NON-ALCOHOLIC FATTY LIVER DISEASE

Testing options to help identify NAFLD and NASH

labcorp

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There is a growing, unmet need in chronic liver disease.

NAFLD

Non-alcoholic fatty liver disease (NAFLD) is a collective term used to describe a group of conditions in which there is an abnormal accumulation of fat in the liver in those who drink little to no alcohol. NAFLD is closely associated with features of metabolic syndrome, such as obesity, insulin resistance, type 2 diabetes (T2D), high blood pressure, and dyslipidemia. NAFLD may range from a non-serious condition called fatty liver to a potentially serious condition called non-alcoholic steatohepatitis.[1]

NASH

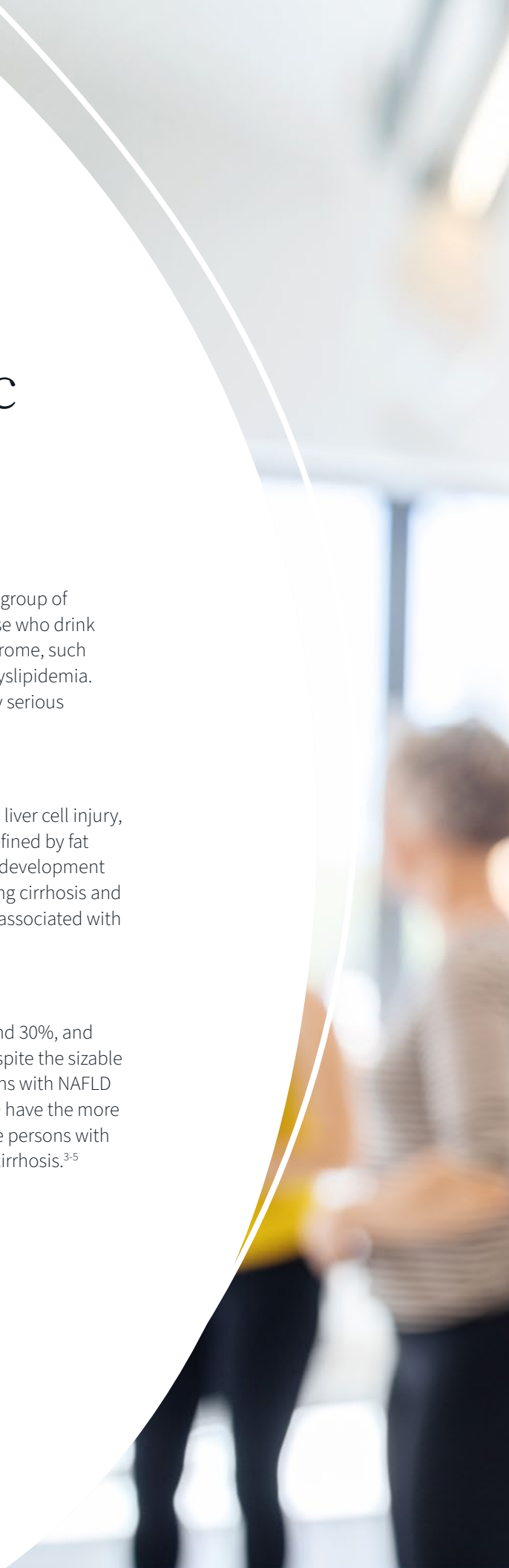
Non-alcoholic steatohepatitis (NASH) is a chronic liver disease characterized by liver cell injury, hepatocellular ballooning and inflammation as a result of steatosis, which is defined by fat accumulation in at least 5% of hepatocytes. This leads to liver scarring and the development of fibrosis (scored F0 to F4). As fibrosis worsens, liver-related morbidity (including cirrhosis and hepatocellular carcinoma) and mortality increase. Like NAFLD, NASH is closely associated with features of metabolic syndrome.[2]

Disease Prevalence

The prevalence of NAFLD in the United States is reported to be between 10% and 30%, and the overall global prevalence of NAFLD is estimated to be greater than 25%. Despite the sizable and growing prevalence, disease awareness remains limited with <5% of persons with NAFLD being aware of their disease. It is estimated that up to 14% of those with NAFLD have the more progressive disease known as NASH. As well, current estimates suggest of those persons with NASH, about 20% could potentially develop significant liver disease including cirrhosis.[3-5]

~80 million

Number of people in the United States living with NAFLD[6]



Those with fatty liver disease with obesity and features of metabolic syndrome that include insulin resistance, T2D, hypertension and dyslipidemia have a higher risk of progression to NASH.

Symptoms

NAFLD and NASH are often asymptomatic. When symptoms are present they can be very non-specific and can include fatigue, daytime tiredness, or abdominal pain early in the disease. Disease is often discovered incidentally due to elevated liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and abnormal imaging studies or surgery. As cirrhosis advances, symptoms may appear.[2]

Screening and diagnosis

NASH is diagnosed by liver biopsy; however, blood-based tests can support screening high-risk populations and assessing the risk of significant fibrosis.[5]

The 2022 AACE guidelines suggest the following for the diagnosis of NAFLD in adult patients:

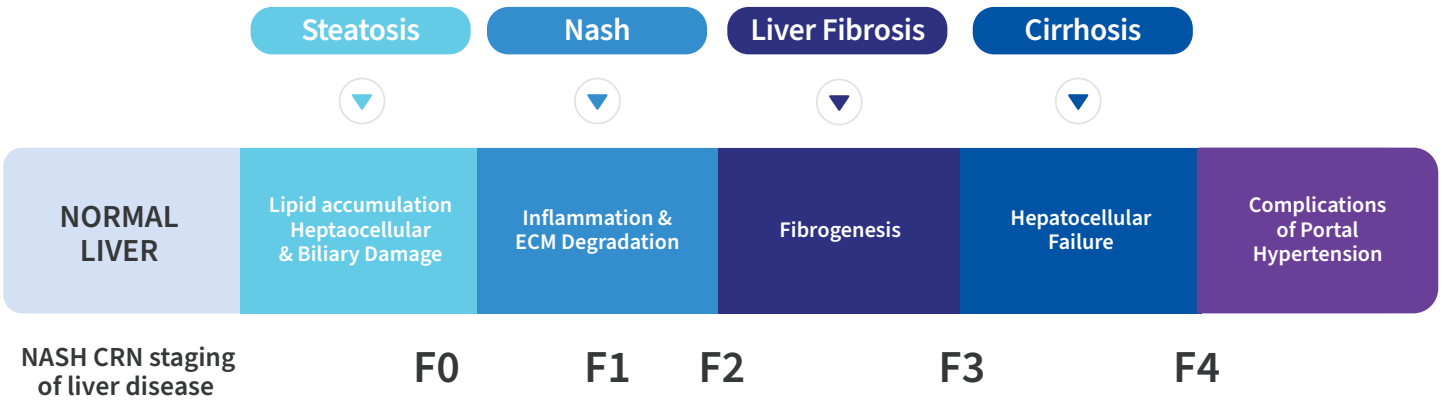
- Consider persons with obesity and/or features of metabolic syndrome, those with prediabetes or T2D, and those with hepatic steatosis on any imaging study and/or persistently elevated plasma aminotransferase levels (over 6 months) to be "high risk" and screen for NAFLD and advanced fibrosis.
- Persons undergoing bariatric surgery should be evaluated for the presence and severity of NASH, and a liver biopsy should be considered at the time of bariatric surgery. Liver biopsy should be recommended if presurgical stratification suggests indeterminate or high risk of liver fibrosis.

Testing for NAFLD and advanced fibrosis as suggested in the AACE guidelines:

- Use liver fibrosis prediction calculations to assess the risk of NAFLD with liver fibrosis. The preferred initial noninvasive, blood-based test is FIB-4.
- Consider persons belonging to the "high risk" group who have an indeterminate or high FIB-4 score for further workup with an imaging test such as LSM (transient elastography) or the blood-based ELF™ test, as available.
- Persons with persistently elevated ALT or AST levels and/or with hepatic steatosis on imaging and indeterminate risk (FIB-4, 1.3-2.67; LSM, 8-12 kPa; or ELF™ test, 7.7-9.8) or high risk (FIB-4, >2.67; LSM, >12 kPa; or ELF™ test, >9.8) based on blood tests and/or imaging (as described in R2.2.1, R2.2.2, and R2.3) should be referred to a gastroenterologist or hepatologist for further assessment, which may include a liver biopsy.

Identification of persons at higher risk of NAFLD, NASH and advanced fibrosis is the first step in optimizing patient management and therapy.

NAFLD Progression



*NASH Clinical Research Network (CRN) Scoring System

Treatment and patient management[5]

The AACE guidelines suggest that clinicians manage adults with NAFLD for comorbidities such as obesity, metabolic syndrome, T2D, dyslipidemia, hypertension, and cardiovascular disease (CVD) based on the current standards of care. Physicians should recommend lifestyle changes with a goal of at least 5%, preferably ≥10%, weight loss. More weight loss is often associated with greater liver histologic and cardiometabolic benefit. Furthermore, clinicians must recommend physical activity that improves body composition and cardiometabolic health.

While there aren't any medications that have been approved by the FDA specifically for NAFLD/NASH, there are medications that are effective for the treatment of liver disease as well as the cardiometabolic conditions associated with NAFLD or NASH. Pioglitazone and GLP-1 receptor agonists are recommended for persons with T2D and biopsy-proven NASH.

To offer cardiometabolic benefit in persons with T2D and NAFLD, clinicians must consider treatment with GLP-1 receptor agonists, pioglitazone, or SGLT2 inhibitors. Due to the lack of evidence of efficacy, metformin, acarbose, dipeptidyl peptidase IV inhibitors, and insulin are not recommended for the treatment of NASH but may be continued as needed for the treatment of hyperglycemia. Clinicians should recommend the use of obesity pharmacotherapy as adjunctive therapy to lifestyle modification for individuals with obesity and NAFLD or NASH with a goal of at least 5%, preferably ≥10 %, weight loss, when this is not effectively achieved by lifestyle modification alone.

For chronic weight management, clinicians should give preference to semaglutide 2.4 mg/week (best evidence) or liraglutide 3 mg/day. Clinicians should consider bariatric surgery as an option to treat NAFLD and improve cardiometabolic health in persons with NAFLD and a BMI of ≥35 kg/m2 (≥32.5 kg/m2 in Asian populations), particularly if T2D is present.

For persons with NASH and compensated cirrhosis, clinicians should exercise caution in recommending bariatric surgery, which should be highly individualized if prescribed and performed at experienced centers, however it is not recommended for persons with decompensated cirrhosis.

Assessment of liver fibrosis risk

FIB-4 (403604)

The FIB-4 index is a simple, accurate, readily available, blood-based test index that can help in evaluation of patients with NAFLD or hepatitis C virus (HCV) for the presence of liver fibrosis, and potentially the indication for liver biopsy. Results from the FIB-4 test include ALT, AST, platelet count and the FIB-4 score.[7]

Liver Fibrosis Risk Profile with Hepatic Function Panel, Complete Blood Count (CBC) With Differential, FIB-4, and APRI (402145)

This profile is intended for use in screening patients suspected to be at risk for liver fibrosis. APRI is a simple, accurate, readily available, blood-based test index that can stratify patients with NAFLD or HCV who are at high or low risk for significant fibrosis and cirrhosis with high degree of accuracy. FIB-4 index is a simple, accurate, readily available, blood-based test index that can help in evaluation of patients with HCV or NAFLD for the presence of liver fibrosis and potentially indication for liver biopsy.[7]

Assessment of "at-risk NASH"

(those with NASH who have a higher risk of progression to end-stage liver disease)

NASHnext™ (504960)

Utilizing NIS4™ technology, NASHnext is a blood-based diagnostic test that quantitatively measures four independent biomarkers (miR34a, CH13L1/YKl40, a2M, and HbA1c) to produce a score that identifies, among patients with metabolic factors, those with at-risk NASH, who are at higher risk of disease progression. NASHnext is the only blood-based test that identifies patients with at-risk NASH with significant liver fibrosis.[8]

Assessment of fibrosis, steatosis and inflammation

NASH FibroSure® Plus (550960)

This blood-based assessment of liver status in patients with NAFLD provides quantitative results of 10 biochemicals (α2-macroglobulin, haptoglobin, apolipoprotein A-1, total bilirubin, ɣ-glutamyltransferase (GGT), ALT, AST, total cholesterol, glucose, triglycerides) in combination with age and gender (BMI not required). These factors 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 NASH (0.0-0.75, N0-N2). The absence of steatosis (S<0.38) precludes the diagnosis of NASH.[9-11]

Prognostic assessment

Enhanced Liver Fibrosis (ELF™) (550659)

The Enhanced Liver Fibrosis (ELF™) test is a simple, accurate, blood-based test that provides a numeric score for use in patients known to have advanced liver fibrosis. The ELF™ score is derived from an algorithm that combines PIIINP, TIMP-1, and HA. It is indicated as a prognostic marker in conjunction with other laboratory findings and clinical assessments in patients with advanced fibrosis (F3 or F4) due to NASH in order to assess the likelihood of progression to cirrhosis and liver-related clinical events.[12]

Reflexive panels

FIB-4 With Reflex to Enhanced Liver Fibrosis (ELF™) (402175)

This panel is aligned to the testing algorithm identified by the 2022 AACE Clinical Practice Guideline for the Diagnosis and Management of NAFLD in Primary Care and Endocrinology Clinical Settings.[5] See individual tests descriptions.

FIB-4 With Reflex to NASH FibroSure® Plus (402146)

See individual tests descriptions.

At Labcorp, we believe proper testing can help slow the trends by helping identify those at risk of developing NAFLD and NASH.

Related Tests

Test Name	Test No.
NASH	
AST and Platelets with APRI	**385375**
Enhanced Liver Fibrosis (ELF™)	**550659**
FIB-4	**403604**
FIB-4 With Reflex to Enhanced Liver Fibrosis (ELF™)	**402175**
FIB-4 With Reflex to NASH FibroSure® Plus	**402146**
Liver Fibrosis Risk Profile with Hepatic Function Panel, Complete Blood Count (CBC) With Differential, FIB-4, and APRI	**402145**
NASHnext™	**504960**
NASH FibroSure® Plus	**550960**
Risk of Cardiovascular Disease and Type 2 Diabetes	
Glucose, Plasma	**001818**
Hemoglobin (Hb) A1c	**001453**
Insulin	**004333**
Lipid Panel Plus ApoB	**123544**
Lipid Panel Plus Diabetes Risk Index	**123525**
Lipid Panel Plus Inflammation	**123510**
Lipid Panel Plus Inflammation and Diabetes Risk Index	**123559**
Lipid Panel Plus Inflammation, Diabetes Risk Index and Apo B	**123567**
NMR LipoProfile® With Insulin Resistance Markers Without Lipids	**123497**
NMR LipoProfile® With Lipids and Insulin Resistance Markers	**123638**
Liver Related Markers	
α2-Macroglobulin, Quantitative	**122135**
Alanine Aminotransferase (ALT/SGPT)	**001545**
Albumin	**001081**
Alkaline Phosphatase	**001107**
Aspartate Aminotransferase (AST/SGOT)	**001123**
Bile Acids	**010330**
Lactic Acid Dehydrogenase (LD)	**001115**
Protein, Total	**001073**
ASH	
ASH FibroSure®	**550180**
Ethyl Glucuronide/Ethyl Sulfate (EtG/EtS), Screen and Confirmation, Urine	**737610**
Hepatitis	
Acute Viral Hepatitis (HAV, HBV, HCV)	**144000**
Hepatitis A Virus (HAV) Antibody, Total	**006726**
Hepatitis A Antibody, IgM	**006734**
Hepatitis B Virus (HBV) Screening and Diagnosis	**144473**

Test Name	Test No.
Hepatitis B Core Antibody, Total	**006718**
Hepatitis B Surface Antibody, Qualitative	**006395**
Hepatitis B Surface Antigen (HBsAg) Screen, Qualitative	**006510**
Hepatitis B Surface Antigen, Quantitative, Monitor	**007130**
Hepatitis B Virus (HBV) Genotype	**551710**
Hepatitis B Virus (HBV) Genotyping Plus Drug Resistance	**551750**
Hepatitis B Virus (HBV), Quantitative, DNA Real-time PCR, (Nongraphical)	**551610**
Hepatitis C Virus (HCV) Antibody With Reflex to Quantitative Real-time PCR	**144050**
Hepatitis C Virus (HCV) FibroSure®	**550123**
Hepatitis C Virus (HCV) GenoSure® NS3 / 4A	**550540**
Hepatitis C Virus (HCV) Genotype 3 NS5A Drug Resistance Assay	**550603**
Hepatitis C Virus (HCV) Genotyping, Nonreflex	**550475**
Hepatitis C Virus (HCV) NS5A Drug Resistance Assay	**550325**
Hepatitis C Virus (HCV) NS5B Drug Resistance Assay	**550505**
Hepatitis C Virus (HCV), Quantitative, Real-time PCR (Graphical)	**550070**
Hepatitis C Virus (HCV), Quantitative, Real-time PCR (Nongraphical)	**550080**
Hepatitis C Virus (HCV), Quantitative, RNA PCR (Graphical) With Reflex to Genotyping	**550100**
Hepatitis C Virus (HCV), Quantitative, RNA PCR (Nongraphical) With Reflex to Genotyping	**550090**
Other	
α-Fetoprotein (AFP), Tumor Marker	**002253**
α-Fetoprotein (AFP), Tumor Marker (Serial Monitor)	**480012**
α-Fetoprotein (AFP) With AFP-L3%, serum	**141300**
α1-Antitrypsin, Serum (preferred) or plasma	**001982**
α1-Antitrypsin Deficiency, DNA Analysis	**511881**
α1-Antitrypsin Phenotyping, Serum	**095653**
γ-Glutamyl Transferase (GGT)	**001958**
Actin (Smooth Muscle) Antibody (ASMA)	**006643**
Ammonia, Plasma	**007054**
Bilirubin, Total and Direct	**001214**
Ceruloplasmin	**001560**
Copper, Serum or Plasma	**001586**
Copper, Urine	**003343**
Hereditary Hemochromatosis, DNA Analysis	**511345**
Liver-Kidney Microsomal (LKM) Antibodies	**163980**
Mitochondrial (M2) Antibody	**006650**
Soluble Liver Antigen (SLA) IgG Antibody	**007441**
Thyroid Peroxidase (TPO) Antibodies	**006668**

Labcorp working to bring NASH technologies to the forefront

Superior testing options with NASHnext™, NASH FibroSure® Plus, ELF™ and more through Labcorp

- 15 NAFLD/NASH studies in 5 years, with 4 global phase 3 studies in progress at Labcorp Drug Development
- 4,000+ biopsy-confirmed patients recruited by Labcorp Drug Development, plus metrics on 700+ sites across 28 countries
- 31 NAFLD/NASH and NASH cirrhosis studies currently being conducted in our labs as of 2019

Drug development leadership & medical testing expertise makes Labcorp your choice for NASH collaboration.

References

1. American College of Gastroenterology website. Non-alcoholic Fatty Liver Disease (NAFLD). https://gi.org/topics/ fatty-liver-disease-nafld/. Accessed October 3, 2019.
2. Non-Alcoholic Steatohepatitis. Understanding NASH, A Major Public Health Issue. The NASH Education Program.
3. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence and outcomes. *Hepatology 2016*; 64(1):73-84
4. National Institute of Diabetes and Digestive and Kidney Diseases website. Treatment for NAFLD & NASH. https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash/treatment. Accessed October 3, 2019.
5. Cusi K et al. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by AASLD Endocr Pract. 2022 May;28(5):528-562. doi: 10.1016/j.eprac.2022.03.010.
6. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology*. 2018 Jan;67(1):123-133.
7. Angulo P, Bugianesi E, Bjornsson ES, et al. Simple noninvasive systems predict long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2013 Oct;145(4):782-789.e4. PubMed 23860502
8. Harrison SA, Ratziu V, Boursier J, Francque, S, Bedossa, P, Majd, Z, et al. A blood-based biomarker panel (NIS4) for non-invasive diagnosis of non-alcoholic steatohepatitis and liver fibrosis: a prospective derivation and global validation study. *Lancet Gastroenterol Hepatol*. 2020;5(11):970-985.
9. Poynard T, Peta V, Munteanu M, et al. The diagnostic performance of a simplified blood test (SteatoTest-2) for the prediction of liver steatosis. *Eur J Gastroenterol Hepatol*. 2019 Mar;31(3):393-402. PubMed 30516570
10. Poynard T, Munteanu M, Charlotte F, et al. Diagnostic performance of a new noninvasive test for nonalcoholic steatohepatis using a simplified histological reference. *Eur J Gastroenterol Hepatol*. 2018 May;30(5):569-577. PubMed 29406435
11. Ratziu V, Massard J, Charlotte F, et al. Diagnostic value of biochemical markers (FibroTest-FibroSURE) for the prediction of liver fibrosis in patients with non-alcoholic fatty liver disease. *BMC Gastroenterol*. 2006 Feb 14;6:6. PubMed 16503961
12. ADVIA Centaur® Enhanced Liver Fibrosis (ELF™) [package insert]. Tarrytown, NY. Siemens Healthcare Diagnostics Inc. Rev. 01, 2021-08.

For more information about NASH-NAFLD and how it can benefit your patients, visit **Labcorp.com/NASH**

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