turnaround time continues to be a factor in assessing laboratory performance and reinforces the challenge of collectively searching for innovative solutions to improve every phase of the laboratory process (2). Lean tools such as 5S (sorting, set in order, shine, standardize, sustain), the Kaizen Blitz, process mapping and value stream mapping can be easily adapted for use in the clinical laboratory. Six Sigma improvement principles can also enable the laboratory team to monitor projects, allocate resources, and ensure that each step of the process has been completed in an efficient manner (20). Measurable differences between laboratories that have embraced these strategies (Lean labs) and those that have not (conventional labs) have been demonstrated using accepted metrics. For example, 88% of Lean labs achieved a turnaround time for tro-

ponin of 40 min or less; only 15% of conventional labs attained this level of performance. Moreover, 89% of Lean labs had a turnaround time of 12 min or less for STAT complete blood counts (CBC) as compared to 16% for conventional labs (21).

In reference to these findings, particular attention is being focused on the application of Lean and Six Sigma strategies to the preanalytical phase. By implementing these tools to maximize process flow, eliminate waste, and recognize the variations that can hinder the delivery of high-quality services, laboratory professionals can reach their efficiency goals, reduce costs and ultimately improve patient care.

Preanalytical quality indicators

External quality assurance (''EQA'') programs are increasingly been developed for ''PAPA'' incidents in clinical laboratories. Beside the ongoing efforts of the WG-LEPS, there are several examples of similar programs settled on a national basis worldwide, such as those developed by the Sociedad Española de Bioquímica Clínica y Patología Molecular (SEQC) (22), a national EQA scheme developed in Croatia for monitoring the extra-analytical areas of testing (23), as well as a series of pilot PAPA programs that have been developed and trialed in multiple volunteer pathology laboratories throughout Australia and New Zealand over a 12-year period (24). In this last case, the earliest pilot programs focused on unselected PAPA incidents, which allowed information to be gathered on the frequency, severity, apparent cause and root cause of detected incidents. Data from these pilot studies were used to define a subset of PAPA incidents which represented either the most frequent or serious incidents, or which represented incidents with the greatest opportunity for inter-laboratory benchmarking and improvement. From these were developed the current KIMMS EQA program, which is now sufficiently robust to be offered for routine diagnostic laboratory use. The KIMMS program requires participating laboratories to monitor a range of PAPA incidents, from which a subset of incidents are aggregated and entered into the KIMMS system. Strict data definitions ensure comparability of data collection and reporting. Participating laboratories are de-identified and their data is pooled to form a national frequency distribution of PAPA incidents, with each laboratory then able to compare their performance to that of the pool. Stratification of laboratories to permit peer benchmarking is currently being developed.

For the most recent KIMMS EQA cycle, there were 59 participating laboratories, which reported 3.9 million specimens. The overall PAPA incident rate was 1.22%. The single most significant incident was inadequate patient or sample identification (0.28%), with 96% of these being rejected or unable to be analyzed by the laboratory service. Sample hemolysis was the most common extra-analytical incident, with the majority of these being traceable to the collection phase. Only 0.06% of incidents related to post-analytical incidents or errors. Of all reported incidents, the root cause was under the laboratory's direct control in 30% of cases,

with the remaining 70% of cases requiring interaction of the laboratory with other players in the healthcare system. The KIMMS EQA Program has evolved into a mature quality assurance program capable of identifying and driving improvements in health care. As additional laboratories enrol, it is anticipated that the range of incidents included in and considered by the program will expand.

Sources of in vivo and in vitro hemolysis

Hemolysis is traditionally defined as the release of intracellular components of erythrocytes and other blood cells into the extracellular space (25). The breakdown of red blood cells with subsequent release of hemoglobin and other intracellular contents into the plasma can occur either inside the blood vessels due to pathological conditions (i.e., ''in vivo'' hemolysis) or during collection, handling and processing of specimens before the analytical measurements (i.e., ''in vitro'' hemolysis).

In vivo hemolysis can be caused by a large number of clinical conditions, including several infections by bacteria (especially Gram-positive, such as Streptococci, Enterococci and some Staphylococci) or parasites. *Plasmodium* species are also responsible for nearly 250 million cases of malaria, killing between one and three million people, the majority of whom are young children in sub-Saharan Africa (26). An additional case of in vivo hemolysis are autoantibodies, either secondary to a sensitizing event, such as in the Rh-D or ABO blood group incompatibility, or primitive such as in the warm antibody autoimmune hemolytic anemia (AIHA) or in the cold agglutinin disease. Other frequent causes of in vivo hemolysis include hereditary, acquired and iatrogenic conditions, hemoglobinopathies, drugs, intravascular disseminated coagulation (DIC), other less common transfusion reactions, heart valves and HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome.

In vivo hemolysis is one of the leading challenges for clinical laboratories, since it is independent of the technique used for collecting blood and is therefore both virtually unavoidable and potentially insurmountable (27). Conversely, in vitro hemolysis depends mainly on blood collection technique and can also occur due to inappropriate collection, handling, storage and processing of the specimens (28). As such, the leading factors that can trigger in vitro hemolysis include anatomical and physiological characteristics, as well as equipment, techniques and ability of blood collection (29). Nevertheless, the sources of in vitro hemolysis associated with venipuncture are as yet prevailing (4). Blood forced through a very fine needle or IV catheter frequently produces injury or even breakdown of blood cells. In addition, unusual location of venipuncture, specific antiseptics used before phlebotomy, long application of the tourniquet, too vigorous or no mixing of the primary tubes, tubes under-filled or filled from syringes are important causes (30).

After collection of the blood samples, at least other three preanalytical phases must be carefully managed to prevent deterioration: transport, centrifugation and storage. Transport

by courier, especially for long time or under extreme temperature conditions, can damage the cells inside the tubes, causing their rupture. Pre-transport centrifugation also increases the percentage of hemolyzed specimens. For in-patients, the pneumatic tube transport system has also been implicated in in vitro hemolysis (31). Critical conditions for centrifugation include the time between collection and processing, extreme conditions of temperatures and speed, poor separator barrier integrity and re-centrifugation. Finally, inappropriate conditions (i.e., time and temperature) of storage can negatively affect the integrity of specimens. As such, the huge number and complexity of all these possible causes of in vitro hemolysis highlight the importance of education and training of the staff with the responsibilities of blood collection.

Detection and management of hemolytic specimens

The presence of cellular components in a serum and/or plasma sample released by breakdown of blood cells, namely RBCs, may cause a significant bias in the measurement result of several analytes. If this interference exceeds a certain threshold, a clinically relevant bias in the measurement is very likely to occur. As mentioned previously, improper procedures for venipuncture, specimen transport and processing (e.g., such as prolonged use of venous stasis, delayed centrifugation and blood collection through intravenous catheters) have been implicated in the etiology of in vitro hemolysis. In particular, the technique of blood aspiration, difficulty of blood draw, prolonged tourniquet time (>1 min), and the use of pneumatic tubes are also mentioned among the most frequent causes of hemolysis. Blood collection is therefore considered to be the most critical activity in the PAPA phase of the total testing process (32).

Hemolyzed specimens may be detected either manually (i.e., by visual inspection) or by means of automated detection [i.e., the hemolysis index (HI)]. The visual approach is rather arbitrary, highly subjective, non-standardized and not reproducible. Laboratory personnel cannot reliably rank the degree of hemoglobin interference in serum or plasma, even if a good coloured standard for comparison is available. Visual assessment of the degree of actual concentration of hemolysis is therefore highly unreliable and is now being increasingly replaced by the use of automated systems for detection of serum indices in many developed Western countries. However, some less developed countries still rely on visual inspection of samples to detect and grade the degree of hemolysis.

Automated detection of serum hemolysis is undeniably superior to visual detection (33). Nowadays, many automated chemistry analyzers are equipped with automated serum indices detection system. Such systems use a semiquantitative spectrophotometric measurement, and grade interfering substances into categories, usually reporting a qualitative or quantitative HI, which is proportional to the concentration of free hemoglobin in serum (34). The HI is then compared with alert values specific for the analyte. The decision to perform or suppress testing is based on this information. This approach is reproducible, it decreases the error rate and increases productivity and the reliability of test results (35). Moreover, it substantially improves the detection of mildly hemolyzed specimens, in which the concentration of serum free hemoglobin ranges from 0.3 to 0.6 g/L (i.e., the visual detection limit).

Although the routine use of these systems provides the basis for standardization and harmonization of practices across different laboratories worldwide, there is still no universally accepted recommendation on i) the way to detect the degree of hemolysis, ii) index decision thresholds, and iii) the reporting policies. A joint effort is needed to adopt the uniform error reporting schemes and harmonize the way hemolyzed samples are processed (7). Nevertheless, a globally agreed policy to deal with hemolyzed specimens is to always ask for new samples to replace those that are hemolyzed. When these cannot be obtained, it is the responsibility of the laboratory specialist to communicate the problem with the requesting physician and seek a solution that is best for patient care (e.g., suppressing all results affected by in vitro hemolysis) (34, 35).

Hemolysis index as indicator of preanalytical sample quality

Unsatisfactory blood collection practices that jeopardize patient safety in primary health care (PHC) centers, have been reported as the majority of the patients contacts with care (36, 37). Most previous studies have used subjective visual assessment or analysis of free hemoglobin with laborious manual spectrophotometric techniques to evaluate the prevalence of hemolysis (free hemoglobin in serum or plasma). The HI determination in automated analyzers is, however, a much more efficient method for detecting hemolysis, especially mild hemolysis. Although there are some differences among the various instruments, the HI is typically quantified as part of the serum indices by monitoring serum or plasma absorbance at various wavelengths (e.g., 340, 410, 470, 600 and 670 nm). Afterwards, a set of predefined equations enable the calculation of each index, which reflects proportionally the presence of a given interferent such as bilirubin (icterus), free hemoglobin (hemolysis) and turbidity (lipemia). The limits of detection can be adjusted by the single laboratory according to the local technique and policy (33).

For many years, the HI has been used in laboratories to assess sample hemolysis to avoid analytical interference when hemolysis is significant. However, the use of the distribution of free hemoglobin concentrations for all samples above the analyzers detection limit as a marker of overall preanalytical quality has not been previously reported. A retrospective study on the level of free hemoglobin of all samples considered hemolyzed at the pre-set detection limit of 150 mg/L (HI $\geq$ 15) using the Vitros 5.1 analyzer showed that samples collected in a primary care center with the high-

est prevalence of hemolyzed samples were 6.1 times (95% CI 4.0–9.2) more often hemolyzed compared to the center with the lowest prevalence (38). It is noteworthy that this limit is far below the hemolysis levels usually considered for sample rejection. The results demonstrate a significant variation in the prevalence of low-level hemolyzed samples likely to be a reflection of varying preanalytical conditions.

This is the first use of low-level (analyzer detection limit) sample hemolysis of all samples from individual health care units as a quality indicator of the overall preanalytical quality. The method offers several benefits to increase patient safety over collecting or reporting rejection due to hemolysis only. For instance, the distribution curve of hemolysis determined in all samples from individual health care units allows for quantitative analysis so that the effect of intervention on procedures can be studied, and also makes it possible to compare and benchmark preanalytical quality, not only at the laboratory/hospital level, but also down to the health care unit/hospital ward and even to the level of the individual phlebotomist. Future studies are needed to investigate the influence of specific preanalytical practices on the hemolysis distribution of collected samples.

Usefulness of primary sample collection systems in reducing the preanalytical variability

The specimen container is the device that links the preanalytical and analytical phases of the laboratory diagnostics process. The complexity in the preanalytical phase, along with its numerous interrelated stages, leads to the potential for significant variability in the way samples are collected, transported, processed and stored (post-analysis) (39, 40). Preanalytical variability and any resulting error in this phase can adversely affect the quality of the specimen and the subsequent analysis in many different ways, which may lead to sample rejection and erroneous results in some cases. The causes of preanalytical variability and resultant specimen rejection have been defined and extensively reviewed previously in this article. As such, they include the specimen collection devices in the preanalytical phase and their impact on preanalytical variability.

During the sample collection process there are many ways in which the specimen container can reduce preanalytical variability and errors as well. For example, optimizing the label design can facilitate the recoding of all the information needed for correct specimen identification, by using low draw volume blood collection tubes, a six-fold reduction in phlebotomy-induced hemolysis can be achieved. Also, standardisation of the colour coding of blood collection tubes can help users to easily identify the correct tube type as well as the use of the ''order of draw'' that can reduce contamination from additives between tubes and inaccurate test results (e.g., a chart detailing this order should be posted in every phlebotomy room so that it can be easily consulted by the phlebotomist) (41).

There are many innovations in sample collection device designed to ensure the integrity and stability of the sample during transportation and storage after processing. These include the use of specialized additives, such as glycolytic inhibitors for glucose samples, CTAD (i.e., a mixture of citrate, theophylline, adenosine and dipyridamole) for platelet preservation in coagulation samples and the use of gel based separator media in order to isolate the red blood cells from the supernatant.

On arrival in the laboratory, the sample needs to be processed into the appropriate supernatant. The control of this process is crucial to ensure an appropriate and high quality supernatant, yet it is often a cause of preanalytical variability. For example, incorrect centrifugation conditions will not create the required platelet poor plasma for coagulation testing, and insufficient clotting time will result in fibrin formation post-centrifugation. The use of specialized serum tubes can reduce the required clotting time required and formation of fibrin. During the analytical phase there are additional limitations on the analytical method and the type of tests that can be performed, defined by the compatibility between the analyte and the sample additive, most notably those used for immunoassays (42). Finally, maintaining the sample stability during extended storage is of great benefit to the laboratory, particularly for 'add-on' or future testing. In this case, the specimen container supplier should not only provide the aforementioned innovations of additive and gel separator media but should also provide evidence of analyte stability over time.

Standards of safety in blood collection

Percutaneus exposures (PC) represent the most frequent work related accident in the healthcare setting, with the potential of transmitting severe bloodborne infections to healthcare workers, and needlestick injuries due to blood-filled needles used for blood collection carry the highest risk. Reliable estimates on this topic has been gathered by the ''Studio Italiano Rischio Occupazionale da Human Immunodeficiency Virus (HIV)'' (SIROH), which collected data on more than 65,000 PC. They concluded that one hepatitis B virus (HBV), four HIV, and 30 hepatitis C virus infections were observed (Puro V, De Carli G. Personal communication). Overall, 3000 (5%) PC occurred in the laboratory setting, including anatomy-histology labs, mostly due to needles and glass instruments. Clinical-biochemical and pathology labs accounted for the majority of PC, followed by microbiology and virology labs, and to a lower extent in research and transfusion center labs. Among personnel, PC involved lab technicians in approximately 60% of cases, and a non-negligible number of PC also occurred to housekeepers.

Overall, about 50% of PC were needlestick injuries related to blood collection. To assess the effect of implementing needlestick-prevention devices (NPDs) use on injury rates (IRs), detailed occupational exposure records (numerator) and used hollow-bore needle devices (denominator) for NPD and conventional devices (CDs) were collected yearly from those SIROH hospitals which implemented at least one NPD for blood drawing or peripheral venous access (for a mean

of 4, 5 years, range 1–10); in all these hospitals, safe injection practices are standard policy (43). As such, IR was significantly lower for NPD when compared with the corresponding CD: vacuum tube blood drawing set with winged steel needle, 2.18 vs. 6.42 (denominators: NPD 4719620; CD 2087088; 17 hospitals), and with standard needle, 1.63 vs. 4.66 (NPD 1906106; CD 1030773; 14 hospitals); blood gas syringe, 2.87 vs. 11.85 (NPD 418419; CD 84375; 12 hospitals); IV catheter, 3.27 vs. 9.61 (NPD 979073; CD 2611681; 12 hospitals). Analysis of NPD injuries performed in eight hospitals also showed that in 20% of these, NPD were not activated, mostly by workers with a work experience <2 or >15 years, whereas the remaining NPD injuries occurred before safety mechanism activation was possible (35%) or during activation (30%). Remarkably, the safety mechanism failed in 15% of cases, only (44).

More importantly, the IRs tended to decline in the years following their introduction, thereby suggesting that a learning curve exists and that the full benefits of the new devices can be achieved and maintained with their sustained use. However, training for new employees and re-training of other staff must be ensured to avoid misuse and reluctance towards new techniques. The observed CD IR were lower than those reported in the literature before the availability of NPD, possibly because of the high baseline standard of needlestick prevention policy in these hospitals, as well due to a beneficial effect of education and training performed on NPD implementation.

Patient identification errors

Although patient misidentification is not so frequent when compared with other diagnostic errors, it should be considered that the current estimates might be negatively biased since most identification errors might go undetected as long as they do not produce negative outcomes for patients, or because of underreporting, despite that this error is widely acknowledged as a ''sentinel event''. Moreover, despite the relatively low frequency, identification errors are a major healthcare issue because they are potentially associated with the worst clinical outcome due to the potential to generate incorrect diagnosis and lead to inappropriate therapy. Although patient identification errors in transfusion medicine tend to occur in 0.05% of specimens, the rate is much higher in clinical chemistry laboratories, up to 1%. Several factors may contribute to generate identification errors, including malpractice, issues related to workflow, materials used in the identification process, or the approach taken by staff to confirm the identity of individual patients (45).

As such, some actions might be undertaken to prevent this otherwise serious healthcare problem. While most healthcare employees tend to work around problems and fulfil immediate needs, such as the dramatic consequences of an incorrect blood transfusion, the root cause of the error is frequently left over. However, it is advisable to analyze the vulnerable activities [i.e., performing a root cause analysis (RCA)] and reorganize the entire process accordingly. Then,

strict adherence to quality system requirements [e.g., the International Standards Organisation (ISO) 15189: 2007], standard operating procedures (SOPs) as well as guidelines and recommendations for specimen collection and management should be followed. It is noteworthy that the Joint Commission still recommends using at least two patient identifiers when providing every type of care, treatment or services, and to conduct a final verification process to confirm the correct patient, procedure and site using active communication techniques prior to any procedure (National Patient Safety Goals 2011: Goal 1.1) (46). As such, new technologies based on improved safety systems [e.g., bracelets with an α-numeric code that opens a mechanical barrier system, machine-readable bracelets with barcodes or radiofrequency identifier devices (RFID) and machine-readable anthropometric data], request forms, test tubes and labels with a unique identity code for each patient would help to make the process of patient identification much safer. Then, a rigorous ''tolerance zero'' policy of rejecting any potentially mislabelled or misidentified specimen should be established. Finally, the widespread use of innovative technologies is advisable, including informatics data entry to recognize potential biases from previous values and eliminate the manual transcription of data, automated systems for patient identification and specimen labeling.

Sample stability

Clinical laboratories have been at the vortex of the maelstrom affecting medicine over the past years. Various strategies to contain and reduce the overall costs of laboratory services are being implemented or advocated. These include centralization, consolidation and integration of services, reengineering the laboratory and increasing the level of automation, optimizing test usage and decentralizing testing to the point-of-care. The growing trend of closures and mergers of hospital facilities have led to consolidation of laboratory services for a variety of opportunistic, logistic and economic reasons. Moreover, many hospitals, clinics and physician practices find it economic to outsource specimens for testing to private or commercial laboratories. This is because performing low volume or esoteric testing is not considered economically viable anymore. In areas of the country in which healthcare networks with aggressive outreach programs are strong, laboratories in smaller hospitals are increasingly being closed, and the tests sent to a central laboratory. Moreover, due to the tremendous growth in decentralized phlebotomy services, blood specimens may arrive in the central laboratory from varying distances, under variable storage and transportation conditions. As such, central laboratories serving healthcare networks are experiencing an increased workload and are facing emerging challenges due to sample stability. Stability is defined by the ISO as the capability of a sample material to retain the initial property of a measured constituent for a period of time within specified limits when the sample is stored under defined conditions (ISO Guide

30, 1992). Instability is instead present when there are important changes in one or more of those measurements.

The problems in preparation and transporting of samples from a peripheral facility to a centralized laboratory cannot be fully controlled by the laboratory staff because they mostly reside outside the jurisdiction/responsibility of laboratory personnel. A general issue challenging clinical laboratories is the integrity of uncentrifuged specimens for clinical chemistry analyses. The prolonged contact of plasma or serum with cells is in fact a frequent cause of spurious test results, so that plasma and serum should ideally be separated from the blood cells as soon as possible to prevent ongoing metabolism of cellular constituents, as well as the active and passive movement of analytes between the plasma or serum and intracellular compartments. Some plasma proteins and enzyme are inherently labile. Thus, a prolonged elapsed time between sample collection and processing might cause degradation, fragmentation and other problems that induce spurious false elevation or decrease and consequently spurious test results (47, 48). The coagulation laboratory currently performs a large number of distinct tests using a variety of techniques. This leads to remarkable problems when sample quality is not optimal. Clotting assays are the most susceptible to poor standardization of several process of the preanalytical phase and they are strongly influenced by storage conditions before centrifugation. Several pitfalls related to storage conditions and centrifugation (temperature and time) of whole blood samples have also been described. Ideally, the specimens should be transported non-refrigerated at ambient temperature (15–22°C) as soon as possible. Moreover, routine coagulation tests, such as the prothrombin time (PT) and the activated partial thromboplastin time (APTT) should be accomplished within 4 h after collection (more generally, separated plasma samples can be maintained at room temperature or refrigerated for a few hours without adverse effect on coagulation). Extreme temperatures during transportation should be prevented (i.e., the specimens should neither be transported refrigerated or at high temperature). Delays in transport may substantially affect labile clotting factors (e.g., factors V and VIII) (49, 50). Regardless of all these challenging issues, the governance of sample transportation and storage is possible. Basically, the stability of the samples varies depending on a variety of variables such as the blood collection system, whether the samples are stored as whole blood or centrifuged, the temperature samples are maintained at during storage, the reagent/instrumentation used for analysis and the test parameter to be analyzed. First and foremost, the samples should be always transported in an appropriate container and with no delay. Consideration should be made to include temperature and humidity data recorders in transport containers to monitor transport conditions. When delay in sample processing is unavoidable or predicted, immediate centrifugation and separation of serum or plasma, eventually followed by refrigeration and freezing, might be advisable. Typically, the lower the temperature, the longer that the specimens can be maintained for future testing (e.g., testing for samples maintained at –20°C should be performed within two to four weeks of storage, whereas testing for samples maintained at –80°C is still suitable after several months and sometimes years of storage). For clinical chemistry and immunochemistry testing, the use of gel based separator tubes might also be advisable to establish a barrier between serum and blood cells, and thereby increase the stability of a number of analytes. Although several studies have previously assessed the variation of test results occurring over time due to the different storage conditions and recommendations for collection, transport, processing and storage of blood specimens have been drafted by the Clinical and Laboratory Standards Institute (CLSI), formerly known as National Committee for Clinical Laboratory Standards (NCCLS) (51), any laboratory should assess the impact of any potential delay in testing, for each combination of materials and conditions, using both normal and abnormal samples. Statistically significant changes in test results over time might be observed, but it is always important to acknowledge whether such differences are clinically relevant (i.e., modest biases may be tolerated when there is no impact on patient management) (13).

Serum or plasma sample – which one is better?

Serum has long been the most commonly used sample type for clinical chemistry testing. The wide preference for serum can be attributed in large part to the essentially cell-free nature of serum produced from a properly clotted blood specimen. This characteristic allows the serum to remain stable for extended periods of time once it has been separated from the clot, which is especially desirable in settings where samples are not analyzed soon after centrifugation. An additional reason for the widespread use of serum may be the historical development of assays in clinical chemistry, which has for long focused on serum-based methodologies. However, trends in clinical laboratory requirements and expectations over the past decade have prompted instrument vendors to ensure that assays are developed and validated to be compatible also with heparin plasma. As such, heparin plasma is now the sample of choice in clinical chemistry for an increasing number of laboratories. However, heparin plasma represents a more complex sample matrix than serum, with unique considerations that may impact specimen quality and test results. The well-known shortcomings of serum include the potential for longer test result turnaround time due to the time required for blood to clot, and fibrin formation when clotting is incomplete. When blood is collected from patients on anticoagulant therapy, latent fibrin formation in serum may be unavoidable. In contrast, anticoagulated blood can be centrifuged immediately to obtain plasma for testing, and issues with fibrin formation are generally reduced compared with serum. Plasma samples also have reduced potential for pseudohyperkalemia, which can occur when potassium is released from platelets during the clotting of blood (52). These benefits of an anticoagulated specimen are offset by the presence of cells, platelets and fibrinogen in the plasma sample after centrifugation. The presence of these compo-

nents in plasma allows for metabolic and lytic effects of cells and platelets, as well as conversion of fibrinogen to fibrin, both of which will have a time and temperature dependence. These, in turn, have the potential to affect sample quality, instrument operation and test results (53). Analyte stability in separated plasma may also be compromised for certain routine chemistry analytes depending on cell/platelet counts, but can also be comparable to serum (54). Standardized procedures for specimen collection, handling, processing, testing and storage are thus especially important for plasma samples to minimize variation in test results. Rapid serum tubes with new technologies enabling reduced clotting time can provide the fast turnaround time of plasma, while maintaining the sample quality of serum. A careful review of the benefits and limitations of both sample types is warranted to determine if a conversion from one sample type to the other makes sense for a particular institution.

Preanalytical errors in point-of-care testing

Point-of-care testing (POCT) is typically defined as laboratory testing performed at or near the site where clinical care is delivered, as such combining sample collection, analysis, and reporting of results into an integrated testing structure characterized by a very simple user interface. POCT is often analytically reliable when preformed according to the manufacturers instructions. However, since POCT is mostly intended for non-analysts to perform testing for diagnosis, monitoring or therapy purposes, the lack of appreciation of the quality systems in a laboratory can and does lead to a broad array of errors which undermine the perception of the reliability and safety of this testing system. The majority of errors in most clinical testing occur in the preanalytical phase; this is one of the reasons why the International Standard ISO 15189 has been developed for medical laboratories, and why specific international standards such as those issued by the ISO (ISO 22870) (55) and the CLSI (CLSI document POCT07-P) (56), as well as national guidelines [e.g., Società Italiana di Medicina di Laboratorio (SIMeL). Position Statement on POCT – in-hospital setting – of the Italian Society of Laboratory Medicine] (57) have been also been specifically developed for POCT. The causes of preanalytical variability, which is regarded as the most critical aspect of the total testing process where most errors occur, are not present with POCT, in contrast to traditional laboratory diagnostics, namely sample handling, transportation and preparation. In most test cases, the sample does not require preparation (i.e., centrifugation, since whole blood is the most commonly used specimen type), separation and storage (57–59). As such, POCT errors can be broadly categorized as selection of an unsuitable device for the purpose, inappropriateness (i.e., request of an inappropriate test and/or analyte for the clinical purpose), sampling errors (i.e., clotting or in vitro hemolysis) (60), sample introduction errors into the device, inadequate device preparation, inadequate patient identification, inadequate record keeping of what is being done and who did the testing, lack of recorded quality systems as well as inade-

quate analytical performance, e.g., reading a result too early or late and post-analysis data handling and record keeping.

While some high volume POCT suppliers may provide training, too often untrained staff perform POCT. There is a clear need for organisations introducing POCT to ensure staff are trained and have regular updates to ensure correct performance of all steps. This enables a quality system to be established and minimized risk for the organisation. Too often, the introduction of POCT is not seen as a corporate decision, since errors in POCT analyzes constitute a risk to patients and leave the organisation open to litigation (61).

Preanalytical variability in urinalysis

The chemical, physical and morphologic urinalysis has undergone radical changes over the past 10 years. Thus, it is time for introducing further changes and modifications in various steps of this important test. Most frequently, urine samples are collected to diagnose urinary tract infections (bacteria), or other diseases of the kidneys or urinary tract (causing hematuria or proteinuria). As such, there is increasing focus being placed on improving the quality throughout the total process of urinalysis, especially the preanalytical phase (62). The most reliable recommendations for the appropriate performance of this test have been published by the European Confederation of Laboratory Medicine (ECLM), which has provided details of standardized collection and preservation of single-voided urine samples in the consensus document ''*European Urinalysis Guidelines*'' (63). Nevertheless, significant activity still needs to be undertaken to improve traceability of common measurements such, as that of urinary albumin (64). The unawareness or ignorance of the minimum preanalytical issues is a frequent cause of non-diagnostic samples and waste of both economic and human resources. A series of drawbacks is attributed to urinalysis specimens (63), including (i) medical indication, i.e., when the patient is not informed about the medical need of the test, the outcome is questionable. Urinalysis as a ''routine'' screening is no longer indicated; (ii) patient preparation, i.e., oral and written instructions to the patient help in minimizing intra-individual physiological variation, e.g., by reducing excretion of water and by avoiding posture-related proteinuria (65). Written instructions in the language of the patient are helpful to avoid losses in suitability of the specimen; (iii) sample collection, i.e., mid-stream urine needs detailed illustrations on how to collect a suitable sample. It may be difficult to deliver for many disease-related reasons (hip arthritis, rheumatic disease, etc). Disposable collection containers and transportation tubes should be used, with labels used to mark them. Contaminated collection creates difficulty in treatment (''mixed flora'' hides the urinary tract infection). Documentation of success in collection (as reported by the patient) may help afterwards in interpreting low colony counts (down to the level of 10^6 CFB/L or 10^3 CFU/mL); (iv) transport, so that urine specimen should be transferred into the secondary tube (with preservatives as specified) when intended for transportation. Erroneous types of tubes, inappropriate

temperatures (freezing, heating), or extended storage at room temperature may adversely impact on the outcome (66, 67) (true time of collection is thereby needed to be able to assess possible delays); and finally (v) missing or inadequate request, documentation, i.e., detailed (computerized) request should clearly indicate the prescribed laboratory tests, typically by using specific codes. Additional minimum information includes current anti-microbial medication (if bacteria should be cultured), in addition to other preanalytical items.

Automation of the pre-analytical phase

Relevant changes have occurred in organization, complexity and role of clinical laboratories in healthcare, where automation has proven to be a powerful catalyst for these changes. The urgent need to shift our vision of healthcare towards a patient-centered enterprise, to improve efficiency and efficacy, as well as the growing pressure to have reliable and reproducible conditions for analysis have led to a high degree of consolidation and automation of the analytical phase in clinical laboratories worldwide (68). Nevertheless, there is evidence that the lack of standardization of several steps of the preanalytical phase, from sample collection to specimen processing and storage, exert unfavorable influences on test results, consuming healthcare resources and negatively affecting patient outcome (3). Although it may still seem radically innovative in the context of the preanalytical phase, the automation of repetitive, error-prone and bio-hazardous processes has several advantages, including the potential to improve the turnaround time, abate the biological risk associated with operator's exposure to hazardous biological material, reduce errors and costs associated with sample handling and allow a much favorable management of workflows and bottlenecks in the entire preanalytical process (69). This aspect would ultimately contribute to reorganization the total testing process, reorganizing more efficiently human and technological resources, increase flexibility, increasing the professionalism of the laboratory specialists, improving efficiency and quality and, last but not least, decreasing uncertainty and errors in the process of handling of the specimens. As such, some alternative solutions can be followed, including total laboratory automation (TLA), modular laboratory automation, and workcell/workstation automation. Each of these systems has advantages and drawbacks. While TLA seems more suitable for larger, high-volume laboratories characterized by important specimen throughput requirements, ''stand-alone'' automated processing units have been also been developed to fulfil the requirements of the preanalytical section of small- to medium-sized laboratories as well as for those requiring multiple and redundant smaller processing units to achieve better flexibility and a higher processing output capacity. Regardless of the different approaches, all these preanalytical solutions have the potential to automatically inspect, barcode, centrifuge, decap, sort, check sample volume, detect clots, create and apply secondary tube labeling, aliquoting, destination sorting into analyzer racks, and eventually storing the specimens. Additional ben-

efits include the flexible configurations with computer and network controls, the full integration with the most popular analytical platforms, a higher degree of specimens control and a substantial simplification in achieving accreditation/certification. Automated phlebotomy preparation trays, conveyor belts, pneumatic systems and other innovative robotic facilities are also proposed to standardize, ease and accelerate the procedures for sample collection and transportation. The availability of customized solutions, determined on a local basis according to specific needs and individual work-flow (e.g., some ''open system'' configurations can be connect with more than 30 different models of instrumentation from a variety of manufacturers), will allow laboratories to remain competitive in the integrated healthcare network. In contrast, automation of several steps of the preanalytical process also carries some drawbacks, such as a shortage of personnel, the new knowledge required (e.g., business management, informatics and workflow analysis), a higher risk of system failure, increased costs for energy and liquids, a major commitment from healthcare managers, the challenging integration with new and promising techniques such as the ''-omics'' and, last but not least, the potential drive towards manufacturer's-guided laboratories.

Accreditation of clinical laboratories: focus on the pre-analytical phase

Accreditation is a foremost tool to prove that the clinical laboratory has both a quality management system and the competence to warrant high confidence in test results (70). At variance with other healthcare areas, accreditation of medical laboratories is not only focused on the data, but also involves accurate interpretation and counselling. Since it has been consistently shown that the vast majority of laboratory errors occur in the extra-analytical phases of the total testing process, it is important that all the preanalytical activities be included in the assessment for accreditation. The ISO 15189:2007 ''Medical laboratories – Particular requirements for quality and competence'' is the most relevant standard for setting up a quality system in the medical laboratory. It is considered as such not only by all European societies of Clinical Chemistry and laboratory medicine, and those of the IFCC, but also by the National Accreditation Bodies of the European Cooperation for Accreditation (EA). The way it should be used is clearly indicated in this EA-4/17 ''EA position paper on the description of scopes of accreditation of medical laboratories''.

ISO 15189 contains various paragraph very specifically focused on the preanalytical phase (71). The document starts already with a precise definition, which encompasses – in chronological order – clinician's request, preparation of the patient, collection of the primary sample, transportation to the laboratory and storage. For phlebotomy it demands detailed instructions about preparation of the patients, their identification, primary sample collection, and sample labelling. When the sample is to be collected in the laboratory,

adequate accommodation for the patients is also required. Moreover, for samples collected by extra-laboratory personnel, the laboratory is responsible for producing adequate instructions and possibly for training. The document contains clear indications about transportation and storage of the specimens, to ensure stability of the sample properties. Specific criteria for acceptance and rejection of samples must be present within the laboratory, not only for the unequivocally identification of the samples, but for the conditions they are received as well. Special attention is paid to urgent (STAT) requests, since reduction of turnaround time already begins with the sampling procedure, or even before, at the time of the formulation of the test request. An essential element of ISO 15189 is that the services are regularly reviewed by the laboratory in the management review. Part of this is the customer satisfaction, relation with customers and continuous quality improvement. Safety aspects, and risk assessment must be considered as well. The clinical laboratory and not the accreditation body is primarily responsible for this quality. Nevertheless, the assessment of the laboratories adherence to good practice in the preanalytical phase is an essential part of the whole accreditation process (72).

A special item, which should be covered by accreditation as well, concerns POCT. The ISO 22870:2006 ''POCT – Requirements for quality and competence'' was originally set up to form an integral part of ISO 15189. Both International Laboratory Accreditation Cooperation (ILAC) and EA clearly state that ISO 22870 should be used in connection with ISO 15189. A clear responsibility of the laboratory is to take care of the training of the non-laboratory persons, often nurses, who perform POCT. In this specific are of testing, preanalytical aspects are important as well.

Conclusions

There has been a significant improvement in perceiving the importance of patient safety and the need to reduce diagnostic errors – at least those more preventable – over recent years. The most important gauge of quality in laboratory testing is that the test results are accurate and suitable for clinical practice. According to the traditional ''brain-to-brain'' representation of laboratory diagnostics, the total testing process develops through a three-part process, including the preanalytical, analytical and postanalytical phases. Nevertheless, an accurate test result always begins with a high-quality specimen and the preanalytical variability exerts a strong influence on laboratory testing, healthcare organization and clinical outcomes, so that the governance of this crucial phase of the total testing process offers a great potential for improving the total quality in laboratory diagnostics and enhancing satisfaction of stakeholders. Appropriate management and standardization of this phase is also crucial, inasmuch as several preanalytical issues are now comprised within most accreditation programs (e.g., the ISO 15189) and because private laboratories, which are inherently subjected to the greater competition of an open market, are placing major focus on blood sampling issues to prevent patient com-

Table 1 Technological, informatic and computer science advances in the preanalytical phase.

Computerized physician order entry (CPOE)
Positive patient identification by
- Barcode technology
- Smart cards
- Radio-frequency identification (RFID)
- Optical character recognition and voice recognition devices

''Active tubes'' (lab-on-a-chip integrated containers)
- Storage of patient data, measurement of physiological (e.g., temperature/humidity/flow rate) and metabolic data (e.g., glucose concentration)

Transport systems
- Pneumatic tubes conveyer
- Robots
- Transportation monitoring systems (e.g., time of transportation, temperature, humidity, etc.)

Instrumentation tools
- Query-host communication
- Primary tube processing
- Volume/clotting/bubbles sensors
- Serum indices

Informatics tools
- Query-host communication
- Automatic validation
- Expert systems
- Delta check technology
- Error-recording software

plaint or patient dissatisfaction. Most preanalytical errors result from system flaws and insufficient audit with operators involved in specimen collection/handling responsibilities (Figure 1). Therefore, standardization and monitoring preanalytical variables is of foremost importance and is associated with the most efficient and well-organized laboratories, resulting in reduced operational costs and increased revenues. The most reliable approach encompasses thereby the development of a thoughtful risk management strategy, which includes systematic analysis of workflows and bottlenecks in the system, elimination or redesign of flawed/mishandled procedures, identification of solutions to suit local circumstances, awareness that errors are mostly attributable to a ''system'' rather than to a human failure (i.e., do not blame the operators), continuous process monitoring (e.g., development and implementation of suitable ''error identification and recording systems''), continuous education by dissemination of reliable recommendations, improved communication, interpretive rounds within and outside the laboratory, and definition and implementation of representative quality indicators and outcome measures. Technological advances as well as recent developments in technology, informatics and computer sciences (Table 1) will represent valuable opportunities for further advances in this area.

Conflict of interest statement

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