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Harmonization of clinical laboratory information – current and future strategies

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ABSTRACT

According to a patient-centered viewpoint, the meaning of harmonization in the context of laboratory medicine is that the information should be comparable irrespective of the measurement procedure used and where and/or when a measurement is made. Harmonization represents a fundamental aspect of quality in laboratory medicine as its ultimate goal is to improve patient outcomes through the provision of an accurate and actionable laboratory information. Although the initial focus has to a large extent been to harmonize and standardize analytical processes and methods, the scope of harmonization goes beyond to include all other aspects of the total testing process (TTP), such as terminology and units, report formats, reference intervals and decision limits, as well as tests and test profiles request and criteria for interpretation. Two major progresses have been made in the area of harmonization in laboratory medicine: first, the awareness that harmonization should take into consideration not only the analytical phase but all steps of the TTP, thus dealing with the request, the sample, the measurement, and the report. Second, as the processes required to achieve harmonization are complicated, a systematic approach is needed. The International Federation of Clinical

Chemistry and Laboratory Medicine (IFCC) has played a fundamental and successful role in the development of standardized and harmonized assays, and now it should continue to work in the field through the collaboration and cooperation with many other stakeholders.

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INTRODUCTION

Patients, clinicians and other healthcare professionals assume that clinical laboratory tests performed by different laboratories at different times on the same sample and specimen can be compared and that results can be reliably and consistently interpreted (1). Unfortunately, these assumptions are not always justified because many laboratory test results are still highly variable, poorly standardized and harmonized. Harmonization represents a fundamental aspect of quality in laboratory medicine as its ultimate goal is to improve patient outcomes through the provision of an accurate and actionable laboratory information (2). Although the initial focus has to a large extent been to harmonize and standardize analytical processes and methods, the scope of harmonization goes beyond to include all other aspects of the total testing process (TTP), such as terminology and units, report formats, reference intervals and decision limits, as well as tests and test profiles request and criteria for interpretation (3, 4).

Major reasons to focus on a global picture of harmonization are represented by: a) the nature of errors in laboratory medicine and the evidence of the high rates of errors in the pre-and post-analytical phases (5, 6), b) the evidence of large variations in terminology, units and reference ranges (7), c) the increasing demand for improving appropriateness in test request and result interpretation (8), and, finally, d) the risks for patient safety related to previous issues (9).

HARMONIZATION: CURRENT PROJECTS

As recently highlighted by Tate and Coll ”clinical laboratory testing is now a global activity, and laboratories no longer work in isolation” (10). Therefore, there is an increasing awareness of the importance and urgency to achieve harmonization in all steps of the total testing process (TTP) for ensuring comparability and interchangeability of laboratory information.

Harmonizing the pre-analytical phase

Several initiatives and projects are in progress for harmonizing both the pre-pre-analytical as well as the pre-analytical processes. In the initial steps of the cycle, the issue of demand management which focuses on ensuring appropriate requesting is receiving an increasing importance. A step forward in this area has been achieved through the acceptance of the definition of “inappropriate test demand” that appears to be “a request that is made outside some form of agreed guidance” (11). The type of guidance may vary from national and international guidelines to locally agreed behaviours but the basic concept is the application of scientific evidence rather than anecdote to clinical practice (8). Among the several progress, a special attention should be deserved to the National Minimum Retesting Interval Project promoted by the Clinical Practice Section of the Association for Clinical Biochemistry (ACB) in the UK uses a “state of the art” approach to set consensus/evidence based recommendations on when a test should be repeated. (12).

The importance to standardize patient preparation and sample collection requirements to minimize the uncertainty from the pre-analytical phase has already activated efforts to provide better evidence and recommendations. (13, 14). Further work to optimize sample transportation procedures as well as the identification of indicators for their monitoring has been done,

and this is a premise for future harmonization initiatives in this field (15-17). In addition, the harmonization of procedures for evaluating the quality of biological samples, the criteria for their acceptance and rejection even through the use of automated workstations and serum indexes has been largely reported and promoted (18-21).

Harmonizing analytical results

Although the terms "standardization" and "harmonization" define two distinct, albeit closely linked, concepts in laboratory medicine, the final goal is the same: the equivalence of measurement results among different routine measurement procedures over time and space according to defined analytical and clinical quality specifications (22).

While standardization, which allows the establishment of metrological traceability to the System of Units (SI), represents the recommended approach, for a multitude of measurands the SI does not yet apply, in particular when the components in the measurand comprise a heterogeneous mixture. Over the past two decades, several clinical laboratory tests have been standardized through the development of reference measurement procedures, the IFCC playing a major role in this project. In particular, the standardization of glycated haemoglobin contributed to significant improvements in diabetes (23). Other important projects are in progress in order to standardize measurands of high clinical value such as cardiac troponin (24) and carbohydrate-deficient transferrin (25). However, as a matter of fact, for a huge number of measurands neither a reference method nor reference material are available (26). For all these measurands, harmonization of available methods and diagnostic systems should be promoted. In the last few years, significant progress has been done establishing an overarching control system of the harmonization process in all its aspects through improvements in: a) defining the quality and quantity of human samples to be used for standardization and harmonization studies (27, 28), b) identifying new and more robust mathematical models and statistical treatments of the data (29, 30). A major lesson we learnt, is that standardization and harmonization should not be applied only to clinical chemistry measurands, but to the whole field of laboratory medicine, including molecular diagnostics (31). It should be highlighted that one of the most impressive and effective examples of harmonization in laboratory medicine is the expression of prothrombin results as international normalized ratio (INR). PT results are corrected mathematically into INR by raising the PT-ratio to a power equal to the international sensitivity index (ISI) thus harmonizing results stemming from different thromboplastins from patients on treatment with vitamin K antagonists (32). Therefore, the debate on harmonization should not be limited to clinical chemistry scientists but should involve all fields of laboratory medicine to provide comparability and interchangeability of all tests usually performed in clinical laboratories, including "omics".

Under the patient-centered viewpoint, the supposed diatribe between standardization and harmonization should concentrate on more joint efforts to provide equivalence of measurement results among different routine measurement procedures and different clinical laboratories over time and space.

Harmonizing the post-analytical phase

Several issues in the post-analytical phase are increasingly acknowledged as fundamental steps for achieving higher harmonization and effectiveness of laboratory information.

Current evidence collected in the UK and in Australia demonstrates a significant variation in the units used for some tests and even more

widespread variation in the way they are represented on screens and paper, as well as the way they appear in electronic messages (33). This, in turn, creates a potential for misinterpretation of laboratory results and risk for patient safety (7). As test results are increasingly transferred electronically, the argument for adopting a single standardized set of units needs immediate uptake (34).

Reference intervals are the most widely used decision-making tool in laboratory medicine and serve as the basis for many of the interpretations of laboratory results. Numerous studies have shown large variation of reference intervals, even when laboratories use the same assay thus contributing to different clinical interpretation, risk for patients and unnecessary test repetition (35, 36). The importance of obtaining reference intervals traceable to referent measurement systems has been reported (37) and evidence-based approaches to harmonize reference intervals have been promoted (38). The Nordic Reference Interval Project (NORIP) was one of the earliest reference interval harmonization initiatives and established common reference intervals in apparently healthy adult populations from five Nordic countries for 25 of the most common clinical chemistry analytes (39) Several more recent initiatives have already provided data for adopting common reference intervals in huge geographical areas such as Asia (40), Canada (41-43) and Australasia (44). In the Australasian approach, selection of a common reference interval requires a checklist assessment process be adopted to assess the evidence for their use and is based on the criteria summarized in Table 1.

The final decision on the common reference interval to be used involves weighing up each piece of evidence. Importantly, the proposed reference limits should also be supported by flagging rates which provide an indication of the clinical considerations of a reference interval (46). However, the use of asterisks should require further considerations because patients and people who have no training in laboratory medicine now have direct access to their laboratory test results.

Table 1 Selection of common reference interval (RI): criteria to be adopted

1.	Define analyte (measurand)
2.	Define assays used, accuracy base, analytical specificity, method-based bias
3.	Consider important pre-analytical differences, actions in response to interference
4.	Define the principle behind the RI (e.g. central 95%)
5.	Describe evidence for selection of common RIs data sources (literature, lab surveys, manufacturers, data mining and the allowable bias goal as quality criterion for acceptance)
6.	Consider partitioning based on age, sex, etc
7.	Define degree of rounding
8.	Assess clinical considerations of the RI
9.	Consider use of common RI
10.	Document and implement

Adapted from ref 45, modified.

Various practices, a number of different terminologies and extremely different values have been described in the literature affecting the quality of critical results management. Large variability in critical results practices have been reported not only when comparing different geographical areas but even in the same country (47). Very recently, a study on the outcomes of critical values notification, demonstrated that in more than 40.0% of cases, they were unexpected findings, and that notification led to a change of treatment in 98.0% of patients admitted to surgical and in 90.6% of those admitted to medical wards, thus confirming their importance for an effective clinical decision-making (48). Several initiatives and recommendations on the harmonization of critical result management have been released (49-52) and, finally, a better awareness of the importance of this issue for improving the quality of laboratory services and patient safety has been achieved.

Quality indicators

The definition, implementation and monitoring of valuable analytical quality specifications have played a fundamental role in improving the quality of laboratory services and reducing the rates of analytical errors. However, a body of evidence has been accumulated on the relevance of the extra-analytical phases, namely the pre-analytical steps, their vulnerability and impact on the overall quality of the laboratory information. The identification and establishment of valuable quality indicators (QIs) represents a promising strategy for collecting data on quality in the total testing process (TTP) and, particularly, for detecting any mistakes made in the individual steps of the TTP, thus providing useful information for quality improvement projects (53). In addition, QIs represent a fundamental requirement for the accreditation of clinical laboratories according to the International Standard ISO 15189 (54). While some interesting programs on indicators in the TTP have been developed in some countries, there was no consensus for the production of joint recommendations focusing on the adoption of universal QIs and common terminology in the total testing process. A preliminary agreement has been achieved in a Consensus Conference organized in Padua in 2013, after revising the model of quality indicators (MQI) developed by the Working Group on "Laboratory Errors and Patient Safety" of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). The consensually accepted list of QIs, which takes into consideration both their importance and applicability, could be actually tested by all potentially interested clinical laboratories to identify further steps in the harmonization project (55). Preliminary performance criteria based on data collected have been proposed to allow a benchmark between different laboratories and to support improvement initiatives (56).

FUTURE STRATEGIES

Although standardization and harmonization in laboratory medicine have been recognized as essential requirements for improving quality and value for patients for a long time, some major barriers have affected the success of such projects. In fact, the processes required to achieve harmonization are complicated, costly, and time consuming: a systematic approach, therefore, is needed. This should be based on an infrastructure with "well-defined procedures, transparent operations, effective communication with all stakeholders, and a consensus approach to cooperation" (57). This systematic approach and roadmap represent essential steps for more successful harmonization initiatives. The increasing demand for standardization and harmonization in laboratory medicine requires incremental progress in addressing these issues through the cooperation between many stakeholders: laboratory professionals and their

scientific societies and federations, clinicians, in vitro manufacturing industry, accreditation and regulatory bodies, and patients' representatives (2). Several organizations, such as the IFCC, the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM), the American Association for Clinical Chemistry (AACC), the World Health Organization, the recently formed International Consortium for Harmonization of Clinical Laboratory Results (ICHCLR) that are working in the field should cooperate and integrate their efforts to avoid duplication of initiatives and to provide joint programs. Other scientific organizations such as the Clinical and Laboratory Standards Institute (CLSI) and the Joint Committee for Traceability in Laboratory Medicine (JCTLM), are recognized to play a major role in providing guidelines and lists of reference materials and reference procedures. But, first and foremost, laboratory professionals have to better understand the urgent need to improve harmonization in everyday clinical practice and to take a proactive role in efforts to assure comparability and interchangeability of laboratory information.

CONCLUSIONS

According to a patient-centered viewpoint, the meaning of harmonization in the context of laboratory medicine is that the information should be comparable irrespective of the measurement procedure used and where and/or when a measurement is made: this represents the major driver for implementing harmonization initiatives. In recent years, further demanding drivers have increased the need for, and relevance of, efforts for harmonizing laboratory information, first and foremost the evidence that variations in laboratory information not only cause confusion but are potentially dangerous. There is convincing evidence that errors in laboratory medicine affect patient outcomes and affect patient safety (6). Two major progresses have been made in the area of harmonization in laboratory medicine: first, the awareness that harmonization should take into consideration not only the analytical phase but all steps of the TTP, thus dealing with "the request, the sample, the measurement, and the report". Second, as the processes required to achieve harmonization are complicated, a systematic approach is needed. A further achievement is the recognition of the need to also apply the concepts of harmonization and standardization in clinical research and in projects of translational medicine (58). The cooperation between laboratory professionals, clinicians, IVD manufacturers, accreditation and regulatory bodies is essential.

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