

AACE Clinical Practice Guideline on NAFLD in Primary Care and Endocrinology Clinical Settings

Nonalcoholic fatty liver disease (NAFLD) often occurs in patients with obesity, type 2 diabetes (T2D), insulin resistance and atherogenic dyslipidemia and is the manifestation of metabolic disease in the liver.¹ It is estimated that over 80 million people in the United States (US) are living with NAFLD and that 20% of NAFLD patients in the US have nonalcoholic steatohepatitis (NASH), the more severe and progressive stage of NAFLD.² In patients with T2D, the prevalence of NAFLD is 50–75% and NASH is 37%.^{3,4} It is for this reason that the American Association of Clinical Endocrinology (AACE) has published new clinical practice guidelines with the purpose of providing primary care physicians and endocrinologists with practical evidence-based recommendations for the diagnosis and management of NAFLD.¹

The 2022 AACE guidelines suggest the following for the diagnosis of NAFLD in adult patients:¹

- 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.
- Blood based tests:
 - Use liver fibrosis prediction calculations to assess the risk of NAFLD with liver fibrosis. The preferred noninvasive initial test is the FIB-4.
 - Consider persons belonging to the “high risk” group who have an indeterminate or high FIB-4 score for further workup with an LSM (transient elastography) or ELF test, as available.
- Imaging modalities:
 - To stage the risk of fibrosis in persons with NAFLD, clinicians should prefer the use of Vibration controlled transient elastography (VCTE) as best validated to identify advanced disease and predict liver-related outcomes. Alternative imaging approaches may be considered, including shear wave elastography (less well validated) and/or magnetic resonance elastography (most accurate but with a high cost and limited availability; best if ordered by liver specialist for selected cases).
- In persons with T2D, consider screening for clinically significant fibrosis using the FIB-4, even if they have normal liver enzyme levels.
- In persons with T1D, consider screening for NAFLD with clinically significant fibrosis using the FIB-4, only if there are risk factors such as obesity, features of metabolic syndrome, elevated plasma aminotransferase levels (>30 U/L), or hepatic steatosis on imaging.
- Further risk stratify persons with T2D or T1D with cardiometabolic risk factors and/or elevated plasma aminotransferase levels (>30 U/L) using the FIB-4, elastography, and/or ELF test.

Key Recommendations

Patients with one or more of the following features should be screened for NAFLD and advanced fibrosis

- Obesity
- Metabolic syndrome
- Type 2 Diabetes or prediabetes
- Hepatic steatosis on any imaging study
- Persistently elevated ALT or AST levels (over 6 months)

Screening Algorithm

- Use FIB-4 to assess the risk of NAFLD with liver fibrosis
- Consider those with an indeterminate or high FIB-4 score for further workup with an LSM (transient elastography) or ELF test

- 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.
- Refer persons with clinical evidence of advanced liver disease (ascites, hepatic encephalopathy, esophageal varices, or evidence of hepatic synthetic dysfunction) to a gastroenterologist/hepatologist for further care.

For management of NAFLD in adult patients, the AACE guidelines suggest that clinicians manage persons with NAFLD for comorbidities such as obesity, metabolic syndrome, diabetes mellitus, 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 $\geq 10\%$, weight loss. More weight loss is often associated with greater liver histologic and cardiometabolic benefit. Dietary modification that reduces macronutrient content and induces energy deficit and adoption of healthier eating patterns, such as the Mediterranean diet, is recommended. Furthermore, clinicians must recommend physical activity that improves body composition and cardiometabolic health. Physicians must recommend participation in structured weight loss and exercise programs tailored to the individual's lifestyle and personal preferences. 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 $\geq 10\%$, 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.

Given that NAFLD is a growing public health problem that is closely linked to the epidemics of obesity and T2D and other comorbidities and affects many of the patients seen and managed by endocrinologists and primary health care professionals, it is of vital importance to increase awareness, diagnosis and treatment for NAFLD. This is critical for early treatment in order to reduce progression to cirrhosis and hepatocellular carcinoma. The new AACE guidelines are a new tool in the armamentarium of patient care.

Labcorp offers the following tests for use in the assessment of NAFLD:

Test Name	Test No.
FIB-4 Medical decision points: 0.00 – 1.29 Low risk for advanced liver fibrosis 1.30 – 2.67 Indeterminate risk for advanced liver fibrosis >2.67 High risk for advanced fibrosis and for developing of other liver related events	403604
Enhanced Liver Fibrosis (ELF) TM Test* Lower risk < 9.80 Mid risk 9.80 – 11.29 Higher risk >11.29	550659
FIB-4 With Reflex to Enhanced Liver Fibrosis (ELF) TM Test >1.29 FIB-4 will reflex to ELF test	402175

*The ELF reference ranges in this table were based on the FDA's intended use of ELF as a prognostic marker. ELF was cleared in the US to be used in conjunction with other laboratory findings and clinical assessments in patients with advanced fibrosis (F3 or F4) due to NASH to assess the likelihood of progression to cirrhosis and liver-related clinical events. Reference the AACE guidelines for suggested cut-off points of screening patients for advanced liver fibrosis.

References

1. 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 the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract.* 2022 May;28(5):528-562. doi: 10.1016/j.eprac.2022.03.010.
 2. American College of Gastroenterology website. Non-alcoholic Fatty Liver Disease (NAFLD). <https://gi.org/topics/fatty-liver-disease-naflid/>. Accessed October 3, 2019.
 3. Lee Y, Cho Y, et al. Nonalcoholic fatty liver disease in diabetes. Part I: epidemiology and diagnosis. *Diabetes Metab J* 2019;43:31-45. doi: 10.4093/dmj.2019.0011.
 4. Budd J, Cusi K. Nonalcoholic fatty liver disease: what does the primary care physician need to know? *American Journal of Medicine* 2020; 133(5):536-543. doi:10.1016/j.amjmed.2020.01.007
- For more information regarding test options, including specimen requirements and CPT codes, please consult the online Test Menu at www.labcorp.com.

Visit the online test menu at **Labcorp.com** for additional test options and full test information, including CPT codes and specimen collection instructions.

