

## Review

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# Harmonization in laboratory medicine: the complete picture

## Abstract

Evidence of the acute lack of interchangeable laboratory results and consensus in current practice among clinical laboratories has underpinned greater attention to standardization and harmonization projects. Although the focus is mainly on the standardization of measurement procedures, the scope of harmonization goes beyond method and analytical results: it includes all other aspects of laboratory testing, including terminology and units, report formats, reference intervals and decision limits, as well as test profiles and criteria for the interpretation of results. This review provides further insight on the issue of harmonization in laboratory medicine in view of the urgent need for a complete picture now that old and new drivers are calling for more effective efforts in this field. The main drivers for standardization and harmonization projects are first and foremost patient safety, but also the increasing trends towards consolidation and networking of clinical laboratories, accreditation programs, clinical governance, and advances in Information Technology (IT), including the electronic patient record. The harmonization process, which should be considered a three-tier approach involving local, national and international fronts, must go beyond the harmonization of methods and analytical results to include all other aspects of laboratory testing. A pertinent example of the importance of a complete picture in harmonization programs is given by the National Bone Health Alliance working in the field of bone turnover markers in cooperation with scientific societies including the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).

**Keywords:** harmonization; laboratory medicine; patient safety; quality; standardization; total testing process.

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## Introduction

Thanks to constant innovation in strategies, tools and techniques used in the total testing process (TTP), the path leading to quality and patient safety in laboratory medicine is infinite, since it must be ensured that each and every step in the TTP is correctly performed, thus guaranteeing a valuable medical decision making process and effective patient care [1]. While a body of evidence gained in recent years demonstrates the decrease achieved in analytical errors, further efforts are required to address the vulnerability of pre- and post-analytical steps, and to assure comparability and concordance of data obtained by different clinical laboratories [2].

Although the importance of standardization and harmonization in clinical laboratories has been evident for more than four decades [3], harmonization of laboratory information is still the 'holy grail'. In addition, further efforts to achieve harmonization in laboratory medicine have become mandatory thanks to new and highly demanding goals, such as electronic patient records and the growing importance of clinical guidelines. Last but not least, initiatives aiming to improve harmonization of laboratory test results have an ethical dimension, their main purpose being to provide reliable information that, in turn, should assure optimal care for patients in a global world [4]. Although important standardization and harmonization projects are being conducted by major organizations such as the American Association for Clinical Chemistry (AACC) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), an overall picture is still required, as all processes and steps involved in the testing cycle play a relevant role in the ultimate quality and safety for patients. This review aims to contribute to improving the awareness of laboratory professionals on the importance of standardization and harmonization projects dealing with all steps of the TTP.

## Drivers for standardization and harmonization

The main thrust behind standardization and harmonization has been clear and well known for several decades. Service users, namely requesting physicians and patients, need to be able to directly compare results from different clinical laboratories. However, in recent years, further demanding drivers have increased the need for, and relevance of, efforts for harmonizing laboratory data (see Table 1). First and foremost, there is a greater awareness that variations in test results, names, units and reference intervals not only cause confusion but are potentially dangerous. For example, as cardiac troponin I and/or T assay play a key role in the diagnosis and treatment of acute coronary diseases, the harmonization and standardization of these assays are needed in order to improve upon commutability and data comparison. In particular, it should be possible to diagnose acute myocardial infarction irrespective of the choice of analyte (cTnI or cTnI) or analyzer. Yet attempts to standardize and harmonize continue to fail, and discordant classifications of patients and subjects relative to the cut-off have been described [5]. Even a change in the unit for hemoglobin (Hb) expression could potentially affect patient safety. Findings in a recent survey conducted in the UK revealed that 80% of laboratories were using g/dL, although g/L is the recommended unit and this, in turn, changed the reported results by a 10-fold factor [6]. In the seminal concept of ‘patient-centered care’, a key issue is the active engagement of patients in fateful healthcare decisions including the need

for diagnostic tests [7]. In laboratory medicine, supposed ‘patient empowerment’ often translates in mounting pressure from individual patients for direct access to test requests and results interpretation [8]. This, linked to the lack of effective procedures and results harmonization, may trigger cascades of serious and stressful interventions thus incurring a risk of harming patients.

The increased trend towards consolidation and networking of clinical laboratories represents a formidable thrust and incentive for standardization and harmonization as there is the need to enable the safe utilization of laboratory data by a wide range of users in primary and secondary healthcare. Accreditation of medical laboratories according to the ISO 15189: 2007 Standard requires documentation of trueness of measurement (5.5.3c) and of metrological traceability (5.5.3g), which are fundamental requisites of the standardization and harmonization processes [9]. Advances in information technologies and the electronic distribution from different laboratories of data that should be mixed and matched and, even more important, electronic health recording have increased the demand for harmonization in laboratory medicine [10]. Therefore old and new drivers, namely the widespread mobility of the population and the recognition of patient-centeredness as a major attribution for reorganizing healthcare services, call for increased efforts to achieve standardization and harmonization. If a patient intends to travel at home or abroad, it will soon be unjustifiable to tell her or him that s/he must use the same clinical laboratory on the ground that results from different laboratories are neither consistent nor comparable.

Drivers	Negative outcomes
Patient safety	Differences in practice put patients at risk (data misinterpretation, misclassification, misdiagnosis, and inappropriate treatment)
Patient empowerment	Mounting pressure to allow individual patients direct access to test requests and results interpretation linked to a lack of harmonized policies and results
Consolidation and networking	Differences preclude the effective and safe utilization of laboratory data by a wide range of users in primary and secondary healthcare
Accreditation	The ISO 15189 Standard requires records of trueness of measurement (5.5.3c) and of metrological traceability (5.5.3g)
Clinical guidelines	Differences among laboratories compromise the value of practice guidelines and results interpretation according to recommended thresholds and decision limits
Public/patient confusion	Users expect test results to be accurate and comparable, and interpreted in a consistent way
Clinical governance	Differences make clinical laboratories more vulnerable and laboratory professionalism less trustworthy
Advances in computing and IT	Differences prevent the mixing and matching of laboratory data distributed electronically by different laboratories
Electronic patient records	Differences preclude data commutability, and may change patient’s ‘natural history’

**Table 1** Old and new drivers for standardization and harmonization in laboratory medicine.

## Standardization of laboratory results

The terms ‘standardization’ and ‘harmonization’ define two distinct, albeit closely linked, concepts in laboratory medicine. Yet both are based on traceability principles described in the International Organization for Standardization (ISO) standard 17511 [11], in which the term ‘standardization’ is used when results for a measurand are equivalent, and the results are traceable to the International System of Units (SI) through a high-order primary reference material and/or a reference measurement procedure (RMP). The term ‘harmonization’ is generally used when results are equivalent, being either traceable to a reference material or based on a consensus approach, namely in agreement with the mean values obtained with different methods, but neither a high-order primary reference material nor an RMP is available.

The concepts of metrological traceability and calibration hierarchies have been well defined and extensively described in several papers [12, 13]. According to the traceability strategy, a result of measurement in a patient sample should be traceable along a cascade of measurement procedures and calibrators/reference materials of increasing metrological order up to the highest level represented by the definition of the measurand in SI units [14]. In principle, if a reference system is in place for an analyte, its measurement is described as ‘standardized’, thus giving clinical laboratories the best possible opportunity to obtain analytical results close to true values, which are thus harmonized across different routine measurement procedures [12]. However, it should be underlined that in addition to the three commonly cited pillars of a reference system (i.e., RMP, reference materials and accredited reference laboratories), some key characteristics of these components play a relevant role. In fact, the commutability of reference materials, the definition of measurement uncertainty and traceable reference intervals/decision limits are of paramount importance.

### Commutability

Commutability has been defined as ‘The equivalence of the mathematical relationships among the results of different measurement procedures for a reference material and for representative samples of the type intended to be measured’ [11]. A non-commutable reference material cannot be used for calibration traceability because it does not have the same numeric relationship between measurement procedures as do the patient samples. A non-commutable material may therefore produce differences

in calibration, resulting in non-harmonized analytical values among different clinical laboratories and different measurement procedures [15, 16]. However, the need to validate commutability for secondary reference materials has only recently been recognized [17, 18], and clinical laboratories still encounter difficulty in selecting commutable materials from the commercially available sources.

### Uncertainty

Establishing the traceability of results for a test measurement should be inextricably linked to the definition of *acceptable measurement uncertainty* to fit the intended clinical application (‘fitness for purpose’). The uncertainty of measurement must be ‘defined across the *entire traceability chain*, starting with the provider of reference materials, extending through the diagnostic manufacturers and their processes for assignment of calibrator values, and ultimately to the final result reported to clinicians by end users (i.e., the clinical laboratories)’ [19]. This approach should be applied to every analyte measured in the clinical laboratory so as to understand whether the current status of the uncertainty budget of the measurement associated with the proposed metrological traceability chain is suitable for clinical application of the test itself [20]. For example, recently published data demonstrate that the reference measurement system currently available for albumin and the associated uncertainty does not guarantee the accuracy needed for its clinical use [21].

### Reference intervals

The adoption of the metrological approach to standardize assay results significantly modifies the relationship of analyte results to existing reference intervals and decision limits [22, 23]. Therefore, if analytical standardization is not followed by the appropriate revision of reference values and decision limits, pivotal to making the correct interpretation and clinical utilization of laboratory data, patients’ outcomes will be worsened. In a recent paper, Panteghini demonstrated this issue by describing three effective examples: serum creatinine and glomerular filtration rate equations, the prostate-specific antigen recalibration, and glycated hemoglobin [19].

A global consideration of problems linked to commutability, measurement uncertainty and reference values clearly shows that laboratory professionals must close the current gap between the standardization principles and

their application in routine practice in order to counteract the view that manufacturers should bear responsibility for the quality of results. The responsibility of clinical laboratories is not limited to the selection of commercial measurement procedures, but should include items ranging from the definition of the appropriate quality specifications for each measurand to the identification of criteria required for obtaining the optimal interpretation and utilization of results, including reference intervals and decision limits. Moreover, the realization and maintenance of metrological traceability call a new effort from the organizers of Proficiency Testing (PT)/External Quality Assessment (EQA) programs: PT/EQA materials should disclose commutability to allow transferability of analytical performances from participating laboratories to patient samples. Accredited reference laboratories should assign reference measurement procedures to the values of these materials, and the allowable uncertainty of measurement should be defined in order to verify the suitability of laboratory measurements for the clinical setting [24]. Reference values are still an open question for clinical laboratories even though they are an essential step in improving the post-analytical phase [25]. There is therefore an urgent need to link standardization initiatives to new and more effective efforts to provide reference intervals traceable to reference measurement [26].

## Harmonization of laboratory results

The development and implementation of a reference measurement system, a major scientific and organizational challenge, is a long process; this explains why a reference measurement system and a primary reference material are available for only a few measurands, including some clinical chemistry analytes such as glucose, electrolytes and cholesterol, as well as some hormones (e.g., cortisol), most of these having a relatively small molecular weight. The development of reference measurement procedures for a number of hapten assays is possible thanks to the unequivocal definition of the analyte, while it is far more complicated for large molecular weight peptides that may exist in multiple circulating forms or isotypes. In addition to grappling with molecular complexity, sometimes it is impossible to identify which isotype exerts the biological activity [27]. So far, several hundred measurands of clinical interest lack metrological traceability to SI units - either because of the difficulty involved in unequivocally defining the analyte in terms of molecular structure and weight or because primary and secondary reference measurement

procedures are unavailable. This applies in particular to fields other than the traditional 'clinical chemistry' with the inherent risk of considering standardization and traceability as programs exclusively oriented to clinical chemistry measurands. However, all other measurands can be accommodated in one of several calibration hierarchies of the lower metrological order of the ISO 17511 standard [11]. In particular, although no primary reference material is available, the development of reference measurement procedures for many enzymes of clinical interest (category 2 of reference systems) has resulted in significant improvements in commercially available methods and reagents and therefore in a significant enhancement of agreement between different laboratories [28]. The availability of a suitable matrix reference material for the measurement of serum protein (ERM-DA470, previously called CRM470) has led to a high level of harmonization in measurement results for 15 human serum proteins [29]. More recently, a new serum protein reference material (ERM-DA470k/IFCC) has been produced to replace ERM-DA470, and values have been successfully assigned to 12 proteins [30].

An increasing body of evidence demonstrates that patient test results can be harmonized even for analytes present in different molecular forms, for which reference procedures are not available. This applies in particular to immunoassays, relevant examples being thyroid function tests [31–33], insulin [34], PTH [35] and the growth hormone [36].

So even when reference standards are unavailable, major steps towards harmonization can be achieved through inter-method comparison and recalibration to the overall mean or to the value obtained with a high-order measurement procedure (e.g., isotope dilution-liquid chromatography/tandem mass spectrometry, IDMS for insulin assay). Further examples of successful harmonization initiatives in fields other than the traditional clinical chemistry include coagulation tests, the most frequently requested being Prothrombin Time (PT). The expression of PT results following the International Normalized ratio (INR) resulted in an improvement in the harmonization of results with an improvement in the utilization of this test for monitoring vitamin K antagonist therapy (VKAT), thus sparing patients from having to use the same clinical laboratory if they plan to travel [37]. Other initiatives for the harmonization of test results in the field of coagulation have been reported, particularly for the D-dimer measurement [38]. Another example refers to the measurement of the total hemoglobin concentration in blood. This assay should be performed with a conventional reference measurement procedure endorsed by the ICSH, which utilizes an international conventional calibrator (IRMM BCR 522)

with a certified value and uncertainty assigned using calibrated spectrophotometers [39].

The need to harmonize test results across method types, laboratory settings and intended use is increasingly recognized in the field of molecular diagnostics. The proliferation of assay methods, mainly homemade, and the absence of standard reference materials contribute to variability in test results among laboratories. Harmonization initiatives are based on the development of reference materials, appropriate documentary standards and guidelines, and proficiency testing/external quality assessment programs [40]. The importance of harmonization, and its advantages over standardization, has been stressed for innovative biomarkers, particularly when ‘broader implementation is premature or prohibitively expensive’ [41].

## Harmonization: the global picture

According to the Clinical and Laboratory Standards Institute (CLSI) definition, harmonization is ‘the process of recognizing, understanding, and explaining differences while taking steps to achieve uniformity of results, or at minimum, a means of conversion of results such that different groups can use the data obtained from assays interchangeably’ [42]. However, the scope of harmonization goes beyond method and analytical results harmonization to include all other aspects of laboratory testing, such as terminology and units, report formats, reference intervals and decision limits, as well as test profiles and criteria for result interpretation [43]. The above-mentioned concept of ‘patient-centered care’ and current evidence of errors in laboratory medicine call for a global and integrated project on harmonization in laboratory testing that should involve all steps of the process. Table 2 summarizes the main issues concerning harmonization in the laboratory testing.

## Test requesting

Appropriateness in test requesting, a major issue in the debate on quality and efficiency in laboratory medicine, is complex and, as yet, no magic bullet has been found to solve it; yet there is no doubt that differences in test requesting may lead to confusion and put patient safety at risk. Removing tests that offer little incremental information would save money, avoid additional investigations arising from incidental and clinically irrelevant minor abnormalities, and improve the risk to benefit ratio. In a recent bench marking program in the UK, the 49 laboratories subscribing to the initiative listed 11 different liver function profiles [44]. Thanks to improvements in information technology, it is now more feasible to aim for diagnosis- or condition-based testing rather than organ-based testing. Best practices in test requesting should be determined for the most prevalent clinical conditions by interacting with expert clinicians. In theory, this should be done for each and every laboratory test, but particularly for those that are costly, that may affect patient management and may cause the patient psychological or economical difficulty, such as tumor markers [45]. Clinical practice guidelines are systematically developed statements intended to assist practitioners and patients in making decisions about appropriate healthcare for specific clinical circumstances, namely in test requesting. It has recently been observed that the inclusion of laboratory medicine specialists in the guideline development process may increase the focus on important laboratory-related items, including appropriateness in test requesting and related procedures [46]. Therefore, harmonization initiatives based on current evidence should be welcomed, even if the need for a more ‘personalized’ approach based on individual needs and following the mantra ‘the right test for the right patient at the right time’ remains the major goal in improvement initiatives.

Step in TTP	Issues
– Test requesting	Terminology, test and test profiles Re-testing interval and practices
– Sample collection and handling	Time, patient preparation Handling, transportation and storage issues
– Analysis	Acceptance/rejection criteria Analytical procedures (method, calibration, quality control)
– Report	Turnaround times Reporting units and formats Reference intervals, reference change values and decisional limits Critical values and tests

**Table 2** Harmonization in laboratory testing: main issues.

## Re-testing intervals

Minimal re-testing intervals (MRI) are defined as the minimum time before a test should be re-tested based on the properties of the test and the clinical situation in which it is used. The Association for Clinical Biochemistry (ACB) has promoted a project to investigate this issue starting with a survey, an additional literature search, the preparation of recommendations and revision by third party experts [47]. The final recommendations on re-testing times are thus based on evidence, if available, if unavailable, expert opinions are sought.

The repeat testing practice is also useful for the automatic repeat testing of laboratory tests when values trigger automated 'repeat rules', such as critical test results, in the laboratory information system. According to a recently published study, the 'practice of repeat testing for many automated clinical chemistry tests can be stopped', but this step should be taken only after more definitive confirmatory data have been obtained [48].

## Sample collection and handling

Several lines of evidence attest to the fact that the vast majority of errors in laboratory medicine originate in the 'manually intensive' activity undertaken in the pre-analytical phase [49]. The most prevalent pre-analytical errors are those occurring during the collection of blood specimens; so the definition, implementation, and monitoring of suitable sample collection standards are highly conducive to improving the quality of the testing process [50]. In particular, harmonization projects should adhere to standardized protocols for patient preparation, time and use of appropriate devices and techniques for sample collection. In addition, due to the consolidation of laboratory testing facilities, there is an increasing need for systems that assure quality and safety in biological sample transportation; yet little evidence on this aspect is available in the literature [51, 52].

## Report

Some data reported in literature show that in the post-analytical phase, most laboratory errors are attributable to clerical errors, thus stressing the need to avoid manual transcription of data and/or to implement safer manual procedures (e.g., double check) [53]. However, in this phase, not only is there variation in the coding and naming of tests but there is also significant variation in

the units used for reporting [54]. Satisfactory terminology should be: appropriate for the clinical setting, implementable, understandable and acceptable to clinicians, software developers and statisticians and, last but not least, customizable [55]. Harmonization of laboratory test names should therefore be based on those principles. Most professionals believe that units of measure have been standardized following the publication in 1971 of the SI Units, which introduced the *amount-of-substance* with *mole* as a measurement unit [56]. However, 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 [54, 55]. While international consensus on this issue would be welcome, on a local basis a pragmatic solution should be sought, at least by different laboratories in the same geographical area, in order to harmonize the units of measure, and to obviate the reporting of confusing results.

Although the state-of-the-art for reporting units is in a sorry state, reference values are in an even sorer one. The classical approach advocated by the IFCC [25] and recently revised by Ceriotti et al. [57, 58] is well defined and straightforward. However, alternative methods have been advocated. The Pathology Harmony group is encouraging laboratory professionals to find consensus in developing a common set of reference ranges and clinical protocols for wide use across the UK. The assumption of the pragmatic philosophy driving the scheme is that the minor differences between the methods used by laboratories are of little clinical significance. The continuing debate between purists and pragmatists must be tempered against the clinical risk springing from a plethora of different reference ranges [59]. The evidence of different intervals for 'simple' but essential laboratory tests such as potassium for 45 laboratories in central England triggered the recommendation of common intervals [60]. This initiative, welcomed by patients and physicians in the same geographical area, is a simple tool for facilitating clinical reasoning and optimizing current services. Pragmatism cannot replace good science, but there is no justification for delaying the harmonization of reference ranges for many laboratory tests performed in the same geographical area. Consensus should also be achieved on reliable turnaround times (TAT) that take effective clinical needs into account; this is of crucial importance in preventing a widespread and wild point-of-care testing being introduced and conducted without evidence of its effect on patient-management strategies and clinical outcomes [61].

## Critical values

The timely release and effective communication of critical test results may have a significant impact on medical decisions and related patient outcomes. Certification, accreditation and regulatory bodies [9, 62] require laboratories to follow procedures that ensure patient safety, but there is limited guidance on the best practices for attaining this end.

Table 3 summarizes the main issues in the management of critical values and critical tests. The reported variations between procedures and policies used by different laboratories in the same country and by those in different countries [63–65] emphasize the need for harmonization projects, which has become more pressing as the notification of critical values and procedures for the correct management of critical tests has gained increasing importance.

## Quality indicators

The identification of reliable quality indicators (QIs) in the TTP is a crucial step in enabling users to quantify the quality of laboratory services, but the current lack of attention to extra-laboratory factors is in stark contrast with the body of evidence showing the multitude of errors that continue to occur in the pre- and post-analytical phases. Although interesting programs on indicators for the extra-analytical phases have been developed in some countries, there is no consensus on the production of joint recommendations for the adoption of universal QIs and the use of common terminology in the total testing process [66]. In view of the different QIs and terminologies currently used, there is an urgent need to harmonize proposed QIs, which should comply with three main principles: they must be patient-centered, consistent with the requirements of the

International Standard for medical laboratories accreditation, and address all stages of the TTP. Harmonization of QIs consists of two compulsory steps: the identification of common QIs and a standardized reporting system.

The model of quality indicators (MQI), consensually developed by a group of clinical laboratories in a project launched by a working group of the IFCC [68] should be a further driver for a global view of harmonization in laboratory medicine.

## The agenda for harmonization

The increasing demand for standardization and harmonization in laboratory medicine requires incremental progress in addressing these issues through professional organizations, multidisciplinary practice guidelines developed by national and international committees, peer-review publications, the global in vitro manufacturing industry, regulatory bodies and many other stakeholders. Closer interaction with all stakeholders is essential for harmonization projects to be successful and, particularly for critical tests, to enhance clinical effectiveness and guarantee greater patient safety. As standardization and harmonization initiatives in laboratory medicine are long-lasting, some lessons from the past should guide us towards better outcomes.

First, the processes required to achieve harmonization are complicated and therefore an infrastructure with ‘well-defined procedures, transparent operation, effective communication with all stakeholders, and a consensus approach to cooperation’ is mandatory [18]. The systematic approach and roadmap proposed by Miller and colleagues as a result of the conference organized in 2010 by the AACC represent an essential step towards successful harmonization initiatives in laboratory medicine. Underpinning this systematic approach is the recognition that it is important to ‘identify measurands for which harmonization is needed, prioritize the measurands based on clinical importance and technical feasibility, and organize the implementation of harmonization initiatives’ [18].

Second, the responsibilities for the procedures and materials in analytical standardization projects are now defined at different levels, and the Joint Committee for Traceability in Laboratory Medicine (JCTLM), has taken on an increasingly important role [13]. In particular, two working groups are providing a list of reference materials and reference procedures, and are identifying reference measurement laboratories [14]. However, the evaluation and validation of commercially available kits, even for

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1. Definition of critical tests and critical values
2. Identification of critical values
3. Critical values notification procedures
– Data validation
– Timeliness of reporting
– Communication tools (phone, informatics, call centers)
– Personnel responsible for data transmission and receiving results
– Acknowledgment of results and feedback
– Data recording
4. Procedures for evaluating and monitoring the outcomes of critical results management practices.

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**Table 3** Key issues in critical tests and critical values management.

high-order traceable assays, is still the duty and responsibility of laboratory professionals and cannot be ignored. This also applies to assays sold as ‘for Research Use Only’, as underlined in a recent Editorial [69].

Third, regulatory bodies should play an increasing role in standardization and harmonization projects. The state-of-the-art of diagnostic technologies evaluation underlines the need to assess efficacy in the context of the care pathway, including issues such as standardization, harmonization and evidence of impact on patient outcomes [70]. In Europe, current regulation falls under the responsibility of a Directive, CE marking (*Conformité Européenne*), which simply certifies that a product has met health, safety, and environmental standards. However, it obliges diagnostic manufacturers to ensure traceability of their analytical systems to recognized higher-order references [71]. The US procedure for the evaluation of diagnostic technologies is more complicated, multifaceted, and inextricably linked to payment, and does not necessarily take the issues of standardization and harmonization into due consideration [70]. Even if other regulatory frameworks are in place in Canada and Australia, the fundamental role of laboratory professionals in assuring quality in the whole cycle of laboratory investigations is increasingly recognized [71].

Fourth, standardization and harmonization issues should be taken into consideration from the beginning (i.e., as soon as a new assay is under development); this also applies to measurements performed in research. Considerable evidence has been collected to demonstrate several pitfalls in the translational history of new laboratory tests, namely new biomarkers. Ioannidis has recently highlighted a number of aspects that need to be addressed in the biomarker pipeline emphasizing current failures including poor analytical validity, difficulties in standardization, and the lack of large-scale evidence of clinical utility [72]. Recent technological developments have highlighted the need to improve the framework for the evaluation of laboratory tests, namely innovative biomarkers, including the issues of standardization and harmonization ‘to all assay variables from the protocol and raw data acquisition, processing, interpretation, and reporting’ [41].

Fifth, while current evidence underlines the greater vulnerability of extra-analytical procedures and processes [2], greater awareness should be gained of the importance of standardization and harmonization initiatives aiming to reduce errors in the TTP and improve comparability of laboratory information. Standardization and harmonization go hand-in-hand since they are continuous processes that in synchronicity promote further standardization and harmonization efforts. For example, the identification of pre-analytical errors may only be possible because measurements have become more accurate and specific as a result of standardizing the actual measurements. This in turn creates the need to obtain higher quality samples to sustain further standardization projects [73].

The time has come for a global picture of harmonization in laboratory medicine that takes into consideration all the steps and processes of the TTP and prioritizes the implementation of corrective and preventive actions on the basis of identified clinical needs. The projects promoted by the Pathology Harmony in the UK [54], the Royal College of Pathologists in Australasia [43, 55], and on QIs [67, 68] represent a key step toward closing the gap between scientific knowledge and current practice in laboratory medicine.

## Conclusions

The complete picture of harmonization in laboratory medicine must take into account not only initiatives to standardize and harmonize analytical results, but all other steps that may influence the ultimate quality of laboratory information. First, there is a need to improve appropriateness in test requesting, and to identify valuable and safe procedures for sample collection and handling through evidence-based guidelines and expert opinion. The standardization and harmonization of methods and measurement procedures remain the ‘core’ of projects for assuring uniformity of results, but PT/EQA programs in monitoring and improving comparability of laboratory

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- Local: Adoption of international and national recommendations; implementation of ‘ad interim’ laboratory practices for measurement units, reference ranges, decision limits and Standard Operating Procedures
  - National: Diffusion of internationally developed guidelines; development and release of laboratory practices for standardization and harmonization of all TTP steps, including communication of test results and critical values
  - International: standardization and among methods harmonization, clinical practice guidelines for test requesting and result interpretation
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**Table 4** Harmonization as a three-level process.

results play a major role in harmonizing results obtained by different laboratories. Harmonization in TAT, reporting units and formats, reference intervals, reference change values and decision limits – and the definition and notification of critical values – in the post-analytical phase, may contribute to improving the overall quality of laboratory services and may thus, in turn, enhance the quality of care. A pertinent example of the importance of a complete picture in harmonization programs is given in the work on bone turnover marker conducted by the National Bone Health Alliance in cooperation with scientific societies including the IFCC. The project, started by identifying the most valuable markers, assayed harmonization and appropriate quality control/assurance programs, and then established reference population databases [74, 75]. Thanks to this initiative, the harmonization of laboratory information should come into effect. The example given shows that harmonization projects must not only be pursued, but that they should also be successful. Therefore, the harmonization process can be implemented only with the active involvement of numerous stakeholders, including laboratory professionals, international and national medical and clinical organizations, IVD manufacturers, metrology institutes, and regulatory agencies, and a three-tier approach (Table 4) will be required to achieve this: 1) locally, in addition to the

adoption of international and national recommendations and guidelines, pragmatic initiatives will be undertaken to ‘ad interim’ harmonize laboratory practices regarding measurement units, reference ranges and decision limits. These ‘ad interim’ solutions should be adopted until a consensus is achieved at international or national levels; 2) nationally, in addition to the diffusion of internationally-developed guidelines, laboratory practices for the communication of laboratory results, including critical values and should be disseminated; and 3) internationally, standardization and harmonization projects will be pursued and practice guidelines should be released to cover all steps of the TTP, including test requesting and results interpretation.

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