

## ASH FibroSURE™

### Introduction

Alcoholic liver disease covers a wide range of manifestations from simple fatty infiltration to extensive fibrosis, cirrhosis, and/or hepatocellular carcinoma. The spectrum of disease is dependent on the dose and duration of alcohol consumption as well as on genetic and environmental factors that appear to play a role. Cofactors that facilitate progression of liver injury include viral hepatitis infection, iron overload, and obesity with diabetes mellitus.<sup>1,2</sup> Although 90% to 100% of heavy drinkers (defined as >60g-80g in men and >20g in women of alcohol/day have evidence of steatosis (fatty liver), only 10% to 35% develop alcoholic steatohepatitis (ASH), and 8% to 20% develop cirrhosis.<sup>1,3</sup> Steatosis is the earliest manifestation of alcoholic liver damage. It is characterized by the presence of macrovesicular steatosis with minimal or no inflammation.<sup>4</sup> ASH is considered a more histologically advanced form of the disease. It is characterized by the presence of inflammation, primarily neutrophil-rich, hepatocyte necrosis, intracytoplasmic Mallory bodies (alcoholic hyalin), and variable amounts of perivenular or perisinusoidal fibrosis.<sup>4</sup>

Continued alcohol consumption and sustained ASH leads to cirrhosis. Accumulation of the alcohol metabolism product, acetaldehyde, leads to production of reactive oxygen species, upregulation of a variety of cytokines, and activation of hepatic stellate cells that orchestrate fibrogenesis.<sup>5</sup> The most effective therapy is abstinence from alcohol consumption. Alcoholic steatosis with minimal inflammation is usually reversible within a few weeks of discontinuing alcohol consumption.<sup>1</sup> Abstaining from alcohol is also important in stabilizing or reducing more advanced inflammation and fibrosis associated with ASH. Corticosteroid treatment reduces short-term mortality in patients with severe ASH,<sup>6,7</sup> and cytokine-directed therapies and antioxidants are being investigated.<sup>2</sup>

### Laboratory and Diagnostic Features

Since many patients are asymptomatic, screening for alcoholic consumption should be a routine part of annual medical examinations. Overt signs of alcoholic hepatitis such as fever, jaundice, hepatomegaly, ascites, portal hypertension, and bleeding may not be present even in patients with extensive liver fibrosis.<sup>1,2</sup> Laboratory examination often reveals leukocytosis, elevated liver enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lutamyl transpeptidase

(GGT) with an AST/ALT ratio greater than 2.0. Serum bilirubin, albumin and prothrombin time may not become abnormal until cirrhosis develops.<sup>1,2</sup> Ultrasonography may be helpful in identifying evidence of fatty infiltration and/or nodularity and portal hypertension associated with cirrhosis, but negative findings do not exclude the diagnosis.<sup>1</sup>

Despite its invasiveness and potential for complications, liver biopsy has been used to establish a definitive diagnosis, to evaluate the severity of necroinflammatory activity, and to assess prognosis—particularly if corticosteroid or other therapy is being considered.<sup>1,2</sup> Percutaneous liver biopsy may be contraindicated because of the presence of coagulopathy, thrombocytopenia, and ascites, necessitating a transjugular approach.<sup>2</sup> Noninvasive biomarkers (HCV FibroSURE™) for the assessment of liver pathology in viral hepatitis C patients have been available since 2003.<sup>8,9</sup> New research and development efforts have made noninvasive markers available for the management of suspected alcoholic liver disease patients.<sup>10-12</sup>

### ASH FibroSURE™

ASH FibroSURE is a noninvasive assessment of liver status for patients with alcoholic liver disease (ALD). Quantitative results of 10 biochemicals, including  $\alpha_2$ -macroglobulin, haptoglobin, apolipoprotein A<sub>1</sub>, bilirubin, GGT, ALT, AST, total cholesterol, triglycerides, and fasting glucose, in combination with age, gender, height, and weight, are analyzed, using a proprietary algorithm, to provide quantitative surrogate markers for liver fibrosis, hepatic steatosis, and ASH.

**Fibrosis Marker.** ASH FibroSURE includes a quantitative surrogate fibrosis marker (0.00-1.00), corresponding to the Metavir F0-F4 fibrosis staging, that has been evaluated in viral hepatitis patients.<sup>8,9</sup> It has recently been validated in chronic alcoholic liver disease.<sup>10</sup> Among 221 alcoholic patients where 63% had significant alcoholic fibrosis (Metavir F2-F4) and 31% had cirrhosis by liver biopsy, a fibrosis result of >0.3 yielded a sensitivity of 84% and a specificity of 66% for the detection of significant fibrosis. A fibrosis result of >0.7 yielded a sensitivity of 91% and a specificity of 87% for detection of cirrhosis.<sup>10</sup>

**Steatosis Marker.** ASH FibroSURE provides a quantitative surrogate marker (0.00-1.00) for hepatic steatosis grade S0-S3 corresponding to 0% to >66%. The steatosis marker

has been studied in a variety of patient types including chronic hepatitis C patients, alcoholic liver disease, and nonalcoholic fatty liver disease (NAFLD). In a population of 744 patients (583 HCV, 18 HBV, 69 NAFLD, and 74 alcoholic disease patients), where 36% had significant steatosis (>5%) on a liver biopsy, a steatosis score >0.5 had a sensitivity of 71% and a specificity of 72% for identification of significant steatosis.<sup>11</sup>

**ASH Marker.** The ASH FibroSURE test also provides a quantitative surrogate marker (0.00-1.00) for alcoholic steatohepatitis grade (ASH 0-ASH 3). In a population of 225 alcoholic patients where 34% had alcoholic hepatitis features (polynuclear neutrophil infiltrate and hepatocellular necrosis) by liver biopsy, an ASH value >0.5 had a sensitivity of 80% and a specificity of 84% in identifying alcoholic steatohepatitis.<sup>12</sup>

Studies evaluating markers of ASH FibroSURE have used the liver biopsy as the “gold standard” against which noninvasive biomarkers are evaluated; however, it is important to note that sampling variability has been documented in HCV-infected liver biopsies,<sup>13,14</sup> in NASH,<sup>15</sup> and may also be a factor in ALD.

ASH FibroSURE should only be used for patients with suspected alcoholic liver disease. It is not recommended for patient with other liver diseases. HCV FibroSURE is recommended for patients with viral hepatitis, and NASH FibroSURE should be used for patients with suspected nonalcoholic fatty liver disease. None of the FibroSURE tests should be used for patients with Gilbert disease, acute hemolysis, acute viral hepatitis, drug-induced hepatitis, genetic liver disease, autoimmune hepatitis, and/or extrahepatic cholestasis. Any of these clinical situations may lead to inaccurate quantitative predictions of fibrosis.

#### ASH FibroSURE™

**CPT** 82172; 82247; 82465; 82947; 82977; 83010; 83883; 84450; 84460; 84478

**Synonyms** Alcoholic Liver Disease; Noninvasive Liver Biopsy; Steatohepatitis

**Special Instructions** Age, sex, height, and weight are required for this test.

**Specimen** Serum

**Volume** 3 mL

**Minimum Volume** 3 mL

**Container** Red-top tube or gel-barrier tube

**Collection** Separate serum from cells within 1 hour of collection. Protect from light. To avoid delays turnaround time, please submit separate frozen specimens for each test when requesting multiple tests on frozen specimens.

**Storage Instructions** Store at 2°C to 8°C for up to 72 hours. Freeze for longer storage.

**Patient Preparation** Patient should be fasting for at least 8 hours.

**Causes for Rejection** Gross hemolysis; gross lipemia; improper labeling; nonfasting specimen; sample not protected from light

**Use** This test is intended for noninvasive assessment of liver status in patients with alcoholic liver disease. Quantitative results of 10 biochemicals in combination with age, gender, height, and weight are analyzed using a computational algorithm to provide a quantitative surrogate marker (0.0-1.0) of liver fibrosis (Metavir F0-F4), hepatic steatosis (0.0-1.0, S0-S3), and alcoholic steatohepatitis (ASH) (0.0-1.0, H0-H3).

**Limitations** ASH FibroSURE is recommended for patients with suspected alcoholic liver disease. It is not recommended for patients with other liver diseases. It is also not recommended in patients with Gilbert disease, acute hemolysis, acute hepatitis, acute inflammation of the liver, extrahepatic cholestasis, transplant patients, and/or renal insufficiency patients. Any of these clinical situations may lead to inaccurate quantitative predictions of fibrosis.

## References

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