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Opinion Paper

Laboratory network of excellence: enhancing patient safety and service effectiveness

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Abstract

Clinical laboratories have undergone major changes due to technological progress and economic pressure. While costs of laboratory testing continue to be the dominant issue within the healthcare service worldwide, quality, effectiveness and impact on outcomes are also emerging as critical value-added features. Five Italian laboratories are therefore promoting a network of excellence by investigating markers of effectiveness of laboratory services and sharing their experience of using them in clinical practice. In the present study we report preliminary data on indicators of quality in all phases of the so-called total testing process, the key to evaluating all phases of the total testing process, including the appropriateness of test requests and data interpretation. Initial findings in evaluating pre-analytical causes of specimen rejection in three different laboratories and the effects of introducing three laboratory clinical guidelines are reported. These data should stimulate debate in the scientific community and encourage more clinical laboratories to use the same indicators to improve clinical effectiveness and clinical outcomes within the healthcare service.

Keywords: clinical outcomes; errors and risk of error; laboratory network; patient safety quality indicators; total testing process.

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Introduction

Laboratory medicine can be considered a pioneer medical discipline. To promote quality, it has introduced concepts such as ''quality control'', ''quality assurance'' and ''quality management'' (1). However, traditional tools for assessing laboratory efficiency have been limited to the field of indicators of internal quality, such as turnaround time, performances in internal and external quality assessment schemes, productivity and costs. The new environment of ''clinical governance'' calls for a focus on effectiveness and outcome, as well as on efficiency (2). The programs for recognition of clinical laboratories – accreditation in particular – should evolve from the mere assessment of compliance with standards to tools for effective evaluation of the quality of laboratory services and their contribution to the quality of care. Quality monitoring, risk management, continuing education of personnel and monitoring of clinical indicators should have a well-defined place in accreditation programs for recognition of quality in clinical laboratories, namely accreditation (3). The increased interest in evaluating the impact of laboratory testing on clinical and economical outcomes seen in recent years has been driven by the evolution of healthcare systems, pressure to reduce laboratory costs, changes in reimbursement of laboratory tests, the need to demonstrate efficiency and efficacy, new regulatory requirements, and the increasing relevance of appropriateness and patient safety issues. Outcome measurement must include a quantitative assessment of the benefit of medical and clinical interventions, whose final impact on quality of life is probably the most reliable way of assessing outcomes (4). However, as it is difficult to assess long-term outcomes, intermediate disease-related end points can be employed to assess surrogate markers, such as length of hospital stay, and discharge and re-admission rates. For medical laboratories, effectiveness and impact on outcomes are difficult areas to assess because laboratory tests are only part of the diagnostic process and because laboratory information must be acknowledged by clinicians if is to benefit patient care. Randomized controlled trials, considered the ultimate method for assessing the impact of clinical care on outcome, have no place in laboratory medicine, possibly because they are not profitable for the diagnostic industry and because of the widespread and consolidated use of many laboratory tests in clinical practice for patient diagnosis and monitoring. Recently, Waise and Plebani proposed a ten-point list of surrogate markers for assessing and improving the

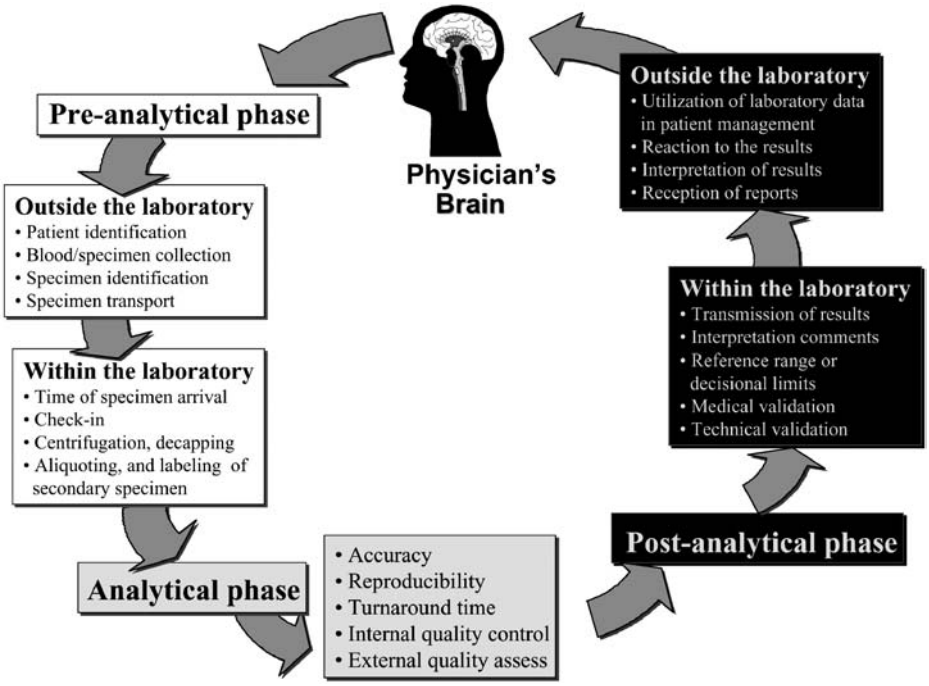

Figure 1 Total testing process: pre-, intra- and post-analytical steps.

efficiency and effectiveness of clinical laboratories (5). However, the authors did not identify specific indicators and targets for benchmarking and for assessing quality in a particular laboratory. The aim of the present paper is therefore to review the list of proposed markers to better detail quality indicators and standards of performance by considering experience gained in discussing and introducing some of the proposed markers into five Italian clinical laboratories, which agreed to take part in a project called ''laboratory network of excellence'' and to share experiences. Preliminary data are reported, and suggestions made as to possible indicators for the future. For the initial three indicators, we report data already obtained, while for all other indicators we present a proposal derived from the discussion and the temporary consensus reached among the five laboratories participating in the network. This opinion paper, therefore, does not report definitive data, but we hope it will stimulate debate in the community of laboratory professionals on the proposed indicators and on reasonable targets of performance to achieve for demonstrating the efficiency and effectiveness of laboratory services.

Errors and risk of error

The report of the Institute of Medicine entitled ''To err is human'' (6) has generated widespread interest in medical error and adverse events in healthcare, as well as strategies for reducing them. Knowledge on real and potential adverse events related to laboratory services has been provided by studies focusing on the rate of laboratory errors and the classification of errors on the basis of their cause, phase of testing, responsible party, and extent of harm to the patient. It is widely agreed that laboratory errors may be defined as ''any defect from ordering tests to reporting results and appropriately interpreting and reacting on these'' (7, 8), but the study of actual and potential adverse events related to laboratory testing would benefit from a rigorous classification scheme identifying preventable problems likely to harm patients, and suggesting solutions to these problems. Therefore, the identification of the most critical steps in the total testing process is a prerequisite for setting up a plan for a corrective and preventive strategy aimed at safeguarding patients. Figure 1 shows the different steps and related quality aspects that make up the so-called ''total testing process'' (TTP) which, in turn, is usually subdivided into the three traditional (pre-, intra-, and post-) analytical phases. However, the pre-analytical phase can be further subdivided into pre-, pre-analytical phase occurring outside the laboratory and consisting of two key activities: 1) formulating a clinical question and selecting appropriate examinations; and 2) ordering, collecting and handling, transportation and reception of samples prior to testing (9). The ''conventional'' pre-analytical phase, which occurs under the control of the laboratory, can be summarized as ''specimen preparation activity''. Specimen preparation involves the activities required to make a sample suitable for analysis: centrifugation, aliquoting, diluting and sorting the specimens into batches for introduction into automated analyzers. The specimen preparation step has attracted considerable attention because of both the recognized risk in terms of hazard for laboratory staff, and the significant contribution to total cost and time of testing. Automated pre-analytical processing units reduce the labor associated with specimen processing, and decrease laboratory errors involved with specimen

Table 1 Quality indicators and specifications of the pre-analytical phase [modified from ref. (11)].

Quality indicator	Specification target, %
Requests	
• Error in patient identification	0.08
• Physician identification missing	0.50
• Erroneous specification of hospital unit	0.60
• Request unintelligible	0.10
• Correction of errors or test ordered	0.30
• Total error in outpatient requests	1.25
Sampling	
• Uncollected phlebotomy request, inpatients	7.00
• Uncollected phlebotomy request, outpatients	0.30
• Tourniquets and holders contaminated with blood	2.50
• Needle stick injuries per 100,000 venipunctures	0.01
• Samples redraw	2.00
• Specimen collected from infusion route	20.6
• Inappropriate container used	0.015
• Errors found in identification wristbands	3.00
Transport and receiving samples	
• Inadequate sample collection and transport	0.004
• Sample rejection, whole blood count	0.45
• Sample rejection, chemistry	0.35
• Sample lost/not received	0.12
• Improperly labeled container	0.002
• Sample damaged in transit	0.002
• Sample clotted, hematology	0.20
• Sample clotted, chemistry	0.006
• Sample hemolyzed, hematology	0.009
• Sample hemolyzed, chemistry	0.20
• Laboratory accident	0.004
• Insufficient sample volume	0.05
Inadequate sample/anticoagulant volume ratio	0.02

sorting, labeling, and aliquoting. Furthermore, these tools improve the integrity of specimen handling throughout specimen processing and increase safety for laboratory staff (10). Intra-analytical activities are better defined, whereas two different sub-processes are involved in the post-analytical stage. One, occurring in the laboratory, consists of the technical and medical validation of results, the production of a report – including interpretive comments – and its transmission to the requesting clinician. The other, occurring outside the laboratory, is the clinician's reaction to the report, and interpretation and utilization of laboratory information for diagnosis and treatment.

While quality indicators for the intra-analytical phase of laboratory activity have been well defined and their specifications internationally recognized for a large number of biological constituents, there is no consensus concerning types of and acceptability limits for extra-analytical quality indicators. A Medline search of quality indicators performed by Ricos and co-workers used the following key words: Q-probes, Q-tracks alone and error, mistake, indicator crossed with quality and laboratory medicine (11). Tables 1– 3 show a list of proposed indicators for errors in the pre-, intra-, and post-analytical phases of TTP.

More recently, we provided all five participating laboratories with a risk analysis; a complex methodology was used with the aim of identifying the most critical steps in the TTP, based on cognitive task analysis, hazard and operability study, and absolute probability judgement (12–14). The analysis allowed the five laboratories to provide us with data for preliminary review and assessment (15). In particular, as

Table 2 Quality indicators and specifications of the analytical phase [modified from ref. (11)].

Quality indicator	Specification target, %
• Number of erroneously rejected analytical runs	5
• Number of repeated samples on the basis of quality control results	TBD
• Unacceptable results in internal quality control	0.07
• Unacceptable results in external quality assessment programs (EQA)	1.4
• Unacceptable performance despite successful quality control data	TBD
• Number of specimens repeated for flags or analytical alarms	TBD
• Isolated malfunctioning of instruments (P/C) (with consequent erroneous results)	2.6
• Analytical methods/techniques changed or improved on the basis of unsatisfactory EQA results (per year)	TBD

TBD, to be defined.

Table 3 Quality indicators and specifications of the post-analytical phase [modified from ref. (11)].

Quality indicator	Related to	Specification target
Report validation	Number of reports	
• Reports with test requested but not completed		1.4%
• Reports with test completed but not requested		1.1%
• Reports with erroneous reference values		TBD
• Reports with physician name discrepancies		1.9%
Intra-laboratory reports	Number of reports	
• Laboratory reporting errors		0.05%
• Delivery outside the specified time		11%
• Reports altered		TBD*
Consulting service	Number of telephone inquiries	
• Average time to communicate critical values for inpatients		6 min
• Average time to communicate critical values for outpatients		14 min
• Telephone inquires not resolved		21.3
• Clinical advice requested but not adequately performed		TBD
Laboratory computer availability	In 30 days	
• Number of downtime episodes		3 episodes
• Cumulative median downtime		4 h
Employee competence	Number of employees	
• Non-technical employee failure rate		0.9–2.9%
• Technical employee failure rate		0.9–6.4%
Physicians' reaction	Min	
• Time interval between report generation and inspection by a clinician		TBD

TBD, to be defined.

shown in Figure 2, a curve describing the relative risk and the most vulnerable activities was obtained for each laboratory. All laboratories, despite some differences, did not demonstrate a severe and unacceptable systematic risk in performing their activities, but the analysis allowed each laboratory to focus on the most critical steps. This approach is consistent with the recent ISO technical specification draft ''Medical

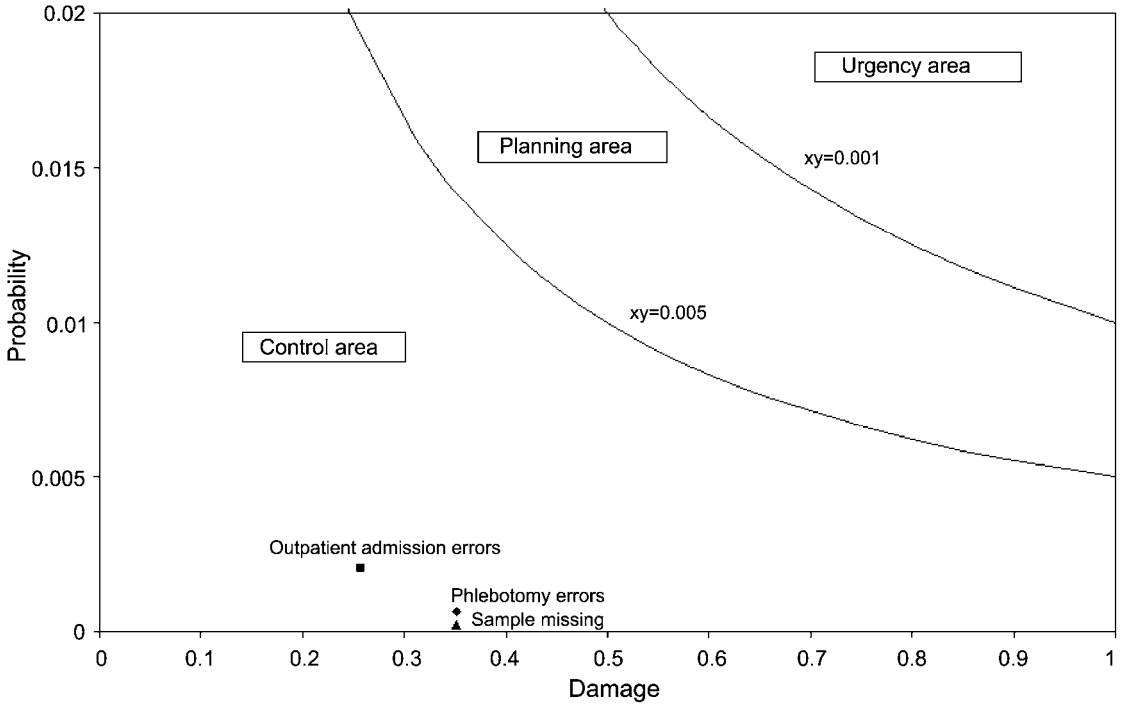

Figure 2 ISO-risk curve representing the most critical processes as a result of the cognitive analysis, hazard and operability study, and absolute probability judgement. In this case (laboratory 1), the analysis does not demonstrate any significant risk in the pre-analytical processes.

Table 4 Pre-analytical errors in three Italian laboratories.

	Laboratory 1, ppm		Laboratory 2, ppm		Laboratory 3, ppm	
	Inpatients	Outpatients	Inpatients	Outpatients	Inpatients	Outpatients
Hemolyzed sample	3286	100	4300	120	1105.5	621
Insufficient sample	1200	50.1	1250	34.5	995.3	149.6
Incorrect sample	705.9	142.2	823.5	80.7	490.2	235.9
Clotted sample	306.5	39.3	380.7	40.5	928.9	414.3
Incorrect identification	111	0.4	31.3	0.65	NA	NA
Empty tube	92	3.9	80.7	–	4488	759.6
Lack of signature (blood group)	103.0	0	NA	85.0	NA	NA
Lack of or wrong compilation accompanying module	46.0	0	127.5	0	NA	NA
Sample not in ice	29.0	2.9	148.9	3.8	250.3	126.6
Tube broken in the centrifuge	22.0	17.7	25.8	27.7	NA	NA
Urine not acidified	9.2	0	155.3	2.9	NA	NA
Urine volume not indicated	1.9	0	187	3.8	118	28.0

Tests registered during a 1-year period: laboratory 1, 258,3850 for inpatients and 2,032,133 for outpatients; laboratory 2, 3,560,135 for inpatients and 2,870,253 for outpatients; laboratory 3, 2,876,524 for inpatients and 173,764 tests for outpatients. NA, not applicable; ppm, parts per million.

laboratories – reduction of error through risk management and continual improvement – complementary elements'' (16) and should allow clinical laboratories to effectively work on the reductions of errors and risk of errors.

Pre-analytical procedures for the rejection/acceptance of specimens

Analytical quality remains the ''core'' of clinical laboratory activity, and pre- and post-analytical aspects are of crucial importance in assuring the ultimate quality of laboratory services. Specimen adequacy, a critical pre-analytic factor, affects test result accuracy and usefulness (17). Therefore, standard operating procedures for evaluating submitted specimens are an integral component of laboratory quality procedures. Specimens failing to meet acceptability criteria should be rejected: accepting specimens unsuitable for analysis can lead to erroneous information that could compromise patient care. Other important aspects of this issue are the desire to minimize the amount of blood taken from patients, to avoid delay in diagnosis and treatment due to a lack of laboratory results, and the need to improve the relationship between the laboratory and personnel dedicated to sample collection. Finally, collection and monitoring of data, and giving reasons for specimen rejection is a fundamental part of quality indicators in laboratory medicine. Table 4 shows the comparison made between types of pre-analytical errors registered throughout 2003 in three Italian clinical laboratories involved in the network project. Differences in the number and relative frequency of errors may be related to the volume and complexity of examinations performed, to different inpatient vs. outpatient ratios, and other differences among centers. The greatest difference between the rate of errors in outpatient and inpatient specimens was found between laboratories 1 and 2. The most rational explanation for this finding is that blood-drawing procedures are performed by laboratory staff for outpatients and by hospital ward personnel for inpatients. In other settings, namely in the US, where phlebotomists under laboratory control take care of specimens collection for inpatients, differences between out- and inpatients are expected to be relatively small. On monitoring the same indicators, a significant error reduction was found in 2003 compared to 2002, with the decrease ranging between 2.1% and 1.3% (mean 1.46%) in the three laboratories; this demonstrates efficacy of monitoring in achieving continuous quality improvement. Therefore, the participants to the network agreed to collect data on pre-analytical errors and encourage other clinical laboratories to do the same to make possible reliable benchmarking and future definition of acceptable targets for any pre-analytical error (e.g., acceptable rate of hemolyzed, clotted and insufficient samples). Table 5 shows some suggested indicators for the pre-analytical phase.

Clinical laboratory guidelines

Clinical practice guidelines, an increasingly common element in clinical care worldwide, aim to improve

Table 5 Suggested quality indicators for the pre-analytical phase.

a) Standard operating procedures for specimen acceptance/rejection
b) Identification and monitoring of reasons for specimen rejection
c) Effects of improvement initiatives in decreasing the rate of specimen rejection
d) Comparisons between clinical laboratories (benchmarking) of frequency and reasons for specimen rejection

health outcomes by recommending effective intervention and advising against unnecessary, ineffective or sometimes harmful treatment (18). Guidelines combine scientific evidence with patients' choices, clinicians' experience, and the availability of resources. Clinical guidelines help healthcare professionals to decide on appropriate and effective patient care. A recent review gave a summary of the various reasons why guidelines are developed; the authors proposed a ten-step process and listed criteria for the development of laboratory guidelines (19).

Current indications are that while specific scientific evidence is crucial to their development and implementation, guidelines are inadequate if their local applicability is not evaluated. Therefore, as part of a project to develop a laboratory network of excellence, three Italian clinical laboratories evaluated and monitored the impact of the development and use of common guidelines in their own setting. The choice of the diagnostic areas for developing guidelines was made on the basis of the following considerations: a) the clinical relevance and prevalence of the health condition; b) the volume of related diagnostic activity; c) the level of appropriateness or, rather, the evidence of inappropriate test requests; and d) the existence of guidelines developed following a systematic, standardized and explicit methodology.

After careful selection, three major areas for laboratory diagnosis were identified: 1) thyroid disease (20); 2) acute coronary syndrome (21); and 3) autoimmune disease (22). For cardiovascular and thyroid diseases, the clinical impact of the guideline was significantly different in the five different settings, as shown in Figure 3 and 4. In particular, the creatine kinase isoenzyme MB (CK-MB) requests were very significantly different among the five clinical laboratories, despite the body of evidence suggesting the more accurate and effective role of cardiac troponin. Irrespective of the baseline situation, we observed a significant difference in compliance with the guideline. One laboratory had completely removed the CK-MB request from the menu, while in other laboratories the number of requests for this marker was equal to or slightly reduced in comparison to that of cardiac troponin (recommended marker). Regarding the free thyroxine/thyroid stimulating hormone (FT_4/TSH) ratio, one of the markers for successful implementation of the guideline for thyroid disease,

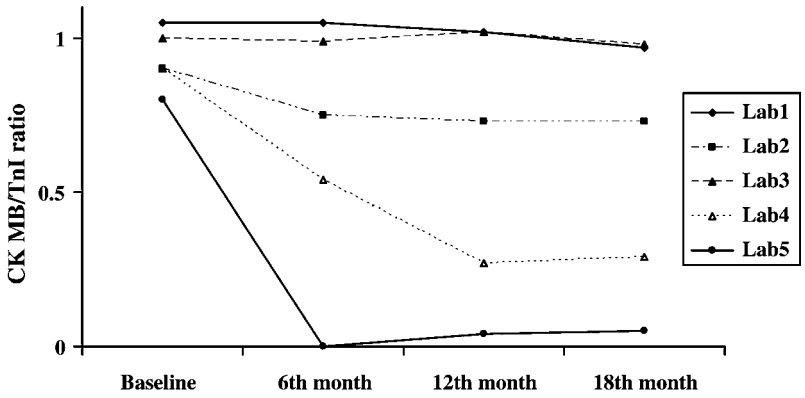

Figure 3 CK-MB/troponin I ratio as an indicator of successful implementation of the guideline on acute coronary disease. According to the guideline, the recommended test is cardiac troponin I, while the CK-MB request is discouraged. In fact, CK-MB requests dramatically decreased (near to zero) in laboratory 5, while in laboratory 1 they remain at a very high level (CK-MB/troponin I ratio approx. 1). Intermediate values were observed in the other three laboratories.

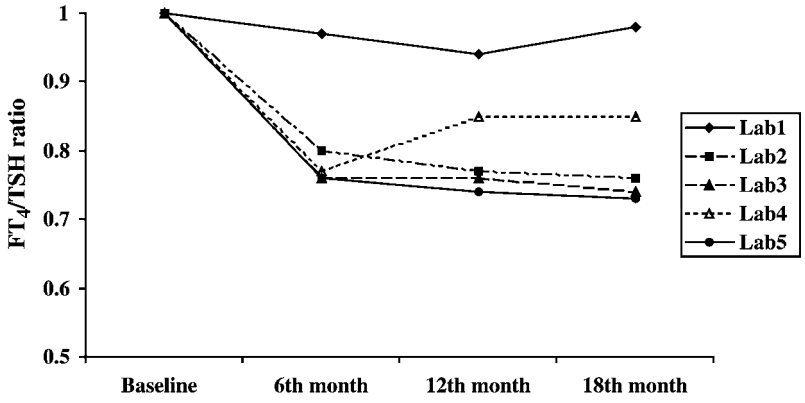

Figure 4 FT_4/TSH ratio as an indicator of successful implementation of the guideline on thyroid disease. The guideline suggests the utilization of TSH as the initial biochemical marker in asymptomatic subjects and, therefore, recommends the measurement of FT_4 only in selected samples. However, while in laboratories 2, 3 and 5 the FT_4 requests are significantly decreased and currently present FT_4/TSH ratios of approximately 0.70, laboratory 1 presents a higher ratio that means that the number of FT_4 requests parallels that of TSH.

Table 6 Quality indicators for efficiency and efficacy of clinical laboratory guidelines.

- Number of guidelines developed and introduced in the last 2 years
- Criteria for selection of diagnostic areas and related guidelines
- Identification of indicators of the impact of guidelines in terms of efficiency and efficacy
- Monitoring of identified indicators and initiatives for improving diffusion, adherence and compliance
- Regular reviewing and updating of guidelines
- Audit for evaluating efficacy of introduced guidelines in improving clinical and economic outcomes

wide differences among the five laboratories have been described and in one case (laboratory 4), after a transitory decrease in the ratio, a trend to a ''return to the initial habit'' was found. This underlines the importance of local conditions of care, adaptability, practicability and the relationship between physicians and laboratory scientists. The indicators proposed on the basis of this experience are listed in Table 6.

Consultant advisory service and its documentation

ISO 15189: 2003, the new, specific international standard for medical laboratory accreditation, recognizes the importance of a consultant advisory service (23). This activity covers all aspects of laboratory investigations, including appropriateness of test requesting (the right test, for the right question, for the right patient), as well as the interpretation of results and advice on further appropriate investigation. To evaluate the quality and effectiveness of consultant advisory activity, an efficient system must be used for its registration and documentation, as shown in Table 7.

Table 7 Documentation of consultant advisory services.

1. Provision, in the request form, of a space for adding clinical information required for addressing the testing process, including results interpretation; for some tests, particularly complex and costly ones, the ''gating policy'' requires analytical activity to be authorized only if the requester has answered specific questions to demonstrate the appropriateness of the test in relation to the clinical context or problem
2. Registration of any request received from clinicians for clinical advice in test ordering, result interpretation or any other laboratory-related question
3. Implementation of an advisory service in specific clinical areas where there is consistent record of the existence of particular expertise
4. Documentation of initiatives and meetings for improving appropriateness in test request/result interpretation
5. Documentation of interdepartmental activities aiming to implement and divulge guidelines and recommendations for improving appropriateness and utilization of laboratory information
6. Identification of ''contact'' physicians in any ward/clinical department
7. Attendance at clinical audit or improvement initiatives within the institution

Interpretative comments

Interpretation of laboratory test results is a post-analytical activity. With the increasing complexity of some laboratory tests that call for a knowledge of analytical and biological characteristics, test interpretation is no longer a purely clinical activity. Increasingly often, laboratory professionals are asked to give advice and co-operate with clinicians to help them to interpret new, complex tests, including genetic analyses (24). Other factors underpinning the greater need for interpretative comments are well summarized in a recent paper (25). Currently, while it is widely accepted that there is a need for patient-specific clinical laboratory narrative interpretations and comments, the ways in which such interpretation can be achieved have yet to be defined. Physicians and laboratory specialists agree that local clinical needs point to a requirement for interpretative comments to be issued on demand by physicians, and by the laboratory in particular cases (e.g., macro-amylase, macro-AST, mitochondrial form of CK), or constantly as a component of a test result in some cases (e.g., serum protein electrophoresis). However, we believe that quantitative goals cannot be either identified or achieved because the issue is so complex and because the clinical context of different laboratories varies so greatly. Moreover, the percentage of reports accompanied by interpretative comments strongly depends on the test menu and its complexity. However, a list of items related to the quality of interpretative comments is given in Table 8.

Setting and communicating quality specifications to clinicians

The level of performance required to facilitate clinical decision-making has been given a number of names, such as quality goals, quality standards, analytical goals and desirable standards. Currently, the most widely used term is ''quality specifications'' (26). We can further subgroup quality specifications into reliability and practicability characteristics. The latter deal with details of executing the procedure (e.g., speed of analysis, volume and type of sample required) that affect intra-laboratory quality. The former, however, by dealing with the scientific facets of assays such as

Table 8 Quality issues in interpretative comments.

- Identification of diagnostic areas in which the clinical laboratory can provide an effective clinical interpretation of laboratory results
- Documentation of the policy for clinical authorization and reporting of interpretative comments
- Documentation of the training and accreditation programs of laboratory scientists qualified to provide interpretative comments
- Percentage of reports with interpretative comments (on total reports)
- Audit system for evaluating the quality of interpretative comments
- Performance in the external quality assessment of quality of interpretative comments, if available

Table 9 Classification of laboratory tests.

Type of test	Quality specifications
1. Test with a unimodal distribution	Very demanding; analytical uncertainty around the decision limit should be close to zero
2. Test with bimodal distribution	Total allowable error, according to the biological variability
3. Test for patient monitoring	Reference changes value (RCV)
4. Test requiring interpretative comments	Clinically useful but must be accompanied by clarification/explanation by interpretative comments
5. Test requiring pre- and post-analytical counseling	Mandatory for genetic testing

bias and precision, significantly affect not only intra-laboratory quality, but also clinical interpretation and decision-making. It is increasingly widely recognized that it is of crucial importance to inform clinicians of the quality specifications of laboratory tests. According to a recent proposal aimed at improving on the process of informing clinicians of quality specifications, laboratory tests belong to five different categories (27), as shown in Table 9.

Therefore, as clinicians require quality informative and practical explanations, some indicators should be collected, as shown in Table 10.

Pro-active role of clinical laboratories

The pro-active role of clinical laboratories is another aspect of efforts made to improve the efficacy of laboratory services. First, the policy of introducing new tests that are of greater clinical effectiveness, and of discontinuing obsolete and useless tests is an important aspect of the quality policy. Clinical needs should be continuously assessed and re-evaluated and this should be done in strict co-operation with physicians, particularly in some diagnostic areas in which new insights have paved the way for the development of more informative laboratory tests. Second, laboratory results and findings may indicate that further testing is required for a better understanding of the cause underlying the result itself and for speedier diagnosis and treatment. This applies to the characterization and typing of suspected monoclonal bands (M-proteins) on protein serum electrophoresis by immunofixation/immunosubtraction (28), the measurement of haptoglobin and free hemoglobin in hemolyzed specimens if in vivo hemolysis is suspected (29), and antimicrobial susceptibility testing in the case of bacterial growth in biological specimens (particularly bacteriuria) (30). Third, reflex testing when the initial laboratory tests are performed may suggest that further investigations are required for a clearer diagnosis. This applies to cases such as: the measurement of FT_4 when TSH levels show a moderate increase or decrease with respect to reference values (31); and confirmatory tests for lupus anticoagulant positive data obtained with the screening procedure (32). Table 11 shows a list of possible indicators of the pro-active role of clinical laboratories.

Table 10 Quality indicators in communicating laboratory data to clinicians/informing clinicians of laboratory data.

- Number and percentage of tests with indicated quality specifications or clinical limits and value related to quality specifications
- Number and percentage of tests with defined critical/decisional limits
- Number and percentage of tests with defined reference change values and computer-aided calculation of the RCV based on a comparison between two serial data
- Number and percentage of tests with decision limits and evaluation of the analytical functional imprecision at selected clinical threshold

Percentage of control vs. patient specimens

Internal quality control (IQC) is an essential component of the strategy for evaluating and improving quality in clinical laboratories. However, current laboratory practice cannot be described simply as quality control, but is rather process control, with IQC being a part of the process. Howanitz and co-workers evaluated laboratory IQC processes using the College of American Pathologists Q-Probes program (33), and concluded that IQC practices are complex and highly variable among participants, with the cost of control samples ranging from 6.8% to 37.0% for four common analytes (hemoglobin, cholesterol, calcium and digoxin); the highest costs incurred were for the quality control of digoxin. Costs and, mainly, the number of control samples in relation to patient samples are important indicators: an excessively high ratio (many control samples in comparison to total samples in the analytical run) may not only reveal the excessive costs of control procedures, but should also prompt the laboratory management to reappraise the use of the test within the institution, or to refer the test to another laboratory. It has been well demonstrated that, mainly for complex testing, quality is assured if the laboratory receives and examines an adequate number of specimens, hopefully with a mix of ''nor-

Table 11 Indicators for documenting the pro-active role of clinical laboratories.

- New tests introduced by the laboratory (number/last 24 months)
- Tests considered obsolete and discontinued by the laboratory (number/last 24 months)
- Tests introduced or discontinued by clinicians and laboratory specialists together
- Diagnostic algorithms in anomalous and pathological laboratory findings
- Percentage of samples for which additional test are requested and performed by the laboratory
- Reflex testing when anomalous results are obtained at screening or first-level tests
- Percentage of samples for which reflex testing is performed

Table 12 Quality indicators related to the control/patient specimens ratio.

- Setting out/designing a policy for establishing the correct ratio between control and patient specimens according to the nature of the test required, and its complexity
- Fixing a ''maximum'' control/patient specimen ratio to keep the test in house or to refer it to another laboratory
- Continually monitoring the control/patient specimen ratio, particularly for costly and complex tests
- Recognizing any differences between control procedures for the same analyte when performed in a routine vs. an emergency (stat) setting

mal'' and ''pathological'' results. The competence of laboratory staff not only in measurement of the test, but also in selecting appropriate reference and decision levels and in interpreting the results, is related to the number and types of specimens received (Table 12).

Reference values

The differences between an analytical result and a laboratory finding have been well described in the literature (34). A numerical result without any further information (reference values, decision limits, etc.) is useless for clinical decision-making and patient management. The concept of reference values, first introduced in 1969 by Saris and Grasbeck, is not yet used by laboratory scientists and clinicians as rigorously as it should (35). Although documents issued by national and international accreditation bodies involved in accreditation of clinical laboratories specify requirements regarding the provision of reference values in laboratory reports, available evidence demonstrates that this issue receives scanty attention. Recent years have seen a significant improvement in interlaboratory agreement on issues such as analytical quality, but a wide variation in reference values (36). This means that individual laboratories may obtain comparable test results but, because of differences in reference values, these results may be interpreted in different ways, being considered normal or pathological, depending on the different reference values used by the different laboratories. Moreover, regarding the intriguing issue of transferability of reference values, the main question is whether the laboratory can use the reference limits proposed by the manufacturers (mainly after the European directive on in vitro diagnostics) or by other scientists following reports in the literature. Factors influencing the reference values used are the existence of multiple ethnic groups and different styles of life, and the globalization and movement of individuals from one country to another and cohabiting with indigenous populations. A further factor prompting the re-evaluation of this issue is increasing analytical reliability, which allows ever-smaller deviations from the norm to be detected and explained. Furthermore, with the current longer life expectancy and improvement in the overall health status of the elderly, there is an increasing need for reference values for the elderly. Lastly, we need to reappraise theoretical concepts and practical applications of conventional population-based reference values; in particular, further knowledge on underlying biological variations of quantities examined in medical laboratories is crucial for better understanding of the appropriate generation and application of reference values (37).

Table 13 Quality indicators related to reference and decision values.

- Source and modalities for the generation and adoption of reference values
- Existence of specific reference intervals for gender, age, and ethnic group
- Frequency and time-span for reappraisal of reference values
- Experience of transferability and generation of common reference values in a large geographical area
- Evidence of evaluation and reappraisal of reference values following users' suggestions and responding to clinical needs
- Existence of parameters with both reference and decision values

As laboratory scientists are, and will continue to be, responsible for defining reference values and intervals, they should rigorously apply the quality indicators shown in Table 13.

Conclusions

Laboratory data are an integral part of the physicians' decision-making process and current findings show that they influence 70% of medical diagnoses (38). Therefore, quality assessment and improvement of laboratory services play a significant role in programs for assessing and improving quality in healthcare. The availability of an international standard, ISO 15189: 2003, specifically developed and released for clinical laboratories, provides a unique opportunity to harmonize existing accreditation programs worldwide and meet requirements for assessing quality in the TTP. The new international standard identifies clauses and sub-clauses for each phase (pre-, intra-, and post-analytical) of laboratory activity but it does not, and cannot, identify indicators and related quality specifications. In fact, a clinical indicator can be defined as ''a measure that assesses a particular healthcare process or outcome'', and is a tool for producing a quantitative measurement of quality of care (39). However, it is not enough to simply know the level of an indicator: we must also understand whether the defined level is acceptable or not (40). Acceptability must be evaluated in relation to the purpose for which the indicator is to be used; this process, based on existing quality specifications, calls for preliminary data collection when benchmarks are available. Currently, this applies to most of the quality indicators proposed. As yet, no quality specifications are available. Those used are based on literature data obtained with different study designs, different test complexities and volumes, and different statistical

treatments of data. Therefore, in the absence of scientific evidence, clinical indicators should be selected on the basis of consensus between laboratory professionals, and tested in multicenter trials.

The present study, a preliminary reassessment of the proposed list of efficacy markers, provides further specifications on related quality indicators that were evaluated in five different clinical laboratories. It is to be hoped that the initial experience of the laboratories participating in the network of excellence will promote knowledge of the above-reported markers and indicators, and prompt a broader evaluation using a homogeneous study design for each type of indicator. This initiative should, in turn, yield realistic data for benchmarking and defining related quality specifications.

The present paper has some limitations. First, we collected some data and evidence for a limited number of quality indicators. Second, more robust data should be collected on risk analysis and error rates. Third, laboratories must test the practical utility of all the above efficacy markers in routine practice, as well as their effects on the final quality of laboratory services. Fourth, for any indicator, a reasonable target should be identified to make an objective evaluation possible and to prioritize improvement projects. Lastly, different local situations may require different approaches and this should always be taken into account.

In conclusion, the observations and proposals made in the preliminary experience of five Italian clinical laboratories that decided to participate in a network of excellence have allowed a comparison between performances, not only in terms of workload and efficiency indicators, but also in introducing quality and efficacy markers of the entire testing process. Further, more reliable data should be collected by increasing the number of laboratories that agree to share experiences and evaluate the proposed quality indicators.

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