# NASH Guidelines and Quality Measures

| NASH Guidelines | NIDDK (NIDDK, 2016) | AASLD and ACG (Chalasani et al., 2018) | AGA (Chalasani et al., 2012) | EASL (Marchesini et al., 2015) | WGO (LaBrecque et al., 2012) |
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| Definition of NASH | NAFLD is condition where excess fat is stored in liver, not caused by heavy alcohol use → classified into simple fatty liver and NASH<br>• Simple fatty liver: NAFL; fat in liver but little or no inflammation or liver cell damage<br>• NASH: Form of NAFLD with hepatitis and liver cell damage, in addition to fat in liver → inflammation and liver cell damage can cause fibrosis | NAFLD: evidence of hepatic steatosis (HS) through imaging or histology and lack of secondary causes of hepatic fat accumulation → classified into NAFL and NASH<br>• NAFL: presence of >5% HS without evidence of hepatocyte ballooning<br>• NASH: presence of >5% HS and inflammation with hepatocyte injury [can be with or without fibrosis] | NAFLD: evidence of hepatic steatosis (HS) through imaging or histology and lack of secondary causes of hepatic fat accumulation → classified into NAFL and NASH<br>• NAFL: presence of >5% HS without evidence of hepatocyte ballooning<br>• NASH: presence of >5% HS and inflammation with hepatocyte injury [can be with or without fibrosis] | NAFLD is excessive hepatic fat accumulation with insulin resistance, and the >5% of hepatocytes with steatosis → NASH covers the spectrum of disease severity that includes fibrosis, cirrhosis, and hepatocellular carcinoma<br>• Must exclude daily alcohol consumption | NAFLD defined by excessive fat accumulation in form of steatosis in liver; >5% of hepatocytes NASH:subgroup of NAFLD with liver cell injury and inflammation in addition to steatohepatitis; virtually indistinguishable histologically from alcoholic steatohepatitis → liver expression of MetS |
| Risk Factors | • Obese, especially with large waist size<br>• High BP<br>• High triglycerides or abnormal cholesterol levels | • Established link:<br>  ○ Obesity<br>  ○ T2DM<br>  ○ Hypertension<br>  ○ Dyslipidemia<br>• Emerging link:<br>  ○ Sleep apnea<br>  ○ Colorectal cancer | • Obesity<br>• T2DM<br>• Dyslipidemia<br>• MetS<br>• Prevalence of NAFLD increases with age<br>• Male gender is risk | • Obesity<br>• T2DM<br>• Metabolic syndrome<br>• Imaging evidence of fat accumulation<br>• ALT/GGT abnormalities<br>• Waist circumference | • Insulin resistance/ metabolic syndrome<br>• Jejunoileal bypass surgery<br>• Highest risk in 40-65 year olds |

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| | • Type 2 diabetes<br>• Metabolic syndrome<br>Less likely but associated with NASH:<br>• Disorder that causes body to use or store fat improperly<br>• Rapid weight loss<br>• Infections, like hep C<br>• Certain medicines<br>  ○ Amiodarone<br>  ○ Diltiazem<br>  ○ Glucocorticoids<br>  ○ Highly active antiretroviral therapy<br>  ○ Methotrexate<br>  ○ Synthetic estrogens<br>  ○ Tamoxifen<br>  ○ Valproic acid<br>• Exposure to some toxins<br>• Gallbladder removal | ○ Osteoporosis<br>○ Psoriasis<br>○ Endocrinopathies<br>○ Polycystic ovary syndrome [independent of obesity]<br>• Prevalence of NAFLD and stage of liver disease increase with age<br>• Male sex considered risk factor for NAFLD in some cases<br>• PNPLA-3 may explain ethnic differences for NAFLD incidence | factor<br>• Hispanics have higher prevalence<br>• Emerging conditions:<br>• Hypothyroidism<br>• Hypopituitarism<br>• Hypogonadism<br>• Sleep apnea<br>• Polycystic ovary syndrome [independent of obesity] | >94/>80cm for Europid men/women<br>• Arterial pressure >130/85 mmHg or being treated for hypertension<br>• Fasting glucose >100mg/dl or treated for T2DM<br>• Serum triacylglycerols >150mg/dl<br>• HDL cholesterol <40/50 mg/dl for men/women<br>• Fatty diet with excess calorie intake or unhealthy lifestyles and sedentary behavior<br>• PNPLA3 indicates susceptibility to NAFLD | • Higher risk in Hispanics and Asians, lower risk in African-americans<br>• Genetic predisposition<br>• Drugs and toxins |

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| Threshold for Screening | • If patient has family history of NAFLD/NASH<br>• High BMI<br>• Palpate enlarged liver<br>• Signs of insulin resistance<br>  ○ Darkened skin patches over elbows, knees, knuckles<br>• Signs of cirrhosis, like jaundice | • Routine screening for NAFLD in high-risk groups not advised due to lack of knowledge surrounding the long-term benefits and cost effectiveness<br>• Systematic screening of family members for NAFLD currently NOT recommended<br>• Be sure to exclude other options for steatosis origin as well as coexisting common chronic liver disease<br>• Persistently high serum ferritin, increased iron saturation in patients with C282Y HFE mutation → consider liver biopsy<br>• High serum titers of antibodies with >5 ULN aminotransferases, high globulins, or | • Unsuspected hepatic steatosis detected on imaging with signs attributable to liver disease or have abnormal liver biochemistries → full workup<br>• Unsuspected hepatic steatosis detected on imaging with no symptoms and normal liver biochemistries → assess for MetS and alternate causes for hepatic steatosis [ex. Drinking or medications]<br>• Biopsy not needed in patients with normal liver biochemistries and are asymptomatic → even if imaging shows hepatic steatosis<br>• Screening of family members with NAFLD not recommended | • Individuals with steatosis should be screened for metabolic syndrome, independent of liver enzymes<br>• Subjects with obesity or metabolic syndrome should be screened for NAFLD by liver enzymes<br>• Persons with obesity must be screened for NAFLD rigorously<br>• Follow-up with lean persons that indicate IR and altered body fat distribution → disease progression is possible<br>• Screen for NAFLD in patients with T2DM, regardless of liver enzyme levels | • Associated conditions for NASH and should warrant screening:<br>  ○ Hyperlipidemia<br>  ○ Insulin resistance/metabolic syndrome<br>  ○ Type 2 diabetes<br>  ○ Hep C<br>  ○ Rapid weight loss<br>  ○ TPN<br>  ○ Wilson's disease, Weber-Christian disease, beta lipoproteinemia diverticulosis, polycystic ovary syndrome, obstructive sleep apnea<br>• Low risk for NASH<br>  ○ Patient is morbidly obese<br>  ○ Morbidly obese and has one to two of the following: hypertension, T2DM, AST or ALT > 27 IU/l, sleep |

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| | | high total protein to albumin ratio → full work-up<br>• Presence of commonly associated comorbidities [see Established link and Emerging link] | • Persistently high serum ferritin and increased iron saturation in context of C282Y HFE mutation → liver biopsy<br>• High serum titers of autoantibodies seen with high aminotransferases, high globulin → complete work-up<br>• Presence of MetS can target those who should get liver biopsy | | apnea, is non-black<br>• Intermediate risk for NASH<br>○ Morbidly obese and has 3 to 4 of the following: hypertension, T2DM, AST or ALT > 27 IU/l, sleep apnea, is non-black<br>• High risk for NASH<br>○ Morbidly obese and has five of the following: hypertension, T2DM, AST or ALT > 27 IU/l, sleep apnea, is non-black<br>• Very high risk for NASH<br>○ Morbidly obese and has all of the following: hypertension, T2DM, AST or ALT > 27 IU/l, sleep apnea, is non-black |
| Recommendations for Screening | • If patient has any of the risk factors, | • NAFLD and NASH patients with T2DM | • NAFLD fibrosis score to identify | • Biopsy is the only way to differentiate | • Order liver enzyme tests and liver |

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| | especially metabolic syndrome, order liver enzyme tests<br>• If patient has increased ALT/AST levels, order imaging → ultrasound, MRI, CT scans<br>• Only use liver biopsy if patient is more likely to have NASH or if other tests show signs of advanced liver disease or cirrhosis | should be monitored for advanced fibrosis and determined if they are high or low risk using FIB-4 or VCTE<br>• Liver biopsy is most reliable approach to identify steatohepatitis<br>• Presence of MetS → strong predictor for presence of steatohepatitis<br>○ Indicator for liver biopsy<br>• Use of clinical decision aids [NAFLD fibrosis score, FIB-4, AST to platelet ratio index (APRI)], serum biomarkers [ELF panel, Fibrometer, FibroTest, Hepascore], or imaging [TE, MRE, Acoustic radiation force impulse imaging, ultrasound]<br>• NFS or FIB-4 index | NAFLD patients with higher likelihood of having fibrosis or cirrhosis<br>• Cannot recommend CK18 biomarker to identify SH in clinical practice<br>• Use presence of MetS and NAFLD fibrosis score to identify patients with higher risk for SH and advanced fibrosis<br>• Liver biopsy considered in patients that might have co-existing chronic liver conditions that cannot be excluded without liver biopsy | between NAFL and NASH<br>• Moderate and severe steatosis should be identified through imaging<br>• Fatty liver index, SteatoTest, NAFLD liver fat score → reliable to predict presence of steatosis<br>○ Cannot tell severity<br>• If MetS present, start with ultrasound and liver enzyme tests to detect steatosis<br>• H-MRS to quantify liver fat → clinical trials and experimental settings; too expensive for clinic use<br>• Liver biopsy for NASH to show steatosis, hepatocyte ballooning, lobular inflammation<br>• Serum biomarkers, NAFLD fibrosis score, and fibrosis 4 calculator to identify cases at low risk of advanced fibrosis | ultrasound for patients with insulin resistance, metabolic syndrome, diabetes<br>• Order imaging procedures to evaluate for steatosis in patients with elevated liver enzymes<br>• Order liver biopsy if liver enzymes are elevated and ultrasound is positive for steatosis, and patient has metabolic syndrome<br>• Evaluate weight loss, exercise, diet, lifestyle changes after six months<br>• Blood and platelet count, liver biochemical tests, prothrombin time 2 times annually<br>• Consult hepatologist after six months and then yearly |

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| | | useful to identify NAFLD patients with higher likelihood of stage 3 or stage 4 fibrosis and cirrhosis<br>• VCTE or MRE to identify advanced fibrosis in patients with NAFLD<br>• Liver biopsy for patients with NAFLD and are at increased risk for steatohepatitis or advanced fibrosis<br>• MetS, NFS or FIB-4, or liver stiffness measured by VCTE/MRE can identify patients at high risk for advanced fibrosis<br>• Liver biopsy to determine etiology of hepatic steatosis | | and cirrhosis<br>• Advanced fibrosis and cirrhosis should be identified through liver biopsy<br>• High risk of disease progression → 5-year biopsy follow-up<br>• Calculation of HOMA-IR in non-diabetics with proper reference value can be used instead of IR<br>○ Limited use in persons with MetS<br>• Early NASH with increased risk of fibrosis progression: over 50 years old, diabetes, MetS, increased ALT | • Screen for cardiovascular risk every 1-2 years<br>• Liver biopsy every 3-5 years<br>• Imaging tests when indicated |
| Recommendations for management | • NAFLD: Gradual weight loss to reduce fat and inflammation in liver<br>• NASH: Gradual weight loss to | • Pharmacological treatment should be limited to those with biopsy-proven NASH and fibrosis<br>• Weight loss to reduce hepatic | • Weight loss to reduce HS through just hypocaloric diet or in conjunction with increased physical activity | • Screen for diabetes in patients with NAFLD<br>• MetS with no steatosis and normal liver enzymes → follow-up in 3-5 | • NAFLD → weight loss and diet management<br>• If patient is diabetic, control insulin and fat with medications and lipid-lowering agents<br>• NASH can only be |

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| | reduce fat, inflammation, and fibrosis in liver; may recommend vitamin E if no cirrhosis or diabetes<br>• Limit intake of fats, maintain healthy weight, eat healthy diet, limit portion sizes<br>• Avoid heavy alcohol use [>4/day and >14/week for men, >3/day and >7/week for women]<br>• Avoid sugar-sweetened beverages<br>• Cirrhosis: medicine, operation, medical procedures → liver failure needs transplant<br>• Recommend clinical trials for NASH | steatosis through reduction in calories and/or increase in physical activity<br>○ Daily reduction of 500-1000 calories combined with moderately intense exercise<br>• Weight loss of at least 3-5% of body weight to improve steatosis<br>• Weight loss of 7-10% to improve fibrosis<br>• Metformin is not recommended for NASH treatment<br>• Pioglitazone improves liver histology in patients both with and without T2DM<br>○ Can be used to treat patients with biopsy-proven NASH<br>• Vitamin E at a daily dose of 800 IU/day can be considered for biopsy-proven NASH in | • Loss of 3-5% of body weight to improve steatosis<br>• Loss of up to 10% of body weight to improve necroinflammation<br>• Exercise alone can reduce HS in NAFLD<br>• Metformin is not recommended as specific treatment in adults with NASH<br>• Pioglitazone can be used to treat SH in biopsy-proven NASH → may need to be non-diabetic<br>• Vitamin E at dose of 800 IU/day improves liver histology in non-diabetics with biopsy-proven NASH → first-line pharmacotherapy<br>○ Not for NASH in diabetic patients, NAFLD without liver biopsy, | years with ultrasound<br>• MetS with steatosis and determined low risk → follow-up in 2 years with liver enzyme and fibrosis biomarkers<br>• Medium to high risk → recommend to specialist and perform biopsy<br>• Screen for CVD in patients with NAFLD<br>• Daily alcohol consumption up to 30g in men and 20g in women is acceptable<br>• Small amounts of weight loss reduces liver fat and improves hepatic IR<br>• Weight loss associated with NASH regression<br>• Individual tailoring of dietary restrictions and progressive increases in anaerobic exercises and resistance training<br>• 500-1000 calorie energy deficit per | treated through weight loss and diet management |

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| | | nondiabetics<br>• Bariatric surgery can be considered → not an established treatment for NASH<br>  ○ Considered on case-by-case basis<br>• Omega-3 fatty acids can be considered to treat hypertriglyceridemia in patients with NAFLD<br>• Do not consume heavy amounts of alcohol<br>• Statins can be used to treat dyslipidemia in NAFLD and NASH → but not in decompensated cirrhosis<br>• Monitor risk for CVD<br>• Patients with NASH cirrhosis should be screened for gastroesophageal varices<br>• Patients with suspected cirrhosis | NASH cirrhosis, or cryptogenic cirrhosis<br>• Omega-3 fatty acids may be considered as first line agents to treat hypertriglyceridemia<br>• Premature to consider foregut bariatric surgery as established option to treat NASH specifically<br>• Should not consume heavy amounts of alcohol<br>• Statins can be used to treat dyslipidemia in patients with NAFLD and NASH<br>• Patients with NASH cirrhosis should be screened for esophageal varices<br>• Patients with NASH cirrhosis should be considered for HCC screening | week<br>• 7-10% total weight loss target<br>• Use of cognitive behavioral treatment to reinforce lifestyle<br>• Low to moderate fat and moderate to high carb intake<br>• Low carb keto diets or high protein<br>• 150-200 min/week of moderate intensity aerobic physical activity in 3-5 sessions<br>• Resistance training<br>• Drug therapy indicated for progressive NASH and early-stage NASH with increased risk of fibrosis progression or active NASH with high necroinflammatory activity<br>• No firm recommendations for medication treatment but vitamin E and pioglitazone might be used for NASH treatment | |

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| | | suspected should be considered for HCC screening<br>• Routine repeats of liver biopsy not necessary | • Routine repeats of liver biopsy not necessary | | |

## References


Chalasani, N., Younossi, Z., Lavine, J.E., Diehl, A.M., Brunt, E.M., Cusi, K., Charlton, M. & Sanyal, A.J. (2012). The Diagnosis and Management of Non-alcoholic Fatty Liver Disease: Practice Guideline by the American Gastroenterological Association, American Association for the Study of Liver Disease, and American College of Gastroenterology. *Gastroenterology, 142,* 1592-1609. Doi: 10.1053/j.gastro.20212.04.001.

Chalasani, N., Younossi, Z., Lavine, J.E., Charlton, M., Cusi, K., Rinella, M., Harrison, S.A., Brunt, E.M., & Sanyal, A.J. (2018). The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guideline From the American Association for the Study of Liver Diseases. *Hepatology, 67*(1), 328-357. Doi: 10.1002/hep.29367.

LaBrecque, D., Abbas, Z., Anania, F., Ferenci, P., Ghafoor Khan, A., Goh, K.L., Hamid, S.S., Isakov, V., Lizarzabal, M., Mojica Pernaranda, M., Rivera Ramos, J.F., Sarin, S., Stimac, D., Thomson, A.B.R., Umar, M., Krabshuis, J., & LeMair, A. (2012, June). *World Gastroenterology Organisation Global Guidelines: Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis.* Retrieved from http://www.worldgastroenterology.org/UserFiles/file/guidelines/nafld-nash-english-2012.pdf.

Marchesini, G., Day, C.P., Dufour, J.F., Canbay, A., Nobili, V., Ratziu, V., Tilg, H., Roden, M., Gastaldelli, A., Yki-Jarvinen, H., Schick, F., Vettor, R., Fruhbeck, G., & Mathus-Vliegen, L. (2015). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *Journal of Hepatology, 64,* 1388-1402. Doi: 10.1016/j.jhep.2015.11.004.

National Institute of Diabetes and Digestive and Kidney Diseases. (2016, Nov). *Nonalcoholic Fatty Liver Disease & NASH.* Retrieved from https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash/definition-facts.