As clinicians evaluate patients, they first develop problem lists based on the history, physical examination, and basic laboratory studies. Synthesis and analysis result in a differential diagnosis with associated disease probabilities. Experienced clinicians then selectively use diagnostic tests to rule in or rule out these possibilities. For example, in a patient presenting with jaundice, anorexia, fever, and abdominal pain, the relative increases of the serum aminotransferase activity and the serum alkaline phosphatase will help to guide the subsequent evaluation. If the aminotransferase activity is markedly increased, then the subsequent evaluation will be targeted toward identifying an etiology for hepatocellular injury. In contrast, if the alkaline phosphatase is markedly increased, then the evaluation would be targeted toward identifying an etiology for obstructive jaundice. This paper reviews clinical decision making, discusses characteristics of diagnostic tests, and presents examples of how basic clinical information can guide the use of the laboratory in evaluating patients with suspected liver disease.

INDEXING TERMS: sensitivity • specificity • predictive value

The objective of this paper is to discuss how laboratory tests can be used in a rational, cost-effective manner in evaluating patients with liver disease. In this paper, I will first describe an approach to clinical problem solving that illustrates how diagnostic tests are utilized in clinical decision making. Subsequently, I will illustrate how this technique can be used in the evaluation of patients with liver disease. In considering the use of laboratory and diagnostic tests, one must consider the various ways in which studies are used. Tests that are entirely appropriate in one setting may be less appropriate, or even not indicated, in other settings. There are at least three major areas where the laboratory is used. First, much of clinical medicine deals with using laboratory tests in the diagnosis of disease. This area will be the focus of this work. However, tests are also used for other purposes. With an increased emphasis on prevention, more attention is being placed on developing screening tests for detection of early, asymptomatic disease. Finally, laboratory tests are used in management of patients with chronic diseases. This includes monitoring their disease state as well as measuring concentrations of therapeutic agents.

USE OF THE LABORATORY IN DIAGNOSIS OF DISEASE

In considering use of the laboratory in diagnostic evaluations, one should consider the various steps (Table 1) that clinicians use during clinical problem solving. First, the healthcare provider obtains primary data from and about the patient. This includes key information from the history, the physical examination, and basic laboratory tests such as the blood count, glucose, and urinalysis. On the basis of this information, the physician then develops a problem list unique to the patient and clinical setting. Using the problem list, the clinician then develops a differential diagnosis that includes the potential diagnoses most likely to account for the patient’s problems. Experienced clinicians also develop probabilities of disease associated with the likely diagnoses and in doing so develop quantitative estimates for the most likely diagnoses. Then, the clinician will selectively utilize the laboratory and other diagnostic tests in ruling in and (or) ruling out the most likely diagnoses until the probability of a given disease is high enough that the physician feels comfortable treating the disease, or low enough that the physician feels comfortable in not pursuing that diagnosis further.

The probabilities of disease when a clinician feels comfortable in starting treatment or in not pursuing a diagnosis further are referred to as thresholds. The use of thresholds in diagnostic testing has been described well in an article by Pauker and Kassirer [1]. They refer to the test–treatment threshold as the probability of disease where the value of subsequent testing is the same as the
value of treatment. Once the probability of disease exceeds this threshold, then the clinician should consider the disease as "ruled in" and should begin treatment. Similarly, the test–no treatment threshold refers to that probability of disease where the value of testing and no treatment are the same. Thus, when the probability of disease falls below this threshold, then the disease is "ruled out" and the clinician should feel comfortable that the probability of disease is low enough that further evaluation is not necessary.

Thresholds and associated disease probabilities are illustrated in Fig. 1. In this example, the physician's initial differential diagnosis results in an intermediate probability of disease between the thresholds. Subsequently, diagnostic studies A and B are done, which result in the probability of disease remaining in the intermediate range between the thresholds. Then, test C is done, which moves the probability of disease above the test–treatment threshold. After this test, no further testing should be necessary and the clinician would begin treatment.

The test–treatment threshold and the test–no treatment threshold vary with different diseases. There are many variables, such as the costs and consequences of missing a diagnosis, the complications of therapy, and the risk of diagnostic tests, that move these thresholds to higher or lower probabilities. For example, where one suspects liver cancer, the test–treatment threshold would be quite high, given the implications of the diagnosis and therapy. In evaluating possible hepatitis in blood donors, the test–no treatment threshold would be quite low, since a missed diagnosis could result in great risk for the recipient. Thus, in approaching clinical problem solving, the physician uses diagnostic studies to revise the probabilities of diseases so that the diagnoses on the differential diagnosis list move either high enough to justify treatment, or low enough to justify no treatment. As the clinician works to rule in or rule out diagnoses, he or she will use the laboratory and diagnostic testing to revise the probability of disease. By knowing the sensitivity and specificity of a diagnostic study, the clinician is able to go from a pretest probability of disease to a revised posttest probability, which eventually leads to ruling in or ruling out diagnoses.

To appropriately utilize laboratory studies, one should be familiar with the concepts of sensitivity, specificity, and predictive values (also referred to as posttest probabilities). Those who work in the clinical laboratory deal most often with concepts of test sensitivity and specificity—two characteristics that indicate the performance of a diagnostic test in those with and those without a disease. As illustrated in Table 2, sensitivity is the percent of those with the disease who have a positive test. Specificity is the percent of those without a disease who have a normal or negative test. In general, sensitivity and specificity are viewed as constant for a given test and disease; however, it is important that an appropriate spectrum of patients be used in measuring the test's sensitivity and specificity. For example, if sensitivity is determined only in patients with end-stage disease, the test's true sensitivity is likely to be much less when used in a general population of patients with various stages of illness. Similarly, if test specificity is derived in only normal, healthy subjects rather in those who might have the disease, then specificity will also be overstated. These issues, which relate to spectrum and bias in diagnostic testing, are described elsewhere, particularly in a landmark article by Ransohoff and Feinstein [2].

Although the concepts of sensitivity and specificity are critically important to those who work in the clinical laboratory, for clinicians caring for patients the more important issue is the probability that a positive test indicates the disease. This probability is dependent on the test's sensitivity and specificity and on the pretest probability of disease. As shown in Table 2, the positive predictive value indicates the probability that those with a positive test have the disease. The negative predictive value is the percent of those with a negative test who do not have the disease. The marked impact that pretest probability, also referred to as disease prevalence, has on predictive values is illustrated in Tables 3 and 4. For the example in Table 3, when the pretest probability of disease is 10%, a positive test has an associated posttest probability of just 33%. In contrast, a negative test indicates a 99% probability of no disease. In the high pretest

Table 1. Approach to clinical problem solving.
1. Obtain primary data from/about patients: History, physical examination, basic laboratory tests
2. Develop problem list
3. Develop differential diagnoses and probability
4. Selectively utilize the laboratory to rule in or rule out diagnoses

Fig. 1. Disease probability, thresholds, and diagnostic testing.
disease probability situation illustrated in Table 4, a positive test is associated with nearly certain disease, i.e., a posttest disease probability of 98%, whereas a negative result still has a fairly high likelihood of having disease. (In this example, there is a 47% chance that the patient does not have the disease even after the normal test.) These cases illustrate that in situations in which the pretest probability of disease is low, a negative test is quite helpful in excluding the disease, whereas a positive test may result in only an intermediate disease probability. In contrast, when the pretest probability of disease is high, a positive test tends to be confirmatory, whereas a negative test may result in a relatively high posttest probability of disease. The posttest probabilities in Tables 3 and 4 again emphasize the importance of pretest probability on the interpretation of test results.

The examples in Tables 3 and 4 assume that all positive (or negative) test results are equivalent. Obviously, this is not always the case. For example, a very high serum aspartate aminotransferase (AST) concentration in a patient with suspected hepatitis is more convincing than a minimally increased value. Such information, which is described by some as “signal strength,” can also be used in clinical decision making by utilizing likelihood ratios.

Briefly, a likelihood ratio for a diagnostic test is calculated by dividing the percent of patients who have the disease, e.g., hepatitis, and a certain test result, e.g., a serum AST concentration of 500–800 U/L, by the percent of patients who do not have hepatitis but have the same concentration of serum AST activity. Multiplying the likelihood ratio by the pretest odds of disease gives the posttest odds that the disease is present. [The pretest odds of disease is calculated by dividing the pretest disease probability by (100% − pretest probability).] A detailed description of the concepts of likelihood ratios and disease odds, which is beyond the scope of this introductory article, can be found in a chapter by Suchman and Dolan [3].

### APPLICATION TO PATIENTS WITH LIVER DISEASE

As illustrated in Table 1, as a clinician evaluates a patient, he/she follows several steps in reaching a diagnosis. One of the key steps is developing the differential diagnosis and associated probabilities of disease for the differential diagnoses. This step results in the transformation of much information, including extensive qualitative material, into quantitative disease probabilities that are critical in interpreting the results of laboratory studies. For some diagnoses, such as coronary artery disease [4], these probabilities are relatively well known. My colleagues at the University of Rochester have developed approaches for estimating pretest probabilities of disease for common medical problems [5]. In situations where the pretest probabilities are less certain, experienced clinicians should still be able to at least estimate the pretest disease probability as high, intermediate, or low, and even this stratification can greatly assist in interpreting the results of laboratory studies. Some of the factors that influence the accuracy of these estimates have been detailed by Dawson [6].

In approaching patients with jaundice and suspected liver disease, it is difficult to come up with a specific algorithm for all patients. However, I believe that a general approach would include the following four major steps (also listed in Table 5): First, demonstrating that the increased bilirubin is due to liver disease or biliary obstruction rather than another cause such as hemolysis; second, determining the relative increases in serum AST

### Table 2. Characteristics of diagnostic tests.

<table>
<thead>
<tr>
<th>Test Result</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>False-positive</td>
<td>C</td>
<td>D</td>
</tr>
</tbody>
</table>

Note: Sensitivity = A/(A + C) Positive predictive value = A/(A + B)
Specificity = D/(B + D) Negative predictive value = D/(C + D)
Prevalence (or pretest probability) = (A + C)/(A + B + C + D)

### Table 3. Posttest probabilities of disease when the pretest probability of disease is 10%.

<table>
<thead>
<tr>
<th>Test Result</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>90</td>
<td>180</td>
</tr>
<tr>
<td>Negative</td>
<td>10</td>
<td>720</td>
</tr>
</tbody>
</table>

Note: Prevalence = (90 + 10)/(90 + 180 + 10 + 720) = 10%
Sensitivity = 90/(90 + 10) = 90% Positive predictive value = 90/(90 + 180) = 33%
Specificity = 720/(180 + 720) = 80% Negative predictive value = 720/(10 + 720) = 99%

### Table 4. Posttest probabilities of disease when the pretest probability of disease is 90%.

<table>
<thead>
<tr>
<th>Test Result</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>810</td>
<td>20</td>
</tr>
<tr>
<td>Negative</td>
<td>90</td>
<td>80</td>
</tr>
</tbody>
</table>

Note: Prevalence = (810 + 90)/(810 + 20 + 90 + 80) = 90%
Sensitivity = 810/(810 + 90) = 90% Positive predictive value = 810/(810 + 20) = 98%
Specificity = 80/(20 + 80) = 80% Negative predictive value = 80/(90 + 80) = 47%

### Table 5. Approach to patients with jaundice and possible liver disease.

1. Verify liver disease as source of jaundice
2. Determine relative increases in aminotransferase enzyme activity and alkaline phosphatase.
3. Determine etiology for hepatocellular injury or obstructive jaundice
4. Assess hepatic synthetic function
and (or) alanine aminotransferase (ALT) activity vs serum alkaline phosphatase; third, on the basis of the relative enzyme increases, determining the likely etiology for hepatocellular disease or obstructive jaundice; and fourth, in most situations, also assessing hepatic synthetic function.

In demonstrating that the increased bilirubin is due to liver disease, I generally measure both the total and conjugated (direct) bilirubin concentrations, since in most adults with jaundice from liver disease the conjugated bilirubin is increased, whereas in other causes such as hemolysis, the increased bilirubin is usually unconjugated. Once a liver source has been identified as the cause of jaundice, the next step is determining the relative increase of serum aminotransferase activity (AST, ALT) compared with the increase in serum alkaline phosphatase activity. In many cases, it is sufficient to measure either the serum AST or serum ALT activity. However, because the AST concentration can reflect other sources such as muscle, in some situations it may be useful to measure both concentrations because serum ALT activity is more specific for liver disease. This decision should be guided by the clinical situation, and often both AST and ALT are measured when there is uncertainty about the presence of liver disease or concern exists about alcoholic hepatitis. Nevertheless, although both enzymes may be measured during initial evaluation, it is rarely necessary to measure concentrations of both enzymes in following patients.

This approach, shown in Fig. 2, then should help to guide the remainder of the work-up. If the primary abnormality is in the aminotransferase activity, evaluation of hepatocellular dysfunction should proceed, with attention primarily to viral infections but also to hepatotoxic agents. On the other hand, if enzyme increases point mainly to obstructive disease through an increase in the alkaline phosphatase, then studies looking for intra- or extrahepatic obstruction should proceed.

The following cases illustrate the application of this approach to clinical medicine.

Case. J.G. is a 65-year-old man who presents with jaundice. For the past week he has felt anorectic and has also noticed dark urine. He has felt warm, but has not checked his temperature. He has had some discomfort in his upper abdomen. He has recently traveled overseas and enjoys eating raw seafood. He has had no recent surgery, no blood transfusions, and has no prior history of hepatitis. He does not use intravenous drugs. His examination was remarkable only for a low-grade fever, jaundice, and mild right upper quadrant discomfort with a liver span that was ~12 cm.

After obtaining this primary information, the clinician would develop a problem list. For this patient, it would likely include jaundice, low-grade fever, anorexia, and eating raw seafood. The primary differential diagnoses would be malignancy, especially metastatic disease, and viral hepatitis. My pretest probabilities of disease would be ~35–45% for malignancy and ~25–35% for hepatitis. My next steps would be to determine that the increased bilirubin was of hepatic origin and then to assess the relative increases of serum AST and (or) ALT and alkaline phosphatase.

For the first case, let us assume that the bilirubin was primarily hepatic in origin and that the AST was 1200 U/L and the alkaline phosphatase 180 U/L. This enzyme pattern, by using Fig. 2, is quite indicative of hepatocellular dysfunction. Thus, the posttest probability of hepatitis is quite high and the evaluation would emphasize hepatocellular injury, with acute viral hepatitis as a likely cause. Rather than obtaining a complete hepatitis panel at this time, I would likely first obtain serology for hepatitis A IgM antibody, and then proceed with additional, more extensive serology, only if the hepatitis A antibody were negative.

For a second case, let us again assume that the bilirubin was primarily of hepatic origin, but that the AST was 110 U/L and the alkaline phosphatase 480 U/L. In this case, the posttest probability of obstructive liver disease is very high and the evaluation would concentrate primarily on imaging studies of the liver and biliary tree to assess the etiology of the obstructive jaundice. Although the clinical laboratory could play some role in subsequent evaluation, unless there was strong evidence for primary biliary cirrhosis, it is likely that imaging studies would dominate the subsequent work-up. Depending on the local expertise, these studies would include computed tomography scanning, ultrasound, and (or) magnetic resonance imaging of the liver and biliary system. The hepatitis serologies, which were a key part of the first scenario, would have little to add to this case.

Thus, these two scenarios, with two slightly different primary laboratory results, indicate why it is difficult to come up with one algorithm for evaluating all patients with liver disease. However, the cases do illustrate how a general approach can be developed and then individual steps pursued on the basis of a logical, sequential approach. These scenarios also illustrate the approach of many clinicians in focusing on one or two likely diagnoses and attempting to rule in or rule out these likely diag-

![Fig. 2. Evaluation of hyperbilirubinemia.](image-url)
noses before proceeding with an extensive work-up, which may include multiple diagnostic tests.

The approach described above illustrates how clinical strategies and algorithms can be developed for patients with suspected liver disease. Several of the papers that were presented as part of this Beckman Conference also describe approaches that can be used to evaluate patients with possible liver disease, ranging from screening for hemachromatosis to evaluating patients with possible hepatitis.

**USE OF TESTS IN SCREENING AND PATIENT MANAGEMENT**

Although laboratory tests are used frequently in diagnosis, they are also used extensively both in screening for disease and in patient/disease management. Issues concerning screening for disease are presented well in Witte’s paper dealing with hereditary hemachromatosis [7]. For this paper, screening is defined as identification of disease at an early, often asymptomatic, stage. Principles of screening can also be applied to evaluating units of donated blood to assess risk for hepatitis and other infectious agents.

In deciding whether or not to implement screening for a disease, costs and benefits must be clearly understood. The costs and benefits, expressed generally as dollars per “quality adjusted year saved,” can be estimated with standard approaches; then the relative costs and benefits of different types of screening programs can be compared. Since the costs/benefits of currently accepted maneuvers, such as screening for cervical cancer, are known, the values for proposed new screening programs can be compared with currently accepted procedures. The cost/benefits of some screening maneuvers are described in the paper on hereditary hemachromatosis [7].

In assessing potential screening tests, it is important to consider several issues. First, the disease must be common; second, it must have significant associated morbidity or mortality; there must be effective treatment; and finally, early detection and treatment must be proven to be beneficial. In evaluating potential screening tests, laboratory scientists and clinicians should weigh these issues carefully (summarized in Table 6). In screening for disease, as in ruling out disease, it is best to have a test with high sensitivity, so that the number of false-negative tests is minimal. Thus, a negative test should be reassuring and tends to exclude the disease. However, in the case in which there are several potential screening tests with similar sensitivities, specificity must also be considered because in a screening program, one also must try to minimize the number of false-positive tests. In fact, in some screening tests, because of relatively low disease prevalence, much of the cost of the program, and many of the positive test results, are related to false-positive tests, which add cost to the entire screening program. False-positive results are a concern not only because of the cost of subsequent evaluations, but also because of patient anxiety caused by the positive test.

A final use of laboratory tests is to manage or follow patients with chronic disease. This approach is described in several of the papers discussing viral hepatitis. In assessing the utilization of tests for patient management, it is important to understand the pathophysiology of the disease, and target both the test as well as the timing of the tests to the disease under study. Thus, for a patient with acute hepatitis, one could follow the course of the AST or ALT and bilirubin. Similarly, for obstructive liver disease, one could follow the bilirubin and alkaline phosphatase. The assessment of tests to be used in patient management is illustrated well in the paper describing laboratory evaluation in postliver transplantation patients [8].

Here I have described an approach to clinical decision making and how diagnostic strategies and clinical algorithms can be determined. Indeed, rational approaches for a number of common problems have been developed [5].

The first step in the diagnostic journey begins with a careful history and physical examination as well as obtaining some baseline laboratory studies that should lead to a problem list and then the most likely diagnoses. Then, the laboratory should be used in a selective manner to rule in or rule out the most likely diagnoses. This process should be done understanding both the pretest probability and the laboratory tests’ characteristics, including sensitivity and specificity. This approach can be used to develop strategies of using the laboratory in diagnosis, screening, and disease management. Such strategies are often developed at the local level where there is a good understanding of the common diseases and also an understanding of the strengths of the laboratory. Ideally, such algorithms should be developed jointly by the clinicians and laboratory scientists to use their overlapping, but discreet, expertise to develop an optimal approach.

---

**Table 6. Issues in screening for disease.**

| Identification of early/asymptomatic disease |
| Benefits must outweigh costs and risks |
| Other questions to consider: |
| Common disease? |
| Significant morbidity/mortality? |
| Effective treatment? |
| Early treatment beneficial? |

---

**References**


