



Understanding MASH and the New Therapies for Steatotic Liver Disease

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Financial Disclosures

- Consultant and member of the Speakers Bureau for Madrigal Pharmaceuticals
- I will not reference unlabeled or unapproved uses of drugs or other products

Overview

Definition, pathogenesis, prevalence, risk factors, and natural history of MASLD

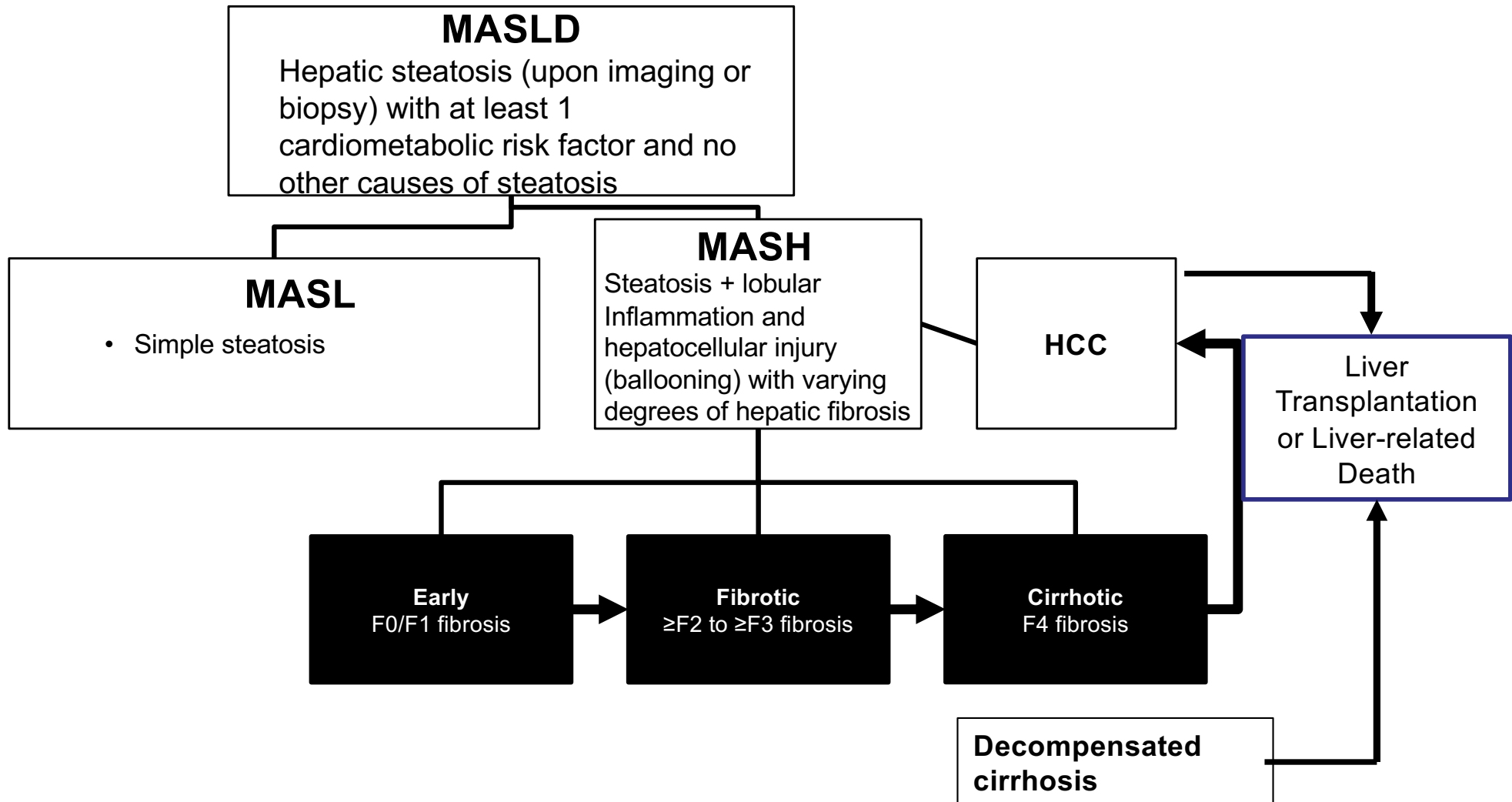
Diagnostic tests to assess fibrosis and identify patients at risk of progression to cirrhosis

Discuss the historical approach to treating MASH

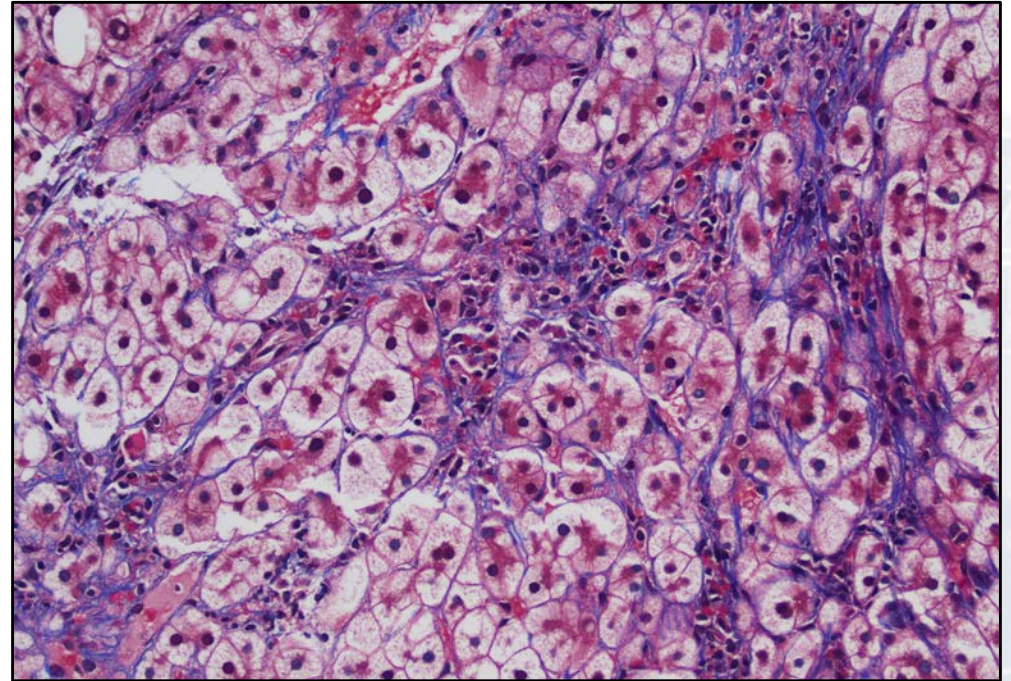
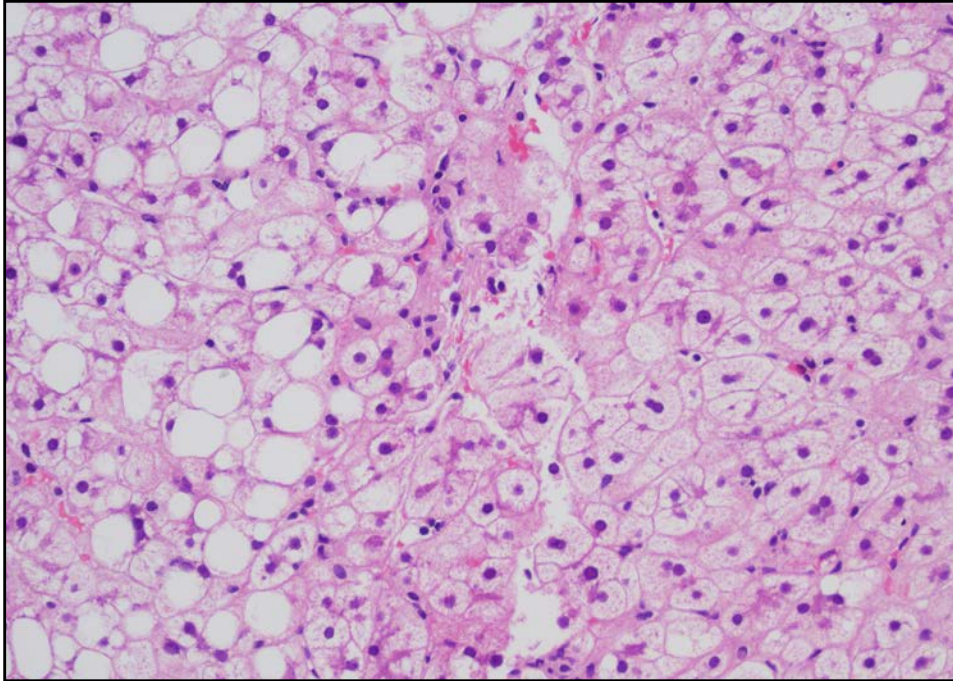
Review therapies newly approved for the treatment of MASH

Ongoing trials and emerging therapies

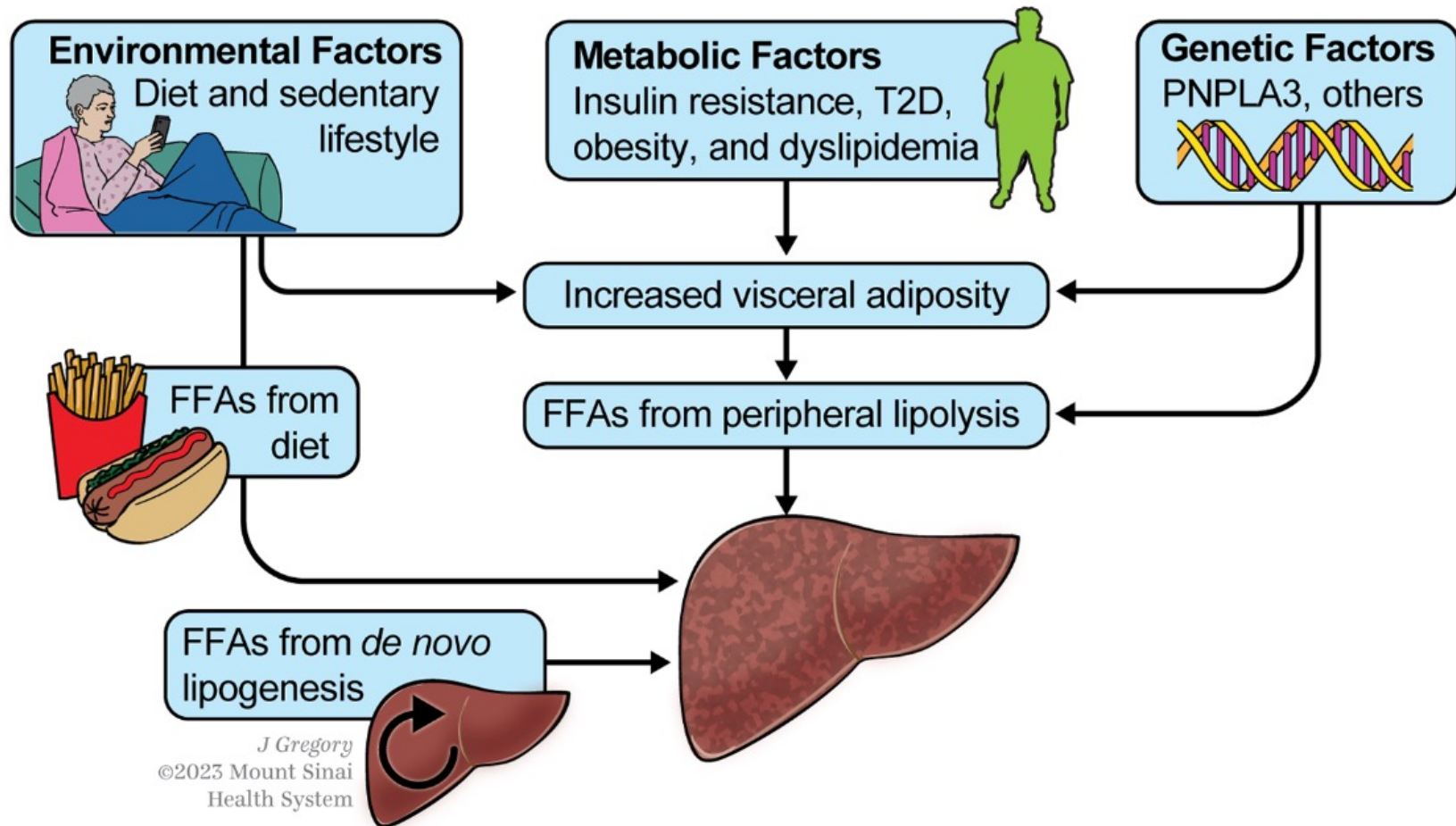
Spectrum of Disease



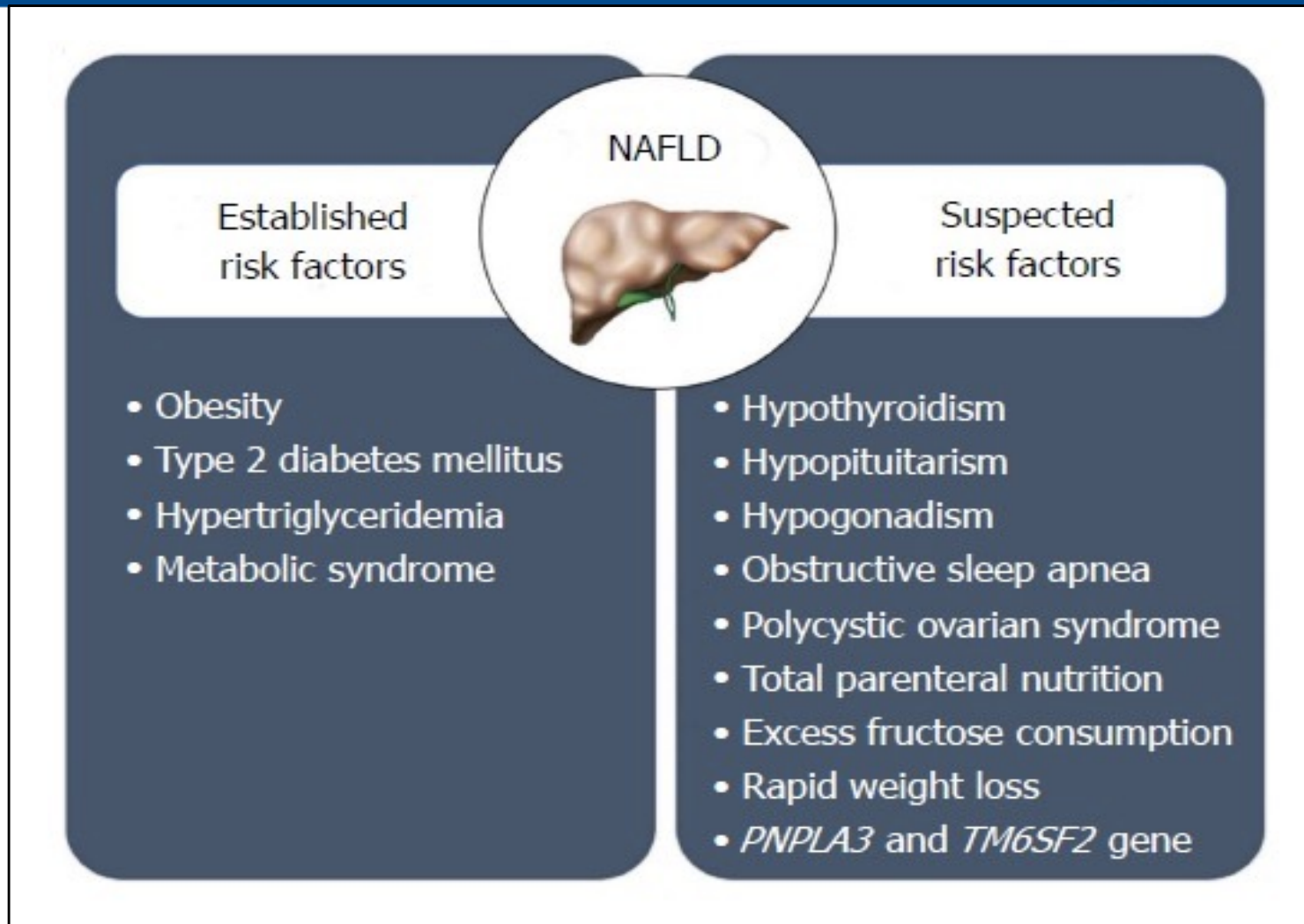
MASH on Liver Biopsy



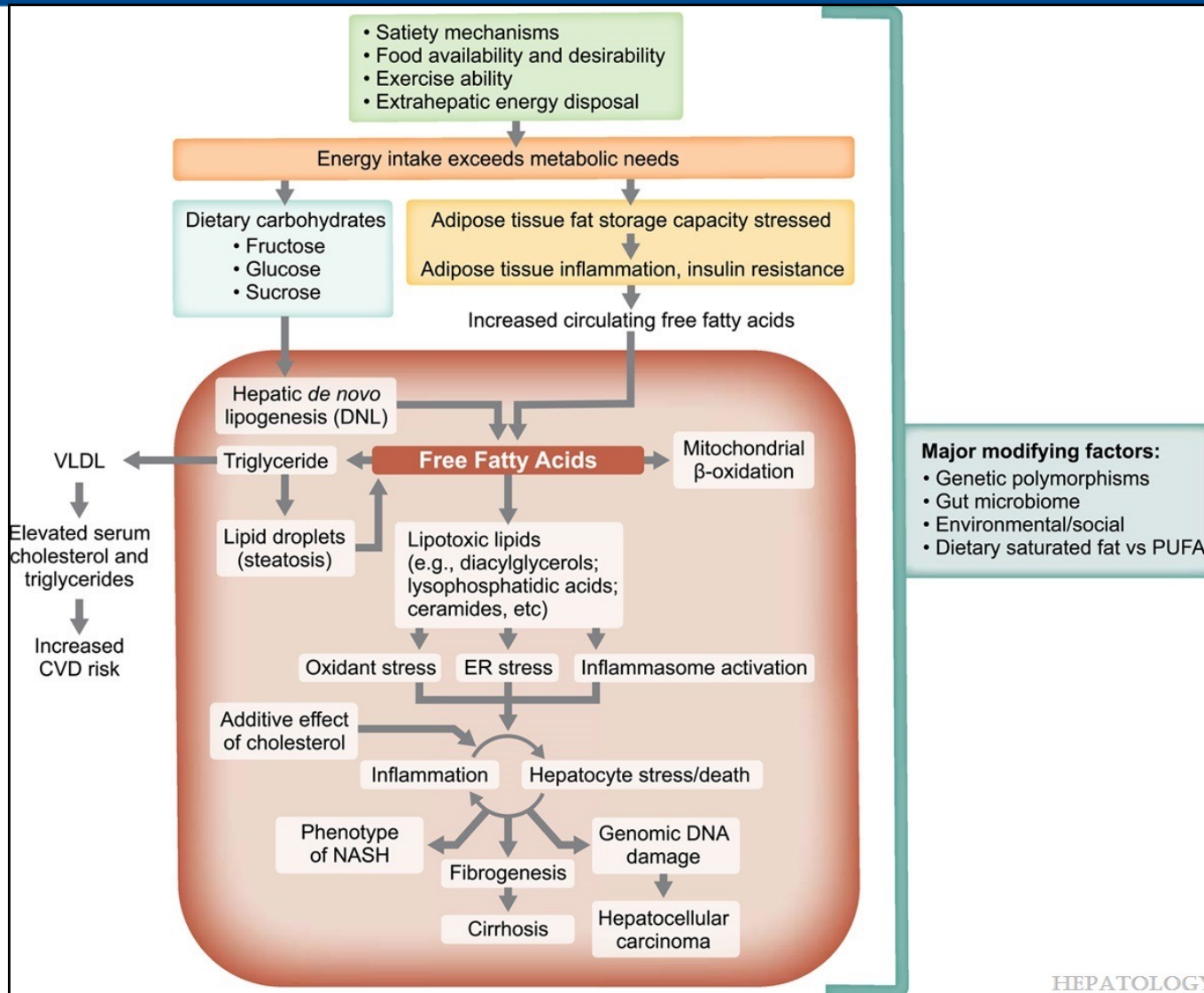
Risk factors for MASH



Factors Associated with MASLD

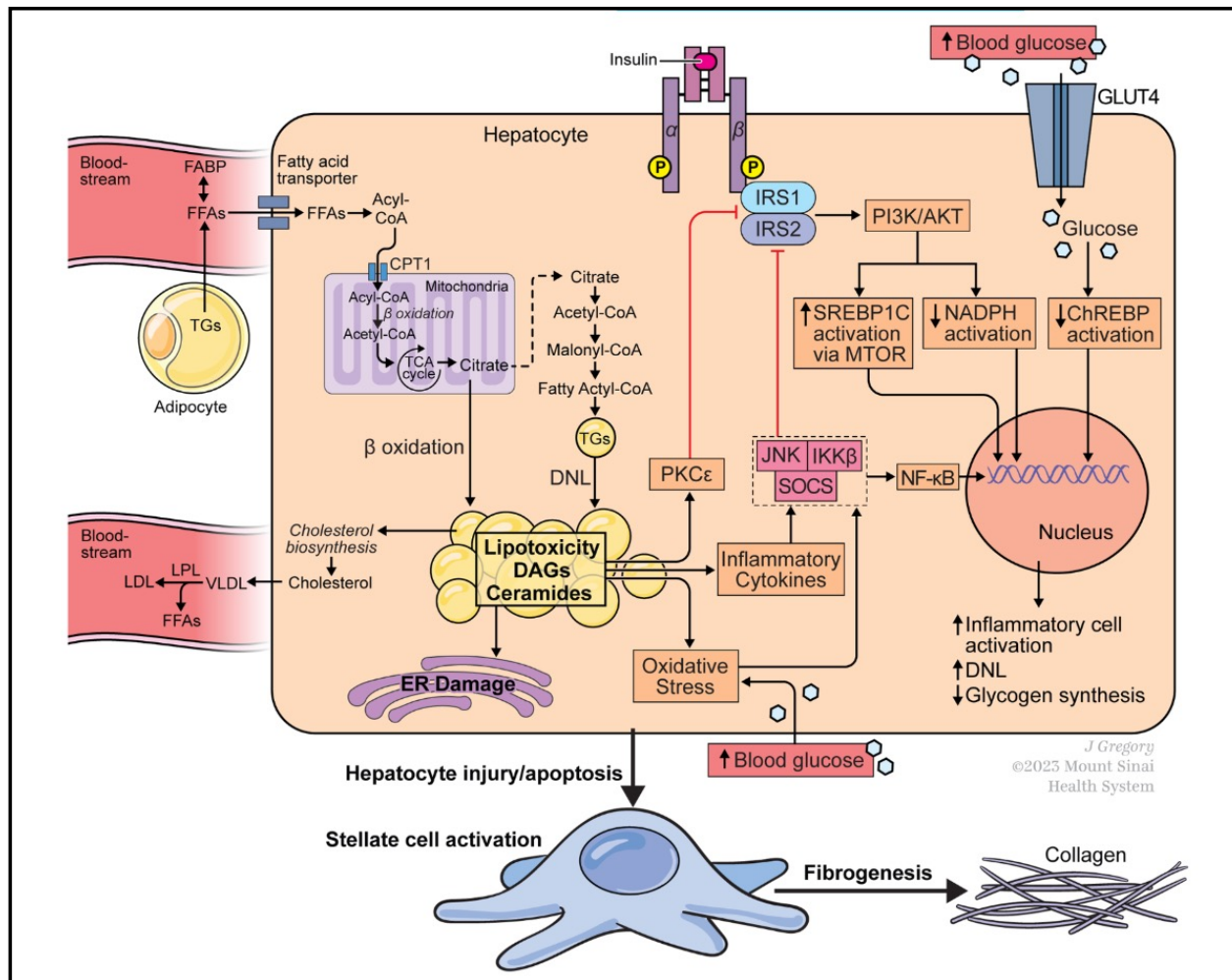


Pathogenesis of MASH



Insulin resistance is nearly universal in MASH!

The generation of lipotoxic species in MASH

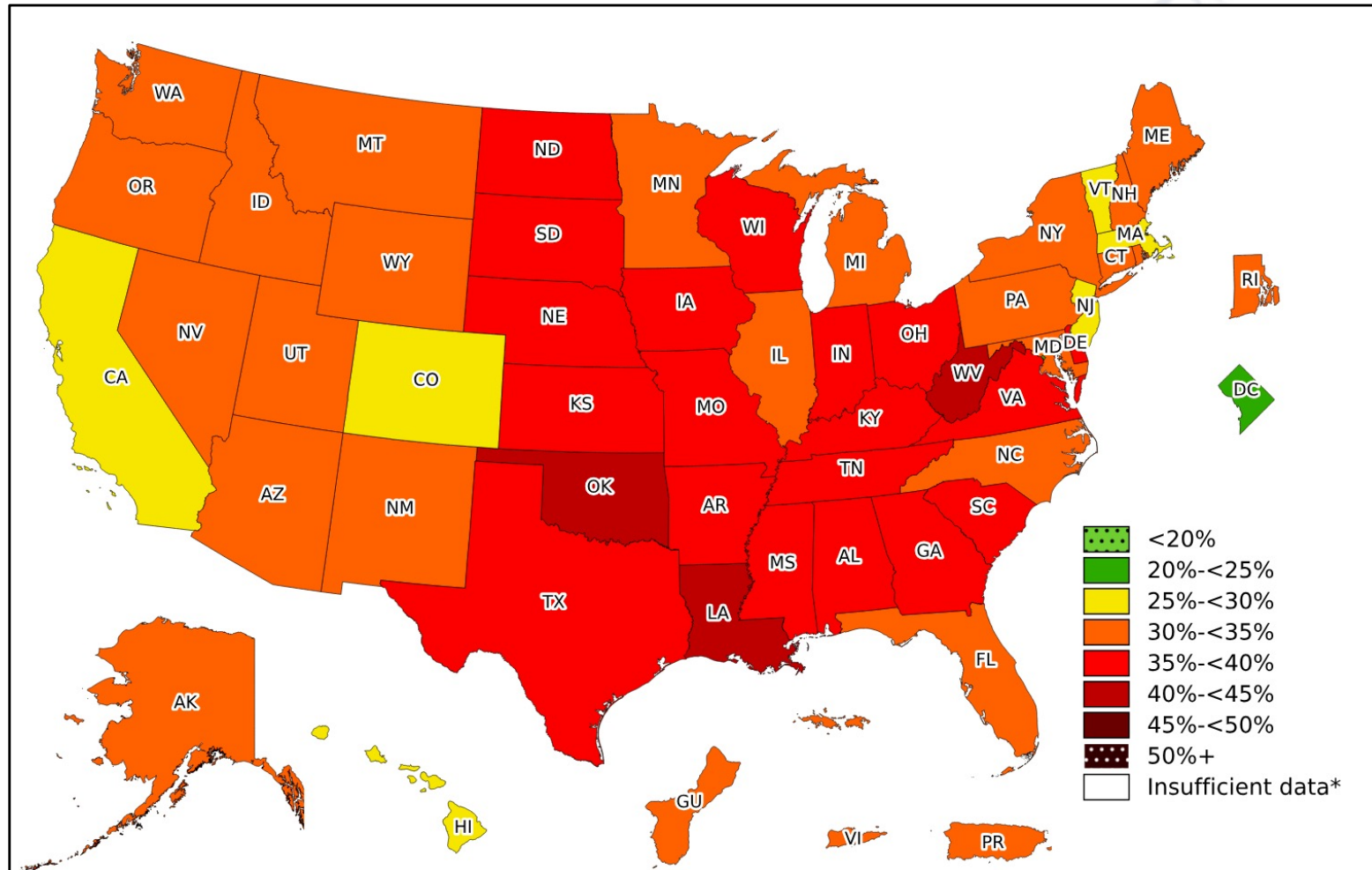


The generation of **lipotoxic species** is what drives hepatocellular injury and fibrosis in MASH

Genetic Risk factors

- Patatin-like phospholipase 3 (PNPLA3)
 - I148M polymorphism (G allele)
- TM6SF2 (Transmembrane 6 superfamily member 2)
 - rs58542926 variant
- MBOAT7

Prevalence of Obesity in U.S. in 2022



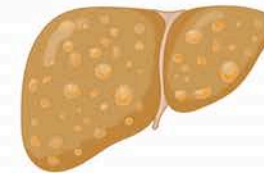
Overall obesity prevalence: 42%

<https://www.cdc.gov/obesity/data/prevalence-maps.html>

Prevalence of Steatotic Liver Disease and MASLD in the U.S.

Prevalence of Steatotic Liver Disease in the US: NHANES 2017-2020

Background and Aims: Following a Delphi consensus process, the term "steatotic liver disease" (SLD) was introduced to replace "fatty liver disease". Using the NHANES dataset from 2017-2020 we aimed to unveil the prevalence of SLD and its sub-categories in the US.



SLD

37.87%
(95% C.I.: 35.1%-40.7%)

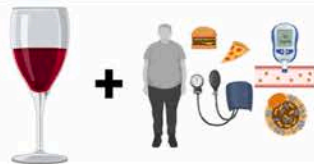
MASLD

32.45%
(95% C.I.: 29.8%-35.2%)



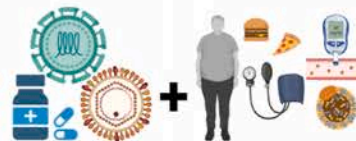
MetALD

2.56%
(95% C.I.: 1.91%-3.41%)



Other Combination Aetiology

1.14%
(95% C.I.: 0.88%-1.49%)



ALD

1.17%
(95% C.I.: 0.71%-1.92%)



Cryptogenic/ Other

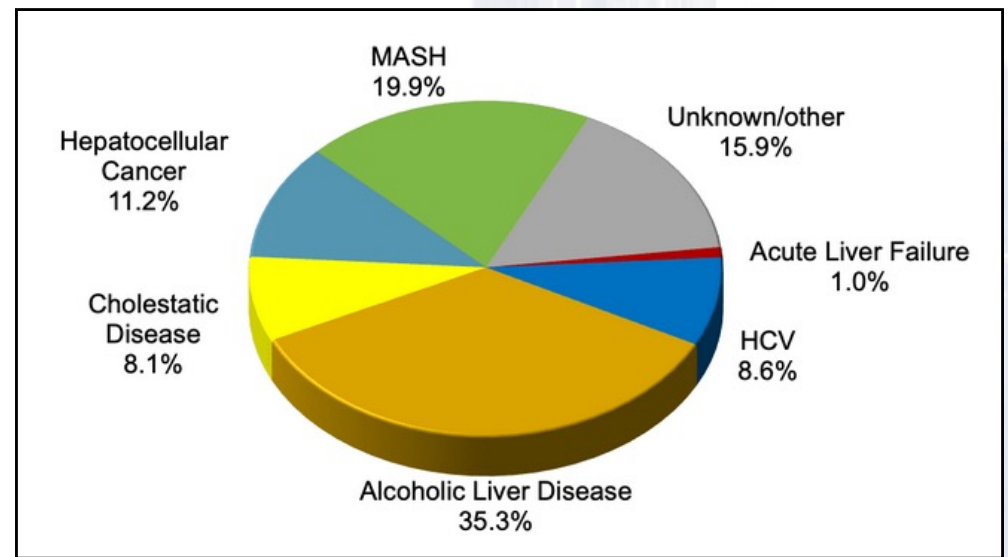
0.32%
(95% C.I.: 0.17%-0.61%)



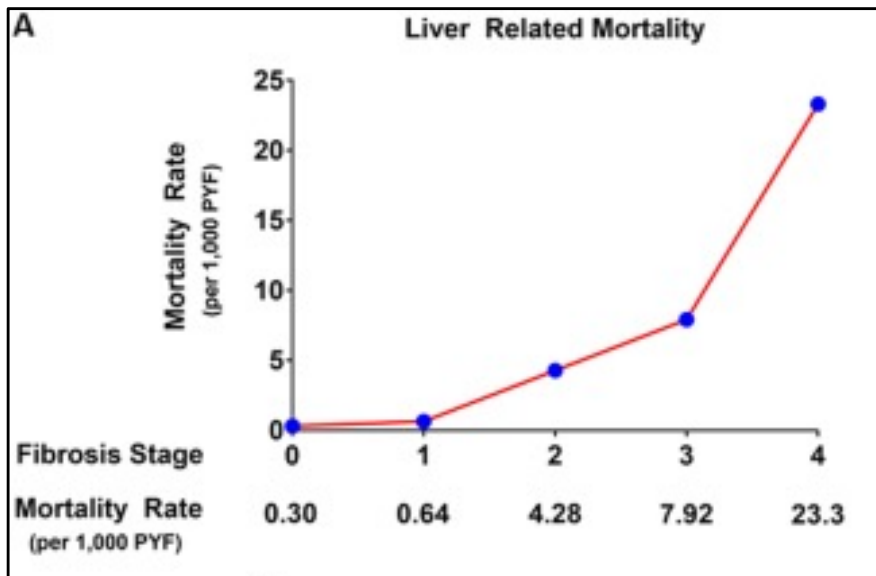
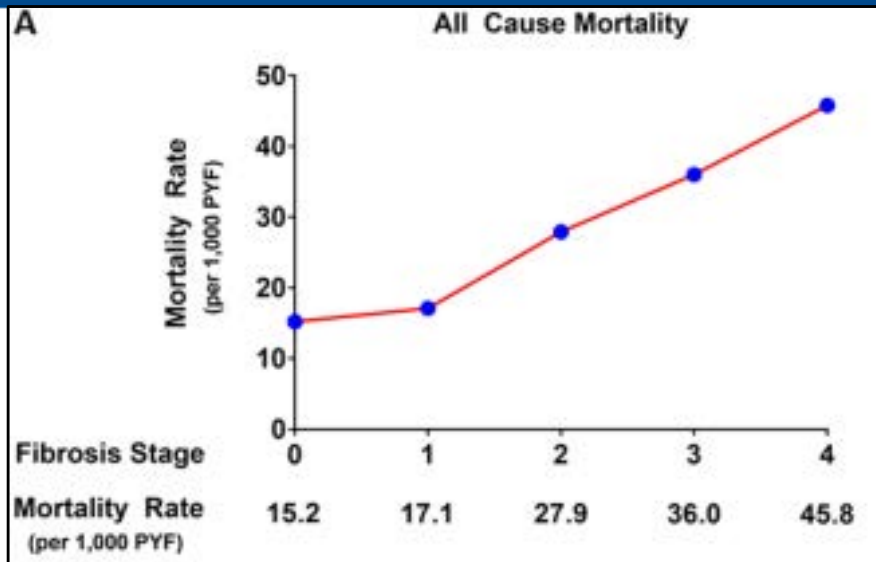
Clinical Gastroenterology and Hepatology

MASH is a major cause liver transplant

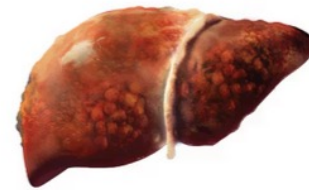
- MASH-related cirrhosis is already the **leading indication for liver transplantation** in women and those > 65 years of age
- The incidence of hepatic decompensation, HCC, and death related to MASH cirrhosis are expected to increase **2-3 fold** by 2030



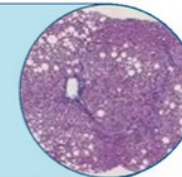
Mortality increases by Fibrosis Stage in MASH



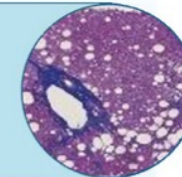
MASH with fibrosis



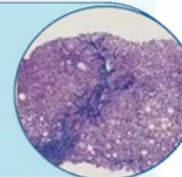
Fibrosis stage 1



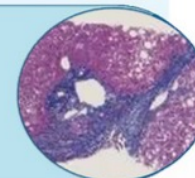
Fibrosis stage 2



Fibrosis stage 3



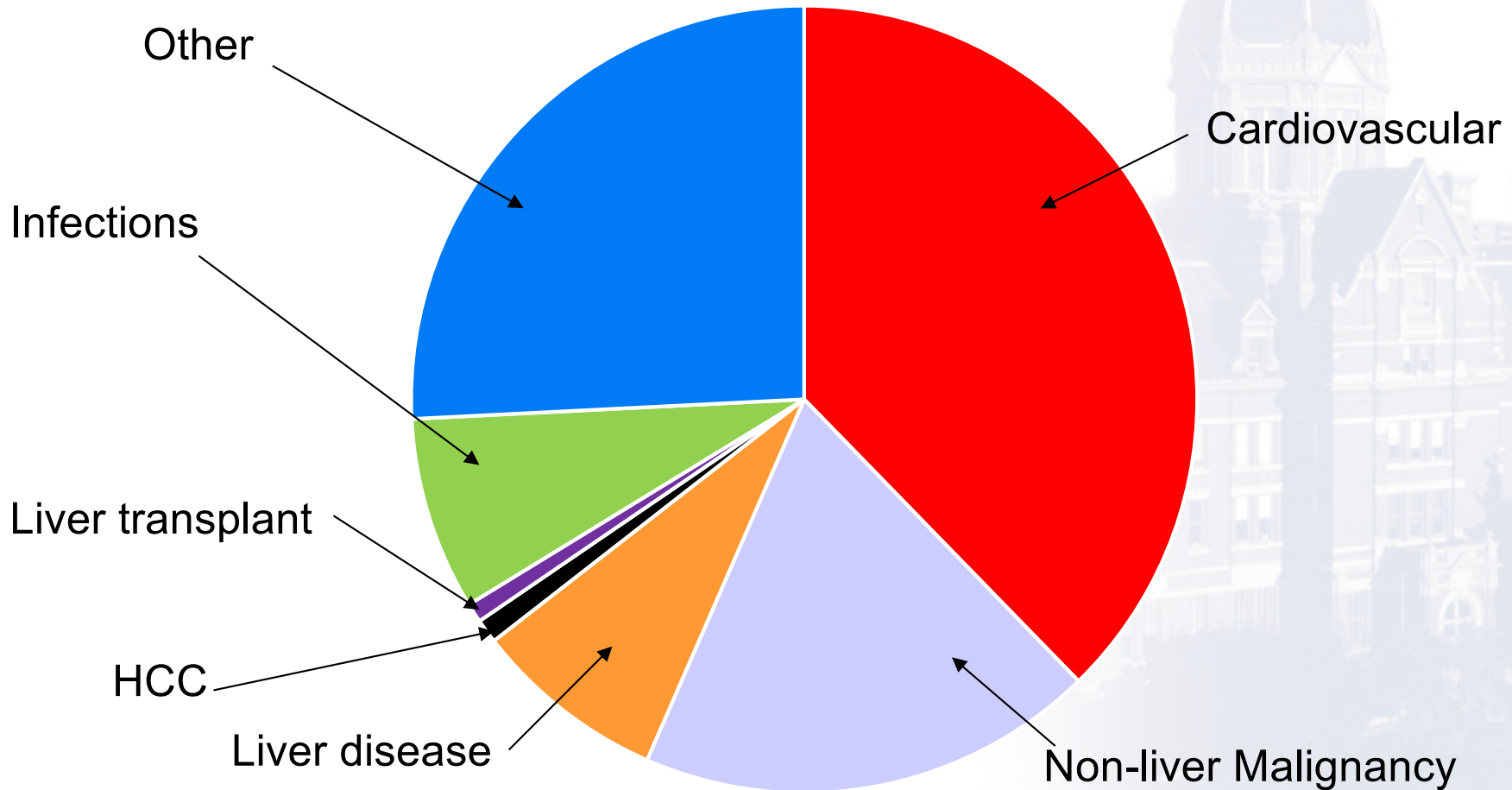
Fibrosis stage 4



We care a lot about **fibrosis!**

Mortality in MASLD

Causes of Death



Overview

Definition, pathogenesis, prevalence, risk factors, and natural history of MASLD

Diagnostic tests to assess fibrosis and identify patients at risk of progression to cirrhosis

Discuss the historical approach to treating MASH

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Ongoing trials and emerging therapies

Non-invasive scoring algorithms to assess fibrosis

FIB-4 index

- Age
- AST
- Platelets
- ALT

FIB-4 Score	Fibrosis Risk
<1.3	Low
1.3-2.67	Intermediate
> 2.67	High

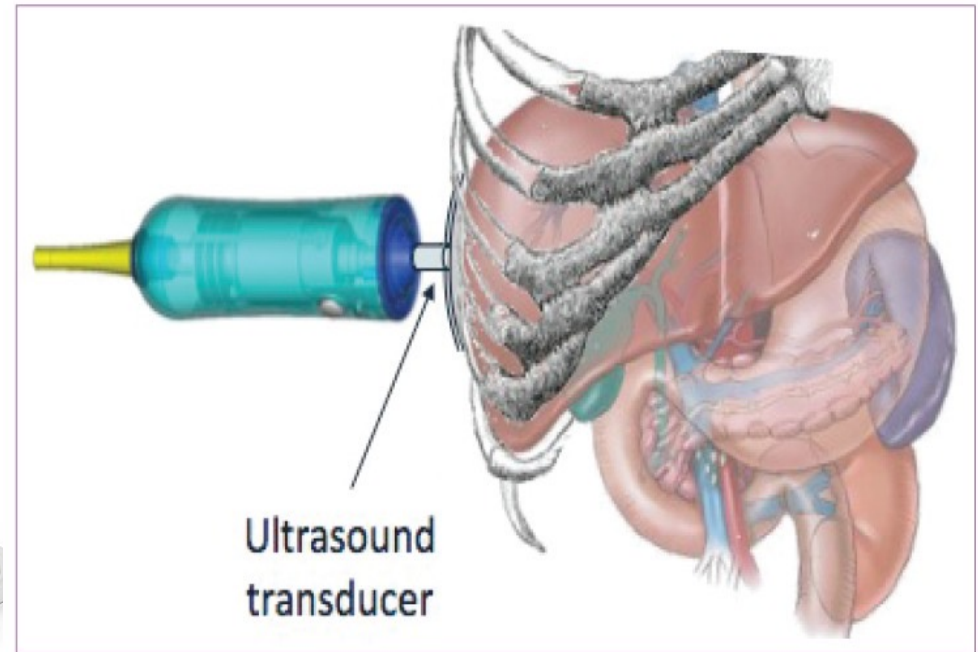
Recommended as a first-line assessment for primary care providers based on simplicity and minimal cost

Enhanced Liver Fibrosis (ELF) Test

- Proprietary blood test consisting of 3 elements involved in matrix turnover:
 - Hyaluronic acid
 - tissue inhibitor of metalloproteinase-1
 - N-terminal procollagen III peptide
- ELF score ≥ 9.8 reliably identifies patients with MASLD at increased risk of progression to cirrhosis and liver-related clinical events

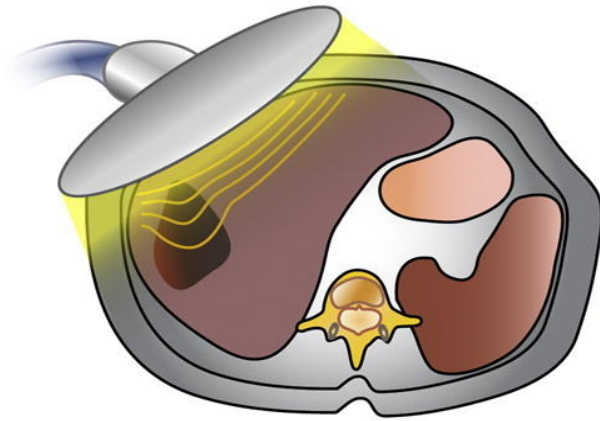
Elastography

Vibration Controlled Transient Elastography (Fibroscan)

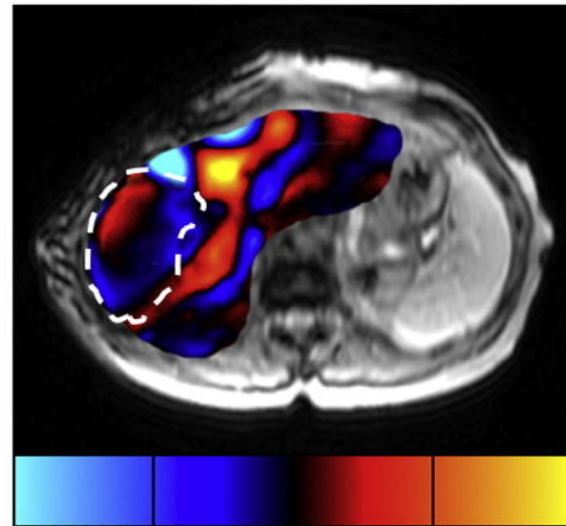


- Liver stiffness measurement (LSM) $< 7 - 8$ kPa can be used to rule out advanced fibrosis, especially if used sequentially after FIB-4
- LSM $8 - 12$ kPa: Moderate to significant fibrosis
- LSM > 12 kPa: Advanced fibrosis

MR Elastography (MRE)

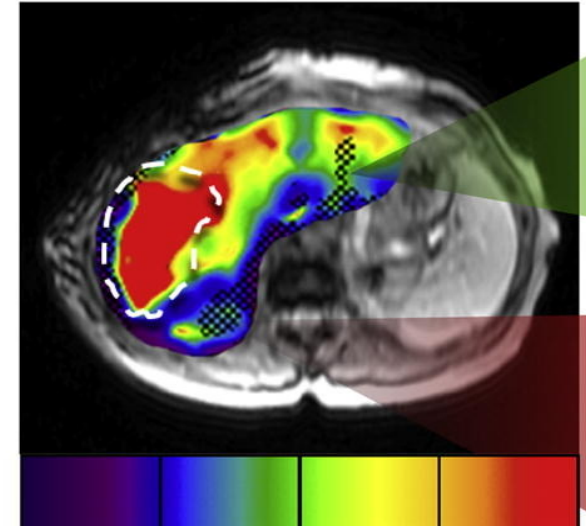


Shear Wave Image



-40 0 +40
Displacement (μm)

Elastogram



0 4 8
Shear Stiffness (kPa)

- MRE more sensitive than VCTE in the detection of fibrosis stage ≥ 2
- The most accurate noninvasive, imaging-based biomarker of fibrosis
- Not first line approach to risk stratification in patients with MASLD due to cost
- LSM by MRE ≥ 5 kPa suggestive of cirrhosis
- Among patients with cirrhosis, baseline LSM by MRE predicts future risk of incident hepatic decompensation and death

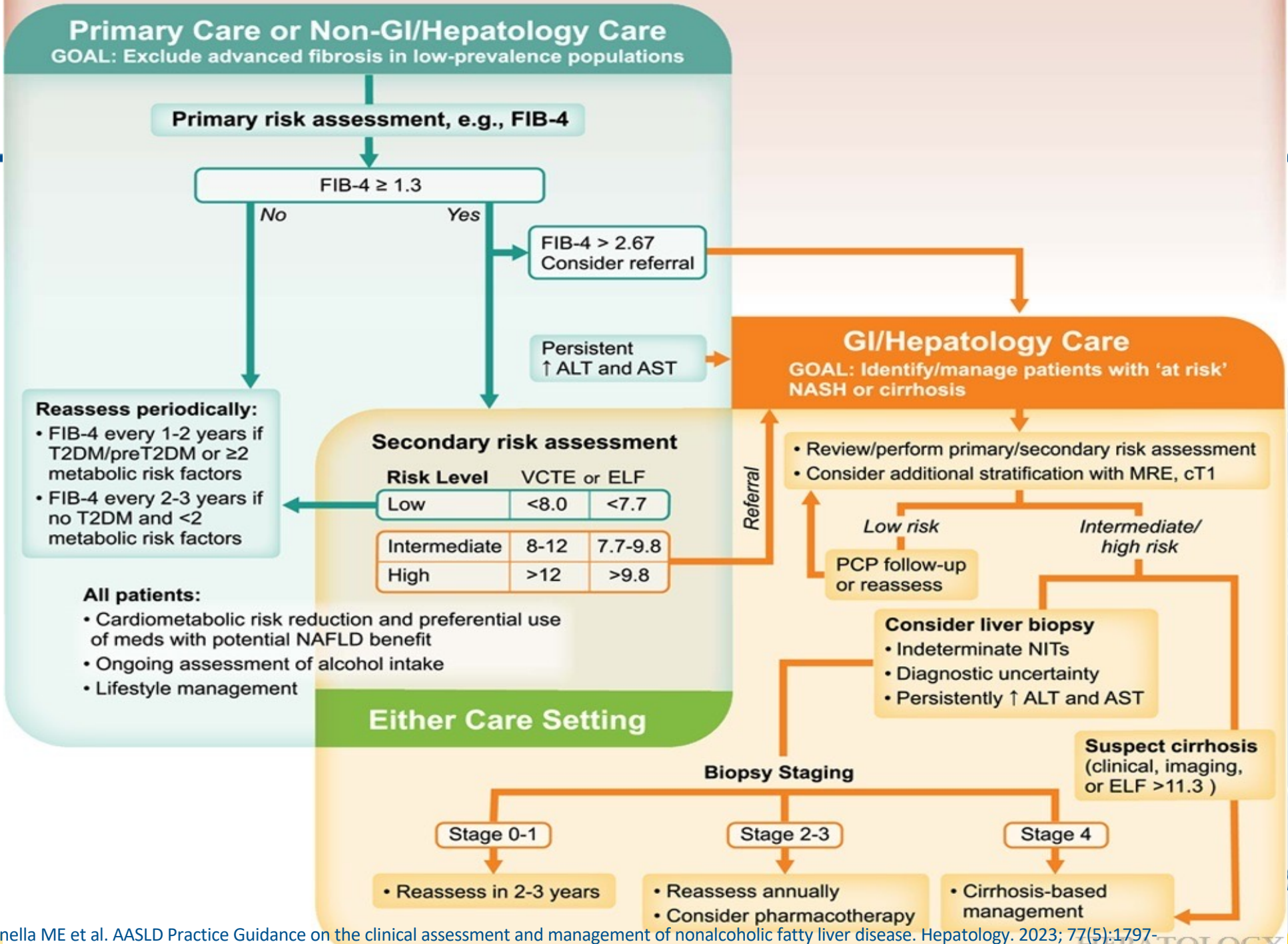
Which high risk populations should be screened for clinically significant fibrosis?

Patients with

- Type 2 diabetes mellitus
- Obesity with metabolic complications
- A family history of cirrhosis
- Significant alcohol use

Early identification of at-risk patients allows for interventions that may prevent progression to advanced liver disease and associated complications

Clinical Suspicion for Fatty Liver Disease



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Ongoing trials and emerging therapies

Goal of MASH Treatment: Disease Reversal

- Resolution of MASH without worsening of fibrosis
- **Improvement in fibrosis by ≥ 1 stage without worsening of MASH**

Treatment approach to prior to 2024

Treatment	Outcome
Weight loss Lifestyle intervention (Diet and exercise) Bariatric surgery	10% weight loss improves steatosis, steatohepatitis, and fibrosis Decreases cardiovascular risk

Targeting Oxidative Stress

Drug	Mechanism	Trial	Primary Endpoint
Vitamin E	Anti-oxidant	PIVENS TONIC	≥ 2 reduction in NAS, no worsening of fibrosis

Targeting Insulin Resistance

Drug	Mechanism	Trial	Primary endpoint
Pioglitazone	PPAR γ agonist	PIVENS and others	≥ 2 reduction in NAS, no worsening of fibrosis

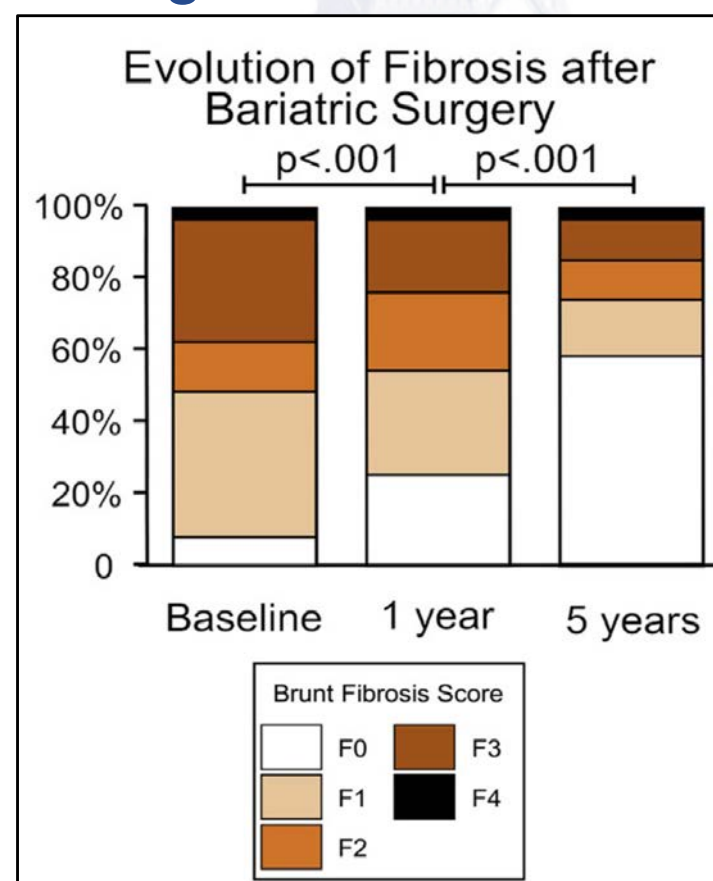
Bariatric Surgery



- Bariatric surgery should be considered as a therapeutic option.

- Metabolic weight loss surgery
- Resolves MASH in majority of patients without cirrhosis
 - 72% with loss of hepatic fat!¹
 - Reversal of fibrosis observed in 6 months¹
- Reduces mortality from CVD and malignancy

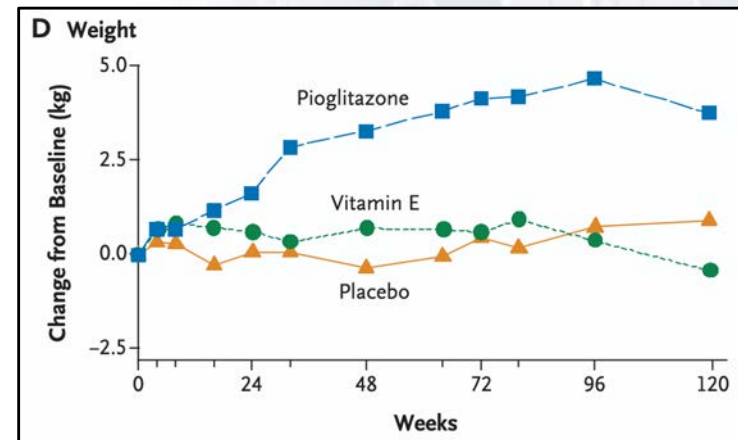
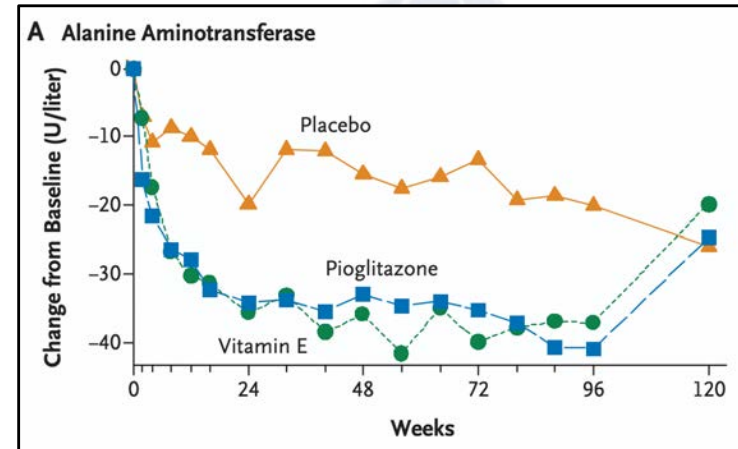
- Long-term data



Vitamin E and Pioglitazone



- Pioglitazone – 30mg/45mg
 - PPAR γ agonist (Type 2 DM)
 - Improves liver histology and insulin resistance
 - **Side effects:** Weight gain, risk of heart failure exacerbation, bone loss
- Vitamin E - 800 IU/day
 - Improves liver histology in nondiabetic adults with biopsy-proven MASH
- **Neither improves hepatic fibrosis**



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The Therapeutic targets of MASH

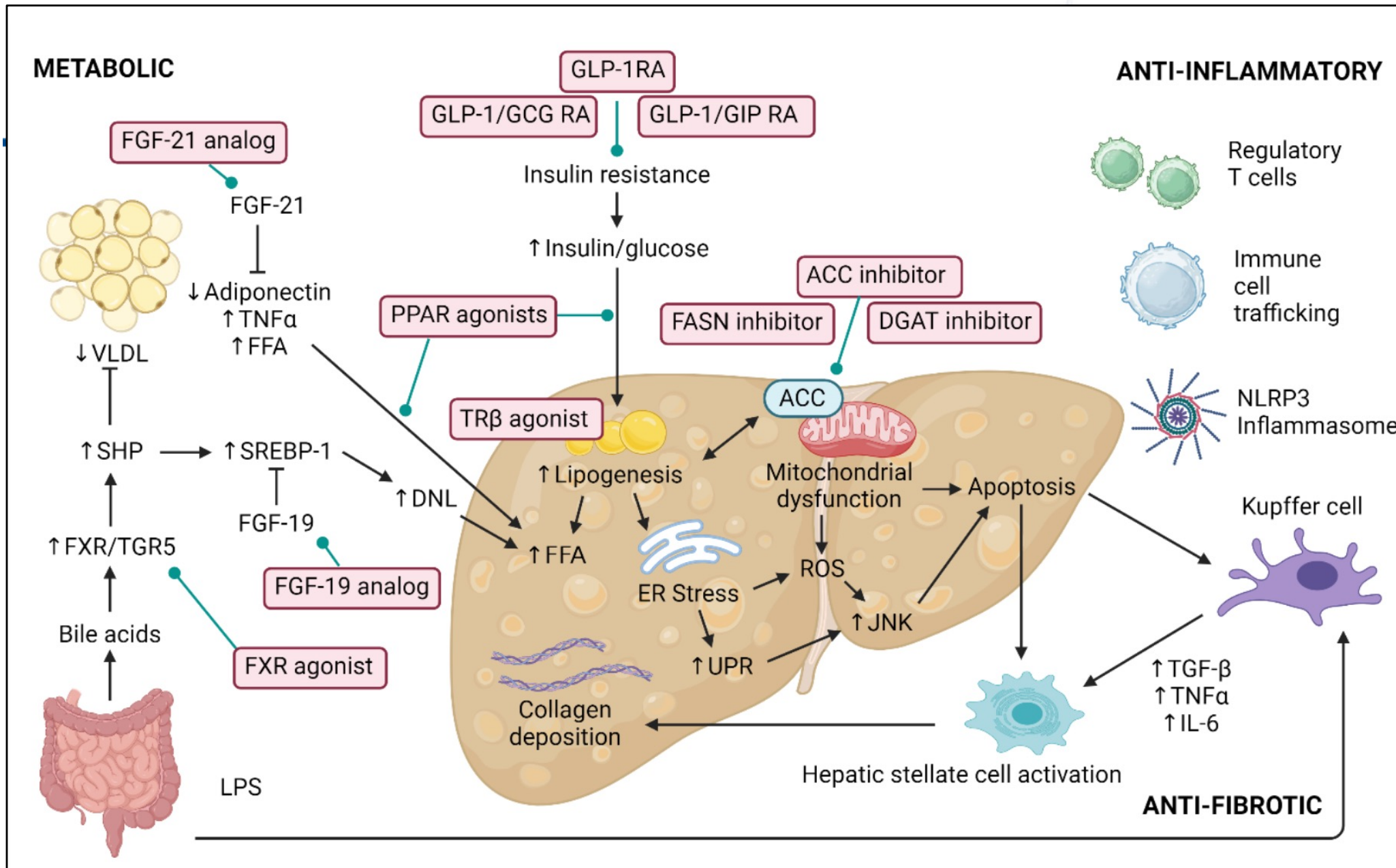
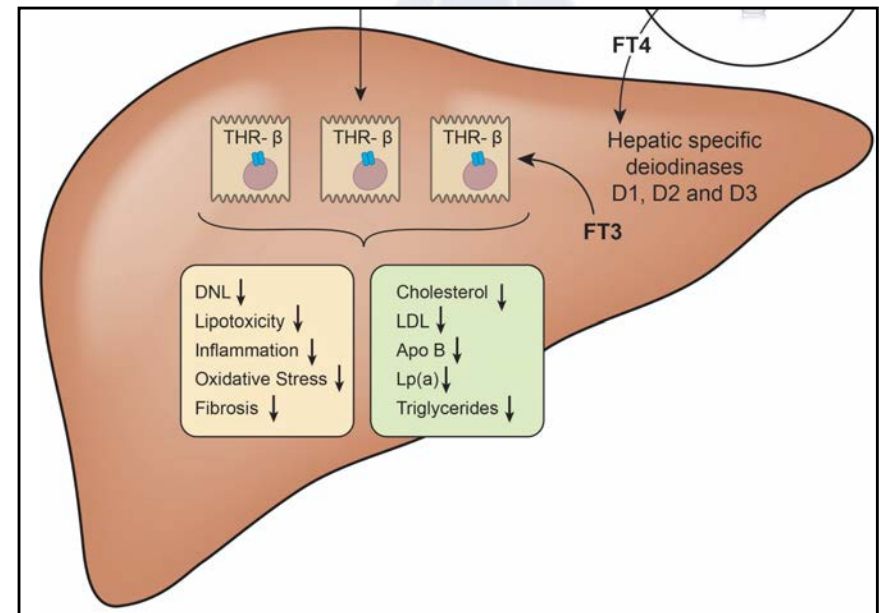
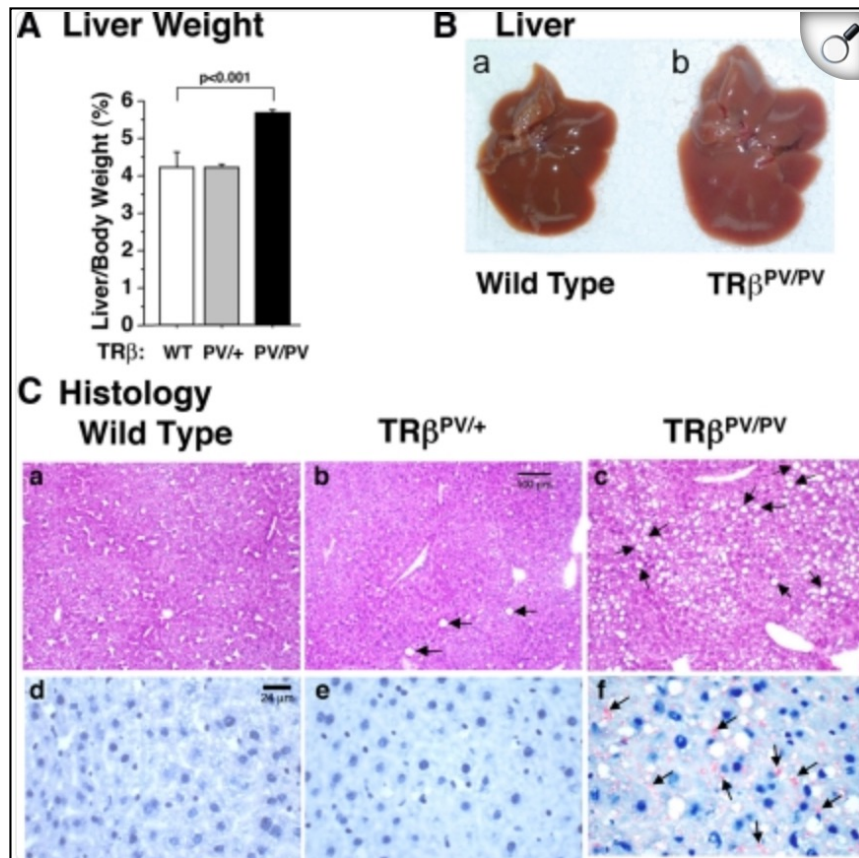


Figure 2: Therapeutic horizons in metabolic dysfunction–associated steatohepatitis

Fatty acid synthesis or lipid droplet targeting	Insulin sensitivity/ glucose lowering	Bile acid synthesis	Antiinflammatory	Antifibrotic early stage	Antifibrotic late stage
<ul style="list-style-type: none"> • THR-β agonist • FASN inhibitors • FGF21 analog • DGAT inhibitors • KHK inhibitors • siRNA PNPLA3 • PPAR agonist 	<ul style="list-style-type: none"> • GLP-1 agonist • GLP-1/GIP agonist • GLP-1/GIP/glucagon agonist • PPAR agonist • SGLT2 inhibitors • FGF21 analog • ANGPTL3 siRNA • Others 	<ul style="list-style-type: none"> • FGF19 analog • Others 	<ul style="list-style-type: none"> • GLP-1 agonist • GLP-1/GIP agonist • GLP-1/GIP/glucagon agonist • DHA • siRNA PNPLA3 • PPAR agonist • HSD17B13 	<ul style="list-style-type: none"> • FGF21 analog • Glucagon agonist • GLP-1 agonist • GLP-1/GIP agonist • GLP-1/GIP/ glucagon agonist • Anti-JNK-1 • PPAR agonist • Nox inhibitors • FGF19 analog • Others 	<ul style="list-style-type: none"> • FGF21 analog • PPAR agonist • ASK-1 inhibitors • Anti-GAL-3 • Anti-CTGF • FGF21/19 analog • Pentraxin-2 • Anti-IL-17 • Anti-TGF-β
Steatosis, ballooning, and inflammation			Stage 1–3 fibrosis	Stage 3–4 fibrosis	
Resolution of MASH			Reduction in the rate of progression of fibrosis or improvement in fibrosis	Reversal of advanced fibrosis or improvement in fibrosis	

Thyroid Hormone Receptor Beta-agonism in MASH



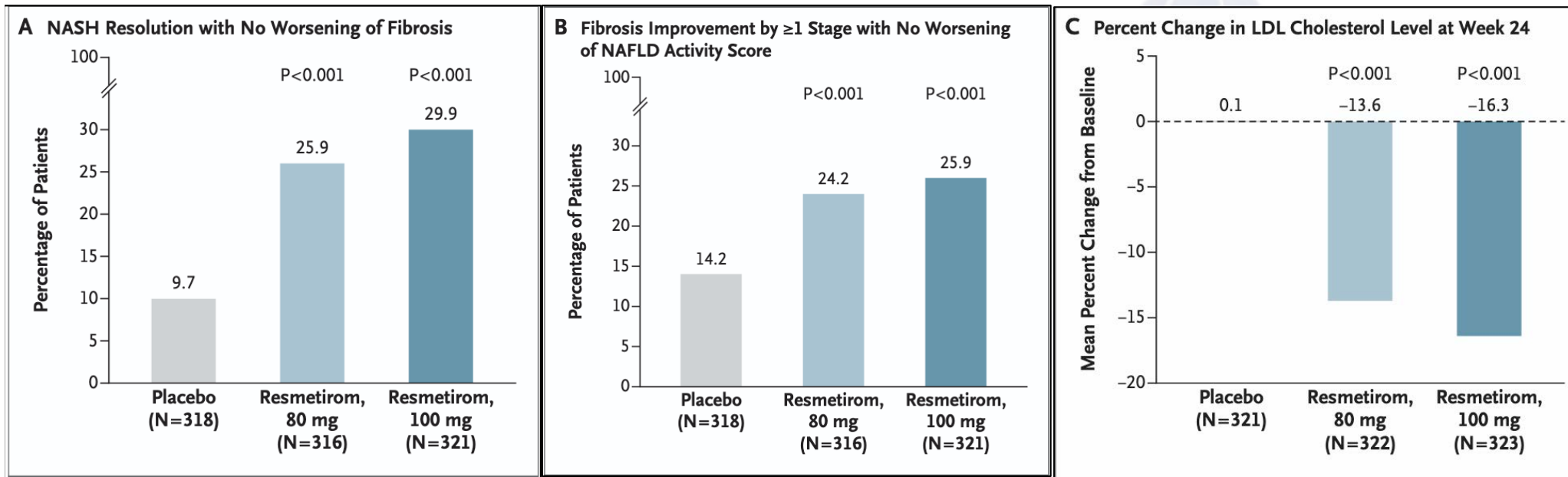
- **THR-B agonism:**
 - Increases beta-oxidation
 - Reduces de novo lipogenesis (DNL)
 - Reduces lipotoxicity

A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis



The NEW ENGLAND
JOURNAL of MEDICINE

S.A. Harrison, P. Bedossa, C.D. Guy, J.M. Schattenberg, R. Loomba, R. Taub, D. Labriola, S.E. Moussa, G.W. Neff, M.E. Rinella, Q.M. Anstee, M.F. Abdelmalek, Z. Younossi, S.J. Baum, S. Francque, M.R. Charlton, P.N. Newsome, N. Lanthier, I. Schiefke, A. Mangia, J.M. Pericàs, R. Patil, A.J. Sanyal, M. Noureddin, M.B. Bansal, N. Alkhouri, L. Castera, M. Rudraraju, and V. Ratziu, for the MAESTRO-NASH Investigators*



- At 52 weeks, THR-B agonism meaningfully reverses MASH and fibrosis!
- FDA approval – **March 14th, 2024**

Prescribing Resmetirom

- **Indication:**

- MASH with stage 2/3 fibrosis
- Minimal to no alcohol use
- No cirrhosis

- **Dose:**

- 80mg (< 100kg)
- 100mg (>100kg)

- **Side effects:**

- Diarrhea (#1)
- Nausea
- Pruritus
- Mild ELE after initiation

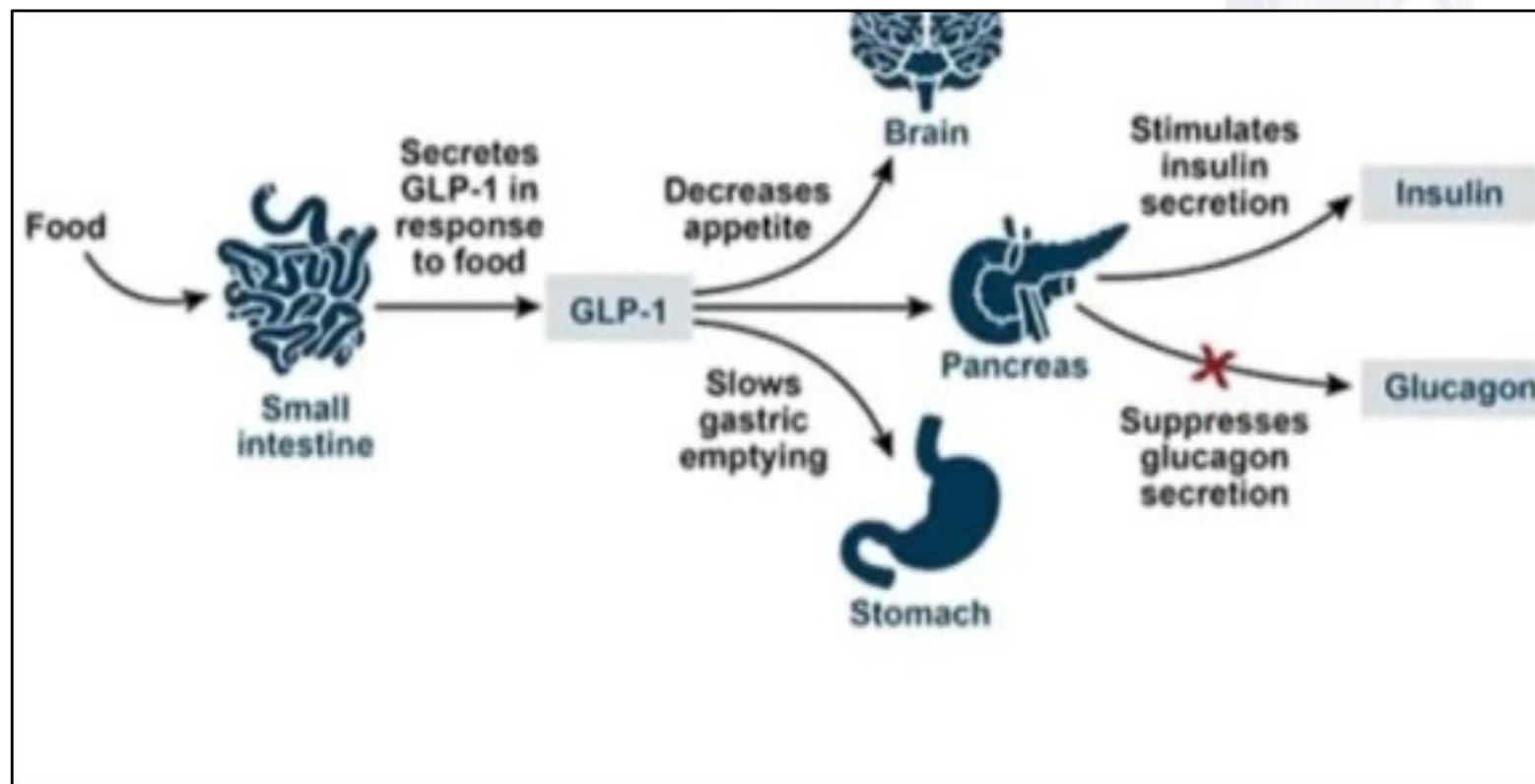
- **Safety**

- Considerations:**

- Thyroid hormone replacement?
- CYP and OATP1B interactions

The GLPs

- A long-acting Glucagon-like peptide-1 (GLP-1) analogue that mimics the effects of native GLP-1



The GLP Timeline

- **2015**: SUSTAIN trials suggest signal for MASH treatment
- **2016**: Liraglutide in MASH (LEAN)– Phase 2 trial

Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study THE LANCET

- **2020**: Semaglutide in NASH – Phase 2 trial
- **2025**: Semaglutide in MASH – Phase 3 trial

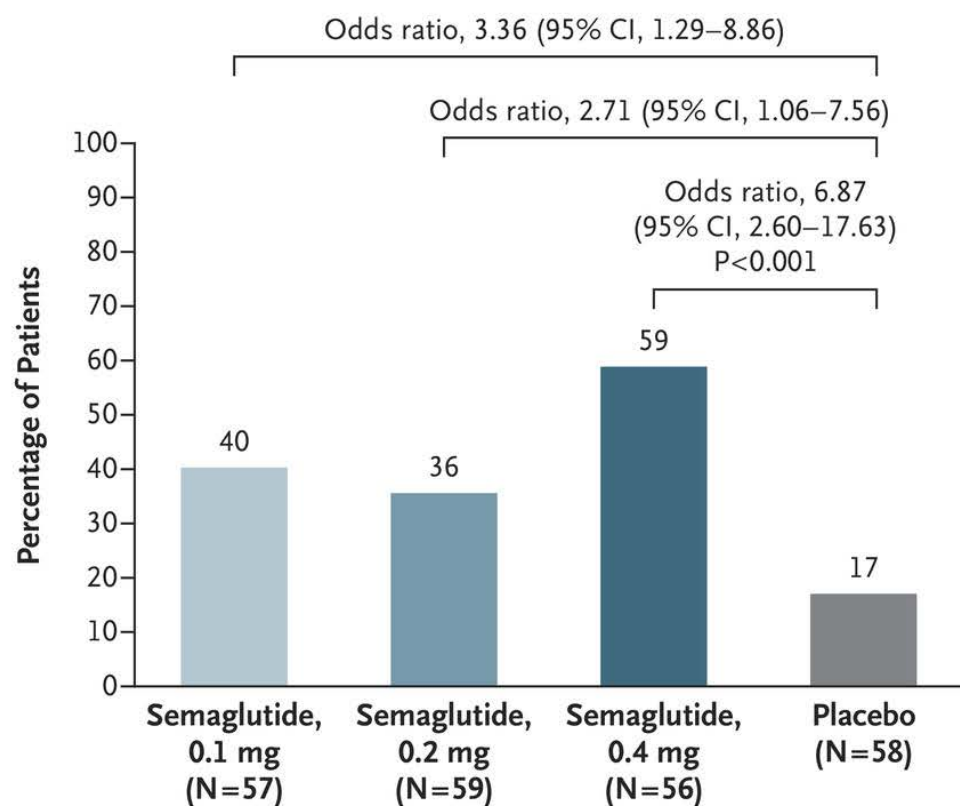
A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis



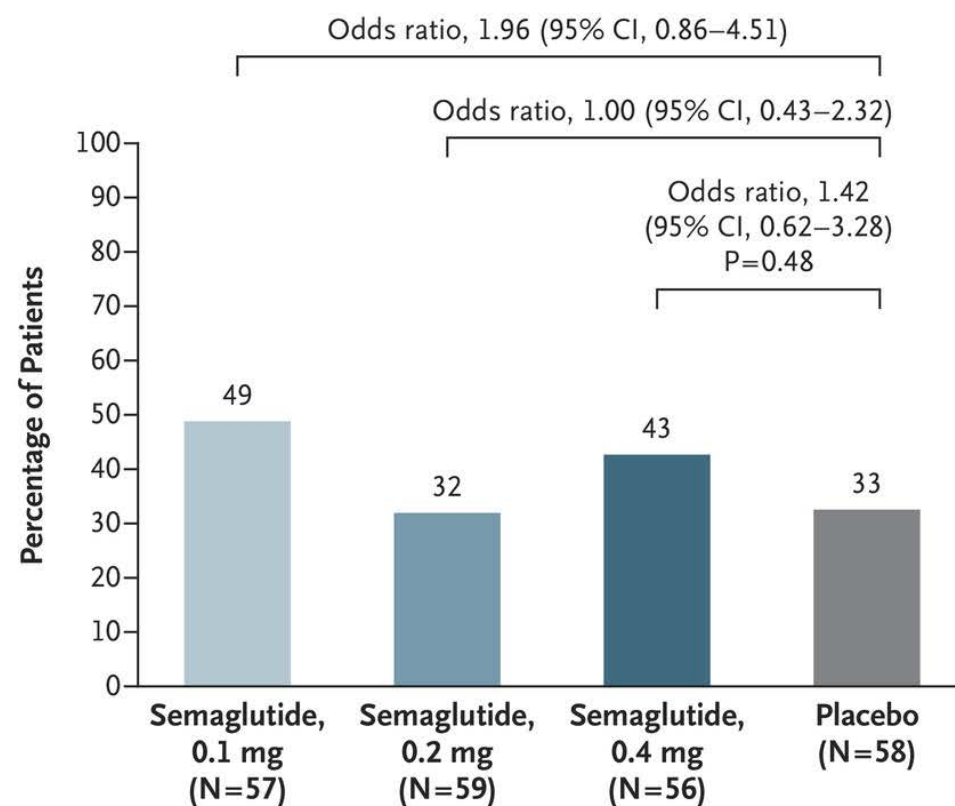
P.N. Newsome, K. Buchholtz, K. Cusi, M. Linder, T. Okanoue, V. Ratziu,
A.J. Sanyal, A.-S. Sejling, and S.A. Harrison, for the NN9931-4296 Investigators*

2020

A Resolution of NASH with No Worsening of Liver Fibrosis (primary end point)



B Improvement in Liver Fibrosis Stage with No Worsening of NASH (confirmatory secondary end point)



ESSENCE TRIAL (Phase 3)

Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis



The NEW ENGLAND
JOURNAL of MEDICINE

2025

Arun J. Sanyal, M.D.,¹ Philip N. Newsome, M.B., Ch.B., Ph.D.,^{2,3} Iris Kliers, M.D.,⁴ Laura Harms Østergaard, M.Sc.,⁴ Michelle T. Long, M.D.,⁴ Mette Skalshøi Kjær, M.D., Ph.D.,⁴ Anna M.G. Cali, M.D.,⁴ Elisabetta Bugianesi, M.D., Ph.D.,⁵ Mary E. Rinella, M.D.,⁶ Michael Roden, M.D.,⁷⁻⁹ and Vlad Ratziu, M.D., Ph.D.,¹⁰ for the ESSENCE Study Group*

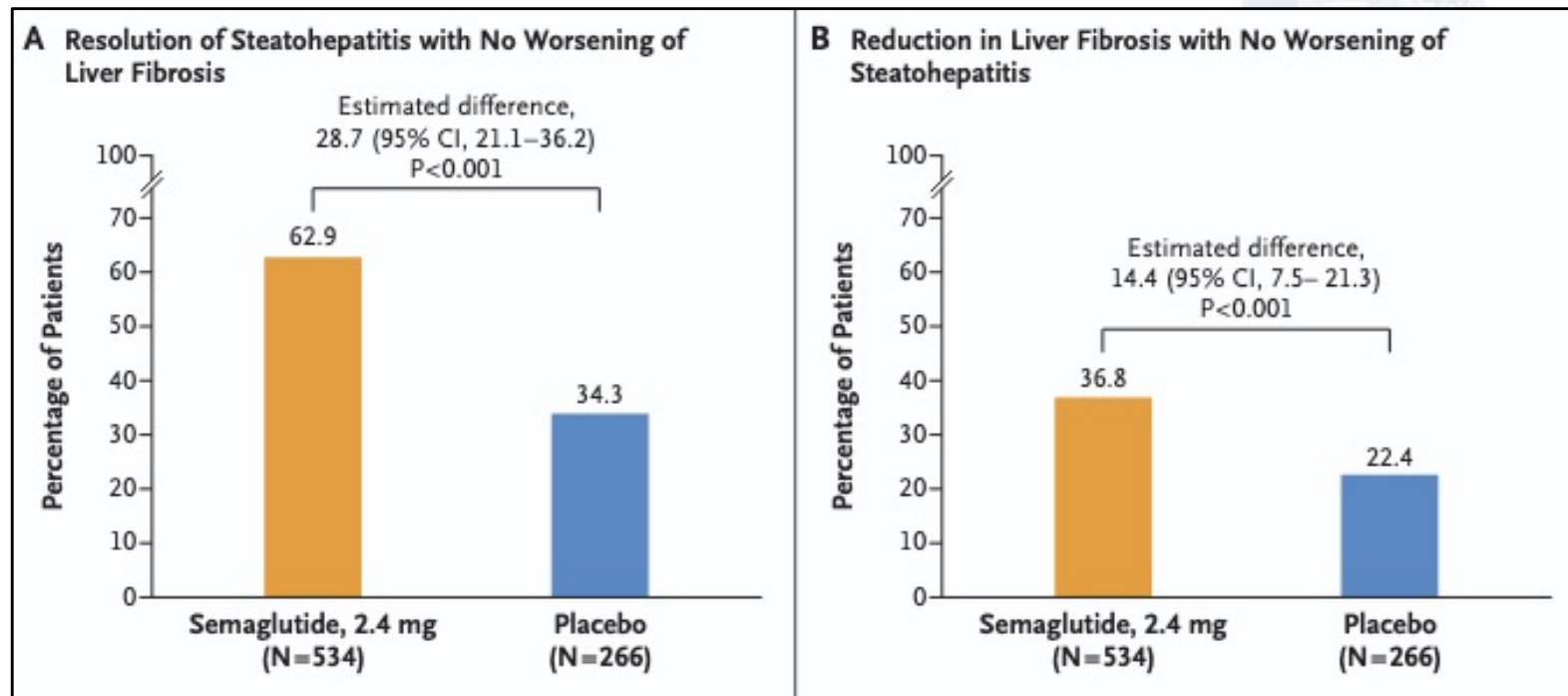
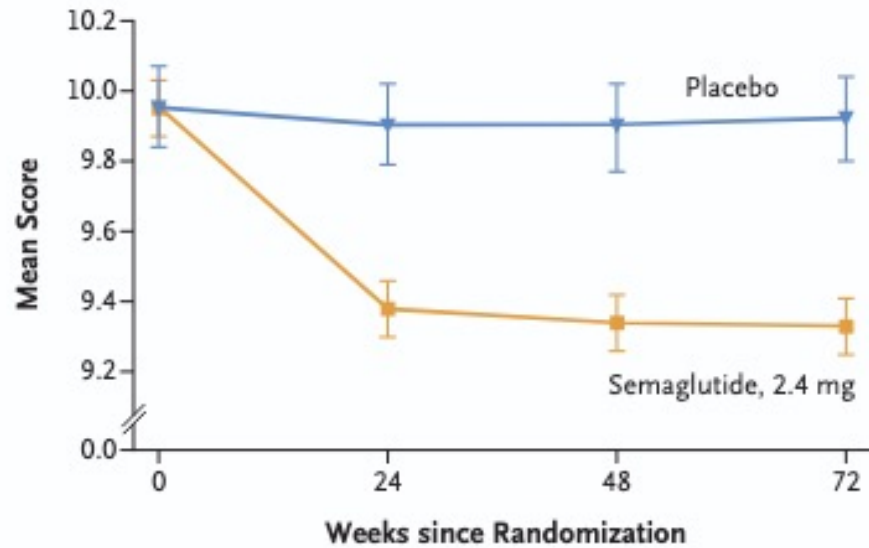


Figure 1. Primary End Points.

The figure shows the percentage of patients with fibrosis stage 2 or 3 who had resolution of steatohepatitis with no worsening of liver fibrosis (Panel A) and reduction in liver fibrosis with no worsening of steatohepatitis (Panel B) after 72 weeks, with the estimated difference expressed in percentage points.

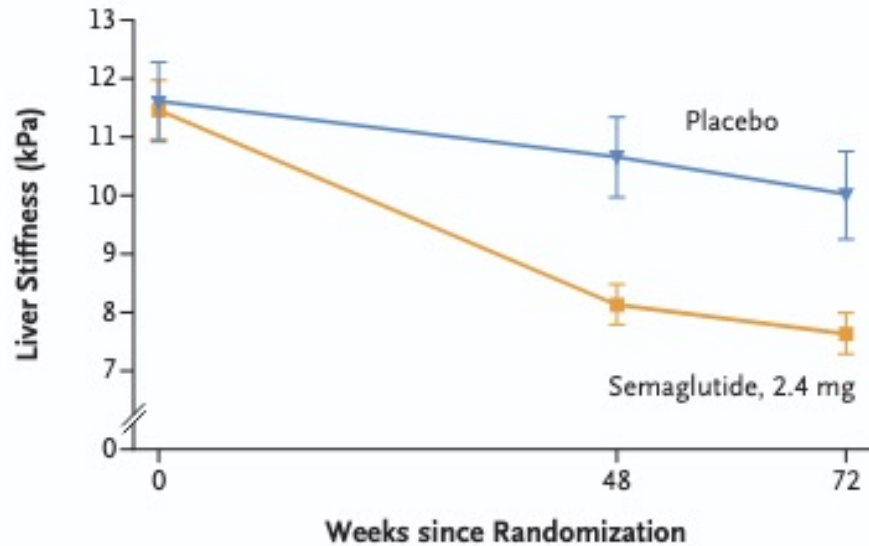
A Enhanced Liver Fibrosis Score



No. of Patients

	0	24	48	72
Placebo	266	252	246	237
Semaglutide, 2.4 mg	534	511	504	492

B Liver Stiffness Measured by Vibration-Controlled Transient Elastography



No. of Patients

	0	48	72
Placebo	216	204	193
Semaglutide, 2.4 mg	417	399	381

ESSENCE

Secondary outcomes

August 2025

BREAKING NEWS

FDA GRANTS ACCELERATED APPROVAL FOR WEGOVY (SEMAGLUTIDE) TO TREAT MASH



wegovy®

2.4 mg

solution for injection
semaglutide

For single-patient use only

Prescribing Semaglutide in MASH

- **Dose:**

- Treatment effect only clearly seen HIGH dose
- **2.4mg/week** (start at 0.25mg – 0.5mg)

- **Side effects:**

- High incidence of nausea, constipation, and vomiting

- **Concerns:**

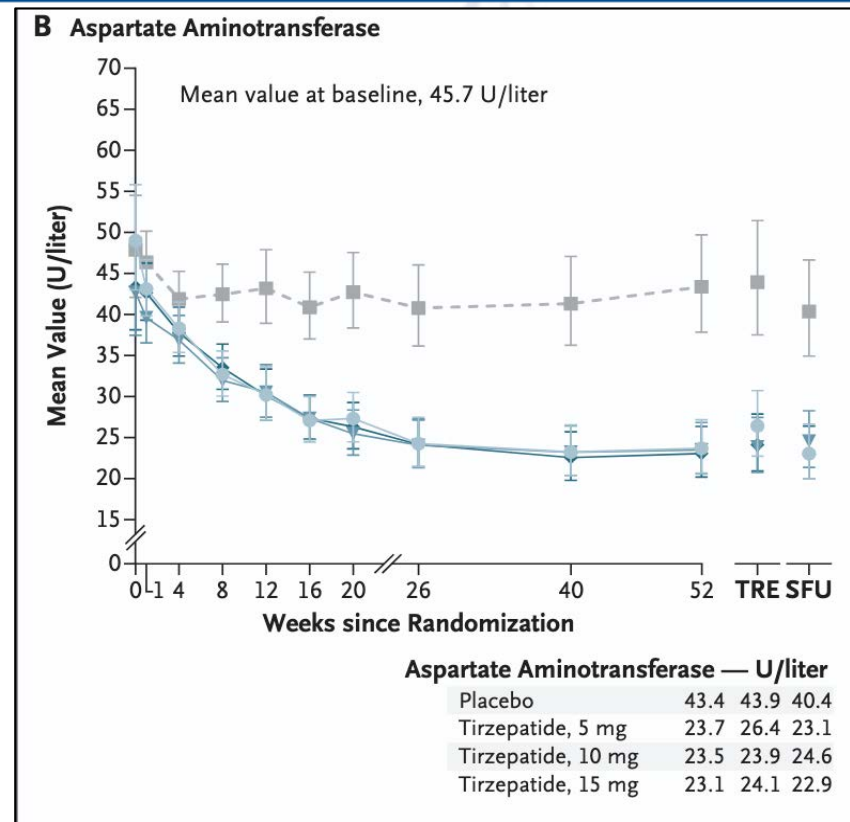
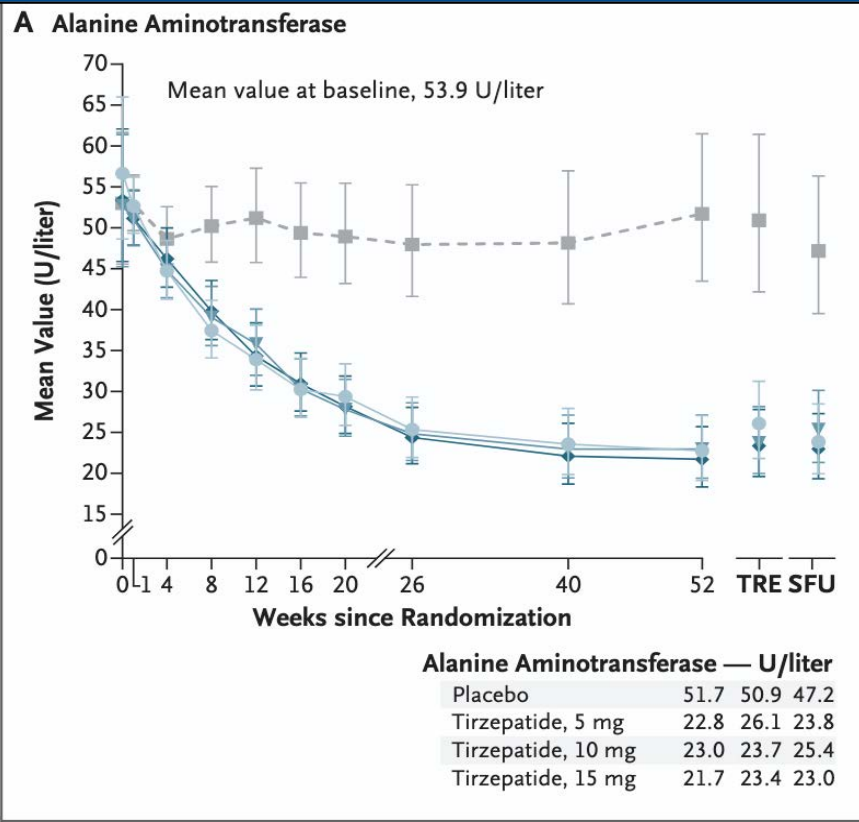
- Ceiling effect?
- Duration of treatment
- Treatment adherence

Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis



R. Loomba, M.L. Hartman, E.J. Lawitz, R. Vuppalanchi, J. Boursier, E. Bugianesi, M. Yoneda, C. Behling, O.W. Cummings, Y. Tang, B. Brouwers, D.A. Robins, A. Nikooie, M.C. Bunck, A. Haupt, and A.J. Sanyal, for the SYNERGY-NASH Investigators*

2024



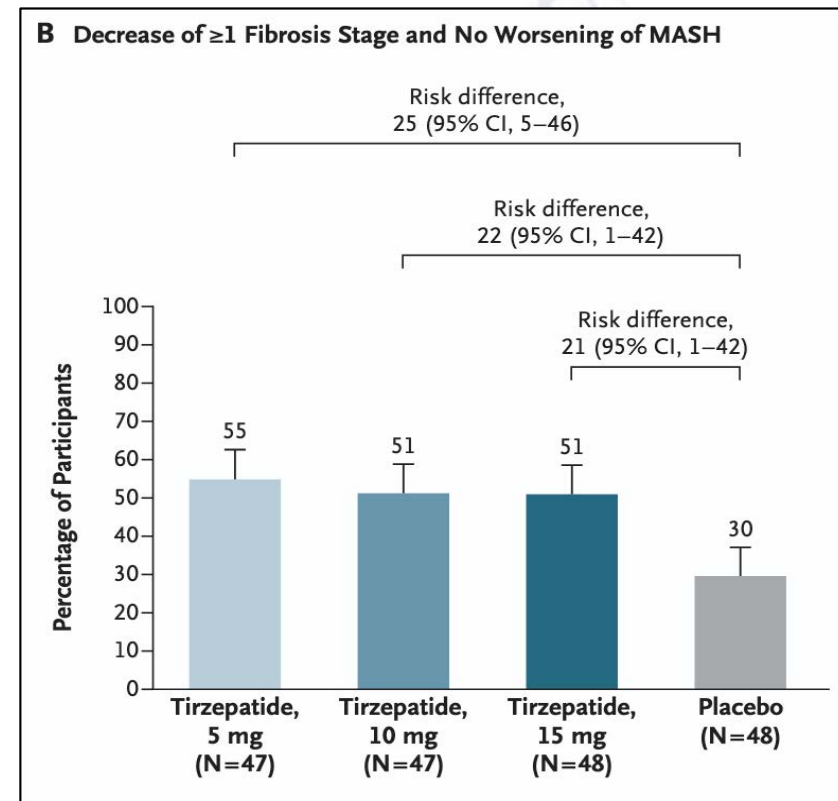
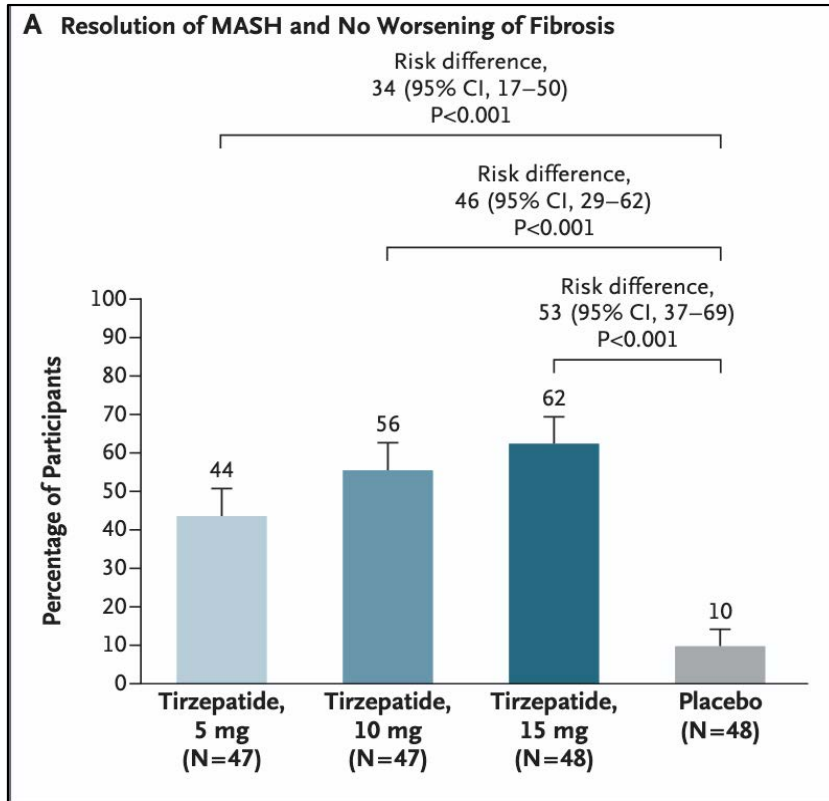
- Phase 2 trial
- Dual GLP/GIP agonism

Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis



R. Loomba, M.L. Hartman, E.J. Lawitz, R. Vuppalanchi, J. Boursier, E. Bugianesi, M. Yoneda, C. Behling, O.W. Cummings, Y. Tang, B. Brouwers, D.A. Robins, A. Nikooie, M.C. Bunck, A. Haupt, and A.J. Sanyal, for the SYNERGY-NASH Investigators*

2024



- All 3 doses of tirzepatide show MASH reversal.
- Strong fibrosis signal!

Tirzepatide: Final Verdict?

- Phase 3 is currently enrolling!
- Be patient

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What is on the horizon?



GLP/glucagon and GLP/glucagon/GIP agonism in MASH

Agent	Trial Design	Results	Upcoming
Cotadutide 2021	Phase 2 834 patients 14 weeks	↓ AST/ALT ↓ Fib4 scores ↓ Pro-C3	Discontinued
Pemvidutide 2025	Phase 1 94 patients 12 weeks	Significant ↓ liver fat concentration (LFC) on MRI- PDFF	<i>Expected</i>
Survodutide 2024	Phase 2 293 patients 48 weeks	62% with MASH improvement ↓ Fibrosis	<i>LIVERAGE, Phase 3 in recruitment</i>
Retatrutide (triple) 2024	Phase 2 98 patients 48 week	Large ↓ LFC ALT/ELF no change	<i>TRIUMPH, phase 3 in recruitment</i>

Nahra R et al., Diabetes Care 2021
Sanyal et al., NEJM 2024
Harrison et al., Journal of
Hepatology 2025
Sanyal et al., Nature 2024

The future of PPAR agonism in MASH

Agent	Trial Design	Results	Upcoming
Saroglitazar (PPAR α/γ) 2024	175 patients 24 weeks	ALT/AST CAP scores LSM reduction*	<i>Phase 2 going</i>
Lanafibranor (PPAR $\delta/\alpha/\gamma$) 2021	Phase 2 247 patients	MASH resolution see at higher dose (1200mg) Improvement in fibrosis at high dose	<i>Phase 3 ongoing, Expect in fall 2026</i>

FGF21 Analogs in MASH

Agent	Trial Design	Results	Upcoming
Efruxifermin 2024	Phase 2 128 patients 24 weeks	Significant improvement in resolving both MASH and fibrosis	<i>SYNCHRONY</i> Phase 3 enrolling
Pegozafermin 2023	Phase 2 222 patients 24 weeks	Similar to above	<i>Phase 3</i> <i>enrolling</i>

Many others

- **Denifanstat** : Fatty acid synthase inhibitor being studied in phase 3
 - Improved MASH resolution and fibrosis
- **Fircostat**, Acetyl-CoA carboxylase inhibitor
- **GLP and FGF21** combination therapies

Summary

- MASLD is everywhere. We need help managing it.
 - Screening for clinically significant fibrosis now recommended for high-risk populations (Type 2 diabetes mellitus, obesity with metabolic complications, family history of cirrhosis, and significant alcohol use)
- FIB-4 (< 1.3), ELF (< 8), VCTE (LSM < 7), and MR elastography (< 3) are outstanding for identifying MASH
- Bariatric surgery should still be considered in patients with morbid obesity with high cardiovascular risk
- **Resmetirom** and **Semaglutide** have demonstrated efficacy in MASH reversal.
- More treatments are coming. Invite us back in a few years.
- We can prevent the number of patients developing MASH cirrhosis and HCC.

Case presentation: My patient

- 52-year-old man with severe obesity, HTN, and newly diagnosed DM (A1c 6.9) referred sonographic evidence of steatosis. Chart reviewed showed an elevated AST/ALT dating back to 2017. (7 years)
- 6' 2", 321lbs, BMI 41, worked at the FDA
- Very unhealthy diet and no exercise (too difficult)
- Little to no alcohol

Labs: AST **44 U/L**, ALT **59 U/L**, AP 109 U/L, total bilirubin 0.4 mg/dL, albumin 3.9 g/dL, Hb 13.1 g/dL, platelet count 219 K/cu mm

Case presentation: My patient

- FIB-4: 1.36, indeterminate
- MR elastography (07/2024):
 - Stiffness measurement: 4.1kPa (stage 3 fibrosis)
 - Fat quantification: 26%
- Management:
 - Started Semaglutide. Uptitrated to 1mg/week. Could not tolerate increase due to GERD
 - 02/2025: 297lbs (BMI 38.1), AST 37, ALT 51. Started Peloton at home. **We agreed to start Resmetirom 100mg**
 - 10/2025: 282lbs (BMI 36.2), AST 29, ALT 36
 - 01/2026: AST 24, ALT 33. Repeat MR elastography
 - Stiffness measurement: 3.4kPa (stage 1-2 fibrosis)

Thank you

