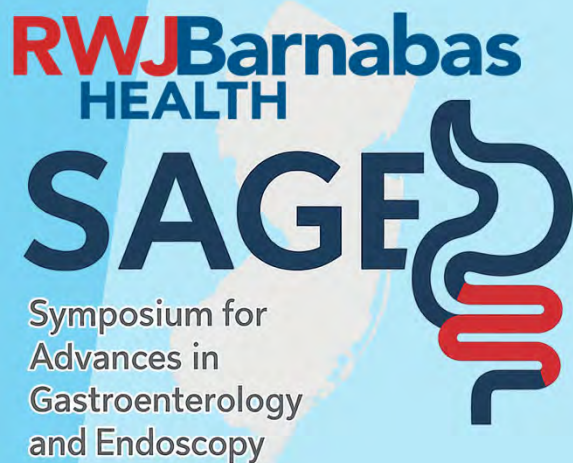




MASLD: What you need to know in 2026 and beyond

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Professor of Medicine

Medical Director: Liver Transplantation

Division Director: Hepatology and Transplant Hepatology

Rutgers New Jersey Medical School

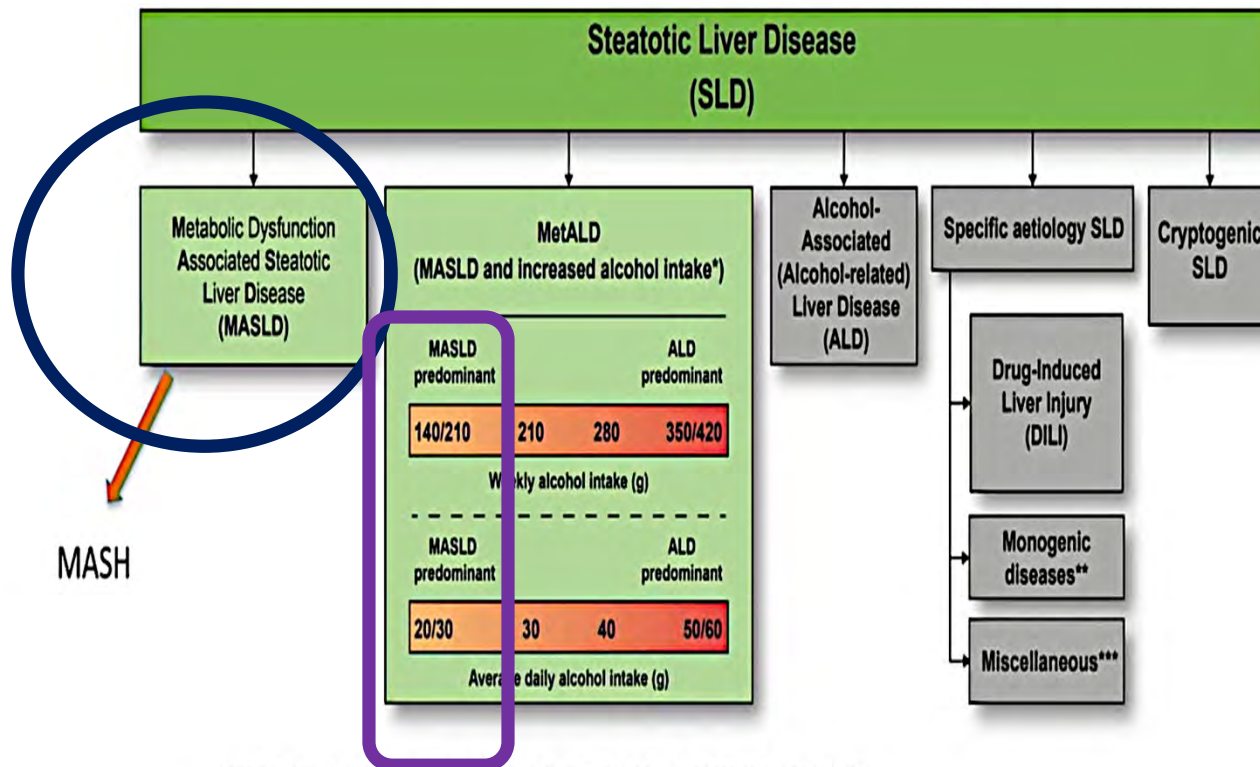
Disclosures

- Advisory Board:
 - Salix
 - Abbvie
 - Gilead
 - Malinkrodt
 - Madrigal

MASLD: Metabolic Dysfunction Associated Steatotic Liver Disease

- ▶ Epidemiology
- ▶ Definitions
- ▶ Natural History
- ▶ Diagnosis
- ▶ Current Therapy
- ▶ Dx paradigms: FDA approved therapies

Consensus nomenclature change for NAFLD



*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)

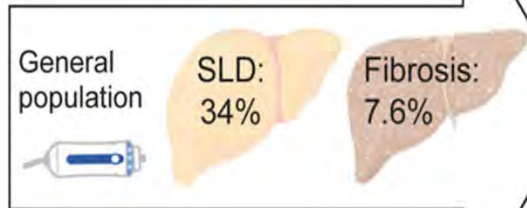
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism

***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease

<https://www.aasld.org/new-masld-nomenclature>

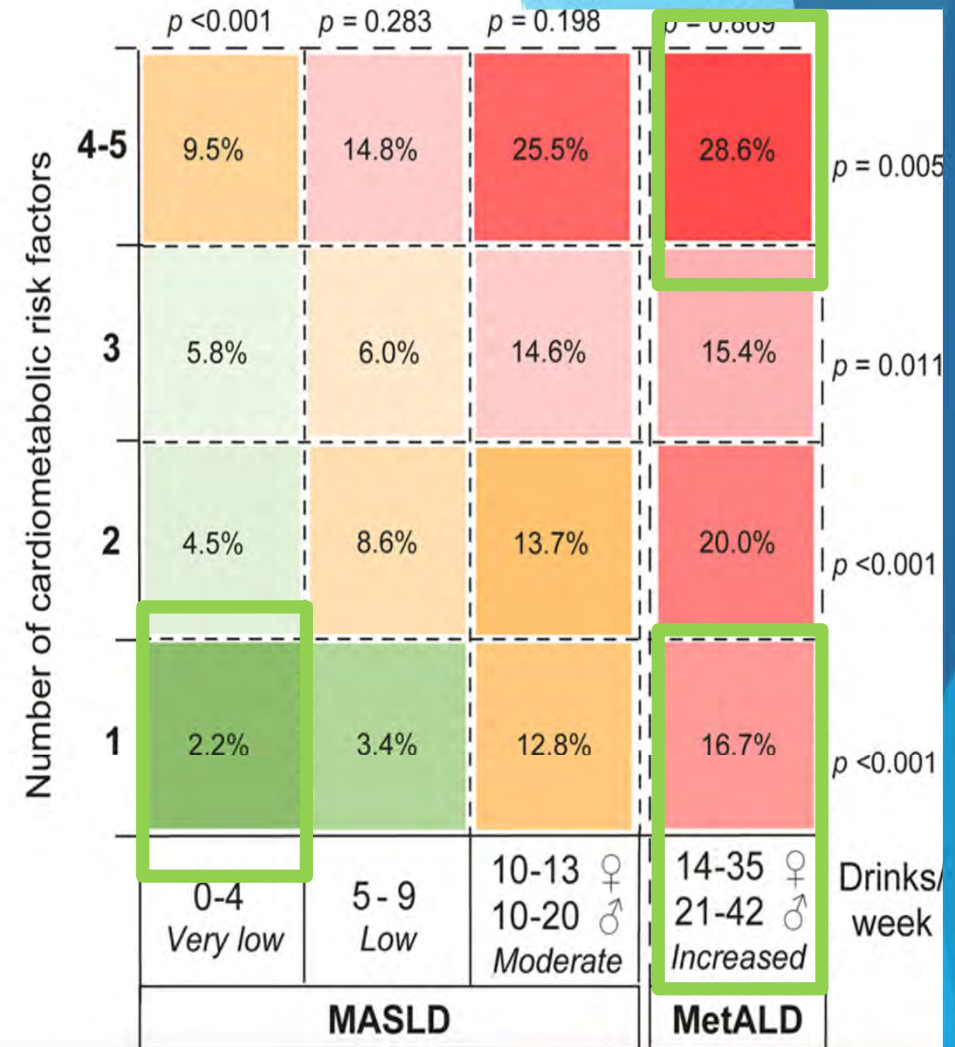
Fibrosis staging unchanged

Derivation sample: Spain,
ETHON cohort (n = 6,826)



Validation sample: U.S.,
NHANES cohort (n = 4,427)

- Steatotic liver disease was defined as CAP ≥ 275 dB/m
- Significant fibrosis was defined as LSM ≥ 8.0 kPa
- Results refers to the derivation cohort
- Analysis was performed with Chi² test



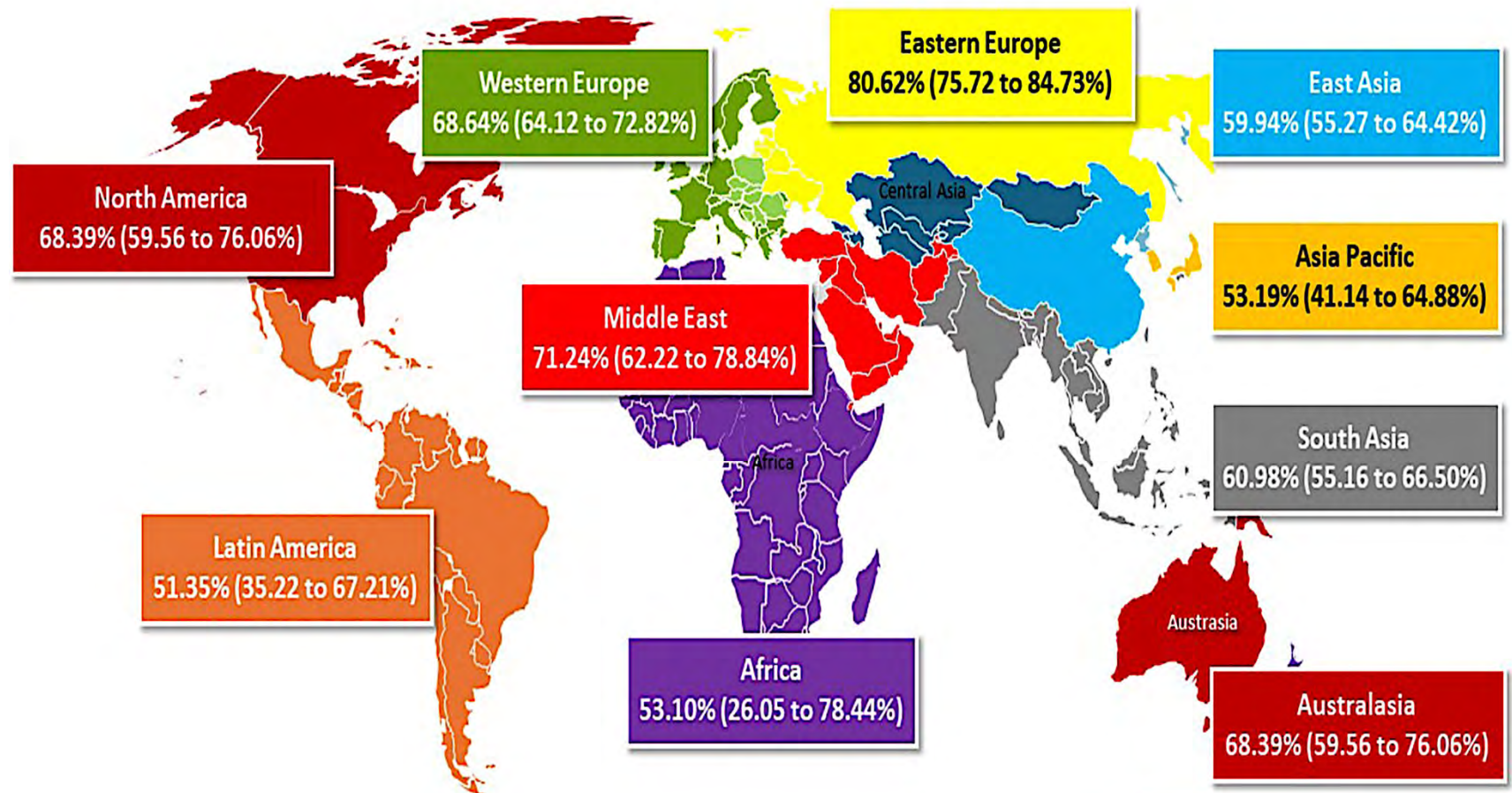
Epidemiology

- ▶ **MASLD** is the most common cause of liver disease in Adults in the US
 - ▶ 2024-2026: leading indication for liver transplantation along with alcohol associated liver disease
 - ▶ Most common cause of abnormal liver tests in Pediatrics
 - ▶ HIV infected patients at high risk of MASLD (with older ARV's)
- ▶ **Race/Ethnicity**
 - ▶ More common in Hispanics>Caucasians>African Americans
 - ▶ Rapidly increasing prevalence in Asians, East Asians ("lean MASLD")
- ▶ **Risk Factors**
 - ▶ Metabolic syndrome (obesity, hyperlipidemia, insulin resistance, HTN)
 - ▶ Genetic association with PNPLA3 and TM6SF2 ("lean SLD")
- ▶ **Diagnosis**
 - ▶ Abnormal liver tests (sometimes), imaging, liver biopsy not required
 - ▶ Exclude other causes of liver disease
 - ▶ A normal ALT does not rule out MASLD
 - ▶ An abnormal ALT does not rule in MASH

Pooled Prevalence of NAFLD: 65.33% (95% confidence interval:62.35 to 68.18%)

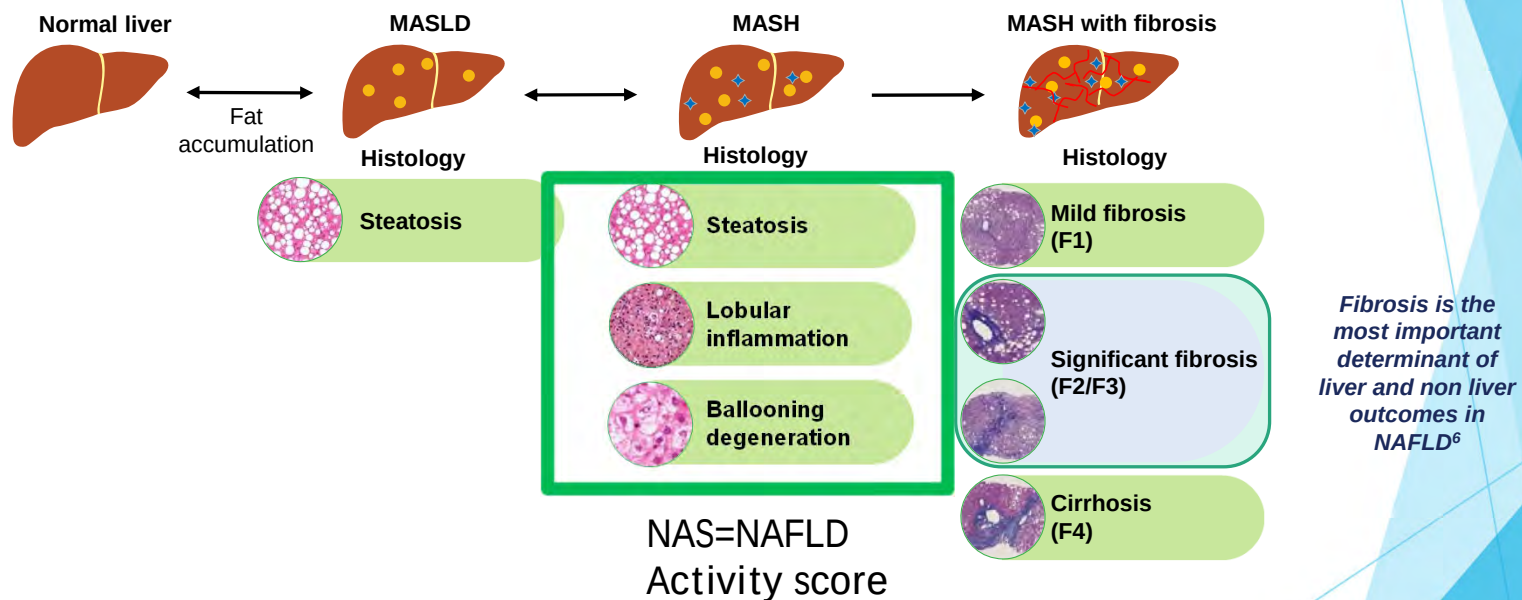
Clinical Gastroenterology and Hepatology

Volume 22, Issue 10, October 2024, Pages 1999-2010.e8



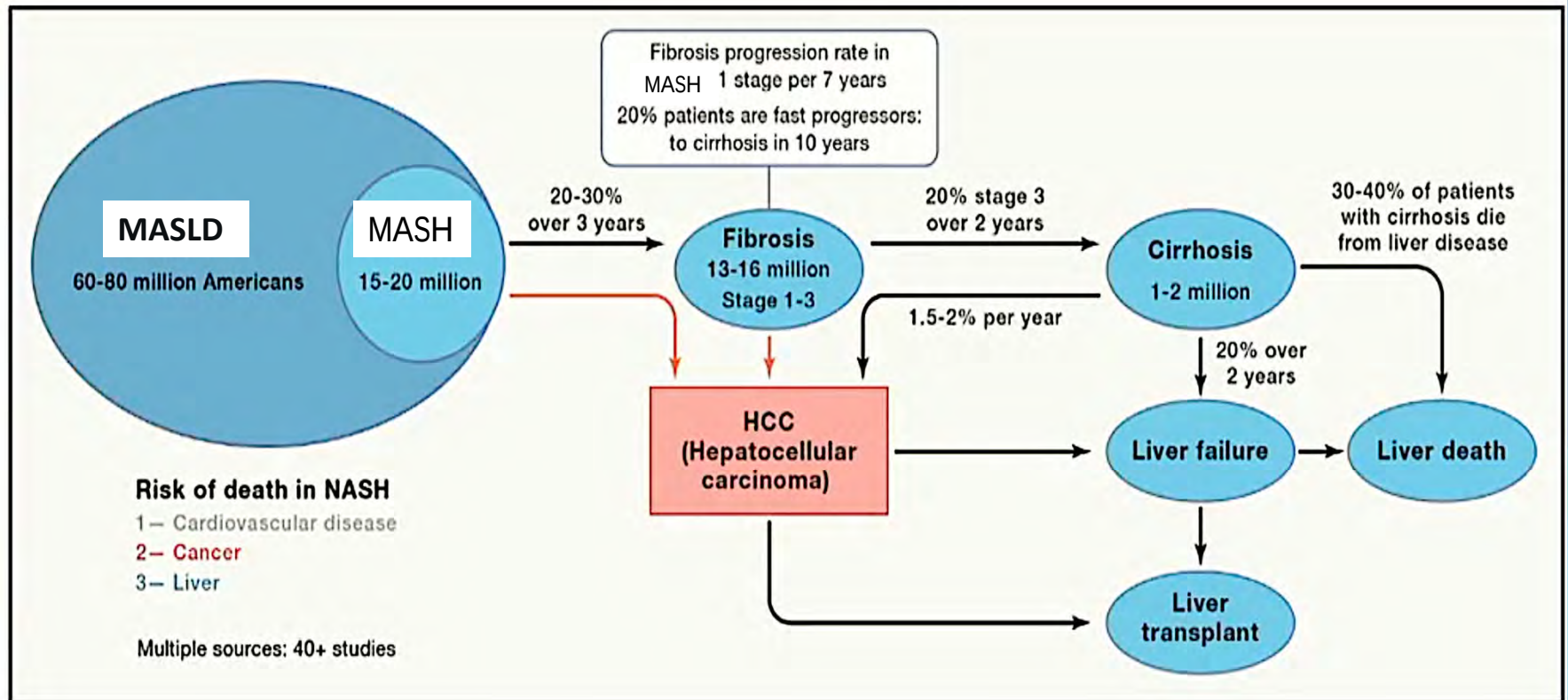
MASLD is chronic and progressive, ranging from simple steatosis to MASH^{1,2}

MASH is the inflammatory subtype of MASLD, which can progress to cirrhosis, liver cancer, or result in death¹⁻⁵



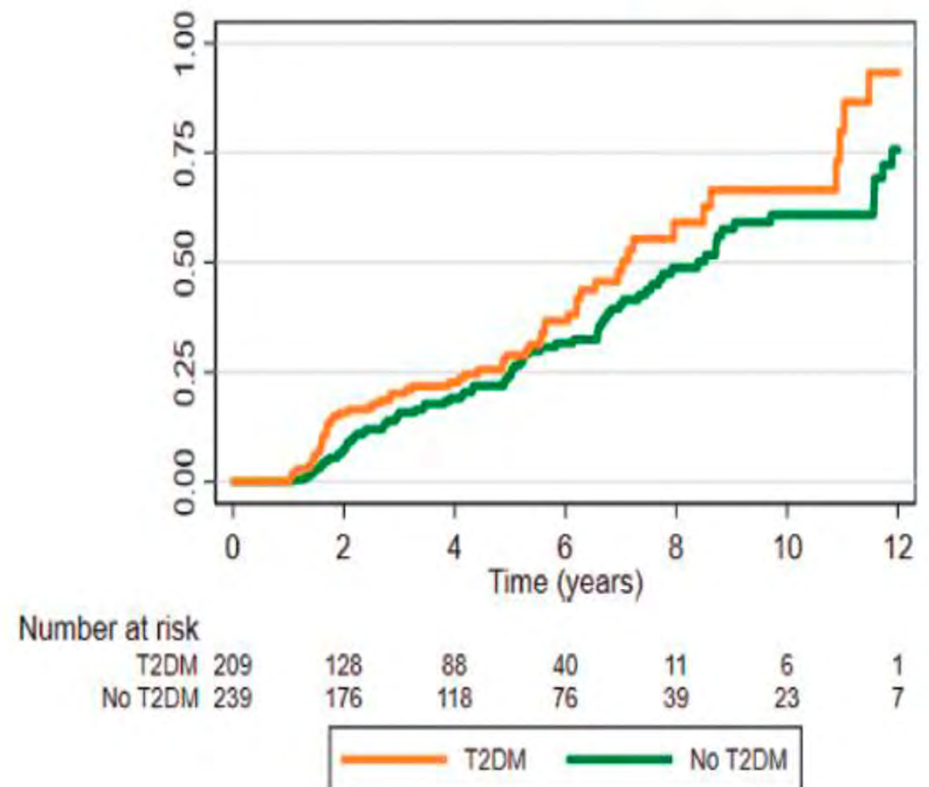
1. Sheka AC, et al. *JAMA*. 2020;323(12):1175-1183.
2. Alkhoury N, McCullough AJ. *Gastroenterol Hepatol (N Y)*. 2012;8(10):661-668.
3. EASL-EASD-EASO. *J Hepatol*. 2016;64:1388-1402.
4. Diehl AM, Day C. *N Engl J Med*. 2017;377:2063-2072.
5. Honda, et al. *Int J Mol Sci*. 2020;21:4039.
6. Kanwal F, et al. *Gastroenterology*. 2021;161(5):1657-1669.

Natural history of MASLD



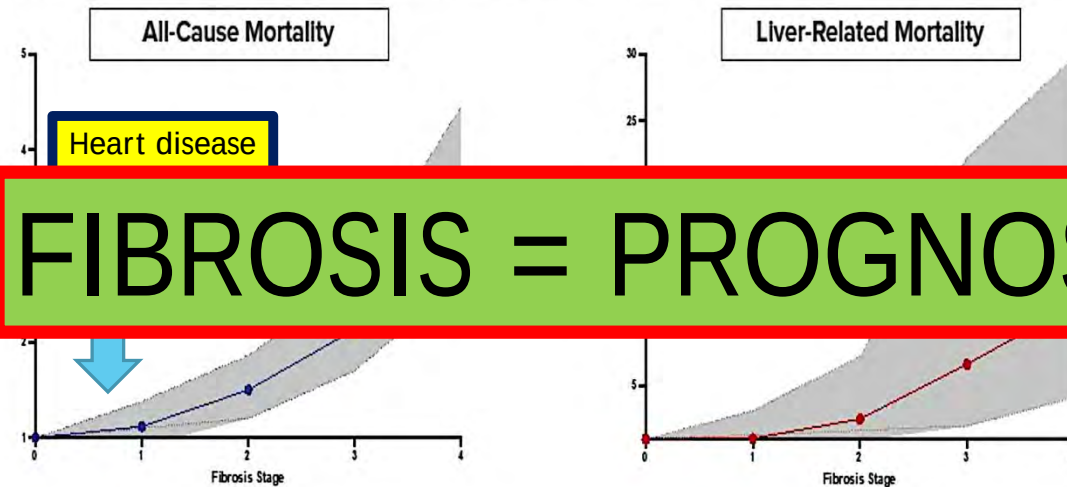
Rate of Progression of Fibrosis is Higher in Diabetic Patients

- 448 adults (239 non-diabetics, 209 diabetics) with ↑ MASLD were prospectively studied
- Diabetics had a significantly higher cumulative incidence of fibrosis progression at 4-years, 8-years and 12-years
 $P=0.003$



Fibrosis Stage and Disease Outcomes in MASLD

Systematic Review and Meta-Analysis of 13 Studies 4,428 NAFLD Patients (2,875 With Histological NASH).



	Stage 0 vs 1 RR (95% CI), P value n/N vs n/N, I ² statistic	Stage 0 vs 2 RR (95% CI), P value n/N vs n/N, I ² statistic	Stage 0 vs 3 RR (95% CI), P value n/N vs n/N, I ² statistic	Stage 0 vs 4 RR (95% CI), P value n/N vs n/N, I ² statistic
All-cause mortality				
8	1.12 (0.91–1.38) 135/843 vs 136/896, 0%	1.50 (1.20–1.86) 135/843 vs 103/425, 0%	2.13 (1.70–2.67) 135/843 vs 86/301, 0%	3.42 (2.63–4.46) 135/843 vs 61/169, 27%
Liver-related mortality				
7	1.05 (0.35–3.16) 3/521 vs 7/755, 0%	2.53 (0.88–7.27) 3/521 vs 10/340, 0%	6.65 (1.99–22.25) 3/521 vs 12/248, 0%	11.13 (4.15–29.84), 0% 3/521 vs 22/151

All-Cause Mortality and Liver-Related Mortality Increase With Fibrosis Stage in NASH.

MASLD

Laboratory Findings

- **Mild Elevation in ALT>AST (unlike ETOH) or WNL labs**
 - **AST>ALT if cirrhotic**
- **Mildly increased Alk phos and GGT**
- **Elevation in cholesterol, triglycerides, HgA1C**
- **Hepatitis A-E, alpha 1, and ceruloplasmin neg/norm, celiac neg**
- **Autoimmune markers (1:80-1:160)**
- **Elevation in ferritin (> 50% pts)**
 - **Absence of homozygous HFE gene**
 - **Heterozygous HFE gene does not impact history**
- **NIT's for everyone (non-invasive tests for fibrosis)**

MASLD

Imaging Studies

- Ultrasound- “increased echogenicity” often overestimates fat
 - ▶ Beware “pseudomass” due to focal fat sparing
- ▶ CT scan- low density parenchyma
- ▶ Imaging can now adequately assess the degree of hepatic fibrosis and/or steatosis
 - ▶ Newer technologies include
 - ▶ Fibroscan: Controlled attenuation parameter (CAP)
 - ▶ ARFI: Acoustic radiation force impulse or Ultrasound Elastography
 - ▶ MR elastography/ iron corrected T1
 - ▶ MR-PDFF (Protein Density Fat Fraction)

VCTE

Vibration Controlled Transient Elastography



FDA accepts proposal for reasonably likely surrogate endpoint for 'MASH' all-cause mortality or liver-related events

review each
measures

check success
rate

control invalid
measurement

[8/27/2025] FDA's Center for Drug Evaluation and Research, Office of New Drugs has accepted a Letter of Intent for the qualification of Liver Stiffness Measurement by

Vibration-Controlled Transient Elastography is a reasonably likely surrogate endpoint for clinical trials in adults with non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate-to-advanced liver fibrosis (scarring).





SUPERSONIC IMAGINE

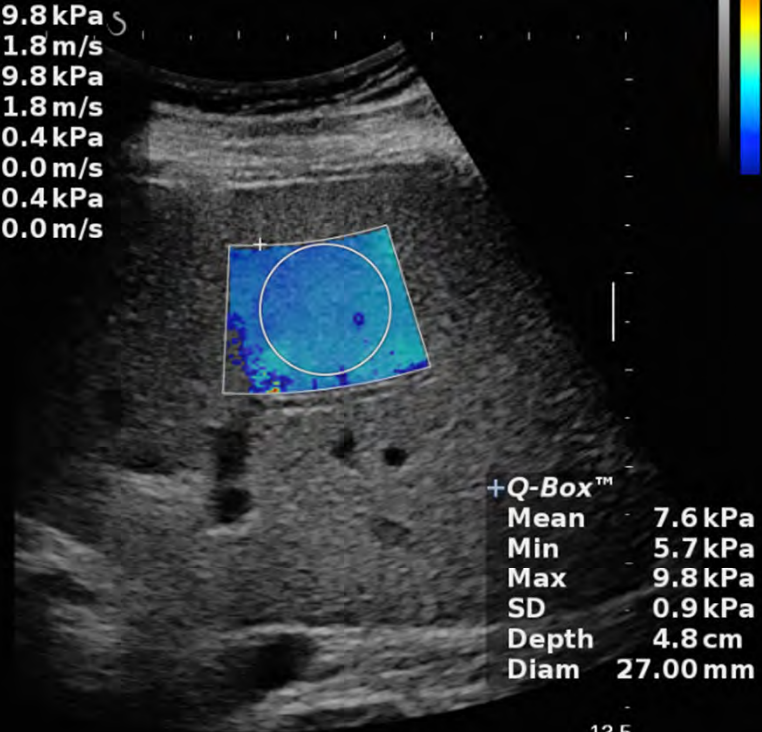
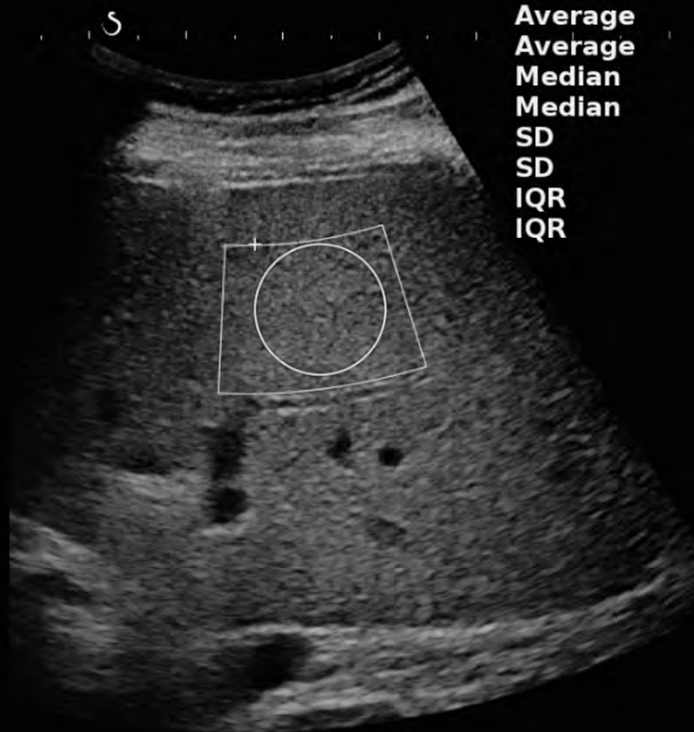
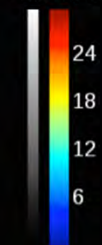
ARFI: acoustic radiation force impulse

08/06/2015 17:43:39
XC6-1 / Abdominal / Liver
MI 1.6 Tib 3.6

Q-Box Liver

Nb Q-Box =	10
Average	9.8 kPa
Average	1.8 m/s
Median	9.8 kPa
Median	1.8 m/s
SD	0.4 kPa
SD	0.0 m/s
IQR	0.4 kPa
IQR	0.0 m/s

≥30 kPa



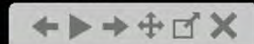
+Q-Box™

Mean	7.6 kPa
Min	5.7 kPa
Max	9.8 kPa
SD	0.9 kPa
Depth	4.8 cm
Diam	27.00 mm

13.5

B
Pen/Med/H
M 12/64 dB/Low
T 1540 m/s/SC/SR 4
G 58 %/Fr. 7 Hz

Z 140 %

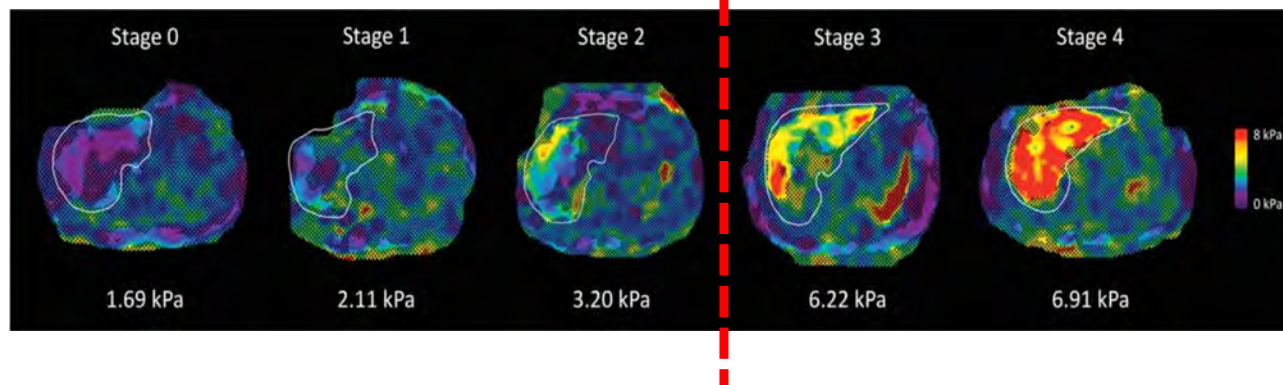


SWE™
Std
M 1/Low
S 5/O 50 %/G 80 %

MR Elastography

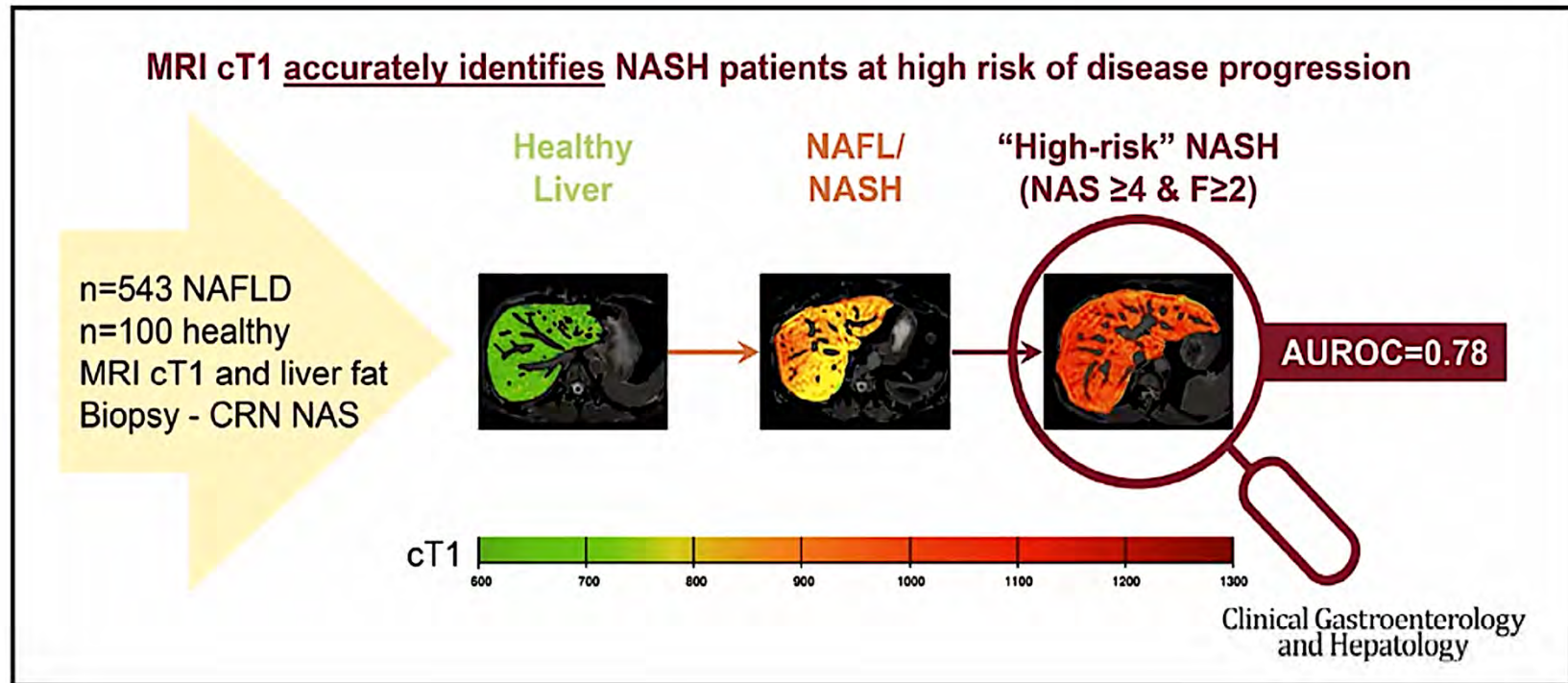
MRE: Detecting Advanced Fibrosis in People With MASLD

- Prospective, cross-sectional analysis of 2D MRE in N = 117 patients with biopsy-proven NAFLD



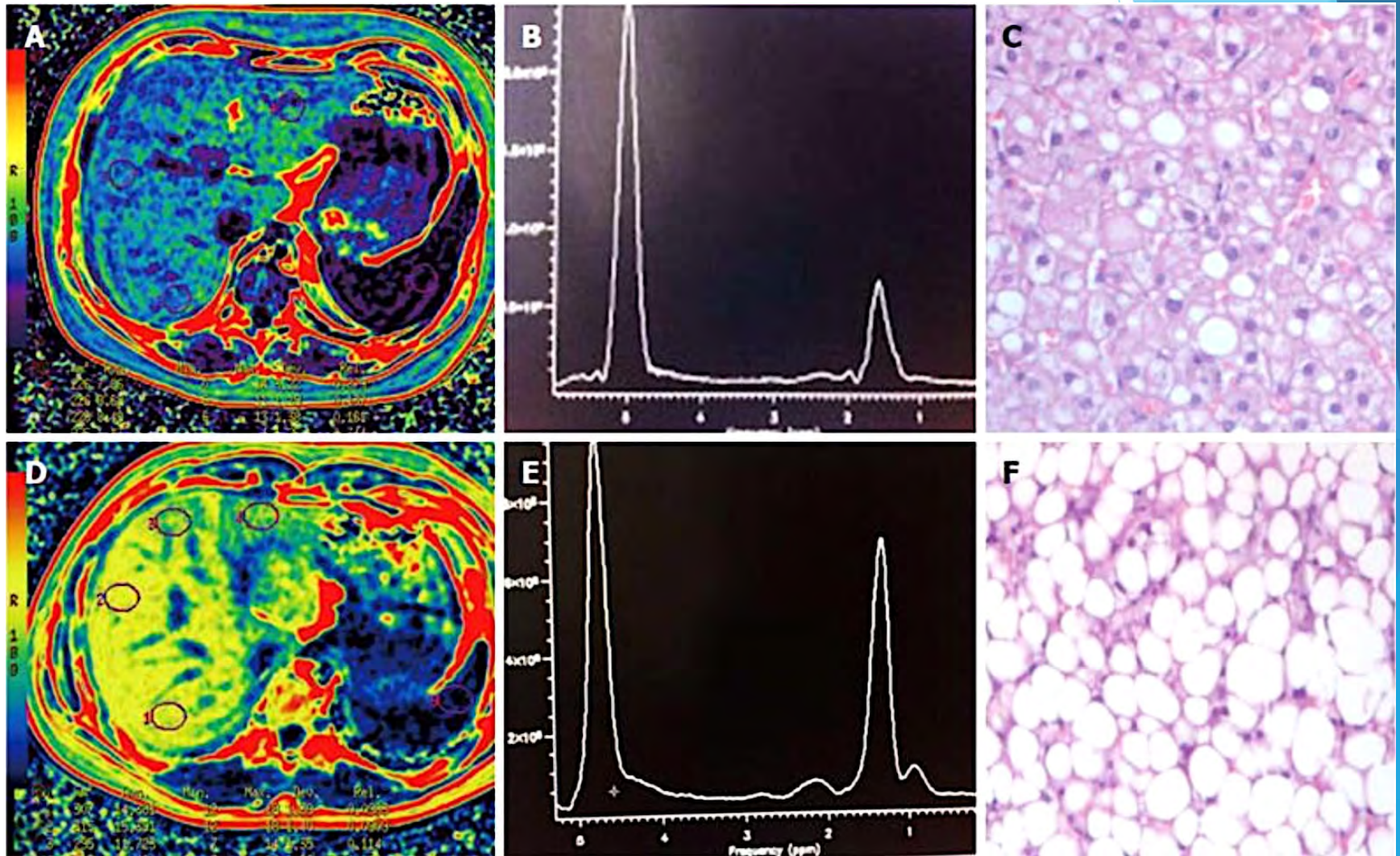
Cutoff for Detecting Advanced Fibrosis $\geq$ F3	Sensitivity	Specificity	AUROC
MRE stiffness > 3.63 kPa	.86	.91	.924

cT1 (MRI iron-corrected T1)



1. Andersson A, et al. *Clin Gastroenterol Hepatol*. 2022;20(11):2451-2461. 2. Rinella ME, et al. *Hepatology*. 2023;77(5):1797-1835.

MRI PDFF (protein density fat fraction)



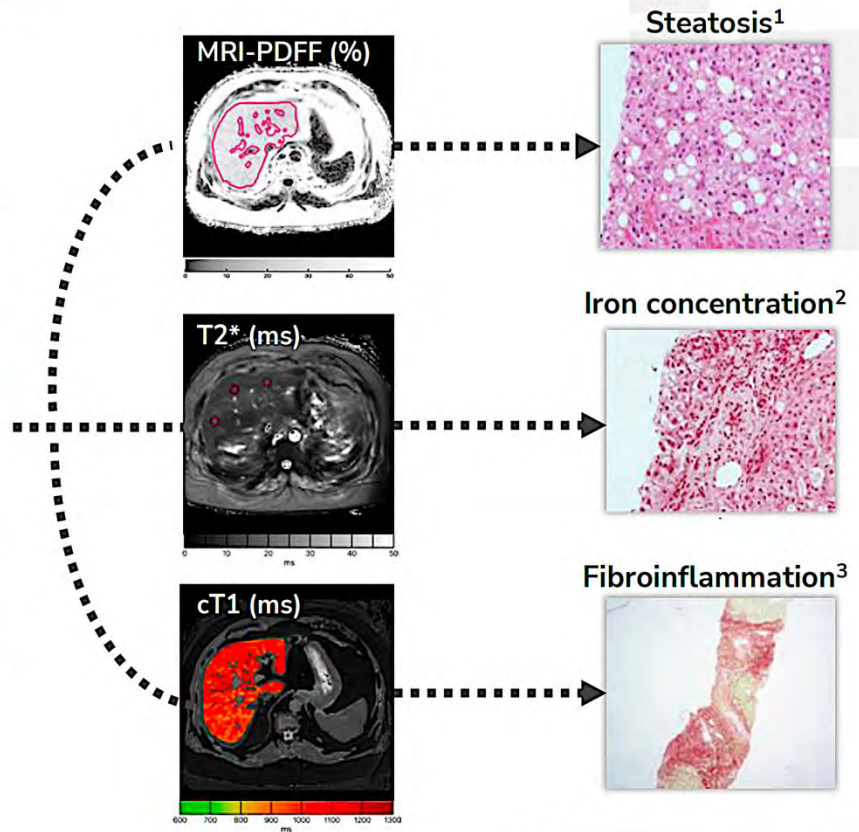
What is **LiverMultiScan**?

Precision imaging for patients with liver disease



In a single contrast-free MRI scan

3 facets of liver disease



Commonly Used Noninvasive Tests (NIT)

NIT's need to be performed on every patient at risk for MASLD

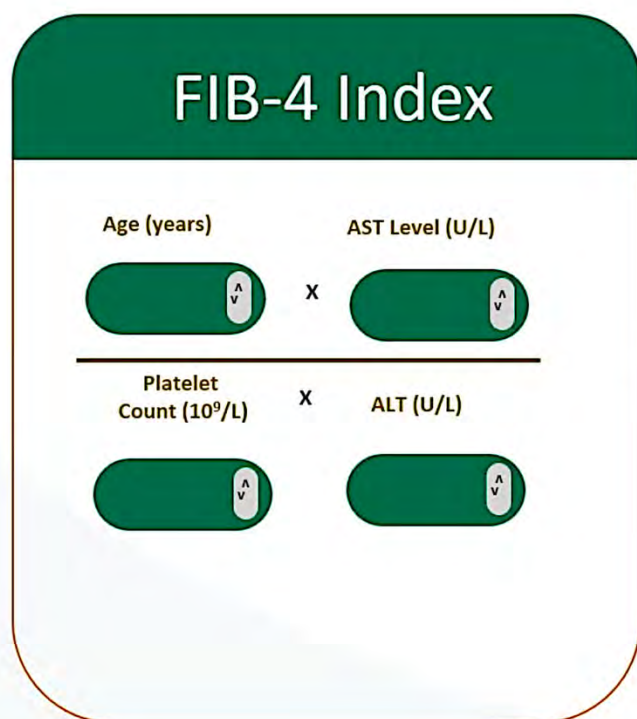
Combine a non-invasive lab test and a non-invasive imaging test

Clinical or Laboratory Scores		Imaging
Simple	Proprietary	Elastography
- Fibrosis-4 (FIB-4)^[1,2] - MAFLD fibrosis score^[4,5] - AST/platelet ratio index^[1]	- Enhanced Liver Fibrosis Test^[1] - ADAPT/Pro-C3^[3] (not available in US) - FibroSure^[1] Labcorp - Hepascore - Fibrotest Quest	- Transient elastography (eg. FibroScan)^[1,2] 2D shear wave elastography^[4] - Magnetic resonance elastography^[1] - Corrected T1 (Liver MultiScan)^[5,6] - MRI-PDFF^[7] - FAST score^[8]

Advanced Fibrosis/Cirrhosis = screening for portal HTN and HCC
> F1 fibrosis: refer

1. EASL. J Hepatol. 2015;63:237. 2. Alkhouri. Gastroenterol Hepatol (N Y). 2012;8:661. 3. Daniels. Hepatology. 2019;69:1075.
4. Sigrist. Theranostics 2017;7:1303. 5. Jayaswal. AASLD 2018. Abstr. 1042. 6. Jayaswal. Liver Int. 2020;40:3071.
7. Idilman. Radiology. 2013;267:767. 8. Newsome. Lancet Gastroenterol Hepatol. 2019;[Epub].

FIB-4: First Line Testing in Primary Care



Rule-Out

Low Probability
< 1.30

Rule-In

Indeterminant
1.30 – 2.67

High Probability
> 2.67

Advantages:
Readily available
No added cost
Validated in MASLD
High NPV (~90%)

Areas of debate

Should patients with T2DM use lower cutoffs/other tests?
Performance declines in high-prevalence settings
Optimal testing intervals
When to stop screening

Steatosis-Associated Fibrosis Estimator (SAFE) Score

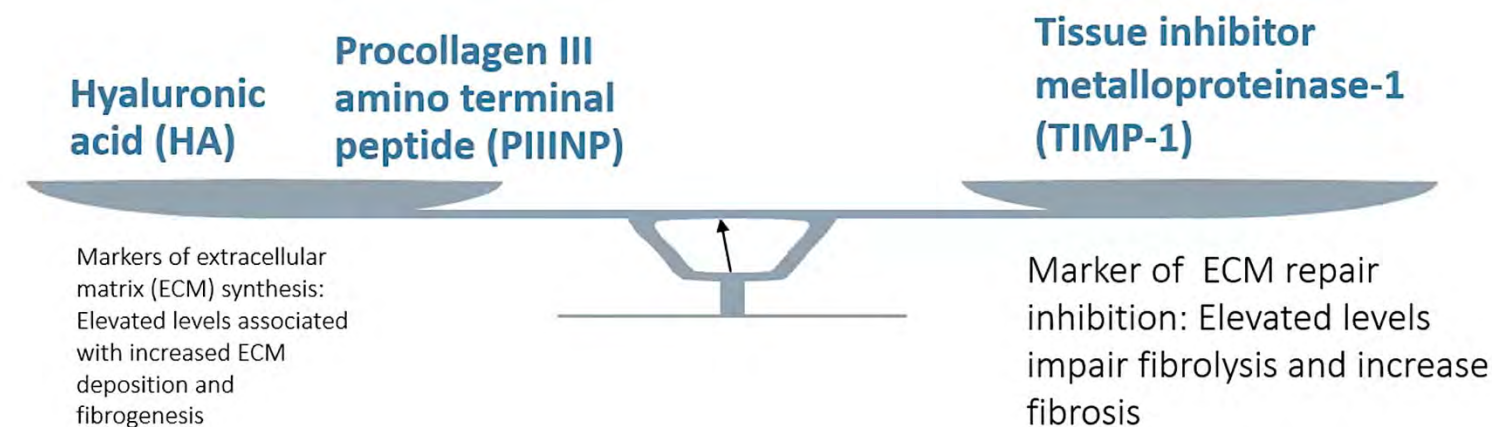


Estimates the risk of moderate to advanced liver fibrosis (stages 2 or higher) among patients with metabolic dysfunction-associated steatotic liver disease (MASLD).

When to Use	Pearls/Pitfalls	Why Use
Age		years
<u>BMI</u>	Norm: 20 - 25	kg/m ²
Diabetes	☒ No ☐ Yes	
<u>AST</u>	Norm: 10 - 40	U/L
<u>ALT</u>	Norm: 10 - 55	U/L
Albumin	Norm: 3.5 - 5	g/dL ↔
Total protein	Norm: 6 - 8.5	g/dL ↔
Platelets	Norm: 150 - 350	× 10 ³ /μL ↔

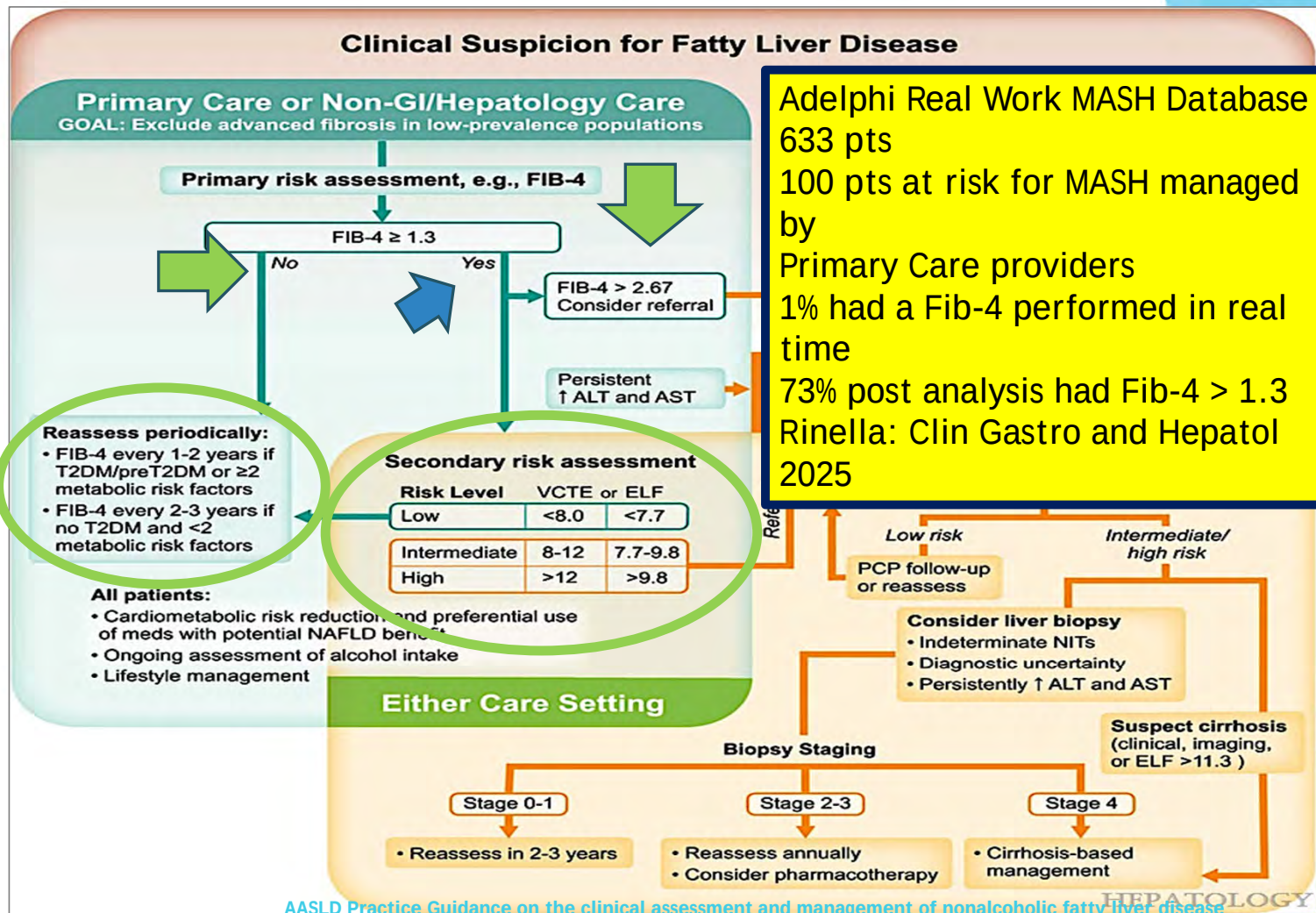
Hepatology
. 2026;83):591-602

Enhanced Liver Fibrosis (ELF™) Test for prognosis in advanced MASH



Fully Automated: ELF Score Calculated and Reported





Adelphi Real Work MASH Database
633 pts
100 pts at risk for MASH managed by Primary Care providers
1% had a Fib-4 performed in real time
73% post analysis had Fib-4 > 1.3
Rinella: Clin Gastro and Hepatol 2025

AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease

Guidelines Across Disciplines Agree

	AASLD	AGA	ADA	AACE
Screening philosophy	Targeted case-finding in high-risk groups, not mass screening	Stepwise clinical care pathway	FIB-4 screening embedded in T2D annual care standards	Routine screening in all T2D + pre-diabetes
Who to screen	T2D, obesity + metabolic risk factors, incidental steatosis, elevated AST/ALT	T2D, >2 metabolic risk factors, incidental steatosis, elevated AST/ALT	All patients with T2D or pre-diabetes with elevated ALT or hepatic steatosis	T2D, pre-diabetes, obesity, MetS, >2 metabolic risk factors
Step 1: Initial NIT	FIB-4	FIB-4	FIB-4	FIB-4
Step 2: Second-line test	VCTE or ELF	VCTE	Defers to AASLD/AGA pathways	VCTE or ELF
Key distinction	Age adjusted FIB-4 thresholds	2026 updated adds MASLD + pharmacotherapy	Embeds MASLD screening into annual T2D care	Only guideline recommending routine screening in all T2D

The Goals for MASH Management – Then & Now

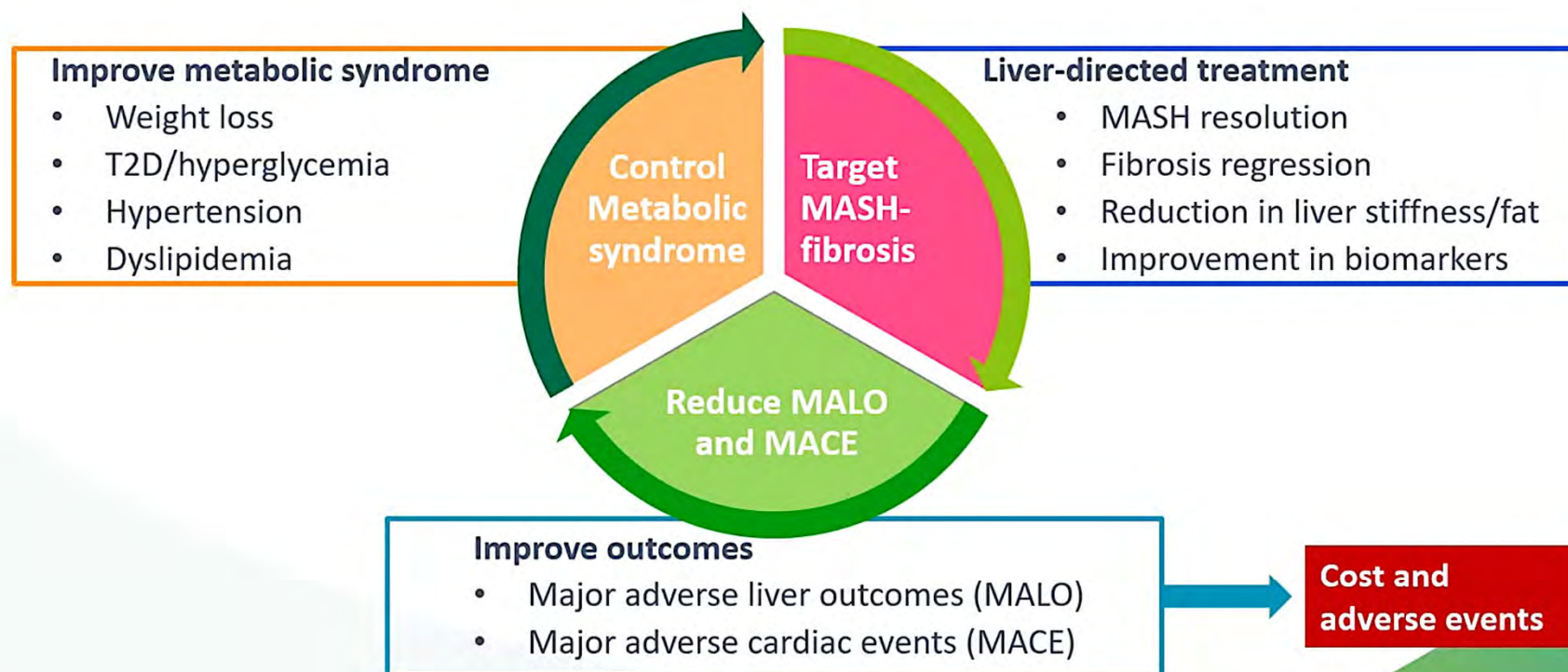
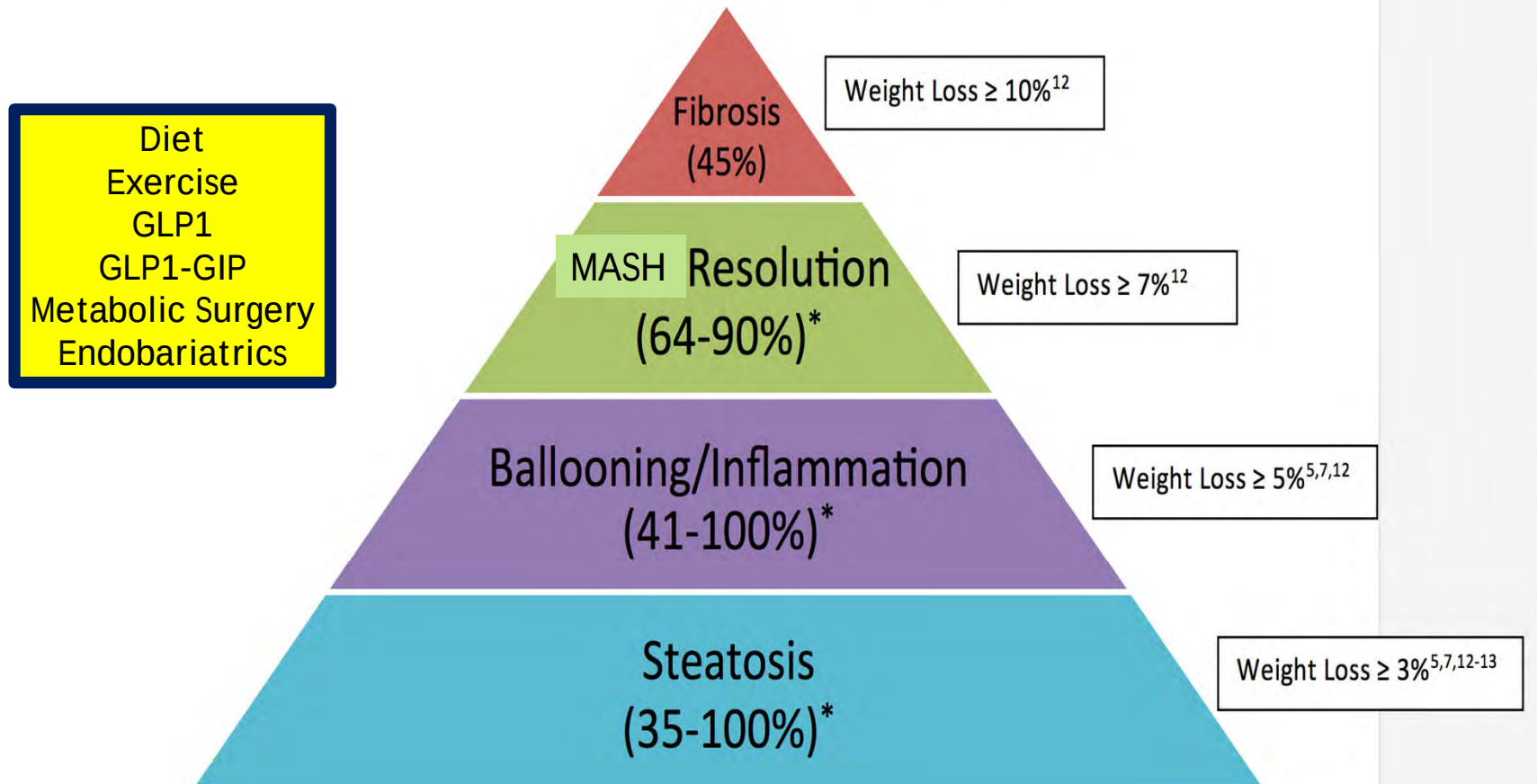


Figure 1 - Weight Loss Pyramid

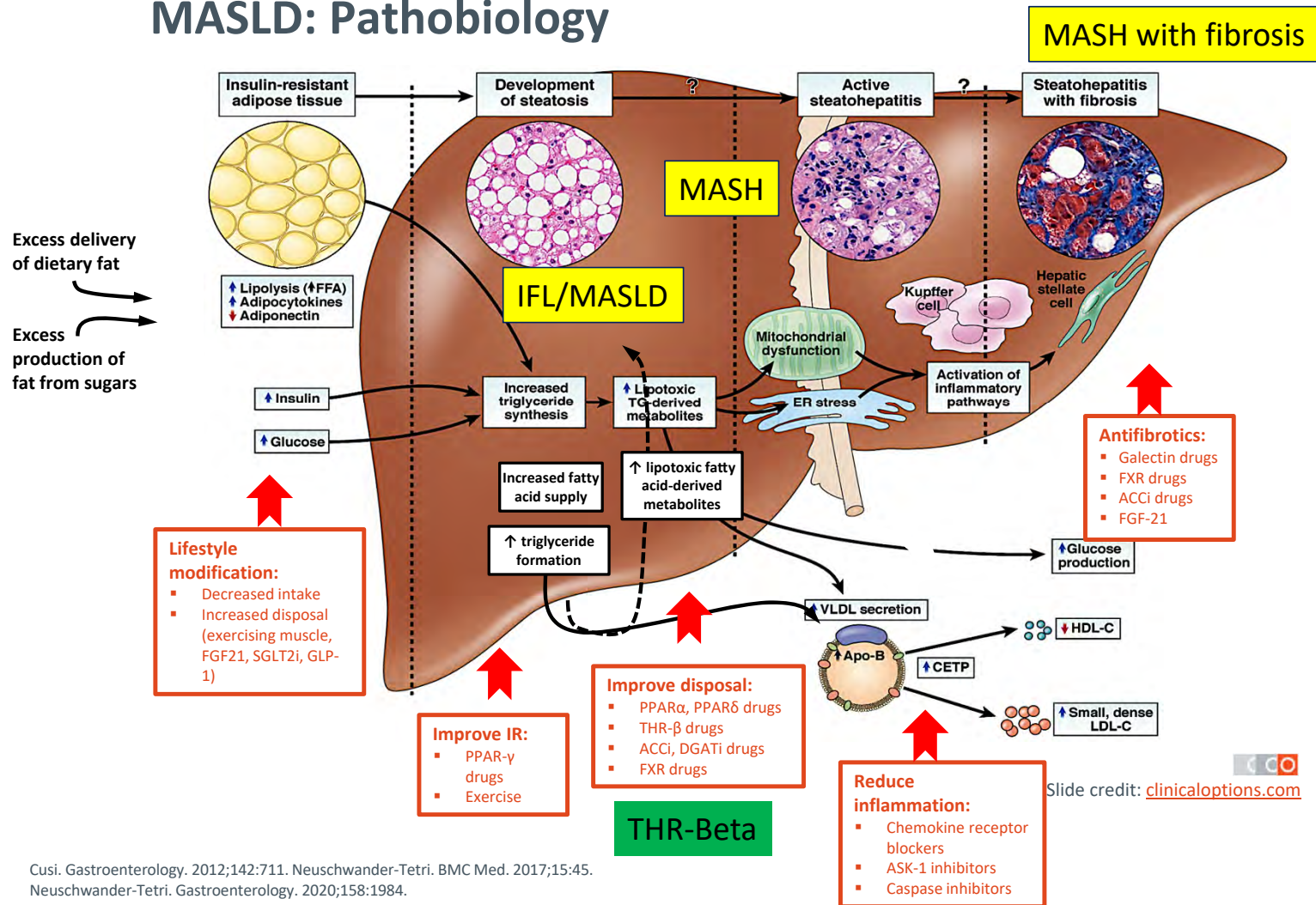


Harrison S Clin Liver Dis. 2016 May;20(2):339-350.



“Medical Therapies for MASLD” FDA Approved

MASLD: Pathobiology



Cusi. Gastroenterology. 2012;142:711. Neuschwander-Tetri. BMC Med. 2017;15:45.
Neuschwander-Tetri. Gastroenterology. 2020;158:1984.

MAESTRO-NASH Phase 3 Trial Design

KEY ELIGIBILITY CRITERIA

Presence of ≥ 3 metabolic risk factors

NASH on biopsy: NAS ≥ 4
(with ≥ 1 in each component)

Fibrosis stage F1B, F2, or F3

$\geq 8\%$ hepatic fat by MRI-PDFF

MAESTRO-NASH

1:1:1
Randomization

Placebo

Resmetirom 100 mg

Resmetirom 80 mg

△ Liver biopsy ▲ LDL-C/Biomarkers
▲ MRI-PDFF/MRE ▲ VCTE/CAP

Screening D1

W16

W24

W52

52 Week
Primary Endpoint

Month 54

54 Month Outcome
Primary Endpoint

**DUAL PRIMARY
END POINT
AT WEEK 52**

NR: NASH resolution (ballooning score=0,
inflammation score=0/1,
& ≥ 2 -point reduction in NAS)
with no worsening of fibrosis

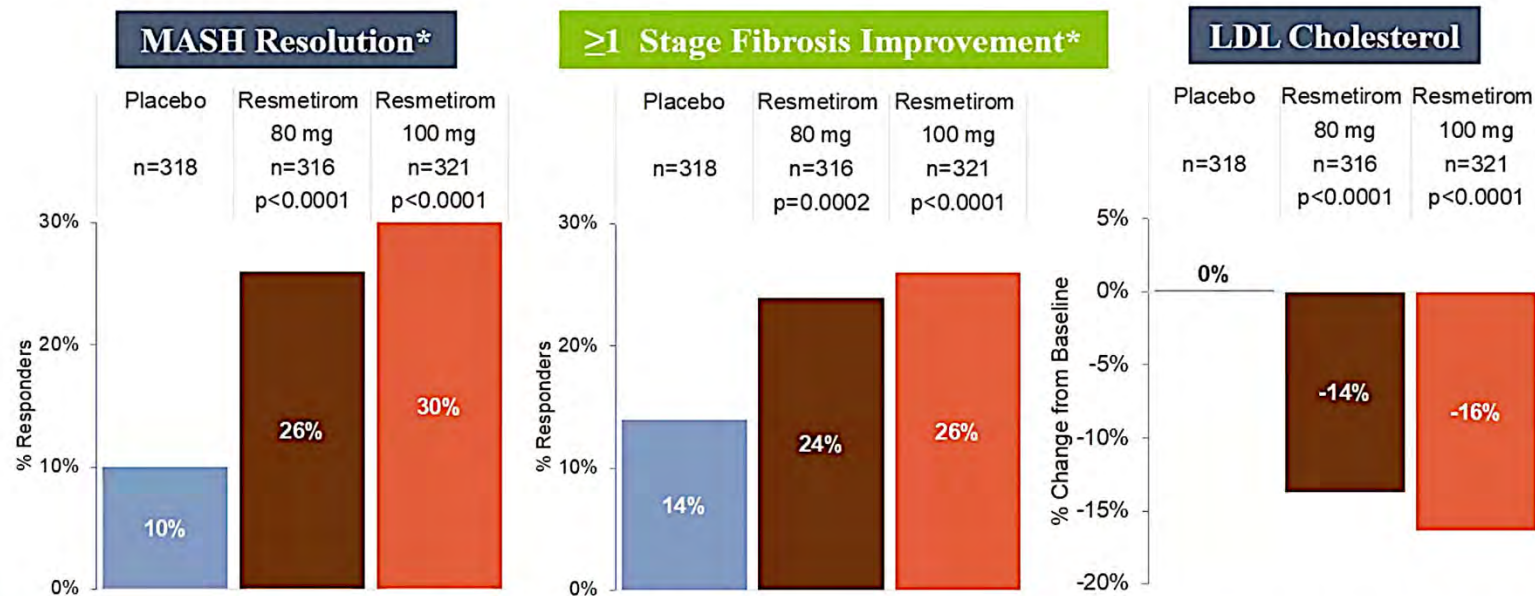
FI: ≥ 1 -stage improvement in fibrosis
with no worsening of NAS

- Patients in this serial liver biopsy trial were counseled on moderate diet and exercise at each study visit
- Patients on baseline GLP-1 therapy with $\geq 5\%$ weight loss at 52 weeks were evaluated for achievement of NR and FI liver biopsy end points or percent change from baseline in MRI-PDFF at Week 52

PI: Baseline Characteristics – MAESTRO NASH

Assessment of baseline disease severity			Overall (N=888)
Liver Biopsy	Fibrosis stage, n (%)	F2	328 (37)
		F3	560 (63)
Other Assessments	VCTE, kPa, median (Q1, Q3)*		12 (10, 15)
	CAP, dB/m, median (Q1, Q3)*		349 (320, 378)
	FIB-4, median (Q1, Q3)*		1.3 (1.0, 1.8)
	ELF, median (Q1, Q3)*		9.7 (9.2, 10.4)

MAESTRO Phase 3 Trial: Dual Primary Endpoints (Week 52)



Both primary liver biopsy endpoints and the key secondary endpoint of LDL cholesterol lowering were met

Patients will continue to be followed for at least 5 years for clinical outcomes
FDA provided accelerated approval March 14, 2024

MAESTRO-NASH: Adverse Events

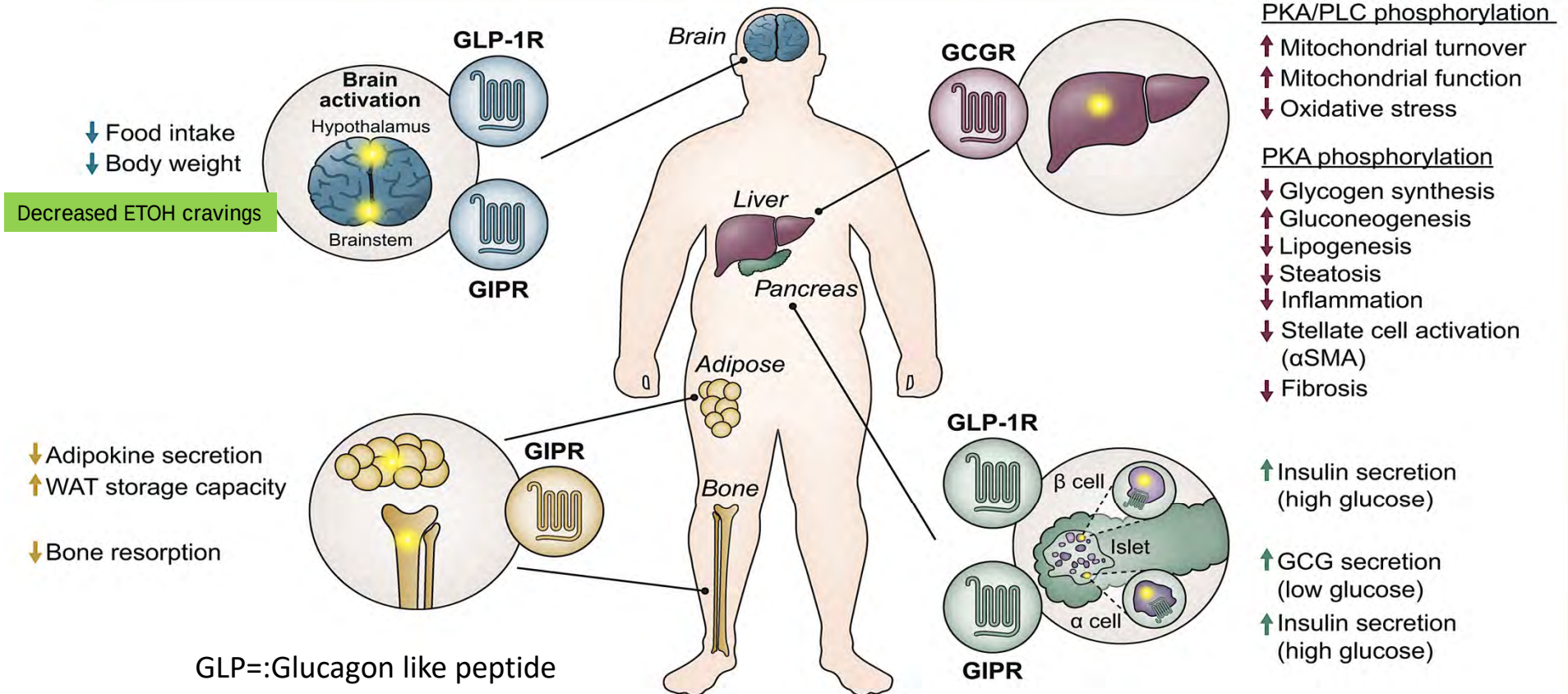
Safety Summary

AE Term	Resmetirom 80 mg (n=316)	Resmetirom 100 mg (n=321)	Placebo (n=318)
SAEs	11.8%	12.7%	12.1%
Study discontinuation for AEs	2.8%	7.7%	3.7%
Diarrhea	28%	34%	16%
Nausea	22%	19%	13%

- Resmetirom was **safe and well-tolerated**
- Consistent with previous Phase 2 and Phase 3 data, the most common adverse events reported with greater frequency in the resmetirom groups vs placebo were an excess of generally mild and transient diarrhea and generally mild nausea at the beginning of therapy

Incretin targets

Released from GI tract
In response to food



GLP=:Glucagon like peptide

GCGR: glucagon receptor

GIP: glucose dependent insulinotropic polypeptide = gastric inhibitory peptide

WAT: white adipose tissue

Newsome PN, Ambery P. *J Hepatol.* 2023;79:1557-1565.

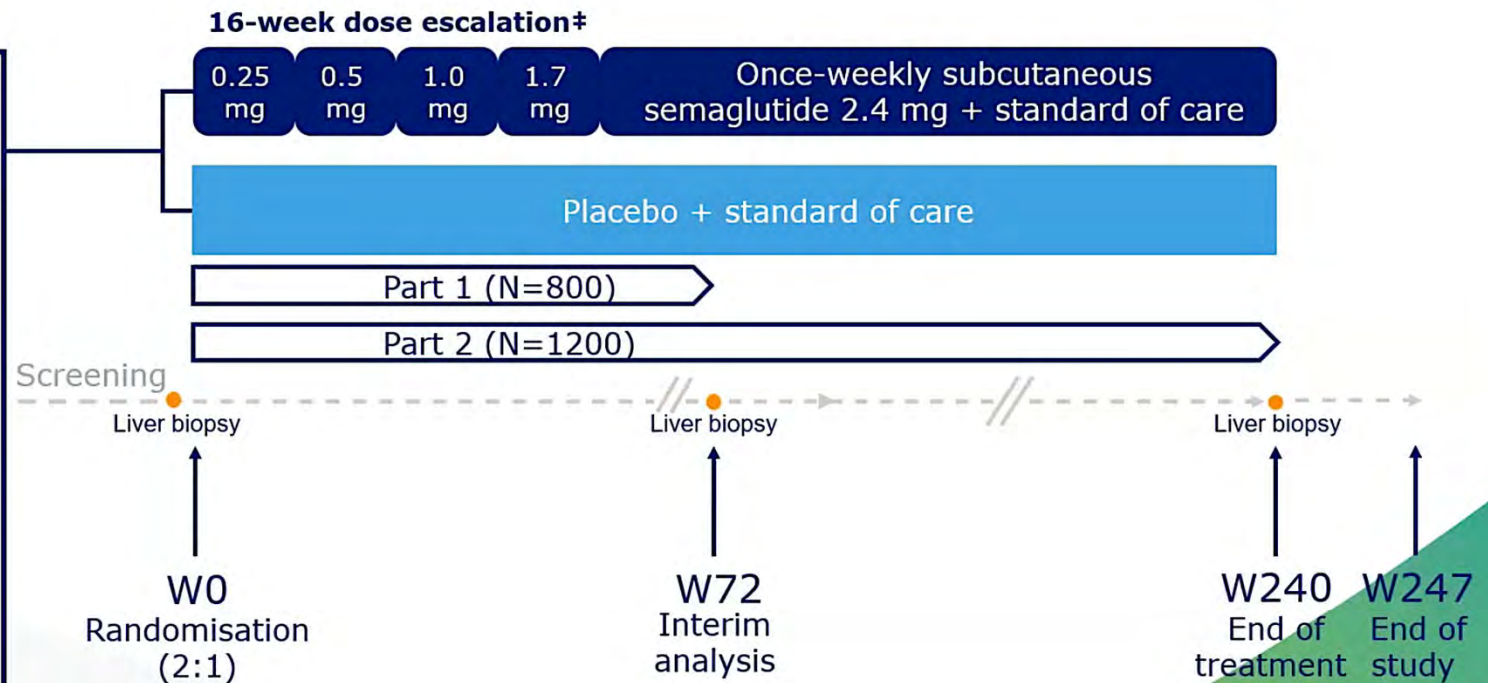
ESSENCE Phase 3 with Semaglutide: Design

Key inclusion criteria

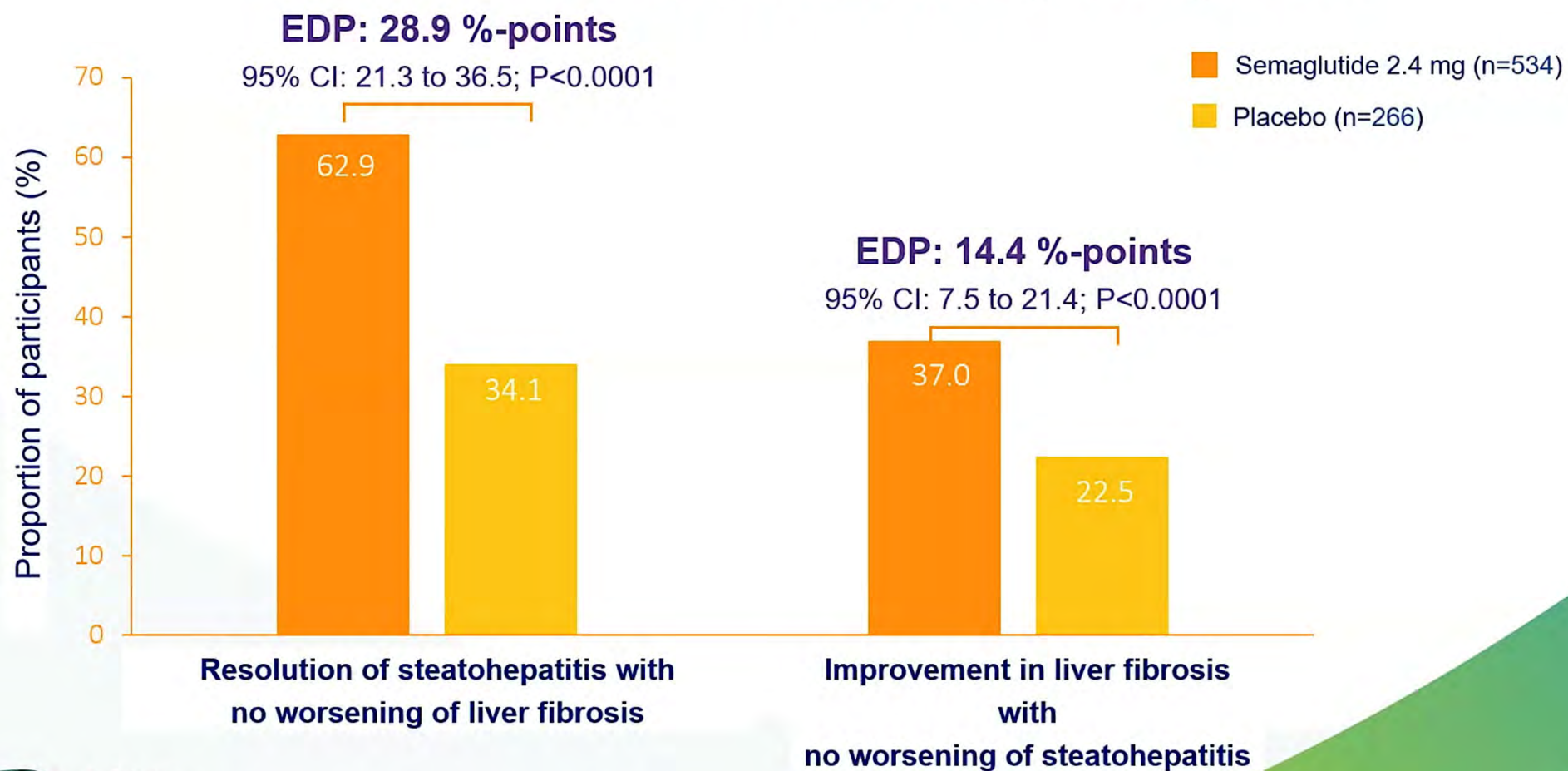
- Age ≥ 18 years old
- Histological evidence of fibrosis stage 2 or 3*
- NAS $\geq 4^{\dagger}$

Key exclusion criteria

- Chronic liver diseases other than MASLD
- Known or suspected excessive consumption of alcohol (>20 g/day for women or >30 g/day for men)
- Treatment with GLP-1RAs or unstable use of other glucose-lowering, lipid-lowering or weight loss medications within 90-days prior to screening



ESSENCE Phase 3: Primary Endpoints



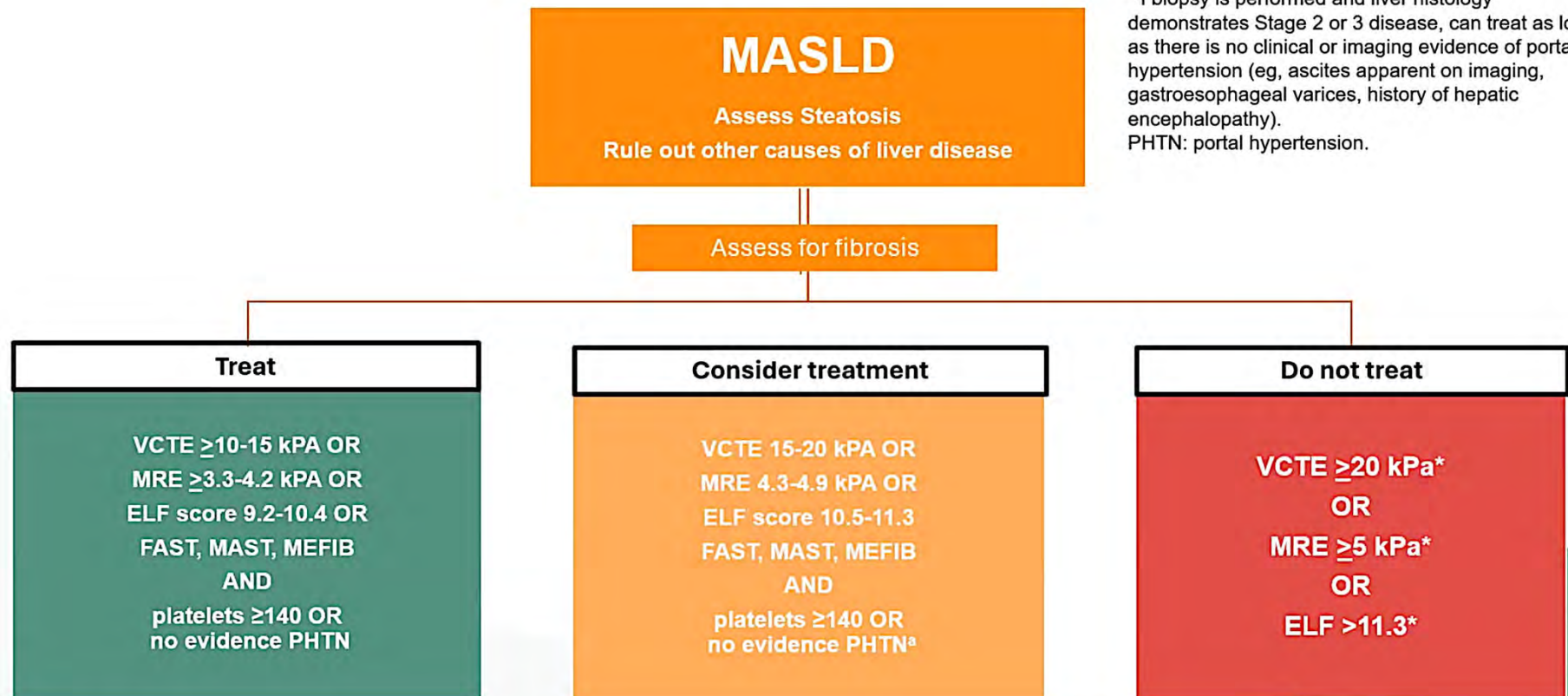
Semaglutide: Phase 3 Trial Safety

Safety Analysis Set (1195 participants)

AE, n (%)	Semaglutide 2.4 mg (n=800)	Placebo (n=395)
All AEs	690 (86.3)	315 (79.7)
Fatal AEs	3 (0.4)	6 (1.5)
Serious AEs	107 (13.4)	53 (13.4)
AEs leading to trial discontinuation	21 (2.6)	13 (3.3)
AEs affecting $\geq 10\%$ of participants		
Nausea	290 (36.3)	52 (13.2)
Diarrhea	215 (26.9)	48 (12.2)
Constipation	178 (22.3)	33 (8.4)
Vomiting	149 (18.6)	22 (5.6)
COVID-19	134 (16.8)	74 (18.7)
Decreased appetite	112 (14.0)	11 (2.8)

Treatment Decision Based on NITs

*If biopsy is performed and liver histology demonstrates Stage 2 or 3 disease, can treat as long as there is no clinical or imaging evidence of portal hypertension (eg, ascites apparent on imaging, gastroesophageal varices, history of hepatic encephalopathy).
PHTN: portal hypertension.



MASLD: Summary.

- ▶ **MASLD is the most common cause of liver disease in the US (and most of the rest of the world)**
- ▶ **MASLD**
 - ▶ most common indication for liver transplantation in the US in women
 - ▶ second most common for men
- ▶ **Natural History: MASH w/ fibrosis = bad liver outcomes =MALO's**
- ▶ **Use FIB-4 to assess for fibrosis**
 - ▶ **Fib-4 < 1.3, treatment by PCP, Endocrinologist, APP**
 - ▶ **Fib-4 > 1.3**
 - ▶ Serum tests for Fibrosis (ELF)
 - ▶ US elastography or VCTE, refer if >F1
- ▶ **Treatment is directed at modifying the metabolic syndrome and improving insulin resistance**
 - ▶ Diet, Exercise, Blood sugar, obesity control, Treat elevated Lipids and Cholesterol,
 - ▶ Resmetirom F2/F3
 - ▶ Semaglutide F2/F3