Diabetes and Metabolic Associated Steatotic Liver Disease (MASLD) - Evaluation and Treatment

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Disclosure

Advisory Board: Abbott; Eli Lilly; MannKind; Novo Nordisk

Consultant: Eli Lilly; Novo Nordisk

Research Grant: AbbVie; Bayer Pharmaceuticals; Eli Lilly; Novo Nordisk

Speaker's Bureau: Abbott; Eli Lilly; MannKind; Novo Nordisk

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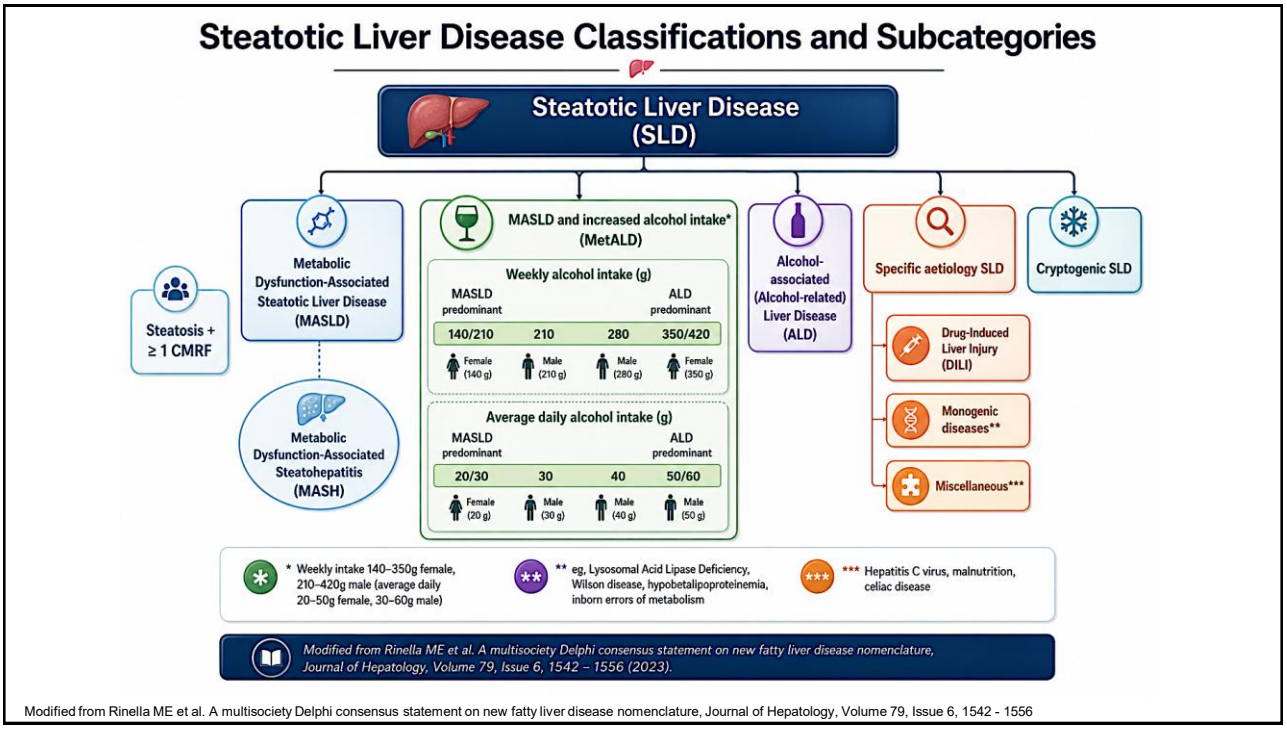

Modified from Rinella ME et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature, Journal of Hepatology, Volume 79, Issue 6, 1542 - 1556

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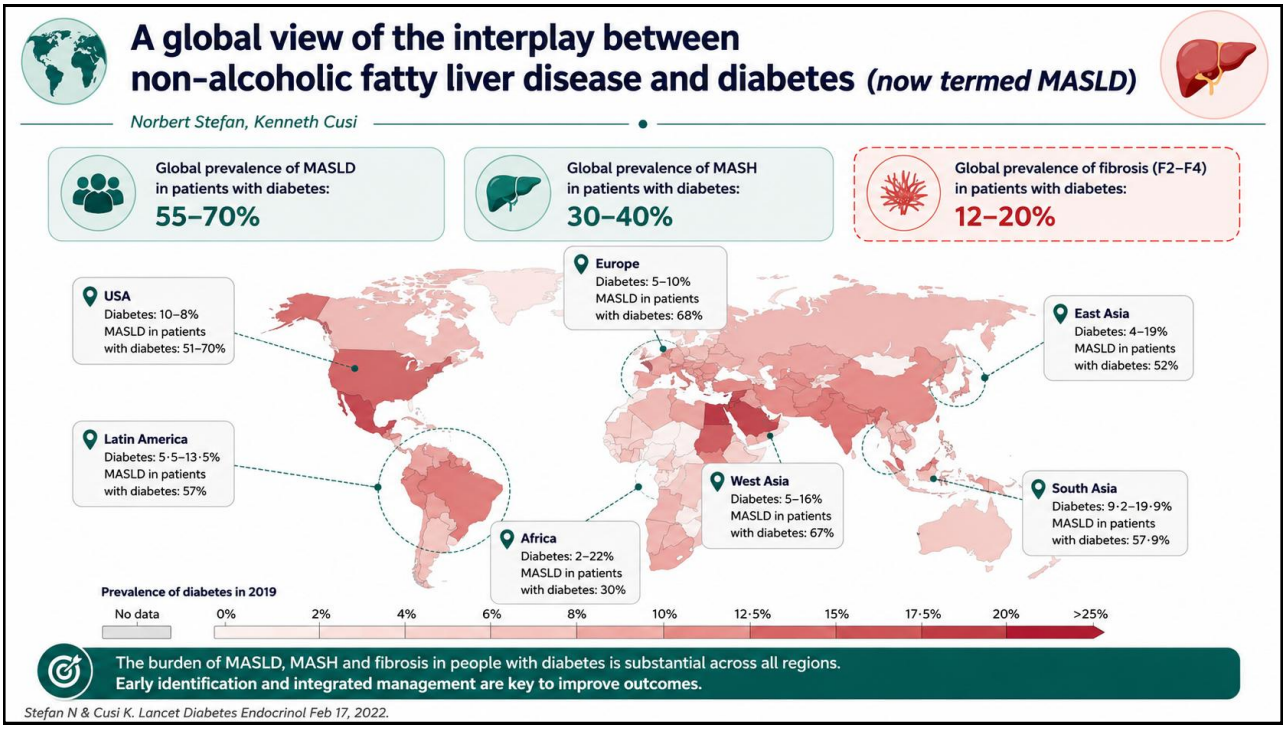

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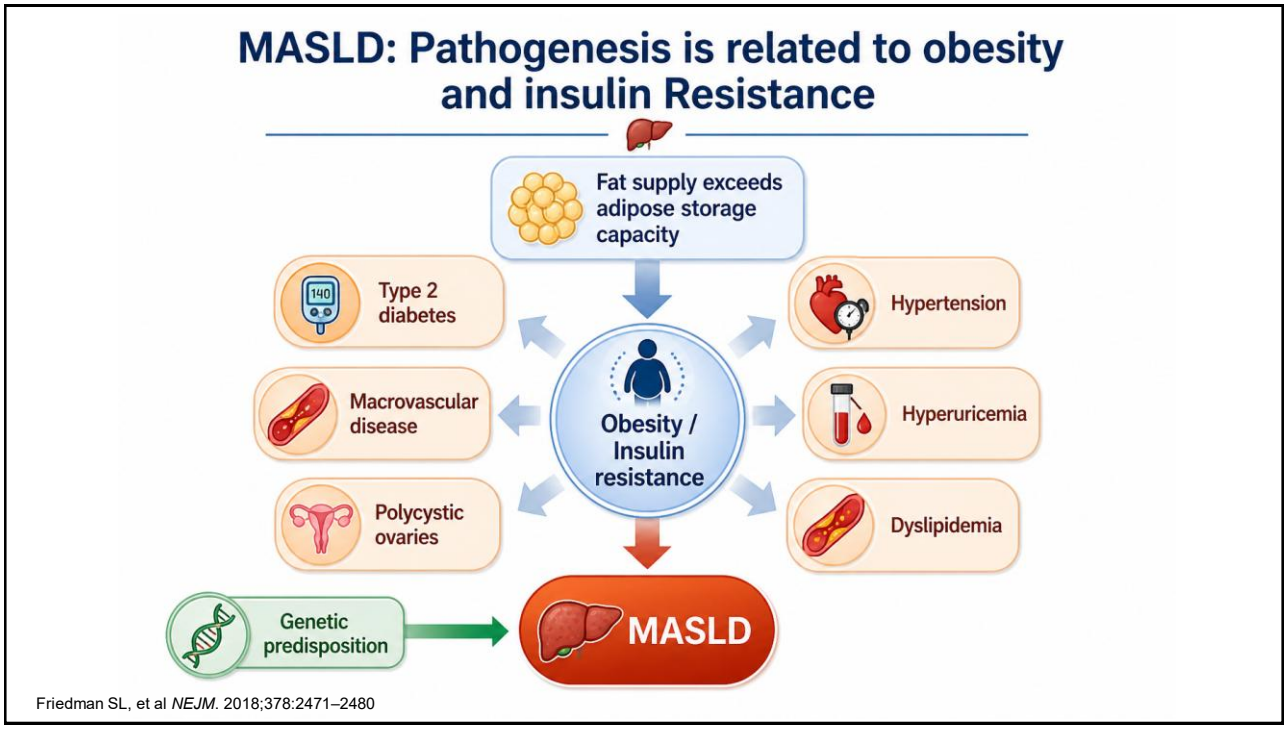

Friedman SL, et al *NEJM*. 2018;378:2471–2480

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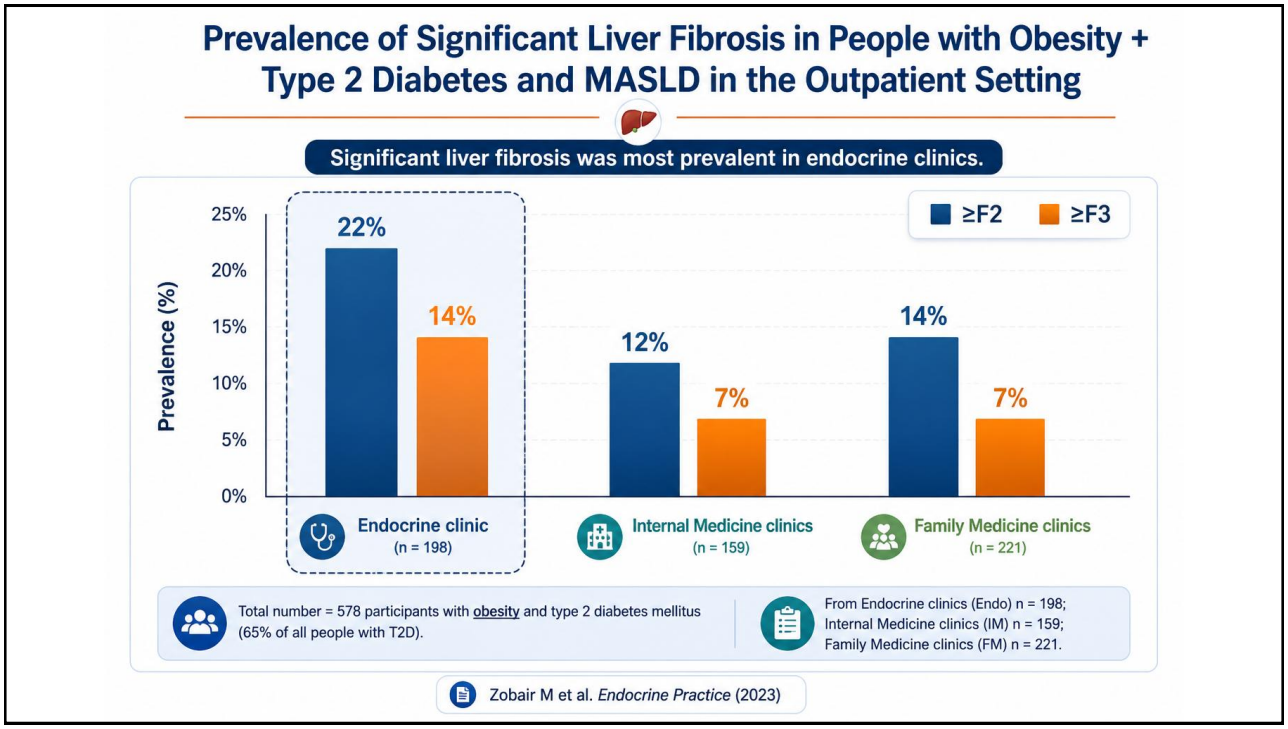

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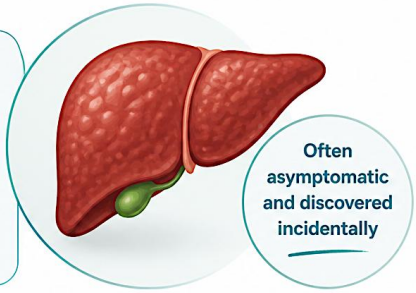
How does MASLD Present?

Symptoms

- Usually asymptomatic; majority discovered by chance
- Fatigue frequently present
- Right upper quadrant discomfort



Often asymptomatic and discovered incidentally

Often an "Incidental Finding"

- Incidental abnormal LFTs
- Incidental "bright liver" on imaging
- Incidental hepatomegaly

Early detection through screening and routine evaluation is key to preventing progression.

De Alwis. *Dig Dis.* 2016;34:19.

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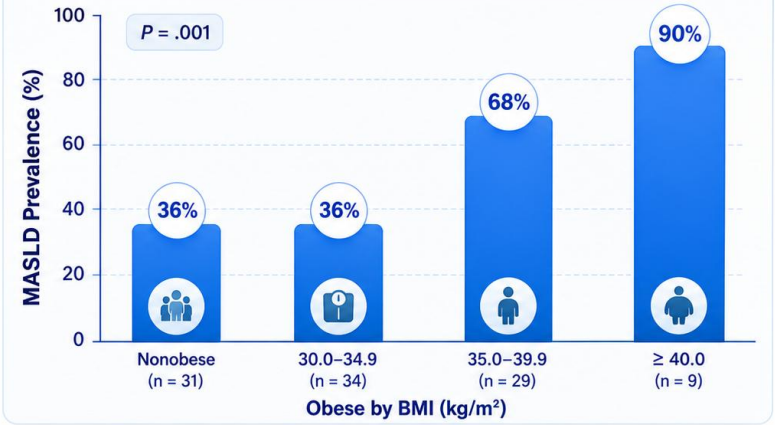
Prevalence of MASLD in Patients with T2DM and Normal AST/ALT

Prevalence of MASLD by Obesity (BMI)



Patients with T2DM and normal AST or ALT evaluated for liver triglyceride content by H-MRS, insulin sensitivity, and adipose tissue insulin resistance (N = 103)

Prevalence of MASLD in overall cohort: **50%**

Among these patients, prevalence of MASH: **56%**

Paola Portillo-Sanchez et al. *J Clin Endocrinol & Metab* (2015)

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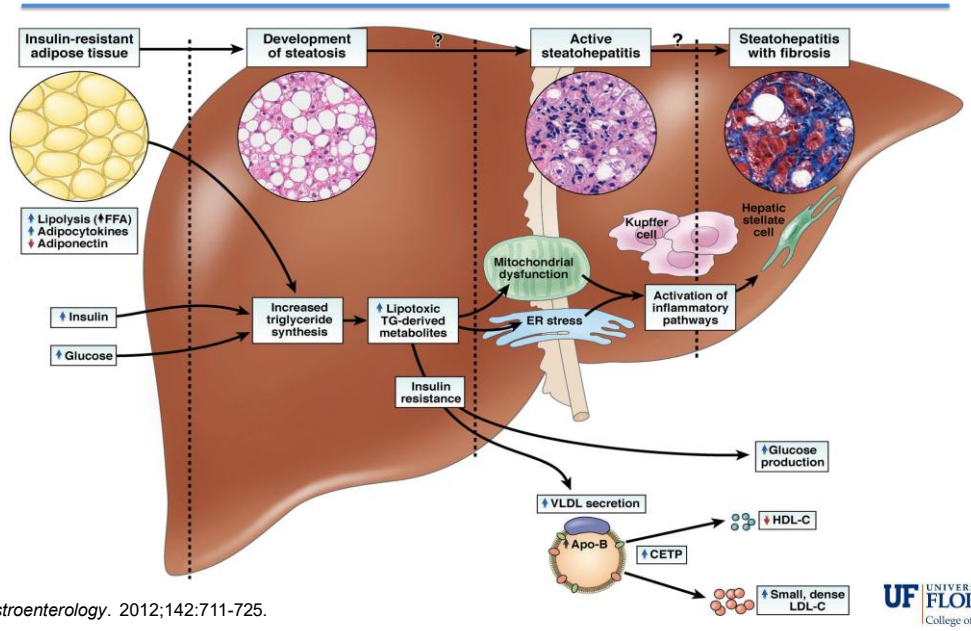
From Obesity and T2D to MASH with Cirrhosis



Cusi K. *Gastroenterology*. 2012;142:711-725.

UF UNIVERSITY of FLORIDA College of Medicine

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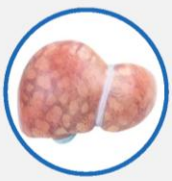
MASLD Is a Chronic and Progressive Liver Disease

MASLD: Metabolic Associated Steatotic Liver Disease

Normal Liver	MASLD – Steatotic Liver	MASH: Metabolic Associated Steatohepatitis	MASH with fibrosis	Cirrhosis
				
Fat accumulation	▪ Isolated steatosis (fat in ≥5% of hepatocytes)	▪ Steatosis ▪ Ballooning ▪ Inflammation	▪ **F1:** fibrosis stage 1 = **Mild** *Moderate to Advanced* ▪ **F2:** fibrosis stage 2 ▪ **F3:** fibrosis stage 3	▪ **F4:** fibrosis stage 4 = **Cirrhosis**

MASH is the more advanced form of MASLD which can progress to cirrhosis, liver failure, hepatocellular carcinoma

Hepatocytes, liver cells. **Steatosis,** excess fat in liver cells. **Steatohepatitis,** build up of excess fat in liver cells causing inflammation and damage.

1. Sheka AC, et al. JAMA. 2020;323(12):1175-83. 2. Alkhouri N, McCullough AJ. Gastroenterol Hepatol (N Y). 2012;8(10):661-8. 3. EASL–EASD–EASO. J Hepatol. 2016;64:1388-402. 4. Diehl AM, Day C. NEJM. 2017;377:3063-72. 5. Honda et al. Int J Mol Sci. 2020;21:4039.

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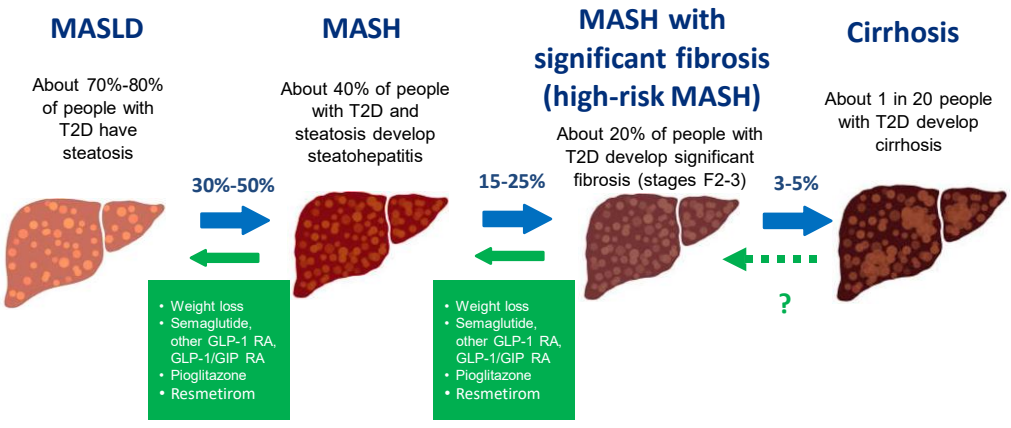
Progression of MASLD in People with T2D



Main factors of disease progression:
T2D, insulin resistance, obesity, genetic factors (i.e., PNPLA3), and male sex

Adapted from Nogueira & Cusi et al. *Diabetes Spectrum*. February 2024;37:20-28.

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Why is it imperative to diagnose MASLD?

- **High prevalence:** ~25–38% of U.S. adults (≈100M people)
- **Silent disease:** majority asymptomatic, normal AST/ALT common
- **All stages of MASLD** are associated with increased risk for other comorbidities (T2D, CVD, CKD, cancers)
- **Fibrosis drives outcomes:** ≥F2 linked to ↑ liver-related & all-cause mortality
- **Actionable:** noninvasive screening (FIB-4 → elastography) identifies high-risk patients
- **Treatment era:** lifestyle, GLP-1 RAs, and resmetirom for MASH with fibrosis

Early identification and intervention can prevent progression and improve liver and cardiometabolic outcomes.

Alqahtani SA et al. Hepatol Commun. 2021; Rinella ME et al. Hepatology. 2023; Kanwal F et al. Gastroenterology. 2026

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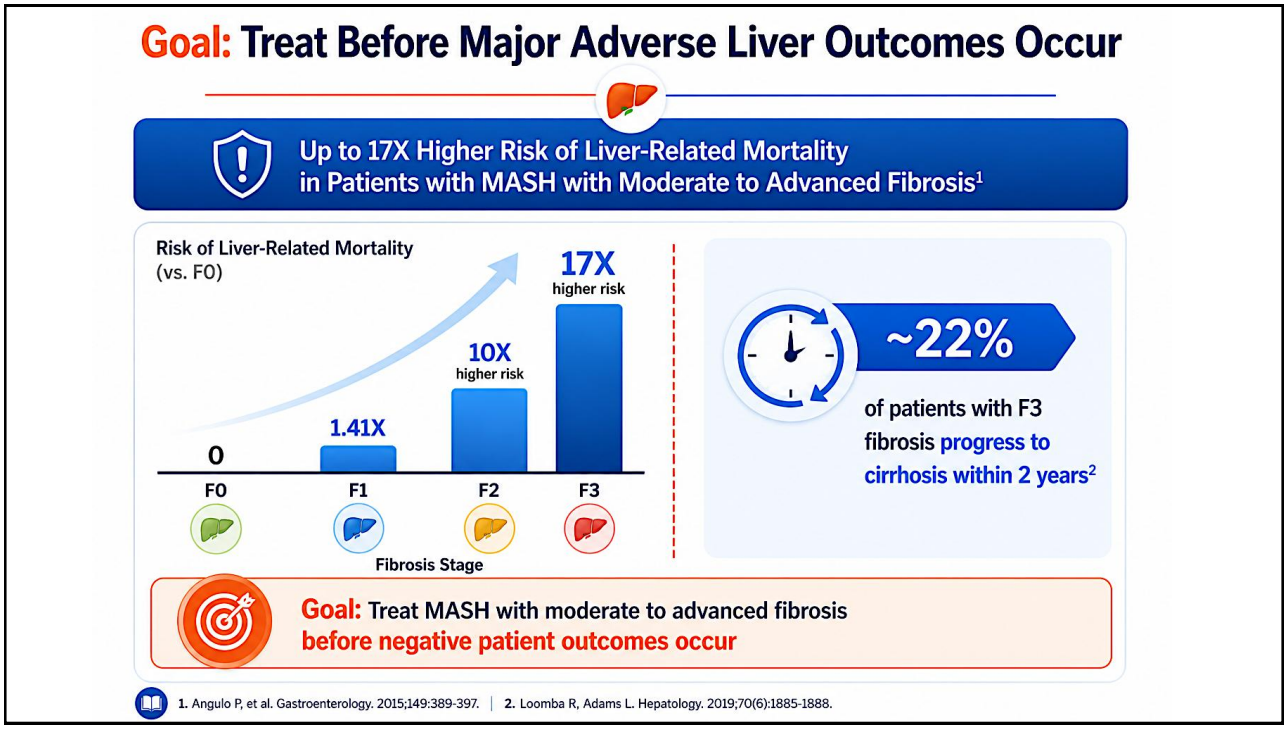
Goal: Treat Before Major Adverse Liver Outcomes Occur
Up to 17X Higher Risk of Liver-Related Mortality in Patients with MASH with Moderate to Advanced Fibrosis[1]
Risk of Liver-Related Mortality (vs. F0)
0
1.41X
10X higher risk
17X higher risk
F0
F1
F2
F3
Fibrosis Stage
~22%
of patients with F3 fibrosis progress to cirrhosis within 2 years[2]
Goal: Treat MASH with moderate to advanced fibrosis before negative patient outcomes occur
1. Angulo P, et al. Gastroenterology. 2015;149:389-397. | 2. Loomba R, Adams L. Hepatology. 2019;70(6):1885-1888.

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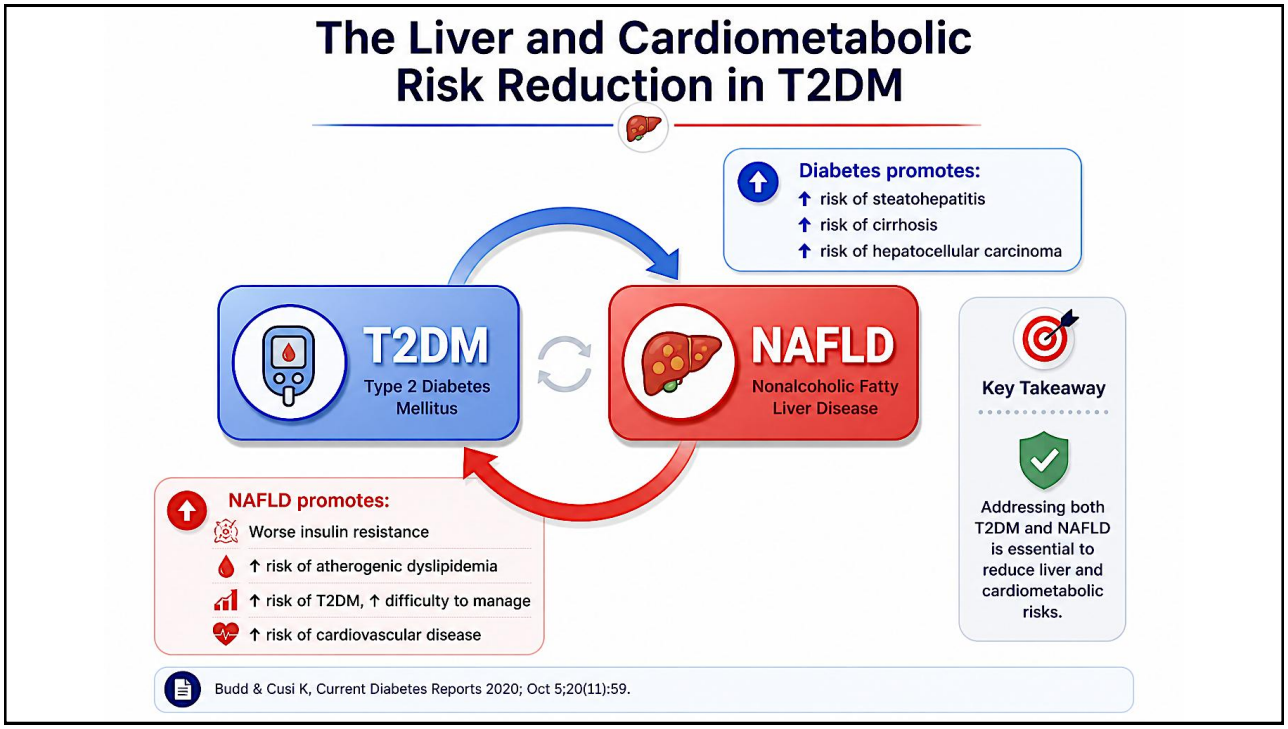
The Liver and Cardiometabolic Risk Reduction in T2DM
Diabetes promotes:
↑ risk of steatohepatitis
↑ risk of cirrhosis
↑ risk of hepatocellular carcinoma
T2DM
Type 2 Diabetes Mellitus
NAFLD
Nonalcoholic Fatty Liver Disease
NAFLD promotes:
Worse insulin resistance
↑ risk of atherogenic dyslipidemia
↑ risk of T2DM, ↑ difficulty to manage
↑ risk of cardiovascular disease
Key Takeaway
Addressing both T2DM and NAFLD is essential to reduce liver and cardiometabolic risks.
Budd & Cusi K, Current Diabetes Reports 2020; Oct 5;20(11):59.

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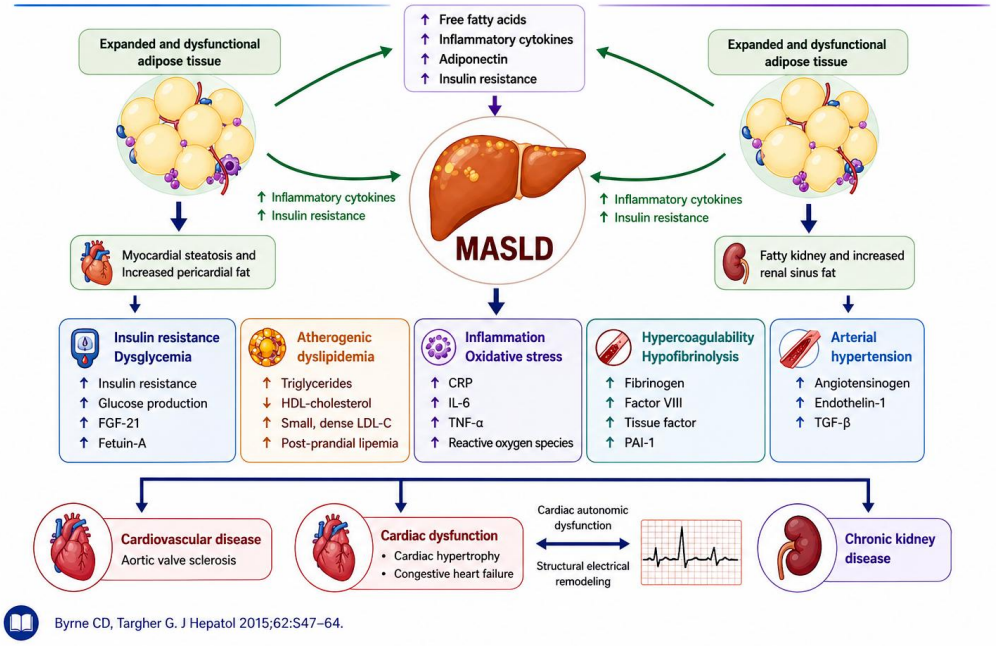
Putative connection between MASLD, CVD and CKD



Byrne CD, Targher G. J Hepatol 2015;62:S47–64.

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MASH Screening

WHO TO SCREEN

- **T2DM/insulin resistance**
- **Obesity** with 1 or more metabolic risk factor
- **Hepatic steatosis** or abnormal LFTs

HOW TO SCREEN (NON-INVASIVE)

- **FIB-4**
- **Enhanced Liver Fibrosis Score (ELF)**
- **Fibroscan (VCTE)**

Early identification of patients at risk for advanced fibrosis allows timely intervention to prevent progression and improve outcomes.

FIB-4 = Fibrosis-4 Index; ELF = enhanced liver fibrosis test; VCTE = vibration-controlled transient elastography
Kanwal F, et al. *Gastroenterology* 2026 (online ahead of print) DOI: 10.1053/j.gastro.2026.01.047

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Initial Evaluation

- **FIB-4;** smartphrase in EMR
- **A1C, lipids**
- Rule out **viral hepatitis**

$$\text{FIB-4} = \frac{\text{Age} \times \text{AST}}{\text{Platelets} \times \sqrt{\text{ALT}}}$$

FIB-4 RISK STRATIFICATION AND REFERRAL TO GI

FIB-4 SCORE		
< 1.3	Management by PCP	Repeat risk assessment q2–3 years
1.3–2.67	Consider GI/Liver Referral	If MASLD established, return to PCP
> 2.67	Refer to GI/Liver	Longitudinal specialty care as appropriate

Best Practice for ALL MASLD Patients *Regardless of Fibrosis Stage*

- Referral to MOVE!
- CV Disease Risk Factor Management
- Alcohol Abstinence
- Viral Hepatitis Immunization

US Dept of Veterans Affairs. Viral Hepatitis and Liver Disease. Available at: https://www.hepatitis.va.gov/nafl/diagnosis.asp

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Limitations of FIB-4 for Screening in MASLD

Important constraints that limit FIB-4 as a stand-alone screening test

1. Large Indeterminate Range
Large numbers report in the indeterminate range → requires second-line testing

2. Age-Related Misclassification
False positives in older adults; reduced sensitivity in < 35

3. Does Not Screen for Early Fibrosis
Limited ability to detect early (stages F0–F1) disease

4. Susceptible to Confounders
AST/ALT (alcohol, muscle), platelets (inflammation) can skew results

5. Not Disease-Specific
Cannot distinguish MASLD from other chronic liver diseases

6. Unreliable in Acute Illness
Reduced reliability due to laboratory variability and acute inflammatory states

CLINICAL IMPLICATION: AASLD recommends FIB-4 as a first-line triage tool, not stand-alone screening; **requires confirmatory testing** (e.g., elastography, ELF, or other validated assessments)

AASLD Practice Guidance (2023–2024) | EASL Guidelines (2021–2024) | Sterling et al. Hepatology 2006
McPherson et al. Gut 2017 | Castera et al. J Hepatol 2019

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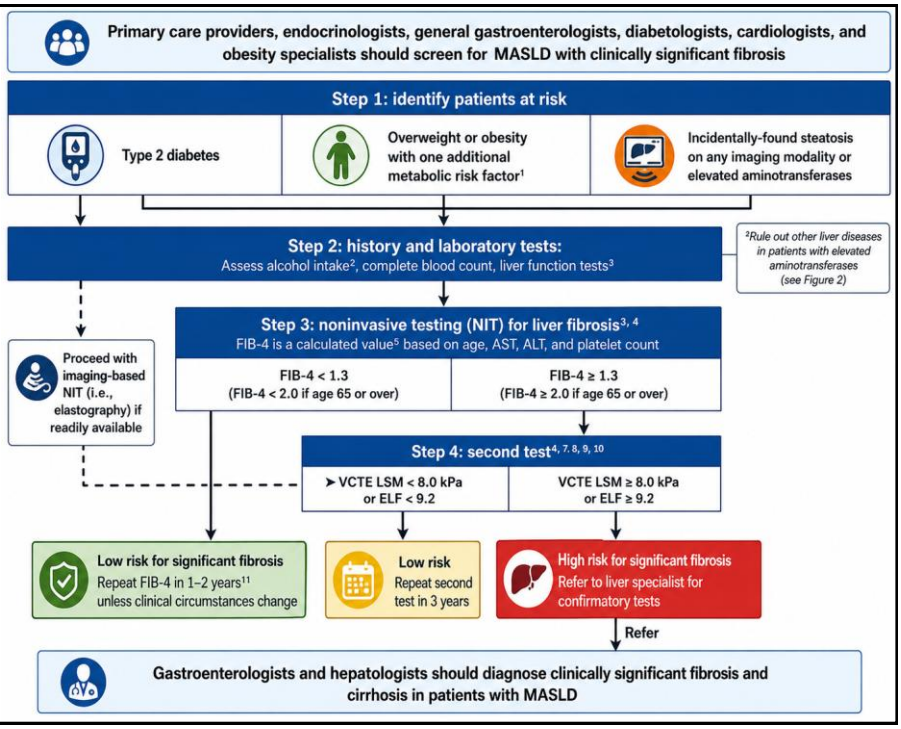
AGA MASLD Clinical Care Pathway



Adapted from Kanwal F, et al. *Gastroenterology* 2026 (online ahead of print) DOI: 10.1053/j.gastro.2026.01.047

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IMAGING

Abdominal ultrasound
not needed

Vibration-Controlled Transient Elastography (VCTE)
AKA **FibroScan®** to stage

Non-invasive

Quick (~10 minutes)

Accurate staging of fibrosis

VCTE (FibroScan®) provides a reliable, non-invasive way to assess and stage liver fibrosis.

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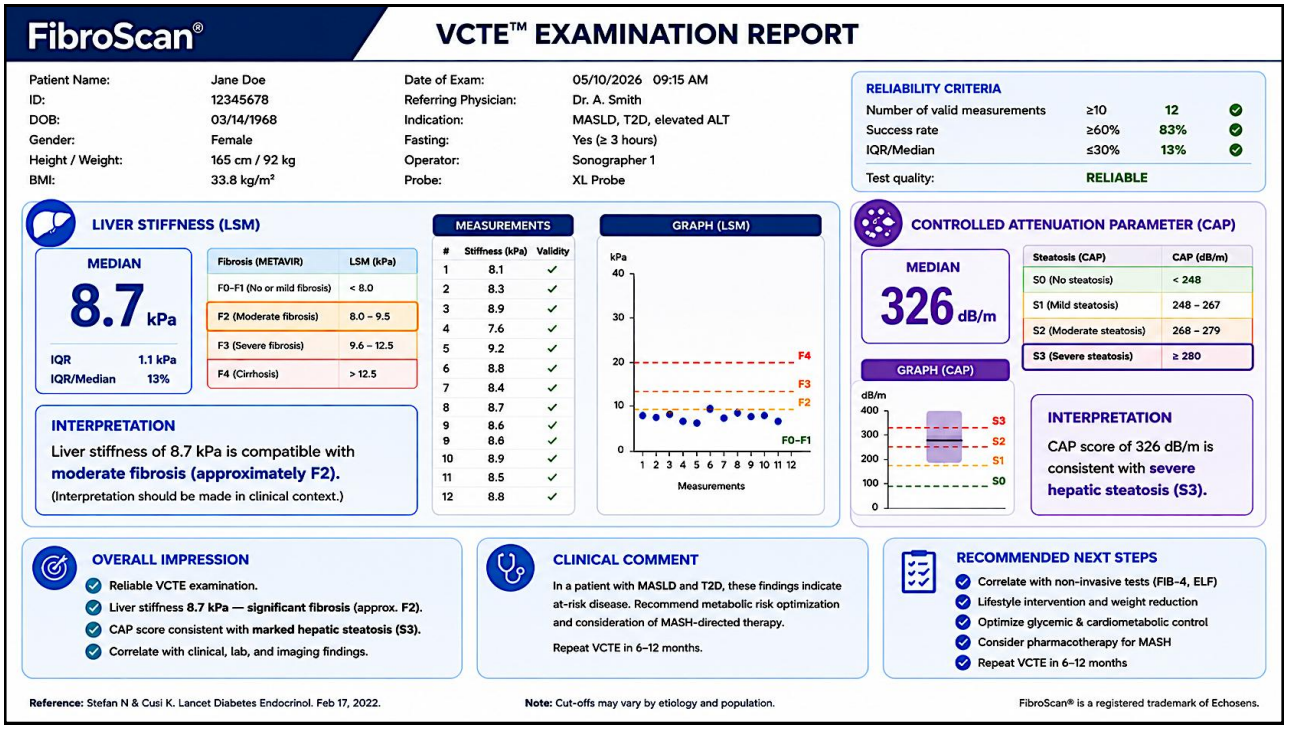
FibroScan®
VCTE™ EXAMINATION REPORT
Patient Name: Jane Doe
ID: 12345678
DOB: 03/14/1968
Gender: Female
Height / Weight: 165 cm / 92 kg
BMI: 33.8 kg/m²
Date of Exam: 05/10/2026 09:15 AM
Referring Physician: Dr. A. Smith
Indication: MASLD, T2D, elevated ALT
Fasting: Yes (≥ 3 hours)
Operator: Sonographer 1
Probe: XL Probe
RELIABILITY CRITERIA
Number of valid measurements ≥10 12
Success rate ≥60% 83%
IQR/Median ≤30% 13%
Test quality: RELIABLE
LIVER STIFFNESS (LSM)
MEDIAN
8.7 kPa
IQR 1.1 kPa
IQR/Median 13%
Fibrosis (METAVIR) LSM (kPa)
F0–F1 (No or mild fibrosis) < 8.0
F2 (Moderate fibrosis) 8.0 – 9.5
F3 (Severe fibrosis) 9.6 – 12.5
F4 (Cirrhosis) > 12.5
MEASUREMENTS
Stiffness (kPa) Validity
1 8.1 ✓
2 8.3 ✓
3 8.9 ✓
4 7.6 ✓
5 9.2 ✓
6 8.8 ✓
7 8.4 ✓
8 8.7 ✓
9 8.6 ✓
9 8.6 ✓
10 8.9 ✓
11 8.5 ✓
12 8.8 ✓
GRAPH (LSM)
kPa
F4
F3
F2
F0–F1
Measurements
INTERPRETATION
Liver stiffness of 8.7 kPa is compatible with moderate fibrosis (approximately F2).
(Interpretation should be made in clinical context.)
CONTROLLED ATTENUATION PARAMETER (CAP)
MEDIAN
326 dB/m
Steatosis (CAP) CAP (dB/m)
S0 (No steatosis) < 248
S1 (Mild steatosis) 248 – 267
S2 (Moderate steatosis) 268 – 279
S3 (Severe steatosis) ≥ 280
GRAPH (CAP)
dB/m
S3
S2
S1
S0
INTERPRETATION
CAP score of 326 dB/m is consistent with severe hepatic steatosis (S3).
OVERALL IMPRESSION
Reliable VCTE examination.
Liver stiffness 8.7 kPa — significant fibrosis (approx. F2).
CAP score consistent with marked hepatic steatosis (S3).
Correlate with clinical, lab, and imaging findings.
CLINICAL COMMENT
In a patient with MASLD and T2D, these findings indicate at-risk disease. Recommend metabolic risk optimization and consideration of MASH-directed therapy.
Repeat VCTE in 6–12 months.
RECOMMENDED NEXT STEPS
Correlate with non-invasive tests (FIB-4, ELF)
Lifestyle intervention and weight reduction
Optimize glycemic & cardiometabolic control
Consider pharmacotherapy for MASH
Repeat VCTE in 6–12 months
Reference: Stefan N & Cusi K. Lancet Diabetes Endocrinol. Feb 17, 2022.
Note: Cut-offs may vary by etiology and population.
FibroScan® is a registered trademark of Echosens.

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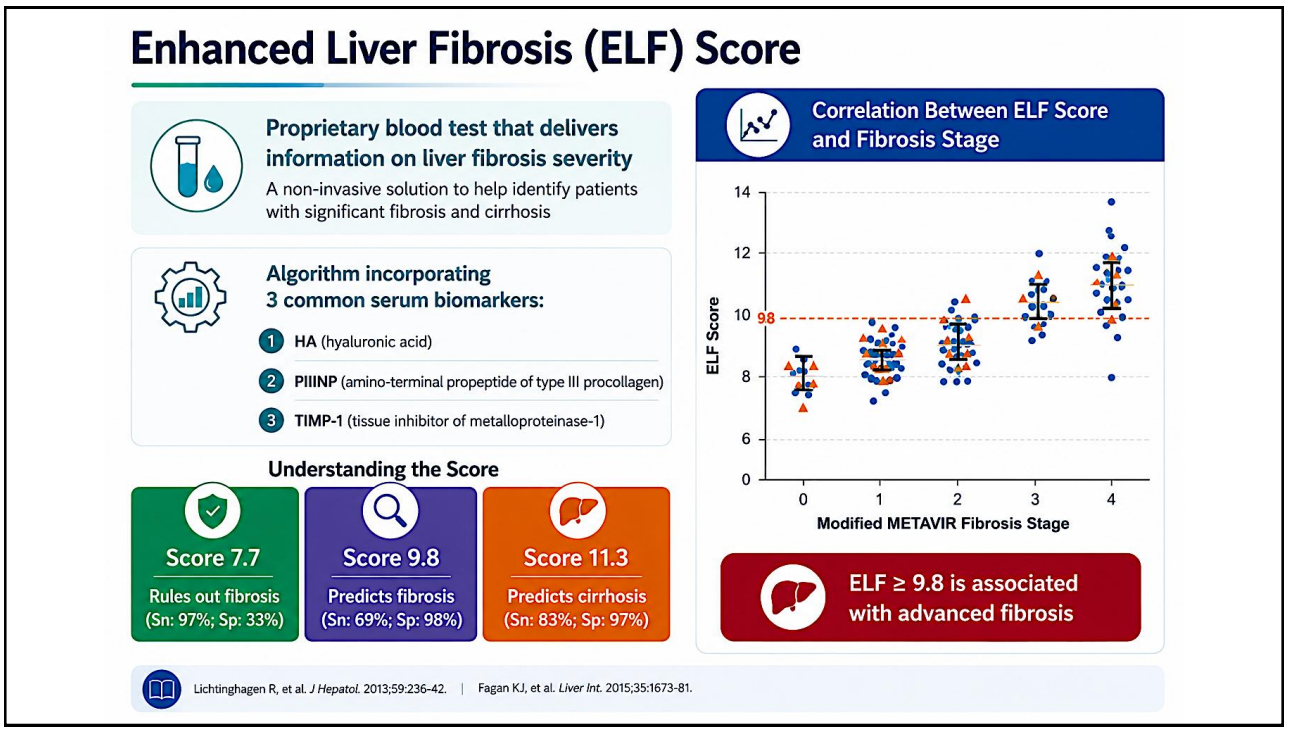
Enhanced Liver Fibrosis (ELF) Score
Proprietary blood test that delivers information on liver fibrosis severity
A non-invasive solution to help identify patients with significant fibrosis and cirrhosis
Algorithm incorporating 3 common serum biomarkers:
1 HA (hyaluronic acid)
2 PIIINP (amino-terminal propeptide of type III procollagen)
3 TIMP-1 (tissue inhibitor of metalloproteinase-1)
Understanding the Score
Score 7.7
Rules out fibrosis
(Sn: 97%; Sp: 33%)
Score 9.8
Predicts fibrosis
(Sn: 69%; Sp: 98%)
Score 11.3
Predicts cirrhosis
(Sn: 83%; Sp: 97%)
Correlation Between ELF Score and Fibrosis Stage
ELF Score
9.8
Modified METAVIR Fibrosis Stage
ELF ≥ 9.8 is associated with advanced fibrosis
Lichtinghagen R, et al. J Hepatol. 2013;59:236-42. | Fagan KJ, et al. Liver Int. 2015;35:1673-81.

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Role of ELF in Clinical Algorithms

GUIDELINE-BASED APPROACH (AASLD/EASL)

STEP 1

FIB-4 (rule-out)

Use FIB-4 to identify patients at low risk for advanced fibrosis

STEP 2

ELF or VCTE (risk stratification)

Use ELF or VCTE to further stratify risk of advanced fibrosis

BEST USE CASES FOR ELF

1. INDETERMINATE FIB-4

Clarify risk in patients with indeterminate FIB-4 results

2. FAILED OR UNRELIABLE VCTE

Useful when VCTE is not feasible, failed, or results are unreliable

3. LONGITUDINAL MONITORING

Track changes in fibrosis over time to monitor disease progression or treatment response

AASLD 2023–2024 | EASL 2021–2024 | Newsome PN J Hepatol 2020 | Vali Y BMJ 2020 | Day JW Hepatology 2021

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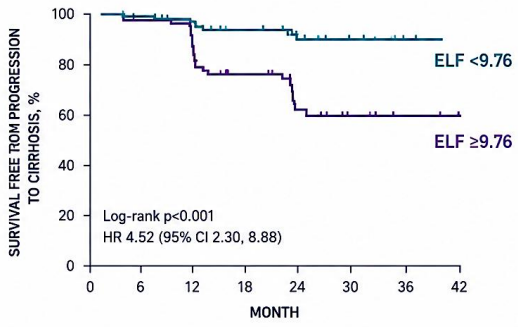
ELF Predicts Progression More Accurately than Biopsy

Phase 2 simtuzumab in NASH and F3–F4

PROGRESSION TO CIRRHOSIS ACCORDING TO BASELINE ELF



PREDICTORS OF PROGRESSION TO CIRRHOSIS

Parameter	Adjusted HR (95% CI)	p-value
Baseline ELF	3.20 (2.33, 4.39)	<0.001
Change in ELF	1.60 (1.19, 2.16)	<0.01
Ishak stage 4 vs 3	0.87 (0.47, 1.59)	0.64

Optimal threshold of baseline ELF: 9.76
(sensitivity 77%, specificity 66%)

Higher baseline ELF and greater change in ELF were associated with increased risk of progression to cirrhosis

Note: ELF was approved by FDA on basis of ability to predict adverse clinical outcomes

Saarinen K, et al. JHEP Rep. 2023;5(7):100765.

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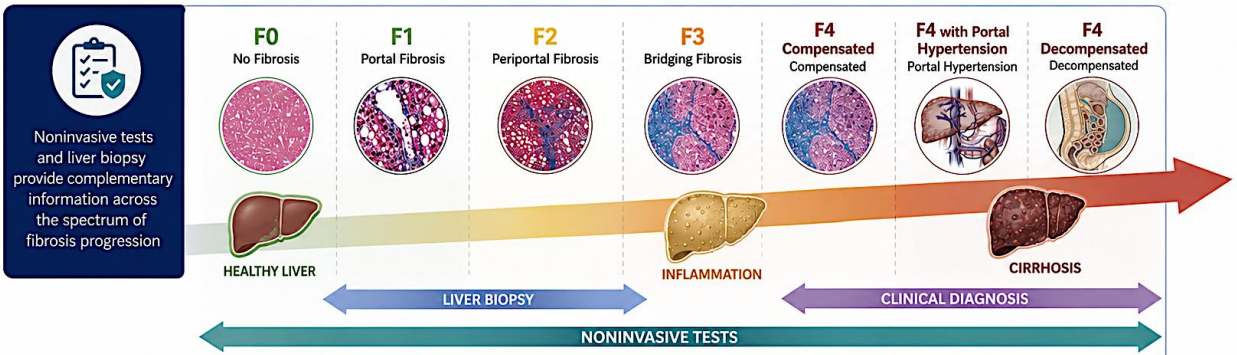
Summary of Noninvasive Testing with Staging of MASLD

Noninvasive tests provide a continuous assessment of disease progression across the MASLD spectrum



NONINVASIVE TESTS	LOW / NO FIBROSIS (F0–F1)	SIGNIFICANT FIBROSIS (F2)	ADVANCED FIBROSIS (F3)	CIRRHOSIS (F4)
FIB-4	<1.3	1.3 – 2.67	>2.67	—
ELF	—	>9.8	>11.3	>11.3
VCTE (kPa)	<5	>10	>20	>25
MRE (kPa)	<2.65	>3.14	>3.53	>4.45

Castera L, Rinella ME and Tsochatzis M. *NEJM* 2025

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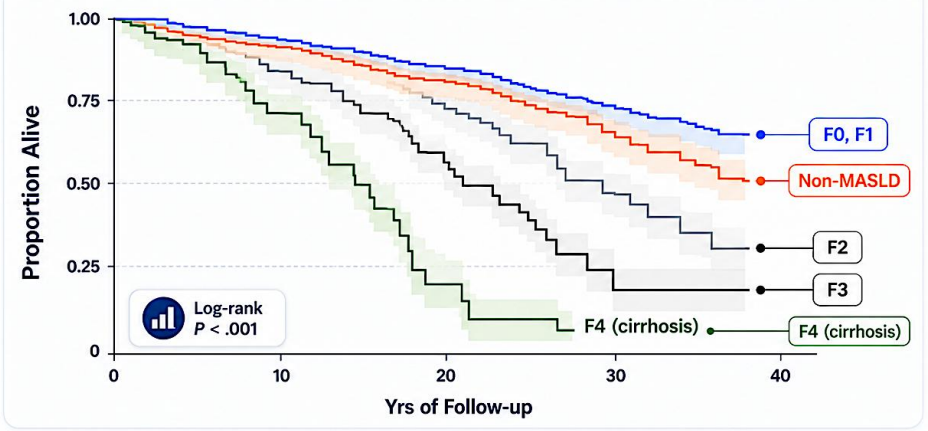
Stage of Liver Fibrosis is Associated with Increased Mortality

Retrospective survival analysis of 646 MASLD patients and matched controls



Compared with patients with F0–F1 fibrosis:

- **Non-MASLD** ~1.4x higher risk
- **F2** ~2.0x higher risk
- **F3** ~2.8x higher risk
- **F4 (cirrhosis)** ~4.5x higher risk

Risk of mortality increases progressively with advancing liver fibrosis stage

Hagström. *J Hepatol.* 2017;67:1265.

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Testing to rule out other causes of liver disease

VIRAL HEPATITIS PANELS: Hepatitis B surface antigen (HBsAg) and Hepatitis C antibody (anti-HCV)

ALCOHOL HISTORY & TESTING: IRON STUDIES: Serum iron, total iron-binding capacity (TIBC), and ferritin are used to rule out hereditary hemochromatosis.

AUTOIMMUNE MARKERS: Antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), and sometimes anti-liver kidney microsome (LKM) antibodies for autoimmune hepatitis.

METABOLIC & GENETIC SCREEN: Ceruloplasmin (for Wilson's disease, especially in younger patients)

THYROID FUNCTION TESTS: Thyroid-stimulating hormone (TSH) to rule out hypothyroidism

Newsome PN, et al. *Gut* (2018) DOI: 10.1136/gutjnl-2017-314924

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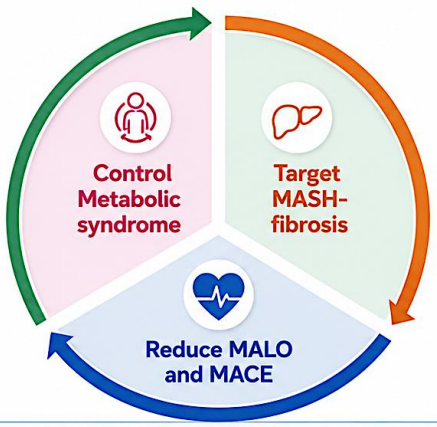
The Goals for MASH Management

Improve metabolic syndrome

- Weight loss
- T2D/hyperglycemia
- Hypertension
- Dyslipidemia



Liver-directed treatment

- MASH resolution
- Fibrosis regression
- Reduction in liver stiffness/fat
- Improvement in biomarkers

Improve long term outcomes

- Major adverse liver outcomes (MALO)
- Major adverse cardiac events (MACE)

Ref: Finney AC et al. Front Cardiovasc Med. 2023 May 2;10:1116861. | Younossi ZM et al. Hepatol Commun. 2023 Dec 22;8(1):e0352. | Targher G et al. Gut. 2024 Mar 7;73(4):691-702.

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Management of NAFLD/NASH: Weight Loss

52 week intervention of physical activity and calorie restricted diet (-750 kcal deficit)

Mean weight loss: **4.6 kg** (83 kg baseline)

Results with ≥5% Total Body Weight (TBW) Loss

30% of patients

58% had resolution of NASH

82% had a 2-point reduction in NAFLD activity score (NAS)

Results with ≥10% Total Body Weight (TBW) Loss

10% of patients

100% had reduction in NAFLD score

90% had resolution of NASH

45% had regression of fibrosis

Sustained weight loss is the cornerstone of MASH management, leading to histologic improvement and fibrosis regression.

Vilar-Gomez *et al.* Gastroenterology. 2015

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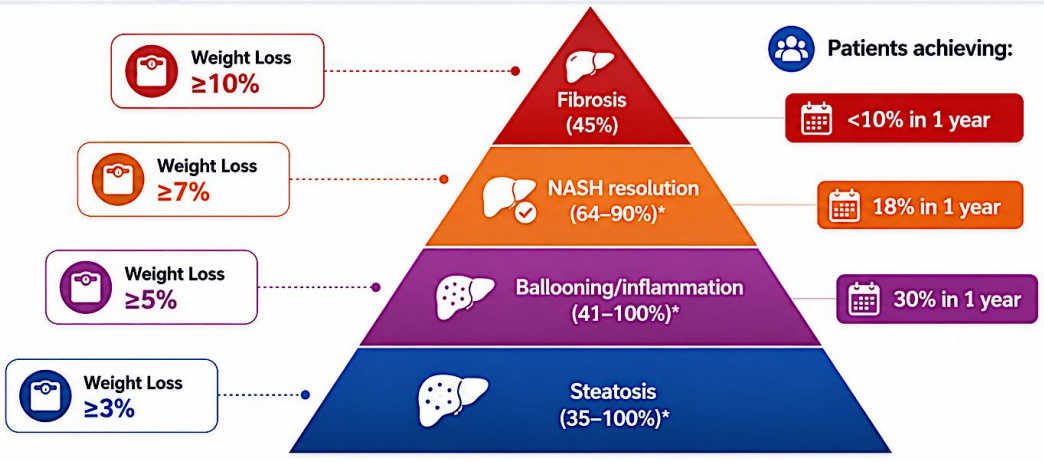
Lifestyle Therapy for MASLD

Sustained weight loss is the foundation of MASLD management and is associated with resolution of steatosis, inflammation, and fibrosis.



Vilar-Gomez E, et al. *Gastroenterology.* 2015;149:367–378. | Promrat K, et al. *Hepatology.* 2010;51:121–129. | Harrison SA, et al. *Hepatology.* 2009;49:80–86. | Wong VWS, et al. *J Hepatol.* 2013;59:536–54.

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Mediterranean Diet in NAFLD: Observational Study

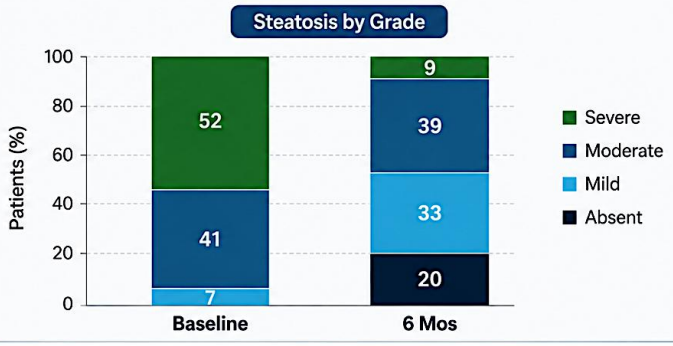
DESIGN

6-month observational study of **Mediterranean diet** intervention with monthly nutrition counseling in patients with NAFLD

N = 46

RESULTS

Frequency of grade ≥ 2 steatosis decreased in **> 80%**, with resolution in **20%**



Gelli. World J Gastroenterol. 2017;23:3150.

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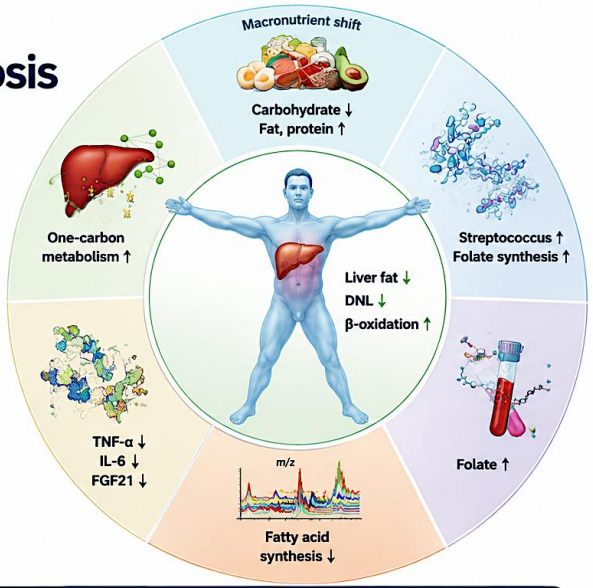
Carbohydrate Restriction has Rapid Benefits in Hepatic Steatosis

14 day study of low carbohydrate diet on liver fat content (by MRS)

- **10 obese subjects** with high liver fat
- **Diet:** <30 gm CHO, isocaloric to minimize impact of weight loss
- **Weight loss:** 1.8%
- **Mean reduction of liver fat:** 43.8%
- **Returned to baseline** 1 – 3 mos

43.8% Reduction in liver fat



Short-term carbohydrate restriction rapidly reduces liver fat and favorably modulates metabolic, inflammatory and microbial pathways.

Rapid metabolic benefits beyond weight loss.

Mardinoglu, A et al. 2018, Cell Metabolism 27, 559–571

32

Is there an optimal diet for MASLD?

Mediterranean diet

good choice for a balanced diet with **strong evidence for benefit**

Low carbohydrate diets

are effective in the short term, but **adherence** is difficult and **long-term data are lacking**

Avoidance of **added sugars** (especially fructose in beverages) is **recommended**. None of the diets have evidence of consistent superiority.

Key is likely to be **patient preference and adherence**.

Rinella M et al. *Hepatology* 2023

33

Exercise in MASLD:
Effect on Liver Fat and ALT

28 randomized trials
of exercise-based interventions in patients with NAFLD and underlying metabolic disorders (N = 1644)

Reduction in intrahepatic lipid content

Standardized mean difference:
-0.69
(95% CI: -0.90 to -0.48)

Reduction in ALT

Weighted mean difference:
-3.30 IU/L
(95% CI: -5.57 to -1.04)

Regular exercise is associated with significant reductions in liver fat and ALT in patients with MASLD.

Orci. Clin Gastroenterol Hepatol. 2016;14:1398.

34

Lifestyle Modification in Fatty Liver Disease: EASL Multidisciplinary Clinical Practice Guideline

Energy restriction
- Calorie restriction (500–1,000/day)
- 7–10% weight loss target
- Long-term maintenance approach

Fructose intake
- Avoid fructose-containing food and drink

Coffee consumption
- No liver-related limitations

Comprehensive lifestyle approach

Daily alcohol intake
- Strictly below 30 g men and 20 g women

Macronutrient composition
- Low-to-moderate fat
- Moderate-to-high carbohydrate
- Low-carbohydrate ketogenic diets or high protein
- Mediterranean diet is suggested

Physical activity
- 150–200 min/week moderate intensity in 3–5 sessions
- Resistance training to promote musculoskeletal fitness and improve metabolic factors

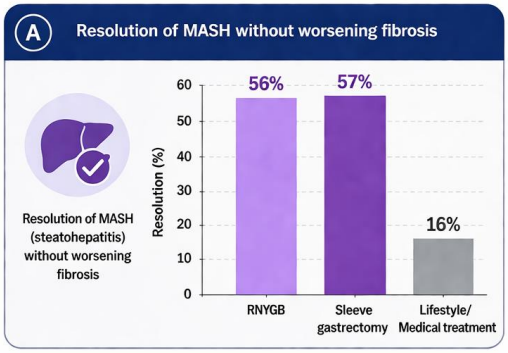
EASL–EASD–EASO CPG NAFLD. *J Hepatol* 2016; 64:1388–402

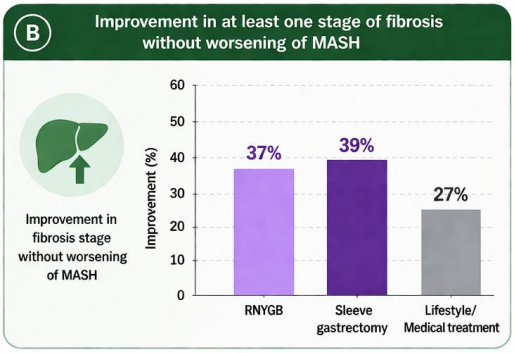
35

BRAVES Study: Bariatric surgery is superior to lifestyle/medical treatment in MASH

288 subjects with MASH, randomized 1:1:11 to: RNYGB | Sleeve gastrectomy | Medical treatment

Medical treatment included vitamin E (Pioglitazone and/or Liraglutide in subjects with T2D)





Bariatric surgery (RNYGB or sleeve gastrectomy) significantly outperforms lifestyle/medical treatment in achieving histologic benefits in MASH.

Verrastro O et al. Lancet. 2023;401:1786-1797.

36

Medications to treat diabetes and their efficacy in MASLD

Medication	Liver fat	Disease activity (steatohepatitis/NAS)
Metformin	Unchanged	Neutral
Pioglitazone	Decreased	Improved[a]
Insulin	Decreased	Effect unknown
GLP-1 RAs (semaglutide and liraglutide)	Decreased	Improved[a]
SGLT2 inhibitors (dapagliflozin, empagliflozin, and canagliflozin)	Decreased	Effect unknown
DPP-IV inhibitors (sitagliptin and vildagliptin)	Unchanged (in RCTs)	Effect unknown

[a] *Improvement in some histological features, but not consistently in all studies.*

Chan W et al. *J Obes Metab Syndr* 2023; 32: 197-213

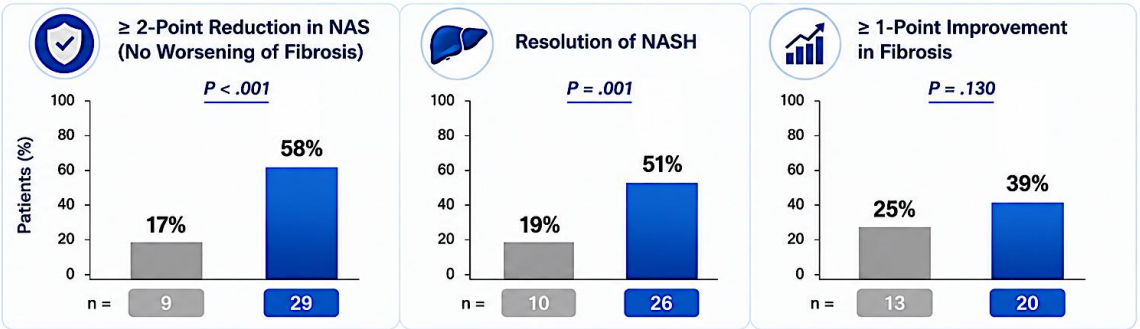
37

Pioglitazone in NASH With Prediabetes/T2D: 18-Mo Outcomes *(not approved for MASH)*

Randomized, placebo-controlled, double-blind phase IV study of patients with NASH and prediabetes or T2D (N = 101)[1]

Placebo (N = 51)
Pioglitazone 45 mg QD (N = 50)

PRIMARY ENDPOINTS AT 18 MONTHS



Pioglitazone 45 mg daily significantly improved liver histology in patients with NASH and prediabetes/T2D, including greater **reduction in NAS** and higher rates of **NASH resolution**.

[1] *Cusi. Ann Intern Med. 2016;165:305.*

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SGLT-2 Inhibitors: Effects on Liver Fat and Measures of Fibrosis *(not approved for MASH)*

LIVER FAT

SGLT-2 inhibitors consistently **reduce liver fat independent** of weight loss.

- Significant reductions in liver fat (MRI-PDFF) demonstrated in multiple randomized controlled trials.
- Effects on liver fat occur even with **minimal or no weight loss.**
- Consistent improvements observed across different SGLT-2 inhibitors.

FIBROSIS (NONINVASIVE MEASURES)

SGLT-2 inhibitors show **favorable effects** on measures of fibrosis.

- Significant **reductions in liver stiffness** measured by transient elastography (VCTE).
- Decreases in serum **fibrosis biomarkers** (e.g., Pro-C3, PIIINP).
- Suggested **antifibrotic potential**, though histologic data are limited.

KEY TAKEAWAY: SGLT-2 inhibitors reduce liver fat independent of weight loss and improve noninvasive measures of fibrosis, supporting their role as a **promising therapy in MASLD.**

Sources: Armstrong MJ, et al. J Hepatol. 2023;79:1351–1366.
Zelber-Sagi S, et al. Liver Int. 2024;44:1179–1196.

39

SYNERGY-NASH Study: Tirzepatide in MASH with fibrosis *(not approved for MASH)*

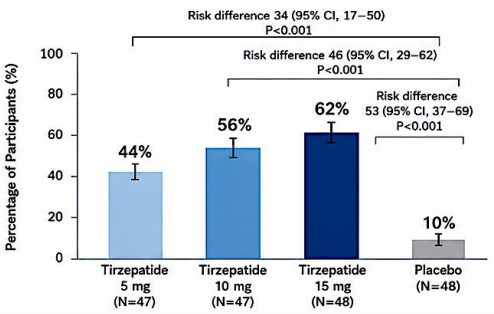
52-week phase 2 study
of 190 subjects with MASH with stage 2–3 fibrosis

Intervention
Tirzepatide 5 mg, 10 mg, 15 mg vs Placebo

Randomized, double-blind, placebo-controlled

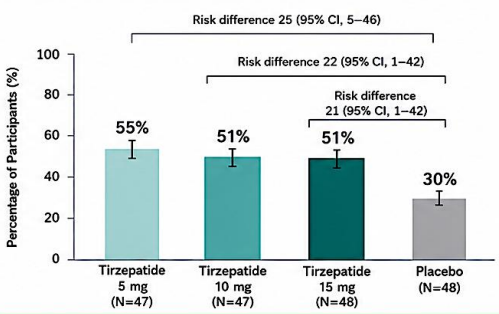
PRIMARY

A Resolution of MASH and No Worsening of Fibrosis



KEY SECONDARY

B Decrease of ≥1 Fibrosis Stage and No Worsening of MASH



Tirzepatide demonstrated dose–dependent superiority over lifestyle/medical treatment in achieving MASH resolution and fibrosis improvement.

Loomba R et al. *N Engl J Med.* 2024;391:299–310.

The NEW ENGLAND JOURNAL of MEDICINE

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Essence Trial: Semaglutide 2.4 mg in MASH – Results of primary endpoints at 1.5 years in first cohort

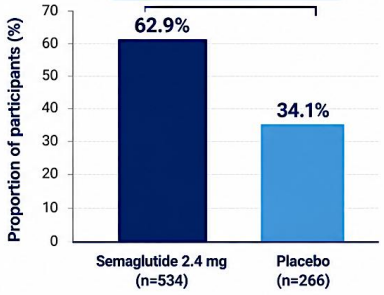
Ongoing phase 3 study of semaglutide 2.4 mg in 800 subjects

Population NASH with fibrosis stage 2 – 3

Primary endpoints assessed at 1.5 years in first cohort

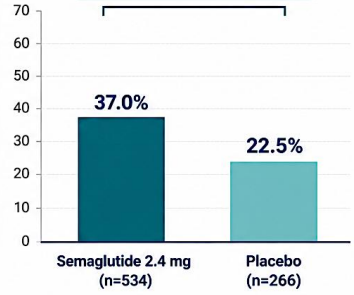
Resolution of steatohepatitis with no worsening of liver fibrosis

EDP: 28.9 %-points
95% CI: 21.3 to 36.5; P<0.0001



Improvement in liver fibrosis with no worsening of steatohepatitis

EDP: 14.4 %-points
95% CI: 7.5 to 21.4; P<0.0001



Semaglutide 2.4 mg (n=534)
Placebo (n=266)

Adverse events: Consistent with those known to be associated with GLP-1 RA class

Presented at The Liver Meeting 2024, November 15–19, San Diego, USA. Newsome PN et al. (Essence Trial Investigators) | *Hepatology*. 2024.

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Real-World Discontinuation of Subcutaneous Semaglutide in MASLD Patients

A retrospective cohort study using Optum Market Clarity data (2017–2024)

BACKGROUND

MASLD and its progressive subtype, MASH, are chronic liver conditions with progression to the latter underdiagnosed in clinical practice. SC semaglutide is being investigated for MASH in the ESSENCE clinical trial (NCT0482218), where >89% of participants remained persistent at 72 weeks.

STUDY AIM

To assess alignment between real-world medication compliance and that observed in the ESSENCE trial among MASLD patients starting SC semaglutide for an approved indication.

METHODS

- Retrospective cohort of MASLD patients initiating SC semaglutide (Ozempic® or Wegovy®) from 2017–2024 in Optum Market Clarity data
- 12-month baseline period prior to index date (first prescription claim) used for sample selection and covariate measurement
- Excluded patients with other liver diseases (e.g., viral hepatitis) or severe MASH complications (e.g., cirrhosis)
- Discontinuation: gap in medication coverage ≥45 days
- Follow-up: index date to death, dropout, or end of data availability
- Outcomes: Kaplan-Meier (KM) persistence and time-to-discontinuation

KEY RESULTS

36,531 adults included

- 69.5% (n=25,371) had type 2 diabetes
- Mean (SD) age: 52.6 (12.0) years
- 63.0% (n=23,021) female

Patients who discontinued SC semaglutide:

64.3% (n=23,473)

DISCONTINUATION TIMING

- 56.3% (n=20,566) discontinued within 1 year
  60.1% (n=21,966) discontinued within 72 weeks
- Mean time-to-discontinuation: 24.7 weeks (SD 28.6)
- Mean follow-up time: 77.9 weeks (SD 57.6)

KM ESTIMATES (accounting for censoring)

- 64% (95% CI: 63%–64%) discontinued by 1 year
- 72% (95% CI: 71%–72%) discontinued by 72 weeks

CONCLUSION

The majority of MASLD patients discontinued SC semaglutide, with 72% doing so within 72 weeks of initiation. Results are consistent with findings from similar observational studies and highlight the importance of monitoring SC semaglutide use patterns in a real-world setting, especially with respect to the resultant impact on liver outcomes as well as BMI and glycemic goals.

Abbreviations: MASLD, metabolic dysfunction–associated steatotic liver disease; MASH, metabolic dysfunction–associated steatohepatitis; SC, subcutaneous; KM, Kaplan-Meier; CI, confidence interval; SD, standard deviation; BMI, body mass index.

Clark S et al. Presented at AASLD 2026

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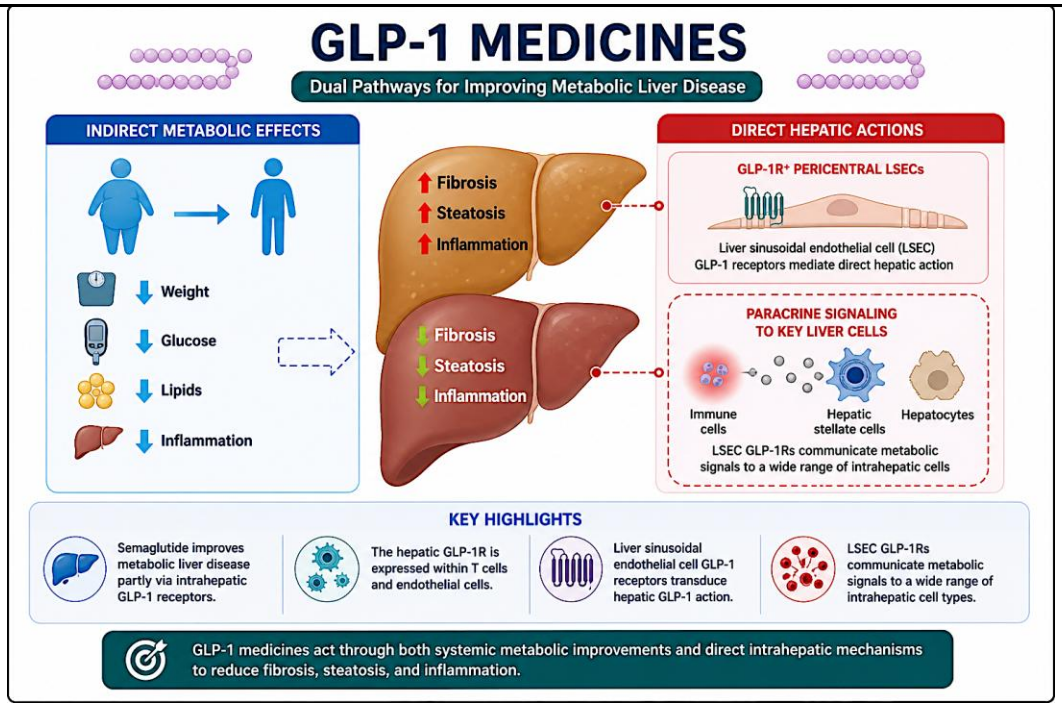

Gonzalez-Rellan, M et al. Cell Metabolism. 2026;38:1–20

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Follow-Up of At-Risk MASH on Semaglutide

Monitoring :
- Clinical (q3–6 mo): weight, BP, adherence | Target ≥10% weight loss
- Laboratory (q3–6 mo): AST/ALT, platelets, HbA1c, lipids

⚠ ALT normalization ≠ fibrosis regression[1–3]

Fibrosis Surveillance:
- FIB-4 (q6–12 mo): rising value should trigger escalation[4]
- Elastography (q1–2 yr): track liver stiffness trend[5]

→ Fibrosis trend > single measurement[5]

Escalation:
- Rising fibrosis markers, weight loss <5–7%, persistent metabolic risk[2,4]
- Intensify therapy, consider combination[6]

Advanced Disease (≥F3):
- Referral to gastroenterology for HCC surveillance q6 mo (US ± AFP)[7]

Management success = fibrosis stability[5,8]

References

1. Chalasani N, et al. *Hepatology.* 2018;67(1):328-357.
2. EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction–associated steatotic liver disease (MASLD). *J Hepatol.* 2024;81(3):492-542.
3. Rinella ME, et al. *Hepatology.* 2023;77(5):1797-1835.
4. Sterling RK, et al. *Hepatology.* 2006;43(6):1317-1325.
5. European Association for the Study of the Liver (EASL) Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol.* 2015;63(1):237-264.
6. Younossi ZM, et al. *Hepatology.* 2023;78(6):1878-1911.
7. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology.* 2018;67(1):358-380.
8. Singh S, et al. *Lancet Gastroenterol Hepatol.* 2015;1(3):196-208.

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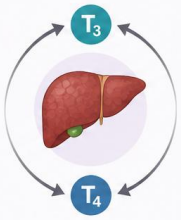
Resmetirom: Rationale of Using Selective Thyroid Hormone β as Treatment of MASH

1 Thyroid hormone affects metabolism of fatty acids[1]

- Fatty acid uptake
- Lipogenesis
- Lipolysis
- Beta-oxidation
- Bile acid metabolism



Thyroid hormone signaling in the liver

2 Key biological and clinical rationale[2]

- Hypothyroidism is associated with higher risk of NAFLD/NASH
- Thyroid hormone receptor β predominates in liver parenchymal cells
- Free T4 levels are lower in NAFLD patients
- Low Free T3 is independent risk factor for advance fibrosis

Resmetirom is a selective thyroid hormone receptor β agonist designed to target liver-specific pathways to improve steatohepatitis and fibrosis in MASH.

1. Wirth E et al. Exp Rev Endocrine & Metab 2022;17:425-434;
2. Li et al. JCEM 2023;108:1602-1613.

45

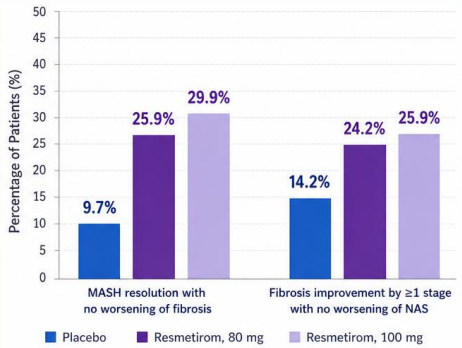
Maestro Study: Resmetirom for Treatment of MASH with Fibrosis

52-week, phase 3, randomized double-blind study of 955 subjects with MASH with fibrosis 1B – 3

Randomized 1:1:1 Resmetirom 80 mg, Resmetirom 100 mg, or Placebo

Well-powered study evaluating key **histologic** and **metabolic** endpoints over 52 weeks

PRIMARY ENDPOINTS (52 weeks)



KEY EFFICACY FINDINGS

MASH resolution with no worsening of fibrosis *[Primary endpoint]*
→ *Resmetirom 80 mg, 100 mg > placebo*
(25.9% & 29.9% vs 9.7% resp., P<0.001)

Fibrosis score improvement ≥ 1 with no worsening of NAS *[Primary endpoint]*
→ *Resmetirom 80 & 100 mg > placebo*
(24.2% & 25.9% vs 14.2%, resp., P<0.001)

Percent change in LDL at week 24
→ *Resmetirom 80 & 100 mg > placebo*
(-13.6% & -16.3% vs 0.1%)

SAFETY SUMMARY

Adverse events were mild/moderate and more frequent in resmetirom groups 80 mg & 100 mg vs placebo:
- Diarrhea (27% & 33.4% vs 15.6%), self-limited with time
- Nausea (22% & 18.9% vs 12.5%)

Resmetirom 80 mg and 100 mg significantly improved **MASH resolution** and **fibrosis** without worsening of NAS, with a favorable safety profile over 52 weeks.

Harrison S et al. *N Engl J Med* 2024; 390: 497-509; Leff P, Rich N. *Evidence-Based GI* April 2024: 6-13.

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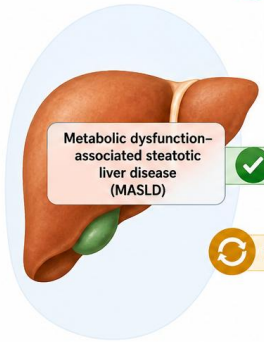
Selection of Patients for Therapy with Resmetirom



Metabolic dysfunction–associated steatotic liver disease (MASLD)

NOT RECOMMENDED

- Cirrhosis, including LSM via VCTE >20 kPa or MRE >5 kPa
- Concomitant active liver disease
- Excess alcohol use (>20/30 g/d in women/men)
- Active thyroid disease

RECOMMENDED

Imaging-based NILDA	VCTE: LSM 8–15 kPa[a] MRE: LSM 3.1–4.4 kPa[a]
Liver histology	MASH with F2–F3[b]

MAY BE USED

Individualized decisions by a specialist experienced in liver fibrosis for:

- LSM values outside the recommended ranges
- Other NILDA data consistent with F2–F3[c]

OTHER CONSIDERATIONS

- Not recommended for alcohol intake > 20 g/d in women or >30 g/d in men
- Not recommended for autoimmune hepatitis, primary biliary cirrhosis or those with active gallbladder disease
- **Lower dose if on clopidogrel**
  - TSH within 6 months of initiation
  - Address abnormal thyroid function
  - Consider TSH at 3 to 6 mo intervals
- If on statin, reduce dose at initiation as long as LDL goals are met

Careful patient selection and monitoring help maximize benefits and minimize risks with resmetirom.

[a] Modified from the AASLD NILDA guidelines.[5]
[b] MASH = metabolic dysfunction–associated steatohepatitis.
[c] F2–F3 = moderate to advanced fibrosis.

Chen, V. Hepatology 81(1):312-320, January 2025. doi: 10.1097/HEP.0000000000001112 81

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Recommended follow up before and first 12 months after initiation of therapy with Resmetirom

Timeframe	Safety/Efficacy assessments	Safety assessments		Efficacy assessments	
	Hepatic function panel[a]	Thyroid function[b]	Lipid profile[c]	Noninvasive measurement of liver stiffness[d]	MRI-PDFF[e]
Before treatment initiation	✓	✓	✓	✓	Consider
3 months	✓				
6 months	✓	✓	✓		
12 months	✓	✓	✓	Repeat if imaging NILDA was used at baseline	Consider repeating if baseline data are available

[a] Hepatic function panel includes ALT, AST, ALP, total billirubin. [b] TSH. [c] Lipid profile includes total cholesterol, LDL-C, HDL-C, triglycerides. [d] VCTE or MRE. [e] MRI-PDFF (MRI proton density fat fraction).

Chen, V. Hepatology 81(1):312-320, January 2025. doi: 10.1097/HEP.0000000000001112

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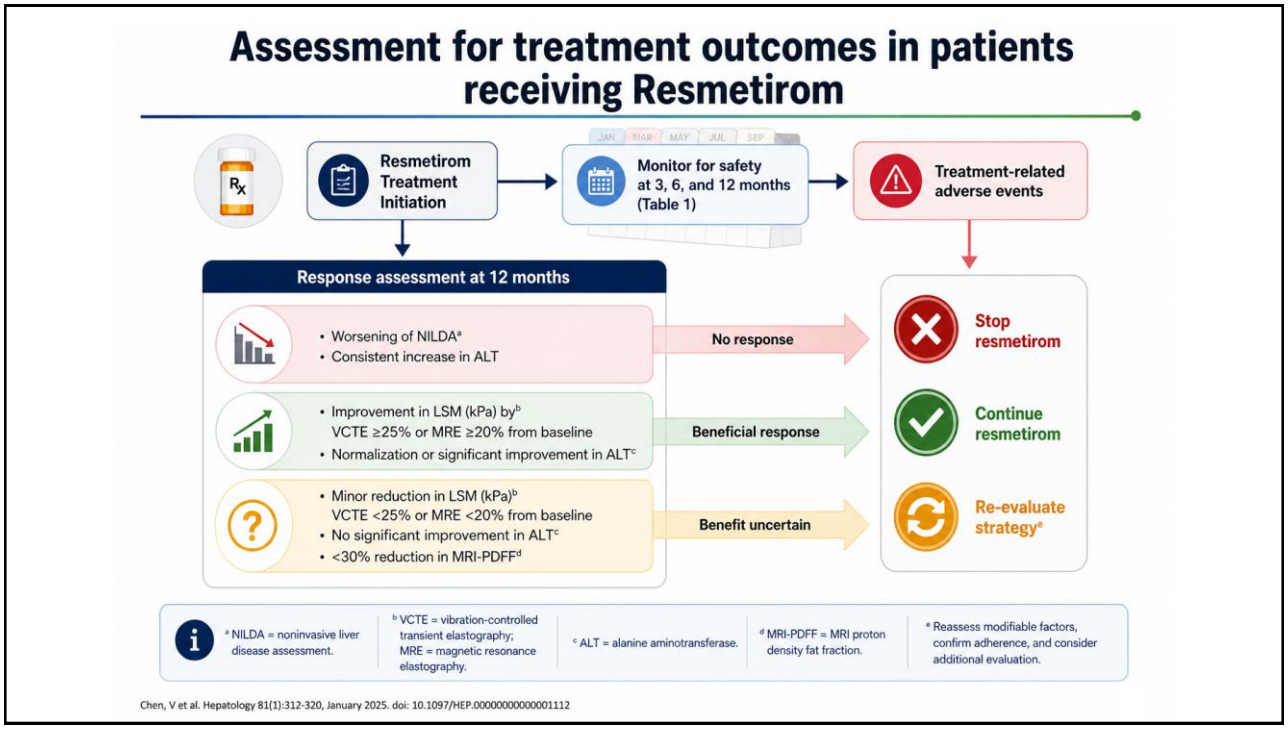
Assessment for treatment outcomes in patients receiving Resmetirom
Resmetirom Treatment Initiation
Monitor for safety at 3, 6, and 12 months (Table 1)
Treatment-related adverse events
Response assessment at 12 months
• Worsening of NILDA[a]
• Consistent increase in ALT
No response
Stop resmetirom
• Improvement in LSM (kPa) by[b] VCTE ≥25% or MRE ≥20% from baseline
• Normalization or significant improvement in ALT[c]
Beneficial response
Continue resmetirom
• Minor reduction in LSM (kPa)[b] VCTE <25% or MRE <20% from baseline
• No significant improvement in ALT[c]
• <30% reduction in MRI-PDFF[d]
Benefit uncertain
Re-evaluate strategy[e]
[a] NILDA = noninvasive liver disease assessment.
[b] VCTE = vibration-controlled transient elastography; MRE = magnetic resonance elastography.
[c] ALT = alanine aminotransferase.
[d] MRI-PDFF = MRI proton density fat fraction.
[e] Reassess modifiable factors, confirm adherence, and consider additional evaluation.
Chen, V et al. Hepatology 81(1):312-320, January 2025. doi: 10.1097/HEP.0000000000001112

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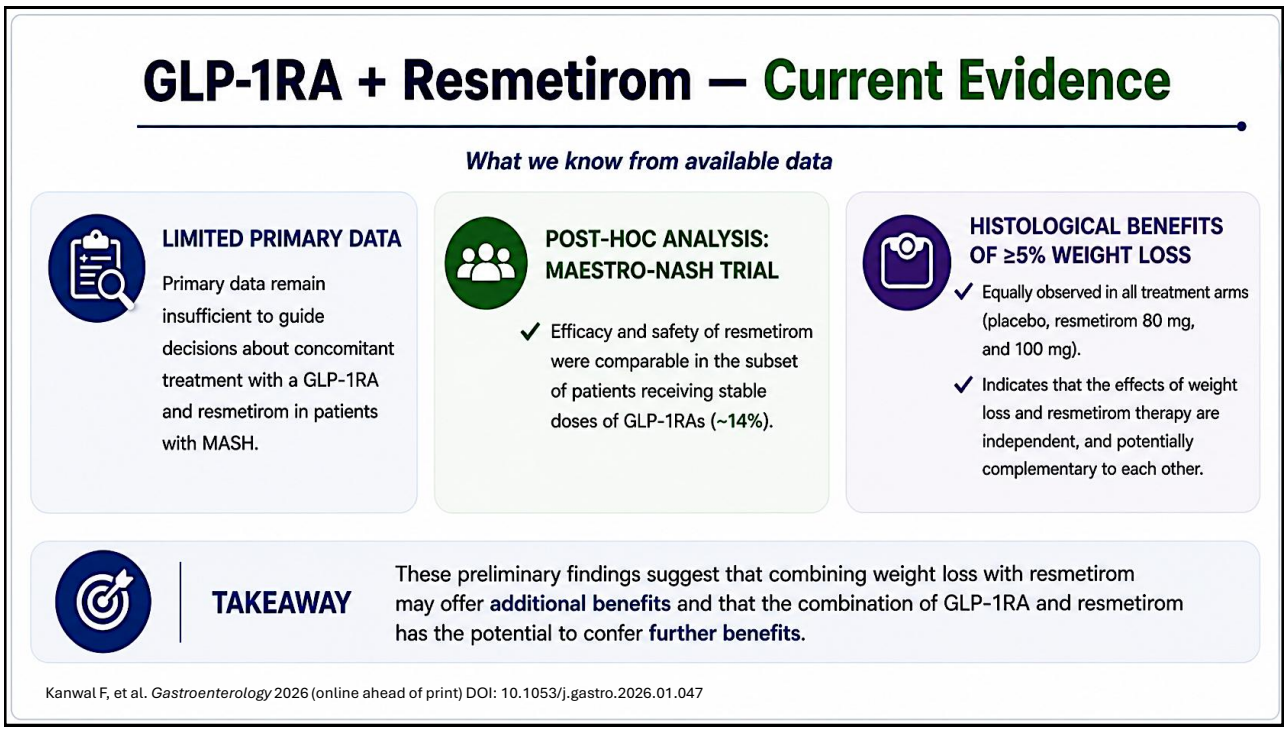
GLP-1RA + Resmetirom — Current Evidence
What we know from available data
LIMITED PRIMARY DATA
Primary data remain insufficient to guide decisions about concomitant treatment with a GLP-1RA and resmetirom in patients with MASH.
POST-HOC ANALYSIS: MAESTRO-NASH TRIAL
✓ Efficacy and safety of resmetirom were comparable in the subset of patients receiving stable doses of GLP-1RAs (~14%).
HISTOLOGICAL BENEFITS OF ≥5% WEIGHT LOSS
✓ Equally observed in all treatment arms (placebo, resmetirom 80 mg, and 100 mg).
✓ Indicates that the effects of weight loss and resmetirom therapy are independent, and potentially complementary to each other.
TAKEAWAY
These preliminary findings suggest that combining weight loss with resmetirom may offer additional benefits and that the combination of GLP-1RA and resmetirom has the potential to confer further benefits.
Kanwal F, et al. Gastroenterology 2026 (online ahead of print) DOI: 10.1053/j.gastro.2026.01.047

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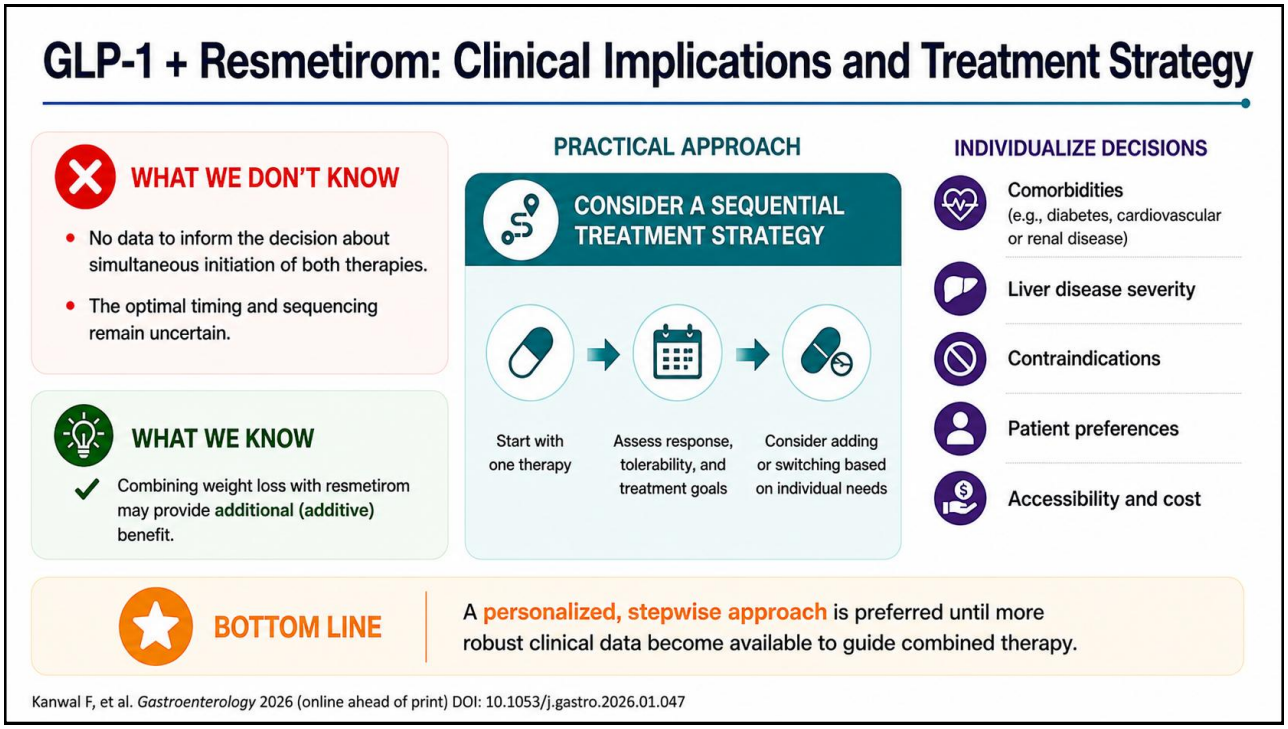
GLP-1 + Resmetirom: Clinical Implications and Treatment Strategy
WHAT WE DON'T KNOW
No data to inform the decision about simultaneous initiation of both therapies.
The optimal timing and sequencing remain uncertain.
WHAT WE KNOW
Combining weight loss with resmetirom may provide additional (additive) benefit.
PRACTICAL APPROACH
CONSIDER A SEQUENTIAL TREATMENT STRATEGY
Start with one therapy
Assess response, tolerability, and treatment goals
Consider adding or switching based on individual needs
INDIVIDUALIZE DECISIONS
Comorbidities (e.g., diabetes, cardiovascular or renal disease)
Liver disease severity
Contraindications
Patient preferences
Accessibility and cost
BOTTOM LINE
A personalized, stepwise approach is preferred until more robust clinical data become available to guide combined therapy.
Kanwal F, et al. Gastroenterology 2026 (online ahead of print) DOI: 10.1053/j.gastro.2026.01.047

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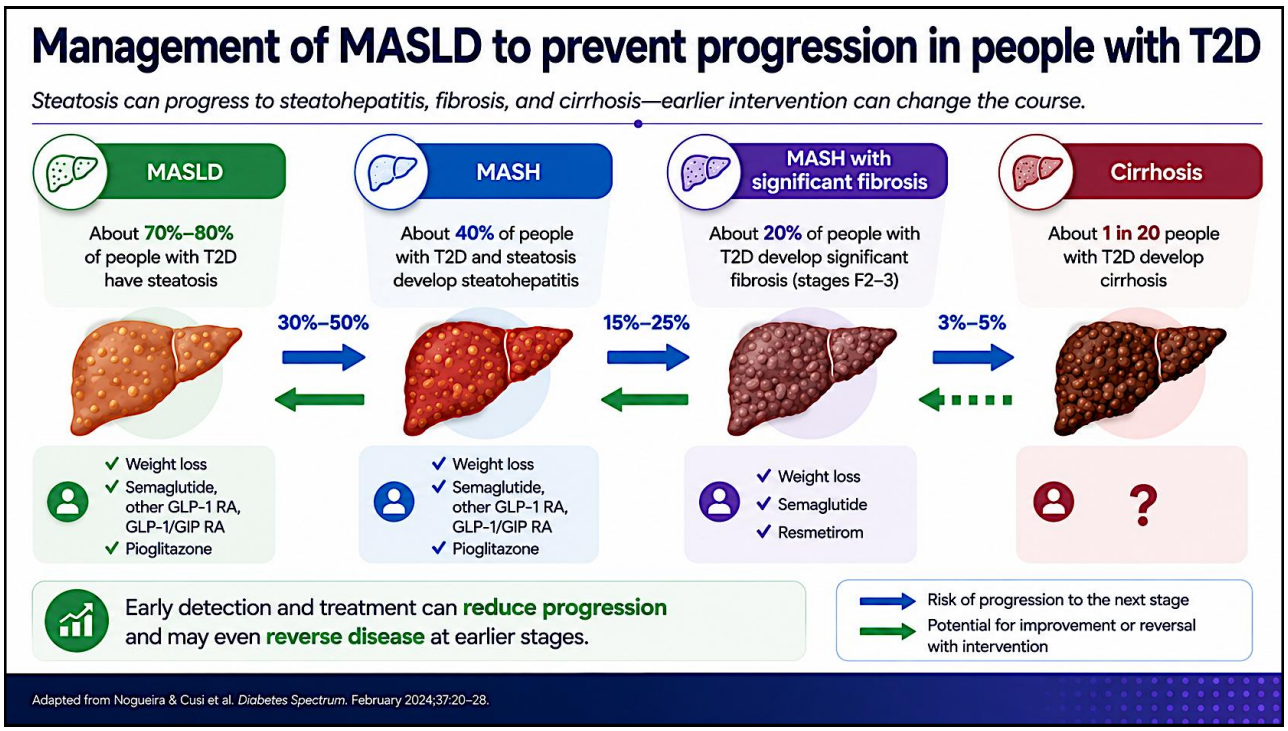
Management of MASLD to prevent progression in people with T2D
Steatosis can progress to steatohepatitis, fibrosis, and cirrhosis—earlier intervention can change the course.
MASLD
About 70%–80% of people with T2D have steatosis
MASH
About 40% of people with T2D and steatosis develop steatohepatitis
MASH with significant fibrosis
About 20% of people with T2D develop significant fibrosis (stages F2–3)
Cirrhosis
About 1 in 20 people with T2D develop cirrhosis
30%–50%
15%–25%
3%–5%
Weight loss
Semaglutide, other GLP-1 RA, GLP-1/GIP RA
Pioglitazone
Weight loss
Semaglutide, other GLP-1 RA, GLP-1/GIP RA
Pioglitazone
Weight loss
Semaglutide
Resmetirom
?
Early detection and treatment can reduce progression and may even reverse disease at earlier stages.
Risk of progression to the next stage
Potential for improvement or reversal with intervention
Adapted from Nogueira & Cusi et al. Diabetes Spectrum. February 2024;37:20–28.

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How to choose between semaglutide and resmetirom

in a patient with comorbid T2D and high risk MASH?

1 INITIAL CHOICE

Start Semaglutide

If obese and not already on incretin therapy, start semaglutide **0.25 mg QW** and titrate up to **2 mg.**

OR

Consider Resmetirom

If intolerant to semaglutide or if lean MASLD, consider **resmetirom.**

2 CONSIDER REFERRAL TO GASTROENTEROLOGY

- To rule out **secondary causes** of liver disease (if you are not comfortable doing so)
- To **monitor** efficacy of treatment
- To institute **non-GLP-1RA** therapies (ie: resmetirom)
- To use established **clinical pathways** to follow for progression/ hepatocellular carcinoma

GOAL

Reduce liver inflammation and fibrosis progression, prevent cirrhosis and liver-related complications, and improve cardiometabolic outcomes.

Note: Treatment decisions should be individualized based on patient characteristics, preferences, tolerability, and access.

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MASH THERAPEUTICS PIPELINE: LATE-STAGE DEVELOPMENT

A diverse set of mechanisms advancing toward potential approval

MECHANISM CLASS	THERAPY (PROGRAM)	COMPANY	MECHANISM OF ACTION	DEVELOPMENT PHASE	KEY DIFFERENTIATORS / POSITIONING
FGF21 ANALOGS (FIBROSIS REVERSAL & METABOLIC REMODELING)	Efruxifermin (EFX)	Akero Therapeutics	FGF21 analog	PHASE 3	• Strong fibrosis improvement including advanced fibrosis/cirrhosis • Differentiated FGF21 profile
	Pegozafermin	89bio (Roche)	GlycoPEGylated FGF21 analog	PHASE 3	• Potent metabolic and weight effects • Broad cardiometabolic benefit
	Efimosfermin alfa	Boston Pharmaceuticals	Long-acting FGF21 analog	PHASE 2	• Long half-life, once-monthly dosing • Robust biomarker and imaging data
INCRETIN-BASED THERAPIES (METABOLIC & WEIGHT BENEFIT)	Semaglutide (high-dose)	Novo Nordisk	GLP-1 receptor agonist	PHASE 3	• Strong MASH resolution data • Established safety and CV benefit
	Pemvidutide (ALTB-801)	Altimmune	Dual GLP-1 / Glucagon RA	PHASE 2	• Significant weight loss • Marked hepatic fat reduction
	Survodutide (BOE072)	Boehringer Ingelheim / Zealand Pharma	Dual GLP-1 / Glucagon RA	PHASE 2	• High efficacy on MASH endpoints • Once-weekly dosing
LIVER-DIRECTED METABOLIC AGENTS (STEATOSIS & INFLAMMATION)	VK2809	Viking Therapeutics	THR-β agonist	PHASE 2	• Oral, once-daily • Direct hepatic gene regulation
	Denifanstat (TVB-2640)	Sagimet Biosciences	FASN inhibitor	PHASE 2	• Oral agent • Attractive combination partner
	Ervogastat + Clesacostat	Pfizer	DGAT2 inhibitor + ACC inhibitor	PHASE 1	• Complementary MOAs • Potential best-in-class combination

MECHANISM COLOR KEY: FGF21 ANALOGS — Fibrosis reversal & metabolic remodeling; INCRETIN-BASED THERAPIES — Metabolic improvement & weight reduction; LIVER-DIRECTED AGENTS — Steatosis, inflammation & lipid metabolism

DEVELOPMENT STAGE KEY: Completed; In Progress / Ongoing; Planned / Next Step

RA = Receptor Agonist; FASN = Fatty Acid Synthase; THR-β = Thyroid Hormone Receptor Beta; DGAT2 = Diacylglycerol O-Acyltransferase 2; ACC = Acetyl-CoA Carboxylase; CV = Cardiovascular.

Source: Company pipelines, investor presentations, clinicaltrials.gov, press releases (May 2024)

OUTLOOK

MASH treatment is rapidly advancing across multiple mechanisms. Combination therapy is likely to define the standard of care.

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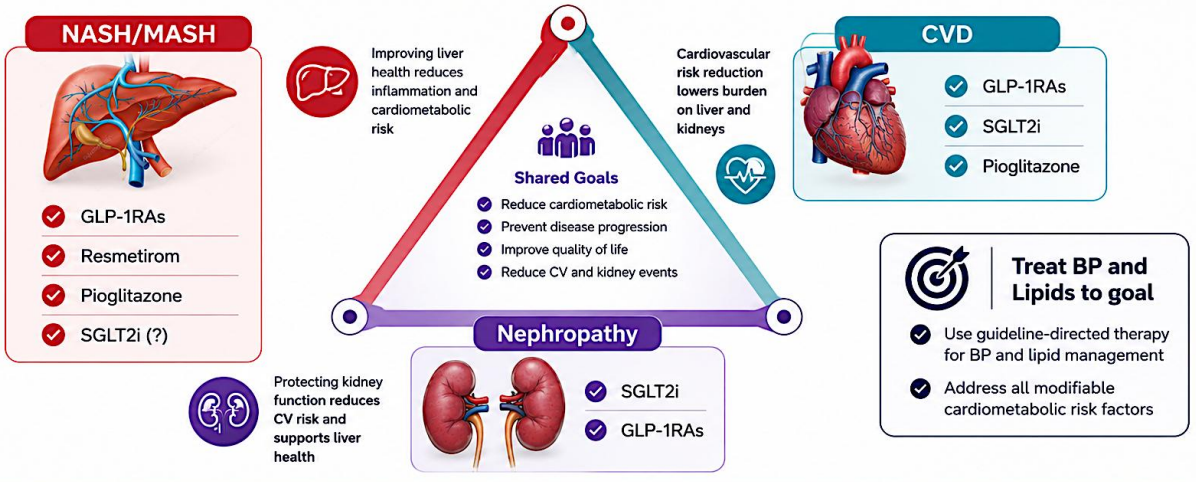
Incorporate MASLD in the Management of Cardiometabolic Risk Reduction in Obesity and T2DM: A "triangle of care"



Cusi K (unpublished 2026)

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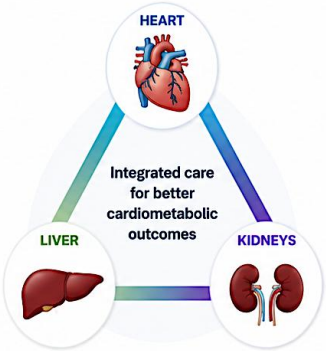
MASLD Clinical Implications

Addressing MASLD is essential to reduce cardiometabolic risk and improve outcomes.

1. **MASLD and diabetes (i.e., T2D or T1D w/cardiometabolic risk factors [CMRFs])** interact as "disease enhancers" of each other.
2. **In endocrine clinics** about **≥40%** of people with **T2D** have **MASH** and **≥20%** are at risk of cirrhosis (have "at-risk" MASH).
3. **People with T2D (or T1D with obesity/CMRFs) should be risk-stratified** for "at risk" MASH (i.e., having significant liver fibrosis).
4. **Multiple mechanisms at play.** From a treatment perspective, obesity, insulin resistance, hyperglycemia and other CMRFs benefit from lifestyle changes, pharmacotherapy for obesity (i.e., GLP-1RA) or T2DM (i.e., pioglitazone and/or GLP-1RA) and metabolic surgery.
5. **When diagnosed with MASLD,** lifestyle management and newer generation antihyperglycemic agents (incretin therapies and SGLT-2 inhibitors) can prevent progression and increase likelihood of regression.
6. **In patients with at-risk MASH,** treatment with semaglutide and/or resmetirom has the potential to induce regression.
7. **Develop a multidisciplinary team** and refer to GI/liver specialists if additional risk stratification and treatment (i.e., resmetirom) needed.



Early identification and comprehensive management of MASLD can reduce liver disease progression, cardiovascular events, and kidney complications.

Treat the whole patient. Improve outcomes.

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