

Quality in laboratory diagnostics: from theory to practice

Giuseppe Lippi^{1*}, Mario Plebani², Ana-Maria Simundic³

¹Laboratory of Clinical Chemistry and Hematology, Department of Pathology and Laboratory Medicine, University Hospital, Parma, Italy

²Department of Laboratory Medicine, University Hospital of Padova, Italy; Leonardo Foundation, Abano Terme General Hospital (PD), Italy

³University Department of Chemistry, Sestre Milosrdnice University Hospital, Zagreb, Croatia

*Corresponding author: glippi@ao.pr.it, ulippi@tin.it

Received: March 23, 2010

Accepted: May 1, 2010

More than ten years ago, the Institute of Medicine (IOM) reported alarming data on the causes and impact of medical errors in the US, demanding for urgent national efforts to address this problem. Despite large initiatives to improve patient safety throughout the managed care have growth exponentially since the release of *"To Err is Human"*, the outcome has however been much lower than expected. It is still undeniable, however, that the worldwide galloping movement of patient safety, boosted by Governments, national healthcare systems and consumers unions, has catalyzed important changes in healthcare and laboratory medicine as well. Some of these changes have introduced important innovations in the current medical and laboratory practice, towards establishment of a foremost culture of quality and safety.

The very issue we have to face is natural to the real meaning of "healthcare quality". Quality is generally defined as "a high degree or grade of excellence", but the translation of this concept in healthcare is somehow challenging, since we all know that "quality" means rather different things to different people. Someone thinks that getting quality healthcare means seeing the doctor right away, being treated courteously by the doctor's staff, or having the doctor spend a lot of time with him/her. While all these things are important, the "clinical" quality of healthcare is indeed much more pervasive. The Agency for Healthcare Research and Quality (AHRQ) of the U.S. Department of Health & Human Services brings a helpful example to defi-

ne healthcare quality. Getting quality healthcare is like taking a car to the mechanic; the people in the garage can be pleasant and take note of complaints, but the most important thing is whether they can be able to fix the problems and, hopefully, to return the car timely and with no additional malfunctioning. Accordingly, healthcare quality can be seen as receiving the most appropriate care, whilst minimizing the risk of side effects and adverse events not directly related to the presence of the original disease (e.g., medication errors, wrong site surgery or retained instrument after an operation, wrong drug or wrong route of administration of drugs, adverse drugs reactions, hospital acquired infections, etc). In other words, according to the current definition of the US Institute of Medicine (IOM) healthcare quality is the degree to which health services increase the likelihood of desired health outcomes and are consistent with current professional knowledge.

While several areas of healthcare are still struggling with the issue of patient safety, diagnostics has been forerunner in pursuing this issue, so that the concept and practice of Total Quality Management (TQM) has now become commonplace throughout radiology, pathology and laboratory medicine. This does not mean, however, that the various branches of diagnostics are completely free from errors. In radiology, the level of error varies depending on the type of the investigation, but the range is 2–20% for clinically significant or major errors (1). At the practice level of pathology, the

error rate is comprised between 13 and 14% (2). In the field of laboratory medicine, the error rate ranges widely, from 0.1 to 3.0% of laboratory results. Since these extreme limits do not probably mirror closely the reality, a more probable error rate is that ranging from 0.3 to 0.6%. Of these errors, three-fourth generate "normal" results, one-sixth produce "absurd" results (which would be thereby identified before translating into a real harm for the patient), but approximately one-sixth might be so significant to have an adverse impact on patient care (3). Due to both an increasing consciousness of this important problem and a pervasive policy of education, the laboratory error rate has undergone a further reduction during the past 10 years (e.g., from 0.47% in 1997 to 0.33% in 2007) (4,5), a trend particularly accentuated for analytical errors, so that the analytical variability is now frequently less than 1/20th of what it was 40 years ago (6,7).

Since laboratory practice is traditionally divided into three stages (preanalytical, analytical and postanalytical), all of these must be targeted for improving the quality throughout the total testing process. Therefore, this special issue of *Biochimica Medica* is aimed to provide the readers with important updates on total quality management in the various aspects of laboratory diagnostics.

In the first article, Lippi *et al.* provide a comprehensive overview on patient safety in healthcare and laboratory diagnostics. Basically, patient safety is regarded as the basic healthcare discipline that emphasizes reporting, analysis, and prevention of medical errors. Besides carrying serious harms to the patient health, it is widely acknowledged that medical errors might translate into a huge amount of money wiped out of the national and international economy, so that new solutions are urgently needed to make the healthcare system work more efficiently and safely. In this article, the basic concepts of medical as well as diagnostic errors are reviewed, and the most reliable solution for prevention and governance are discussed.

In the second article, entitled "*Quality and diagnostic perspectives in laboratory diagnostics*", Mathias M. Müller deals with the true concept of quality in

the field of laboratory medicine. The article is a thoughtful piece, aimed to make anybody think about the scope of this profession, which should be inevitable less technology- and more patient-oriented.

Although the analytical process has a minor impact on the total number of errors in laboratory medicine as compared with the pre- and post-analytical phases, these mistakes should be minimized as much as possible. As such, Oswald Sonntag discusses valuable options on how to further improve the analytical phase. For examples, an extensive database dealing with drug interferences, effects of herbs and has been developed, and will be helpful to prevent misleading interpretation of lab results. Accurate statistical analysis and appropriate approaches for comparing results of different methods are necessary for a better interpretation of data. An increase in the knowledge of calibration process is also necessary to reduce the costs for extra testing or mishandled therapies. The quality control process in the clinical laboratory is also necessary for preventing errors, although the accurate selection of the material is mandatory for commutability. It is finally highlighted that the most appropriate reference interval for the population (e.g., according to age, sex, ethnicity) should be provided, otherwise laboratory data would be of limited value for the clinicians.

Assay interferences have long been underestimated and unfortunately too often overlooked in the daily laboratory practice. Nevertheless, the extra-analytical phase of the laboratory testing process is now recognized as the major source of laboratory errors and the preanalytical phase accounts for the vast majority of mistakes encountered in the total testing process. Among these, hemolysis is the leading problem and the most prevalent interference in laboratory testing. The traditional visual inspection of the sample to detect hemolysis is typically arbitrary and therefore mostly unreliable because it may over- and underestimate the actual prevalence of hemolyzed serum specimens. The recent advances in laboratory technology have however made available new and more reliable means for the automated detection of the

serum indices, including the hemolysis index, which is also being increasingly used to monitor the quality of the collection process. These technological innovations are highly appealing for the optimal reproducibility and the improved detection of even mildly hemolyzed specimens. The article of Simundic *et al.* reviews the analytical performance of the hemolysis index and discusses the leading opportunities to deal with hemolyzed specimens in the daily laboratory practice. It is finally suggested that in the presence of hemolysis the laboratory personnel should always ask for new sample(s). In case new sample(s) can not be obtained, the laboratory specialist should inform the wards about the problem and seek for the most reliable solution.

The role of External Quality Assessment (EQA) and proficiency testing (PT) is to provide reliable information to allow laboratories to assess and monitor the quality status of internal procedures and processes, the suitability of the diagnostic systems, the accountability and competence of the staff, along with the definition of measurement uncertainty in laboratories results. Sciacovelli *et al.* highlight that only the correct use of information provided from EQA/PT might produce real improvements of laboratory performance. As such, the definition, the strengths and the limitations of current policies of EQA/PT are reviewed, focusing on the leading aspects of uncertainty in this area, that comprehend the major responsibility of laboratory professionals to appropriately analyze EQA/PT samples and reports, to detect trend or bias that might not be apparent in single results, to investigate the root causes producing unacceptable performances, to apply and monitor the opportune actions for removing the underlying cause/s, to verify the effectiveness and, above all, to determine whether the problem could have somehow affected the clinical decision making. It is also highlighted that laboratory accreditation plays an essential role; the administrators have to validate the management of EQA/PT, verifying that the laboratory chose EQA/PT schemes in agreement with the international recommendations and the national guidelines and handles the EQA/PT information correctly.

The traditional, widespread and more practiced approach for interpreting results of laboratory testing relies on a "transversal" comparison of patient's data with an established reference interval. The establishment of appropriate reference intervals requires however careful planning, monitoring and documentation of each single aspect of the process, especially the selection of an appropriate reference population (which might be selected among a group of subjects homogeneous in terms of ethnicity, geographical origin and environmental conditions), the stratification of the values according to major demographic and clinical characterizes (e.g., age, sex, health status) along with the use of the most appropriate statistics for the final calculation. The definition of reference ranges or intervals of reference represents therefore an essential part of total quality management in laboratory diagnostics. In the next article of this issue, Guidi and Salvagno offer a comprehensive overview on how this process should be handled appropriately to prevent misleading interpretation of laboratory data and, especially, they introduce the key concept of "longitudinal comparison of laboratory results", which might probably replace the use of reference intervals in the very next future.

Although it is widely known that clinicians must be timely informed of abnormal laboratory results representing a life-threatening condition for the patient as well as for any values for which delays in reporting can result in adverse outcomes, the criteria for considering tests results as critical are still controversial. The next article of Plebani M. and Piva E. gives a comprehensive overview on the ongoing efforts for improving actual consensus on the definition and notification of laboratory critical values and for evaluating their contribution to improve clinical outcomes and patient safety, providing also some highlights on a valuable experience of automated notification, which is a reliable tool for improving the timeliness of communication and avoiding potential errors for which accreditation programs require read-back of the results.

Urinalysis comprehends the physical, chemical, and microscopic examination of the urine, comprehen-

ding a variety of biochemical and morphological analyses. As in other areas of laboratory diagnostics, however, improved standardization of performance is needed, not only for a compelling clinical need (i.e., adoption of consistent reference intervals and appropriate interpretation of results), but also because urinalysis continues to be one of the most frequently laboratory tests requested by clinicians. In the article of Caleffi *et al.*, the European Confederation of Laboratory Medicine (ECLM) – European Urinalysis Guidelines are critically discussed, providing useful information on the desirable specimen to be collected, the best procedures for sample collection, handling and storage, as well as additional indications on how to further improve the postanalytical phase. The principal suggestions provided in this article include control and standardization of preanalytical processes (that are the most vulnerable to uncertainty and errors), the definition of precise levels of preanalytical related information and data on the samples), the identification of criteria for sample acceptance and rejection, the introduction of universal approaches for including comments and notes of unsuitability of the specimen within the laboratory report, and the appropriate interpretation of test results.

Haemostasis, *in vivo*, is the homeostatic process whereby blood flow is maintained within the vasculature and, *in vitro*, represents one of the most complex areas of diagnostic laboratory testing. As such, the results of coagulation testing play an essential role for the screening, diagnosis and therapy of bleeding and thrombotic disorders. Unfortunately, however, there are many steps in the process of laboratory testing where the process can go awry and therefore must be controlled. In the next chapter by Favalaro *et al.*, the test methodologies for investigating common hemostatic disorders are deeply reviewed, as well as the clinical relevance of each single assay. It is specifically highlighted that the preanalytical phase of the total testing process is the most vulnerable to uncertainties and errors in the haemostasis laboratory, so that it is essential that the specimen is appropriately collected, transported and stored. It is also suggested that the internal quality control (IQC) must be

performed with each assay, using appropriate levels of the analyte as well as suitable time intervals to assess the ongoing assay performance. The participation to EQA, which is often a requirement of the accreditation of medical laboratories, offers also the important opportunity for evaluating long-term performances of laboratories, and especially for comparing each single lab with like and unlike methodologies. The multitude of EQA that offer programs specific to haemostasis testing provide valuable information on assay specific diagnostic error rate, assay precision, accuracy, sensitivity and assessment of overall assay performance, so that the incorporation of both IQC and EQA into a laboratory program will indeed improve the quality of coagulation testing.

Point-of-care testing (POCT) is traditionally defined as diagnostic testing at or near the site of patient care, driven by the need to bring the test conveniently and immediately to the patient. POCT is generally accomplished with the use of transportable, portable, and handheld instruments and test kits. Recently, cheap, small, fast, and smart devices have increased the diffusion of POCT, by making it cost-effective for many conditions. As for other areas of laboratory diagnostics, governance of POCT is however required for ensuring reliable and reproducible results. The article of Giavarina *et al.* provides therefore a synopsis of a recent document endorsed as a Position Statement on POCT (in-hospital setting) of the Italian Society of Laboratory Medicine (Società Italiana di Medicina di Laboratorio, SIMeL), which is inspired by the official documents and International standards for generalities (ISO 15189/2007) and specific items (ISO 22870/2006). This document represents a valuable enterprise, in that it refers to professional standards, guidelines and peer reviews documents for the governance of POCT, including solution for reliable implementation and potential problems in this innovative area of testing.

Clinical laboratories make a wide use of commercial diagnostic products throughout the total testing process. These products can be divided into two major categories, that are *in vitro* diagnostic (IVD) devices (e.g., laboratory instruments, reagents, assays and blood collection tubes) and me-

dical devices (e.g., specimen collection devices). Likewise laboratory professionals, commercial companies are expected to manufacture high quality products to enable a high degree of confidence and safeness in diagnostics. In the next article of this issue, Ana Stankovic synthesizes all the processes that the IVD industry has arranged to assure the maximum quality of its offerings, including designing products that meet customer needs, manufacturing them within developed specifications and very little variability, assuring both safety and efficacy in their use, fulfilling regional regulatory requirements and monitoring performance after release into the marketplace. The article also provides an overview on the key role that regulators play in maintaining product quality by setting performance standards enforced through formal product approval processes before allowing their distribution in the marketplace.

At the beginning of the 21st century there are widely accepted priorities in laboratory medicine such as laboratory automation, laboratory consolidation, molecular diagnostics, and accreditation of laboratories. Although the first systems or levels of quality management systems in laboratories are IQC, EQA or PT, the concept of accreditation or certification is now the core of laboratory practice.

The current definition of accreditation (as for ISO/IEC regulations) encompasses the formal recognition that the clinical laboratory is competent to carry out specific tests or specific types of tests. As such, laboratory regulation through quality in the healthcare arena must be based on accreditation, certification, quality monitoring, patients' rights, standard operation processes and standards of healthcare quality. In the last article of this special issue of *Biochemia Medica*, Tomáš Zima provides a comprehensive overview on the certification/accreditation processes worldwide, discussing the main theoretical and practical aspects. It is also emphasized that the first step before accreditation is building an enthusiastic team with education on quality management system, as well as appropriate selection of methods, description of the various processes in the lab, development or improvement of the metrology system, definition and structure of documents, preparation of a quality manual and standard operation practices.

We hope that you should enjoy the collection of articles in this special issue of *Biochemia Medica* devoted on quality in laboratory diagnostics, and we thank all the authors for their foremost contributions.

References

1. Goddard P, Leslie A, Jones A, Wakeley C, Kabala J. Error in radiology. *Br J Radiol* 2001;74:949-51.
2. Zarbo RJ, Meier FA, Raab SS. Error detection in anatomic pathology. *Arch Pathol Lab Med* 2005;129:1237-45.
3. Lippi G, Guidi GC. Readers' response and author's reply to "Laboratory results that should be ignored". *MedGenMed* 2006;8:38.
4. Plebani M, Carraro P. Mistakes in a stat laboratory: types and frequency. *Clin Chem* 1997;43:1348-51.
5. Carraro P, Plebani M. Errors in a stat laboratory: types and frequencies 10 years later. *Clin Chem* 2007;53:1338-42.
6. Plebani M. Laboratory errors: How to improve pre- and post-analytical phases? *Biochem Med* 2007;17:5-9.
7. Lippi G, Simundic AM. Total quality in laboratory diagnostics. It's time to think outside the box. *Biochem Med* 2010; 20:5-8.