The Impact of Laboratory Practice on Patient Outcomes

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We've been warming up with the previous topics. Now we're going to see where the "rubber meets the road". We're going to talk about the impact of laboratory practice on patient outcomes. I'm here to tell you that laboratory practice does have an impact on patient outcomes, and I hope you'll agree after I am finished.

Although I think I'm going to raise more questions today than I answer, I specifically want to answer these 5 questions:

1. What is an outcome?

2. Does laboratory testing have an impact on patient outcomes? I think it does, at least in certain situations.

3. Does *all* laboratory testing have an impact on outcomes? I think we'll find the answer to this is not at all clear.

4. Who cares?

5. And most importantly, for us in academia at least, what is needed to perform outcomes research in clinical laboratory practice?

First of all, what's an outcome? We've already heard that it's hard to define. I like the definition that David Eddy, a health policy and management consultant, uses: An outcome is "something that happens."

Let us examine some examples of outcomes. We can look at the length of the patient's stay in the hospital. This is a crude clinical outcome, with the assumption being that if the patient gets out of the hospital quickly, this is a good clinical outcome. If the length of stay is long, maybe that's not such a good clinical outcome. Length of stay could also be considered a patient outcome. Patients are usually happier if they get out of the hospital quicker. Of course, there's one way to get out of the hospital real quick and that's if you die.

Cost of care is a financial outcome that seems to be driving the health-care system more and more. The assumption here is that care is better if it costs less to take care of the patient, but you still get a good outcome. If care is expensive, it may be due to complications or unnecessary procedures. A big bill is often related to a longer length of stay.

Complication rates are another way of looking at clinical outcomes and quality. Notice that, as we move down this list of outcomes measures, we are moving from the older concepts of quality assurance to a total quality management approach to defining quality and outcomes. We can look at complications, such as postoperative infections or people falling out of bed in the hospital. But we really need to focus on the clinical conditions of the patients. Has the patient's condition improved? Ultimately, I think we need to look at the condition of the

population. Is the health of the whole population improving? We need to get away from focusing on individual episodes of care, the practice of individual physicians, or even the health of the individual patient. We need to focus on population health.

Let's look further at some patient outcomes. A rather crude measure of patient outcome is death. You can look at the signs and symptoms with which the patient presents and how they improve over time as the result of treatment. We may even look at quality of life issues. How long does it take patients to get back to a certain level of performance after they've had an episode of care or they've been hospitalized? How long does it take them to get out of bed? How long before they get back to performing daily activities? How long before they get back to a full schedule of activities? How long before they resume playing tennis or skiing? Those activities are very important to patients. Ultimately, we need to worry about the satisfaction of patients. How do they feel about their care? The final step in this focus on patient satisfaction is the idea that patients should really be delighted with their medical care. They should feel better after interfacing with the health-care system than they did before. This is a concept I've heard articulated very clearly by Leland Kaiser, one of America's leading futurists. We should be asking our patients the same kinds of questions that the hotel asks us or that Disneyland asks us. Patients should feel better because they interacted with the health-care system. There is a progression from the older concept of quality assurance, where we worried a lot about death rates from procedures such as open-heart surgery, to the concept of total quality management, where the emphasis is on patient delight.

What are the challenges in outcomes research, particularly as it relates to laboratory testing? The first challenge is to study conditions where you can actually measure differences in clinical outcomes. You need to have a medical condition with treatment alternatives that result in different clinical outcomes. Then you can ask the question: Are the different outcomes related to different treatments? Finally, you can ask the question: Does laboratory testing influence the choice of treatments? It is a rather daunting challenge.

Complicating all of this are the well-known test performance characteristics and how they influence the predictive value of a test. Figure 1 depicts the well-known 2-by-2 matrix for a test that can either be positive or negative; the patient can either have a disease or not have a disease; and there are 4 possible combinations of test results and disease status. Outcomes research investigates the consequences of each of those possibilities in terms of the costs and benefits. Having an impact on all of this are the test performance characteristics: sensitivity (positivity in disease); specificity (negativity in health); and, of course, the predictive value of a positive or negative test. Predictive value is tremendously influenced not just by sensitivity and specificity, but also by the prevalence of the disease. This relates to what Dr. Reed was talking about earlier today. Depending on your patient population (age, socioeconomic status, ethnic make-up), you may start with a different disease prevalence. For example, the predictive value of a test in the office laboratory of a physician who sees primarily ambulatory patients is going to be different than the predictive value of the same test performed at the academic medical center, because the disease prevalence will be

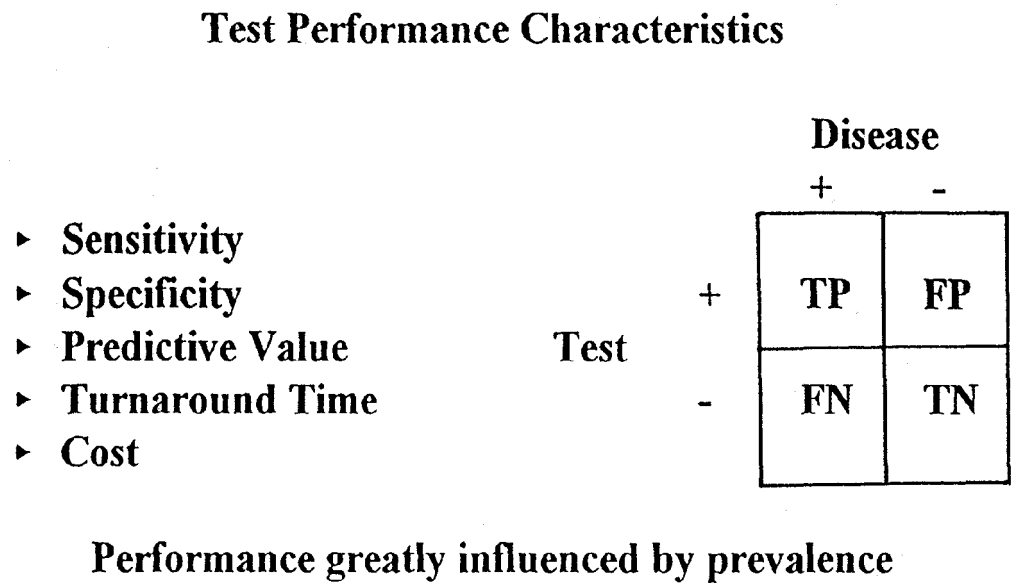

Figure 1. Test performance characteristics influenced by the prevalence of disease.

different in the two distinctly different patient populations.

In addition to these fundamental characteristics of a test, we must consider turnaround time. Whether you can obtain the test result rapidly or not influences whether that test can have an impact on patient care. And of course, there is the cost. Is the cost of the test justified when you look at the outcome?

If you look at the 4 boxes in the matrix, you can think of various scenarios. For example, if you're screening for a disease that has catastrophic consequences if it's not diagnosed early, then you are willing to endure a few false positives to ensure that you pick up all of the true positives. Phenylketonuria (PKU) is an example of such a disease. The concerns are different when screening for a chronic condition for which we don't have a very good therapy, such as multiple sclerosis. It's questionable whether it really helps to know whether the patient has the disease or not. You probably want to have a test that gives you very few false positives. You are less concerned about false negatives because there's not much of a consequence. As you can see, test performance characteristics complicate the whole issue of laboratory testing outcomes research.

If I haven't convinced you yet, I want to emphasize that patient outcomes research and research on the impact of clinical laboratory testing on patient outcomes is difficult work. However, there are a lot of examples in the literature that demonstrate that laboratory practice does, in fact, have an impact on patient outcomes. I'm going to talk about the following few examples: pre-

natal and newborn screening, therapeutic drug monitoring and pharmacokinetics consultation, prostate specific antigen testing, chest pain management, and blood component therapy.

This slide summarizes the cost/benefit analysis of PKU screening in Japan. The Japanese cost/benefit ratio was about 1/2.5. The cost of the testing process was $12,577 per detected PKU case and the cost-avoidance was $31,444 per case,[1] a very favorable cost/benefit ratio. You saw similar data from Dr. Laessig in Wisconsin. We can change certain variables within a system that will change the cost/benefit ratio. For example, Coody[2] showed the impact of cost-containment measures on the timing of newborn PKU screening. There was pressure to decrease the length of stay after parturition, particularly with babies that were born by normal vaginal delivery. Length of stay in the hospital was frequently less than 24 hours. More than 30% of the babies were being tested for PKU less than 24 hours after birth. When PKU testing takes place between 12 and 24 hours of age, there is at least a 10% failure rate to detect PKU. So here you have a relatively useful screening test for congenital disease, for which the cost benefit ratio can increase if you are not careful about controlling the conditions of administration.

Screening for invasive cervical cancer reduces the incidence and mortality due to cervical cancer. A study published by Dr. Eddy, whom I quoted earlier, compared the lifetime risk per 10,000 patients between unscreened women and women who were subjected to Pap Smear screening every 3 years from age 22 to age 65.[3] The incidence of invasive cervical carcinoma in the unscreened population is about 250 and is approximately 35 in the screened population. There is about a 90% reduction in the incidence of this disease. A similar reduction occurs in the death rate, which in the unscreened population is about 118 per 10,000 and about 11 in the screened population. Clearly, Pap smear screening is a very effective screening strategy and certainly has a very positive outcome on health.

Let us now look at a few examples of therapeutic drug monitoring. Witte, in a recent article in *Clinical Chemistry*, showed the relationship between serum amino-glycoside levels and death due to gram negative sepsis.[4] As the peak concentration of amino-glycoside increases, mortality due to gram negative sepsis decreases. Interestingly, when you ask most people why they monitor drug levels for amino-glycosides, they say "to avoid kidney failure or loss of hearing." In fact, more people probably die from under-dosing amino-glycosides than they do from over-dosing. Can laboratory practice have an impact on the success of animo-glycoside therapy? The answer is yes. Destache published a cost-benefit analysis of a pharmacokinetics consultation service for patients receiving amino-glycosides.[5] The control population was treated by the attending physicians as they normally treated their patients. The study group patients were subjected to vigorous and aggressive pharmacokinetics consultation. The latter group showed a definite decrease in the length of stay, the amount of time that the patients were febrile, and the direct costs. The shortened length of stay was probably due to fewer complications, and the cost of care decreased by 50%. Clearly, the aggressive pharmacokinetics intervention in the dosing of amino-glycosides had an impact on patient outcome.

Dr. Winkelman and his colleagues in Boston looked at Medicare claims data to monitor clinical outcomes following several different laboratory tests. This particular study focused on prothrombin time (PT) testing.[6] These workers screened data from about 14,000 Medicare patients. They looked for patients who had a PT and then looked for downstream events occurring within 6 days that they could also pick up from the Medicare claims. If the PT test was done in a laboratory that did less than 40 PT tests per month, the risk of hospitalization due to stroke or myocardial infarction was increased 2-fold and 3-fold, respectively. If the PT test was done in a laboratory different from the preceding PT test, there was also increased risk of hospitalization due to stroke or myocardial infarction (MI). You can't definitively conclude that the hospitalization was related to the PT testing circumstance. But, it's a little suspicious in view of the very large number of patients reviewed.

What about Prostatic Specific Antigen (PSA)? Brawer and colleagues used test sensitivity, specificity, and actuarial models to estimate the impact of adding the PSA test to the digital rectal exam over a 10-year period. I don't know if these data actually have been published, but I heard them at a meeting a few weeks ago. They concluded that it resulted in a shift to detection at an earlier stage of carcinoma, longer survival, and a decreased number of terminal care patients. All of these benefits would be achieved with a minimal increase in the per member per month cost, from $1.24 to $1.50.[7] This is my slide that reminds me to caution you. When it comes to analyzing outcomes data, it's buyer beware. Everybody that does outcomes research today has a bias and probably always will. What is the potential bias here? One of the co-authors of this work happens to work for Hybritech, which manufactures the PSA tests. I'm not trying to say that this fact invalidates the results. I'm just saying that when you interpret outcomes results, you have to pay attention to these kinds of biases, because all outcomes research requires making a lot of assumptions. Such research also requires a lot of statistical analysis and a lot of data manipulation. I'm convinced that one can come up with almost any result they want by manipulating these parameters. You really have to be careful. You have to analyze not just the data but from where the data come. Which axe do the authors have to grind? What do they have to benefit? From what I know about PSA testing--I wouldn't necessarily agree with these conclusions. Maybe that will be a point for some discussion later.

We have a very active group in chest pain management at the Medical College of Virginia. In fact, some of you may have seen us on national TV recently. We had a short segment on the CBS network sometime in the last few weeks that reported on our chest pain management program. It's a multi-disciplinary program that involves clinicians, laboratorians, and radiologists. It's a big effort. Among other things, we've shown that some improvements in chest pain management are related to laboratory practice.[8] There are two particular groups of patients for whom we find aggressive laboratory testing very helpful: One is the group that presents with a non-diagnostic EKG and relatively low clinical suspicion but who eventually rule in with acute MI. The second group includes those who present with a very good clinical picture of acute MI but eventually rule out. Among patients who eventually rule in to actually have MI, a very

aggressive management protocol in the form of a critical pathway that defines every single management step, including laboratory testing, lowers the length of stay from 4.7 to 3.3 days. The total cost of care for these patients decreased from $7,824 to $6,562. Interestingly, the lab costs actually decreased. Among the historical control patients, where the laboratory testing for acute MI included batch testing for creatine kinase iso-enzymes and LDH iso-enzymes, the tests were only run once or twice a day. With the new protocol, we employed 24-hour-a-day, immediately available, mass assays for CKMB and myoglobin. If you look at those patients who actually have acute MI, the mean time to diagnosis now is 3 hours instead of 20 hours with the old laboratory strategy. Patients who need percutaneous transluminal coronary angioplasty (PTCA) get treatment faster, and more of them get treated. With the old protocol only 5 out of 10 patients who needed PTCA got treated, whereas with the new protocol 6 out of 8 are treated. No patients were treated within 24 hours under the old protocol, but 3 patients are treated within 24 hours with the new protocol. These are very small numbers, and obviously we cannot draw a lot of conclusions. We believe these results will hold up with additional patients accrued. Dr. Phil Anderson, who was the lead lab person in these studies, is here at this meeting today. You can find the details of this study at the poster area.

An even larger impact, in terms of dollars and cents, comes from the patients who eventually rule out for acute MI. Their length of stay decreased from 4.4 to 3 days. Total cost of care was reduced from $7,449 to $5,965. The variable cost decreased by about 25%. Again, even the laboratory costs were less. In both cases, the decreased lab cost probably relates to a decreased length of stay. If patients are not in the hospital, you can't run lab tests on them. There are about 280 or so patients in this group. The cost savings in our institution was more than $1 million dollars. If you extrapolate this nationwide, you could come up with more than $4 billion dollars annually in potential savings. I think that the rapid availability of markers for MI is certainly cost-effective and helpful to patient management.

The final example I would like to look at is in the improvement of platelet therapy as the result of changes in laboratory practice. This study was published in *Transfusion* by Mark Simpson a few years ago.[9] It's based primarily on his experience at Walter Reed Army Medical Center where I did my residency in pathology. There were mainly three interventions: First was the development of very specific criteria for when to transfuse patients--specific platelet count thresholds, and clinical conditions that would warrant transfusions. Second, there was concurrent review of the transfusion orders. When the platelet transfusion orders came in, a blood bank physician immediately evaluated that order and evaluated the patient. Third, the blood bank physician consulted with the clinician before deciding whether or not the patient would be transfused. This had a tremendous impact on the platelet ordering and utilization. When the study began, about 58% of the platelet transfusion requests were actually denied by the blood bank physician because they weren't indicated. After the program operated a few years, that number dropped to about 8%. The physicians became much more skillful and much more thoughtful about their platelet requests. A 56% reduction in platelet usage was realized.

That's not just a decreased cost. It meant that when patients really needed platelets, there were platelets in the blood bank to give them. The old system was plagued by the fact that it was first come, first served. It was a 7-11 Store approach to blood banking. If somebody asked for it, and you had it, you gave it to them. Often you would have someone on chemotherapy who was having a bleeding episode, and you had no platelets. This system helped manage the platelet inventory and it really benefitted patient care from our perspective. Unfortunately, we really don't know the ultimate patient outcomes, but there was no perceived degradation in quality of care. This lack of objective patient outcomes data points out the deficiency we have in many published outcomes studies.

These are my success stories. Let's look at the other side of the coin. Clearly some, and one might even say, a lot of laboratory testing provides very little patient benefit. I've often had that fact pointed out to me by an administrator who is looking to downsize my lab. Some examples of ineffective testing are pre-op screening in general and pre-op coagulation studies in particular. There is no substitute and no better test to evaluate a patient's potential to bleed during surgery than a good medical history and physical examination. Routine screening tests for coagulation disorders in a general population of patients are essentially worthless. Routine utilization of a standard admissions profile is similarly ineffective. Someone mentioned earlier today that when a manufacturer came up with the ability to do 20 tests at a time on one small sample, we suddenly thought good medical care required everybody to get a SMAC-20 when they got admitted to the hospital. Extensive chemical profiling probably generated more false positive results (which had to be resolved) than it prevented bad outcomes.

Improperly collected specimens are another source of low value testing. You can only do good lab work if you have a good specimen. Blood cultures are notorious because they're often collected by non-laboratory personnel who are in a hurry, who don't particularly know what they're doing, and don't particularly have a lot of interest in what they're doing. They don't scrub the patient's arm well, they're sloppy with collecting the blood cultures, or they only draw blood from one site. As a result, you get worthless or even misleading results. The test is only as good as the specimen collection. Another example of specimens that are frequently inadequate is sputum. If you don't have a method for evaluating sputum specimens, then you're going to be culturing a lot of saliva.

Finally, low-yield specimens may be very cost ineffective. Culturing cerebrospinal fluid (CSF) for tuberculosis (TB) almost never yields positive results. Positive specimens almost always have specific findings in the CSF, such as inflammatory cells or protein. Culturing CSF that is negative for cells and protein is almost useless.

Lieu[10] studied the cost-benefit of testing for cystic fibrosis prenatally. The cost of routine screening in all pregnancies in the U.S. would be about $83 million. You could probably save about $12 million by preventing the birth of some children with cystic fibrosis. The net cost would be about $71 million or $1.4 million per unwanted cystic fibrosis birth averted. You hate to put a dollar value on a human life, but these are the kinds of studies that are needed before you start mass screening programs. It is reasonable to ask if this is where we want to

put $1.4 million. From a public policy point of view, there may be better uses for the money.

So who cares about the impact of laboratory testing on patient outcomes? I think patients care. They want to get good care, and they want to pay a reasonable price for it. The payers clearly care, whether they are private or public. Employers care, because they really are the payers to a large extent. Providers care, I think, because more and more providers are being evaluated on the basis of their outcomes. Finally, suppliers care because the way care is prescribed has an impact on how you use medical equipment and supplies.

The scope of outcomes research may vary. It may be very limited. An individual hospital may be worried about individual practice patterns and specific physicians. The focus is to decrease the variation in care--for example, how to get all the orthopedic surgeons to use the same protocol when they do a hip replacement, or to have all the cardiac surgeons use the same protocol when they do a coronary artery by-pass. Simply limiting or decreasing that variation will improve outcomes because members of the care team all have a better understanding of what they're doing.

To really get at the question of understanding whether we're going to improve the outcomes or not, we have to widen the scope of study and include health systems or regional outcome studies. These would include systems like Columbia HCA or Bon Securs. They can pool their data and get a better idea of which treatment protocols work. At the national level, our professional societies are able to develop practice guidelines that then can be adapted at the local level to provide more standardized, effective care.

Let us now consider what is needed for outcomes research. Probably the single biggest need is information systems. We have to learn how to integrate information across the whole spectrum of care, including clinical, demographic, administrative, claims, financial, and survey information. Only then can you begin to answer the question: How satisfied are the patients? One approach is the Central Data Repository, also called a Permanent Patient Record, and a variety of other names, used to capture information (*i.e.*, clinical, financial, demographic, etc.) on patients from birth to death, wherever they may be treated. This will allow us to integrate that information and truly measure outcomes.

We need standard data definitions. We need to standardize the way we code diagnoses and procedures. We need objective measures of outcomes. If you can't measure it, you can't evaluate or manage it. There has to be much better access to the data. Providers and researchers must be able to use and evaluate the data. I think we need practice guidelines to standardize care. Unless you begin to standardize how you treat patients, it's difficult, if not impossible, to evaluate clinical outcomes. We can do data pooling and meta-analysis.

The most successful research approach is going to be programmatic, such as what is being done at the University of Alabama-Birmingham. Their Laboratory and Health Services Research Program is a multi-disciplinary program with five different areas of interest. This is difficult work. We have to bring together clinicians, statisticians, and laboratorians. This is not the kind of research where you go into your laboratory or you sit at your PC and work by yourself.

Who is going to pay for outcomes research? We always look to the

government. Certainly, the Agency for Health Care Policy and Research is a source of funding. Also, there are CDC (we're here today) and NIH. Professional societies have also taken a leadership role. The American Association for Clinical Chemistry has funded several outcomes research studies over the last few years. I think you will see a lot of opportunities with insurers, with health systems and suppliers--especially the people who manufacture the testing kits and equipment. All of these are funding opportunities.

References

1. Hisashige, A. Health Economic Analysis of the Neonatal Screening Program in Japan. *Int J Technol Assess Health Care*. 1994;10:382-391.

2. Coody, D., et al. Early Hospital Discharge and the Timing of Newborn Metabolic Screening. *Clin Pediatr*. 1993;32:463-466.

3. Eddy, DM. Screening for Cervical Cancer. *Ann Intern Med*. 1990;113:214-216.

4. Witte, DL. Measuring Outcomes: Why Now? *Clin Chem*. 1995;41:775-780.

5. Detache, CJ., et al. Impact of a Clinical Pharmacokinetic Service on Patients Treated with Aminoglycosides: A Cost-Benefit Analysis. *TDM*. 1990;12:419-426.

6. Mennemeyer, ST., and Winkelman, JW. Searching for Inaccuracy in Clinical Laboratory Testing Using Medicare Data. *JAMA*. 1993;269:1030-1033.

7. Brawer, et al. Assessing the Cost and Utilization Impact after 10 Years of Serial Testing DRE vs. DRE/Tandem® PSA for Prostate Cancer Using an Actuarial Approach. Univ. of WA. Hybritech (Tandem PSA). Unpublished.

8. Anderson, P., et al. The Costs and Effectiveness of a Rapid Diagnostic and Treatment Protocol for Myocardial Infarction. Medical College of Virginia. Unpublished.

9. Simpson, MB. The Clinical Use of Platelet Preparations. *Transfusion*. 1987;27:192-195.

10. Lieu, TA., et al. The Cost-Effectiveness of Prenatal Carrier Screening for Cystic Fibrosis. *Obstet Gynecol*. 1994;84:903-912.