NONINVASIVE TOOLS (NITs) FOR MASH DIAGNOSIS

Liver biopsy to diagnose metabolic dysfunction–associated steatohepatitis (MASH) has largely been replaced by NITs due to its invasiveness, adverse events, interobserver variability, and potential for sampling error. There are multiple laboratory-, serum-, and imaging-based NITs regularly used in clinical practice.

Calculating a patient's Fibrosis-4 (FIB-4) score is often the first step to identifying patients at risk for advanced fibrosis.

FIB-4 calculation

Initial Measures and Advanced Fibrosis Cutoff	Subsequent Measures and Advanced Fibrosis Cutoff
FIB-4, >2.67	MRE, >3 kPa
	TE, ≥12 kPa
	ELF score, ≥9.2

Cutoff values to identify advanced fibrosis for each test have been established, though further conditions apply to determine whether a patient is eligible for pharmacotherapy.

INITIATING RESMETIROM AND LONG-TERM MONITORING

Resmetirom is the first pharmacotherapy approved for treatment of MASH, specifically for patients with F2 or F3. As it is not approved for use in patients with F1 or F4, using NITs to identify eligible patients is critical.

	MASH F2 or F3 (Resmetirom Eligible)		Cirrhosis	
Metric	**AASLD Guidance**	**Expert Panel Recommendations**	**AASLD Guidance**	**Expert Panel Recommendations**
TE	8-15 kPa	10-19.9 kPa	>20 kPa	≥20 kPa
MRE	3.1-4.4 kPa	3.3-4.9 kPa	>5 kPa	≥5 kPa
ELF		• 9.2-9.7 (+ second NIT) • 9.8-11.3 (if in isolation)		>11.3
Other		• FAST, ≥0.67 • MAST, ≥0.242 • MEFIB, FIB-4 ≥1.6 + MRE ≥3.3 kPa	Concomitant active liver disease, excess alcohol use (>20/30 g/d in women/men), active thyroid disease	Concomitant active liver disease, excess alcohol use, platelets ≤140,000/µL, evidence of PHTN

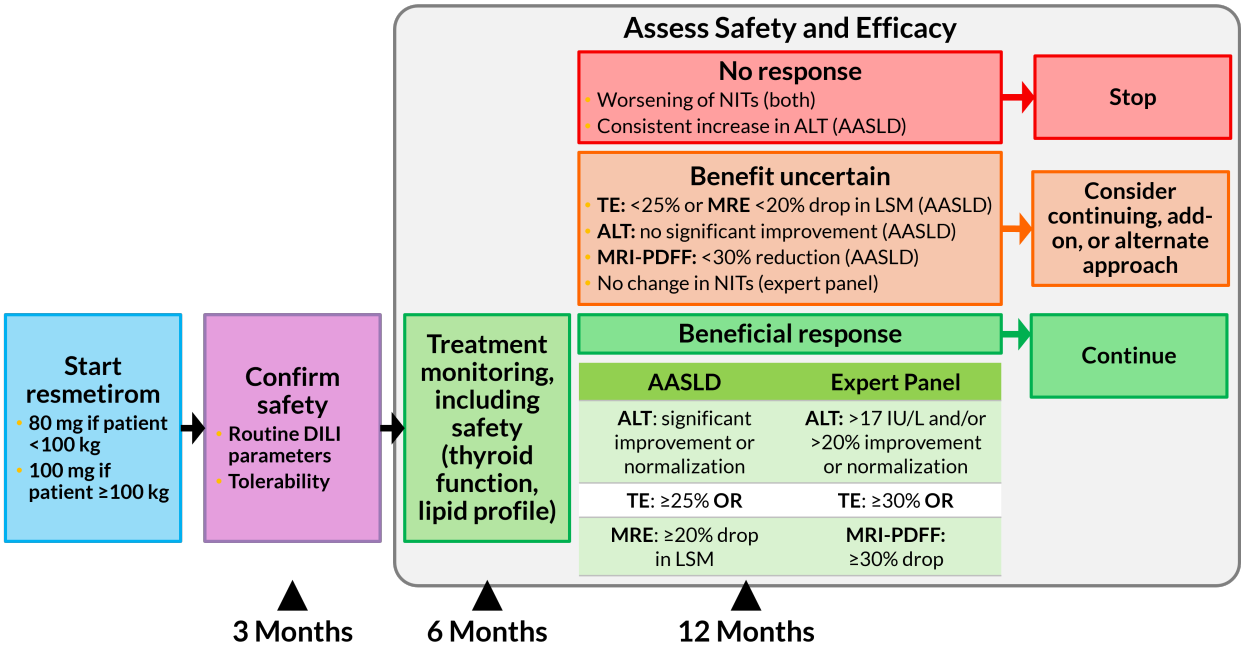
AASLD, American Association for the Study of Liver Diseases; FAST, FibroScan-aspartate aminotransferase (AST); MAST, magnetic resonance imaging-AST; MEFIB, MRE + FIB-4; PHTN, pulmonary hypertension.

AASLD Guidance

If a patient is eligible, resmetirom is initiated, then safety is monitored for the first year. Efficacy may not be apparent until after 12 months. Additional guidance is provided by the AASLD and Expert Panel Recommendations.

Expert Panel Recommendations

Guidance for Resmetirom Initiation and Monitoring



ALT, alanine aminotransferase; DILI, drug-induced liver injury; MRI-PDFF, magnetic resonance imaging-proton density fat fraction.

ADDRESSING COMMON CARDIOMETABOLIC COMORBIDITIES

While lifestyle modification has historically been the cornerstone of MASH management and should still be discussed with patients, a shift to pharmacotherapy has arisen with the approval of glucagon-like peptide-1 (GLP-1)–targeting therapies that treat both type 2 diabetes (T2D) and obesity.

Semaglutide Indications	Semaglutide Dosing	Tirzepatide Indications	Tirzepatide Dosing
Obesity			
To reduce excess body weight and maintain weight reduction long term in patients aged ≥12 years with obesity or adults with overweight in the presence of ≥1 weight-related comorbid condition	Initiate at 0.25 mg subcutaneously (SQ) weeks; titrate every 4 weeks to 2.4 mg SQ	To reduce excess body weight and maintain weight reduction long term in adults with obesity or with overweight in the presence of ≥1 weight-related comorbid condition	Initiate at 2.5 mg SQ weekly; titrate by 2.5 mg after 4 weeks until maintenance dose is achieved (5mg, 10mg, or 15 mg SQ weekly)
To reduce the risk of major adverse cardiovascular events (MACE) in adults with established cardiovascular disease (CVD) and either obesity or overweight		To treat moderate to severe obstructive sleep apnea in adults with obesity	Initiate at 2.5 mg SQ weekly; titrate by 2.5 mg after 4 weeks until maintenance dose is achieved (10mg or 15 mg SQ weekly)
T2D			
As an adjunct to diet and exercise to improve glycemic control in adults with T2D	Initiate at 0.25 mg SQ weekly; titrate to 0.5 mg after 4 weeks. Dosage may be titrated up to 2 mg for glycemic control or 1 mg for CKD	As an adjunct to diet and exercise to improve glycemic control in adults with T2D	Initiate at 2.5 mg SQ weekly; titrate to 5 mg SQ weekly after 4 weeks. May be increased by 2.5 mg to a maximum of 15 mg, as required
To reduce the risk of MACE in adults with T2D and established CVD			
To reduce the risk of sustained eGFR decline, end-stage kidney disease and cardiovascular death in adults with T2D and chronic kidney disease (CKD)			

The American Diabetes Association provides guidance on initiation of GLP-1–targeting therapies for patients with T2D, including those with obesity.

ADA Guidelines

GLP-1–targeting therapies may also provide benefits for MASH. Semaglutide recently demonstrated significant improvement in resolution of MASH, with no worsening of fibrosis, and improvement in fibrosis, with no worsening of MASH. Tirzepatide demonstrated significant improvement in resolution of MASH, with no worsening of fibrosis, but no significant improvement in fibrosis stage.

CREATING COMPREHENSIVE TREATMENT PLANS

Comprehensive treatment plans for patients with MASH may involve pharmacotherapy for both MASH and T2D or obesity. Though data on the combination of resmetirom and GLP-1–targeting therapies are limited, the AASLD guidelines and Expert Panel Recommendations, highlighted above, discuss staggered initiation of these therapies. Dosage changes are not required for either medication.

Bariatric surgery may also be an option to manage obesity, and potentially improve MASH and fibrosis:

- Patients with body mass index (BMI) ≥35 kg/m^2 regardless of comorbidities
- May be considered in patients with BMI 30 to 34.9 kg/m^2 who have cardiometabolic comorbidities

Bariatric Surgery Guidelines

A multidisciplinary team individualized to each patient should be established, and may include:

- Endocrinologists
- Cardiologists
- Primary care providers
- Nutritionists or dieticians