SPECIAL ARTICLE

Screening in Liver Disease: Report of an AASLD Clinical Workshop

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This report summarizes an AASLD Clinical Workshop that was presented at Digestive Diseases Week 2003 on screening in liver diseases. As newer diagnostic tests become available, many liver diseases and complications of liver disease can be detected at an early asymptomatic stage. In many cases, early detection can lead to earlier treatment and an improved outcome. However, screening for liver diseases in asymptomatic persons has the potential for adverse consequences, including discrimination and stigmatization. The cost of screening programs is significant, and access to screening tests varies in different countries. Future screening programs require careful planning and implementation to balance the benefits, risks, and cost-effectiveness. This review outlines the concepts of screening and their application to a broad range of liver diseases. (HEPATOLOGY 2004;39:1204–1212.)

Screening can be defined as the examination of asymptomatic people to classify them as likely or unlikely to have the disease of interest.[1] Screening tests are usually administered to individuals who do not have current symptoms but who may be at high risk for certain adverse health outcomes. The sensitivity and cost-effectiveness of screening increases when the screening specifically addresses populations known to be at higher risk for the abnormality (*e.g.*, screening of Northern Europeans for hemochromatosis). Most present-day screening programs are based on the premise that treatment will slow or stop the progression of established cases of disease that are detected early, while later treatment is less likely to be effective. Looking for additional illnesses in individuals with medical problems is termed *case finding*; therefore, screening is limited to individuals who are apparently well. Many screening programs are regarded as surveillance rather than screening (*e.g.*, screening for hepatocellular carcinoma [HCC] in patients with preexisting cirrhosis). Surveillance is usually conducted over time; for example, repeat screening tests may be conducted once every 10 years on a single individual. The terms *screening*, *case finding*, and *surveillance* are not uniformly used in the medical literature.[2]

The screened disease should be medically important, and its prevalence should be reasonably high. The natural history should be known, and an effective intervention must exist. The ideal screening test is valid and reliable; the operating characteristics of ideal screening tests have been well established (Table 1). There are a variety of screening tests available for specific liver diseases and the complications of liver disease (Table 2).

Overview of Cost-Effectiveness Evaluations *(Dawn Provenzale)*

It is increasingly common to use decision analysis models to assess the cost-effectiveness of screening. These models are often complicated, and it is beyond the scope of this review to discuss all of the inherent assumptions of such analyses.[3–5] In the study of screening test cost-effectiveness, a hypothetical cohort is screened and then compared with another unscreened hypothetical group. The natural history of the disease must be clearly understood to create these models. The lack of a clear natural history has been the greatest limitation when models have been applied to many liver diseases, including viral hepatitis, HCC, or hemochromatosis. Incremental cost-effectiveness ratios have been used to compare different strategies. It is unusual for screening programs to save money, and

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PIIINP, N-terminal peptide of collagen type III; ALT, alanine aminotransferase.

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Received June 18, 2003; accepted December 11, 2003.

This article comes from a Clinical Research Workshop sponsored by the AASLD at Digestive Diseases Week, May 17, 2003, Orlando, FL.

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Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.20169

Table 1. Operating Characteristics of Screening Tests

Sensitivity	The property of the screening test that allows cases to be detected early and is derived from the following formula: [number who test positive/total number tested with disease].
Specificity	The property of test that allows nondiseased people to be identified: [number who test negative/total number tested without disease].
Positive predictive value	The number with disease/number who test positive. The positive predictive value is dependent on the prevalence of the condition; thus a test with a moderate sensitivity may have a low positive predictive value in an uncommon condition. Other test measurements that are not dependent on prevalence are odd ratios and likelihood ratios.
Lead time bias	When the date of diagnosis is early but the death date is unchanged, falsely suggesting improved survival (Fig. 1).
Length time bias	Can also be seen in screening; for example, slower-growing liver tumors are identified more readily in a screening program (Fig. 2).

therefore thresholds for funding or acceptability as much as $50,000 per quality-adjusted life-year saved are commonly cited. A sensitivity analysis in a decision analysis model can be used to alter baseline assumptions to assess the effects these changes would have on costs. For example, if untreated hepatitis C always progressed to cirrhosis, an expensive treatment with a low success rate may seem cost-effective. However, if many patients with chronic hepatitis C do not progress to cirrhosis, the cost-effectiveness of an expensive medication becomes more controversial. In the case of surveillance for HCC, the cost and availability of an expensive treatment—such as that required for liver transplantation—may be the most important variable to consider.

When estimating the cost of an intervention, both its face value cost and the downstream costs of working up true positives, false positives, and any incidental findings should be considered. A seemingly inexpensive test, if suggested for a large number of subjects, can rapidly become an expensive program. If a test has high sensitivity and poor specificity, even something as inexpensive as a guaiac fecal occult blood test can be costly as a result of the colonoscopies that must eventually be performed. Likewise, a more expensive test with better operating characteristics (fewer false negatives and false positives) may actually be a better investment.

Table 2. Screening for Liver Disease and Its Complications

Medical Condition	Available Screening Tests	Comments
Hepatocellular carcinoma	Ultrasound, alpha-fetoprotein	Better tests and treatment options are needed
Hemochromatosis	Transferrin saturation, ferritin, C282Y genetic test	TS and ferritin detect iron overload; genetic test defines a predisposition to iron overload
Hepatotoxicity	Serial ALT, alkP monitoring	Stop drug if ALT is more than three times the upper limit of normal Cholestatic drugs may have long-term effects
Hepatitis C	Anti–hepatitis C virus	For high-risk groups
Hepatitis B	HBsAg for disease Anti-HBs for need for vaccination	Potential harm from identifying asymptomatic carriers
Cirrhosis	Algorithms using multiple tests	Many current tests have indeterminate results
Portal hypertension	Endoscopic evaluation for esophageal varices	Risk of bleeding is compared with side effects of treatments

Abbreviations: ALT, alanine aminotransferase.

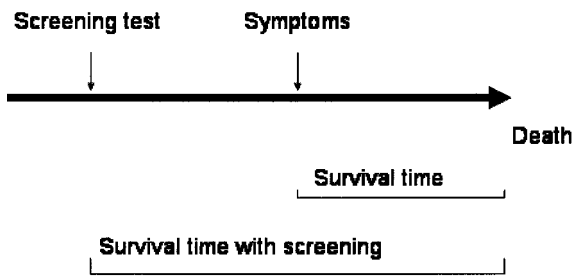

Fig. 1. A screening test detects the disease at an earlier asymptomatic stage, but the death date does not change. An apparent increase in survival time is misleading (lead time bias).

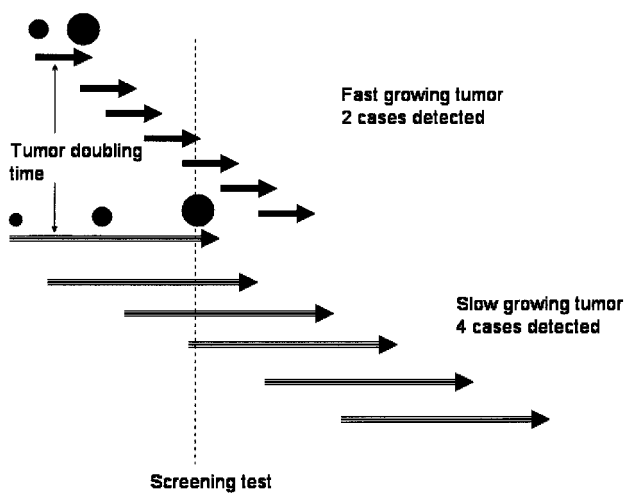

Fig. 2. A screening test is more likely to detect a slow-growing tumor than a rapidly growing tumor, leading to a length time bias.

Potential for Genetic Discrimination
(Mark Hall)

A growing number of genetic blood tests may be used to predict the risk of developing a medical illness. In the United States, there is widespread concern about genetic discrimination by health insurers, and most states have adopted legislation limiting health insurers' use of genetic information.[6] The premise of this legislation is the belief by the public and the medical genetics community that there is a real threat of discrimination by insurance companies in the United States. However, the best evidence indicates that genetic discrimination by such health insurers is rare or nonexistent. In a prominent study, in-depth interviews were conducted in seven states with 77 representatives from the insurance industry (agents, actuaries, underwriters, and regulators).[7] In addition, 148 health insurance application forms were collected and analyzed, and 142 insurance agents were contacted with inquiries about purchasing insurance using a scripted scenario that presented a fictitious case of a positive test for "the breast cancer gene." The conclusion from this extensive effort was that health insurers do not inquire about predictive genetic test results and do not use this information, nor is this type of information included in their underwriting guidelines.[7]

Segments of the population potentially exposed to genetic discrimination are those who purchase individual health coverage outside the workplace or those who obtain health insurance as part of small employer groups (fewer than 20 workers). This is the portion of the United States population in which health insurers appear to project future medical costs based on an assessment of individual health risks. For this segment, a 1991 survey of health insurers found that, among various groupings of insurers, 36% to 64% would decline or limit coverage if presymptomatic genetic testing revealed "the likelihood of a serious chronic future disease."[8] However, this assumes that insurers learn about predictive genetic test results. Over half the states now prohibit some or all health insurers from using or inquiring about predictive genetic tests results.[7] Genetic testing may reveal a predisposition to previously unsuspected disease that requires immediate treatment in the form of preventive care or corrective genetic therapy. If this care is expensive, health insurers would likely seek out and act on this type of genetic information for insurance products that are not issued to larger groups. However, when genetic conditions require immediate treatment, it is debatable whether definitions of unfair discrimination are met. These same factors apply to other predictive tests (*e.g.*, blood sugar and cholesterol), and many would argue that there should not be "genetic exceptionalism."[9]

The situation is different for life and other types of health-related insurance, such as long-term care or disability income insurance. For these types of insurance, predictive medical information has much greater salience. Life insurers are now routinely using predictive genetic information in the form of family history[7] and argue strenuously that they must be able to consider the results of predictive genetic testing as this technology becomes more commonplace.

Screening for Specific Liver Diseases and/or Complications of Liver Diseases

If we begin to look for the complications of liver disease, it is more appropriate to label it surveillance rather than screening. The detection of asymptomatic liver disease or a complication of liver disease requires that a beneficial and acceptable treatment be available.

Surveillance for Hepatocellular Carcinoma
(Adrian Di Bisceglie)

Patients at risk for HCC include those with cirrhosis, chronic viral hepatitis, and certain metabolic diseases such as hemochromatosis and alpha-1-antitrypsin deficiency. Because of the poor prognosis of HCC when it is diagnosed at an advanced stage, early detection is most desirable. Small HCC is amenable to potentially curative treatment by liver transplantation, resection, or local ablation by alcohol injection or radiofrequency ablation. Early diagnosis of HCC is possible through the use of imaging techniques such as ultrasound, computed tomography, or magnetic resonance imaging combined with regular measurement of serum alpha-fetoprotein levels.

What has not yet been established is (1) whether initial surveillance for HCC among patients with liver disease is associated with prolonged patient survival and (2) whether this approach is cost-effective.[10] Scant data are available on the benefits of surveillance from randomized controlled trials. In fact, Sherman et al.[11] found that such a trial was not practical in North America, and most of the available data come from cohort or retrospective studies. For example, McMahon et al.[12] found that serial measurement of alpha-fetoprotein is valuable in diagnosing HCC among Alaska natives with chronic hepatitis B virus. Tong et al.[13] screened 173 patients with cirrhosis due to hepatitis C and found 31 who developed HCC. Unfortunately, only 18 of these tumors were single and of a size potentially amenable to treatment at the time of diagnosis. Potentially curative treatments were possible in only 12 of the patients in this group (39%) (resection in four,

liver transplantation in eight). There have been several studies of the cost-effectiveness of surveillance for HCC. Estimates for the cost per tumor detected have ranged between $11,000 and $25,000. Costs per year of life saved have been estimated to be between $26,000 and $112,996[14–16] compared with an estimate of $25,000 per year of life saved by screening for colorectal cancer. A survey of practicing hepatologists in the United States indicated that 83% conduct some form of surveillance for HCC in patients at risk, most frequently using the combination of ultrasound and alpha-fetoprotein, but only about one third consider surveillance to be cost-effective in a nontransplant population. A common reason cited for screening was a fear of malpractice lawsuits.[17] Thus, surveillance for HCC appears to have become standard practice in selected patients, despite the absence of proof of its value. This practice is unlikely to change without new data, which are unlikely to be forthcoming because of a variety of medical and nonmedical issues that adversely affect the possibility of conducting a properly designed scientific study.

Screening for Hemochromatosis *(Paul Adams)*

Hemochromatosis is a common and treatable liver disease, and many studies have been undertaken to assess the role of population screening in the early detection and treatment of this condition. Considering the evidence that is required to make a decision to screen the general population for hemochromatosis, it is important to assess phenotypic–genotypic correlations—in particular, the degree to which individuals with predisposing mutations of the *HFE* gene may manifest abnormal iron markers and may go on to develop clinical features of iron overload.[18,19] Typical screening tools for hemochromatosis include serum transferrin saturation, ferritin, and genetic testing for the C282Y and H63D mutation of the *HFE* gene. Genetic testing has been a major advance in the diagnosis of hemochromatosis, but it has also identified C282Y homozygotes for the *HFE* mutation without iron overload. This is most apparent in population screening studies, but it may also occur during a pedigree investigation. With regard to C282Y homozygotes, a spectrum has been identified that spans from asymptomatic persons with normal iron studies to chronically ill patients with cirrhosis and diabetes.[20] Most studies have advocated initial screening with transferrin saturation and genetic testing in participants with an elevated transferrin saturation.[21] This minimizes the risk of genetic discrimination in nonexpressing cases and allows for the identification of non–*HFE*-related iron overload.[22,23]

An important issue is whether population screening studies have detected patients with significant disease. In the largest screening study to date, 65,238 Norwegians were screened by transferrin saturation twice; cases were confirmed by genetic testing and/or liver biopsy.[24] One hundred forty-seven liver biopsies were performed; of these, four men and none of the women had cirrhosis. An Australian study of 3,011 persons led to liver biopsies in six cases (one with cirrhosis, two with fibrosis).[25] Another screening study of 41,038 persons from San Diego has suggested that the prevalence of significant life-threatening complications of hemochromatosis in C282Y homozygotes may be as low as 1%.[26] In this study, some patients had suspected liver dysfunction; however, liver biopsies were not performed, and most C282Y homozygotes had elevations in transferrin saturation and ferritin. The inclusion of a control group in this study highlights the difficulty of attributing symptoms in hemochromatosis, because a significant proportion of the general population have fatigue, arthralgias, and diabetes. This discrepancy between the morbidity in referred patients and the lack of morbidity in screened patients is not unique to hemochromatosis. At the present time, it appears that men of Northern European ancestry are the highest risk group for C282Y hemochromatosis with iron overload[27] and this group could be considered for screening with transferrin saturation as a preventative health measure. The Hemochromatosis and Iron Overload Screening study has screened 100,000 North American participants and will provide additional information about the use of screening in an ethnically diverse population.[28]

Screening for Medication-Related Hepatotoxicity *(Laurie DeLeve)*

Screening for drug-induced liver disease is often based on the use of liver chemistry tests. Screening with such tests is a form of secondary prevention—that is, early recognition of liver test abnormalities before frank liver injury develops. Several characteristics determine the usefulness of screening using liver chemistry. Foremost, the time interval between onset of liver chemistry abnormalities and subsequent liver injury must exceed the screening interval. Second, the incidence of liver toxicity must be high enough to justify the cost-effectiveness of routine liver chemistry screening. Third, liver test abnormalities need to be a good predictor of the development of liver damage. Unfortunately, this screening strategy has only proven useful in the management of a very limited number of drugs or clinical settings. As a rule, drugs that cause liver toxicity as a result of metabolic idiosyncrasy occur in

the first year of therapy. Isoniazid toxicity can occur any time in the first year, but 50% of cases occur in the first 2 months. Liver tests for individuals on isoniazid alone are usually checked on a monthly basis.[29,30] This strategy may not be effective for drugs for which the interval between onset of liver test abnormalities and liver injury is shorter than the screening interval.[31] Drugs that cause idiosyncratic liver toxicity due to hypersensitivity usually cause symptoms between 2 and 8 weeks after starting the drug; hence monitoring would need to be performed at frequent intervals during a relatively short period.

How should one approach liver test abnormalities in the absence of frank liver injury? For many drugs, the common practice has been to more closely monitor patients with serum aminotransferases of greater than three times the upper limit of normal. Some form of adaptation may occur, for there is often subsequent normalization of serum aminotransferases with continued use of various drugs. When serum aminotransferases are elevated to five to six times the upper limit of normal, the drug may need to be discontinued. The approach to drugs that cause acute cholestasis differs from that of drugs that cause elevations in aminotransferases, because continued use can lead to chronic cholestasis from a vanishing bile duct–like syndrome or a biliary cirrhosis–type syndrome. Thus drugs that cause even mild cholestasis may need to be discontinued, unless dosage adjustment or other changes in therapy can resolve the cholestasis.[32] Perhaps the most important form of tertiary prevention is to educate patients on the symptoms of drug-induced hepatitis; counsel them to immediately stop a potentially hepatotoxic drug when symptoms appear; and counsel them to consult their physician for guidance, rather than to simply wait for the next available clinic appointment.

The future of screening for drug-induced liver disease is likely to be in the area of pharmacogenomics. This will require identification and characterization of candidate genes and polymorphisms related to drug toxicity, correlation of genotype to drug response and clinical outcome, and ultimately the development of molecular tests to individualize drug therapy. There are two approaches that are likely to be applied. First, an attempt can be made to classify individuals with toxicity based on currently known polymorphisms. This approach would be particularly invaluable for unique drugs that are of great assistance to many patients but highly toxic to a small number of individuals. The limitation of this strategy is that very few polymorphisms have been identified that can be related to drug toxicity. The second approach is to develop a database of gene expression profiles of known hepatotoxins and compare the gene expression profile of a new drug during development. This approach holds promise for the prevention of marketing of hepatotoxic compounds and may also identify unexpected polymorphisms that can be applied for individual screening.

Table 3. Screening for Hepatitis C

Persons who have injected illicit drugs in the recent or remote past, even if only once
Persons with medical conditions that may increase exposure to hepatitis C virus
Persons who received clotting factor concentrates before 1987
Persons who have ever been on chronic hemodialysis
Persons with persistently abnormal aminotransferase levels
Prior recipients of transfusions or organ transplants
Persons identified as having received a blood transfusion later found to be positive for hepatitis C virus
Persons transfused prior to July 1992
Persons who received an organ transplant prior to July 1992
Health care workers, emergency medical technicians, and public safety workers after a needle stick injury
Children born to mothers positive for hepatitis C virus
Persons from areas of high prevalence

Screening for Chronic Viral Hepatitis
(Leonard Seeff)

Hepatitis C. Screening for hepatitis C is currently recommended for high-risk groups by most (but not all) public health authorities (Table 3). Detection is important for patient treatment and to prevent further infection of contacts. Current treatments are not ideal because of the continuing problem of treatment resistance (particularly among African Americans) and the distressingly common and unpleasant side effects. Currently successful treatment (defined by the achievement of an sustained viral response) has not been proven to extend useful life expectancy.[33] However, loss of virus, return of serum enzymes to normal, and improvement of the liver biopsy provide a reasonable assumption of such a favorable effect.[34]

Screening has had an impact in selected populations. Transmission from patients to the health care worker is not uncommon, but the reverse situation is far less common.[35,36] This raises the question of whether routine testing of health care workers should be performed. This only has relevance if the worker is to be removed from performing exposure-prone procedures, a strategy that is not recommended in the United States but is practiced in the United Kingdom. In the latter country, a health care worker found to be positive for hepatitis C virus (HCV) is removed from direct patient care and can only return if treatment eradicates the virus.[37] Although sexual transmission is uncommon, the use of barrier protection (*e.g.*, a condom) is helpful in reducing the likelihood of HCV transmission and can be recommended in some situations. Screening has had its most profound impact among

Table 4. High-Risk Groups for Screening for Hepatitis B

All pregnant women
High-risk adolescents
Health care workers
Clients and staff of institutions for the developmentally disabled
Hemodialysis patients
Recipients of clotting factor concentrates
Persons from areas of high prevalence
Household and sexual contacts of a hepatitis B virus carrier
Injection drug users
Sexually active homosexual and bisexual men
Sexually active heterosexual men and women
Inmates of long-term correctional facilities
Persons with abnormal liver tests of unknown cause
Persons infected with other viruses, such as hepatitis C virus and/or HIV.

blood donors. With the introduction of sensitive donor screening assays in 1992, transfusion-associated hepatitis C has become an issue of the past. Thus screening appears to be helpful in some settings and is demonstrated to be effective in reducing transmission in others; hence it is warranted on this basis alone.

Hepatitis B. Screening for hepatitis B seems justified but is confined to specific target groups (Table 4).[38] The numbers of groups for whom screening is warranted should begin to dwindle with the introduction of routine hepatitis B vaccination. Numerous excellent drugs are now available to treat chronic hepatitis B, although treatment is difficult, particularly for persons infected with mutant strains of hepatitis B virus.[39] Like chronic hepatitis C, chronic hepatitis B virus infection can induce slow evolution to cirrhosis and—more commonly than occurs with chronic HCV—to the development of HCC. Unlike hepatitis C, hepatitis B can progress to HCC without preceding cirrhosis. Accordingly, the potentially serious nature of chronic hepatitis B warrants the need to screen at-risk individuals so that appropriate treatment can be instituted.

Screening to identify a carrier permits the determination of whether sexual and household contacts require prophylaxis if the carrier is not immune to hepatitis B. The factor that sets this process on course is the identification of the index carrier recognized through screening. Screening is important to identify persons who are unaware that they are infected with hepatitis B virus, which would warrant specific treatment of the disease.

The potential impact of the diagnosis of chronic hepatitis or a carrier state on an individual's job security, income, stigmatization (if the diagnosis is known), marital or other relationships, and future insurability must be discussed with the patient. For example, a dentist who has been referred for abnormal liver enzymes may need to know the implications of a positive hepatitis test on his or her future practice. The identification of asymptomatic persons with viremia and normal liver tests who go on to lose their employment has to be carefully weighed against the potential treatment benefits and the reduction of the spread of infection. Future research in this area will need to include input from public health experts, ethicists, and legal advisors.[40,41]

Surveillance for Cirrhosis *(Michael Arthur)*

There is an increasing clinical need to be able to define the extent of liver fibrosis to determine whether therapeutic intervention is appropriate in chronic HCV infection, steatohepatitis, hemochromatosis, and other liver diseases. As more effective treatments become available for chronic liver disease, there will be an increased need for repeated assessments of the extent of liver fibrosis to help determine efficacy in individual cases. This will be a key issue as new antifibrotic therapies are brought into clinical development over the next decade. To date, there are no universally accepted methods of determining the extent of liver fibrosis despite many different investigational approaches to the problem. Liver biopsy is currently the most common method of staging the severity of liver fibrosis, with histopathological appearances graded according to validated criteria. Imaging techniques may be used to screen patients for the presence of cirrhosis, but they are not sufficiently accurate at determining the earlier stages of liver fibrosis. There is no single serum marker that can accurately predict the stage of disease in all cases, but of those evaluated to date, the best results are obtained with serum levels of hyaluronic acid, the N-terminal peptide of collagen type III (PIIINP), or more recently with a marker called YKL-40. A direct comparison of the performance of hyaluronic acid to PIIINP in predicting the stage of liver fibrosis in 326 patients with chronic hepatitis C found that hyaluronic acid had greater diagnostic performance than PIIINP as determined by their respective receiver operating characteristic curves.[42] The search for other serum markers continues to highlight new options, such as YKL40, with recent preliminary studies; this suggests they may outperform PIIINP and hyaluronic acid as a single marker.[43,44]

In an attempt to improve on the results obtained with single markers, another approach has been to investigate the value of algorithms formed from either multiple serum markers alone or in combination with clinical criteria. The ratio of aspartate aminotransferase/platelets was demonstrated to predict fibrosis and cirrhosis in 192 hepatitis C patients.[45] The main difficulty with many algorithms is that they can only assign approximately half of the patients, while the remainder fall into an indeterminate group.[46,47]

A European collaborative study focused on an algorithm based around 10 markers that included PIIINP, c-terminal procollagen III propeptide, hyaluronic acid, 7S type IV collagen, undulin, tenascin, TIMP-1, MMP-2, collagen VI, and laminin P1, all of which were analyzed in patients with a wide variety of chronic liver diseases. Algorithms were formulated using discriminant analysis initially in a test group of 321 patients, who were then tested prospectively in another 600 patients. For all cases this algorithm had a negative predictive value for clinically significant fibrosis of 79.1%. In some diagnostic categories, the negative predictive value was in excess of 96% (*e.g.*, nonalcoholic fatty liver disease, hemochromatosis, and posttransplant liver disease). Longitudinal studies are currently being analyzed to determine if these algorithms can be used to follow changes in liver histology over time.[48]

Surveillance for Portal Hypertension *(Tom Boyer)*

Because the diagnosis of portal hypertension requires measurement of hepatic vein pressure gradient using an invasive test, surveillance for portal hypertension usually means looking for ascites or varices. The physical examination is a poor screening test for the presence of portal hypertension. The presence of visible venous collaterals or ascites is specific but is not sensitive for the diagnosis of portal hypertension. Splenomegaly is also an insensitive test for the presence of portal hypertension, even though those with splenomegaly are more likely to have portal hypertension than are those without this physical finding. Low levels of albumin and prolongation of the prothrombin time or international normalized ratios in patients with chronic liver disease suggest the presence of cirrhosis but provide no estimate of the severity of portal hypertension. Serum levels of laminin and amino-terminal propeptide of type III procollagen have been suggested to correlate with hepatic vein pressure gradient. Although there may be some relationship between the levels of these tests and portal hypertension in alcoholics, in other forms of liver disease they do not provide an estimate of the severity of the portal hypertension or the risk of bleeding from esophageal varices.

Imaging studies have been used extensively to screen for portal hypertension; abdominal ultrasound has been used most commonly. The findings of splenomegaly, portal vein diameter greater than 13 mm, and presence of collaterals or ascites are all indicative of portal hypertension. However, the size of the portal vein and spleen do not correlate with the severity of portal hypertension or the presence or absence of varices.[49,50] Similarly, computed tomography and magnetic resonance imaging are subject to the same problem in that they can identify features suggestive of portal hypertension in some patients, but the findings do not correlate quantitatively with portal pressure or size of varices. These techniques cannot be used to screen patients for portal hypertension when the goals are making decisions about therapy or predicting outcome.

The most widely used surveillance test for portal hypertension is upper endoscopy looking for varices. This test is useful because if varices are found, then portal hypertension is present and the appearance of the varices is predictive of bleeding. There is good agreement among observers, and endoscopic surveillance for varices is now recommended for all patients with cirrhosis. If high-risk varices are found, then treatment—either pharmacological or endoscopic—is recommended. If varices are small or absent, endoscopy should be repeated in 2 years. The presence of splenomegaly or thrombocytopenia is predictive of the presence of high risk varices.[51] This practice has recently been questioned, however, because it may not be a cost-effective approach to the management of these patients.[35,36] Modeling was performed comparing treatment of all cirrhotic patients with beta-blockers to endoscopic screening and treating only those with high-risk varices. In one of the two studies, screening was shown to be cost-effective only in patients with good liver function. In all other scenarios it was more cost-effective to treat all cirrhotic patients with beta-blockers without endoscopic surveillance.[52,53] However, there have been no published studies comparing the treatment of all cirrhotic patients with beta-blockers to the endoscopic surveillance strategy, so at this time no conclusions can be reached as to which approach is best. Future studies on pharmacological therapy would be greatly enhanced by a noninvasive method for the measurement of portal hypertension.

Summary *(Theodore Levin)*

Because screening targets apparently healthy people, the ethics differ from those for patients who come to a physician for evaluation and treatment of a bothersome symptom. Harm as a result of screening can arise directly (*e.g.*, a colonic perforation from colonoscopy performed to screen for colon cancer) or indirectly by discovering cases of disease that might never cause symptoms (*i.e.*, pseudodisease) as well as subjecting patients to invasive diagnostic evaluations or harmful treatments.

The availability and use of screening tests varies widely between different countries and health care systems. Many health care systems are unable to deliver a one-time screening test for hepatitis or hemochromatosis. In addition, screening for HCC in cirrhotic patients would cause a large increase in ultrasound

examinations. If there are delays in obtaining ultrasound examinations for symptomatic patients, any screening program based on ultrasound will have to figure in the cost of purchasing additional machines and hiring and training additional technicians. Will the investment in personnel or equipment translate into lower treatment costs, improved survival, or better quality of life?

The practicing physician is often faced with making management decisions based on clinical practice guidelines. Unfortunately, these guidelines often represent the consensus of experts and are not always supported by evidence-based medicine.[54] The future will require prospective studies on the efficacy of screening and surveillance to prevent the morbidity and mortality of liver diseases. Many of these studies are already in progress and, despite their limitations, will likely guide our management decisions into the next decade.

Acknowledgment: The authors acknowledge the administrative support of Janeil Klett and Julie Deal and editorial assistance from Heidi Blanck.

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