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# “Navigating the transition from NAFLD to MASLD - A Call to action for Non-GI Physicians”

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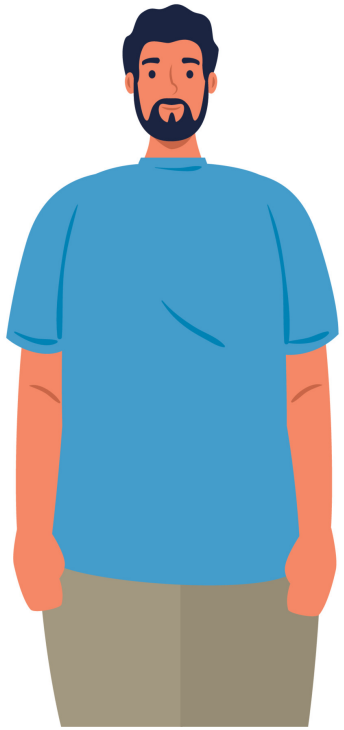
# Objectives

- Explain the new Nomenclature
- Recognize patients at risk
- Outline the connection between MASLD, obesity and T2 Diabetes Mellitus
- Review Society guidelines and algorithms for identifying, risk stratifying and managing low risk patients in the community

# Disclosures

- No financial disclosures

# Case: 55 year-old Hispanic male with Obesity, T2DM and AST/ALT elevation



## Reason for referral

- Aminotransferase elevations
- RUQ discomfort
- 20 lb weight gain over 5 years
- Mostly “normal” liver chemistries over previous 5 years
- Mild intermittent ALT/AST elevation ALT 45 AST 50

## Past Medical History

- Obesity (230lbs, BMI 35)
- Pre-diabetes (HbA1c 6.3%)
- Hypertension

## Family History

- Mother: T2DM, Hypothyroid
- Father: CAD
- No hx of liver disease or alcohol abuse

## Drug History

- Lisinopril

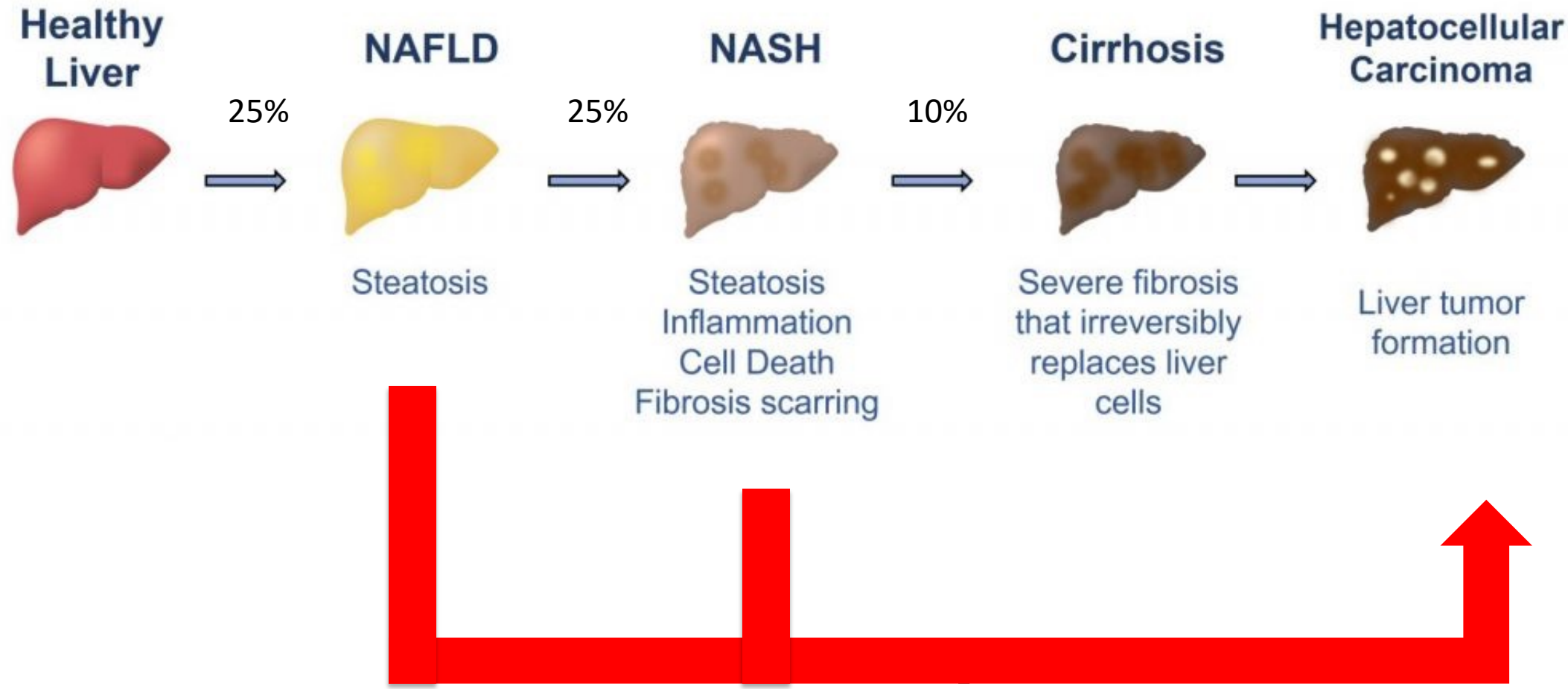
## Social History

- Rare alcohol consumption
- Works in IT

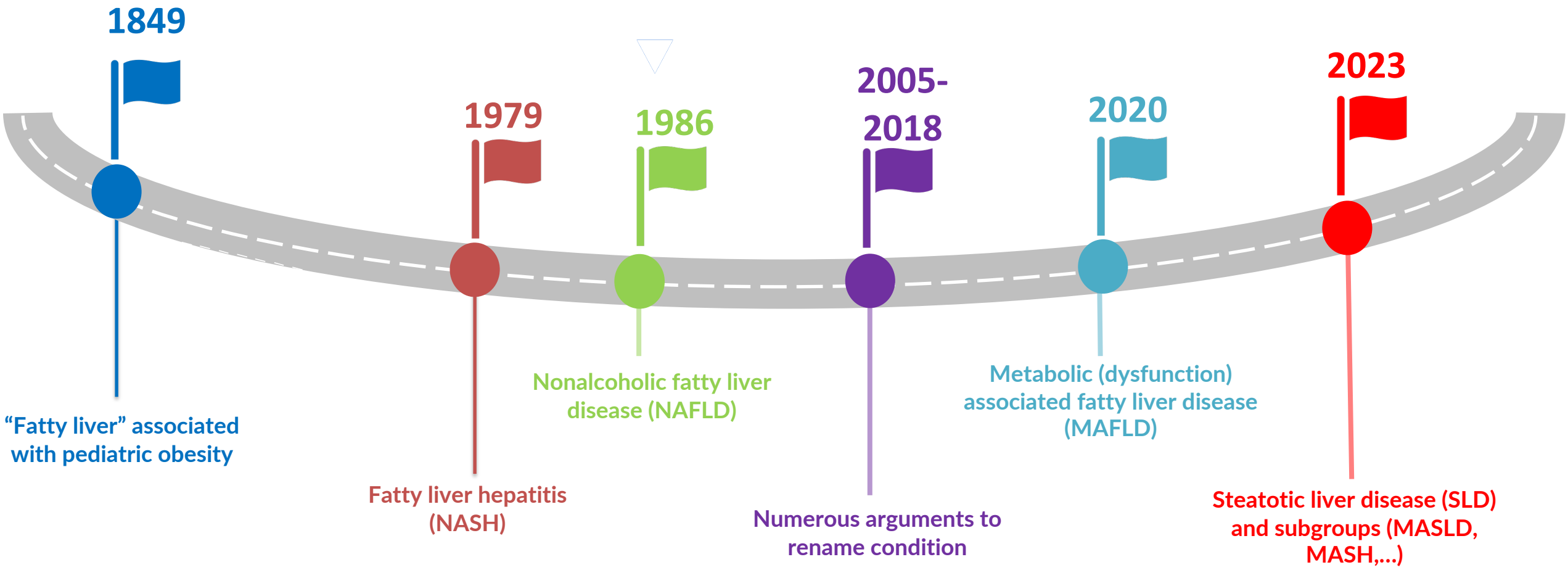
## Physical Exam

- BP 130/85
- BMI: 35
- Central adiposity (WC 110cm)
- Acanthosis nigricans
- No stigmata of chronic liver disease, liver 3cm below costal margin.

# Features of Non-Alcoholic Fatty Liver Disease



# In search of a name…



# What was wrong with calling it NAFLD?

exclusionary stigmatizing

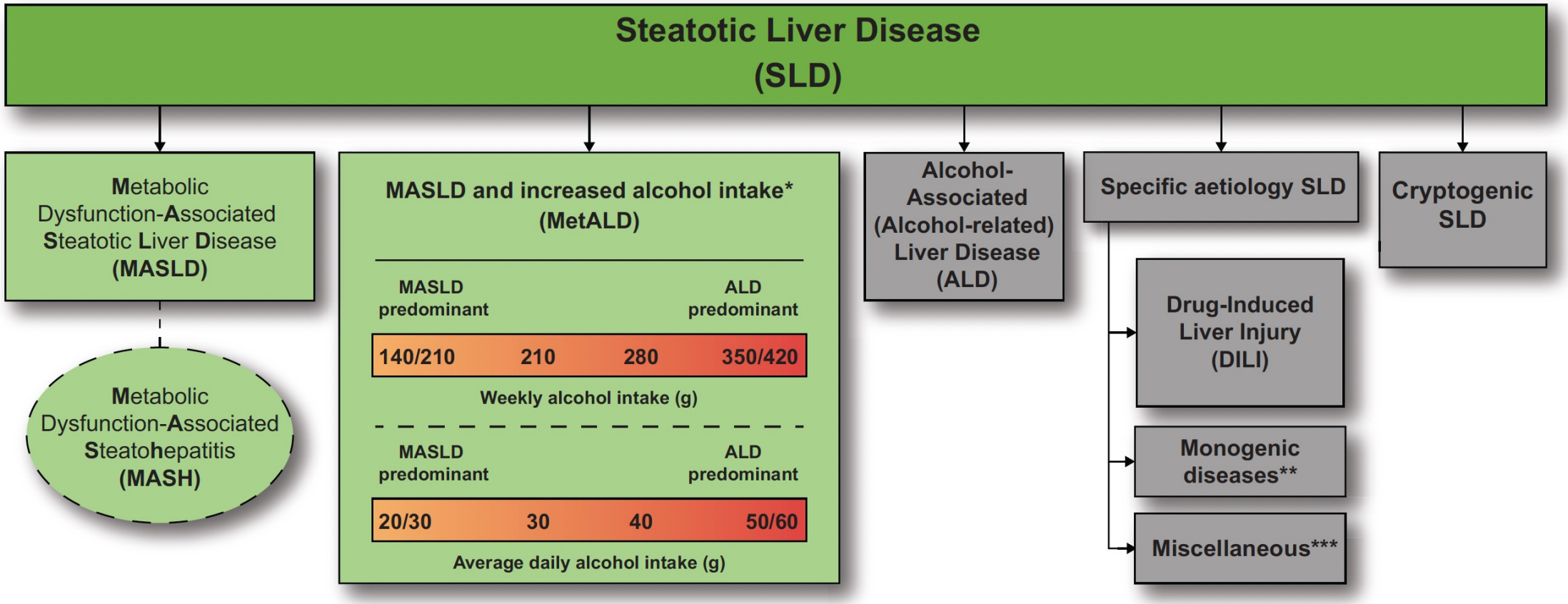
**Name**

**Nonalcoholic fatty liver Disease (NAFLD)**

**Definition**

Steatosis in the absence of other etiologies (≥ moderate alcohol use, viral hepatitis, etc)

# NAFLD is out; MASLD is in!




*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease, human immunodeficiency virus (HIV)



The NAFLD nomenclature is changing. AASLD 2023. ***Rinella et al, Hepatology, 2023***

# What was wrong with calling it NAFLD?

**Name**

exclusionary stigmatizing

**Nonalcoholic fatty liver Disease (NAFLD)**

→ Metabolic dysfunction-associated steatotic liver disease (MASLD)

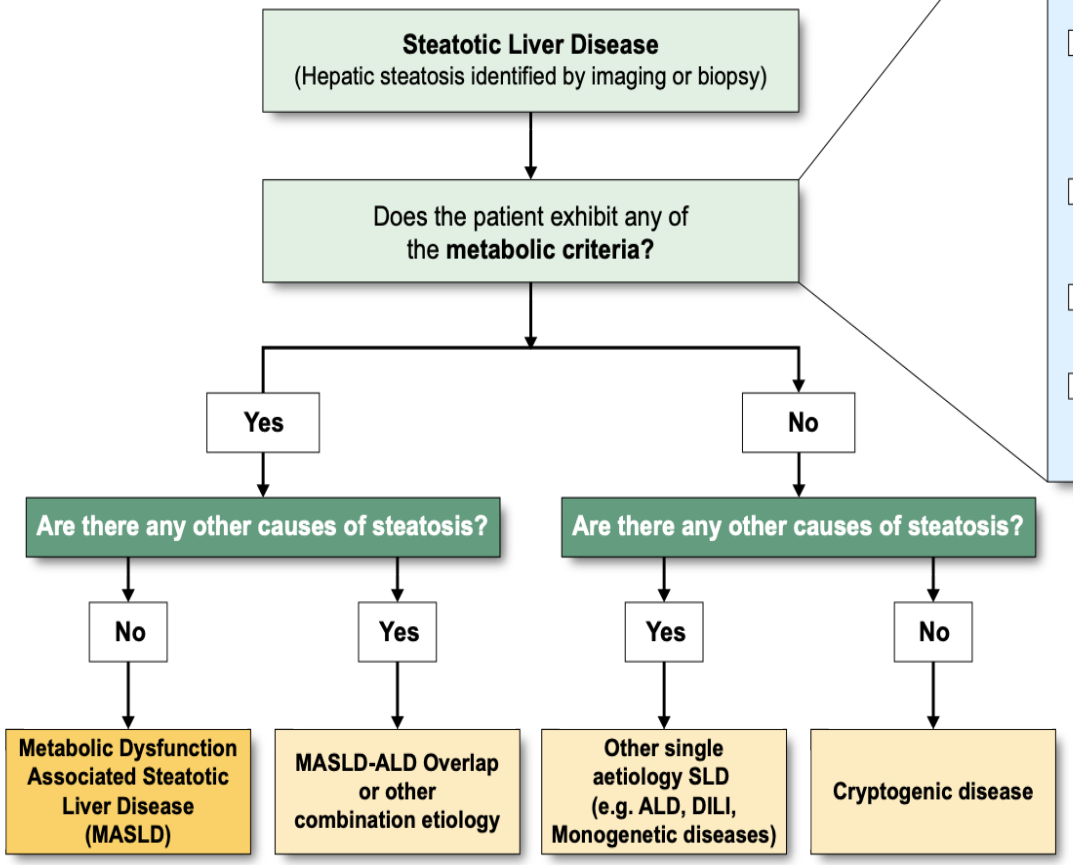
**Definition**

Steatosis in the absence of other etiologies (≥ moderate alcohol use, viral hepatitis, etc)

→ Steatosis in the presence of at least 1 metabolic comorbidity

# A new approach to steatotic liver disease

Table 2: MASLD definition in context of steatosis




**Adult Criteria**

**At least 1 out of 5:**

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

**Pediatric Criteria**

**At least 1 out of 5:**

- ☐ BMI ≥ 85th percentile for age/sex [BMI z score-1] **OR** WC > 95th percentile **OR** ethnicity adjusted
- ☐ Fasting serum glucose ≥ 5.6 mmol/L [≥ 100 mg/dL] **OR** serum glucose ≥ 11.1 mmol/L [≥ 200 mg/dL **OR** 2-hour post-load glucose levels ≥ 7.8 mmol [140 mg/dL] **OR** HbA1c ≥ 39 mmol/L **OR** already diagnosed/treated type 2 diabetes **OR** treatment for type 2 diabetes
- ☐ Blood pressure age < 13y, BP ≥ 95th percentile **OR** ≥ 130/80 mmHg (whichever is lower); age ≥ 13y, 130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides < 10y, ≥ 5.6 mmol/L [≥ 100 mg/dL]; age ≥ 10y, ≥ 1.70 mmol/L


*Each drink shown above represents one U.S. standard drink and has an equivalent amount (0.6 fluid ounces) of "pure" ethanol or approximately 14 grams of alcohol.*

*Rinella et al, AASLD 2023*
*Allen et al, Gastroenterology, 2023*

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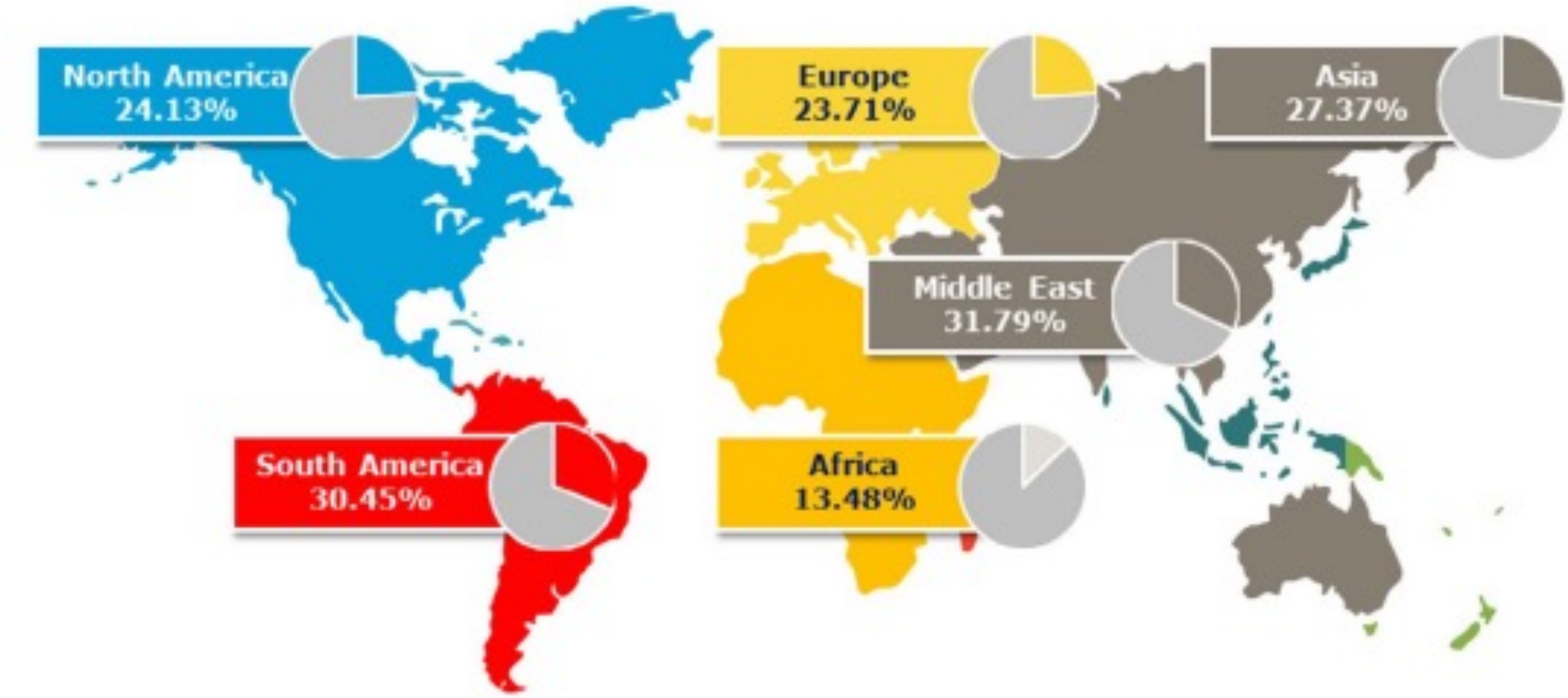
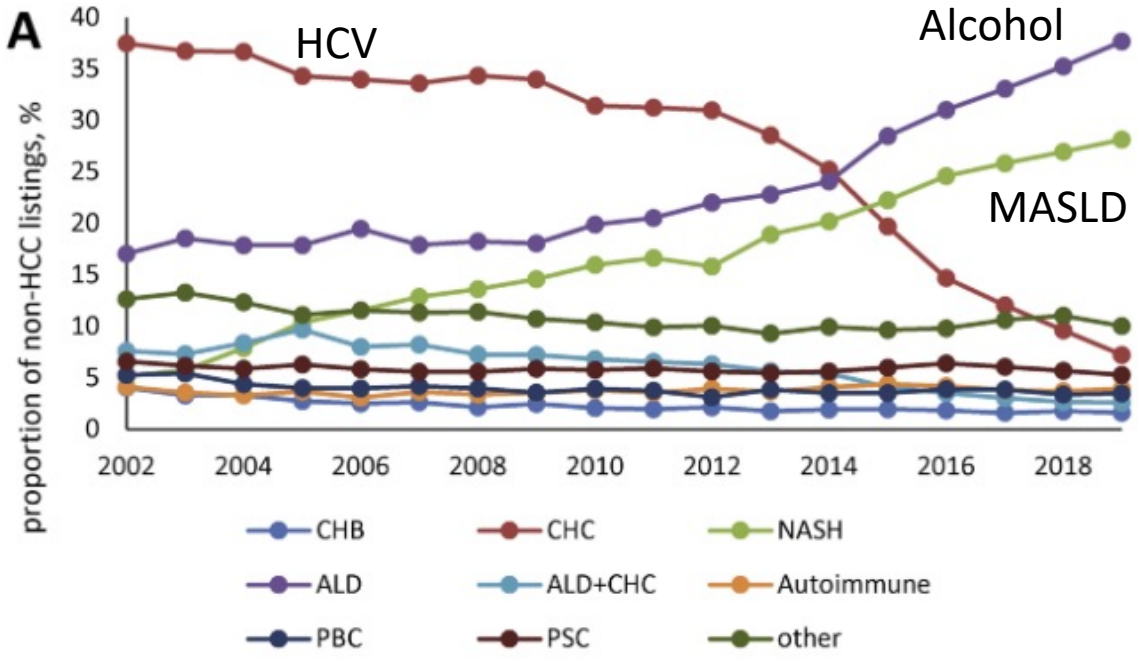
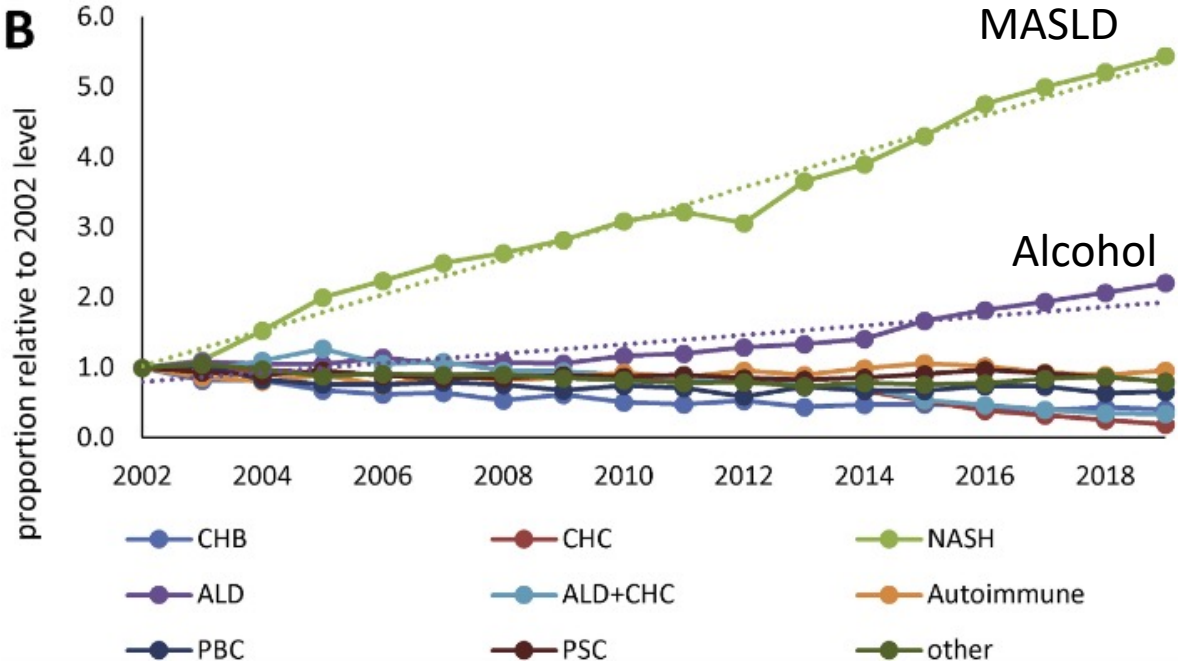
# A global burden; a pandemic




*Younossi et al, Hepatology, 2019*

# Most rapidly growing indication for Transplantation




*Younossi et al, Clinical Gastroenterology and hepatology, 2021*

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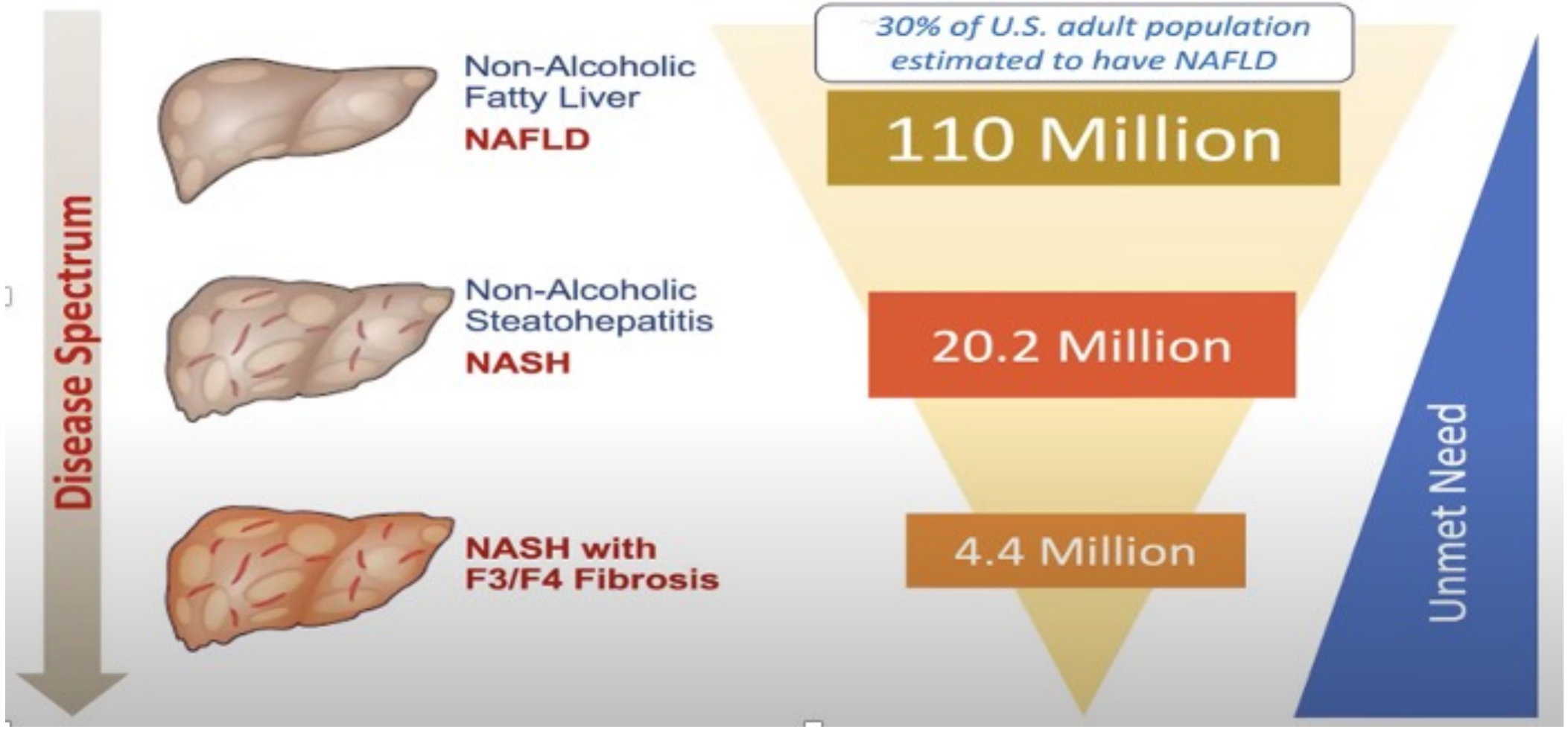
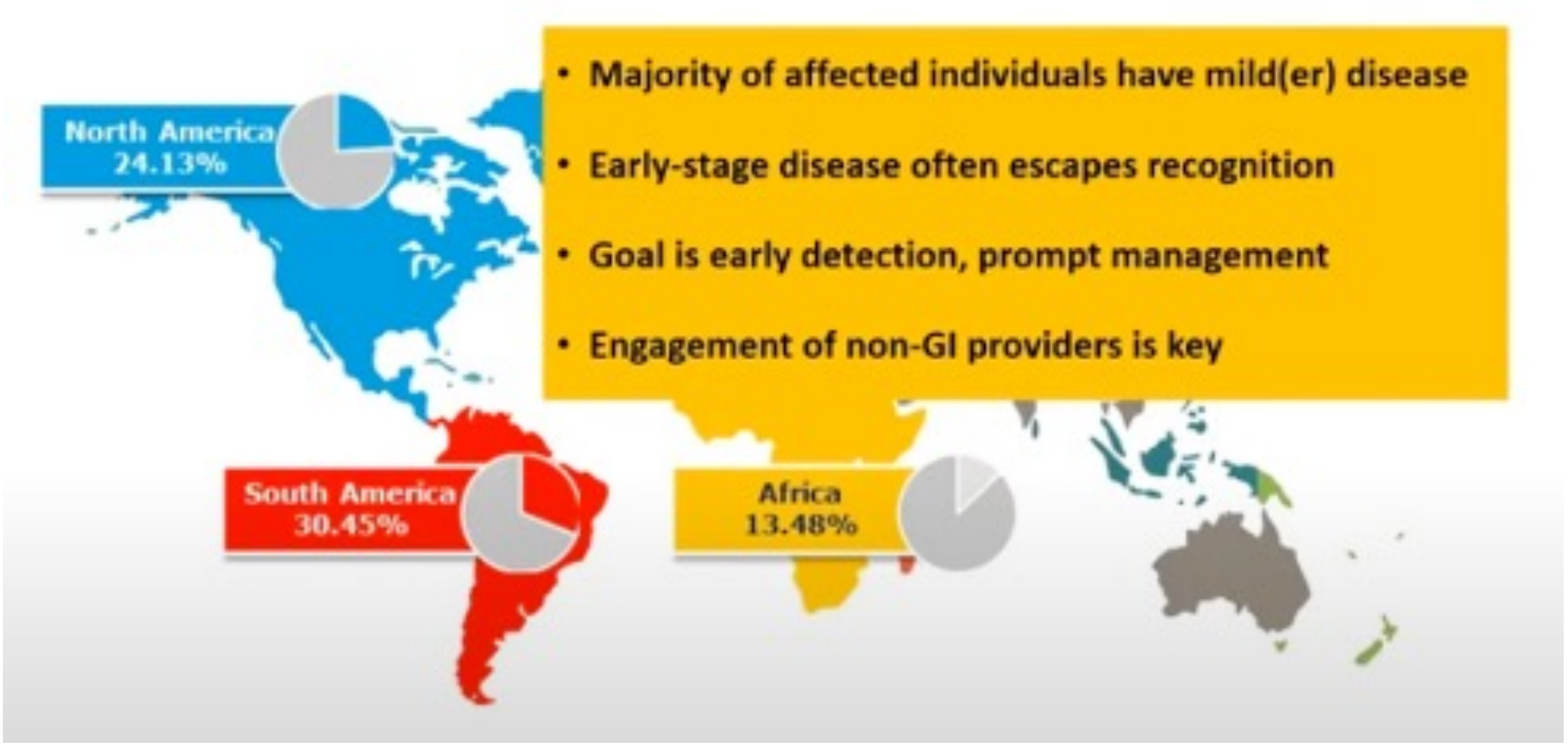
# Burden of disease in the U.S




*Estes c et al, Hepatology, 2017*

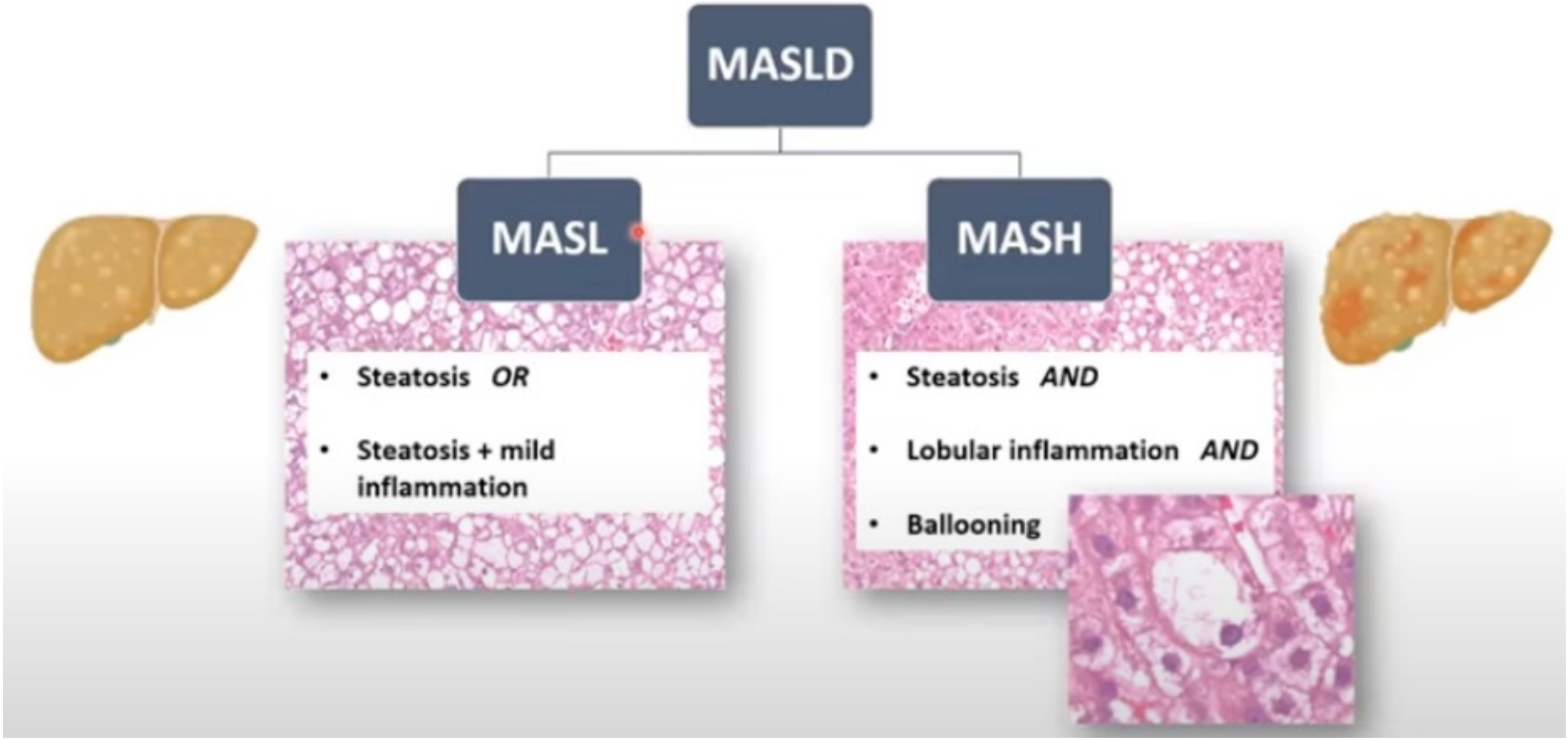
# 110 million may be an underestimate…



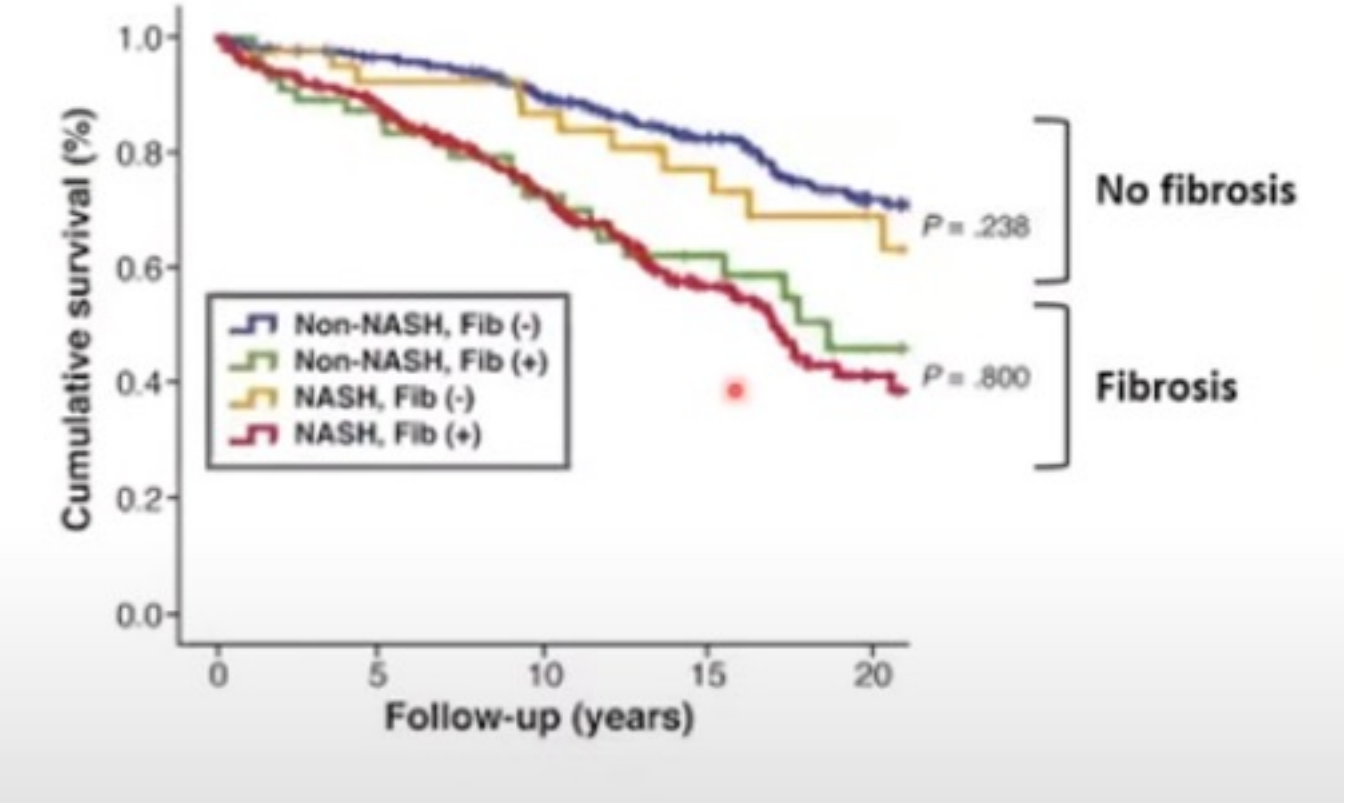

*Younossi et al, Hepatology, 2019*

# MILLIONS OF LIVERS SUFFER IN SILENCE

# MASLD sub-categories



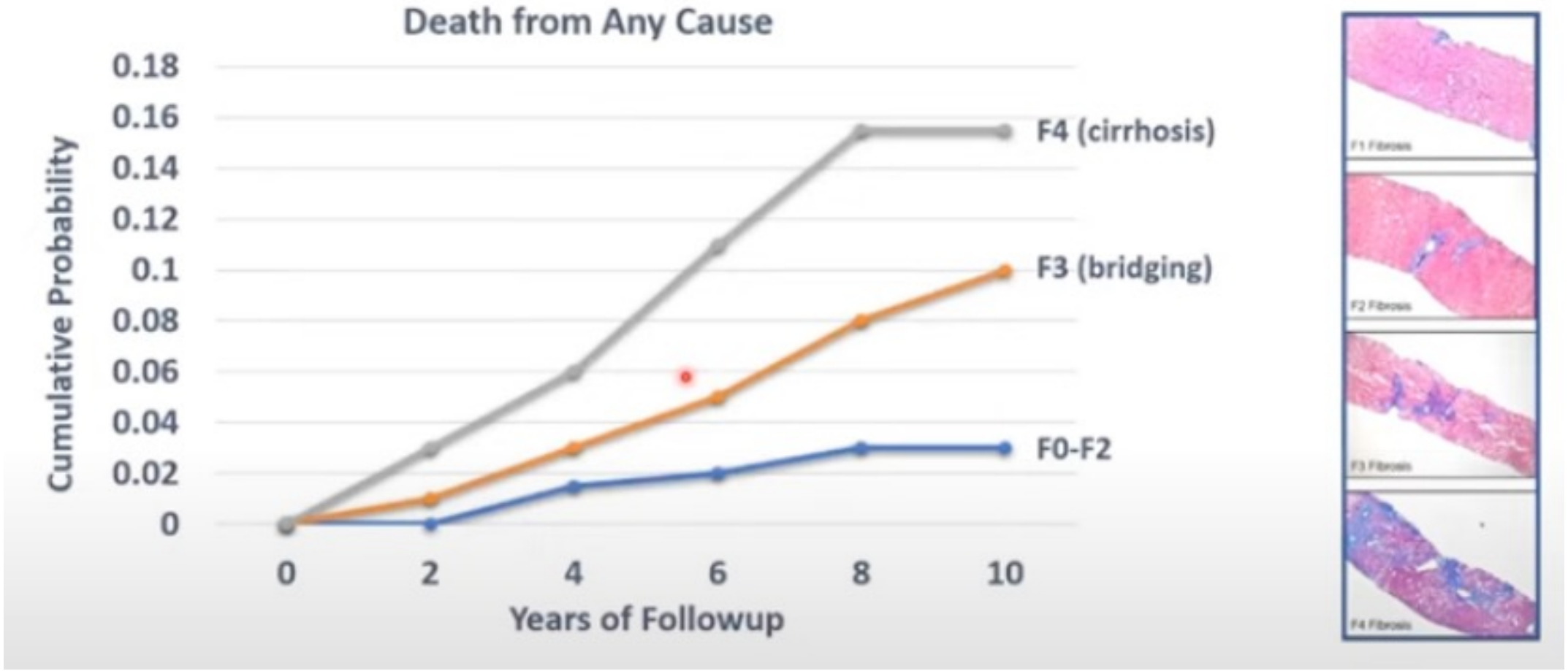
# Fibrosis is the greatest predictor of mortality in MASLD




Liver fibrosis portends mortality in MASLD, with or without MASH (steatohepatitis)

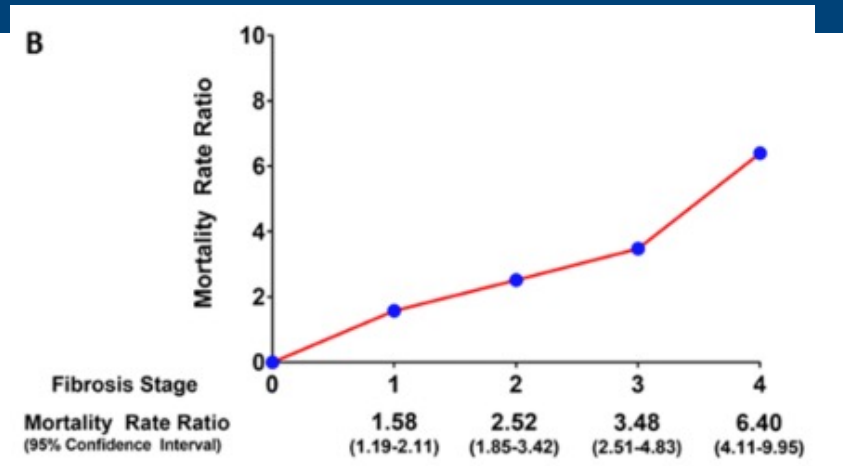
*Angulo et al, Gastroenterology, 2015*

# More fibrosis = higher mortality

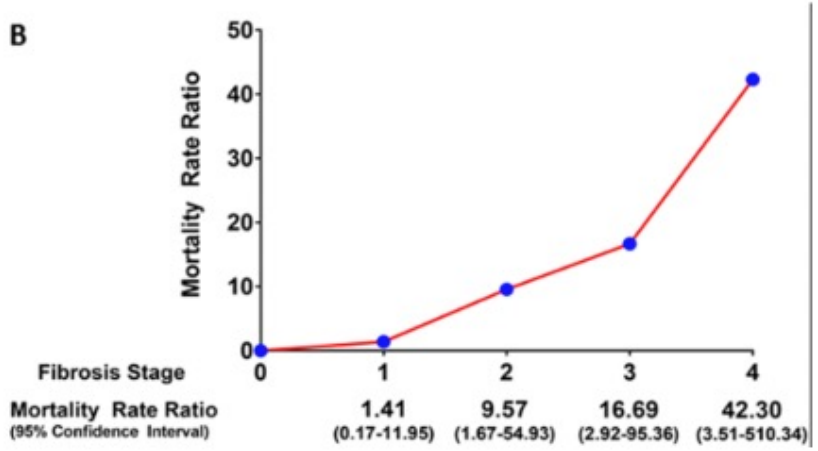



*Sanyal et al, NEJM, 2021*

# Progressive Fibrosis Associated With Increased Mortality



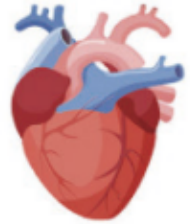

All cause mortality



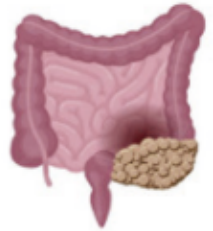

Liver related mortality

**Causes of Mortality in NAFLD**

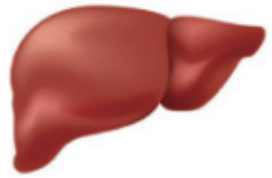
1. Cardiovascular



2. Extrahepatic cancer



3. Liver disease



4. Diabetes

Dulai et al, Hepatology, 2017.

# Barriers to early diagnosis

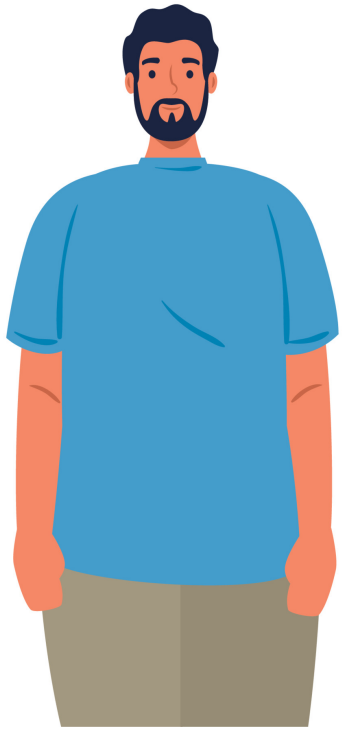
1. Volume: 1 in 3 adults in US now have MASLD

2. No symptoms until end stage liver disease although some will complain of RUQ discomfort

3. Liver enzymes are ***normal*** in most MASL and in 50% of patients with MASH

Early diagnosis allows timely intervention to prevent disease progression to cirrhosis and HCC

# Case: 55 year-old Hispanic male with Obesity, T2DM and AST/ALT elevation



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- Aminotransferase elevations
- RUQ discomfort
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- Mostly “normal” liver chemistries over previous 5 years
- Mild intermittent ALT/AST elevation ALT 45 AST 50

## Past Medical History

- Obesity (230lbs, BMI 35)
- Pre-diabetes (HbA1c 6.3%)
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## Family History

- Mother: T2DM, Hypothyroid
- Father: CAD
- No hx of liver disease or alcohol abuse

## Drug History

- Lisinopril

## Social History

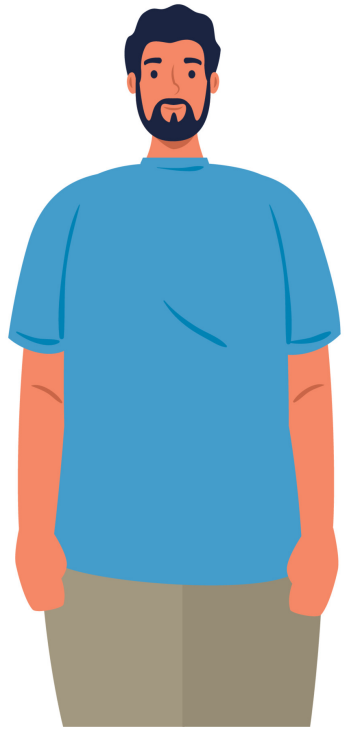
- Rare alcohol consumption
- Works in IT

## Physical Exam

- BP 130/85
- BMI: 35
- Central adiposity (WC 110cm)
- Acanthosis nigricans
- No stigmata of chronic liver disease, liver 3cm below costal margin.

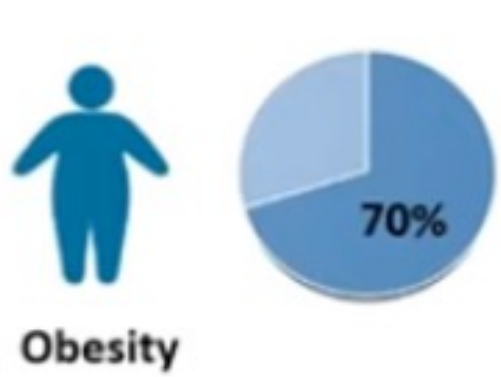
# Patient Evaluation: Secondary causes of steatosis

- Detailed medical history: alcohol, medications, secondary causes of steatosis, family history

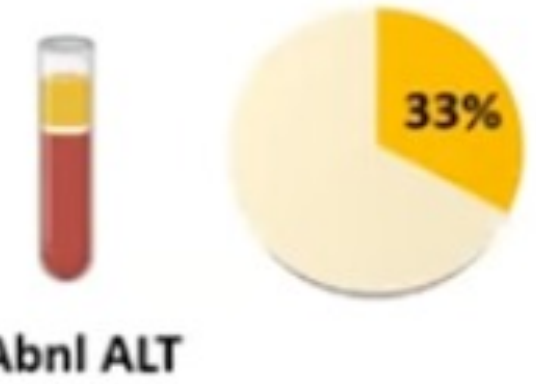


| Medications | Other Etiologies |
| --- | --- |
| • Amiodarone | • HCV, Wilson's Disease, HH |
| • Methotrexate | • Lipodystrophy/HIV |
| • Tamoxifen | • Starvation/Malnutrition/Celiac |
| • 5-FU | • Post Whipple |
| • Corticosteroids | • Parenteral nutrition |
| • Valproate | • Inborn errors of metabolism |
| • Antiretrovirals | • LAL-D |
| | • Abetalipoproteinemia |

# Pre-test probability of MASLD based on common comorbidities










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

*Noureddin et al, Hepatol commun, 2022*
*Quek et al, Lancet Gastro Hep, 2023*

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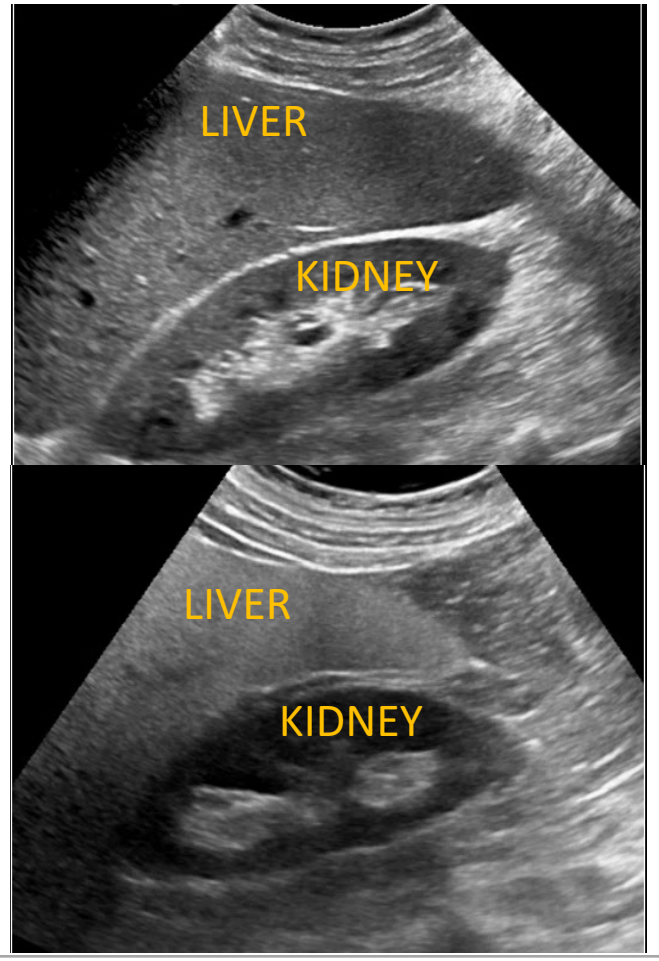
# Laboratory Evaluation

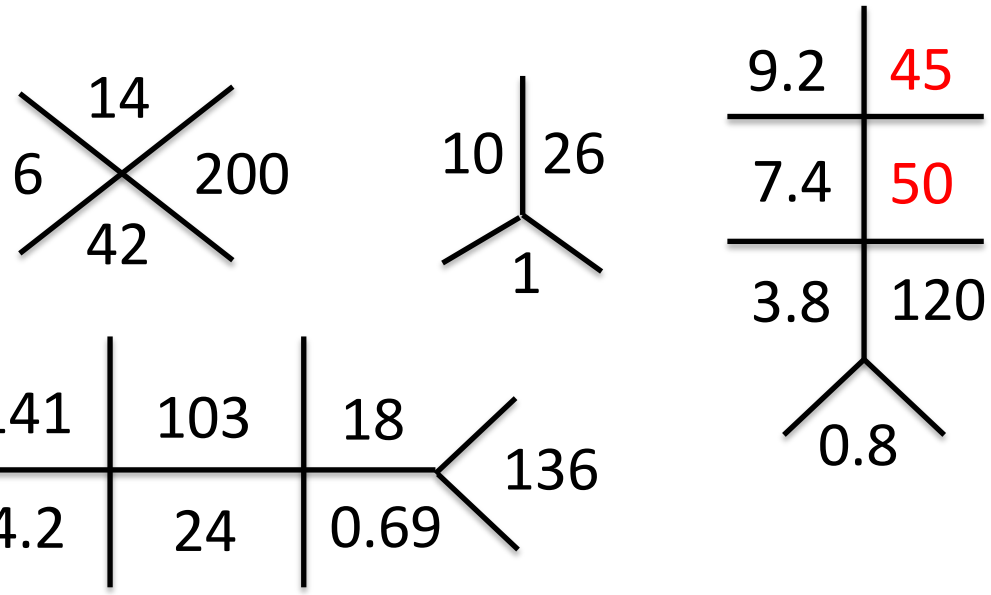
- Viral hepatitis serologies
- Ferritin*
- ANA*, ASMA*, IgG
- A1AT
- Ceruloplasmin
- CBC, CMP, INR
- HIV Ab
- Lipid panel
- HbA1c
- Thyroid function

- Imaging: Abdominal ultrasound




**Ultrasound-based imaging only detects moderate-severe hepatic steatosis**

# Back to our patient




Ultrasound Liver:

- Increase in hepatic echogenicity with typical regions of focal sparing
- The contour appears smooth
- Spleen size 9.5 x 9.4 x 3.5 cm
- **Impression: Hepatic steatosis. No evidence of portal hypertension.**

# Using the algorithm

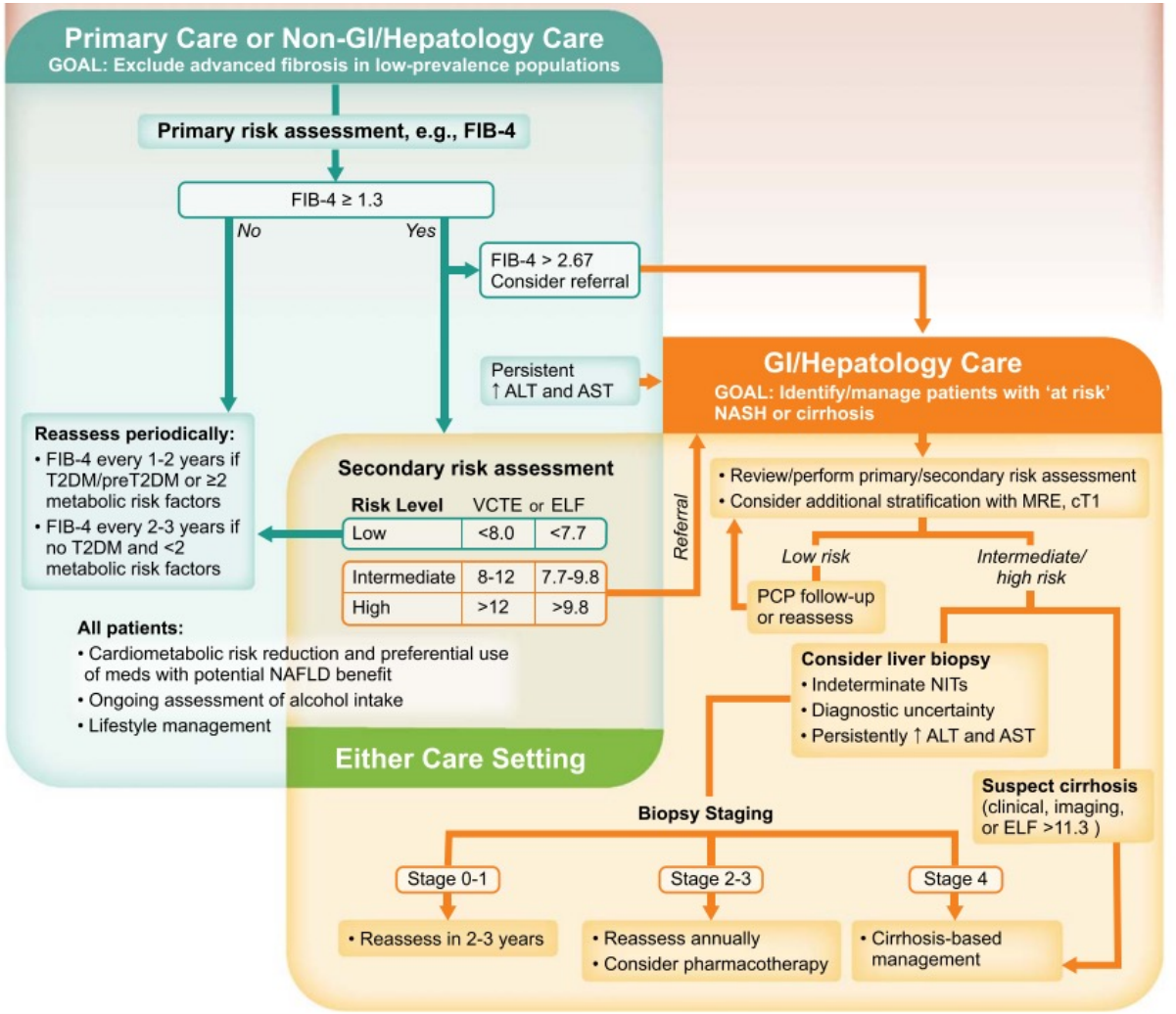
Table 2: MASLD definition in context of steatosis

| Adult Criteria | Pediatric Criteria |
|---|---|
| At least 1 out of 5: | At least 1 out of 5: |
| | 85th percentile for age/sex [BMI e-1] OR WC > 95th percentile hnicity adjusted |
| | g serum glucose ≥ 5.6 mmol/L 0 mg/dL] OR serum glucose ≥ 11.1 L [≥ 200 mg/dL OR 2-hour post-load se levels ≥ 7.8 mmol [140 mg/dL] bA1c ≥ 39 mmol/L OR already osed/treated type 2 diabetes OR ent for type 2 diabetes |
| | pressure age < 13y, BP ≥ 95th ntile OR ≥ 130/80 mmHg (whichever er); age ≥ 13y, 130/85 mmHg ecific antihypertensive drug ent |
| | a triglycerides < 10y, ≥ 5.6 mmol/L mg/dL]; age ≥ 10y, ≥ 1.70 mmol/L mg/dL OR lipid lowering treatment |
| | a HDL-cholesterol ≤ 1.0 mmol/L mg/dL] OR lipid lowering treatment |

## Primary questions to answer:

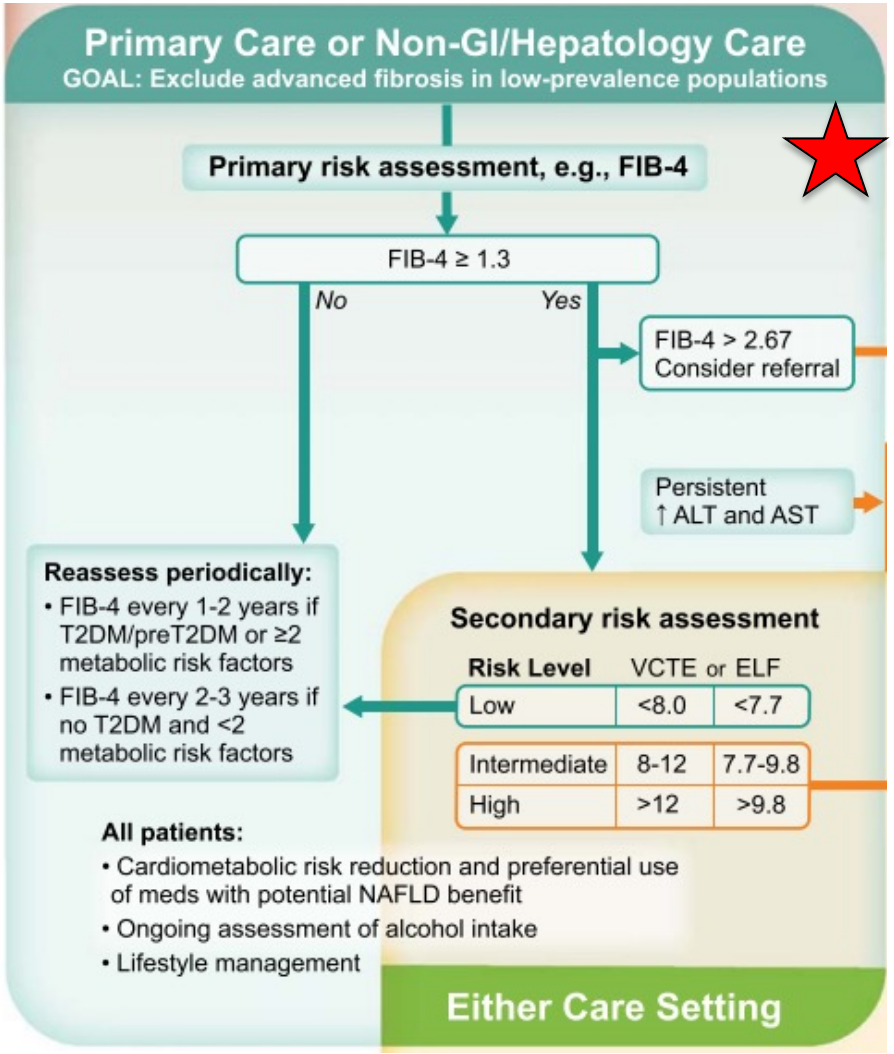
- Does this patient have underlying steatohepatitis (MASH)?
- Does this patient have any fibrosis?
- Does this patient have advanced (F3/F4) fibrosis?

# Risk Stratification




Rinella, et al. *Hepatology,* 2023.

# Risk Stratification




App Store Preview

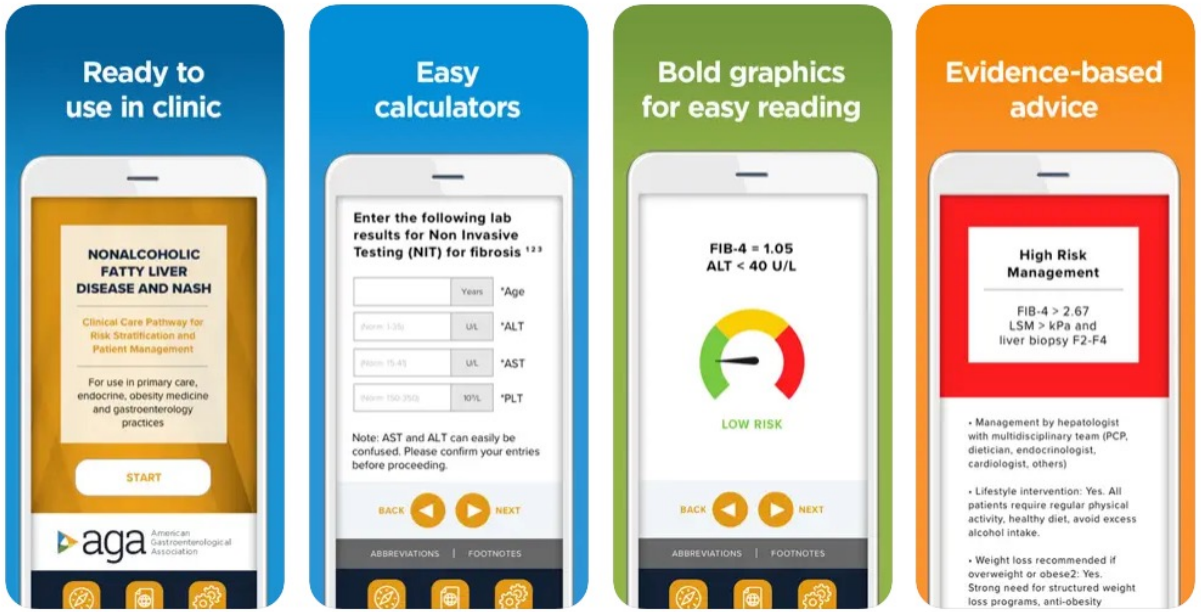
**AGA NASH App** 17+

American Gastroenterological Association

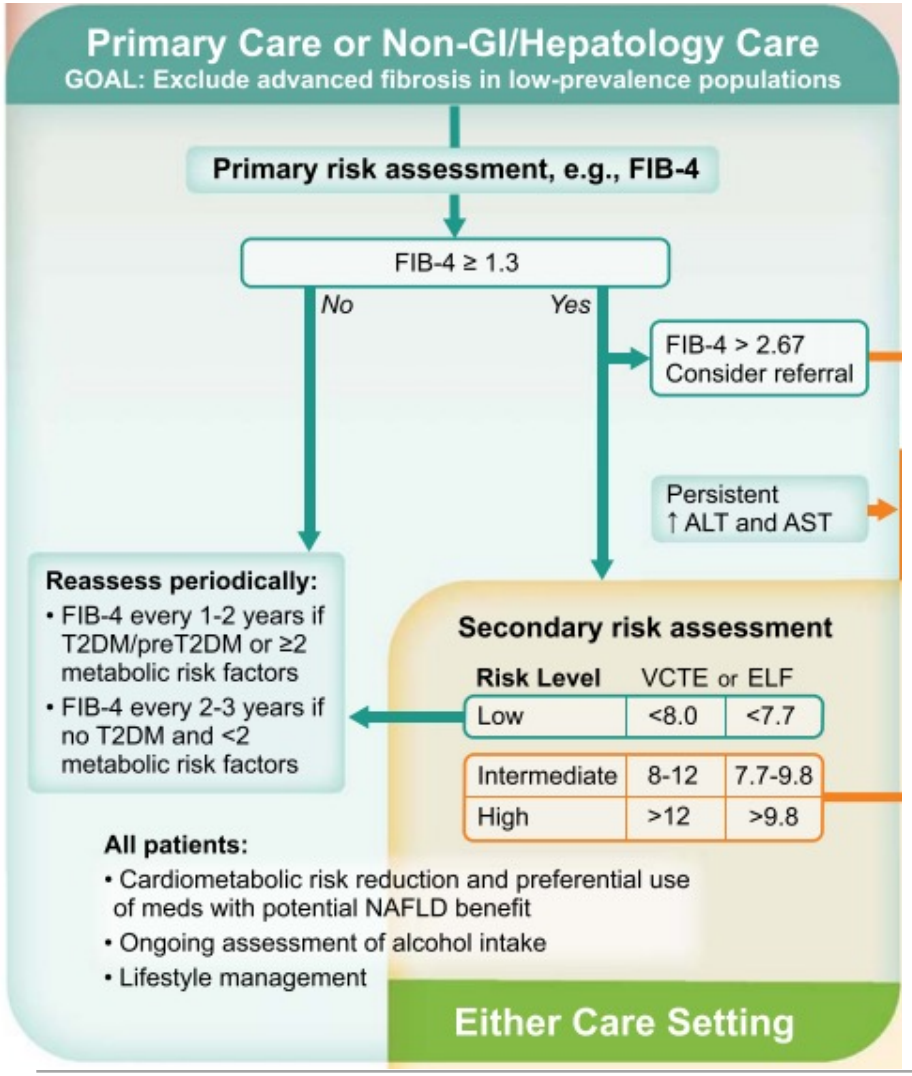
★★★★★ 5.0 • 1 Rating

Free

**iPhone Screenshots**

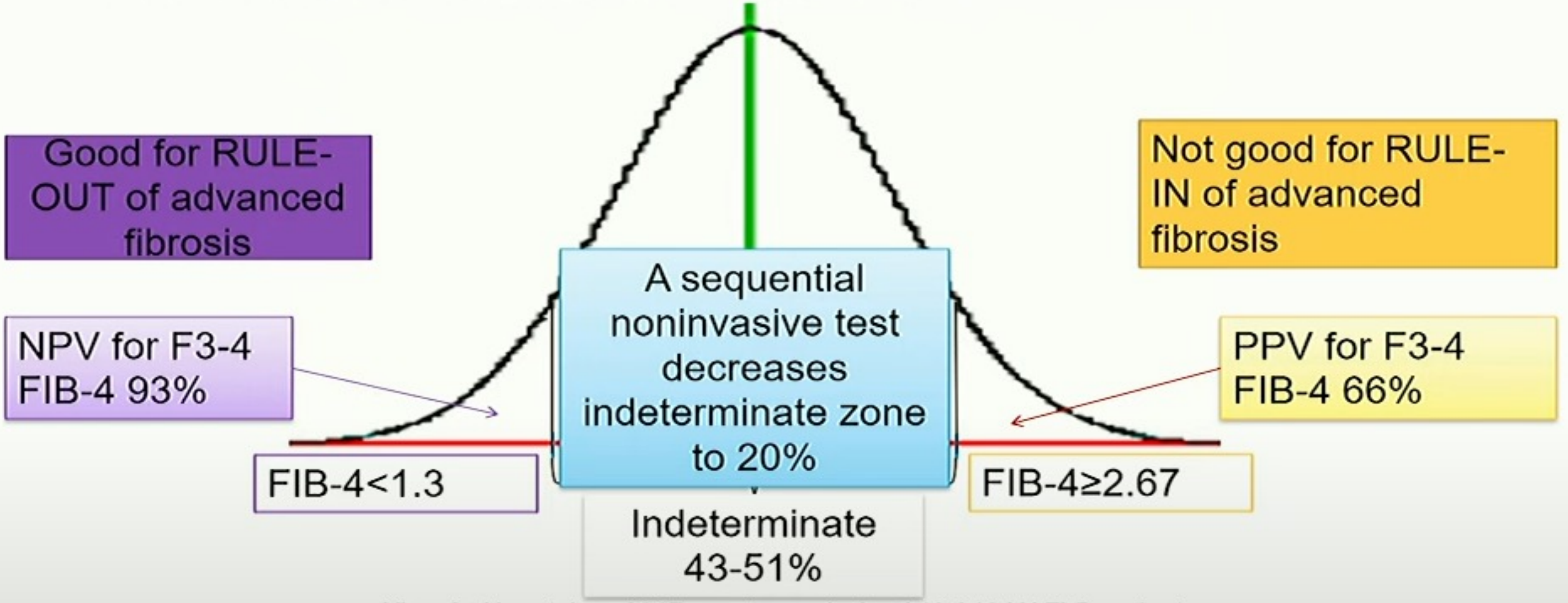


# Risk Stratification




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

# NEED 2 CUT-OFFS AND UP TO HALF OF PATIENTS HAVE INDETERMINATE VALUES




Xiao G, *Hepatology* 2017 – meta-analysis of 13,046 NAFLD patients
Anstee Q Hepatology 2019 – 3,202 patients in clinical trials

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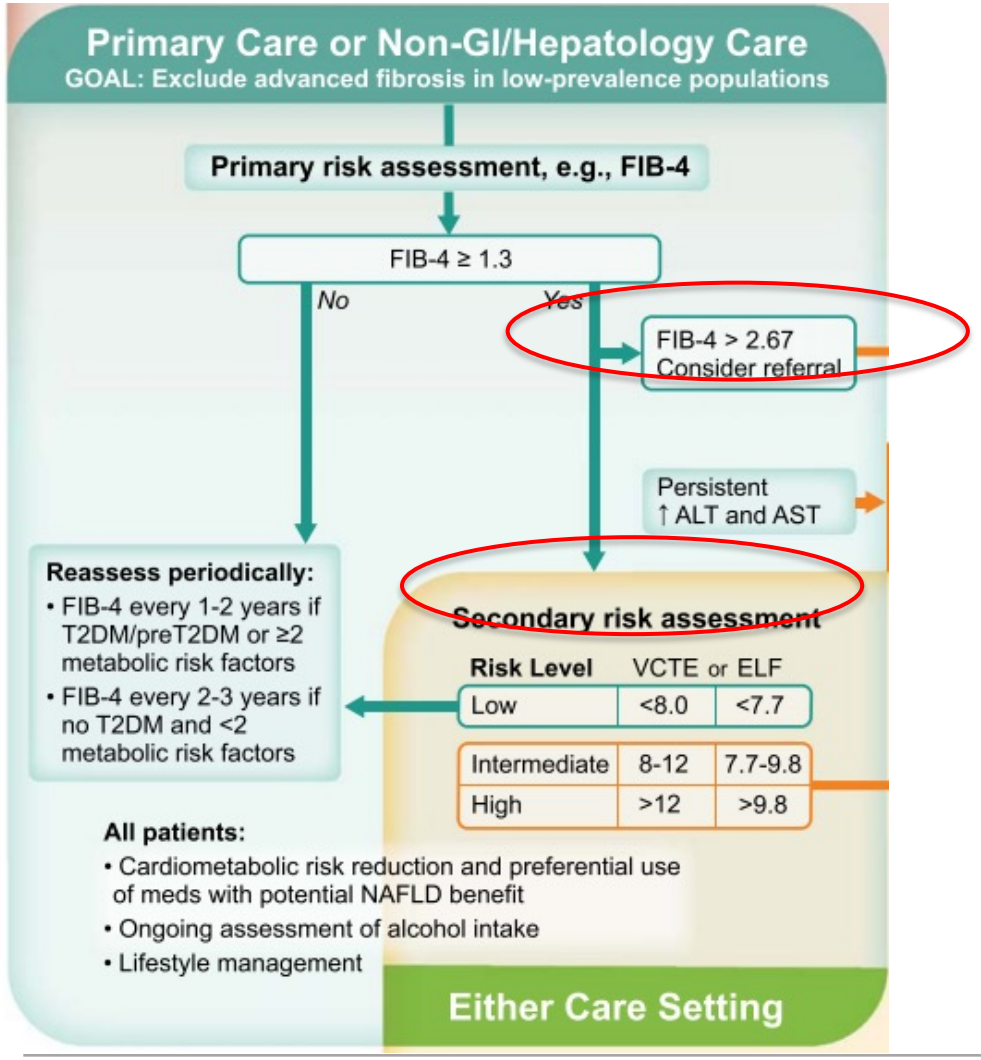
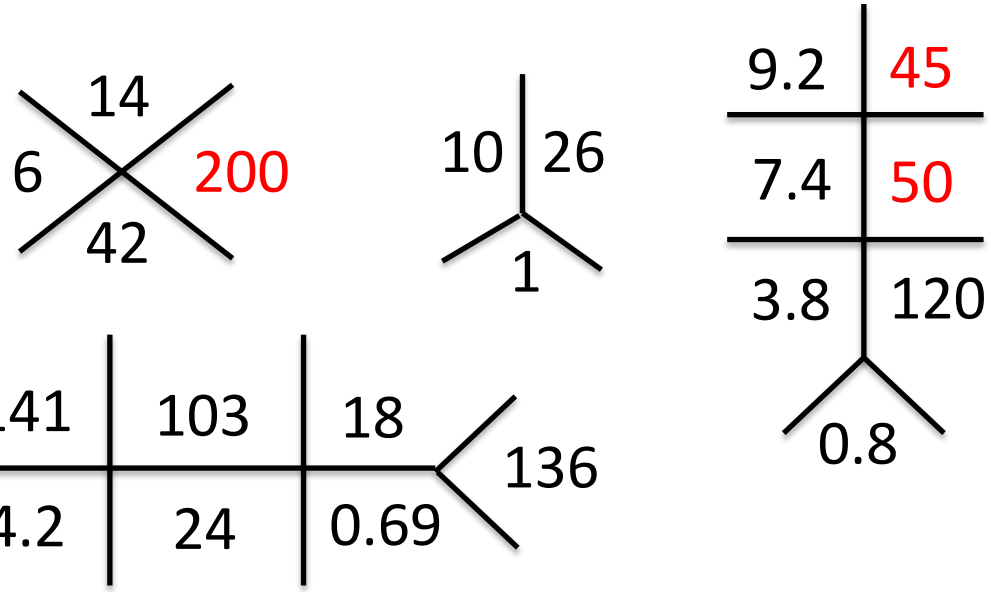
# Our Patient



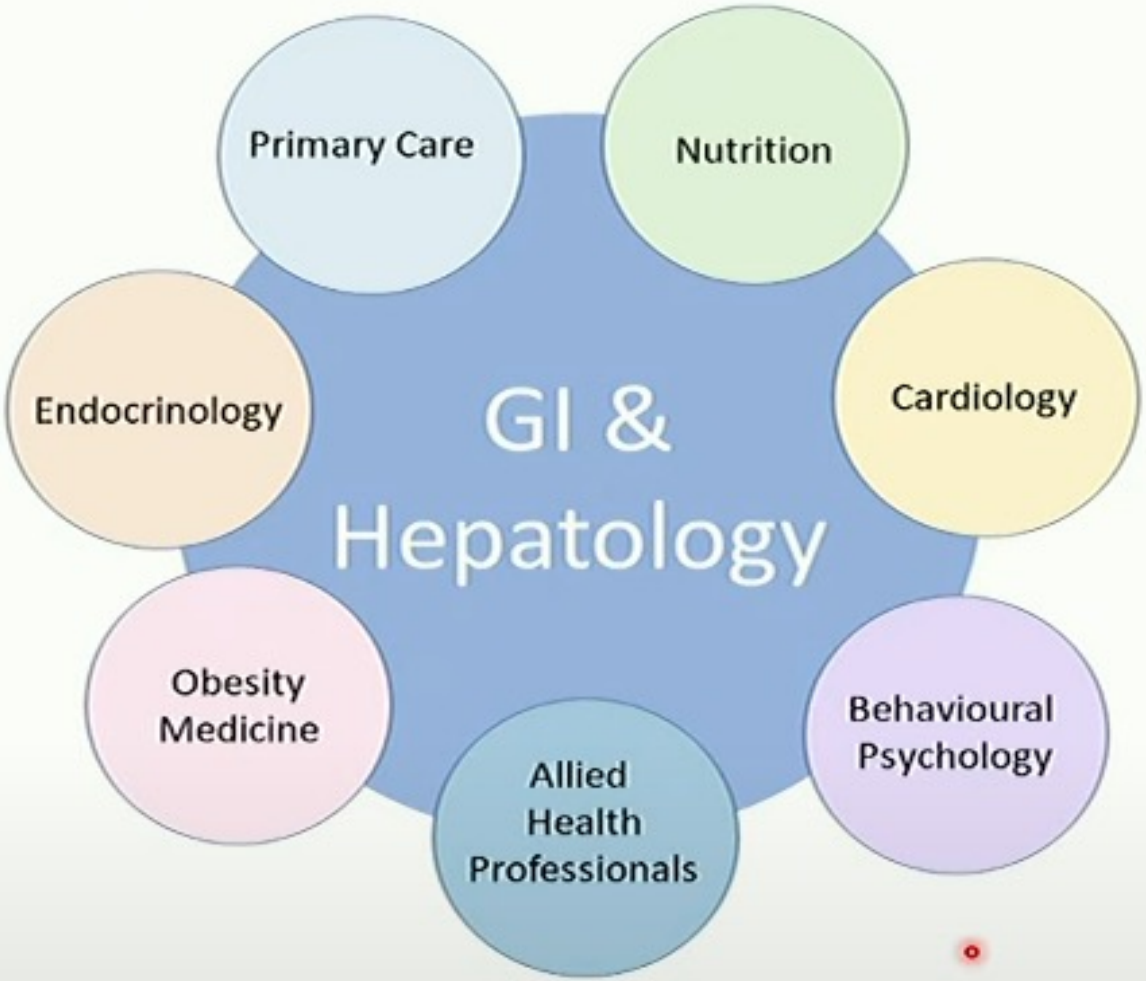

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}} = \frac{55 \times 45}{200 \times \sqrt{50}} = 1.75$$



# What happened to our patient

- Underwent RNY gastric bypass
- In 14 months, lost approximately 60 pounds (~25% of body weight)
- Improved dysglycemia HbA1c 6.3 → 5.1
- Normalization of liver chemistries: AST 18, ALT 20
- Improvement in estimates of steatosis and fibrosis via MRE/MRI-PDFF

# MASLD requires multidisciplinary care




Brennan PN…Allen AM *et al.* Beyond a liver-gut focus: the evolution of gastroenterology and hepatology in challenging the obesity and steatotic liver disease paradigm. *Gut.* 2023

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# Management of the low risk patient

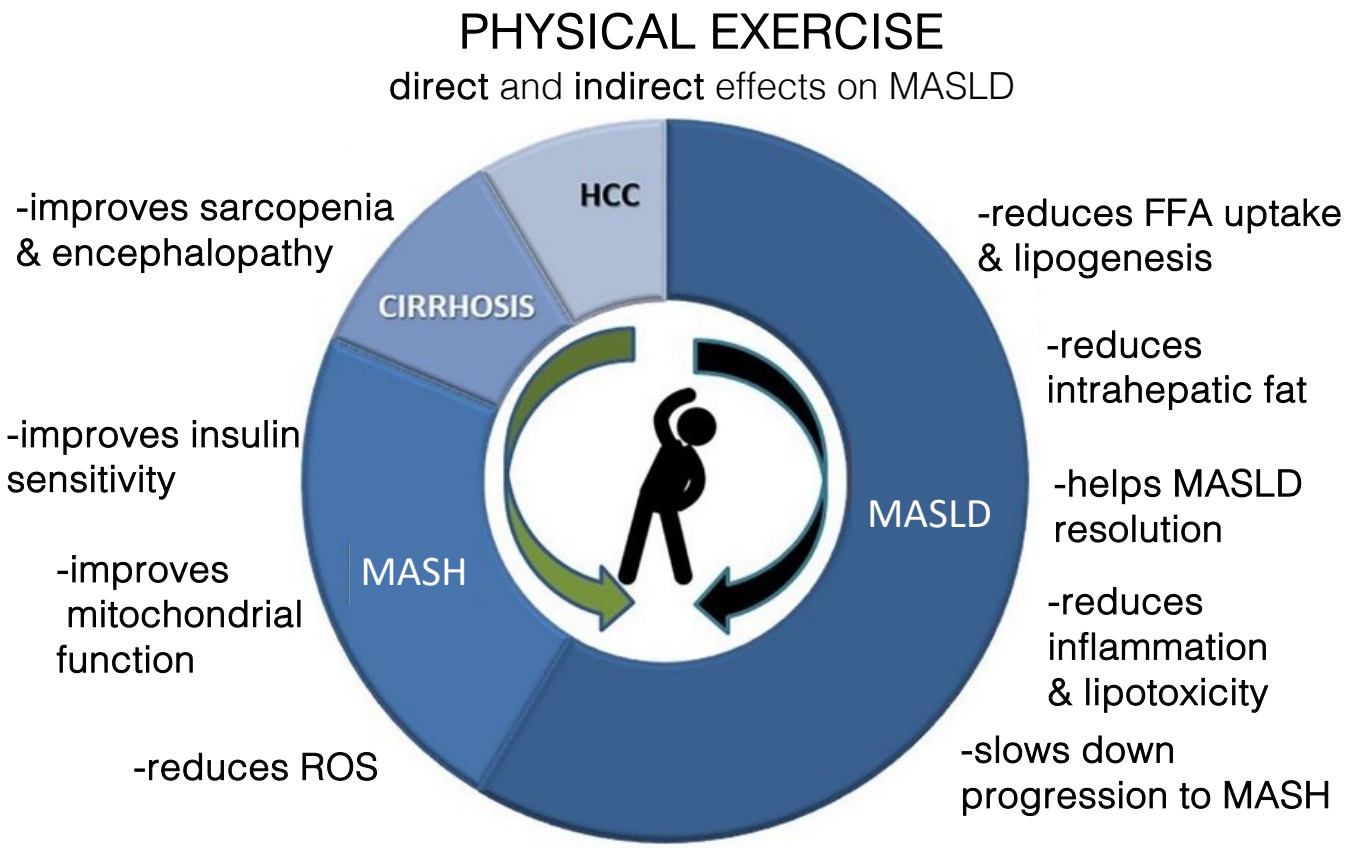
| | LOW RISK<br>FIB-4 < 1.3 or<br>LSM < 8 kPa or<br>liver biopsy F0-F1 | INDETERMINATE RISK<br>FIB-4 1.3 - 2.67 and/or<br>LSM 8 - 12 kPa and<br>liver biopsy not available | HIGH RISK[1]<br>FIB-4 > 2.67 or<br>LSM > 12 kPa or<br>liver biopsy F2-F4 |
|---|---|---|---|
| | Management by PCP, dietician, endocrinologist, cardiologist, others | Management by hepatologist with multidisciplinary team (PCP, dietician, endocrinologist, cardiologist, others) | |
| Lifestyle intervention[2] | Yes | Yes | Yes |
| Weight loss recommended if overweight or obese[3] | Yes<br>May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery | Yes<br>Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery | Yes<br>Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery |
| Pharmacotherapy for NASH | Not recommended | Yes[4, 5, 6] | Yes[4, 5, 6, 7] |
| CVD risk reduction[8] | Yes | Yes | Yes |
| Diabetes care | Standard of care | Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA) | Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA) |

Kanwal, et al. *Gastroenterology,* 2021.

# Management: Diet Composition

- Prescribed a diet that leads to a caloric deficit
- Mediterranean diet (limited carbs and sat fat; enriched in fiber and unsat fat) generally recommended due to cardiovascular benefits
- Excessive fructose should be avoided
- Tailor dietary modifications to patient's cultural and personal preferences
- Coffee consumption: ≥3 cups/d reduces risk of NAFLD and liver fibrosis

# Management: Impact of Exercise

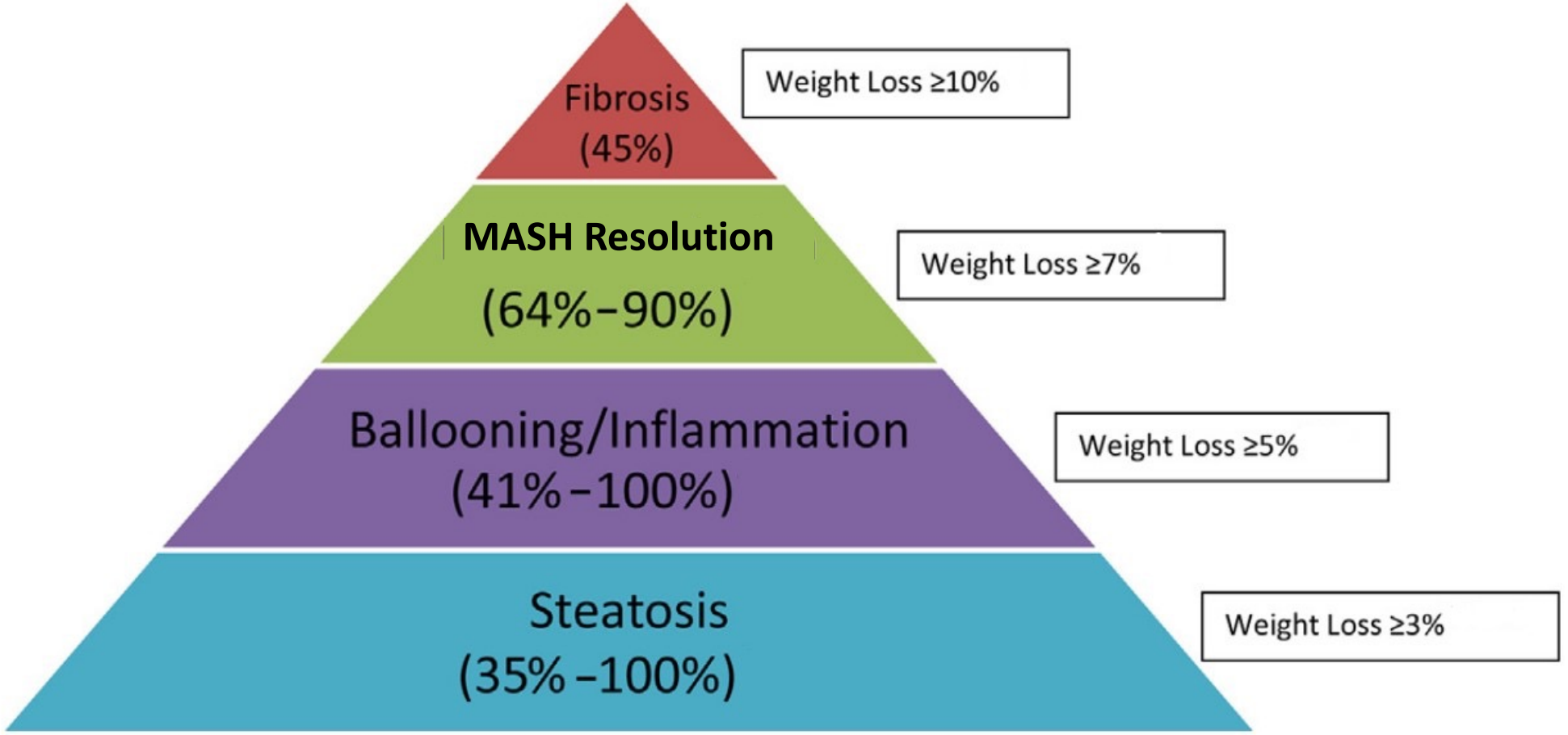



EXTRAHEPATIC BENEFITS

↓visceral fat, whole body fat, ↑muscle strength and bulk, ↑bone density, ↑flexibility, ↓blood pressure, ↑cardiorespiratory fitness, improved mood and sleep patterns, ↑energy levels

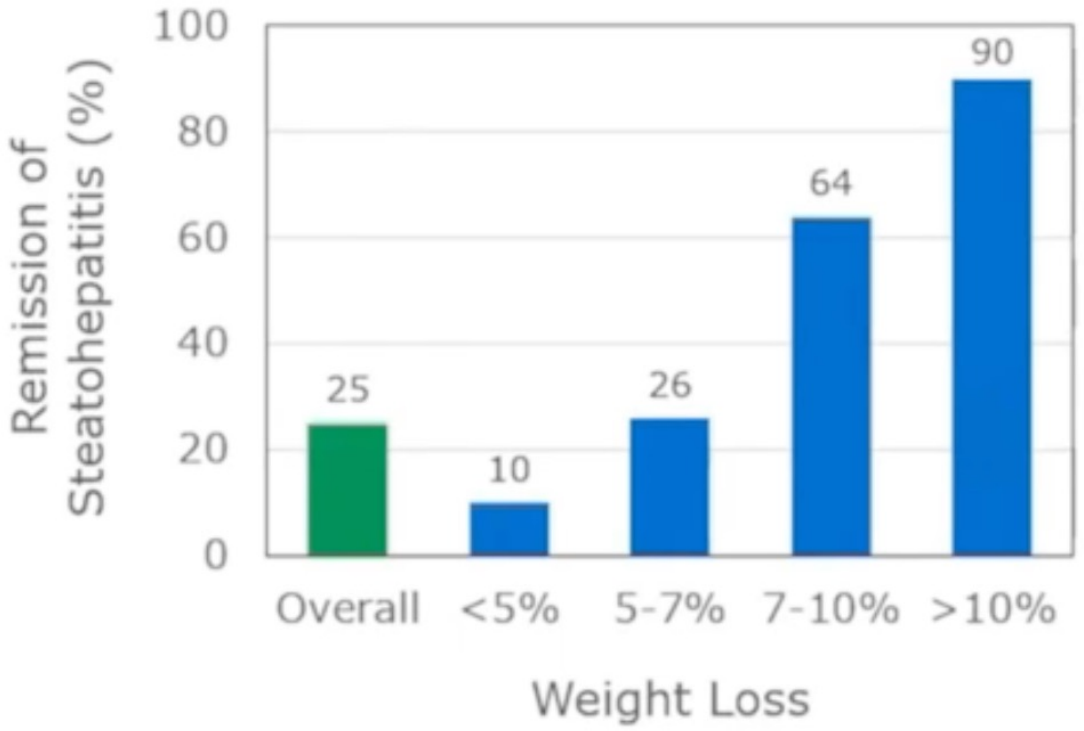
- Exercise alone may prevent/reduce hepatic steatosis irrespective of weight loss
- Both aerobic exercise and resistance training reduce liver fat; tailor to patient preferences

# Management: Obesity Management




Hanna et al, *Clinical liver disease*, 2016.

# Lifestyle changes




**293 adults** with NAFLD

Average NAS **4.8**

**61% F0**, 8% F1, 20% F2, 11% F3 (no F4)

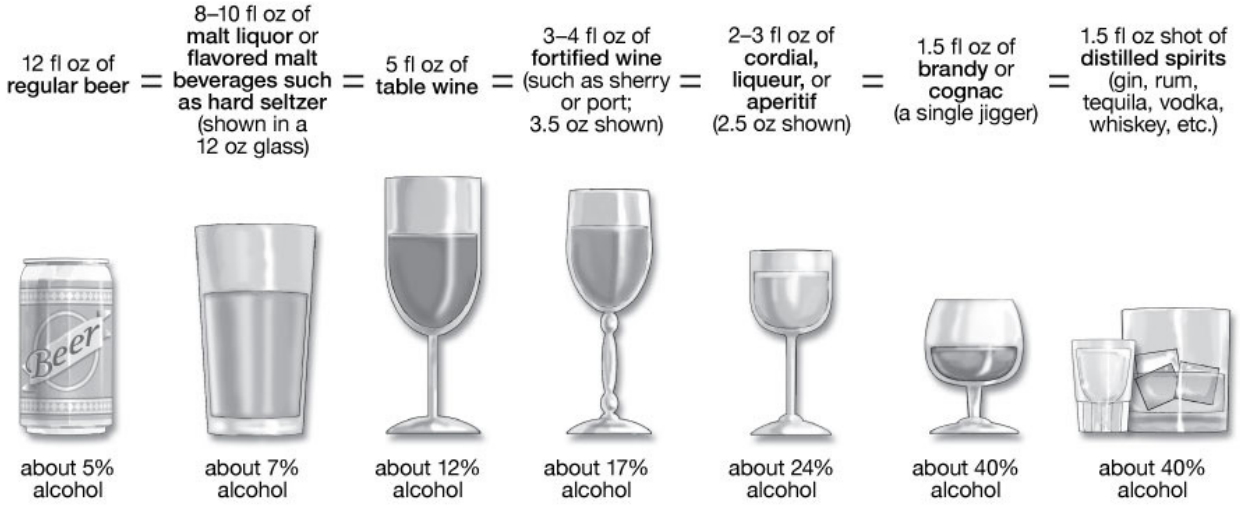
52 week treatment
750 kcal/day deficit diet
200 min/week exercise

- Average change in NAS Score **-1.58**

Vilar-Gomez E *et al.*, *Hepatology* 2015

# Management: Alcohol Consumption

- Patients with clinically significant hepatic fibrosis (≥F2) should abstain from alcohol use completely
- Abstinence, particularly for patients with moderate-heavy alcohol intake, can lower risk of fibrosis progression
- In patients with MASLD, alcohol can be a cofactor for liver disease progression, and intake should be assessed on a regular basis




*Each drink shown above represents one U.S. standard drink and has an equivalent amount (0.6 fluid ounces) of "pure" ethanol.*

# Management: Therapeutics – Impact of Available Medications on Patients with MASLD

| Medication | FDA Indication | Patient Population | Liver Benefit | Side Effects | Non-liver Benefit |
|---|---|---|---|---|---|
| **Vitamin E** (rrr-alpha) 800 IU daily | N/A | MASH **without** T2DM or cirrhosis | Improves steatosis, NASH and transplant-free survival<br>No proven benefit on fibrosis | Increased risk of stroke, bleeding, worsens IR, prostate CA, ?mortality | None |
| **Pioglitazone**<br>30–45mg po daily | T2DM | MASH with and without T2DM | Improves steatosis, activity and NASH<br>Fibrosis improvement? | Weight gain,<br>HF exacerbation,<br>bone loss in postmenopausal women | Improves insulin sensitivity, prevention of DM, CV risk reduction, stroke prevention |
| **Liraglutide**<br>1.8mg SC daily (T2DM), 0.6–3mg SC daily (obesity) | T2DM, obesity | MASH without cirrhosis | Improves steatosis,<br>No proven impact on fibrosis | Gastrointestinal, Gallstones, pancreatitis | Improves insulin sensitivity, weight loss, CV risk reduction, may slow renal dz progression |
| **Semaglutide**<br>0.4mg SC daily, 0.25–2.4mg SQ weekly | T2DM, obesity | MASH without cirrhosis | Improves steatosis, activity and NASH; No proven impact on fibrosis- *may* slow progression | | Improves insulin sensitivity, weight loss, CV, and renal outcomes; stroke prevention |
| **Tirzepatide (GIP/GLP)** | T2DM | T2DM or obesity with MASLD | Reduces steatosis on imaging | Gastrointestinal, Gallstones, pancreatitis | Improves insulin sensitivity; significant weight loss;<br>CV benefit unknown |
| **SGLT2i (Empagliflozin)** | T2DM | T2DM and MASLD | Reduction in steatosis by imaging | Risk of genitourinary yeast infection, volume depletion, bone loss | may improve insulin sensitivity, improves CV renal outcomes; benefit in HF, modest weight loss |

# MASLD: GLP-1 for all?

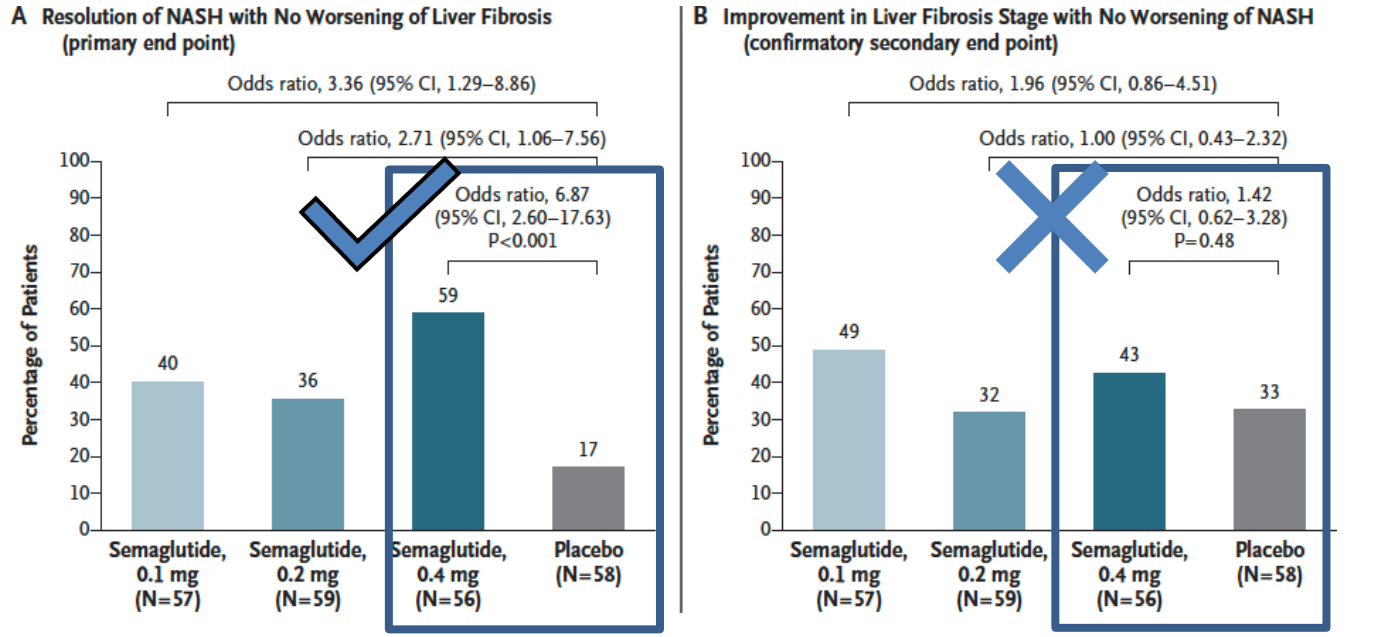
ORIGINAL ARTICLE

N ENGL J MED 384;12 NEJM.ORG MARCH 25, 2021

## 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*

- Phase 2 trial of NASH and **F1*, F2 or F3**
- Sema **0.1, 0.2 or 0.4mg** v placebo SC **qd** X **72w**



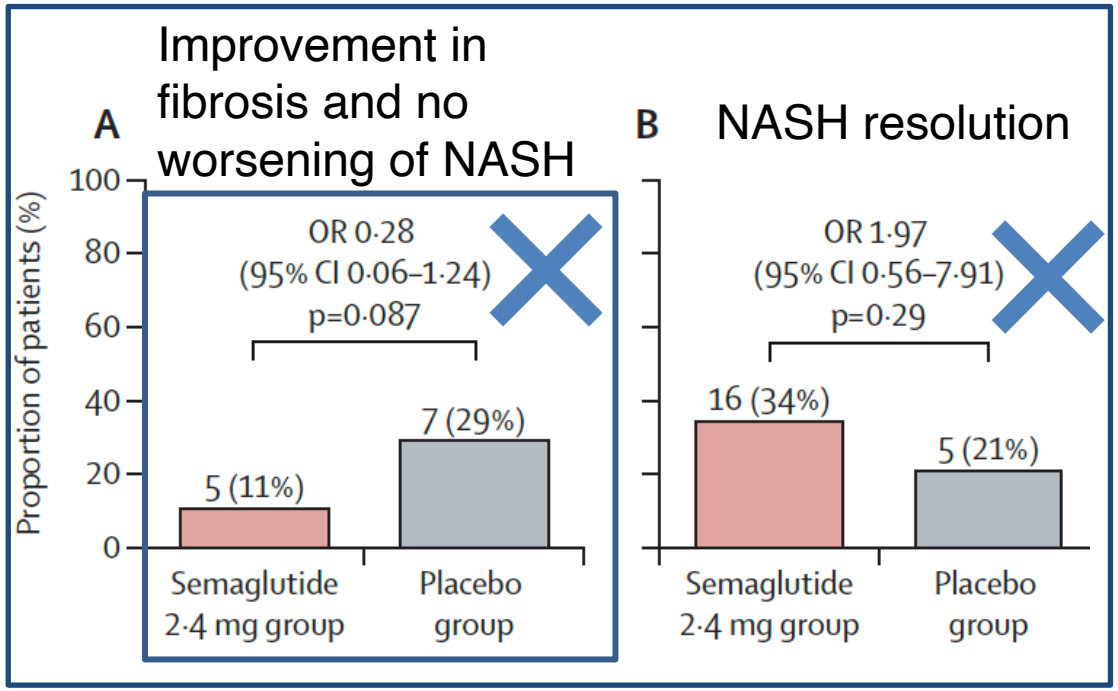

*F1 was added during trial

www.thelancet.com/gastrohep Published online March 16, 2023

## Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial**

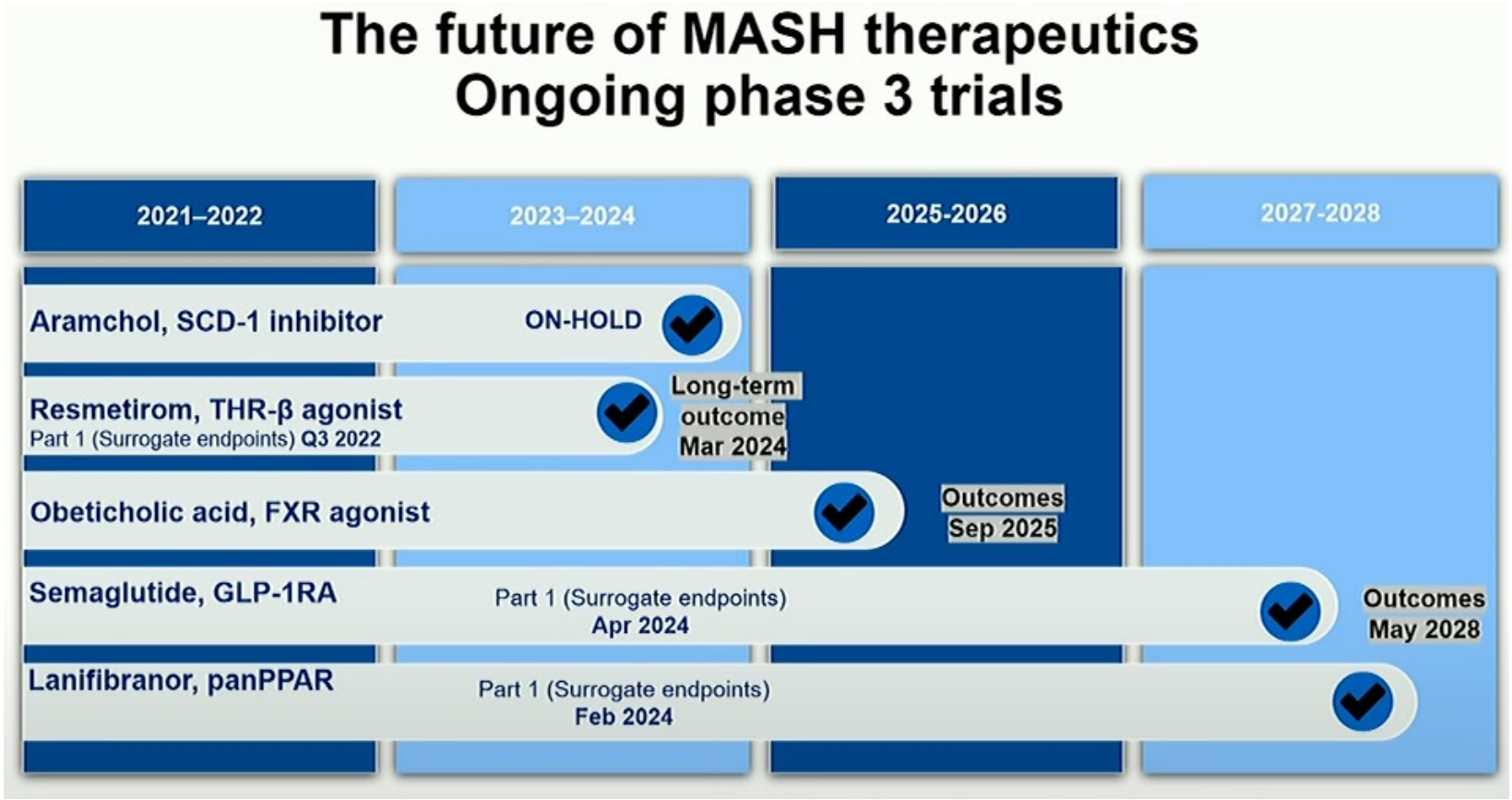
Rohit Loomba*, Manal F Abdelmalek, Matthew J Armstrong, Maximilian Jara, Mette Skalshøi Kjær, Niels Krarup, Eric Lawitz, Vlad Ratziu, Arun J Sanyal, Jörn M Schattenberg, Philip N Newsome*, on behalf of the NN9931-4492 investigators†

- Phase 2 trial of NASH **F4** (cirrhosis)
- Sema **2.4 mg** vs. placebo SC **qw** X **48w**




**primary endpoint changed from MRE to histology mid-trial

# The future of MASH therapeutics
## Ongoing phase 3 trials

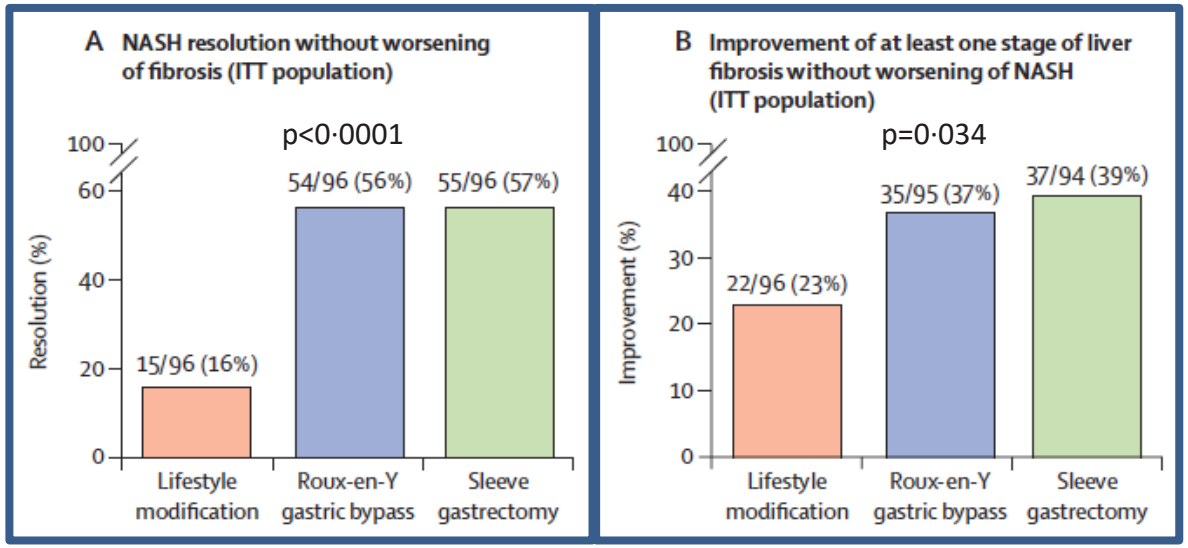


# MASLD: Surgery for all?

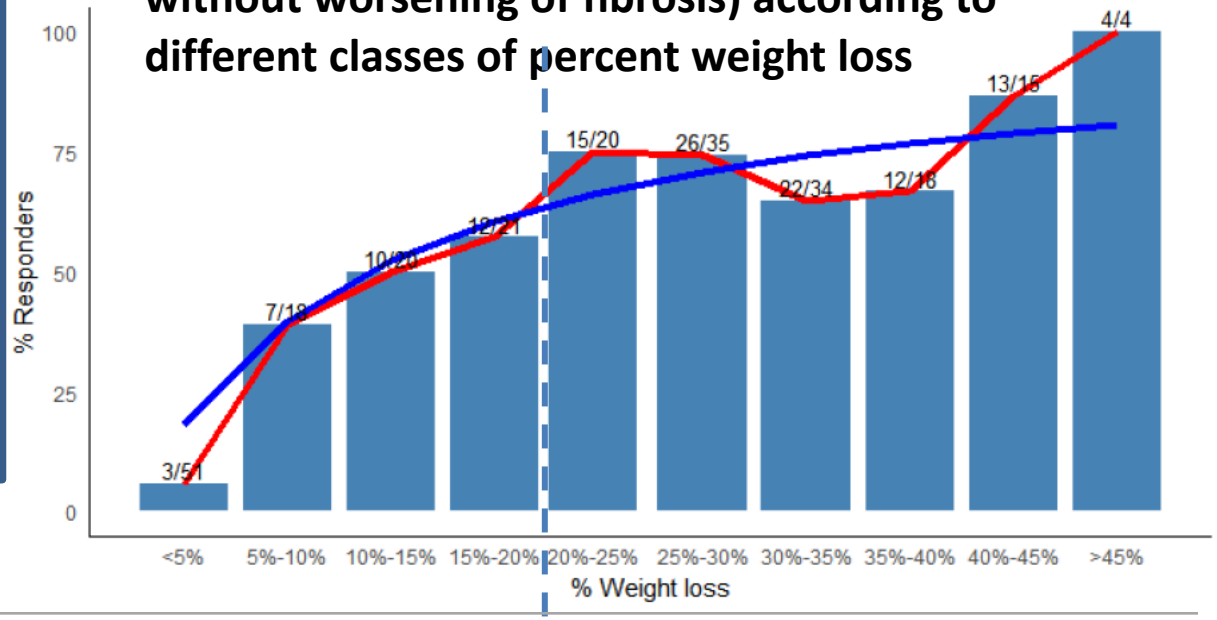
## Bariatric–metabolic surgery versus lifestyle intervention plus best medical care in non-alcoholic steatohepatitis (BRAVES): a multicentre, open-label, randomised trial

*Ornella Verrastro*, Simona Panunzi*, Lidia Castagneto-Gissey, Andrea De Gaetano, Erminia Lembo, Esmeralda Capristo, Caterina Guidone, Giulia Angelini, Francesco Pennestrì, Luca Sessa, Fabio Maria Vecchio, Laura Riccardi, Maria Assunta Zocco, Ivo Boskoski, James R Casella-Mariolo, Pierluigi Marini, Maurizio Pompili, Giovanni Casella, Enrico Fiori, Francesco Rubino, Stefan R Bornstein, Marco Raffaelli, Geltrude Mingrone*

Published online April 20, 2023 https://doi.org/10.1016/S0140-6736(23)00634-7




**Percentage of responders (MASH resolution without worsening of fibrosis) according to different classes of percent weight loss**





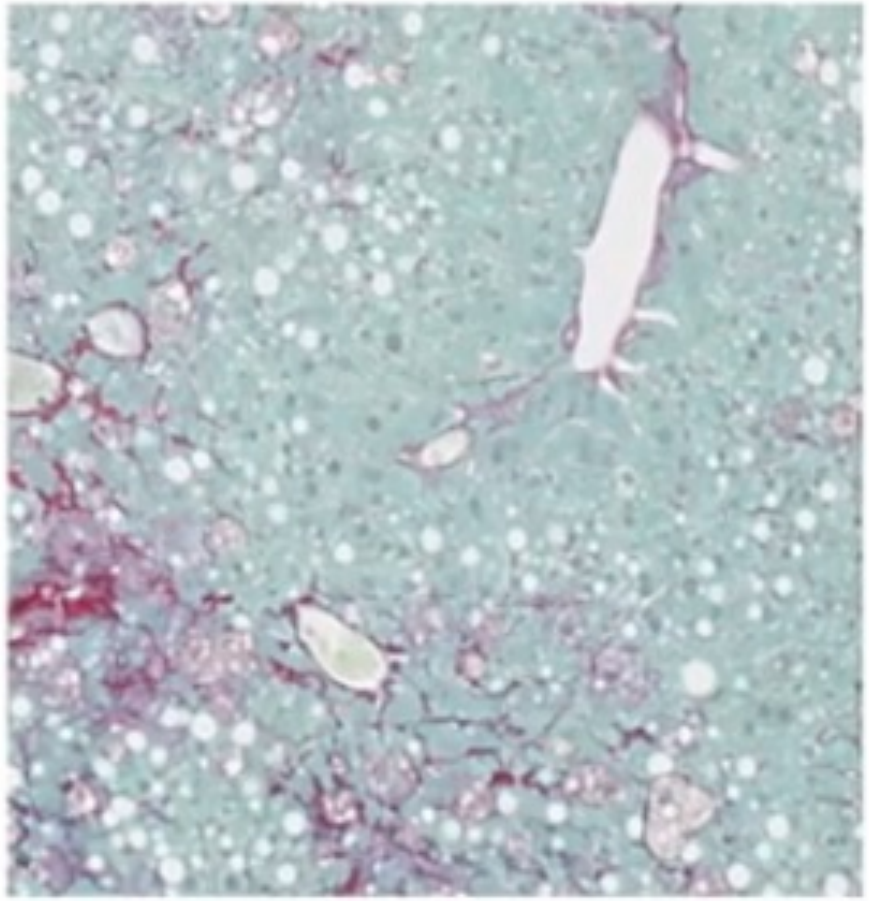

Verrastro et al. Lancet

# Summary 1: MASLD "call to action"

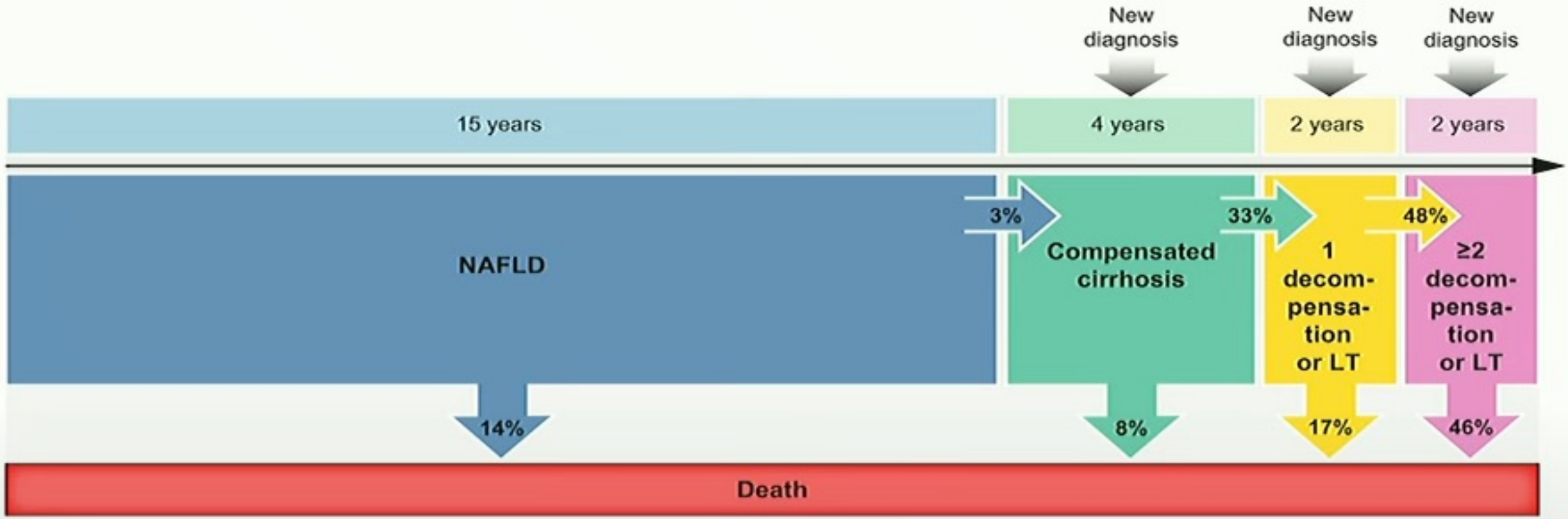
**Addressing the MASLD epidemic cannot be accomplished by GI specialists alone**

**GI societies are going all-in to:**

- Heighten awareness of MASLD in primary care and non-GI specialties
- Encourage the use of algorithms/apps for risk stratification
- Educate providers to take advantage of evidence-based treatment options

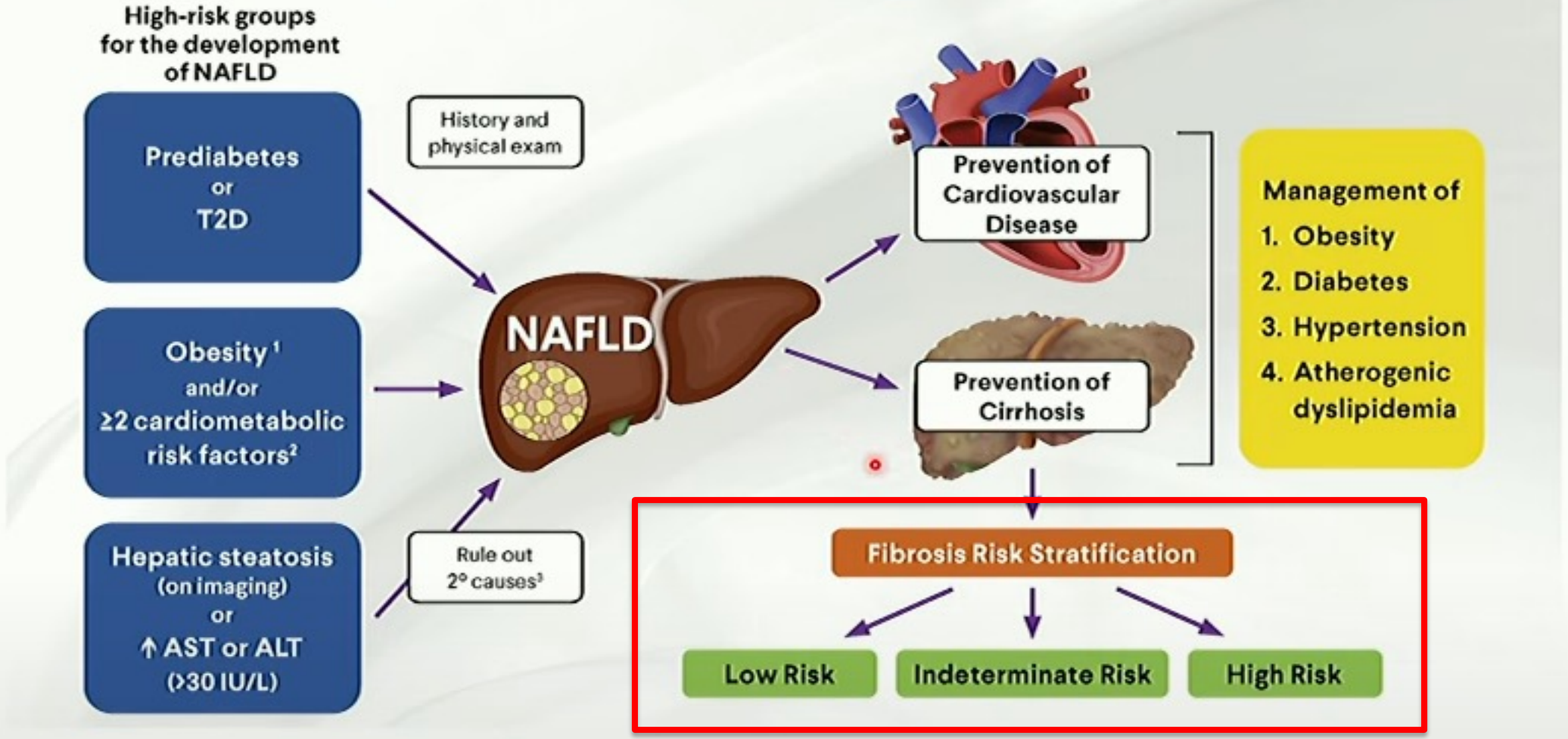


# MASLD has a slow clinical course…until cirrhosis onset




Allen AM, Therneau TM…Kamath PS. Clinical course of non-alcoholic fatty liver disease and the implications for clinical trial design. *J Hepatol*. 2022

# Management Algorithm for NAFLD – Overview




Cusi K et al. 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 *Endocr Pract.* 2022

# Summary

- MASLD continues to grow at an alarming rate
- Screen for SLD in those with 1 or more components of the metabolic syndrome
- MASLD vs MetALD
- Risk stratification: FIB-4 followed by elastography
- Refer to hepatology if greater than F2 fibrosis
- Weight loss is the mainstay of therapy and includes lifestyle changes, pharmacotherapy and surgery
- Good MASLD care is multidisciplinary and invludes good control of DM, dyslipidemia, hyerptension and OSA given high risk of cardiovascular disease
- Multidiscioplinary care pathways are needed
- Liver directed therapies on the horizon: 2024-2025

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Please answer today's CME questions at menti.com

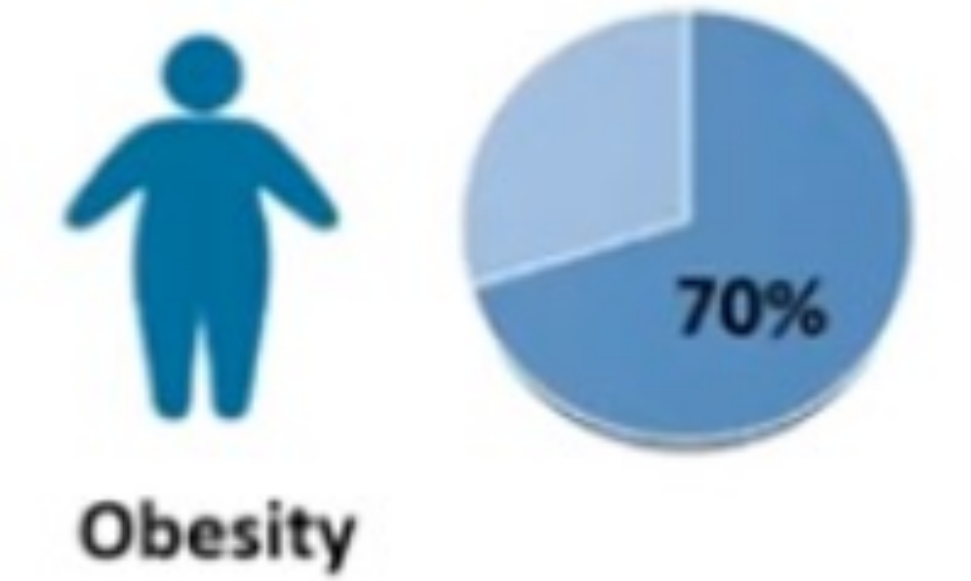
Menti.com
CODE:
33801580

# CME Question:

What is the pre-test probability that a patient with obesity has MASLD?

A. 55%
B. 97%
C. 33%
D. 90%
E. 70%

# ANSWER



# Acknowledgements

Dr Maddie Kubiliun, Transplant hepatologist at UT Southwestern

# Thank You for Listening

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