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Non-Alcoholic Fatty Liver Disease:

Diagnosis and Treatment in 2023

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Disclosures

I have no financial disclosures related to the contents of this presentation

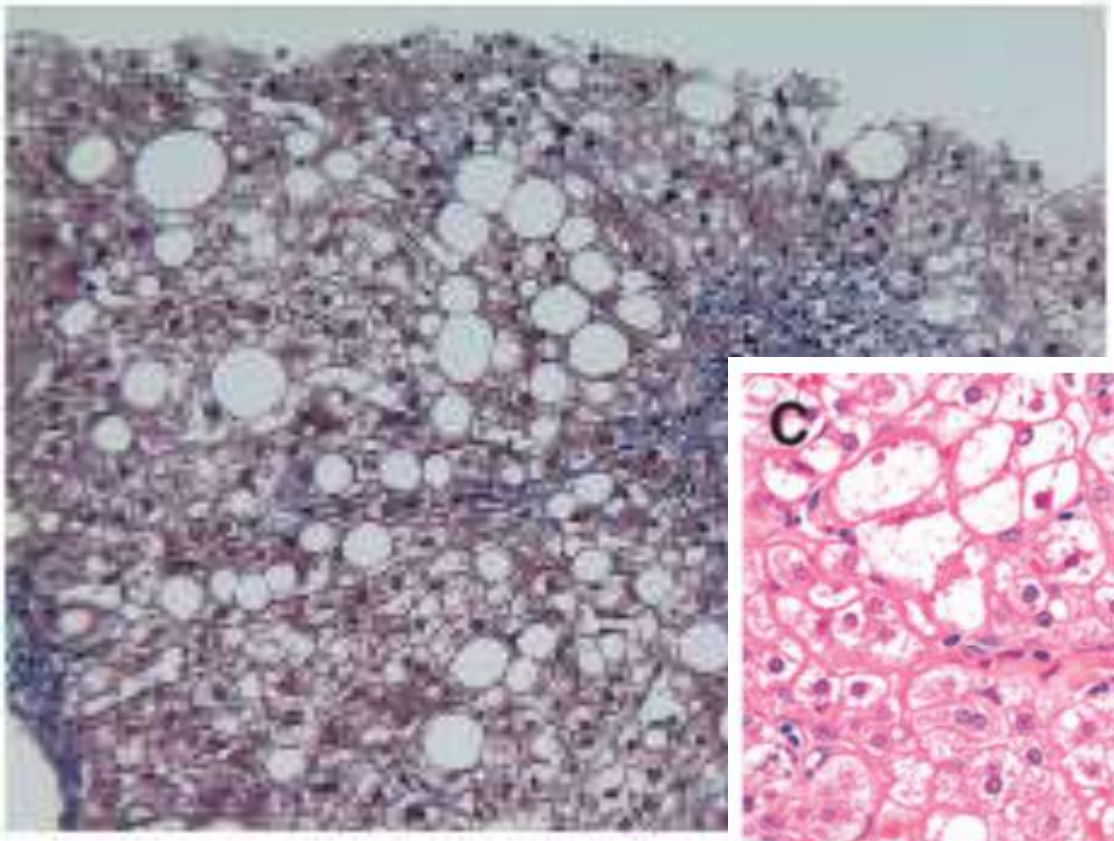
DEFINITIONS

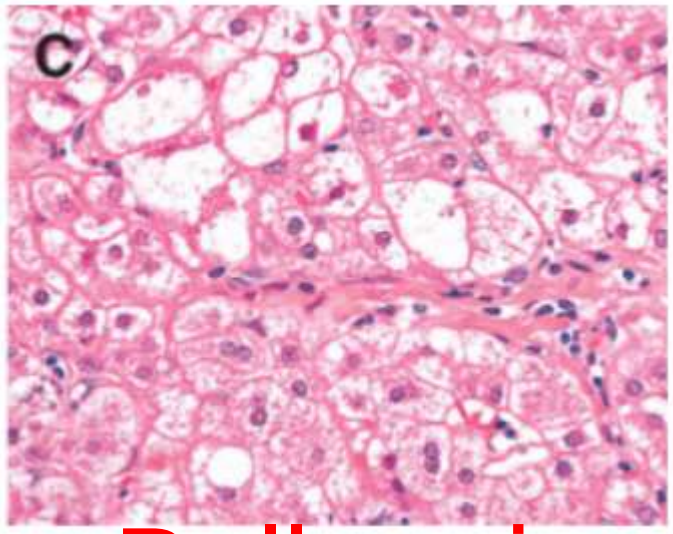
Non-alcoholic fatty liver disease (NAFLD)	• Includes all grades and stages • 5% or more hepatocytes with evidence of macrovesicular steatosis • Alcohol intake less than 20 g/day (women) 30 g/day (men) • Rule out alternative causes of steatosis
Non-alcoholic fatty liver (NAFL)	• Macrovesicular steatosis +/- mild inflammation

Non-alcoholic steatohepatitis (NASH)	• NAFLD plus:
	  • Inflammation
	  • Ballooning (cellular injury)
	  • +/- Fibrosis

Rinella et al. AASLD Practice Guidance on the Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease. *Hepatology.* 2023

Histology





Ballooning

Brunt, E. Histological assessment of nonalcoholic fatty liver disease in adults and children. Clin Liv Dis 2012.
Kleiner et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005.

TABLE 1. Common Causes of Secondary HS

Macrovesicular steatosis
- Excessive alcohol consumption
- Hepatitis C (genotype 3)
- WD
- Lipodystrophy
- Starvation
- Parenteral nutrition
- Abetalipoproteinemia
- Medications (e.g., mipomersen, lomitapide, amiodarone, methotrexate, tamoxifen, corticosteroids)

Microvesicular steatosis
- Reye's syndrome
- Medications (valproate, antiretroviral medicines)
- Acute fatty liver of pregnancy
- HELLP syndrome
- Inborn errors of metabolism (e.g., lecithin-cholesterol acyltransferase deficiency, cholesterol ester storage disease, Wolman's disease)

Chalasani et al. Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance and Guidelines From the American Association for the Study of Liver Diseases. *Hepatology.* 2018

Histologic Patterns: Drug-induced steatosis

	Hepatic Steatosis	Steatohepatitis
5-FU	X	
Amiodarone	X	X
Irinotecan		X
Tamoxifen	X	X
Methotrexate	X	X
Corticosteroids	X	

Rinella et al. AASLD Practice Guidance on the Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease. *Hepatology.* 2023

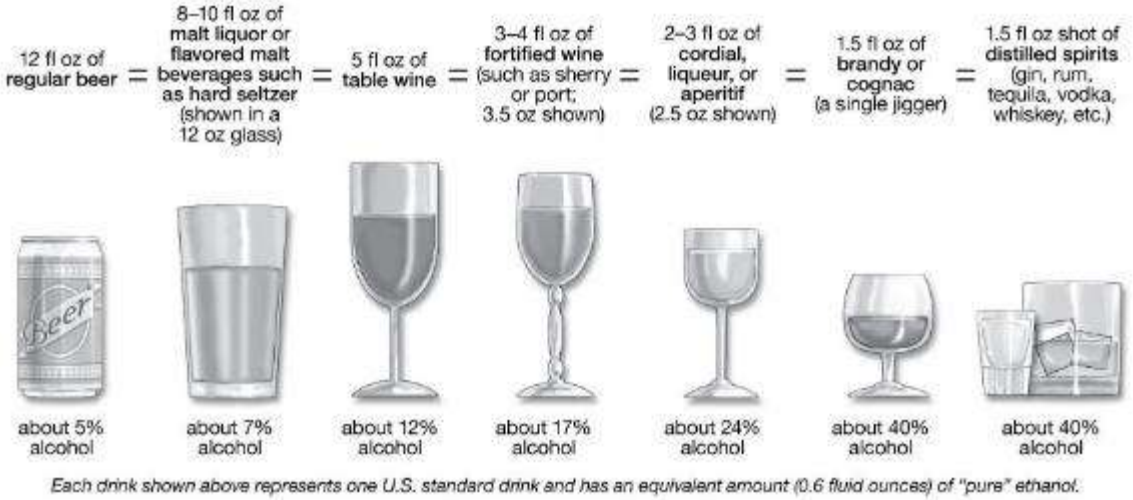
Alcohol consumption

- Alcohol intake contributes for fatty liver disease progression
- Variability in individual susceptibility related to alcohol

	Mild intake	Moderate intake	Heavy intake
Men	Up to 30 g/day	31-59 g/day	60 g/day or more
Women	Up to 20 g/day	21-39 g/day	40 g/day or more

Lower odds of NASH Resolution

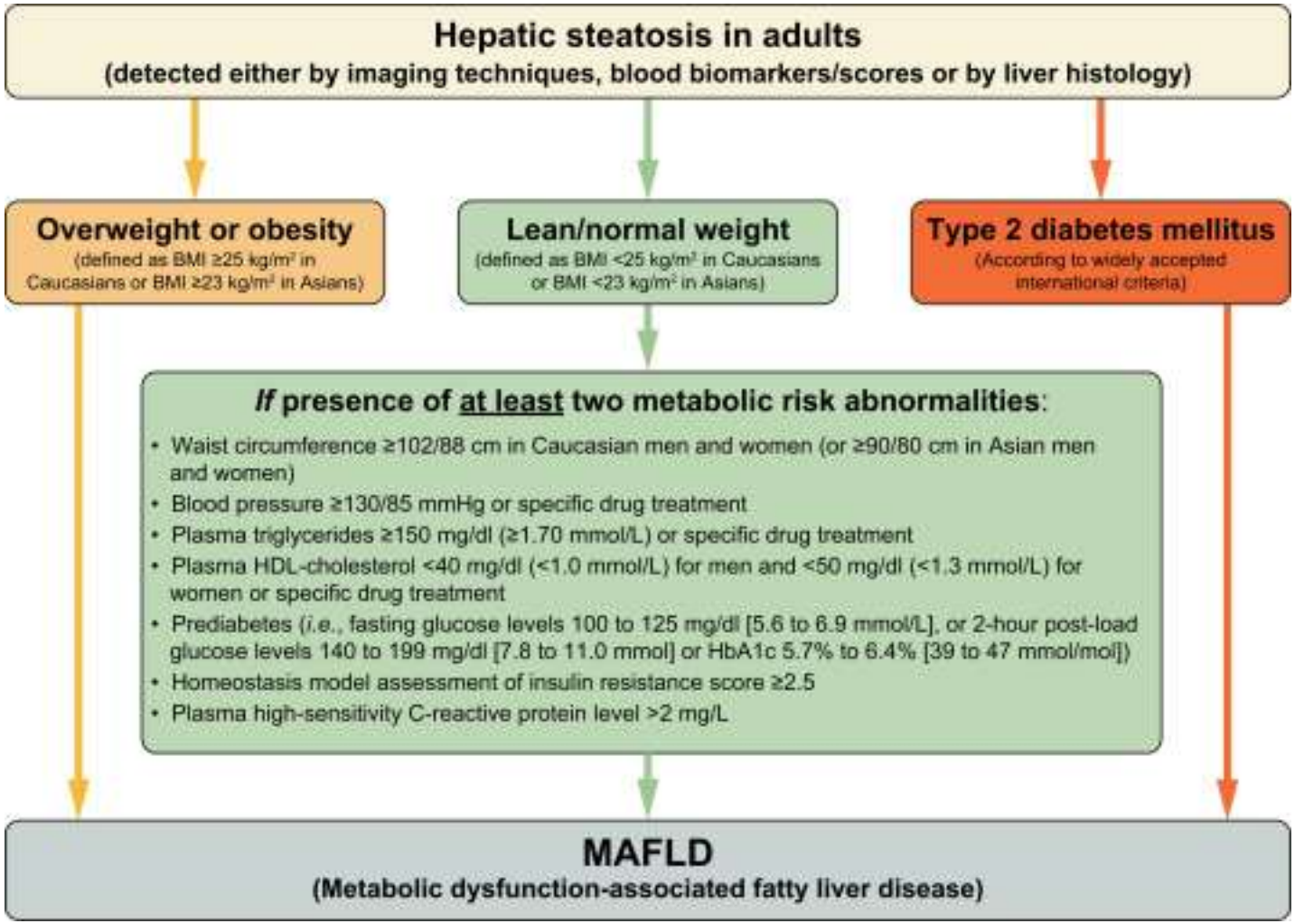
Fibrosis Progression



One standard drink
= 14 g of alcohol

1. https://www.niaaa.nih.gov/sites/default/files/standard-Drink-June2022.jpeg
2. Rinella et al. AASLD Practice Guidance on the Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease. *Hepatology.* 2023

Newer Definition: MAFLD



Eslam et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *JHep.* 2020

New Terminology: NAFLD to **MAFLD**

- Old terminology is based on focus of excluding other causes of liver disease including **excess alcohol intake**

- We now have better understanding of the pathophysiology of this class of liver disease – hepatic dysfunction as part of the spectrum of systemic metabolic dysfunction

- Shift from negative criteria to identifying positive criteria in making a diagnosis of **Metabolic dysfunction associated fatty liver disease (MAFLD)**

- Terminology that is based on a definition that is independent of other diseases

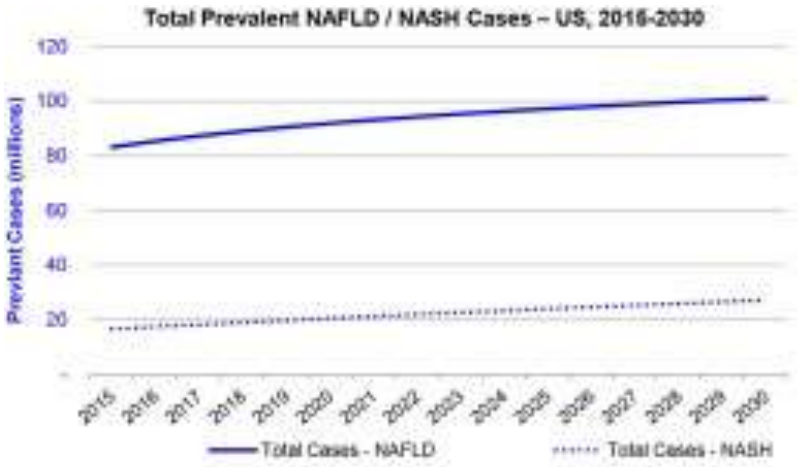
Global NAFLD Prevalence

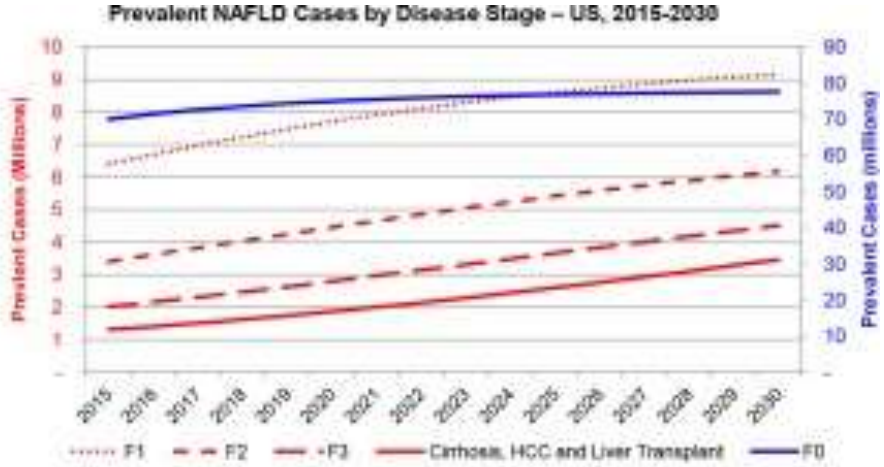
Table 1. NAFLD Prevalence Stratified by Region

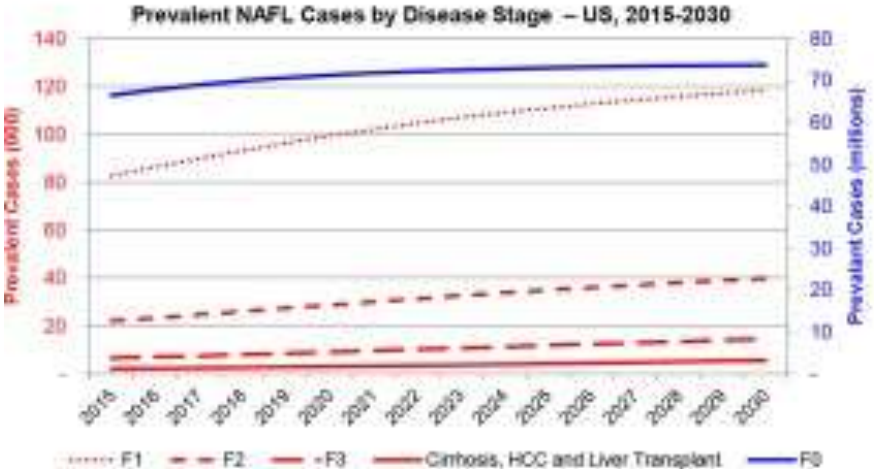
Region	N	Prevalence (%)	95% CI (%)	I^2 (%)
Africa	2	13.48	(5.69-28.69)	84.37
Asia	14	27.37	(23.29-31.88)	99.17
Europe	11	23.71	(16.12-33.45)	98.78
Middle East	3	31.79	(13.48-58.23)	99.14
North America	13	24.13	(19.73-29.15)	99.19
South America	2	30.45	(22.74-39.44)	69.10
Overall	45	25.24	(22.1-28.65)	99.07

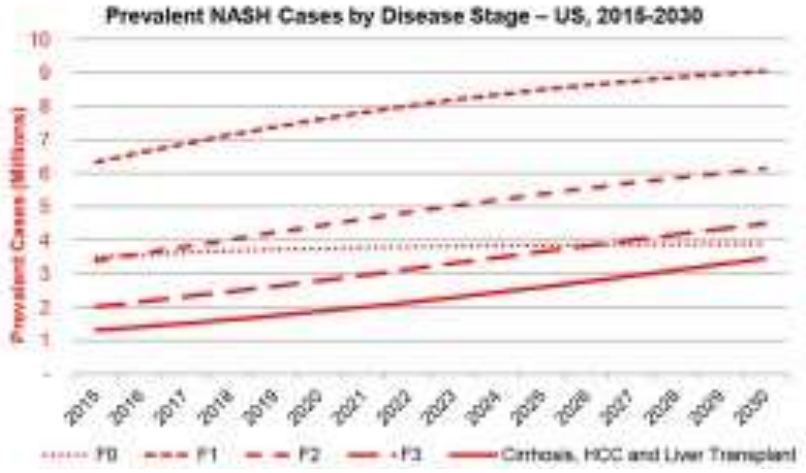
Younossi, Z.M., Koenig, A.B., Abdelatif, D., Fazel, Y., Henry, L. and Wymer, M. (2016),
Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes.
Hepatology, 64: 73-84. https://doi.org/10.1002/hep.28431

Excepted exponential increase in NAFLD disease burden



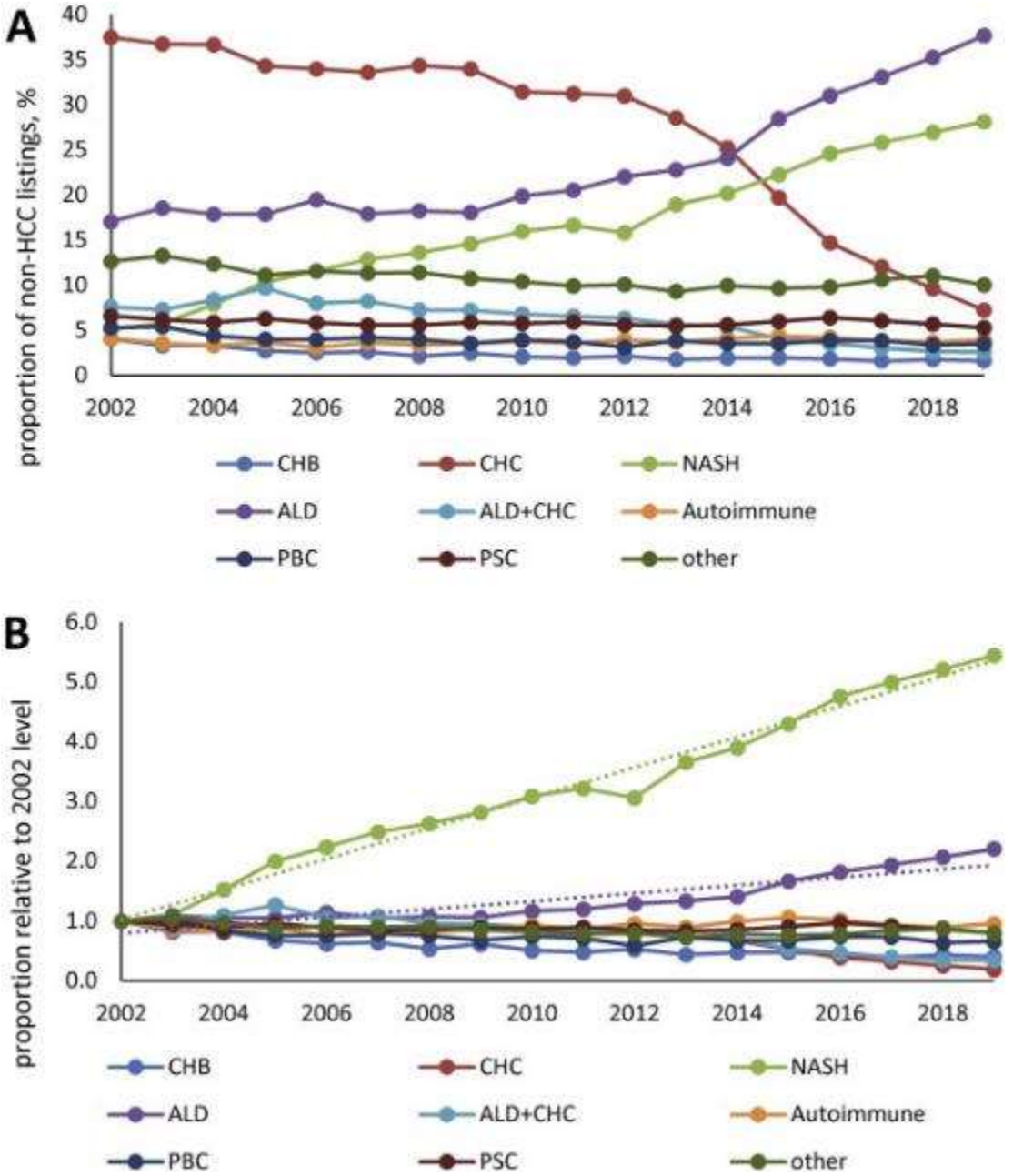






Estes et al. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology.* 2018

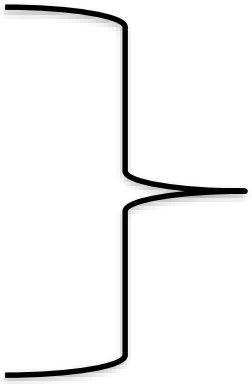
Trends in etiologies of chronic liver disease amongst non-HCC waitlisted patients



Younossi et al. Nonalcoholic Steatohepatitis is the most rapidly increasing indication for liver transplantation in the United States. *CGH.* 2021

Risk Factors and Associations

- Risk Factors
  - **Obesity**
  - **Type 2 Diabetes Mellitus**
  - Dyslipidemia
  - Hypertension



- **Metabolic syndrome**
- **INSULIN RESISTANCE**

- Associated Diseases
  - Cardiovascular disease (most common cause of mortality)
  - Hypothyroidism
  - Obstructive Sleep Apnea
  - GH Deficiency
  - Polycystic Ovarian Syndrome

Chalasani et al. Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance and Guidelines From the American Association for the Study of Liver Diseases. *Hepatology.* 2018

Obesity and NAFLD

- Body fat distribution affects the role of obesity in NAFLD
  - Visceral fat > subcutaneous fat
  - Android body fat distribution > gynoid body fat distribution

- Android body fat distribution
  - Increased truncal subcutaneous fat and visceral fat
  - Associated with (regardless of BMI):
    - Cardiovascular disease
    - Insulin resistance
    - Hepatic fibrosis

- Gynoid body fat distribution
  - Subcutaneous fat in the hip and buttocks
  - Protective against NAFLD

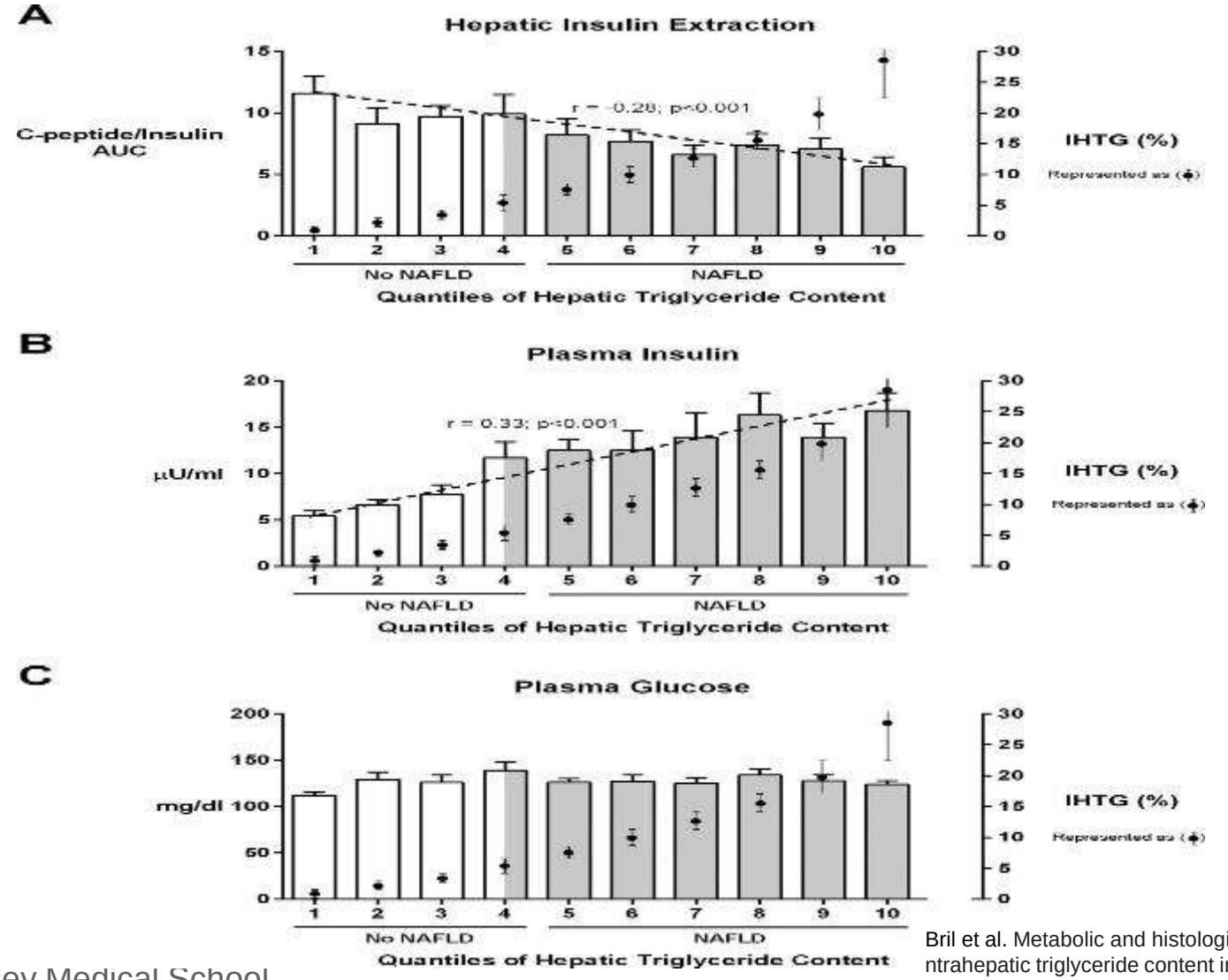
Rinella et al. AASLD Practice Guidance on the Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease. *Hepatology.* 2023

Type 2 Diabetes and NAFLD

- NAFLD is associated with a 2- to 5-fold increase risk for Type 2 Diabetes
  - Screening for type 2 diabetes should be completed at NAFLD diagnosis
- Type 2 diabetes patients have a 30% to 75% prevalence of NAFLD
- Type 2 diabetes is the **strongest risk factors for:**
  - **NAFLD**
  - **Hepatic Fibrosis**
  - **HCC**

Rinella et al. AASLD Practice Guidance on the Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease. *Hepatology.* 2023

Insulin resistance contributes to NAFLD



Bril et al. Metabolic and histological implications of I ntrahepatic triglyceride content in nonalcoholic fatty liver Disease *Hepatology.* 2016

Why Does Hepatic Fibrosis Matter?

- Reflective of disease chronicity
- Identifies those at risk for hepatocellular carcinoma and in need for screening
- Predicts risk of future liver related decompensation
- Predicts risk prior to invasive procedures/surgery
- Hepatic fibrosis is dynamic with possibility of improvement
- **Identifies those at increased risk for liver related mortality**

Need to identify “at risk” NASH = NASH + at least stage 2 fibrosis

Who should be screening for significant fibrosis?

- Type 2 diabetes patient (6-9% fibrosis prevalence)
- Significant alcohol use (17% fibrosis prevalence)
- Family history of cirrhosis (18% fibrosis prevalence)
- Obesity + metabolic complications (4-33%)

Rinella et al. AASLD Practice Guidance on the Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease. *Hepatology.* 2023

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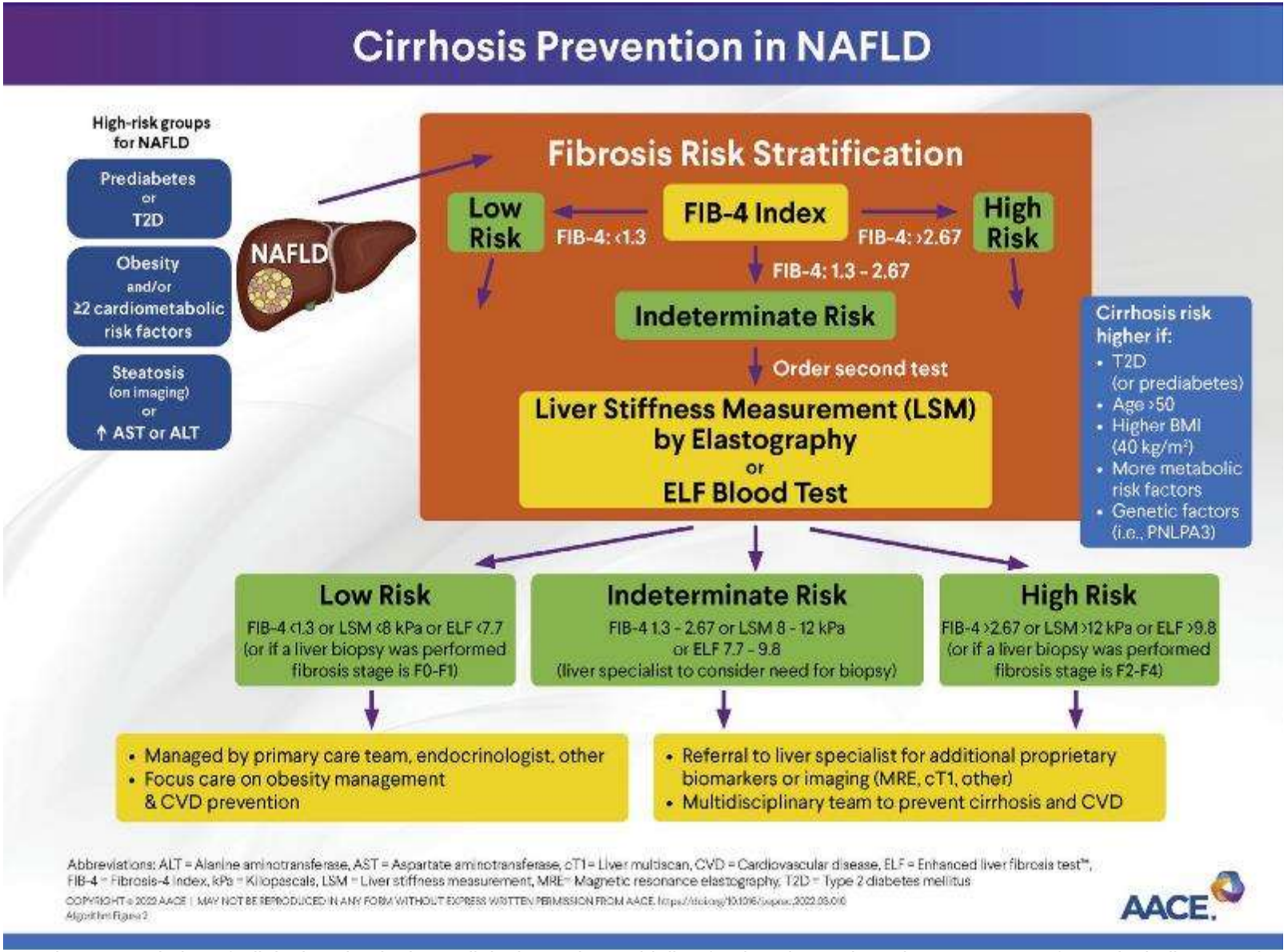


Cusi et al. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings. Endocrine Practice. 2022

Diagnostic considerations: Gastroenterologist & Hepatologist

- Correctly identified “at-risk” NASH or the presence of advanced fibrosis

- Indeterminate NIT or not consistent with clinical presentation
  - MR elastography

- Discordance amongst NITs or between NITs and other related workup
  - Liver biopsy

- Assess for a competing or secondary diagnosis
  - Liver biopsy

Non-invasive assessment of hepatic steatosis

- B-mode ultrasound
  - Poor sensitivity for smaller amounts of steatosis
- Controlled attenuation parameter (CAP)
  - Point of care estimation of fat
  - Poor at monitoring changes in hepatic steatosis
- MRI-protein density fat fraction (PDFF)
  - Fat quantification superior to CAP
  - Not readily available and higher costs

US is no longer recommended as a method to detect undiagnosed hepatic steatosis

Non-invasive tests (NIT) for hepatic fibrosis

Serologic (patented and non-patented)

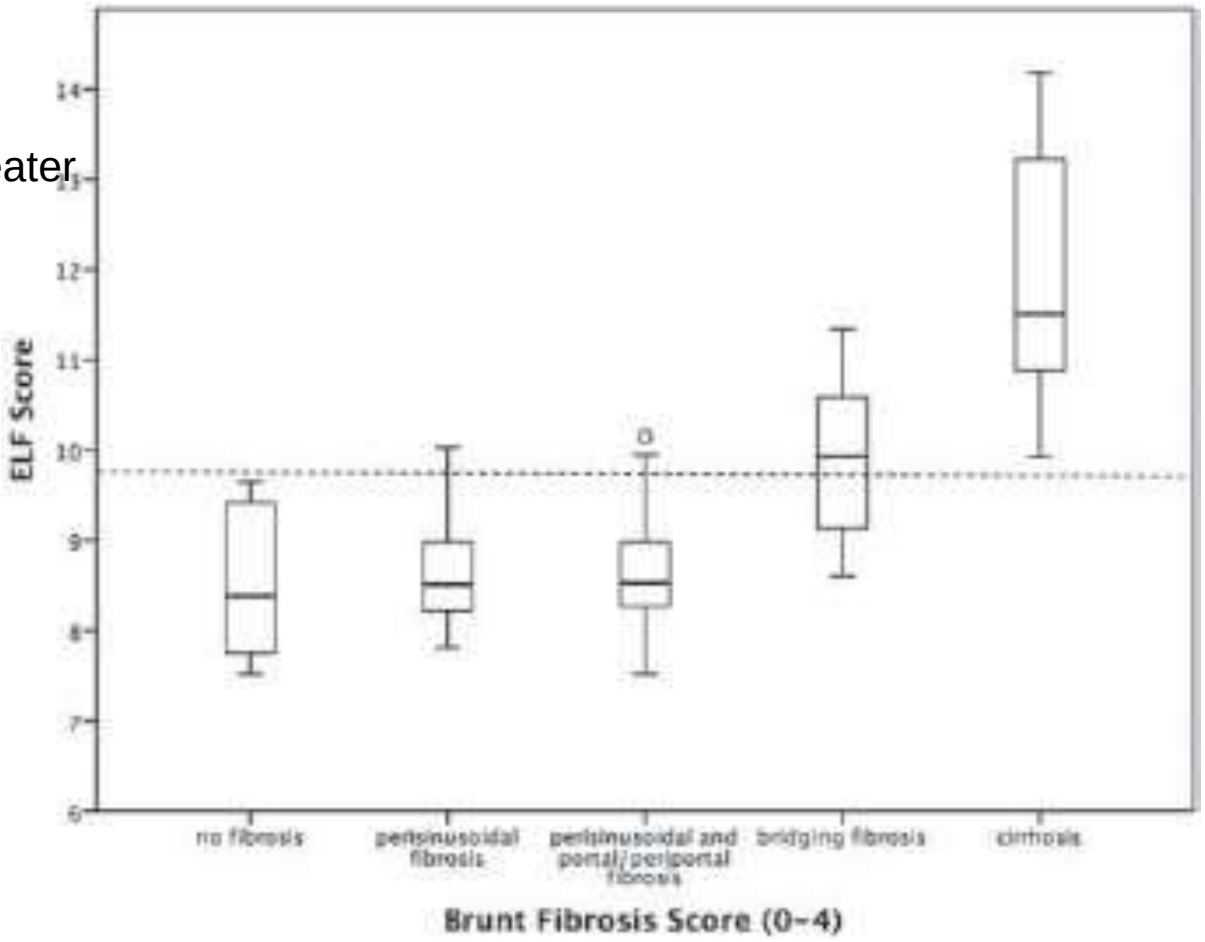
- Panels of indirect markers
- Direct markers

Radiologic Testing

- Transient Elastography (TE)
- Two-dimensional shear wave elastography (2D-SWE)
- Acoustic radiation force impulse (AFRI) imaging
- Magnetic Resonance Elastography (MRE)

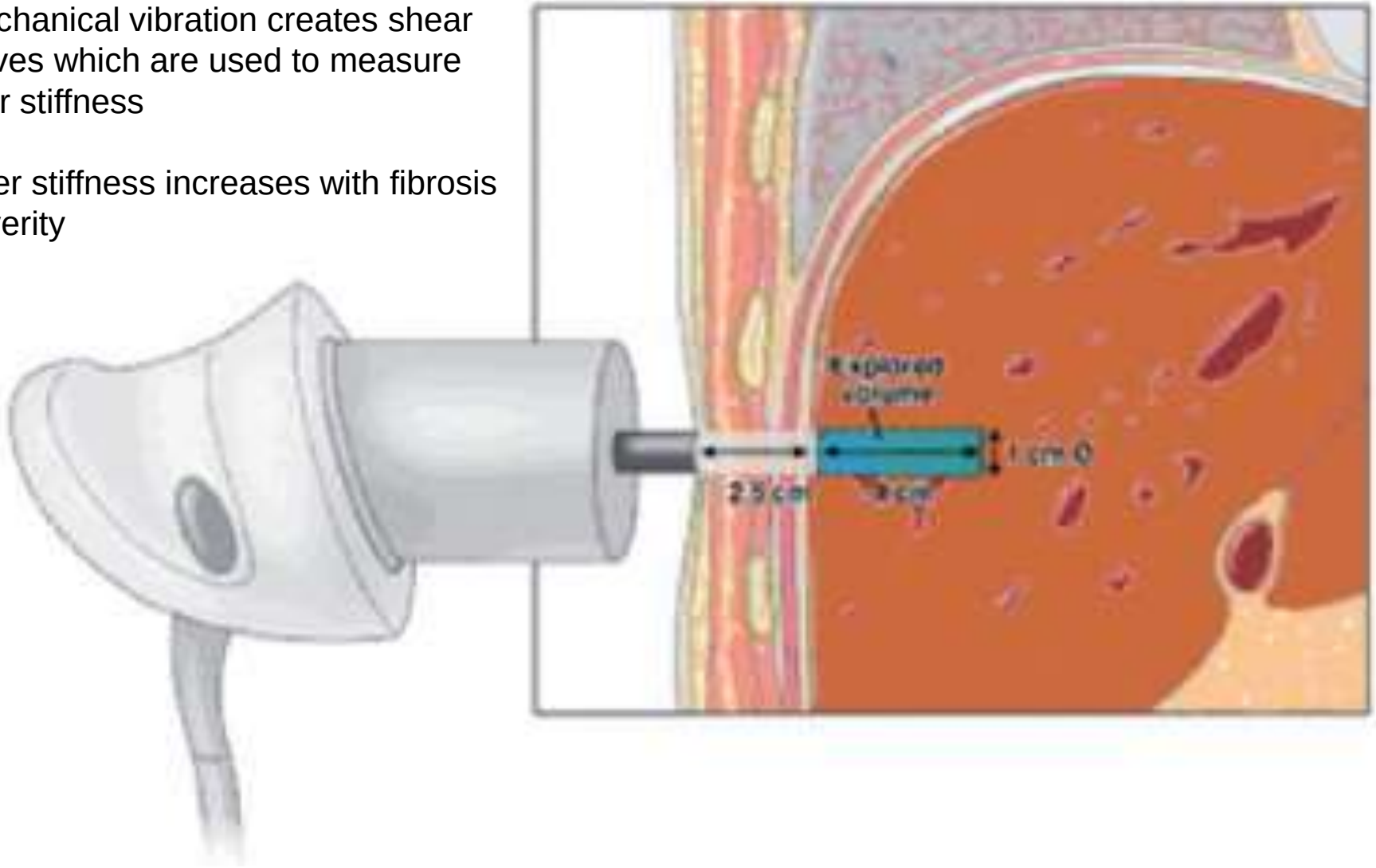
ELF: Proprietary blood test to assess for fibrosis

- Manufacturer Cutoff: 9.8 or greater
- Sensitivity: 86.7%
- Specificity: 92.5%
- PPV: 72%
- NPV: 97%
- Consists of three elements involved in matrix turnover



Miele L, De Michele T, Marrone G, et al. Enhanced Liver Fibrosis Test as a Reliable Tool for Assessing Fibrosis in Nonalcoholic Fatty Liver Disease in a Clinical Setting. *The International Journal of Biological Markers*. 2017

- Mechanical vibration creates shear waves which are used to measure liver stiffness
- Liver stiffness increases with fibrosis severity



Ledinghen et al. *Gastroenterologie Clinique et Biologique*. 2008; 32(6): 58-67

Elastography in the diagnosis of NAFLD

- LSM < 8 kPa rules out advanced fibrosis
- LSM between 8 and 12 kPa is associated with fibrotic NASH
- LSM > 12 kPa is associated with advanced fibrosis
- Changes in LSM can predict disease progression

Rinella et al. AASLD Practice Guidance on the Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease. *Hepatology.* 2023

Pearls: NAFLD Diagnosis

- Assess for secondary causes of steatosis including a careful assessment of alcohol intake
- Assess for risk factors for NAFLD to help determine risk for NASH and fibrosis
- ”At risk” NASH should be identified during diagnostic workup
  - NASH + stage 2 fibrosis (F2)
- ”At risk” patients should be screened for fibrosis using FIB-4 first
  - Secondary screening for intermediate or high-risk patients using VCTE
- ”At risk” patients should be referred to a specialist

Diagnostic highlights from the updated AASLD guidance document

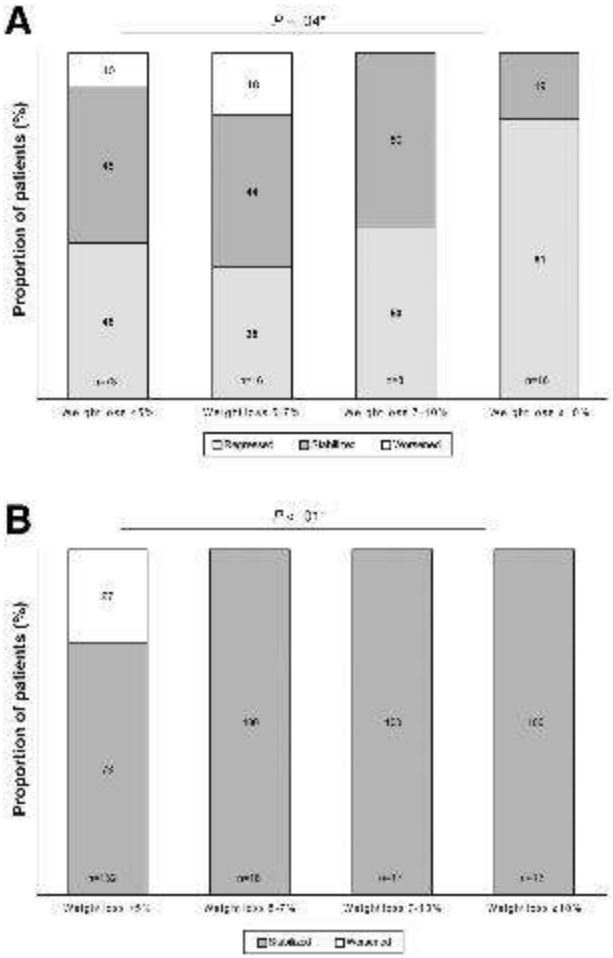
- General population-based screening for NAFLD is not advised
- All patients with hepatic steatosis or clinically suspected NAFLD based on the presence of obesity and metabolic risk factors should undergo primary risk assessment with FIB-4
- High-risk individuals, such as those with type 2 diabetes, medically complicated obesity, family history of cirrhosis, or more than mild alcohol consumption should be screened for advanced fibrosis.
- In patients with pre-DM, type DM or more metabolic risk factors (or imaging evidence of hepatic steatosis), primary risk assessment with FIB-4 should be repeated every 1-2 years

Rinella et al. AASLD Practice Guidance on the Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease. *Hepatology.* 2023

	LOW RISK FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1	INDETERMINATE RISK FIB-4 1.3 - 2.67 and/or LSM 8 - 12 kPa and liver biopsy not available	HIGH RISK[1] FIB-4 > 2.67 or LSM > 12 kPa or 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 May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Yes 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. Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. *Gastroenterology.* 2021

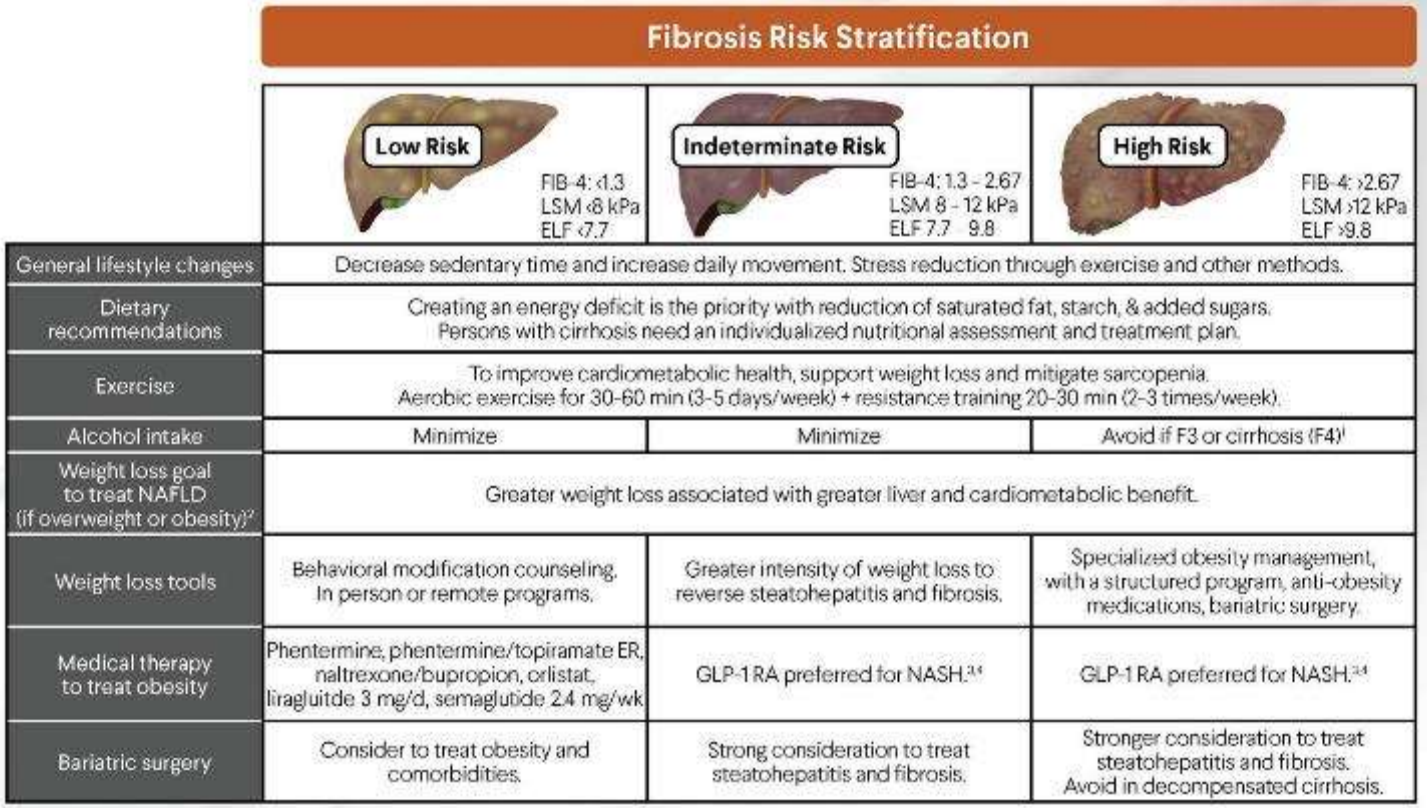
Impact of weight loss on NASH with fibrosis



- 5% or more weight loss can result in improvement in NASH
- 10% or more weight loss
  - 90% **resolution** of NASH
  - 45% **regression** of fibrosis

Vilar-Gomez et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology.* 2015

Weight Management in NAFLD



	Fibrosis Risk Stratification		
	Low Risk FIB-4: <1.3 LSM <8 kPa ELF <7.7	Indeterminate Risk FIB-4: 1.3 - 2.67 LSM 8 - 12 kPa ELF 7.7 - 9.8	High Risk FIB-4: >2.67 LSM >12 kPa ELF >9.8
General lifestyle changes	Decrease sedentary time and increase daily movement. Stress reduction through exercise and other methods.		
Dietary recommendations	Creating an energy deficit is the priority with reduction of saturated fat, starch, & added sugars. Persons with cirrhosis need an individualized nutritional assessment and treatment plan.		
Exercise	To improve cardiometabolic health, support weight loss and mitigate sarcopenia. Aerobic exercise for 30-60 min (3-5 days/week) + resistance training 20-30 min (2-3 times/week).		
Alcohol intake	Minimize	Minimize	Avoid if F3 or cirrhosis (F4)[1]
Weight loss goal to treat NAFLD (if overweight or obesity)[2]	Greater weight loss associated with greater liver and cardiometabolic benefit.		
Weight loss tools	Behavioral modification counseling. In person or remote programs.	Greater intensity of weight loss to reverse steatohepatitis and fibrosis.	Specialized obesity management, with a structured program, anti-obesity medications, bariatric surgery.
Medical therapy to treat obesity	Phentermine, phentermine/topiramate ER, naltrexone/bupropion, orlistat, liraglutide 3 mg/d, semaglutide 2.4 mg/wk	GLP-1 RA preferred for NASH.[3,4]	GLP-1 RA preferred for NASH.[3,4]
Bariatric surgery	Consider to treat obesity and comorbidities.	Strong consideration to treat steatohepatitis and fibrosis.	Stronger consideration to treat steatohepatitis and fibrosis. Avoid in decompensated cirrhosis.

Abbreviations: GLP-1 RA = Glucagon-like peptide-1 receptor agonists, HCC = Hepatocellular carcinoma, NASH = Nonalcoholic steatohepatitis

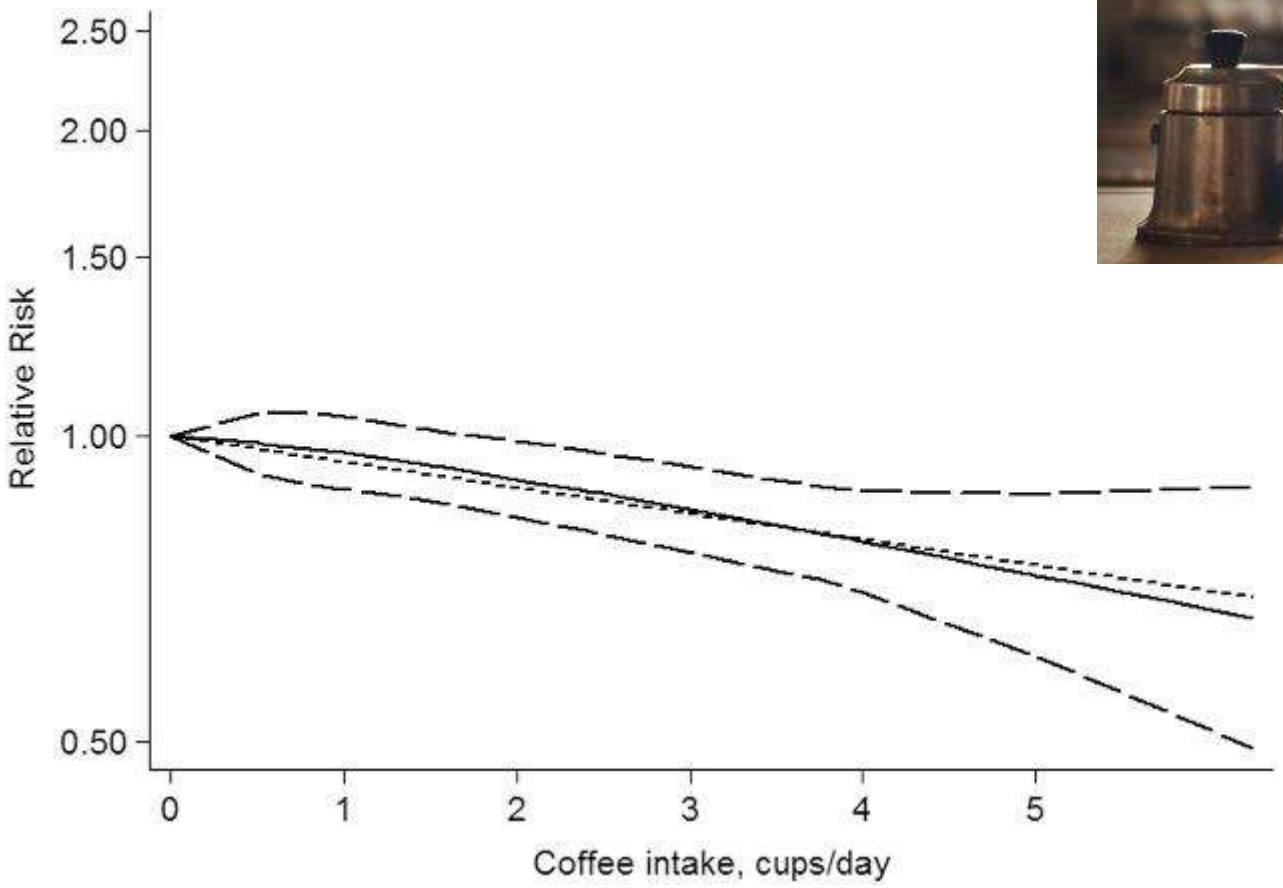
1. Persons with confirmed cirrhosis based on biopsy or high likelihood based on LSM >13.6kPa from vibration controlled transient elastography (FibroScan®), ELF ≥9.8 or >5.0 kPa on MRE) should undergo HCC surveillance. Varices screening is recommended if LSM >20 kPa or platelet count of <150,000/mm³.
2. These goals should only be taken as a broad guidance. NAFLD/NASH may also improve by changes in macronutrient content, exercise and other factors beyond magnitude of weight loss. All high quality studies available limited to a maximum of 12 month duration.
3. No high-quality evidence for pharmacotherapy in persons with NASH cirrhosis. Treatment should be individualized and used with caution only by liver specialists.
4. Among GLP-1 RAs, semaglutide has the best evidence of benefit in persons with steatohepatitis and fibrosis.

Algorithm Figure 2

AACE.

Cusi 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. Endocrine Practice. 2022

Dose–response relationship of coffee intake (cups per day) with the risk of occurrence of NAFLD



Chen et al. A systematic review and a dose-response meta-analysis of coffee dose and nonalcoholic fatty liver disease. *Clin Nutr.* 2019

Bariatric surgery for the management of NAFLD/NASH

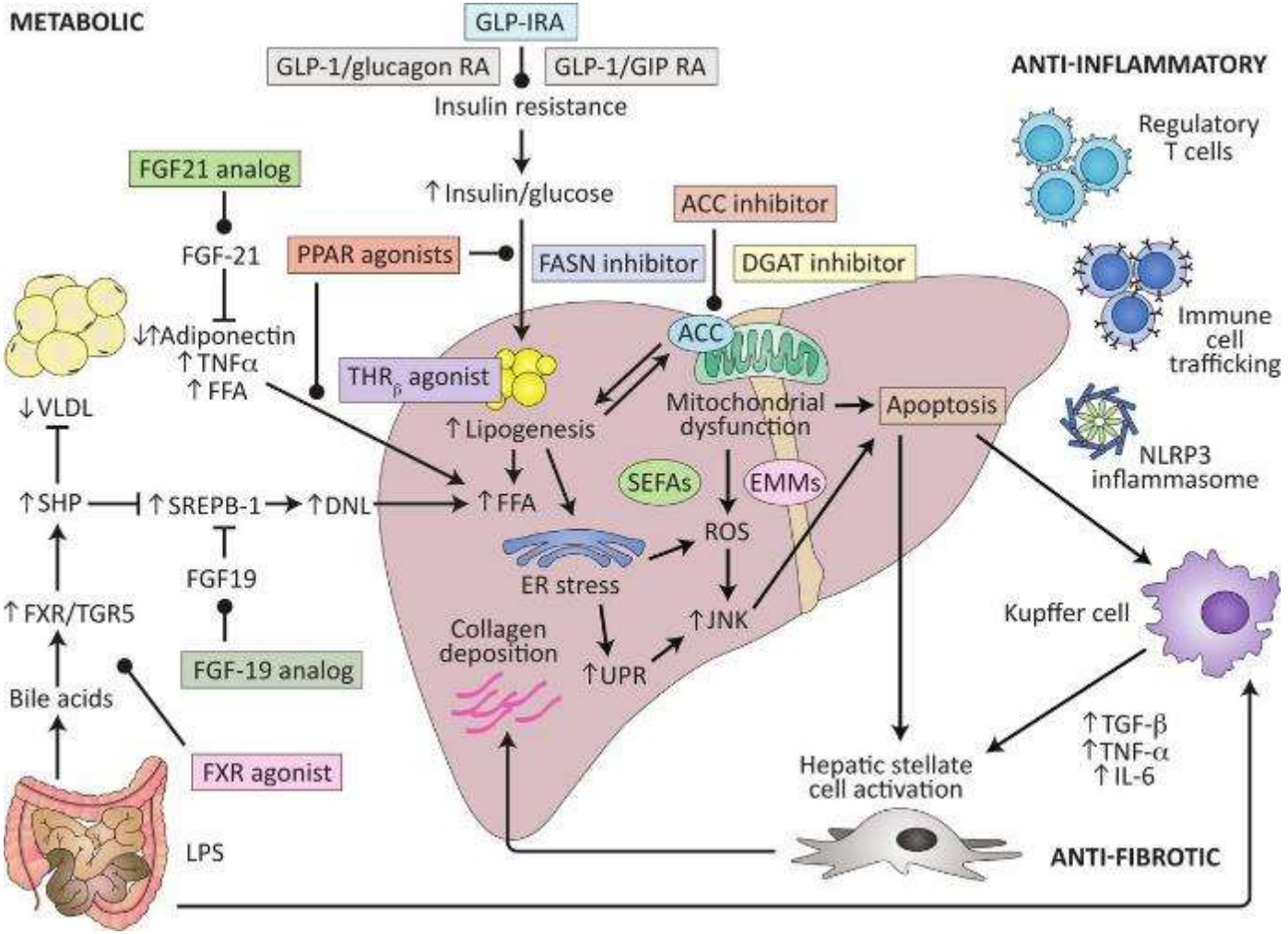
- Consider in those meeting criteria for metabolic weight loss surgery

- Benefits of bariatric surgery:
  - Resolution of NASH
  - Improvement in hepatic fibrosis
  - Resolution of diabetes
  - Sustained weight loss (up to 30%)

- Decompensated cirrhosis is a contraindication for bariatric surgery
  - *Consider if performed with liver transplantation at high volume centers*

Rinella et al. AASLD Practice Guidance on the Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease. *Hepatology.* 2023

Potential therapeutic targets



Dufour et al. Current therapies and new developments in NASH. *GUT.* 2022

Pharmacotherapy for NAFLD/NASH

- **No FDA approved treatment at any stage of disease**

- Consider medications approved for other indications that have shown benefits for NASH in trials

Considerations:

- High dose vitamin E
- Thiazolidinediones
- GLP-1 RAs

The role of vitamin E in NASH

Table 2. Primary Outcome and Changes in Histologic Features of the Liver after 96 Weeks of Treatment.

Variable	Placebo	Vitamin E	Pioglitazone	P Value*	
				Vitamin E vs. Placebo	Pioglitazone vs. Placebo
Primary outcome†					
No. of subjects randomly assigned	83	84	80		
Subjects with improvement (%)	19	43	34	0.001	0.04
Changes from baseline in histologic features					
No. of subjects with biopsy specimens at baseline and 96 wk	72	80	70		
Steatosis					
Subjects with improvement (%)	31	54	69	0.005	<0.001
Mean change in score	−0.1	−0.7	−0.8	<0.001	<0.001
Lobular inflammation					
Subjects with improvement (%)	35	54	60	0.02	0.001
Mean change in score	−0.2	−0.6	−0.7	0.008	<0.001
Hepatocellular ballooning					
Subjects with improvement (%)	29	50	44	0.01	0.08
Mean change in score	−0.2	−0.5	−0.4	0.03	0.01
Total NAFLD activity score (mean change)	−0.5	−1.9	−1.9	<0.001	<0.001
Fibrosis‡					
Subjects with improvement (%)	31	41	44	0.24	0.12
Mean change in score	−0.1	−0.3	−0.4	0.19	0.10
Resolution of definite nonalcoholic steatohepatitis (% of subjects)	21	36	47	0.05	0.001

* P values were calculated with the use of the Mantel–Haenszel chi-square test, stratified according to clinic, for the primary outcome; Fisher's exact test for the binary secondary outcomes; and analysis-of-covariance models, regressing change from baseline to 96 weeks on treatment group and baseline value of the outcome, for secondary outcome scores.

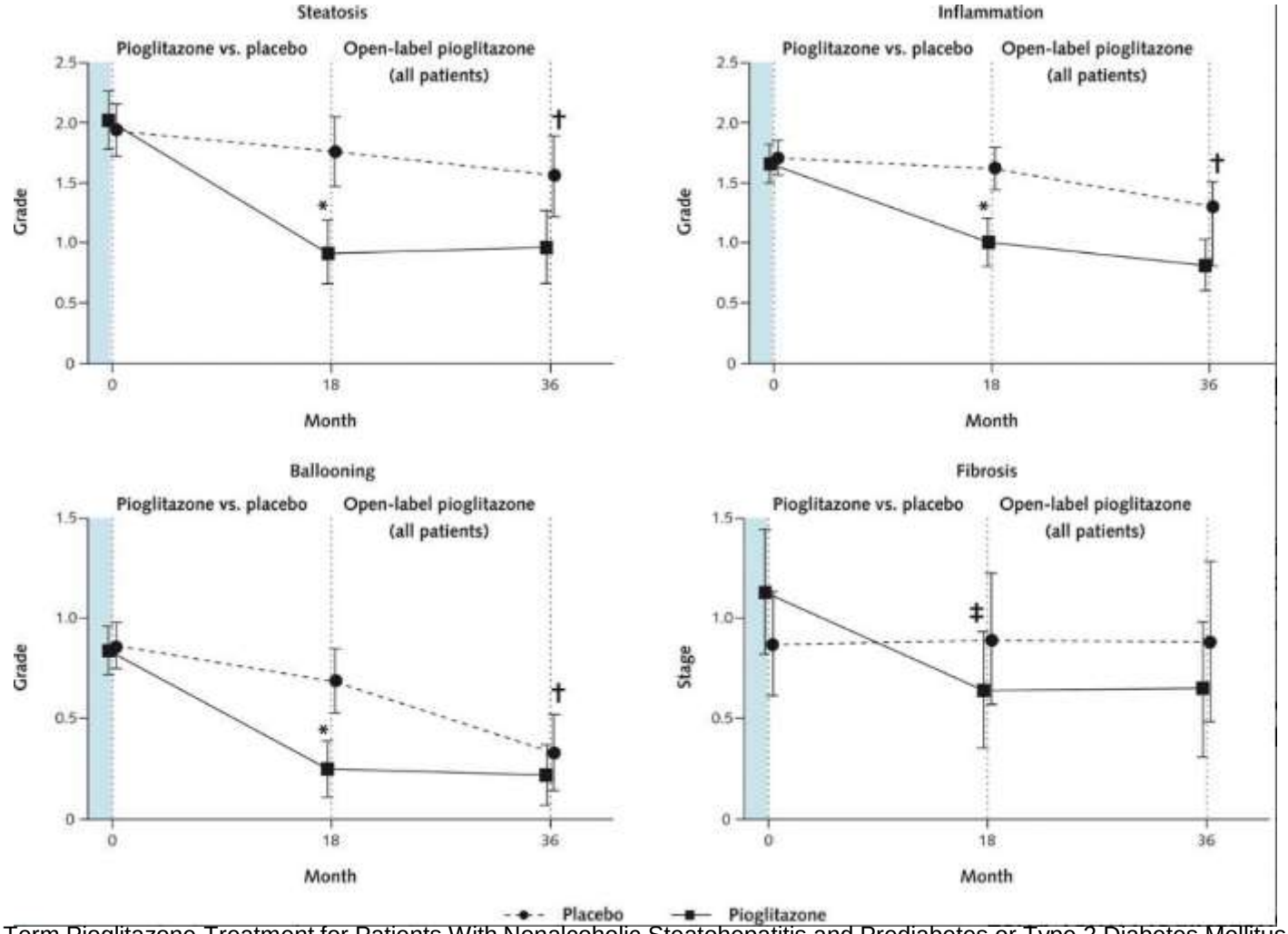
† The primary outcome was an improvement in histologic findings, which required improvement by 1 or more points in the hepatocellular ballooning score; no increase in the fibrosis score; and either a decrease in the activity score for nonalcoholic fatty liver disease to a score of 3 points or less or a decrease in the activity score of at least 2 points, with at least a 1-point decrease in either the lobular inflammation or steatosis score. A total of 11 subjects in the placebo group, 4 in the vitamin E group, and 10 in the pioglitazone group had missing histologic data at week 96, and the results for these subjects were imputed as a lack of improvement. The NAFLD activity score was assessed on a scale of 0 to 8, with higher scores indicating more severe disease; the components of this measure include steatosis (assessed on a scale of 0 to 3), lobular inflammation (assessed on a scale of 0 to 3), and hepatocellular ballooning (assessed on a scale of 0 to 2).

‡ Fibrosis was assessed on a scale of 0 to 4, with higher scores indicating more severe fibrosis.

- 800 IU daily for 96 weeks
- Improved histology (2 or more point reduction in NAS)
- Reduction in liver transaminases
- Increased risk of hemorrhagic stroke
- Questionable relationship between prostate cancer and Vit E

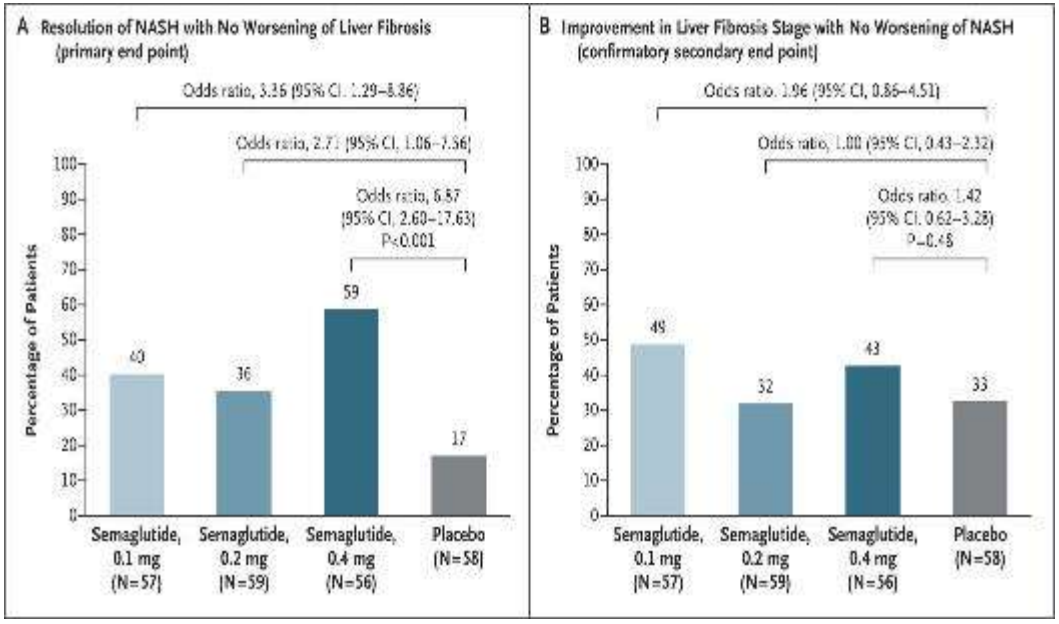
Sanyal et al. Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis. NEJM, 2010

Pioglitazone has shown benefits in NASH



Cusi et al. Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus. Ann Int Med, 2016

GLP-1 RAs



- Several approved for type 2 diabetes and obesity, none approved for the treatment of NASH
- Phase 2b RCT
  - Daily subcutaneous semaglutide in 320 patients with NASH
  - Fibrosis stages 1 to 3
  - 59% treatment group vs 17% of placebo group had NASH resolution
  - Fibrosis improvement in the treatment group was not statistically significantly different compared to placebo
  - Phase 3 trial underway

Newsome et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis . NEJM, 2021

Other agents

- SGLT-2i
  - Role in management/treatment of NAFLD is limited
  - Small studies
  - No histologic assessments
  - Trend towards improvement in hepatic steatosis

- Metformin
  - No histologic improvement in NASH

- UDCA
  - No histologic benefit based on RCT

- Milk Thistle
  - Evidence is inconclusive
  - No improvement in NASH histology

Dyslipidemia management

- Moderate to high intensity statins
  - Assess ASCVD risk scores
- Combination with other hypolipemic agents when necessary
  - Ezetimibe
  - PCSK-9 inhibitors
  - Fibrates
  - Omega 3 fatty acids
- Safety
  - Safe including patients with compensated cirrhosis
  - Risk of statin related liver adverse effects higher in decompensated cirrhosis

Rinella et al. AASLD Practice Guidance on the Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease. *Hepatology.* 2023

Treatment Highlights

- Multidisciplinary management to address metabolic risk factors
- No current FDA approved treatments for NASH
- Weight reduction results in histologic improvement in NASH
- Bariatric surgery should be considered in patients with NASH but not decompensated cirrhosis if criteria for metabolic weight loss surgery are present
- Diabetes mellitus should preferably be managed with agents that have proven benefit in NASH including pioglitazone and semaglutide
- Statins are safe across the NASH disease spectrum but should be used with extreme caution in decompensated cirrhosis