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Harmonization of laboratory testing — Current achievements and future strategies

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ABSTRACT

Harmonization in laboratory testing is more far-reaching than merely analytical harmonization. It includes all aspects of the total testing process from the "pre-pre-analytical" phase through analysis to the "post-post-analytical" phase. Harmonizing the pre-analytical phase requires use of standardized operating procedures for correct test selection, sample collection and handling, while standardized test terminology, and units and traceability to ISO standard 17511 are required to ensure equivalency of measurement results. Use of harmonized reference intervals and decision limits for analytes where platforms share allowable bias requirements will reduce inaccurate clinical interpretation and unnecessary laboratory testing. In the post-analytical phase, harmonized procedures for the management of critical laboratory test results are required to improve service quality and ensure patient safety. Monitoring of the outcomes of harmonization activities is through surveillance by external quality assessment schemes that use commutable materials and auditing of the "pre-pre-analytical" and "post-post-analytical" phases. Successful implementation of harmonization in laboratory testing requires input by all stakeholders, including the clinical laboratory community, diagnostics industry, clinicians, professional societies, IT providers, consumer advocate groups and governmental bodies.

1. Introduction

Clinical laboratory testing is now a global activity and laboratories no longer work in isolation. Therefore, it is in the best interests of patients to work towards a closer agreement or harmonization of laboratory procedures and test results. Once achieved, this approach generates clinical information which is widely useful for disease management and medical intervention. It is important to recognize that harmonization in laboratory testing is more far-reaching than merely analytical harmonization. It includes all aspects of the total testing process [1], from the "pre-pre-analytical" phase ('Right test choice at the Right time on the Right patient') through analytical steps ('Right results in the Right form') to the "post-post-analytical" phase ('Right interpretation with the Right advice as to what to do next with the result').

There are now powerful drivers for broader harmonization to occur across all aspects of laboratory testing. Patient safety concerns arising from use of the Electronic Health Record (EHR) are driving the need for harmonized methodology, terminology and units of reporting in Laboratory Medicine. Analytical tests can use different methods that may not have been harmonized, possibly with different units of reporting. Those who request laboratory tests and receive laboratory reports, the information systems developers and even the laboratorians themselves may be unaware of these differences, especially if the transfer of results from the laboratory to the report recipient does not clarify differences in units of reporting or in assay methods in use. Inevitably the assumption made by clinicians is that the differing numbers can be directly compared. This situation has the potential for misinterpretation of results, wrong treatments and adverse patient outcomes [2].

It is, therefore, a main responsibility of laboratory professionals to identify where harmonization in laboratory testing is still lacking and involve the relevant stakeholders (including the laboratory community, clinicians using tests, IT staff, General Practitioners, patients' associations and regulatory bodies) to ensure optimal use and reporting of laboratory results, thereby minimizing their misinterpretation (Table 1).

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EFLM, European Federation of Clinical Chemistry and Laboratory Medicine; EHR, Electronic Health Record; EQAS, External Quality Assurance Scheme; IFCC C-NPU, International Federation of Clinical Chemistry and Laboratory Medicine Committee on Nomenclature for Properties and Units; IFCC C-RIDL, IFCC Committee on Reference Intervals and Decision Limits; IFCC WG-LEPS, IFCC Working Group on Laboratory Errors and Patient Safety; ISO, International Organization for Standardization; IT, information technology; IUPAC, International Union of Pure and Applied Chemistry; IVD, In Vitro Diagnostics; JCTLM, Joint Committee for Traceability in Laboratory Medicine; NORIP, Nordic Reference Interval Project; QIs, quality indicators; SOPs, standard operating procedures; WG, working group.

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Table 1
Summary of features and requirements for achieving harmonization in laboratory testing.

Phase	Requirements	Vested stakeholders
Pre-pre-analytical	1. Use of evidence-based guidelines for appropriate test selection. 2. Plan for implementation and educational phases.	1. Clinicians; the laboratory community; guideline organizations. 2. Professional societies; the laboratory community.
Pre-analytical	1. Standardize pre-laboratory/external pre-analytical processes. 2. Implement SOPs to reduce error and ensure patient safety.	1. Healthcare practitioners e.g. phlebotomist; laboratory personnel. 2. WHO World Alliance for Patient Safety; CLSI; IFCC WG-LEPS.
Analytical	1. Harmonize patient results through a standardization and/or harmonization process. 2. Harmonize laboratory test names and units. 3. Standardize test requesting and reporting for the EHR. 4. Harmonize report formats where there are patient safety issues. 5. Monitor reliability of analytical systems and analytical quality of measurements.	1. JCTLM; national metrology institutes; reference material providers; IFCC; IVD manufacturers; EQAS organizers; clinical laboratories. 2–4. Clinical terminology and information systems providers; IUPAC; IFCC C-NPU; Governments; patient safety groups. 5. IVD manufacturers; EQAS organizers; clinical laboratories.
Post-analytical	1. Harmonize reference intervals and clinical decision limits. 2. Plan for implementation and educational phases. 3. Report critical patient values according to an agreed critical test list.	1–2. Professional societies; IFCC C-RIDL; the laboratory community; clinicians. 3. Laboratory personnel; clinicians; GPs.
Post-post-analytical	1. Educate users about the meaning of laboratory tests. 2. Develop an on-going laboratory-clinical systems provider working relationship for long-term sustainability of pathology harmonization.	1. Clinicians; GPs; consumer advocate groups; patients. 2. The laboratory community; clinicians; systems providers.

CLSI, Clinical and Laboratory Standards Institute; EQAS, external quality assurance scheme; EHR, electronic health record; GPs, general practitioners; IFCC WG-LEPS, International Federation of Clinical Chemistry and Laboratory Medicine Working Group on Laboratory Errors and Patient Safety; IFCC C-NPU, IFCC Committee on Nomenclature for Properties and Units; IFCC C-RIDL, IFCC Committee on Reference Intervals and Decision Limits; IUPAC, International Union of Pure and Applied Chemistry; IVD, In Vitro Diagnostics; JCTLM, Joint Committee for Traceability in Laboratory Medicine; SOPs, standard operating procedures.

2. Harmonizing the pre-analytical phase

For reasons of patient safety, it is important that healthcare practitioners and laboratory professionals recognize the need to use standardized operating procedures for pre-analytical processes to reduce error and make possible obtaining an accurate test result. These procedures include among others correct test selection, sample collection and handling.

2.1. Appropriate test selection and test profile requesting

Test availability and the composition of test profiles for different clinical conditions can vary between laboratories resulting in confusion to clinicians who may use both private and public laboratories, and in added expense at no additional benefit to the patient [3]. The European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Working Group (WG) on Guidelines is systematically addressing ways of harmonizing test selection for specific diseases. Already through the UK Pathology Harmony project, guidelines relating to tumour marker requesting have been recommended [4]. The group examined the use of tumour markers in oncology practice in the UK for which no standard guidance was available. Best practice was determined for each of the common tumour markers following recommendations from professionals with appropriate expertise [4].

2.2. Optimizing sample handling

Correct sample handling including sample collection and sample preparation and appropriate tube type are critical to providing accurate test results [5]. Furthermore, it is important to harmonize collection procedures to minimize the uncertainty from the pre-analytical phase. The EFLM is specifically addressing pre-analytical issues such as standardization of sample collection requirements through its WG on Pre-analytical Phase, with manufacturers of collection tubes participating in this activity. Laboratories may introduce procedures to reduce high frequencies of hemolyzed samples, e.g. collection of troponin requests by trained phlebotomists in Emergency Departments [6].

2.3. Quality indicators

The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) WG on Laboratory Errors and Patient Safety is addressing the need to establish a global program of continual improvement to ensure the quality of patient care and safety. The WG has applied the use of quality indicators (QIs) to detect pre- and post-analytical errors in laboratory testing [7]. A total of 16 QIs have been developed for the pre-analytical phase, including those traditionally outside the control of the laboratory, e.g. test requesting, patient and sample identification, and sample collection (so-called "pre-pre-analytical phase" QIs), as well as QIs that cover all steps of the laboratory "pre-analytical phase", e.g. sample preparation and storage. Through an understanding of the risks to patients undergoing laboratory testing, standardized operating procedures should be developed to reduce errors and improve patient safety [7–9].

3. Harmonizing analytical issues

3.1. Harmonization of test units and terminology

There is a need for standardization of units of reporting and terminology. Current reporting practices are heterogeneous and may lead to an increased risk of interpretation errors, possibly endangering patient safety. It is these factors which are driving the requirement for standardization of IT structures and terminology. Currently both in the UK through the Pathology Harmony project and in Australia and New Zealand through the Royal College of Pathologists of Australasia Pathology Units and Terminology Standardisation (PUTS) Quality Use of Pathology project, there are important contributions being led by the respective pathology professions. Assessment of units, terminology and which tests to combine for display as a graph or cumulative report (i.e. code harmonization) will provide the structure for future pathology test requesting and reporting [10,11].

3.2. Standardization vs. harmonization of assay results

Clinical laboratories understand standardization to mean the closer equivalence of measurement results through calibration to a higher-order reference method and/or reference material. The standardization of measurements is of high priority in laboratory medicine and aims to achieve closer comparability of results obtained using routine measurement procedures [12]. The use of the standardization process ensures the traceability of results to a widely accepted reference measurement system and greater certainty that a result is close to the true value [12,13]. However, measurements of heterogeneous analytes with inherent molecular variability, e.g. cardiac and tumour markers, rely on assays showing differences in antibody specificity and the antigenic epitope measured.

Consequently, these measurements are usually traceable only to a lower-order manufacturer's selected measurement procedure and calibrators as neither reference material nor reference method is available.

3.3. Standardization and traceability to the International System of measurement (SI)

The metrological concepts of standardization, calibration traceability to reference materials and measurements, and measurement uncertainty are described in the International Organization for Standardization (ISO) standards ISO 17511 [14] and 18153 [15], which describe criteria for assuring the accuracy and equivalence of clinical laboratory results. It is the reference measurement system that links higher-order reference methods and reference materials to field calibrators and methods used in clinical laboratories through an unbroken, metrologically-based, hierarchical traceability chain. Once suitable reference materials are available, these materials and the manufacturer's testing procedures can be used by industry to assign values to working calibrators by a value transfer process. Through this calibration process, clinical laboratories using commercial procedures with validated calibrators to measure patient samples will obtain traceable values, with little or no calibration bias among the different commercial procedures.

3.4. Harmonization of non-SI traceable analytes

Compared with the described standardization process, the harmonization process is not based on traceability to a higher-order reference measurement system and, therefore, may be biased in terms of trueness. Nevertheless, if commercial measurement procedures have similar analytical specificity for a measurand and a commutable calibrator material is available for value transfer, then harmonization is feasible [16]. An international consortium for harmonization of clinical laboratory results is currently being formed to organize these global harmonization efforts [17].

4. Harmonizing the post-analytical phase

4.1. Reference limits and decision levels

Numerous studies have shown that the variation in reference intervals for clinical analytes may be much greater than the analytical inaccuracy of their measurements [18,19]. Hence, the same patient result obtained by two laboratories that use the same assay, but different reference intervals can contribute to different clinical interpretation and unnecessary additional laboratory testing, with some risk to the patient of inappropriate investigation or treatment. One solution to the problem is to define “common” reference limits and decision points. The implementation of harmonized reference intervals at a local, national or international level has implications for use of the analyte in clinical guidelines.

Reference limits and decision points can be classified based on their quality using the Stockholm hierarchy as a classification standard [20]. Decision thresholds based on clinical outcome studies constitute the highest level of quality, with the clinical expectation that all methods employed in the clinical setting are harmonized. By contrast, reference limits based on an assay's kit insert data constitute the lowest quality level, usually having the least harmonization with little possibility of shared reference limits.

In between these extremes there are other approaches to achieving harmonized reference limits. The Nordic Reference Interval Project (NORIP) established common reference intervals in adults for 25 of the most common clinical chemistry analytes using apparently healthy adult populations from five Nordic countries [21]. One hundred and two participating laboratories analyzed reference samples they had collected together with reference material and control sera that were value-assigned by reference measurement procedures or traceable to a trueness reference.

Expert local groups can provide professional recommendations. In New Zealand, a practical model developed by the Auckland Regional Quality Assurance Group more than 35 years ago provides a mechanism by which reference limits can be harmonized across laboratories within a region after a checklist assessment process including the evidence for merging of reference intervals [22]. In Australia and New Zealand an initiative is currently underway to achieve harmonized reference limits through an evidence-based approach and understanding the various physiological factors that affect reference intervals [20,23]. Using Bhattacharya analysis of hundreds of thousands of data points for samples from ‘the walking well’, and partitioning by age, gender and gestational age in pregnancy, it is possible to tease out the physiological factors that contribute to changes in reference intervals in health. While laboratories are well-versed in method verification and validation to determine if assays are fit-for-purpose, they are less aware of the importance of selecting the most appropriate and evidence-based reference intervals.

An important aspect of harmonized reference intervals is development of the criteria for a laboratory to use a common reference interval, i.e. the allowable bias and imprecision. Information about method comparability through an assessment of the between-method bias using biological samples [24] is required before common reference intervals can be implemented. It is the analytical quality of the assays we use that will ultimately determine those analytes which can share common or harmonized reference intervals. Assays traceable to reference measurement systems will be most capable of harmonization [25]. The clinical laboratory can adopt common reference intervals provided that there is verification of similar pre-analytical conditions, of traceability of the analytical method used, and of similar characteristics of the population being tested.

4.2. Management of critical laboratory results

An important area needing attention is that of critical laboratory results and their communication to clinicians. The literature on current standards and recommendations for critical result management indicate that there is considerable variation among laboratories for critical tests and limits, notification procedures and monitoring of outcomes [26–28]. Harmonized best practice laboratory guidance preferably based on outcome studies or failing that expert consensus is needed to improve service quality and assure patient safety [29]. The Clinical and Laboratory Standards Institute (CLSI) is currently preparing a guideline on the topic that will aid in harmonizing critical result management policies and procedures worldwide.

5. Surveillance of the success of harmonization activities

Surveillance of harmonization activities is required to determine whether they are successful. In the case of method standardization/harmonization, there are external quality assurance schemes (EQAS) that provide commutable materials and value assignment with reference procedures to assess the analytical quality of measurements for selected analytes. This aspect is of particular relevance when clinical decision limits recommended by international guidelines and/or traceable reference intervals are in use. In the case of “method harmonized” analytes, it will be important to have an ongoing monitoring of assays to detect any systematic drift in assay performance by the evaluation of patient samples that are validated for commutability.

Reporting the source of laboratory reference intervals along with EQA data will provide useful information about the harmonization status of both the analyte measurement and corresponding reference interval.

A number of quality indicators have been suggested for audit of the ‘post-post analytical phase’ to assess, for example, the timeliness of

laboratory reporting, the number of critical results communicated, the use of evidence-based commenting on reports including advice given to clinicians by laboratories [7–9,30]. Harmonization criteria should be patient-centred and possibly incorporate standardized reporting systems for data management handling. Laboratories need to work closely with IT staff, General Practitioners and patient-management system vendors to ensure optimal use and reporting of laboratory results, and to avoid misinterpretation of longitudinal results in the same individual. On the other hand, consumer education about the meaning of laboratory tests is becoming more important while patients are expected to understand and manage their own healthcare. On-line education modules for specific diseases and for appropriate laboratory testing are required [31].

6. Conclusion

Harmonization initiatives have a central role in laboratory medicine and require input from a range of national and international stakeholders to gain momentum and uptake. Their development will require the close interaction of all stakeholders, including the clinical laboratory community, diagnostics industry, clinicians, professional societies, IT providers, consumer advocate groups and governmental bodies. A well-planned communication and marketing strategy is required in order to be able to roll out the relevant changes, to educate clinicians and to gain acceptance of these processes by all stakeholders.

Whatever the laboratory discipline, the same goals of harmonization apply. As potential consumers of laboratory testing ourselves, we above all have the expectation of receiving not only the Right result on the Right patient at the Right time in the Right form, but also the Right test choice with the Right interpretation with the Right advice as to what to do next with the result irrespective of the laboratory that produced it. It is only by having a harmonized approach to laboratory testing that we can achieve these expectations.

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