

NASH FibroSURE™

Introduction

Nonalcoholic fatty liver disease (NAFLD) covers a spectrum of liver disease from simple fatty infiltration (steatosis) to progressive fibrosis. Nonalcoholic steatohepatitis (NASH), first described in 1980 by Ludwig et al,¹ refers to the progressive form of NAFLD, which can lead to cirrhosis and hepatocellular carcinoma. It is now recognized as the most common cause of cryptogenic cirrhosis.² The prevalence of NAFLD in the US population is estimated at 3% to 24%.³ Prevalence is higher for special populations—particularly the obese and/or those with the metabolic syndrome characterized by type II diabetes mellitus, hypertension, and hypertriglyceridemia.

The pathogenesis of NASH is not yet fully understood, but insulin resistance, accumulation of triglycerides in the hepatocytes, oxidative stress, cytokine effects, and fatty acid toxicity are all suspected to be involved in the progression from simple steatosis to NASH. No single therapy is available for patients with NASH, but efforts are generally aimed at modifying the conditions associated with NASH, including obesity, hypertriglyceridemia, and diabetes mellitus. As more is learned about the underlying pathogenesis of NASH, new targeted therapeutic approaches are being investigated.

Laboratory and Diagnostic Features

Laboratory abnormalities of NAFLD include mildly to moderately elevated liver enzymes (ALT and/or AST), rarely exceeding 10 times the upper limit of normal. An AST/ALT ratio greater than 1 often indicates more severe disease.³ Serum bilirubin, prothrombin time, and albumin are typically normal, except in NAFLD-associated cirrhosis. Hepatic ultrasound may reveal increased echogenicity of the liver due to fatty infiltration, but negative findings do not exclude the diagnosis of NAFLD.⁴ Furthermore, none of the radiographic modalities can differentiate between NASH and other forms of NAFLD.⁴

Despite its invasiveness and potential for complications, liver biopsy has been used to diagnose and stage NAFLD. Depending on the severity of the disease, a liver biopsy may reveal simple macrovesicular steatosis—with or without inflammatory changes—or (in advanced cases) hepatocyte ballooning, necrosis, perisinusoidal fibrosis, and/or cirrhosis. The NASH Clinical Research Network recently validated a histological feature scoring system that takes into consideration steatosis, lobular

inflammation, and hepatocellular ballooning to assist in diagnostic categorization as “NASH,” “borderline NASH,” or “not NASH.”⁵ Noninvasive biomarkers (HCV FibroSURE™) for the assessment of liver pathology in viral hepatitis C patients have been available since 2003.^{6,7} New research and development efforts have made noninvasive markers available for the management of suspected NAFLD patients.⁸⁻¹⁰

NASH FibroSURE™

NASH FibroSURE is a noninvasive assessment of liver status for patients with nonalcoholic fatty liver disease (NAFLD). Quantitative results of 10 biochemicals, including α_2 -macroglobulin, haptoglobin, apolipoprotein A₁, bilirubin, γ -glutamyl transpeptidase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (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 NASH.

Fibrosis Marker. NASH FibroSURE includes a quantitative surrogate fibrosis marker (0.00-1.00), corresponding to the Metavir F0-F4 fibrosis staging, that has been validated in viral hepatitis^{6,7} and in alcoholic hepatitis¹¹ but only recently evaluated in NAFLD patients. In a study of 171 NAFLD patients where 23% had significant NAFLD-associated fibrosis (Metavir F2-F4) and 11% had cirrhosis by liver biopsy, a fibrosis result of >0.3 yielded a sensitivity of 83% and a specificity of 78% for the detection of significant fibrosis.⁸

Steatosis Marker. NASH 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, alcoholic liver disease, and 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 liver biopsy, a steatosis score >0.5 had a sensitivity of 71% and a specificity of 72% for identification of significant steatosis.⁹

NASH Marker. The NASH FibroSURE test also provides a diagnostic assessment of the presence of NASH using three broad categories N0-N2 corresponding to “Not NASH,” “Borderline NASH,” and “NASH” per the Kleiner classifica-

tion.⁵ In a population of 257 NAFLD patients, where 62% had at least borderline ASH by liver biopsy, a prediction of NASH had a sensitivity of 88% for identifying NASH and a specificity of 50%.¹⁰

Studies evaluating markers of NASH FibroSURE have used liver biopsy as the “gold standard” against which noninvasive biomarkers are evaluated; however, sampling variability and heterogeneity in NAFLD and NASH liver biopsy evaluations pose a significant challenge for such evaluations. Sampling error has been documented in liver biopsies of HCV-infected individuals^{12,13} and is even more pronounced in NAFLD and NASH where the uneven distribution of histologic lesions of NASH can lead to substantial misdiagnosis and staging inaccuracies.^{14,15}

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

Synonyms Fatty Liver Disease; NAFLD; Nonalcoholic Fatty 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; improperly labeled specimen; non-fasting specimen; sample not protected from light

Use This test is a noninvasive assessment of liver status in patients with nonalcoholic fatty liver disease (NAFLD). 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 non-alcoholic steatohepatitis (NASH) (0.0-0.75, N0-N2). The absence of steatosis (S<0.38) precludes the diagnosis of NASH.

Limitations NASH FibroSURE is recommended for patients with suspected nonalcoholic fatty 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, autoimmune hepatitis, extrahepatic cholestasis, transplant patients, and/or renal insufficiency patients. Any of these clinical situations may lead to inaccurate quantitative predictions of fibrosis.

NASH FibroSURE should only be used for patients with suspected nonalcoholic fatty liver disease. It is not recommended for patients with other liver diseases. HCV FibroSURE is recommended for patients with viral hepatitis, and ASH FibroSURE should be used for patients with suspected alcoholic 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.

References

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