

Navigating MASLD: Clinical Updates for Frontline Providers

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Disclosure

Advisory Board: Madrigal

Consultant: Alpha Insights; Antheneum Partners;
Gerson Lehrman Group; Slingshot Insights

Research Grant: Akeru; Madrigal; W.L. Gore &
Associates



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Learning Objectives

At the completion of today's talk, learners will:



Discuss the new nomenclature, epidemiology and risk factors for MASLD and MASH



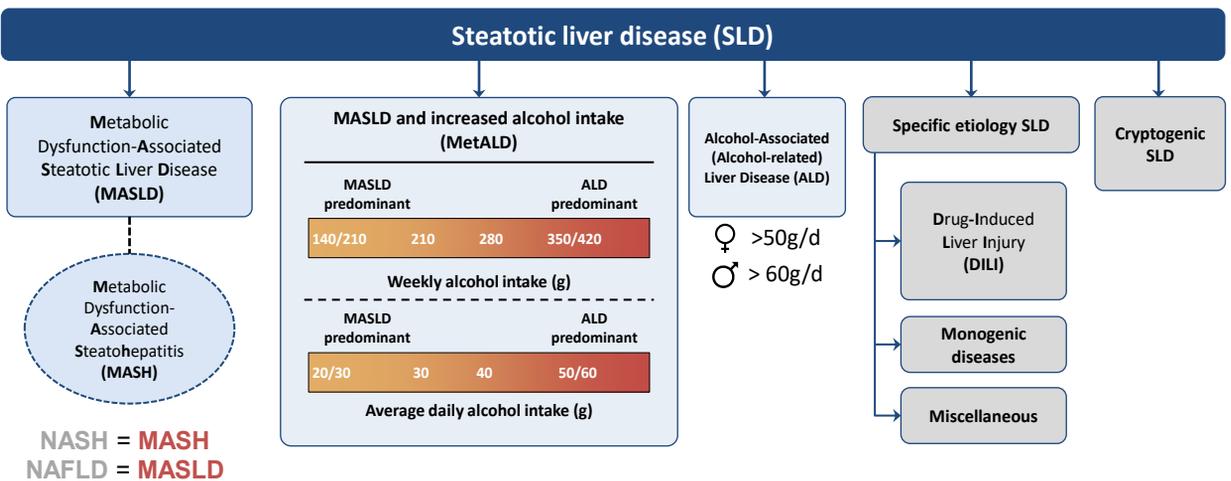
Describe the diagnosis, staging, and natural history of MASLD/MASH



Understand treatment goals and potential therapeutic modalities in MASLD/MASH

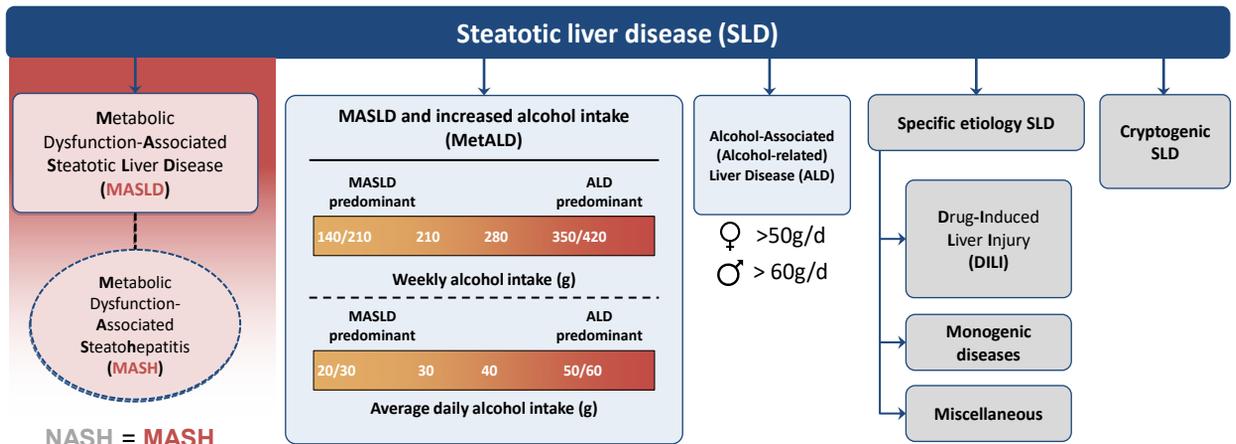
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New Nomenclature: Steatotic Liver Disease and Beyond



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New Nomenclature: Steatotic Liver Disease and Beyond



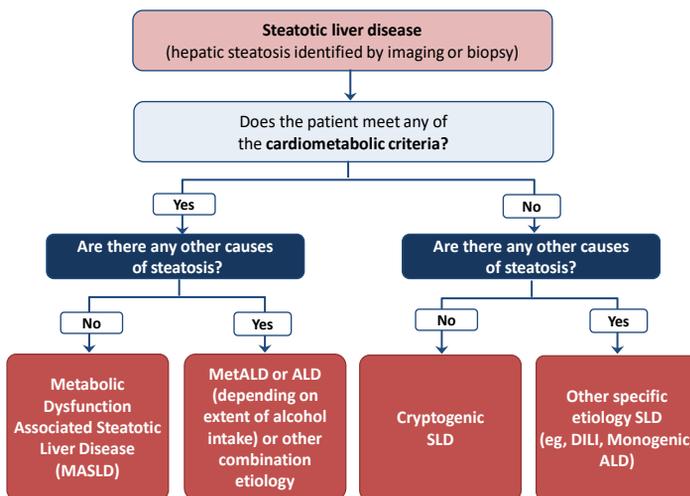
NASH = MASH
NAFLD = MASLD

Rinella ME et al. *Hepatology*. 2023;78:1966-1986.

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Categorizing Steatotic Liver Disease



Adult cardiometabolic criteria

At least 1 out of 5:

- BMI ≥ 25 kg/m² [23 Asia] WC >94 cm (M) / >80 cm (F) OR ethnicity-adjusted equivalent
- Fasting serum glucose ≥ 5.6 mmol/L (100 mg/dL) OR 2-hour post-load glucose levels ≥ 7.8 mmol/L (≥ 140 mg/dL) OR HbA1c $\geq 5.7\%$ (39 mmol/L) OR type 2 diabetes OR treatment for T2DM
- Blood pressure $\geq 130/85$ mmHg OR specific antihypertensive drug treatment
- Plasma triglycerides ≥ 1.70 mmol/L (150 mg/dL) OR lipid lowering treatment
- Plasma HDL-cholesterol ≤ 1.0 mmol/L (40 mg/dL) (M) and ≤ 1.3 mmol/L (50 mg/dL) (F) OR lipid lowering treatment

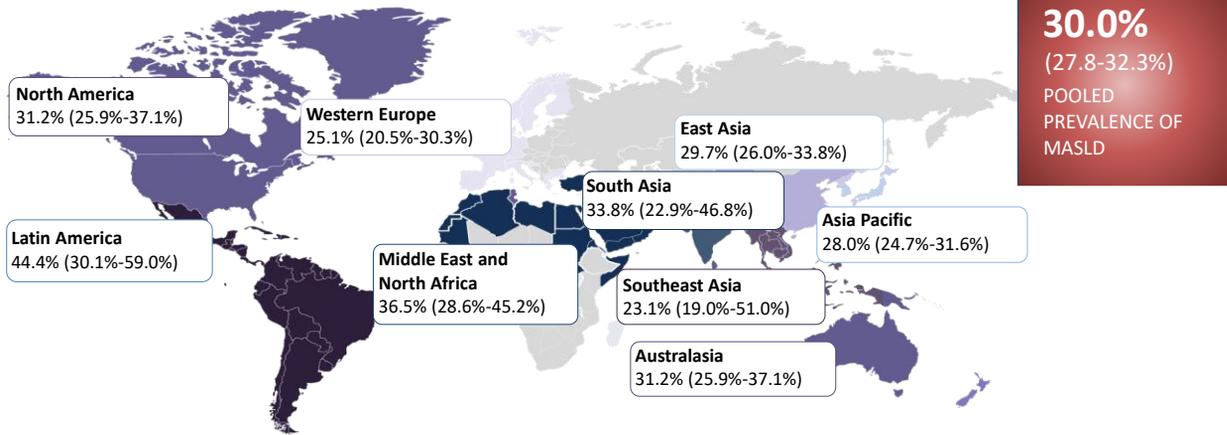
ALD, alcohol-related liver disease; BMI, body mass index; DILI, drug-induced liver injury; SLD, steatotic liver disease; T2DM, type 2 diabetes mellitus; WC, waist circumference.
Rinella ME et al. *Hepatology*. 2023;78:1966-1986.

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MASLD Is a Crisis in the US and Worldwide

Prevalence (95% CI) of MASLD by global regions data, 1990-2019

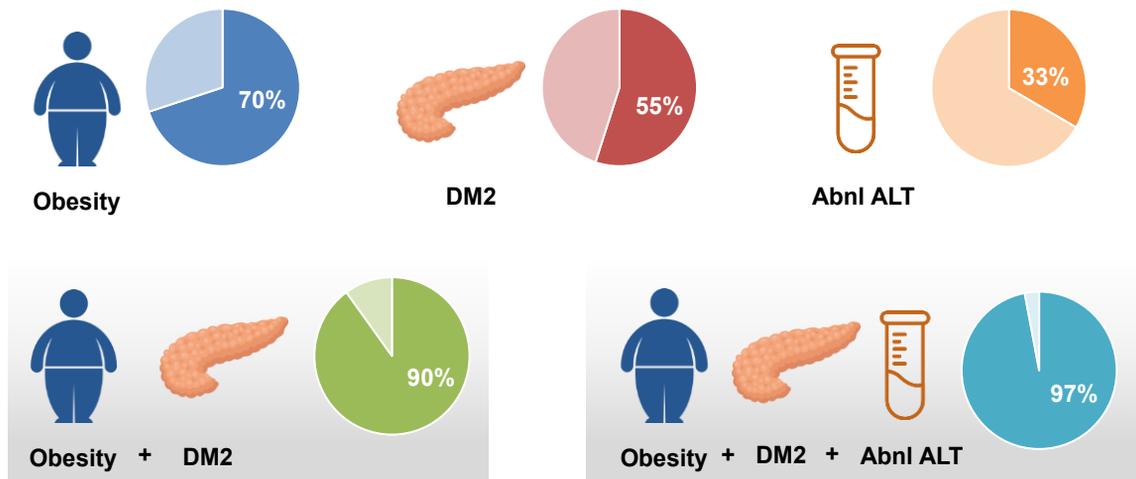


Younossi Z et al. *Hepatology*. 2023;77:1335-1347.

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MASLD Prevalence in General Practice



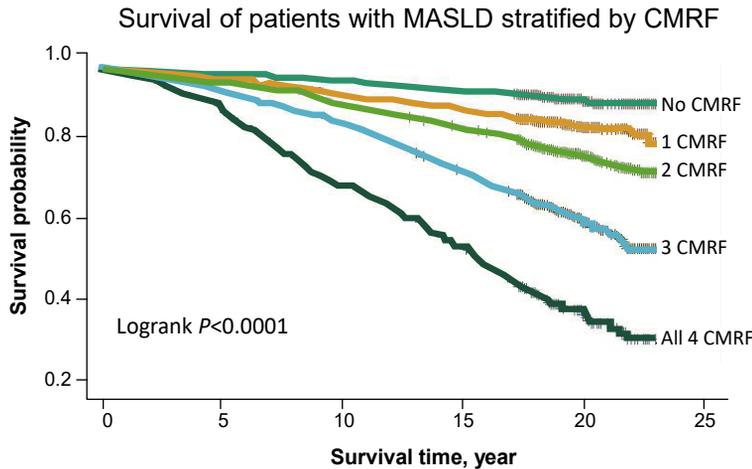
Younossi et al, *Hepatology*, 2019
Nabi et al, *Gastroenterology*, 2020

Noureddin et al, *Hepato Comm*, 2022
Quek et al, *Lancet Gastro Hep*, 2023

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Clinical Predictors of Outcomes in MASLD: Impact of Cardiometabolic Risk



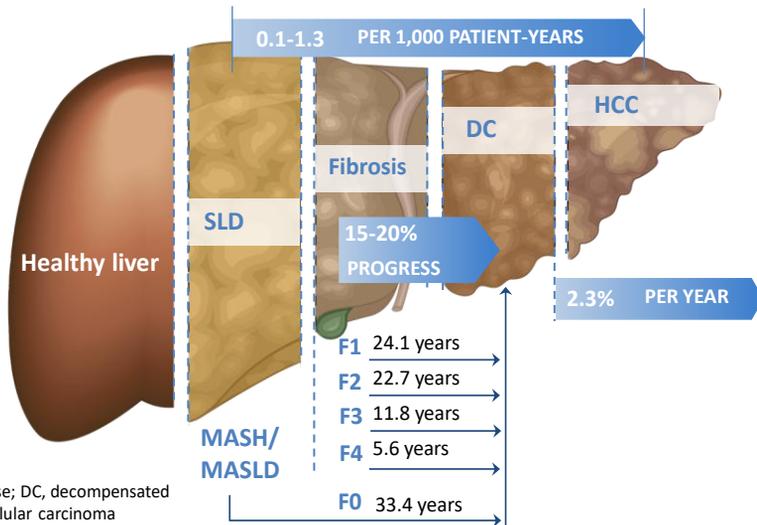
Increasing number of cardiometabolic risk factors (CMRF) are associated with mortality

Golabi P et al. *Medicine*. 2018;97(13):e0214.

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Natural History of MASLD and MASH



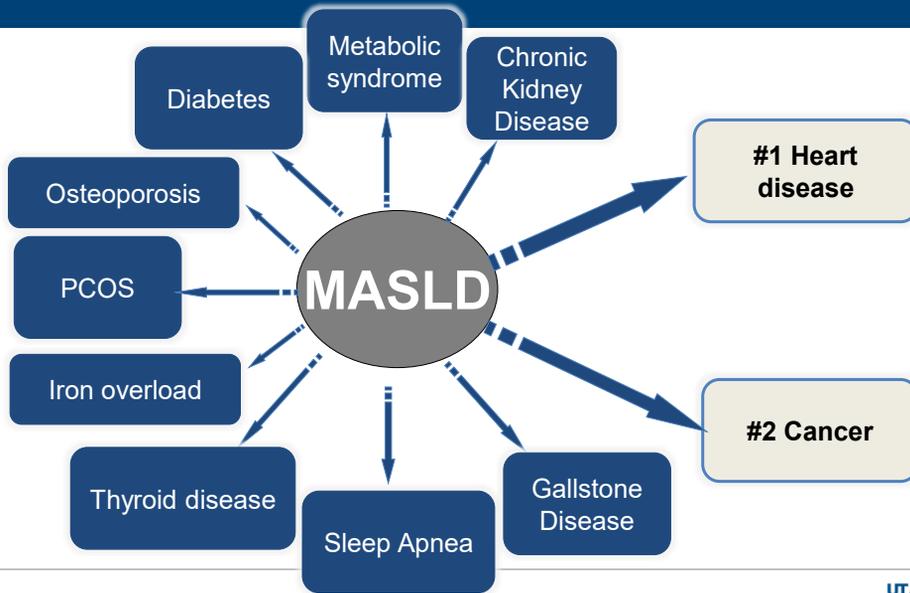
SLD, steatotic liver disease; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma

1. Younossi Z et al. *EMJ Hepatol*. 2022; 2. Sayiner M et al. *Clin Liver Dis*. 2016;20(2):205-214; 3. Younossi ZM et al. *Hepatology*. 2016; 64(5):1577-1586; 4. Lequoy M et al. *Horm Mol Biol Clin Invest*. 2020;29:41(1); 5. Younossi Z et al. *Hepatology*. 2018; 6. Younossi Z.J. *Hepatology*. 2019.

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MASLD Affects More Than Just the Liver

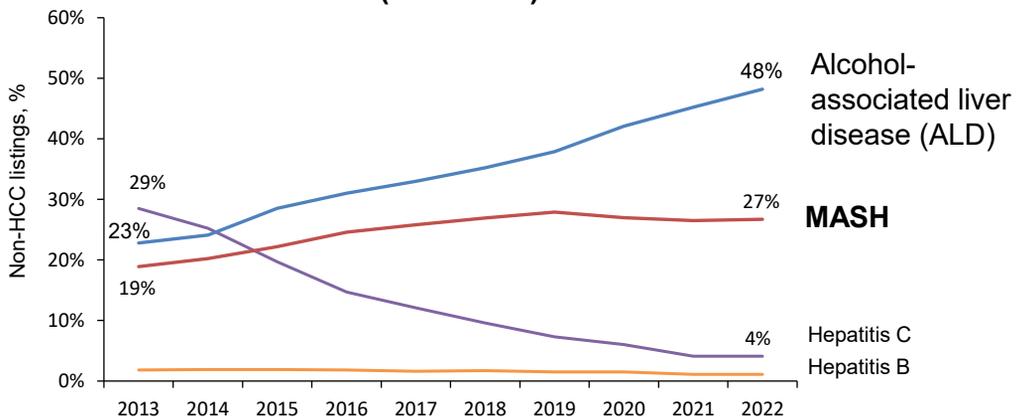


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Consequences of MASH: Liver Transplantation

Liver transplantation in the United States (Non-HCC)

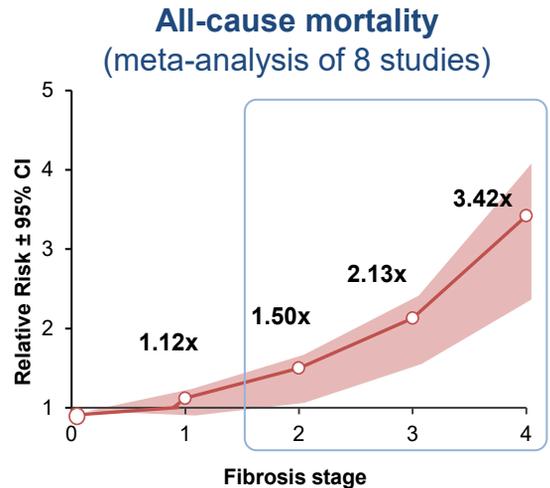
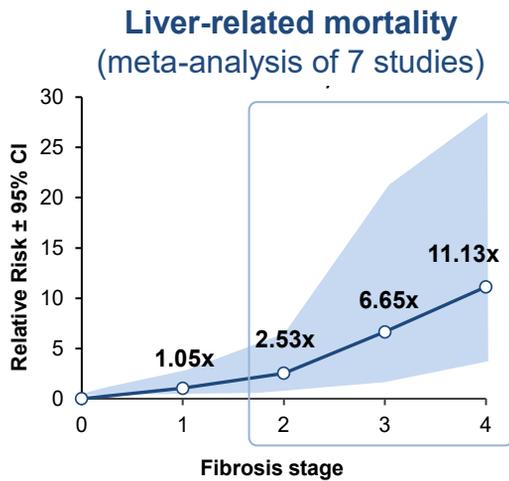


Younossi ZM. *Hepatal Commun.* 2023 22;8(1):e0352.

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Fibrosis Stage Predicts Liver Outcomes and Mortality



Taylor RS et al. *Gastroenterology*. 2020;158:1611-25.



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Describe the diagnosis, staging, and natural history of MASLD/MASH



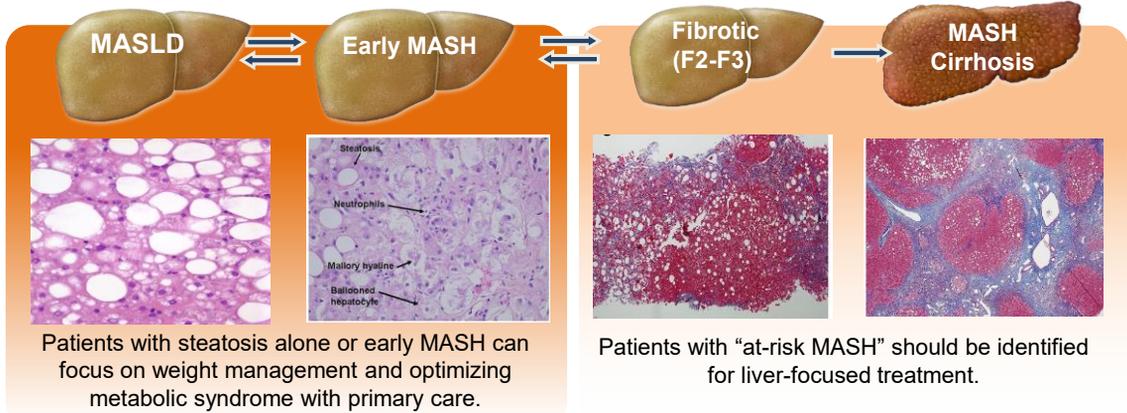
Understand treatment goals and potential therapeutic modalities in MASLD/MASH



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Disease Staging

Historically, MASH has been diagnosed by liver biopsy. **Currently, non-invasive tests (NITs) can distinguish between lower risk patients and patients with “at-risk MASH” with reasonable reliability.**

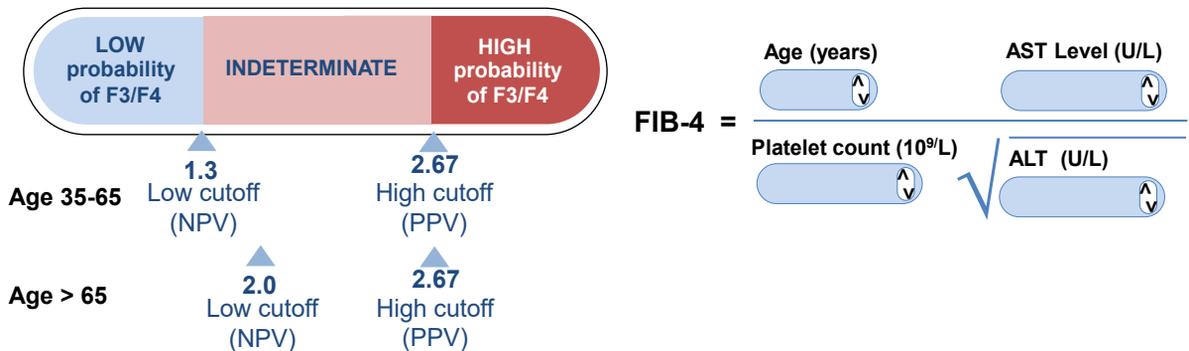


Provided by Mazen Nouredin, MD, MHSc Reproduced for educational purposes only.

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NIT Staging: Fibrosis-4 (FIB-4) Score

FIB-4 for MASLD/MASH screening

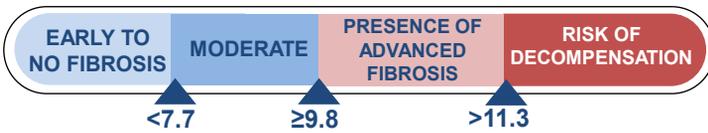


1. Sterling et al. *Hepatology*. 2006. 2. Eddowes et al. *Gastroenterology*. 2019. 3. Vali Y et al. *J Hepatology*. 2020;73(2):252-262. 4. Day J et al. *J Appl Lab Med*. 2019;3(5):815-826. 5. Newsome et al; *Lancet Gastro Hep*. 2020.

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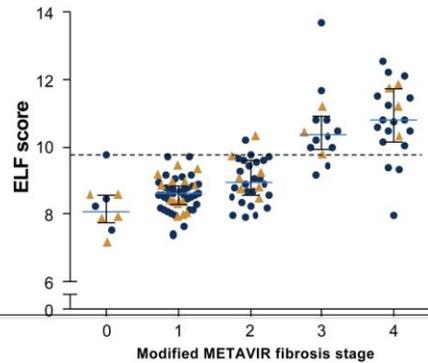
NIT Staging: Enhanced Liver Fibrosis (ELF) Score

ELF cut-off scores and accuracy for measuring advanced fibrosis



ELF is a blood test that measures 3 biomarkers involved in collagen homeostasis (fibrosis): HA, PIIIINP, and TIMP-1.

ELF score according to modified METAVIR fibrosis stage for patients with overweight/obesity and steatosis on liver biopsy²



HA, hyaluronic acid; PIIIINP, procollagen III amino terminal peptide; TIMP-1, tissue inhibitor of metalloproteinase.

1. Lichtinghagen R et al. *J Hepatol.* 2013;59:236–42. 2. Fagan KJ et al. *Liver Int.* 2015;35:1673–81. 3. Vali Y et al. *J Hepatology.* 2020;73(2):252-262. 4. Day J et al. *J Appl Lab Med.* 2019;3(5):815-826.



NIT Staging: Enhanced Liver Fibrosis (ELF) Score

Quest

Test Code: **10350**
CPT: 0014M

LabCorp

Test Code: **550659**
CPT: 0014M

1. Lichtinghagen R et al. *J Hepatol.* 2013;59:236–42. 2. Fagan KJ et al. *Liver Int.* 2015;35:1673–81. 3. Vali Y et al. *J Hepatology.* 2020;73(2):252-262. 4. Day J et al. *J Appl Lab Med.* 2019;3(5):815-826.



NIT Staging: Elastography

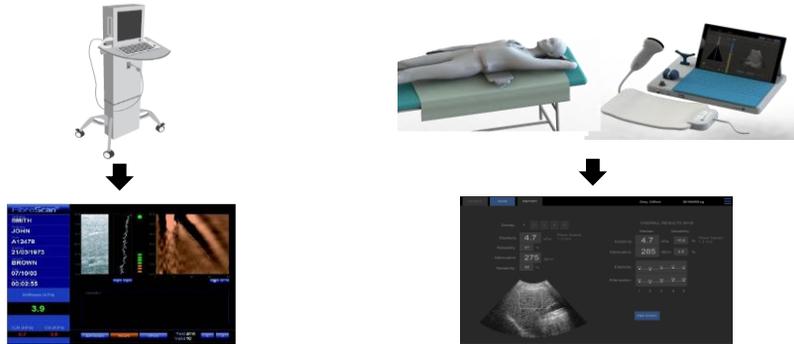
Provides Two Values

1. Stiffness Score (kPa)*

Estimates fibrosis
Reported in kilopascals (kPa)

2. CAP Score

Estimates fat quantity
Only good if >30% liver has fat



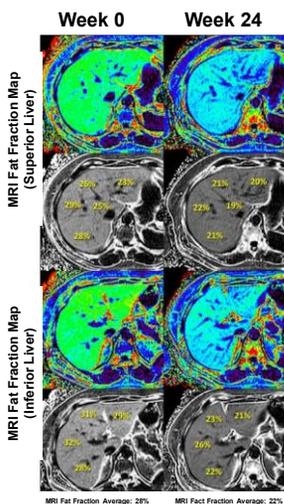
	Transient Elastography (kPa)	3D S-WAVE Ultrasound Elastography (kPa)
Advantages	<ul style="list-style-type: none"> Can be performed in clinic with real-time results 	<ul style="list-style-type: none"> Can be performed in clinic with real-time results
Disadvantages	<ul style="list-style-type: none"> Increased failure rate with obesity Expensive device Cutoff values with XL probe are slightly different from M probe 	<ul style="list-style-type: none"> More time consuming than TE (although time can be reduced significantly with training) Limited availability

Fibroscan (VCTE) kPa ≠ shear wave kPa; CAP, controlled attenuation parameter.

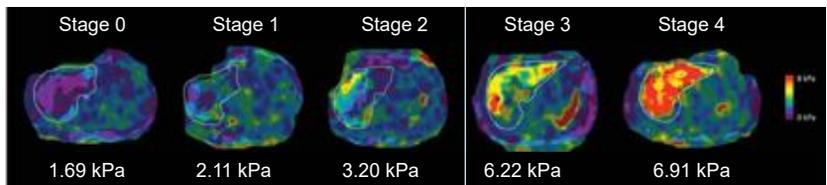


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NIT for MASLD Staging: MRI-PDFF and MRE



Modified phase-contrast pulse sequence to visualize rapidly propagating mechanical shear waves (~60 Hz)



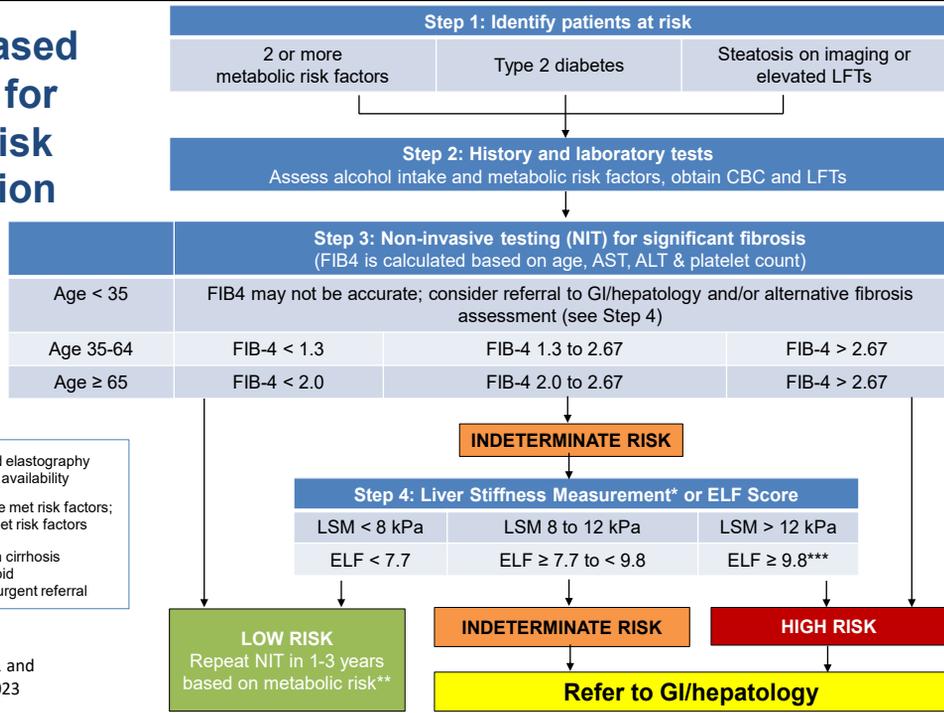
Cutoff for Detecting Advanced Fibrosis	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
MRE stiffness ≥3.64 kPa	0.86 (0.65-0.97)	0.91 (0.83-0.96)	0.68 (0.48-0.84)	0.97 (0.91-0.99)

Noureddin. *Hepatology*. 2013; Loomba. *Hepatology*. 2015; Loomba *Hepatology*. 2014; Patel et al. *Ther Adv Gastroenterol*. 2016; Han, Noureddin. *Liver Int*. 2020.



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Practice-Based Guidance for MASLD Risk Stratification



*VCTE (preferred) or ultrasound elastography (shear wave or ARFI) based on availability
 **1-2 years if T2DM or 2 or more met risk factors; 2-3 years if no T2DM and <2 met risk factors
 ***ELF ≥ 11.3 is consistent with cirrhosis
 ELF ≥ 13 is associated with rapid decompensation and requires urgent referral

Adapted from Kanwal et al. *Gastroenterology* Nov 2021 and Rinella et al. *Hepatology* 2023

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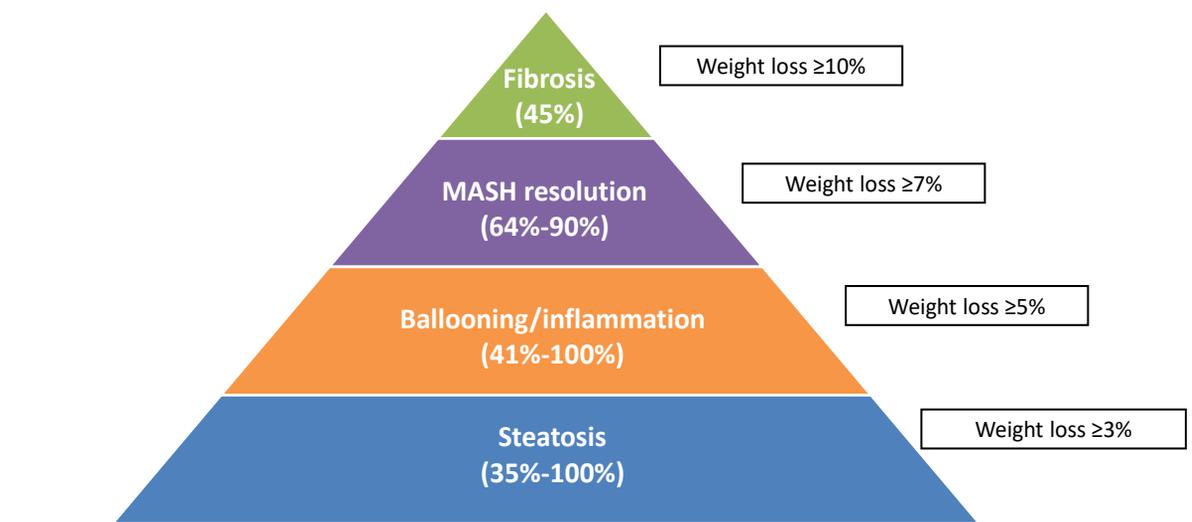
Understand treatment goals and potential therapeutic modalities in MASLD/MASH

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First Step in MASLD/MASH Management: Lifestyle Modifications



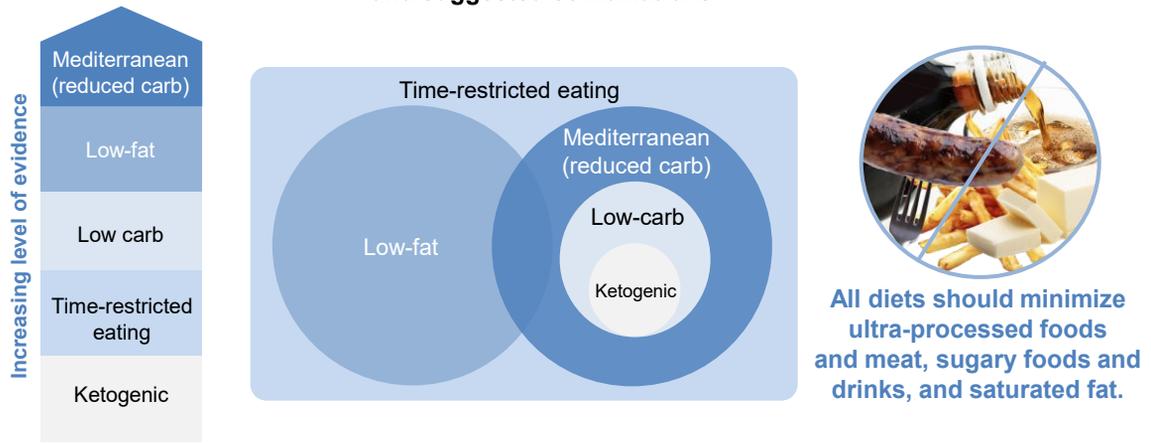
MASLD Management: Address Weight



Hannah. Clin Liver Dis. 2016;20:339.

Type of Diet for the Treatment of MASLD

Conceptual summary of level of evidence of diets for MASLD treatment and suggested combinations



Zelber-Sagi S. *Liver International*. 2022;42:1731-1750.

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MASLD Diet: Clinical Pearls

- Prescribe a diet that leads to a caloric deficit
- Tailor dietary modifications to patient’s cultural and personal preferences
- **Coffee** consumption: ≥3 cups/day reduces risk of MASLD, fibrosis and HCC
- NO support for other nutraceuticals
- Minimize alcohol
 - NONE in MASH F2 or greater
 - Emphasize risks of binge drinking on liver health

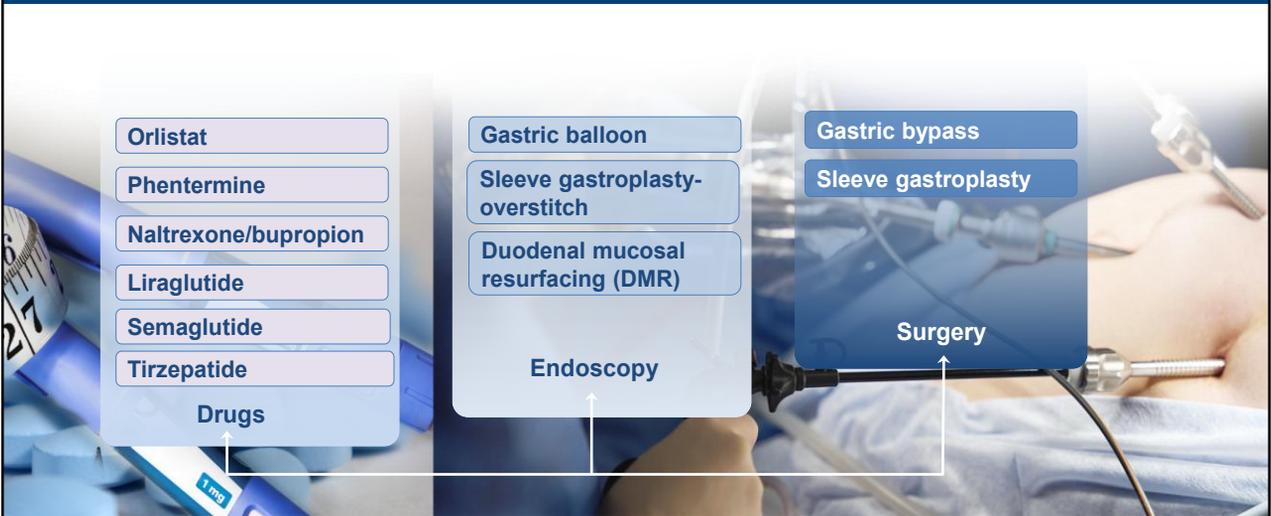


EASL-EASD-ESO MASLD Clinical Practice Guidelines 2024

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Weight Loss Beyond Lifestyle Modifications



NOTE: None of the strategies listed are approved for the treatment of MASH.
Adapted from © 2020 AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES. WWW.AASLD.ORG.

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Recommendations for Physical Activity

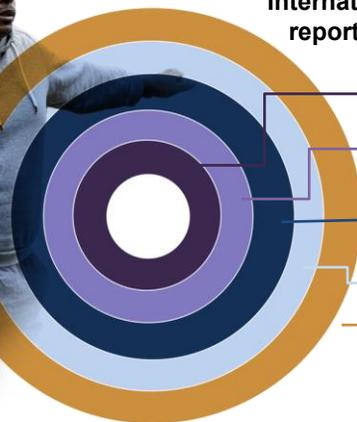
Tailor to the patient

Aim for >150 min/week of moderate-intensity or 75 min/week of vigorous-intensity physical activity

Minimize sedentary time



American College of Sports Medicine (ACSM) International Multidisciplinary Roundtable report on physical activity and MASLD



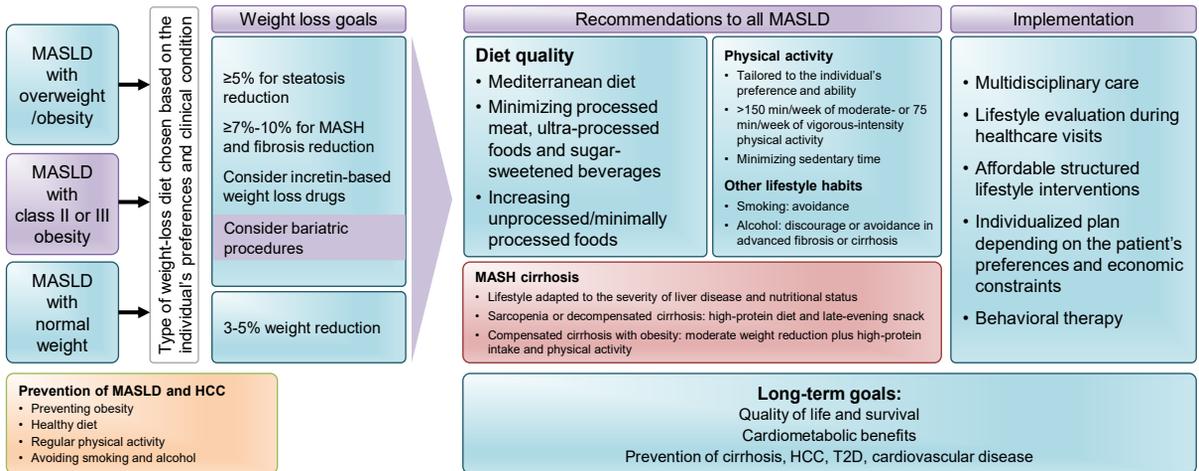
- Liver fat
- CV health
- Body composition
- Cardiorespiratory fitness
- Health-related QoL

© World Obesity.
Stine JG. *Hepatal Comm.* 2023;7(4):e0108.

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Lifestyle: Optimizing Cardio-Metabolic Risks



EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD)
 Tacke, Frank et al. Journal of Hepatology, Volume 81, Issue 3, 492 - 5



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Second Step of MASH Management: Liver Targeted MASH Treatment



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Major 2025 Updates in MASH Pharmacotherapy



FDA Accepts Letter of Intent for VCTE as a Surrogate Endpoint in MASH trials¹



Semaglutide Receives Conditional Approval (F2–F3)^{2,3}



Next-Generation Agents Move Toward Registration

Resmetirom entering post-approval outcomes phase.

FGF21 analogs (e.g., pegozafermin) show *fibrosis + NASH resolution*.

Dual agonists (GLP-1/GIP, GLP-1/GCGR) advance as combination-strategy candidates.

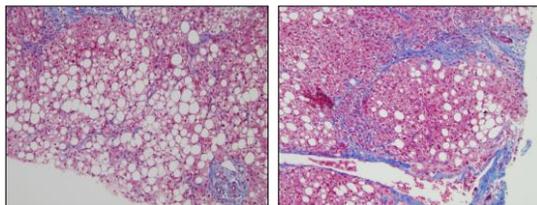
1. U.S. Food and Drug Administration. WEGOVY (semaglutide) injection, for subcutaneous use: Official prescribing information. Aug 2025. 2. Sanyal AJ et al. *N Engl J Med* 2025 Jun 5; 392:2089;



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Currently Accepted FDA Endpoints for Non-cirrhotic MASH Conditional Approval

Resolution of MASH, no worsening of fibrosis



Stage 2-3

Stage 3-4

Resolution or improvement of MASH could reflect disease progression

Reduction in fibrosis, no worsening of MASH

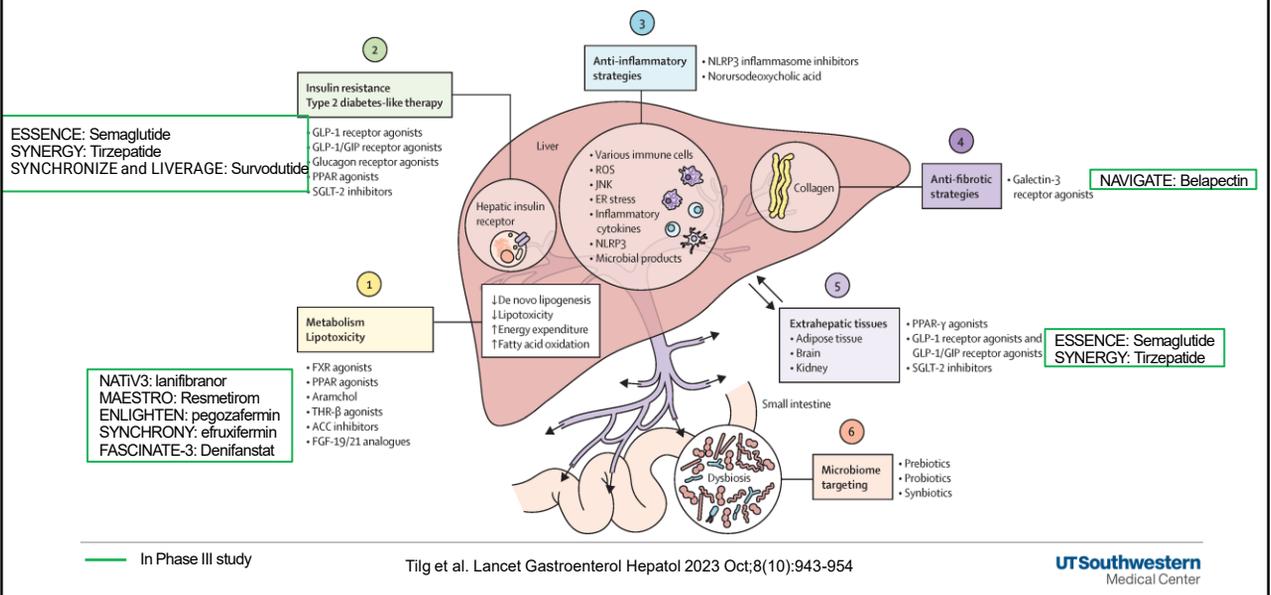
- Fibrosis linked to hard clinical outcomes
- Needs to not adversely impact metabolic or inflammatory activity

Courtesy of M. Rinella



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Targeting Pathophysiological Processes in MASH



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Resmetirom Was the First Approved Drug for MASH



Oral, partial agonist of thyroid hormone receptor-beta (THR-β)¹

Approved March 2024 for the treatment of adults with **NASH^a with moderate-to-advanced fibrosis in conjunction with diet and exercise²**

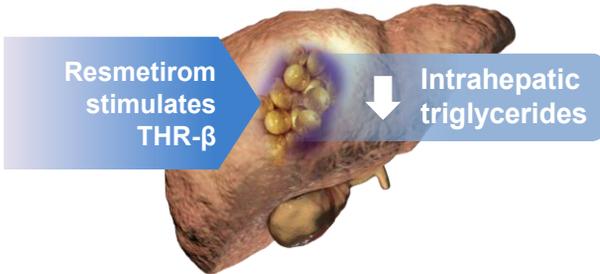
Cost: ~\$47,000 per year

^aNASH used due to publication date.

1. Harrison SA et al. *N Engl J Med*. 2024;390(6):497-509; 2. Rezdiffra [prescribing information]. Madrigal Pharmaceuticals, Inc.

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Resmetirom Mechanism-of-Action



Liver-targeted activity

- Stimulates THR-β receptors in the liver
- Selectively effective in activating THR-β over THR-α outside the liver (heart and bones)

Reduces hepatic steatosis

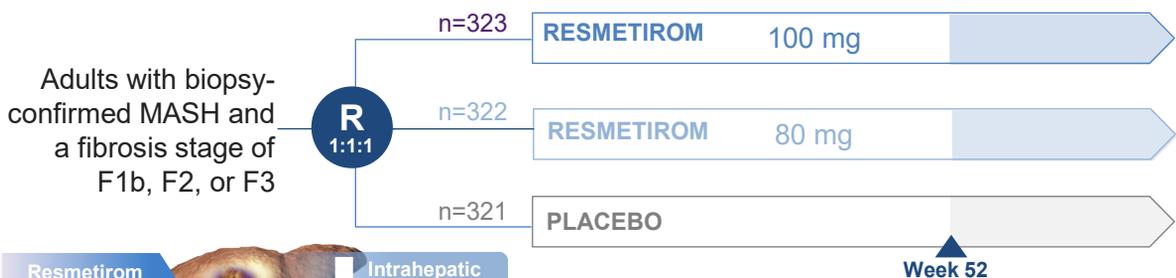
- Stimulates lipophagy
- Stimulates mitochondrial biogenesis
- Inhibits lipogenesis

May interfere with fibrogenesis by inhibiting TGF-β signaling

1. Harrison SA et al. *N Engl J Med.* 2024;390(6):497-509; 2. Rezdiffra (resmetirom) [prescribing information]. Madrigal Pharmaceuticals, Inc.; West Conshohocken, PA; 2024.

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MAESTRO-NASH: Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis



Primary endpoints

- 1 MASH resolution including a reduction in NAS by ≥ 2 points with no worsening of fibrosis
- 2 Improvement (reduction) in fibrosis by ≥ 1 stage with no worsening of NAS

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Resmetirom Phase 3 (MAESTRO) Study: Patient Population

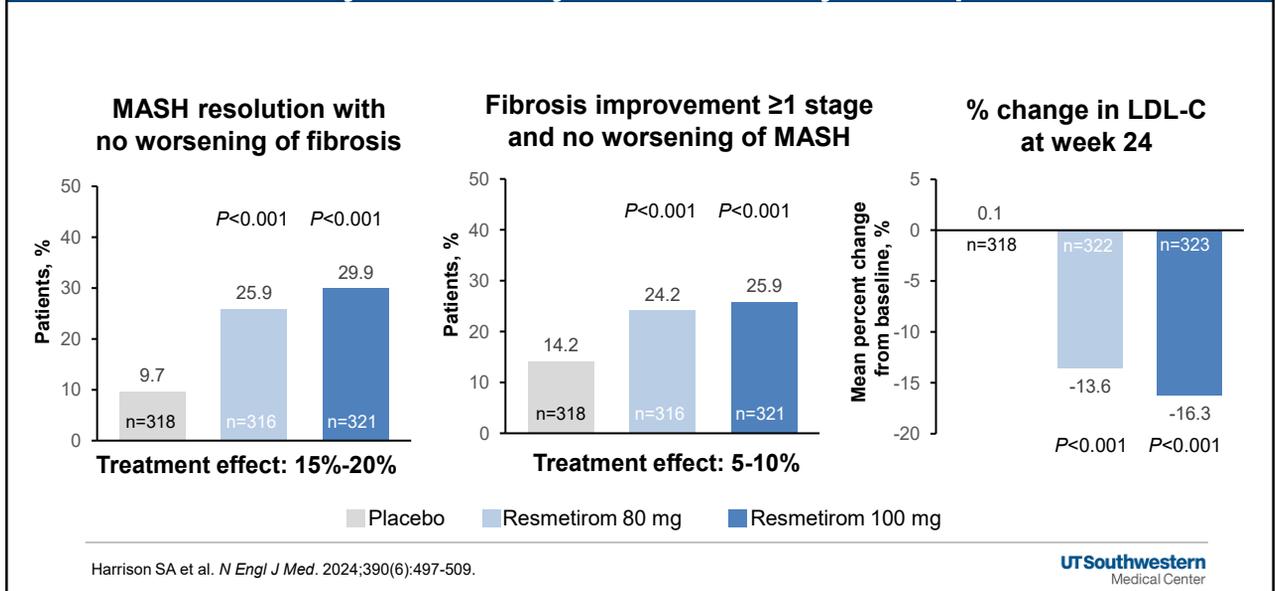
Characteristic	Overall (N=966) %
Fibrosis stage	
F1b	5.1
F2	33.0
F3	61.9
Type 2 diabetes	67.0
Hypertension	78.1
Dyslipidemia	71.3
Statin use	48.9
GLP-1 receptor agonist use	14.3

Harrison SA et al. *N Engl J Med.* 2024;390(6):497-509.

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Resmetirom Phase 3 (MAESTRO) Study: Primary and Key Secondary Endpoints



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Resmetirom: Phase 3 Safety (MAESTRO Study)



Adverse events >10% of patients in any group

	Resmetirom 80 mg (n=322) %	Resmetirom 100 mg (n=323) %	Placebo (n=321) %
Diarrhea	27.0	33.4	15.6
Covid-19	21.4	16.7	20.6
Nausea	22.0	18.9	12.5
Arthralgia	14.9	10.8	12.5
Back pain	10.9	8.4	11.8
Urinary tract infection	10.2	8.4	8.4
Fatigue	10.2	8.0	8.7
Pruritus	8.1	11.5	6.9
Vomiting	8.7	10.8	5.3

NOTE: Increases in mean ALT and AST (<1.5x baseline) were observed in the first 4 weeks after initiating treatment. Values returned to baseline ~8 weeks after initiating treatment.

Harrison SA et al. *N Engl J Med.* 2024 Feb 8;390(6):497-509.

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Resmetirom Dosing and Other Considerations

Dosing

<100 kg (220 lbs)
80 mg QD

≥100 kg (220 lbs)
100 mg QD

- Rule out additional causes of liver disease, including autoimmune hepatitis
- Resmetirom is **not approved** in patients with **cirrhosis**
- Prior to starting therapy, review for possible drug-drug interaction potential, including **statins, gemfibrozil, clopidogrel, cyclosporine**

Rezdiffra (resmetirom) [prescribing information]. Madrigal Pharmaceuticals, Inc.; West Conshohocken, PA; 2024.

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Semaglutide 2.4 mg Is the Second FDA Conditionally Approved Drug for MASH



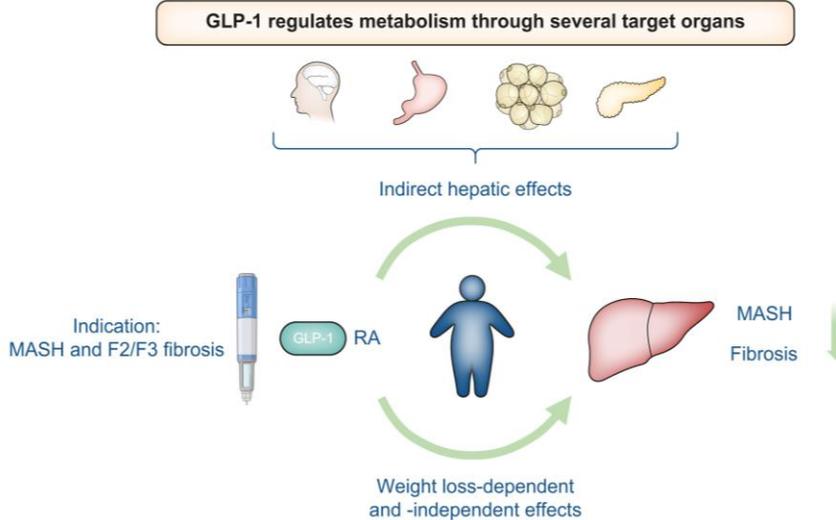
Injectable, GLP-1 Agonist

Approved August 2025 for the treatment of adults with **MASH with moderate-to-advanced fibrosis in conjunction with diet and exercise²**

Cost: ~\$16,200 per year

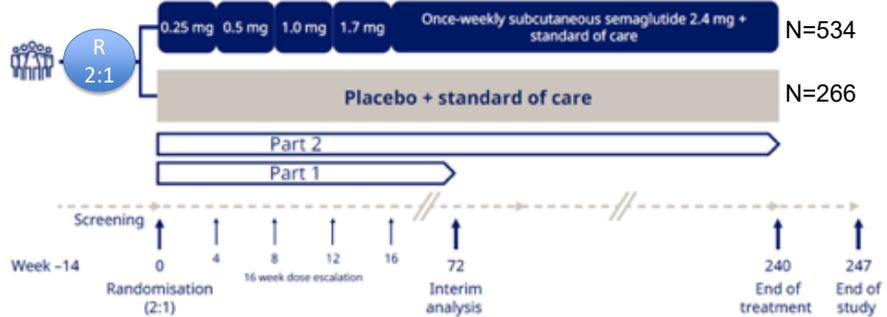
1. Sanyal A. et al. N Engl J Med 2025;392:2089-2099; 2. Wegovy [prescribing information]. Novo Nordisk, Inc

GLP-1 Agonists in MASH



ESSENCE Study: Phase 3, Randomized, Controlled Trial of Semaglutide in MASH with Liver Fibrosis

Adults with biopsy-confirmed MASH and a fibrosis stage of F2, or F3



The NEW ENGLAND JOURNAL of MEDICINE

Primary endpoints

- MASH resolution including a reduction in NAS by ≥ 2 points with no worsening of fibrosis
- Improvement (reduction) in fibrosis by ≥ 1 stage with no worsening of NAS

Sanyal A. et al. N Engl J Med 2025;392:2089-2099

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Semaglutide Phase 3 (ESSENCE) Study: Patient Population

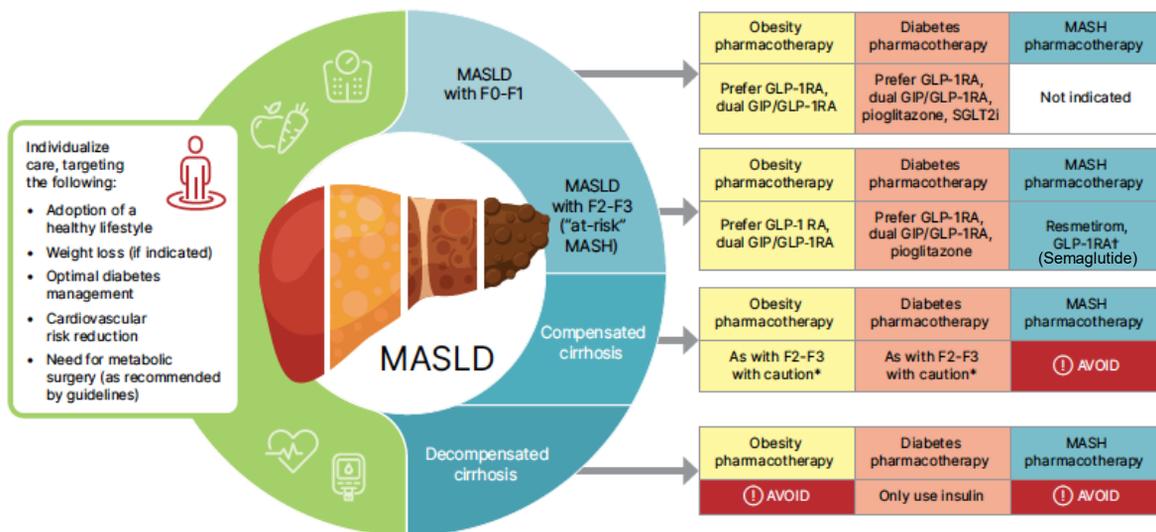
Characteristic	Overall (N=800) %
Age, year (SD)	56.0 \pm 11.6
BMI, kg/m ²	34.6 \pm 7.2
Fibrosis stage, %	
F2	31.3
F3	68.8
Type 2 diabetes, %	55.9
FIB-4, median (IQR)	1.56 (1.12-2.27)
Liver stiffness (VCTE), kPa	12.8 \pm 16.9

Sanyal et al. NEJM Apr 30, 2025. ePub

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Bringing it Home: MASLD Management in 2026



Cusi K et al. Diabetes Care 2025; 8:1-26 | <https://doi.org/10.2337/dci24-0094>

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When You Identify Hepatic Steatosis in a Patient with Metabolic Risk Factors, What Is the *Best Next Step*?

- Reassure if ALT/AST are normal
- Order ultrasound and follow clinically
- Calculate FIB-4
- Refer directly to GI/hepatology
- Screen for viral hepatitis

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What Do You Usually Emphasize to Patients with MASLD as Their *Greatest Long-term Health Risk*?

- A. Progression to cirrhosis
- B. Hepatocellular carcinoma
- C. Liver Transplantation
- D. Cardiovascular disease
- E. Diabetes mellitus

Which Patient with MASLD Should Be Referred to GI/Hepatology for *Consideration of Liver-directed MASH Therapy*?

- A. Steatosis on imaging with normal labs
- B. Low-risk FIB-4 (score <1.3)
- C. Compensated cirrhosis
- D. Confirmed stage 2 or 3 (F2-F3) fibrosis
- E. Decompensated cirrhosis

Key Take Aways

MASLD for Frontline Providers



New nomenclature recognizes a continuum between metabolic risk and alcohol use on steatotic liver disease



Risk stratification in MASLD starts with use of the FIB4 score followed by VCTE or ELF and/or referral to GI/Hepatology



Lifestyle modification remains the backbone
Resmetirom and semaglutide 2.4 mg are FDA-approved* for F2–F3 MASH

*conditionally approved

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