



[A technical review]

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 classification.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}

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.

NASH FibroSURE™ 550140

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

Test Includes α_2 -macroglobulin; alanine aminotransferase (ALT); apolipoprotein A₁; aspartate aminotransferase (AST); bilirubin, total; cholesterol, total; γ -glutamyl transpeptidase (GGT); glucose; haptoglobin; triglycerides

Specimen Serum

Volume 3 mL

Minimum Volume 3 mL (**Note:** This volume does **not** allow for repeat testing.)

Container Red-stopper tube or gel-barrier tube

Collection Separate serum from cells within one hour of collection and refrigerate at 2°C to 8°C. **Protect from light.** Specimen is stable for as long as three days. Freeze if storage longer than 72 hours is needed.

Storage Instructions Refrigerate at 2°C to 8°C for as long as 72 hours; **freeze** if longer storage required.

Patient Preparation Patient should fast for at least eight hours.

Causes for Rejection Gross hemolysis; gross lipemia; improperly labeled specimen

Methodology Patented artificial intelligence algorithm combines patient’s age, gender, and the results of 10 biomarkers to generate a measure of nonalcoholic fatty liver disease

Contraindications NASH FibroSURE should **not** 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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