



METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Testing options to help identify MASLD and MASH



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

MASLD

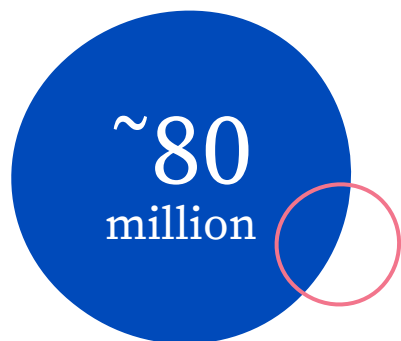
Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease (NAFLD), is a collective term used to describe a group of conditions in which there is an abnormal accumulation of fat in the liver in those who drink little to no alcohol. MASLD is 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



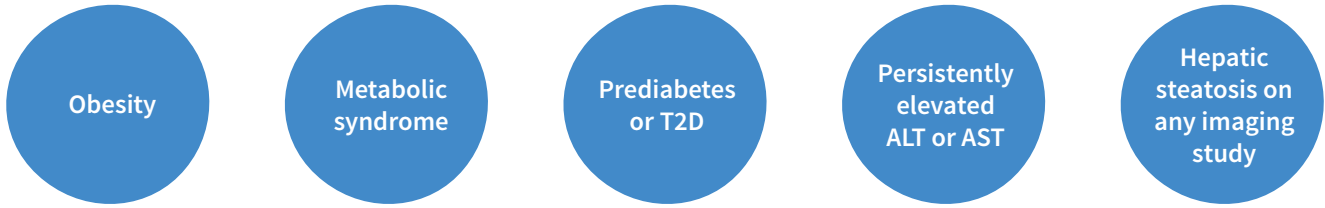
Number of people in the United States living with MASLD⁵



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}



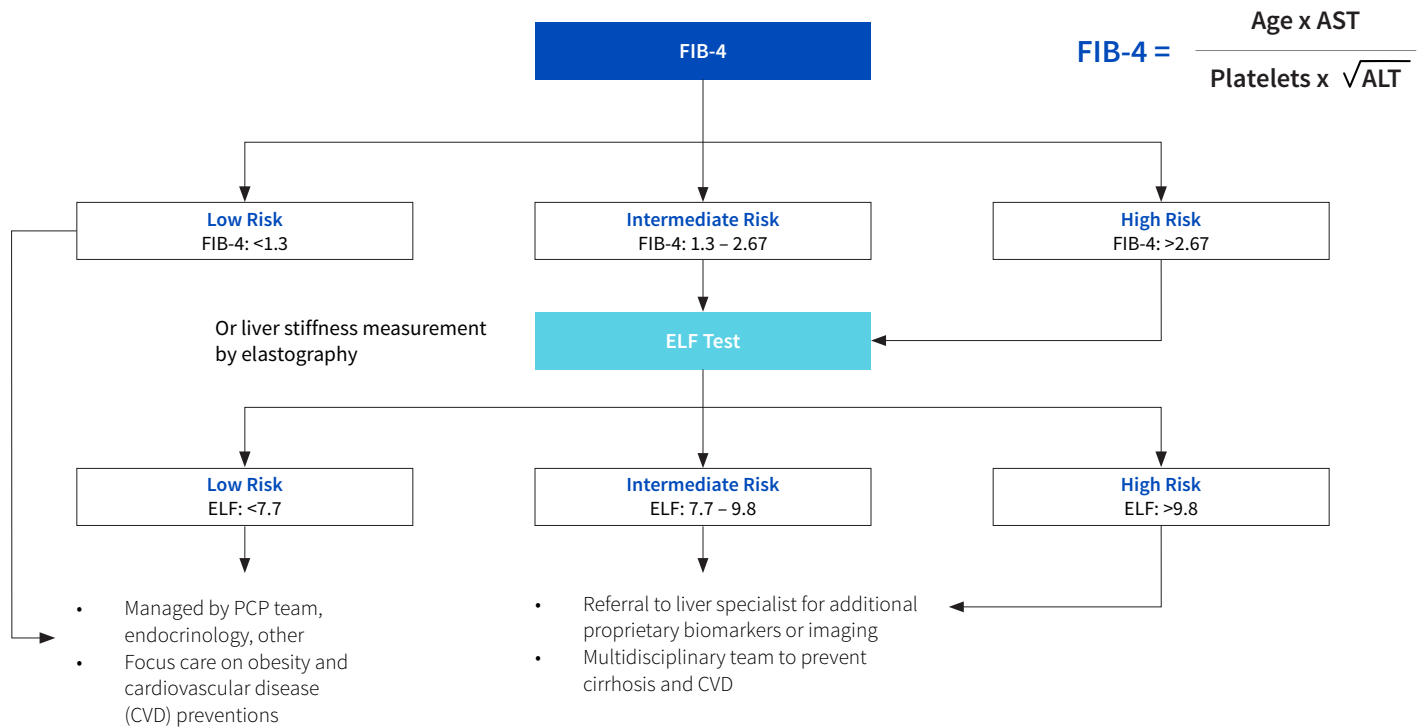
Testing for MASLD and advanced fibrosis as suggested in recent guidelines:

- 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 AASLD⁶



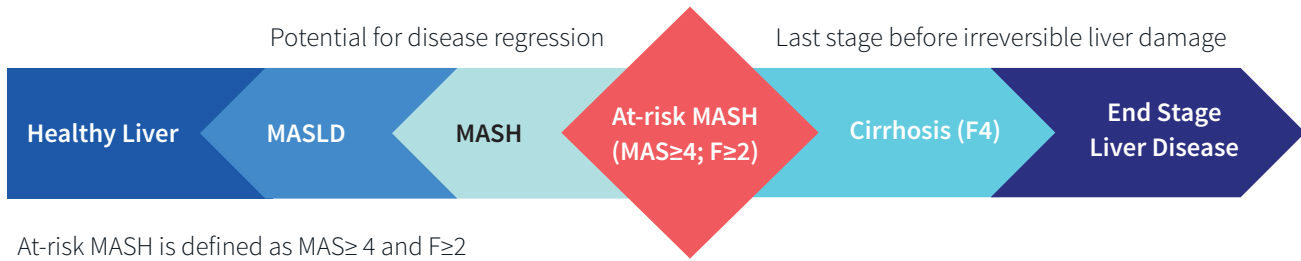
ELF cut points recommended by AASLD differ from the FDA sanctioned cut points. The AASLD cut points are purposed for referral to specialist for evaluation. FDA cut points are purposed for risk prognostication.

FDA Cut Points¹³

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 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 management¹⁻³

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 \geq 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 \geq 35 kg/m² (\geq 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.

NASH FibroSure® Plus with Reflex to Enhanced Liver Fibrosis (ELF)™ Test (550978)

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 metabolic-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
NASH FibroSure® Plus with Reflex to Enhanced Liver Fibrosis (ELF)™ Test	550978
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
Hepatitis B Surface Antibody, Qualitative	006395

Test Name	Test No.
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
Hepatitis D Virus (HDV) Antibody, IgG and IgM	144012
Hepatitis D Virus (HDV) RNA, Quantitative PCR	550653
Hepatitis B Virus (HBV) Triple Panel With Reflex to Hepatitis D Virus (HDV) Antibody	144103
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.



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For more information about MASH-MASLD and how testing can benefit your patients, visit [Labcorp.com/NASH](https://www.labcorp.com/NASH).

