Review

Simona Ferraro, Federica Braga and Mauro Panteghini*

Laboratory medicine in the new healthcare environment

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Abstract: The 21st century challenge is to redesign healthcare systems to be safe, efficient, effective, timely, equitable and patient-centred. Although laboratory medicine is integral to many of these objectives involving prevention, diagnosis, treatment, and managing disease of patients, it suffers from poor visibility as a medical discipline and as a profession and fewer rewards for educational efforts when compared to other medical disciplines. Laboratory scientists are often perceived as managing machinery and equipment, but conversely they need to take a position of shared clinical leadership, showing the role of laboratory tests to guarantee optimal care for patients. This is however challenging because of some reluctance by laboratory professionals to involve themselves in test structuring and requesting and in the inspection of work as it arrives because it is assumed that all requests are clinically necessary; there is a poor communication and integration between clinical wards and laboratory; and, importantly, there is the need for an excellent cultural and scientific background of laboratory professionals for implementing outcome research and to act as knowledge managers and skilled clinical consultants. By combining the unique talent of performing quality laboratory assays with knowledge of the pathophysiologic rationale behind the tests, laboratory professionals have the expertise to advise their clinical colleagues in regard to the appropriate test selection and interpretation of laboratory results, thereby creating opportunities to define the added value and the pivotal role of laboratory medicine on healthcare delivery.

Keywords: analytical validity; laboratory-clinic interface; laboratory medicine; patient outcomes.

***Corresponding author: Prof. Mauro Panteghini,** Department of Biomedical and Clinical Sciences 'Luigi Sacco', University of Milan, Via GB Grassi, 74, 20157 Milano, Italy,
E-mail: eflmpresident@efcclm.eu
Simona Ferraro and Federica Braga: Department of Biomedical and Clinical Sciences 'Luigi Sacco', University of Milan, Milan, Italy

Introduction

Many of the current changes in the healthcare environment, such as changes in demography, population ageing, patient expectations (and the new era of the "informed/expert" patient), chronic disease growth, movement of clinical practice to prevention, evolution in information technology, and reduced cost of services, will significantly impact laboratory medicine. The patient more and more is becoming the main objective of the healthcare system. In 2001, the Institute of Medicine observed that the healthcare delivery in the United States was unable to provide consistent, high-quality medical care to all people. It predicted that the main challenge for the 21st century was to redesign the healthcare system in order to assure safe, efficient, timely, equitable, effective and patient-centred care to meet patient needs [1]. On the other side of the Atlantic Ocean, the UK Department of Health has similarly proposed a vision for diagnostic services in 2020 and beyond by putting the patient at the centre of service design, delivery and evaluation [2]. Particularly, three main goals have been suggested: a) to improve the availability and access to information by the patient, b) to accelerate the adoption of new evidence-based diagnostic technologies, and c) to redesign diagnostic pathways to facilitate access to well-integrated services [2].

In this setting, it is easy to recognise that laboratory medicine has a pivotal role as it is integral to many clinical decisions on prevention, diagnosis, treatment and management of patient disease. Laboratory tests supply clinicians with information necessary to provide high-quality, safe, effective and appropriate care to patients [3]. The often quoted "70% claim" according to which laboratory data affect ~70% of medical decisions, ~70% of clinical diagnoses are dependent on laboratory and ~70% of the information in the medical record consists of laboratory results is, however, quite anecdotal, as systematic evidence of the laboratory contribution to the overall process of diagnosis and management of patients is hard to produce [4]. Certainly the wind of change is coming for laboratory medicine: the test repertory (currently at least

3500 tests), as well as the laboratory workload, is further increasing, and this, at least partly, results in and reflects the uncontrollable demand and the requesting of unnecessary/redundant tests. Furthermore, the test utilisation is varied and heterogeneous, with often limited evidence supporting the introduction of novel tests and their impact on patient outcomes.

Laboratory medicine: a "profession without a face"

Laboratory medicine, as a medical discipline and as a profession, suffers from lower visibility and few rewards for educational efforts compared to other medical disciplines [5]. Laboratory scientists are often perceived as managing machinery and equipment without any position of shared clinical leadership [6]. Hence the central question is, "what paths should we follow to ensure we become relevant to healthcare?".

There are currently two main forces driving the clinical laboratory organisation: the important technological advances (e.g. total laboratory automation, molecular diagnostics techniques, including high-throughput microarrays, next generation sequencing, genome-wide association studies, new point-of-care [POC] solutions, etc.) and the economic pressures, with the need to align to increasingly limited budgets. As a consequence, cost savings is frequently realised by consolidation and, in some cases, regionalisation of laboratory services with the creation of individual laboratories serving multiple healthcare facilities. This may undermine the influence of laboratory professionals, isolating them from clinical problems and leading to some degree of "deprofessionalisation".

Clinical optimisation of operational efficiencies

In our view, laboratory specialists have the opportunity to be proactive in clinically optimising these operational efficiencies. As an example, the creation of a core laboratory (core-lab) structure in a hospital setting, which is generally viewed as an approach increasing efficiencies by moving from a compartmentalised laboratory department to a consolidated laboratory activity, may provide the occasion to create a decision making-based laboratory department, where the core-lab, using total laboratory automation, should include first-line tests, and satellite laboratories execute specialised tests. This model, characterised by a very short turnaround time (TAT) for all tests performed in the core-lab, may represent a new paradigm to improve the predictability and reliability of the laboratory service, working to avoid delays in clinical decision-making that may cause overcrowding and boarding of clinical wards [7]. Accordingly, tests in the core-lab menu no longer are prioritised to be performed as urgent, because all tests, having short TAT, become "equally urgent". On the other hand, the satellite laboratory sections (e.g. haematology, endocrinology, infectiology, oncology, etc.), performing tests requiring a specialised knowledge, may more fruitfully cooperate with care teams for specific medical conditions assuring that their results may effectively work in the correct clinical setting. This laboratory organisation model applies well with the medical decision-making model based on the probabilistic reasoning that core-lab tests are considered as first-level analyses ordered according to the initial hypothesis/clinical suspicion, and the specialised laboratory sections perform those tests to exclude or confirm the presence of the disease (Figure 1).

Covering all phases of the laboratory examination

Previously, we described how a laboratory result coming from an appropriate request should enable a decision to be made, which leads to an action being taken, yielding an improved outcome for the patient [8]. Starting from the request appropriateness, large variations in clinicians' requesting have, however, been demonstrated and cannot easily be explained by differences in disease prevalence [9]. For instance, in UK the annual rate of use for carbohydrate antigen (CA) 125 ranged (after outlier exclusion) from 0.9 to 8.4 per 1000 practice population, a ~9-fold variation. This may be associated with differences in professional practice and in the uptake by physicians of new scientific evidence after the release of National Institute for Health and Clinical Excellence guidelines on ovarian cancer (OC) detection [10]. The framework of tumour markers represents a typical laboratory area where the simple implementation of recommendations based on their correct use may largely decrease the number of inappropriately ordered tests and related costs, without any detrimental impact on clinical outcomes [11, 12].

The main challenge for laboratory medicine is certainly to connect laboratory testing to patient outcomes. Often this is reliant on linking the test with processes,

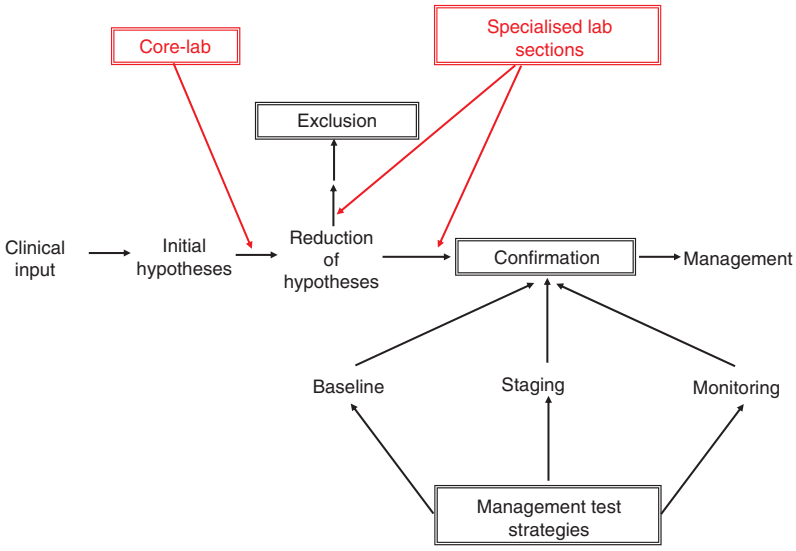

Figure 1: The contribution of a decision making-based laboratory department, organised in a core-lab section and satellite specialised laboratory areas, to the sequence of diagnostic reasoning.
Modified from Benson ES, Rubin M. The sequence of diagnostic reasoning, 1978.

such as clinical decisions and actions, which in turn directly impact health-related outcomes [13]. The potential for a laboratory test to improve outcomes therefore depends upon a wide range of variables including, e.g. the effectiveness of the therapeutic intervention and features of the investigated patient population. Three kinds of patient outcomes are described: a) clinical hard outcomes (i.e. morbidity, mortality and quality of life); b) surrogate outcomes (metric, such as length of stay, readmission/complication rates, episode/treatment costs, or medical, such as therapeutic TAT or some disease markers); and, more recently, c) additional outcomes concerning emotional/cognitive (e.g. well-being), social and behavioural effects (e.g. adherence to treatment). Linking these outcomes to laboratory tests is difficult for several reasons: in addition to the disconnect between health-related outcomes and test performance, the high cost of studies relative to potential financial profit to corporate funders, risk of loss of financial profits if favourable outcomes are not achieved, the requirement for a large number of patients/volunteers (sample size) to do outcome studies, as well as other methodological issues [14]. To try to simplify the process and make it more practical, three hierarchical levels of laboratory-related outcomes can be considered [15]. The lowest level refers to the performance of the test in actual practice and basically reflects its analytical validity; the intermediate level is related to the clinical validity of the test and depends on its predictive value; and the highest level of laboratory-related outcomes accounts for the clinical utility of the test estimated from the probability of a change in health status of the patient based on the test results.

The analytical validity as first-level laboratory-related patient outcome

To guarantee the analytical validity of a laboratory test the implementation of the standardisation of measurements represents an absolute priority [16]. Laboratory customers (i.e. clinicians and patients) expect laboratory results to be equivalent regardless of time, location, laboratory and assay system employed. This can be reached only if results obtained by routine procedures are calibrated in terms of the values obtained at the highest available level of the calibration hierarchy [17]. In this regard, it is essential to build an unbroken metrological traceability chain that starts from the unequivocal definition of the measurand and ends, through a calibration hierarchy, at the level of the patient's result. The correct implementation of this metrology-based approach also allows the use of common reference intervals and decision limits, enabling effective application of evidence-based medicine [18]. Finally, the standardisation of laboratory test results reduces the average aggregate cost of follow-up procedures and achieves an important ethical dimension as it aims to affect the way diagnostic tests are used in order to guarantee optimal care for patients in a global world [19, 20]. Overall, analytical improvements are therefore a matter of patient safety [21].

Establishing traceability of in vitro diagnostic (IVD) medical systems depends on some basic requirements being fulfilled. First, it is essential to establish a calibration hierarchy starting from the unequivocal definition of the measurand as the quantity subject to measurement [22]. The assay selectivity for the measurand at each level of the traceability chain is a crucial aspect and in a standardisation project correlation studies should preliminarily be performed to test the relationship among commercial methods and to demonstrate the harmonisation potential [23]. Elimination of measurement bias by the applied implementation strategy enables the reliable transfer of the measurement trueness from the highest level of the metrological hierarchy to commercial calibrator values, thereby lead to unbiased results on clinical samples [24]. Finally, an adequate estimation of all sources of measurement uncertainty should be performed [25].

The European Union (EU) Directive 98/78/EC on IVD devices, created to ensure that IVDs do not compromise the health and safety of patients and to attain the performance levels attributed to them by their manufacturer, supports the application of metrological concepts [26]. Its main aim is indeed to improve comparability of measurement results through more structured and understood approaches for standardisation, which have further been described in the companion ISO standards [27]. This clearly gives to our profession a unique role in promoting and applying these concepts to the clinical setting. The new EU regulatory framework under discussion will further enhance the laboratory profession involvement, asking us for post-market surveillance activities, for example, and for external expertise advice. Already now laboratory professionals have the responsibility to verify the availability and quality of information about IVD metrological traceability and uncertainty and to survey the IVD system traceability [25]. We recently recommended that clinical laboratories should be able to easily access the information on which higher order references (materials and/or procedures) has been used by manufacturers of diagnostic assays to assign traceable values to calibrators, which internal calibration hierarchy has been applied by the manufacturer and on the combined uncertainty value of commercial calibrators [25]. The description of the traceability implementation steps and of their corresponding uncertainties is important as the selection of different types of traceability chains for the same analyte may lead to different combined uncertainties at the level of commercial calibrators and patient samples [25, 28].

Once the IVD system has been introduced into daily practice, the possible sources of degradation of its performance are numerous. It is, therefore, essential to put in place a continuous surveillance of the quality of performance of commercial assays. This surveillance basically relies on quality control programmes, which should, however, be redesigned to meet metrological criteria [25, 29, 30]. Particularly, the Internal Quality Control (IQC) has to be reorganised into two independent components: one devoted to checking the alignment of the analytical system and verification of the consistency of declared traceability during routine operations performed in accordance with the manufacturer's instructions (IQC component I) and the other structured for estimating the measurement uncertainty due to random effects (IQC component II) [30]. The participation to External Quality Assessment Schemes (EQAS) that meet specific metrological criteria is also mandatory for the evaluation of performance of participating laboratories in terms of standardisation and clinical suitability of their measurements. The requirements for this type of EQAS have been extensively described in previous publications [25, 29–33]. Briefly, in addition to the use of commutable control materials, it is necessary to assign values (and uncertainty) to them with reference measurement procedures performed by an accredited laboratory and to define and apply a clinically allowable performance goal. Unfortunately, there are few EQAS that can meet all of these requirements because some practical constraints, including technical (lack of certified materials, difficulties to prepare commutable samples, complicated logistics of distribution of frozen samples), psychological (lack of awareness of which quality factors make an EQAS important) and economic (higher costs) aspects, which limit their introduction [34]. It is, however, clear that EQAS which meet metrological criteria have unique benefits that add substantial value to the practice of laboratory medicine (Table 1).

Table 1: Unique benefits of External Quality Assessment Schemes meeting metrological criteria.

– Giving objective information about quality of individual laboratory performance
– Creating evidence about intrinsic standardisation status/ equivalence of the examined assays
– Serving as management tool for the clinical laboratory and IVD manufacturers, forcing them to investigate and eventually fix the identified problem
– Helping those manufacturers that produce superior products and systems to demonstrate the superiority of those products
– Identifying analytes that need improved harmonisation and stimulating and sustaining standardisation initiatives that are needed to support clinical practice guidelines
– Abandonment by users (and consequently by industry) of nonspecific methods and/or of assays with demonstrated insufficient quality

In implementing standardisation of measurements it is essential that our profession clearly defines the clinically acceptable measurement error that is fit for purpose for each analyte and its clinical application [29]. The definition of analytical performance specifications for each analyte is essential to make laboratory determinations clinically usable and to ensure that the measurement error does not invalidate the result [35]. In the IFCC-IUPAC conference held in 1999 in Stockholm, a hierarchy of sources for deriving the analytical specifications of a laboratory measurement was first established [36]. After 15 years, a new conference recently held in Milan has revisited the Stockholm consensus, investigating to what extent the advocated hierarchy is still valid or if it has to be changed or expanded [37]. Although the essence of the previously established hierarchy was supported, new perspectives have evolved prompting simplification and explanatory additions [38]. Basically, the recommended approaches for defining analytical performance specifications should preferentially rely on the effect of analytical performance on clinical outcomes or on the biological variation of the measurand (Table 2) [38]. Once again, the attention is primarily directed towards the measurand and its biological and clinical characteristics, some models being therefore better suited for certain measurands than for others.

When is evaluating clinical validity alone adequate as laboratory-related patient outcome?

According to Lord et al. [39], accuracy studies evaluating the clinical validity of a laboratory test suffice in showing the impact on the patient outcome when a novel diagnostic test is safer (or cheaper) or more specific than, but of similar sensitivity to, an old test used in same clinical setting. This is, for instance, the case of serum human epididymis protein 4 (HE4), a novel marker for OC detection proposed to replace CA 125. In a recent meta-analysis we showed that CA 125 and HE4 have the same diagnostic sensitivities (79%), but HE4 is superior to CA 125 for specificity (93% vs. 78%, respectively), decreasing the rate of false positive results and thus avoiding unnecessary treatment [40]. Therefore, new trials assessing treatment efficacy in the OC cases detected by HE4 are not needed.

However, where a new test is more sensitive than an old test, assuming specificity, harms and costs are the same, the new test will lead to the detection of additional cases of disease. In this case, randomised trials are required to assess treatment efficacy in cases detected by the new diagnostic test, unless the new test detects the same spectrum and subtype of disease as the old one [39, 41]. Indeed, diagnostic accuracy is not a "true" health outcome as this type of study answers the question "Does the result of the laboratory test predict an outcome of interest (e.g. classification of the clinical condition)?" whereas health outcome studies ask if use of the test is associated with improved patient outcomes [42]. Randomised trials provide higher quality evidence about the impact on patient management using laboratory tests and how it affects patient health (Figure 2) [43]. George Lundberg explained that "A laboratory test is an intervention, and an intervention of any kind (diagnostic or therapeutic) is appropriate only if it is more likely to benefit than to harm the patient and can be done at a reasonable cost and with reasonable risk" [44].

Table 2: Recommended models to be used for defining analytical performance specifications. Adapted from ref. [38].

Model 1: Based on the effect of analytical performance on clinical outcomes
a. Done by direct outcome studies – investigating the impact of analytical performance of the test on clinical outcomes;
b. Done by indirect outcome studies – investigating the impact of analytical performance of the test on clinical classifications or decisions and thereby on the probability of patient outcomes, e.g. by simulation or decision analysis
Model 2: Based on components of biological variation of the measurand
Model 3: Based on state of the art of the measurement, defined as the highest level of analytical performance technically achievable

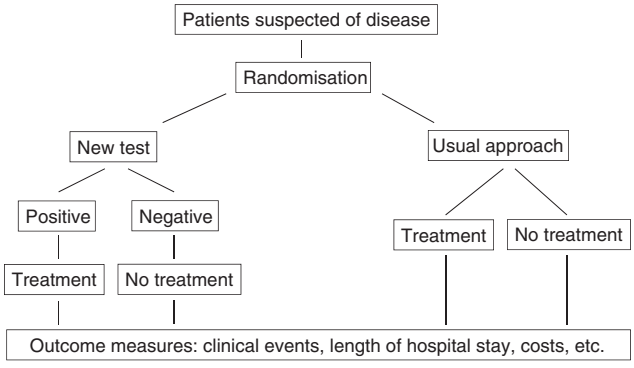

Figure 2: Scheme of a cost-effectiveness trial for a new laboratory test.

Introducing cardiac troponin: a paradigm example of the laboratory role

Today, the measurement of cardiac troponins (cTn) represents the biochemical "gold standard" that is central to the new millenium's diagnostic criteria for acute, evolving or recent myocardial infarction (MI) [45, 46]. Quoting Sharkey, "Perhaps no other laboratory test has the authority to alter a patient's clinical course and cost of care so broadly" [47]. Just after its availability, when compared to the traditional diagnostic enzymatic approach, the cTn measurement was shown to impact patient management by enabling early discharge from hospital and resulting in significant cost savings, both in Europe and United States healthcare systems [48, 49]. The introduction of cTn strongly impacted on the diagnostic classification of patients with suspected acute coronary syndrome. Collinson et al. [50] estimated that ~5% of all hospital admissions, who were diagnosed as non-ST elevation MI with World Health Organisation enzymatic criteria, had actually normal cTn values that classified them as false positive. The potential annual drug cost for treatment of these cases as MI patients was estimated to be approximately £56,000, with a 10-year estimated cost close to half a million pounds in wasted resources [50]. Together with the introduction of new biomarkers that significantly impact health outcomes, laboratory professionals assume a central role in removing from the menu those tests that have become obsolete and useless. Removing tests that offer little incremental information reduces costs, avoids additional investigations arising from incidental and clinically irrelevant abnormalities, and improves the risk to benefit ratio. In the field of MI diagnosis, deleting myoglobin, total creatine kinase (CK) and CK-MB isoenzyme determinations from laboratory order forms in patients admitted to the emergency department leads to significant cost savings and reduces possible confusion in data interpretation and patient management [51].

Even the introduction of new generations of cTn assays [the so-called "high sensitivity" assays (hsTn)] has been supported by their ability to significantly impact on patient clinical outcomes, with a consistent reduction in morbidity and mortality due to the enhanced capability of hsTn to identify patients at high risk for cardiovascular events [52]. By comparing the hsTn 3-h diagnostic protocol with the traditional 10-h protocol using the conventional cTn assay, the incremental cost-effectiveness ratio (or cost per total quality-adjusted life years gained) was ~4-fold lower by using the hsTn 3-h testing [53].

Working to promote laboratory medicine as the science that underpins medicine

With the implementation of hsTn, emergency department physicians and cardiologists have been rather confused about the interpretation of marker results and a plethora of editorials published in cardiology journals have highlighted the difficulties to manage the more frequent cTn positive results [54–59]. It is curious to note that cardiology societies recommended using the 99th percentile cut-off when assays were unable to measure low cTn concentrations accurately [60]. However, when the new generation of hsTn assays can finally fulfil the recommendations reliably, cardiologists generally have not welcomed their introduction [61]. We recently discussed the issue in this journal and emphasised that application of powerful biomarkers such as cTn requires laboratory professionals to be involved in closely scrutinising proposed assays and limiting their clinical use before the evidence for them is solid [62]. If laboratory professionals are not involved from the beginning, this type of "original sin" is very difficult to reverse later.

There are examples showing that clinical investigators are often too quick in publishing data without collecting and including thorough evidence of assay performance [41]. Some years ago, soluble CD40 ligand, a platelet activation marker, was shown to predict mortality in patients with unstable angina and to be useful for guiding antiplatelet treatment [63, 64]. However, these studies were performed on serum samples and clotting releases significant and variable amounts of soluble CD40 ligand. The subsequent investigations revealed important confounding influences of sample type and handling on measured marker concentrations that invalidated previously published clinical studies [65, 66]. Several issues should be considered when evaluating clinical studies on laboratory test use and most of them concern pre-analytical and analytical characteristics of the assays often ignored or not adequately described. Researchers need to know how the samples should be collected and/or preserved to assure accurate measurements as well as the stability of the samples over time, in particular when planned studies will use archived samples [67]. The advantages of including laboratory medicine specialists early-on in the design of study protocols as well as in the guideline development process are clear and only this approach may increase the focus on important laboratory-related items even when this information is fragmentary [68].

POC testing is also an issue of laboratory governance. We believe that any tensions that have existed between POC practitioners and laboratories are likely to ease in the future. It is apparent now that in certain situations POC testing is a better option and in other cases it is better and cheaper to send the sample through the main laboratory [69]. Laboratory professionals are better now at helping understand the balance between POC and centralised laboratory testing. It is quite clear that the trueness and precision of POC assays are probably not adequate for some applications, and, as for all IVD devices, more outcome-based research related to POC testing is needed.

The laboratory-clinical interface

Table 3 lists the laboratory-related sources of diagnostic mistakes [70]. It is apparent that the vast majority of them happen at the laboratory-clinical interface, involving test demand (pre-pre-analytical phase) and the result interpretation (post-post-analytical phase) [71]. To improve this situation, the establishment of a partnership between clinicians and laboratory professionals is basic to assure the correct clinical management of patients and to increase the clinical efficacy of laboratory testing [72]. Managing upstream demand, down-stream interpretation of laboratory results, and subsequent appropriate action, through close relationships between laboratory specialists and clinicians, is a crucial aspect of the laboratory examination process [8].

Active initiatives by laboratory professionals to improve physicians' acknowledgment of laboratory data and their interpretation are needed in order to assure quality and safety in the extra-analytical phases of the total testing process. The periodicity of (re)testing (i.e. how often should tests be requested) should be better managed by laboratory professionals. While a very small group of tests may be ordered as often as necessary, in the majority of cases a minimum retesting interval should be introduced (Table 4) [73]. For instance, an automated rejection rule based on 48-h minimum retesting interval for serum C-reactive protein (CRP) has been reported as a sustainable method for reducing unnecessary repeat of CRP, thereby improving workload and expenditure, and influencing clinician-requesting behaviour [74]. The recently released consensus recommendations by the UK Association for Clinical Biochemistry and Laboratory Medicine for minimum retesting intervals in clinical biochemistry can be very helpful to harmonised laboratory behaviour in this field [75].

Table 3: Laboratory-related causes of diagnostic mistakes. Adapted from refs. [70] and [71].

- Inappropriate test ordered (20% of total)
- Appropriate test not ordered (45% of total)
- Appropriate test result not used properly because:
  - Knowledge deficit
  - Failure of synthesis (no results integration)
  - Misleading result (unaware of test limitations)
- Appropriate test result delayed/missed
- Appropriate test result inaccurate

Table 4: Options of retesting policy based on evidence. Adapted from ref. [73].

- As often as necessary (very small group of tests, including, e.g. plasma electrolytes, hemoglobin, prothrombin time)
- Once in a lifetime (e.g. genetic test for hereditary disorders)
- Never ordered on inpatients (e.g. lipoproteins as cardiovascular risk factors)
- Never ordered again once a positive result has been obtained (e.g. *Treponema pallidum* particle agglutination)
- Not ordered more frequently than daily or longer (e.g. C-reactive protein)
- Not ordered more frequently than monthly (e.g. antibody testing for hepatitis B or C virus infection)
- Not ordered more frequently than every 3 months (e.g. HbA_{1c})
- Ordered no more frequently than annually (e.g. renal function in diabetics)
- Never be ordered (e.g. vitamin D for population-based screening)

The report underpins the effectiveness of the laboratory products, being a synthesis of data, knowledge, and information. A problematic report format may prevent the correct use and interpretation of laboratory test results, when it lacks information, is difficult to understand or when it reports widely variable reference intervals across laboratories. Approximately 20% of the recently surveyed primary care physicians in the United States still experience uncertainty and challenges in interpreting different laboratory report formats, this problem potentially affecting ~13 millions patients/year and raising significant concerns about the safety and efficient use of laboratory tests [76]. The lack of harmonisation of terminology used in the laboratory reports is still a disturbing issue. For instance, a recent survey performed by the Italian Society of Clinical Biochemistry – Laboratory Medicine (SIBioC) has shown that for reporting of urine albumin results the wrong terminology of "microalbuminuria" is still used by >40% of national laboratories [77].

Although the concept of reference intervals is part of the laboratory culture, today two fundamental aspects are driving improvement in defining and using reference

values in clinical practice, emphasising the need for a more careful consideration of the issue [8, 78]. ISO 15189:2012 states that "biological reference intervals shall be periodically reviewed" and they should be verified every time a variation in analytical and/or pre-analytical procedures occurs [79]. Furthermore, there is the need to link the analytical standardisation based on the previously discussed principles of metrological traceability with the identification of appropriate reference intervals [16, 18, 80]. Prior to the traceability era most of laboratory results were method-dependent and their interpretation was based on method-dependent reference intervals. However, with the implementation of measurement standardisation, the traceable results obtained by metrologically aligned assays can be appropriately interpreted only by using traceable reference intervals (Figure 3) [31]. The introduction of common traceable reference intervals should hopefully cause the disappearance of different intervals employed for the same analyte and provide more congruent and effective information to clinicians. Laboratory professionals can play a relevant role also when reference intervals are not appropriate because the biological individuality of the analyte is high, in which case the longitudinal evaluation of significance changes in serial results of an individual patient should be applied through the use of the reference change value (RCV) concept [81]. Laboratory professionals should ensure that RCVs are fit-for-purpose by checking that analytical performance fulfils specified precision goals and educating clinicians in appropriate interpretation of results [82, 83].

An additional tool for improving data interpretation is the use of patient-specific laboratory-generated interpretive comments (LGIC). Anecdotal reports have estimated the impact of LGIC in aiding clinicians to increase diagnostic accuracy [84, 85]. By comparison, another report showed the potential negative consequences of using laboratory staff with inadequate expertise for commenting [86]. In 2006, Plebani et al. [87] identified the key issues to be considered for a reliable introduction of LGIC. Nevertheless, the practice of attaching individualised comments to laboratory reports still varies among countries and even among laboratories within a country, thus highlighting the need for improvement [8, 88].

Another responsibility of laboratory professionals is the definition and communication of critical laboratory results, a key issue in maximising patient safety. However, the reported variations between procedures and policies used by different laboratories emphasise the need for harmonisation of approaches [89]. International accreditation standards are probably needed to allow a timely and reliable communication of critical results to clinical personnel responsible for patient care. In particular, harmonised procedures are required to state responsibilities and contents of the alert list and to describe details concerning the communication of critical values (timeframe, who should deliver and receive alert results, way to acknowledge receipt, etc.). Also relevant is the measurement of the performance and impact of laboratory communication procedures on patient outcome and safety [90].

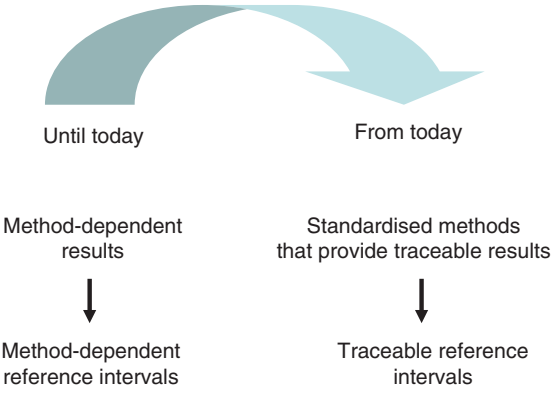

Figure 3: Linking the analytical standardisation based on the principles of metrological traceability with the identification of appropriate reference intervals.
Modified from ref. [31].

Concluding remarks

The main scope of this review is to highlight to readers that laboratory professionals should play a central role in improving clinical effectiveness in the new healthcare environment in which no one single medical specialty can hold all the answers to patient care. We provided examples on how laboratory professionals may clinically optimise operational efficiencies, should survey the analytical performance and testing appropriateness, educate clinicians and work to ameliorate the cost-effectiveness of tests and improve patient outcomes (Figure 4). We cannot of course ignore some problems [91]. It is noteworthy that there is a certain reluctance by laboratory professionals to engage themselves in test structuring and requesting as well as in the inspection of work as it arrives because it is assumed that all requests by clinicians are necessary. In addition, the communication between laboratory and wards is sometimes poor and the integration hard to build. Last but not least, there is a need for a viable culture and scientific background for laboratory professionals for implementing outcome research and act as knowledge

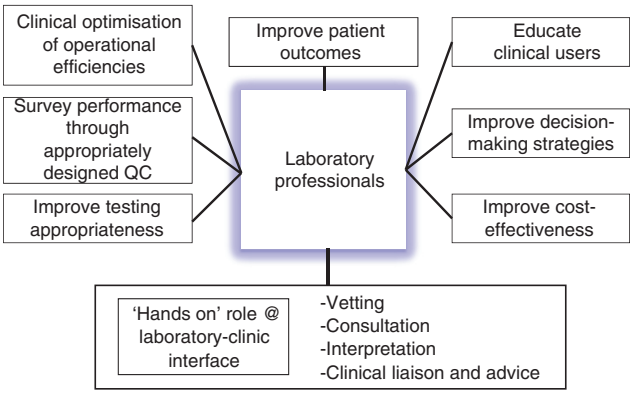

Figure 4: Role of laboratory medicine as medical discipline and profession.

managers and skilled clinical consultants. However, in order to become relevant in the healthcare environment, laboratory professionals have to change their attitude from one of being introspective and defensive to one that is outward looking and innovative. By combining the talent of performing quality laboratory assays with knowledge of the pathophysiologic rationale behind the tests, laboratory professionals have the unique opportunity to use their expertise to advise their clinical colleagues in regard to the appropriate test selection and interpretation of laboratory results, and to create opportunities to define the value and the pivotal role of laboratory medicine by focusing on its overall impact in healthcare delivery.

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