**Editorial**

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# Time for a holistic approach and standardization education in laboratory medicine

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The value of laboratory medicine is closely related to the impact of its laboratory services on patient outcome. The perception of patients and medical doctors regarding medical laboratory services is that diagnostic laboratories deliver accurate test results, which guarantee an unequivocal and similar risk classification, diagnosis, treatment and patient outcome across hospitals. External quality assurance (EQA) programs, which structurally evaluate laboratory test performance, demonstrate that this perception is not true, not even for routine medical tests [1–3]. This situation is undesirable because patients live in a global world, and therefore, it is essential that diagnostic test results produced in accredited medical laboratories across the globe are comparable in time and space, enabling unequivocal diagnosis, treatment, and monitoring of patients. To that end, global standardization and harmonization of medical tests should be key for sustainable patient care with universal application of reference values and decision limits, as well as preparing for future exchange and interoperability of electronic health records. Beyond the relevance of global standardization and harmonization of routine diagnostic tests, the need to standardize and harmonize tests also holds for innovative biomarkers which have the potential to become medical tests. After all, new scientific findings based on for example disruptive *-omics* technologies (such as genomics, transcriptomics, proteomics, and metabolomics) are expected to undergo rapid translation and should be standardized right from the outset of their development [4].

Stakeholders involved in diagnostic testing – in vitro diagnostic (IVD) industry, medical laboratories, and EQA-providers – are faced with a multitude of legislations and regulations which are not attuned to each other and variably affect medical test performance and test standardization due to varying interpretations. First, standards from authoritative bodies such as ISO 15189:2012 and ISO 17025 for accreditation of medical laboratories, and EN 14136 and ISO 17043 for accreditation of EQA/proficiency testing providers verify the competences of its target groups in a generic way, leaving room for variable interpretation. Second, guidelines from scientific organizations such as the RiliBÄK guidelines in Germany can lead the way in defining analytical requirements regarding test performance, which is the case in German medical laboratories. Third, the former European IVD directive 98/79/EC, which is currently under revision, demands traceability of test results to standards of higher order without being clear about the exact reference measurement system that is required. Finally, the review work of the Joint Committee for Traceability in Laboratory Medicine (JCTLM) – established in 2002 – is highly relevant, as JCTLM working groups periodically evaluate the potential of new reference materials, reference methods, and reference laboratories for test standardization. Unfortunately, JCTLM has no legal status and no references are made to its database either in ISO 15189:2012 and ISO 17025 or in the IVD 98/79/EC directive. Notwithstanding this confusing situation on how to standardize tests, it is assumed by regulators and legislators that IVD industry implements the metrological traceability concept in the same unequivocal way.

Independent evaluation of test accuracy and interlaboratory comparability of medical test results is structurally done by EQA organizers that provide blinded EQA samples for analysis in laboratories that participate in specific EQA programs. The first EQA surveys were set up by Belk and Sunderman back in 1947 [5]. Currently, six types of EQA programs with different evaluation capabilities exist, depending on the EQA sample characteristics and the quantities intended to be measured [6]. In essence, all EQA programs aim to improve the quality of medical testing and to reduce interlaboratory variation among laboratories. Only types 1 and 2 EQA programs make use of commutable, value-assigned EQA samples, and have the capability of evaluating trueness and imprecision of medical tests.

In this issue of *CCLM*, Infusino et al. [7] report on the progress of traceability implementation and standardization for routine enzyme measurements. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) had established Reference Measurement Procedures (RMPs) for seven frequently requested enzymes in the period 2002–2011. These IFCC-RMPs were positioned as

the highest "anchor" in the traceability chain for enzyme standardization. IVD manufacturers were expected to assign values to their commercial calibrators in order to make them traceable to the IFCC-RMPs, to achieve equivalent results in clinical samples, independent of reagents, analyzers, and laboratories. Notwithstanding the fact that most IFCC-RMPs have been in place for about 10 years, recent multicenter studies demonstrated only for creatine kinase satisfactory standardization, improvement in γ-glutamyl transferase standardization and inadequate aspartate transaminase, alanine transaminase, lactate dehydrogenase, and amylase standardization [2, 6]. The main reasons for this are related to the fact that IVD manufacturers continue to manufacture kits based on different experimental conditions leading to test results that are not traceable to IFCC-RMPs. Also, end-users still use diagnostic reagents that do not have the correct specificity for measuring the enzymes of interest. In another contribution to this *CCLM* issue, Braga et al. [8] evaluated trueness of alkaline phosphatase measurements by means of an EQA experiment with commutable, value-assigned serum pools in 13 Italian laboratories and demonstrated that only 3 out of 13 laboratories met the desirable bias specifications and only one laboratory provided test results with a dispersion within the uncertainty of the target value. Infusino et al. and Braga et al. criticize the fact that, notwithstanding the presence of the IVD directive 98/79/EC and the existence of JCTLM-listed IFCC-RMPs for enzyme measurements, the implementation of the metrological traceability concept for routine enzyme measurements by the IVD-industry is slow, variable and inadequate. According to these authors, the way forward for standardization in clinical enzymology is adoption of analytical performance specifications based on clinically acceptable measurement uncertainty for each enzyme, together with the provision of EQA programs using commutable materials and an evaluation approach exclusively based on trueness. Yet, as the number of types 1 and 2 EQA programs based on native, commutable and value-assigned EQA samples is limited, rapid progress along this line seems unrealistic.

One can wonder what the deeper root causes of resistance to test standardization may be. Firstly, it seems that standardization of medical tests such as enzyme measurements is presumed by its stakeholders as a minor issue and not an essential part of Test Evaluation. Stakeholders apparently do not understand the entire picture of Test Evaluation or the relevance of test standardization for patient care. Several frameworks for Test Evaluation are in place, such as the framework from the European Federation of Laboratory Medicine (EFLM) Working Group on Test Evaluation, in which all key components of test evaluation and their interdependences are presented [9]. The test evaluation framework illustrates that in the case of inaccurate test results, desirable analytical performance specifications cannot be met, negatively impacting clinical performance and clinical effectiveness of medical tests. If the IVD industry and laboratory professionals do not perceive the mutual influence of analytical on clinical performance specifications, and vice versa, they do not fully appreciate the need for standardization. Therefore, the importance of equivalence of test results especially for analytes which have a reference measurement system in place should be shown explicitly by documenting the degree of patient harm in its absence. This could be investigated in straightforward simulation studies, such as the one described for example by Langlois et al. [10]. Second, there is a lack of education on standardization in laboratory medicine. Looking into best practices of successful standardization efforts in other branches such as the food industry (Nestlé) and the mobile industry using mobile communications technology standards (with migration of the market from the 2G to 3G arena) may help to understand the reasons for resistance to standardization of medical tests on the one hand and how to overcome these on the other hand. After all, these industries also had to solve similar resistances. To increase global efficiency, Nestlé, a leading nutrition, health, and wellness company did a SAP® software installation, the world's largest at that time. There were 15,000 processes to reconcile and the project encountered lots of resistance. Nestlé's CEO continued to push for adaptation and standardization of the processes first, and cost savings and benefits soon became clear. In 2 years, the percentage of standardized processes at Nestlé jumped from 30% to 80%. Among other benefits, standardization made it easier for Nestlé to integrate acquired companies. Also, with the explosive growth of internet in the late 1990s, the pro-active stakeholders in the mobile industry sensed that the future lay in multimedia services delivered through the Internet. Notwithstanding the huge obstacles these companies encountered in order to transform the circuit-switch 2G voice systems to packet-switch 3G multimedia systems, they were successful. The examples from the food and mobile industries demonstrate that these companies managed resistances by analyzing the sources of resistance and by developing leader strategies to overcome the resistances [11–13]. One of the most elementary strategies appeared to be the demonstration of the need for change, tied to the mission of the branch. Beyond that, participation, training, and active support of stakeholders or employees were also essential to overcome resistance. Finally, overarching and defined

processes for standardization were essential in order to get standardization prioritized as a key factor for success.

By analogy, global test standardization in laboratory medicine is only feasible using a holistic and coordinated approach, similar to the ones used in successful industries. Beyond that, global test standardization also needs an educational approach with a curriculum that encompasses or integrates standardization education [14]. Several dimensions of test standardization should be addressed in such a curriculum, namely: (a) the scale for standardization is relevant (e.g. national, international); (b) the disciplines or sectors involved should be inventoried; (c) the subject matter areas such as quality, safety and interoperability should be clear; (d) the kinds of standards needed should be considered e.g. terminology, reference materials, reference methods and reference laboratories, compatibility, quality; (e) overarching global processes of test standardization should be considered and designed, including the selection of standards-setting organizations, drafting, decision-making, distribution, selection, implementation, use and impact; and finally, (f) several aspects of standardization (physical, psychological, economic, and ethical) should be investigated, including characterization of standardization (variety reduction) and the importance per stakeholder.

Global test standardization is the way forward for better patient care worldwide. Notwithstanding the good intentions of several stakeholders and organizations, the current standardization process is fragmented, allows permissiveness and does not clarify the degree of patient harm caused by non-standardization. Global standardization efforts are key for future success and demand holistic and strongly coordinated approaches with matched legislation and regulation. Furthermore, standardization of tests should no longer be considered a pastime of those interested in metrology; instead, scientifically underpinned standardization education should become an integral part of curricula of future specialists in laboratory medicine.

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