

# MASLD / MASH: Core Concepts & Cutting Edge

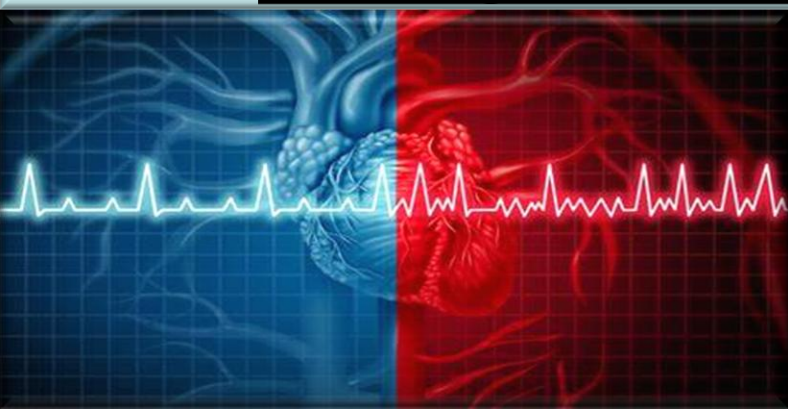
## An 'Unrecognized' Public Health Crisis

**'Navigating the Maze': Growing Public Health Care Challenge Affecting Millions**

**Navigate Complexities MASLD/MASH Evolving Clinical Landscape**

**What Clinical Outcomes Most Concerned About For Patients With MASLD/MASH?**

**'Turning the Tides' For the Future Making What is Invisible... Visible**



The Link Between

Obesity and

Cancer



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**Kalamazoo, Michigan**

**MOA Spring Conference – Troy 5/15/2026 5 PM**

**Fatty Liver Disease**

**A Silent Killer**



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**Prediabetes**  
is **NOT** a warning.

It's late-stage insulin resistance.

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# What Was Quietly Destroying The Doctor?

- ❌ **Constant Snacking**: Eating Every 2-3 Hours Kept Insulin Elevated. The Liver Never Stops Making Fat. That 3pm Granola Bar? Triglyceride Spike.
- ❌ **Ultra-Processed Foods**: Raise Triglycerides Even at Normal Calories. My "Low-Fat" Yogurt Was Packed With Sugar.
- ❌ **Late-Night Carbs**: Post-Shift Cereal Went Straight to Liver Fat When Metabolism Was Slowest.
- ❌ **Alcohol As Stress Relief**: Liver Converts it to Triglycerides Like Sugar.
- ❌ **Sleep Deprivation**: One Week of 6-Hour Nights Disrupts Insulin Signaling. Fat Storage Overdrive.



# What Actually Worked?

✓ 30-40g Protein Breakfast: (Eggs, Plain Greek - Yogurt, Avocado).

Stack

✓

Dro

✓

✓

Trig

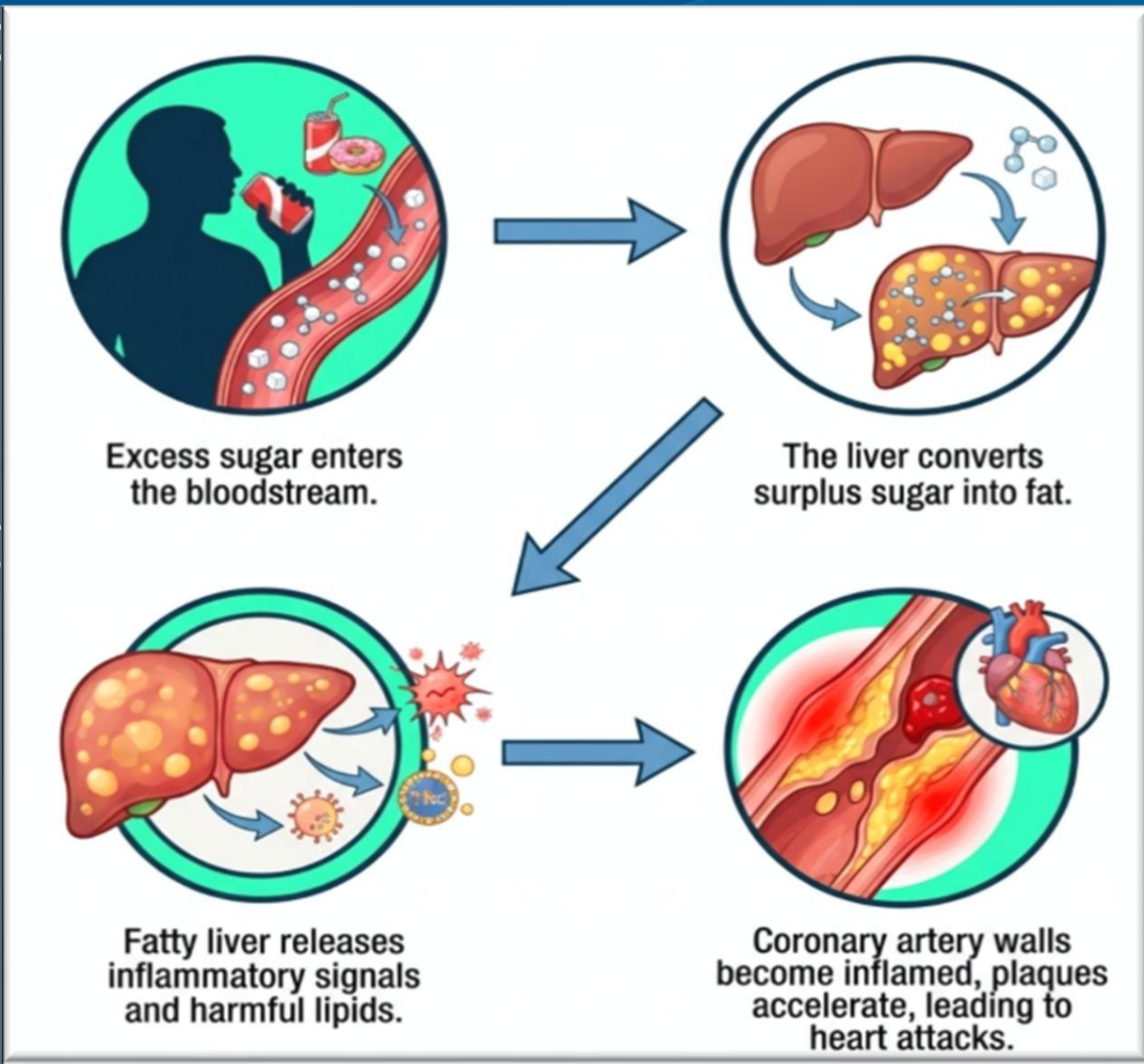
✓

Abs

✓

Fat

✓



# INSULIN

**IR / Sugar & Heart Attacks: The Liver Connection**

We treat glucose. We ignore insulin.

les

r

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# What Are We Really Eating?

## Ultra-Processed Foods, Insulin Resistance & the Quiet

R

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& Preserv



**“Low fat” and “sugar free” are usually code words for chemically laden, overly processed, and unnatural. DON'T BE FOOLED!**



When You  
our,  
al Colors,

What is This Food

Body?



# Ultra-Processed Foods Aren't Designed for Metabolic Health

- ◀ Highly Processed Foods Are Engineered For:
  - Long Shelf Life
  - Maximum Palatability
  - Repeat Consumption
- Not For Blood Sugar Stability or Long-Term Metabolic Health.
- These Foods Digest Rapidly, Spike Blood Sugar, & Demand Large Insulin Responses, Often Multiple Times a Day.
- Over Time, This Constant Insulin Stimulation Teaches The Body to Stop Responding Efficiently to Insulin = Insulin Resistance.

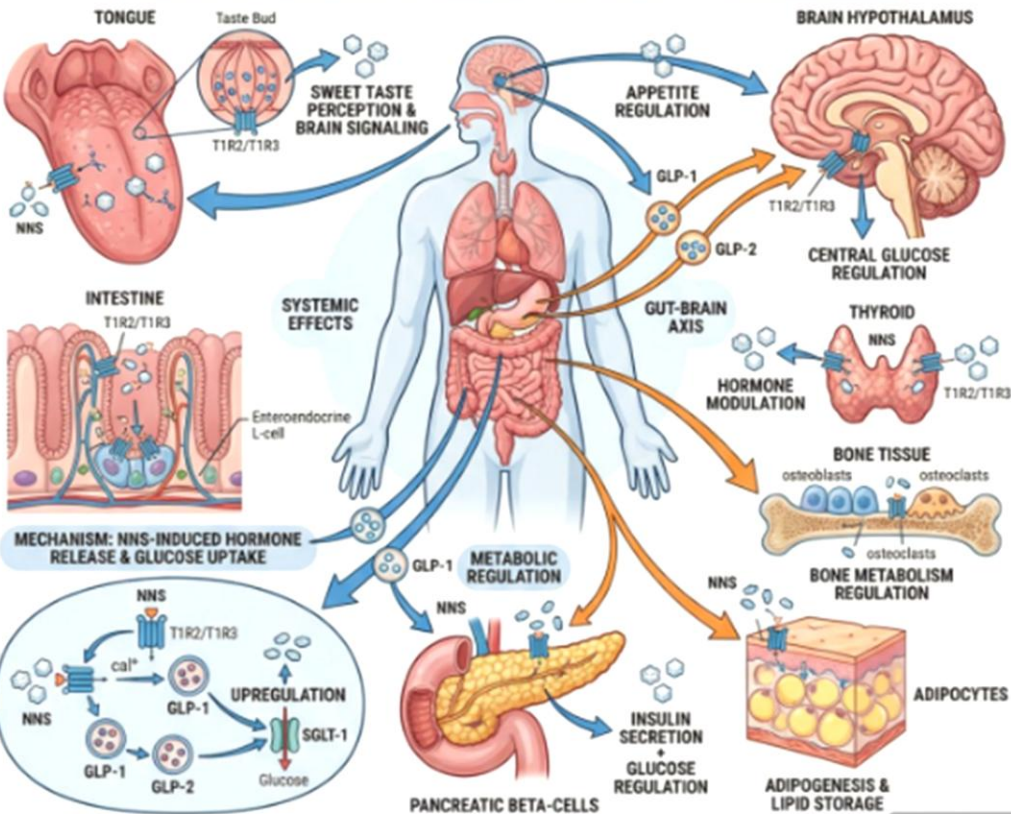


# Glycemic Impact of Non-Nutritive Sweeteners in Health and Type 2 Diabetes

## KEY BACKGROUND & RECOMMENDATIONS



## ANATOMICAL DISTRIBUTION & MECHANISMS OF SWEET TASTE RECEPTORS (T1R2/T1R3) WITH NNS INTERACTION



# Miss the Bigger Picture Same Calories Can Produce Very Different Hormonal Outcomes.

***Instead of Asking:***  
**“How Many Calories is This?”**  
**Try Asking:**  
**“What is This Food Teaching My Metabolism To Do?”**  
**Because Food Doesn’t Just Fuel Us.  
It Programs Us.**

How Food Impacts Insulin, Blood Sugar, & Hormones That Support Health Rather Than Quietly Hijacking Real Food, Stable Blood Sugar, & Metabolic Homeostasis of Health Dramatically.

✓ The **Most Dangerous** Things I've Seen About Liver Disease is This:

✓ **Most People Feel Completely Normal in the Early Stages. And That's Exactly Why Liver Disease is Often Detected Late.**

✓ Globally, Liver Disease is Rising Rapidly.

✓ **Closely Linked to Obesity, Insulin Resistance, Poor Metabolic Health, & Ultra-Processed Diets.**

✓ What Concerns Me Most is How Silent it Can Be Early On. Patients Often Expect Liver Problems to Feel Obvious.

✓ In Practice, The Early Signs are Usually Subtle & Easy To Dismiss:

- Persistent Fatigue
  - Brain Fog
- Bloating or Abdominal Heaviness
- Gradual Weight Gain Around The Abdomen
  - Elevated Triglycerides or Blood Sugar
- Mild Abnormalities On Routine Bloodwork

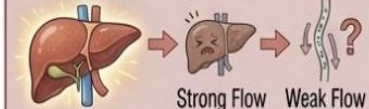
## **EARLY SIGNS OF LIVER PROBLEMS**

(What I pay attention to clinically)

EARLY LIVER DISEASE IS OFTEN SILENT. AND MANY PEOPLE HAVE NO IDEA THEY HAVE IT.

### 1 LIVER-RELATED SIGNS

- Persistent fatigue
- Brain fog / poor concentration



→ Sign of Poor Metabolism

### 2 METABOLIC & INFLAMMATORY SIGNS

- Mildly elevated liver enzymes
- High triglycerides + rising blood sugar
- Elevated inflammation markers



→ SIGNAL OF LIVER STRESS

### 3 ABDOMINAL & TOLERANCE SIGNS

- Increased abdominal fat (visceral)
- Bloating or abdominal heaviness
- Poor tolerance to alcohol or heavy meals



→ Linked to Metabolic Dysfunction

### 4 DERMATOLOGICAL & SYSTEMIC SIGNS

- Darkening around neck/armpits (insulin resistance signs)
- Poor sleep + low recovery



→ Signals Metabolic Strain

**KEY CONTEXT:** Non-alcoholic fatty liver disease (NAFLD) now affects ~30% of adults globally.

- The encouraging part: Early liver dysfunction is often reversible when identified early.
  - That's why recognizing subtle signs matters.
- 👉 Prevention is far easier than advanced reversal.



### REBOOT YOUR GUT-LIVER AXIS

- What commonly drives it:
- Excess visceral fat
  - Insulin resistance
  - Ultra-processed diets
  - Constant eating/snacking
  - Poor sleep
  - Low muscle mass
  - Sedentary lifestyle

- ✓ Individually, None of These Immediately “Feel” Like Liver Disease. But Physiologically, They Often Point Toward Metabolic Dysfunction Affecting the Liver.
- ✓ The Liver is Deeply Connected to:
  - Blood Sugar Regulation
  - Fat Metabolism
  - Inflammation
  - Hormone Processing
- ✓ So Early Liver Dysfunction Rarely Stays Isolated.
- ✓ **Another Major Misconception:** People Assume Liver Disease Only Happens From Alcohol. Today, I See Fatty Liver Routinely in:
  - > Non-Drinkers
  - > Younger Adults
  - > People Who Consider Themselves “Fairly Healthy”
- ✓ Because Modern Liver Stress is Increasingly Driven by:
  - Excess Visceral Fat
  - Constant Eating Patterns
  - Liquid Calories
  - Poor Sleep
  - Low Muscle Mass
  - Insulin Resistance
- ✓ The **Good Part** is: Early Liver Dysfunction Is Reversible When Identified Early.

**Simple Framework With Patients to Help Identify:**

- Early Warning Signs
- Metabolic Patterns Linked to Liver Stress
- What Deserves Attention Before Advanced Disease Develops

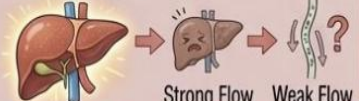
## 🍷 EARLY SIGNS OF LIVER PROBLEMS ⭐

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What commonly drives it:

→ Excess visceral fat	→ Constant eating/snacking
→ Insulin resistance	→ Poor sleep
→ Ultra-processed diets	→ Low muscle mass
	→ Sedentary lifestyle

# Disclosures

- ❖ I Have the Following Financial Relationships to Disclose:
- ❖ Pharmaceutical Based Research On Safety, Efficacy, Outcome Trials And
- ❖ Speaker's Bureau for: BI / Lilly, Abbott, DexCom, Novo-Nordisk, Corsept Therapeutics, Abbvie, Amgen
- ❖ All Planners, Reviewers, And Course Directors Have No Relevant Financial Relationships With ACCME-Defined Commercial Interests.
- ❖ My Presentation Today Will Be Fair, Balanced, Free of Commercial Bias & Fully Supported By Scientific Evidence



# Objectives

- 1. Define NAFLD (Now MASLD) & Its Different Stages, Including Non-Alcoholic Steatohepatitis (Now MASH) & Fibrosis
- 2. Explain the Pathophysiology of MASLD Including the Role of Insulin Resistance & Fat Accumulation in the Liver (More Than Just 'No Alcohol')
- 3. Recognize Clinical Manifestations, Burden & Associated Complications of MASLD / MASH
- 4. Identify Patients at High Risk for MASH for Screening & If Needed Diagnostic Work-Up
- 5. Incorporate Guidelines, Best Practices & Timely Multidisciplinary Care into the Management of MASH with its Metabolic Comorbidities
- 6. Discuss New & Emerging Therapies for MASH with Respect to Mechanisms, Clinical Trial Data & Recommendations or Potential Place in Therapy

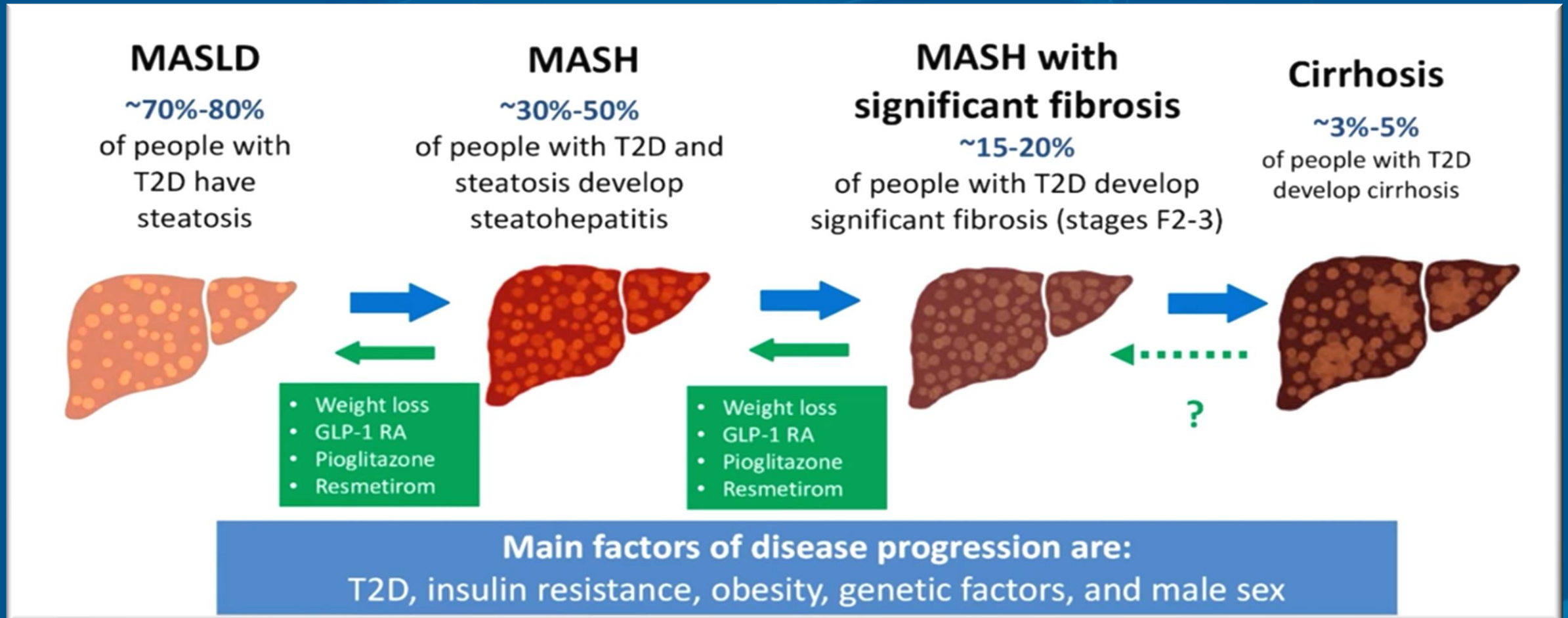


# History of NAFLD & NASH

- ❖ A Casual Relationship Btw Hepatic Fat Accumulation & The Development of Fibrosis Had Been Observed in 1839 Followed By The Microscopic Finding That 'Fatty Degeneration' Develops Close To Inflammatory Deposits & Scarring
- ❖ The Term 'Fatty Liver Hepatitis' First Appeared in 1962 in German Literature While The Term 'Non-Alcoholic Steatohepatitis' (NASH) Was Coined in 1980. Defined By The Histopathological Hallmarks of Steatosis, Lobular Inflammation, Liver Cell Damage With Ballooning – Eventually Appearance of Mallory-Denk Bodies.
- ❖ Why Should We Care?



# Prevalence of MASLD and MASH



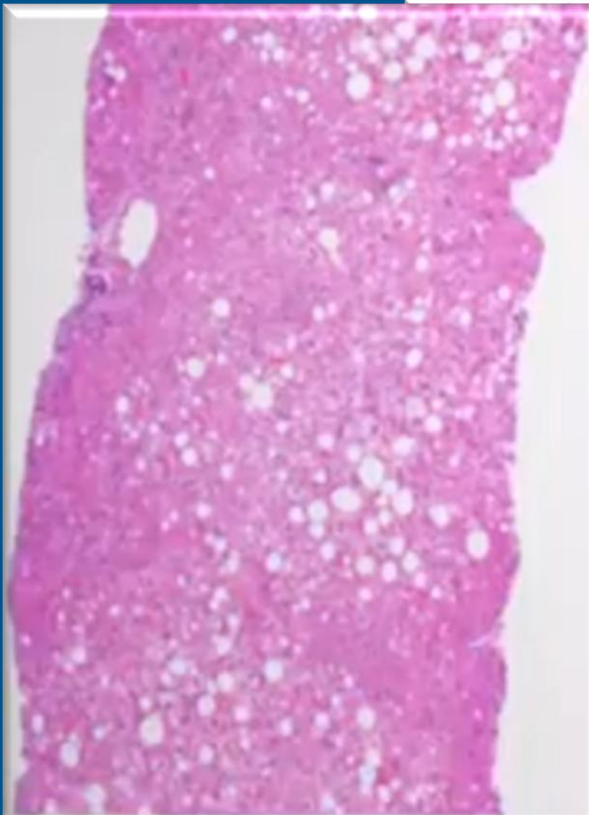
Based on a Meta-Analysis of 35 Studies Estimating Prevalence of 3% in General Practice Setting and 14% in Inpatient Setting/Referrals for Biopsy.

Wang. Front Pharmacol. 2024;14;13362216. Miao. Trends Endocrinol Metab. 2024;35:697.

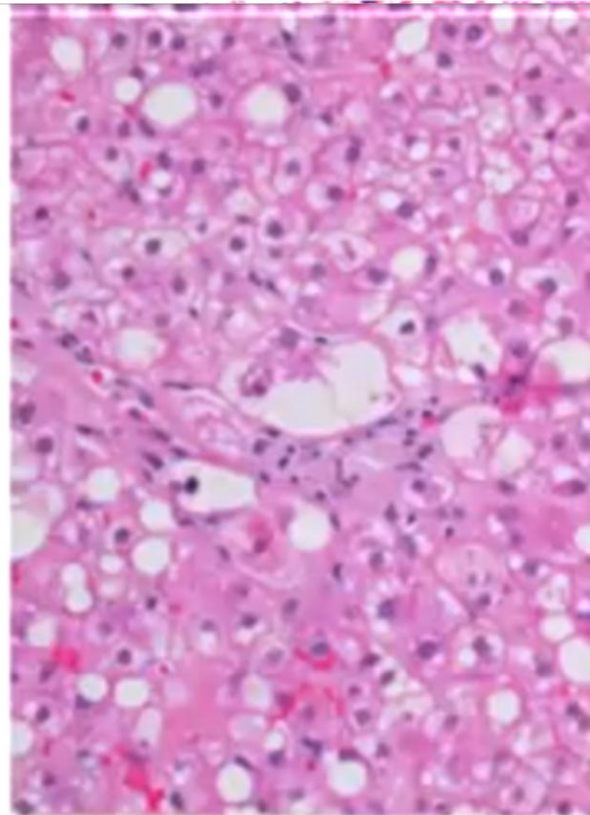
Lee. J Clin Med. 2023;12:7634. Owrangi. Ailment Pharmacol Ther. 2025;61:433.



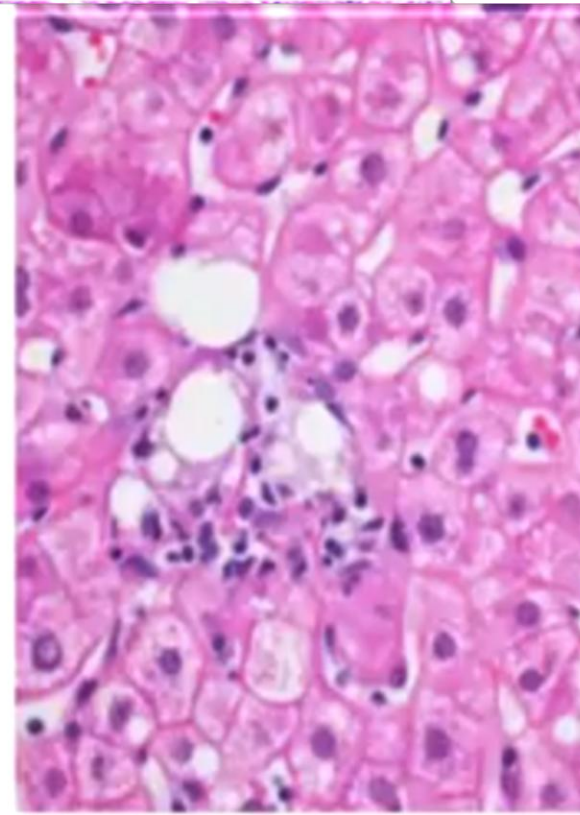
# If You Treat Diabetes & / Or Obesity, It Is Important To Understand Fatty Liver Disease: It Is Common & It Can Be Deadly



Steatosis  
(0-3)



Ballooning  
(0-2)



Lobular Inflammation  
(0-3)

**GRADE = NAFLD Activity Score (NAS) of 0 to 8**

**New York Times**

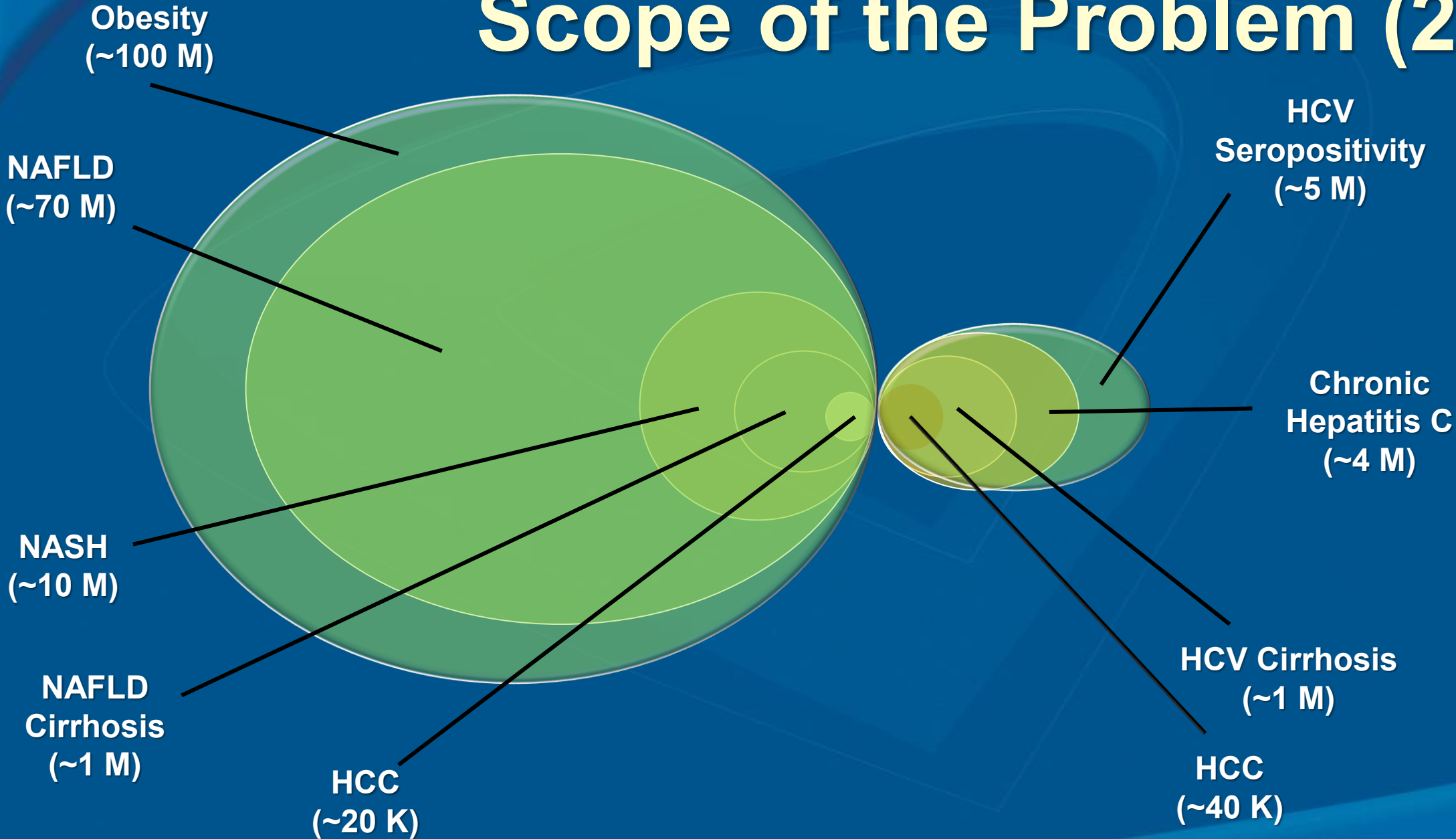
GIVE THE TIMES

## Fatty Liver Disease Can Be Deadly

### Ballooning Of Hepatocytes Best Prediction of Fibrosis

are thought to be serious liver disease as MASLD. It is possible if you catch

# Scope of the Problem (2014)



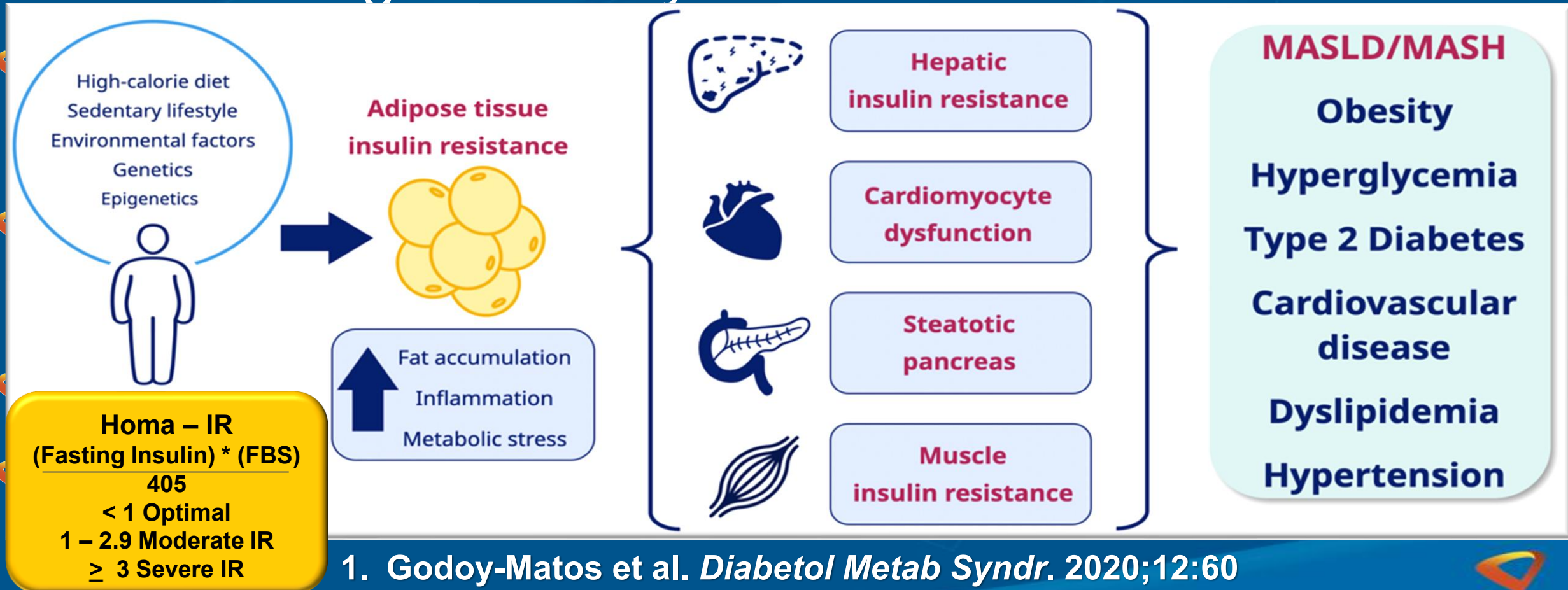
# Future Projections

- ▶ Trends In Liver Transplantation: 2014 Hepatitis C Was the Leading Cause. Now Curable
- ▶ Today There is a Competition Btw ETOH Liver Disease / NASH Cirrhosis For The Leading Cause of Transplantation
- ▶ Global Epidemic of Obesity Fuels Metabolic Conditions – Increasing the Clinical / Economic Burden of NAFLD.
- ▶ Models Predict Growth ~ 30% in Total NAFLD Cases by 2030
- ▶ NASH Prevalence Predicted To Increase ~ 50% While Advanced Liver Dz Will More Than Double As A Result of Ageing Western Populations



# More Than A Liver Dysfunction

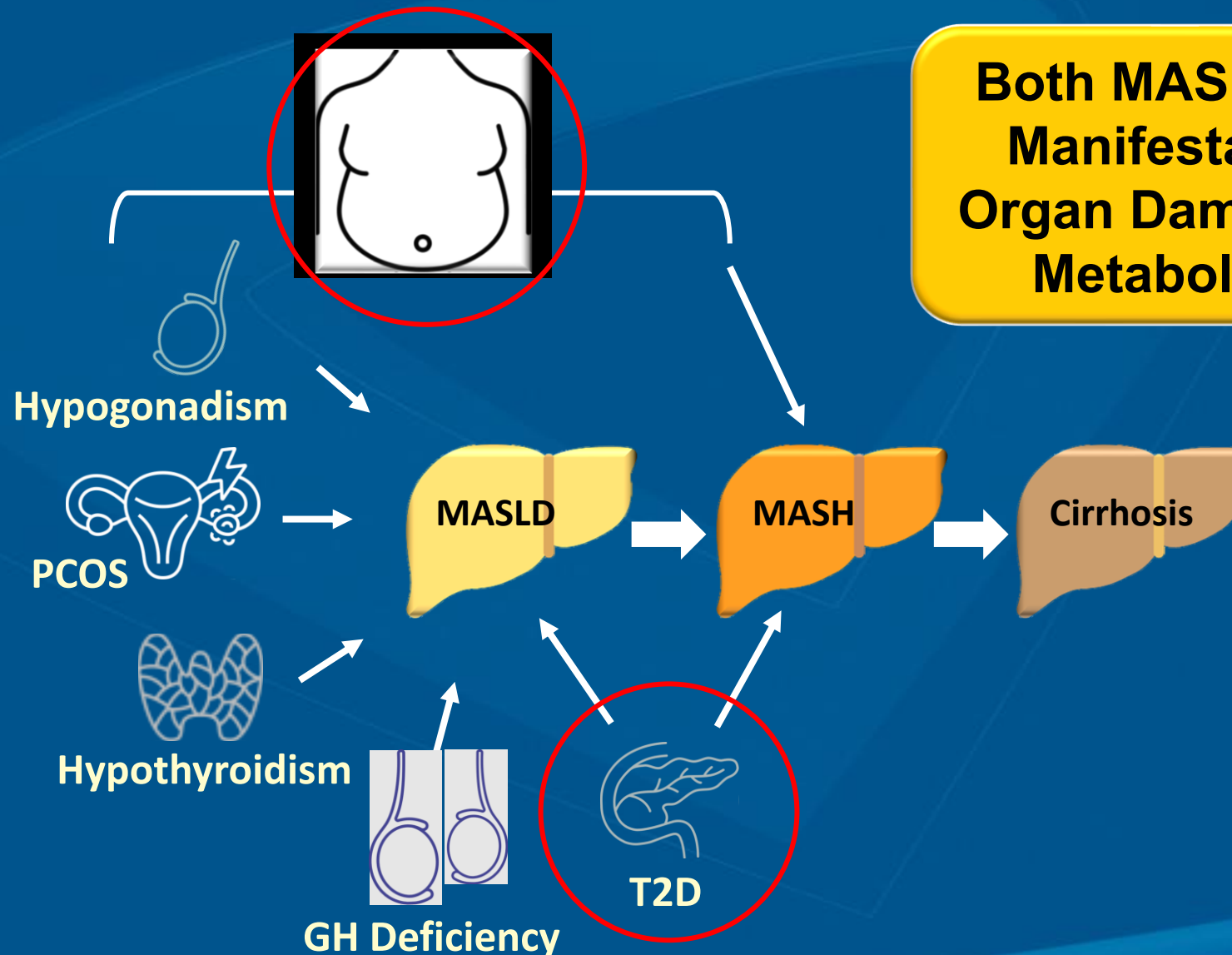
- ▶ Reclaim This Condition & Route It Where It Belongs
- ▶ Name Change Is Timely



1. Godoy-Matos et al. *Diabetol Metab Syndr.* 2020;12:60
2. Chakravarthy MV. *Endocrinol Diabetes.* 2020;3(4):e001122



# Endocrine Factors Associated With MASLD



# MALSD / MASH Is A Problem

MASH  
Inflammatory  
Subtype of  
MASLD

- ❖ Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) (Non-Alcoholic Fatty Liver Disease [NAFLD])
  - Most Common Cause Chronic Liver Disease.
  - Prevalence of MASLD in People with Obesity and/or T2DM is 70-80%.
- ❖ MASLD Can Lead to Metabolic Dysfunction-Associated Steatohepatitis (MASH) (Non-Alcoholic Steatohepatitis [NASH])
  - Which Can Lead to Cirrhosis and Hepatocellular Carcinoma (HCC).
- ❖ Early Screening for MASLD, & Treatment of Obesity and T2DM, Can Help in Preventing Progression to Cirrhosis and HCC.
  - ~ 5% of Persons with MASLD are Aware of Such. (~ 1 in 80 Dx ICD-10)

# MALSD / MASH Is A Problem

- ▶ Most Common Causes of Death in Patients with MASLD Overall are CVD Followed by Non-Hepatic Malignancy, Lastly Liver Dz.
  - Amount of Liver Fibrosis Identified Histologically in MASLD Strongly Linked to the Development of Liver-Related Outcomes and Death.
- ▶ MASLD is Under-Diagnosed and Under-Treated ...Why??
  - Clinicians Have Inadequate Knowledge of MASLD
  - Until Recently, Guidelines Varied Considerably / Inconsistent Guidance & Risk Stratification / Inconsistent Application In Clinical Practice as There was an Absence of a Unifying Strategy Encompassing All Disciplines in the Management of the MASLD Spectrum
  - Shift in the Understanding / Recent Progress in Understanding the Pathophysiology of MASLD / MASH

80 – 100 Million Americans

~ 2 in 3 Adults in U.S + Diabetes Tripled Since 2004

# Tsunami Silent & Deadly

MASLD: 30% and MASH: 5.3%

## Prevalence of Steatotic liver disease

(N=7,367 NHANES '17-'20) CAP score  $\geq 288$  dB

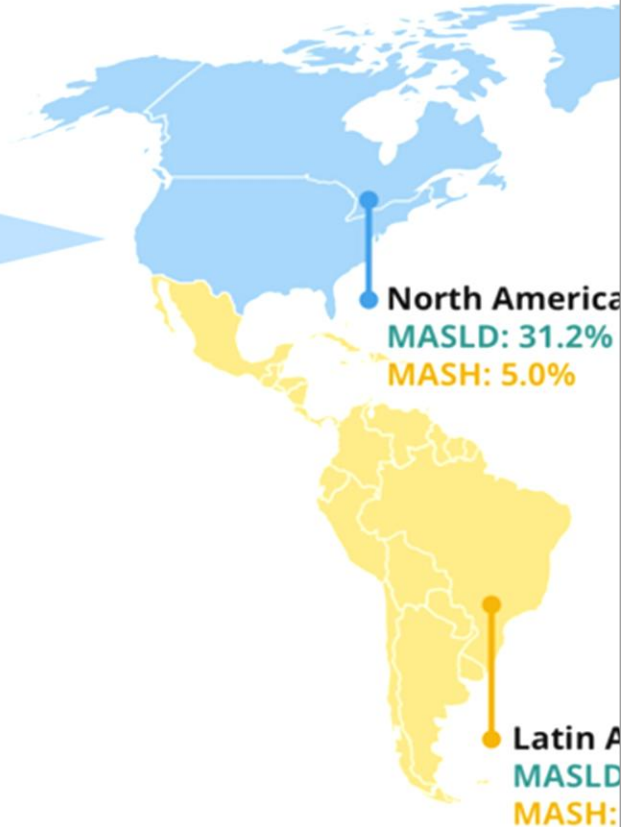


SLD  
34.2%



% of SLD  
92% MASLD  
6% MetALD  
2% ALD

~1 in 3 adults in the United States have MASLD



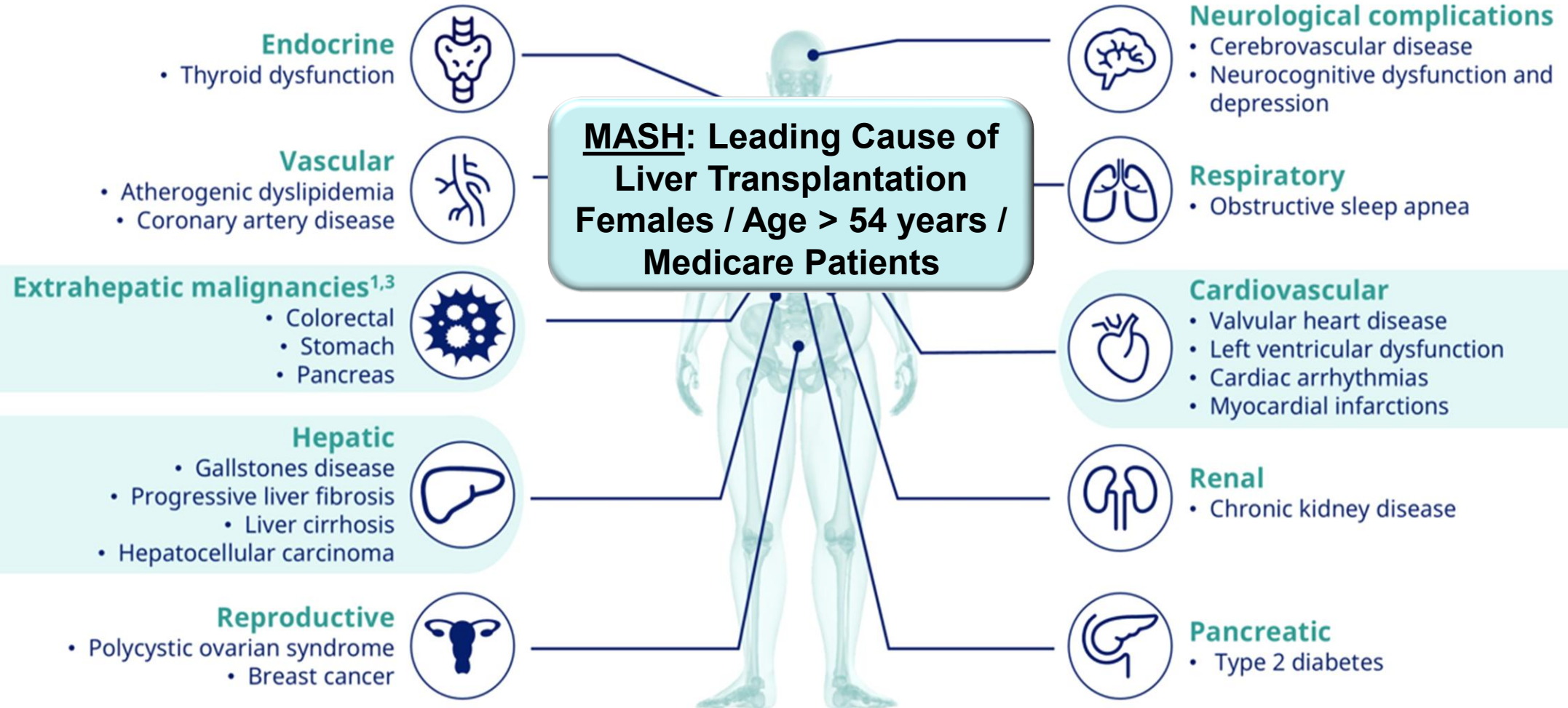
# What We Don't See In Obesity?

THIS IS ONLY THE BEGINNING

5.1% (1.8-8.4) Realize They Have A 'Liver Disease'

- Ticking Time Bomb
- Unrecognized Major Public Health Crisis
- Hiding In Plain Sight

Fatty Liver

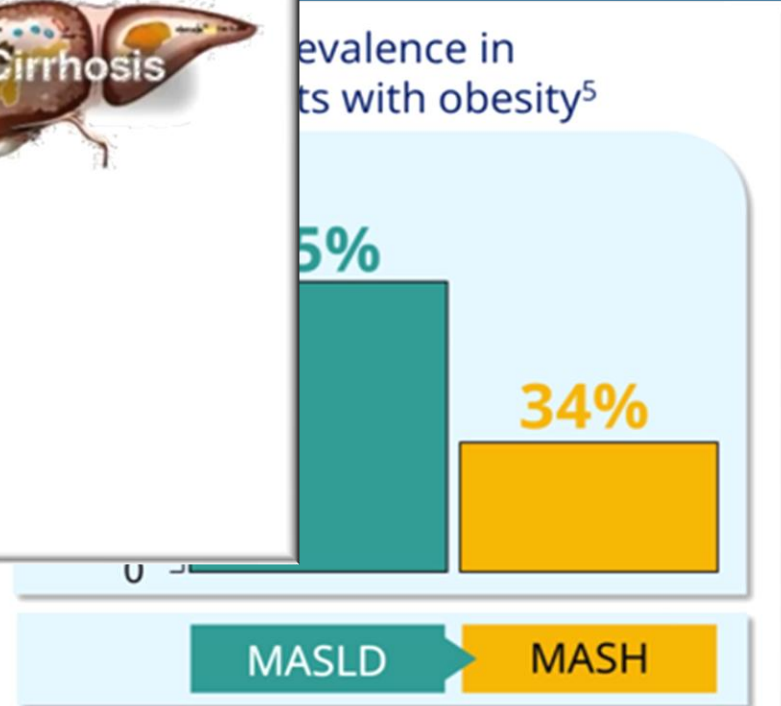
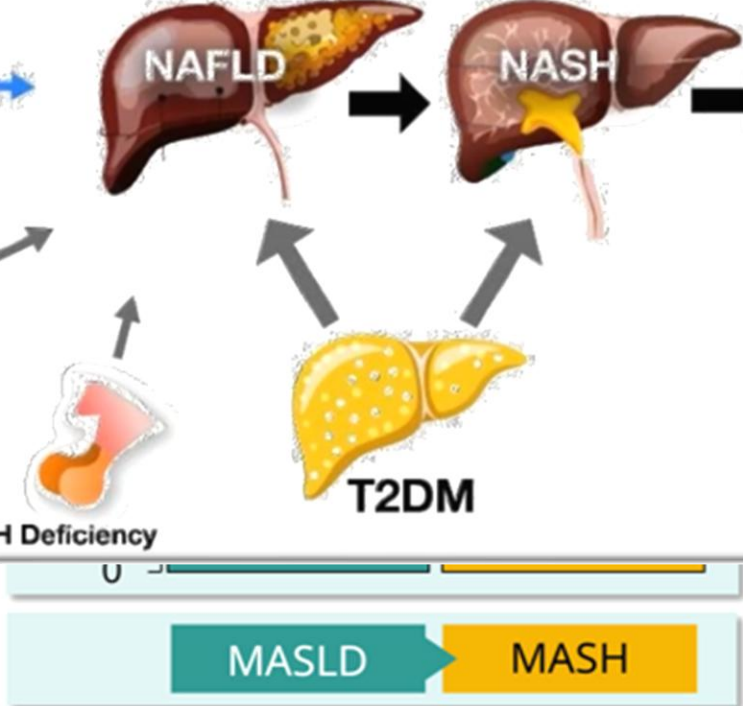
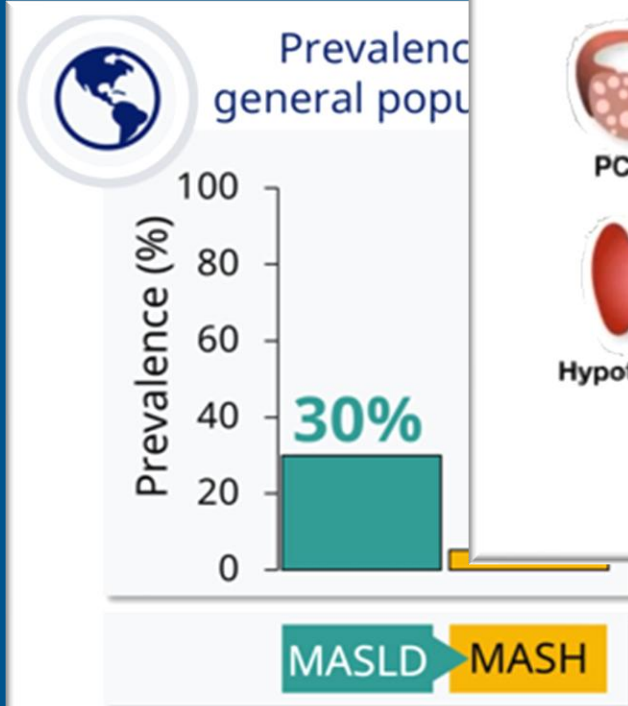
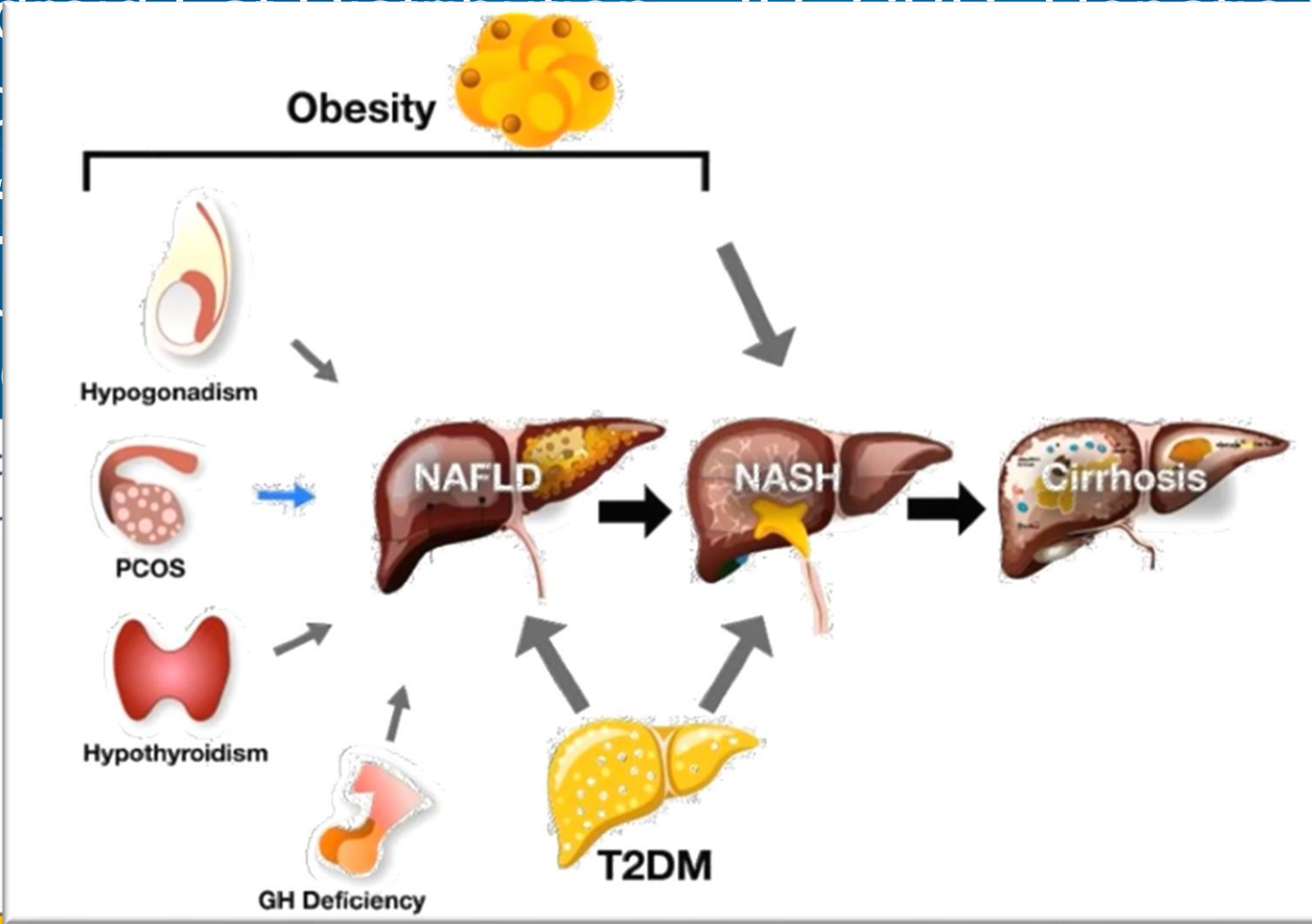


# Co-Morbid Conditions

Obesity: And... Fibrosis

Regardless of...

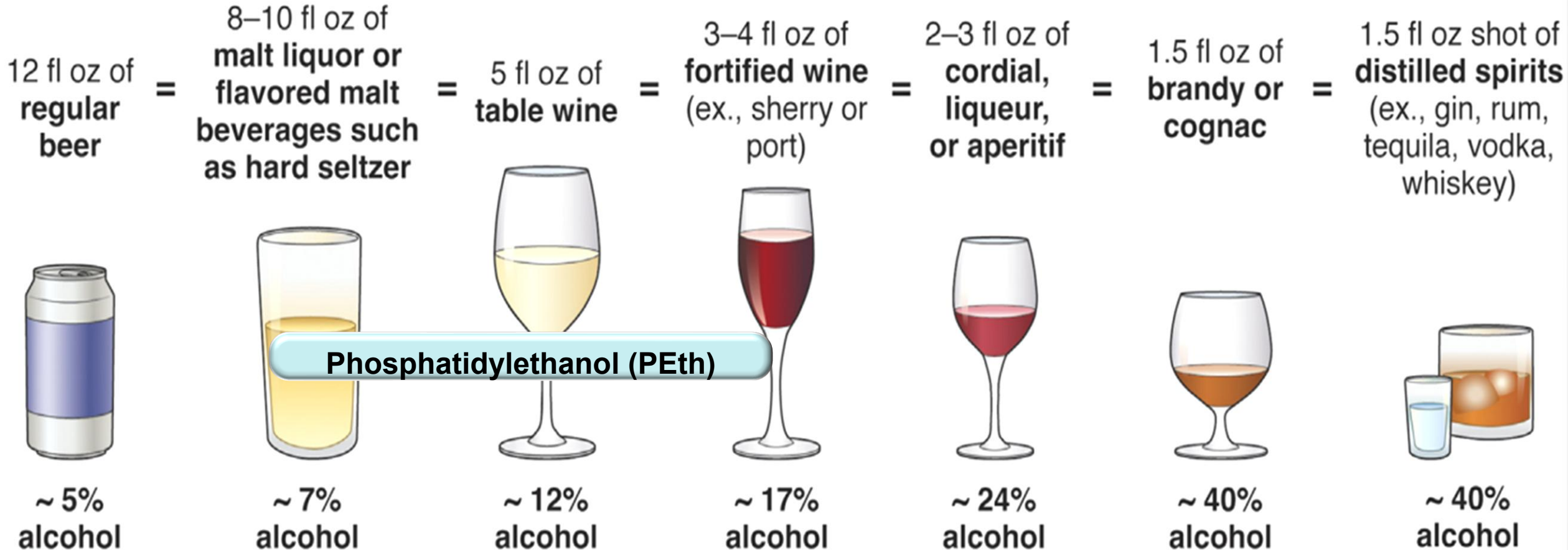
T2DM: Most Ass'd w Cellular Screened (H...  
 The Organs



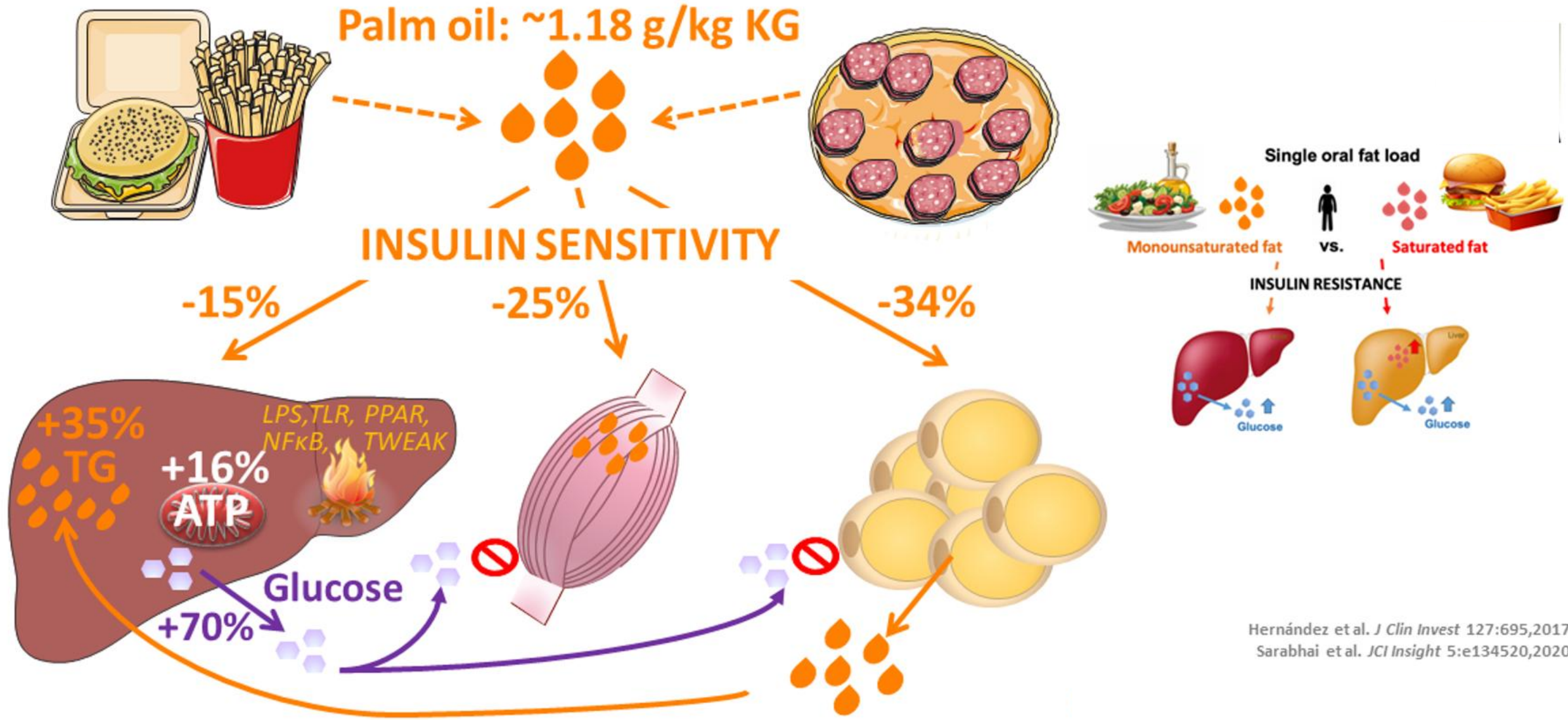
# Definition

> 5% Steatosis (Macrovesicular) & the Absence of Other Causes  
With Little or No ETOH (< 20 g/d W; < 30 g/d M)

## Standard drink (SD) in the US

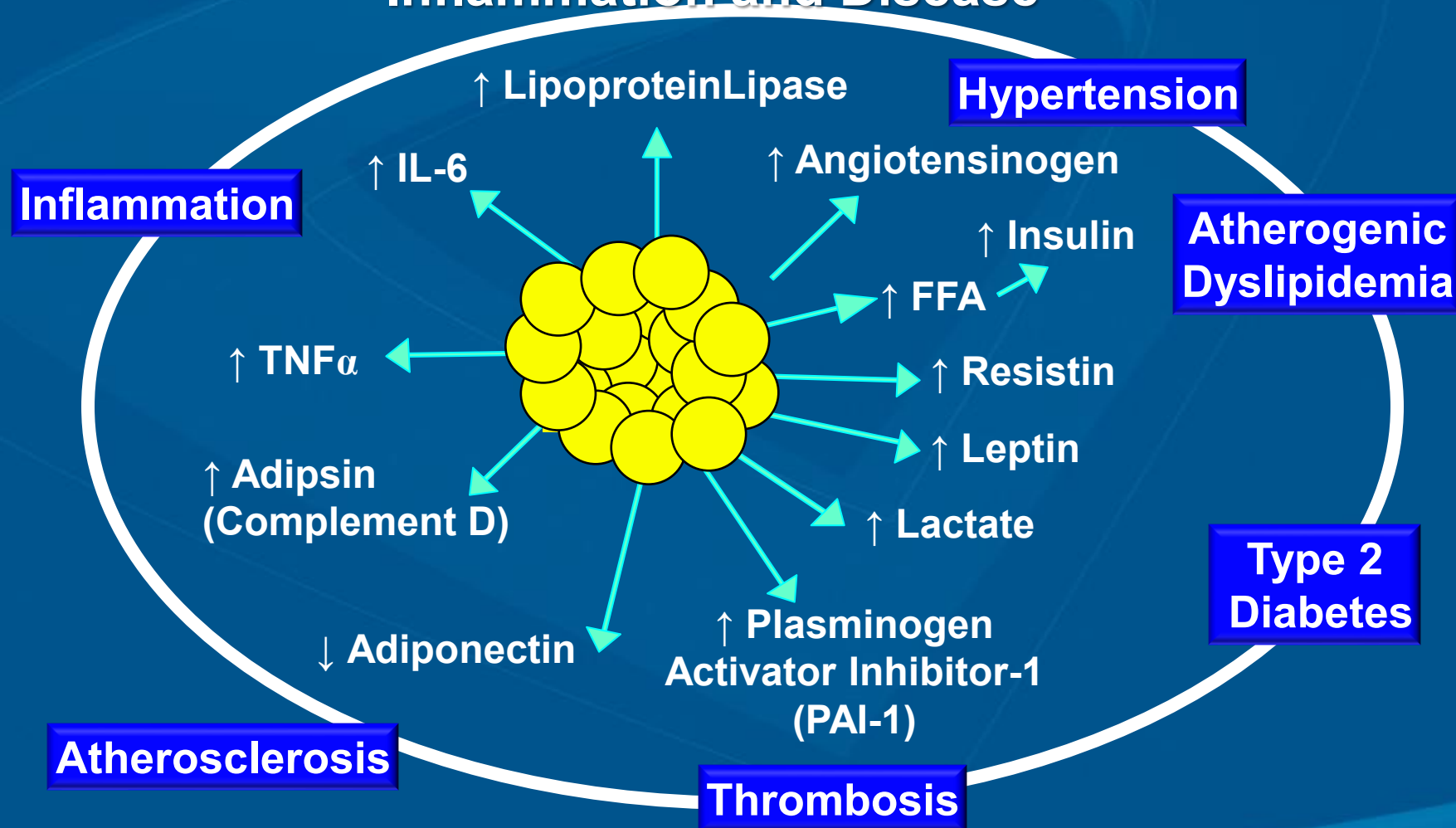


# Chronic Liver Injury: Disease Progression & Fibrosis In MASLD / MASH



# How Intra-Abdominal Visceral Adiposity Causes Disease?

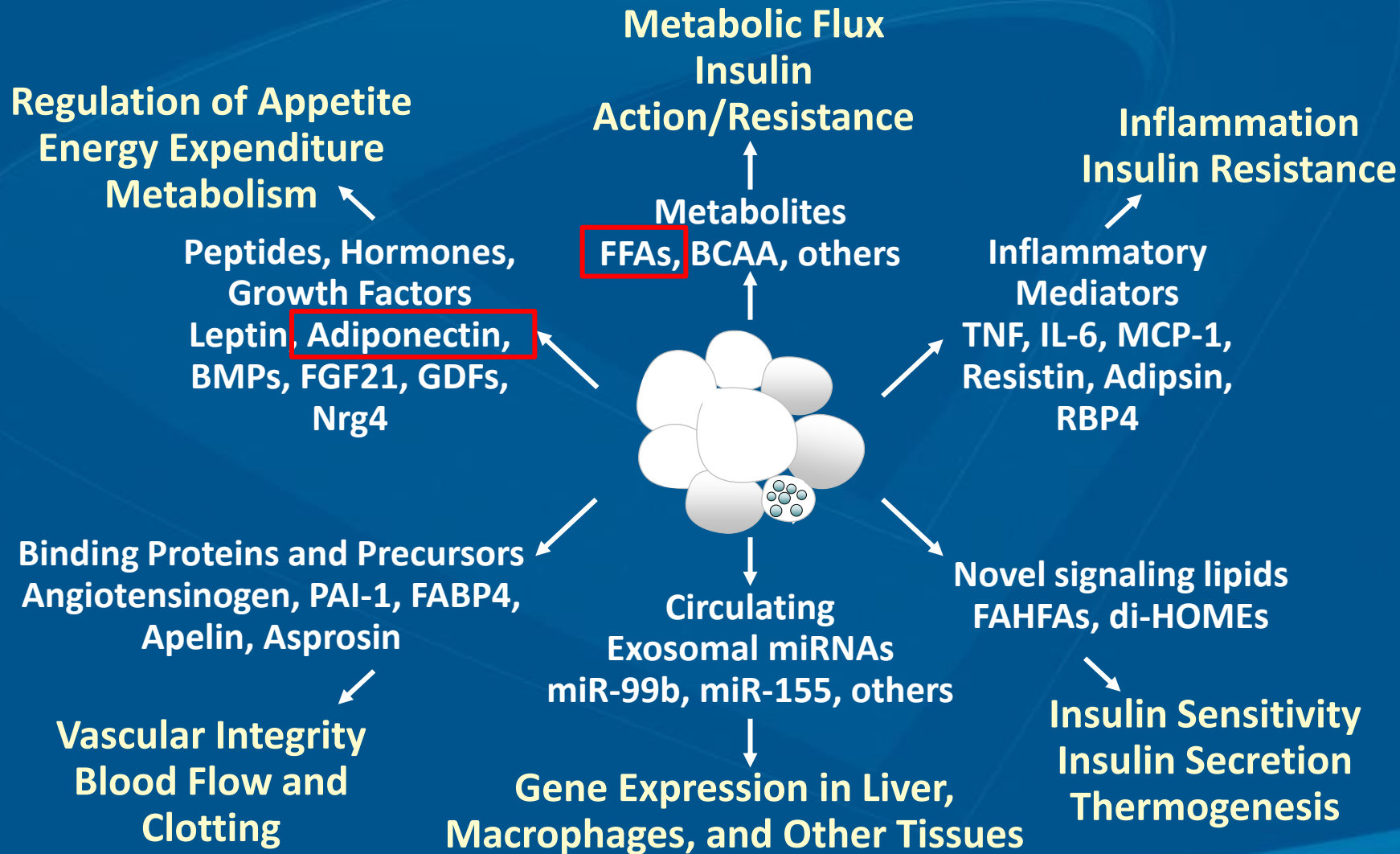
Increased Expression of Some Hormones, Suppression of Others, Leads to Inflammation and Disease



Lyon 2003; Trayhurn et al 2004; Eckel et al 2005

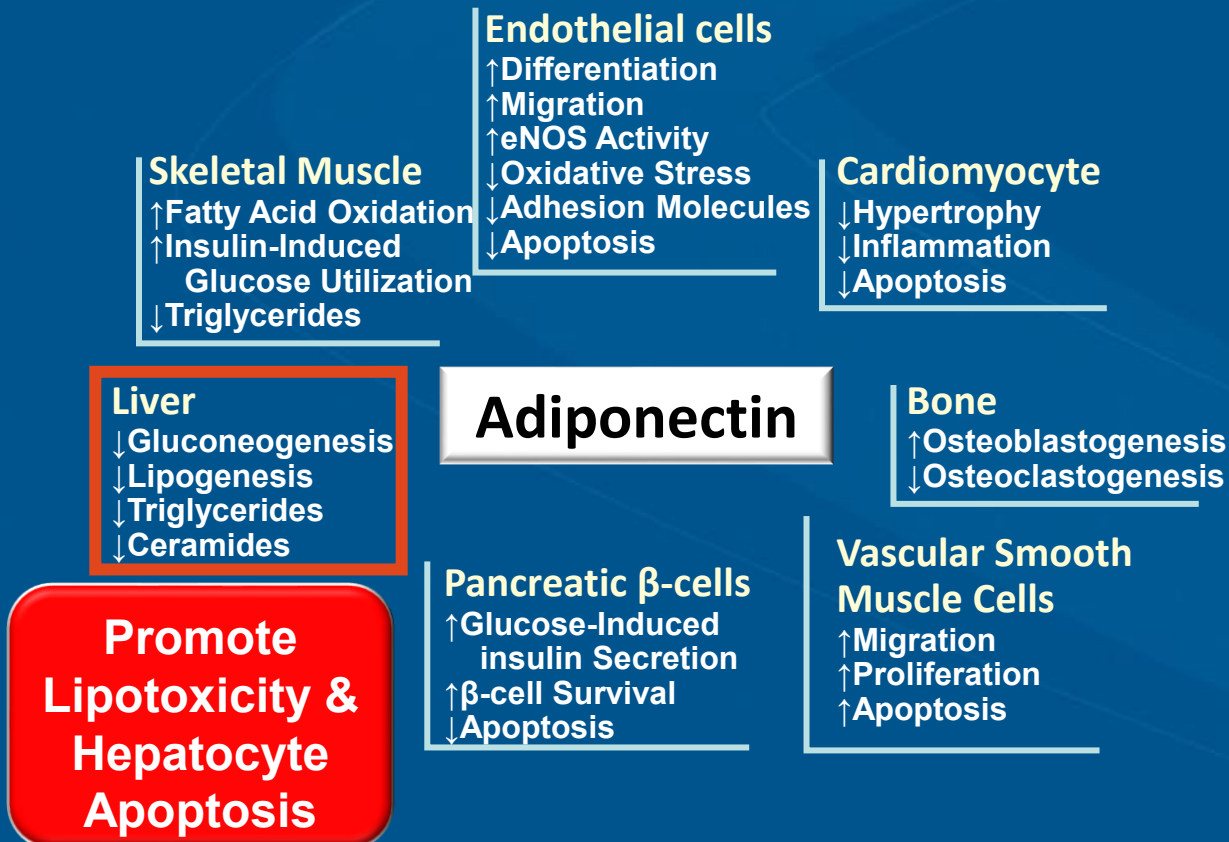


# Adipose Tissue: Dynamic Metabolic Organ

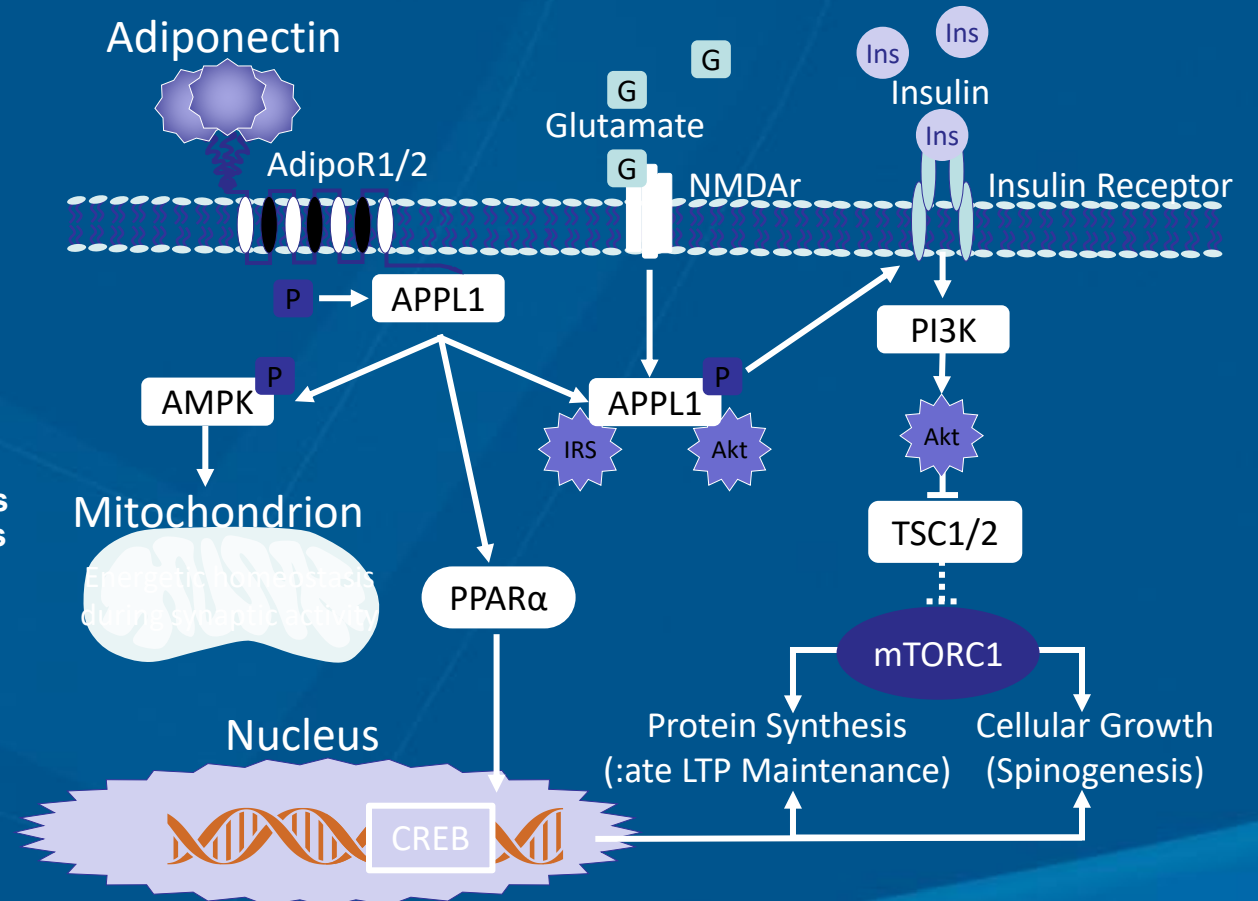


# Adipose Tissue as a Metabolic Organ: Adiponectin

## Tissue-Specific Adiponectin Signaling<sup>1</sup>



## Regulation of Neuronal Plasticity by Adiponectin Signaling<sup>2</sup>



1. Roy. Cell Biosci. 2021;11:77. 2. Formolo. Brain Plasticity. 2022;8:79  
<https://content.iospress.com/articles/brain-plasticity/bpl220138>.



# Stressed Adipose Tissue

## Normal Adipose Development

Normal Nutrition  
Normal Microbiome  
Adipocyte Growth Factors



Normal Adipose Development  
Different Adipocyte Populations and Other Adipocyte Precursors



Adipose Expansion  
Preadipocyte Proliferation  
Adipocyte Hyperplasia

## Healthy Adipose Expansion

Increased Number of Small Adipocytes  
Low inflammation



↑MCP-1  
Adipose Remodeling  
More Adipocyte Hyperplasia and Hypertrophy  
Changing Adipose Hormones Inflammation

## Metabolically Unhealthy Obesity

Insulin Resistance  
Ectopic Fat Deposits  
Metabolic Syndrome



↑di-HOMEs  
↓FAHFs  
Δ Exosomal miRNAs

↑Leptin  
↓Adiponectin  
Δ Other Adipose Hormones

↑TNF- $\alpha$ , IL-1 $\beta$ , etc

FFA

Preadipocyte subtypes



Mature adipocyte subtypes



Lipodystrophic adipocytes



Resident macrophages (M2)



Proinflammatory macrophages (M1)



Distinct types of macrophages



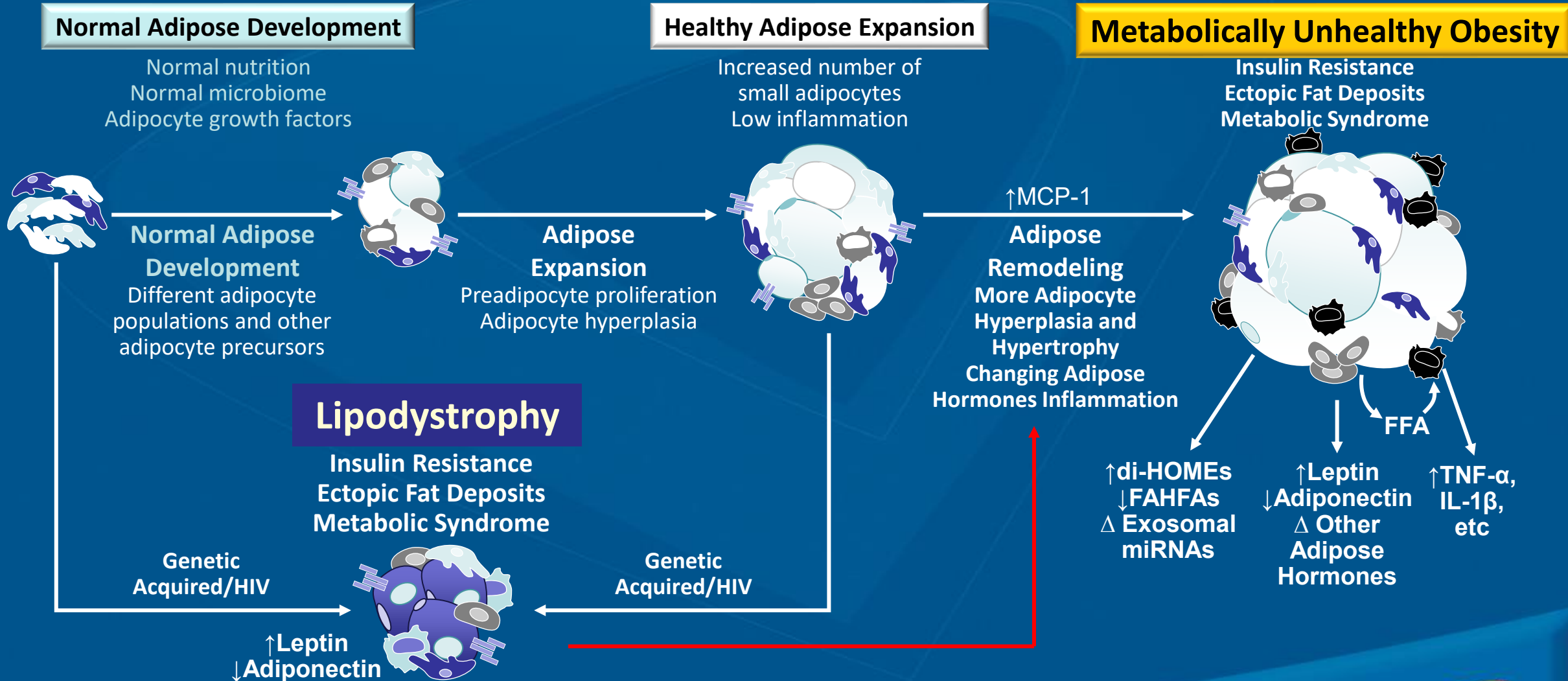
Stromovascular cells



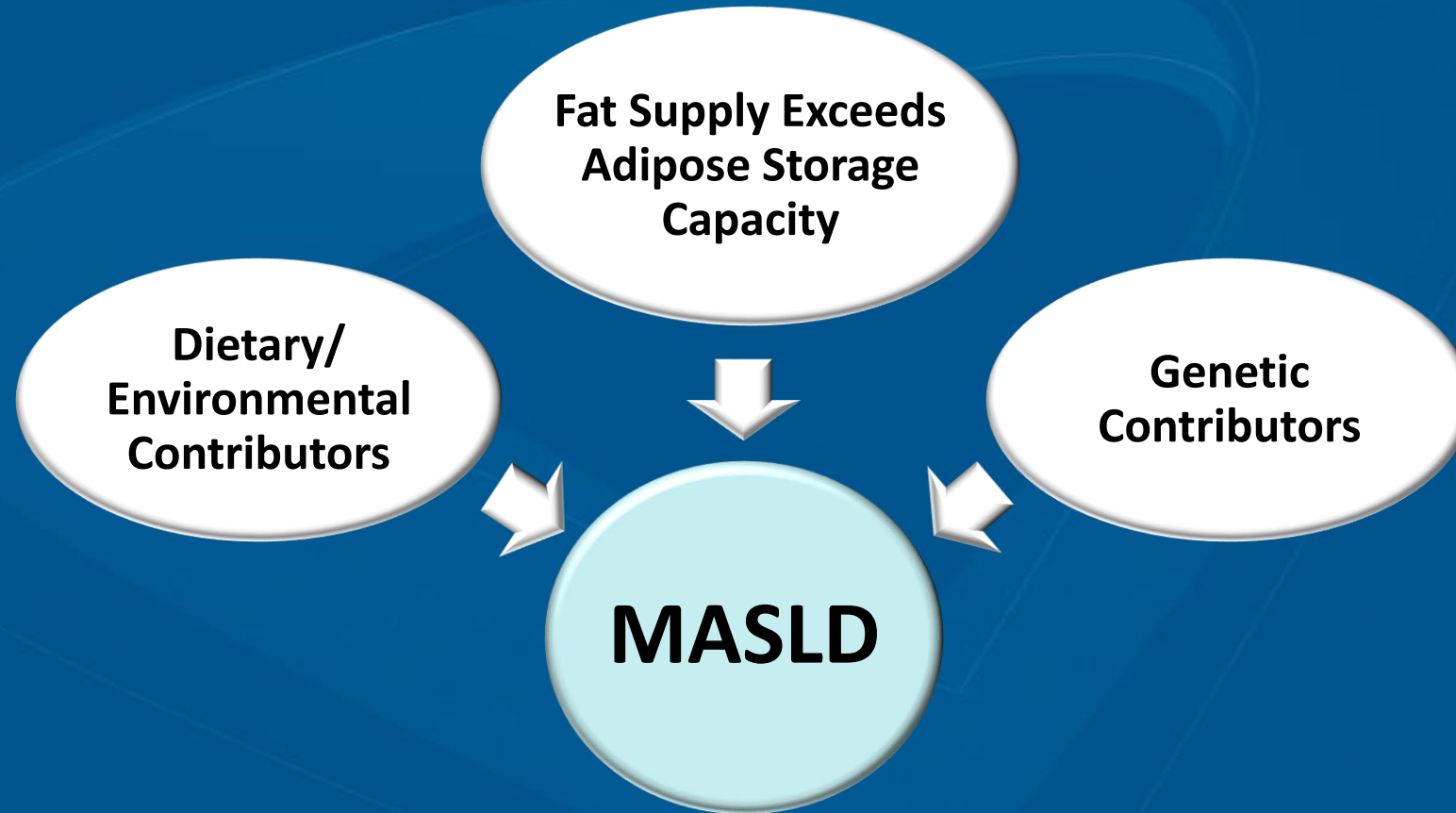
Insulin receptors



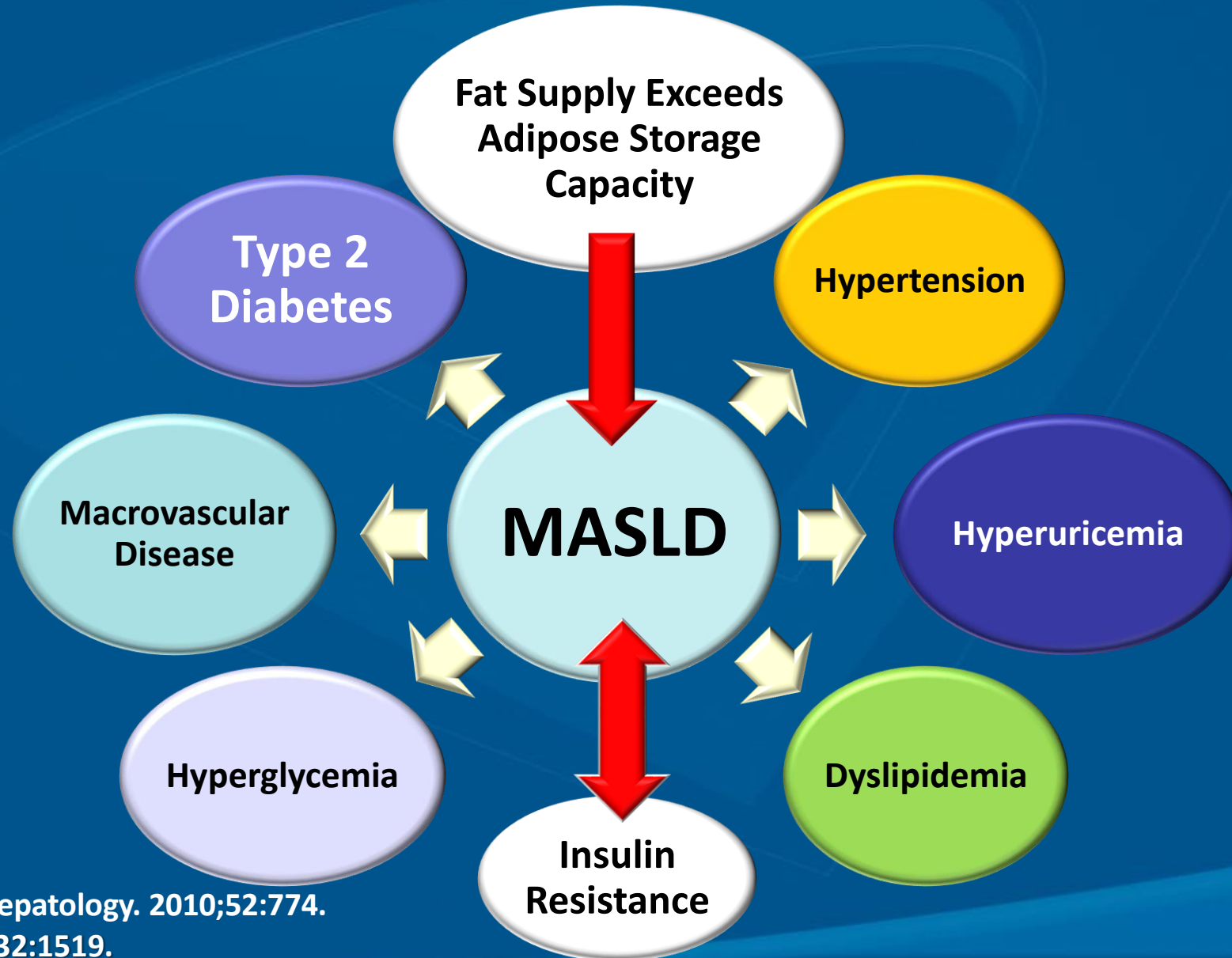
# Stressed Adipose Tissue



# MASH Pathogenesis: Role of Metabolic Comorbidities



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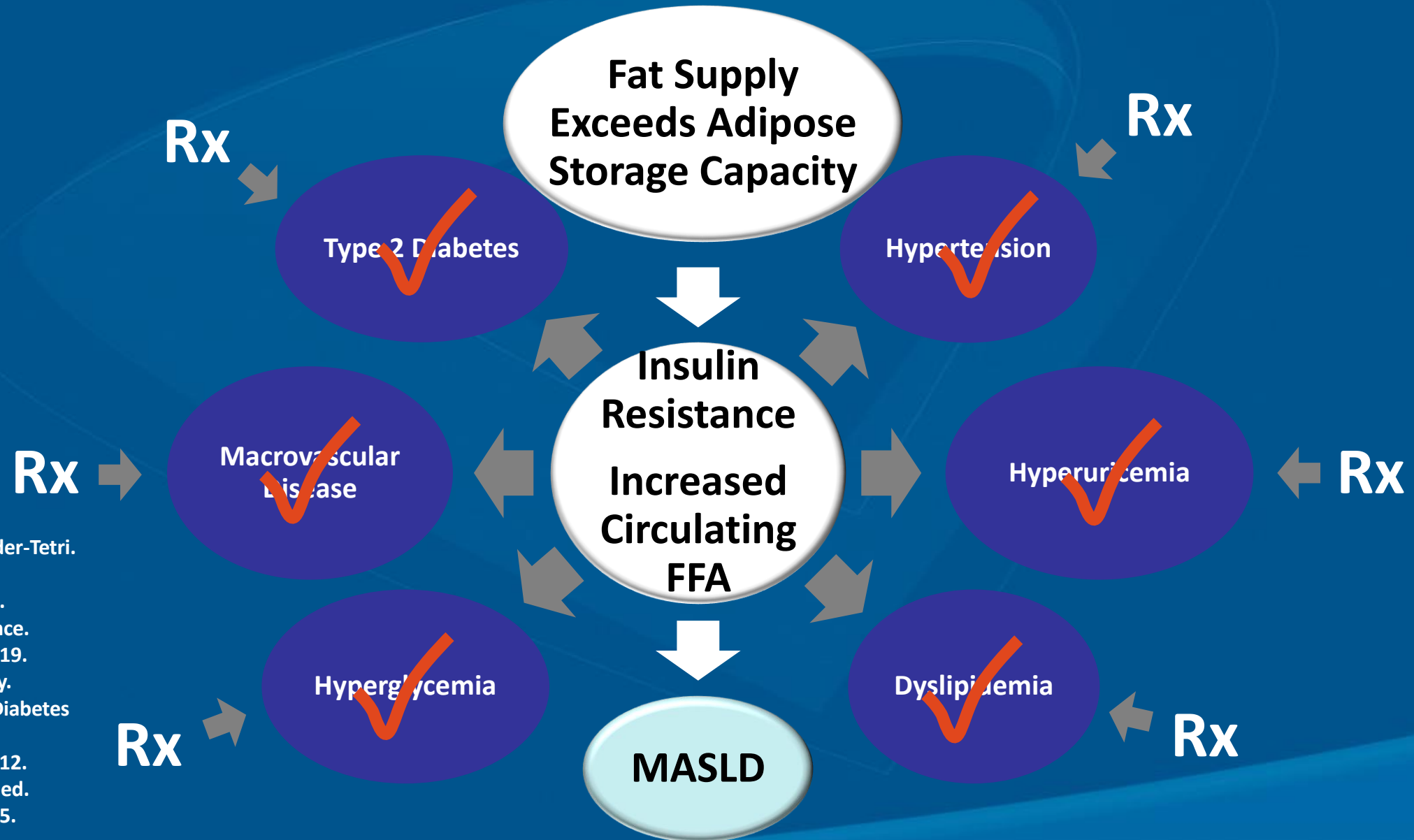


1. Neuschwander-Tetri. Hepatology. 2010;52:774.

2. Cohen. Science. 2011;332:1519.



# MASH Pathogenesis: Role of Metabolic Comorbidities



Neuschwander-Tetri.  
Hepatology.  
2010;52:774.  
Cohen. Science.  
2011;332:1519.  
Chakravarthy.  
Endocrinol Diabetes  
Metab.  
2020;3:e00112.  
Yen. J Clin Med.  
2022;11:1445.



# MASH Pathogenesis: Role of Metabolic Comorbidities

# INSULIN RESISTANCE

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The root cause of metabolic disease  
— still not a diagnosis.

Ideal  
Metabolic  
Rx?

Neuschwander-Tetri.  
Hepatology. 2010;52:774.  
Cohen. Science. 2011;332:1519  
Chakravarthy. Endocrinol  
Diabetes Metab. 2020;3:e0011  
Yen. J Clin Med. 2022;11:1445.

We treat glucose. We ignore insulin.



# Guideline Recommendations: Who Is at Risk for MASH and Advanced Fibrosis?

## AASLD<sup>1</sup>

- **Advanced Fibrosis Screening Recommended at High Risk (T2D, Obesity with Metabolic Complications, Family History)**
- **Increasing Number of Metabolic Diseases = Increasing Risk of Progressive Liver Disease**

## ADA<sup>2</sup>

- **MASLD/MASH w/ Fibrosis Screening Recommended with T2D or Prediabetes, Especially in Persons with Obesity, Cardiometabolic Risk Factors, or Current Cardiovascular Disease, or Incidental Hepatic Steatosis on Imaging or Elevated Plasma Aminotransferases**

## AACE<sup>3</sup>

- **MASLD/MASH with Fibrosis Screening Recommended with T2D or Prediabetes, Especially in Persons with Obesity, Cardiometabolic Risk Factors, or Features of Metabolic Syndrome, or Incidental Hepatic Steatosis on Imaging, or Elevated Plasma Aminotransferases**

**AASLD, ADA, and ACCE Guidelines Call Out Patients with T2D as Warranting Workup**

1. Rinella. Hepatology. 2023;77:1797.

2. ADA Professional Practice Committee. Diabetes Care. 2025;48:S59. 3. Cusi. ACCE. Endocrine Practice. 2022;28:528



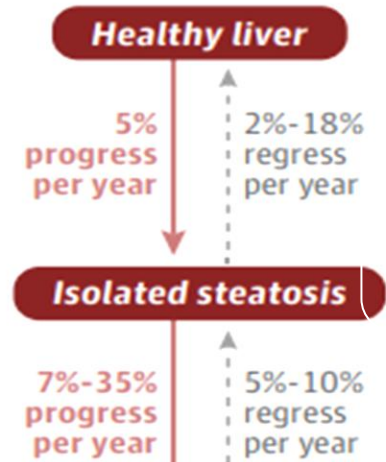
# Fibrosis P

Increased **Fibrosis**: Increased Mortality; Increased All-Cause Hepatic Malignancies

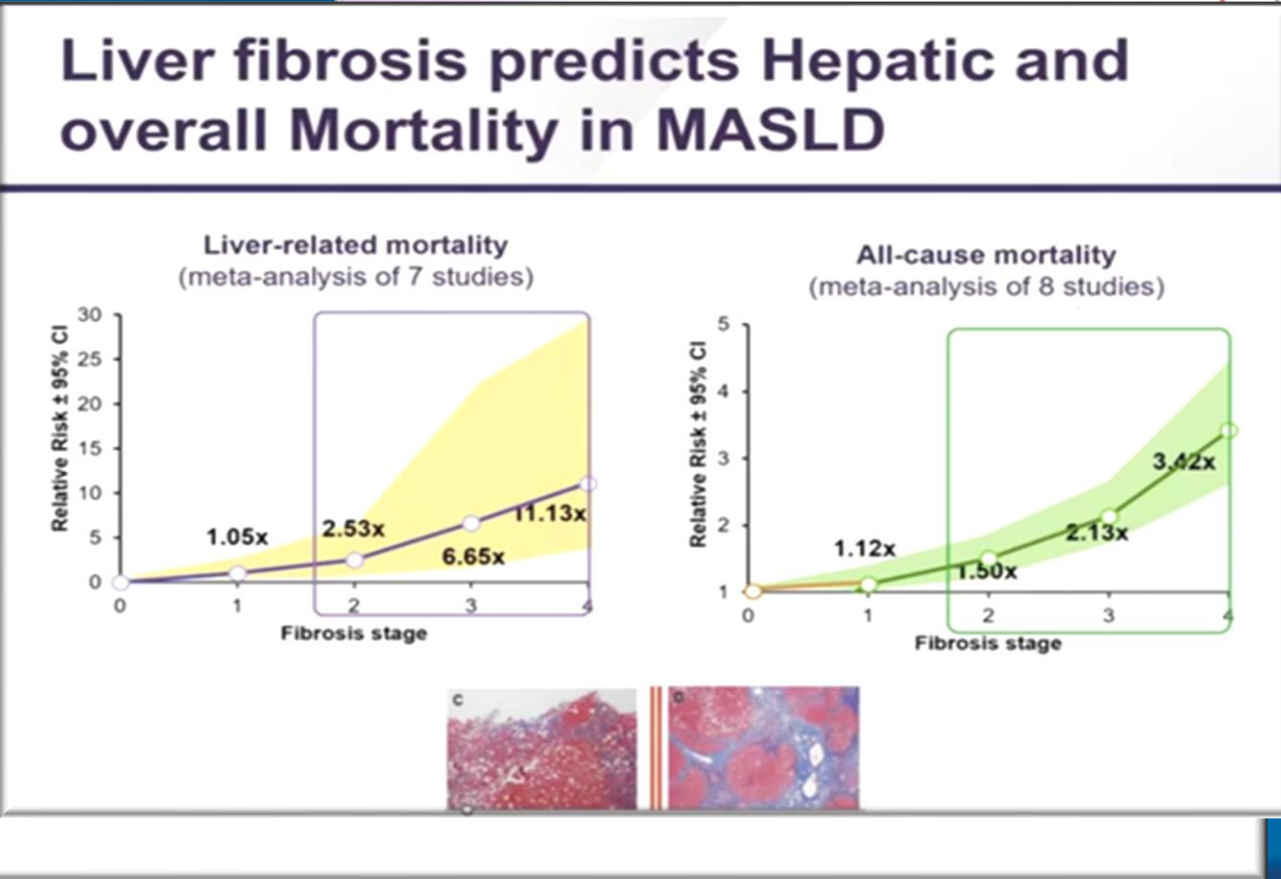
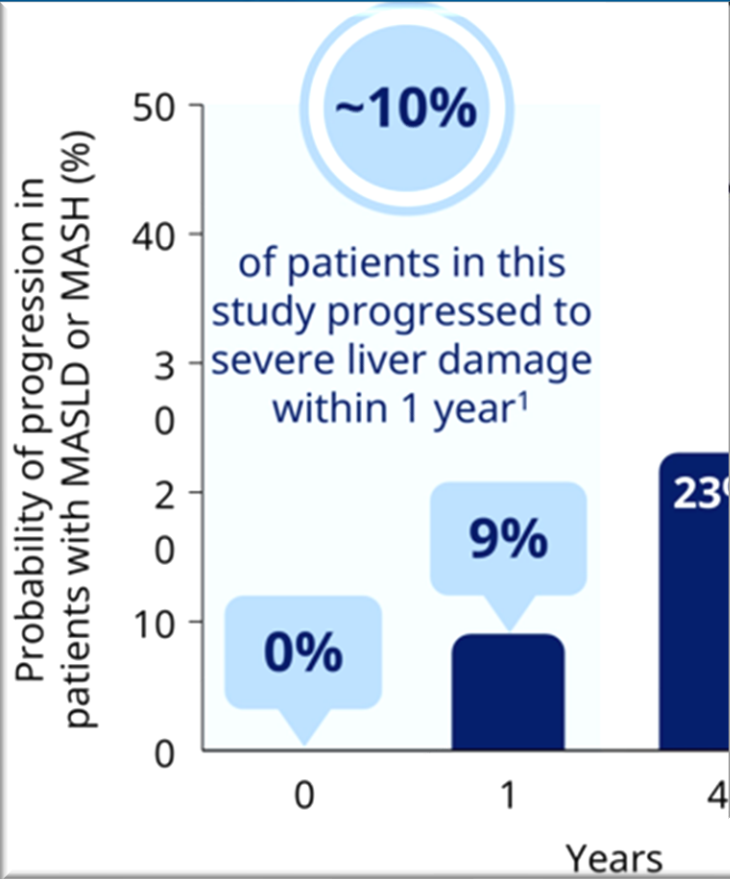
## MASLD progression

**F0-F1 fibrosis**  
30-35 y to cirrhosis or hepatic decompensation

**F2 fibrosis**  
15-20 y to cirrhosis or hepatic decompensation



JAMA.doi:10.1001/jama.2025.19615  
11/10/25



Function-  
hepatitis

1%-10% regress per year

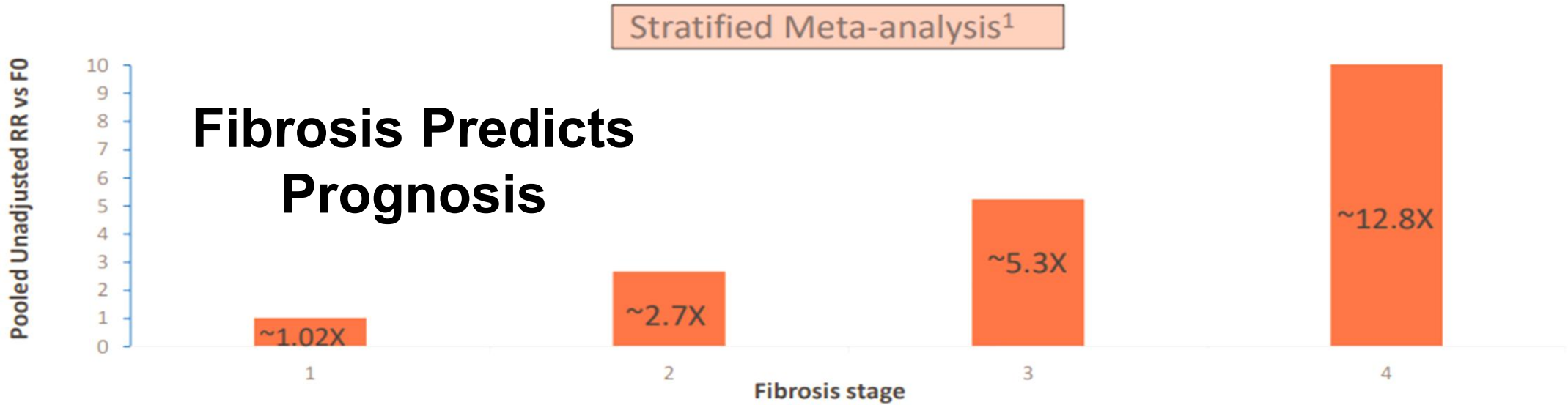
is

10% progress per year

Hepatic decompensation



# Fibrosis Severity & Liver Morbidity: Retrospective Meta-Analysis Derived From Multiple Studies



Fibrosis Stage	1	2	3	4
Pooled unadjusted RR Vs. F0 (95% CI)	1.02 (0.58-1.89)	2.67 (1.58-4.51)	5.24 (3.97-9.98)	12.78 (6.85-23.85)

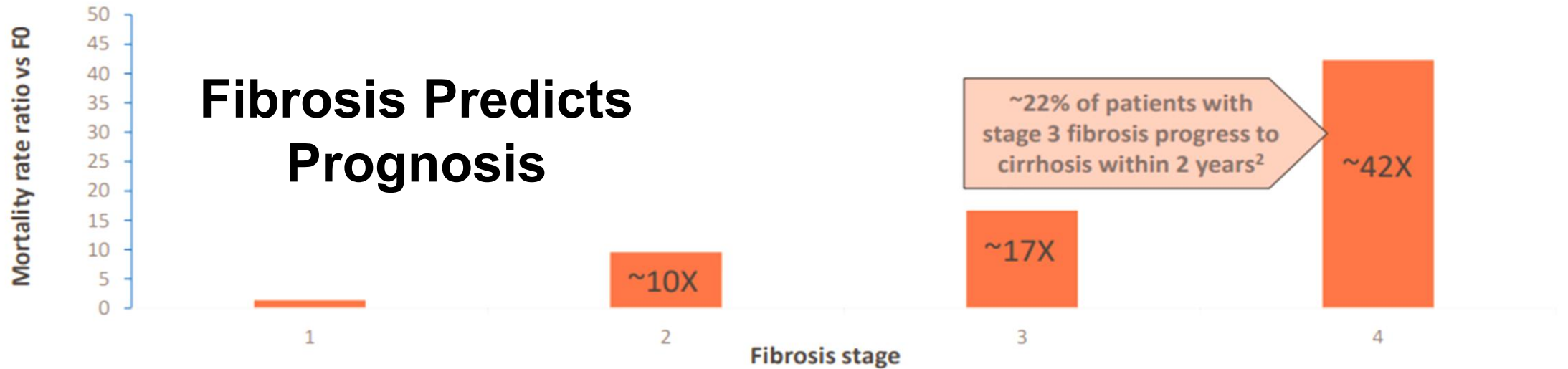
\*Liver morbidity defined differently across multiple studies in Metanalysis - Search terms included: ascites, esophageal varices, cirrhosis, cancer, decompensation, encephalopathy

1. Taylor RS et al. *Gastroenterology* 2020. May;158(6):1611-1625.e12.



# Fibrosis Severity & Liver Mortality From A Retrospective Analysis Derived From Multiple Studies

Risk Of Liver Related Death Statistically Higher After Progression To F2



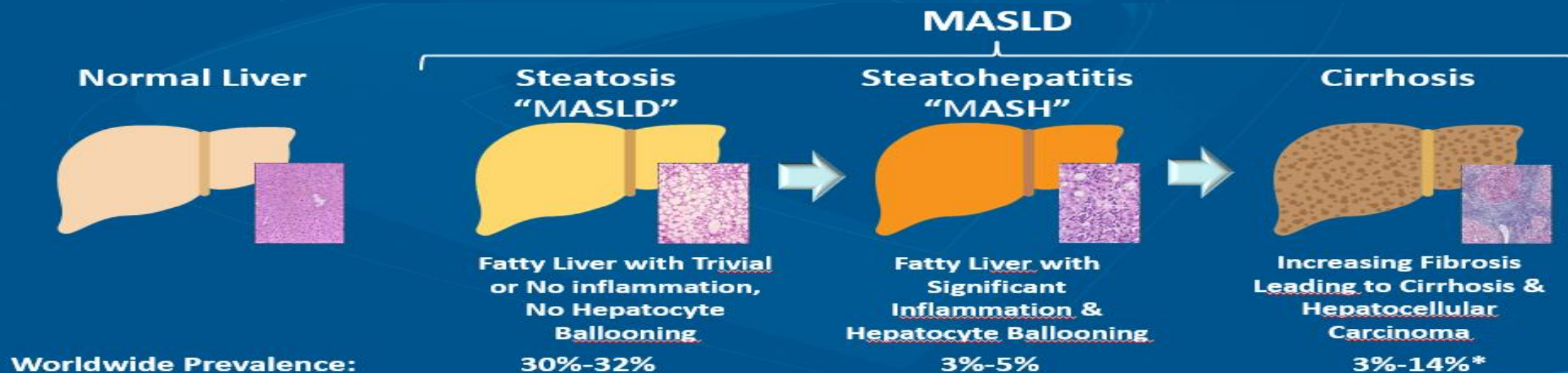
Fibrosis Stage	1	2	3	4
Mortality Rate Ratio (95% CI)	1.41 (0.17–11.95)	9.57 (1.67–54.93)	16.69 (2.92–95.36)	42.30 (3.51–510.34)

1. Dulai PS et al., *Hepatology*. 2017;65:1557-1565. 2. Loomba R. *Hepatology* 2019;70(6):1885-1888



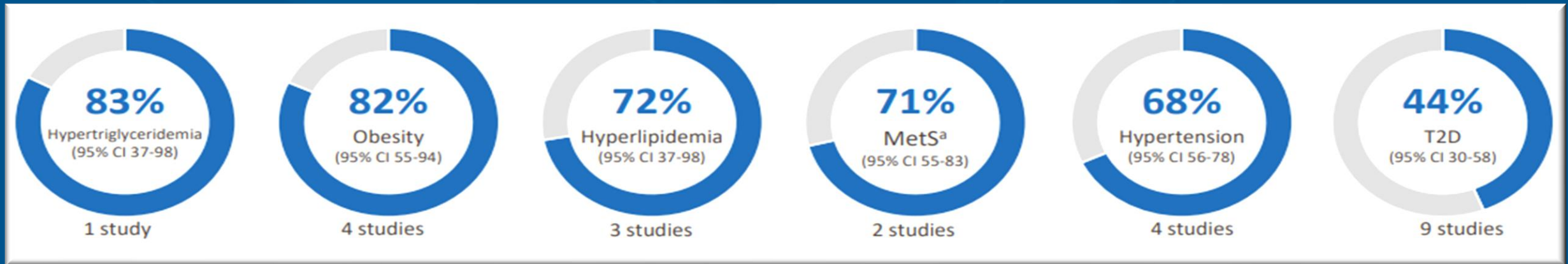
# Progression of MASLD / MASH: Cirrhosis & Hepatocellular Carcinoma

- ▶ MASH Can Progress to Cirrhosis, End-Stage Liver Disease & Need for Liver Transplant
  - 10 Year Cumulative Incidence HCC 1.7 per 1000 Pts w MASLD
  - ~ 20% MASH - Related HCC Identified in Pts Without Cirrhosis
  - Risk of Progression From Compensated Cirrhosis to Decompensation & Death is ~ 10% / Year



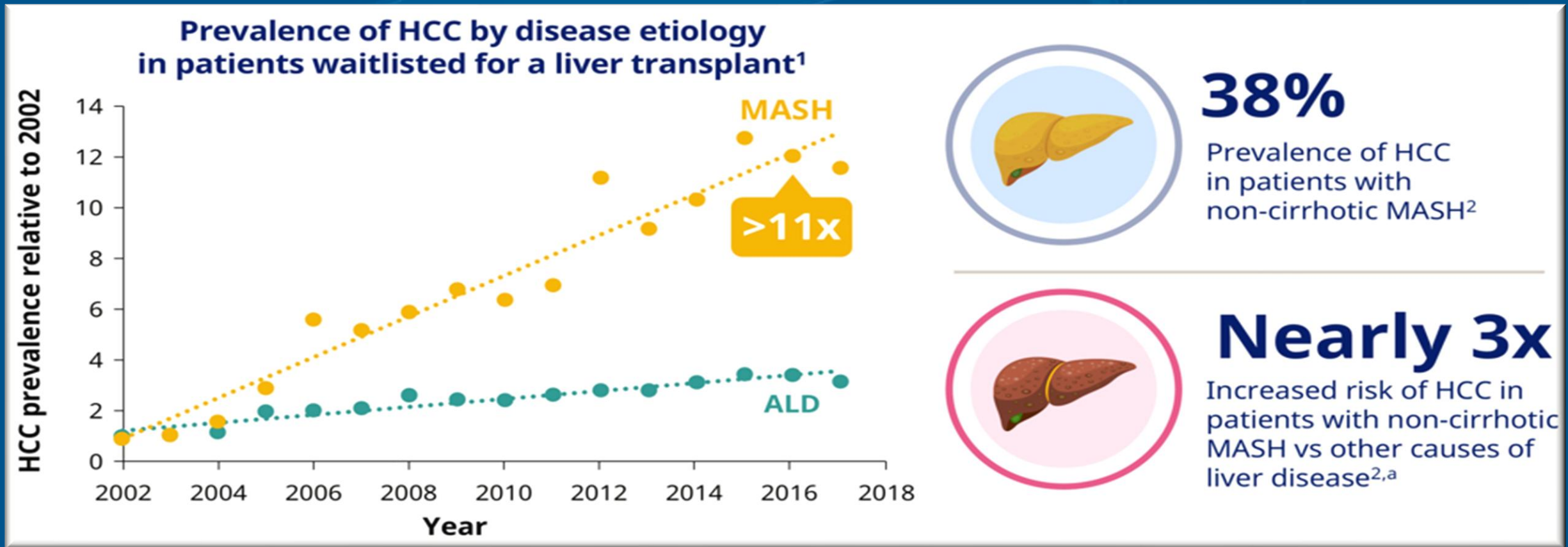
# Comorbidities Among Pts With MASH – Retrospective Meta-Analysis

- Simultaneously, Patients With These Conditions May Experience MASH as a Comorbidity, Highlighting Reciprocal Relationship
  - MASH Can Occur Without Met S, Obesity, or DM but Comorbidities Are Common



1. Younossi ZM et al., *Hepatology*. 2016;64(1):73-84.
2. Chalasani N et al., *Hepatology* 2018;67(1):328-357.
3. Rinella ME et al., *Gastroenterol Hepatol*. 2014;10.
4. Allen AM. *J Hepatol*. 2022 Nov;77(5):1237-1245.

# MASH Comorbidities / Morbidity & Mortality From Retrospective Meta-Analysis



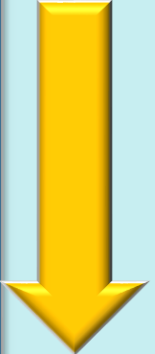
a. Composite ALD, Chronic Hep B/C, Autoimmune Liver Dz, Cholestatic Liver Dz, Wilson's Dz, Hereditary Hemochromatosis

1. Younossi Y et al. *Hepatology*. 2016;64(1):77-84. / Younossi Z et al. *Gastroenterol Hepatol*. 2019;17(4):748-755. 2. Angulo et al. *Gastroenterology*. 2015;149:389-397



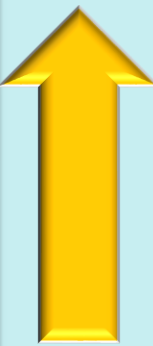
# MASLD & Extra-Hepatic Cancers

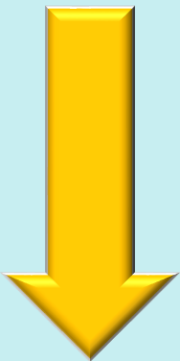
## MASLD

- 
- Adiponectin
  - Insulin Receptors
  - IGFBP-1 & 2


- 
- Insulin Resistance
  - IGF-1
  - Leptin
  - Inflammatory Factors (TNF- $\alpha$ , IL-6)

## Intestinal Dysbiosis

- 
- Micro-Ass'd Molecular Patterns (MAMP's)
  - Toll-Like Receptors
  - IL-6
  - Bile Acids
  - ROS

- 
- FXR (Intestinal Farnesoid X Receptors)
  - IL-18

**Bacterial Translocation**

- 
- **Breast (50%  $\uparrow$ )**
  - **Esophageal Cancer**
  - **Gastric**
  - **Pancreatic**
  - **Colo-Rectal**
  - **Renal Cell**
  - **Colangio-Carcinoma**



# MASLD & CVD

Zheng et al. *Cardiovascular Diabetology* (2024) 23:346  
<https://doi.org/10.1186/s12933-024-02434-5>

Cardiovascular Diabetology

REVIEW

Open Access

Metabolic dysfunction-associated steatotic liver disease and cardiovascular risk: a comprehensive review



# MASLD & Cardiac Function

ANNALS OF MEDICINE

2024, VOL. 56, NO. 1, 2306192

<https://doi.org/10.1080/07853890.2024.2306192>

RESEARCH ARTICLE

 OPEN ACCESS

 Check for updates

The association of metabolic dysfunction-associated steatotic liver disease (MASLD) with the risk of myocardial infarction: a systematic review and meta-analysis



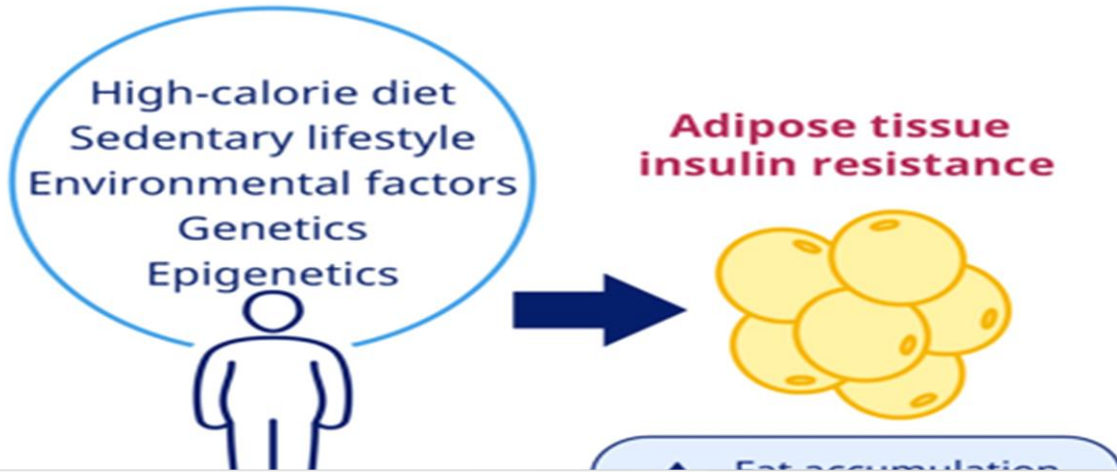
# MASLD & Cardiac Function

## Gut Microbiota Alteration

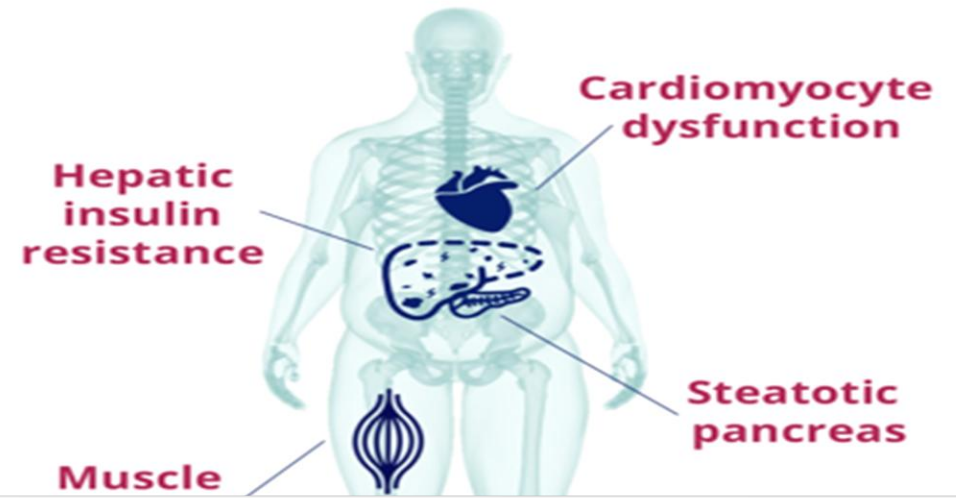
- ▶ High Saturated Fats
- ▶ Sucrose Sweetened Drinks
- ▶ Caloric Dense / Energy Poor Processed Foods
  - Shape the Microbiota To A Less Favorable Profile
- ▶ **Specific Microbiota Signature Unique to MASLD / MASH**
  - Increased CAD
  - Increased Ischemic Stroke
  - Vascular Calcification
  - Prothrombotic Effect

**Microbiome is the Seed of the Problem. Alterations In Gut Bacteria Fueling Inflammation. Gram (–) Rods Producing Cytokines / Toxic Products. Bacterial Translocations. Integrity of Gut Disrupted – Toxins Flow into Portal / System Circulation Causing Havoc**

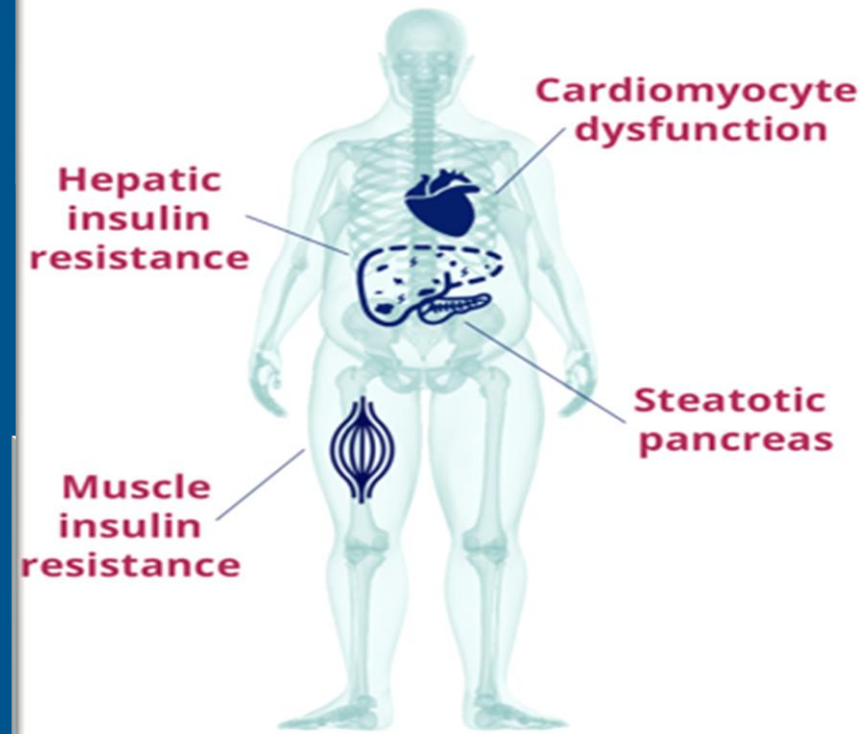
## Underlying Metabolic Impairment



## Multiorgan Dysfunction



## Multiorgan Dysfunction



## Potential Metabolic Conditions



# Accelerated Renal Disease

- ▶ Meta-Analysis – 13 Studies; 1.3 Million Patients, 28.1% with NAFLD 33,840 with Incident CKD Stage  $\geq 3$
- ▶ Median F/U 9.7 Years
- ▶ NAFLD Higher Risk CKD (HR 1.43)
- ▶ Risk Independent Age, Sex Obesity, HTN, DM, & Other CKD Risk Factors
- ▶ The Kidney Is Also A Target Organ

Alessandro Montovani MD et Al.,

[https://eprints.soton.ac.uk/445427/1/NAFLD\\_CKD\\_Risk\\_metaanalysis\\_accepted.pdf](https://eprints.soton.ac.uk/445427/1/NAFLD_CKD_Risk_metaanalysis_accepted.pdf)



# Obesity Is Common, Serious, And Costly

Obesity Impacts Our Nation's Health, Economy, Military Readiness



**1 in 5 Children & 1 in 3 Adults** Struggle With Obesity



The US Spends **\$147 B** Annually Obesity Related Health Costs



Only **2 in 5 Young Adults** Are Weight Eligible & Physically Prepared For Basic Training

Americans Don't Eat Healthy Or Get Enough Physical Activity

**Fewer Than 1 in 10** Eat Recommended Daily Amount of Vegetables

**Fewer Than 1 in 4 Youth** Get Enough Aerobic Physical Activity

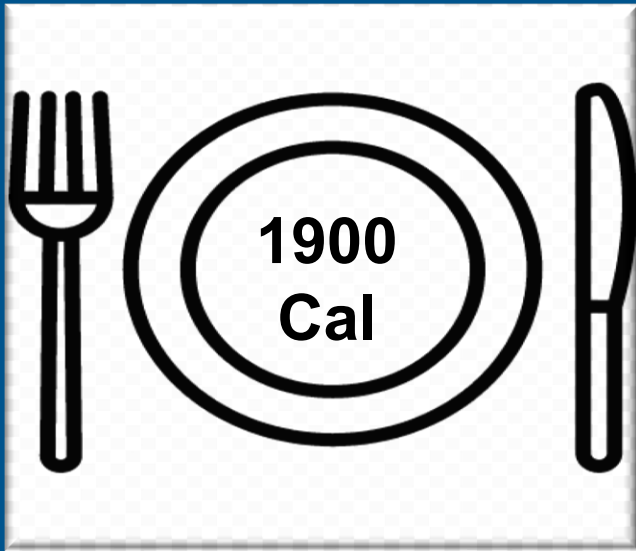
**Just 1 in 4 Adults** Meet the Physical Activity Guidelines

Many Americans Lack Healthy, Affordable Foods / Places To Be Active

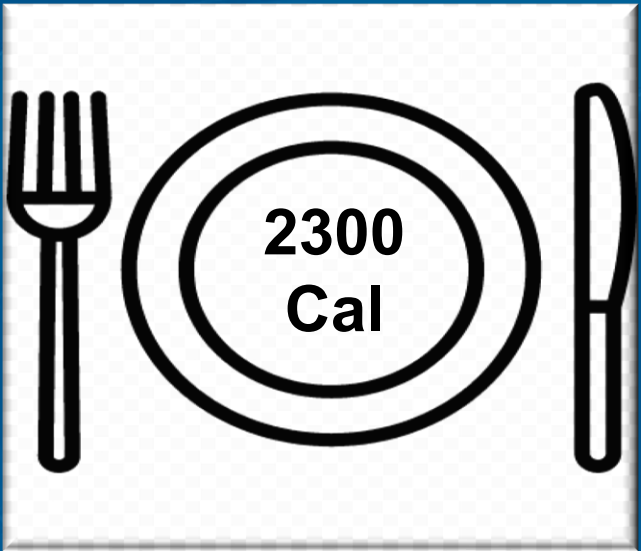
**More Than Half of Americans** Don't Live Within Half A Mile of a Park

**40% of All US Households** Do Not Live Within One Mile of Healthier Food Retailers

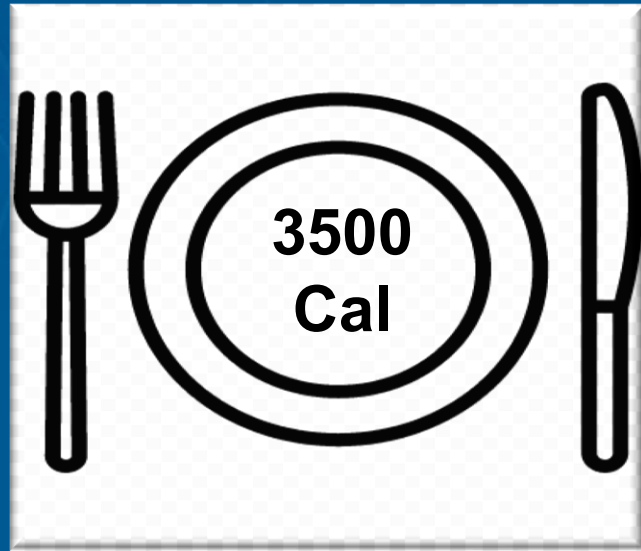




**1970**



**2000**



**2020**

**Calories Up / Exercise Down  
Eating Out Up / Cooking At Home Down**





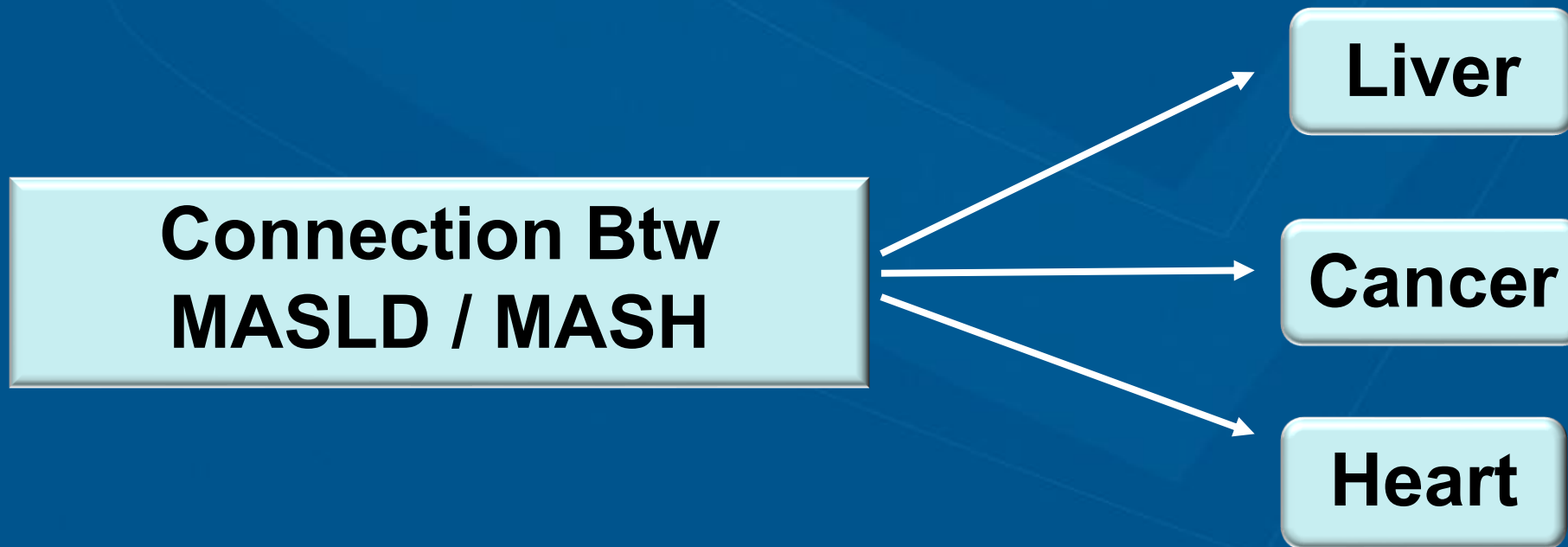
WHAT

NOW?



# Education

- ▶ **MASLD / MASH** is A Cardiac, Hepatologic & Oncologic Disorder With Significant Morbidity & Mortality
- ▶ Drive Awareness, Drive Urgency, & Call To Action



# Screen, ID, Risk Stratify

- ▶ Patients Must Be Identified & Appropriately Risk – Stratified
- ▶ Delay In Dx: Silent Dz – No Sx Until Progressed
- ▶ Similar To Screening For CKDz, Annual Dilated Eye Exam, Comprehensive Foot Exam – Screen For MASLD / MASH

**Make Visible What Is  
Invisible**

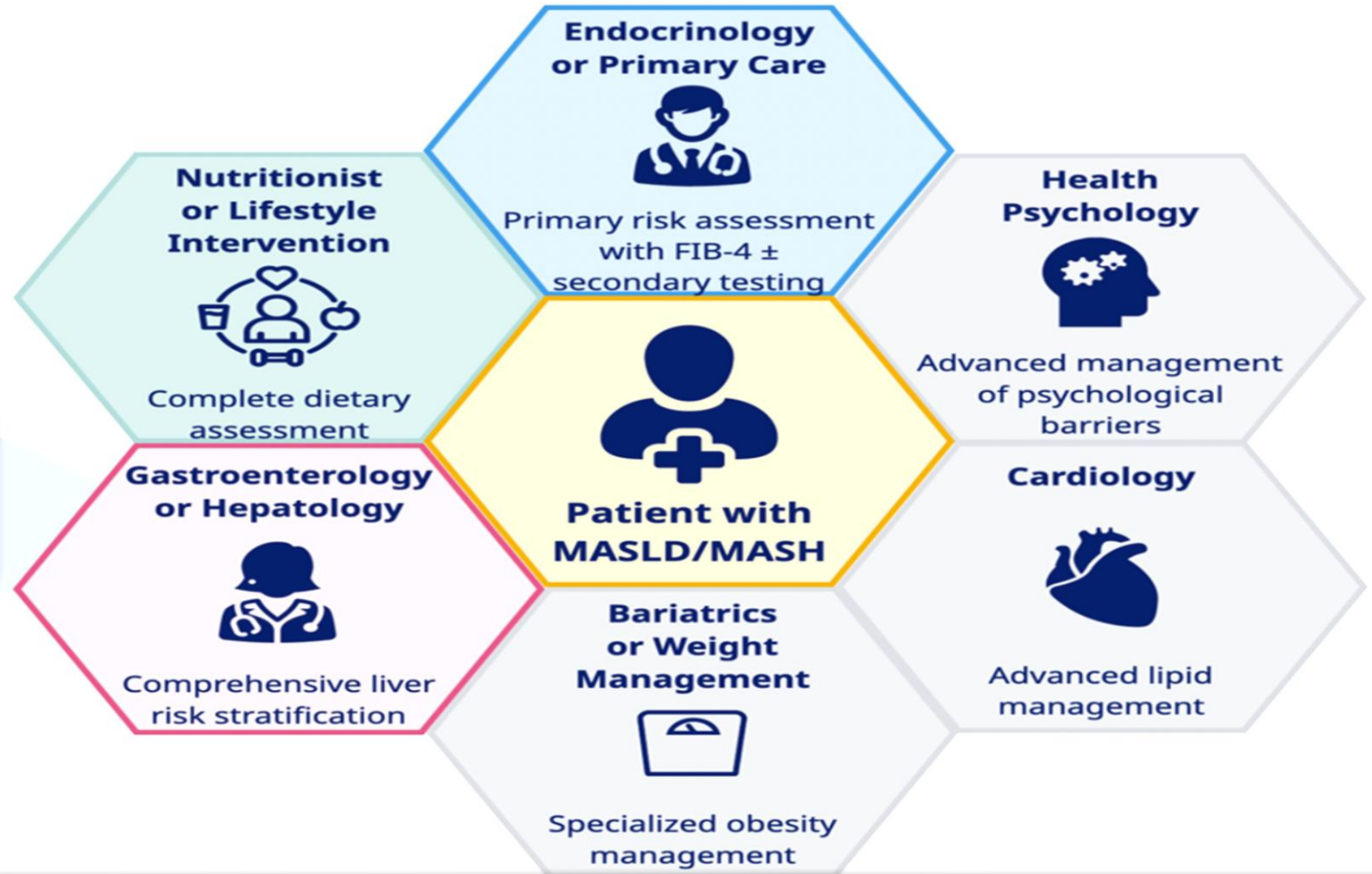


# This is The **New** Paradigm



# Disease Centered vs. Patient Centered Care

**A collaborative approach to managing cardiometabolic risk is important in the care of patients with MASH**



# MASLD & T2DM

**JIM**

Journal of  
Internal Medicine

Founded in 1863

Original Article

Open Access



## Evaluating the prevalence dysfunction-associated steatotic liver disease type 2 diabetes mellitus in

- ✓ 59% MASLD
- ✓ 7% Signs of Advanced Fibrosis
- ✓ Obesity Increased Risk Fibrotic MASLD 8x
- ✓ MASLD Linked to CV Changes / Ectopic Fat
- ✓ Screening Needed DM Primary Care

First published: 16 June 2025 | <https://doi.org/10.1111/jim.15700>

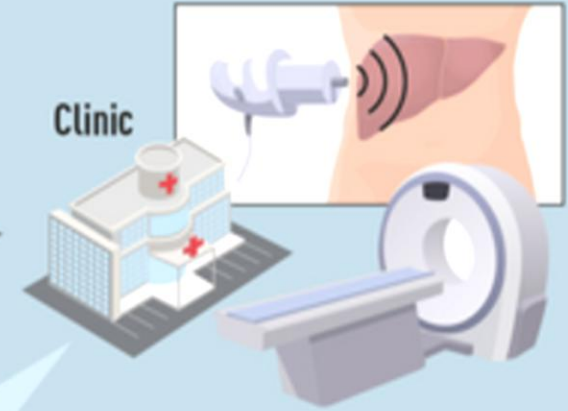
Evaluating the prevalence and severity of MASLD in patients with type 2 diabetes mellitus in primary care

Balkhed et al.

Primary care  
Individuals  
with T2D  
n = 308



Clinic



T2D

59%



MASLD

7%



≥10 kPa

1.9%



≥ 15 kPa/  
clinical cirrhosis

T2D and MASLD

11%



≥10 kPa

2.8%



≥ 15 kPa/  
clinical cirrhosis

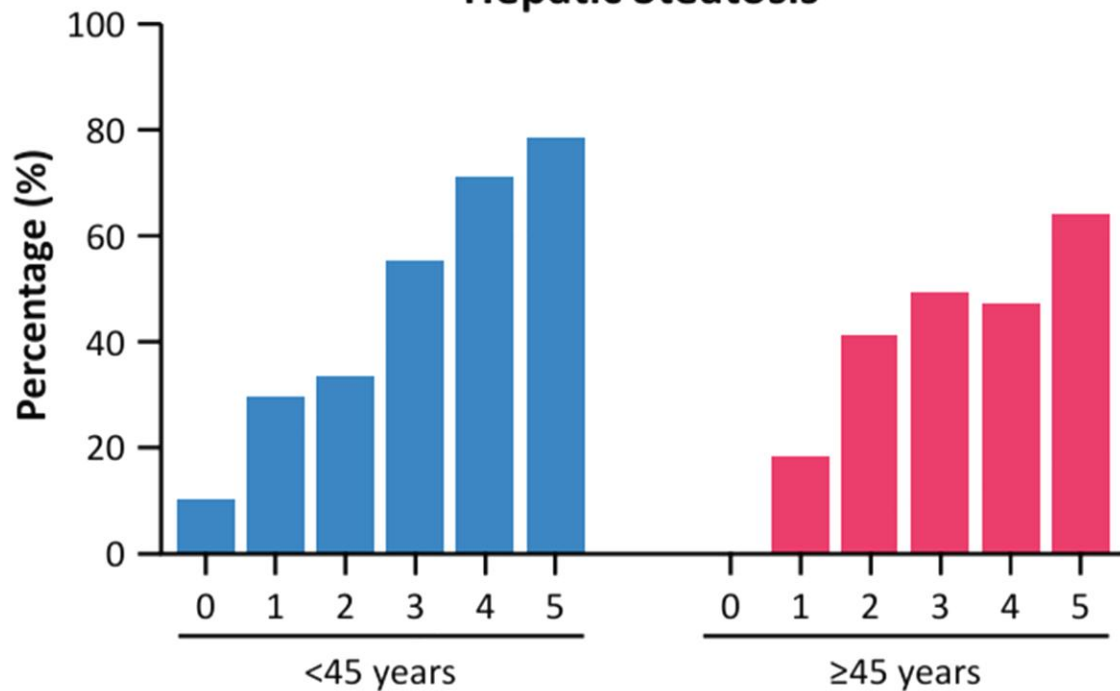
Descr

# The Need To Screen: Obesity Increases Hepatic Fibrosis In Young Adults With T2DM

**Population:** 1420 individuals with (63%) or without type 2 diabetes mellitus who attended internal medicine or endocrinology clinics and did not have a known history of MASLD. **A total of 243 participants were ages <45 years.**

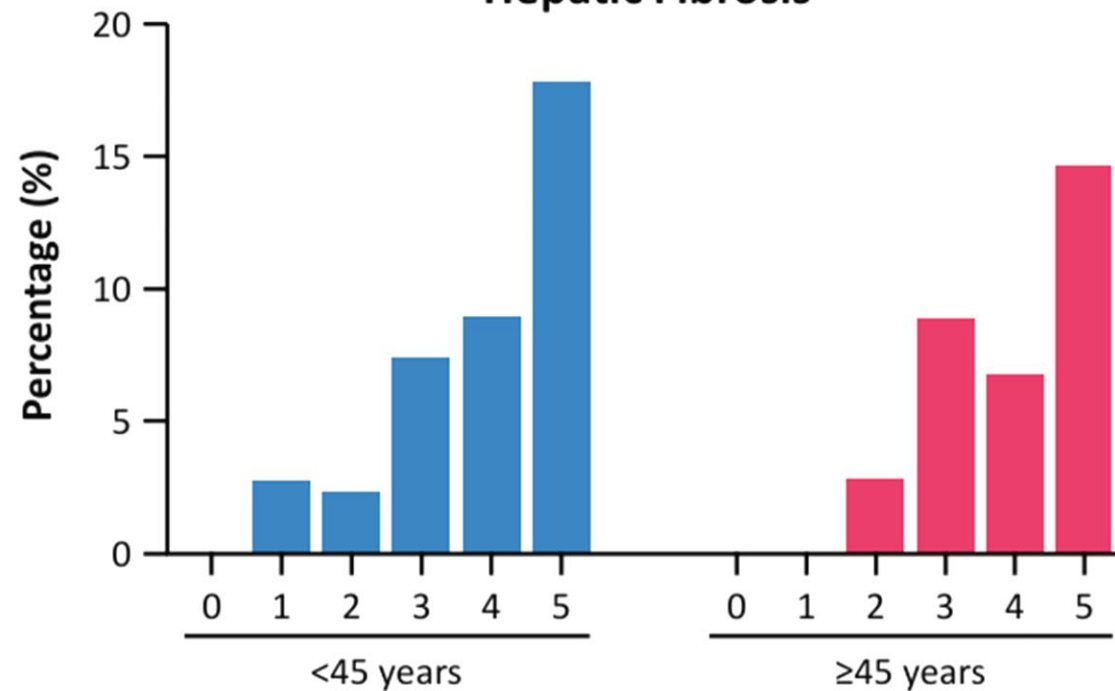
**Screening:** transient elastography for steatosis and LSM; if LSM $\geq$ 6.5 kPa MRE, cT1 and liver biopsy if  $\geq$ F2 suspected.

### Hepatic Steatosis



Number of Metabolic Syndrome Risk Factors

### Hepatic Fibrosis

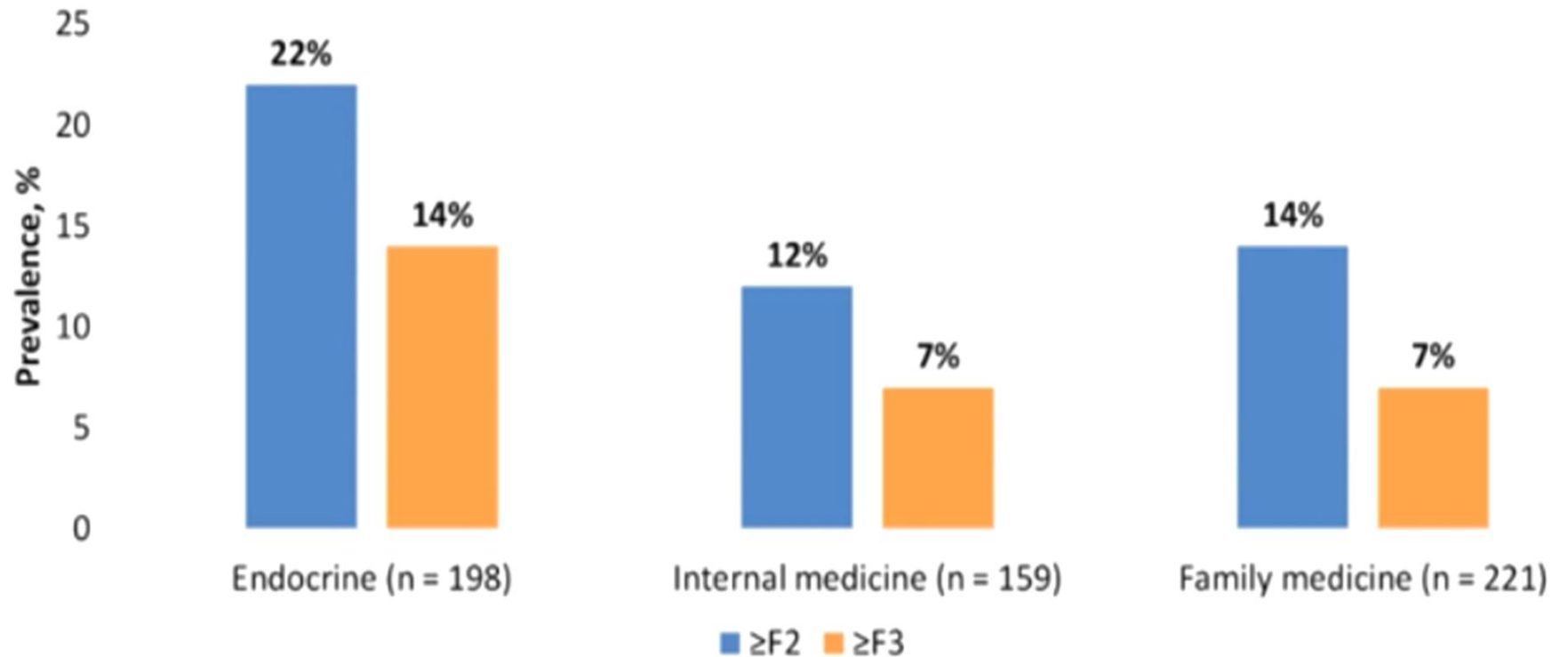


Number of Metabolic Syndrome Risk Factors



# LFT Abnormalities In Steatosis / Fibrosis: T2DM Not Previously Dx MASLD / MASH

Prevalence of Advanced Fibrosis in Outpatient Clinics



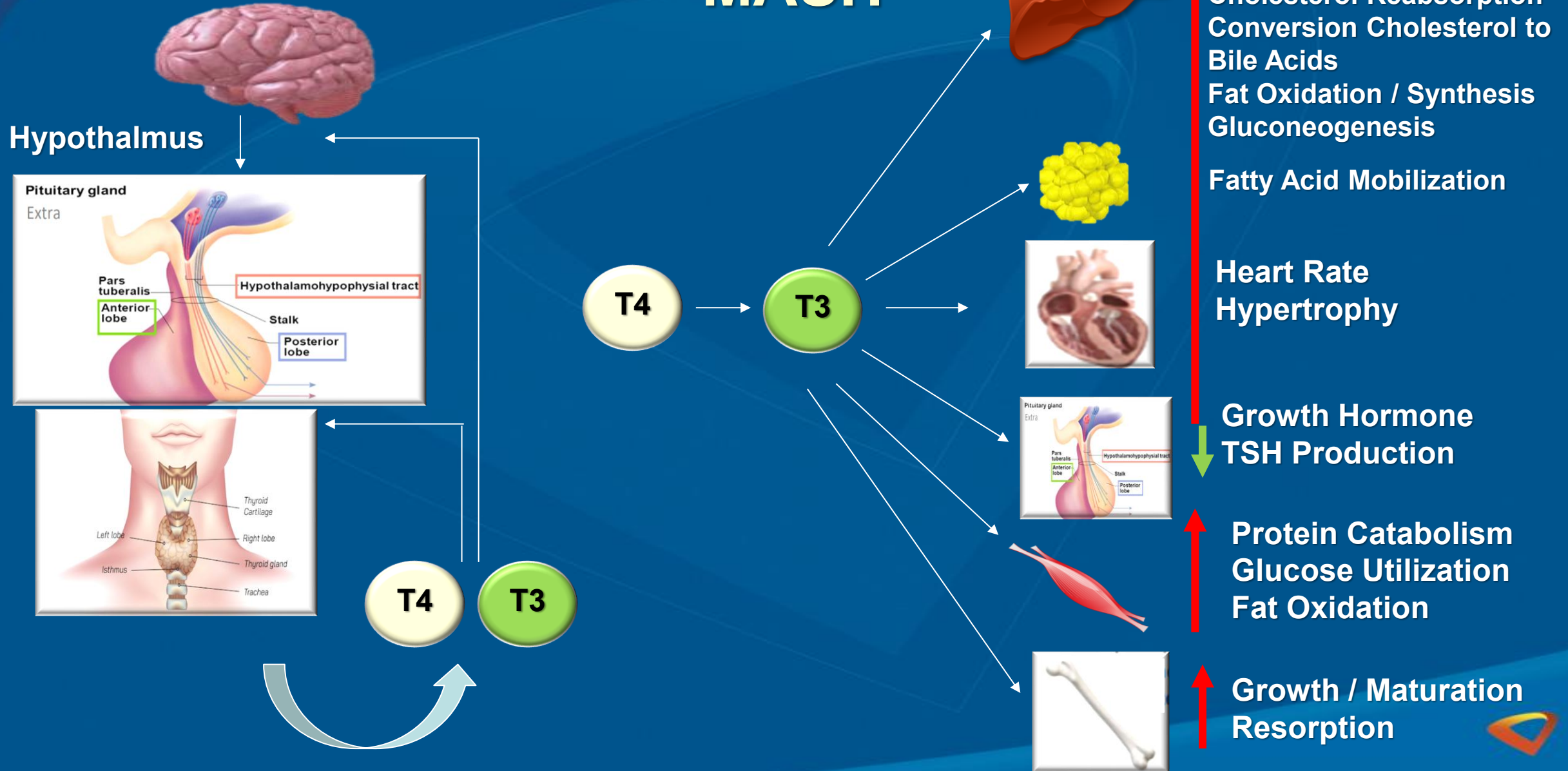
## Population:

578 individuals with obesity, T2D, and MASLD seen in endocrine, internal medicine, or family medicine clinics

Specialists who see patient populations with high rates of cardiometabolic risk factors are critically important for improving MASLD detection.



# Role Of Thyroid Hormone Dysregulation In MASLD / MASH



# Thyroid Hormone Receptor Alpha / Beta

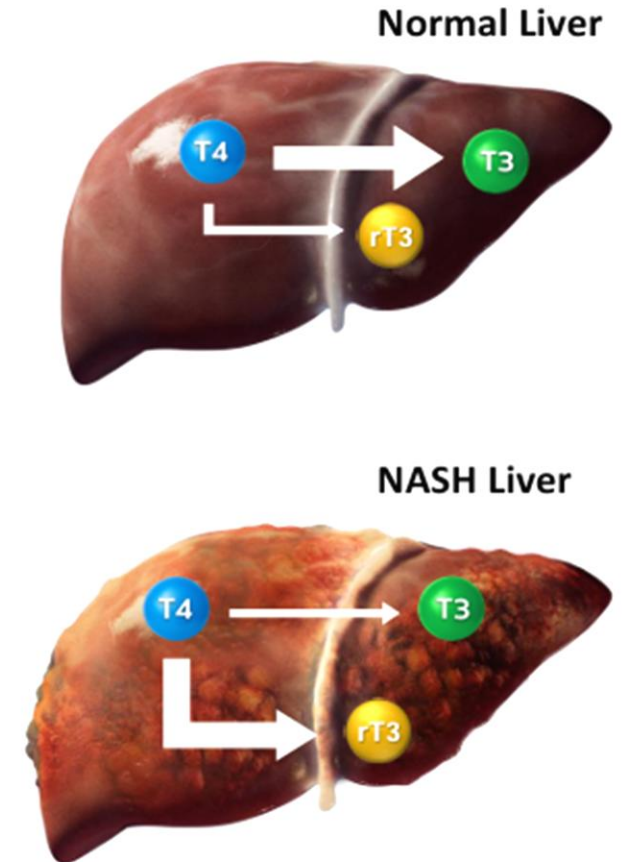
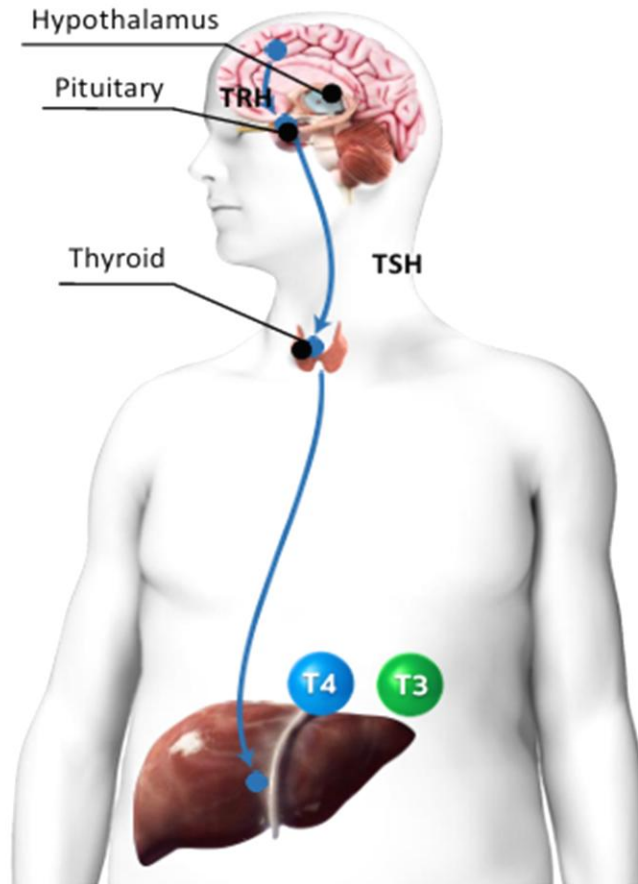
- ❖ THR-Alpha – Predominantly In Heart, Brain & Bone
  - Responsible For Effects In Heart & Bone, Thyrotoxicosis Side Effects of TH Excess
- ❖ THR-Beta - Predominantly In Liver, Kidney & Pituitary Gland
  - Responsible For Effects On Metabolism
  - Crucial Role In The Liver, Including Activation of Liver Fat Oxidation
- ❖ The Liver is the Only Organ Where THR-B is Expressed Higher Than THR-A



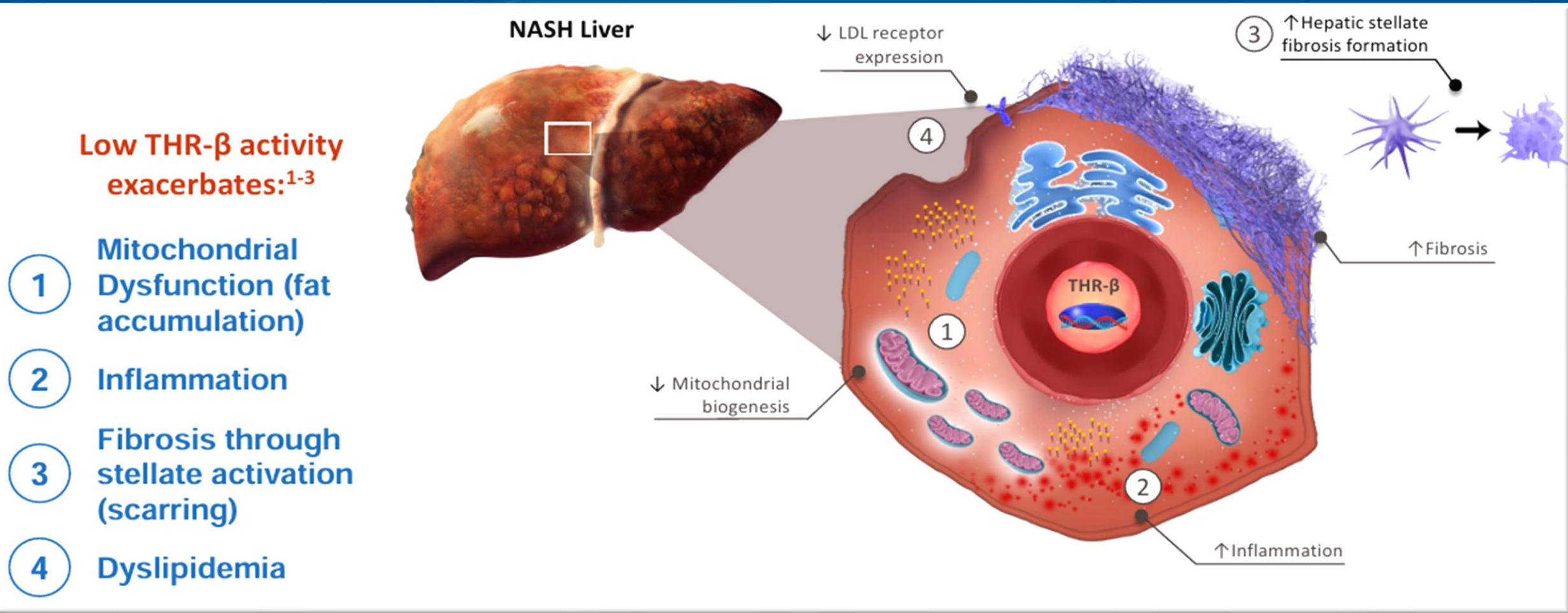
# Role Of Thyroid Hormone Dysregulation In MASLD / MASH

- Altered patterns of gene expression in fatty liver
  - T3 conversion genes downregulated
- Inflammation is a hallmark of NASH
  - Disruption of thyroid hormone conversion (T4 to T3) pathway occurs
    - rT3 is inactive
- Hypothyroidism In The Liver**

Hypothyroidism Ass'd ↑ Risk MASLD / MASH  
Free T4 Levels Lower MASLD  
Low Free T3 = Risk Factor Advanced Fibrosis



# Thyroid Hormone Dysfunction Influences Key Pathways Involved In MASLD / MASH



1. Sinha RA, et al. *Nat Rev Endocrinol*. 2018;14:259-269. 2. Karim G, Bansal MB. *touchRev Endocrinol*. 2023;19:60-70. 3. *Proc Natl Acad Sci USA*. 2016;113(24):E3451-E3460



# MASLD Guidelines For PCP's / Endocrinologists

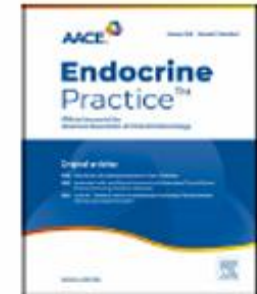
Endocrine Practice 28 (2022) 528–562



Contents lists available at [ScienceDirect](#)

Endocrine Practice

journal homepage: [www.endocrinepractice.org](http://www.endocrinepractice.org)



## Clinical Practice Guidelines

### American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings

Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD)

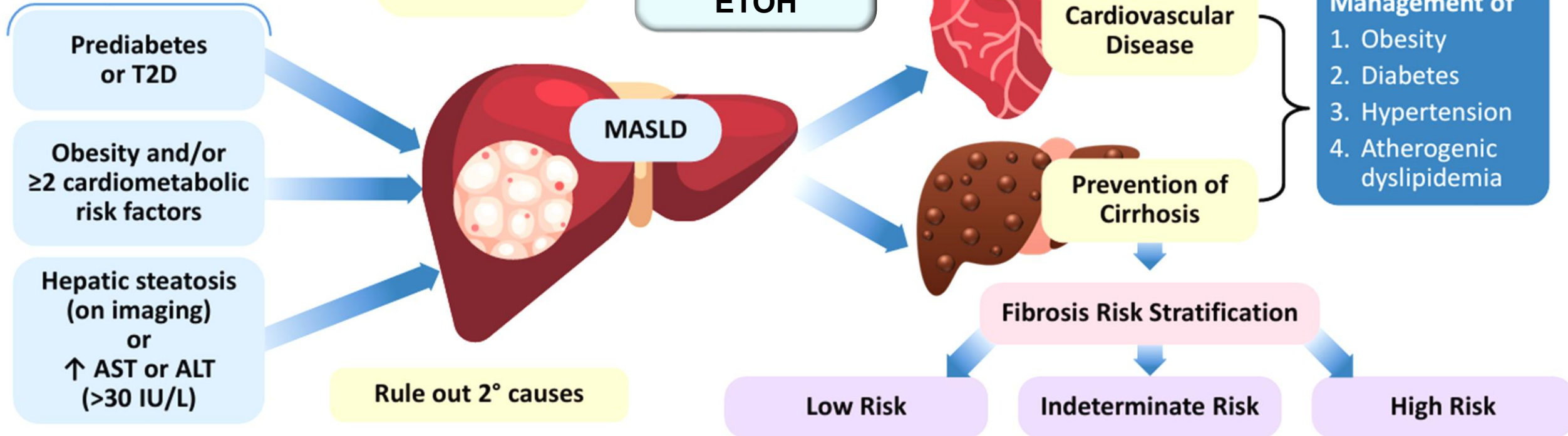


Kenneth Cusi, MD, FACE, FACP, Co-Chair <sup>1,\*</sup>, Scott Isaacs, MD, FACE, FACP, Co-Chair <sup>2</sup>,  
Diana Barb, MD, ECNU <sup>3</sup>, Rita Basu, MD <sup>4</sup>, Sonia Caprio, MD <sup>5</sup>,  
W. Timothy Garvey, MD, MACE <sup>6</sup>, Sangeeta Kashyap, MD <sup>7</sup>,  
Jeffrey I. Mechanick, MD, ECNU, MACE, FACP, FACN <sup>8</sup>, Marialena Mouzaki, MD, MSc  
Karl Nadolsky, DO, FACE, DABOM <sup>10</sup>, Mary E. Rinella, MD, AASLD Representative <sup>11</sup>,  
Miriam B. Vos, MD, MSPH <sup>12</sup>, Zobair Younossi, MD, AASLD Representative <sup>13</sup>

**PCP's Gate-Keepers  
Crucial For Timely  
Identification  
Standardized  
Screening Guidelines**

# MASLD / MASH Algorithm

## High-risk groups for the development of MASLD



AST > 40 w / DM = Concern  
ALT > AST = MASLD  
AST > ALT  $\uparrow$  Prob Adv Fib

Cusi K et al. *Endocrine Practice* 2022;28:528-562



# Monday AM Clinic: Meet Patient

## Ms Smith

- 60 y/o F Returns to Clinic for Incidental Abnormal LFT's, Long-Standing Hx Obesity Refractory to Lifestyle Changes.
- PMHx: T2DM (A1c 7.1%), Obesity, Metabolic Syndrome.
- Meds: Metformin
- Labs: AST 49 IU/L, ALT 61 IU/L  
Hepatitis C Serology Negative

**Which of the Following Is Required to Estimate Ms. Smith's Risk for Hepatic Fibrosis?**

- A. Abnormal LFT's**
- B. Bilirubin**
- C. BMI**
- D. Creatinine Clearance**
- E. Platelet Count**



# Risk Stratification Tools

## FIB-4 Score<sup>[1-3]</sup>

$$\text{FIB-4} = \frac{\text{Age (y)} \times \text{AST level (U/L)}}{\text{Platelet count (10}^9 \text{/L)} \times \sqrt{\text{ALT (U/L)}}} = \text{○}$$

< 1.3

≥ 2.67

**Absence of advanced fibrosis**

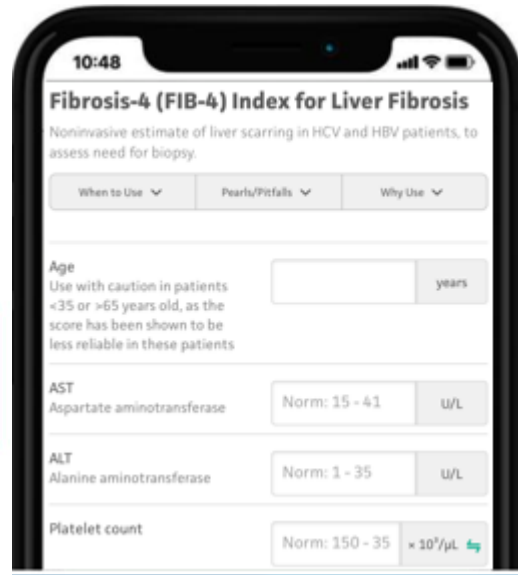
Manage in primary care and treat comorbid conditions

**Indeterminate**

Need additional information from alternate NIT or refer to liver specialist

**Presence of advanced fibrosis**

Refer to liver specialist



## Enhanced Liver Fibrosis Test<sup>[2,3]</sup>

Combines 3 biomarkers of fibrosis: Hyaluronic acid, TIMP-1, and P3NP

< 7.7

≥ 9.8

**Early or no fibrosis**

**Moderate**

**Presence of advanced fibrosis**

Sensitivity of 85%  
15% of patients with advanced fibrosis are missed

Specificity of 90%  
10% of patients are wrongly diagnosed with advanced fibrosis

## Fibroscan<sup>®</sup>[2]

Uses elastography to assess liver stiffness, which increases with fibrosis severity

< 8

≥ 12

**Early or no fibrosis**

**Moderate**

**Presence of advanced fibrosis**

# American Diabetes Association (ADA) 2026 Guidelines: Focus on Fibrosis Risk Stratification To Prevent Cirrhosis

**MASLD with clinically significant fibrosis: Stages 2, 3 and 4 = or “at risk” MASH (i.e., at risk for cirrhosis)**

Histological stages of fibrosis:

Stage 0: no fibrosis

Stage 1: mild

Stage 2: moderate

Stage 3: advanced (“precirrhosis”)

Stage 4: cirrhosis

**Associated with increased risk of liver cirrhosis,  
hepatocellular carcinoma and CVD**



# ADA 2026 MASLD Consensus Report

## Key Tests Primary Care / Endocrinology



### Blood-based biomarkers<sup>1,2,a</sup>

<b>FIB-4</b>	Age, platelets, AST, and ALT
<b>ELF™</b>	TIMP-1, hyaluronic acid, PIIINP
<b>NFS</b>	Age, platelets, AST:ALT ratio, albumin, BMI, impaired fasting glucose, and/or diabetes



### Imaging biomarkers<sup>1,2,a</sup>

<b>VCTE (eg, FibroScan®)</b>	Measure liver stiffness through elastography to detect and diagnose fibrosis or cirrhosis
<b>MRE</b>	
<b>SWE</b>	
<b>cT1</b>	Iron-corrected T1 from MRI



### Combination biomarkers<sup>1,a</sup>

<b>FAST</b>	FibroScan® and AST
<b>MAST</b>	MRI-PDFF, MRE, and AST
<b>MEFIB</b>	MRE and FIB-4



# FIB - 4 Score Reflects Long –Term Health Outcomes

## Risk of major adverse liver outcomes<sup>b</sup>

>4x  
greater

High FIB-4  
vs  
Low FIB-4  
(>2.67 vs <1.3 at baseline)



Decrease in FIB-4 score from high to low/indeterminate



decrease in MALO<sup>b</sup> and expanded MACE<sup>c</sup>

## Risk of heart failure hospitalization

>2x  
greater

High FIB-4  
vs  
Low FIB-4  
(>2.67 vs <1.3 at baseline)



Increase in FIB-4 score from low to indeterminate/high



increase in MALO<sup>b</sup>, expanded MACE<sup>c</sup>, and HFH

**The risk of certain adverse events increases and decreases in proportion with changes to the FIB-4 score**

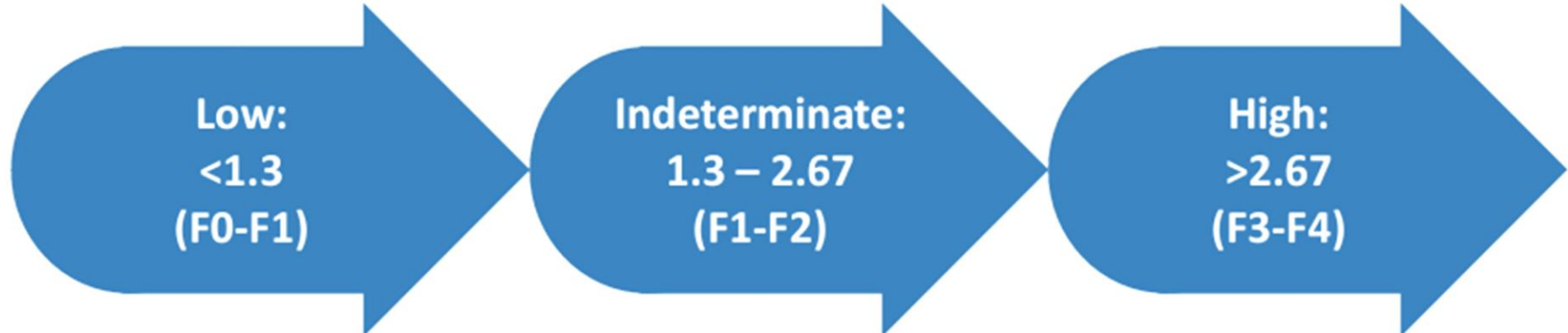
<sup>a</sup>Based on a retrospective analysis of a cohort of patients (Objective 1: 19,395, 18,828, 19,435, and 17,511 patients for the 2- and 3-point MACE, expanded MACE, HFH, and MALO outcomes, respectively; Objective 2: 11,934, 11,570, 11,991, and 10,655 for 2- and 3-point MACE, expanded MACE, HFH, and MALO outcomes, respectively) diagnosed with MASH between Oct 1, 2015, and June 30, 2022, utilizing the Optum Clinformatics database. Adult patients with MASH were indexed on their first NIT 180 days prior to and up to 180 days following the diagnosis of MASH. MASH was defined as the presence of  $\geq 1$  ICD-10-CM diagnostic code for the disease (K75.81) in the absence of other competing diagnoses that could induce liver damage. It consisted of 2 objectives: 1. Investigate the association between baseline NIT scores and major clinical outcomes (mortality, MALO, MACE, and other cardiac endpoints); 2. Investigate the association between changes in NIT scores and major clinical outcomes (MALO, MACE), and other cardiac endpoints. <sup>b</sup>Defined as occurrence of any of the following: cirrhosis (or complications attributable to cirrhosis), hepatocellular carcinoma, liver transplant recipient, or all-cause mortality. <sup>c</sup>Included AMI, coronary revascularization, stroke, HFH, and all-cause mortality. AMI, acute myocardial infarction; FIB-4, Fibrosis-4 index; HFH, heart failure hospitalization; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; MACE, major adverse cardiovascular events; MALO, major adverse liver outcomes; MASH, metabolic dysfunction-associated steatohepatitis; NIT, noninvasive test.  
Data on File; 2024-Liv-RWE-00004



# FIB - 4 Risk of Advanced Fibrosis

## FIB-4

Risk of advanced fibrosis (stages 3-4)



### PARAMETERS

- Age
- AST
- ALT
- Platelets

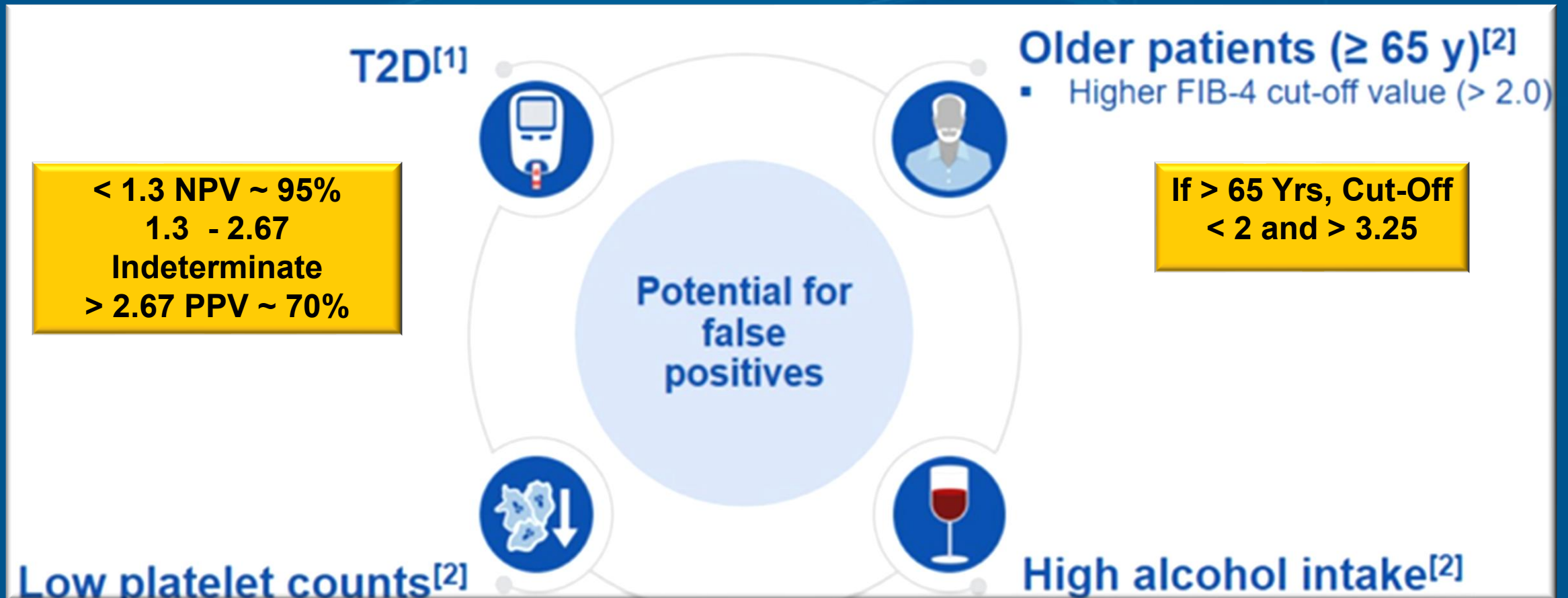
$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count (10}^9\text{/L)} \times \sqrt{\text{ALT (U/L)}}} = 2.69$$

The equation is displayed with interactive input fields for each parameter: Age (60), AST Level (49), Platelet Count (140), and ALT (61).

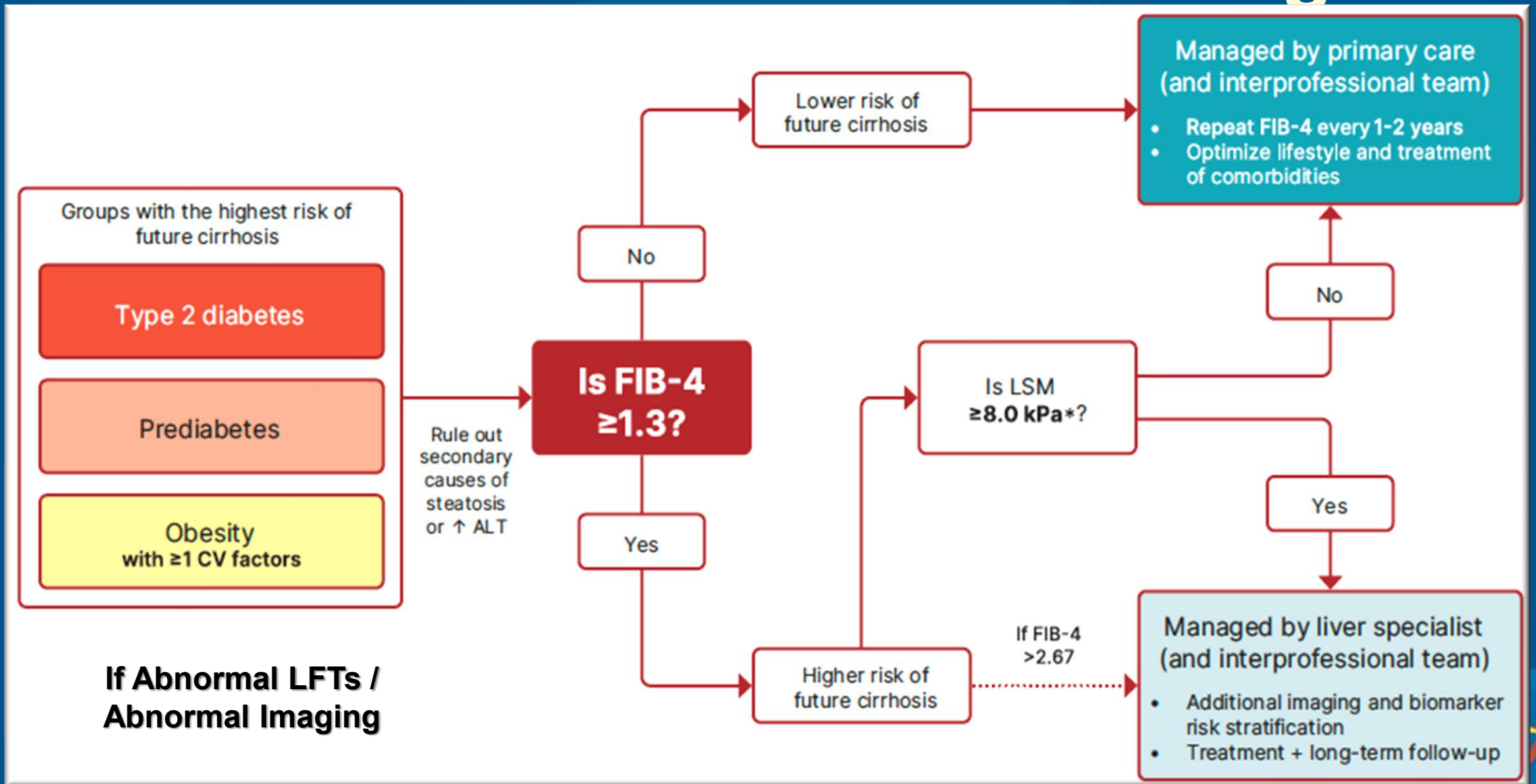
**Plat < 150 Concern For Portal HTN. Liver Makes Platelet Growth Factor. Decreased With Scarring + Blood Backs Up Spleen = Hypersplenism**



# Limitations of FIB - 4 In Certain Populations



# ADA 2026 Guidance: MASH Dx Algorithm



# Patient Ms Smith

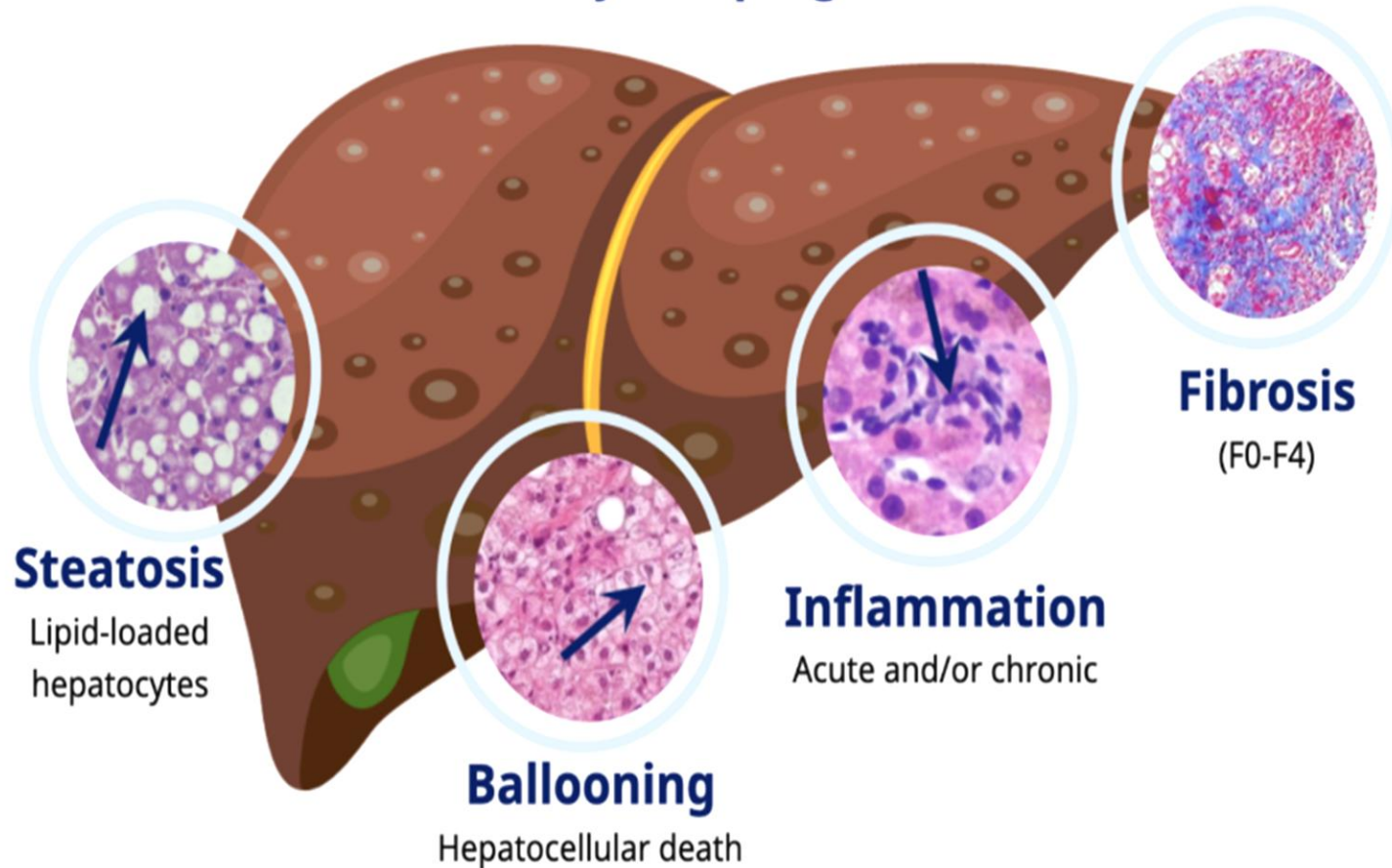
- ▶ 60 y/o F With Abnormal LFT's, Hx Obesity Refractory to Lifestyle Changes.
- ▶ PMHx: T2DM (A1c 7.1%), Obesity, Metabolic Syndrome.
- ▶ Social: CAGE ? Negative (PEth)
- ▶ Meds: Metformin
- ▶ Labs: AST 49 IU/L, ALT 61 IU/L Hepatitis C Serology Negative, Platelets 140 (150-400)
- ▶ FIB - 4 Index 2.69

**Which of the Following Would Be Your Next Step In Management?**

- A. Watchful Waiting Given Low Risk For Hepatic Fibrosis**
- B. Liver Transient Elastography**
- C. Liver U/S**
- D. Liver Biopsy**

# Elastography – Based Imaging For Fibrosis In MASLD

Disease activity and progression<sup>3,4</sup>

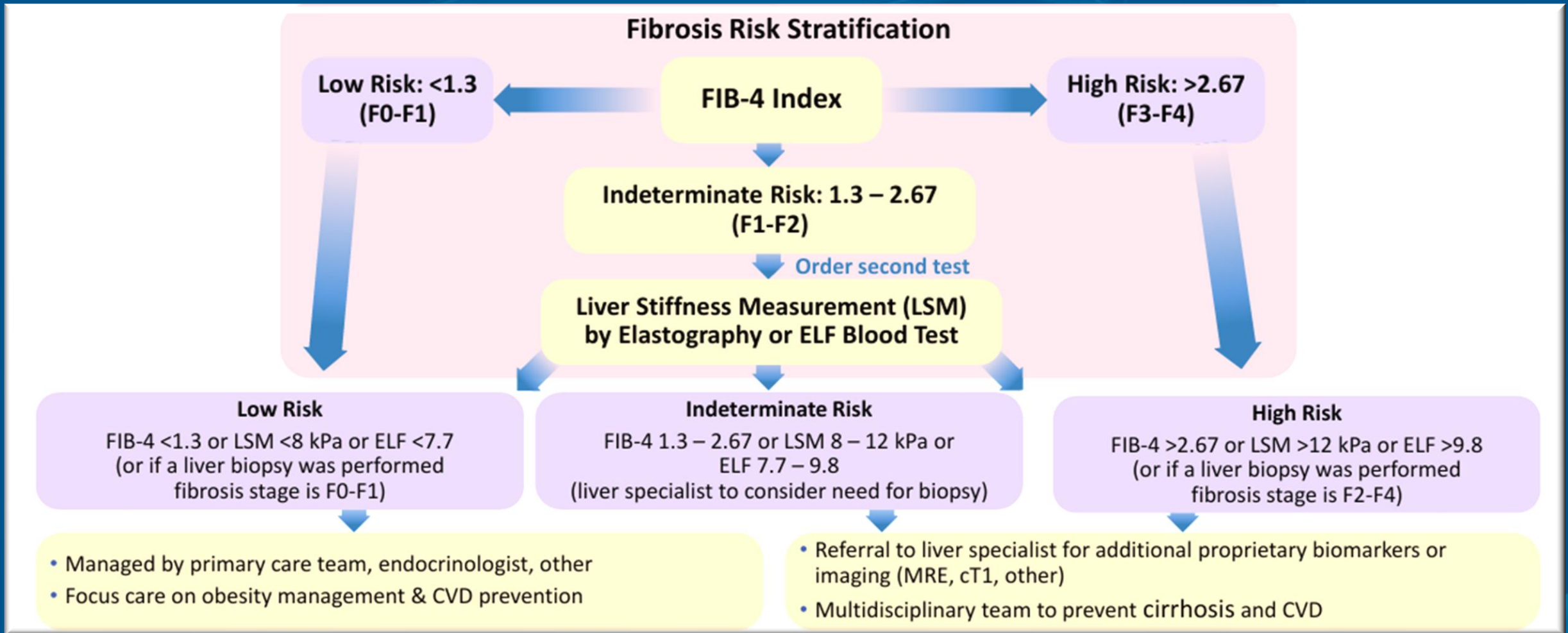


LFTs & U/S Not Considered Screening. Lack Sensitivity / Specificity For Screening  
**Liver biopsy is costly, invasive, and carries risk of potentially serious complications<sup>5</sup>**

**Small Pieces**  
1-1.5 cm Length, 1.2-2 mm Diameter  
**Mis-Staging in 40% Cases**  
~1/50,000 of the Liver / Sampling Variability  
**Bleeding (0.35%)**

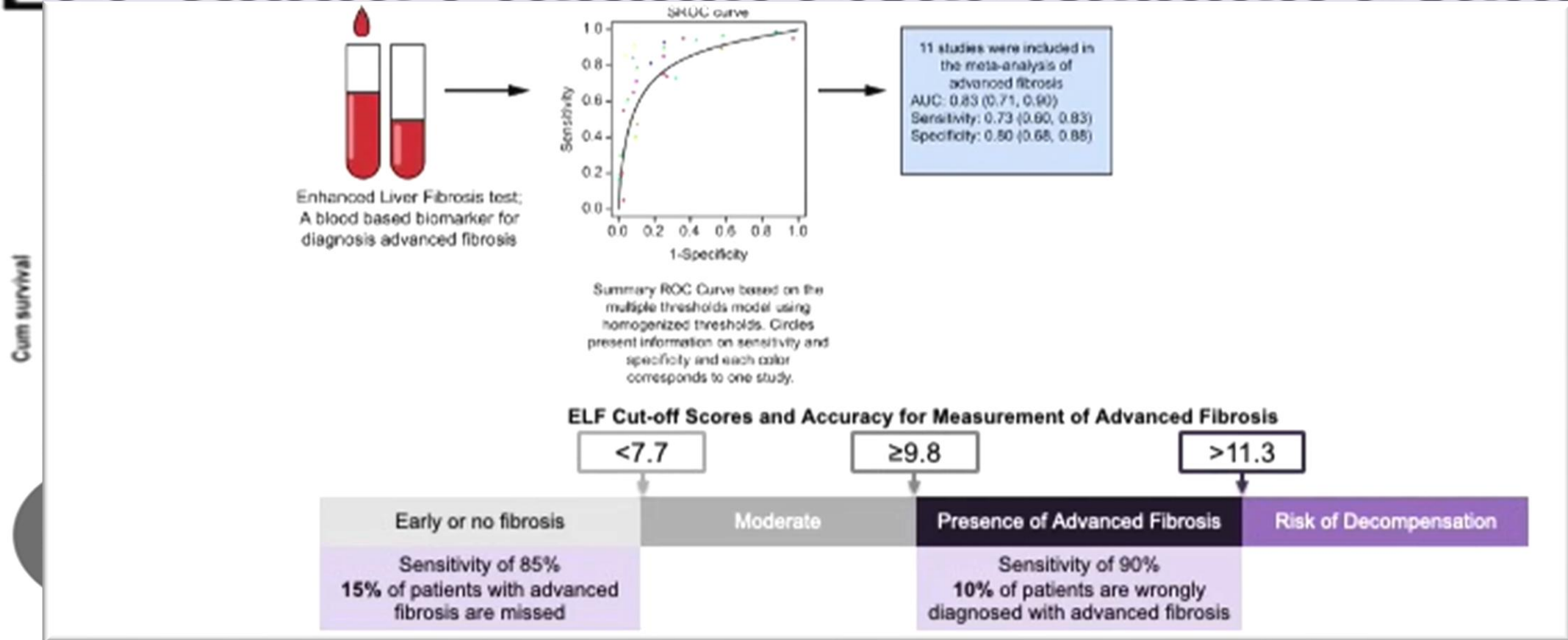


# Cirrhosis Prevention in MASLD



# Enhanced Liver Fibrosis (ELF) Blood Test

## ELF Score Predicts Liver-Related Events

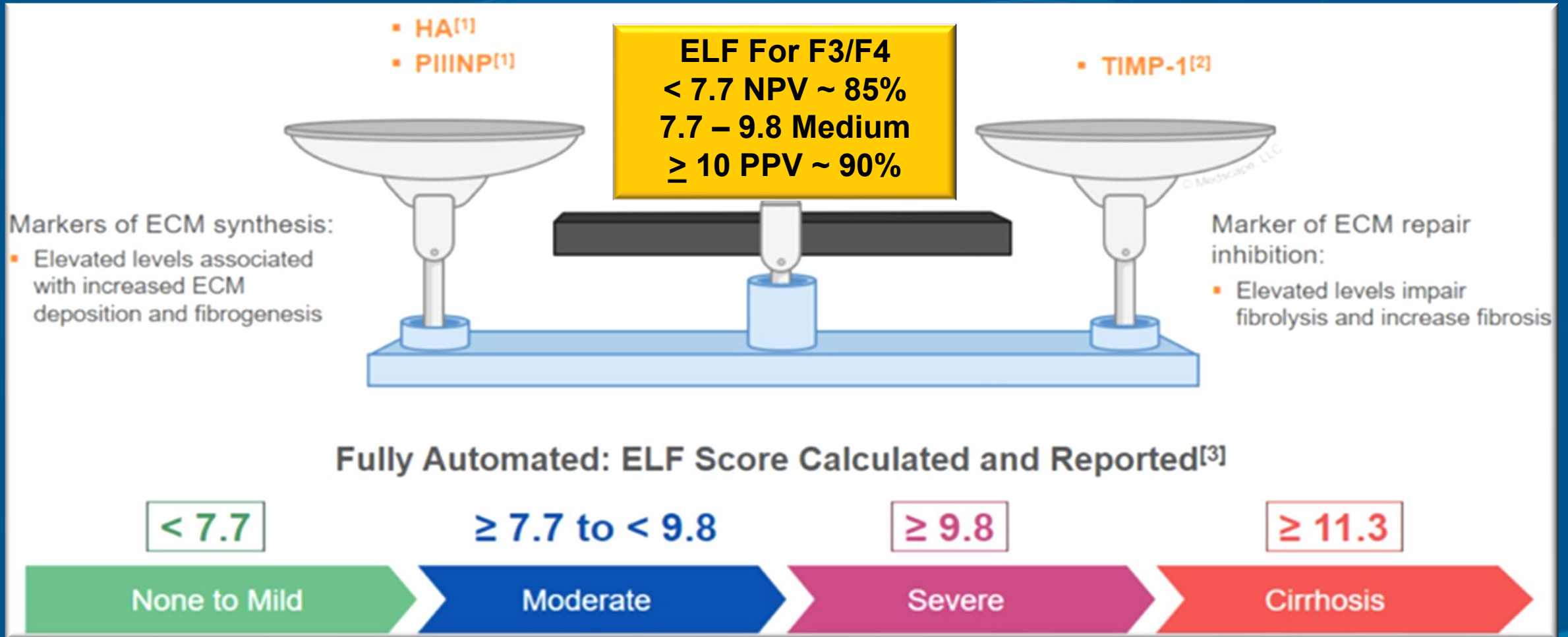


Day J. J Appl Lab Med. 2019 Mar;3:815-26

@scottisaacsmd

Liguori A, D'Ambrosio F, Viceconti N, et al. Prognostic Significance of ELF Test Compared to Liver Biopsy in Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). Abstract Presented at: AASLD 2024; November 15-19, 2024. San Diego, CA. Abstract 874.

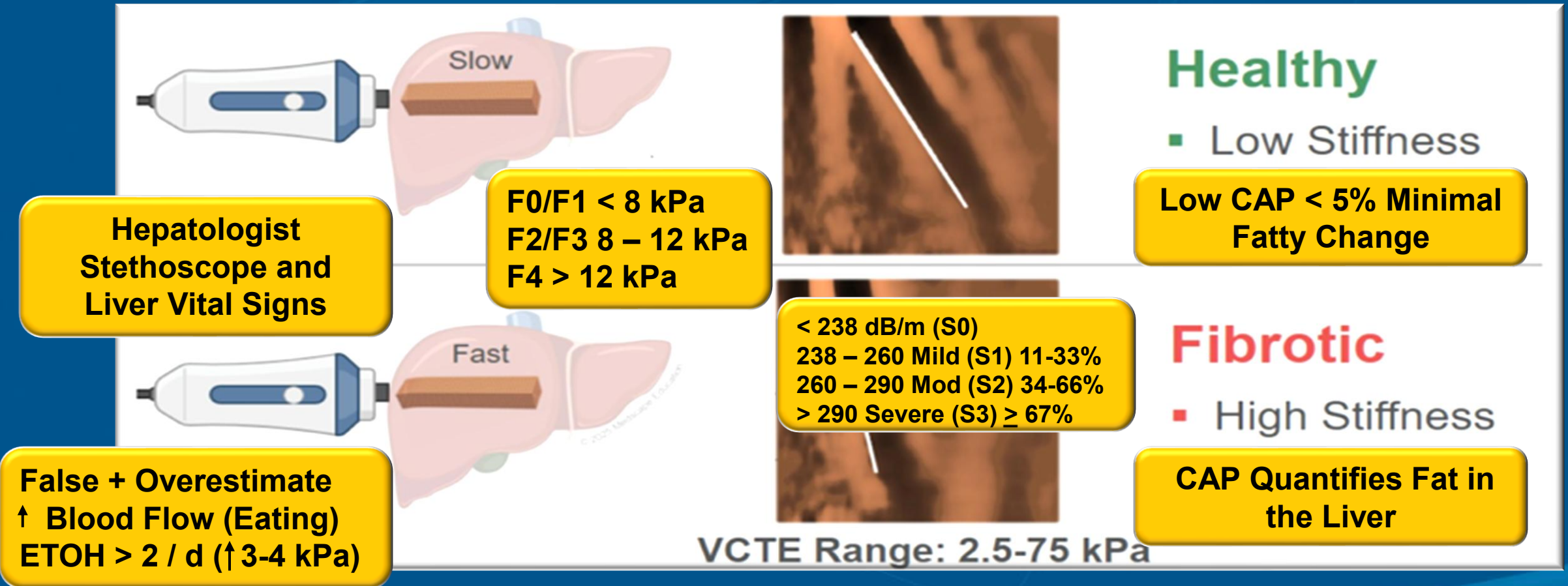
# ELF Test For Prognosis In Advanced MASH



1. Rosenberg WM et al., *Gastroenterology*. 2004;127:1704-1713. 2. Arpino V et al., *Matrix Biol*. 2015;44:247-254. 3. Tamaki N et al., *Diagnostics*. 2024;14:1317



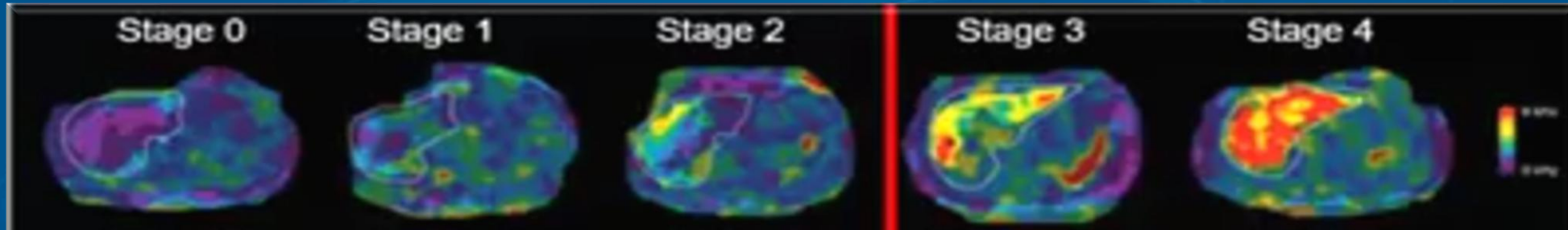
# Vibration Controlled Transient Elastography: Liver Stiffness Correlates To Fibrosis Level



Eddowes PJ et al., *Gastroenterology*. 2019;156:1717-1730



# Magnetic Resonance Elastography (MRE)



MR elastography estimates of hepatic stiffness (at 60 Hz) correlate with hepatic fibrosis stages as:

- <2.5 kPa: Normal
- 2.5 - 2.9 kPa: Normal or Inflammation
- 2.9 - 3.5 kPa: Stage 1 to 2 Fibrosis
- 3.5 - 4 kPa: Stage 2 to 3 Fibrosis
- 4 - 5 kPa: Stage 3 to 4 Fibrosis
- >5 kPa: Stage 4 Fibrosis or Cirrhosis

## MRE Advantages

- Accuracy
- No Impact Ascites / BMI

## MRE Limitations

- Availability (Cost)

- MRI-PDFF (0 – 30%)  
Quantifies Steatosis
- Normal < 5%
- Mild 5 – 10%
- Moderate 10 – 20%
- Severe > 20%



# Revisit Patient Ms Smith

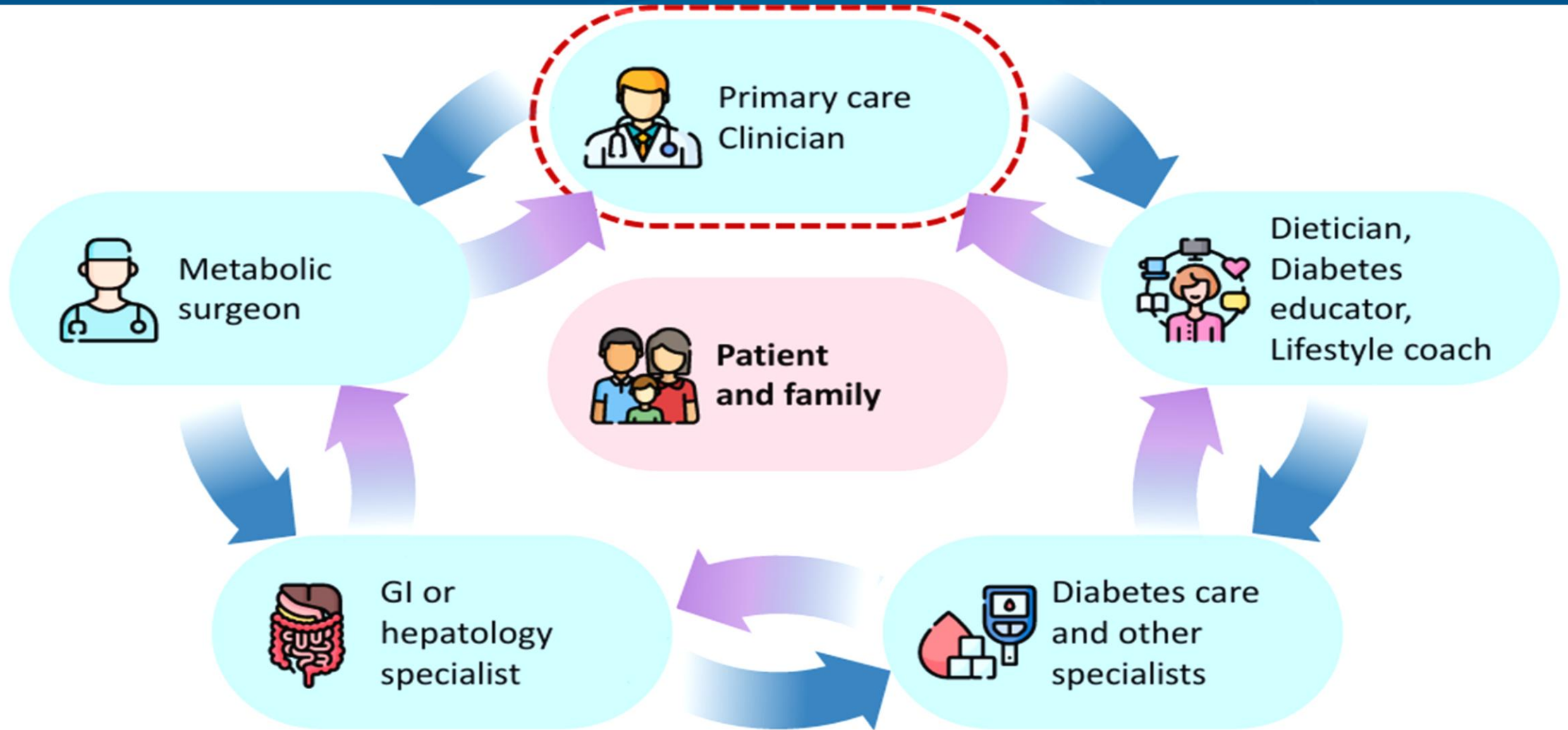
- ▶ 60 y/o F With Abnormal LFT's
- ▶ PMHx: T2DM (A1c 7.1%), Obesity (BMI 34.6 kg/m<sup>2</sup>), Metabolic Syndrome (Refractory to LSM).
- ▶ Social: CAGE ? Negative (PEth)
- ▶ Meds: Metformin
- ▶ Labs: AST/ALT 49 / 61 Plat 140, Hepatitis C Serology Negative
- ▶ FIB-4 Index 2.69
- ▶ VCTE: LSM 10.9 kPa (MASH with Fibrosis F3)

**What is the Most Appropriate Next Step in Management?**

- A. Wait & Watch**
- B. Re-Emphasize LSM**
- C. Optimize Pharmacologic Rx For DM Benefits For MASH**
- D. Refer to Hepatology**



# The Multi-Disciplinary Team For MASLD



Cusi K et al. Diabetes Spectr 2024;37(1):29-38.



# Management Approach

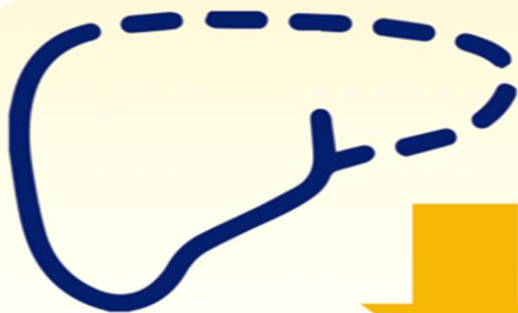
❖ Avoidance of ETOH

❖ Weight Loss:

Vilar-Gomez E et al. *Gastroenterology* 2015;149(2):367-378  
Aminian A et al. *JAMA*. 2021;326(20):2031-2042  
Rinella ME et al., *Hepatology* 2023;77(5):1797-1835



**Bariatric surgery in patients with MASH and obesity was associated with<sup>1</sup>:**



**12.4%**

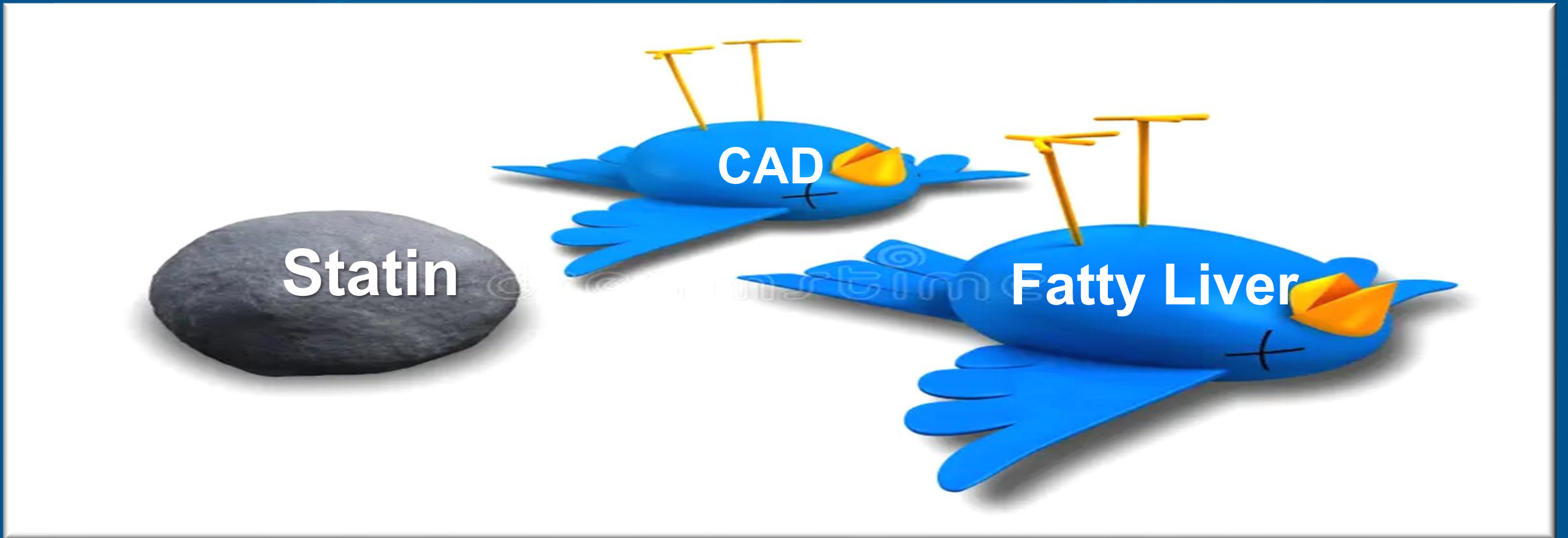
Adjusted 10-year absolute risk difference of major adverse liver outcomes<sup>a</sup>



**13.9%**

Adjusted 10-year absolute risk difference of major adverse cardiovascular events<sup>b</sup>

# ADA 2026 Recommendations: Recommendations For CV Risk Reduction



# Medications For T2DM

## Effects In MASLD

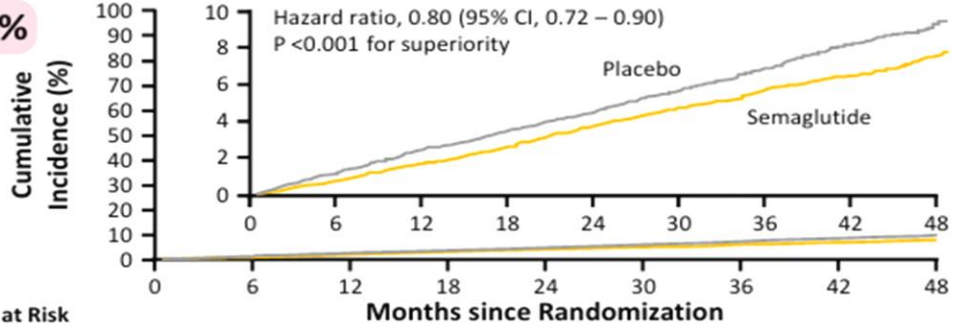
Drug/Drug Class	Steatosis	Steatohepatitis	Fibrosis	Cardiovascular Risk
Pioglitazone	↓	↓	Reduces progression	↓
GLP-1 receptor agonists	↓	↓	Reduces progression	↓
SGLT2 inhibitors	↓	?	?	↓



# SELECT Trial: Semaglutide, MACE, Mortality

## A. Primary Cardiovascular Composite End Point

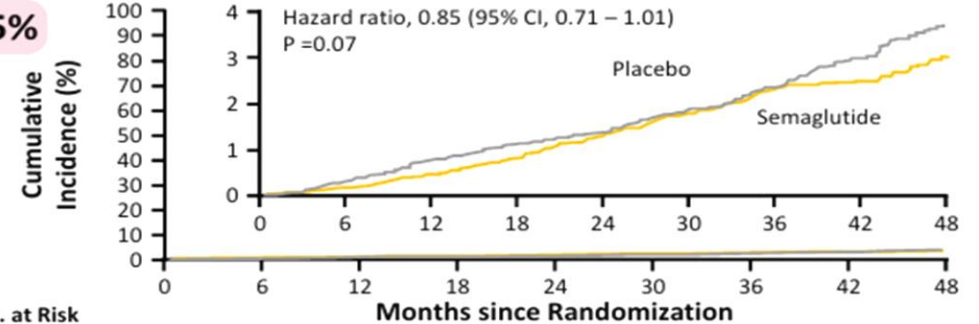
↓ 20%



No. at Risk	0	6	12	18	24	30	36	42	48
Placebo	8801	8652	8487	8326	8164	7101	5660	4015	1672
Semaglutide	8803	8695	8561	8427	8254	7229	5777	4126	1734

## B. Death from Cardiovascular Causes

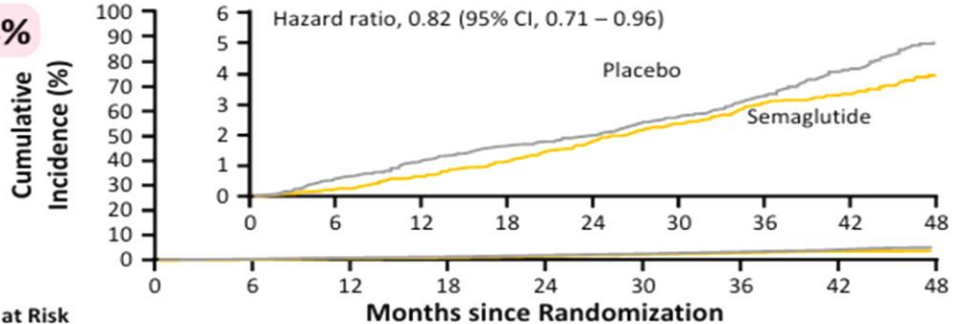
↓ 15%



No. at Risk	0	6	12	18	24	30	36	42	48
Placebo	8801	8733	8634	8528	8430	7395	5938	4250	1793
Semaglutide	8803	8748	8673	8584	8465	7452	5988	4315	1832

## C. Heart Failure Composite End Point

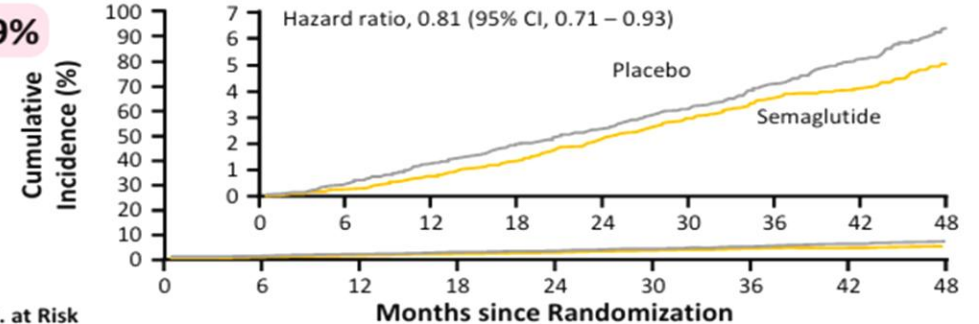
↓ 18%



No. at Risk	0	6	12	18	24	30	36	42	48
Placebo	8801	8711	8601	8485	8381	7341	5885	4198	1766
Semaglutide	8803	8740	8654	8557	8425	7409	5944	4277	1816

## D. Death from Any Cause

↓ 19%



No. at Risk	0	6	12	18	24	30	36	42	48
Placebo	8801	8733	8634	8528	8430	7395	5938	4250	1793
Semaglutide	8803	8748	8673	8584	8465	7452	5988	4315	1832



# Studies Of GLP-1 RA MASLD

## Primary outcome: relative reduction in liver fat on imaging

Author	GLP1-RA	Weight change	Reduction in liver fat content
Vanderheiden et al, 2016	Liraglutide	↓ 2.2%	↓ 31%
Feng et al, 2017	Liraglutide	↓ 6.4%	↓ 19%
Petit et al, 2017	Liraglutide	↓ 4.4%	↓ 19%
Frossing et al, 2018	Liraglutide	↓ 5.7%	↓ 32%
Kuchay et al, 2020	Dulaglutide	↓ 2.6%	↓ 20%

## Primary outcome: percentage of patients with resolution of MASH (by liver histology)

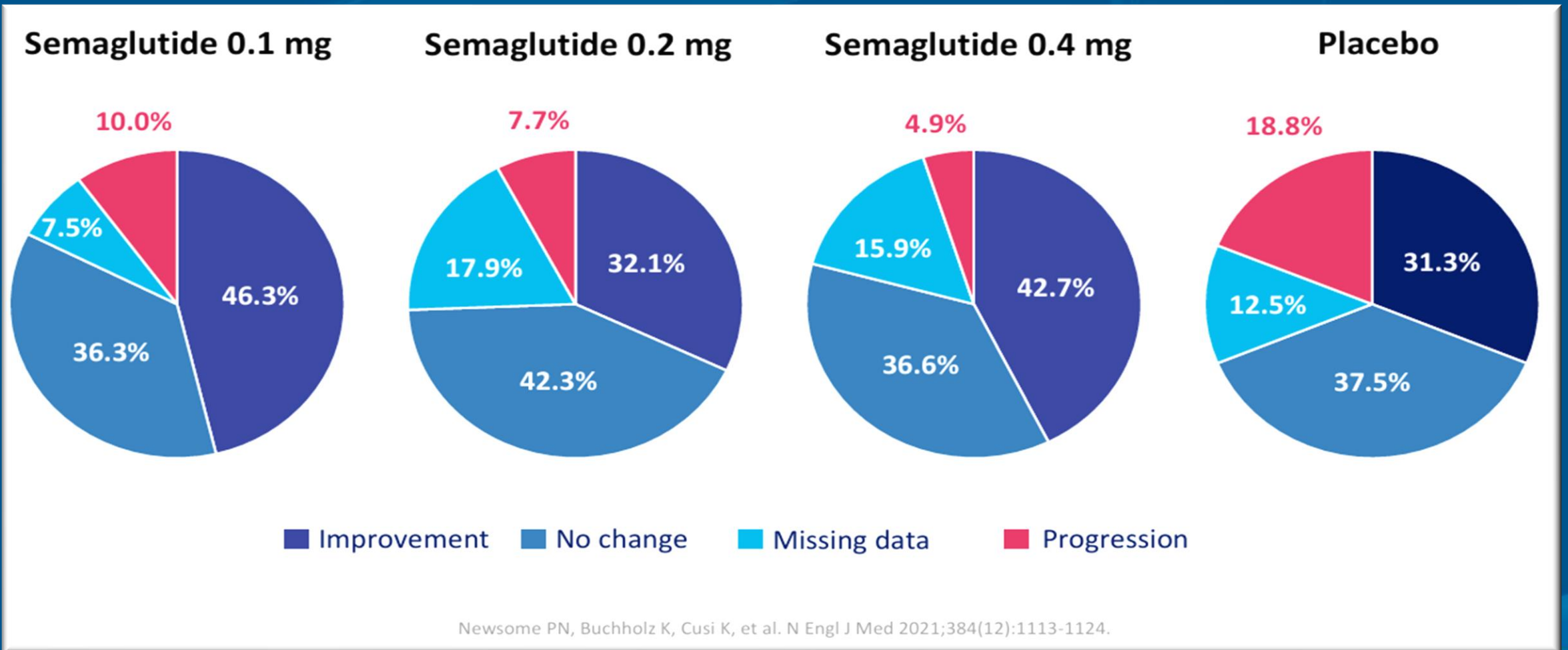
Author	GLP1-RA	Weight change	NASH resolution
Armstrong et al, 2016	Liraglutide	↓ 4.8%	30%
Newsome et al, 2020	Semaglutide	↓ 4%-12%	19%-42%

Studies with a minimal treatment period of ≥24 weeks and ≥50 patients. Arrows indicate statistically significant changes vs comparator. Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; RCT, randomized controlled trial.

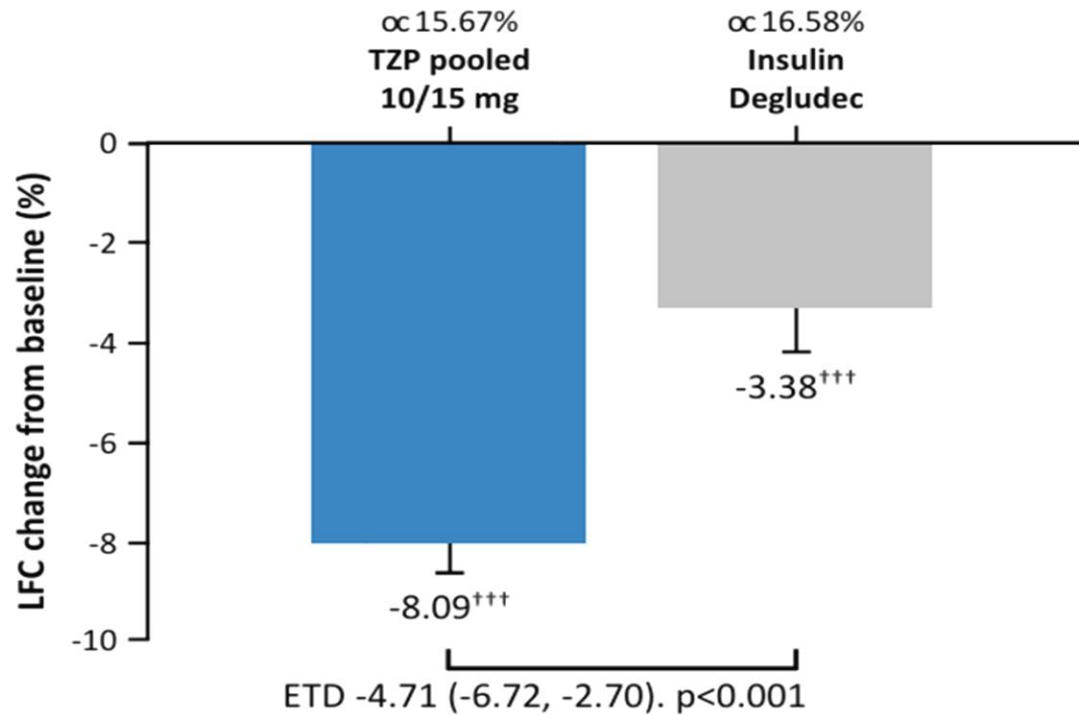
Chavez C, Cusi K, and Kadiyala S. JCEM 2022;107:29-38.



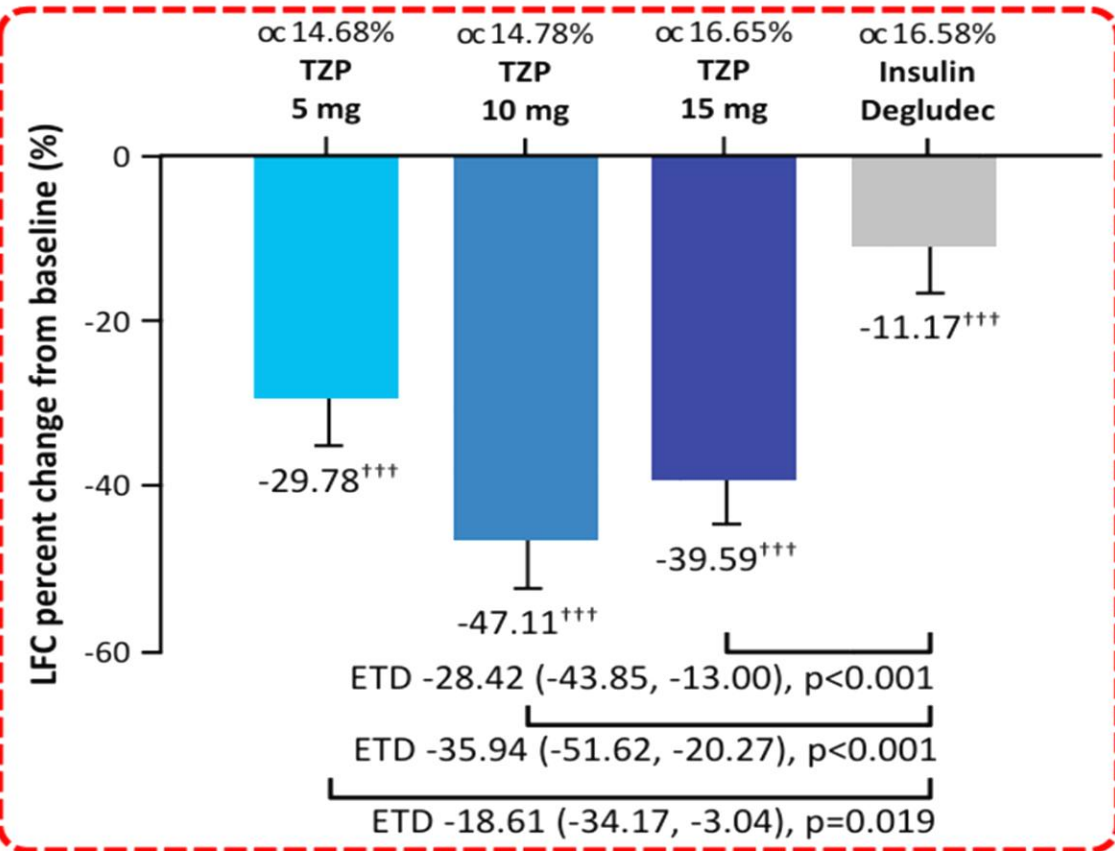
# MASH In Patients On Semaglutide



# SURPASS-3 Trial: Tirzepatide, Insulin, & Liver Fat Content



Data are LSM (SE) at 52 weeks. Estimated treatment differences (ETD) at 52 weeks are LSM (95% CI); mITT (MRI analysis set). ANCOVA analysis. † p<0.05; ††† p<0.001 vs. baseline within treatment group. α represents the mean value at baseline for the respective group.



# SYNERGY-NASH: MASH In Patients On Tirzepatide

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Tirzepatide for Metabolic Dysfunction– Associated Steatohepatitis with Liver Fibrosis

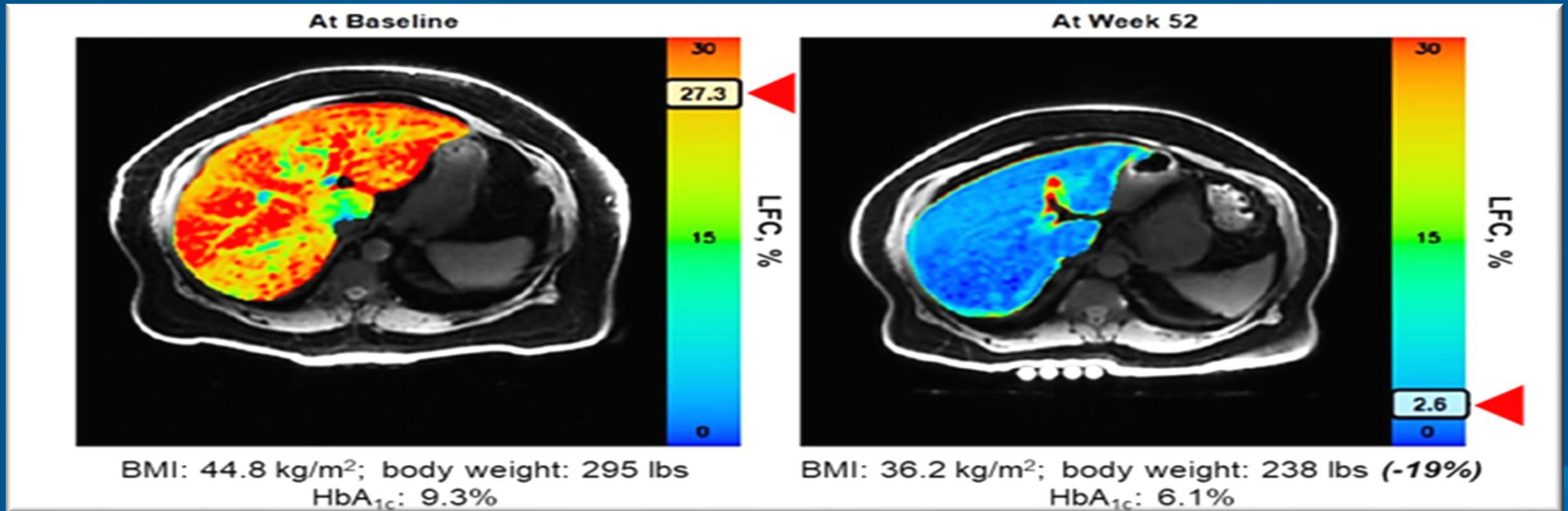
R. Loomba, M.L. Hartman, E.J. Lawitz, R. Vuppalanchi, J. Boursier,  
E. Bugianesi, M. Yoneda, C. Behling, O.W. Cummings, Y. Tang, B. Brouwers,  
D.A. Robins, A. Nikooie, M.C. Bunck, A. Haupt, and A.J. Sanyal,  
for the SYNERGY-NASH Investigators\*

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



# SURPASS-3 MRI Sub-Study: MASLD Before & After 52 Weeks Tirzepatide

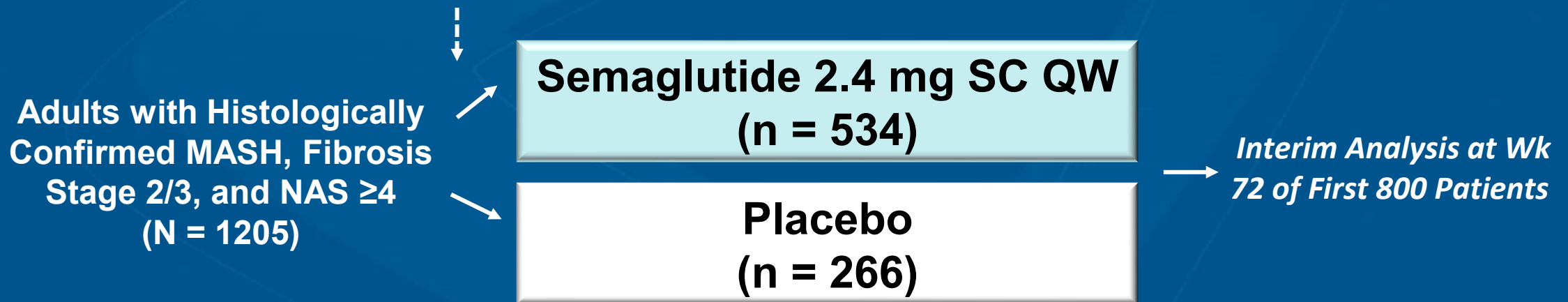
59 y/o Male: Metformin / SGLT-2i: Randomized to 5 mg Tirzepatide QWeek



# ESSENCE: Semaglutide in Patients With MASH

- ❖ **Multicenter, Double-Blind, Placebo-Controlled, Randomized Phase III Trial**

*Stratified by T2D Diagnosis, Fibrosis Stage, and Region*




- ❖ **Primary Endpoints:** Steatohepatitis Resolution with No Liver Fibrosis Worsening & Liver Fibrosis Improvement with No Steatohepatitis Worsening (Part 1 / Interim Analysis); Cirrhosis-Free Survival (Part 2)
- ❖ **Key Secondary Endpoints:** Weight Loss, Combined Steatohepatitis Resolution & Liver Fibrosis Improvement, Liver Enzyme Levels, Noninvasive Fibrosis Markers, & Safety



# ESSENCE – New Top - Line Data

## Semaglutide & MASH

### Phase 3 Trial of Semaglutide in Metabolic Dysfunction–Associated Steatohepatitis

**Authors:** Arun J. Sanyal, M.D., Philip N. Newsome, M.B., Ch.B., Ph.D., Iris Kliers, M.D., Laura Harms Østergaard, M.Sc., Michelle T. Long, M.D., Mette Skalshøi Kjær, M.D., Ph.D. , Anna M.G. Cali, M.D., Elisabetta Bugianesi, M.D., Ph.D., Mary E. Rinella, M.D., Michael Roden, M.D., and Vlad Ratziu, M.D., Ph.D., for the ESSENCE Study Group\* [Author Info & Affiliations](#)

Published April 30, 2025 | N Engl J Med 2025;392:2089-2099 | DOI: 10.1056/NEJMoa2413258

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**63.3%**

of participants  
had FIB-4  $\geq 1.3$

**64.0%**

of participants  
had liver stiffness  
VCTE  $> 8$  kPa

**55.5%**

of participants  
had ELF  $\geq 9.8$

with Semaglutide

(Mod – Advanced Fibrosis)

Fib-4 ~ 1.58

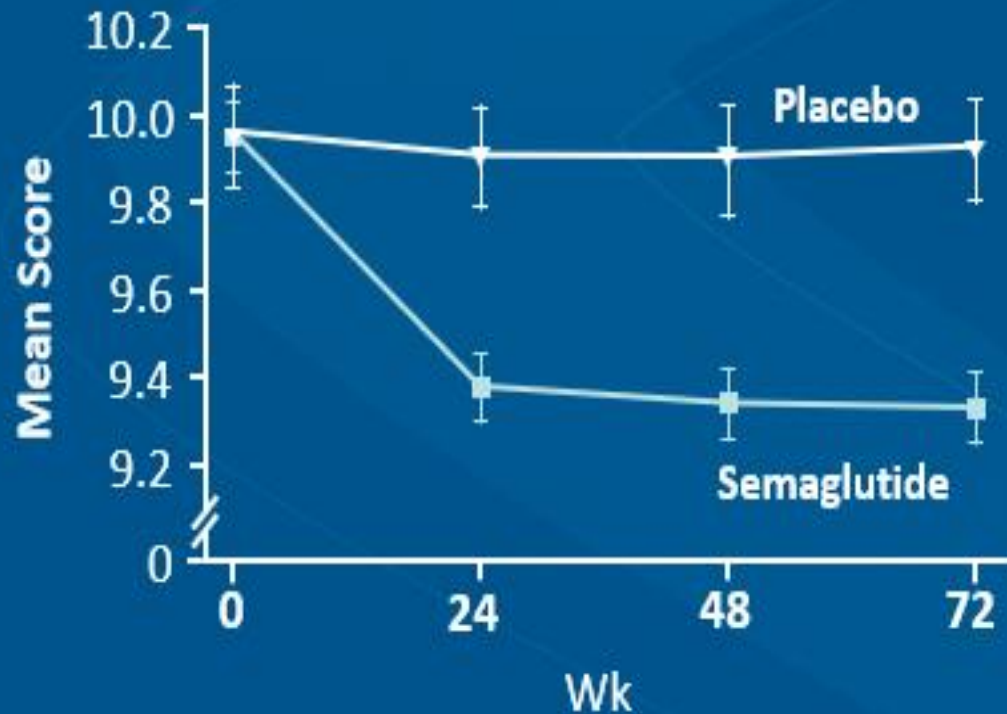
Mean CAP ~ 330 dB/m

Liver Stiffness ~ 12.9 kPa

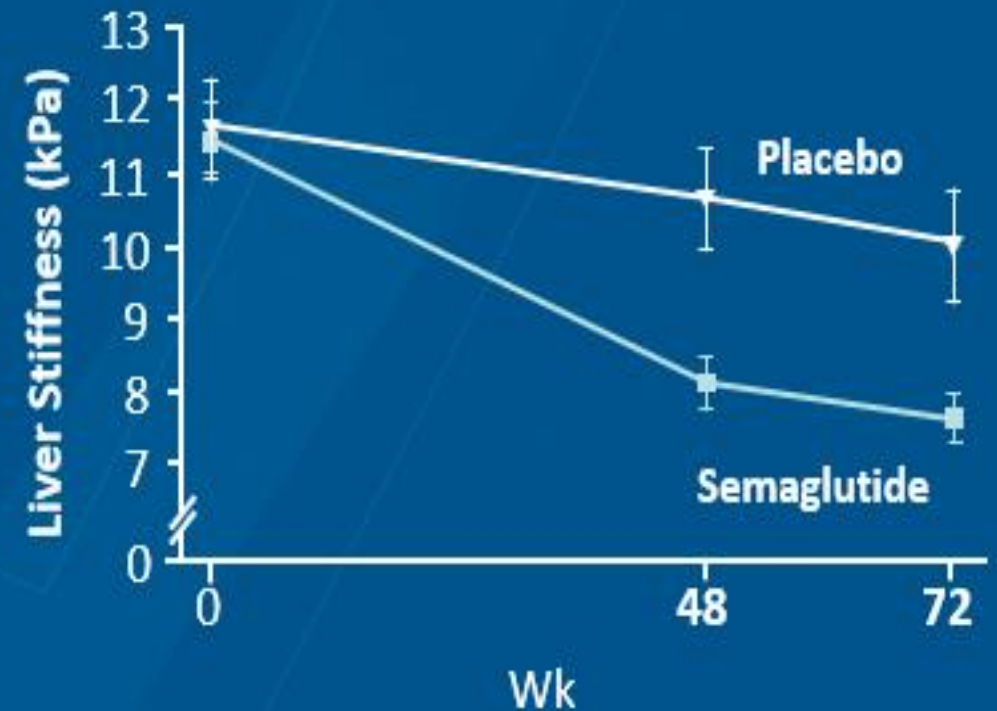


# Semaglutide In MASH: ESSENCE Trial Primary Endpoints

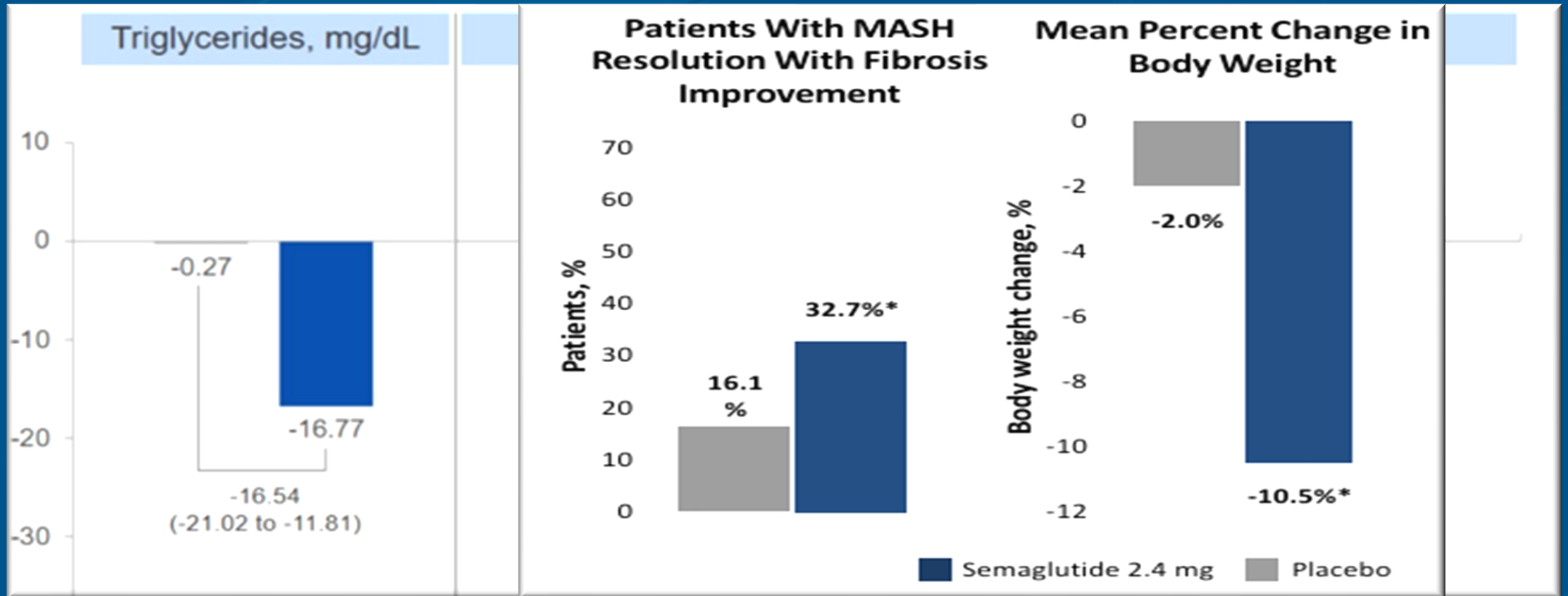
## Enhanced Liver Fibrosis Score



## Liver Stiffness per VCTE



# Semaglutide In MASH: Effects On Lipids / Weight



# ESSENCE: Safety

**Any AE's** 86.3% (Semaglutide) vs 79.7% (Placebo)

**Serious AE's** 13.4% in Both Groups

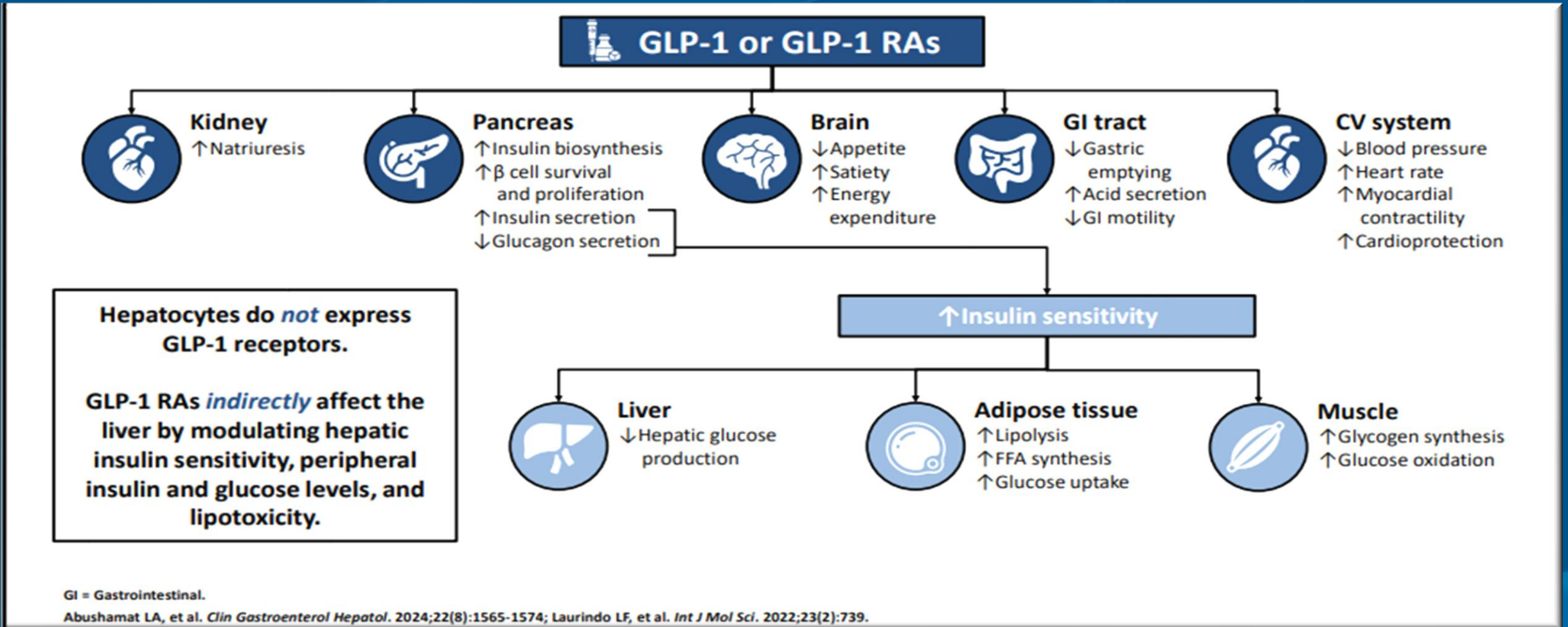
**Discontinuation d/t AE's** 2.6% (Semaglutide) vs 3.3% (Placebo)

**Most Common AE's:** Gastrointestinal (Nausea, Diarrhea, Constipation, Vomiting)

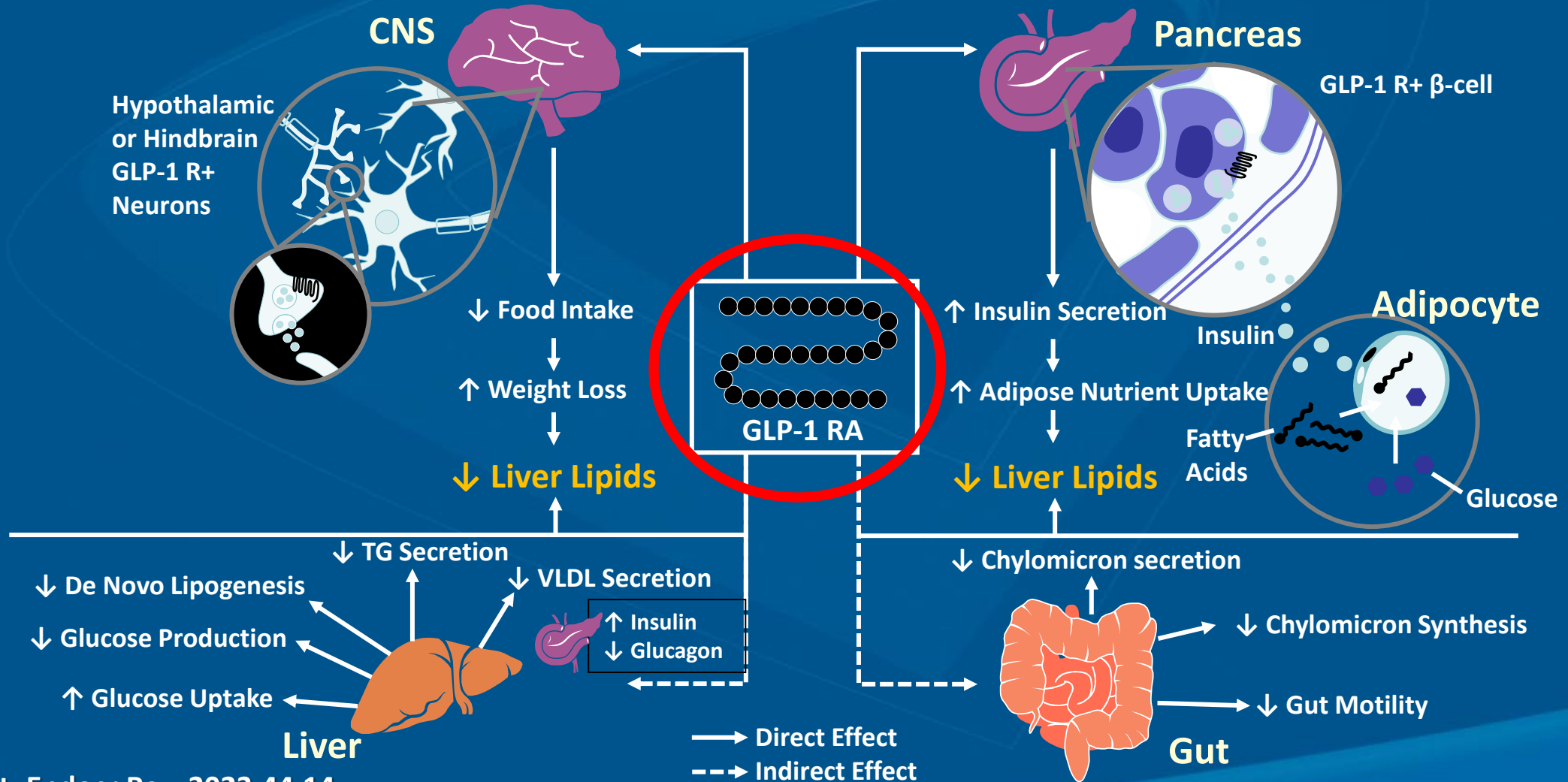
**No Liver - Specific or New:** Safety Concerns Identified



# Benefits GLP1-RA's In Patients With MASLD



# Role of GLP-1 in MASH



# GLP-1 RA Induce Improvement Pathology MASH Mostly Via Extrahepatic Actions

## Cell Metabolism



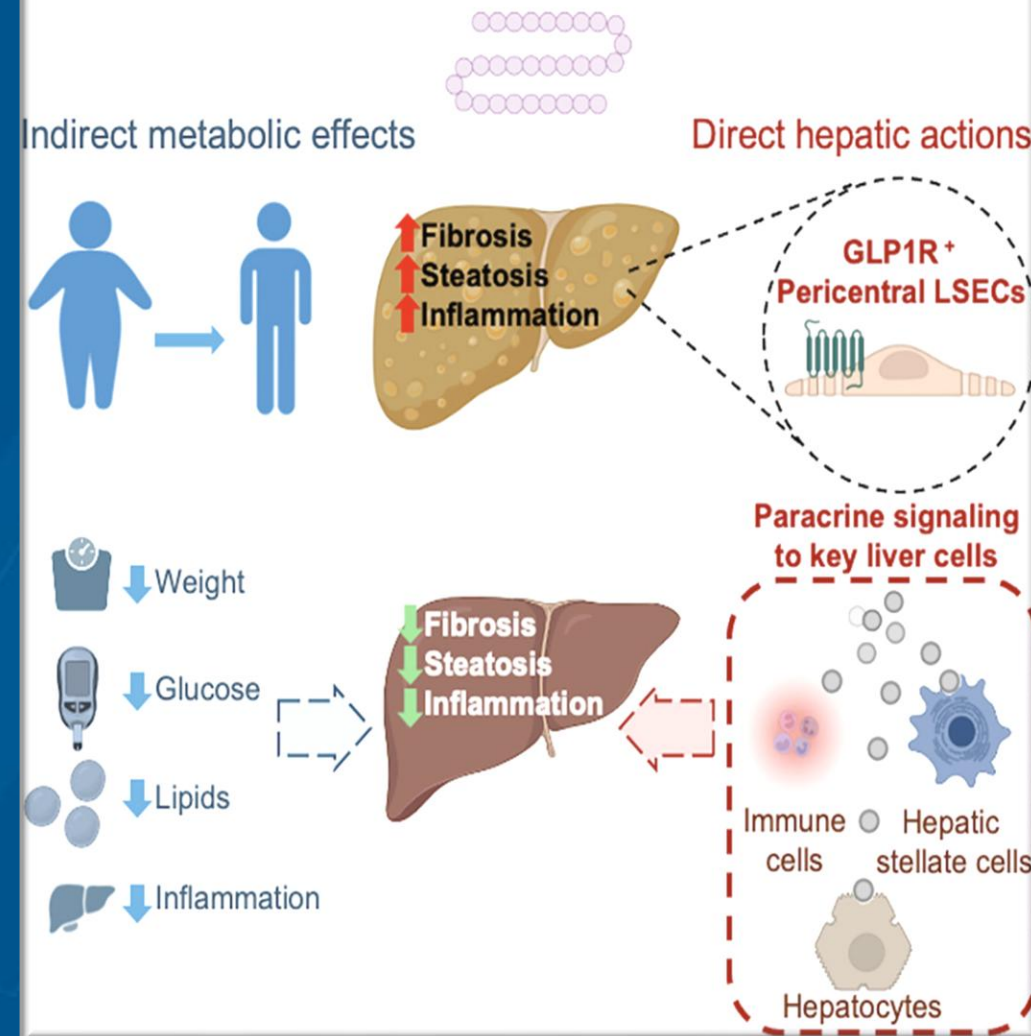
Available online 14 April 2026

In Press, Corrected Proof [What's this?](#)

<https://doi.org/10.1016/j.cmet.2026.03.011>

Article  
The weight-loss-independent hepatoprotective benefits of semaglutide are orchestrated by intrahepatic sinusoidal endothelial GLP-1 receptors

### GLP-1 Medicines



# SGLT2 Inhibitors: Antioxidant Effects

- Reduce oxidative stress
- Enhance contractility
- Normalize mitochondrial function
- Reduce cardiomyopathy
- Reduce coronary microvascular damage

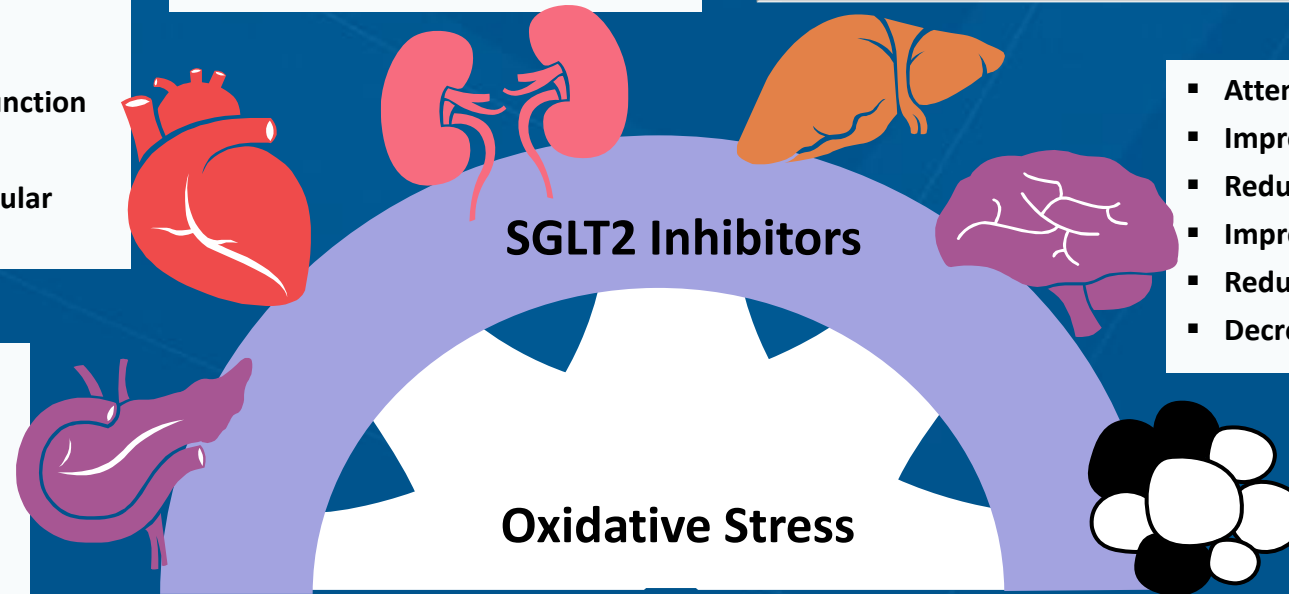
- Better glucose control
- Reduce insulin resistance
- Optimize hemodynamic effects
- Lowering free radical generation
- Enhance antioxidant capacity

- Reduce albuminuria
- Reduce tubular injuries
- Suppress ROS generation
- Reduce renal interstitial inflammation and fibrosis
- Optimize endothelial function
- Improve mitochondrial function

- Normalize Liver Enzymes
- Ameliorate Fat Deposition
- Attenuate Fibrosis
- Reduce Oxidative Stress
- Enhance Antioxidant Capacities
- Reduce Inflammation

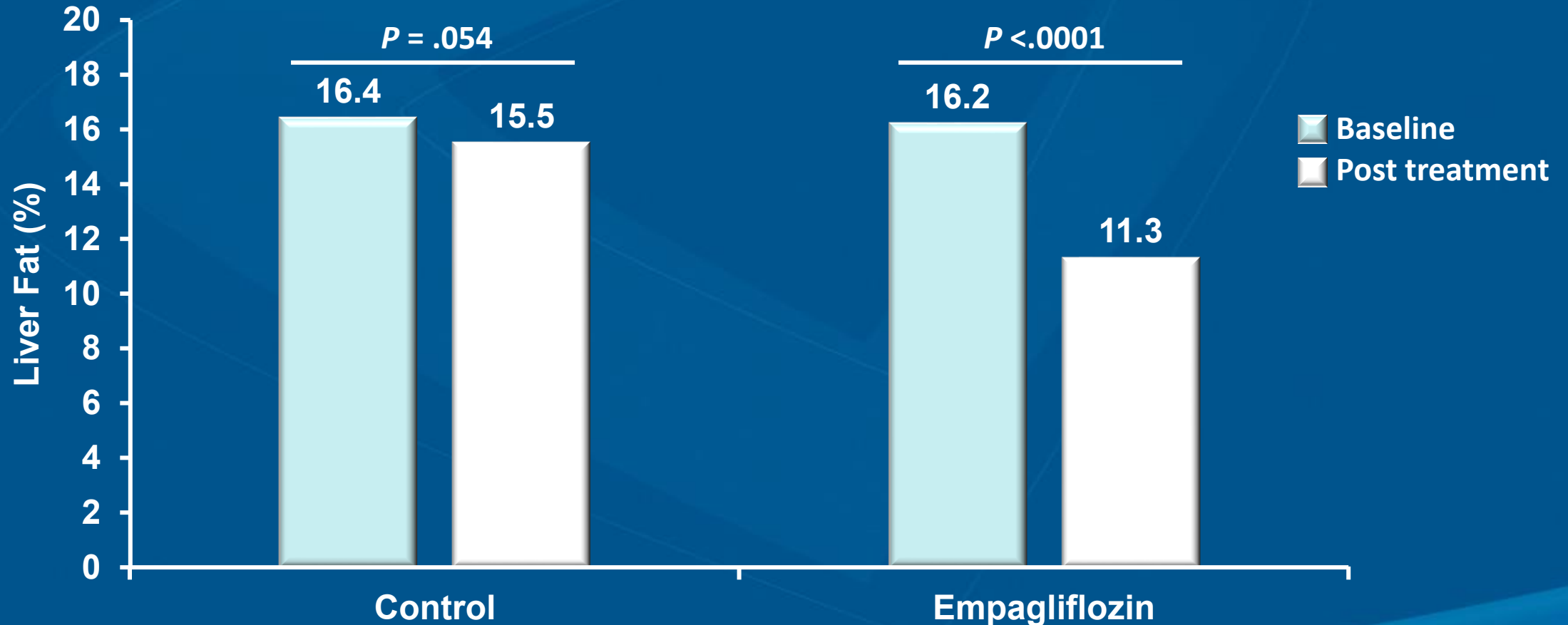
- Attenuate cerebral oxidative stress
- Improve cognitive function
- Reduce infarct size
- Improve motor function
- Reduced senile plaque density and amyloid  $\beta$
- Decrease seizure activity

- Reduce free radical production
- Inhibit tumor neovascularization
- Attenuate oncogenic inflammation
- Inhibit tumor cell proliferation

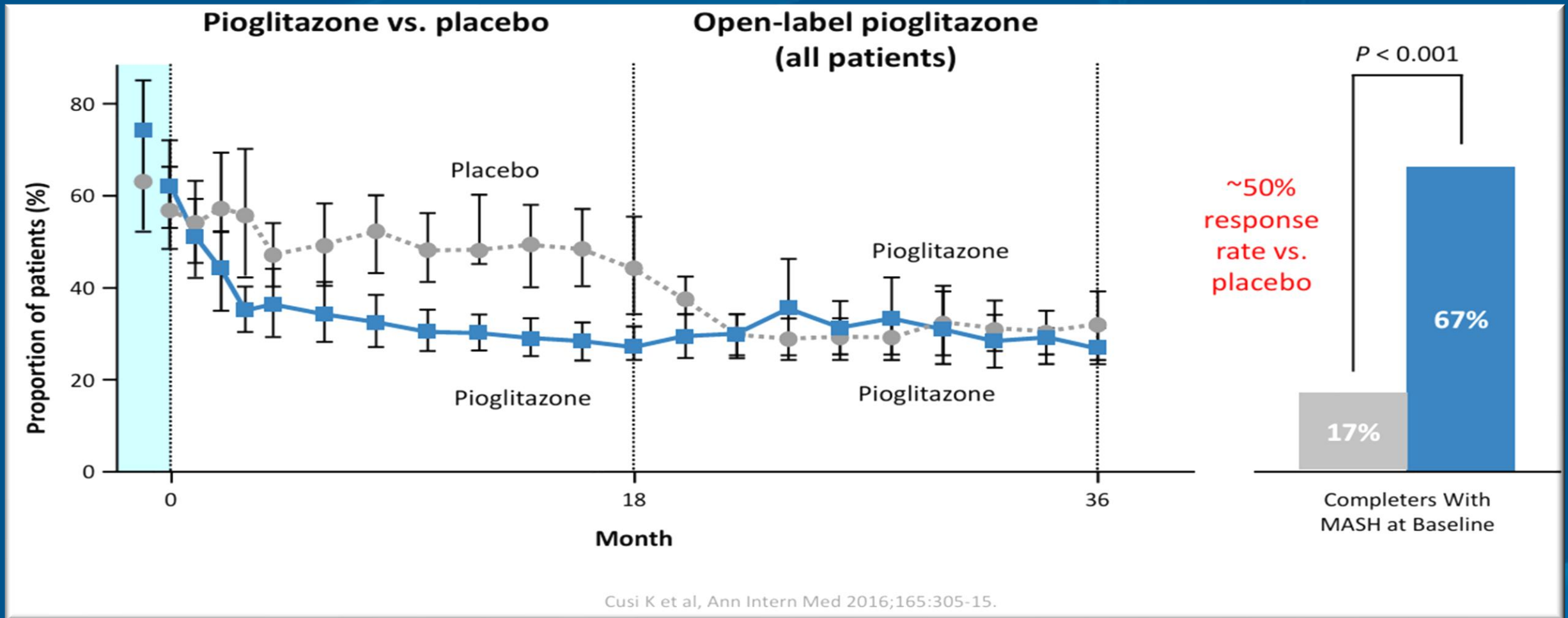


# SGLT2 Inhibitor: Empagliflozin

Change in Liver Fat Relative to BL Assessed by MRI-PDFF



# Plasma ALT & Pioglitazone Compared To Placebo



Cusi K et al, Ann Intern Med 2016;165:305-15.



# Pioglitazone & CVDz In MASLD

Medicine<sup>®</sup>

Systematic Review and Meta-Analysis

OPEN

## **Pioglitazone on nonalcoholic steatohepatitis** **A systematic review and meta-analysis of 15 RCTs**

Yan Zhao, Master<sup>a,b</sup>, Wenli Zhao, PhD<sup>c,d</sup>, Hongwu Wang, PhD<sup>e</sup>, Ye Zhao, PhD<sup>f</sup>, Huaien Bu, PhD<sup>g</sup>, Hirokazu Takahashi, PhD<sup>h,\*</sup>



# PPAR: Pioglitazone

Study	N	Duration	Improvements in NASH			
			ALT/AST	Steatosis	Inflammation	Fibrosis
Pomerat 2004 <sup>1</sup>	18	48 wk	✓	✓	✓	✓
Belfort 2006, <sup>2</sup> Gastaldelli 2021 <sup>3</sup>	55	6 mo	✓	✓	✓	✓
Aithal 2008 <sup>4</sup>	74	12 mo	✓			✓
Sanyal 2010 <sup>5</sup> (PIVENS)	247	96 wk	✓	✓	✓	
Cusi 2016 <sup>6</sup>	101	18 mo		✓	✓	✓
Huang 2021 <sup>7</sup>	90	24 wk	✓	✓	✓	
Meta-analysis (Musso 2017 <sup>8</sup> )	392	6-24 mo	--	--	--	✓
Meta-analysis (Boettcher 2012 <sup>9</sup> )	271	6-24 mo	--	✓	✓	✓

1. Pomerat. Hepatology. 2004;39:188. 2. Belfort. NEJM. 2006;355:2297. 3. Gastaldelli. Liver Int. 2021;41:2659.

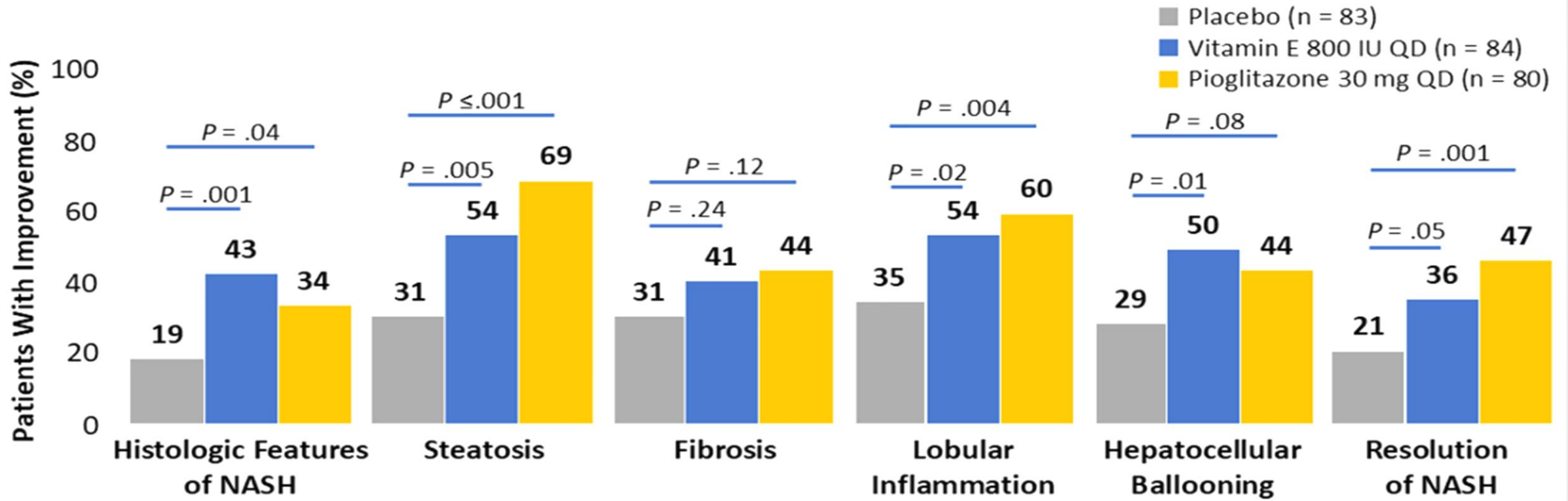
4. Aithal. Gastroenterology 2008;135:1176. 5. Sanyal. NEJM. 2010;362:1675. 6. Cusi. Ann Intern Med. 2016;165:305.

7. Huang. Hepatol Int. 2021;15:1136. 8. Musso. JAMA Intern Med. 2017;177:6339. 9. Boettcher. Aliment Pharmacol Ther. 2012;35:66.



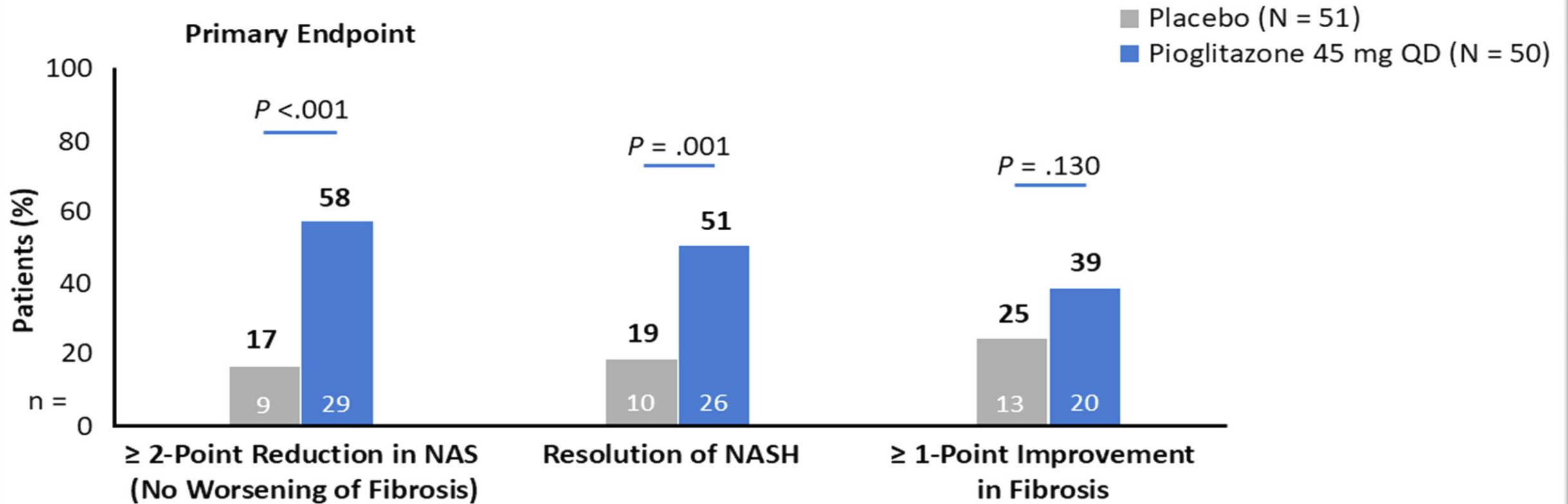
# PIVENS: Pioglitazone & Vitamin E In MASH @ 96 Weeks

- Double-blind, placebo-controlled, randomized phase III study in adults with biopsy-proven NASH and no diabetes or cirrhosis (N = 247)



# Pioglitazone In MASH With Pre-DM / Diabetes: 18 Month Outcomes

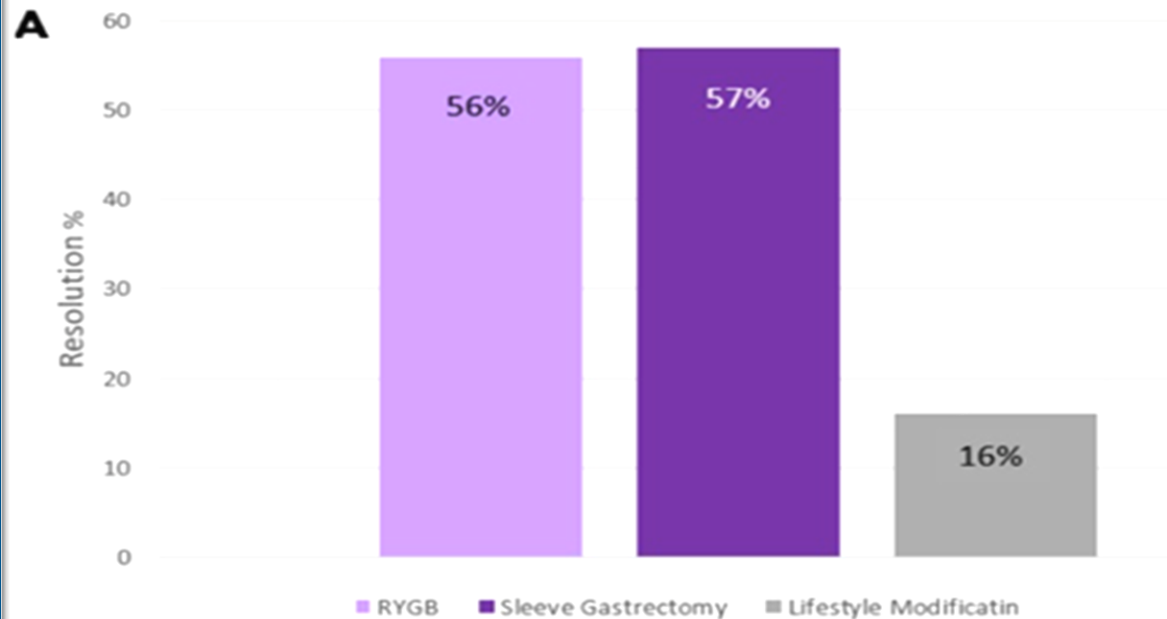
- Randomized, placebo-controlled, double-blind phase IV study of patients with NASH and prediabetes or T2D (N = 101)<sup>[1]</sup>



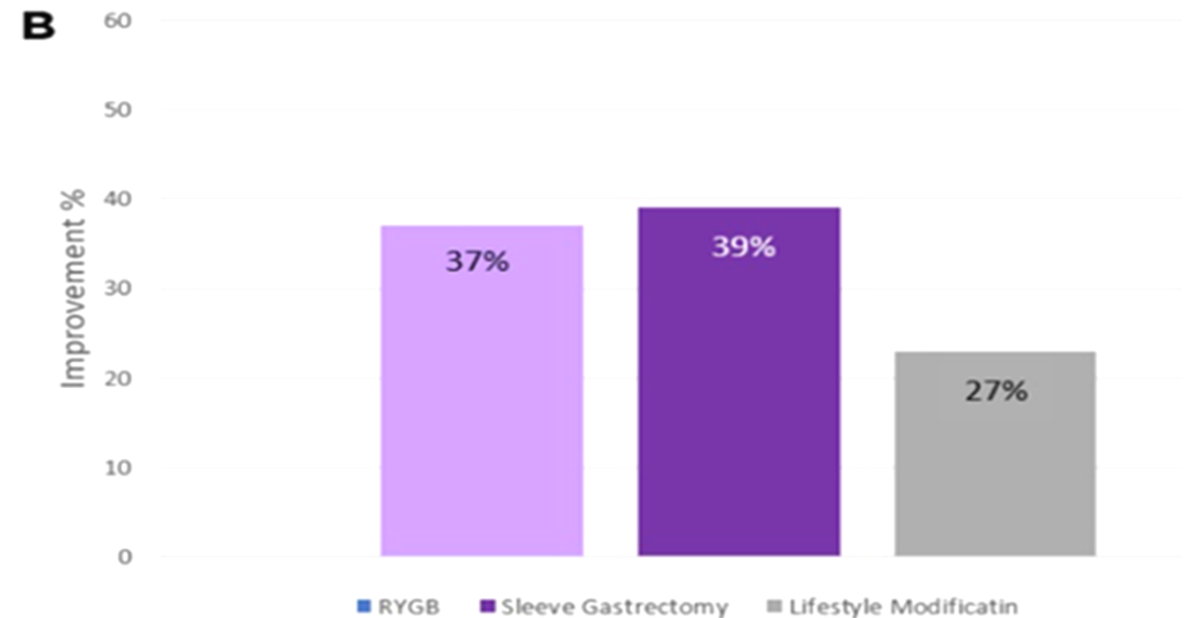
# BRAVES Study: Bariatric Surgery Superior To Lifestyle / Medical Treatment In MASH

288 subjects with MASH, randomized 1:1:1 to RNYGB, Sleeve gastrectomy or medical treatment  
Medical treatment included vitamin E (Pioglitazone and/or Liraglutide in subjects with T2D)

Resolution of MASH without worsening fibrosis



Improvement in at least one stage of fibrosis without worsening of MASH



1. Aminian. JAMA. 11/11/21. doi:10.1001/JAMA.2021.19569.
2. Verrastro O. et al., *Lancet*. 2023;401:1786-1797



# New Emerging Therapies

- ◊ Resmetirom (THR-Beta Agonist)
- ◊ FDA Approval March 2024: Indicated In Conjunction With Diet & Exercise Treatment of Adults with:
  - Non - Cirrhotic Non - Alcoholic Steatohepatitis (NASH) With
  - Moderate – To – Severe Liver Fibrosis (F2 – F3)



# Role THR - Beta In Hepatic Lipid Metabolism

## Mechanism of Action

Selective stimulation of THR- $\beta$ , a nuclear receptor primarily found in hepatocytes that is responsible for regulating critical liver processes

Differential THR- $\alpha$  and THR- $\beta$  expression mediates liver selectivity

THR- $\beta$  >>> THR- $\alpha$



THR- $\alpha$



- **Increased THR- $\beta$  signaling in the liver has been associated with:**
  - Improved lipid metabolism, leading to reduced levels of triglycerides and free fatty acids
  - Reduced liver inflammation
- **As a result, resmetirom can promote liver health and decrease damage to the liver**

THR = Thyroid Hormone Receptor

Karim G, et al. *touchREV Endocrinol.* 2023;19(1):60-70; Petta S, et al. *Liver Int.* 2024;44(7):1526-1536.

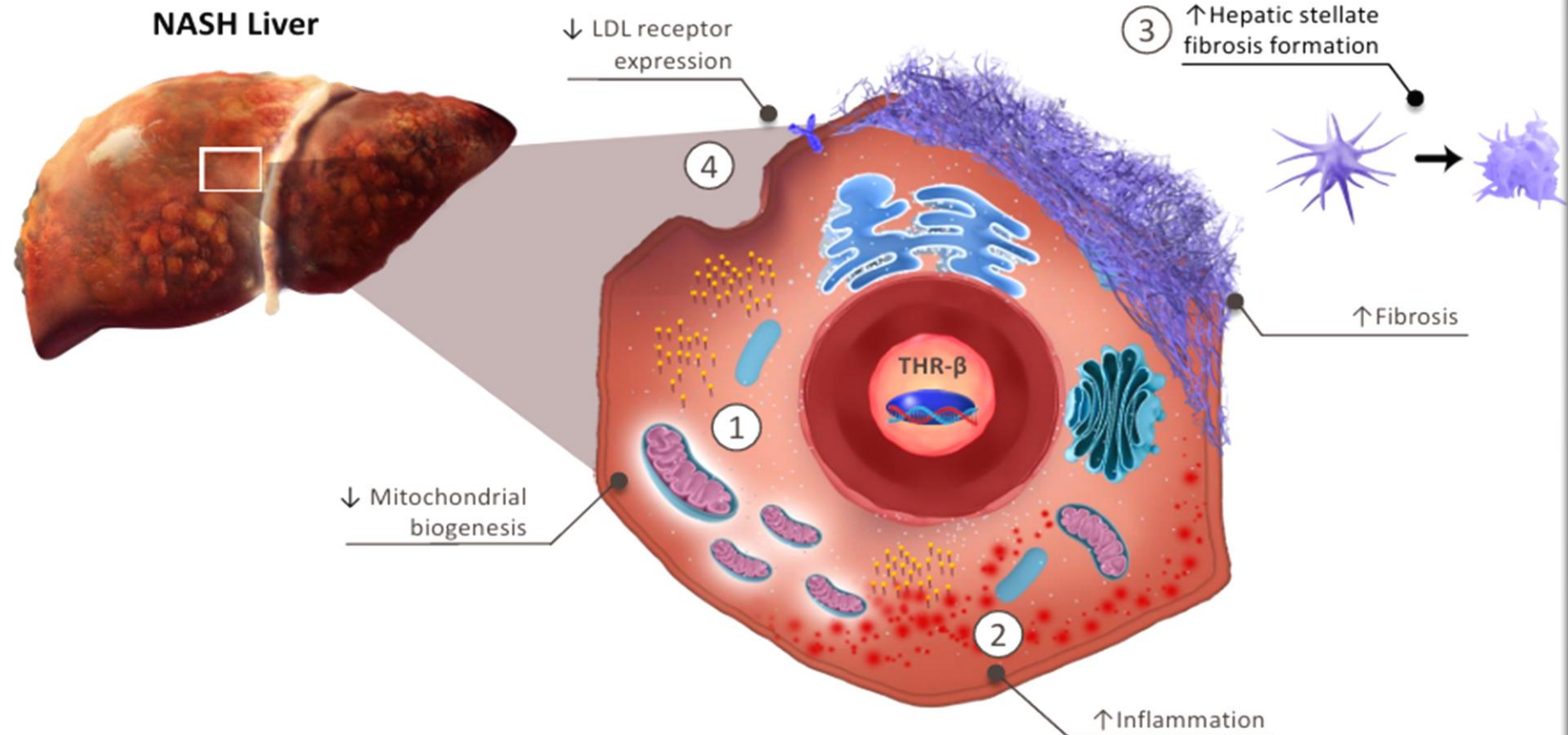
1. Ritter MJ et al., *Hepatology.* 2020;72:742-752.
2. Sinha RA et al., *Nat Rev Endocrinol.* 2018;14:259-269.
3. Taub R et al, *Atherosclerosis.* 2013;230:373-380.
4. Harrison SA et al., *Lancet* 2019;394:2012-2024



# Thyroid Hormone Dysfunction Influences Key Pathways Involved In MASLD / MASH

Low THR- $\beta$  activity exacerbates:<sup>1-3</sup>

- 1 Mitochondrial Dysfunction (fat accumulation)
- 2 Inflammation
- 3 Fibrosis through stellate activation (scarring)
- 4 Dyslipidemia

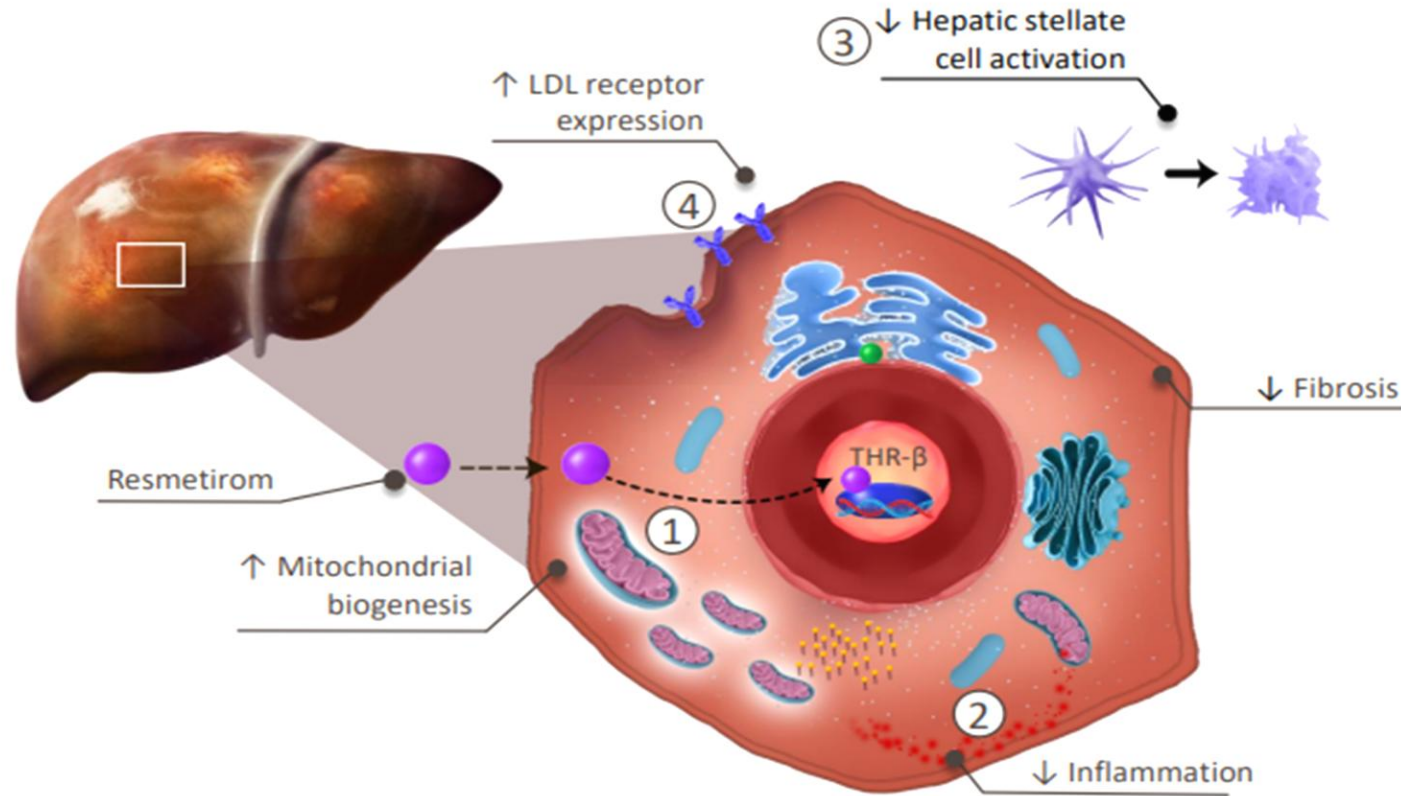


1. Sinha RA, et al. *Nat Rev Endocrinol*. 2018;14:259-269.
2. Karim G, Bansal MB. *touchRev Endocrinol*. 2023;19:60-70.
3. *Proc Natl Acad Sci USA*. 2016;113(24):E3451-E3460



# Key Pathways Involved In NASH Pathology

## Resmetirom MOA



### Resmetirom MOA<sup>1-4</sup>

- 1 Mitochondrial biogenesis
- 2 Reduced inflammation
- 3 Reduced activation of hepatic stellate cells → decreased fibrosis
- 4 Increased LDL receptor expression

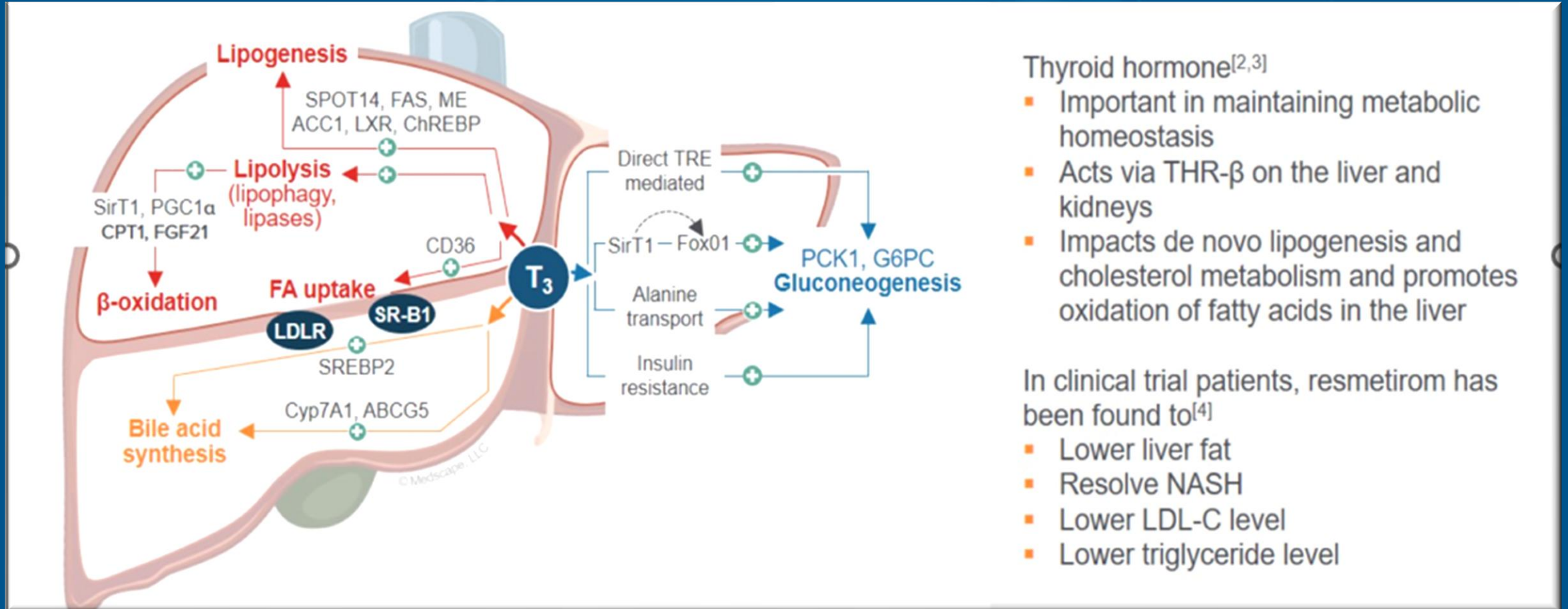
1. Sinha RA et al., *Nat Rev Endocrinol.* 2018;14:259-269.

2. Alonso-Merlino. *Proc Natl Acad Sci USA.* 2016;113(24):E3451-E3460.

3. Karim G, Basnsal MB. *touchRev Endocrinol.* 2023;19:60-70. 4. Harrison SA. *N Engl J Med.* 2024 Feb 8;390(6):497-509



# Resmetirom MOA: THR-Beta Agonist



Thyroid hormone<sup>[2,3]</sup>

- Important in maintaining metabolic homeostasis
- Acts via THR-β on the liver and kidneys
- Impacts de novo lipogenesis and cholesterol metabolism and promotes oxidation of fatty acids in the liver

In clinical trial patients, resmetirom has been found to<sup>[4]</sup>

- Lower liver fat
- Resolve NASH
- Lower LDL-C level
- Lower triglyceride level

1. Sinha RA et al., *Trends Endocrinol Metab.* 2014;25:538-545. 2. Ritter MJ et al., *Hepatology.* 2020;72:742-752.  
3. Sinha RA et al., *Cell Biosci.* 2016;6:46. 4. Harrison SA et al., *Lancet* 2019;394:2012-2024



# Resmetirom PK / PD

## Specificity/Selectivity<sup>1-5</sup>

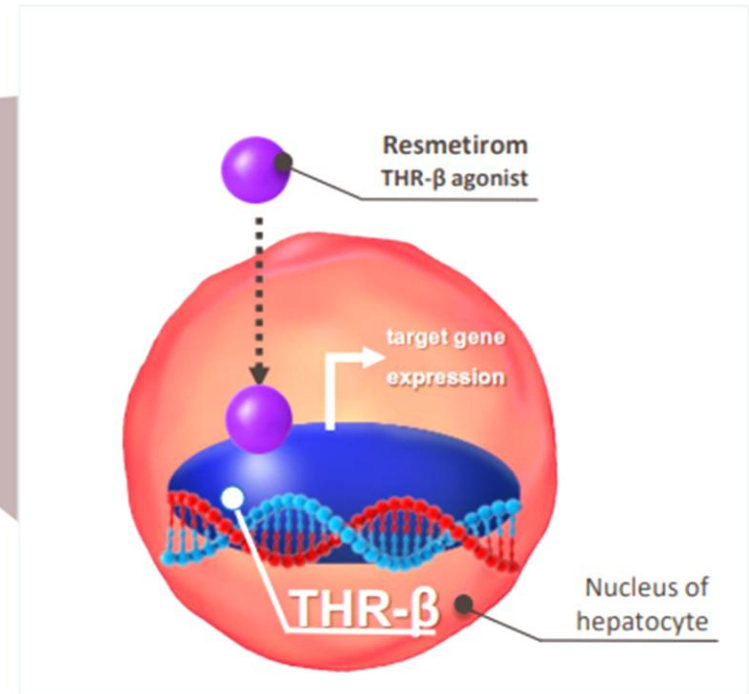
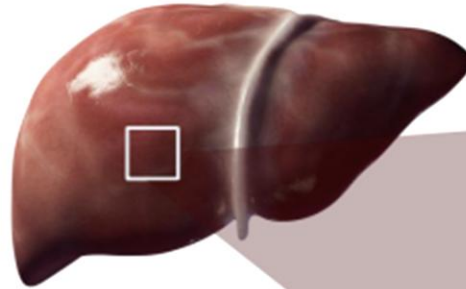
- Liver: Plasma ratio = 10:1
- 18-28x selective for Beta:Alpha
- 99% protein bound
- Half life = 4.5 hours
  
- No observed side effects on **THR- $\alpha$**  receptor present in:



**Bone**  
(osteoporosis)



**Heart**  
(rate and rhythm)







1. Kelly MJ et al., *J Med Chem.* 2014;54:3912-3923.
2. Taub R et al, *Atherosclerosis.* 2013;230:373-380.
3. Harrison SA et al., *Lancet* 2019;394:2012-2024.
4. Harrison SA et al., *Hepatol Commun.* 2021;5:573-588.
5. Harrison SA et al., *N Engl J Med.* 2024 Feb 8;390(6):497-509



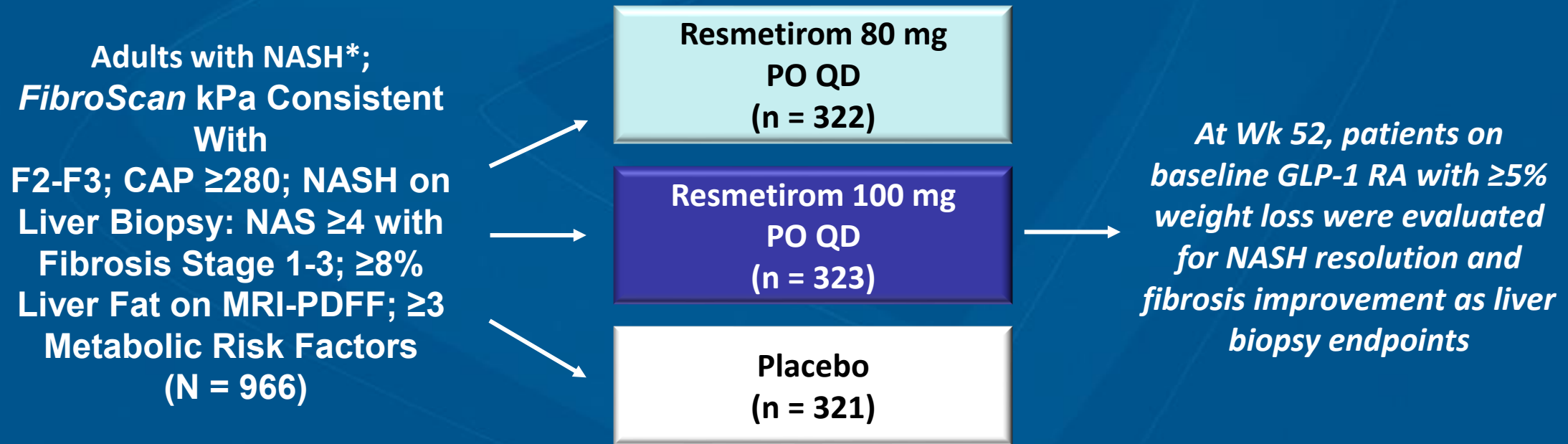
# MAESTRO Clinical Development Program

MAESTRO clinical trials are intended to provide a comprehensive data set in patients with NASH

			
<b>MAESTRO NAFLD-1</b>	<b>MAESTRO NAFLD-OLE</b>	<b>MAESTRO NASH</b>	<b>MAESTRO NASH OUTCOMES</b>
Safety & tolerability as measured by incidence of Adverse Events (AE)	Safety & tolerability as measured by incidence of AEs (Extension to MAESTRO-NAFLD-1)	NASH resolution and/or fibrosis improvement on liver biopsy and composite clinical events	Event-driven trial evaluating progression to hepatic decompensation in patients with well-compensated NASH cirrhosis
52 weeks	52 weeks	52 weeks biopsy (completed) 54 months clinical outcomes	~36 months
~1200 patients (Completed)	~700 patients (Ongoing)	~1700 patients (Ongoing)	~700 patients (Recruiting)

# MAESTRO-NASH: Resmetirom in Patients With MASH

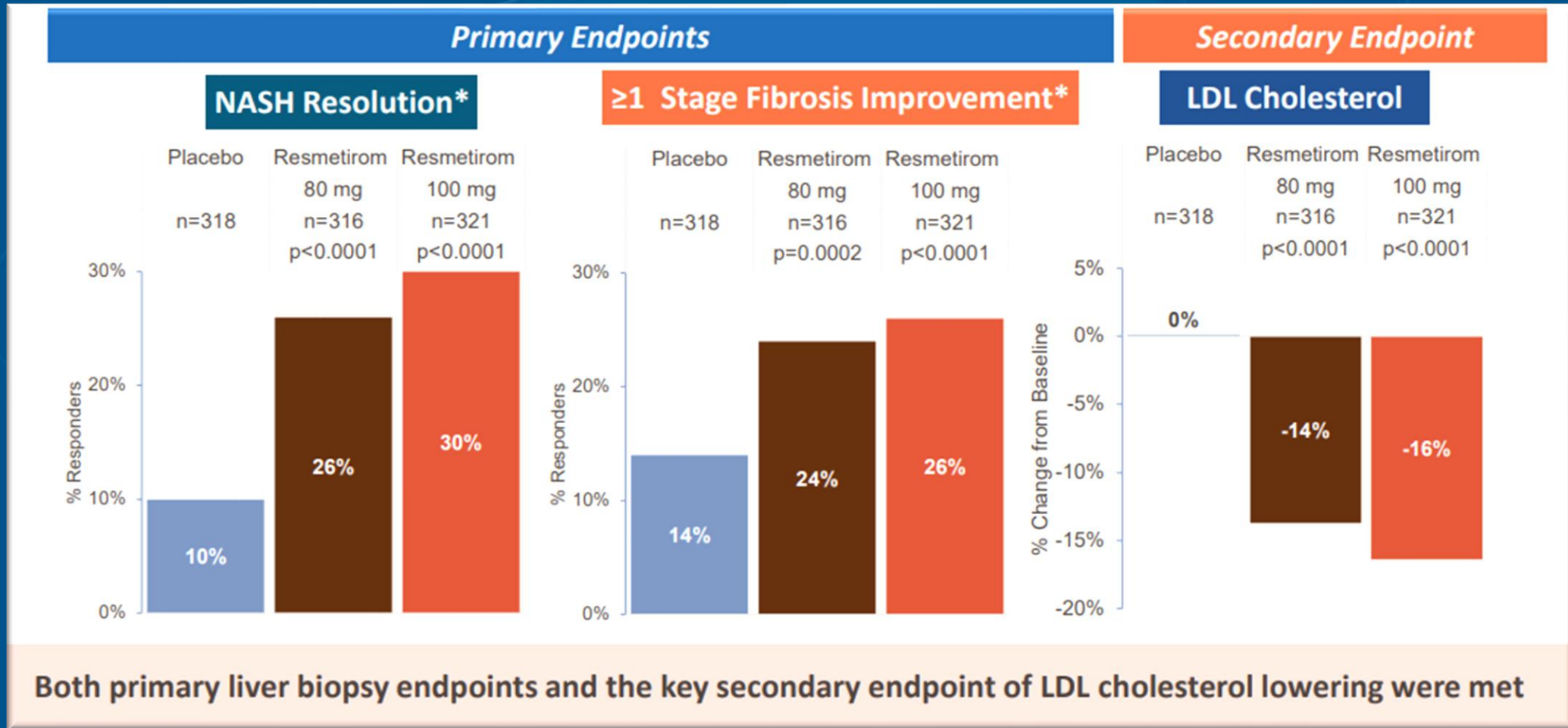
- ❖ Multinational, Double-Blind, Placebo-Controlled, Randomized Phase III Trial



- ❖ Coprimary Endpoints: NASH Resolution at Wk 52, Improvement in Fibrosis by  $\geq 1$  Stage with No Worsening of NAFLD Score
- ❖ Key Secondary Endpoint: Percent LDL-C Change From Baseline at Wk 24

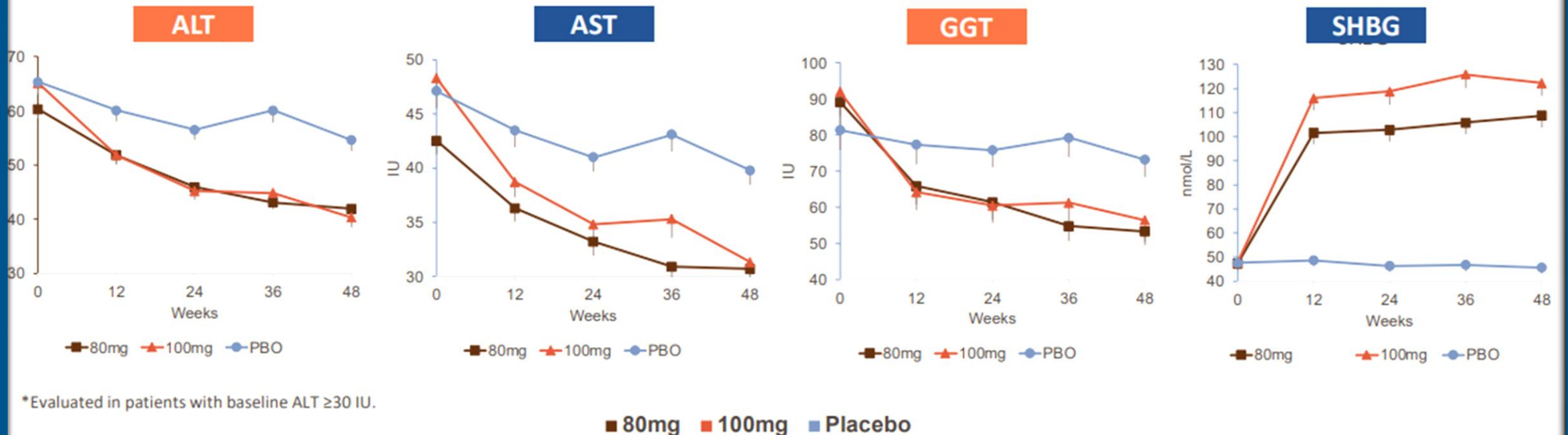


# Biopsies At Baseline & Week 52



# Change From Baseline Liver Enzymes & SHBG

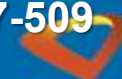
- Reduction of liver enzymes relative to placebo, both percentage change and absolute reduction
- Associated with the neutral biomarker SHBG that increased in proportion to resmetirom target engagement (exposure)



# Trends Observed Non-Invasive Tests After Resmetirom Use

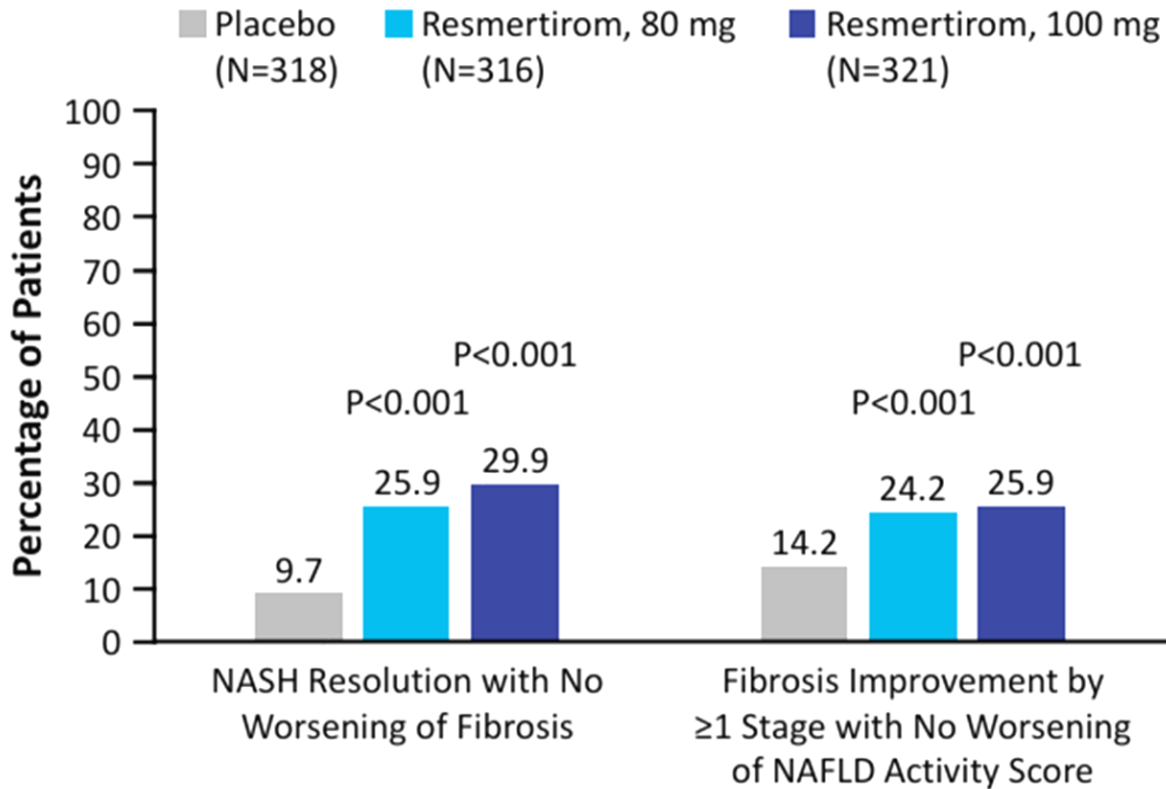
## MAESTRO-NASH

Test type	Steatosis and inflammation marker (NASH resolution)	Fibrosis marker
MRI-PDFF % liver fat	↓	
Fibroscan CAP	↓	
Liver volume	↓	
Liver enzymes	↓	↓
ELF		↓
MRE kPa		↓
Fibroscan LSM		↓

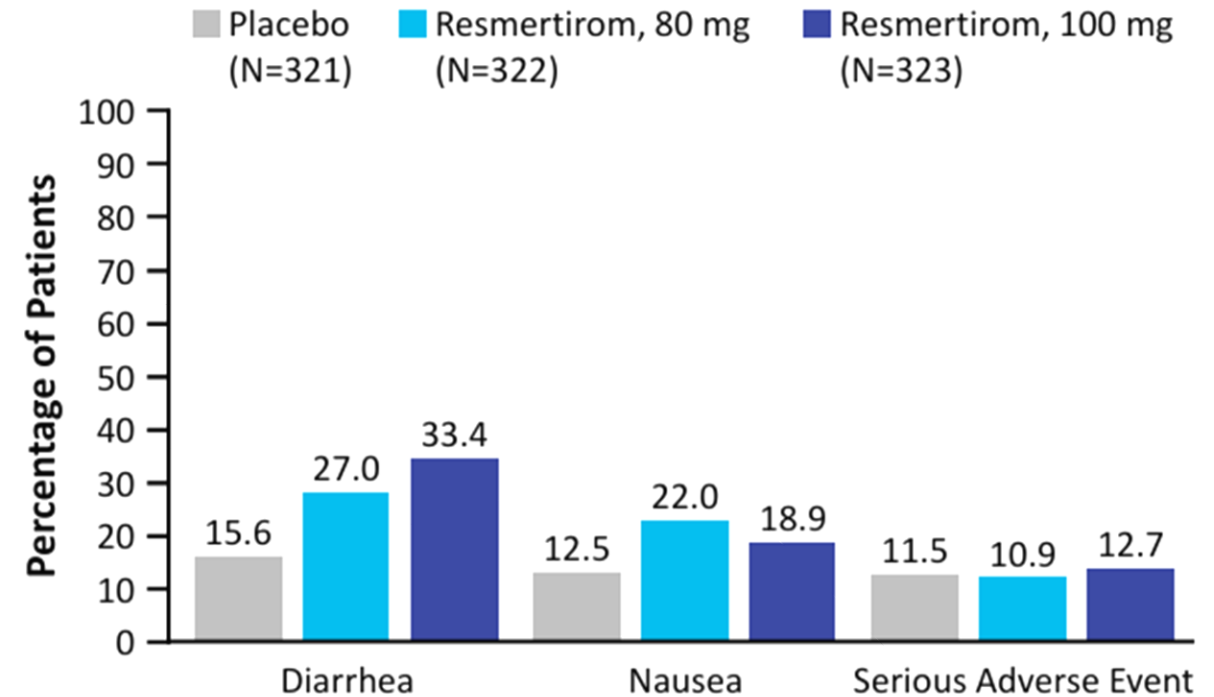


# MAESTRO-NASH Trial: Resmetirom

## Primary End Points



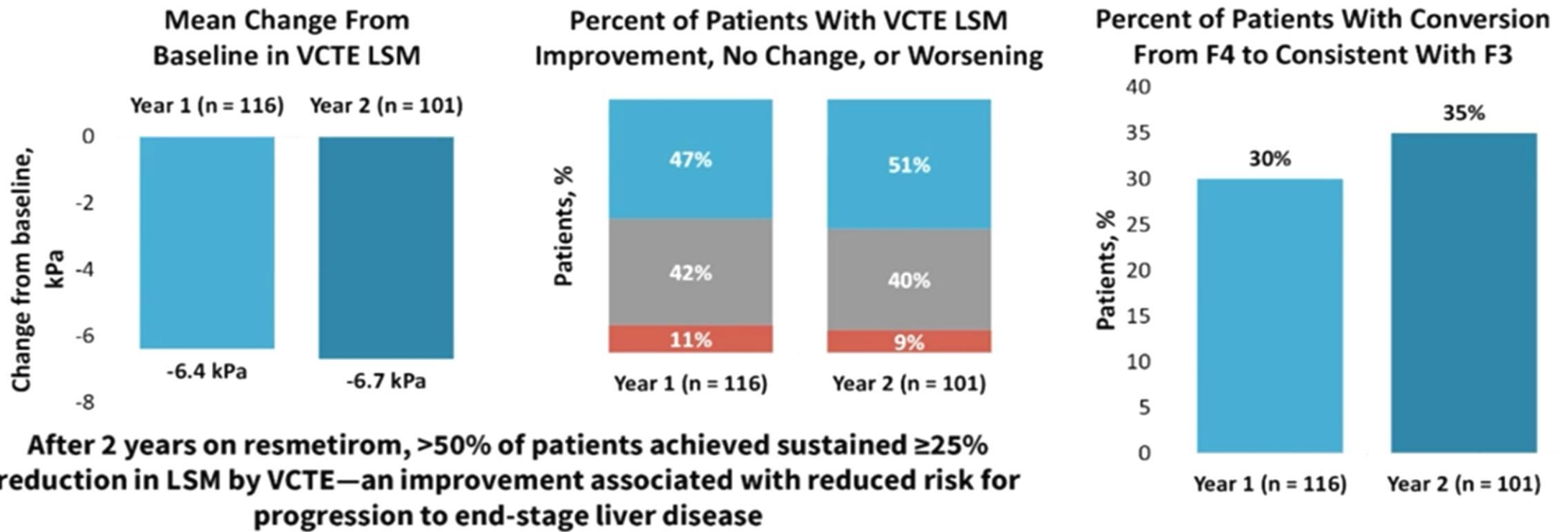
## Safety



In March 2024, the US FDA approved resmetirom for the treatment of adults with noncirrhotic NASH with moderate to advanced liver fibrosis, to be used along with diet and exercise

# Sustained Reduction in LSM With 2 Years of Resmetirom in Patients With MASH and Well-Compensated Cirrhosis

Cirrhosis cohort from MAESTRO-NAFLD-1 phase 3 trial, which enrolled patients with well-compensated MASH cirrhosis (F4 fibrosis) treated with 52 weeks of resmetirom 80 mg followed by a 52-week open-label extension



LSM = Liver Stiffness Measurement

Alkhoury N, et al. Presented at: European Association for the Study of the Liver; Amsterdam, Netherlands: May 7-10, 2025; Lin H, et al. *JAMA*. 2024;331(15):1287-1297.

# Common Adverse Events With Resmiteron

Adverse Reaction	Placebo (n = 294) n (EAIR)	Resmetirom 80 mg (n = 298) n (EAIR)	Resmetirom 100 mg (n = 296) n (EAIR)
Diarrhea	52 (14)	78 (23)	98 (33)
Nausea	36 (9)	65 (18)	51 (15)
Pruritus	18 (4)	24 (6)	36 (10)
Vomiting	15 (4)	27 (7)	30 (8)
Constipation	18 (4)	20 (5)	28 (8)
Abdominal pain	18 (4)	22 (5)	27 (7)
Dizziness	6 (1)	17 (4)	17 (4)

## Adverse reactions leading to discontinuation:

- Resmetirom 100 mg (8 per 100 PY), 80 mg (5 per 100 PY) vs placebo (4 per 100 PY)
- Diarrhea and nausea were the most common causes of treatment discontinuation



# ✓ Emerging Agents: Where Are We

## Agents in Late-Phase Development for the Treatment of MASH Fibrosis

Drug	Mechanism of action	Administration	Phase 3 status	Support (trial)
<b>Lanifibranor</b>	Pan-PPAR agonist	Oral, once daily	Ongoing	MASH resolution and improvement in fibrosis stage (NATIVE phase 2b)
<b>Survodutide</b>	Dual GLP-1 RA/ GCG agonist	SC, once weekly	Ongoing	MASH resolution and improvement in fibrosis stage (1404-0043 phase 2)
<b>Tirzepatide</b>	Dual GLP-1 RA/ GIP agonist	SC, once weekly	Planned	MASH resolution and improvement in fibrosis stage (SYNERGY-NASH phase 2)
<b>Efruxifermin</b>	FGF21 analogue	SC, once weekly	Ongoing	MASH resolution and improvement in fibrosis stage (HARMONY phase 2)
<b>Pegozafermin</b>	FGF21 analogue	SC, once every 2 weeks	Ongoing	MASH resolution and improvement in fibrosis stage (ENLIVEN phase 2)

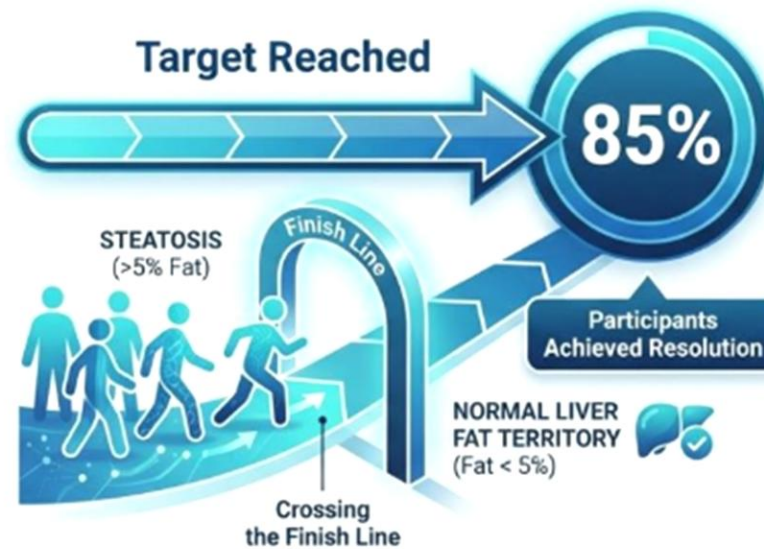
FGF21 = Fibroblast Growth Factor 21; GCG = Glucagon; PPAR = Peroxisome Proliferator-Activated Receptor; SC = Subcutaneous.

Francque SM, et al. *N Engl J Med.* 2021;385(17):1547-1558; Harrison SA, et al. *Lancet Gastroenterol Hepatol.* 2023;8(12):1080-1093; Loomba R, et al. *N Engl J Med.* 2023;389(11):998-1008; Loomba R, et al. *N Engl J Med.* 2024;391(4):299-310; Sanyal AJ, et al. *N Engl J Med.* 2024;391(4):311-319.

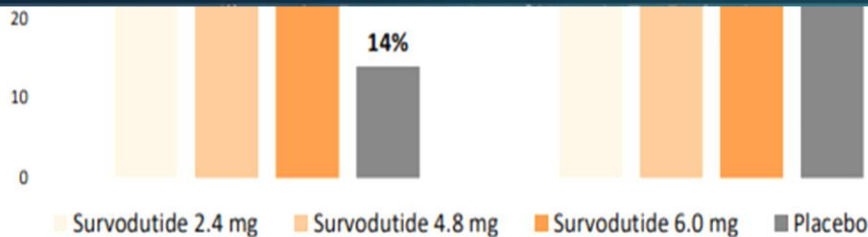
# Triple Agonists GLP-1 / GIP / Glucagon Receptor In Clinical Development For Obesity

## STEATOSIS RESOLUTION

- ✓ **Definition:** Liver fat < 5%
- ✓ **Outcome:** >85% of participants achieved resolution by week 48
- ✓ **Implication:** Reversal of the metabolic driver of fibrosis
- ✓ **Future:** Pending biopsy data for MASH resolution



Phase 3 studies of survodutide in MASH with F2 or F3 fibrosis (LIVERAGE) or in patients with MASH and cirrhosis (LIVERAGE-CIRRHOSIS) are planned.



[doi.org/10.1038/s41591-024-03018-2](https://doi.org/10.1038/s41591-024-03018-2)

## retatrutide ated zed

- Delayed gastric emptying

### Liver:

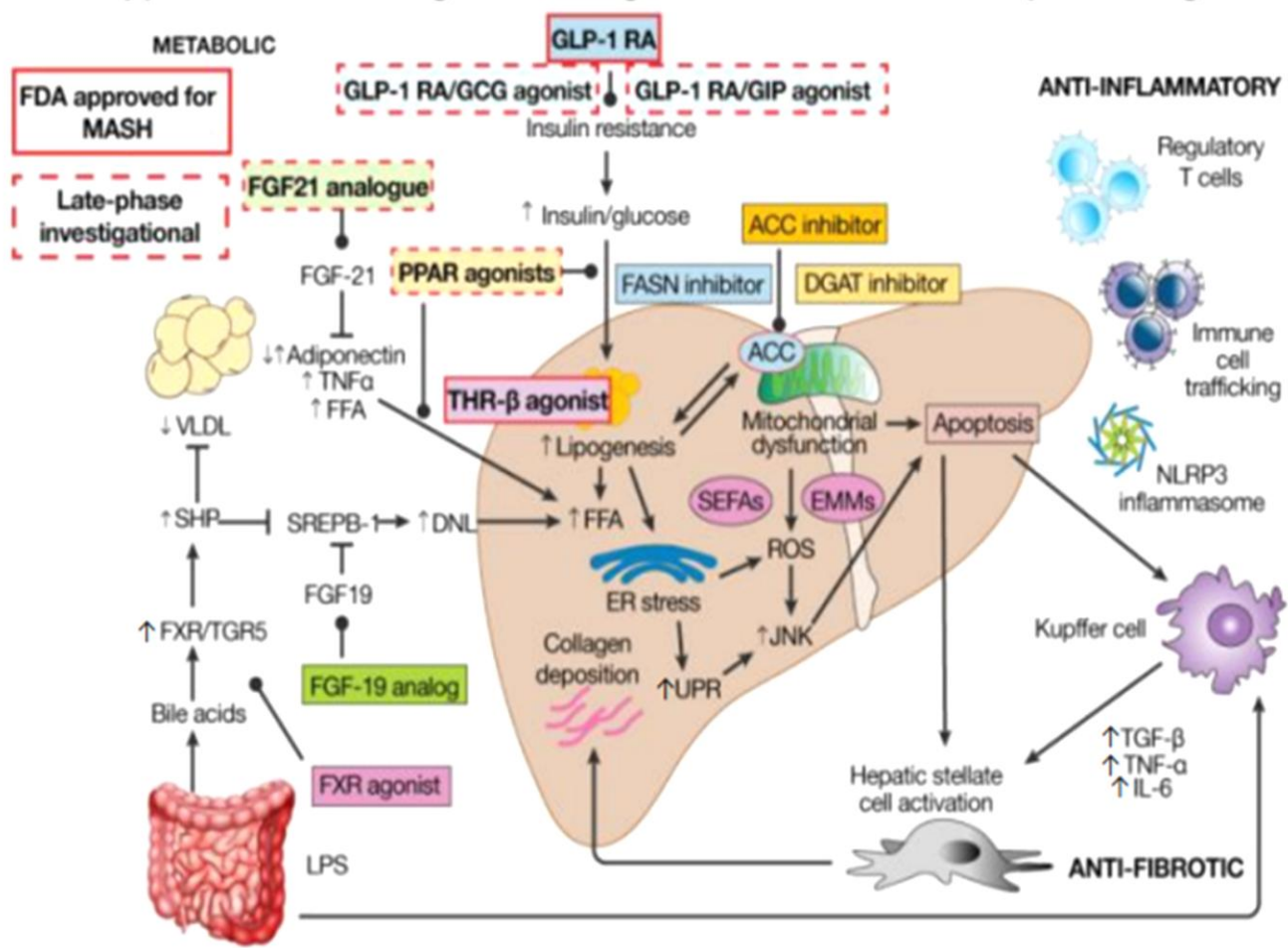
- ↑ glycogenolysis/gluconeogenesis
- ↑ hepatic glucose output
- ↑ fatty acid oxidation
- ↑ amino acid catabolism



appetite

# Take Home Message: Call To Action

## Approved and Investigational Drug Classes and Their Therapeutic Targets



## FDA-Approved Treatments for MASH

	Resmetirom	Semaglutide
<b>MoA</b>	THR- $\beta$ agonist	GLP-1 RA
<b>Administration</b>	Oral, once daily	SC, once weekly
<b>Regulatory status (MASH)</b>	Accelerated approval in 2024	Accelerated approval in 2025
<b>Indication for MASH</b>	Treatment of adults with MASH with moderate to advanced liver fibrosis (F2 to F3)	Treatment of adults with noncirrhotic MASH with moderate to advanced liver fibrosis (F2 to F3)
<b>Additional indications</b>	N/A	<ul style="list-style-type: none"> <li>Established CVD and obesity or overweight</li> <li>Obesity or overweight with <math>\geq 1</math> weight-related comorbidity</li> <li>T2D (to improve glycemic control)</li> <li>T2D and CKD (to reduce the risk of eGFR decline, progression to ESKD, or CV death)</li> </ul>

– Treat Obesity / T2DM GDMT and if Appropriate Liver Directed Rx to Reduce MALO / CVDz / Malignancy

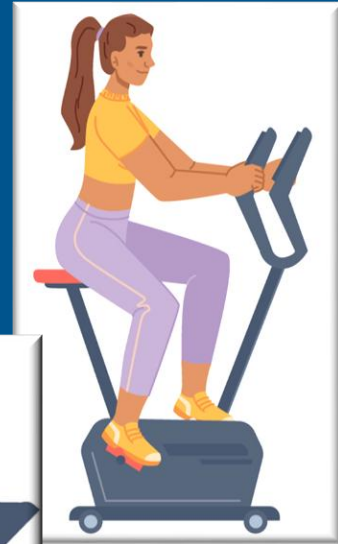
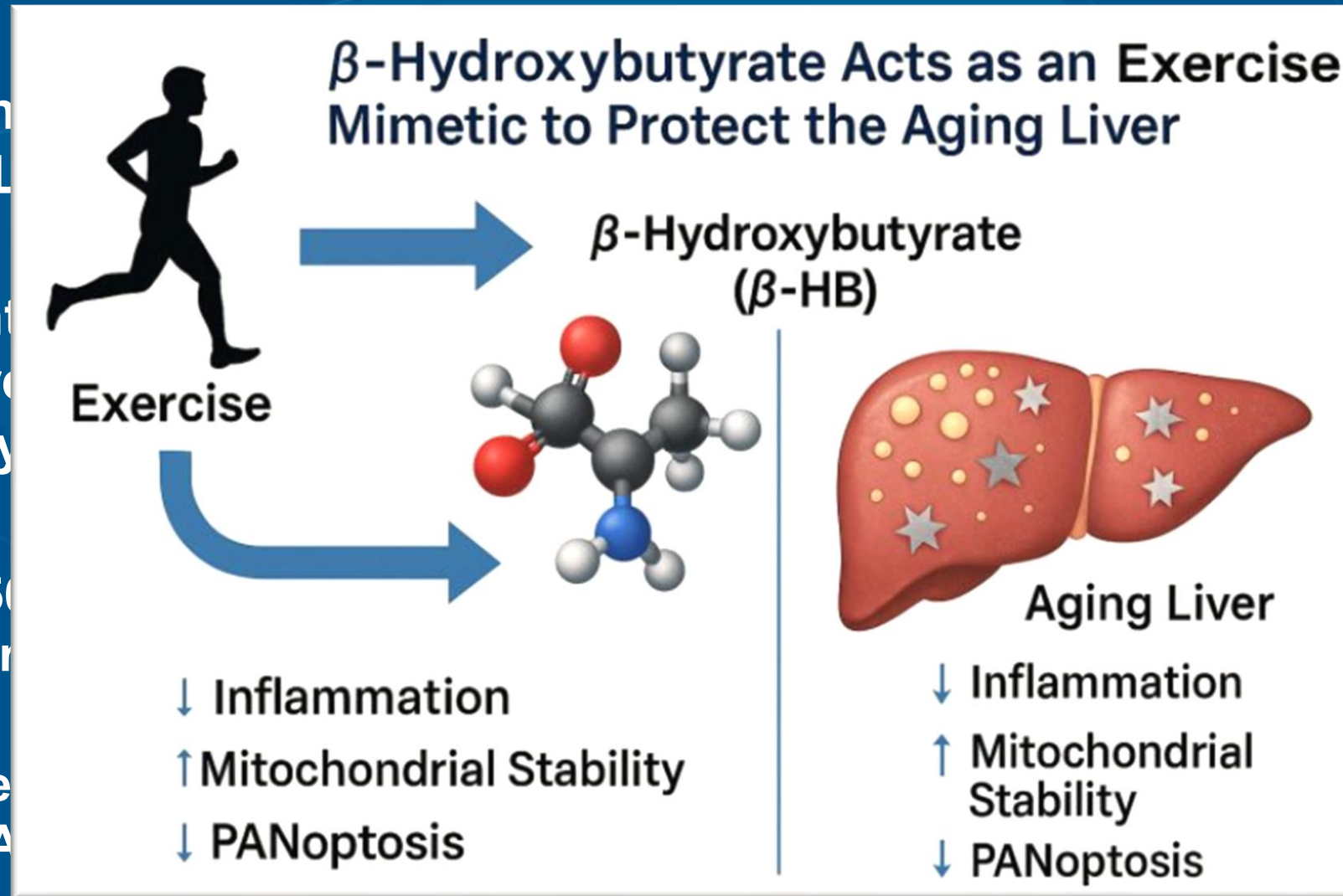
# Example Diet: Mediterranean Diet

- ▶ Rich in Vegetables, Fresh Fruit, Unsweetened Cereals  
Rich in Fiber, Nuts, Fish or White Meat, Olive Oil
- ▶ Limited Simple Sugars and Red / Processed Meats
- ▶ Associated with Reduced Hepatic Steatosis, Improved Insulin Sensitivity, Lower Mortality

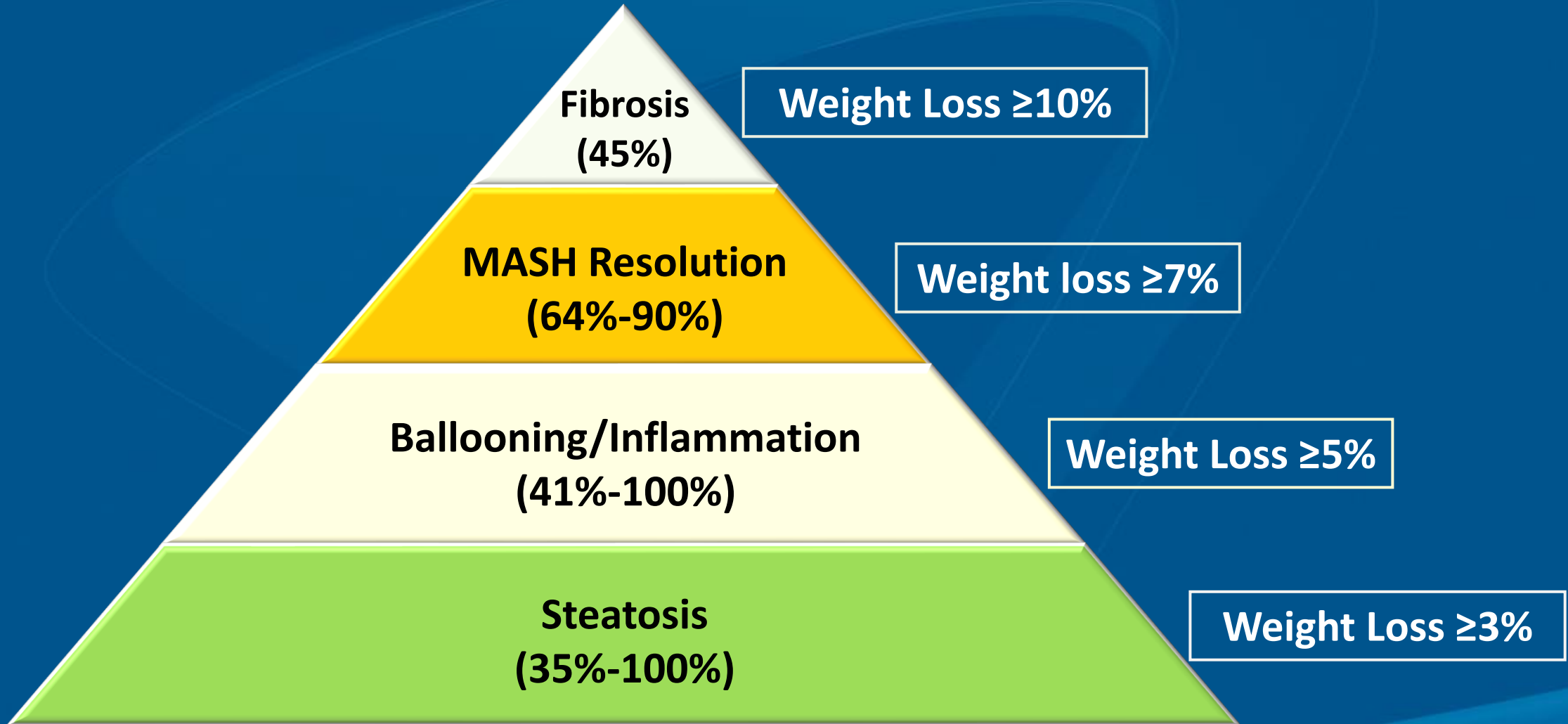


# Exercise

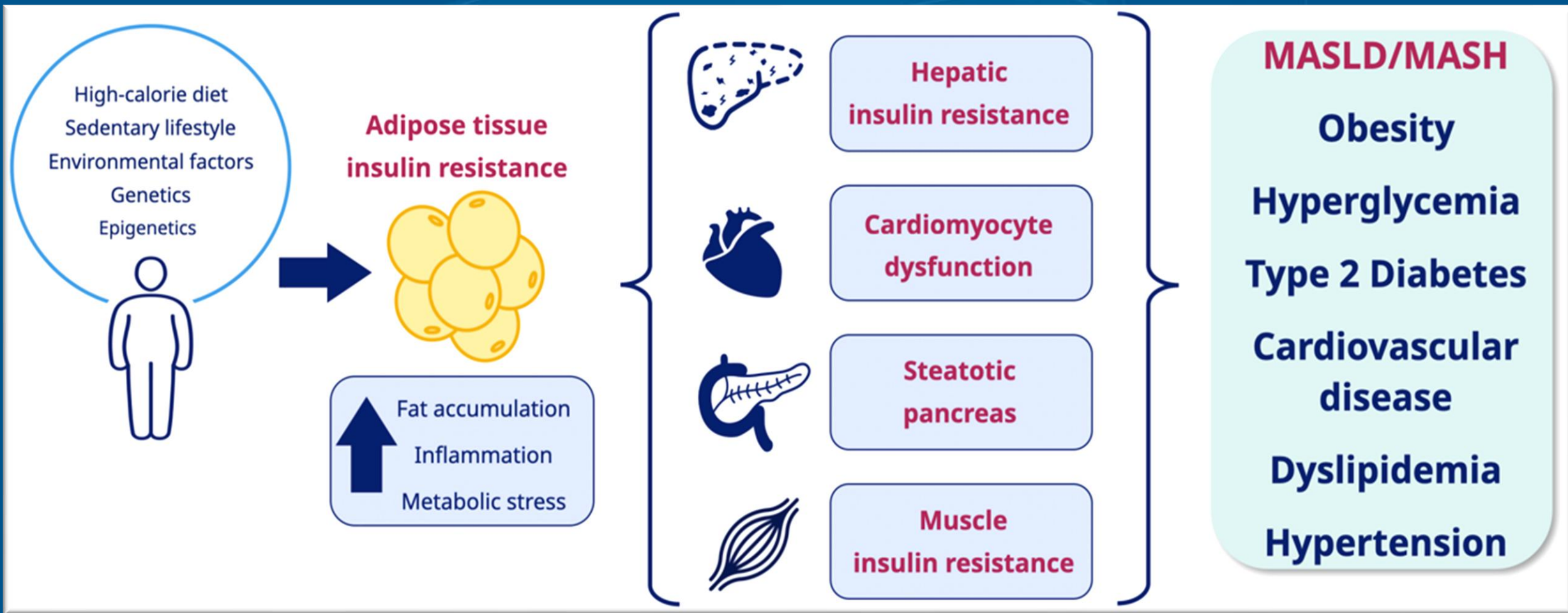
- Increased Phospholipid Steatosis & Liver Inflammation in the Absence of Obesity
- When Weight is Stable, Intense Exercise is Associated with Low Intensity
- Options
  - Aerobic 150-300 minutes/week at Moderate Intensity or 75-150 minutes/week at Vigorous Intensity
  - Resistance Training 2-3 Days/Wk, At Least 8-10 Exercises



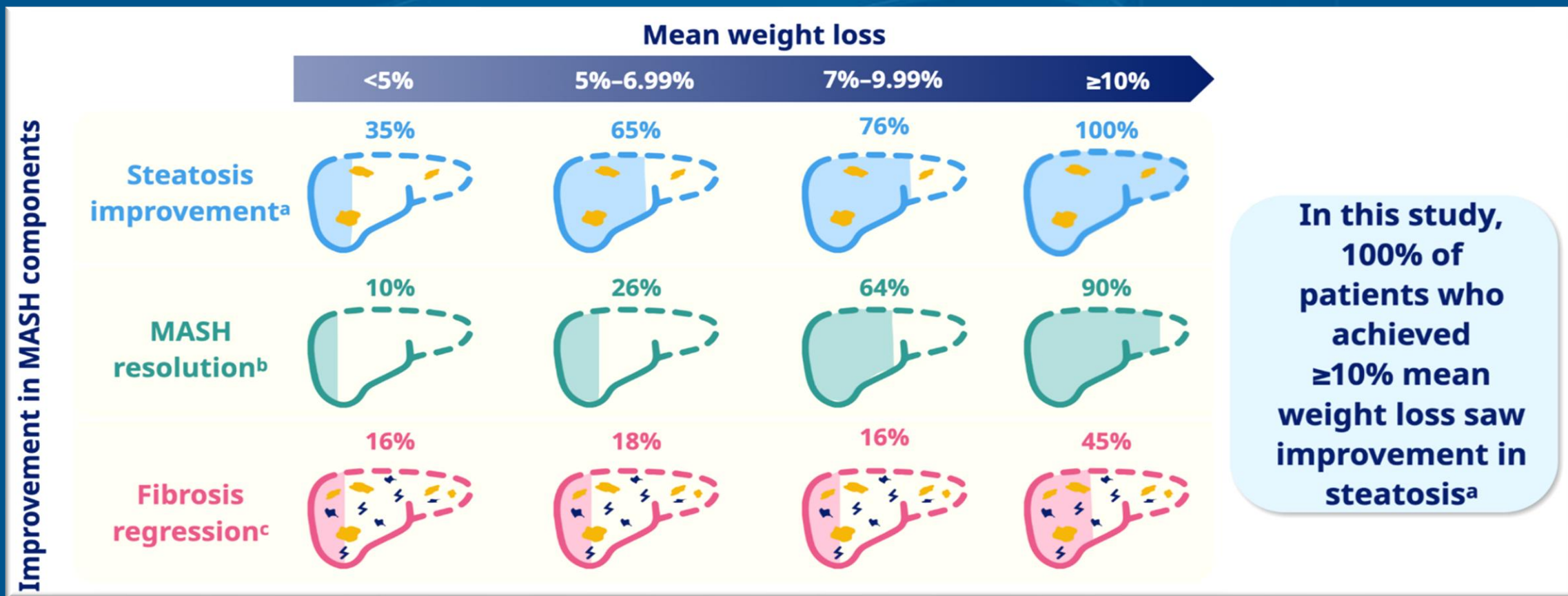
# Weight Loss Thresholds and Impact on MASLD



# Questions ?



# Questions ?



Vilar-Gomez E et al. *Gastroenterology* 2015;149(2):367-378  
Aminian A et al. *JAMA*. 2021;326(20):2031-2042



# Questions ?

- What Is Most Accurate Regarding The Use of Statins In Patients With MASLD & MASH?
  - A. They Are Generally Safe For The Prevention & Reduction Of Cardiovascular Disease
  - B. They Are Contraindicated In This Population
  - C. They Can Only Be Used In Patients With Cirrhosis
  - D. They Cannot Be Used If Patients Have Decompensated Cirrhosis

**Overall, Statin Use Reduced Risk for HCC (HR, 0.53; 95% CI, 0.48-0.59), Hepatic Decompensation (HR, 0.54; 95% CI, 0.49-0.59), & All-Cause Mortality (HR, 0.65; 95% CI, 0.52-0.81) Among Patients with Cirrhosis.**

**Researchers Have Determined Statins Are Safe & Recommended For 1\*/2\* Prevention CVDz. Ample Evidence: Reduction All-Cause Mortality / Cancer Mortality. Statins Potentially Prevent Development Progression of HCC. #1 COD = CVDz / Non-Hepatic Cancers. AASLD – 'Statins: Safe & Recommended Across Dz Spectrum Including Compensated Cirrhosis. Limited Data With Decompensated Cirrhosis'**

# Questions ?

- ◊ What Is The Most Common Arrhythmia Associated With MASLD?
  - A. Atrial Fibrillation
  - B. Atrial Flutter
  - C. Ventricular Fibrillation
  - D. Ventricular Tachycardia

**CVDz Most Common COD. MASLD Strongly Ass'd With Various CV Complications: ASCVDz, Heart Dz, Heart Failure, & Arrhythmias. AFib Particularly Common in MASLD**



# Questions ?

- ◀ Which Test For New – Onset Diabetes Is Most Appropriate For Patients With Cirrhosis Due To MASLD?
  - A. A1c Measurement
  - B. Fasting Blood Sugar Measurement'
  - C. Random Blood Glucose Test
  - D. Oral Glucose Tolerance Test

**2 Hour Postprandial 75 – Gram Oral GTT Found To Outperform FBS, A1c In Patients With Cirrhosis. A1c Especially Susceptible To Inaccuracy d/t Changes In Erythrocyte Turnover, Hemolysis Caused By Splenomegaly, Impaired Erythropoiesis d/t Bone Marrow Suppression & Repeated Blood Transfusions**



# Questions ?

PRACTICE GUIDELINE

AASLD Practice Guideline  
and management



Management  
Case

Patients at low risk for MASH with advanced fibrosis at initial assessment (FIB-4 <1.3)

Prediabetes, T2D, or  $\geq 2$  metabolic risk factors (eg, obesity, dyslipidemia, hypertension)

Yes

No



Repeat FIB-4 every 1-2 years

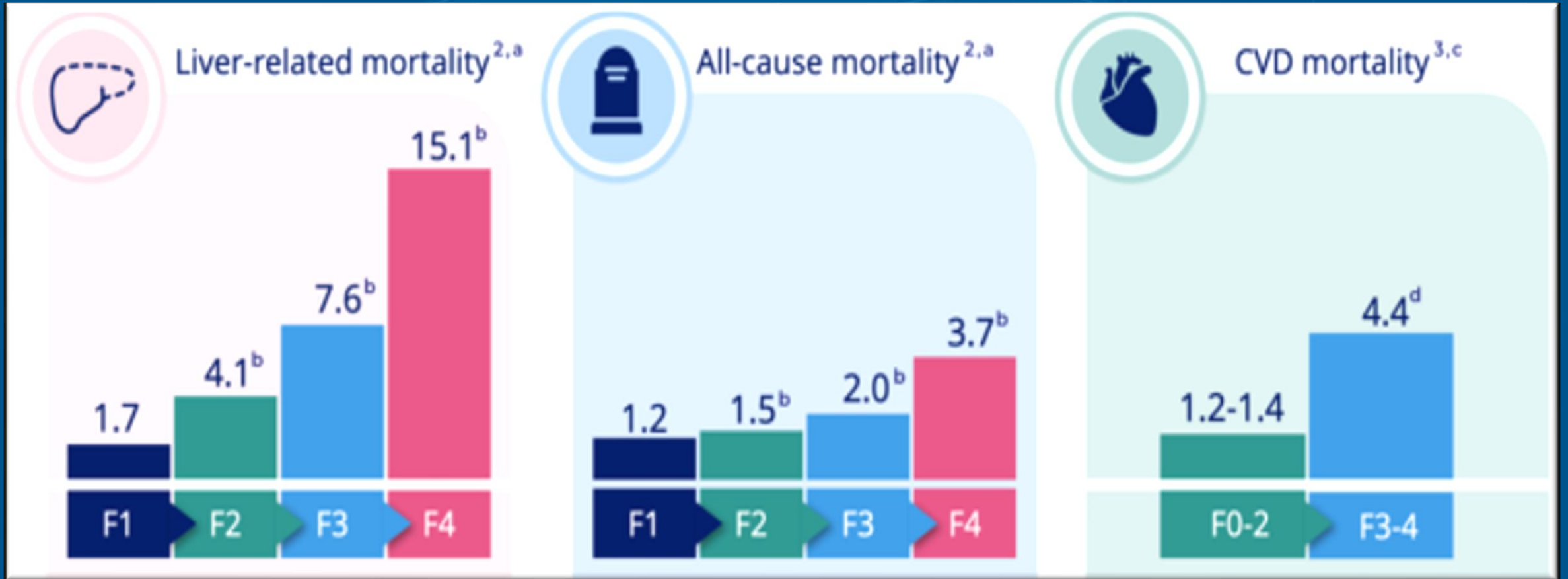


Repeat FIB-4 every 2-3 years

- D. Every 5



# Questions ?



1. Rinella ME et al., *Hepatology* 2023;77(5):1797-1835.

2. Ng CH et al. *Clin Gastroenterol Hepatol.* 2023;21(4):931-939.

3. Ekstedt M et al. *Hepatology.* 2015;61(5):1547-1554. 4. Shroff H et al. *Curr Hepatol Rep.* 2020;19(3):315-326



# Questions ?

- What Role Does Oxidative Stress Play In The Progression From Simple Steatosis to MASH
  - A. It Causes Bile Duct Obstruction & Cholestasis
  - B. It Leads To Direct Suppression Of Insulin Signaling In Muscle Tissue
  - C. It Promotes Hepatocellular Injury & Activation Of Inflammatory Pathways
  - D. It Neutralizes Excess Free Radicals & Reduces Inflammation

**Oxidative Stress, Mainly From Dysfunctional Mitochondria, Results In The Accumulation Of Reactive Oxygen Species That Damage Hepatocytes Via Lipid Peroxidation & DNA Fragmentation. These Processes Stimulate Hepatic Inflammation & Fibrogenesis**





# Guideline-based Management of MASH in the Primary Care Setting

## Screening

### Recommended in adults with:

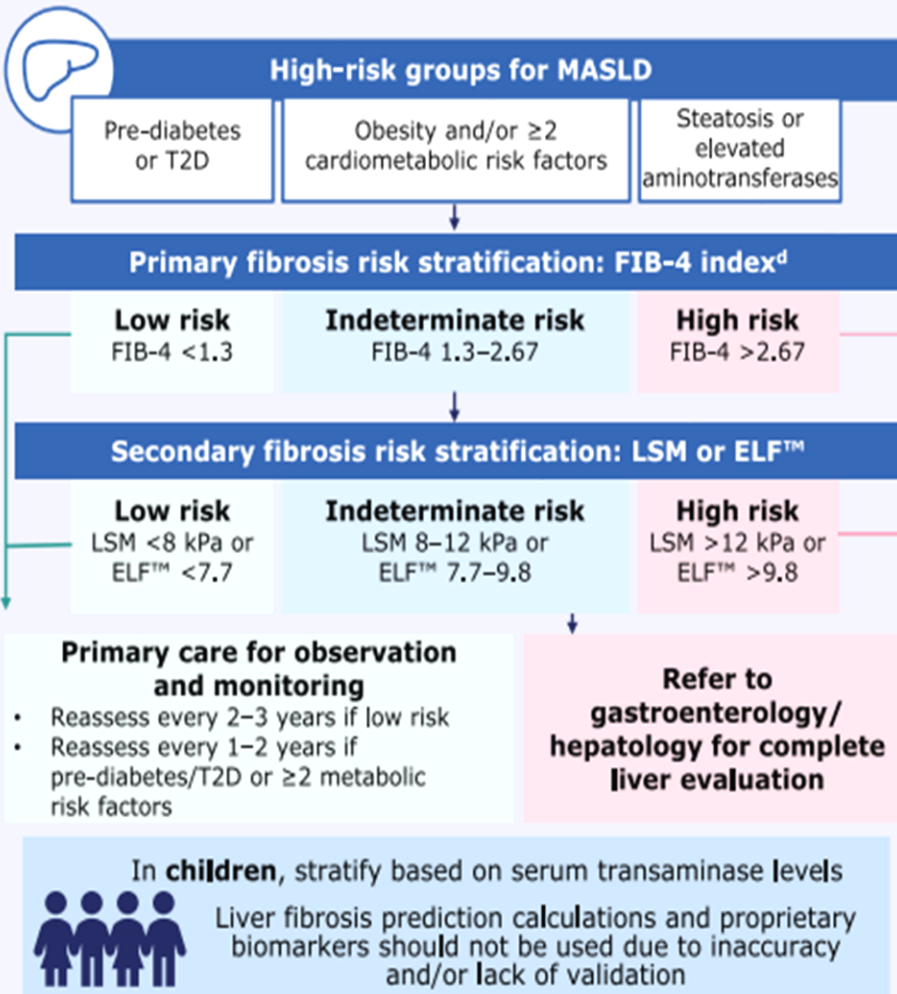
Cardiometabolic and other risk factors, including:<sup>a</sup>

- T2D
- Pre-diabetes
- Insulin resistance
- Obesity
- Aged >50 years
- >Mild alcohol intake<sup>b</sup>
- Family history of cirrhosis

Hepatic steatosis

Persistently elevated liver enzymes

## Risk Stratification



## Management

**Lifestyle interventions**

- Healthy diet (e.g. Mediterranean)
- Physical activity
- Avoid excess alcohol intake

**Weight loss targets**

**$\geq 10\%$  preferred**  
(minimum goal of  $\geq 5\%$ )

**Bariatric surgery**

Consider in appropriate individuals with clinically significant fibrosis<sup>e</sup> and obesity with comorbidities

**Pharmacotherapy**

- MASH + T2D**: GLP-1RAS<sup>f</sup> and/or pioglitazone
- MASH (no T2D)**: Consider vitamin E
- MASH + obesity**: AOM<sup>f</sup> adjunct to lifestyle intervention

**CVD risk reduction**

- Manage comorbidities according to current standards of care
- Statins safe and recommended<sup>g</sup>**

Alina Allen et al.,  
Recommended in children with:

T2D, T1D, Not recommended

245, DOI: 10.1080/00032548.2024.2325332

**Any  
Questions?**



**“Traditional Wisdom is Short on Wisdom and Long on Tradition”**

*Mark Twain*

**“We Can’t Solve Problems Using the Same Kind of Thinking We Used When We Created Them.”**

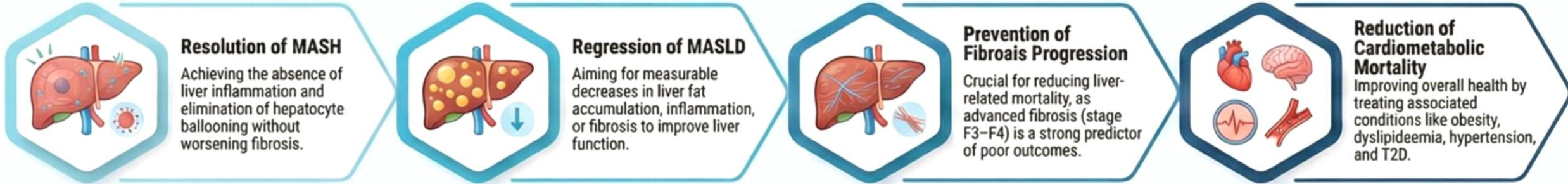
*Albert Einstein*

*ValituttoMichael@Gmail.com*



# The Role of Anti-Diabetic Medications in Managing MASLD

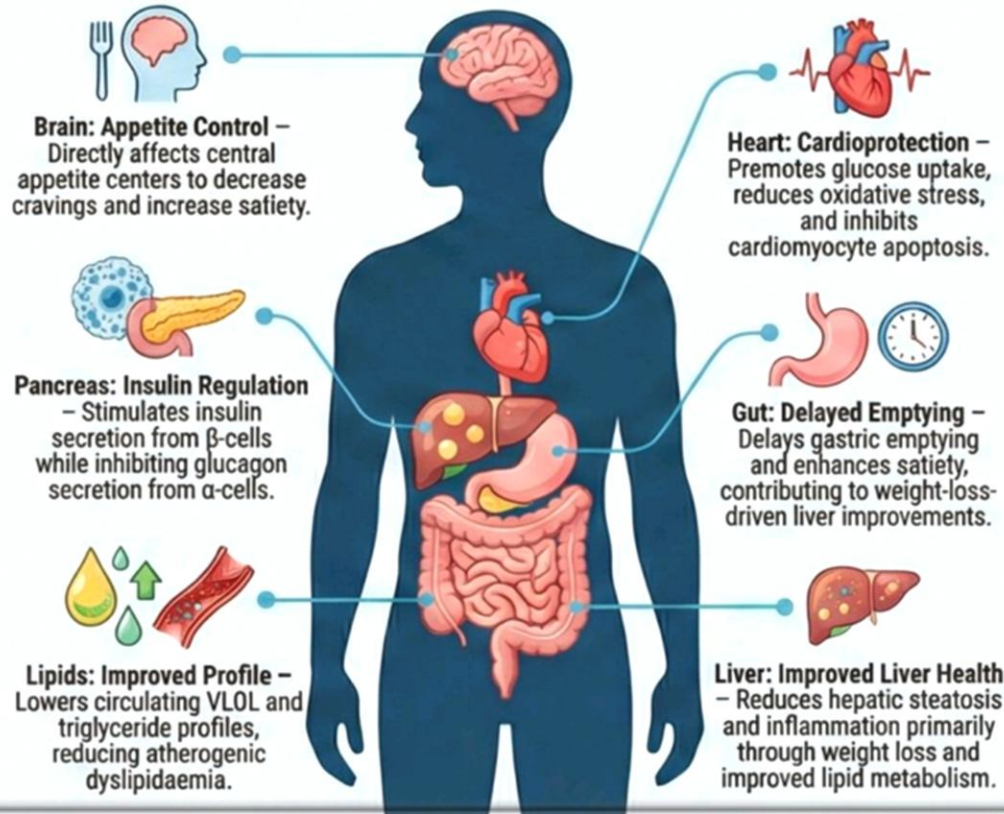
## FOUR EVIDENCE-BASED THERAPEUTIC GOALS



## PRIMARY PHARMACOTHERAPY OPTIONS

- Pioglitazone: The First MASH Reverser**  
A cost-effective PPAR $\gamma$  agonist that improves insulin sensitivity and can reverse MASH, though it may cause weight gain and bone loss.
- GLP-1 RAs: Weight & Liver Protection**  
Medications like Semaglutide reduce hepatic steatosis and inflammation primarily through weight loss and improved lipid metabolism.
- Tirzepatide: Dual Action Efficacy**  
A dual GLP-1 and GIP receptor agonist that has shown up to 62% MASH resolution in high-dose clinical trials.
- SGLT2 Inhibitors: Cardio-Renal Guardians**  
These block glucose reabsorption in the kidney; while they reduce liver fat and stiffness, histological evidence for MASH resolution is still pending.

## MULTISYSTEMIC EFFECTS OF GLP-1 RECEPTOR AGONISM



## MEDICATION EFFICACY COMPARISON

Medication	Liver Enzymes	Hepatic Steatosis	MASH Resolution	Fibrosis Regression
Pioglitazone	●	●	●	●
GLP-1 RA*	●	●	●	●
Tirzepatide	●	●	●	●
SGLT2 Inhibitors	●	●	●	●
Insulin	●	●	●	●
Metformin	●	●	●	●
DPP-4 Inhibitors	●	●	●	●
Sulfonylureas	●	●	●	●

● Beneficial ● Possible Benefit ● Neutral ● Unknown  
\*Histological evidence available for semaglutide. © NotebookLM