Update on Metabolic-dysfunction Associated Steatotic Liver Disease

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Objectives

By the conclusion of this talk, you will be able to:

- Know the **new nomenclature** for fatty liver disease
- Know the definition, prevalence, risk factors, and natural history of MASLD
- Understand the importance of MASLD as a public health problem
- Describe the diagnostic tests to assess fibrosis and identify patients at risk of progression to cirrhosis
- Learn about the management strategies of MASLD including the need for a multidisciplinary treatment approach

New NAFLD Nomenclature

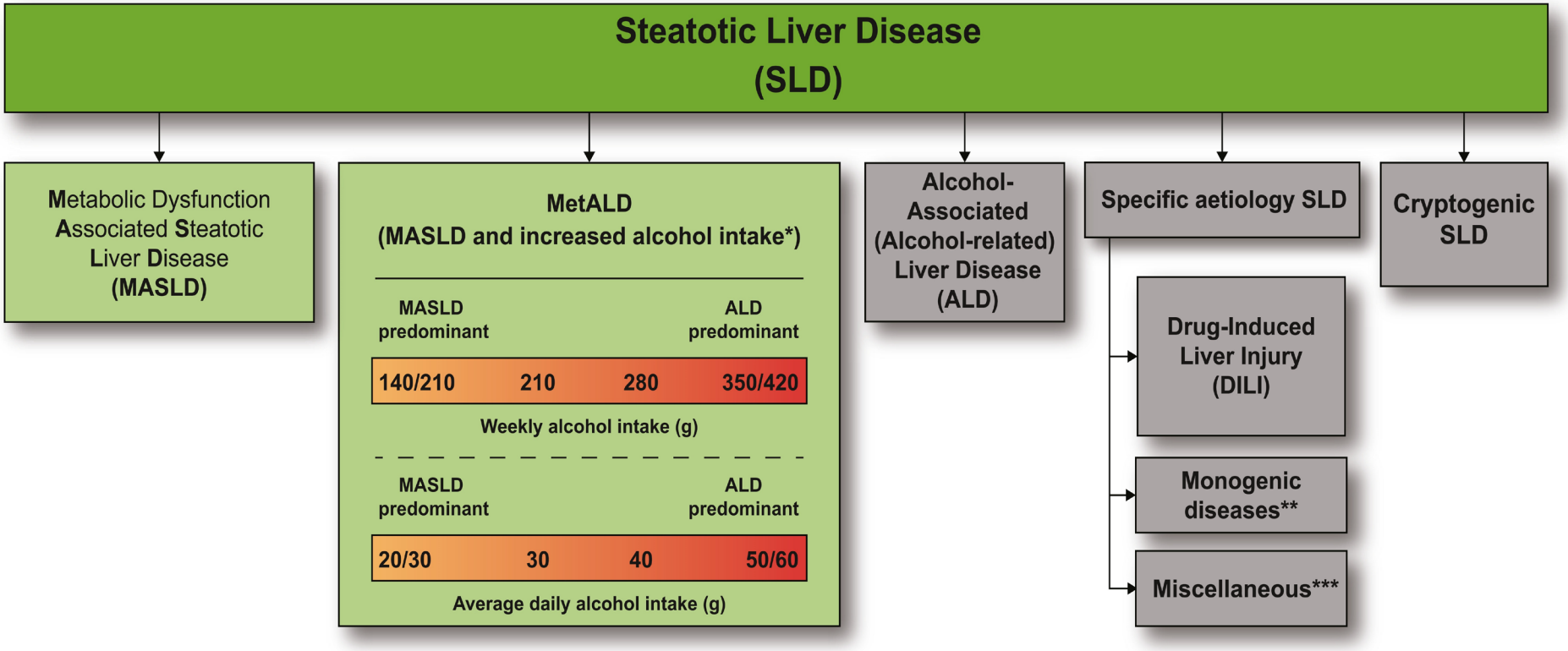
- Announced in June 2023 with multi-society (including AASLD, EASL, APASL) consensus statement
- No more NAFLD!
  - Terms ’Non-alcoholic’ and ‘fatty liver’ stigmatizing
- **Steatotic Liver Disease** is the overarching term
- NAFLD is now **MASLD (metabolic dysfunction-associated steatotic liver disease)**

What to know about the new nomenclature

- **Steatotic liver disease** (SLD) was chosen as an overarching term to encompass the various etiologies of steatosis
- The term steatohepatitis was felt to be an important pathophysiological concept that should be retained
- **Nonalcoholic fatty liver disease (NAFLD) will now be metabolic dysfunction-associated steatotic liver disease** (MASLD)
- MASLD encompasses patients who have hepatic steatosis and have at least one of five cardiometabolic risk factors

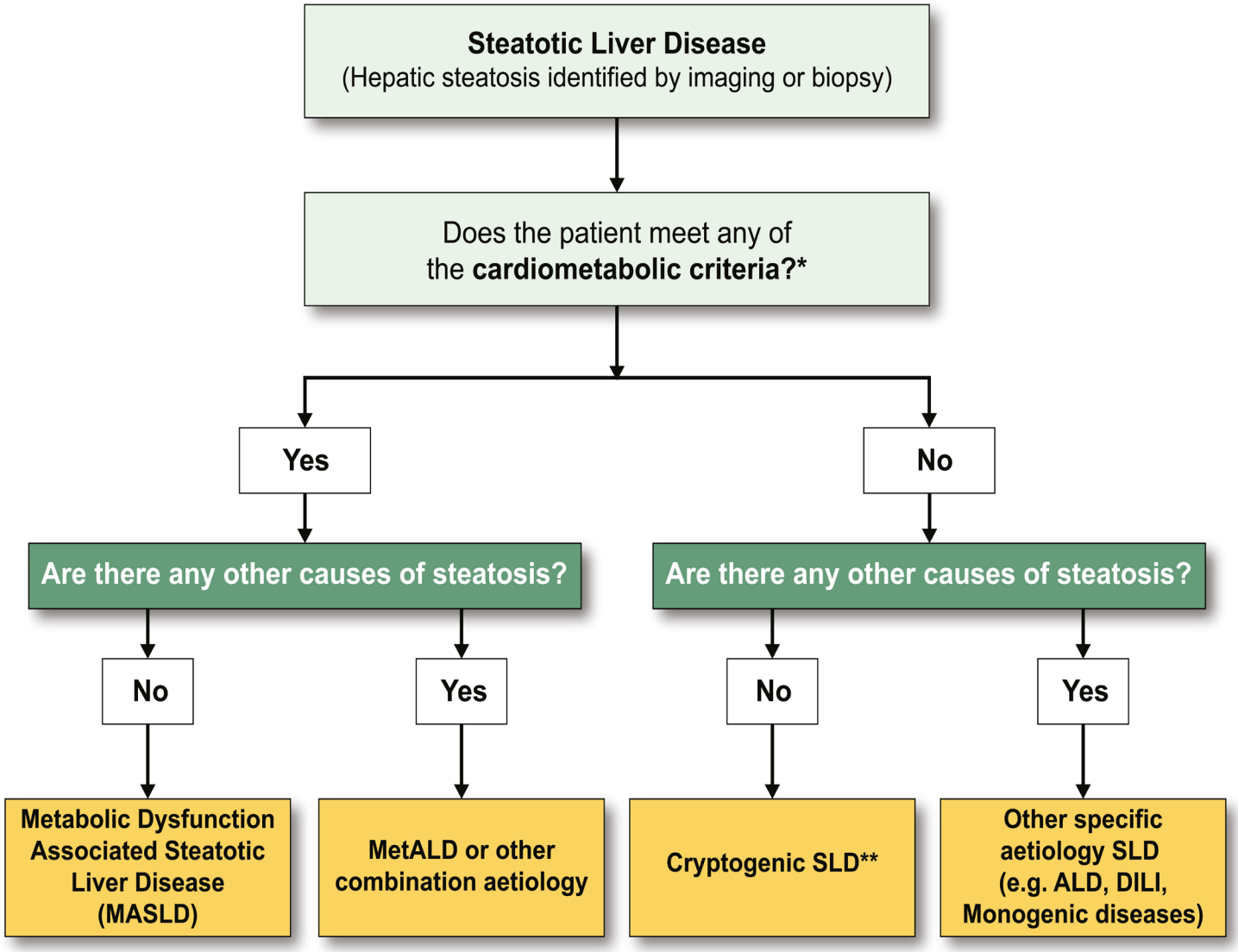
What to know about the new nomenclature

- A new category, outside pure MASLD, termed MetALD (pronunciation: Met A-L-D) was selected to describe those with MASLD who consume greater amounts of alcohol per week (140 g/week and 210 g/week for females and males respectively)
- **Metabolic dysfunction-associated steatohepatitis (MASH) is the replacement term for NASH**
- Those with no metabolic parameters and no known cause have cryptogenic SLD



*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

Rinella, Mary E. et al; on behalf of the NAFLD Nomenclature consensus group. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. Hepatology ():10.1097/HEP.0000000000000520, June 24, 2023. | DOI: 10.1097/HEP.0000000000000520


Steatotic Liver Disease
(Hepatic steatosis identified by imaging or biopsy)
Does the patient meet any of the cardiometabolic criteria?*
Yes
No
Are there any other causes of steatosis?
Are there any other causes of steatosis?
No
Yes
No
Yes
Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD)
MetALD or other combination aetiology
Cryptogenic SLD**
Other specific aetiology SLD (e.g. ALD, DILI, Monogenic diseases)

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*Cardiometabolic criteria

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
- ☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) **OR** lipid lowering treatment

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 ≥ 5.7% [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, ≥ 1.15 mmol/L [≥ 100 mg/dL]; age ≥ 10y, ≥ 1.70 mmol/L [≥ 150 mg/dL] **OR** lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [≤ 40 mg/dL] **OR** lipid lowering treatment

Summary of New Nomenclature

- MASLD diagnostic criteria: In the presence of hepatic steatosis, the finding of any of a cardiometabolic risk factor, would confer a diagnosis of MASLD if there are no other causes of hepatic steatosis.
- If additional drivers of steatosis are identified, then this is consistent with a combination etiology. In the case of alcohol this is termed MetALD
- In the absence of overt cardiometabolic criteria, other etiologies must be excluded and if none is identified, this is termed cryptogenic SLD, although depending on clinical judgment could also be deemed to be possible MASLD and thus would benefit from periodic reassessment on a case-by-case basis

Case Presentation - HPI

- 31-year-old woman who presents to the Johns Hopkins Healthful Eating, Activity & Weight Program for evaluation of MASH
- She was first told that she had elevated liver enzymes in 2019
- She does not eat a healthy diet:
  - She eats fast food (McDonalds, Taco Bell, KFC) daily
  - She likes chocolate and eats Hershey's kisses almost daily
  - She drinks Pepsi soda - 1-2 bottles (20 oz) every other day
- She does not regularly exercise

Case Presentation

- Current weight is 262 lbs. Height is 5'5''.
- Lowest weight was 150 lbs 15 years ago when she lived in Bolivia with her family for 9 months and was walking daily
- **Social History**: She works in retail. She previously drank alcohol socially but stopped after her diagnosis of NASH in 2019. Never smoker. No history of illicit drug use.
- **Family History:** Type 2 diabetes in her mother and father. Her mother is from Brazil and her father is from Bolivia.

Case Presentation

- Physical Exam:
  Weight 262 lbs; Height is 5'5''. **BMI 43 kg/m^2**
  Abdominal obesity. No hepatosplenomegaly.

- Labs:
  - **AST 54 U/L**, **ALT 90 U/L**, AP 109 U/L, total bilirubin 0.4 mg/dL, albumin 3.9 g/dL, WBC 9.9K, Hb 13.1 g/dL, platelet count 319 K/cu mm
  - ANA negative, smooth muscle antibody negative, AMA negative, IgG 1626 (normal 700-1600),
  - HCV antibody negative, Hepatitis B surface antigen, Hepatitis B total core antibody negative
  - Ferritin 145, % sat 17%
  - Alpha-1 antitrypsin 120
  - Ceruloplasmin 25.6

Case Presentation

- Ultrasound abdomen:
  Liver: Moderate diffuse hepatic steatosis. Normal liver contour. No focal lesions.

- NAFLD Fibrosis score: -2.61 (F0-F2)
- FIB-4 index: 0.55 (F0-F1)

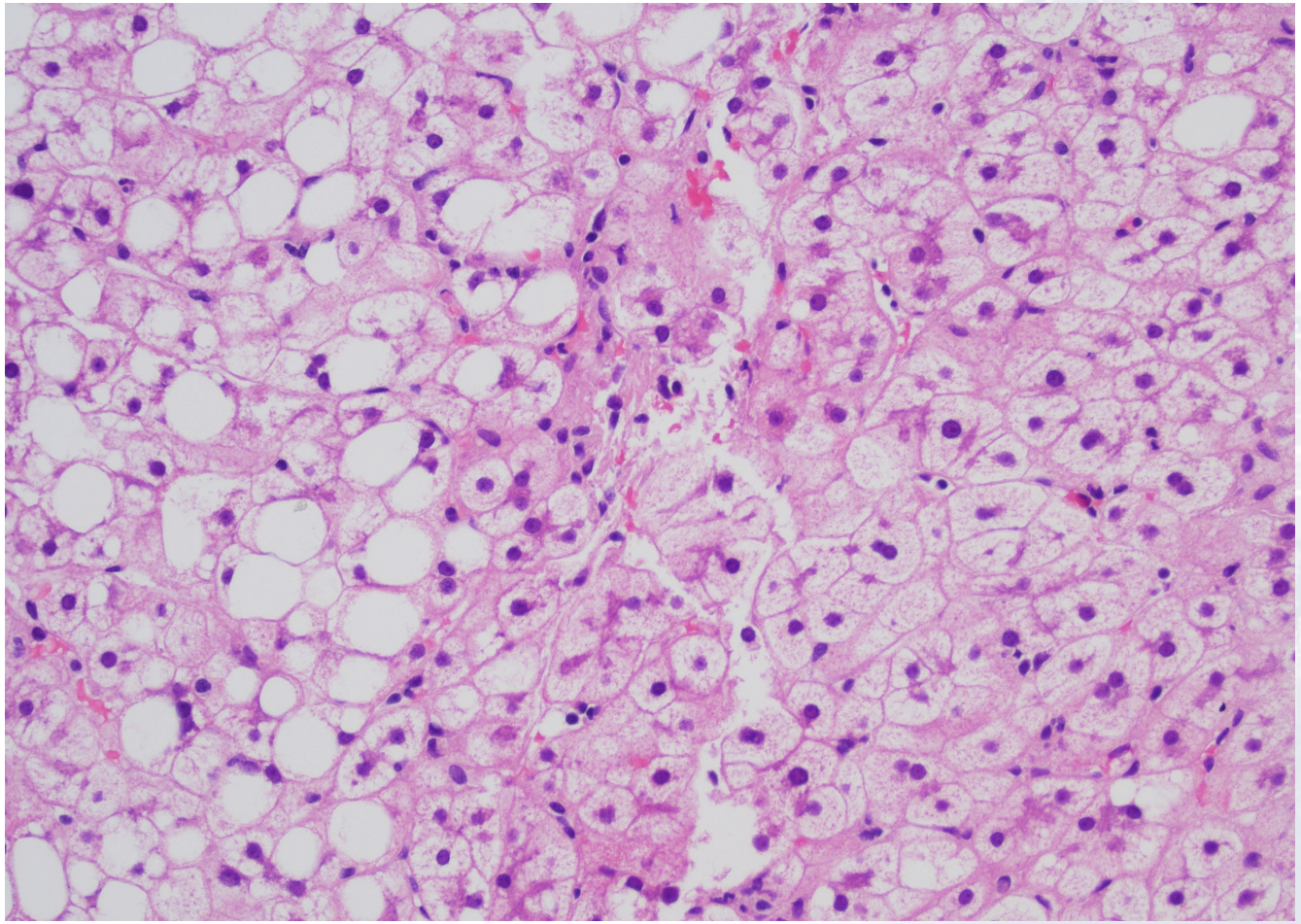
- FibroScan:
  - Elastography: **7.0 kPa** (borderline score between minimal and moderate fibrosis)
  - Controlled attenuation parameter (CAP) score: **280 dB/m** (moderate steatosis)

Liver Biopsy - Pathology

Liver, Left Lobe (Core Biopsy):

- Moderate to severe steatohepatitis with marked macrovesicular steatosis (70%), ballooning degeneration, and rare Mallory Denk bodies
- Mild portal and moderate pericellular fibrosis without bridges (Trichrome and reticulin stains)
- Mild lobular and portal inflammation (lymphocytes, plasma cells, rare neutrophils, rare eosinophils)

Liver Biopsy – H&E Stain



Courtesy of liver pathologists Dr. Robert Anders and Dr. Jackie Birkness

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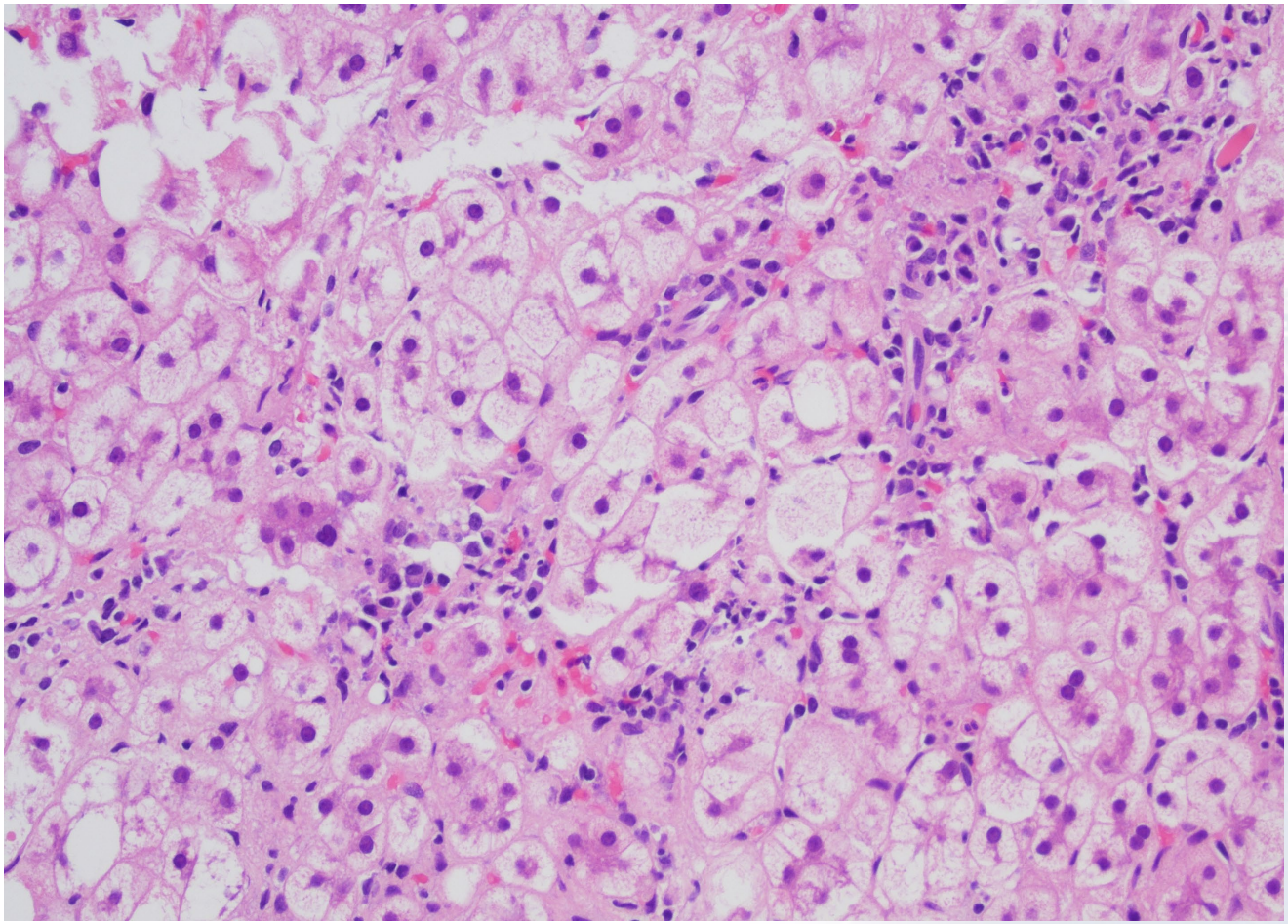
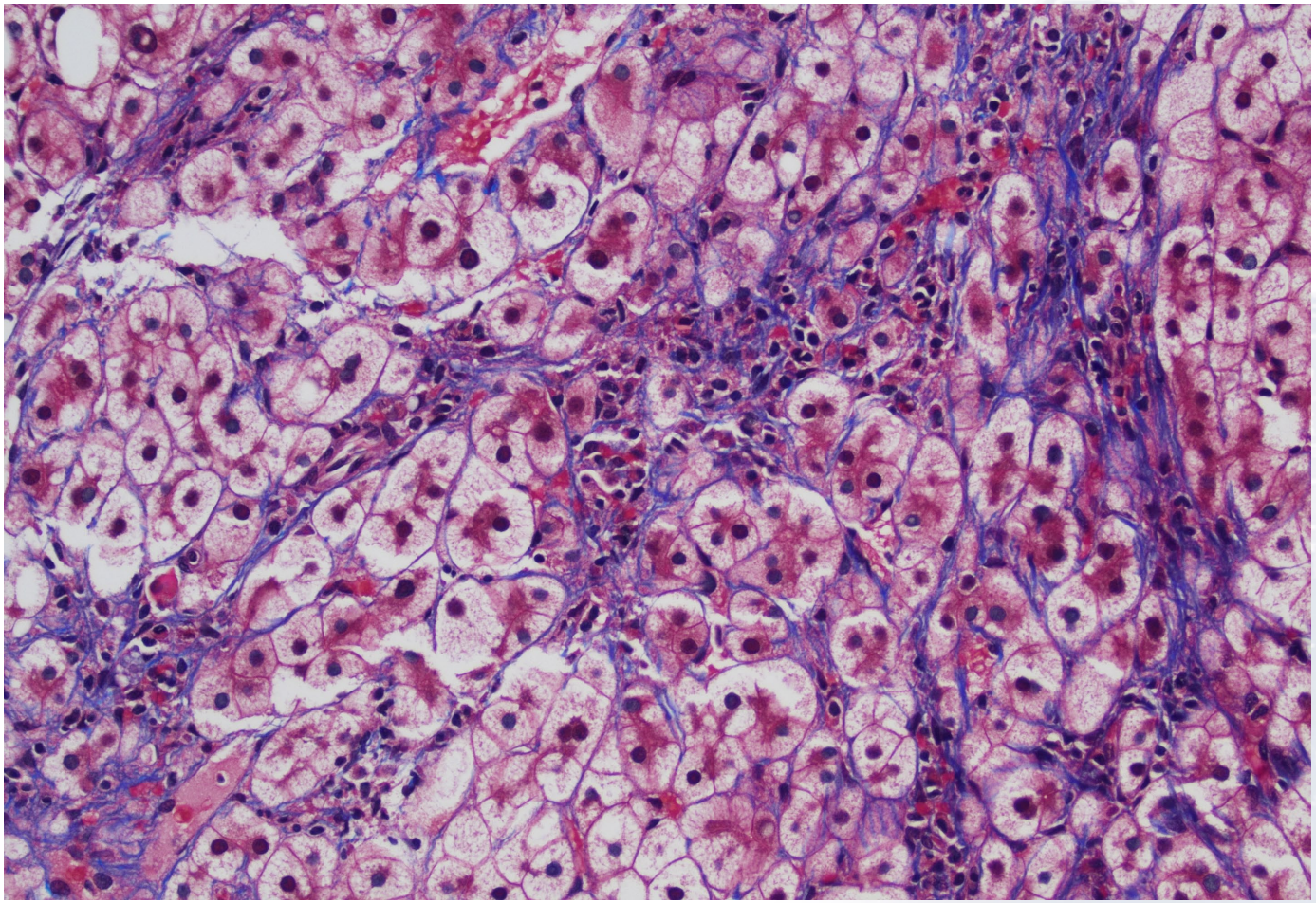
Liver Biopsy – H&E Stain



Courtesy of liver pathologists Dr. Robert Anders and Dr. Jackie Birkness

Liver Biopsy – Trichrome Stain



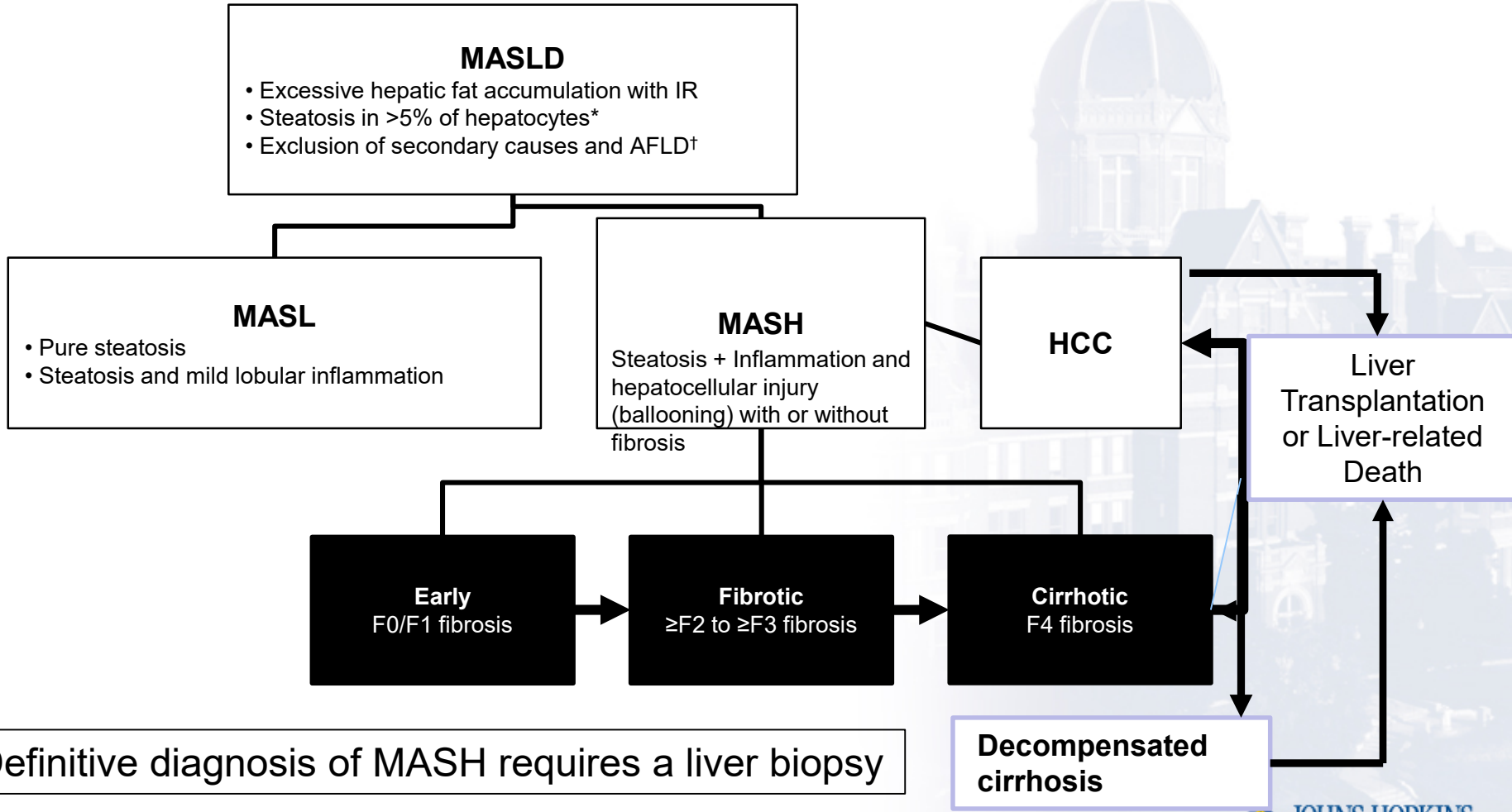
Courtesy of liver pathologists Dr. Robert Anders and Dr. Jackie Birkness

Management

- Recommend 10% total body weight loss (26 lbs) over the next 6 months -> Low carbohydrate/Mediterranean diet and starting a regular cardiovascular exercise program (30 minutes at least 5 days per week)

- What else can you offer her?
  - ? Vitamin E
  - ? Pharmacotherapy

Spectrum of Liver Disease in MASLD



Definitive diagnosis of MASH requires a liver biopsy

EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016 Jun;64(6):1388-402

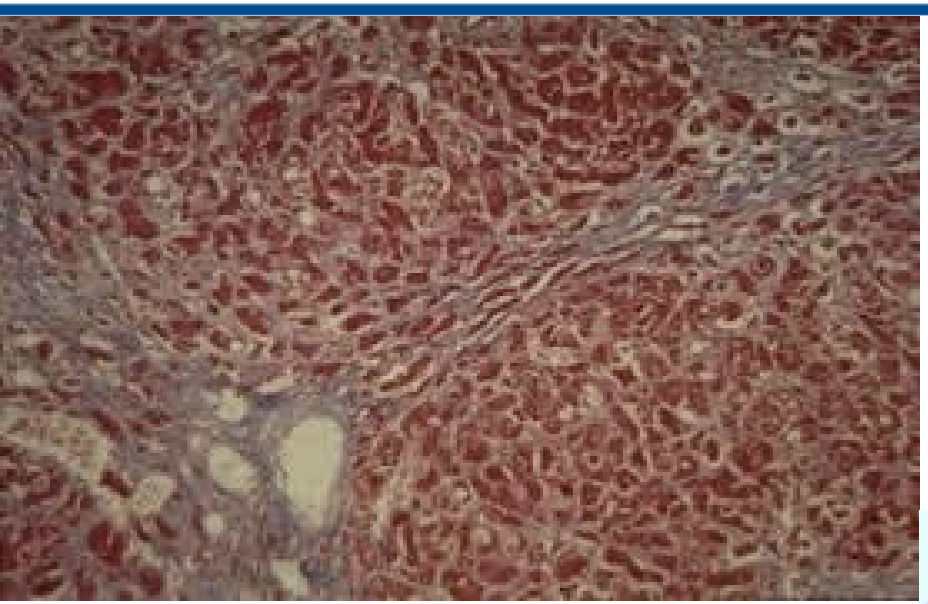
Liver Biopsy: Staging systems for fibrosis

Score	Knodell	Ishak	Scheuer	Metavir
0	None	None	None	None
1	Portal	Portal	Portal	Portal
2		Periportal	Periportal	Septae
3	Bridging fibrosis	Focal bridging	Architectural distortion without cirrhosis	Bridging fibrosis
4	Cirrhosis	Diffuse bridging	Cirrhosis	Cirrhosis
5		Extensive bridging		
6		Cirrhosis		

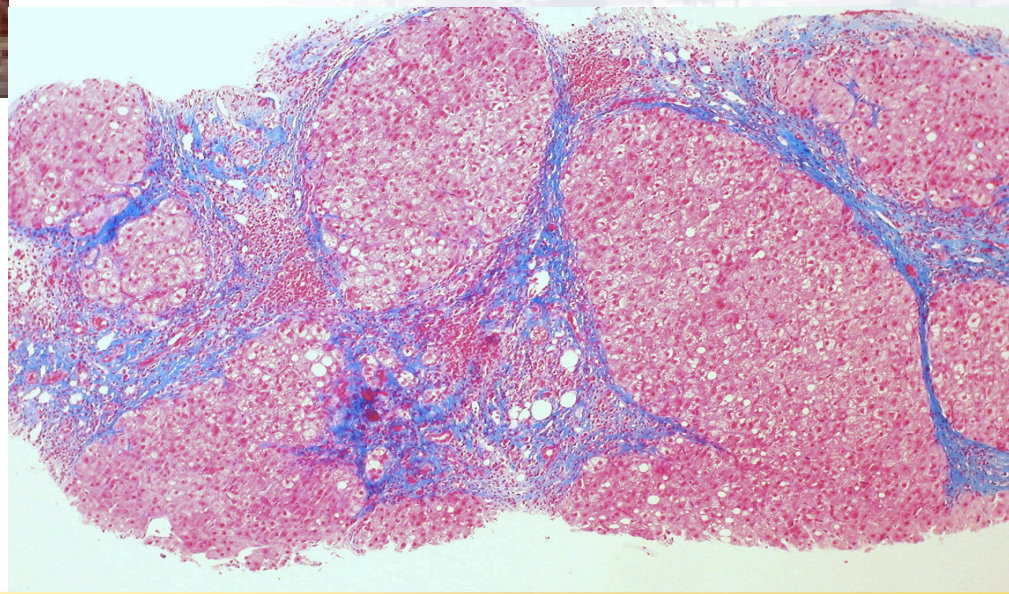
Schiff's Diseases of the Liver 2012

Liver Biopsy

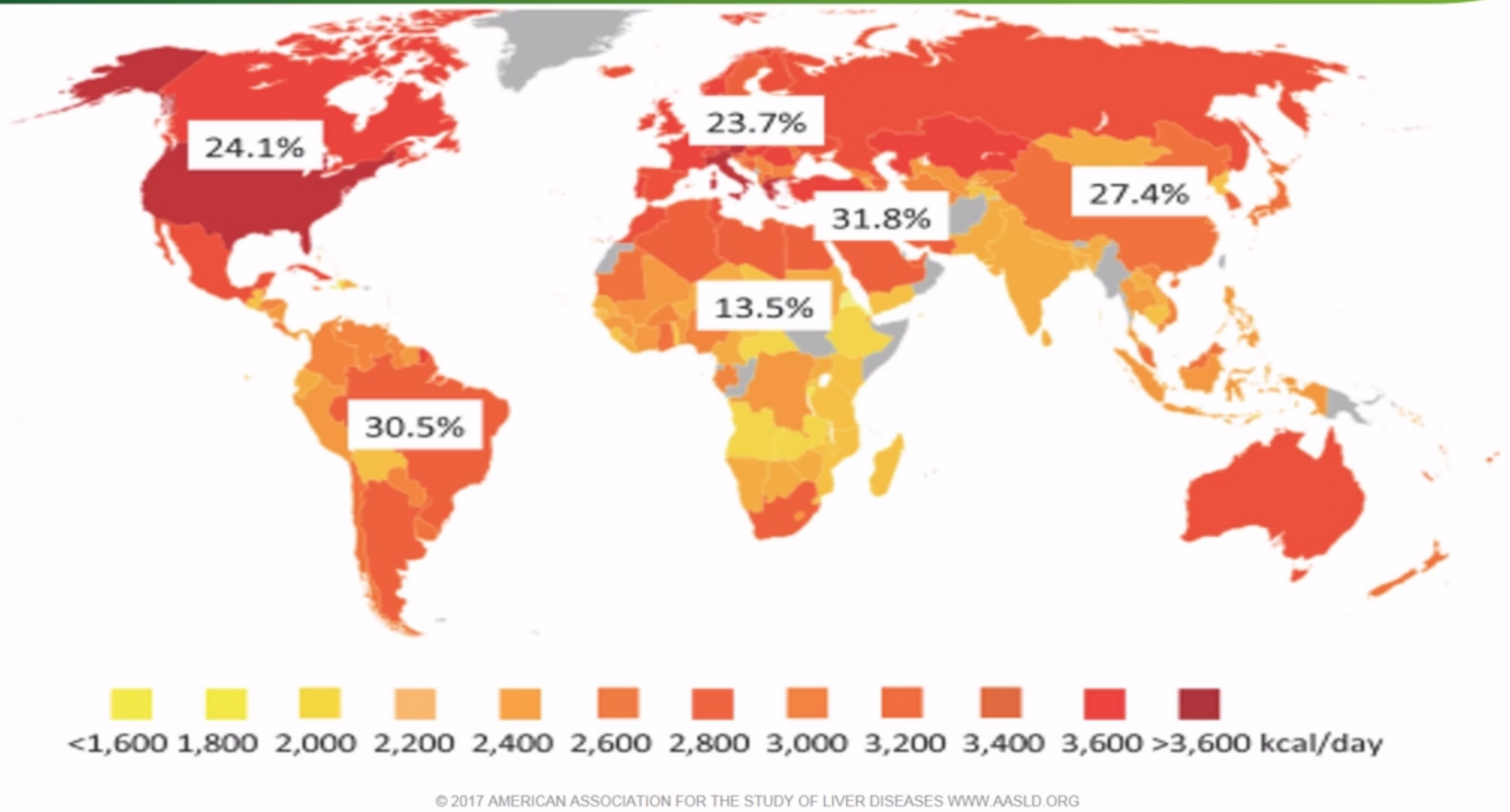
Bridging Fibrosis (Stage 3)



Cirrhosis (Stage 4)



NAFLD seen Globally



Rinella. Hep 2016

Global Prevalence: 25-30%

- As a consequence of pandemic of obesity, MASLD is the most common cause of liver disease worldwide
- The highest rates are in South America and the Middle East, followed by Asia, the U.S., and Europe

Prevalence of MASH

- Challenging to determine with certainty
- MASH identified in 14% of asymptomatic patients undergoing colon cancer screening, 6% of them with significant fibrosis

Harrison SA et al. Prospective evaluation of the prevalence of non-alcoholic fatty liver disease and steatohepatitis in a large middle-aged US cohort. J Hepatol. 2021 Aug;75(2):284-291.

Public Health Implications

- NASH-related cirrhosis is already the leading indication for liver transplantation in women and those > 65 years of age
- NASH is the most rapidly increasing indication for liver transplantation in the U.S.
- NAFLD is fastest growing cause of HCC in liver transplant candidates

Younossi Z et al; Global Nonalcoholic Steatohepatitis Council. Nonalcoholic Steatohepatitis Is the Fastest Growing Cause of Hepatocellular Carcinoma in Liver Transplant Candidates. Clin Gastroenterol Hepatol. 2019; 17(4):748-755.e3.

Rinella ME et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023; 77(5):1797-1835.

Public Health Implications

- Prevalent NAFLD cases are projected to increase 21% by the year 2030

  NAFLD prevalence among the adult population is projected at 33.5% in 2030

- Prevalent NASH cases are expected to increase 63%, with a disproportionate increase in number of patients with advanced liver fibrosis

Estes C et al. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology 2018; 67(1):123-133.

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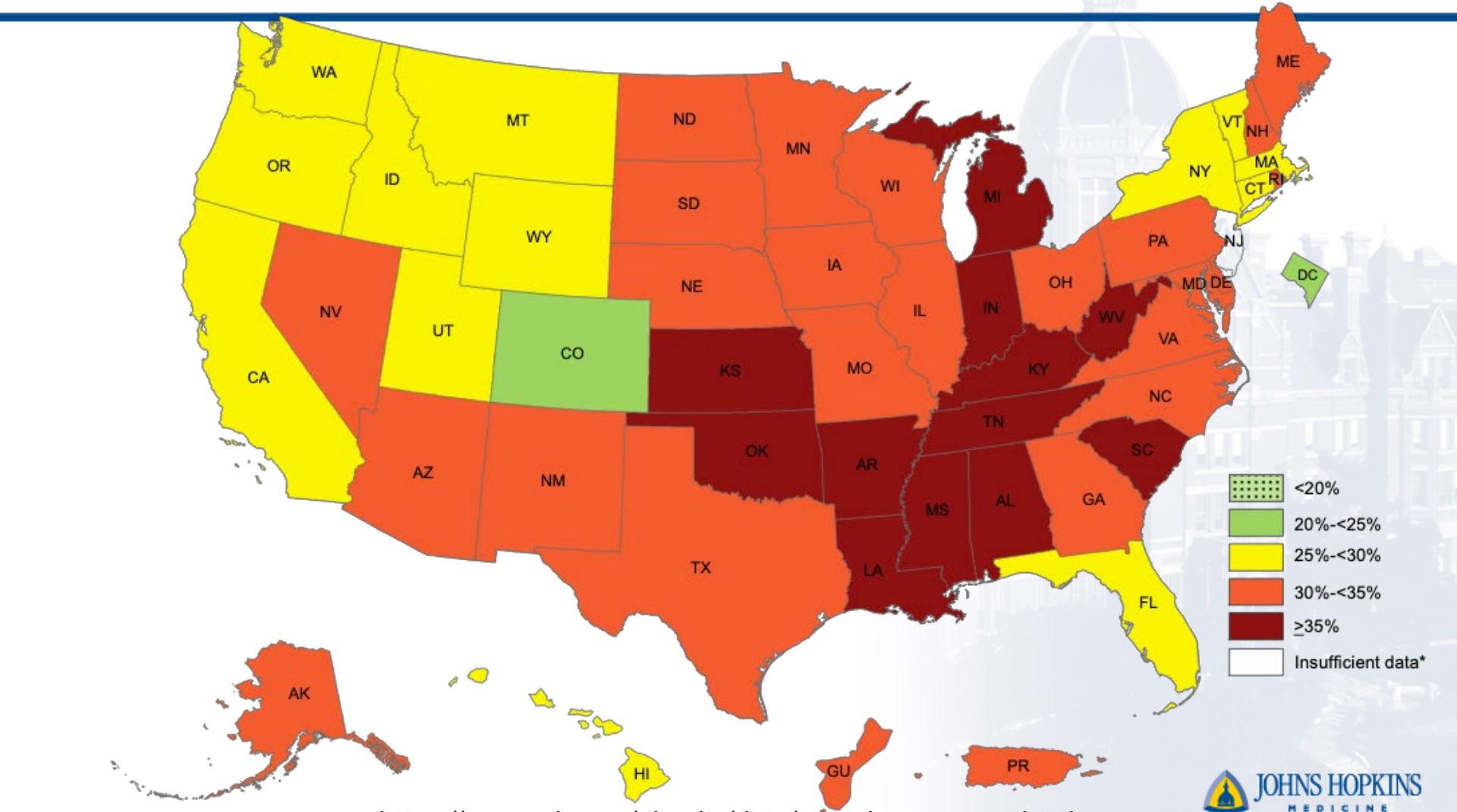
Public Health Implications

- Incidence of decompensated cirrhosis will increase 168%
- Incidence of HCC will increase by 137%
- Liver deaths will increase 178%

Estes C et al. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology 2018; 67(1):123-133.

Prevalence of Obesity in U.S. in 2019



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

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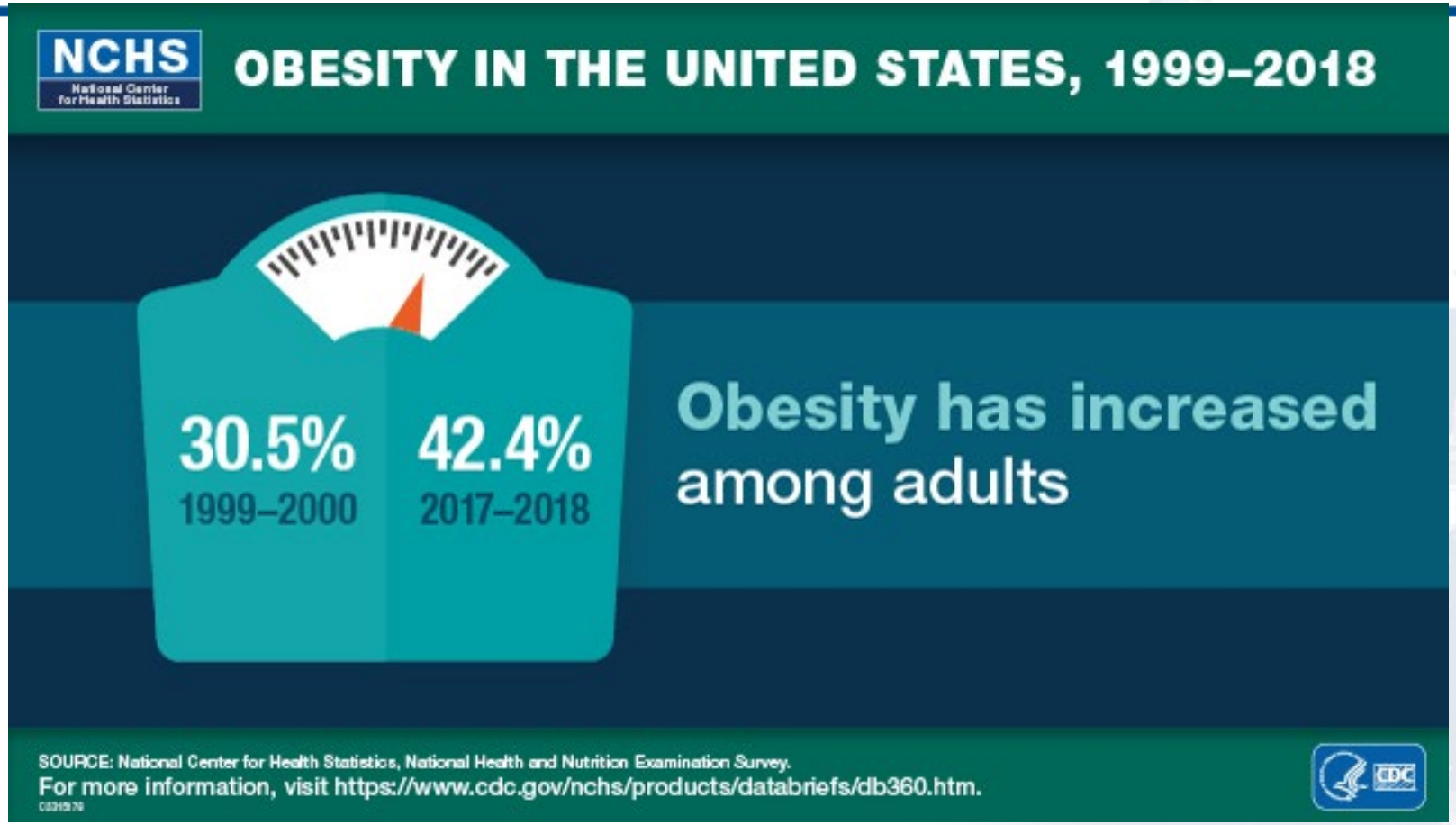
Obesity



- Prevalence of severe obesity increased from 4.7% to **9.2%**
- Prevalence of obesity 18.5% in children and adolescents ages 2-19

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The Culprit: The Western Diet

Overconsumption of over-refined sugars, highly refined and saturated fats, animal protein and a reduced intake of plant-based fibers

https://www.mdedge.com/internalmedicine/article/197770/gastroenterology/western-diet-linked-lower-microbiome-diversity

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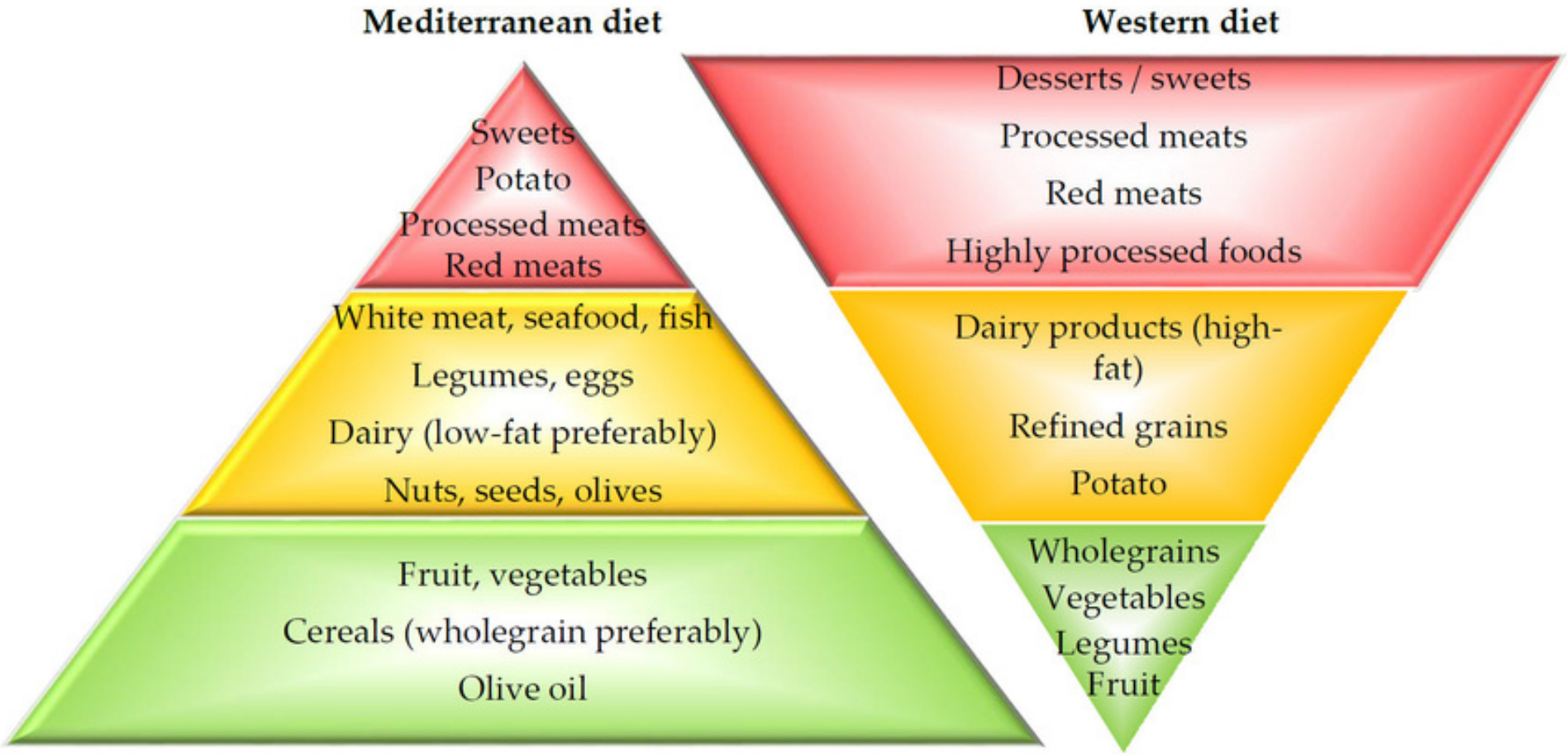
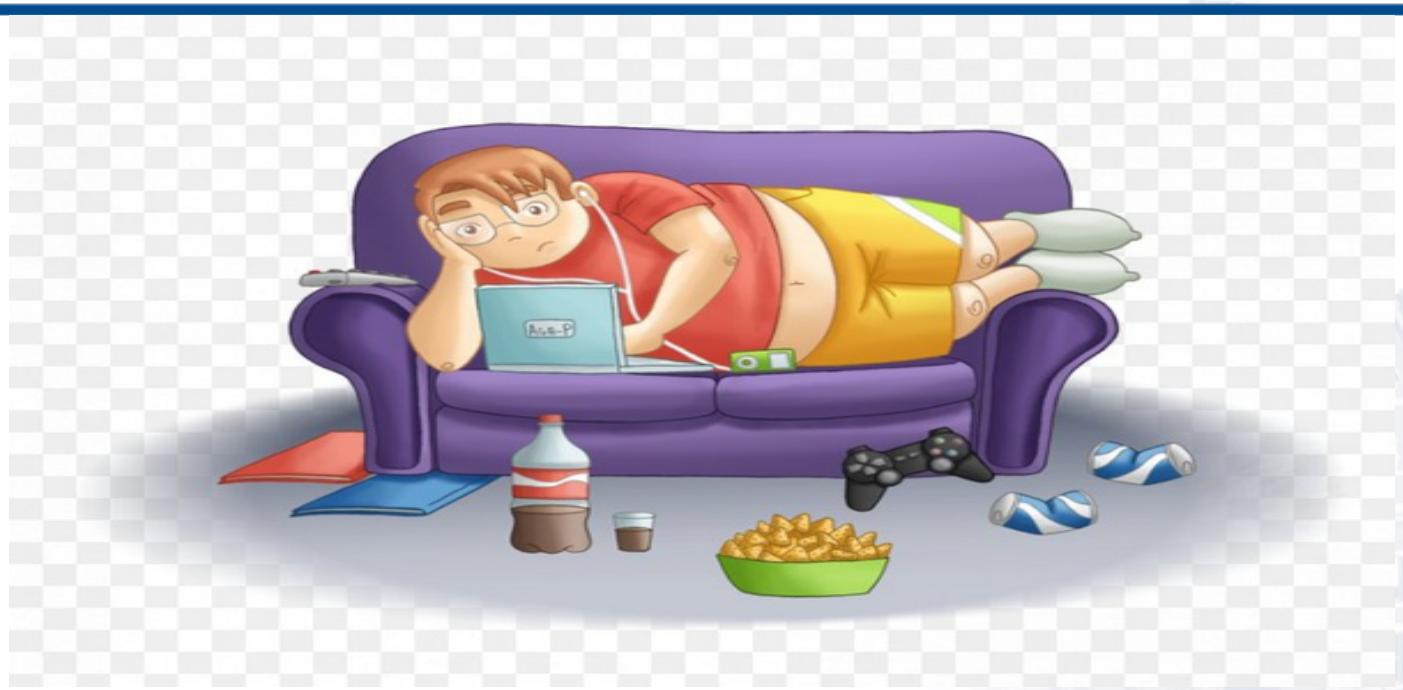


- According to the CDC from 2013-16, 36.6% adults consumed fast food on a given day

https://www.researchgate.net/figure/Characteristics-of-Mediterranean-and-Western-diets-The-Mediterranean-dietary-pattern-is_fig1_320939659

The Second Culprit: Sedentary Lifestyle



https://www.quora.com/Can-you-lead-a-sedentary-lifestyle-and-remain-healthy

- > 60 percent of U.S. adults do not engage in the recommended amount of physical activity
- 25 percent of U.S. adults are not physically active at all

https://www.cdc.gov/nccdphp/sgr/adults.htm#:~:text=More%20than%2060%20percent%20of,Women%20than%20men.

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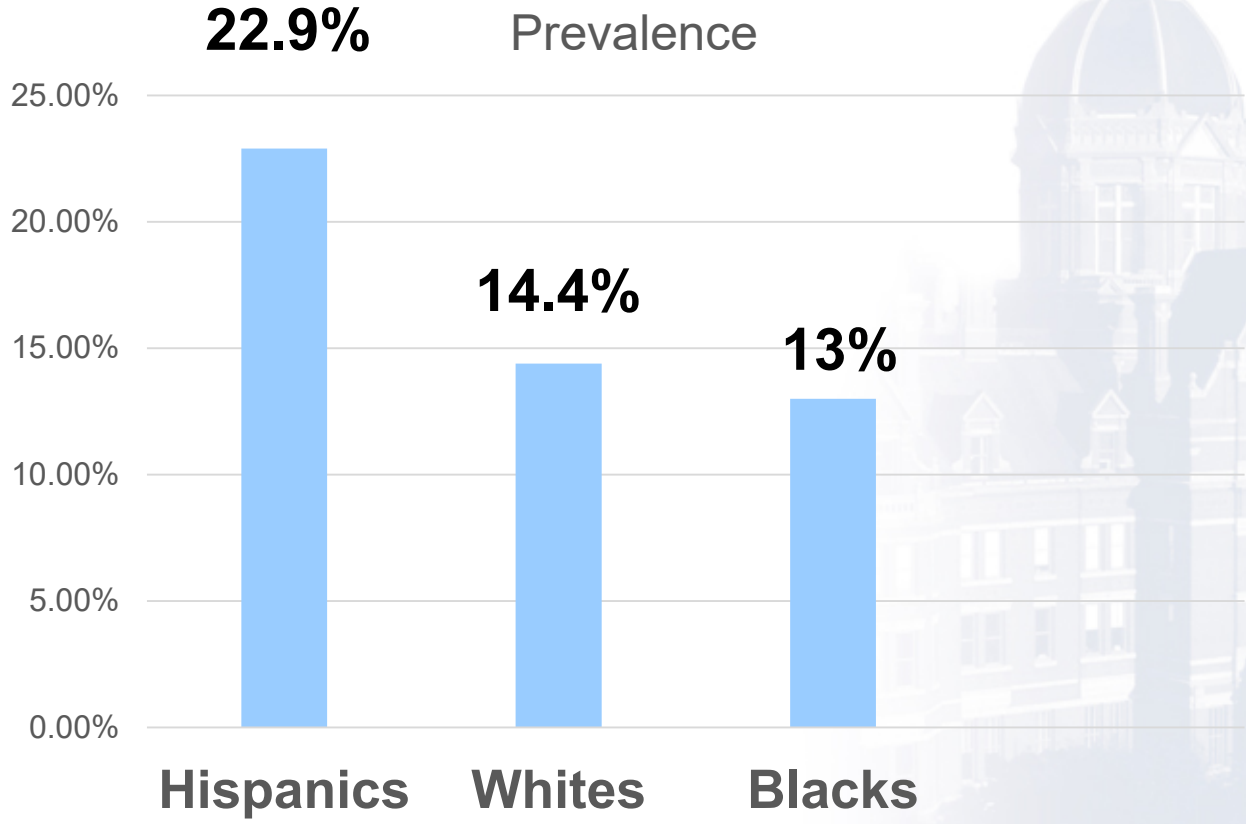
Disparities in NAFLD Prevalence by Race/Ethnicity



Single nucleotide polymorphisms in genes such as the PNPLA3 gene partially accounts for the higher prevalence of NAFLD in Hispanics

Rich NE et al. *Clin Gastroenterol Hepatol*. 2018 Feb;16(2):198-210

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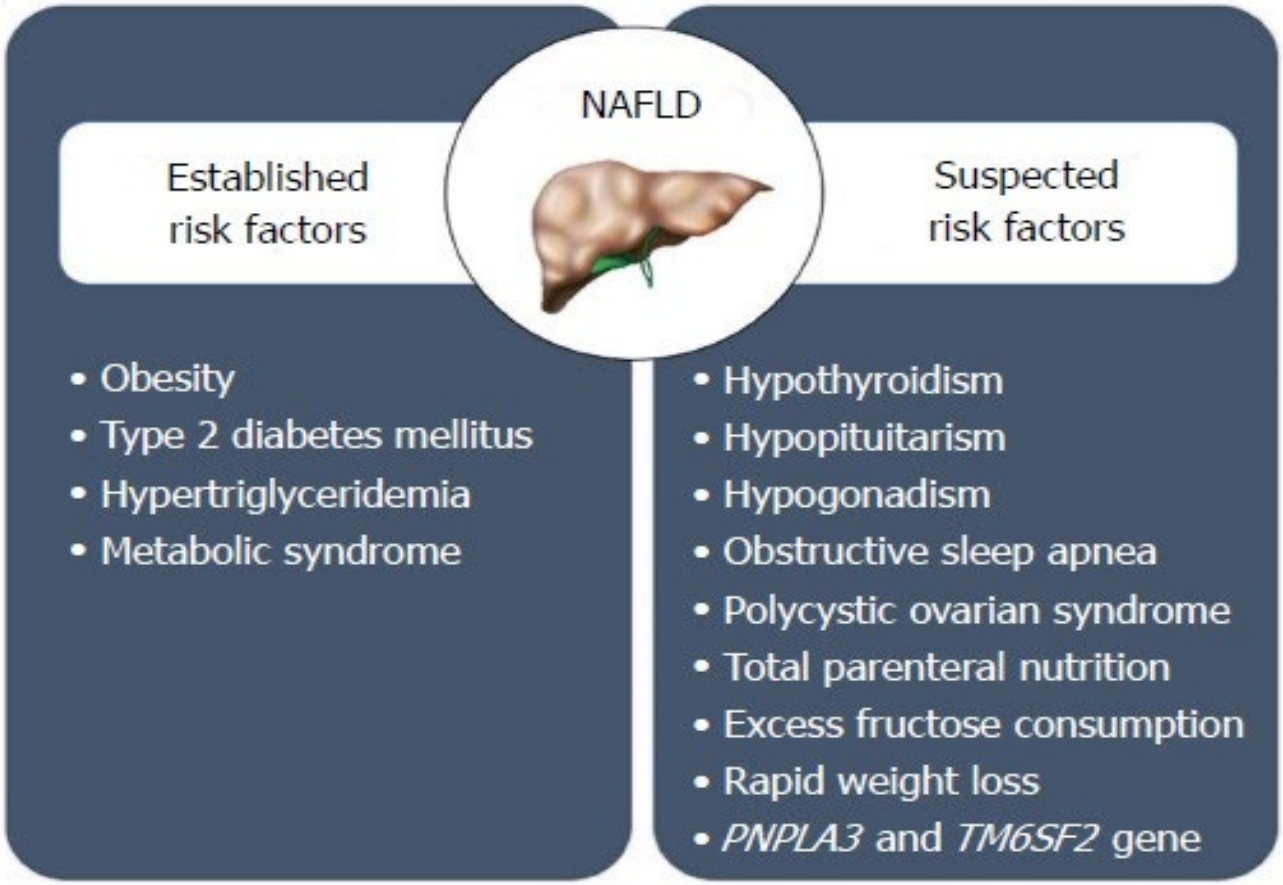
Factors Associated with MASLD



Perumpail BJ et al. *World J Gastroenterol* 2017

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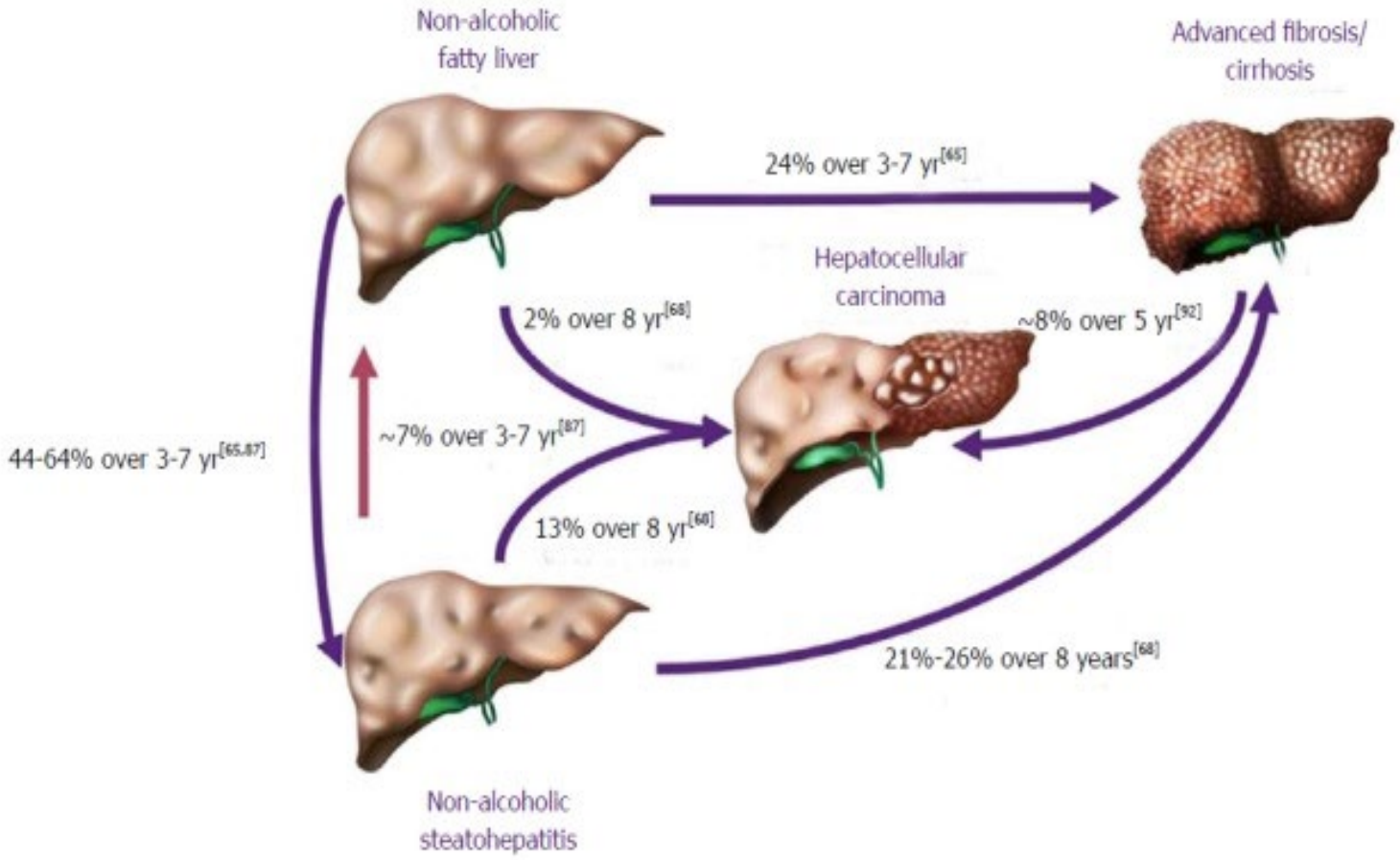
MASLD: Natural History of Disease Progression



Perumpail BJ e al. Clinical epidemiology and disease burden of nonalcoholic fatty liver disease. World J Gastroenterol. 2017;23(47):8263-8276.

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Complications of Cirrhosis

Once patients develop cirrhosis:

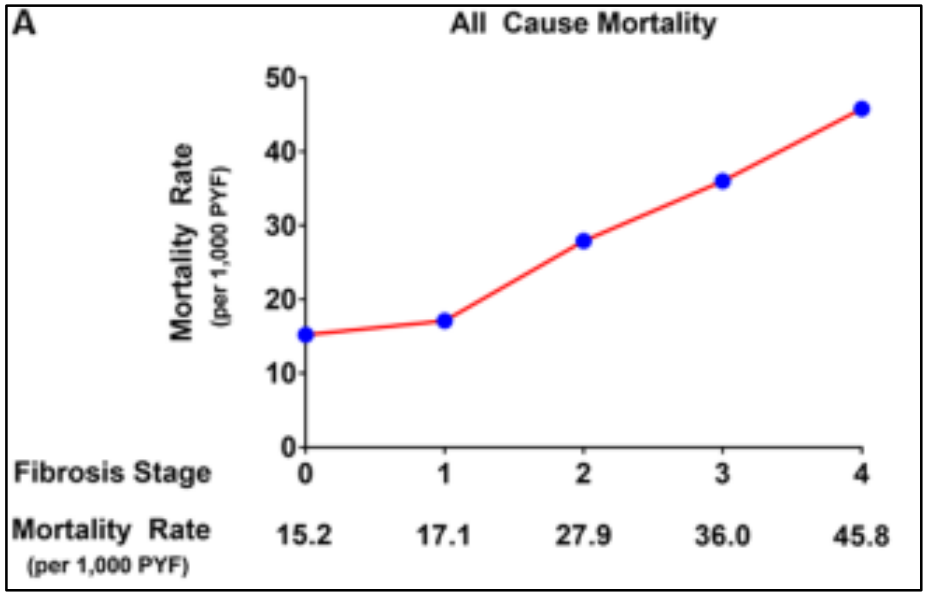
- Progression to clinical decompensation occurs at an incidence of 3-20% per year
- Development of HCC occurs at an incidence of 0.5-2.6% per year

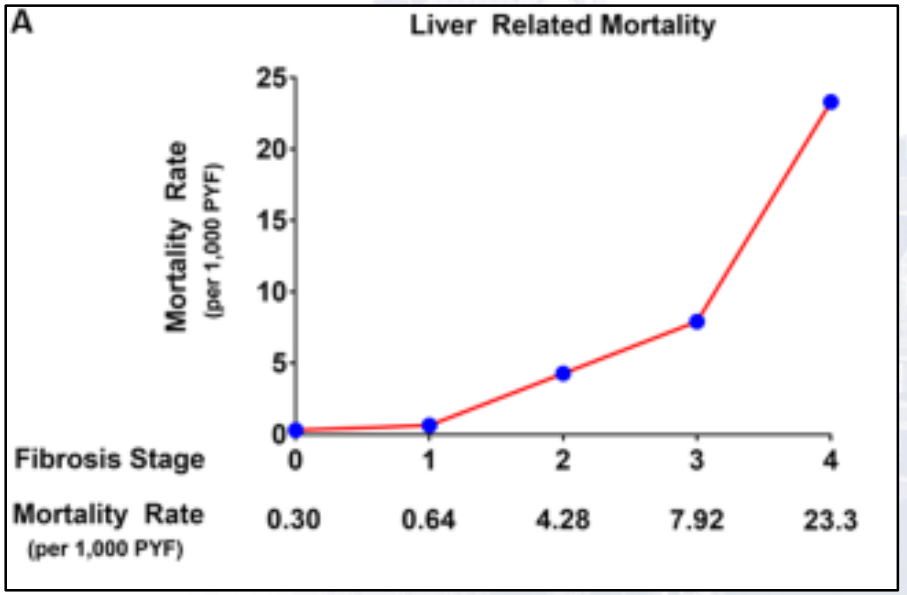
Rinella ME et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023; 77(5):1797-1835.

Huang DQ e al. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2021; 18(4):223-238.

Mortality increases by Fibrosis Stage in MASLD

Meta Analysis of 5 studies with 1,495 MASLD patients and 17,452 patient years





Dulai et al. *Hepatology* 2017

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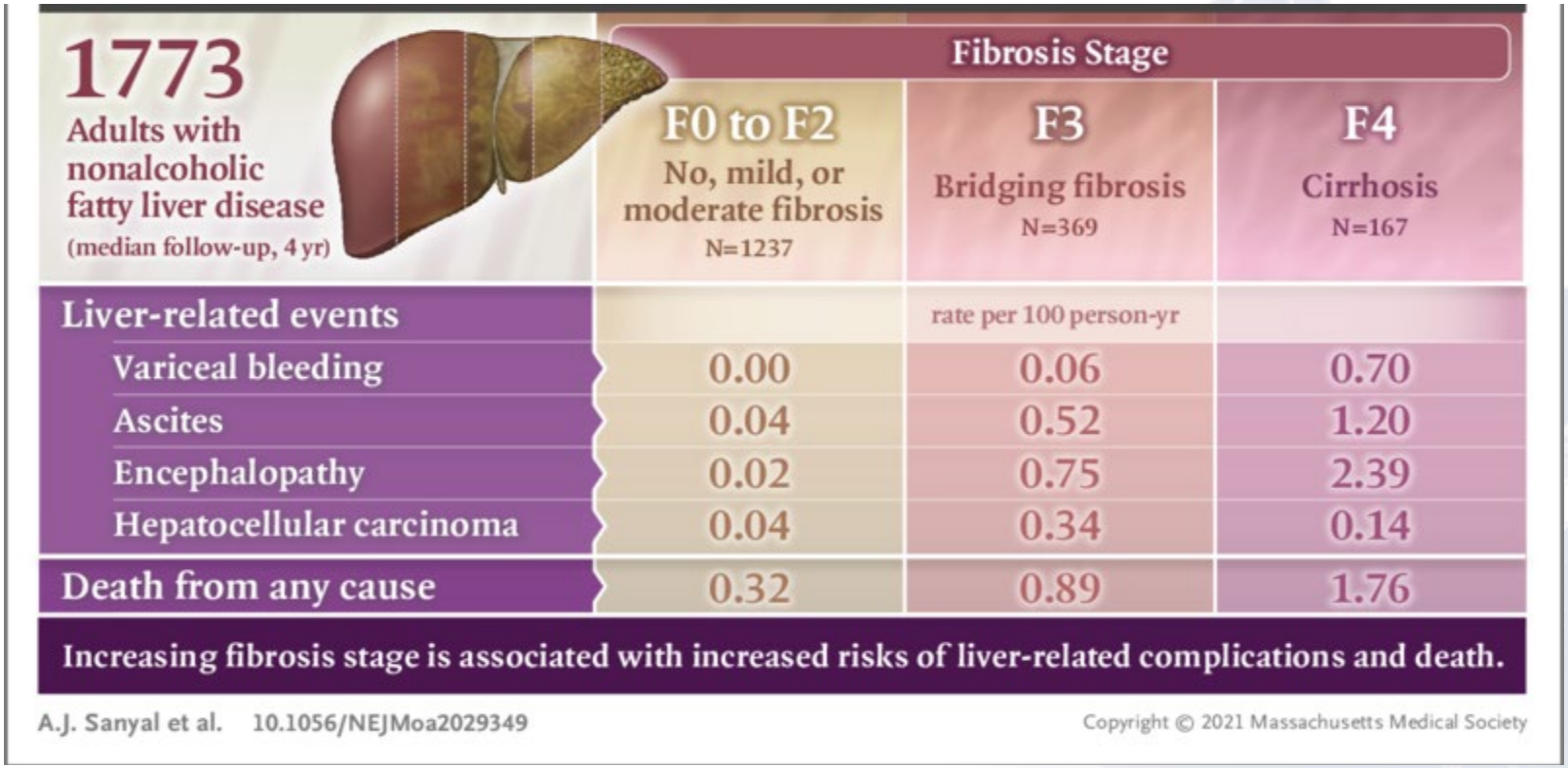
- Patients with **”at-risk” MASH**, defined as MASH with at least stage 2 fibrosis have higher risk of liver-related morbidity and mortality

- Patients with bridging fibrosis (Stage 3) and cirrhosis (Stage 4) have an exponentially higher risk of liver-related morbidity and mortality compared to earlier stages of fibrosis

Rinella ME et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023; 77(5):1797-1835.



Sanyal et al; NASH Clinical Research Network (CRN). Prospective Study of Outcomes in Adults with Nonalcoholic Fatty Liver Disease. N Engl J Med. 2021; 385(17):1559-1569.

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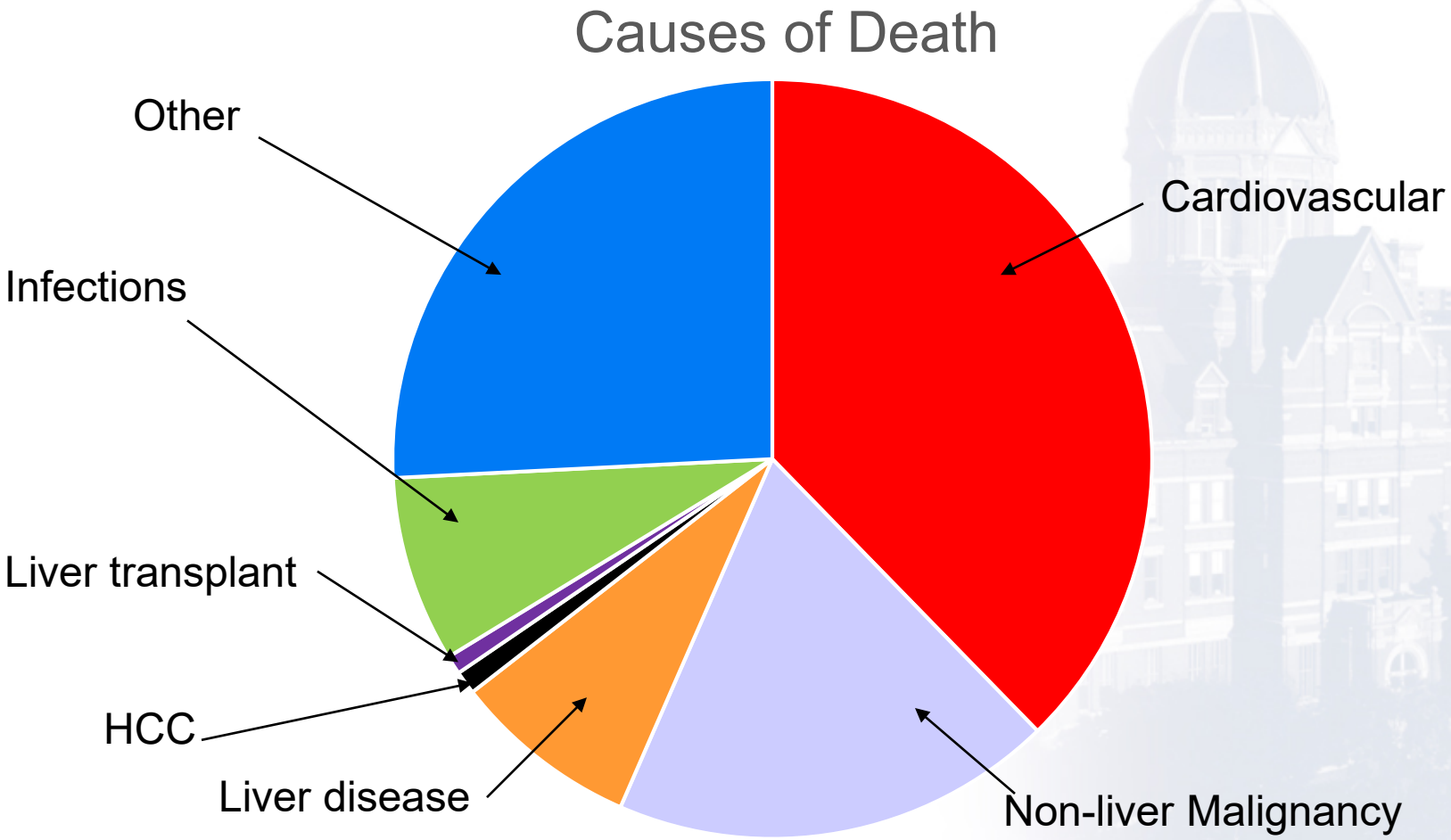
Mortality in MASLD



Angulo et al. *Gastro* 2015

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2 Keys parts of Evaluation/Diagnosis

1. Rule out other causes of chronic liver disease (i.e.: confirm diagnosis)
   - Alcohol history is important: Cut-off is < 3 drinks/day for men, 2 drinks/day for women to be considered MASLD vs. MetALD
   - Chronic viral hepatitis (Hepatitis B and C), hereditary hemochromatosis, autoimmune hepatitis, alpha-1 antitrypsin deficiency, and Wilson disease
2. Distinguish between MAFL and MASH and assess stage of fibrosis
   - FIB-4 index
   - Vibration-controlled transient elastography (VCTE or FibroScan) or MR elastography (MRE)
   - Liver biopsy
     - Consider in patients with metabolic syndrome
     - If there are competing etiologies of liver disease

Non-invasive scoring algorithms to assess fibrosis

NAFLD fibrosis score

- Age
- BMI
- Impaired fasting glucose/diabetes
- AST/ALT ratio
- Platelet count
- Albumin

NAFLD Score	Correlated Fibrosis Severity
< -1.455	F0-F2
-1.455 – 0.675	Indeterminant score
> 0.675	F3-F4

FIB-4 index

- Age
- AST
- Platelets
- ALT

FIB-4 Score	Approximate fibrosis stage*
<1.45	0-1
1.45-3.25	2-3
>3.25	4-6

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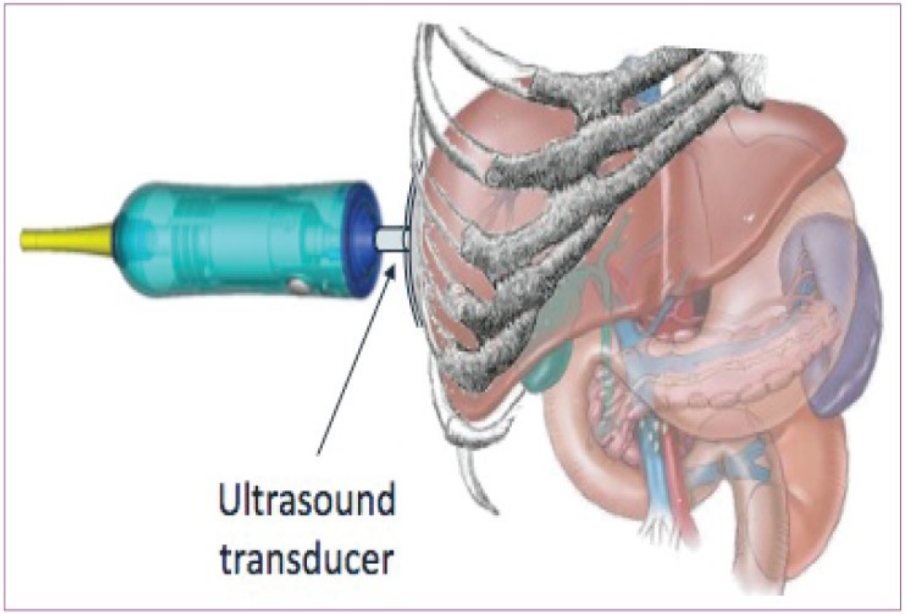
Imaging tests that measure liver stiffness: Vibration Controlled Transient Elastography (FibroScan)



- Probe is positioned in an intercostal space near the right lobe of the liver
- A 50-MHz wave is passed into the liver from a small transducer on the end of the probe
- Device measures velocity of the shear wave as it passes through the liver
- Measurement is converted to a liver stiffness measurement in kPa
- Controlled attenuation parameter (CAP) algorithm calculates the attenuation of the ultrasound signal by fat (dB/m) and provides an estimate of hepatic steatosis

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Image courtesy of Echosens

FibroScan Result Interpretation

Median Liver Stiffness Measurement Interpretation Guidelines

- < 7 kPa: minimal to no fibrosis (metavir 0-1)
- 7.0 kPa – 12.5 kPa: moderate to significant amount of fibrosis (metavir 2-3)
- > 12.5 kPa: significant amount of fibrosis and cirrhosis (metavir 4)

Controlled Attenuation Parameter Interpretation Guidelines

CAP correlates with percentage of liver steatosis and steatosis grade (S0-S3) as follows:

- < 238 dB/m: healthy (S0), where <10% of hepatocytes contain lipid droplets
- 238 – 260 dB/m: mild steatosis (S1), where >10 – 33% of hepatocytes contain lipid droplets
- 260 - 290 dB/m: moderate steatosis (S2), where >34– 66% of hepatocytes contain lipid droplets
- > 290 dB/m: severe steatosis (S3), where >67% of hepatocytes contain lipid droplets

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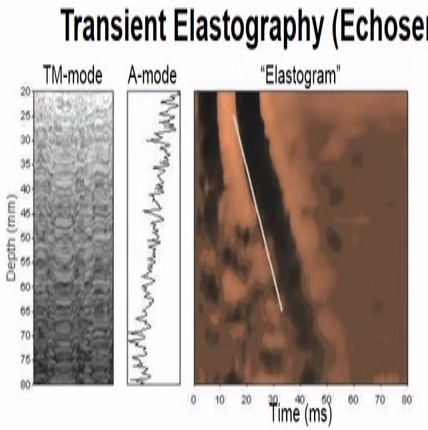
FibroScan Advantages

Modality	Results	**Advantages and Disadvantages**
Vibration controlled transient elastography (FibroScan) with controlled attenuation parameter	E (kPa) (> 12.5 kPa: cirrhosis) CAP (dB/m)	- Relatively inexpensive - Easy to perform - XL probe can be used for obese patients - Not reliable in the setting of significant liver inflammation or ascites



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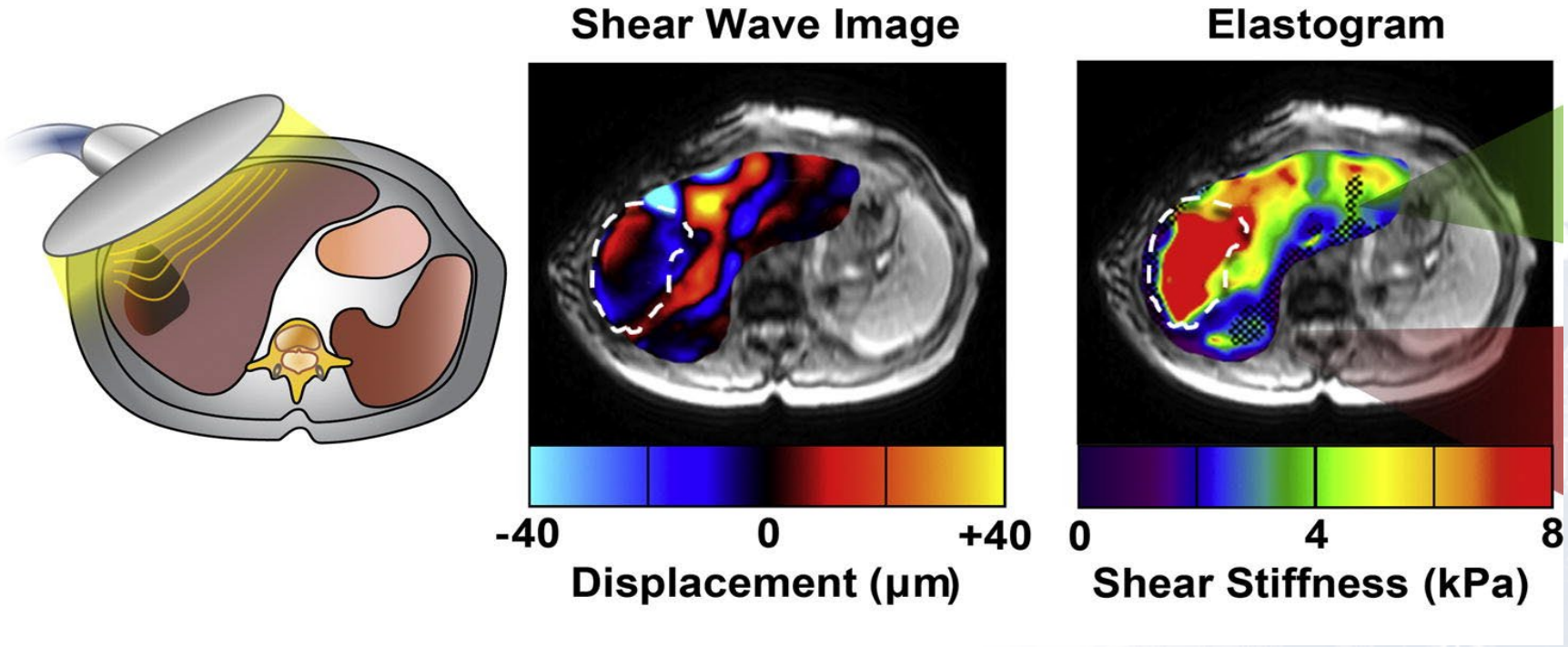
Imaging tests that measure liver stiffness: MR Elastography (MRE)



- MRI is coupled with a device that generates shear waves within liver
- Shear wave velocity is then measured to calculate quantitative results
- Create a visual map (elastogram) that shows stiffness of liver

Prog Nucl Magn Reson Spectrosc. 2015 Nov;90-91:32-48.

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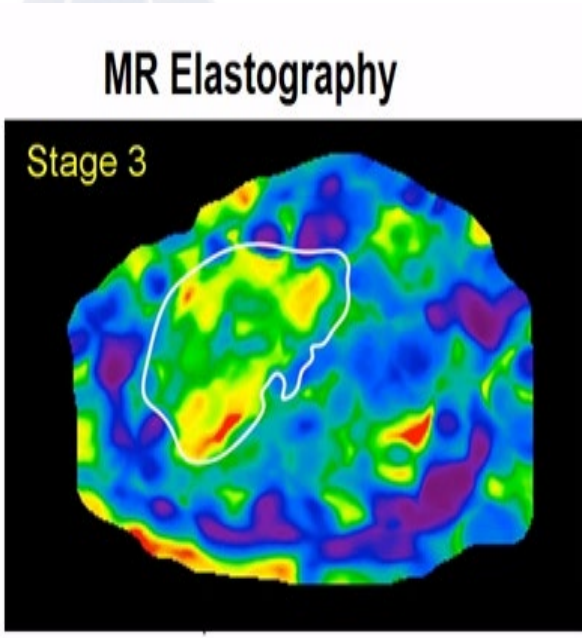
MRE Advantages and Disadvantages

Modality	Results	**Advantages and Disadvantages**
MR elastography	kPa	Can quantify steatosis precisely Can quantify iron concentration More expensive than ultrasound-based techniques

= 2.5 kPa	normal
>2.5-3 kPa	normal or inflammation
>3-3.5 kPa	stage 1-2 fibrosis
>3.5-4 kPa	stage 2-3 fibrosis
>4-5 kPa	stage 3-4 fibrosis
> 5 kPa	stage 4 to cirrhosis



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Diagnostic accuracy of non-invasive methods of fibrosis assessment

Diagnostic Test	Area under the Receiver Operating Curve (AUROC) for detection of moderate fibrosis	AUROC for detection of advanced Fibrosis
NAFLD Fibrosis Score	0.82	0.86
FIB-4 Index	0.83	0.86
FibroScan	0.82	0.88
MR elastography	0.91	0.89

Imajo et al. *Gastroenterology* 2016;150:626–637

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Strategies for Early Detection of MASLD

- General population-based screening for MASLD is currently not recommended
- Targeted screening of populations at increased risk for advanced liver disease is recommended to identify and manage those with clinically significant fibrosis (stage ≥ 2)

Rinella ME et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023; 77(5):1797-1835.

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

AASLD 2023 Practice Guidance

Patients with

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

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

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American Diabetes Association 2023 Recommendation

- Adults with type 2 diabetes or prediabetes, particularly those with obesity or cardiometabolic risk factors/established cardiovascular disease, should be screened/risk stratified for nonalcoholic fatty liver disease with clinically significant fibrosis (defined as moderate fibrosis to cirrhosis) using a calculated fibrosis-4 index (FIB-4 index; derived from age, ALT, AST, and platelets), even if they have normal liver enzymes

Addendum. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Care in Diabetes—2023*. Diabetes Care 2023;46(Suppl. 1):S49–S6

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How should MASLD be managed in primary care settings and when to refer to GI/Hepatology clinic?

- Prevalence of advanced liver disease lower in primary care practices than in hepatology clinics
- Patients suspected to have MASLD based on metabolic risk factors or incidentally found to have fatty liver by imaging in the absence of secondary causses should undergo **primary risk assessment** with **FIB-4 index**
- FIB-4: noninvasive test; score <1.30 - 90% negative predictive value
- Objective of primary risk assessment: Identify patients who are not likely to have advanced fibrosis [low risk, FIB-4 < 1.3]
- Patients in low-risk category can be managed in the primary care setting

Rinella ME et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023; 77(5):1797-1835.

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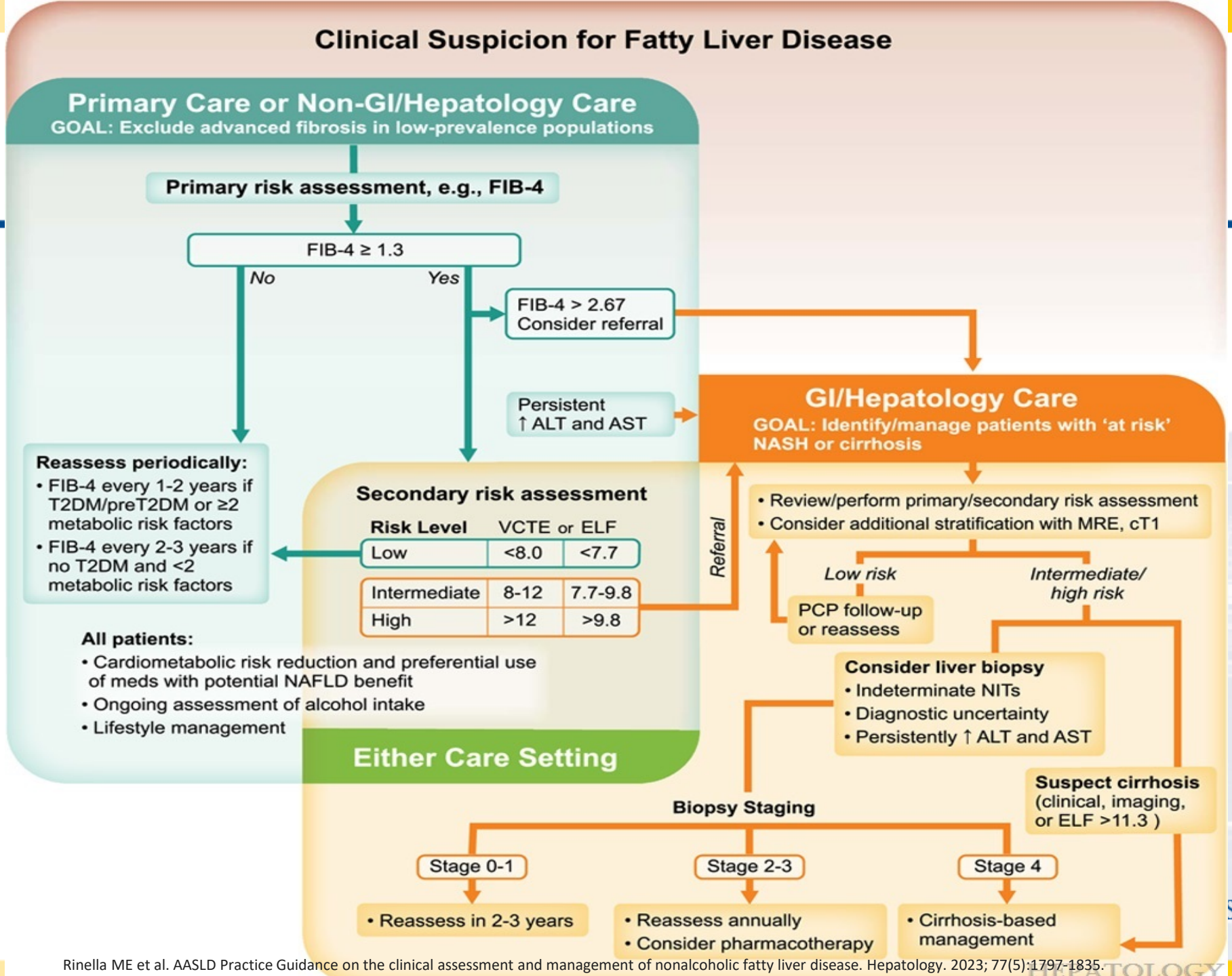
How should MASLD be managed in primary care settings and when to refer to GI/Hepatology clinic?

- In patients with pre-DM, Type 2 DM, or ≥ 2 metabolic risk factors, primary risk assessment with FIB-4 should be repeated every 1-2 years
- Otherwise can repeat FIB-4 every 3-4 years

Rinella ME et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023; 77(5):1797-1835.



Rinella ME et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023; 77(5):1797-1835.

How should MASLD be managed in primary care settings and when to refer to GI/Hepatology clinic?

- Patients with moderate or high risk of advanced disease based on FIB-4 (FIB-4 ≥ 1.3) should undergo **secondary risk assessment** with **vibration-controlled elastography (VCTE)** or Enhanced Liver Fibrosis (ELF) test

- If secondary assessment still consistent with intermediate or high risk of fibrosis, patients should be referred to Hepatology care for further evaluation and intervention

Rinella ME et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023; 77(5):1797-1835.

Enhanced Liver Fibrosis (ELF) Test

- Proprietary blood test consisting of 3 elements involved in matrix turnover:
  - hyaluronic acid
  - tissue inhibitor of metalloproteinase-1
  - N-terminal procollagen III peptide

- ELF score ≥ 9.8 reliable identifies patients with NAFLD at increased risk of progression to cirrhosis and liver-related clinical events

Miele L et al. Enhanced liver fibrosis test as a reliable tool for assessing fibrosis in nonalcoholic fatty liver disease in a clinical setting. Int J Biol Markers. 2017 Oct 31;32(4):e397-e402.

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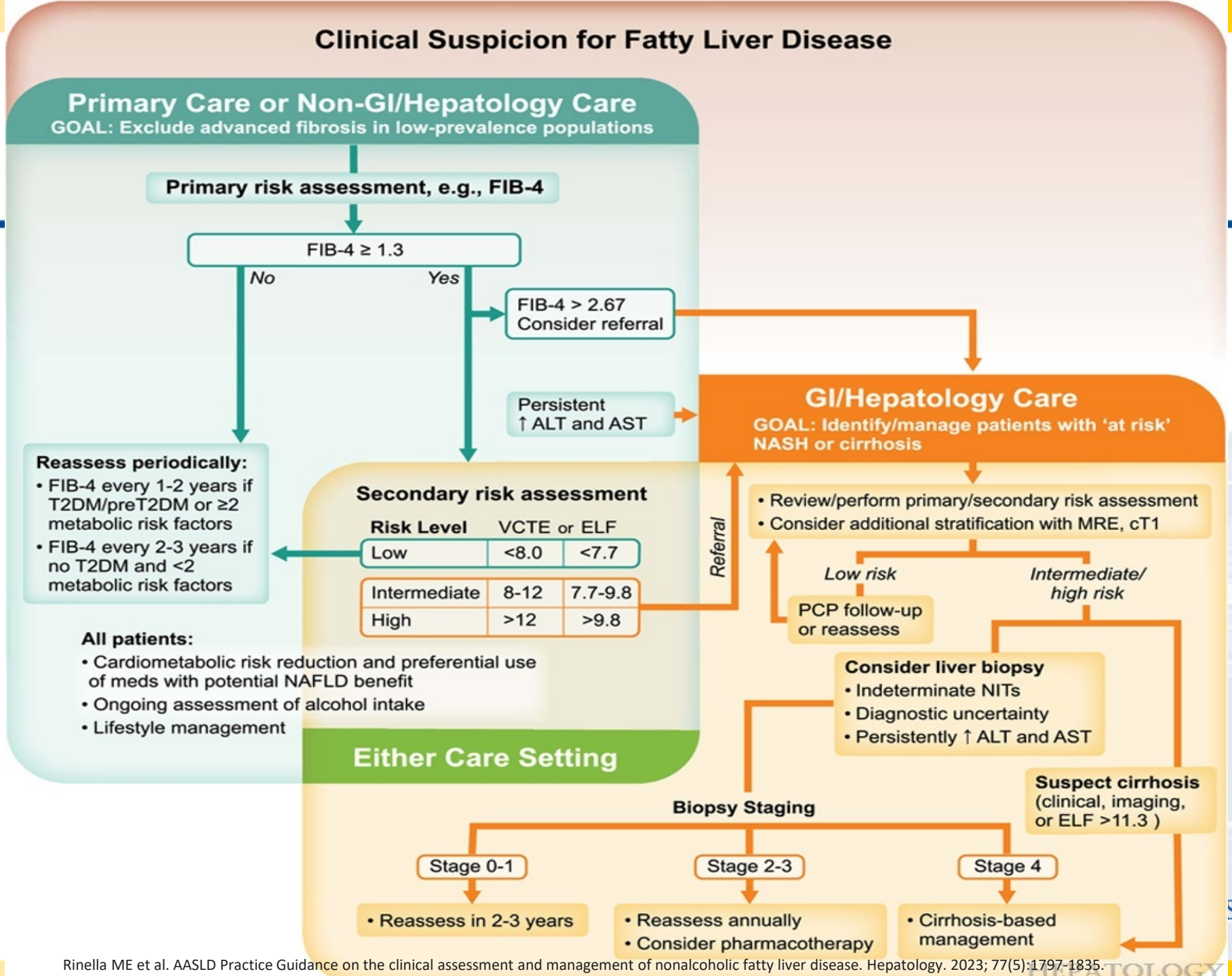


Rinella ME et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023; 77(5):1797-1835.

Further Risk Stratification in Gastroenterology/Hepatology Clinics

- Primary goal in the specialty care setting is identification of patients with “at-risk” MASH or advanced fibrosis
- MR elastography can be used to further risk stratify patients in whom other noninvasive tests have been indeterminate or not reflective of clinical suspicion
- Liver biopsy should be considered when there is diagnostic uncertainty

Rinella et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 2023; 77(5): 1797-1835.

MASLD: 4 Targets of Treatment

- **Obesity**
  - Lifestyle: diet and exercise
  - Bariatric procedures
- Metabolic Syndrome
  - Insulin resistance/type 2 diabetes
  - Dyslipidemia
- Liver disease
  - Steatohepatitis/fibrosis
- Minimize complications
  - HCC/CVD

Summary of Currently Available Treatments for MASH

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

Targeting Oxidative Stress

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

Targeting Insulin Resistance

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

- **There are currently no approved pharmacologic treatments for MASH in 2022!**

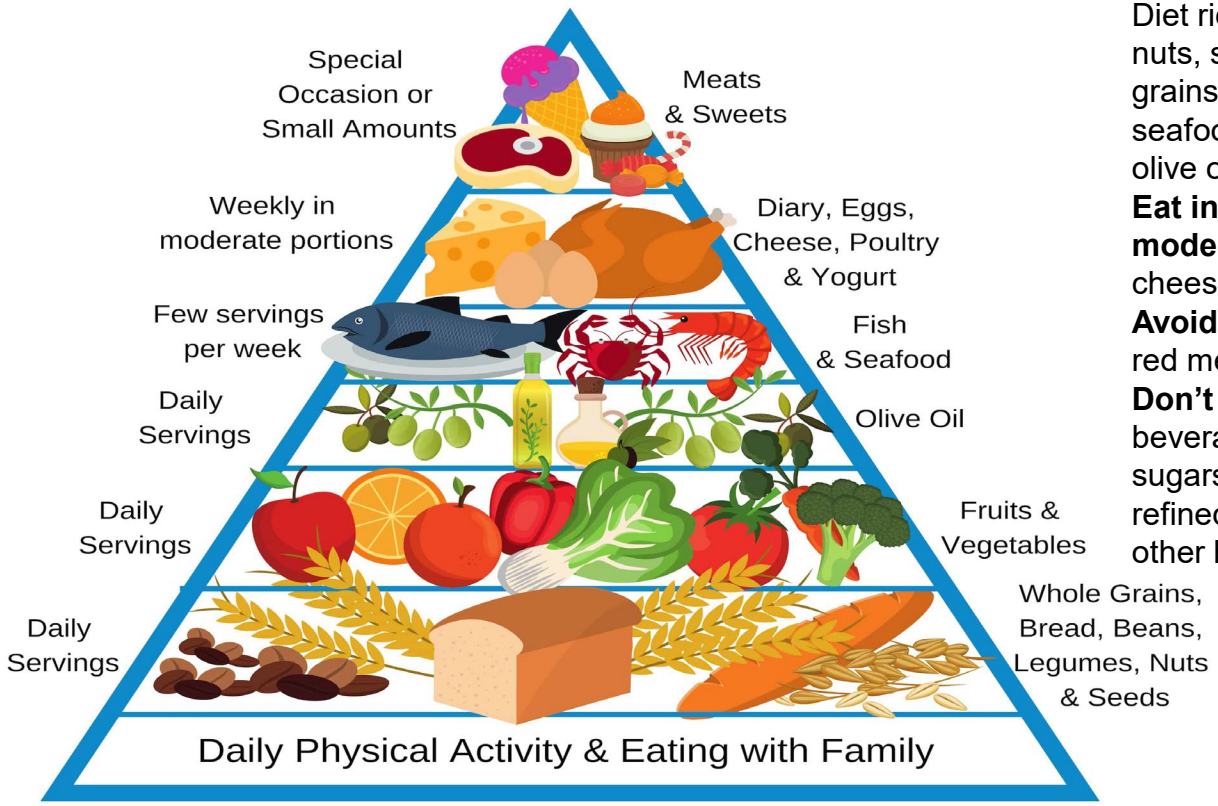
Weight Loss

Backbone of Treatment	Outcome
Weight loss Diet and exercise Bariatric surgery	10% weight loss improves steatosis, steatohepatitis, and fibrosis Decreases cardiovascular risk

- A combination of a hypocaloric diet (daily reduction by 500-1,000 kcal) and moderate-intensity exercise is likely to provide the best likelihood of sustaining weight loss over time

The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance From the American Association for the Study of Liver Diseases, 2018

Mediterranean Diet



Diet rich in vegetables, fruits, nuts, seeds, legumes, whole grains, herbs, spices, seafood, and extra virgin olive oil

Eat in moderation: Chicken, eggs, cheese and yogurt.

Avoid: Saturated fats and red meat.

Don't eat: Sugar-sweetened beverages, added sugars, processed meat, refined grains or oils, and other highly processed foods

Mediterranean Diet

Low carbohydrate, Mediterranean diet – limited carbohydrates and saturated fat and enriched with high fiber and unsaturated fats

https://shimacrobiotics.org/mediterranean-diet-vs-macrobiotics/

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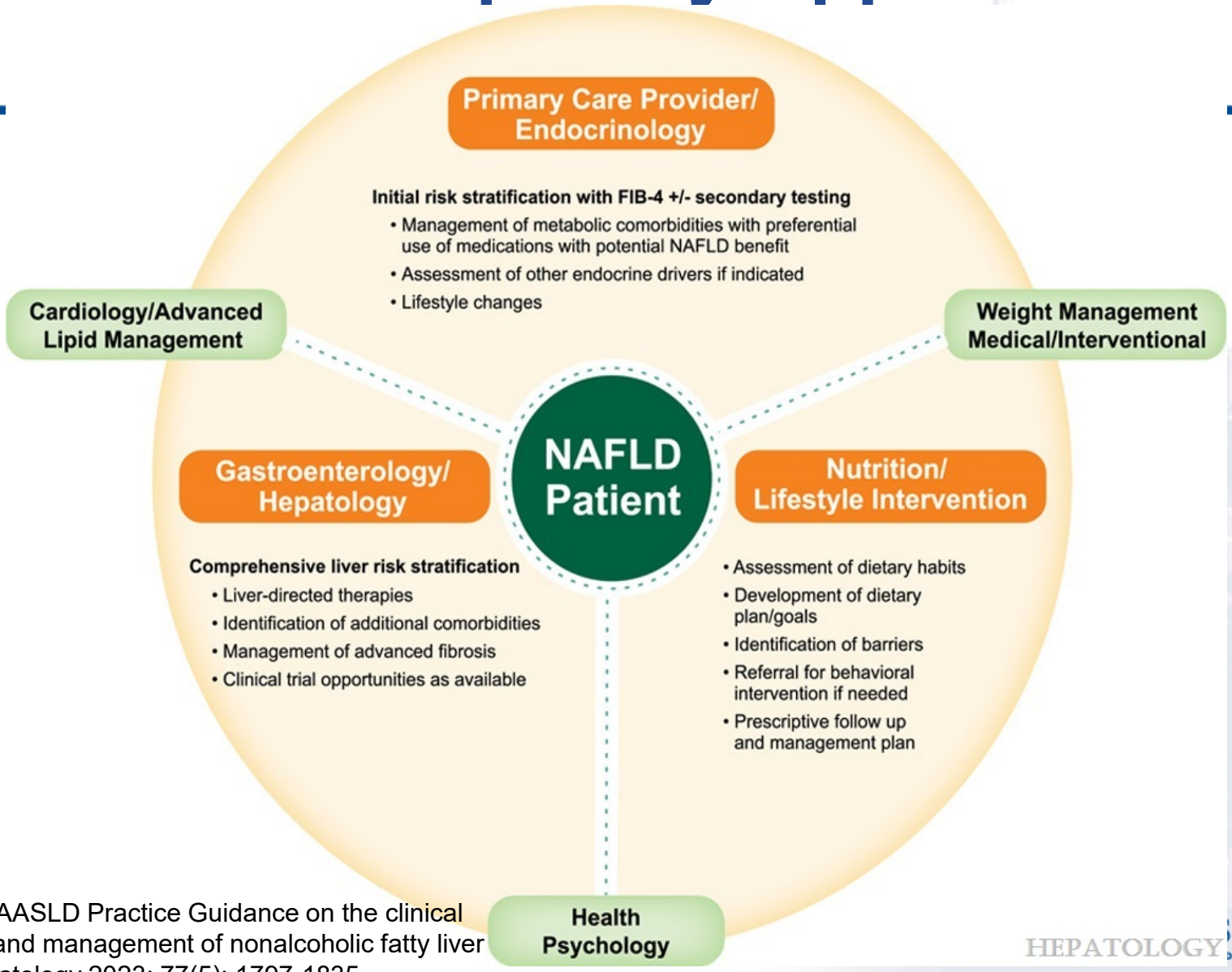
How can we help patients succeed in achieving weight loss?

Multidisciplinary Approach



Rinella et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 2023; 77(5): 1797-1835.

Johns Hopkins Healthful Eating, Activity & Weight Program (HEAWP)

Your Program Experience | For Healthcare Providers | Research

Overview

The Johns Hopkins Healthful Eating, Activity & Weight Program focuses on working with patients to make long-term lifestyle changes to prevent chronic disease and improve their health. We combine scientifically proven strategies with a compassionate and supportive approach to deliver high-quality care for women and men.

Started in June 2020
Location: Green Spring Station

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HEAWP

- **Multi-disciplinary, collaborative program** for the management of patients with overweight/obesity and it associated complications including MASLD

- Main Goals:
  - Help patients succeed with achieving and maintaining weight loss
  - Prevent and manage multiple medical co-morbidities associated with MASLD and decrease risk for cardiovascular disease
    - Obesity
    - Prediabetes and diabetes
    - Hypertension

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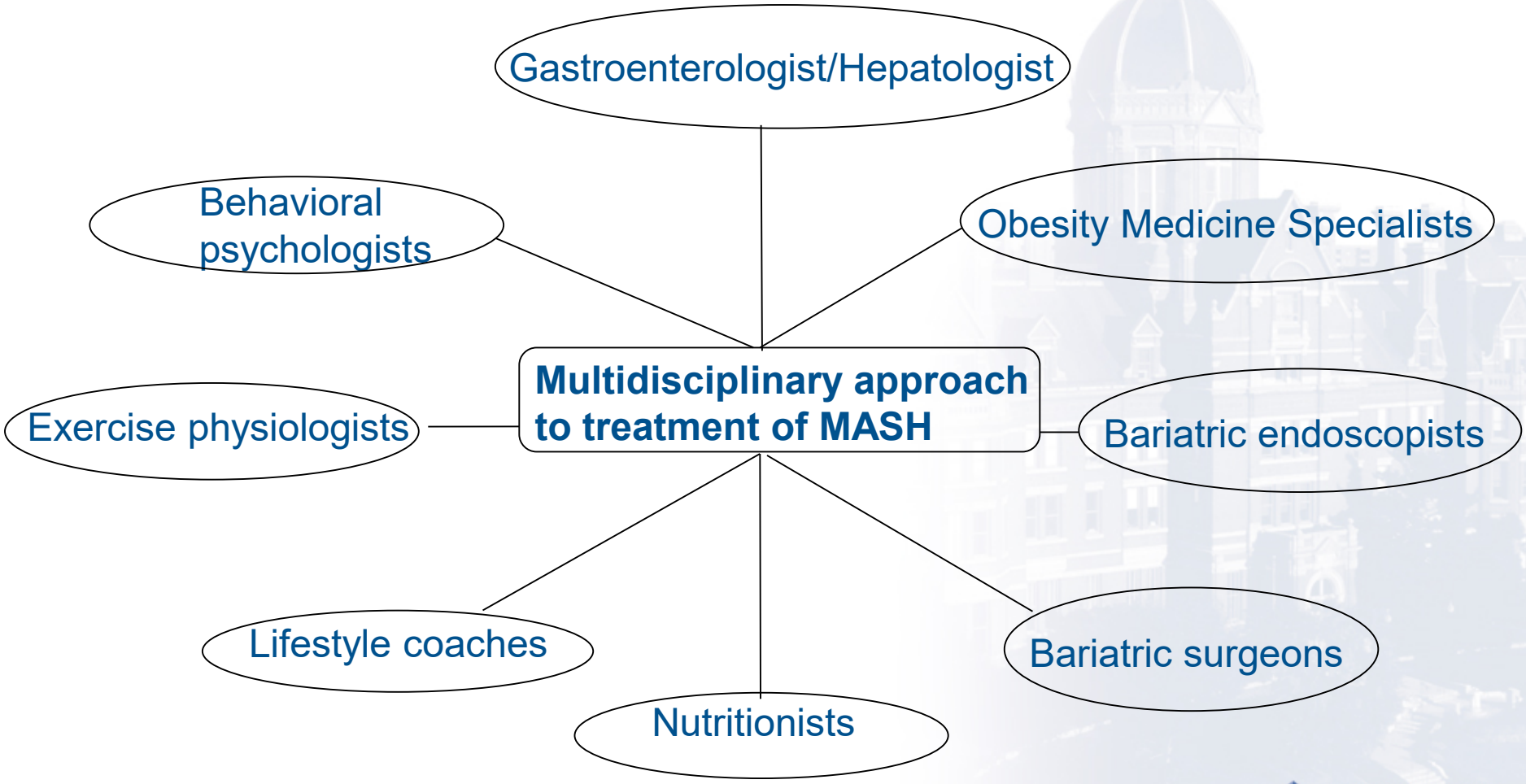

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Current Multidisciplinary Team

Program Director

Kimberly Gudzune, MD, MPH

Obesity Medicine Specialists

Zoobia Chaudhry, MBBS, MD

Selvi Rajagopal, MD, MPH

Larry Cheskin, MD

Craig Hales, MD, MPH

Marci Laudenslager, MD, MHS

Jessica Schwartz, MD,

Hepatologists

James Hamilton, MD

Tinsay Woreta, MD, MPH

Bariatric Surgeons

Michael Schweitzer, MD

Gina Adrales, MD, MPH

Medical Assistants

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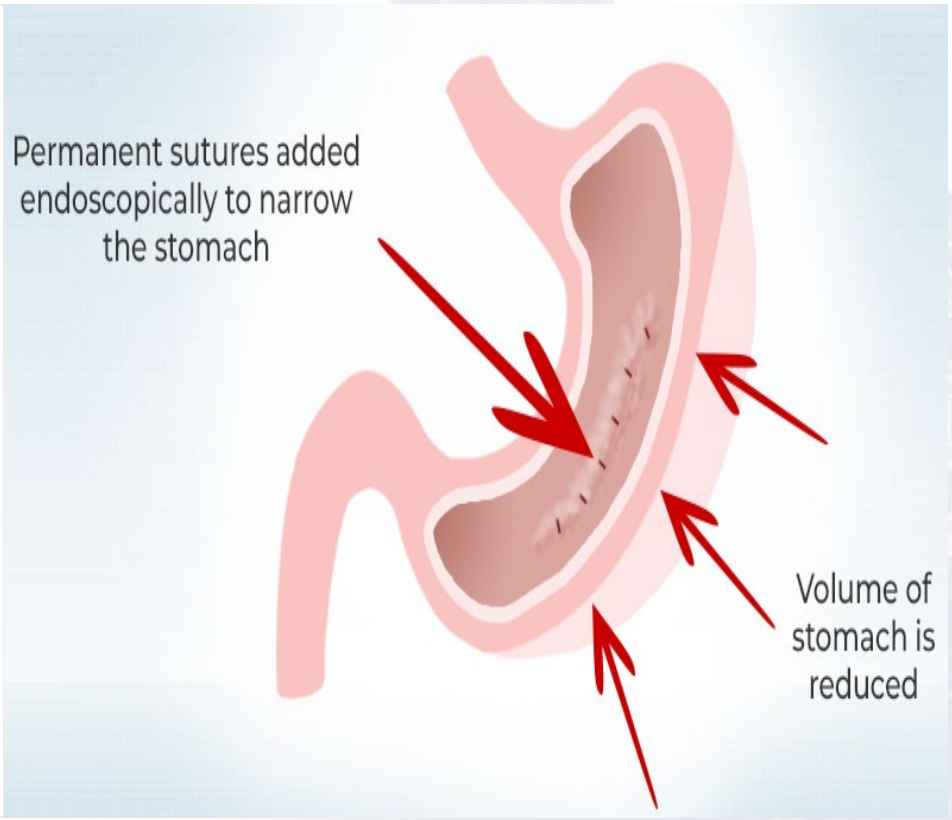
Services provided to assist with weight loss

- 1 hour consultation with detailed history and physical exam
  - Assess for co-morbidities such as obstructive sleep apnea, stress, obesogenic medications
- Intensive lifestyle counseling
- Tracking of diet and physical activity using app (e.g., My Fitness Pal app)
- Basal metabolic rate testing
- Meal replacement
- Pharmacotherapy (e.g., psyllium, phentermine, GLP-1 analogues)
- Visits with obesity medicine physician every 4-6 weeks
- Referral for bariatric endoscopy or surgery

Endoscopic Bariatric Therapies (EBT)

Intragastric balloon (IGB) placement

Endoscopic sleeve gastroplasty (ESG)



- Newer addition to the treatment arsenal for obesity
- Exciting alternative to bariatric surgery as a tool for weight loss that can be performed endoscopically

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Intragastric Balloon Placement Induces Significant Metabolic and Histologic Improvement in Patients With Nonalcoholic Steatohepatitis

Fateh Bazerbachi,[*] Eric J. Vargas,[‡] Monika Rizk,[‡] Daniel B. Maselli,[‡] Taofic Mounajjed,[§] Sudhakar K. Venkatesh,[‖] Kymberly D. Watt,[‡] John D. Port,[‖] Rita Basu,[¶] Andres Acosta,[‡] Ibrahim Hanouneh,[‡] Naveen Gara,[#] Meera Shah,[**] Manpreet Mundi,[**] Matthew Clark,[**] Karen Grothe,[**] Andrew C. Storm,[‡] Michael J. Levy,[‡] and Barham K. Abu Dayyeh[‡]

[*]Division of Gastroenterology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts; [‡]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; [§]Department of Pathology, Mayo Clinic, Rochester, Minnesota; [‖]Department of Radiology, Mayo Clinic, Rochester, Minnesota; [¶]Division of Endocrinology, Department of Medicine, University of Virginia School of Medicine, Charlottesville, Virginia; [#]Gastroenterology and Liver Institute, Escondido, California; and [**]Division of Endocrinology, Mayo Clinic, Rochester, Minnesota

Clinical Gastroenterology and Hepatology 2021;19:146–154

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IGB and NASH

Methods:

- 21 patients with early hepatic fibrosis underwent MRE and endoscopic ultrasound with core liver biopsy collection at the time of IGB placement and removal
- Primary outcome measure: Changes in liver histology parameters after IGB, including change in NAS and fibrosis score

IGB and NASH

Results:

- Six months after IGB, mean total body weight loss was **11.7%**
- Waist circumference decreased by 14.4 cm
- NAS improved in 18 of 20 patients (90%), with a median decrease of 3 points
- Fibrosis improved by 1.17 stages in 15% of patients, and MRE-detected fibrosis improved by 1.5 stages in 10 of 20 patients (50%)
- Half of patients reached endpoints approved by the Food and Drug Administration for NASH resolution and fibrosis improvement

Conclusion: IGB appears to be safe and effective for NASH management when combined with a prescribed diet and exercise program.

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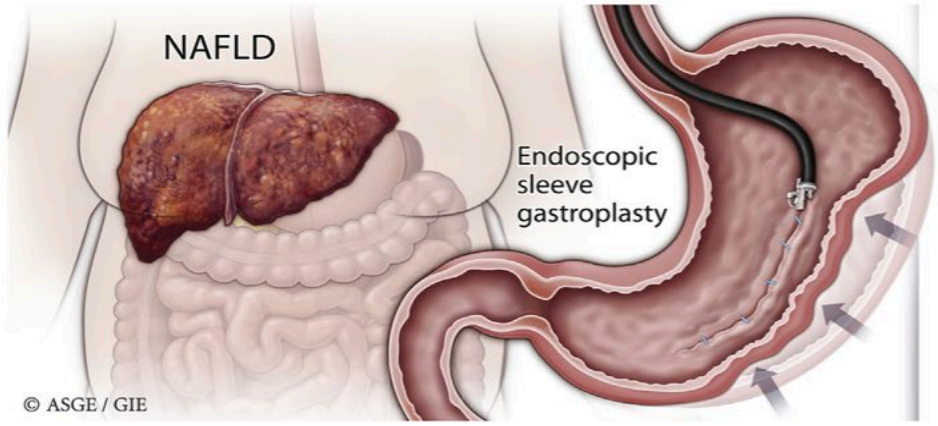
Endoscopic Sleeve Gastroplasty (ESG) and NASH

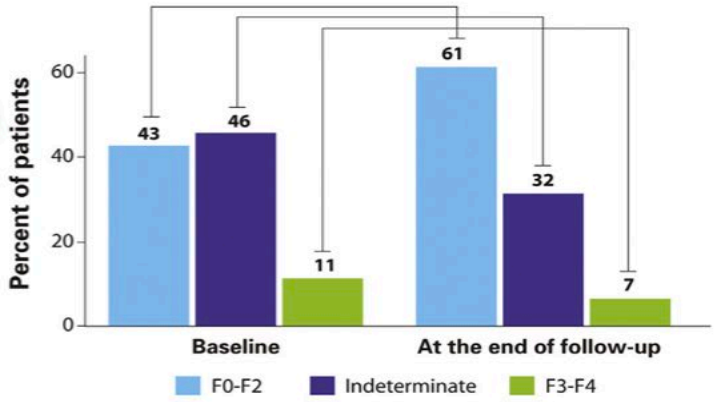
Improvement in insulin resistance and estimated hepatic steatosis and fibrosis after endoscopic sleeve gastroplasty CME

Kaveh Hajifathalian, MD, MPH,[1] Amit Mehta, MD,[1] Bryan Ang, MD,[2] Daniel Skaf, MD,[2] Shawn L. Shah, MD,[1] Monica Saumoy, MD,[3] Qais Dawod, MD,[1] Enad Dawod, MD,[2] Alpana Shukla, MD,[4] Louis Aronne, MD,[4] Robert S. Brown, MD MPH,[1] David E. Cohen, MD PhD,[1] Andrew J. Dannenberg, MD,[5] Brett Fortune, MD,[1] Sonal Kumar, MD,[1] Reem Z. Sharaiha, MD, MSc[1]

New York, New York; Philadelphia, Pennsylvania, USA

GRAPHICAL ABSTRACT





Gastrointest Endosc. 2021 May;93(5):1110-1118

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Endoscopic Sleeve Gastroplasty (ESG)

- 118 patients with obesity and NAFLD underwent ESG and were followed for 2 years
- At 2 years, mean total body weight loss was **15.5%**
- HOMA-IR significantly improved from 6.7±11to 3.0±1.6 after only 1 week from ESG (p=0.019) with continued improvement up to 2 years (p=0.03)
- Hepatic Steatosis Index (HSI) score significantly improved, decreasing by 4 points per year (p value for trend<0.001).
- NAFLD Fibrosis score significantly improved, decreasing by 0.3 point per year (p value for trend=0.034).
- Twenty-four patients (20%) improved their risk of hepatic fibrosis from F3-F4 or indeterminate to F0-F2

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ALCOHOL USE IN MASLD

- Heavy alcohol consumption is a risk factor for chronic liver disease and should be avoided by patients with NAFLD and NASH
  - National Institute for Alcohol Abuse and Alcoholism (NIAAA) defines heavy or at-risk drinking as
    - More than 4 standard drinks on any day or more than 14 drinks per week in men
    - More than 3 drinks on any day or 7 drinks per week in women

- There are insufficient data to make recommendations with regard to nonheavy consumption of alcohol by individuals with NAFLD
  - Counsel patients that no safe threshold for alcohol use has been established

The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance From the American Association for the Study of Liver Diseases, 2018

Pharmacotherapy for MASH

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The role of vitamin E in the Treatment of NASH

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The role of vitamin E in the Treatment of NASH

Vitamin E administered at a daily dose of 800 IU/day improves liver histology in nondiabetic adults with biopsy-proven NASH and therefore may be considered for this patient population.

Risks and benefits should be discussed with each patient before starting therapy.

The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance From the American Association for the Study of Liver Diseases, 2018

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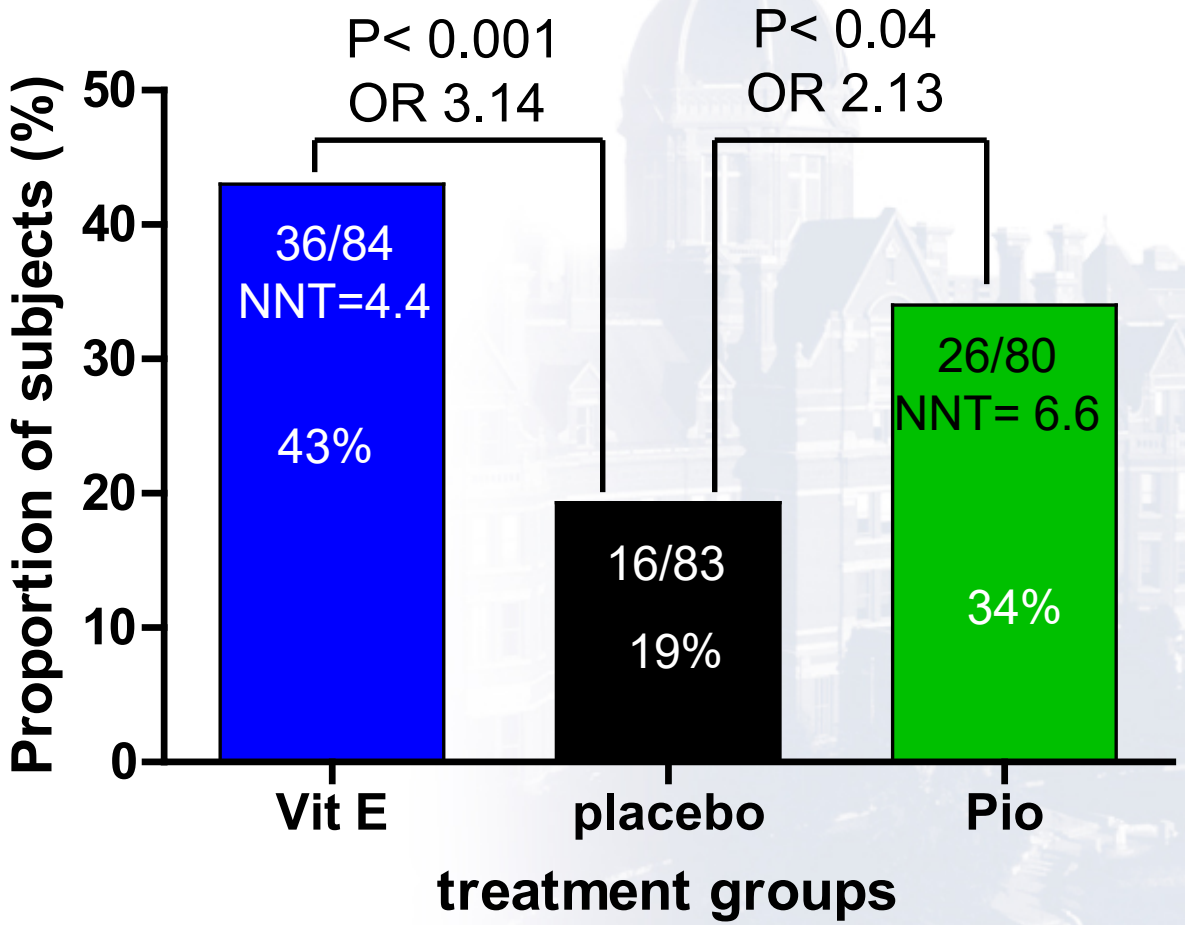
Vitamin E/Pioglitazone: 247 non-diabetic patients with biopsy proven NASH. Biopsied again after 96 weeks

- Primary Endpoint:
  - -2 point NAS reduction (including reduced ballooning)
  - -No worsening of fibrosis
- Only Vitamin E reduced ballooning
- Neither Vitamin E nor Pioglitazone reduced fibrosis

PIVENS trial: Large multicenter RCT in non-diabetic patients with NASH
247 patients randomized to pioglitazone (30 mg/day), vitamin E (800 IU/daily) or placebo for 24 months



Sanyal et al. *NEJM* 2010

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Vitamin E: Summary of data

- Associated with decrease in transaminases
- Improves liver histology in nondiabetic patients with biopsy proven NASH
- No effect on hepatic fibrosis
- Not recommended by AASLD for diabetic patients

Safety concerns

- Vitamin E
  - Increase in all cause mortality at > 800 IU daily (Miller 2005. Bjelakovic 2007)
  - Increase in hemorrhagic stroke (Schwarts 2010)
  - Increase in prostate cancer (Lipmann 2009, Klein 2011)
    - 1.6 per 1000 person years
- Pioglitazone
  - Edema and weight gain (Basu 2006, Sanyal 2010)
  - Osteoporosis (Schwartz 2006)
  - Bladder cancer in some studies (Toccori 2016, Lewis 2015) likely spurious

Use of these agents should be personalized for selected patients after considering the risk benefit ratio

Chalasani et al. *Hepatology* 2017

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CVD most important cause of death in patients with NASH

- NASH patients not at increased risk of DILI from statins
- Meta-analysis of 121,058 patients: 46% lower risk of hepatic decompensation
- Appropriate for patients with increased CVD risk
- Fish oil also useful for hypertriglyceridemia

Chalasani *Hepatology* 2017, Kim *CGH* 2017

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Coffee

- Caffeine - anti-fibrotic effect in all liver diseases (anti-TGF-β)
- Improves liver enzymes in all forms of liver disease
- Reduces all cause mortality
- Reduced risk of HCC in case-control and cohort studies
  - Meta-analysis (14 studies, 2733 HCC)
  - 43% decline in HCC risk
  - Each cup reduced HCC risk by 23%
- Coffee consumption of at least 3 cups daily is associated with less advanced liver disease

Gelatti U et al. J Hepatol 2005, Inoue M, JNCI 2005, Bravi F et al. Hepatology 2009
Saab S et al. Liv Int 2014

What's on the horizon?

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Phase 3 Clinical Trials:

Promising novel agents with anti-inflammatory, anti-fibrotic, or insulin sensitizing properties

Compound	MOA	Trial	Endpoint
Obeticholic acid	**FXR Agonist**	**REGENERATE** **REVERSE**	**Improvement in fibrosis** **Resolution of NASH**
Semaglutide	**GLP-1 Agonist**	Research Study on Whether Semaglutide Works in People With Non-alcoholic Steatohepatitis (ESSENCE)	**Improvement in fibrosis** **Resolution of NASH**

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Obeticholic Acid (OCA): Phase 2 Clinical Trial

Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial

*Brent A Neuschwander-Tetri, Rohit Loomba, Arun J Sanyal, Joel E Lavine, Mark L Van Natta, Manal F Abdelmalek, Naga Chalasani, Srinivasan Dasarathy, Anna Mae Diehl, Bilal Hameed, Kris V Kowdley, Arthur McCullough, Norah Terrault, Jeanne M Clark, James Tonascia, Elizabeth M Brunt, David E Kleiner, Edward Doo, for the NASH Clinical Research Network**

- Phase 2 study
- 141 patients received 25 mg of OCA daily for 72 weeks, 142 received placebo
- 45% of 110 patients in the OCA group had improvement in liver histology compared with only 21% of patients receiving placebo

Neuschwander-Teter et al. *Lancet* 2015

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Obeticholic Acid: Phase 3 Clinical Trial (REGENERATE)

Randomized Global Phase 3 Study to Evaluate the Impact on NASH With Fibrosis of Obeticholic Acid Treatment (REGENERATE)

- Estimated enrollment: 2370 participants
- Study dates: September 2015 – October 2022
- 3 Arms: 10 mg OCA daily
  25 mg OCA daily
  Placebo
- Primary endpoints include:
  - At least one stage of liver fibrosis improvement with no worsening of NASH
  - NASH resolution with no worsening of liver fibrosis

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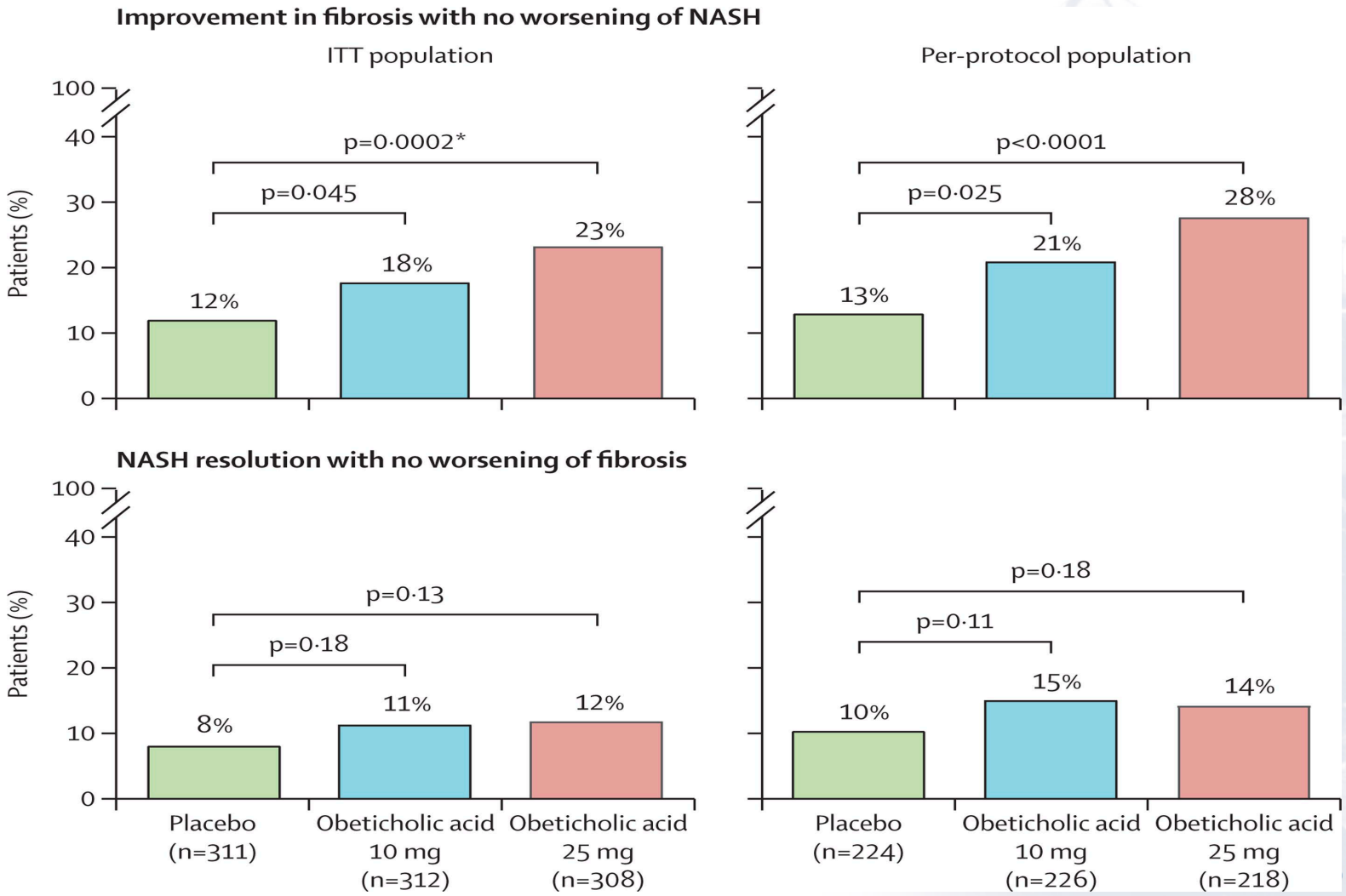
Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial



Safety and Tolerability

- Adverse events were mild to moderate in severity and the most common were consistent with the known profile of OCA
- Most common adverse event: **Dose-related pruritus** (19% in placebo, 28% in OCA 10 mg and 51% in OCA 25 mg).
- OCA treatment was associated with an **increase in LDL cholesterol**
  - Peak increase of 22.6 mg/dL at 4 weeks
  - Subsequently reversing and approaching baseline at month 18 (4.0 mg/dL increase from baseline).
- Triglycerides rapidly and continually decreased in the OCA treatment arms through month 18.
- More patients (3%) on OCA 25 mg experienced gallstones or cholecystitis compared to <1% on placebo and 1% on OCA 10 mg.

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FDA panel votes against obeticholic acid approval for NASH due to unfavorable benefit-risk profile

- FDA panel voted 12-2 against approval for obeticholic acid for pre-cirrhotic patients with liver fibrosis due to MASH
- Advisors reported a “concerning” benefit-risk profile for obeticholic acid

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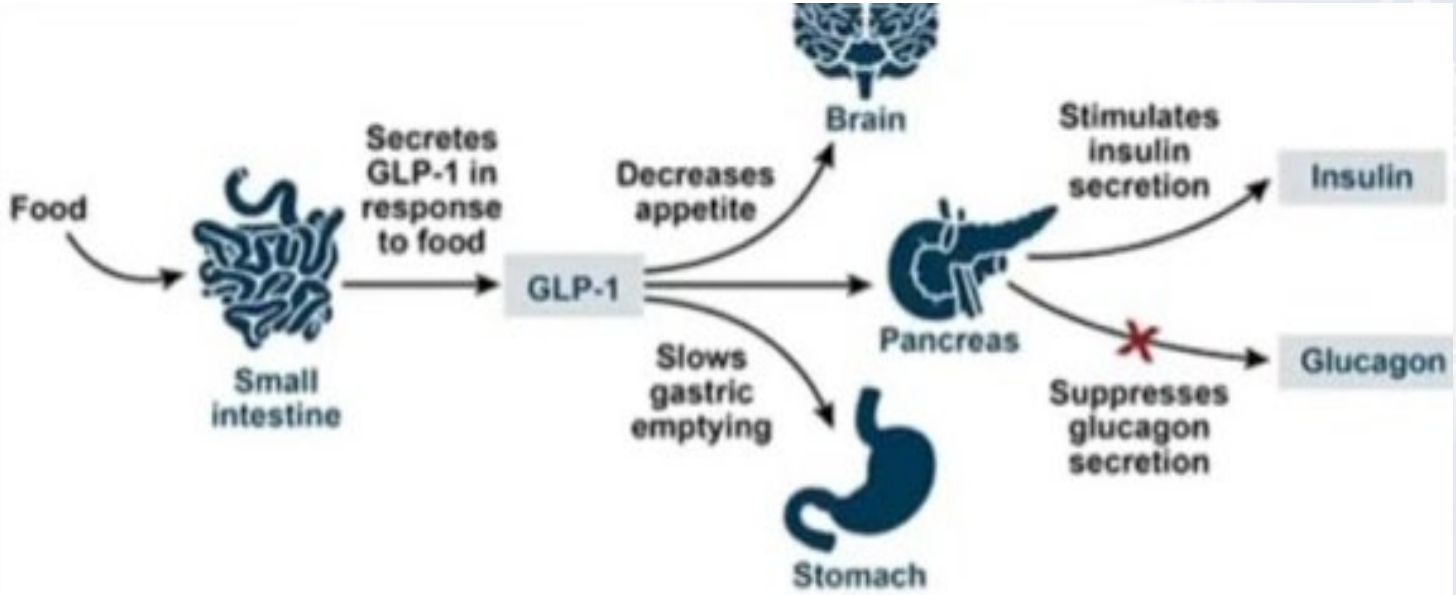
Phase 2 Clinical Trials

- Glucagon-like peptide-1 (GLP-1) receptor agonist **semaglutide**
- Approved for the treatment of Type 2 diabetes and weight management (as of June 2021)
- Induces weight loss and improves glycemic control in patients with obesity and Type 2 diabetes

Semaglutide: Mechanism of Action

- A long-acting Glucagon-like peptide-1 (GLP-1) analogue that mimics the effects of native GLP-1
- Promotes weight loss by reducing energy intake, increasing satiety, and reducing hunger, and enhancing glycemic control



- **Semaglutide significantly reduced ALT in clinical trials in subjects with obesity and/or type 2 diabetes**

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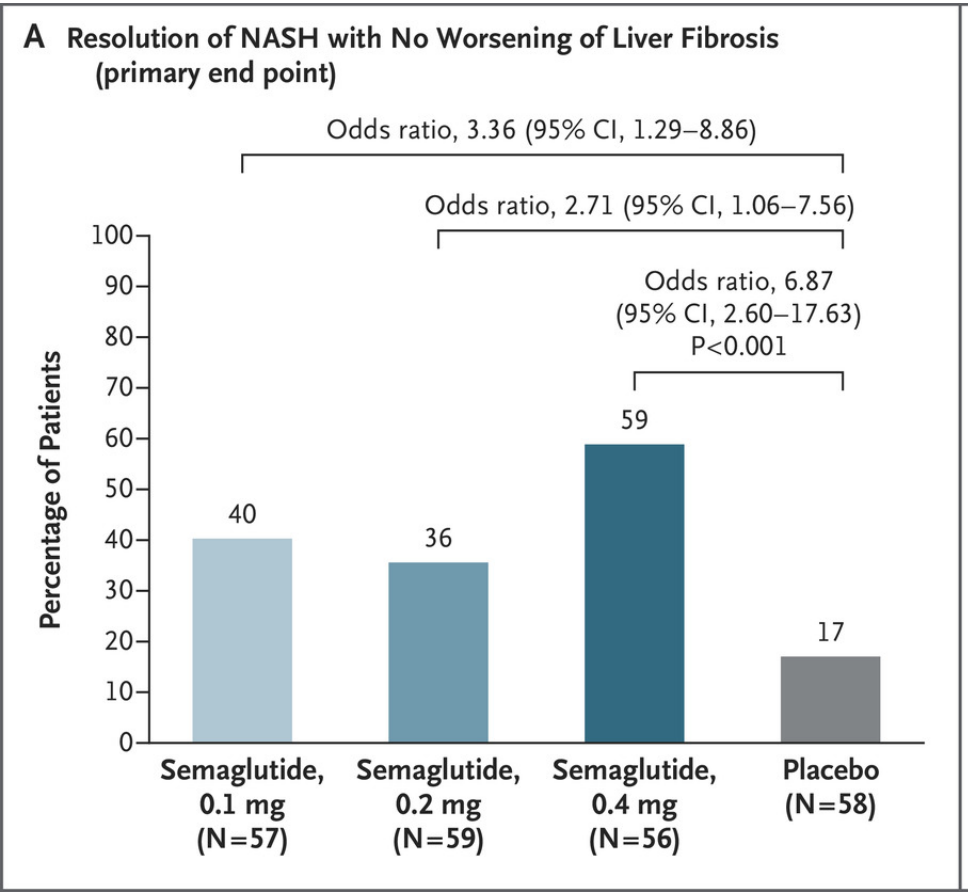
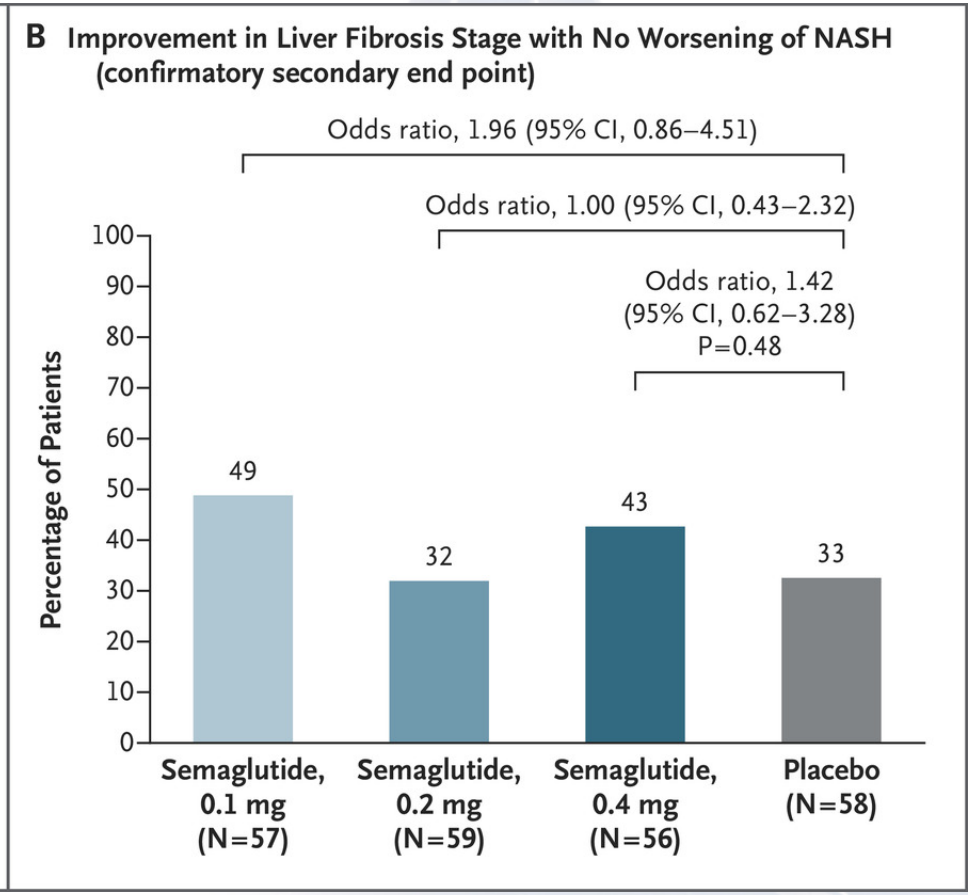
A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis (N = 320)

Phase 2 trial – Treatment with semaglutide resulted in a significantly higher percentage of patients with NASH resolution than placebo





Newsome et al. *N Engl J Med* 2020.

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Semaglutide in NASH

- Mean percent weight loss: 13% in the 0.4 mg group vs. 1% in placebo group

- Safety:
  - Most common adverse events: Gastrointestinal disorders
    - Incidence of nausea, constipation, and vomiting higher in 0.4 mg group compared to placebo group
  - Malignant neoplasms reported in 3 patients who received semaglutide (1%) vs. 0 in placebo group
  - Overall neoplasms reported in 15% of patients who received semaglutide vs. 8% in placebo group

- Phase 3 trials initiated

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Tirzapetide

- A novel glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist
- In **May 2022**, the FDA approved tirzepatide (Mounjaro) for the treatment of Type 2 diabetes in adults and in November 2023 for **overweight/obesity**

ORIGINAL ARTICLE

Tirzepatide Once Weekly for the Treatment of Obesity

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- Lilly receives U.S. FDA Fast Track designation for tirzepatide for the treatment of adults with obesity, or overweight with weight-related comorbidities

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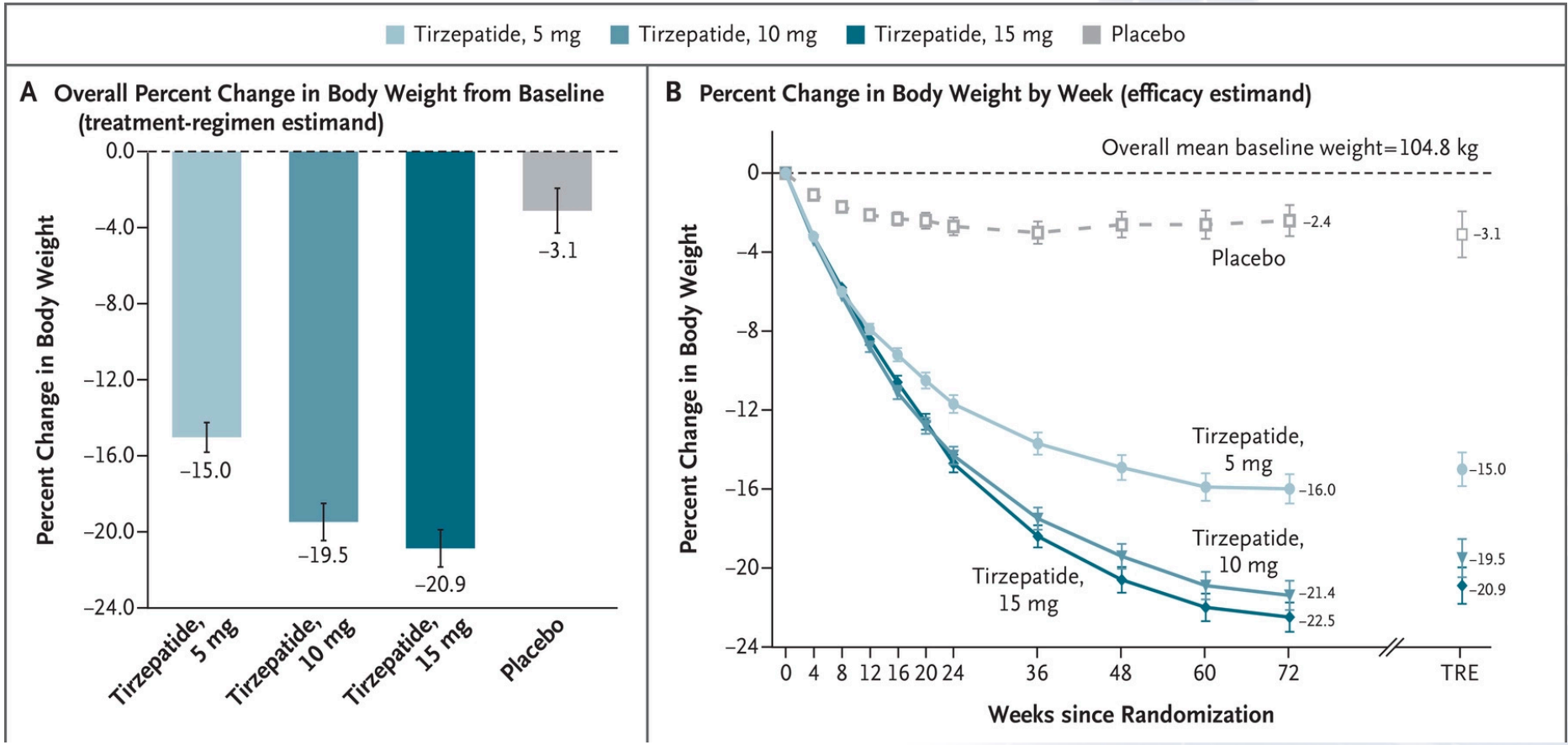
Tirzapetide



Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial

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Summary

Background Tirzepatide is a novel dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 receptor agonist under development for the treatment of type 2 diabetes. The aim of this substudy was to characterise the changes in liver fat content (LFC), volume of visceral adipose tissue (VAT), and abdominal subcutaneous adipose tissue (ASAT) in response to tirzepatide or insulin degludec in a subpopulation of the SURPASS-3 study.

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- From an overall mean baseline liver fat content (LFC) of 15·71% (SD 8·93), the absolute reduction in LFC at week 52 was significantly greater for the pooled tirzepatide 10 mg and 15 mg groups **(–8·09%,** SE 0·57) versus the insulin degludec group (**–3·38**%, 0·83)

- The estimated treatment difference versus insulin degludec was –4·71% (95% CI –6·72 to –2·70; p<0·0001)

- The reduction in LFC was significantly correlated with reductions in visceral adipose tissue, abdominal subcutaneous adipose tissue, and body weight in the tirzepatide groups

Summary

- The MASLD epidemic is being driven by the rise in obesity prevalence
- New nomenclature is less stigmatizing and exclusionary
- Screening for clinically significant fibrosis recommended for high-risk populations (Type 2 diabetes mellitus, obesity with metabolic complications, family history of cirrhosis, and significant alcohol use)
- FIB-4 recommended for primary risk assessment followed by secondary risk assessment with FibroScan if FIB-4 ≥ 1.3

Summary

- Mainstay of treatment is currently still lifestyle intervention (Mediterranean diet and exercise) to achieve weight loss
- Need for more innovative approaches to help patients achieve weight loss
  - **Multidisciplinary approach** may increase rates of success with weight loss
  - **Endoscopic bariatric therapies** (IGB and ESG) appear to be promising treatments for NASH
- Reducing CVD risk profiles is important
  - statins, fish oil, diabetic control
- Vitamin E can improve steatohepatitis but no effect on liver fibrosis
- Promising novel agents with anti-inflammatory, anti-fibrotic or insulin sensitizing properties are in Phase 3 clinical trials
  - **Obeticholic acid -> FDA voted against approval**
  - **GLP-1 receptor agonists (semaglutide)**

Thank you

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Questions?

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