MASLD & MASH (formerly NAFLD / NASH)

Fibrosis stage is the only prognostic number · normal LFTs exclude nothing · and cardiovascular disease is what kills these patients

FIB-4 first
it costs nothing

RENAMED IN 2023 *and the change is practical, not cosmetic*

THE NEW NAMES

NAFLD → MASLD, **NASH → MASH**, under the umbrella **steatotic liver disease (SLD)**. The old names defined the disease by what it was *not* ("nonalcoholic") and required excluding alcohol first. **MASLD is a POSITIVE diagnosis**: steatosis plus **≥ 1 cardiometabolic criterion** (overweight or increased waist, hyperglycemia or T2D, hypertension, high triglycerides, low HDL). "Fatty" was judged stigmatizing.

MetALD: THE NEW MIDDLE CATEGORY

MASLD criteria **plus meaningful alcohol intake** (roughly 20-50 g/day women, 30-60 g/day men). Previously these very common patients fell between two diagnoses; now **both drivers get treated**. Above those thresholds it is alcohol-related liver disease. **Exclude first:** hepatitis B and C, drug-induced steatosis (methotrexate, amiodarone, tamoxifen, valproate, steroids), Wilson disease in the young, hypothyroidism.

⚠ WHAT ACTUALLY KILLS THEM

Cardiovascular disease is the leading cause of death in MASLD, ahead of liver-related mortality, then extrahepatic malignancy. **Finding MASLD is a cardiometabolic risk finding**: the visit should produce a lipid panel, an ASCVD estimate, a blood pressure plan and a statin decision, not only a hepatology referral. Prevalence is ~30% of adults, far higher in T2D and obesity.

RISK-STRATIFY: FIB-4 FIRST *the question is not "is there fat" but "is there F2 or worse"*

Step	Detail
Who	Risk-stratify rather than population-screen: **type 2 diabetes** (highest yield, systematic FIB-4 supported), obesity with metabolic risk, persistently elevated aminotransferases, and **incidental steatosis on any imaging**
Step 1 · FIB-4	Age, AST, ALT, platelets: **free, from labs you already have**. **< 1.3 = low risk** (strong negative predictive value; recheck in 1-3 years). **> 2.67 = high risk → hepatology. 1.3-2.67 = indeterminate**, the zone needing a second test. Performs less well under 35 and over 65
Step 2 · the indeterminate zone	**Elastography (FibroScan) or ELF.** Low stiffness reassures and returns the patient to primary care; high stiffness routes to hepatology. **Do not "watch and repeat LFTs" instead**
⚠ Normal LFTs	**Normal ALT and AST do NOT exclude advanced fibrosis**: many F3-F4 patients have normal enzymes, which can even fall as hepatocyte mass declines. **Using LFTs as the gate is how cirrhosis gets missed for years**
Biopsy	**Now the exception**: diagnostic uncertainty, suspected coexisting disease (autoimmune hepatitis, hemochromatosis), or trials. The noninvasive pathway answers the practical question
The rest of the workup	**Exclude the mimics:** hepatitis B and C serologies, alcohol quantified with AUDIT-C rather than "social drinker", ferritin and iron studies; add autoimmune serologies, ceruloplasmin and alpha-1 antitrypsin where the picture fits. **Complete the cardiometabolic side, because it is the actual prognosis:** A1c, full lipid panel, blood pressure, formal ASCVD risk estimate
If cirrhotic	**HCC surveillance with ultrasound ± AFP every 6 months** and variceal screening. MASLD cirrhosis is now among the leading transplant indications, and HCC can arise in MASLD cirrhosis (rarely without it)
Restage over time	**Repeat FIB-4 every 1-3 years** in low-risk patients, more often with diabetes or ongoing metabolic risk. **Fibrosis is dynamic in both directions**, so a reassuring result today is not a permanent discharge

⚠ LEAN MASLD IS REAL

Roughly 10-20% of MASLD occurs in patients with a normal BMI, driven by visceral adiposity, insulin resistance, or genetic factors (PNPLA3), and it is routinely missed because the clinician is looking for obesity. **A normal BMI does not exclude the diagnosis**, waist circumference is the better measure, and outcomes in lean MASLD are not benign. The same FIB-4 pathway applies.

THE TWO ERRORS TO UNLEARN

1. "Fatty liver, normal LFTs, reassure." Enzymes are a poor filter: risk-stratify everyone with FIB-4 regardless. **2. "Hold the statin, the LFTs are up."** Statins are safe here and treat the leading cause of death in this population, so withholding them over mild transaminase elevation is a net harm. A third to unlearn: **MASLD is not a diagnosis of exclusion any more**, it is a positive one.

TREATMENT: WEIGHT LOSS WITH NUMBERS ATTACHED *"lose some weight" accomplishes nothing; a target does*

Intervention	Detail
The weight thresholds	**3-5% improves steatosis. 7-10% improves MASH inflammation and ballooning. ≥ 10% can regress fibrosis.** Quote the numbers to the patient: they convert vague advice into a goal
Diet and exercise	Mediterranean pattern; **eliminate fructose-sweetened beverages** (direct driver of de novo lipogenesis). **150-300 min/week of moderate exercise reduces liver fat independent of weight loss**: the most useful thing to tell a patient whose scale has not moved. Coffee associates with less progression
Alcohol	Minimize in MASLD; **abstinence in MetALD and advanced fibrosis**, because alcohol and metabolic injury are synergistic rather than additive
Resmetirom (Rezdiffra) *first approved drug*	**MASH with F2-F3 fibrosis, noncirrhotic**, alongside diet and exercise (FDA accelerated approval, March 2024). Liver-directed **thyroid hormone receptor-beta agonist**: local hepatic thyroid signaling reduces steatosis and fibrosis without systemic thyrotoxicosis. **NOT for cirrhosis (F4)** or for steatosis without fibrosis. Early GI effects, monitor LFTs, **mind statin interactions**
Let one drug do two jobs	**GLP-1 receptor agonists** (semaglutide, tirzepatide) where obesity or T2D coexists: weight loss, steatohepatitis resolution and independent cardiovascular benefit. **Pioglitazone** improves MASH histology in T2D but brings weight gain, fluid retention (avoid in heart failure) and fracture risk. **Vitamin E 800 IU only in selected NONdiabetic biopsy-proven MASH**, with its safety debate discussed. **Bariatric surgery** is the most durable option and deserves formal consideration
⚠ Statins	**Safe in MASLD including compensated cirrhosis, and indicated for the disease that will actually kill the patient.** Mildly abnormal aminotransferases are not a reason to withhold or stop one. Vaccinate for hepatitis A and B

PEARLS & PITFALLS

- **Only a minority progress.** Simple steatosis is largely benign for the liver; MASH with fibrosis is what advances, which is why fibrosis stage rather than the presence of fat drives every decision.
- **Restage every 1-3 years** (sooner with diabetes or ongoing risk): fibrosis is dynamic in both directions, and a reassuring FIB-4 today is not a permanent discharge.
- **In a patient with MASLD and type 2 diabetes, the diabetes regimen is a liver decision**: pick an agent with hepatic benefit rather than treating the two problems in separate clinics.
- **The renaming is not trivia.** A resident who still says "NAFLD, exclude alcohol first" will miss MetALD entirely and skip the cardiometabolic workup the new criteria force.

References: Multisociety Delphi consensus statement on new fatty liver disease nomenclature (2023) · AASLD practice guidance on the clinical assessment and management of MASLD · FDA accelerated approval of resmetirom for MASH with moderate to advanced fibrosis (March 2024) · ADA standards of care.