Analytical Goals, the Total Testing Process, and Patient Outcomes

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Abstract: Specifications are routinely required to address the total testing process that includes all pre-analytical, analytical, and post-analytical variables. Rigorous specifications must be developed to address the issues of collection of appropriate specimens as well as the increasing use of bar-coding, optical scanning and information technology links in sample identification. Efforts to fully automate sample accessioning and processing are creating new needs for goals to drive emerging engineering concepts. As electronic reporting of data becomes commonplace, there is a growing need for clinically relevant specifications to connect expert systems and object-oriented database management systems to improved patient outcomes.

Analytical goals also need to reflect diagnostic impact and patient outcomes. In developing cardiac protein assays (CKMB, cardiac troponin) or thyroid hormone assays (TSH, free thyroxine), the specification of specificity and functional sensitivity are a necessary first step. However, only rigorous clinical trials and use of receiver operator characteristic plots can answer key diagnostic questions. Can mass CKMB as a single biochemical marker (together with clinical findings and EKG) appropriately diagnose myocardial infarction, or is concurrent testing with LD1 or cardiac troponin required for optimal diagnostic efficacy? What level of functional sensitivity is required to diagnose hypothyroidism in hospitalized patients with nonthyroidal illness? Is use of a test with rigorous analytical goals sufficient to contribute to improved health of the patient?

Introduction

This presentation has one overarching theme: seizing opportunities in and developing standards and specifications for the management of information in improving patient care. Development of standards in bar coding and data streams has immeasurably improved the laboratory's ability to identify specimens and transfer data with virtually no errors and high levels of productivity. Interchange of clinical information among independent health care-oriented computer systems is now a reality through standards developed for peer-to-peer data transfer or for the use of smart interfaces. Automation of sample preparation and distribution is the focus of work in developing standards and specifications so that robotic systems and clinical laboratory analyzers can effectively interface. Expert systems - under used in laboratory medicine - can be extremely helpful in managing analytical processes and in analyzing complex laboratory data.

Managing information to better meet clinical needs is discussed with reference to cardiac markers and thyroid-stimulating hormone (TSH). Statistically measuring diagnostic performance of, for example, creatinine kinase MB isoenzyme (CKMB) effectively requires the use of well designed clinical trials and of receiver operator characteristic (ROC) curves. Only such approaches can determine whether use of

CKMB alone, or in combination with other cardiac proteins, can effectively aid in diagnosing myocardial infarction. Performance guidelines developed by the American Thyroid Association[1] for thyroid-stimulating hormone are effectively challenging our views on the value of the clinical information provided by first-, second-, and third-generation immunoassays.

Information Management

Altschuler[2] tells us that the practice of medicine consists largely of information management, that health professions do not always use objective data appropriately and, when data are not used appropriately, care is often poorer and costs higher than they would otherwise be.

In analyzing mistakes occurring in laboratory testing, Boone and Ross[3] showed that only 7% were due to analytical problems, while 93% were due to pre- and post-analytical errors. However, recent advances in information technology have significantly improved the areas of sample identification and data streams, while robotics are advancing rapidly in improving control of pre-analytical variables and expert systems are emerging to deal with post-analytical variables.

The American Society for Testing and Materials (ASTM) has developed a standard (E 1466-92) for the form, placement and content of bar code labels on specimen tubes that are used on clinical analyzers. By specifying the use of Code 39 with standard check digit or code 128 in place of older, error-prone symbologies, unparalleled levels of reliability in sample identification are now achievable in clinical laboratories. ASTM standard E 1394-91 covers the transfer of information between clinical instruments and computer systems. If widely adopted by manufacturers of laboratory information systems (LIS) and clinical analyzers, the standard would obviate the need for developing LIS-specific interfaces and would provide a true '"plug and play" environment. An "interpretation box," such as provided by Dawning Technologies, can yield the same reliability even if a manufacturer's data stream is not compatible with E 1394-91.

While information technology is available to dramatically improve the reliability of sample identification and data streams, it is found in less than half of U.S. hospitals. Far fewer hospitals have moved to the next stage, the electronic interchange of patient demographics, orders and results for laboratory tests, imaging studies, etc., among multiple sites. This can be achieved by using a global peer to-peer data transfer standard such as Health Level Seven or by using smart interfaces that adapt to various protocols and legacy (i.e., existing) systems. Medical imaging has taken the lead in this area and, through the use of customized digital imaging systems, captures images from multiple types of diagnostic equipment and display and print them on file anywhere in the network, allows the radiologist to view images and provide consultation from home or office, and provides greater coverage and greater utilization of human resources. The implications for the clinical laboratory are obvious.

The significant unmet need in clinical laboratories is automating sample preparation and distribution. As very large and very expensive robotic systems arrive to meet this need, a parallel need arises for worldwide standards to facilitate optimizing, interfacing and integrating clinical analyzers. The Clinical Testing Automation Standards Steering Committee, formed in 1994 by representatives from clinical laboratories and

manufacturers, has embarked on a multi-year process to develop standards for laboratory automation.

Expert systems, also known as decision-support systems, are now seen with increasing frequency in industrial settings[4] but, disappointingly, are rarely encountered in clinical laboratories. Focused on an appropriate problem, the rule-based, decision tree-based or case-based reasoning expert systems can be powerful tools in managing laboratory processes, in troubleshooting clinical analyzers in analyzing laboratory data and in diagnosing illness. The reasons why expert systems seem to fail is either that technology integration into an already turbulent environment is difficult or that the system is being grafted onto an existing, outmoded workflow, or that the system is not continually "refreshed" with new knowledge.

Analytical Goals and Patient Outcomes

Typical analytical goals (reproducibility, assay linearity, sensitivity, accuracy, correlation, etc.) are essential in developing an assay but alone may not be sufficient to deliver a product with the requisitive diagnostic sensitivity, specificity and efficiency. This will be illustrated using cardiac proteins and thyroid function tests as examples of how to improve the diagnostic information provided by these tests and, in turn, to positively impact patient outcomes.

Well designed and executed clinical trials are an essential first step; in assessing an assay for free thyroxine (FT4), for example, diagnostic performance must be assessed in all patient groups usually encountered, including patients with non-thyroidal illness and extreme binding-protein anomalies.[5] The second essential step is to analyze the clinical data so collected using ROC plots and predictive value theory.

ROC plots[6] provide a graphical description of test performance representing the relationship between the true-positive fraction (sensitivity) and the false-positive fraction (specificity). Clinical accuracy, in terms of sensitivity and specificity, is displayed for the entire spectrum of decision levels. In understanding the value of diagnostic information provided by various cardiac protein assays, ROC plots have been used to optimize clinical performance.

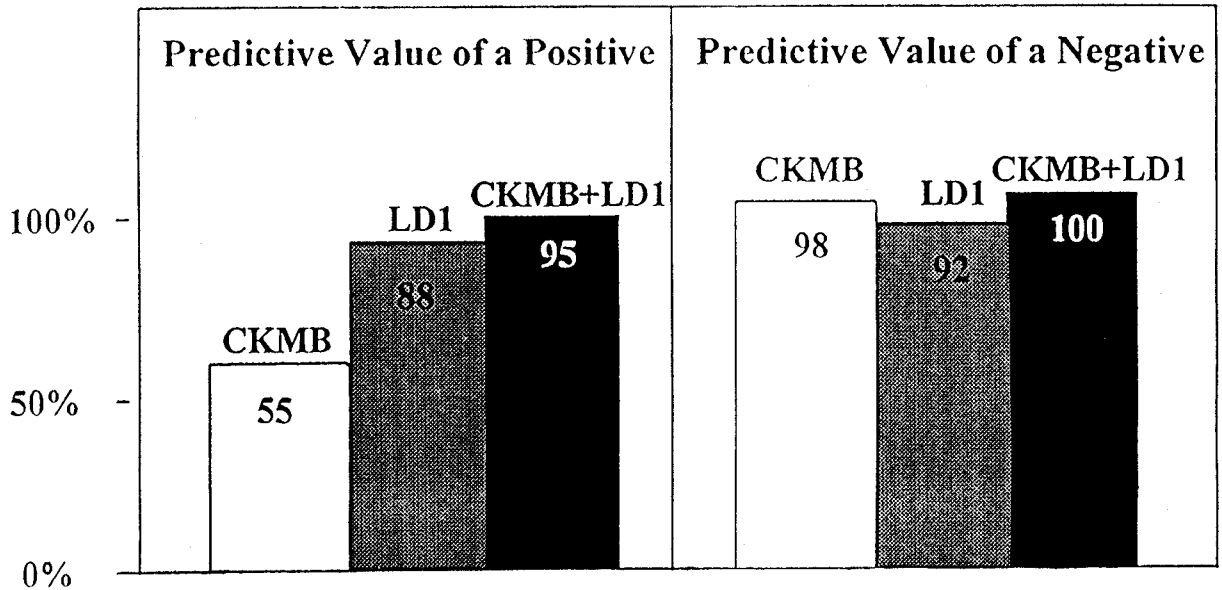
The Power of Receiver Operator Characteristics (ROC) Plots

- ROC plots allow direct comparison of assays using equivalent or different units
- ROC plots provide a means of comparing various reporting units for a given assay
- ROC plots allow direct comparison of clinical performance between assay having significant biases
- ROC plots allow optimization of clinical performance

Ideally, while we want to use a single, powerful test to help rule in or rule out a disease state, applying predictive value theory to the clinical trial data demonstrates the virtual necessity of some form of combination testing. The commonly used cardiac protein tests (myoglobin, CKMB, troponin I (cTnI), troponin T (cTnT) and lactate dehydrogenase isoenzyme 1 (LD1)) all demonstrate distinct temporal rise and fall curves. For example, applying predictive value theory demonstrates the diagnostic performance of CKMB testing alone or in combination with LD1 testing (Table 1).

Similarly, Wu and colleagues[7] have used

Effect of Combination Testing on Predictive Values



The value of using LD1 beomes apparent when the predictive value of the combination, CKMB+LD1, is compared to each test individually. The chart above shows that the predictive value of a positive combination test (CKMB and LD1 both positive) is greater than either test alone. This means that when both CKMB and LD1 are positive at any time during the sampling period, the probability that the patient has had an MI is 95%. The predictive value of a negative for the combination is also improved to 100% versus either test alone.

Table 1. Effect of combination testing on predictive values.

ROC plots to show that the diagnostic information provided by CKMB testing is superior to that provided by CTnT from 6 to 24 hours after acute myocardial infarction (AMI), that the information provided by both tests is equivalent from 24 to 48 hours after AMI and that cTnT provides more information from 48 to 96 hours after AMI. They also conclude that CKMB is more specific for diagnosing AMI and propose that cTnT is more sensitive to myocardial injury. These findings appear to indicate that combination testing of CKMB and cTnT yields optimal diagnostic information.

In thyroid function testing, the quest for improved diagnostic information has been aided by the development of the American Thyroid Association's performance guidelines for TSH.[1,8,9] These guidelines are perhaps the most definitive consensus specifications available for an analyte, and particularly challenge the assay developer with regard to assay reproducibility at subnormal TSH levels. Spencer[8,9] has popularized the concept of first-, second- and third-generation TSH assays, based on functional sensitivity performance.

Functional Sensitivity of TSH Assays

The lowest TSH concentration that achieves an interassay CV of 20%:

Generation	Functional Sensitivity Limit
First (RIA)	1.0 - 2.0 mIU/L
Second (Immunometric)	0.1 - 0.2 mIU/L
Third (Immunometric)	0.01 - 0.02 mIU/L

Functional sensitivity in clinical practice is usually suboptimal in comparison with that reported by the manufacturer.

By combining data from ROC plots and by assessing functional sensitivity, various authors who have studied newer TSH assays raise two intriguing points about the quality (and cost) of diagnostic information provided by these assays.[10,11]

- Second generation TSH assays with appropriate functional sensitivity can match the diagnostic information provided by third-generation assays, but at lower cost.

- TSH values alone, even when obtained from third-generation assays, may not always indicate whether a patient is hyperthyroid; thus, combination testing (TSH and FT4) may be an appropriate strategy to maximize diagnostic information.

Postscript

The current focus on managing diagnostic information, whether through using information technology to minimize pre- and post- analytical variables or developing more powerful assays that maximize diagnostic information, is providing major benefits in laboratory medicine. Five areas of information management, however are suggested that are expected to provide ample benefits for laboratorians:

- driving the benefits of bar-coded sample identification and laboratory information systems into most clinical laboratories

- developing systems for peer-to-peer information transfer that combine and display laboratory data, imaging studies, etc., across multiple geographic sites

- encouraging the use of decision-

support tools to improve laboratory productivity and to maximize the informational content of laboratory data

- seeking a consensus on the design of clinical trials and a uniform manner of expressing the resulting performance data

- achieving a consensus on the coherent use of cardiac proteins in diagnosing AMI.

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