METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Testing options to help identify MASLD and MASH

labcorp

METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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

MASLD

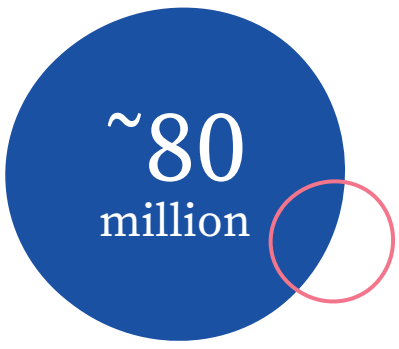
Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease (NAFLD), is a collective term used to describe a group of conditions in which there is an abnormal accumulation of fat in the liver in those who drink little to no alcohol. MASLD is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

MASH

Metabolic dysfunction-associated steatohepatitis, previously known as 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 MASLD, MASH is closely associated with features of metabolic syndrome.

Disease Prevalence

The prevalence of MASLD in the United States is reported to be between 10% and 30%, and the overall global prevalence of MASLD is estimated to be greater than 25%. Despite the sizable and growing prevalence, disease awareness remains limited, and <5% of persons with MASLD are aware of their disease. It is estimated that up to 14% of those with MASLD have the more progressive disease known as MASH. Current estimates suggest of those persons with MASH, about 20% could potentially develop significant liver disease including cirrhosis.[2-4]



Number of people in the United States living with MASLD[5]

Those with fatty liver disease with obesity and features of metabolic syndrome including insulin resistance, T2D, hypertension or dyslipidemia have a higher risk of progression to MASH

Screening in the primary care and endocrinology setting

Recent guidelines suggest persons with any of the following should be considered “high risk” and screened for MASLD and advanced fibrosis:[1,2]

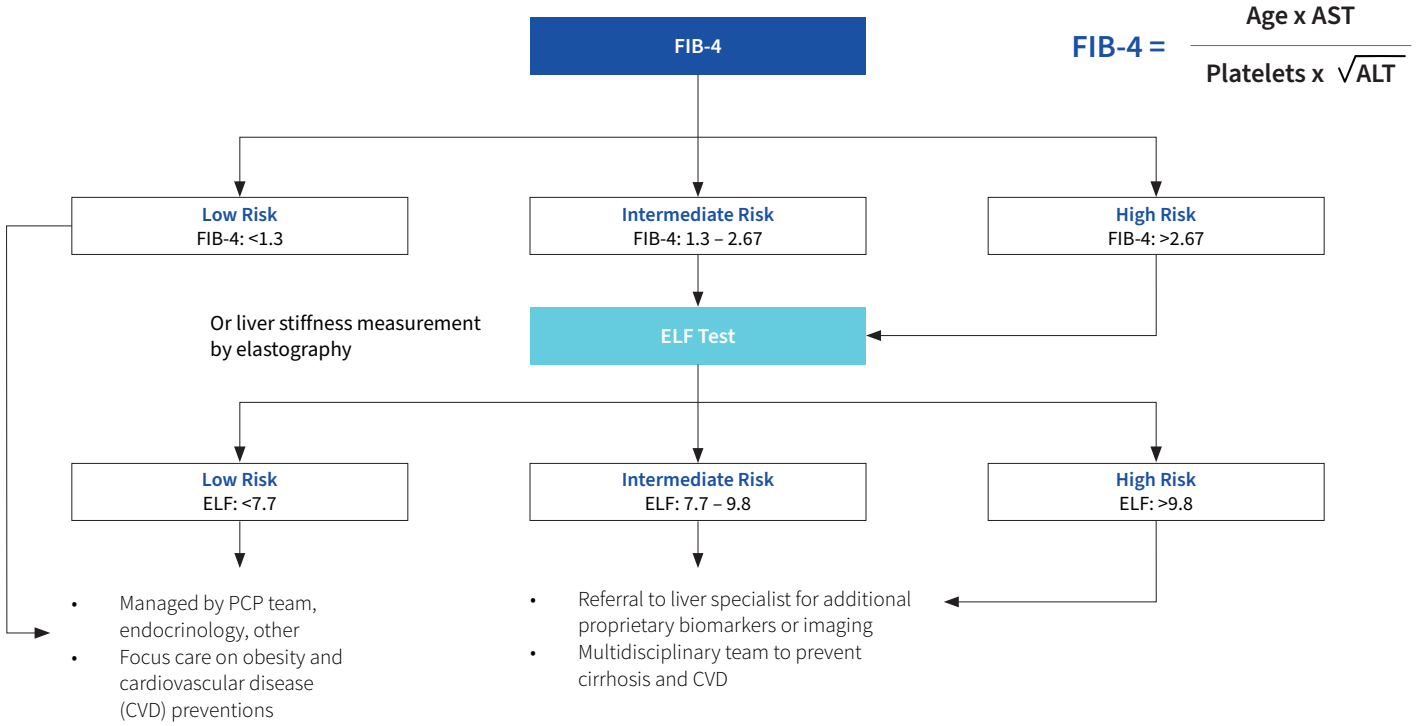
- Obesity
- Metabolic syndrome
- Prediabetes or T2D
- Persistently elevated ALT or AST
- Hepatic steatosis on any imaging study

Testing for MASLD and advanced fibrosis as suggested in recent guidelines:

- The FIB-4 is the preferred calculation to assess the risk of MASLD with liver fibrosis
- Further workup with the blood-based ELF test is recommended for “high risk” persons with an indeterminate or high FIB-4 score

Serum aminotransferase levels are often used clinically to identify patients with liver disease but can be normal in patients with diabetes, MASH and advanced hepatic fibrosis.

Screening guidance from AASLD[6]



ELF cut points recommended by AASLD differ from the FDA sanctioned cut points.

The AASLD cut points are purposed for referral to specialist for evaluation.

FDA cut points are purposed for risk prognostication.

FDA Cut Points[13]

ELF < 9.8 is associated with a lower prognostic risk, but disease progression is still possible for patients with ELF measurements below this threshold.

ELF ≥ 11.3 is associated with a higher prognostic risk, but disease progression may not occur in patients with ELF measurements above this threshold.

Identification of at-risk MASH

At-risk MASH is defined as MAS≥ 4 and F≥2

At-risk MASH refers to a disease stage where there is both a higher risk of liver-related morbidity/mortality but also the potential to reverse active injury in the liver and regress the disease. It is the last stage before irreversible damage occurs. If left untreated, at-risk MASH can progress to cirrhosis and end-stage liver disease and introduce the risk of hepatocellular carcinoma. At-risk MASH has been used as selection criteria for clinical trials which seek to identify individuals eligible to participate in the assessment of new therapies. Separately, clinically identifying patients who should receive targeted therapies is also critical as they can greatly benefit from intensified intervention and regress the disease.[6,7]

Steatosis: 0-3
Lobular Inflammation: 0-3
Hepatocellular ballooning: 0-2
Total MAS: 0-8

MAS 4	Steatohepatitis is highly probable
MAS 5	Steatohepatitis is conclusive
F2	Moderate fibrosis
F3	Bridging fibrosis (most severe)
F4	Cirrhosis

It is estimated that up to 16 million people in the United States are living with MASH, and the prevalence of MASH will increase by 63% by the year 2030.[1]

Treatment and patient management[1-3]

Recent guidelines suggest that clinicians manage adult persons with MASLD for comorbidities such as obesity, metabolic syndrome, T2D, dyslipidemia, hypertension and cardiovascular disease (CVD) based on the current standards of care. The guidelines recommend lifestyle changes with a goal of at least 5%, and preferably ≥10%, weight loss. Higher weight loss is associated with greater liver histologic and cardiometabolic benefit. Furthermore, the guidelines also recommend physical activity that improves body composition and cardiometabolic health. Patient compliance is a concern when suggesting lifestyle changes. A broad and general approach to lifestyle changes should be replaced with patient-centered regimens. Individuals tend to adhere to personalized programs such as structured weight loss and exercise programs tailored to their lifestyle and preferences.

In March 2024, the FDA approved the first therapy developed specifically for the treatment of patients with MASH. Resmetirom (brand name REZDIFFRA) is a thyroid hormone receptor-beta (THR-β) agonist that is indicated, in conjunction with diet and exercise, for the treatment of adults with at risk MASH, with moderate to advanced liver fibrosis (liver scarring consistent with stages F2 to F3 fibrosis). In addition to the benefits resmetirom provides for improvements in MASH and liver fibrosis, it also reduced LDL-C levels, which may confer a reduction in cardiovascular risk in patients who are often dyslipidemic and at high risk for cardiovascular disease.

To offer cardiometabolic benefit in persons with T2D and MASLD, clinicians may also consider treatment with GLP-1 receptor agonists, pioglitazone or SGLT2 inhibitors. Guidelines recommend the use of these anti-diabetic and weight loss therapies as adjunctive therapy to lifestyle modification for individuals with obesity and MASLD or MASH, when this is not effectively achieved by lifestyle modification alone. The guidelines also recommend that clinicians consider bariatric surgery as an option to treat and improve cardiometabolic health in persons with MASLD and a BMI of ≥35 kg/m2 (≥32.5 kg/m2 in Asian populations), particularly if T2D is present.

Assessment of liver fibrosis risk

FIB-4 (403604)

The FIB-4 index is a simple, accurate and readily available blood-based test index that can help in evaluation of patients with MASLD or hepatitis C virus (HCV) for the presence of liver fibrosis, who are potentially indicated for liver biopsy. Results from the FIB-4 test include ALT, AST, platelet count and the FIB-4 score.[8]

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 and readily available blood-based test index that can stratify patients with MASLD 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 and readily available blood-based test index that can help in evaluation of patients with HCV or MASLD for the presence of liver fibrosis who are potentially indicated for liver biopsy.[8]

Assessment of at-risk MASH

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 MASH, who are at higher risk of disease progression. NASHnext is the only blood-based test that identifies patients with at-risk MASH with significant liver fibrosis.[9]

Assessment of fibrosis, steatosis and inflammation

NASH FibroSure® Plus (550960)

This blood-based assessment of liver status in patients with MASLD provides quantitative results of 10 biochemicals (α2-macroglobulin, haptoglobin, apolipoprotein A-1, total bilirubin, γ-glutamyltransferase (GGT), ALT, AST, total cholesterol, glucose, triglycerides) in combination with age and sex (BMI not required). These factors are analyzed using a computational algorithm to provide a quantitative surrogate marker of liver fibrosis, hepatic steatosis and NASH. The absence of steatosis precludes the diagnosis of MASH.[10-12]

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 MASLD in Primary Care and Endocrinology Clinical Settings.[4] See individual tests descriptions.

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

See individual test descriptions.

Prognostic assessment

Enhanced Liver Fibrosis (ELF™) (550659)

The Enhanced Liver Fibrosis (ELF™) test is a simple, accurate and readily available 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 MASH in order to assess the likelihood of progression to cirrhosis and liver-related clinical events.[13]

FIB-4 (403604)

Besides the assessment of liver fibrosis risk, FIB-4 has been shown to assess the likelihood of progression to cirrhosis and liver-related clinical events and mortality.

Metabolic Vulnerability Index (MVX) by NMR (123590)

The Metabolic Vulnerability Index (MVX) captures the metabo-inflammatory components of MASLD. It is based on two sub-panels of biomarkers: the Inflammation Vulnerability Index (IVX), calculated from circulating levels of small-high density lipoprotein particles (S-HDL-P) and GlycA; and the Metabolic Malnutrition Index (MMX), derived from circulating branched chain amino acids (leucine, isoleucine and valine) and citrate levels. An increase in MVX correlates with increased liver-related mortality and enhances prognostic utility.

We believe proper testing can help slow the trends by helping identify those at risk of developing MASLD and MASH.

Related Tests

Test Name	Test No.
MASH	
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**
Metabolic Vulnerability Index (MVX)	**123590**
Metabolic Vulnerability Index (MVX) Plus by NMR	**123601**
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**
Autoimmune Liver Disease Profile (RDL)	**520197**
Hepatitis A Virus (HAV) Antibody, Total	**006726**
Hepatitis A Antibody, IgM	**006734**
Hepatitis B Virus (HBV) Screening and Diagnosis	**144473**
Hepatitis B Core Antibody, Total	**006718**

Test Name	Test No.
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**
Anti-Mitochondrial Ab by IFA (RDL)	**520103**
Anti-GP-210 Ab (RDL)	**520139**
Anti-SP-100 Ab (RDL)	**520112**
Anti-Mitochondrial M2 Ab (RDL)	**520117**
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**
Primary Biliary Cholangitis (PBC) Profile (RDL)	**520192**
Soluble Liver Antigen (SLA) IgG Antibody	**007441**
Thyroid Peroxidase (TPO) Antibodies	**006668**

Labcorp is working to bring MASH technologies to the forefront

In addition to offering superior testing options like NASHnext, NASH FibroSure Plus and ELF, Labcorp also supports the development of new MASH therapies. This includes:

- 70 MASLD/MASH studies conducted in the last five years, with four global phase 3 studies in progress
- 31 current MASLD/MASH and MASH cirrhosis studies
- Recruitment of more than 4,000 biopsy-confirmed patients, with metrics on over 700 sites across 28 countries

Extensive clinical testing capabilities and drug development laboratory services make Labcorp your choice for MASH 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. 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
3. 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.
4. 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.
5. 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.
6. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology*. 2023 May 1;77(5):1797-1835. doi: 10.1097/HEP.0000000000000323.
7. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology*. 2005;41(6):1313-1321. doi:10.1002/hep.20701
8. 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
9. 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.
10. 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
11. 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
12. 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
13. ADVIA Centaur® Enhanced Liver Fibrosis (ELF™) [package insert]. Tarrytown, NY. Siemens Healthcare Diagnostics Inc. Rev. 01, 2021-08.

For more information about MASH-MASLD and how testing can benefit your patients, visit **Labcorp.com/NASH.**

labcorp

L21737_BRO. 0425-9