Editorial

The future of clinical laboratories: more testing or knowledge services?

Over the last 20 years laboratory medicine has played an increasingly dominant role in clinical decision-making and patient management. Laboratory tests are essential to safeguarding health, screening for disease, making a diagnosis and monitoring patients (1). With the constant development of more complex tests, medical practice will become increasingly dependent on laboratory medicine (2), and this process will be underpinned by the forthcoming translation into clinical practice of new insights from promising research areas such as genomics, transcriptomics, proteomics and other “omics”, particularly for achieving an early diagnosis and “personalized medicine” (3). However, laboratory tests and data are useful only if translated into clinical information that can be used effectively by physicians to improve clinical reasoning and patient management (4). The effectiveness of laboratory tests must therefore be evaluated and measured on the basis of the clinical benefit they provide in terms of an improved diagnostic process and/or therapeutic strategy, with consequent maximization of the overall health outcome. A growing body of evidence collected in recent years demonstrates inappropriateness in test requesting, interpretation and utilization (1). It has, moreover, been observed that diagnostic tests do not appear to have a major impact on patient outcome (5) and that laboratory testing is a “commodity”, thus creating a gap between clinical practice and laboratory services. There are many signs of this:

• It is widely believed laboratory medicine costs are high, without there being an awareness of the fact that high-quality laboratory services give true value for money. Competition between laboratories seems to be increasingly based on one element: cost per test. For example, the competitive bidding demonstration project promoted by the US Congress in 2003 hinges upon the assumption that laboratory products available in the marketplace are of equal quality; they are therefore considered commodities (6).

• There is widespread pressure on clinical laboratories to reduce direct costs (reagents, instrumentation and personnel) and to create highly automated megastructures, without making any attempt to evaluate the appropriateness of test request/interpretation, or to improve the utilization of laboratory data in patient management (7).

• The outsourcing of laboratory services is widely promoted in many countries, as for other services (e.g., food, canteens, washing areas) that are not considered “core business” in the healthcare system (8).

• The point-of-care testing option is generally accepted by administrators, who focus on rapid turnaround time rather than making an effective evaluation of its true clinical and operational benefits (9).

• As physicians and scientists no longer consider laboratory medicine “attractive” for economic and professional reasons, fewer graduates in medicine or in biology are trained in the discipline.

• Finally, some standardization projects promoted by laboratory professionals and their associations are underpinned by the idea that improvements in analytical quality specifications of laboratory tests automatically translate into better diagnoses and treatments. However, a growing body of evidence demonstrates that clinical benefits can be achieved only by focusing on the quality of the total testing process, and, in particular, on the appropriateness of test requesting and interpretation.

Recently, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) developed a reference standard based on the mass spectrographic analysis of a glycated peptide fragment of hemoglobin designed to remove non-specific elements of HbA1c measurement (10). Use of the new standard in reporting HbA1c results should reduce the extent of errors in the measurement of this parameter, and might promote inter-laboratory harmonization. However, the international diabetes community has expressed concern regarding clinical use of the new values for HbA1c which are markedly lower than the traditional ones. Philip Home and colleagues have expressed the fear that this scientific advance could worsen overall blood-glucose control and may involve the risk of losing the benefits of years of professional education in the quantitative relation between overall blood-glucose control and diabetes complications (11). It would be unreasonable not to make use of the advance introduced by the IFCC, but a coordinated program is mandatory to assure not only improved analytical data, but also education and criteria for allowing the comparison and interpretation of new and “old” data in patient monitoring.

A growing body of evidence has been accumulated in recent years to demonstrate that apolipoprotein B (apoB) and apoA-I are more effective markers than plasma lipids in diagnosing and guiding treatment of atherogenic dyslipoproteinemias (12). In particular, the apoB/apoA-I ratio better reflects the lipoprotein “atherogenic balance” in blood than any of the cholesterol ratios (13). The IFCC standardization project for measurements of apoB and apoA-I resulted in improved inter-laboratory comparability of analytical...
results by use of an international reference material (14). However, apolipoprotein measurements were never promoted or introduced into clinical/therapeutic trials or into clinical practice, thus representing a missed link in the standardization project. In fact, currently available clinical guidelines are still based on the measurement of total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol. Therefore, improvements in analytical standardization alone not only fail to automatically translate into better care, but they must also be accompanied by major education initiatives and efforts to assure total quality of laboratory data, including their appropriate interpretation and utilization.

Cardiac troponin is another intriguing issue. The conclusions of a recently published review on alternative causes for elevated cardiac troponin levels when acute coronary syndromes have been ruled out underline that “while troponin is a sensitive biomarker to ‘rule out’ non-ST segment elevation myocardial infarction, it is less useful to ‘rule in’ this event because it is not specific for acute coronary syndromes” (15). This contradicts evidence demonstrating that cardiac troponin is effective in diagnosing myocardial damage because of its high positive predictive value, allowing cardiologists and emergency physicians to correctly identify “acute myocardial infarction” in around 30% of ST-negative patients with chest pain and clinical evidence of ischemia (16). The idea that the specificity of cardiac troponin is “poor” depends on the observation that many clinical situations other than myocardial ischemia lead to myocardial injury and necrosis. However, the clinical context and the kinetics of the marker in patients with acute coronary syndrome differ significantly from those in patients with other clinical conditions, thus allowing appropriate interpretation, diagnosis, risk stratification and patient management. Cardiac troponin is not only a milestone in the biochemical approach to the diagnosis and risk stratification of acute coronary syndrome, but, thanks to its specificity, is also increasingly used as a valuable tool in ruling out or in significant myocardial injury after trauma, high-dose chemotherapy and inflammatory disorders such as pericarditis and myocarditis. The conclusions of the above-cited paper, however, stress that efforts to improve analytical methods for cardiac troponin measurement, made by the Committee on Standardization of Markers of Cardiac Damage of the IFCC (17) and other laboratory associations (18), fail to address an important issue: the need to close the gap between the excellent clinical specificity and sensitivity of the marker and its inappropriate request/interpretation in clinical practice. As with any other laboratory test, if troponin measurement is used indiscriminately in populations with a low pre-test probability of disease, its positive predictive value is greatly diminished. If laboratory professionals and their associations, as well as manufacturers, are to promote projects to improve the analytical quality and standardization of a marker with a pivotal role in the management of patients with chest pain, a greater effort should be made to work together with cardiologists and clinicians to ensure that the requesting and utilization of such a marker is appropriate to clinical practice. The troponin saga also shows that a distinction must be made between the clinical value of a laboratory test (troponin) and current methods for its measurement. Performance characteristics strongly affect the clinical value of the test, and laboratory specialists have a duty to promote the continuous improvement of analytical quality specifications, as well as to recommend the appropriate clinical interpretation/utilization of results obtained with currently available assays, thus avoiding excessive underlining of their limitations. Clinical laboratories must report results in a way that allows physicians to appreciate and understand the fundamental quality specifications (bias, imprecision, any decisional levels) that are needed to correctly interpret laboratory findings (19). Communication to clinicians of the current limitations of available assays must not undermine confidence and belief in the clinical value of the marker, especially as its analytical performance characteristics are constantly being improved upon.

The controversy over this issue is not new: Karel G.M. Moons and co-workers have stressed that we need to shift from the traditional “test research” approach, focusing on a particular test to quantify its generic sensitivity, specificity and likelihood ratio, to more consistent “diagnostic research” (20). By “diagnostic research” we mean studies aiming to quantify the extra contribution of a test, which involves more than making test results readily available to the physician in determining the presence or absence of a particular disease. From this perspective, laboratory results are evaluated in the real world, with real patients and real physicians. The recent STARD initiative should contribute to improving the quality of studies on diagnostic accuracy and might show that this is not simply a “laboratory” problem, but an issue concerning all clinical interventions made and information provided (21). A recent paper supporting Bayesian reasoning in framing and revising differential diagnosis recommends the judicious interpretation of diagnostic tests. Bayesians interpret any test result not simply as a categorical probability of a false positive (or negative), but as the degree to which a positive or negative result adjusts the probability of the presence of a given disease (22). In this respect, the following statement deserves attention: “Clinical diagnosis ultimately rests on the ability to interpret diagnostic test results. But what is a diagnostic test? Clearly blood tests, radiography, biopsies, and other technology based evaluations qualify. However, this view is far too restrictive. In truth, any patient feature that varies in a given disease also qualifies. This definition would include each step in the clinical algorithm above, and importantly, virtually all elements of the clinical history and physical examination” (22). Some positive lessons deriving from this conceptual foundation are available in the current literature. In particular, the suitability of the D-dimer assay to exclude venous thromboembolic disease was firmly
demonstrated in the 1980s (23). However, only recently consensus has been reached on the effective use of this laboratory test in clinical practice, linking its negative value to the pre-test odds, which implies the rational use of this laboratory test in the context of other clinical information (24). The first step, which laboratory professionals are responsible for, is to evaluate the performance characteristics of D-dimer assays and to use a method with high sensitivity and, therefore, an adequate negative predictive value. A balanced consideration of sensitivity, specificity, analytical turnaround time and cost is mandatory. The second step is to discuss with “local” physicians the correct interpretation of D-dimer results in a patient with suspected deep venous thrombosis (DVT). Findings in the literature demonstrate that in patients with low/intermediate pre-test probability, a negative D-dimer significantly reduces the post-test odds and provides a reasonable certainty of ruling out thromboembolic disorders. A negative D-dimer finding, therefore, substantially reduces the need for both initial and serial ultrasonography and, in some cases, contrast venography, magnetic resonance venography or CT, thus allowing the physicians to safely save time for the patient and money for the healthcare system. The third step is to activate a diagnostic pathway to be used effectively by physicians for patients with suspected DVT or pulmonary embolism (PE) based not only on available scientific evidence, but also on the acceptance of a shared responsibility to assure accurate data (laboratorians) and correct interpretation (physicians).

Laboratory medicine has introduced seminal concepts such as diagnostic sensitivity and specificity, likelihood ratio and post-test odds for a disease (25) into the medical arena. These concepts must be applied to any clinical practice, not to laboratory tests alone. This also means that laboratory professionals and their scientific associations must continuously improve analytical quality specifications and the standardization of laboratory tests, and work in close cooperation with clinicians and their associations to provide state-of-the-art interpretation and utilization of laboratory tests in the real world, on every possible occasion and in every possible place.

The crucial question is therefore whether laboratory professionals are to control and improve only the analytical part of the total testing process, including at most pre-analytical aspects, or whether they should share with clinicians the responsibility for appropriate requesting, interpretation and utilization of laboratory data that might result in improved outcomes. The issue should be viewed from a general perspective as the need to clarify whether laboratory medicine is an academic discipline, integral to modern medicine, or whether clinical laboratories are simply a testing service dedicated to assuring analytically reliable, efficient and speedy laboratory results without any consideration of their clinical efficacy and their impact on clinical outcomes.

The healthcare system has been defined as “a set of connected or interdependent parts or agents bound by a common purpose and acting on their knowledge” (26). Clinical laboratories are not only a testing service, but are also a knowledge service that utilizes all the means of communications available; they do not simply give assay results, but also offer knowledge and education (27). Laboratory tests cannot be externalized if laboratory professionals are to act as an integral part of the healthcare system, strictly cooperating with clinicians and effectively demonstrating credibility and status within their local communities.

References