Review Article

Enhancing the Clinical Value of Medical Laboratory Testing

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Abstract
The value of medical laboratory testing is often directed to the cost of testing however the clinical benefits of these tests are at least as important. Laboratory testing has an acknowledged widespread role in clinical decision making, and therefore a role in determining clinical outcome. Consequently, the value of laboratory testing should be considered in its role in affecting beneficial actions and outcomes. This includes both the requesting phase of choosing tests which will influence clinical decision making as well as the reporting phase in a way that guides clinical decisions and actions. Clinical decision support systems and software can enhance the value of medical laboratory testing if they are directed toward facilitating those clinical decisions where there is either evidence, or agreed consensus, addressing patient outcomes.

Introduction

Value is often expressed in terms of "quality, clinical efficacy and effectiveness, patient centre-edness, patient satisfaction, timeliness, clinical efficiency, cost effectiveness, productivity affordability and cost".[1] Laboratory value should ideally be judged in a manner consistent with the main goals of a health system which include disease prevention, early detection, establishing an accurate diagnosis, selecting the right treatment, avoiding delays in treatment, facilitating recovery, reducing disability, preventing relapse or retarding disease progression and reducing the need for long term care.[2] Since laboratory testing can help to guide each of these clinical decision points,[3] these health goals are also the primary goals of laboratory testing.

The often stated claim that 70% of clinical decisions depend on laboratory testing may have been established on little evidence,[4] but the claim is supported by recent surveys of specialist clinicians in Germany and the USA which found 60-70% of clinical decisions were affected by laboratory test results, both in the hospital setting and outside.[5] Furthermore, surveys of evidence based clinical guidelines show that at least 80% of guidelines which are aimed at establishing a diagnosis or managing disease require laboratory testing.[3]

The funding of laboratory medicine is typically focused on the *cost* of testing rather than the clinical value of testing.[6] Laboratory specialists may be entitled to be cynical about cost surveys of laboratory testing because, in the words of Oscar Wilde, a cynic is someone who knows the price of everything and the value of nothing.[7]

Defining the Value of Medical Laboratory Testing

Whilst value can be defined as 'the importance, worth or usefulness or something', cost is a simple definition and simply 'the amount that has to be paid for something'. The dependence between cost and value involves the benefit of the product; therefore a cost-benefit relationship can be defined as the amount that has to be paid to gain a financial benefit or 'profit' or alternatively a non-financial benefit or one that is difficult to define in purely financial terms, such as 'quality of life'. Since the goals of healthcare are ultimately defined in improving health outcome, the simplest definition of value in healthcare is 'health outcome achieved per dollar spent'.[8] I would note that the comparison of health outcome to cost asks us to put a dollar value on someone else's life and wellbeing, which is at least as problematic as putting a dollar value on your own. It may be appropriate to compare the costs and health outcomes separately, such as (a) the health outcomes

associated with obtaining healthcare against the health outcomes when not obtaining that care, and/or (b) the cost of obtaining healthcare against the costs of not obtaining that care. We would then still have the ethical challenges inherent in matching outcome differences with the cost differences.[9]

While the value of medical laboratory testing could be regarded as the health benefit compared to cost, we should not neglect the supportive factors for benefit which include technical quality and timeliness.[5] Recent hospital accreditation standards focus heavily on turnaround times for all pathology disciplines in order to reduce length of stay.[10] While we are told, "time is money", the benefits of efficiency include not only reduced costs but also earlier treatment and therefore improved clinical outcomes. While economic measures such as cost of laboratory testing can be added to the cost of an episode of care, the trade-off between these costs and improved health benefits is much harder to define. Analytical quality (precision and trueness) must also be considered in essential prerequisites of laboratory test value, however the clinical impact of those tests to reflect health and disease (specificity and sensitivity) are better measures of clinical utility.[2]

The International Federation of Clinical Chemistry (IFCC) co-sponsored a meeting of world experts in Stockholm during 1999 which aimed at identifying the various strategies used to define quality in laboratory medicine, but also to develop a hierarchy which lists and ranks the preferred strategies for determining quality.[11] The agreed five level hierarchy has since been applied, for example to set allowable quality limits for analytical performance for external quality assurance (proficiency testing).[12] However the hierarchy was rarely applied to non-analytical areas of laboratory quality[13] perhaps suggesting the hierarchy may have been too complex to apply routinely. Fifteen years after the Stockholm meeting, a similar group of experts met in Milan during 2014 and together agreed to simplify the number of levels in the hierarchy from five to three; (a) quality based on clinical outcomes, (b) quality based on biological variation and lastly (c) quality based on state of the art.[14] The Milan meeting also hoped this simplified system would facilitate the broader consideration of laboratory quality beyond the analytical phase, drawing attention to the critical phases before analysis (i.e. test selection and sample processing)[15] as well as those after analysis (i.e. interpretation and clinical action).[16] While the focus of laboratory for many years has been improving analytical quality, Plebani and his co-workers have established that most errors occur in the extra-analytical phases.[17]

Clinical Wisdom

According to Berte & Nevalainen, the potential impact of laboratory tests on clinical outcome can be summarised in a sequence of three questions:[18]

(1) Does a laboratory test change the way a clinician thinks about a patient? Then if so:
(2) Does that change in thinking alter the way the clinician manages the patient? Then if so:
(3) Does that change in patient management affect clinical outcome (i.e. mortality/morbidity)?

With increasing access to computerised health data, clinicians face a modern challenge in knowing what to do with all this information. Zelany was one of the first to try and define the stages of modern informatics starting from 'knowing nothing', and progressing through 'knowing what it is', 'how it happened', 'why it is important' and concluding with 'what is the best thing to do in response to that importance'.[19] In simpler words; 'Know Nothing', 'Know What', 'Know How', 'Know Why', 'Know Best'. Even in earlier times, author T.S. Eliot may have understood this sequence of importance and relevance when he wrote:

(1) Where is the Life we have lost in living?
(2) Where is the wisdom we have lost in knowledge?
(3) Where is the knowledge we have lost in information? [20]

This philosophy of the value of data and information is commonly referred to as the 'Data-Information-Knowledge-Wisdom (DIKW) framework' and it is becoming popular across the expanding science of 'Informatics' including the sub-discipline of 'Health Informatics'.

The DIKW framework can be directly applied to the process of interpreting laboratory test results:

DATA:	Reliably highlight abnormalities in laboratory data
INFORMATION:	Create new information by identifying data patterns
KNOWLEDGE:	Apply medical knowledge to interpret the clinical significance of patterns
WISDOM:	Translate clinical significance into an action that can improve outcome. [21]

Prior to interpretation, a clinician's initial thoughts are to choose suitable laboratory tests and once the report is received, to think about the clinical significance of the results of those chosen tests. The clinicians 'Brain to Brain Loop' was initially defined by Lundberg.[22] More recently Lundberg together with Plebani and Laposata, have reminded us that there are at least two other 'brains' that might facilitate the value of laboratory testing i.e. the laboratorian's brain and the

patient's brain.[23] The laboratorian can assist with appropriate test requesting and interpreting reports. The patient has the ultimate motivation in considering and agreeing to have the tests done in the first place, as well as considering and agreeing to any clinical management consequently indicated by the results of testing.

Patients are often the prime motivators of laboratory testing and have expectations that laboratory testing will relieve (or realise) their anxieties about underlying illness. When clinicians are unsure about the guidelines for screening, it is very likely that patient anxiety or expectation will increase the likelihood of patients being tested regardless of guidelines.[24] General practitioners will admit that the perceived need of the patient for reassurance through testing is seen as an easy, cost- and time-effective strategy during consultation.[25,26]

The frequency that general practitioners request laboratory tests varies by geographic location, and may be determined by practitioner availability in that area.[27] While the largest variations in requesting are seen with rarely requested tests,[28] common test request rates can also vary by geography: Prostate Specific Antigen (PSA) testing (which is controversial and a cause of patient anxiety) shows large variation in use by geographic location.[29] Variation of clinical behaviour may also reflect differences or gaps in understanding[30] therefore studies on the regional use of laboratory tests potentially provide an excellent base for educational initiatives.[31] Other studies have also found that requesting behaviour is related to clinician experience but not significantly affected clinicians medico-legal attitude to risk taking.[32]

There have been numerous strategies proposed to influence laboratory test utilisation.[33] These can be categorised as either (a) restricting access to testing, (b) feedback on the level of testing and/or (c) education regarding guidelines for appropriate testing. On their own, educational programs are generally more effective than a feedback strategy,[34] while restricting access to testing will have various degrees of success depending on the degree of the restriction of access. These strategies are more effective when combined. Conversely, easy access to a bank of tests (test profiles), often defined by laboratories, may have a large effect on regional test use.[35] It is important to note that the incremental cost of some routine tests can be so small, that a restriction in the number of tests per request may not lead to a significant change in the overall cost of testing.[36]

Test request influencing strategies are based on the assumption that it is possible to define inappropriate utilisation. With increasing use of laboratory tests since the 1990s, there has been an accompanying exponential increase in the number of published articles auditing test utilisation.[37] Contrary to the widespread expectation that overutilisation is the main problem, a meta-analysis found that 45% of studies found evidence of under-utilisation whereas only 21% found evidence of overutilisation.[38] An example of underutilisation includes lack of diabetes follow-up with HbA1c and urine albumin. The published basis for judging appropriateness of laboratory testing has also shifted from the each author's opinion on what can be defined as appropriate use, to the use of clinical or organisational guidelines as the basis for defining appropriate test use.[38] It is important to note that many clinical guidelines are based on the subjective consensus of chosen experts rather than truly objective evidence. Achieving consensus on what is an appropriate test request is a significant barrier to improving test utilisation.[39] When test requesting by general practitioners is surveyed and compared to what clinical guidelines would mandate, most general practitioner test requests are not compliant and the main difference is adding other tests not specified in the guidelines.[40,41]

Quality Framework Applied to Extra-analytical Phases of Laboratory Testing

The Table applies the three 'Milan' strategies of defining analytical quality (clinical outcome/biological variation/ state of the art) to the extra-analytical phases of laboratory testing.

The baseline for assessing quality is the 'State of the Art', where a peer based approach describes the status quo and should be considered the minimum standard of care. Indeed, the medico-legal standard of appropriate care is often defined as following what the 'reasonable' practitioner would do in the same clinical circumstance. We generally accept (and hope) that the majority of medical practitioners are reasonable, and the commonest practices are the safest.

The second 'biological variation' strategy is a concept that simply states that 'the allowable analytical variation is less than half the day to day intra-individual biological variation of the patient'. In other words, that the inevitable analytical noise seen during measurement is less than the biological signals we are trying to assess in each patient. If analytical noise is too great, the changes in laboratory results will be mainly due to what is happening in the laboratory rather than what is happening to the patient.

Day to day biological variations in patients also relate to the quality of the extra-analytical phases, but this requires some lateral thought to fully appreciate: when defining reference intervals, the inclusion of the analytical measurement uncertainty together with the biological variations seen within and between individuals literally define the reference

Table. The Milan hierarchy for analytical quality reconsidered in terms of all phases of laboratory testing.

	Pre-Pre-Analytical	Pre-Analytical	Analytical	Post-Analytical	Post-Post-Analytical
Clinical Outcome	Choose tests that can improve outcome	Prevent errors that may be harmful	Clinical Outcome	Reports that facilitate follow-up	Clinical action that improves patient outcome
Identify abnormality	Choose tests likely to be abnormal	Detect errors in patient identification or sampling	Biological Variation	Harmonised reference limits define 'abnormals'	Clinical action in response to abnormal result
Peer based standard	Consistent with peers based requesting	Consistent with peer based sampling	State of the Art	Consistent with peer based reports	Consistent with peers based clinical actions

limits. Reference limits, defined by the biological variations within and between individuals, have become the most common method to interpret laboratory results. This cannot be underestimated as reference limits are used to determine the abnormality flags shown on a report and also to draw the clinician's attention to changes presumed to have clinical importance.

How is biological variation, and the ability to reliably define a significant abnormality, related to the pre-analytical requesting phase? In a recent paper, Naugler and Guo introduce a new concept of using the 'Mean Abnormal Result' (MAR) rate as a new metric for benchmarking laboratory test requesting.[42] They observe that the MAR rate is typically about 8 to 9% across all laboratory tests requested. When physicians order many tests per request (more than 9 tests in their study), the detection of abnormalities does not increase suggesting diminishing return and waste of effort. The potential use of this metric is not only to restrict the number of tests, but also to define which tests are the most likely to be abnormal in any particular patient. The pre-test likelihood that a test will be abnormal depends on risk and disease prevalence. In our studies we have shown that some clinical indications are more likely to be associated with vitamin B12 deficiency including: 'vegetarian'/'macrocytic'/'confusion'/'dementia', while other clinical indications including; 'check-up'/'fatigue'/'tiredness'/'lethargy' do not increase the likelihood of an abnormal result.[43]

While MAR focuses on the potential value of an abnormality in some clinical situations focused on excluding abnormality, rather than confirming an abnormality, a 'normal' result has clinical value. An example is when ruling out organic illness (e.g. phaeochromocytoma) so that a psychiatric diagnosis (e.g. panic disorder) can be made.

Diagnostic errors cause the majority of malpractice claims and are commonly due to either failing to request an appropriate diagnostic test, in about one half of cases, or incorrect diagnostic interpretation, in about one third of cases.[44-46]. It is not analytical failures of laboratory testing but extra-analytical failures which ultimately lead to failure of patient follow-up and suboptimal care.[47] We expect that correctly highlighted abnormalities will result in some clinical action. This is precisely why laboratories also set critical phoning limits, to ensure that when a patient's wellbeing is at extreme risk, the clinician has been made aware of the abnormality in person. While continuing education of clinicians should improve the chance of diagnostic errors occurring, clinical decision support software may also be recruited to improve the requesting and interpretation of laboratory tests.

Guideline-based Clinical Decision Support for Laboratory Test Requesting

Since the value of laboratory testing primarily depends on choosing the appropriate laboratory tests, clinical decision support for laboratory test requesting needs to be focused on the clinical circumstance of each particular patient. As mentioned previously, most clinical guidelines include the appropriate laboratory tests to request in specific clinical circumstances. Several guidelines exist for the appropriate tests used in the management of 'diabetes', however many patients aren't simply diabetic, they may also be: children with type 1 diabetes, or pregnant women with overt or gestational diabetes, or have comorbidities such as obesity, hypertension, dyslipidaemia or renal dysfunction with albuminuria. Each of these demographic and comorbidity factors will influence the appropriateness of laboratory testing. While simplified guidelines are desirable, each patient's circumstance may not be as simple. Clinical pathway options for each patient may

vary according to available resources and patient preferences. Clinician adherence to guidelines requires not only promotion and access to the guidelines, but also positive attitude to guidelines including an agreement on guideline content.[48] How easily a guideline can be directly applied to each of the clinician's patients will affect the perceived applicability of the guideline.

There is an understanding that certain laboratory tests will affect what will be done to the patient depending on whether the result is normal/high/low.[49] Ideally there should be clear evidence that requesting certain laboratory tests will improve clinical outcome. Clinical guidelines are generally based on the consensus of experts who through the available evidence and/or their experience, are trusted to understand and agree that certain laboratory tests facilitate improved clinical decision making and therefore improve clinical outcome. Often there is little high level evidence and clinical guidelines depend on the eminence of the expert panel more than the evidence.[50]

The development of clinical decision support tools based on clinical guidelines depends on the availability of agreed profession based guidelines as well as the tailoring of the advice to the specific circumstances of each patient. Studies are now being conducted that show how clinical decision support rules can improve test utilisation,[51-54] however they should ideally also consider the issue of clinical outcome.[55]

Clinical Decision Support for Laboratory Test Interpretation

High quality computerised clinical decision support can increase evidence based prescription and decrease primary care prescription costs.[56] Laboratory tests that matter, or have value, are those that produce actionable results that bring a positive outcome benefit for the patient.[57] Therefore, clinical decision support for laboratory test interpretation would not stop at assisting to define health status, but also to actively encourage appropriate clinical follow-up. In fact it can be argued that the accurate definition of health status (e.g. an accurate diagnosis) is not as important as ensuring the appropriate clinical follow-up. An example is in the histological diagnosis of malignancy where the accurate definition of which type of malignancy it is, is not as important as the fact that it was completely excised. Therefore when judging interpretation of pathology reports, an inaccurate report diagnosis that leads to appropriate treatment (as for the true diagnosis) is not as bad as an accurate diagnosis that has not been translated to appropriate clinical follow-up.

Recently, the IFCC working group on interpretative commenting quality assurance (WG-ICQA) published their guideline on assuring the quality of interpretative comments in clinical chemistry.[58] These principles could be translated to all disciplines of laboratory medicine. The optimal interpretation is one that includes both optimal diagnosis as well as optimal follow-up while unsatisfactory or poor comments lead to inadequate or inappropriate follow-up.

What Should Laboratorians be Doing to Enhance the Clinical Value of Testing?

Medical laboratories have been focused on improving and maintaining analytical quality and they will continue to do so using existing quality assurance tools. The clinical value of testing also revolves around the selection of test that will beneficially influence clinical outcome and the interpretation of results so that the reports facilitate beneficial clinical actions. It is a requirement that an advisory service exists that both understands and liaises with clinicians in the selection and interpretation of tests. The fundamental requirement for laboratorians is therefore to nurture and expand the clinical communications of the medical laboratory which include face to face meetings, telephone consultations, newsletters and interpretative comments on reports.

The selection of clinically appropriate tests ideally requires knowledge of clinical purpose and knowledge of the tests available including their strengths and weaknesses. Clinical guidelines for appropriate test use should therefore always have the input of both clinicians and laboratorians. Clinical decision support for test selection should involve both clinicians and laboratorians and they should collaborate in initiatives to improve test selection.

Ensuring that laboratory results are available in a timely manner appropriate to the urgency of clinical decision making is another example of how laboratories can impact clinical outcomes through encouraging liaison on these issues.

Laboratory reports, which are often focused on reporting the results of analysis, should rather focus on facilitating beneficial clinical actions. Rather than wading through the details of analysis, reports should summarise the significant findings, their clinical implication and the possible beneficial clinical actions that might be indicated. Reports should be structured to highlight interpretation and action, particularly those clinical actions such as further testing on the existing sample (reflex testing), or repeat sampling, which the laboratory could help to facilitate.

Summary

The value of laboratory testing is primarily related to the ability of these investigations to promote actions that will improve health outcomes. The total cost of healthcare devoted

to improving health outcome is a matter for each community while the proportion of cost attributable to laboratory testing depends on its contribution to promoting beneficial outcome. While collecting the evidence for these beneficial impacts has become a recent concern, the facts that laboratory tests affect clinical decision making and laboratory tests are included in clinical guidelines is undeniable. Enhancing the value of medical laboratory testing primarily relates to supporting each clinicians' ability to request and interpret laboratory testing in a way that facilitates clinical decisions that improve health outcome.

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