Fatty Liver- The Silent Epidemic

Practical Guidance on the Evaluation and Management of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

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NORTHEAST DIGESTIVE

Disclosures

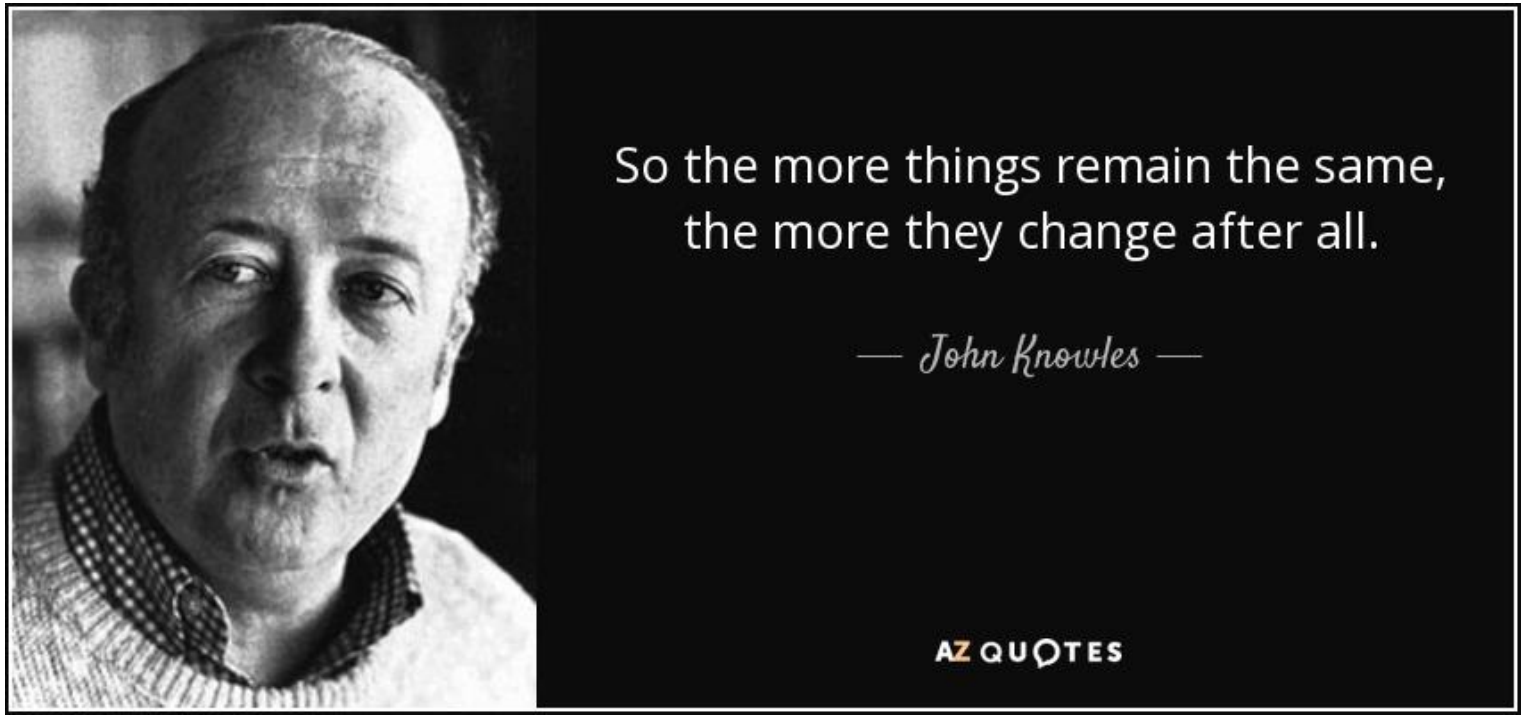
Declaration Statement: I have relevant relationships with ineligible companies to disclose within the past 24 months.

- Prime Therapeutics: Moderator, American College of Gastroenterology National Conference, October 2022
- Objective Health: Sub-investigator for multiple NASH trials, Concluded October 2023

Objectives

- Review updated recommendations on new nomenclature for steatotic liver disease
- Identify at risk populations for steatotic liver disease
- Discuss initial workup of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and Metabolic Dysfunction-Associated Steatohepatitis (MASH) with special attention to noninvasive measures to assess for fibrosis
- Formulate a comprehensive treatment plan
- Summarize updated guidance on pharmacotherapy

New Nomenclature



New Name, Who Dis?

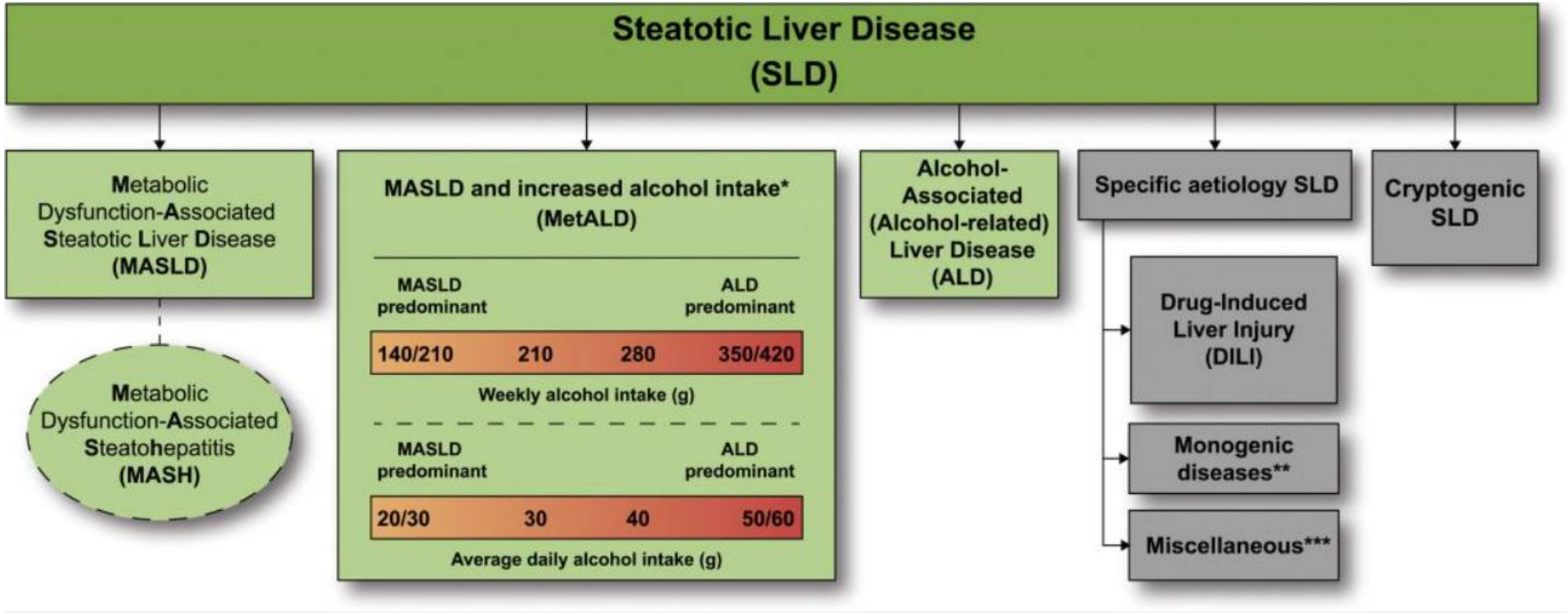
- In 2023, Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH) were renamed
- Multidisciplinary society elected to rename to MASLD* and MASH**
- Reasons for Change
  - "nonalcoholic" and "fatty liver" are stigmatizing
  - "metabolic" and "steatotic liver disease" better characterize the pathophysiology of the disease process
- Added diagnosis for combined MASLD with increased alcohol intake →MetALD

*Metabolic Dysfunction-Associated Steatotic Liver Disease

** Metabolic Dysfunction-Associated Steatohepatitis

Rinella M, et al. Hepatology 2023

Renaming NAFLD to MASLD



* Approximately 17-20 drinks per week or Approximately 2.5-3 drinks per day

Rinella M, et al. Hepatology 2023

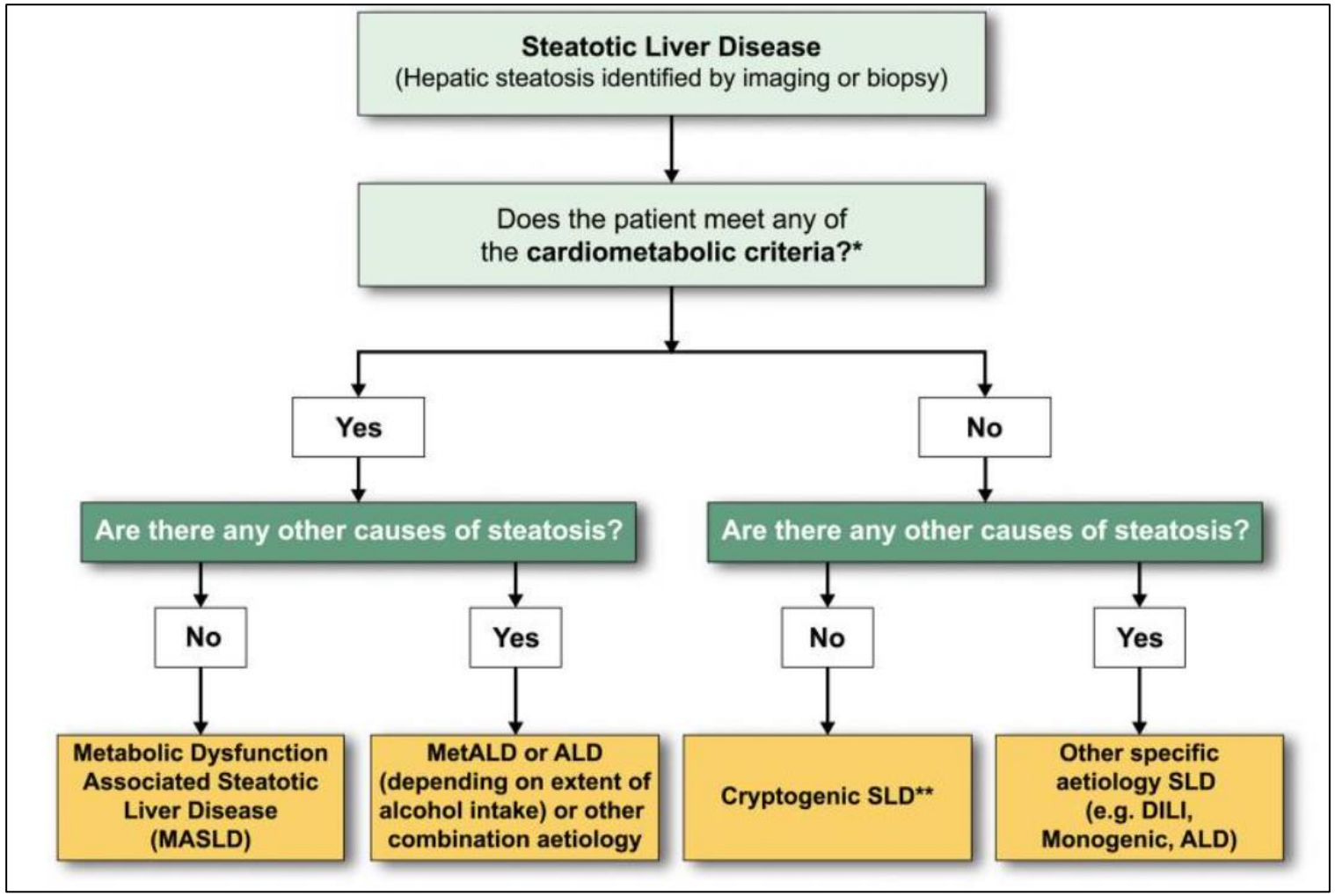
Defining MASLD

Patient must have hepatic steatosis identified on imaging or biopsy AND 1 Cardiometabolic risk factor

Cardiometabolic Risk Factors
BMI≥25 (23 Asia) or Waist Circumference ≥94cm (M) 80cm (F)
Fasting glucose ≥100mg/dL or 2 hour post load glucose ≥140mg/dL or HbA1c ≥5.7% or known Type 2 Diabetes with or without treatment
Blood Pressure ≥ 130/85 or known HTN on specific antihypertensive drug treatment
Plasma triglycerides ≥150mg/dL or on lipid lowering treatment
Plasma HDL ≤ 40mg/dL (M) or 50mg/dL (F) or on lipid lowering treatment

Rinella M, et al. Hepatology 2023

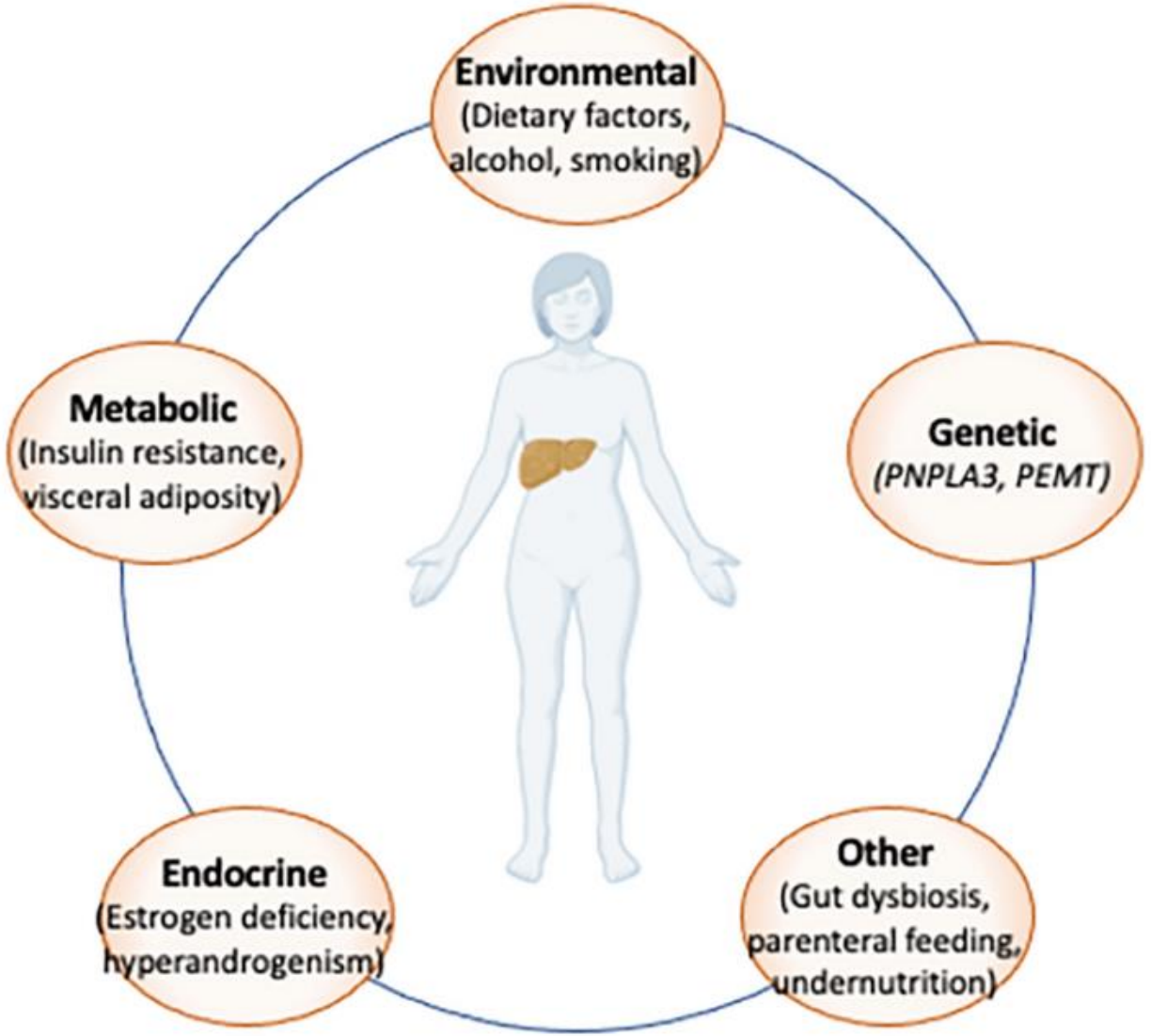
Defining Steatotic Liver Disease



Rinella M, et al. Hepatology 2023

Lean "NAFLD"

- SLD with normal BMI
  - 4-11% of patients in US
- Risk Factors
  - Insulin resistance
  - Visceral adiposity
  - Low muscle mass



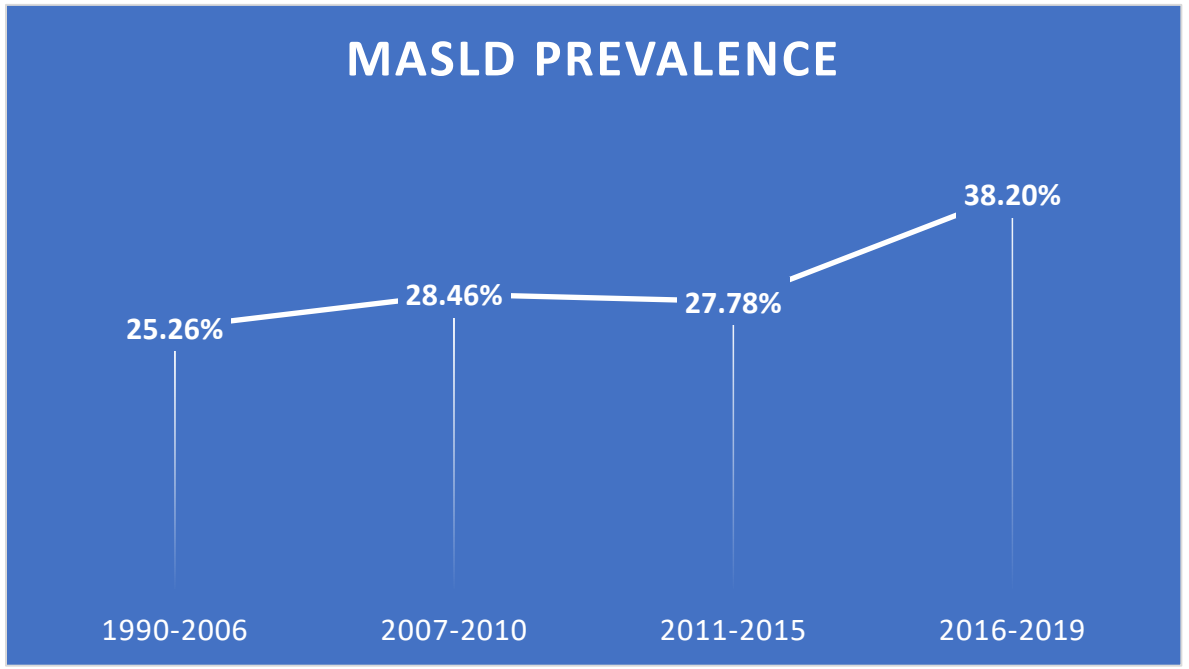
Distefano JK, Gerhard GS, Diabetology and Metabolic Syndrome 2022; 14:45.

Global Burden of MASLD

50.4% increase over 3 decades!

- Global prevalence of MASLD between 30-40%
- Higher in Males 40% vs. Females 26%
- **North America: 31%**

~179,000,000 in N. America



Why the increase?

- Obesity (rates tripled since 1975)
- Type 2 Diabetes Mellitus
- Metabolic Syndrome

Younossi ZM, et al. Hepatology 2023; 77(4): 1335
Hamid O, et al. Annals of Hepatology 2022; 27(5)

Global Burden of MASLD

Why is this a problem?

- Leading cause of cirrhosis
- On trajectory to become leading cause of liver transplant in US
- Mortality secondary to MASLD Cirrhosis expected to increase 2-3 fold by 2030
- Significant economic burden
- Volume of MASLD patients requires multidisciplinary approach

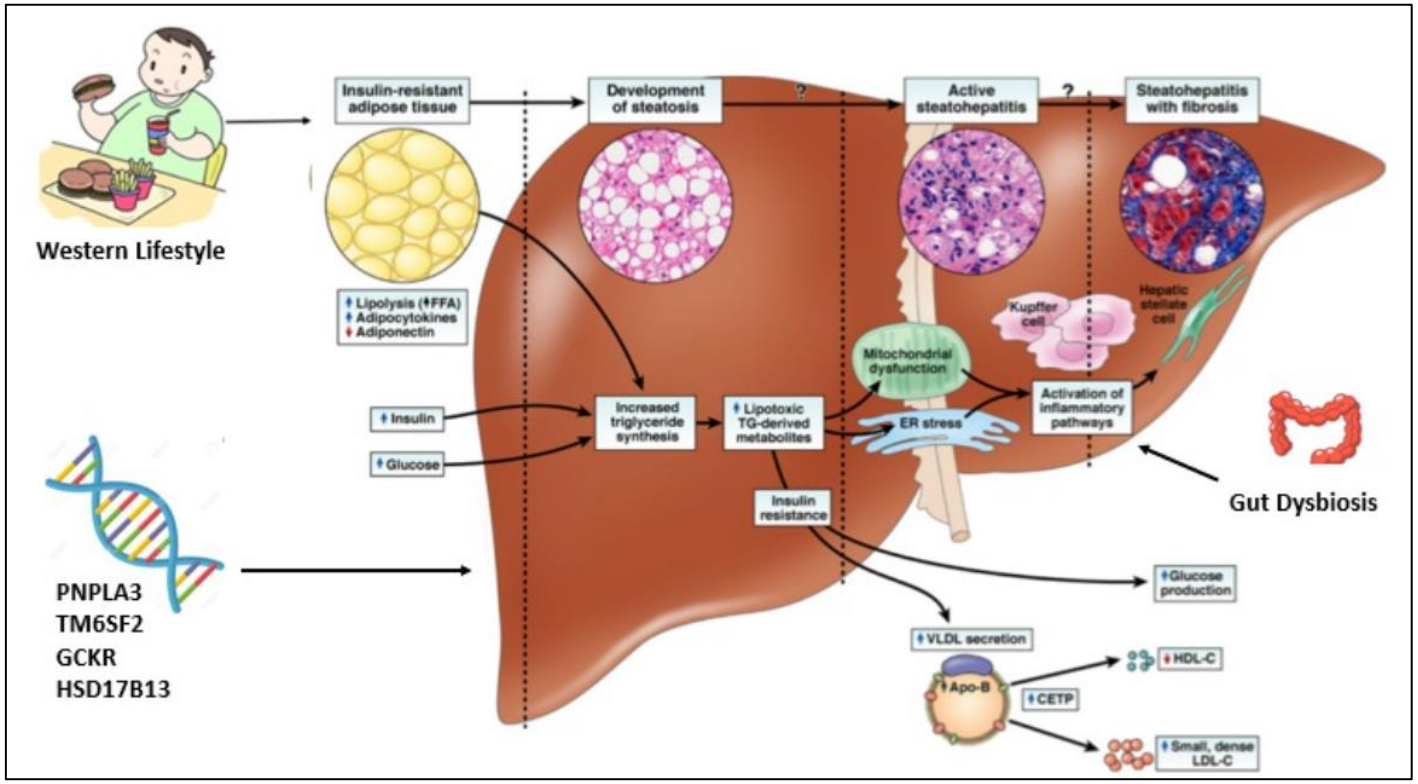
Primary Care	Gastroenterologist	Hepatologist	Endocrinologist	Obesity Medicine

Rinella M, et al. Hepatology 2023

Pathophysiology of MASLD

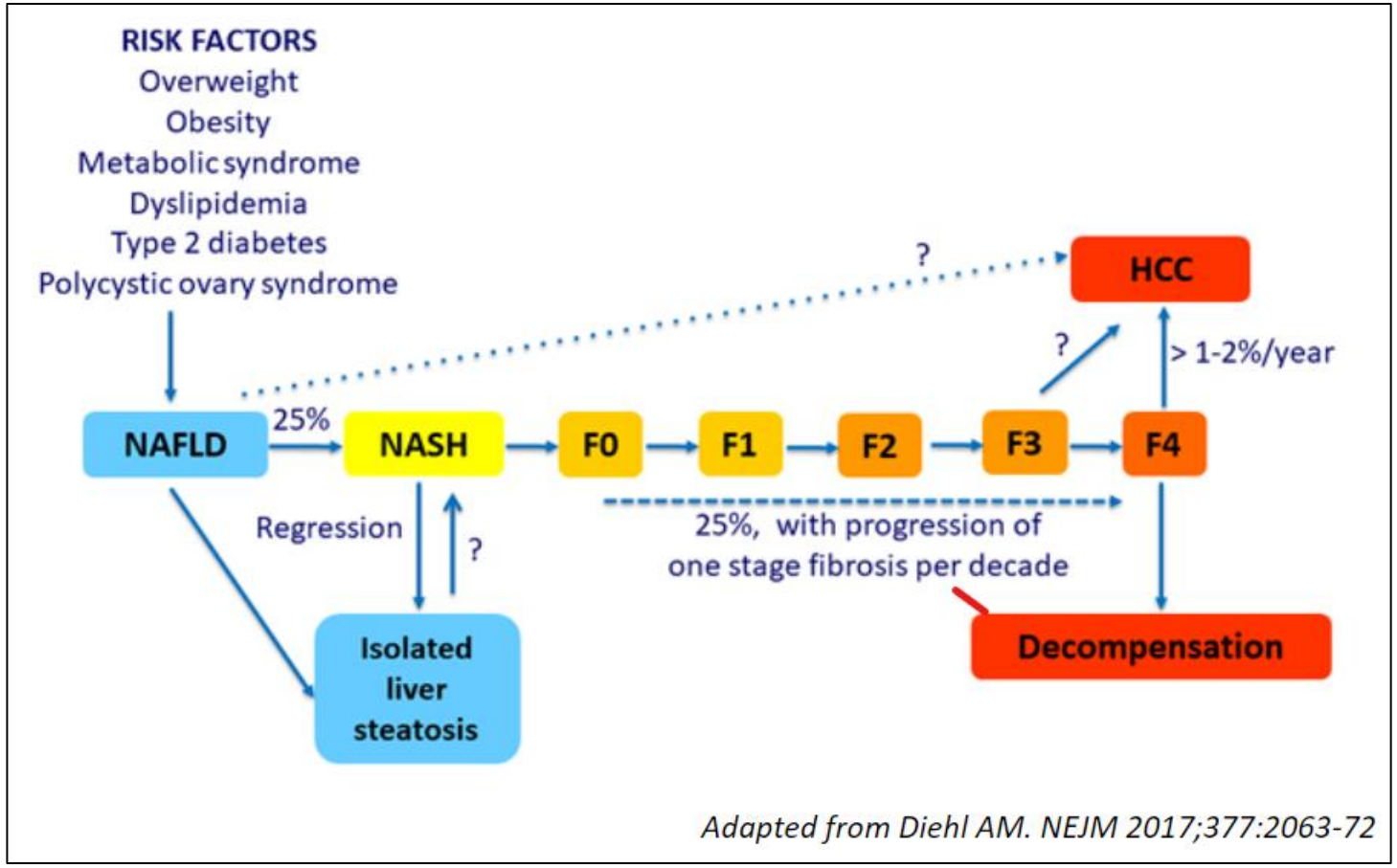
Two hit theory

1. Insulin Resistance
2. Inflammatory Cytokines



Akshintala D,et al. Nonalcoholic Fatty Liver Disease: The Overlooked Complication of Type 2 Diabetes. [Updated 2019 Jul 9]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK544043/

MASLD Progression



Evolution of MASLD/MASH in Primary Care

- 10,334 patients with MASLD/MASH followed over 7 years in primary care
  - Patients referred to nutritionist- 24.2%
  - Patients referred to a hepatologist-0.7%
  - Patients referred to a hepatologist with advanced fibrosis or cirrhosis- 12.8%
    - <4% underwent follow up imaging or biopsies

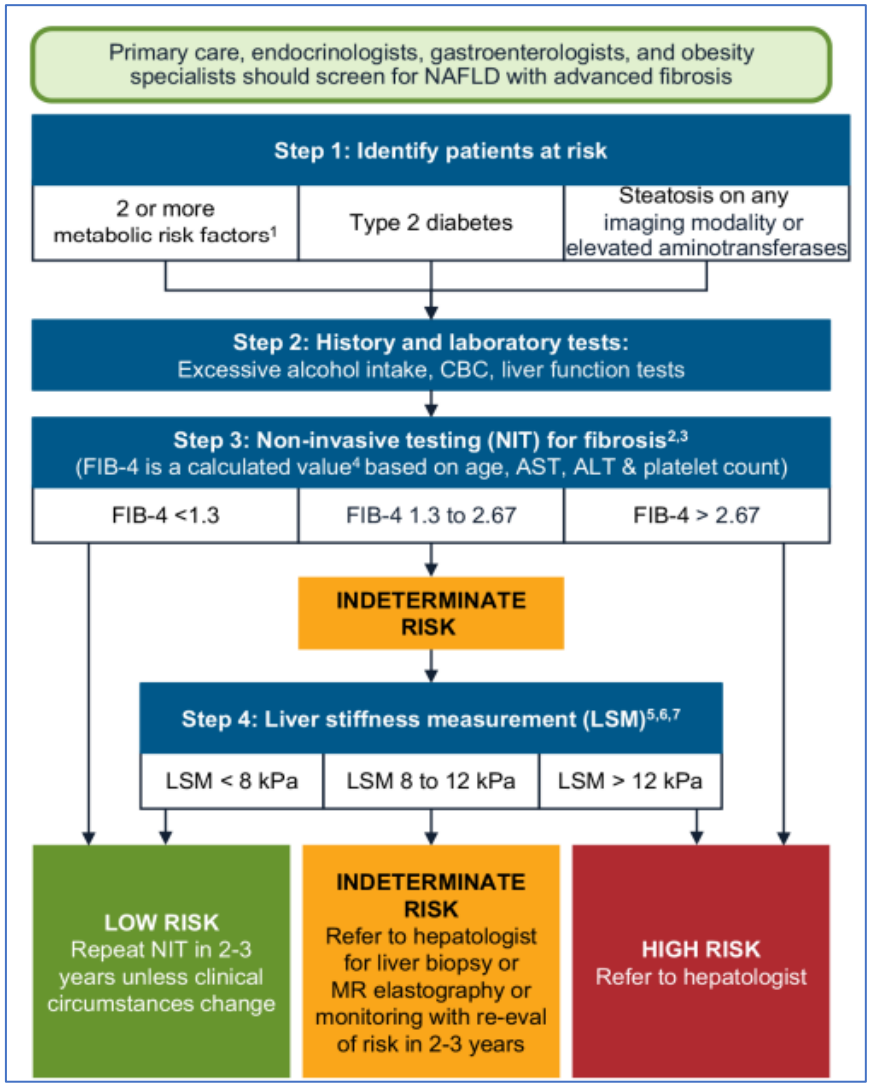
Conclusion: More resources needed for primary care providers on MASLD

Gips JR, et al. Management of nonalcoholic fatty liver disease in a primary care setting. Presented at: The Liver Meeting; Nov. 10-14, 2023; Boston

Initial Evaluation

Clinical Care Pathway for the Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease

Fasiha Kanwal[1,2], Jay H. Shubrook[3], Leon A. Adams[4], Kim Pfotenhauer[5], Vincent Wai-Sun Wong[6], Eugene Wright[7], Manal F. Abdelmalek[7], Stephen A. Harrison[8], Rohit Loomba[9], Christos S. Mantzoros[10], Elisabetta Bugianesi[11], Robert H. Eckel[12], Lee M. Kaplan[10,13], Hashem B. El-Serag[1,2], Kenneth Cusi[14,15]



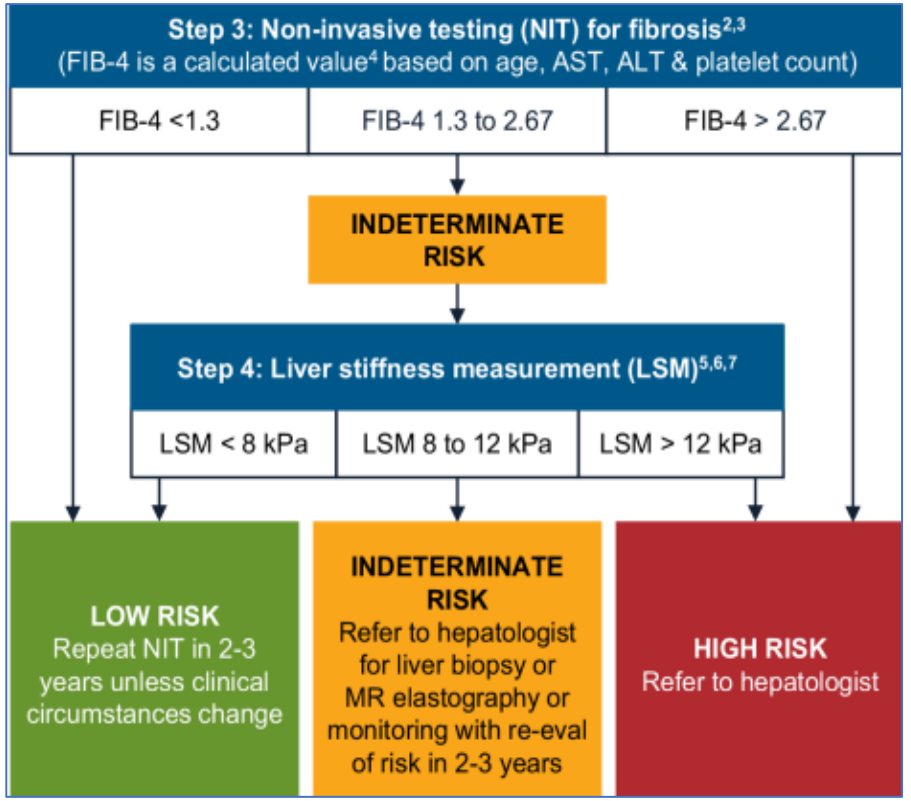
Kanwal F, et al. Gastroenterology 2021.

Noninvasive Testing for Liver Fibrosis

- Benefits
  - Easily available
  - Affordable
  - High Non-Predictive Value (NPV)
  - High correlation to clinical outcomes
  - Factors in Age
- FIB-4: Calculated value based on age, AST, ALT, and PLT

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

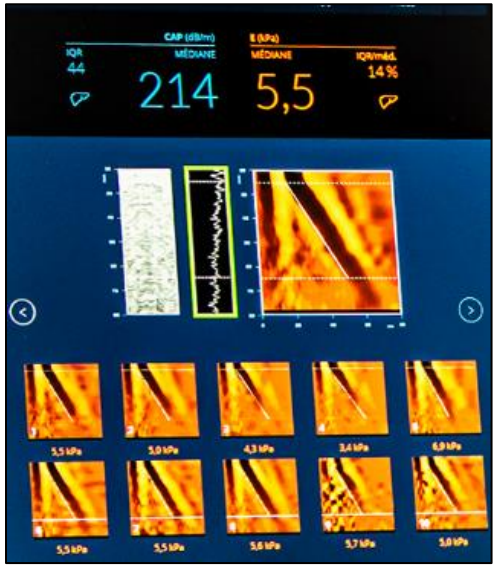
- Can be combined with other biomarker tests for increased accuracy



Kanwal F, et al. Gastroenterology 2021.

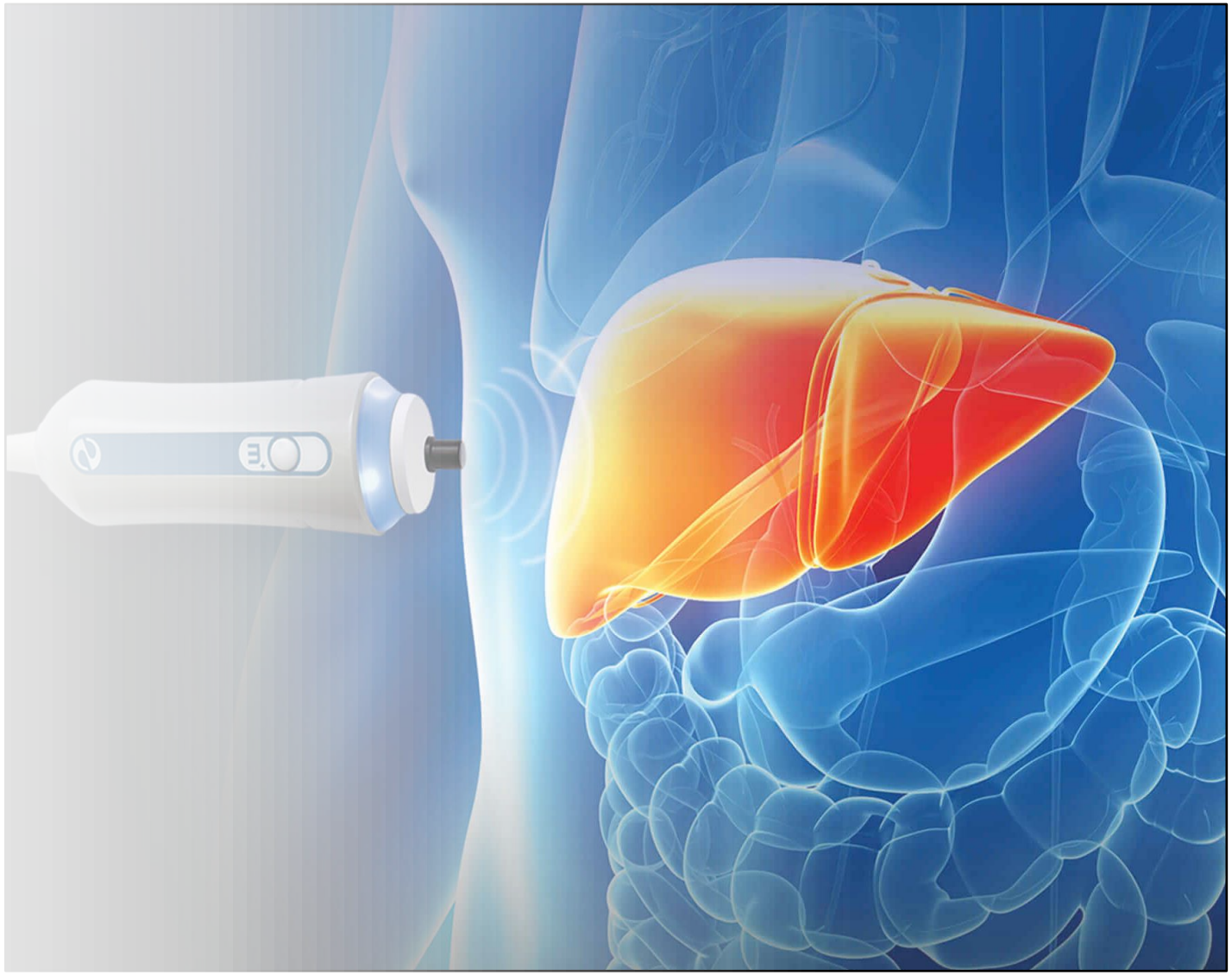
Noninvasive Testing for Liver Fibrosis

- Vibration Controlled Transient Elastography
  - <8.0 kPa excludes clinically significant fibrosis
- Shear Wave Elastography



Limitations of VCTE

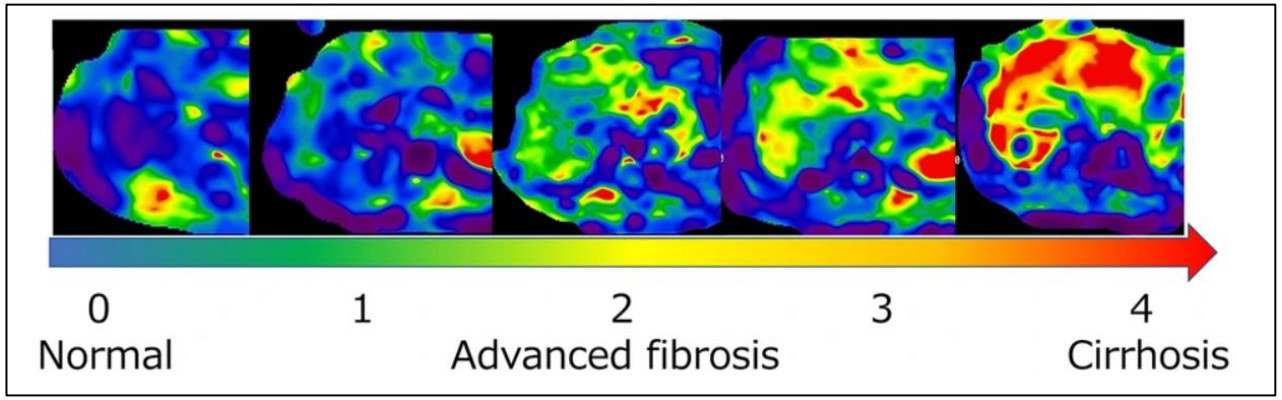
- Dependent on operator experience
- Higher failure rates in obesity, narrow ICS, ascites
- False positives with heavy etoh use, nonfasting states, acute hepatitis
- Variable Reimbursement



MR Elastography

- Pros
  - Most accurate NIT for Fibrosis
  - Less failure rates in obesity

- Cons
  - Costly
  - Not readily available



Nogami A, et al. Sci Rep 2022.

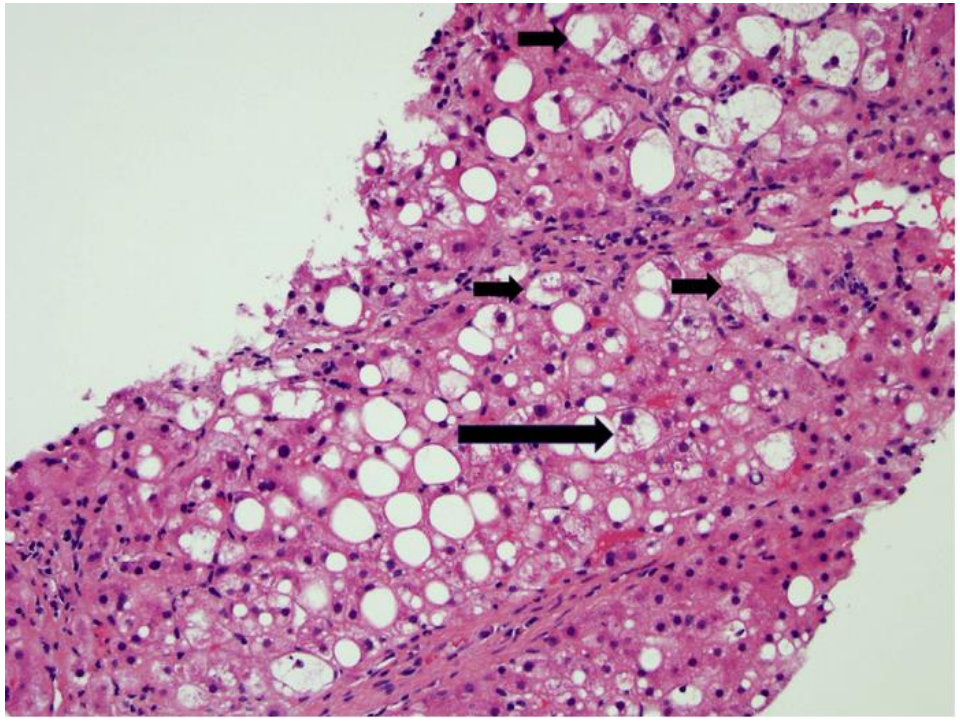
Complex Serum Biomarker Panels

- ELF
  - Decreased false positive rate when used in combination with Fib-4
- FibroSure
- Fibrometer VCTE

- ✓ VCTE/MRE superior to serum biomarker at detecting advanced fibrosis (F3+)
- ✓ Efficient at detecting low risk of fibrosis (high NPV)
- ✓ Reasonable alternative when elastography is unavailable

Liver Biopsy

- Remains gold standard for diagnosis (although rarely required)
- Required for diagnosis of steatohepatitis -MASH
- Useful when NITs are incongruent
- Helpful in ruling out other concomitant liver disease
- Cons
  - Cost
  - Risk of complications
  - Sampling error



Patient Case

John Doe, 52 yrs old, 5’10”, BMI 41

- T2DM, HTN, CAD, Hypercholesterolemia
- Social etoh use 1-2 times per month
- T bili 0.8, ALP 110, ALT 55, AST 48, plt 199
- US shows hepatic steatosis

Next Step?

A. Watch and Wait
B. Calculate Fib-4
C. Refer to hepatology/GI

Patient Case

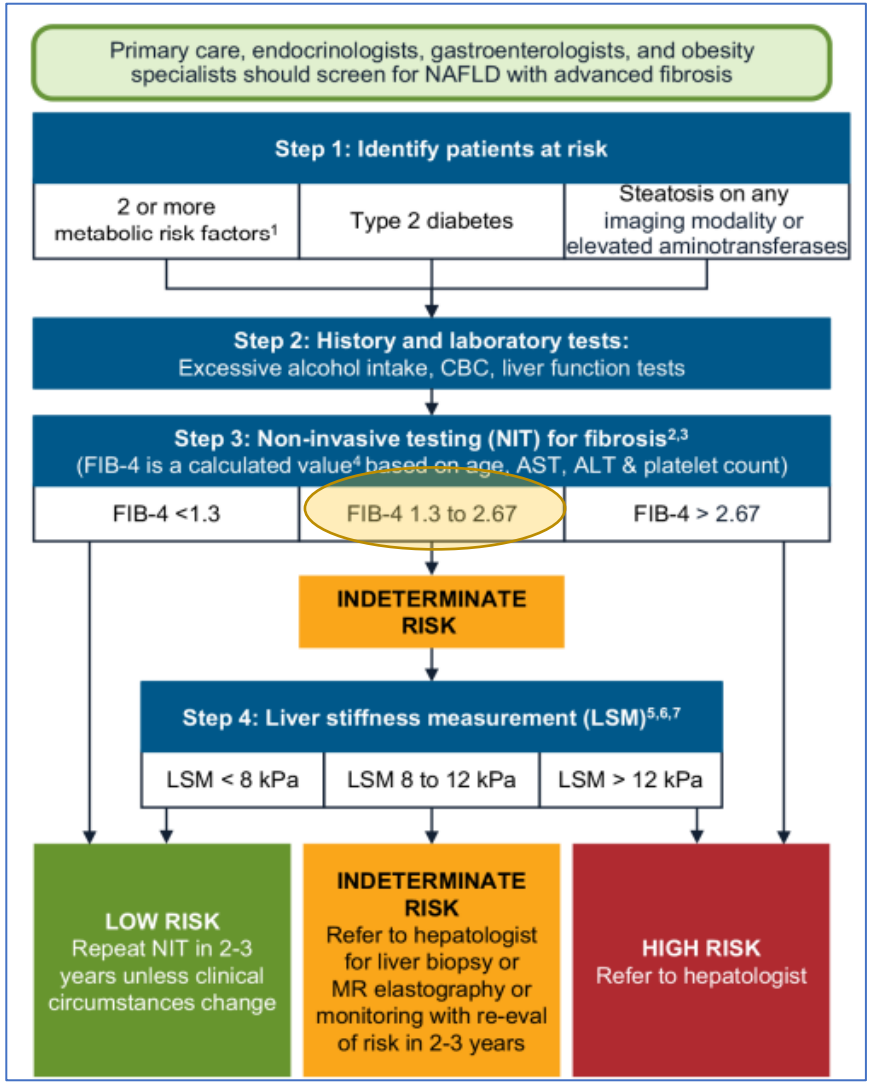
Fib-4

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

1.69

Next Step?

A. Order VCTE/Fibroscan
B. Repeat Fib-4 in 1 year
C. Order Fibrosure blood test



Kanwal F, et al. Gastroenterology 2021.

Patient Case

→Patient referred for VCTE for LSM

VCTE Report

Measurements: 12

Probe size: XL

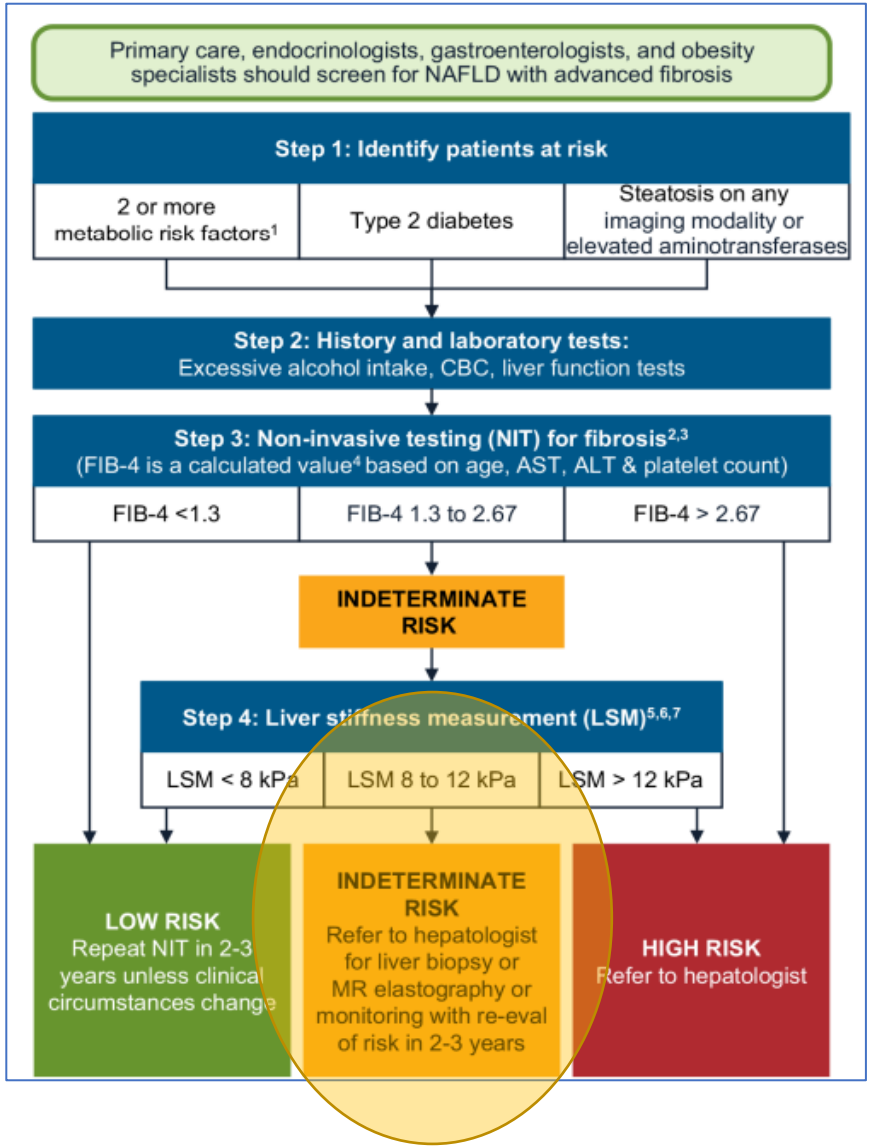
Median kPa: 9.6

Median CAP: 345

IQR: 5%

Next Step?

A. Order ELF blood test
B. Repeat Fib-4 in 1 year
C. Refer to GI/Hepatology

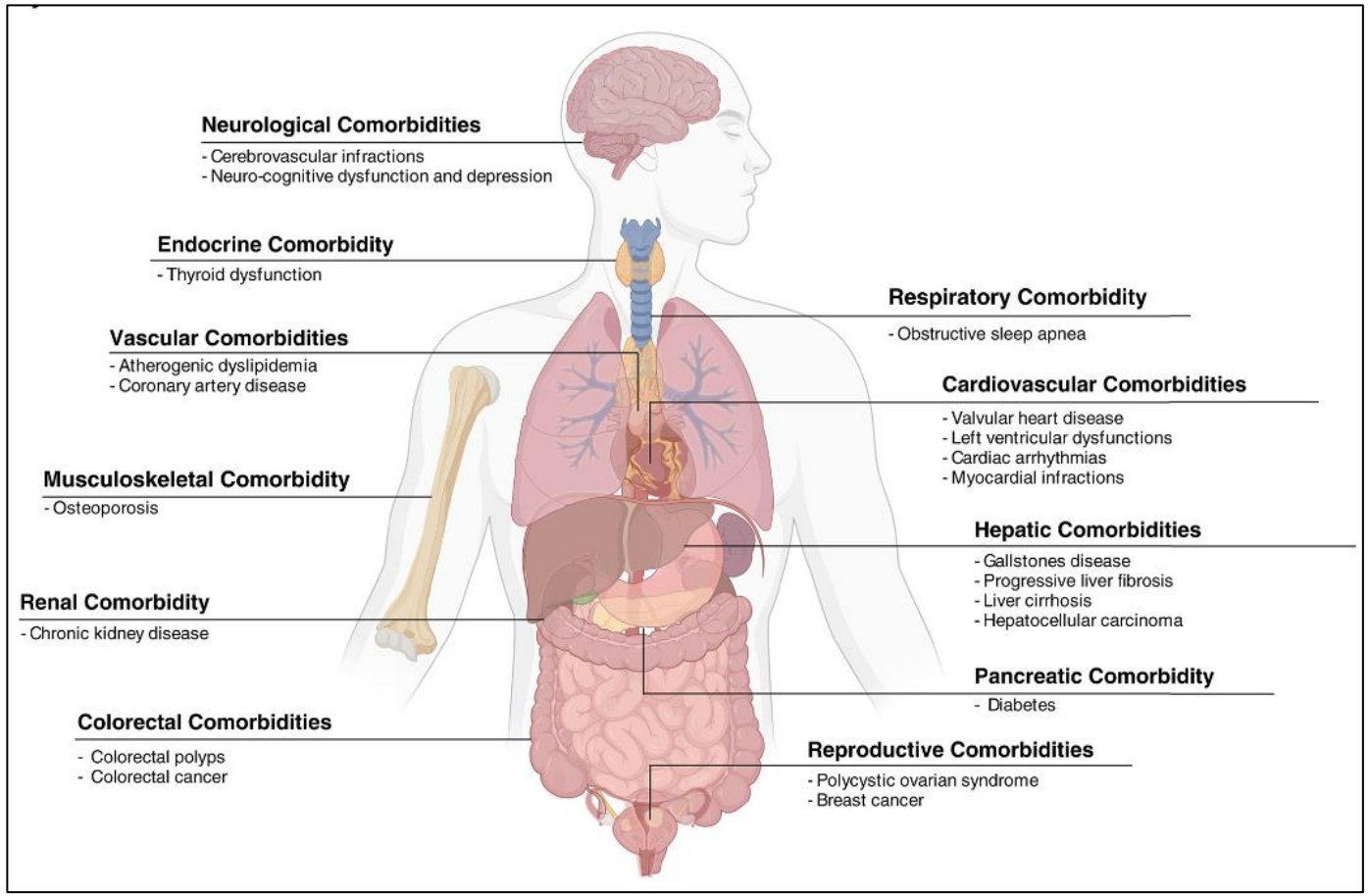


Kanwal F, et al. Gastroenterology 2021.

Patient Case

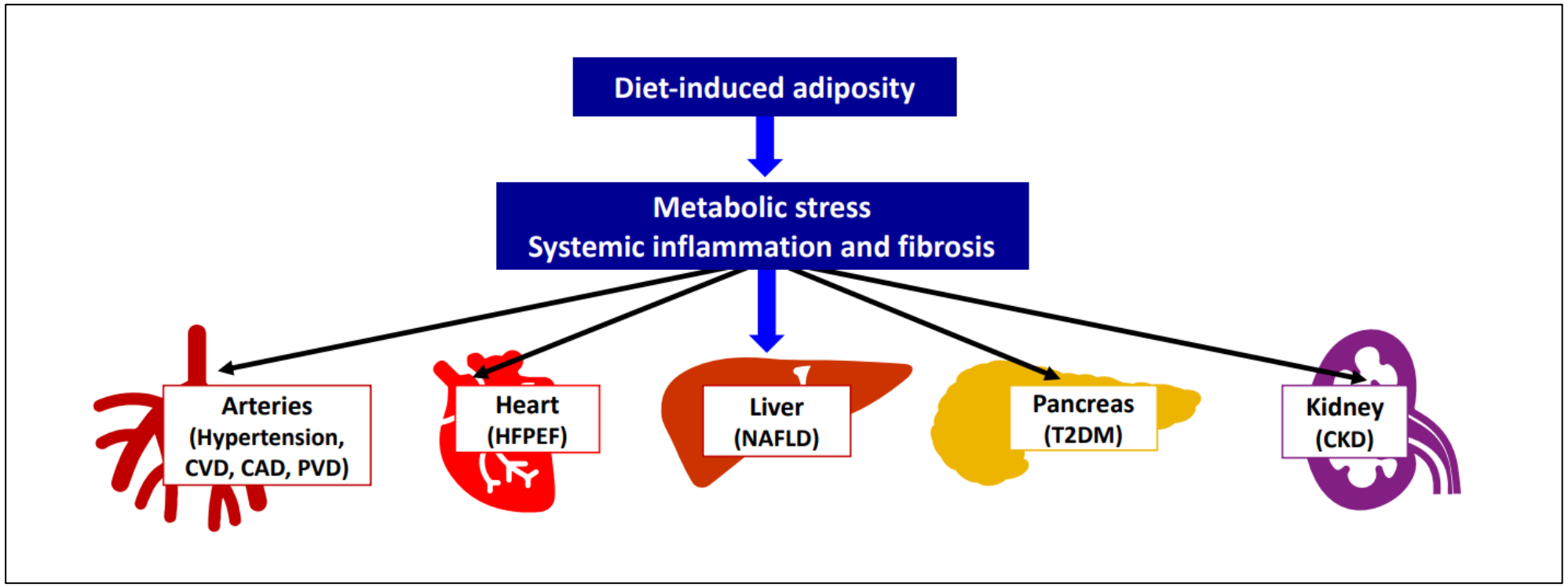
- ✓John Doe was referred to a local GI/hepatologist for further workup, risk stratification and management of MASLD
- ✓Reminder: All patients with persistently elevated transaminases should be referred to GI/hepatology regardless of risk

MASLD Comorbidities



Muthiah MD, et al. *Diabetes, Obesity, and Metabolism* 2022

Treating Disorders of Metabolism



→Leading cause of mortality in MASLD/MASH patients is cardiovascular disease

Adapted from Friedman et al. *Nature Medicine* 2018

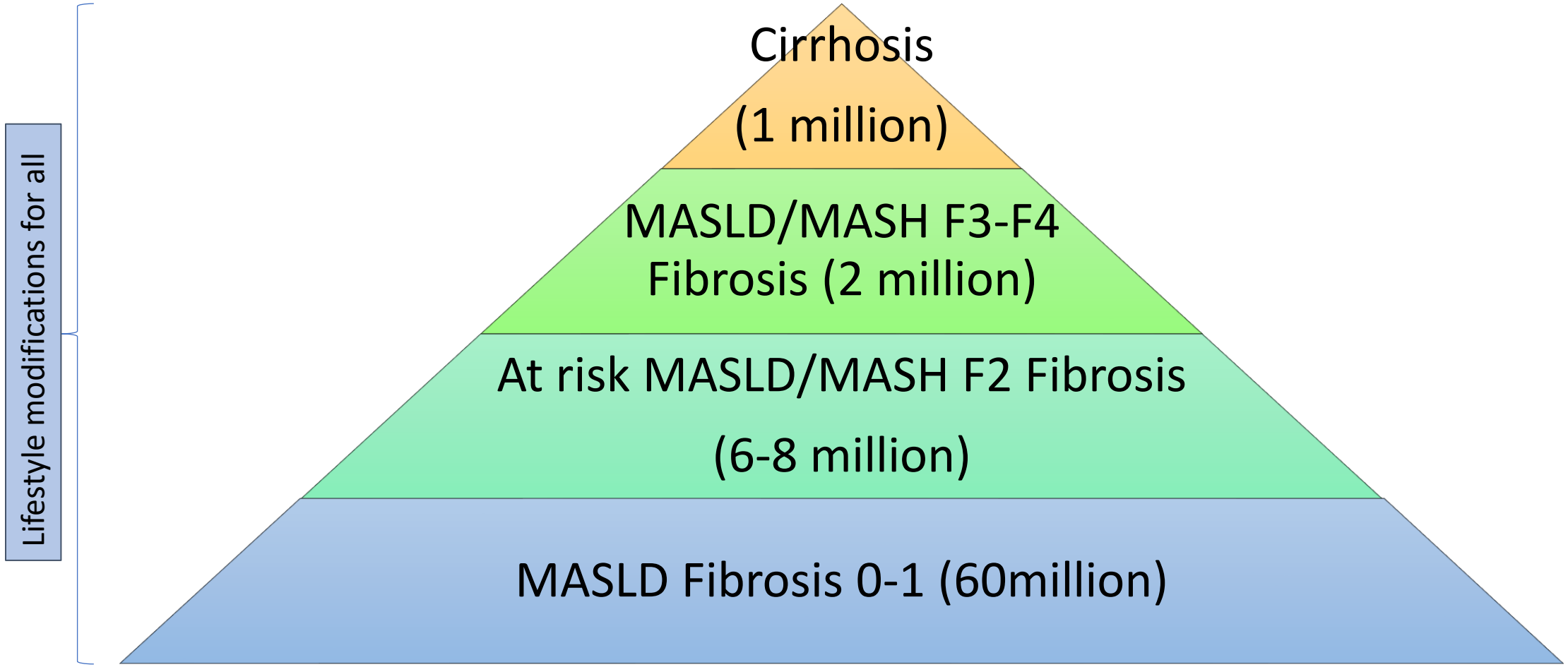
Treating Disorders of Metabolism

Cardiovascular Disease	MASLD	Type 2 Diabetes Mellitus	Chronic Kidney Disease	Heart Failure
Weight Loss	Weight Loss	Weight Loss	Weight Loss	Weight Loss
GLP1	GLP1	GLP1	GLP1	SGLT2i
ARBs	?SGLT2i	SGLT2i	SGLT2i	ARBs
*Statins/Fibrates	THR-β agonists	ARBs	ARBs	

- ✓ Consider statins in patients with CVD and MASLD. May decrease fibrosis and decreases overall mortality risk.

Torres-Pena, et al. Frontiers in Cardiovascular Medicine 2021.

Tackling MASLD



Treatment for Low Risk Fibrosis

Healthy Diet

- Mediterranean diet, Intermittent Fasting, Low Carbohydrate, Caloric Restriction are comparable
- Mediterranean diet may be most sustainable with CV benefit
- Nutrition referral
- Avoidance of fructose containing food and drink
- Minimize ETOH use
- Coffee (3 cups daily) may be beneficial in the absence of contraindications

	LOW RISK FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1
	Management by PCP, dietician, endocrinologist, cardiologist, others
Lifestyle intervention[2]	Yes
Weight loss recommended if overweight or obese[3]	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended
CVD risk reduction[8]	Yes
Diabetes care	Standard of care

Kanwal F, et al. Gastroenterology 2021.

Treatment for Low Risk Fibrosis

Exercise

- Moderate exercise recommended for 150-200 min/week
- Combination of cardiovascular and resistance training is superior to cardiovascular exercise alone

Weight Loss

- 10% weight loss target for MASLD
- Long term approach
- Consider obesity medications or referral for bariatric surgery in patients with comorbidities and qualifying BMI.

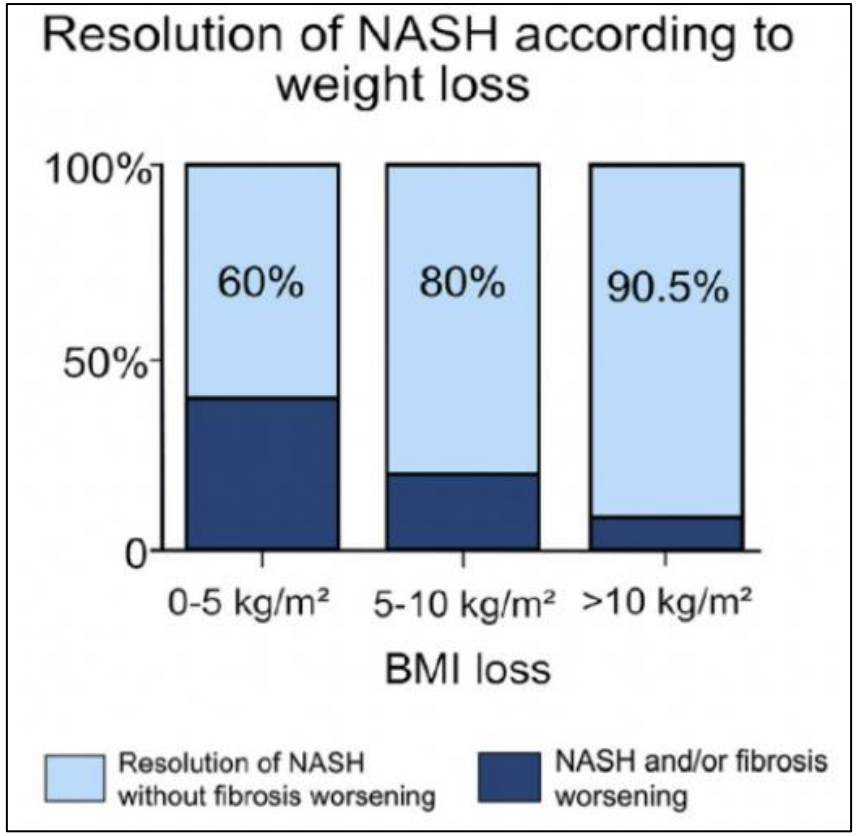
Minimize Alcohol Use

Smoking Cessation

	LOW RISK FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1
	Management by PCP, dietician, endocrinologist, cardiologist, others
Lifestyle intervention[2]	Yes
Weight loss recommended if overweight or obese[3]	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended
CVD risk reduction[8]	Yes
Diabetes care	Standard of care

Kanwal F, et al. Gastroenterology 2021.

Bariatric Surgery and MASLD/MASH



Lassailly G, et al. Gastroenterology 2020; 159:1290.

Available MASLD Treatments

Medication	Study Patients	FDA indication	Benefits	Side Effects
Vitamin E 800 IU daily	MASH w/o T2DM or Cirrhosis	None	• Improves steatosis • Lower risk of decompensation • No definite fibrosis regression	Bleeding, hemorrhagic CVA, potential increase in prostate cancer risk
Pioglitazone	MASH +/- T2DM	T2DM	• Improves steatosis • NASH improvement • Possible Fibrosis improvement • Improved insulin sensitivity	Weight gain, bone loss, heart failure exacerbation
SGLT2i	MASLD and T2DM	T2DM	• Improved steatosis • Better renal outcomes • May improve insulin sensitivity	Urinary infections, volume depletion, bone loss
Semaglutide 0.4mg sc daily, 0.25-2.4mg sq weekly	MASH w/o cirrhosis	T2DM Obesity	• Improves steatosis • NASH resolution • Improved insulin sensitivity • Weight loss • No definite fibrosis regression	Multiple GI side effects, gallstones, pancreatitis
Tirzepetide Sq weekly	MASLD +/- obesity and T2DM	T2DM Obesity	• Improved steatosis • Improved insulin sensitivity • Weight loss	Multiple GI side effects, gallstones, pancreatitis
Resmitirom	MASH with biopsy proven F2/F3 fibrosis	MASLD/MASH with F2/F3 fibrosis	• Resolution of steatosis • Regression of fibrosis • Improved LDL and TRG	Diarrhea, Nausea, Arthralgia

Rinella ME, et al. Hepatology 2023; Bril F, et al. Clin Gastro Hep 2018; Cusi K, et al. Ann Intern Med 2016; Sanyal A, et al. NEJM 2010; Vilar-Gomez E, et al. Hepatology 2020; Armstrong MJ, et al. Lancet 2016; Newsome PN, et al. NEJM 2021; Loomba R, et al. Lancet Gastro Hep 2023; Jastreboff AM, et al; NEJM 2022; Kahl S, et al. Diabetes Care 2020

Statins

- Utilized in patients with MASLD and existing dyslipidemia and/or CAD
- Moderate to high intensity statins indicated
- Decreases risk of cardiovascular morbidity and mortality
- Some studies suggest decreased risk of hepatic decompensation and HCC risk
- Safe in advanced fibrosis

AASLD Guidance recommendation: **Statins are safe and recommended for CVD risk reduction in patients with MASLD across the disease spectrum, including compensated cirrhosis.**

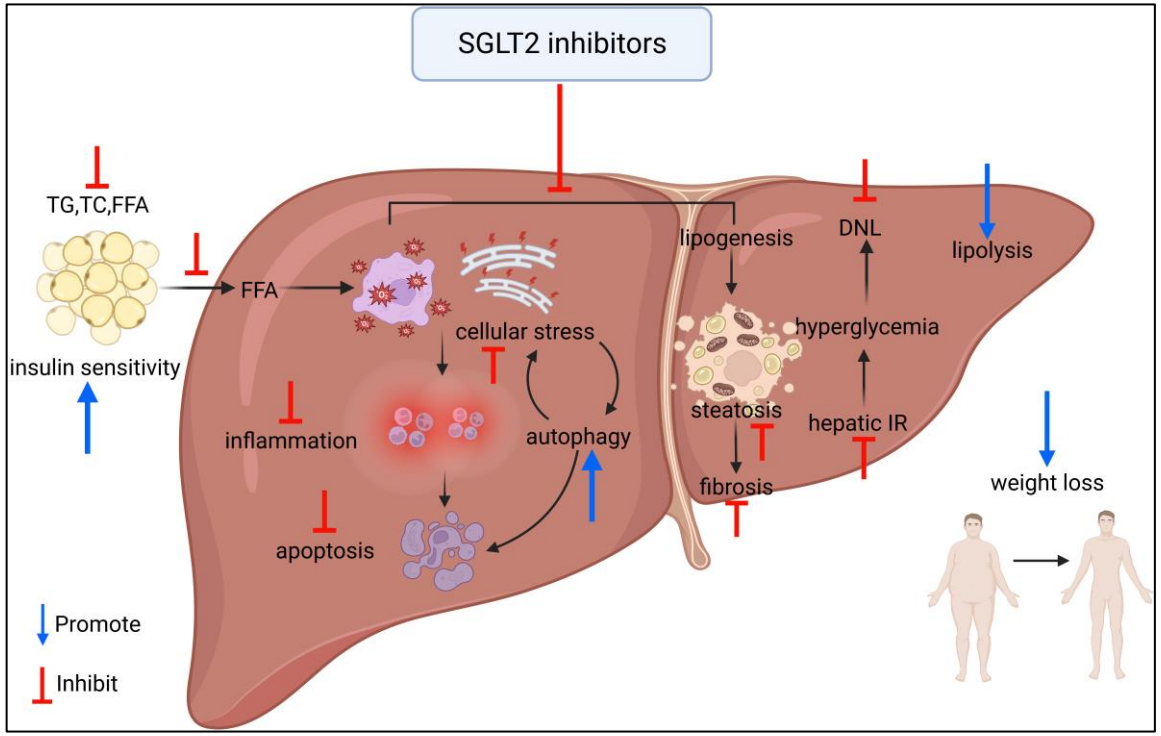
Rinella M, et al. Hepatology 2023

Vitamin E

- Indicated in Biopsy proven MASH
- 800 IU daily
- Improvement in steatosis
- No proven regression of fibrosis
- Increased rate of transplant free survival
- Lower risk of hepatic decompensation
- Caution: Patients with Type 2 DM, may increase risk of prostate cancer
- May increase risk of bleeding and hemorrhagic CVA, interacts with some blood thinners

SGLT2i

- Reduced serum AST and ALT after 3 months of treatment
- Decreased hepatic steatosis
- Decreased FIB-4 and APRI scores after 12 months of treatment
- May result in weight loss
- Improved cardiac and renal risk factors

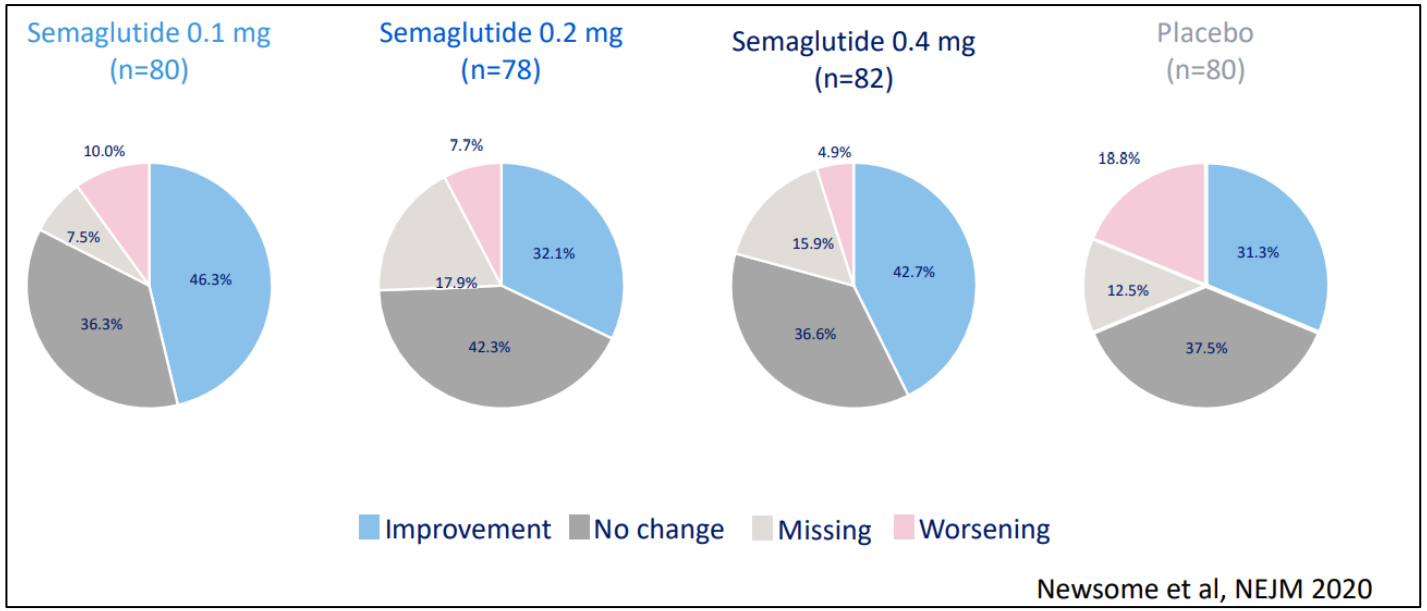


Xu R, et al. *Front Biosci*. 2023, 28(7), 134.

Yanai H, et al. *Int J Mol Sci*. 2023.

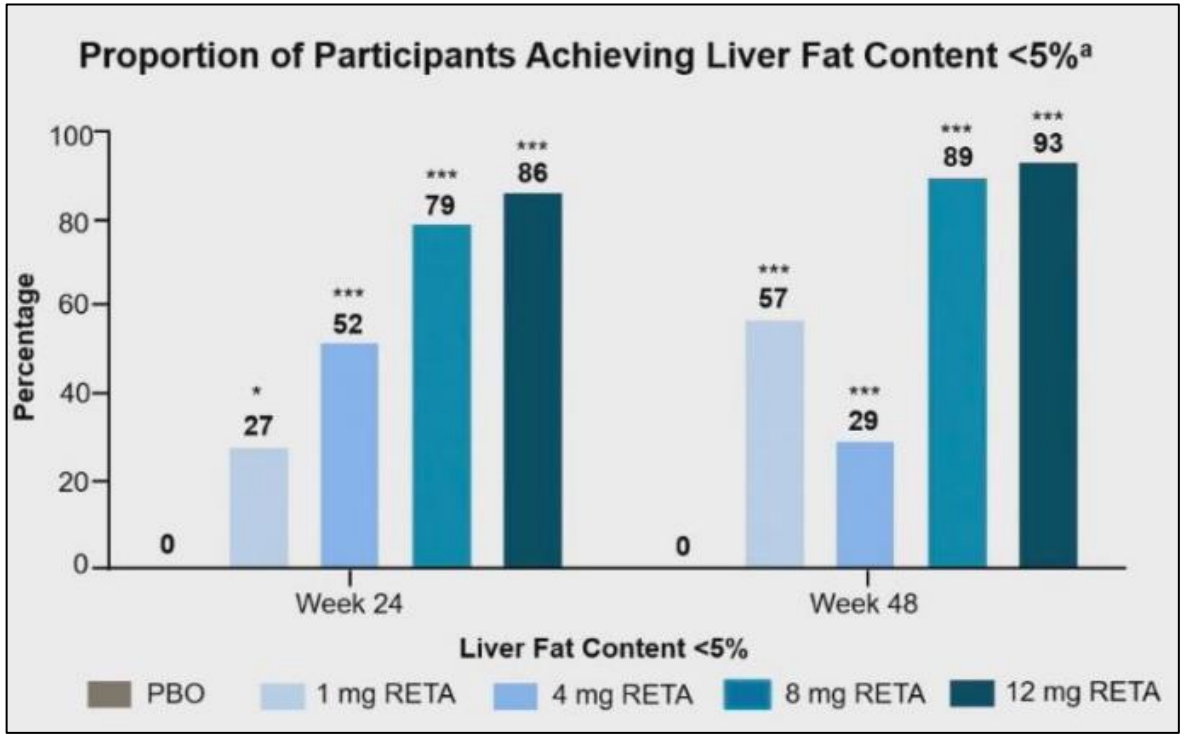
GLP-1 and dual GIP/GLP-1 Agonists

- Approved for use in T2DM and Obesity
  - Liraglutide, Semaglutide, and Tirzepatide approved for Obesity
- Associated MASLD resolution
- Improved steatosis
- Increased insulin sensitivity
- Extremely favorable weight loss profile
- Data inconsistent on fibrosis regression
- Concerns: Multiple GI side effects, gallstones, pancreatitis



Retatrutide

- Triple mechanism-GIP/GLP-1/Glucagon receptor agonist
- Phase 2 Obesity and T2DM trial
  - Up to 24% weight loss observed
  - Subset of patients studied with MASLD
  - 80-90% achieved resolution of hepatic steatosis with 12mg dose



Sanyal et al, ADA 2023

Pioglitazone

- PPAR-Peroxisome proliferator-activated receptor agonist
  - Nuclear receptors that decrease hepatic triglyceride accumulation, increases glucose and lipid metabolism

- In patients with Type 2 DM and MASH:
  - Improves steatosis and MASH
  - Possible fibrosis improvement
  - Improved insulin sensitivity

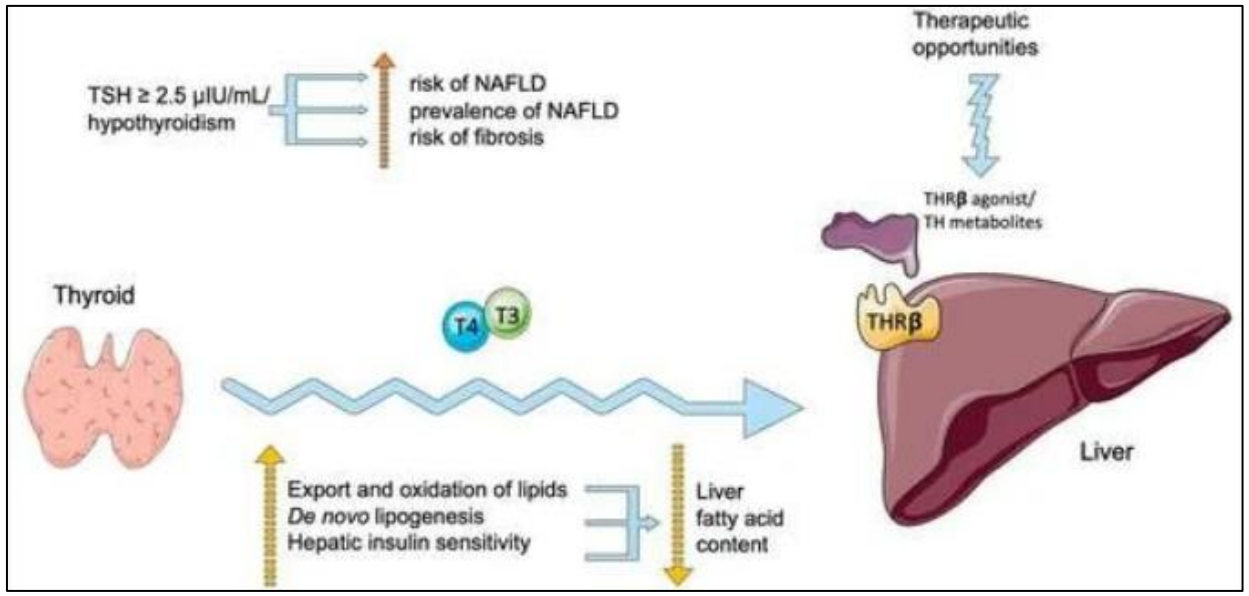
Concerns: Weight gain, bone loss, heart failure exacerbation, may increase bladder cancer risk

PPAR in development

Lanifibranor (pan-PPAR)
Saroglitazar (PPAR α/γ)

THR-β agonists

- Thyroid hormone through activation of the THR-β in hepatocytes, plays an important role in liver function with impacts on serum cholesterol, triglycerides, and buildup of fat in the liver
- Thyroxine Beta Receptor Agonists
  - Decrease hepatic fat
  - Improve MASH
  - Decrease LDL-C
  - Decrease triglycerides
- In Development: Resmitirom



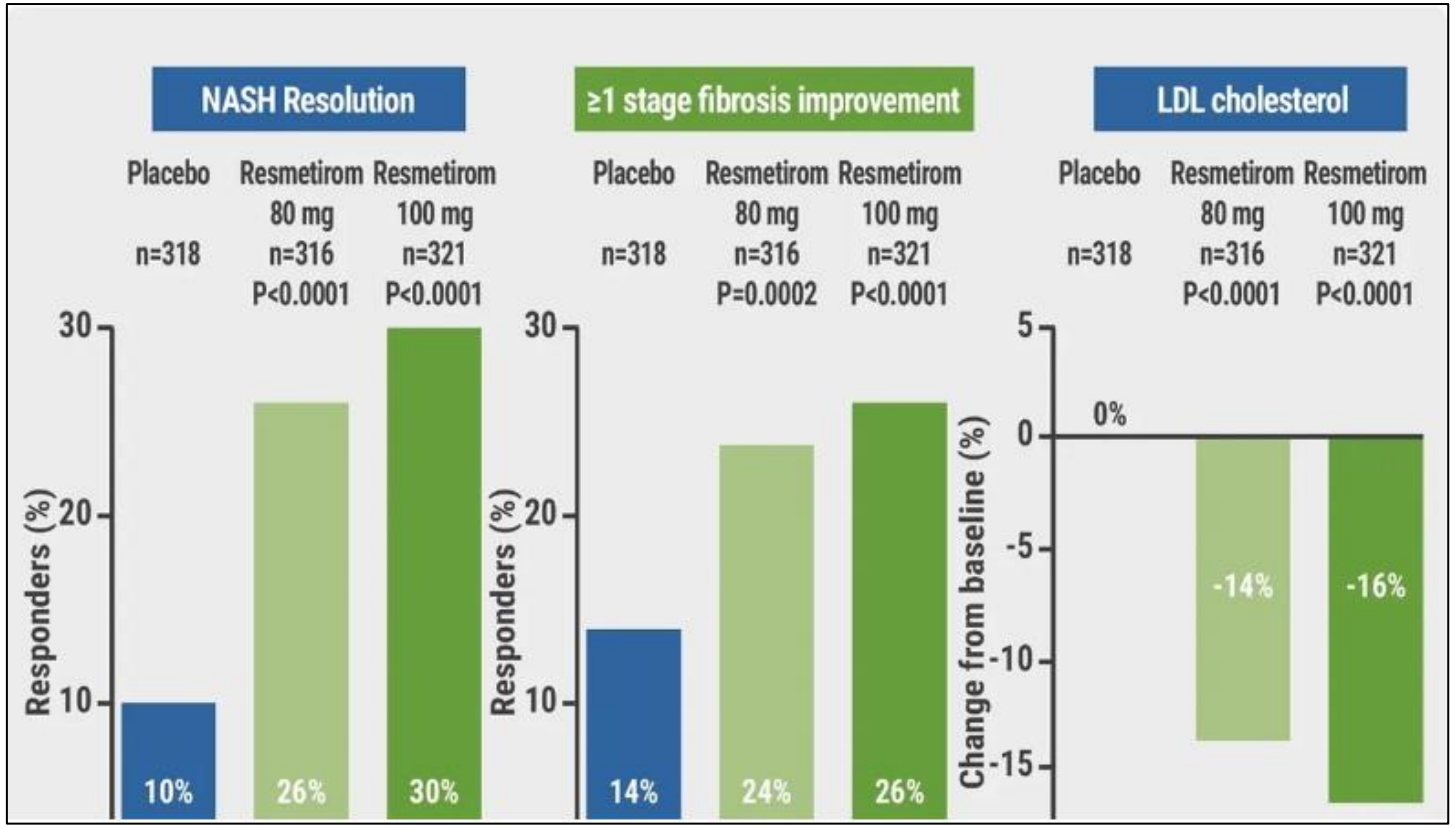
Vidal-Cevallos, et al. Int J Mol Sci 2023

Resmitirom

- First FDA approved treatment for MASLD
- Approved for stage 2 and stage 3 fibrosis
- No biopsy required
- Met primary endpoints
  - Resolution of steatohepatitis and no worsening of fibrosis
  - At least 1 stage of improvement in fibrosis without worsening of steatohepatitis
- Weight-based Dosing: 80mg (<220lbs), 100mg (>220lbs) tablets
- Common side effects: Diarrhea, nausea, pruritis, vomiting
- Drug interactions: moderate to strong CYP2CB inhibitors

Harrison SA, et al. *NEJM* 2024

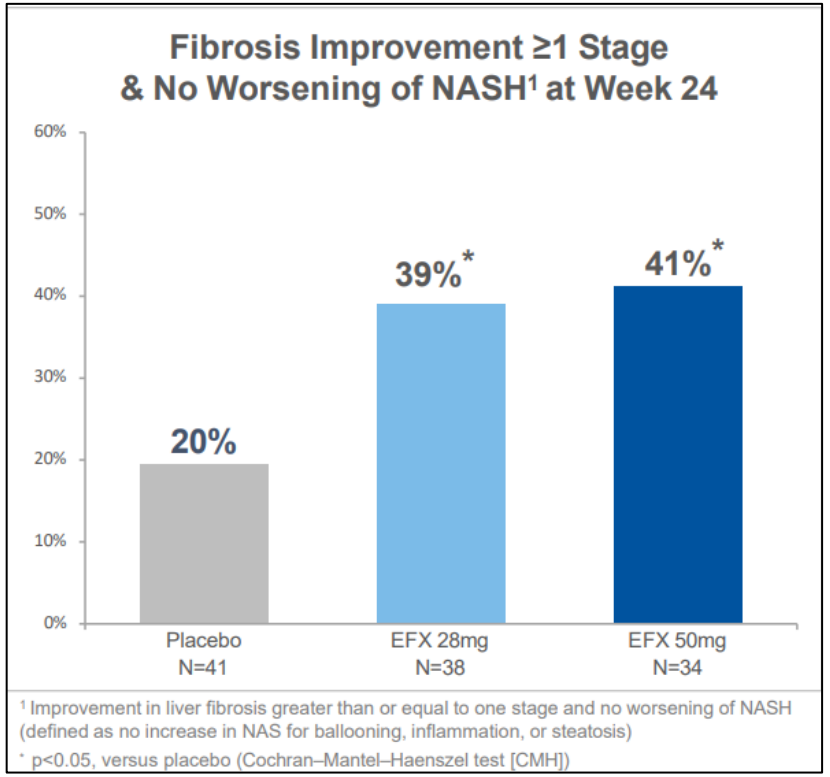
Resmitirom



Harrison SA, et al. *NEJM* 2024

Bile Acids in MASLD

- Farnesoid X receptor is a bile acid sensor that helps regulate bile acid metabolism and lipid homeostasis
- Decreases intracellular fatty acid levels
- Farnesoid X Receptor Agonists
  - Obeticholic Acid ← Development stopped
  - Multiple 2nd generation FXR Agonists in development
- FGF21 analogue- Efruxifermin, Pegozafermin
- FGF19 analogue- Aldafermin



*Efruxifermin data released at AASLD

Harrison et al, AASLD 2022

Special Population: Cirrhosis

- All patients with MASLD/MASH Cirrhosis should be referred to GI/Hepatologist
- More research needed on targeted MASH therapies for cirrhosis
- Presence of T2DM increases risk of HCC 2-fold in cirrhosis
- Presence of metabolic syndrome increases risk of HCC 5-fold in cirrhosis
- MASLD associated HCC: increased risk of mortality in comparison to other causes of HCC

Younossi ZM, et al. Hepatology 2023; 77(4): 1335

Patient Case

John Doe, 52 yrs old, 5’10”, BMI 41

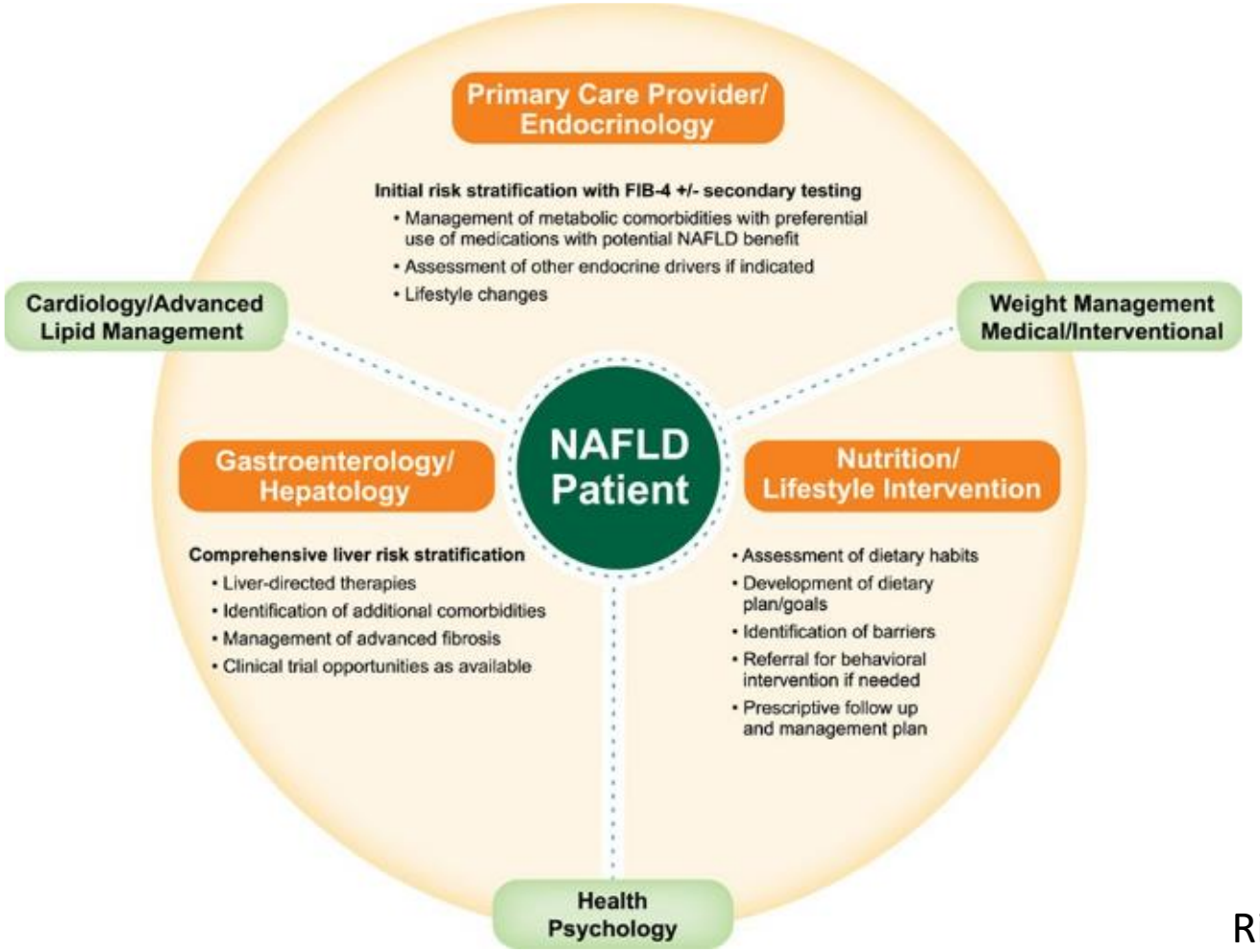
- T2DM, HTN, CAD, Hypertriglyceridemia
- Social etoh use 1-2 times per month
- T bili 0.8, ALP 110, ALT 55, AST 48, plt 199
- US shows hepatic steatosis
- FIB-4 1.69, VCTE 9.6 kPa
- Referred to hepatologist
- Patient expressed no interest in bariatric surgery referral

Patient Case

John Doe, 52 yrs old, 5’10”, BMI 41

- T2DM: Tirzepatide 7.5mg (higher dose trialed but patient tolerated poorly due to GI side effects)
- Hypercholesterolemia: atorvastatin titrated to 40mg
- Referred to nutritionist
- Exercise program
- Recommended initial 10% weight loss goal

Take Home Points



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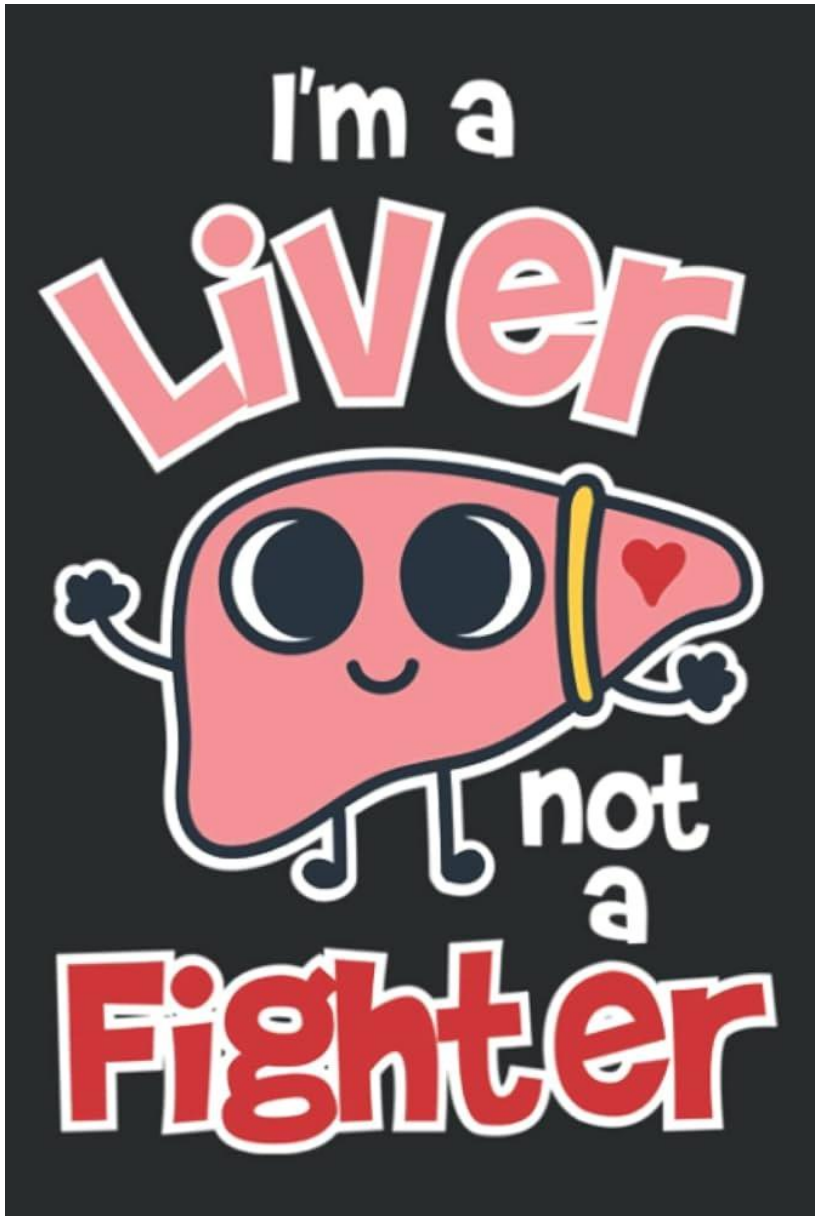
Take Home Points

- The global burden of MASLD is enormous
- Majority of patients with MASLD will receive care outside of GI/hepatology
- Non-invasive tests can help identify patients at risk (FIB-4)
- Refer patients to GI/Hepatology who are at risk for advanced fibrosis
- Lifestyle modifications remain cornerstone of MASLD Care
- Consider use of approved medications in patients with comorbidities (GLP-1, SGLT2i, Statins)
- New treatments are in development- stay tuned regarding FDA decisions for treatments with MASLD indication

Thank You



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