In this review, we define hepatotoxicity as injury to the liver that is associated with impaired liver function caused by exposure to a drug or another noninfectious agent. The distinction between injury and function is important, because it is mainly when function is impaired that symptoms and clinically significant disease follow. We are especially concerned with serious drug-related hepatotoxicity that is disabling or life-threatening or that requires hospitalization. Although drug-related hepatotoxicity is uncommon— for many drugs, the reported incidence is between 1 in 10,000 and 1 in 100,000 patients—its true incidence is difficult to determine. The numbers may be much higher, because of underreporting, difficulties in detection or diagnosis, and incomplete observation of persons exposed. In an effort to improve on the reporting of rates, a group of physicians in France were trained to investigate and report possible causes of hepatic injury from drugs and found a crude incidence rate of about 14 per 100,000 inhabitants per year, 12 percent of whom were hospitalized and 6 percent of whom died. This rate was about 16 times as great as the spontaneously reported rates of adverse hepatic drug reactions in France but was still a possible underestimate.

In most cases, there is no effective treatment other than stopping the drug and providing general supportive care. Prompt use of N-acetylcysteine after acetaminophen overdose and intravenous carnitine for valproate-induced mitochondrial injury are exceptions. In the United States, drug-related hepatotoxicity is now the leading cause of acute liver failure among patients referred for liver transplantation—most of whom have had no prior liver disease—because of an intentional or unintentional overdose of acetaminophen, the drug most often implicated in such cases. When a drug is found to cause even rare hepatotoxicity but is used by millions, it may be removed from clinical use. Although such a drug poses great danger to only a few patients, its removal leads to the loss of drug availability to many. For practicing physicians, drug-related hepatotoxicity is a liability risk; for the pharmaceutical industry, it leads to financial losses; and from a regulatory perspective, it is the most common reason for regulatory actions on the part of the Food and Drug Administration (FDA).

Given its rarity, drug-related hepatotoxicity may not occur during clinical trials, which are usually limited to a few thousand participants. However, after approval of a drug for use and subsequent marketing, large numbers of patients are exposed, and rare toxic effects may emerge. In this article we provide information on the detection, evaluation, possible prevention, and management of drug-related hepatotoxicity. Although our discussion focuses primarily on hepatotoxicity associated with prescribed and over-the-counter medications, the same principles apply to other agents, including dietary supplements and complementary or alternative remedies.
Liver Injury and Its Patterns

In 1989, a panel of 12 European and American experts by consensus defined liver injury as an increase of more than twice the upper limit of the normal range in the levels of serum alanine aminotransferase or conjugated bilirubin, or a combined increase in the levels of aspartate aminotransferase, alkaline phosphatase, and total bilirubin, provided that one of these was more than twice the upper limit of the normal range. The clinical patterns of liver injury were further characterized as hepatocellular, with a predominant initial elevation of the alanine aminotransferase level, or cholestatic, in which the serum alkaline phosphatase level is first elevated. These patterns of liver injury are not mutually exclusive and may be termed mixed if intermediate. It was later suggested, before a February 2001 conference cosponsored by the FDA Center for Drug Evaluation and Research, the Pharmaceutical Research and Manufacturers of America, and the American Association for the Study of Liver Diseases, that an alanine aminotransferase level of more than three times the upper limit of normal and a total bilirubin level of more than twice the upper limit be used as a combined test to define clinically significant abnormalities on liver tests, with further verification through the analysis of additional clinical data. Elevations in serum enzyme levels (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase) were taken as indicators of liver injury, whereas increases in both total and conjugated bilirubin levels were measures of overall liver function. It is important to recognize the pattern of liver injury, since certain drugs tend to create injury predominantly according to one pattern or the other (Fig. 1).

True measures of conjugated bilirubin are seldom obtained, and the direct-reacting bilirubin fraction is an overestimate. The concept of combining the measures of liver injury and function was derived from the observation of the late Hyman Zimmerman that “drug-induced hepatocellular jaundice is a serious lesion. The mortality rate ranges from 10 to 50 percent.” This observation, referred to by Dr. Robert Temple as “Hy’s Law,” has shown notable consistency, and it continues to be used by the FDA to initiate close evaluation of patients with elevated liver tests. Two recent surveys, from Sweden and Spain, provide support for the observation that drug-induced hepatocellular injury with jaundice is associated with greater mortality or the need for transplantation than is cholestatic or mixed injury. However, in each case, additional clinical information is required to determine whether the elevated values were drug-induced or disease-induced.

Injury vs. Function
Liver injury is generally indicated by elevations in serum aminotransferase levels, but increases of far more than three times the upper limit of normal may not lead to clinically significant liver damage. This is because of the great capacity of the liver to heal injury, with the subsequent development of adaptive tolerance, as frequently

<table>
<thead>
<tr>
<th>Hepatocellular (Elevated ALT)</th>
<th>Mixed (Elevated ALP + Elevated ALT)</th>
<th>Cholestatic (Elevated ALP + TBL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>Aminopyrine</td>
<td>Amoxicillin–clavulanic acid</td>
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<tr>
<td>Acetaminophen</td>
<td>Azathioprine</td>
<td>Anabolic steroids</td>
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<td>Allipurinol</td>
<td>Captopril</td>
<td>Chlorpromazine</td>
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<td>Amiodarone</td>
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<td>Baclofen</td>
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<td>Oral contraceptives</td>
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<td>Bupropion</td>
<td>Ciproheptadine</td>
<td>Erythromycins</td>
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<td>Fluoxetine</td>
<td>Enalapril</td>
<td>Estrogens</td>
</tr>
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<td>HAART drugs</td>
<td>Flutamide</td>
<td>Ibesartan</td>
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<tr>
<td>Herbas: kava kava and germander</td>
<td>Nitrofurantoin</td>
<td>Mitazapine</td>
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<td>Isoniazid</td>
<td>Phenobarbital</td>
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<td>Trovafloxacin</td>
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<td>Valproic acid</td>
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Figure 1. Liver Injury and Its Patterns.
Liver injury is defined as an alanine aminotransferase (ALT) level of more than three times the upper limit of the normal range, an alkaline phosphatase (ALP) level of more than twice the upper limit of normal, or a total bilirubin (TBL) level of more than twice the upper limit of normal if associated with any elevation of the alanine aminotransferase or alkaline phosphatase level. Liver injury is further characterized as hepatocellular when there is a predominant initial elevation of the alanine aminotransferase level or as cholestatic when there is a predominant initial elevation of the alkaline phosphatase level; a mixed pattern comprises elevations of both the alanine aminotransferase and alkaline phosphatase levels. Recognizing the pattern of liver injury helps to categorize it, since drugs tend to create injury predominantly in one or another pattern. The injury patterns are not mutually exclusive, and a mixed pattern of injury may occur in many instances of drug-related hepatotoxicity. HAART denotes highly active antiretroviral therapy, and NSAIDs nonsteroidal antiinflammatory drugs.
seen with initial exposure to drugs such as isoniazid and tacrine. Tests reflecting liver injury alone do not necessarily predict or indicate serious hepatotoxicity. Vague symptoms such as fatigue, anorexia, nausea, discomfort in the right upper quadrant, and dark urine may be the first clues that hepatotoxicity has occurred. Drug-related hepatotoxicity should be considered when such symptoms occur in conjunction with biochemical evidence of liver injury, and especially with concurrent impaired liver function. The regulation of serum enzyme activity is not a function of the liver, which is more accurately assessed according to the levels of total bilirubin or conjugated bilirubin — reflecting the liver’s ability to move bilirubin from plasma into bile. Another measurable liver function is protein synthesis, which is reflected in the albumin concentration and the prothrombin time (or its international normalized ratio [INR]).

**CLINICAL PATTERNS OF HEPATOTOXICITY**

Hepatotoxicity may be predictable or unpredictable. Predictable reactions typically are dose-related and occur in most persons who are exposed shortly after some threshold for toxicity is reached. Acetaminophen is a fairly predictable hepatotoxin, as are chemicals such as carbon tetrachloride, phosphorus, and chloroform that are no longer used as drugs. Unpredictable hepatotoxic reactions occur without warning, are unrelated to dose, and have variable latency periods, ranging from a few days to 12 months. Many drugs create a pattern of injury that has characteristic biochemical, clinical, histologic (Fig. 2), and chronicologic features, or a combination of them. Together, these features form what is termed a drug’s signature disease.

Several patterns of drug-related hepatotoxicity may be recognized, each with a different mechanism of injury. Hepatocellular or cytolitic injury involves marked elevations of serum aminotransferase levels, usually preceding increases in total bilirubin levels and modest increases in alkaline phosphatase levels; examples of this type of injury include that attributable to isoniazid or troglitazone. Cholestatic injury is characterized by increases in alkaline phosphatase levels that precede or are relatively more prominent than increases in the alanine aminotransferase or aspartate aminotransferase levels and is associated with amoxicillin–clavulanic acid or chlorpromazine. Hypersensitivity or immunologic injury is often somewhat delayed or occurs on repeated exposure, as exemplified by injury associated with phenytoin, nitrofurantoin, or halothane. This has been referred to as a drug-hypersensitivity syndrome. Mitochondrial injury involves microvesicular steatosis on liver biopsy, lactic acidosis, and modest elevations of aminotransferase levels and may be caused by valproic acid or high-dose parenteral tetracycline.

**MECHANISMS OF HEPATOTOXICITY AND SUSCEPTIBILITY FACTORS**

Drug-related hepatotoxicity cannot be viewed as a single disease. Many different mechanisms lead to hepatotoxicity, including disruption of the cell membrane and cell death resulting from covalent binding of the drug to cell proteins, which creates new adducts that serve as immune targets, thus inciting an immunologic reaction; inhibition of cellular pathways of drug metabolism; abnormal bile flow resulting from disruption of subcellular actin filaments or interruption of transport pumps, leading to cholestasis and jaundice, sometimes with minimal cell injury; programmed cell death (apoptosis), occurring through tumor-necrosis-factor and Fas pathways; and inhibition of mitochondrial function, with accumulation of reactive oxygen species and lipid peroxidation, fat accumulation, and cell death. More detailed discussions of these and other mechanisms have been presented by Lee and by Kaplowitz.

Adults are generally more susceptible to hepatotoxicity than are children, and women are more commonly affected than men. Obesity and malnutrition — particularly in the case of acetaminophen, which, when used in patients with malnutrition, may deplete glutathione — are susceptibility factors. Death attributable to the ingestion of acetaminophen is usually associated with doses of 15 to 25 g; some evidence suggests that alcohol use and fasting lower the threshold for hepatotoxicity from acetaminophen. Pregnancy, concomitantly administered medications, and a history of drug reactions also increase susceptibility. Preexisting liver disease and coexisting illnesses may have a greater effect on the ability of the patient to recover from liver injury than on the likelihood that it will develop.
Possibly the most important susceptibility factor for hepatotoxicity is genetic variability. Genetic polymorphisms have a strong influence on drug metabolism and may increase risk. For example, polymorphism of the N-acetyltransferase 2 gene differentiates fast from slow acetylators; the latter have increased susceptibility to isoniazid toxicity. The recent linkage of irinotecan toxicity to a diminished capacity for glucuronidation in patients with Gilbert syndrome is another example.

Approximately 1.8 percent of the U.S. population carries antibodies to the hepatitis C virus; 74 percent have viremia and are at risk for chronic liver disease. Nonalcoholic fatty liver disease is even more common. Patients with hyperlipidemia frequently have elevations in aminotransferase levels due to nonalcoholic fatty liver dis-

Figure 2. Liver-Biopsy Specimens Showing Common Histologic Features of Drug-Related Hepatotoxicity.
Panel A shows microvesicular steatosis, in which small fat droplets (arrow) are present within the hepatocytes and do not displace the nucleus. Examples of drugs that can induce such an injury include valproic acid and tetracycline. A typical hepatic enzyme pattern in such a reaction includes moderate elevations of the alanine aminotransferase and aspartate aminotransferase levels. Panel B shows acute hepatitis, with hepatocellular swelling, inflammation (black arrow), disarray of the hepatic lobule — which comprises the central vein, the portal triad (the portal vein, hepatic artery, and bile duct), and the hepatic cords — and hepatocellular necrosis with acidophil bodies (white arrow). An example of a drug that can induce such an injury is isoniazid; the predominant biochemical abnormality is hepatocellular, with elevations of the alanine aminotransferase and aspartate aminotransferase levels and less prominent elevations of the alkaline phosphatase and total bilirubin levels. Panel C depicts a cholestatic injury, with bile-stained hepatocytes (arrow), cellular swelling, and minimal inflammation. Typical agents that can cause this injury include amoxicillin–clavulanic acid and chlorpromazine. Alkaline phosphatase is the enzyme that is most prominently abnormal. Panel D shows an eosinophil-rich (arrow) inflammatory infiltrate in the portal triad. Such a histologic pattern may be seen in phenytoin-induced injury, with hepatic enzymes showing a predominantly hepatocellular (alanine aminotransferase, aspartate aminotransferase) pattern of inflammation, although a concurrent cholestatic component (alkaline phosphatase) is not unusual.
ease; such patients do not appear to be at increased risk for statin-associated hepatotoxicity.39

**DIAGNOSIS**

The appearance of symptoms ranging from non-specific anorexia, nausea, and fatigue to obvious jaundice in the setting of the use of prescription or nonprescription medication or dietary supplements should raise the suspicion of drug-related hepatotoxicity. Other causes of liver injury must be ruled out, including hepatitis A or B infection (and, less often, acute hepatitis C infection), alcoholic or autoimmune hepatitis, biliary tract disorders, and hemodynamic problems (Fig. 3). Viral hepatitis can be evaluated by measuring hepatitis A IgM antibody, hepatitis B surface antigen, and hepatitis C antibody or hepatitis C RNA, which are positive in acute hepatitis A, B, and C, respectively. In developing countries, liver injury may result from hepatitis E infection, in which case the presence of antibody should be determined. Biliary abnormalities may lead to liver injury through obstruction or infection, as occurs in cholecystitis or cholangitis. Imaging of the biliary tree, with ultrasonography followed by cross-sectional imaging with computed tomographic scanning or magnetic resonance imaging, is appropriate. The use of endoscopic retrograde cholangiopancreatography allows for the coupling of diagnosis with interventions to relieve obstruction.

Liver injury attributable to alcohol should be suspected if there is a history of recent consumption, a detectable serum alcohol level, or an aspartate aminotransferase level greater than that of alanine aminotransferase by a ratio of 2:1. Autoimmune disease should be suspected if liver injury occurs in the presence of antinuclear or smooth-muscle antibodies or of elevated globulin levels. Hemodynamic abnormalities, such as cardiovascular shock or heart failure, may cause liver injury. In this situation, a history of hypotension or syncope is common. Finally, genetic and metabolic disorders may produce liver injury: elevations in ferritin and iron levels and in total iron-binding capacity may suggest the presence of hemochromatosis; a low α1-antitrypsin level and an abnormal phenotype may suggest disease associated with a deficiency of this protein; and a low ceruloplasmin level in a young person with liver injury suggests the possibility of Wilson’s disease. Liver injury in the absence of another cause may be drug-related but requires additional information, such as that obtained through a careful drug history, in relation to the onset of injury.

Serum-chemistry tests must be supplemented by additional clinical evidence to determine accurately whether the injury has been caused by disease or a drug.40 Various methods have focused on scoring factors, including the timing of exposure, age, alcohol use, pregnancy, the concomitant use of medications, the exclusion of nondrug causes, known information about drug reactions, and the response to rechallenge.41-45 Each factor is given points, which, when summed, allow the clinician to diagnose hepatotoxicity with varying levels of confidence. Table 1 lists the key elements.

![Figure 3. Diagnosis of Drug-Related Hepatotoxicity.](image-url)
Table 1. Key Elements of and Caveats in Assessing Cause in the Diagnosis of Drug-Related Hepatotoxicity.

| Exposition to a drug must precede the onset of liver injury for diagnosis as drug-induced. |
| Caveat: The latent period for the onset of injury after drug use is highly variable. |
| Disease as a cause of liver injury should be ruled out before concluding that hepatotoxicity is drug-related. |
| Caveat: Drugs taken concurrently should also be evaluated. |
| Injury may improve when administration of a drug is stopped (so-called dechallenge). |
| Caveat: Liver injury may first worsen for days or weeks. In severe cases, falling enzyme levels may indicate impending liver failure, not improvement, especially if accompanied by worsening function. |
| Liver injury may recur more rapidly and severely on repeated exposure, especially if immunologic in nature. |
| Caveat: Worsening on rechallenge may not occur if adaptive tolerance has occurred. |

of the assessment of cause in the diagnosis of drug-related hepatotoxicity. Lee and Senior⁴⁶ point out that there are several limitations to these methods, including the facts that age and alcohol use have not been shown to cause worse outcome in patients with acute liver failure, that the time course of liver injury as well as the onset and resolution of hepatic impairment may be highly variable, and that rechallenge does not always lead to a recurrence of hepatotoxicity.

The clinical presentations of hepatotoxicity that are most readily distinguished are acute hepatocellular injury and cholestatic liver disease.¹⁰ Acute hepatocellular injury often is associated with symptoms of malaise, abdominal pain, and jaundice. The alanine aminotransferase level is markedly elevated, with minimal elevations in the alkaline phosphatase level. The combination of jaundice, impaired hepatic function (indicated by an increased prothrombin time or its INR), and encephalopathy indicates particularly severe liver injury. The development of these signs less than 26 weeks after the onset of illness in a patient without preexisting cirrhosis is the hallmark of acute liver failure. This syndrome has a poor prognosis without liver transplantation³ and is a problem of great concern.

Cholestatic liver disease is characterized by jaundice and pruritus, with the alkaline phosphatase level being the most prominently elevated of the liver-enzyme levels initially. Recovery is usually complete but may take several weeks or months. In rare cases, chronic liver injury may occur owing to a self-perpetuating injury termed the vanishing bile duct syndrome.⁴⁷,⁴⁸ Cholestatic drug-induced hepatotoxicity is less likely to be immediately serious but may be prolonged.

**MANAGEMENT**

In the presence of symptoms, particularly jaundice, and of impaired hepatic function or clinical signs of acute liver failure (e.g., encephalopathy), the use of any agent suspected of causing hepatotoxicity should be stopped. Liver injury should be assessed biochemically, immediately and serially,³ with prompt consultation from a hepatologist or gastroenterologist. Rechallenge usually should not be performed, since a recurrent injury may be more severe than the initial insult, especially if the injury is immunologic.

Improvement occurs in most cases, although at variable rates, and is not always immediate after the offending drug is stopped. In fact, liver injury may worsen or follow a protracted course of recovery over weeks or months. Not infrequently, drugs cause transient and asymptomatic but not progressive elevations of aminotransferase levels even while the exposure to a drug continues, and this may represent adaptation.¹⁴ Statins have been shown to cause elevations of aminotransferase levels and severe liver injury in animals; in humans such elevations are common but rarely, if ever, lead to clinically significant hepatotoxicity.⁴⁹ Isoniazid is another example of a drug that commonly causes elevations of liver enzyme levels, yet such increases require permanent cessation of the administration of the drug in only about 1 in 1000 patients.¹³

**PREVENTION**

**THE DRUG-DEVELOPMENT PROCESS**

The first opportunity to prevent hepatotoxicity arises in the early stages of drug development, when animals are exposed to a drug and assessments with regard to toxicity are made. Preclinical studies in animals are more useful for detecting dose-related, predictable hepatotoxicity than they are for detecting unpredictable hepatotoxicity in humans. Phase 1 safety studies provide the first opportunity to identify drug-related hepatotoxicity in humans. These studies are limited by their small number of participants — 12 to 30 healthy subjects — and the brief exposure of these subjects to low doses of a given drug. During effi-
cacy testing, more patients are exposed to a drug, and the likelihood that hepatotoxicity will become evident is higher; however, the limited number of participants involved in controlled clinical trials means that a 95 percent or greater chance of even one case of a rare event occurring with a true incidence of 1 in 1000 subjects requires that almost 3000 be observed.50

The case of troglitazone highlights the importance of recognizing signs of hepatotoxicity during drug development. Troglitazone (Rezulin) was the first peroxisome-proliferator-activated receptor γ agonist approved for use in achieving blood glucose control in patients with non-insulin-dependent diabetes. During clinical trials, 12 of 2510 patients treated with troglitazone had alanine aminotransferase levels of more than 10 times the upper limit of the normal range, and 5 had levels of more than 20 times the upper limit of normal; biopsies were performed in 2 patients, including 1 in whom jaundice developed.51 These observations proved to be predictive of adverse events after troglitazone was marketed, when liver failure developed in 94 of the nearly 2 million patients who used the drug.52 Ultimately, troglitazone was withdrawn from the market, in March of 2000. This situation highlighted the need to appreciate signals that predict hepatotoxicity while a drug is being developed.53

### POST-MARKETING SURVEILLANCE

Currently, the period after a drug is approved is the most important for identifying hepatotoxicity. At present, the FDA’s MedWatch program is a good way to report suspected drug-related hepatotoxicity.54,55 This voluntary reporting system is limited in the use and adequacy of reported clinical details. Case reports that appear in the literature also draw attention to potential hepatotoxins,56-58 particularly substances that are not studied by the manufacturer or regulated by the FDA, such as herbal and over-the-counter complementary and alternative medications.

### MONITORING OF LIVER TESTS IN CLINICAL PRACTICE

There is no evidence to show that, despite instructions and warnings on drug labels, routine monitoring of liver enzymes prevents clinically significant hepatotoxicity, most of which is unpredictable and quite uncommon. Thus, an argument can be made that a more effective and efficient method of detecting and preventing hepatotoxicity would involve vigilance on the part of the patients themselves in recognizing symptoms,13 followed by prompt medical evaluation. Admittedly, such an approach may not apply to all drugs. Table 2 lists key points that may be broadly applied in the recognition and prevention of drug-related hepatotoxicity in clinical practice.

### PHARMACOGENOMICS

Exploitation of the growing body of knowledge of genetic polymorphisms, through the field of pharmacogenomics, should revolutionize our ability to prevent hepatotoxicity. The emerging fields of proteomics and metabonomics also promise insights into the mechanisms of drug-related hepatotoxicity.

It has been postulated that tailoring drug therapy to individual patients may maximize therapeutic effects while minimizing hepatotoxicity, but as yet no genetic tests have come into routine clinical use.30,59

### Table 2. Key Guidelines in the Recognition and Prevention of Hepatotoxicity in Clinical Practice.

<table>
<thead>
<tr>
<th>Do not ignore symptoms</th>
<th>When a drug is being used, even vague symptoms such as nausea, anorexia, malaise, fatigue, and right upper abdominal discomfort as well as specific symptoms such as itching or jaundice should prompt consideration of hepatotoxicity. Testing for liver injury and abnormal function should be performed.</th>
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<tbody>
<tr>
<td>Take a careful history</td>
<td>Elicit a detailed history of the use of prescribed and nonprescribed over-the-counter herbal and other medications or remedies, with dates and amounts.</td>
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Only large prospective trials can provide missing information on drug-related hepatotoxicity, such as its true incidence and associated risk factors, and allow access to biologic samples to learn more about its mechanisms. The multicenter Acute Liver Failure Study collects information on cases of acute liver failure at 50 liver-transplantation centers across the United States. This ongoing study has made several important contributions to the understanding of hepatotoxicity, including the finding that drugs are the most frequent cause of acute liver failure.5,6,9 The National Institutes of Health has funded a multicenter network of five institutions aimed at studying drug-induced liver injury.6

In an attempt to better understand the metabolic pathways involved in hepatotoxicity, this study will facilitate pharmacogenomic exploration through the development of a specimen bank of DNA samples from patients who have idiosyncratic drug reactions.

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Dr. Senior is an employee of the FDA and has no conflicts to report. However, the views expressed in this article represent the opinions of the authors and do not reflect an official position statement of either Jefferson Medical College or the FDA.

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