Brigham and Women's Hospital
Founding Member, Mass General Brigham

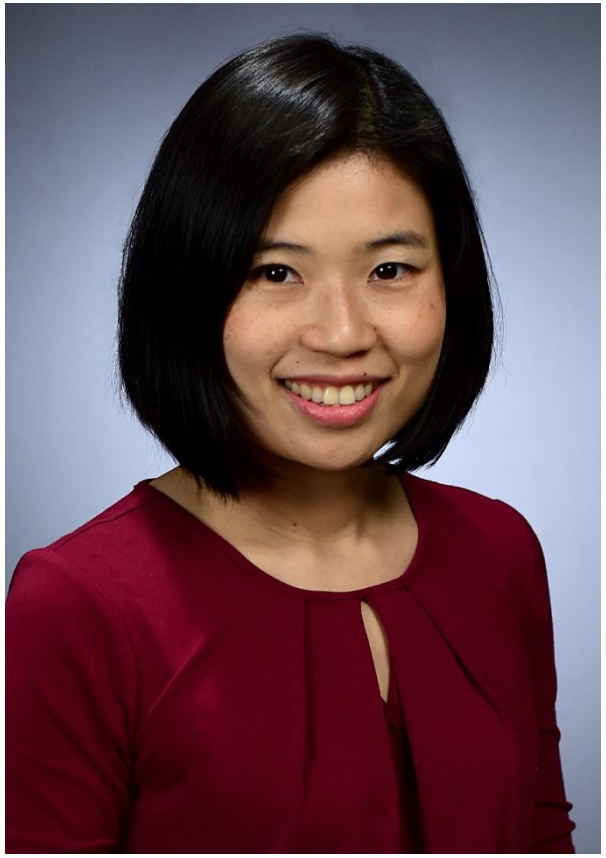
Update in ~~Non-Alcoholic~~ Fatty Liver Disease

M. Valerie Lin, MD

Transplant Hepatologist
Director of Liver Tumor Program
Associate Program Director for Advanced Hepatology Fellowship
Division of Transplant and Hepatobiliary Disease
Department of Surgery
Lahey Hospital & Medical Center

Assistant Professor of Medicine
Tufts University School of Medicine

M. Valerie Lin, MD



- Medicine Residency @ Pennsylvania Hospital, Penn Medicine
- Gastroenterology Fellowship @ Univ of Cincinnati Medical Center
- Advanced/Transplant Hepatology Fellowship @ MGH
- Assistant Professor of Medicine @ Tufts Univ School of Medicine
- Transplant Hepatologist @ Lahey Hospital &Medical Center
- Director of Liver Tumor Program @ Lahey Hospital & Medical Center
- Associate Program Director for Advanced Hepatology Fellowship @ Lahey Hospital & Medical Center
- Clinical focus: chronic liver disease and cirrhosis; liver tumors management; fatty liver disease
- Research focus: HCC outcome in pre- and post- liver transplant patients; Prehabilitation in cirrhosis; Acute on chronic liver failure

DISCLOSURES

- I have no financial disclosures

OBJECTIVES

- To provide an update on the nomenclature and definitions
- To review the natural history and risk factors
- To discuss the diagnosis and monitoring
- To summarize the advances on fatty liver disease management

NOMENCLATURE CHANGES

Old Name	New Name	Definition
NAFLD Nonalcoholic Fatty Liver Disease	**MASLD** Metabolic Dysfunction-Associated Steatotic Liver Disease	Hepatic Steatosis (>5% on bx) + 1 metabolic feature
NASH Nonalcoholic Steatohepatitis	**MASH** Metabolic dysfunction-associated steatohepatitis	HS + inflammation: Mallory bodies, ballooning hepatocytes +/- fibrosis
NASH + ASH	**MetALD** MASLD and significant alcohol	MASLD + 20/30 to 50/60g of etoh daily

REASONS FOR THE NOMENCLATURE CHANGE

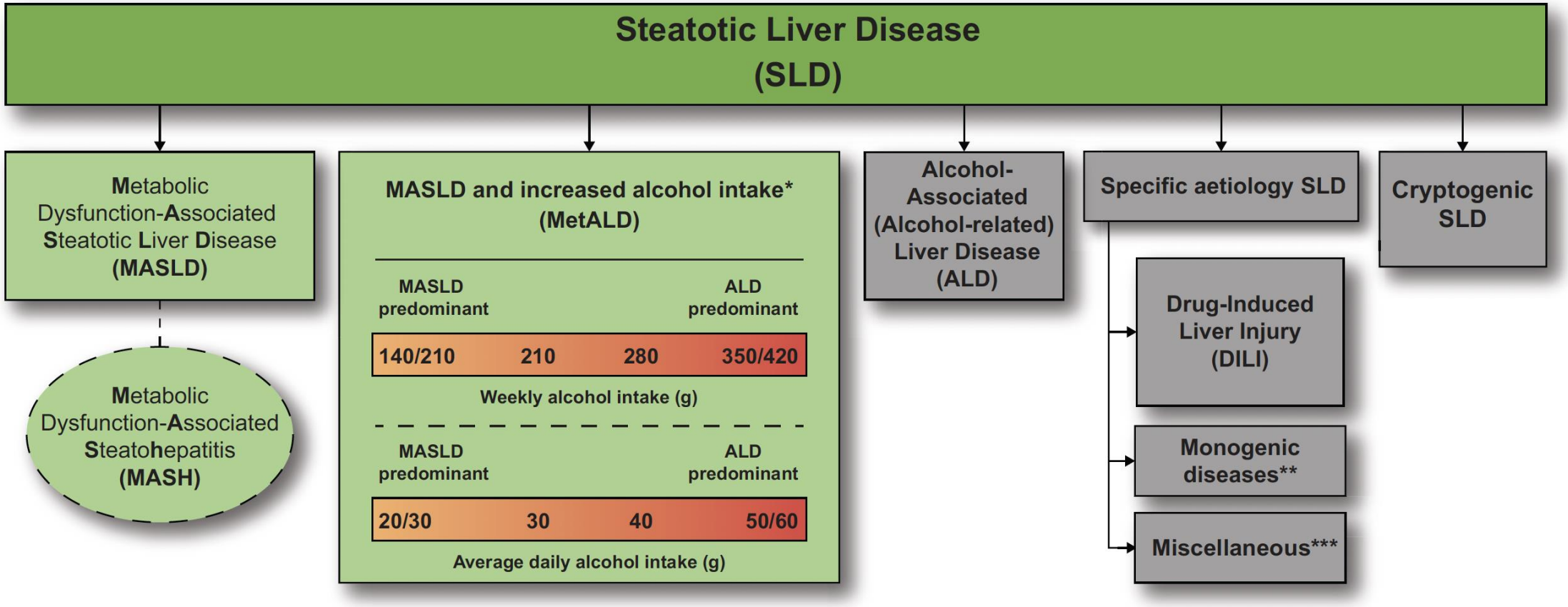
- Non-stigmatizing
- No longer based on exclusion of other disease
- Allows for overlap with alcohol
- Improves understanding that MASLD is “the hepatic manifestation of the metabolic syndrome”

“We will no longer use the previously exclusionary, negative and confounder terms that used potentially stigmatizing language of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH).”

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

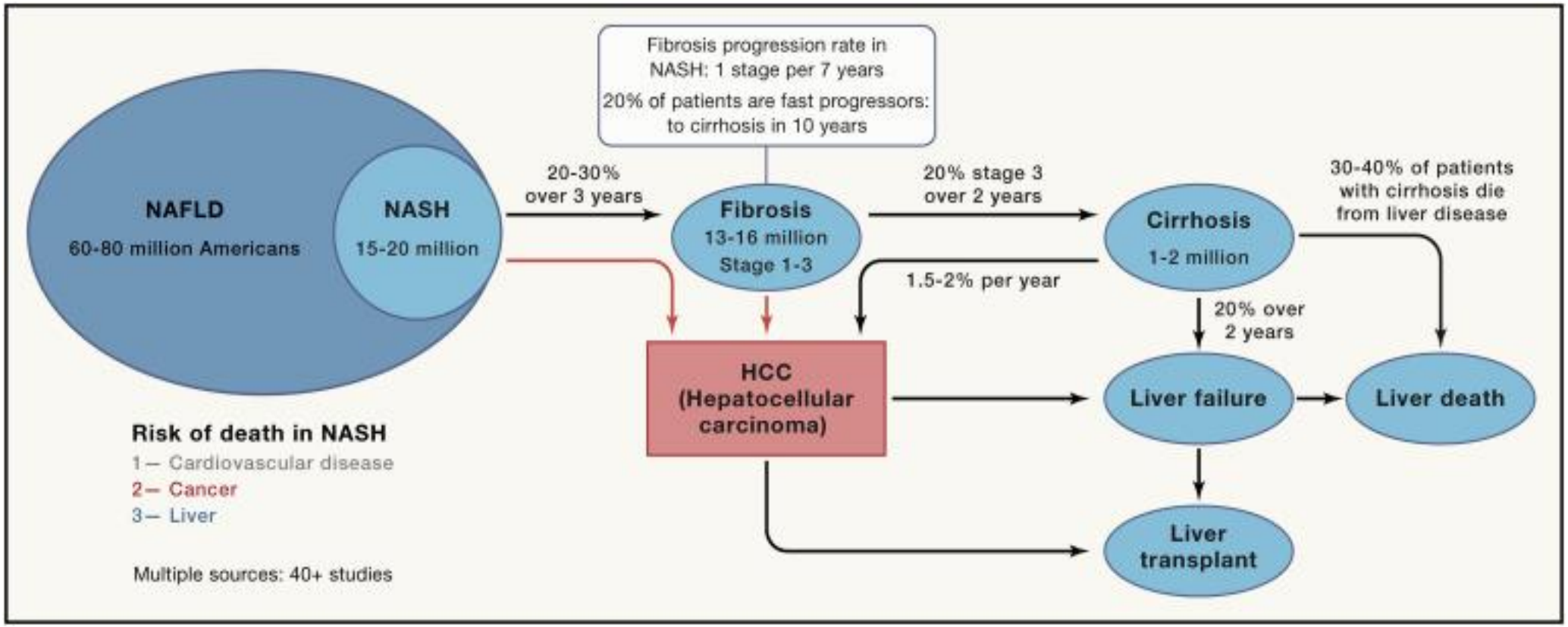
Rinella et al. Hepatology. 2023

STEATOTIC LIVER DISEASE (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, human immunodeficiency virus (HIV)

NATURAL HISTORY OF MASLD



- Risk factors for rapid progressors: DM II, medically complicated obesity, family history, moderate alcohol use and higher ALT

Loomba et al. Cell. 2021.

RISK FACTORS FOR MASLD

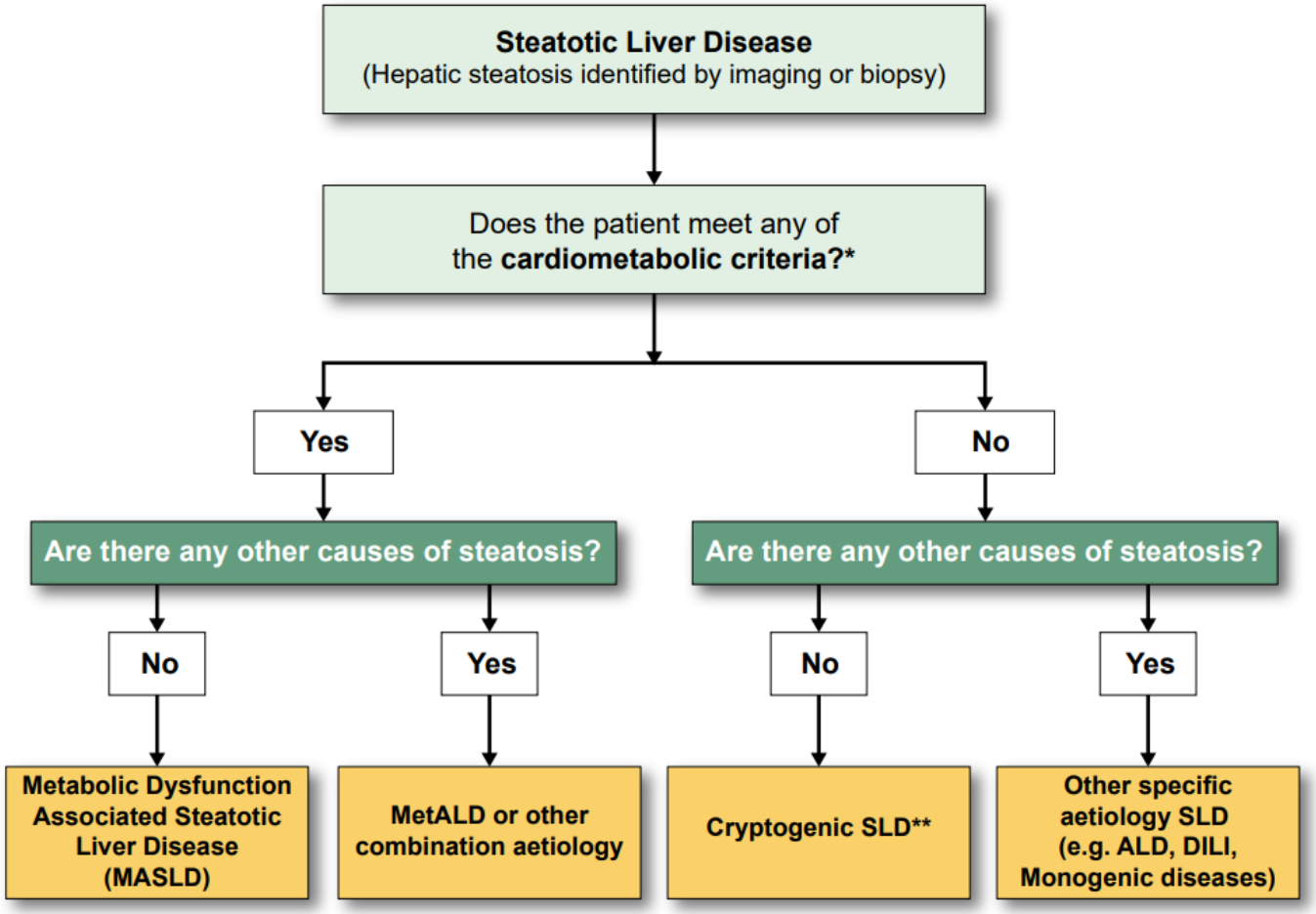
Comorbid conditions	Obesity T2DM (2-5x risk of incidental) HTN Dyslipidemia OSA CVD CKD
Age	Increases prevalence and stage of fibrosis
Gender	2x prevalence M>F
Ethnicity	• Hispanic>non-Hispanic white>American Indian>Alaskan native>African American • Genetic variations

GENETIC MODIFIERS FOR MASLD

- Several genes have been identified
  - PNPLA3/148M
  - TM6SF2
  - MBOAT7
- Have higher liver fat content
- Increased risk of MASH and liver cancer (HCC)
- HSD17B13 may be protective

Rinella et al. Hepatology 2023. Cui et al. Hepatology 2016. Loomba et al. Gastroenterology 2015

DIAGNOSIS OF MASLD



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 equivalent
- ☐ 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

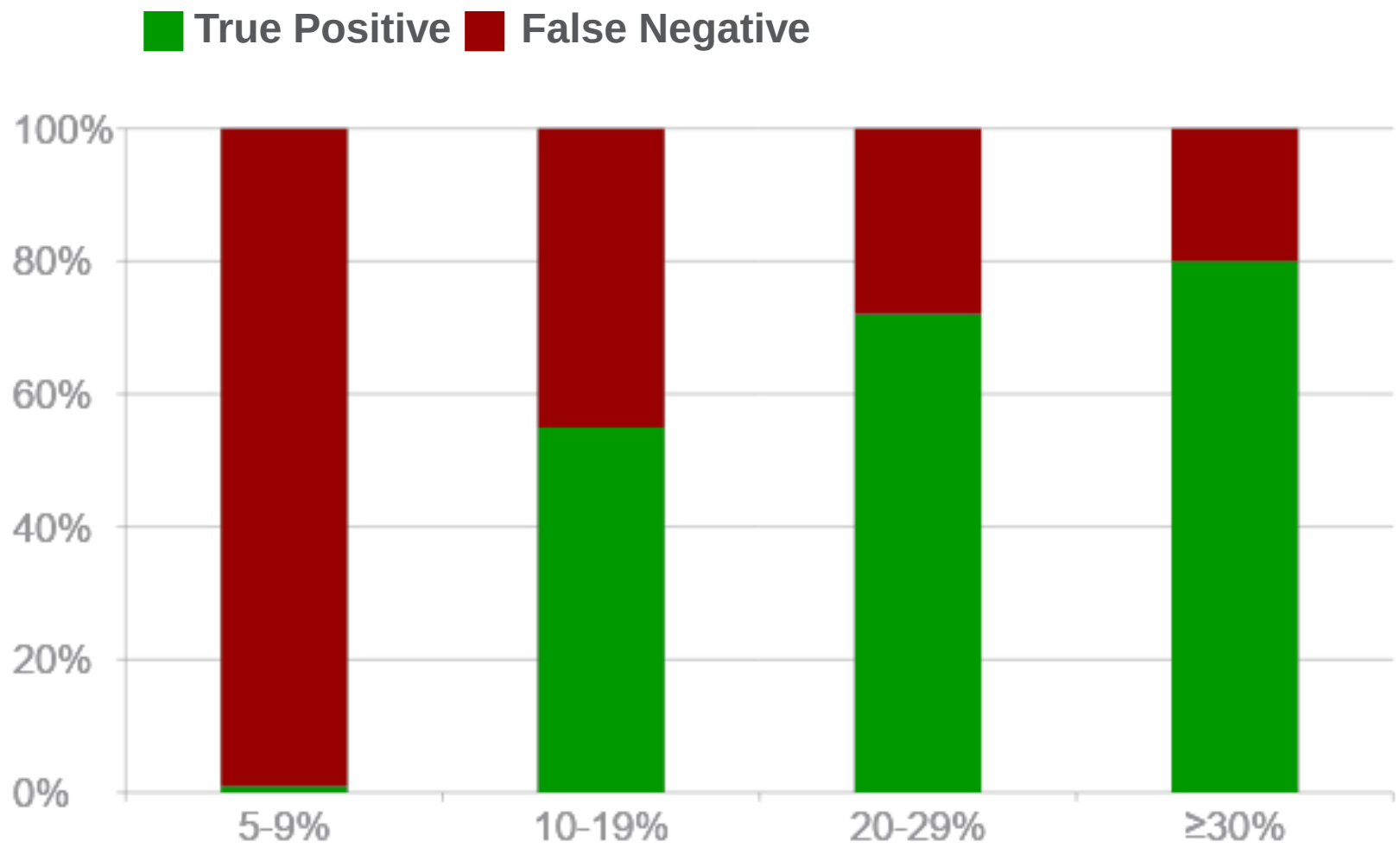
MASLD AND NORMAL AMINOTRANSFERASES

Risk of Severe Liver Disease in Nonalcoholic Fatty Liver Disease with Normal Aminotransferase Levels: A Role for Insulin Resistance and Diabetes

Anna Ludovica Fracanzani,[1] Luca Valenti,[1] Elisabetta Bugianesi,[2] Marco Andreoletti,[3] Agostino Colli,[3] Ester Vanni,[2] Cristina Bertelli,[1] Erika Fatta,[1] Daniela Bignamini,[1] Giulio Marchesini,[4] and Silvia Fargion[1]

- Patients with normal ALT had milder inflammation and steatosis
- 50% of NAFLD patients with normal ALT had NASH
- No difference in prevalence of ≥ F2 fibrosis (22 vs 34%)
- Insulin resistance is associated with severe liver disease in patients with normal ALT

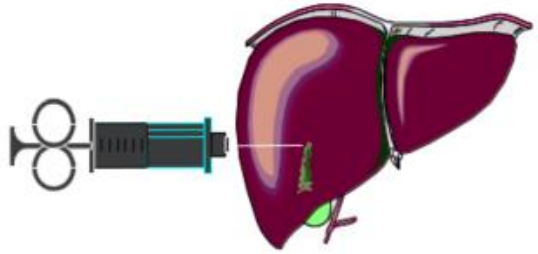
ULTRASOUND FOR DETECTION OF LIVER FAT



Ryan CK, et al., Liver Transpl 2002;8:1114-22

LIVER BIOPSY - GOLD STANDARD OF DIAGNOSIS

Which patients need a liver biopsy?



YES

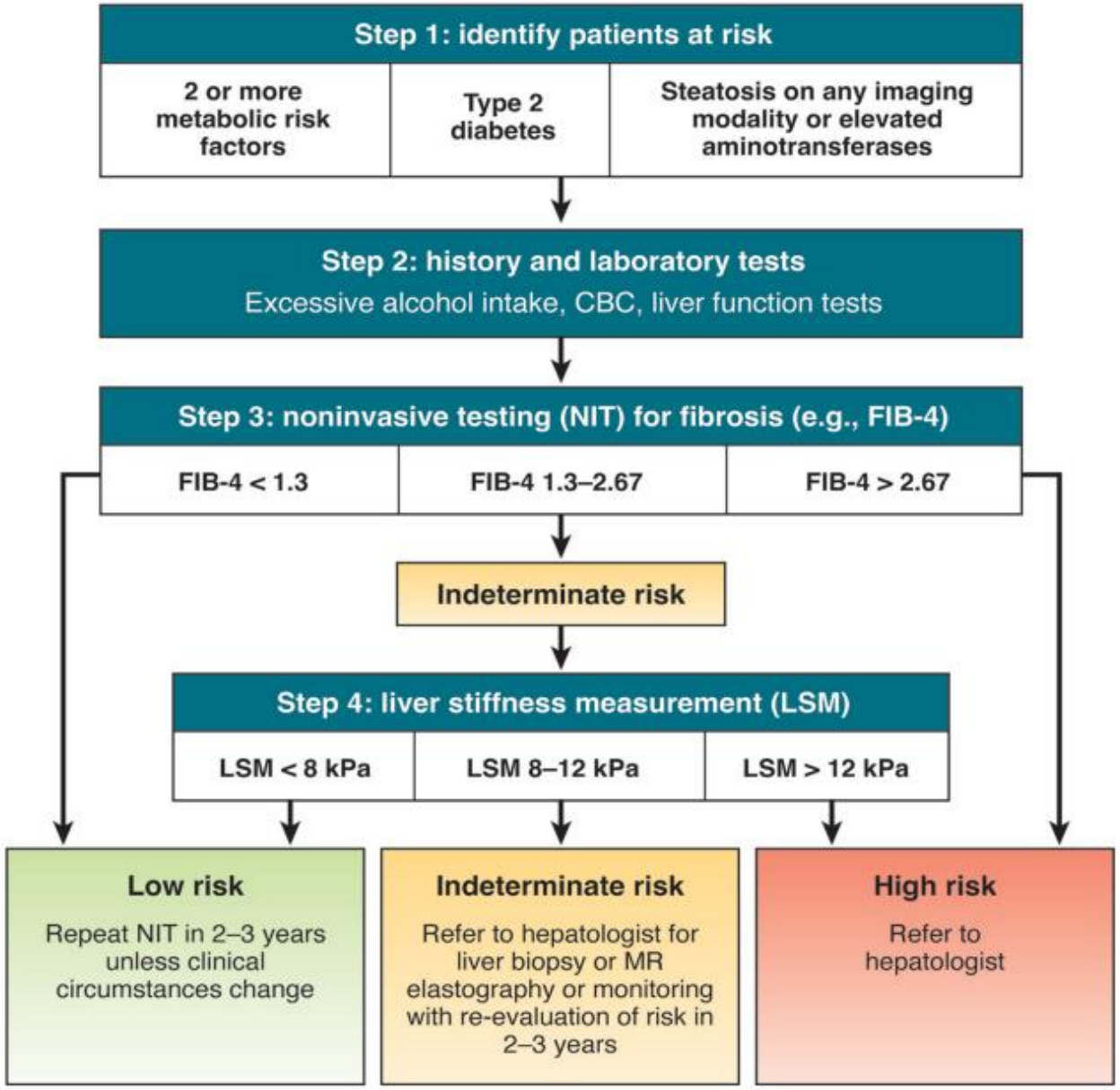
- Establish a firm diagnosis
- Indeterminate or discrepancies
- Clinical trial participation

NO

- Reasonable accuracy of diagnosis with non-invasive methods
- Risk and cost of procedure
- May not alter treatment plan

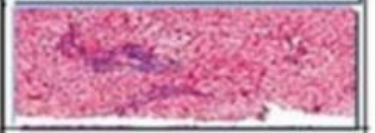
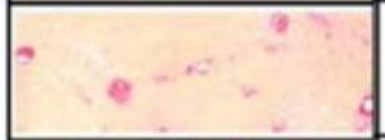
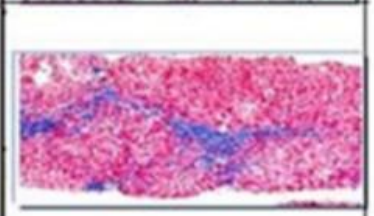
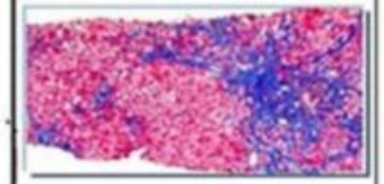
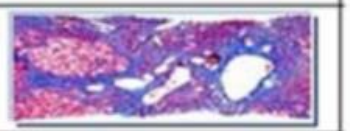
SCREENING FOR HIGH-RISK MASLD

- DM II
- Medically complicated obesity
- Family history of MASLD or cirrhosis
- >Mild alcohol use
- Not recommended for general public



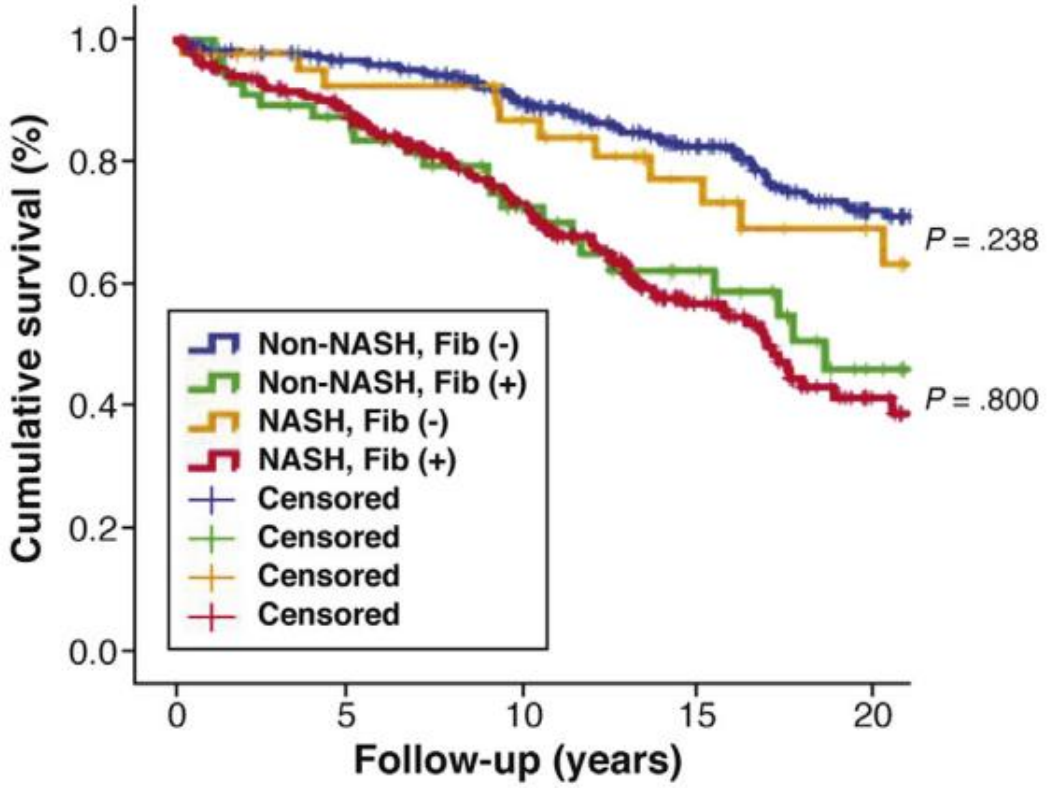
Sanyal et al. Clin Gastroenterol Hepatol. 2023

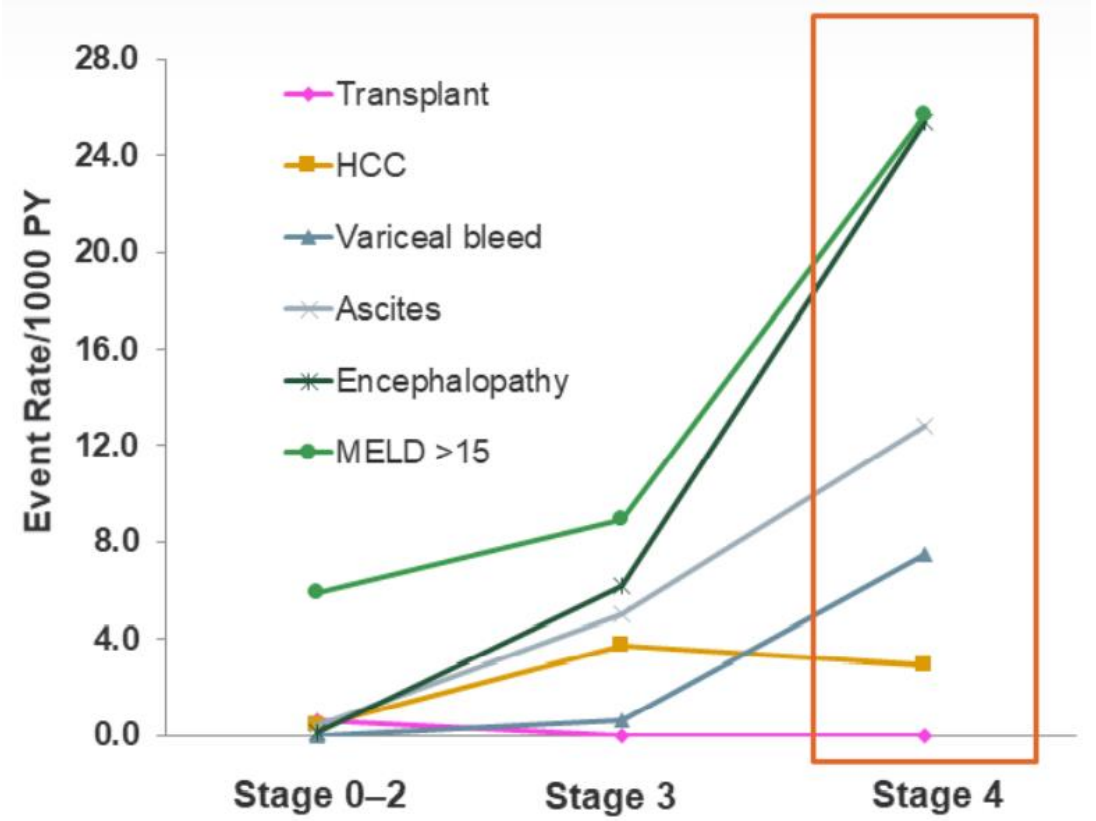
HEPATIC FIBROSIS

Appearance	ISHAK	METAVIR	Appearance
	0	F0	
	1	F1	
	2	F2	
	3		
	4	F3	
	5		
	6	F4	

Bedossa et al. Clinical Liver Disease 2015.6; 5-8

HEPATIC FIBROSIS AND SURVIVAL





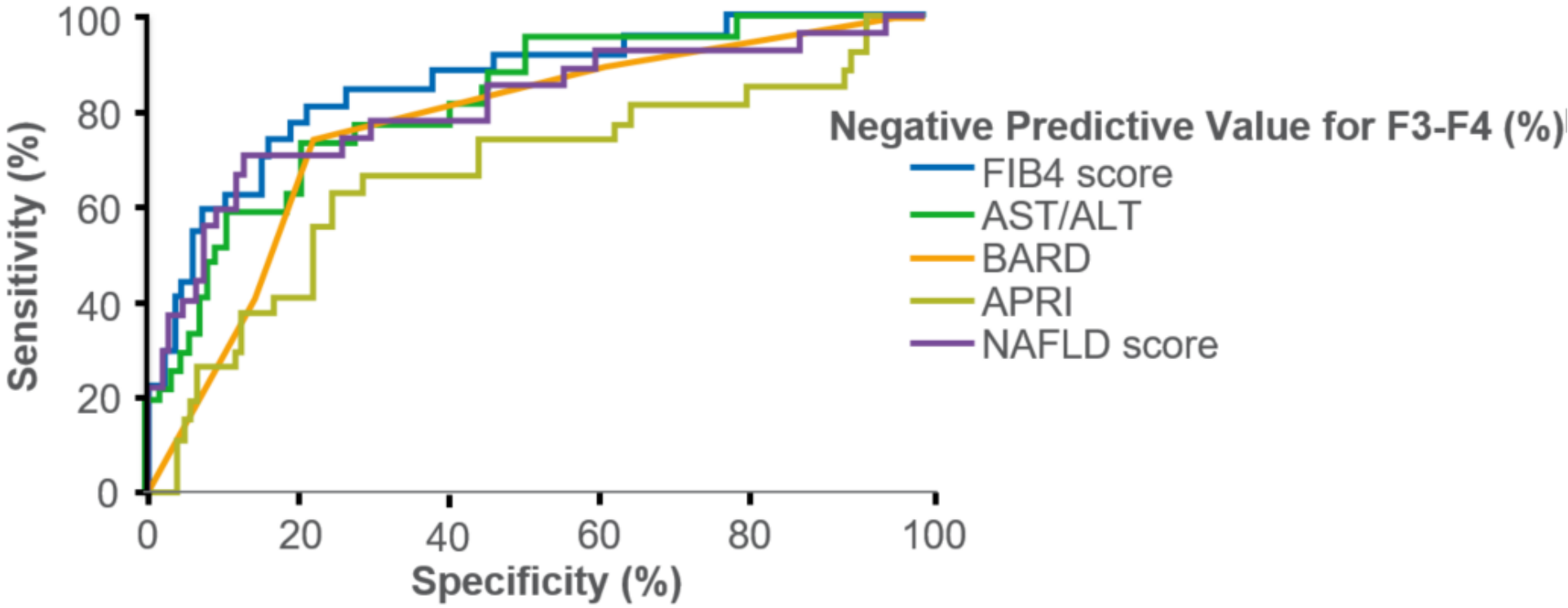
Angulo et al. Gastroenterology. 2015; Sanyal A. et al. NEJM 2021

NON-INVASIVE TESTS OF LIVER FIBROSIS

Clinical or Laboratory Tests		Imaging
Simple	**Complex**	**Elastography**
▪ AST/platelet ratio index ▪ **FIB-4 index*** ▪ NAFLD fibrosis score**	▪ NASH *FibroSure* ▪ **ELF** ▪ HepaScore ▪ FibroTest ▪ Fibrometer ▪ Hepacore ▪ CK-18	▪ **MR Elastography** ▪ VCTE *FibroScan* ▪ pSWE ▪ **2D-SWE**

* Age, AST, ALT, platelets
**Age, BMI, DM/IGF, AST, ALT, platelets, albumin

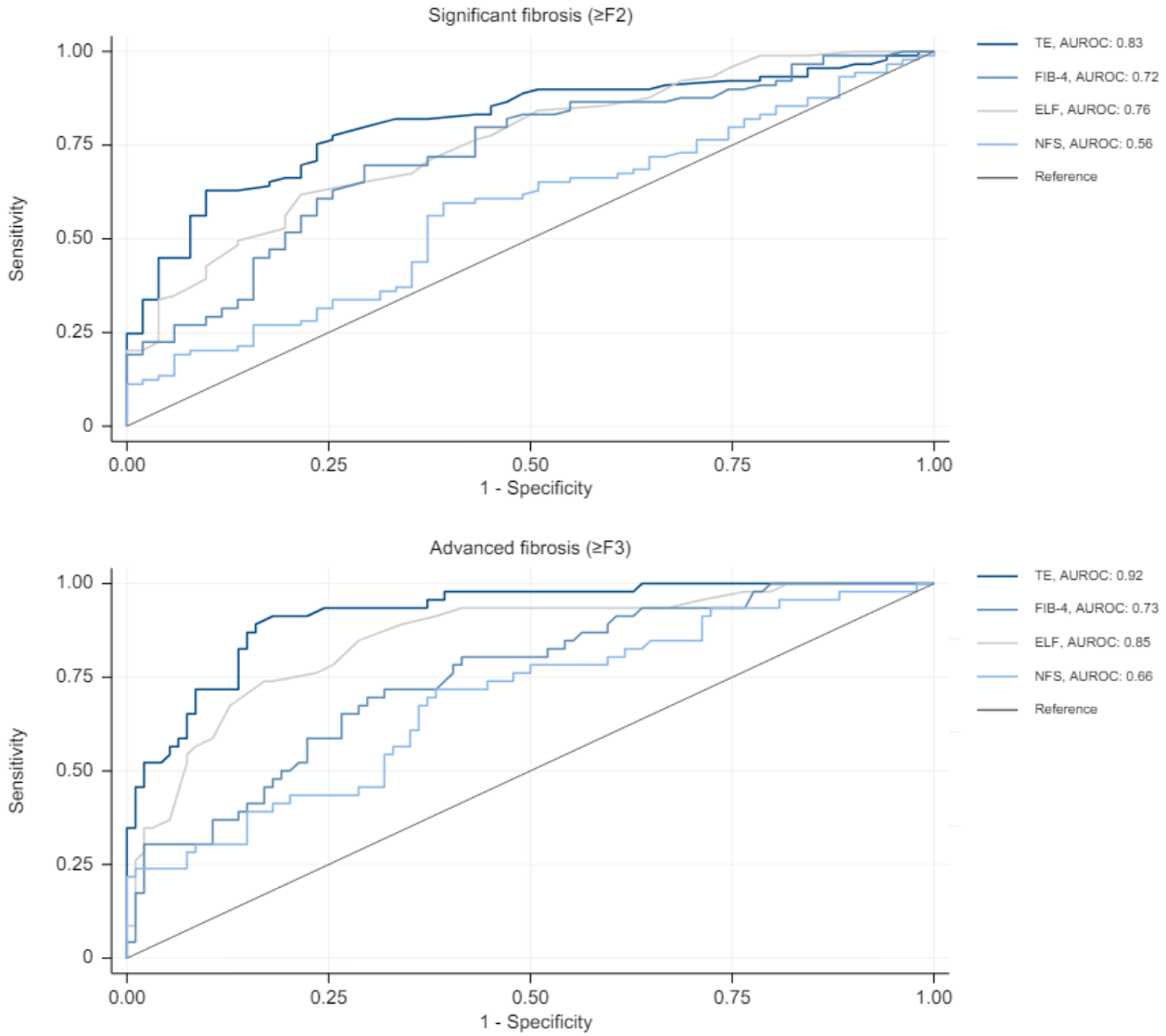
SIMPLE SERUM BIOMARKERS



- **Strength of noninvasive fibrosis predictive tests is in their ability to exclude advanced disease (F3-F4)**
  - **FIB4 NPV>92% but PPV 27%**
  - **≥ 1.3 false positive in 35%. Cut off of 2 is suggested for ≥65 yo**

McPherson S, et al. Gut. 2010; Kjaergaard et al. J of Hepatol. 2023

ENHANCED LIVER FIBROSIS (ELF) SCORE

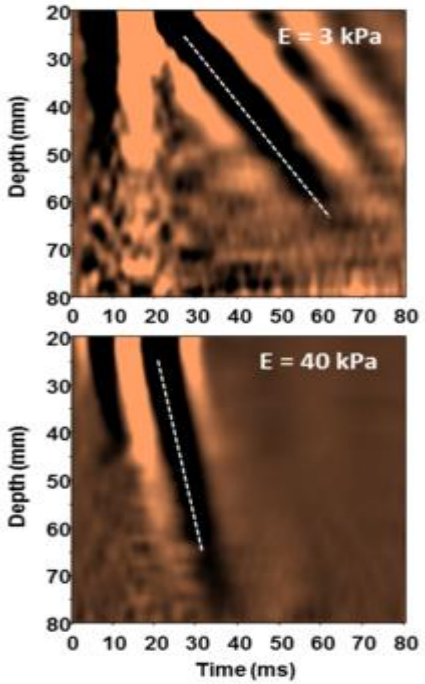


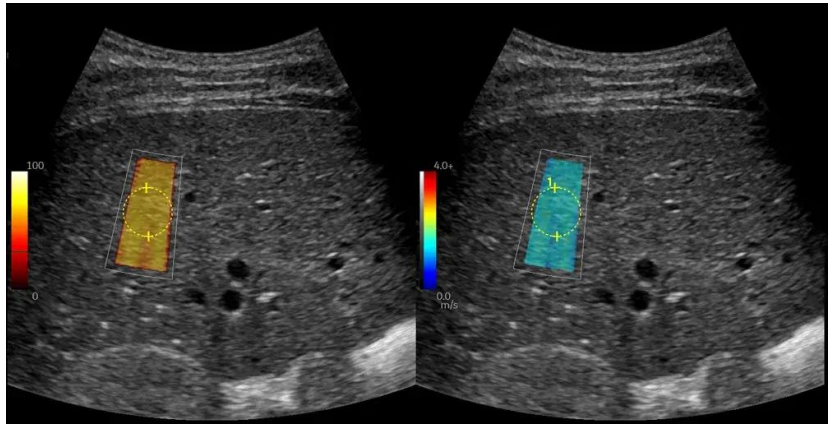
- Biomarker
- PIIINP, hyaluronic acid, TIMP
- Costly
- Less useful for early fibrosis

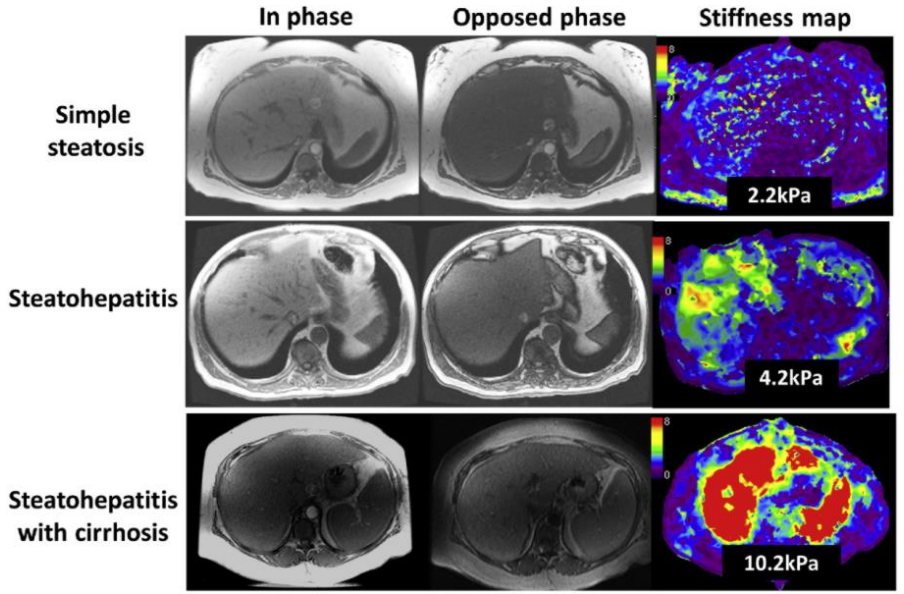
Kjaergaard et al. J of Hepatol. 2023

SOURCES OF VARIABILITY IN ELASTOGRAPHY

- Etiology
- Obesity
- Non-fasting
- Alcohol use
- Inflammation
- Congestion
- Ascites
- Operator experience







Barr RG et al. Radiology 2015;276:845-861

COMBINING NON-INVASIVE TESTS FOR MASLD

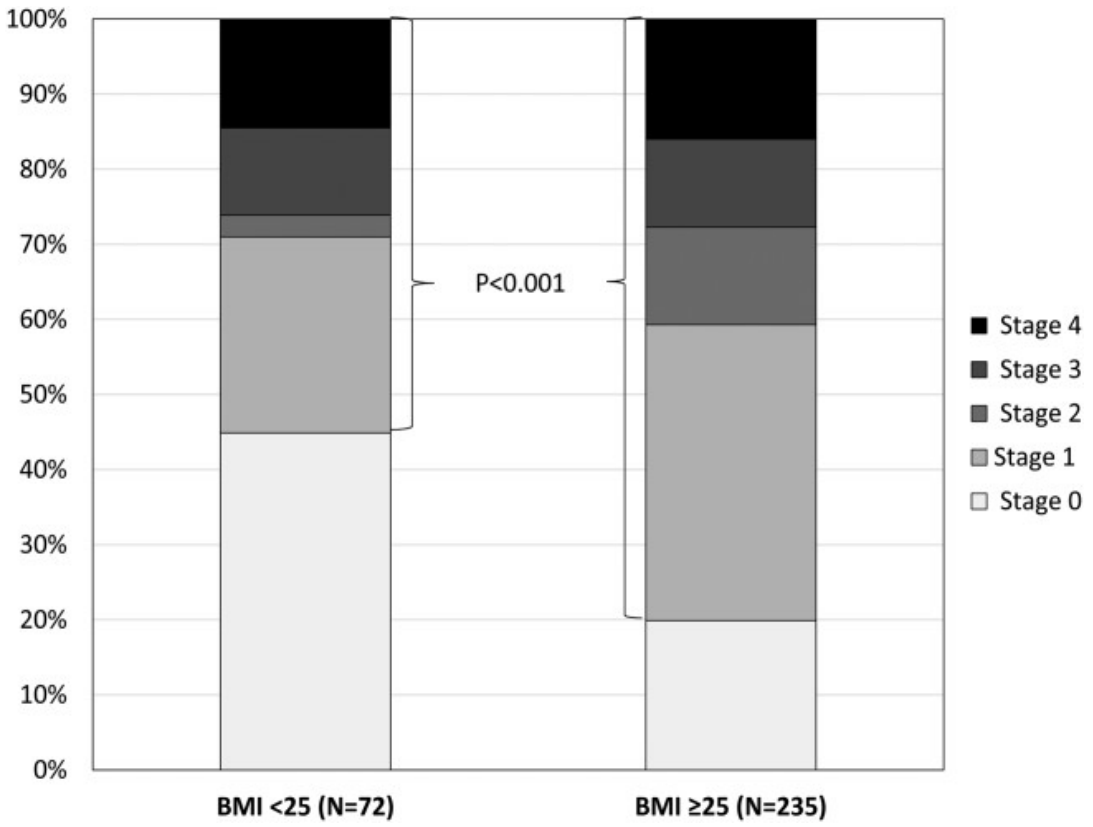
FAST	VCTE CAP, LSM, AST	e-1·65+1·07×ln(LSM)+2·66*10-8×CAP3-63·3×AST-11+e-1·65+1·07×ln(LSM)+2·66*10-8×CAP3-63·3×AST-1
MAST	MRE PDFF, AST	-12.17 + 7.07 log MRE + 0.037 PDFF + 3.55 log AST.
MEFIB	MRE and FIB4	MRE≥ 3.3 kPa and FIB4 ≥ 1.6

Noureddin et al. J of Hepatol 2022.; Ravaioli et al. Gut 2023

LEAN MASLD

- BMI <25 (non-Asians) or <23 (Asians)
- Younger, female, more often Asian, fewer metabolic components
- Prevalence ranges from 4.1% (USA) to 19% (Asia)
- Global NAFLD/NASH registry – 6.8% confirmed MASH have lean body habitus
- MASH is present in 31 to 65% of patients

LEAN MASLD: FIBROSIS STAGE AND PROGNOSIS



- RR of disease progression to advance fibrosis:
  - 6.3% (non-obese) vs. 31.6% (obese) (p-0.079)
- Major events: 8.3% vs. 11.9% (p=0.19)
  - Deaths: 0% vs. 2.6%
  - CV: 4.2% vs. 8.1%
  - HCC: 0% vs. 0.9%
- Needs more data to assess severity of non-obese vs. obese prognosis

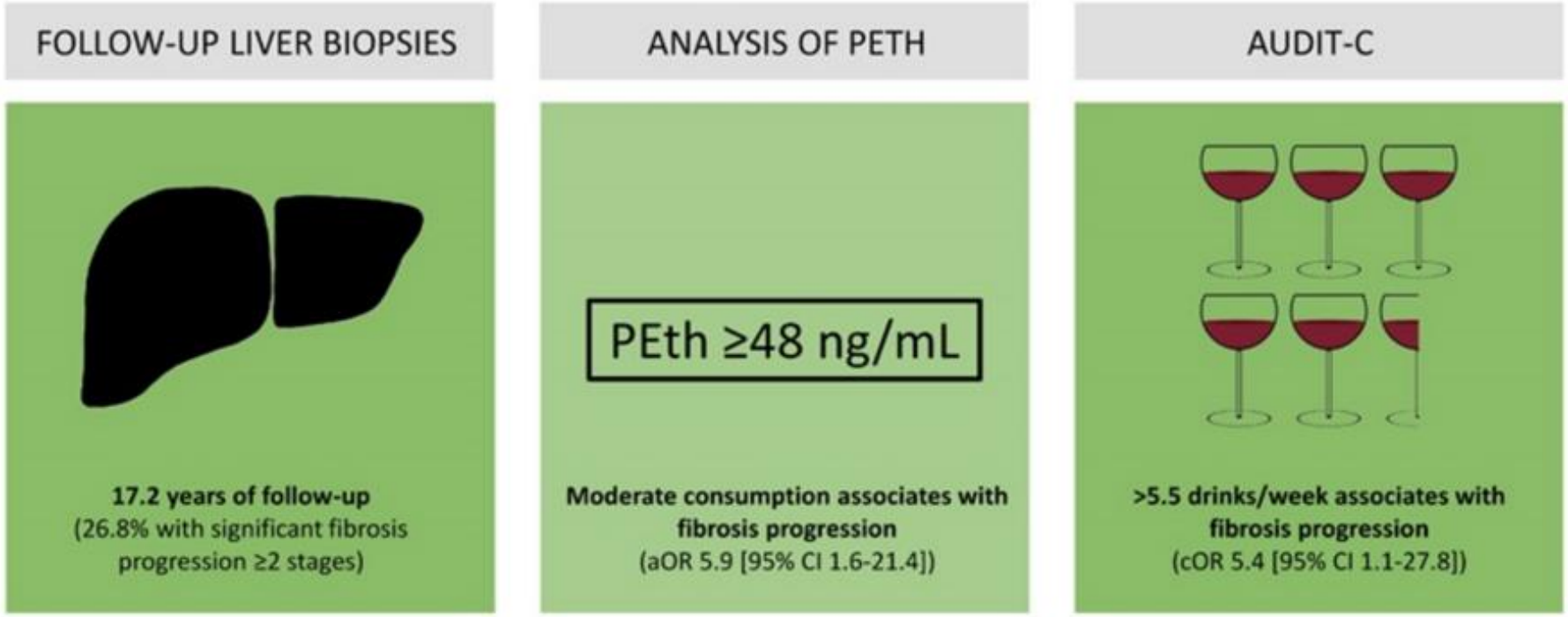
Leung et al. Hepatology 2017;65:54-64

MetALD - MASLD + Alcohol-associated Liver Disease (ALD)

- 1 standard alcohol drink = 14g of alcohol
- Significant alcohol intake is defined as:
  - Women: 20g to 50g of alcohol daily
  - Men: 30g to 60g of alcohol daily
- Binge drinking
  - ≥ 4 drinks/2 hours for women
  - ≥ 5 drinks/2 hours for men
- No safe amount of alcohol
  - Risk of chronic liver disease double for any alcohol when BMI >35
  - Alcohol is NOT recommended if ≥ stage 2 fibrosis

Crabb et al. Hepatology 2019;71:306-333; Newsome. Gut 2018;67:6-19

MODERATE ALCOHOL CONSUMPTION IS ASSOCIATED WITH FIBROSIS PROGRESSION IN MASLD



Moderate (>66-96g/week but <140g) Vs. No/low alcohol consumption

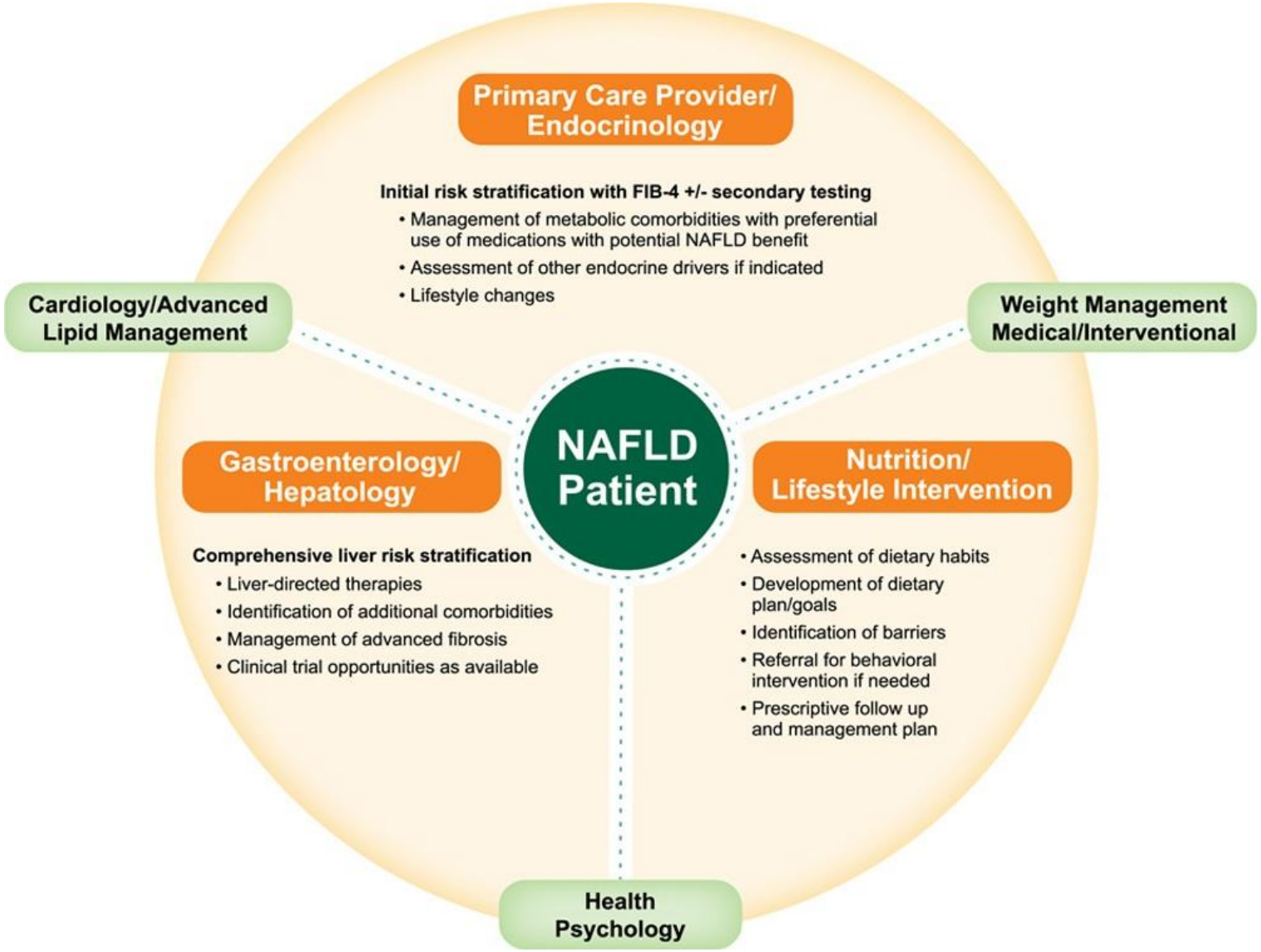
ALCOHOL BIOMARKERS

Test	Source	Detection Time	Cutoff Values	Sensitivity	Specificity	PPV	NPV
CDT/%CDT*	Blood	2-3 weeks	1.7%-2.6%	21%-50%	50%-100%	64%-100%	86%-93%
EtG	Urine	3 days	500 ng/mL	76%-89%	93%-99%	81%-90%	91%-99%
EtG	Hair	Months	30 pg/mg	81%-100%	83%-98%	68%-95%	86%-100%
EtS	Urine	3 days	75 ng/mL	82%	86%	70%	93%
PEth	Blood	2-3 weeks	20 ng/mL	97%-100%	66%-96%	85%	100%

CAUSES OF SECONDARY HEPATIC STEATOSIS

Chronic HCV infection particularly frequent with genotype 3**,#	**Pregnancy-associated#** Acute fatty liver of pregnancy HELLP syndrome
Nutritional/intestinal-related causes# Acute weight loss (bariatric surgery, fasting) Malnutrition Total parenteral nutrition Short bowel syndrome Intestinal failure-associated fatty liver disease* Small intestinal bacterial overgrowth, microbiome changes Coeliac disease Pancreatectomy	**Environmental toxins#, §** Metals: lead, arsenic, mercury, cadmium Herbicides, pesticides Polychlorinated biphenyls Chloroalkenes: - perchloroethylene - trichloroethylene - vinyl chloride **Rare genetic diseases**.#, §** (see Table 2)
Endocrine disorders Hypothyroidism (#, §) Polycystic ovary syndrome (#, §) Hypothalamic/pituitary dysfunction (e.*g.* by tumours, infections)*,# Growth hormone deficiency*,#	**Drug-related*,#, §** cART in HIV (*e.g.* didanosine, stavudine, zidovudine), amiodarone, methotrexate, chemotherapy (*e.g.* irinotecan, 5-fluouracil), tamoxifen, corticosteroids, tetracyclines, valproic acid, amphetamines, acetylsalicylic acid

MULTIDISCPLINARY MANAGMEENT OF MASLD



Rinella et al. Hepatology 2023.

LIFESTYLE INTERVENTION AND WEIGHT LOSS

Weight reduction

Overweight/obesity NAFLD

- 5-10% weight reduction achieved by any healthy diet that the patient can adhere to in the long-term

Non-obesity NAFLD

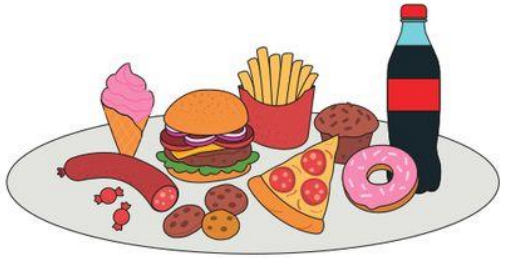
- 3-5% reduction of weight even within the normal BMI range (especially if recent weight gain ocurred or if abdominal obesity is present)

Lifestyle advice for ALL patients with NAFLD

Recommended foods

- n-3 fatty acids found in fish, and walnuts
- Olive oil
- Fruits, vegetables, polyphenols
- Home-cooked meals
- Mediterranean dietary pattern

Non-recommended foods/ minimize consumption



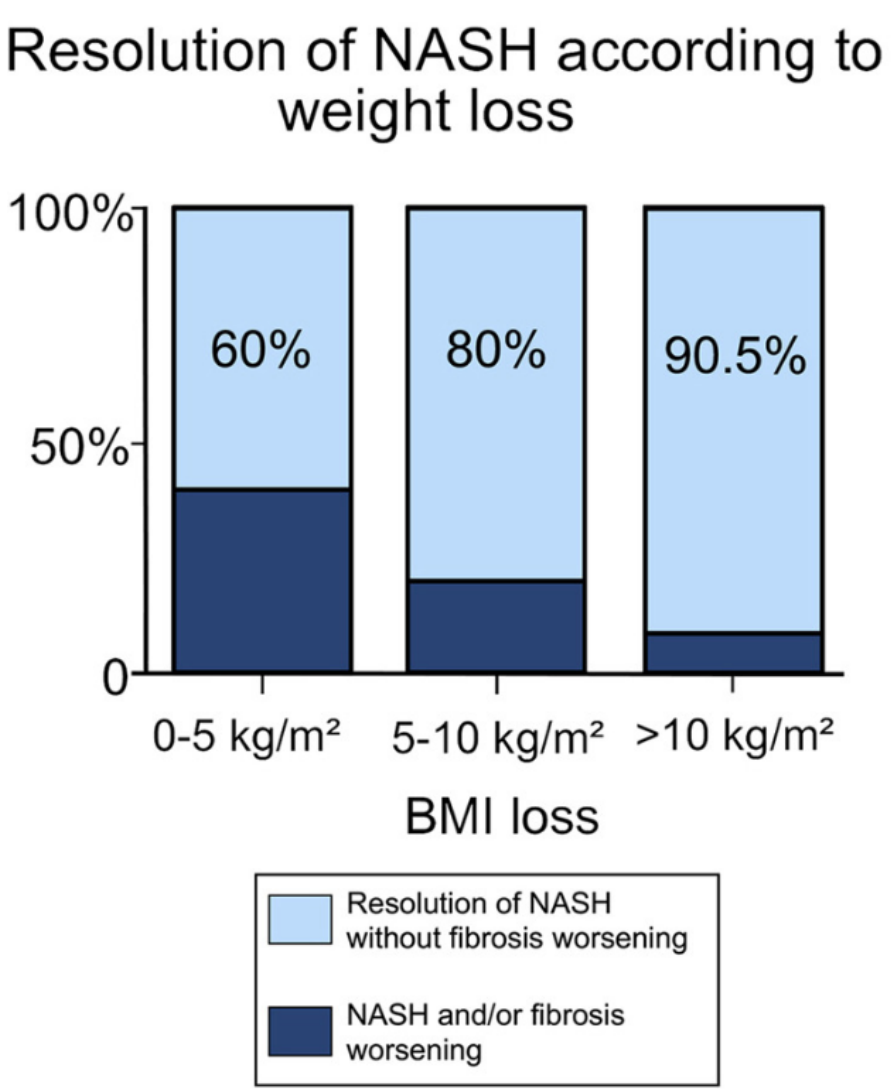
- Added sugar (eg. by reducing sweets, processed foods, sugared dairy products and beverages)
- Saturated fat and cholesterol (eg. by eating low fat meat and low fat dairy products)
- Ultra-processed foods and drinks, red and processed meat

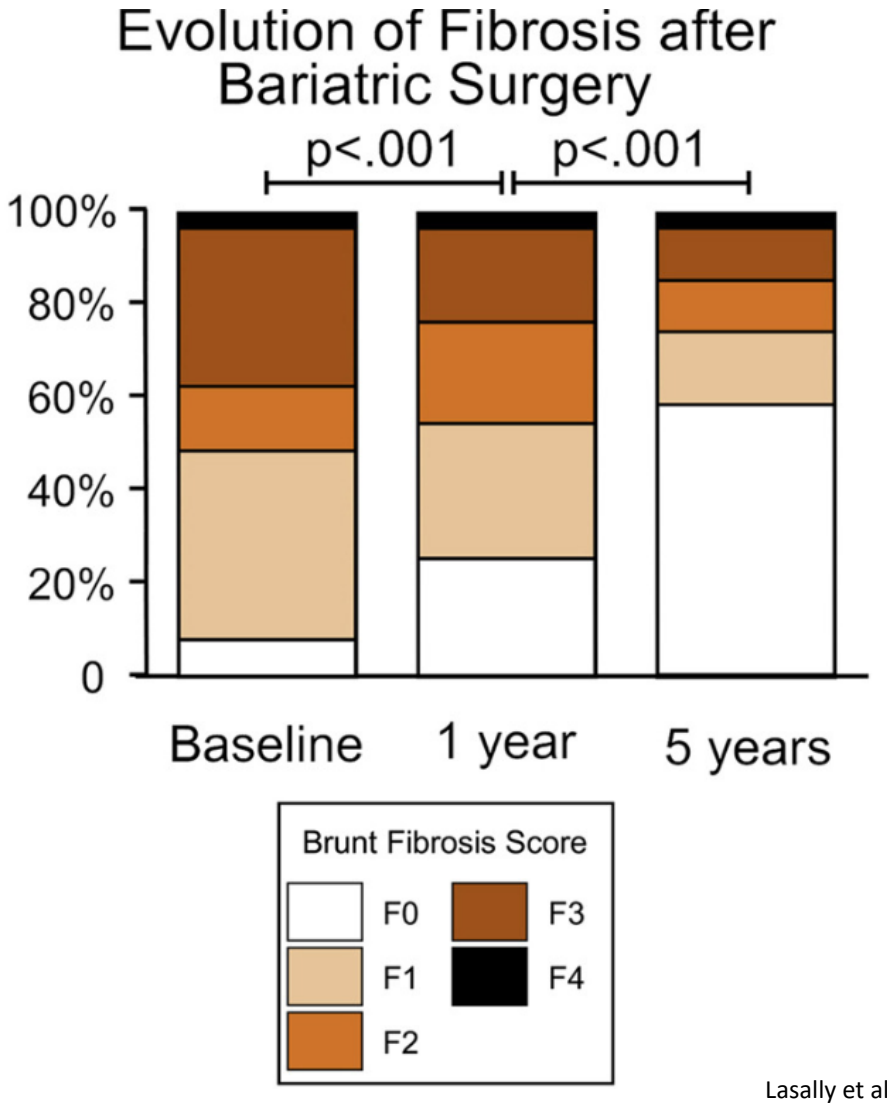
Recommended activity

- Aerobic exercise ≥ 3 days/week (≥ 150min/week moderate intensity)
- Resistance exercise ≥ 2 days/week
- Reduce sedentary behaviour

Patel NS, et al. Clin Gastroenterol Hepatol. 2017

BARIATRIC SURGERY IMPROVES MASLD OUTCOME

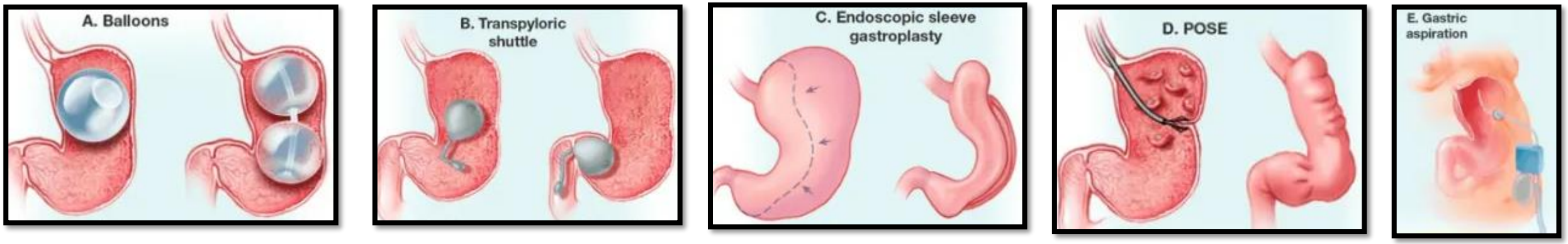




Lasally et al. Gastro 2020

ENDOSCOPIC BARIATRIC METABOLIC THERAPIES (EBMTS)

There are five FDA-approved endoscopic bariatric and metabolic therapies (EBMTs)



OVERVIEW OF AVAILABLE MEDICATIONS FOR MASLD

Medication	FDA indication	Patient population	Liver related clinical benefit	Potential side effects
Vitamin E 800 IU daily	NA	MASH wo T2DM or cirrhosis	improves steatosis	Hemorrhagic stroke, ? Risk of prostate CA
Pioglitazone 30-45mg daily	T2DM	MASH w/wo T2DM	improves steatosis, MASH	Weight gain, bone loss
Liraglutide 1.8mg s.c. daily (T2DM) 0.6 to 3mg sc daily (obesity)	T2DM, obesity	MASH wo cirrhosis	improves steatosis	GI, gallstones, pancreatitis
Semaglutide 0.4mg s.c daily 0.25-2.4mg SQ weekly	T2DM, obesity	MASH wo cirrhosis	improves steatosis, MASH	GI, gallstones, pancreatitis
Tirzepatide	T2DM	MASLD w T2DM or obesity	improves steatosis	GI, gallstones, pancreatitis
SGLT-2i	T2DM	MASLD and T2DM	improves steatosis	GU yeast infection, bone loss

Rinella et al. Hepatology 2023

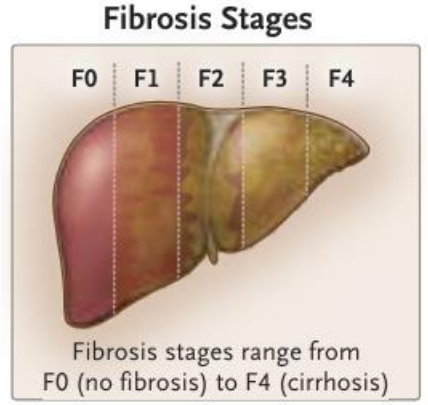
RESMETIROM – THE FIRST FDA APPROVED MASH TREATMENT

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 8, 2024 VOL. 390 NO. 6

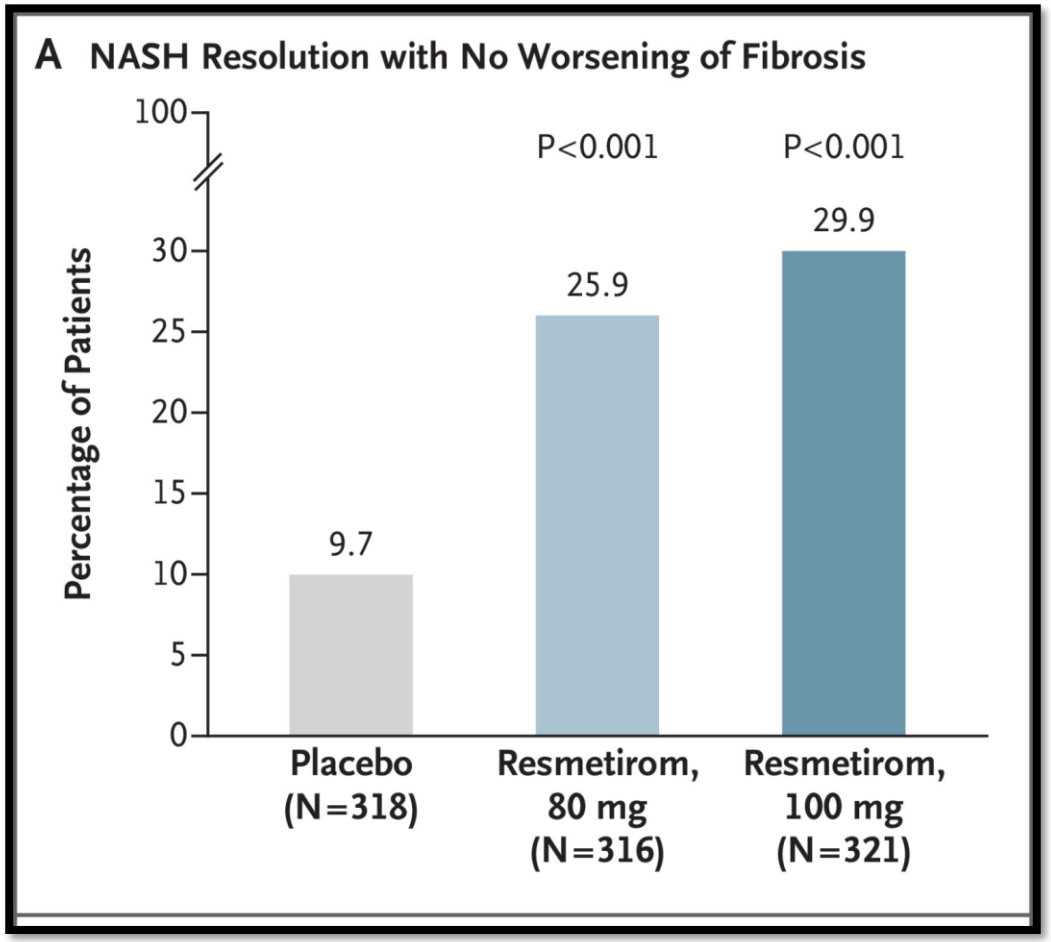
A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

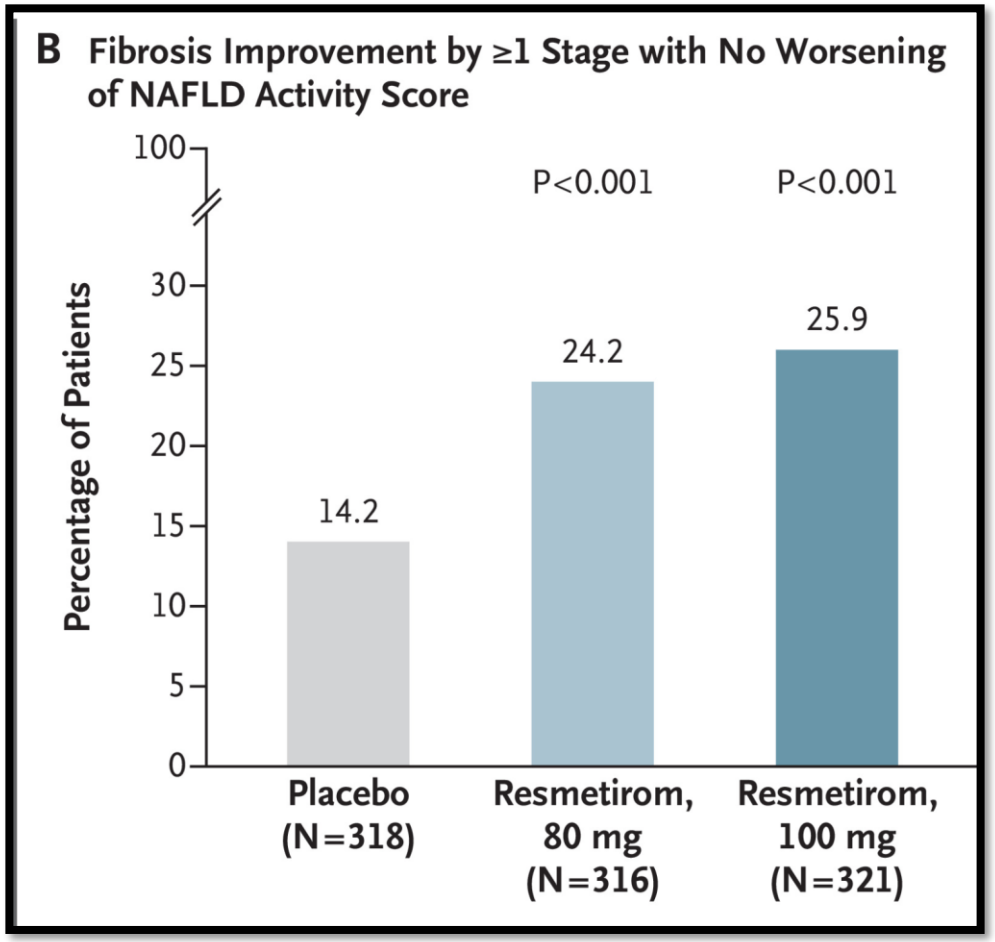
- Oral, liver-directed, thyroid hormone receptor beta agonist
- 966 patients F1B, F2, F3 (>50% were F3)
- Resmetirom 80mg vs. 100mg vs. placebo
- Update at 52 weeks
- Liver biopsy at enrollment and week 52
- Ongoing trial planned for 54 months



Harrison, et al. NEJM 2024

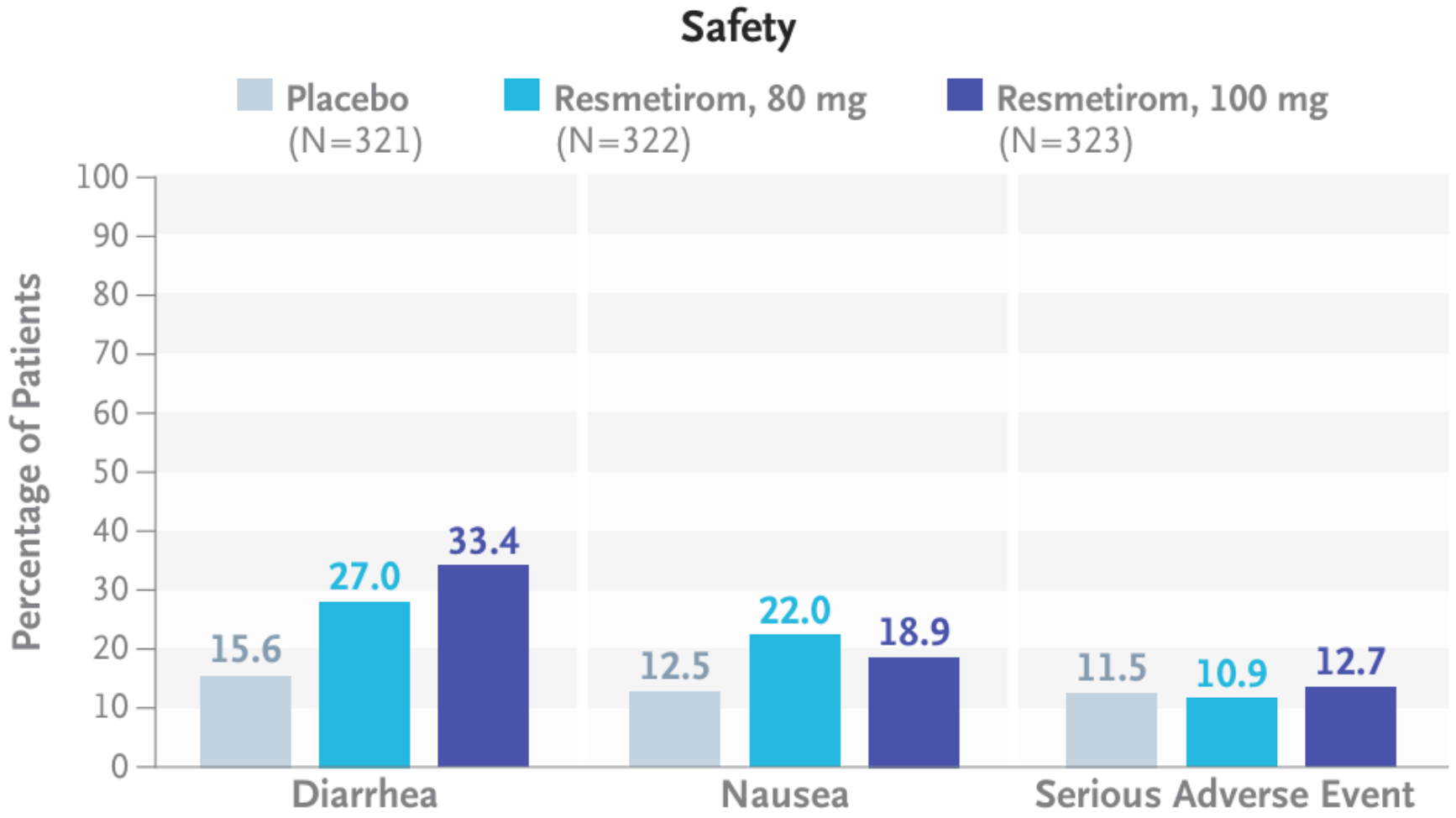
PRIMARY END POINTS FROM MAESTRO-NASH TRIAL





Harrison, et al. NEJM 2024

ADVERSE EFFECTS



PRESCRIBING INFORMATION FOR RESMETIROM

- Name: resmetirom or Rezdiffra
- Indication
  - MASH with F2 or F3 fibrosis
  - Contraindicated in patients with decompensated cirrhosis
- Weight based dosing
  - <220lb/100kg – 80mg/day
  - ≥220 lbs/100kg: 100mg/day
- Drug-drug interactions
  - Avoid gemfibrozil and cyclosporine
  - Statin dose should be decreased
  - Ok to remain on GLP-1 agonists
  - Reduce resmetirom dose if on concomitant clopidogrel

RESMETIROM UNKNOWNS

- Duration of treatment
- Liver profile monitoring during treatment
- How to assess for response
- Use in post transplant patients
- When patient can actually receive the medications (likely “in a few months”)

KEY TAKE HOME POINTS

- MASLD is hepatic manifestation of the metabolic syndrome
- MASLD can occur in lean patient or normal liver enzymes
- Alcohol, T2DM, family history and obesity are risk factors for more significant disease
- Patients with increased fibrosis are at higher risk of cirrhosis and liver-related mortality
- Non-invasive tests is useful in stratifying patients with advanced fibrosis (≥ F3)
- MetALD = MASLD + Alcohol-associated Liver Disease (ALD)
- Best treatment for MASLD is weight loss
- Resmetirom is the first and only FDA approved treatment

QUESTIONS?

- Contact email: valerie.lin@lahey.org