A Success Story for the Biomedical Model: Improved Understanding of Pathophysiologic Processes Coupled with Improved Analytical Procedures

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Abstract: As we attempt to address the question, "How can we improve laboratory testing," it is appropriate to divide the issue and to refine the question. In this writing, I suggest that "testing" from the analytical aspect is quite excellent. Those who are concerned with improvement are aware that test selection and utilization of the data are less optimal. As we consider the subject, it is appropriate to avoid generalizations about "all laboratory testing." That testing which is pathophysiologically based leads to better physician utilization than less clearly defined statistically validated testing. Examples are presented contrasting uric acid and cholesterol with thyroid function testing and measures of myocardial ischemia. Future directions for improving the contribution of laboratory testing are dependent upon continuing advances of pathophysiological understanding. This understanding contributes to the expanding the "evidence-based medicine" database, applying this to the individual longitudinal electronic medical record, and incorporating of artificial intelligence systems to empower physicians. Supporting research should augment the already existing direction of these efforts which are clearly established.

Introduction

The traditional view of the biomedical model holds that if we perform research so that we understand the normal physiology of the human body, and the disturbances associated with pathologic disease states, and we can measure those disturbances, then we can define disease. Along the lines of this model, we have achieved substantial success. Many disease states are definable in terms of precise and accurate analytical measurements performed in the clinical laboratory. This combination should lead to appropriate and successful application of the biomedical sciences to human disease. It is widely held that clinical laboratory testing is often inappropriately utilized and that the data are misinterpreted or ignored. Generalizations, however, may not be appropriate. Testing that reflects integration into pathophysiologic insights may be less of a problem than testing requiring complex statistical validation.

This conference is convened to address clinical laboratory testing and the utilization of the resultant data. The goal is clearly to determine directions for research study to improve upon the current state of affairs. There is a sense that there is too much of the wrong testing and too little of the right testing with inappropriate response to the data. In short, the current state of affairs is unsatisfactory. This response will be on two

levels: the first contrasts two categories of testing in terms of usefulness, clinical applications, success and failure, and proposes consideration which may reflect on how and why tests are used and abused.

On another level, I shall address the limits of physician practice more globally and cite the growing force of "evidence-based medicine" in conjunction with the approaching development of the electronic medical record. Ultimately, we look toward these advances in conjunction with the development of expert systems. When these are linked, we anticipate routine, transparent incorporation of evidence-based medicine to better empower physicians currently overwhelmed by the enormous body of medical knowledge.

Testing Categories

I propose to reclassify clinical laboratory testing into two categories for this discussion, *"Markers"* and *"Integral Component Elements" (ICE)*. This distinction is based on a contrast and comparison of characteristics of the two groups. (Table 1) The former is represented by cholesterol and its association with atherosclerosis, and uric acid with its association with gout. In this sense, it is recognized as contributory, not definitive testing. The *"ICE"* category will be represented in this discussion by measuring of thyrotropin (TSH) and free thyroxine (FT_4) in assessment of thyroid function and creatine kinase-MB isoenzyme (CK-MB) and cardiac troponin I (cTnI) in assessment of ischemic myocardial injury. It is proposed that much of the discussion about the uncertainty of medical relevance goals for analytical testing, reference range debates, issues of predictive value theory applied to clinical medicine, and uncertainty with regard to appropriate utilization relate to the category of "markers." In contrast, there are a growing number of clinical laboratory tests which fit the category of "ICE.". My intent is to use this term as reflecting tests which produce definitive diagnostic evidence. In common parlance, they "ICE" the diagnosis. With these, there is a basis for consensus and appropriate application of medical laboratory testing including assessment of outcomes.

"Markers" are levels of analytes which are associated with disease states based on values observed in populations characterized as diseased or non-diseased. Often, the elements used in the separation of diseased from well individuals are poorly defined because we lack the understanding of the fundamental pathophysiology of the disease or because of the heterogeneity or complexity of those processes. Common properties of this group are the focus on a solitary analytical value, the value is addressed in isolation, little focus on the individual's own reference range in contrast with a population based determination of reference range, and poor linkage between the analyte and the disease state in terms of pathophysiologic understanding. Often this is a labored association. Clinicians find the association vague, producing weak compliance with testing norms for these states. In this group, the application of decision support and predictive value theory is widely applied and essential. The association is statistical.

In contrast, the *"Integral Component Elements" (ICE)* are thoroughly understood in their essential relation to the pathophysiologic state which is addressed. They are commonly interpreted in light of serial trending values rather than in solitary determinations; they are assessed in combination with analytes related by integration into the pathophysiologic understanding; and the individual's own reference range, if defined, plays a critical role in assessment of the differentiation of health versus evolving disease. As a result, they are fundamental to assessing the outcome

associated with the disease process. Physicians intuitively find these analytes appealing because of the relation to the overall process producing better compliance with good medical practice. Bayesian rules, advocated for widespread use by some, do not apply when test results define the very entity being sought. Unfortunately, as reported by Kassirer "[1]... in many instances, Bayesian reasoning and the fundamentals of decision analysis have been incorporated into the curriculum. Yet these methods have limited scope. Bayes' rule does not explain, for example, which diagnoses or how many should be considered or discarded in a given situation, which of many possible tests is likely to have the greatest diagnostic value, or how to incorporate notions of causality into the diagnostic process. And although the principles of decision analysis are worth learning, teaching students how to apply this formal approach has been difficult. In addition, the technique is simply too cumbersome for routine clinical use."[1] While appealing, there is often insufficient information to apply Bayes' rule. We generally do not know the prior probability.[2]

The examples of uric acid in association with gout and cholesterol in association with atherosclerosis are considered in relation to the "MARKER" category. Measurement of these values in isolation provides a weak association with related diseases. Physicians often apply the tests inappropriately and interpret them inappropriately.

In the case of uric acid, the definition of hyperuricemia most commonly applied is a statistical one based on a mean and two standard deviations, reflecting the findings in a randomly chosen population of normal, healthy individuals.[3] However, "the factor(s) responsible for the formation of monosodium crystals in any individual are simply not known ..."[3] Physicians know that "the risk of developing gout increases with increasing hyperuricaemia, but the rise is not proportional and there is no point at which gout is inevitable."[4] It is no wonder that physicians seem to show a lack of respect for this type of laboratory data.

In the case of hypercholesterolemia, the statistical distribution of the "normal range" prevailed for many years, with the result that inappropriately high levels were ignored. In spite of aggressive attempts to now re-educate the physician community, compliance among physicians with regard to dealing with elevated cholesterol measurements is disappointing.[5] This may possibly be explained by continuing debates in the literature which indicate the large differences in absolute mortality from coronary heart disease at a given cholesterol level. It is acknowledged that diet, among other factors, significantly alters outcomes associated with the impact of a given cholesterol level. Physicians recognize that there is a multifactorial process involved and that the underlying pathophysiology remains a subject of debate.[6] Physicians recognize that hypercholesterolemia is a factor; however, given the continuing debate in the literature with regard to the various lipid analytes, it may well be that physicians do not respond as uniformly as the experts desire.[7,8] These observations are not presented to attempt to contradict the significance of lipid abnormality, but rather to identify the confusion which is created in the minds of practicing physicians. It is unlikely that the widespread application of predictive value theory on individual laboratory reports will change this behavior. However, the incorporation of repeated electronic reminders to physicians with specific suggested interventions suggested may be effective in achieving the stated response.[9]

By contrast, as understanding of the pathophysiology of thyroid function and the

acute ischemic coronary process evolves, the application of newer analytes with improved analytical methods permits optimal differentiation of health and disease including prognosis. We now know that the remarkable and successful adoption of the recommendations[10] for thyroid function testing which include thyrotropin (TSH) and free thyroxine (FT_4) measurement is based on the inherent stability of the physiologic relationships of these two analytes.[11] We understand the physiology of thyroid function and the pathophysiologic states which distort this. The analytical measurements are remarkably precise and reproducible, permitting their application in clinical medicine. The reference range for the individual patient is defined by their own "set point." With serial sampling, the data corroborate each other, establishing either the presence of intact physiology or the pathophysiologic abnormalities which characterize a disease state. Indeed, the application of predictive value theory is inappropriate in this setting in that the analyte levels determine the definition of the disease. For example, it is inappropriate to refer to the sensitivity of the TSH measurement for primary hypothyroidism since the TSH must be elevated to make this diagnosis. Indeed, the growing understanding of the pathophysiologic states permits the prediction of outcomes and the measurement of the analyte, TSH, represents a surrogate test which can predict the outcome of atrial fibrillation in the elderly, if untreated.[12] This is a remarkable contrast to the previous use of the laboratory with analytes, such as the uric acid or cholesterol.

A further example of the "ICE" category is now available with the myocardial markers of ischemic cardiac events.[13-15] Progressively, in recent years, we have learned to measure serial samples of CK-MB by ever more precise assays[13] followed by the cardiac troponin T,[14] and now, the completely cardiospecific marker, cardiac troponin I.[15,16] These permit the definition of myocardial injury as characterized by serial elevation and fall of these markers in association with clinically observed events which permit the foreknowledge of prognosis based on the finding of serial elevation of these analytes. They not only predict short term prognosis associated with an acute myocardial event, but in addition, subsequent cardiac mortality over a two-year period.[13]

The relevance of these distinctions to analytical goals for assay methods is self-evident. The methods must be precise and truly define the elements of the pathophysiologic process required. In turn, we have achieved such goals for both thyroid and cardiac testing applications, and these are being rapidly adopted by physicians with appropriate systematic incorporation into the practice of medicine.[10,17] Indeed, failure of physicians to apply analytical testing along these lines will predictably result in increased exposure to malpractice suits because they represent quality standards in medicine.

Improving Laboratory Test Utilization

Frequently, discussions are held relating to the inadequacy of physician utilization of laboratory testing, and the lack of understanding of physicians with regard to the sensitivity and specificity of testing. In short, there is concern with the standards of testing. This leads to assessment of the analytical performance of the laboratory, and further anxieties relating to the analytical process. Rather, the effort to improve "laboratory testing" must relate to the prior steps involved in the sequence and selection of laboratory probes and the appropriate follow-up response to the analytical data, including the interpretation and physician response. The

thesis of this paper holds that physicians will respond to meaningful laboratory testing where the association with disease is conforms to the optimal goal of the biomedical model, that is, the understanding of disease with subsequent intervention.

In the daily routine of medicine, no physician, regardless of level of expertise or training, can call upon and truly master all of the relevant knowledge appropriate to daily problem solving. This must be incorporated into the extensive variability associated with individual patient care including such considerations as age, sex, concurrent medical conditions, medications, and other variables. Consequently, laboratory data reporting reference ranges for well populations are inherently limited and not sufficient.

Evidence-Based Medicine and Expert Systems: Laboratory Implications

Advocates of evidence-based medicine appropriately argue that individual patient evaluation and medical decision making should be based on evidence tailored to the individual. The term "evidence-based medicine" was coined at McMaster Medical School in Canada in the 1980s to label this clinical learning strategy, which people at the school had been developing for over a decade.[18] Four steps are described in evidence-based medicine: 1) Setting the question, 2) Finding the evidence, 3) Appraising the evidence, and 4) Acting on the evidence. This is a growing area which will impact the practice of medicine extensively. The databases are expanding with electronically accessible avenues. The case is persuasive and further research expansion of the concept is needed.[19] Indeed, a joint publishing venture between the British Medical Journal and the American College of Physicians will be launching a new journal based on this concept.[20] Fundamentally, in order to take "evidence-based medicine" beyond the anecdotal report in the literature, we must link this database to the real-time longitudinal electronic medical record with sentinel events triggered by the entry of key laboratory data, pharmacy orders, lists of clinical problems incorporated in the electronic medical record, ongoing addition of the working diagnosis and other components.[21] These sentinels must activate inquiry into the evidence-based electronic database and use sophisticated expert systems.[22] They then will selectively present considerations to the physician for definitive response.

Future Needs

In attempting to cope with the increase in medical knowledge, the profession has explored specialization and sub-specialization. This strategy is successful in one sense, but a failure in the larger sense. As we return to an emphasis on the generalist in medicine, we have no choice but to empower the physician in a new way. Three elements are required to achieve the enhancement described: First, evidence-based medicine must be strengthened and the useable database expanded. This includes further development of pathophysiological understanding of disease. Second, the electronic medical record, a true longitudinal history of the individual, must become a reality with real-time current update of acute episodes. Third, truly sophisticated expert systems must integrate the first two so as to present relative selective considerations to an empowered physician. The technology exists and is not a limiting factor. We, as a society, can achieve this and we have no alternative if long sought goals are to be attained, and in an affordable manner.

Our research direction is clear. The analytical product of the laboratory is satisfactory; in fact, in most cases, it is

exemplary in both precision and accuracy. Now, there is need to improve physician utilization. Augmentation of existing research directions is warranted. If we do this, we will advance the goal of curing or caring.

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