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Promoting clinical and laboratory interaction by harmonization

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ABSTRACT

The lack of interchangeable results in current practice among clinical laboratories has underpinned greater attention to standardization and harmonization projects. Although the focus was mainly on the standardization and harmonization of measurement procedures and their results, 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 limits and decision thresholds, as well as test profiles and criteria for the interpretation of results. In particular, as evidence collected in last decades demonstrates that pre-pre- and post-post-analytical steps are more vulnerable to errors, harmonization initiatives should be performed to improve procedures and processes at the laboratory–clinical interface. Managing upstream demand, down-stream interpretation of laboratory results, and subsequent appropriate action through close relationships between laboratorians and clinicians remains a crucial issue of the laboratory testing process. Therefore, initiatives to improve test demand management from one hand and to harmonize procedures to improve physicians' acknowledgment of laboratory data and their interpretation from the other hand are needed in order to assure quality and safety in the total testing process.

1. Introduction

The importance of standardization and harmonization in clinical laboratories has been evident for more than four decades, but this topic has received the due attention only in the last few years. Although relevant projects have recently been undertaken by scientific associations and committees [1,2], we should still agree with the statement by Hillebrand in 1951, reaffirmed by Rodin in 1967, that "the situation is particularly deplorable just now" [3] and, therefore, the search for harmonization of laboratory information can be compared to that of the "holy grail". A fundamental issue in harmonization and standardization projects is the close interaction and cooperation with physicians, particularly as these approaches should be addressed to improve not only the analytical phase but also all steps of the total testing process (TTP) [4]. As stressed by McLawhon, "a striking majority of our physician and surgeon colleagues still fail to grasp or understand the limitations of current laboratory measurements, the lack of interchangeability of results obtained by different analytical methods, and the resulting effects on interpretation, clinical decision-making, and patient management" [5].

The issue of the interaction between laboratorians and clinicians is long lasting, and paradoxical evidence demonstrates that the more intense is the debate the worse is the state-of-the-art. However, a shift in the pendulum of clinical–laboratory collaboration with laboratory professionals playing a more central role in patient care has been predicted as a result of the translation of "omics" technologies [6]. Clinicians are already struggling to understand laboratory results, but the complexity of the "omics" technologies will require a sea-change in current procedures used for test request and result interpretation. Evidence has been collected to demonstrate that patient safety is compromised by tests that are inappropriately requested and then misinterpreted [7]. Therefore, harmonization of procedures and processes in pre- and post-analytical steps of the TTP, including the communication to clinicians of quality specifications and analytical characteristics of diagnostic tests, plays a key role in improving the ultimate quality of laboratory services. The aim of this paper is to review the most critical issues in the relationships between the clinicians and the laboratory, the so-called 'clinical–laboratory interface', that affect harmonization in the total testing process.

Managing upstream demand, down-stream interpretation of laboratory results, and subsequent appropriate action through close relationships between laboratorians and clinicians remains a crucial issue of the laboratory testing process. These activities are poorly evaluated and monitored, often because the process owner is unidentified and the responsibility falls in the boundaries between laboratory and clinical departments. A body of evidence demonstrates that the risk of errors and patient harm in the "brain-to-brain loop" is significantly decreased within those processes developing within the laboratory, but it is relatively high at the beginning and at the end of the loop, which mostly lie outside the traditional laboratory environment. The increasing concerns towards the first and final procedures in the TTP, the so-called pre-pre- and post-post-analytical steps, highlight the vulnerability of the laboratory–clinical interface and require an innovative approach to harmonization in Laboratory Medicine. According to the Clinical

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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" [8]. However, the scope of harmonization goes beyond method and analytical results including all other aspects of laboratory testing, such as terminology and units, report formats, reference limits and decision thresholds, as well as strategies for test demand and criteria for result interpretation [9].

2. Harmonization of test demand

Many drivers call for managing test demand and they should be grouped into finance, quality and patient issues. The finance perspective is based on the cost of inappropriate requesting that includes not only reagents, consumable and human resources, but also additional and unnecessary consultations, treatments and investigations. However, quality and patient safety issues seem to be more crucial as inappropriate testing is generally related to scarce quality, delayed or missed diagnoses and poor patient experiences [10]. Although there is a large concern regarding the unnecessary requesting of laboratory tests, the evidence is scarce as most studies did not meet methodological standards suggested for clinical audit [11]. In addition, the lack of a consensus on what is an "inappropriate request", resulted in another severe bias in many study designs, thus affecting any possible improvement and harmonization project.

2.1. Inappropriate test demand and practice guidelines

As recently proposed, the definition of inappropriate test demand as a "request that is made outside some form of agreed guidance" should better address the point [12]. In fact, this definition is different from "inappropriate test" that should also design an incorrect test performed for a laboratory error on a correct request, and "unnecessary request", a term that excludes those tests that may be inappropriately late compared with an agreed testing frequency. The focus on "guidance" well reflects one of the major movements that emerged in medicine in the past decade aiming to put medicine on a firm scientific footing, the so-called "evidence-based medicine" [13].

The type of guidance, in turn, may vary from national and international guidelines to locally agreed behaviors, but the "core" of the definition is the need of a reference based on a laboratory and clinical consensus. The application of scientific evidence rather than anecdote to clinical practice has extended to virtually every area of medicine, including Laboratory Medicine. Evidence-based guidelines for standardized test demand represent a formidable tool for improving appropriateness in test request as they are positioned at the crossroads of two developments: one is the arrival of an era of assessment and accountability in healthcare and the other is the increasing belief that clinical practice should be guided by the best available evidence [14]. Professional societies, government panels, and other groups increasingly began developing recommendations to assist laboratory professionals and clinicians in delivering appropriate test demand. In the field of Laboratory Medicine, the National Academy of Clinical Biochemistry (NACB) started producing laboratory medicine practice guidelines and currently eight guidelines published in the last 5 years are available on the NACB website (http://www.aacc.org/publications/practiceguidelines/Pages/default.aspx). These guidelines deal with important topics such as diabetes, emerging cardiovascular risk factors, biomarkers of acute coronary syndrome, expanded newborn screening, and tumor markers. Thereafter many other scientific and professional societies have produced laboratory practice guidelines as well as recommendations for laboratory testing have been introduced as a part of many clinical guidelines.

However, there are some suggestions that the effectiveness of guidelines in influencing clinical practice depends on the way in which the guidelines are developed [15], and implemented [16]. Evidence has been collected to demonstrate the need for an active involvement and inclusion of Laboratory Medicine specialists in the guideline development process as this led to an increase in the number of essential topics such as information on sample type and handling, analytical and biological variation, which, in turn, strongly influence the quality of laboratory data [17]. In addition, some surveys have reported the scarce application in current clinical practice of widely accepted guidelines and the lack of related protocols between clinicians and laboratorians, thus affecting the expected quality improvement [18]. Many barriers delay and/or prevent the compliance with guidelines and behavior modification initiatives are unlikely to be effective if single strategies are used [19]. In particular, a critical issue is the role of defensive medicine in triggering inappropriate laboratory testing, particularly in emergency care setting. It is noteworthy that in a large US-based survey, the vast majority of physicians (i.e., 92%) admitted the prescription of tests and diagnostic procedures as an "assurance behavior" [20], with serious implications for cost, access, technical and interpersonal quality. Therefore, only combined interventions based on national or regional educational initiatives, dissemination of guidelines after adaptation to local situations and other multifaceted approaches may result in significant improvements.

2.2. Strategies to improve appropriateness in test request

A relatively simple but effective initiative is the removal from the test menu of obsolete and unuseful tests. 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. For example, deleting myoglobin, total creatine kinase (CK) and CK MB isoenzyme determinations from standard laboratory electronic order forms in patients admitted to emergency departments for chest pain leads to significant cost saving and reduces possible confusion in data interpretation and patient management [21]. In fact, while the measurement of cardiac troponin in acute coronary syndrome has been proven to be cost-effective, all other "cardiac" markers, including myoglobin and CK MB, do not add useful clinical information [22]. Other consolidated examples are the deletion from order forms of anti-gliadin, anti-reticulin and anti-endomysium antibody tests in patients with suspected celiac disease after the development of anti-transglutaminase assays [23]. However, few reports of the literature deal with experiences in deleting obsolete tests and with the relative economic and patient outcomes and no initiatives to harmonize these projects have been proposed.

A recent and interesting initiative promoted by the Association for Clinical Biochemistry (ACB) aims to harmonize common laboratory test profiles. In a recent bench marking program in the UK, the 49 laboratories subscribing to the initiative listed 11 different "liver function" profiles, thus highlighting the lack of a consensus and huge variability in clinical practice [24]. The ACB proposal for harmonizing test profiles would not only save money, but also remove some of the confusion caused by laboratories using different profiles for the same pathophysiology and reduce some of the additional investigations arising from incidental and clinically irrelevant abnormalities. In addition, it represents an initial step towards problem-based rather than panel-based testing, which should be the ideal solution.

Another issue affecting the inappropriateness of test request is the high rates of re-testing and, recently, some initiatives have been promoted to identify a re-testing policy based on evidence. Minimal re-testing intervals 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. While many laboratories admit to using their laboratory information system (LIS) to identify such tests, there was a lack of published data on recommended minimum re-test interval