to as liver chemistries or liver tests, and should not be referred to as liver function tests. True tests of liver function are not commonly performed but include measurement of hepatic substrates that are cleared by hepatic uptake, metabolism, or both processes (2). Because of the widespread use of the comprehensive metabolic profile testing that is done in routine practice to screen those who present for routine evaluation as well as those who are symptomatic and/or referred for elevation of abnormal liver chemistries, such abnormalities require a rational approach to interpretation. To date, there are no controlled trials that have been performed to determine the optimal approach to evaluate abnormal liver chemistries. This guideline has been developed to assist gastroenterologists and primary care providers in the interpretation of normal and abnormal liver chemistries as well as an approach to prioritize and evaluate those who present with abnormal liver chemistries.

Summary statements:

1. Liver chemistries including ALT, aspartate aminotransferase (AST), alkaline phosphatase and bilirubin are markers of liver injury, not liver function, and should be referred to as liver chemistries, or liver tests.
2. Albumin, bilirubin, and prothrombin time are markers of hepatocellular function that can be influenced by extrahepatic factors.
3. The laboratory measurements of ALT, AST, and alkaline phosphatase are highly reproducible.
4. Elevations of AST and/or ALT, alkaline phosphatase, and bilirubin suggest hepatocellular injury and are the abnormal liver chemistries that require assessment and potential evaluation.
5. ALT is a more specific marker of hepatic injury than AST.
6. An elevated alkaline phosphatase level of hepatic origin may be confirmed by elevation of gamma-glutamyl transferase (GGT) or fractionation of alkaline phosphatase.

The standard comprehensive metabolic profile panel includes AST, ALT, alkaline phosphatase, bilirubin, and albumin. In addition, a prothrombin time may be ordered. Aminotransferases including AST and ALT are enzymes involved in the transfer of amino groups of aspartate and alanine to ketoglutaric acid and are markers of hepatocellular injury and are also referred to as transaminases (3). AST is present in the liver and other organs including cardiac muscle, skeletal muscle, kidney, and brain. ALT is present primarily in the liver, and thus is a more specific marker of hepatocellular cell injury (4–6). AST increase without elevation in ALT is suggestive of cardiac or muscle disease.

Alkaline phosphatase is part of a family of zinc metalloproteinases enzymes that catalyze the hydrolysis of phosphate esters at an alkaline pH (7). This enzyme is found in hepatocytes on the canalicular membrane, not the bile duct cell. In addition to being present on the canalicular membrane of the hepatocyte, alkaline phosphatase is also found in bone, placenta, intestine, and kidney with the most common extrahepatic location originating from bone. Although rarely used in practice, in those with blood type O and B, serum alkaline phosphatase may increase after a fatty meal due to increased levels of intestinal alkaline phosphatase (8). Alkaline phosphatase may be elevated during pregnancy due to placental synthesis of alkaline phosphatase. Typically, alkaline phosphatase elevates with obstruction of the bile ducts, which is due to increased canalicular synthesis of alkaline phosphatase with subsequent translocation to the sinusoid and is also a measure of liver injury (9). This occurs even if the obstruction is minor and insufficient to increase serum bilirubin levels. To confirm hepatic origin of alkaline phosphatase, the canalicular enzyme GGT may be measured. An elevated GGT suggests that the alkaline phosphatase elevation is of hepatic origin (6). Alkaline phosphatase may also be fractionated to better delineate bone, intestinal or hepatic origin of an elevated alkaline phosphatase. In children and the elderly, alkaline phosphatase levels increase, especially females over 50 years of age, in part due to bone turnover (10,11).

Bilirubin comes from the breakdown of senescent red blood cells and predominantly circulates in its unconjugated form tightly bound to albumin. Unconjugated bilirubin is not excreted in the urine. Conjugation by uridine 5'-diphospho (UDP)-glucuronosyltransferase makes bilirubin water-soluble (conjugated bilirubin), allowing it to be excreted in bile where it is converted by bacteria in the colon to urobilinogen, which is subsequently excreted in the urine and stool. The absence of urobilinogen gives stool its classic clay-colored appearance in those with impaired bile flow. Unconjugated bilirubin is reported as indirect bilirubin as determined by the van den Bergh reaction and accounts for ~70% of the total serum bilirubin (12). The total serum bilirubin is usually <1.1 mg/dl and an elevated direct bilirubin (conjugated bilirubin) indicates hepatocellular dysfunction or cholestasis. Fractionation of the bilirubin level to conjugated and unconjugated forms is not done routinely as many laboratories only report total serum bilirubin, which is the sum of conjugated and unconjugated portions. Fractionation of total bilirubin is most helpful when the ALT, AST, and alkaline phosphatase levels are normal or near normal. If the total bilirubin is elevated and fractionation shows the majority of the elevation is unconjugated bilirubin, hepatocellular disease is unlikely to be the explanation. Conjugated bilirubin elevations are present in hepatocellular disorders as well as cholestatic disorders with impairment in bile flow. The delta bilirubin is derived from the reaction of conjugated bilirubin and albumin and has a half-life similar to albumin (5). The delta bilirubin accounts for the prolonged jaundice noted in patients recovering from hepatitis or significant obstruction as its decay is directly related to the half-life of albumin which is 3 weeks.

Two markers of hepatocellular function are albumin and prothrombin time. Albumin is a plasma protein exclusively synthesized by the liver with a circulating half-life of 3 weeks (6). A reduction in albumin (normal ≥3.5 g/dl) usually indicates liver disease of more than 3 weeks duration, although any significant illness can decrease albumin levels due to cytokine effects. Prothrombin time is a far more sensitive measure of liver function than albumin because prothrombin time may be prolonged in patients with severe liver disease of <24 h duration (6). Prothrombin time measures the extrinsic pathway of coagulation. The prothrombin time is a measurement of the clotting tendency of the