The future of Laboratory Medicine: understanding the new pressures (*)

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ABSTRACT

Since the future role of Laboratory Medicine is strongly and equally challenged by economical and new technological pressures, it is essential to take a broad view of the discipline and present to the administrators and other decision makers the full spectrum of activities and benefits Laboratory Medicine can provide. In particular, the importance and the true impact of Laboratory Medicine can only be achieved by assuring an appreciable added value to laboratory tests, represented by their effectiveness in influencing the management of patients and related clinical outcomes.

INTRODUCTION

Clinical laboratories represent an area of healthcare that has always undergone major changes because of technological advances and external economic pressures (1). In the recent past, many new diagnostic techniques and laboratory tests have been introduced as a result of both research on the fundamental pathogenesis of diseases and the development of new methods in themselves. The two Nobel prizes awarded respectively to the inventions of monoclonal antibodies (G. Koehler and C. Milstein, 1984) and the polymerase chain reaction (K.B. Mullis, 1993) are only the more visible tips of a huge iceberg of innovation in the field. Without these techniques, many immunoassays and methods of molecular genetic testing that are currently taken for granted would simply have been impossible. On the other hand, in recent years, significant changes have been made to health care systems and care policy, largely because governments have had to address extremely complex economic issues (2).

EXPERIENCING A PARADIGM SHIFT

Reaction on the part of administrators and decision makers to decreased available funds has begun on several fronts and the funding position of clinical laboratories throughout the world is becoming critical. Laboratories are indeed an easy target for economic restrictions and limitations due to their technological characteristics (2). Furthermore, laboratory testing on hospital inpatients usually is reimbursed under a diagnostic-related group (DRG). Under this arrangement, the hospital is paid a fixed rate for the DRG diagnosis regardless of how many (or how few) tests actually are performed. Reducing laboratory costs will therefore improve the profit margin of the hospital (3).

In clinical laboratories, cost savings have frequently been realized by consolidation of laboratory sections with the creation of central core laboratories. Further economies of scale have been sought through regionalization of laboratory services with the creation of individual laboratories serving different health care facilities (4). In some situation, supposed savings have also been achieved by the addition of automated preanalytic specimen handling using robotic systems (5). Unfortunately, this "technological" approach to lowering costs per assay has frequently been used to undermine the influence of laboratory professionals and to further isolate them from clinical problems (1). On the other hand, laboratorians are usually trained to concentrate on the technical performance and on the achievement and maintenance of the highest quality of test results generated in laboratories. Often forgotten is the value of clinical information associated to clinical laboratory testing. But it is clearly not enough to report the right results if such data are not used for patient care. From the patient's point of view the conversion of data into useful information is the only thing that counts (6). The entire figure depicts a general-knowledge model that moves from laboratory data to information into new knowledge to facilitate medical decisions by caregivers and, ultimately, the intervention and outcome (7). This integration and understanding is the real challenge faced by laboratory physicians and scientists in an era when the number of available test parameters increases enormously and the available funds significantly decrease. Thus, the survival of Laboratory Medicine in such an environment ultimately depends on the ability to add value to the care of patients. The key to appreciating the importance and the true impact of diagnostic testing can only be achieved if the cost aspects are considered in the wider overall context of health economics and not within the more blinkered area of purely laboratory economics, where almost by definition every test represents a cost and its value is outside the scope of the laboratory practice (8).

MEASURING THE OUTCOME OF LABORATORY PRACTICE

How can this thinking be applied in Laboratory Medici-

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ne? It is clear that the "raison d'être" of laboratories should be assessed only in the context of the impact of their output on clinical services affected by care providers and the benefit from the laboratory service always sought outside its confines. In other words, clinical laboratories have to use outcomes research to be competitive in a changed health-care landscape that is characterized by financial problems and excess variation in use of medical procedures and technologies (9). Laboratory professionals must now think more globally and perform studies that demonstrate the impact of laboratory tests on overall patient health, the cost of patient care, and other less tangible humanistic measures, such as quality of life and patient satisfaction (10). Understanding laboratory-related outcomes enables the clinical laboratory to become involved with institutional process improvement, including practice guidelines development, redesign of laboratory services, and application of patient satisfaction measures within the institution (11).

Assessment of clinical outcomes in relation to clinical diagnostics is however difficult (12). Typical measures in outcomes include morbidity, mortality, quality of life, satisfaction with care, and cost of care, but there are many problems performing outcome studies in Laboratory Medicine, such as the gap between remoteness of the outcome measures and the biochemical testing (1). So, frequently there is a role for surrogate markers to be used to assess the clinical impact of laboratory practice (Table 1) (10). In fact, it is easier and shorter to measure changes in utilization of resources, such as the length of hospital stay or the number of clinic visits, than it is to assess the years of life gained. These outcomes may not be traditional, but they are valuable, and we should start using them. One of the best examples of a surrogate outcome is glycated hemoglobin (HbA1c), which can be used as a surrogate marker of glycemic control and for assessing the compliance with therapy in diabetic patients.

Three levels of laboratory-related patient outcomes have been defined (11). The first-order laboratory outcome is simply the performance of a given test result, in terms of sensitivity and specificity, in actual practice. Thus every test has at least four sets of outcomes associated with it, namely, the consequences of a true positive, a true negative, a false positive, and a false negative result. The second-order laboratory outcome is the probability of disease in the patient as estimated by the caregiver receiving the laboratory result, namely, the predictive value of the test as determined using Bayes' theorem. The third-order laboratory outcome is the actual probability of a change in health status of the patient resulting from any therapeutic interventions either instituted or foregone based on the test result. In the end, all healthcare measures, including laboratory tests, should be judged with respect to their ability to maintain or restore a patient's health.

Table 1
Types of outcome measures

Clinical outcome	Surrogate outcome
Mortality	Length of stay
Morbidity	Number of clinic visits
Quality of life, e.g. quality-adjusted life year (QALY)	Disease markers, e.g. HbA1c, LDL cholesterol
Cost of episode	Complication rate
Cost of treatment	Readmission rate

Presently, there are good examples of situations where a judicious choice and use of diagnostic testing can significantly reduce the overall costs of treating the patient, accompanied frequently by a better overall clinical outcome for the patient. In certain clinical situations the introduction of new and more effective laboratory tests has influenced the management of patients and related clinical outcomes directly. One example of this is the introduction of cardiac troponins for the diagnosis and treatment of patients with diseases in the spectrum of acute coronary syndrome (13). Cardiac troponins could be the paradigm of the new role of Laboratory Medicine in many diseases (14). As yet, no other clinical information or any other diagnostic test can replace the information provided by the measurement of troponin. Cardiac troponins are presently regarded as the most specific and sensitive of the currently available diagnostic techniques for myocardial damage and the redefined criterion used to classify acute coronary syndrome patients presenting with ischemic symptoms as myocardial infarction patients is heavily predicated on an increased concentration of these markers in blood (15). Troponins also are the only markers identifying high-risk coronary patients who should be treated with antithrombotic agents, such as glycoprotein IIb/IIIa antagonists, and referred for invasive evaluation at earliest convenience (16). When compared with the traditional enzymatic diagnostic approach, troponin is markedly effective in altering patient management by enabling early discharge of patients, resulting in significant cost savings and increasing bed availability. In a study conducted over six months, as a result of troponin introduction, the hospital saved more than 20,000 pounds from fewer bed days and reduced patient episode cost (17). In another study, including more than 850 consecutive patients presenting to the emergency department with suspected myocardial infarction who were randomized to receive a standard evaluation with serial electrocardiograms and CK-MB tests (control group) or the same plus a serial cardiac troponin evaluation, the length of stay was significantly shorter and hospital charges were less for patients who had troponin measurements, with an impressive potential annual saving of about 4 million of U.S. dollars (18). Collinson et al. (19) recently showed that 5% of all admission in their hospital for suspected acute coronary syndrome was incorrectly classified as myocardial infarction using the traditional WHO enzymatic criteria. The potential annual drug cost for treatment of these patients as infarction patients was approximately 56,000 pounds, with a 10-year estimated cost close to half million pounds in wasted resources (19).

Another example is represented by the use of B-type

natriuretic peptide (BNP) in screening symptomatic patients for left ventricular dysfunction. In a recently published analysis, screening of high risk individuals by BNP before echocardiogram appeared to be more cost-effective than referring all subjects to echocardiography, reducing the cost of screening per detected case of left ventricular systolic dysfunction by 21% (20).

In addition to diagnostic problems, clinical laboratories are now increasingly involved to assist physicians in therapeutic decisions. For instance, the recently updated guidelines of the U.S. National Cholesterol Education Program for treatment of hypercholesterolemia in adults are definitively based on well-defined low-density lipoprotein (LDL) cholesterol values, with regard to the serum concentrations indicating that drug therapy should be initiated and to the treatment goals (21). Another example is represented by HbA1c. The clinical use of this marker as a target for more aggressive therapy in order to reduce the development and the progression of retinopathy, nephropathy, and neuropathy in diabetes mellitus patients is now well recognized. But it has recently been reported that HbA1c also predict mortality in non diabetic men, with an increasing risk throughout the whole range of concentrations, even below the commonly used upper reference limit (22). A last example is a recently published study, demonstrating that a procalcitonin-guided treatment of the lower respiratory tract infections is able to significantly reduce the antibiotic use in this type of diseases without any outcome compromising (23). Low serum procalcitonin concentrations identified patients without clinically relevant bacterial infections, in whom antimicrobial therapy can be safely withheld. Thus, in view of the current overuse of antibiotics in acute respiratory tract infections, treatment based on procalcitonin measurement may have important financial and clinical implications. In addition to lower costs, a reduction of antibiotic use also results in fewer side effects and, in long-term, leads to diminishing drug resistance.

CHANGING ROLE FOR MEDICAL LABORATORY PROFESSIONALS

In order to meet the changing testing needs, the laboratory role in patient management should therefore be improved by assuring an appreciable added value to laboratory tests deriving from appropriate test request and utilization. This brings us to what the laboratory scientist actually does within his own laboratory. Although it is fundamental that he takes responsibility for how laboratory tests are used for patient care, many people still emphasize the development of analytical expertise, at the expense of the application of the laboratory science to the Medicine. Some reasons can be reported to explain this situation:

- reluctance by laboratorian to involve itself in test structuring and requesting and in the inspection of work as it arrives, due the continuous effort required to control it, the unpopularity which a critical approach attracts, and the wrong assumption that all requests are clinically necessary. It is a fact that, once blood has been taken and the request has reached the laboratory, it is easier to perform the test than to discuss its suitability with users;
- poor communication and integration between wards and laboratory, due in part to the uncommunicative attitude of some clinicians to "service" departments;
- and, last but not least, the need for an excellent cultural and scientific background for implementing outcome research. This requires the laboratorian to have knowledge in a diverse group of medical specialties and organizational and leadership skills that are necessary for functioning successfully in interdepartmental multidisciplinary teams.

On the other hand, physicians who frequently request laboratory tests outside of their field of expertise lack the knowledge base to order the optimal sequence of tests and to correctly interpret the results (24). Medical laboratory professionals, combining clinical knowledge with experience in the performance of laboratory assays, can conversely have the unique expertise to advise their clinical colleagues in regard to the appropriate test selection and interpretation of laboratory results (25). Issues of analytical and biological variation, different physiological status, and comorbidities are critical in the interpretation of laboratory results, but many clinicians are unaware of these. For example, the reliability of information derived from a laboratory test may heavily depend on the quality of the analytical performance of the assay being used for the corresponding measurement. It is well demonstrated that the use of the more sensitive cardiac troponin instead of traditional criteria for diagnosis of myocardial infarction leads to an average increase in the number of infarcts from 20 to 30% in patients admitted with suspected acute coronary syndrome (26). However, the percentage of patients re-categorized from angina to myocardial infarction is also critically dependent on the performance of the troponin assay used (27). Since experimental data indicate that various commercial methods have significantly different sensitivities for detection of cardiac troponin in blood samples with very low concentrations of this biomarker, the selection of troponin assay by the clinical laboratory represents one of the major factors influencing the clinical performance of this important biomarker (28).

Biological variation is frequently the most important source of variability in laboratory measurements. Knowing biological variation means to fully understand what is the significance of a laboratory result (Table 2). The importance of the critical difference, also called "reference change value", to determine whether changes in an individual's serial results are really significant is evident. Only by knowing analytical and biological variability, it is possible to calculate this figure (29). Laboratories need to put these tools into everyday practice, ensuring that consumers of our services actually use these aids to test interpretation. Recent studies gave information on the biological variation of BNP and N-terminal proBNP, showing broad fluctuations of the marker concentrations in blood of healthy

subjects (30). For these markers, the critical difference has been calculated as being approximately 70-90%. Therefore, caution should be exercised in interpreting concentration changes of BNP of less than 80% on average as being related to medical therapy regarding decreasing or increasing blood concentrations. Minor changes could simply be related only to the random fluctuation of the biomarker around the homeostatic set point of the individual and not to the effect of a given therapeutic regimen (31).

A demonstration of the possible influence of the physiological situation on the clinical value of laboratory tests can be derived from the behavior of pancreatic amylase in infants and children. Due to the slow development and maturation of some functions of the exocrine pancreas, pancreatic amylase reaches adult concentrations only after the fifth year of life (32). As a consequence, the use of this enzyme for the diagnosis of acute pancreatitis in young children should be avoided and replaced with the measurement of pancreatic lipase. Nevertheless, some pediatricians are unaware of this and continue to ask for an amylase determination in kids with acute abdominal pain and suspected acute pancreatitis (33).

Comorbidities are also critical in the test interpretation, as in the case of the influence of a reduction in the glomerular filtration rate on blood concentrations of C-telopeptide of type I collagen (CTx), a biomarker of bone resorption (34). Thus, in patients with impaired renal function, measurement of serum CTx needs to be interpreted with great caution. In this type of patients, other serum markers of bone resorption, such as tartrate-resistant acid phosphatase 5b isoform, which is not influenced by renal function, should probably be used (35).

It is clear from my personal experience that physicians are greatly confused by the amount of information and make many errors in the selection and interpretation of laboratory tests. As an example, Figure 1 displays an audit experience done in my hospital some years ago on the reasons for the request of measurement of bone turnover markers in different clinical departments. When we asked them the explanation of motives for the request before the test execution, orthopedics were unable to formulate sound reasons in all cases but one, so that the number of profiles dropped from 49 in the 1996 three-month period, monitored before the introduction of the specific request, to only one in the same period of time of the next year, after the introduction of the justification process. Clearly, the exercise helped to identify misconceptions and ignorance on the use of this type of tests. Other authors have shown that the involvement of laboratory professionals in test selection and interpretation can significantly decrease the likelihood of some types of medical errors (24).

Table 2
Practical significance of biological variation: questions to which the knowledge of biological variation for a given analyte aids to answer

- What is the significance of this result?
- When should I measure it again?
- Has this result changed significantly over time?
- Is the performance of the analytical assay appropriate (imprecision, bias)?

PROMOTING THE LABORATORY-CLINIC INTERFACE

The laboratory-clinic interface is, therefore, of fundamental importance to ensure that the patient is given high quality care, because it is the site for exchange of information and provides the boundary for the multidisciplinary style of activity both for improving the appropriateness of test requests and for exchanging information on test results (36,37).

In order to fill the need for better quality health care, avoidance of medical errors, and cost reduction, three strategies have been recommended for supporting and disseminating clinical consultancy in Laboratory Medicine: 1. use of reflex testing and algorithms; 2. providing interpretative comments; and 3. organization of clinical audits (1).

Many examples demonstrate the effectiveness of reflex testing and algorithms for shortening the time of diagnosis and rationalizing the use of laboratory testing. The most common example where a cascade of tests is performed based on an abnormal (frequently chance) biochemical finding is in the case where monoclonal gammapathy is suspected. In this case, an abnormal band found at the protein electrophoresis may trigger the performance of immunofixation and monoclonal protein quantitation to confirm the presence of this abnormality. Fig. 2 shows another example related to an algorithm proposed for the interpretation of hyperamylasemia (38). This workup begins with the measurement of amylase in serum. A high value leads to reflexive testing for pancreatic lipase, followed by serum creatinine or isoamylase assays. The algorithm is able to determine, with a high degree of confidence, if the underlying pathophysiology is the presence of acute pancreatitis or of other causes of hyperamylasemia, such as extrapancreatic abdominal disorders, renal insufficiency, etc. (38).

The second recommended strategy is to provide a patient-specific narrative and, if necessary, graphical interpretation of complex test results in order to allow a more objective utilization of data (39). Adding an interpretative comment to the patient's results and, eventually, giving advice on any action that should be undertaken represents an essential tool for adding value to laboratory reports. An audit of this type of activity in our institution allowed to show the impact of the availability of laboratory-generated interpretative comments in the clinical decision making (40). On a total of 60 requests of cardiac marker tests, the results of our investigation showed that in 70% of cases comments appeared to be useful to better classify patients with suspected acute coronary syndrome. Only in less than 15% of these cases the laboratory comments were

fully ignored by the clinicians (40). Similar findings were recently obtained at the Massachusetts General Hospital in Boston (41). Someone poses questions on the responsibility and accountability for these actions and on potential pitfalls of making a judgment on clinical issues based on learning by biochemical pattern recognition, without necessarily having insight into the clinical process of patient management (42). But, if we consider that in many cases laboratory investigations should aim to identify a pathophysiological process rather to confirm a diagnosis, I don't see any problems in a laboratory comment reporting, for instance, "a significant increase of specific cardiac markers consistent with the presence of myocardial necrosis" or "a significant increase of bone resorption markers consistent with a hyperactivity of osteoclasts". As laboratory specialists, we have to educate physicians to accept laboratory results as information describing a pathophysiological process, not a morphological diagnosis, assuming of course responsibility in order to guarantee reliable laboratory information (43). Using bone disorders as an example, Jabor and Palicka have well illustrated the problem of the rational and non-rational use of laboratory tests (44). If the clinical question is to make the diagnosis of osteoporosis, the correct test is bone densitometry, which can provide a morphological diagnosis. Conversely, biochemical markers should be used if clinicians need to ascertain any modifications in the activity of osteoblasts and osteoclasts in order to identify alterations of bone turnover, including the effect of appropriate therapies (44).

Although the practice of commenting varies among

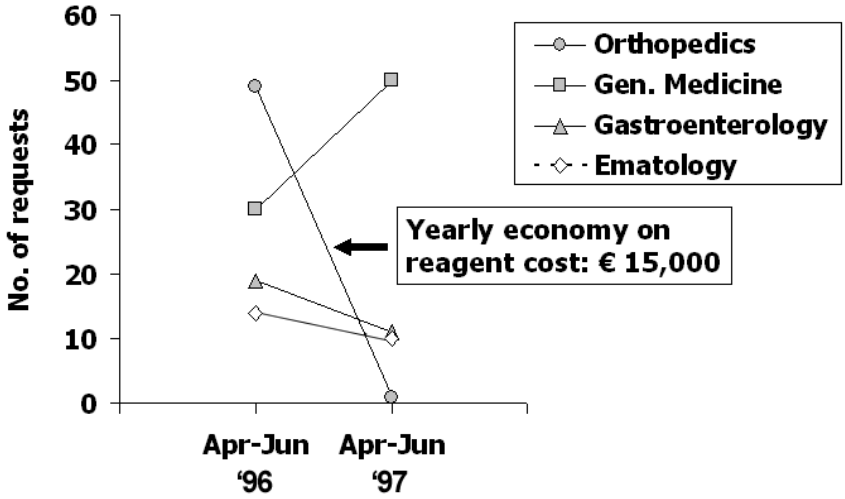

Figure 1
Results of an audit on the reasons of the request of measurement of bone turnover markers. Apr-Jun '96: number of profiles before the introduction of the specific request; Apr-Jun '97: number of profiles after the introduction of the specific request.

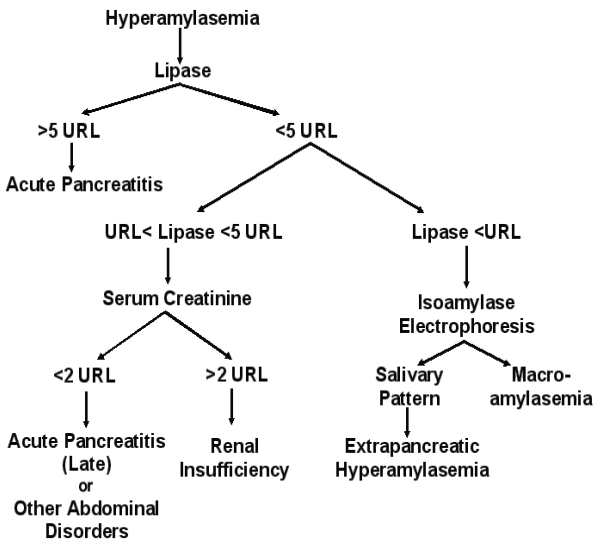

Figure 2
Proposed algorithm for the interpretation of hyperamylasemia. Adapted from ref. 38.
URL, upper reference limit

countries, audit findings show that still too few laboratories regularly add interpretative comments to their reports. In a recent national survey performed in the field of cardiac biomarkers, only 9% of participants declared to perform this type of activity, even if, in 46% of cases, clinicians required advice to the laboratory, especially for interpretative doubts or when test results were not consistent with clinical and instrumental information (45). The largest barrier to the wide implementation of a program to generate narrative interpretations in the clinical laboratory is probably the lack of a sufficient number of specialists in one laboratory to provide adequate interpretations. A recent report clearly shows the potential negative consequences of using interpreters with inadequate expertise for commenting (46).

The third mainstay of the model system of clinical consulting is clinical audit. Audit in Laboratory Medicine may be defined as a process of review and assessment of laboratory performance (47). It is important that laboratories find out whether they are providing a useful service for the clinicians they serve to ensure they provide the optimum service to the patient. Once again, this activity requires cooperation with functional areas outside the laboratory, reflecting the real world of medicine: a cooperative venture among medical specialty fields (48). As an example, in our hospital existing biochemical protocols for diagnosing and monitoring patients with acute coronary syndrome are subjected to constant refinement and, if necessary, to changes in parallel with analytical innovations and new recommendations coming from expert groups (49). The continuous availability of new tests in this field is forcing laboratory and clinicians to revise and compare diagnostic strategies and different protocols to evaluate whether the new tests are to be used in addition to, or instead of, other more traditional tests (50). Our experience shows that the collaboration and cooperation between those with expertise in Cardiology and Laboratory Medicine, working inside the hospital, may permit to achieve a significant delay reduction, through a continuous improvement of the processes and the introduction of changes directed to further improve the obtained results as well, thus ensuring better patient triage (49).

CONCLUSIONS

Some years ago, presidents of European Societies of Laboratory Medicine were asked what they considered to be the most relevant aspects for future development of their profession (51). The implementation of request strategies, the diagnostic validation of tests, together with knowledge of test interpretation were indeed ranked as the most important issues. Today, the complexity of the health-care environment and the ever-expanding array of laboratory tests available have further increased the need for more integration between clinical information and laboratory data (6). This is especially true in genetic testing, because it should be performed as an adjunct to the management of the individual and must be used in conjunction with the total information concerning the patient. The impact of clinical laboratory on the medical environment of the future will be not only to maintain the highest quality of generated data and to improve the total quality of the process of providing laboratory information, but also to maximize the influence of the laboratory results on the management of patients. Advances in science and technology will continue to result in the introduction of more complex, expensive, and difficult-to-interpret tests. By integrating pathophysiologic rationale and preferences of the clinicians responsible for the care of the patient with valid and up-to-date clinical research evidence, Laboratory Medicine, supported by computerized information and reminder systems, will promote the use of this new knowledge in a timely and responsible manner, contributing to provide better care more economically. It's undoubtedly impossible to predict the future, but that does not mean that it's impossible to prepare for it, keeping the best interest of the patient first in mind. As laboratorians, we will remain viable only if we build our own future and educate others about the contribution that the Laboratory Medicine can and does make to health care.

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