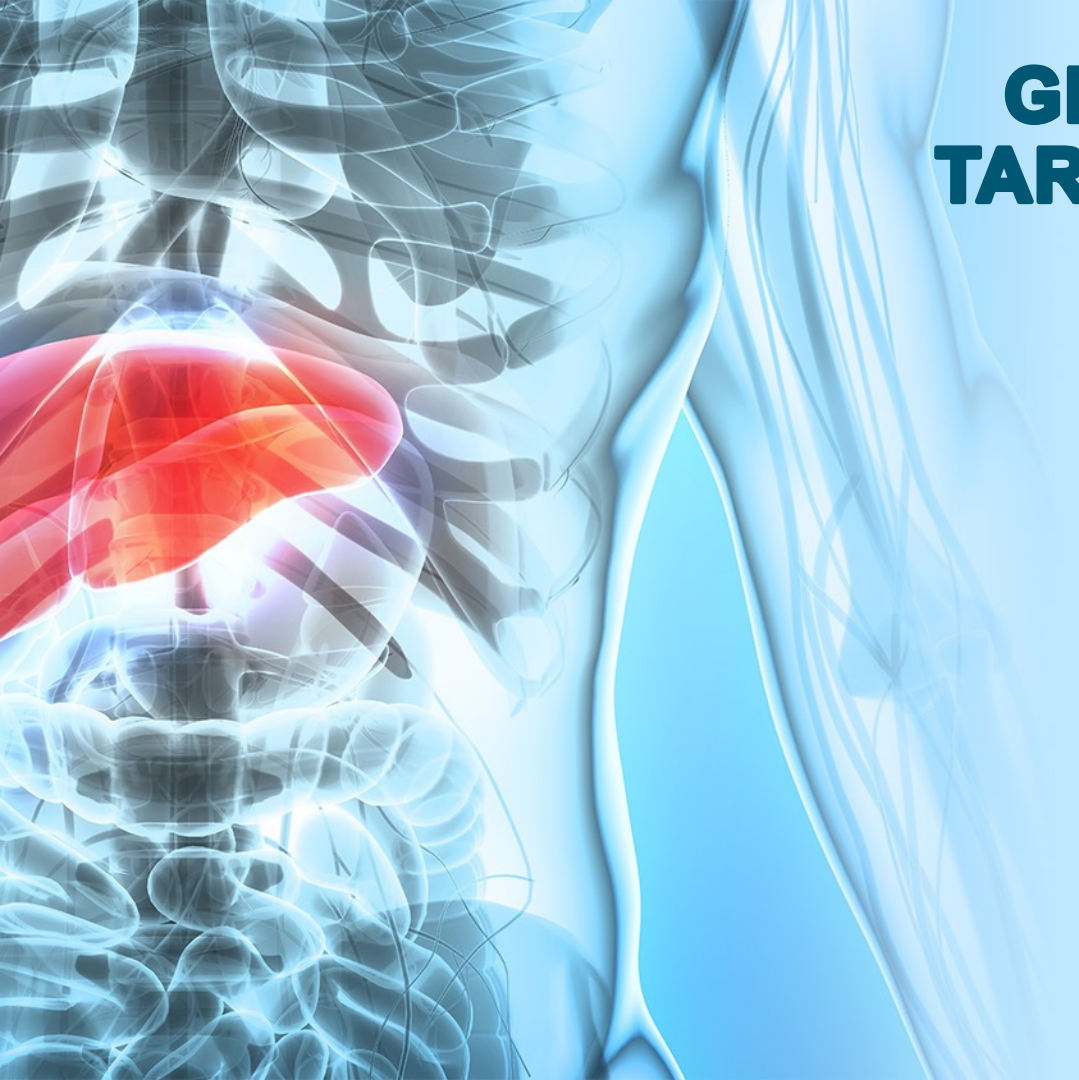

GETTING CLOSER TO TARGETED THERAPIES FOR NASH

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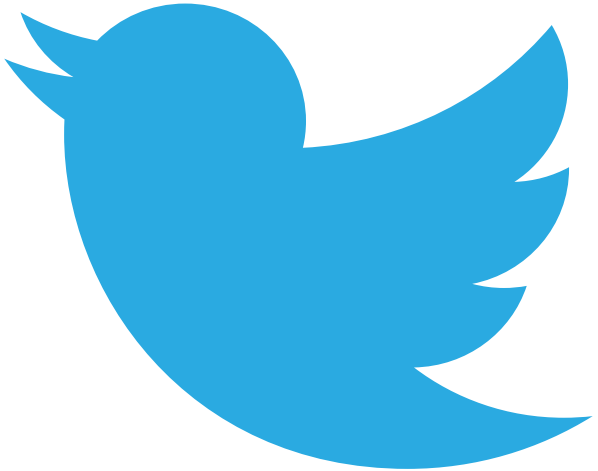

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Chairman, Department of Medicine
Professor of Medicine
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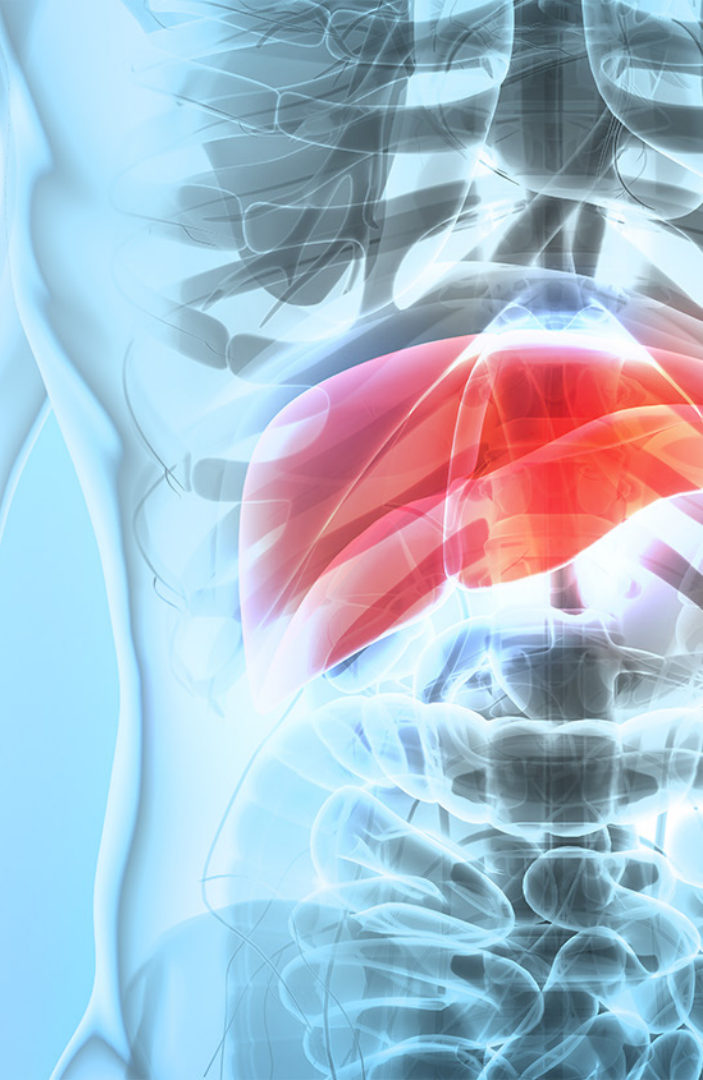
Falls Church, VA



Rohit Loomba, MD, MHSc

Director, NAFLD Research Center
Professor of Medicine
Director of Hepatology and Vice Chief
Division of Gastroenterology
Adjunct Professor
Division of Epidemiology
University of California at San Diego
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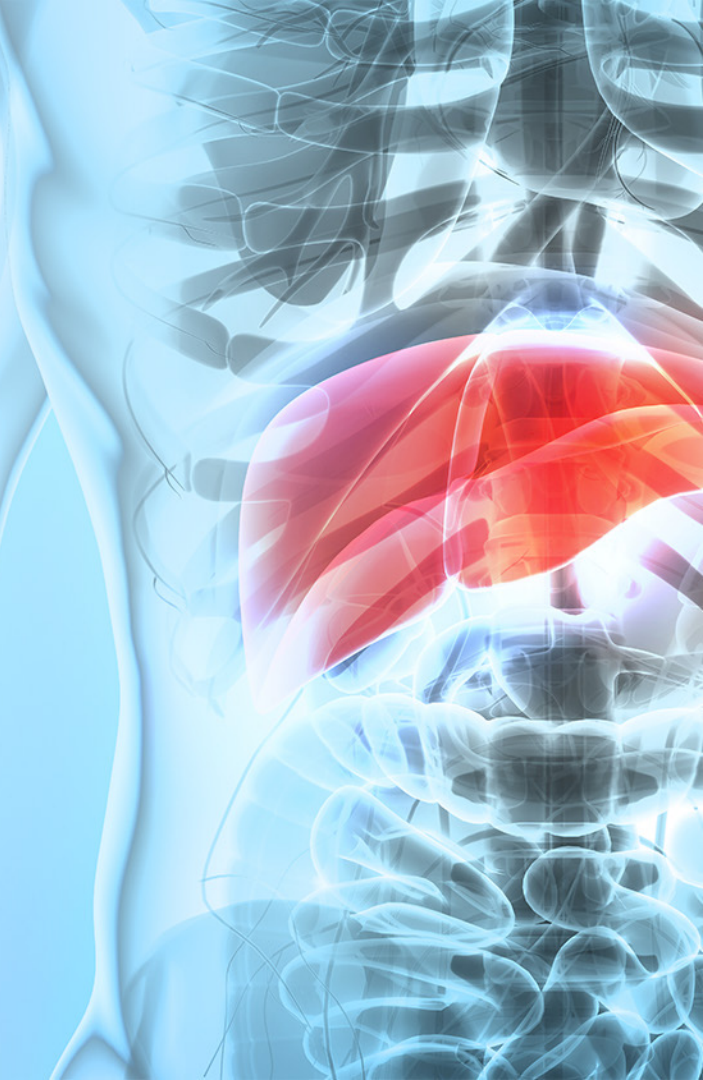


Mazen Noureddin, MD, MHSc

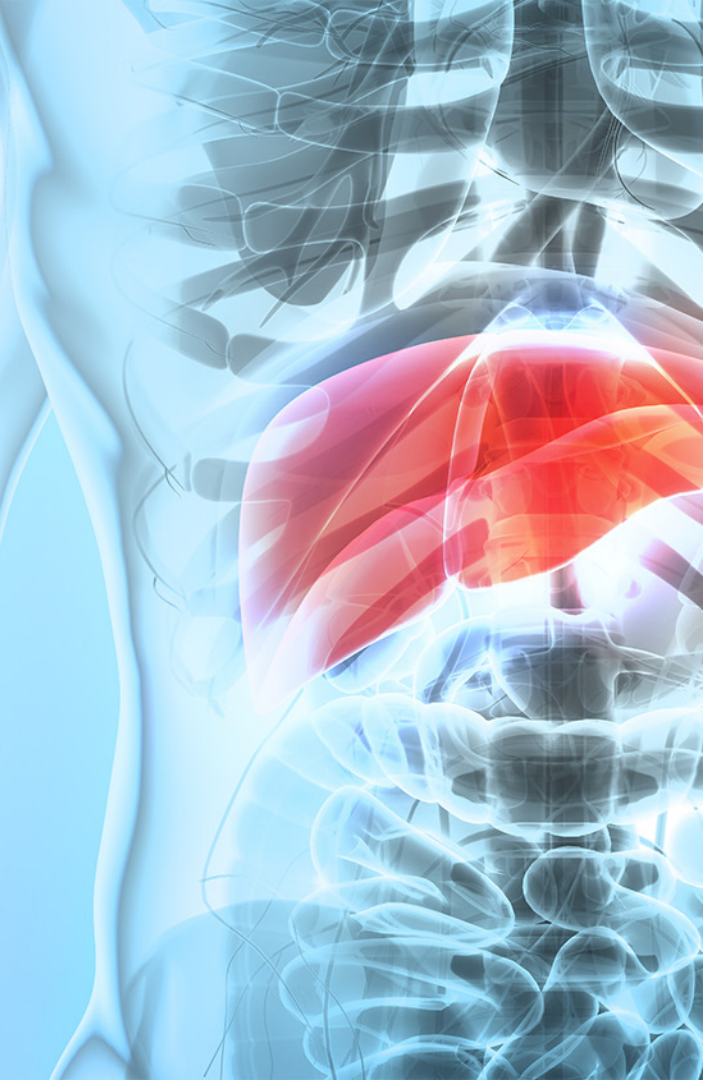
Director, Fatty Liver Program

Karsh Division of Gastroenterology and Hepatology

Comprehensive Transplant Center

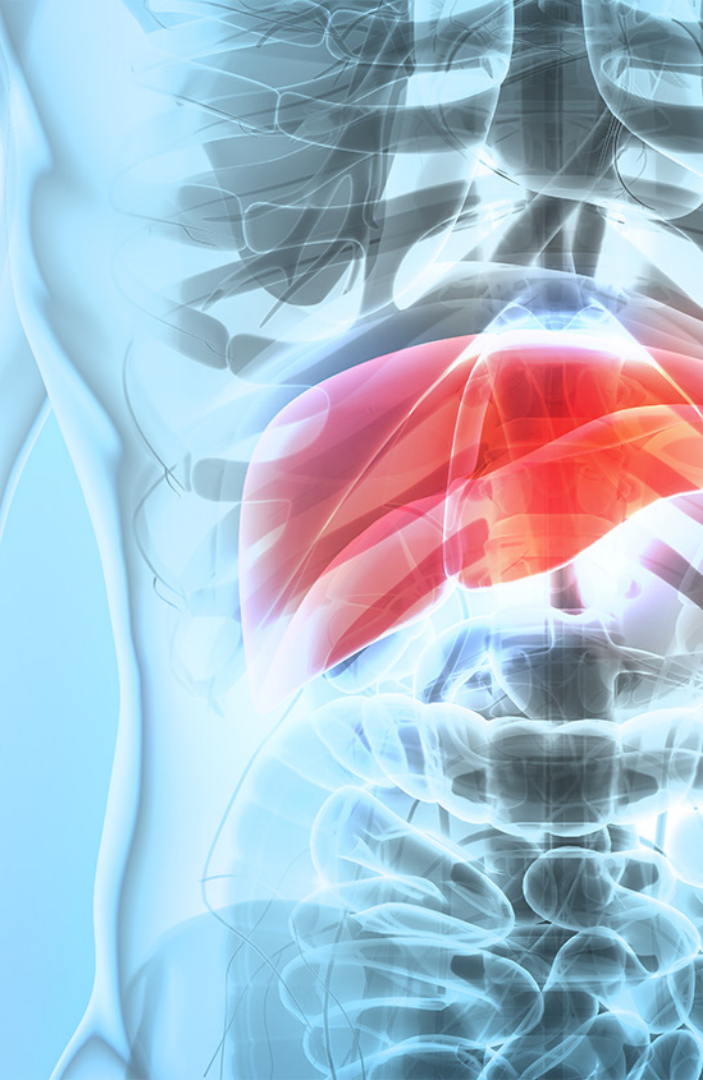
Cedars-Sinai Medical Center

Los Angeles, CA



NAFLD/NASH: An Epidemic Hiding in Plain Sight

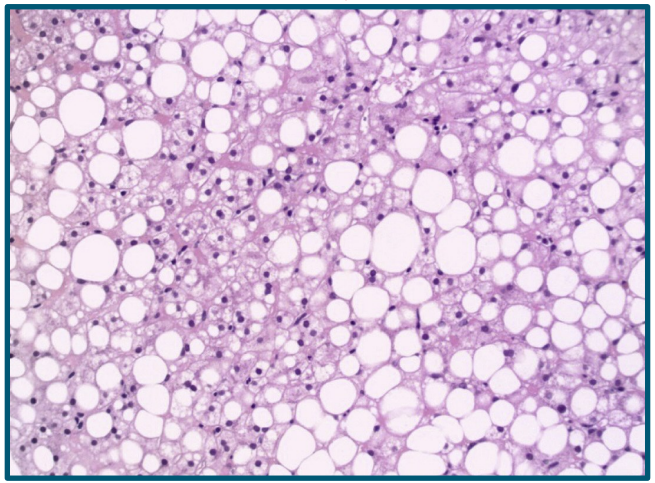
Zobair M. Younossi, MD, MPH



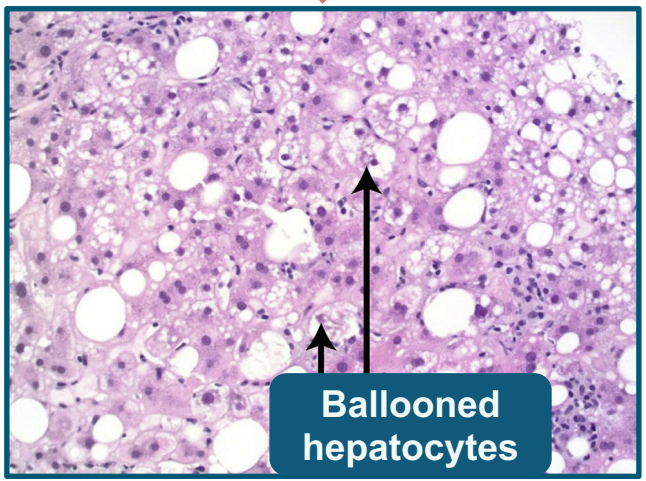
Defining NAFLD and NASH

Nonalcoholic fatty liver disease (NAFLD)

Presence of steatosis in ≥ 5% hepatocytes; minimal alcohol use; biopsy consistent with NAFLD
No other etiology for liver disease; no secondary causes of NAFLD (e.g., meds, HIV, lipodystrophy)



NAFL (nonalcoholic fatty liver)
Non-progressive



NASH (nonalcoholic steatohepatitis)
Progressive

Loomba R, Friedman SL, Shulman GI. *Cell.* 2021;184(10):2537-2564.

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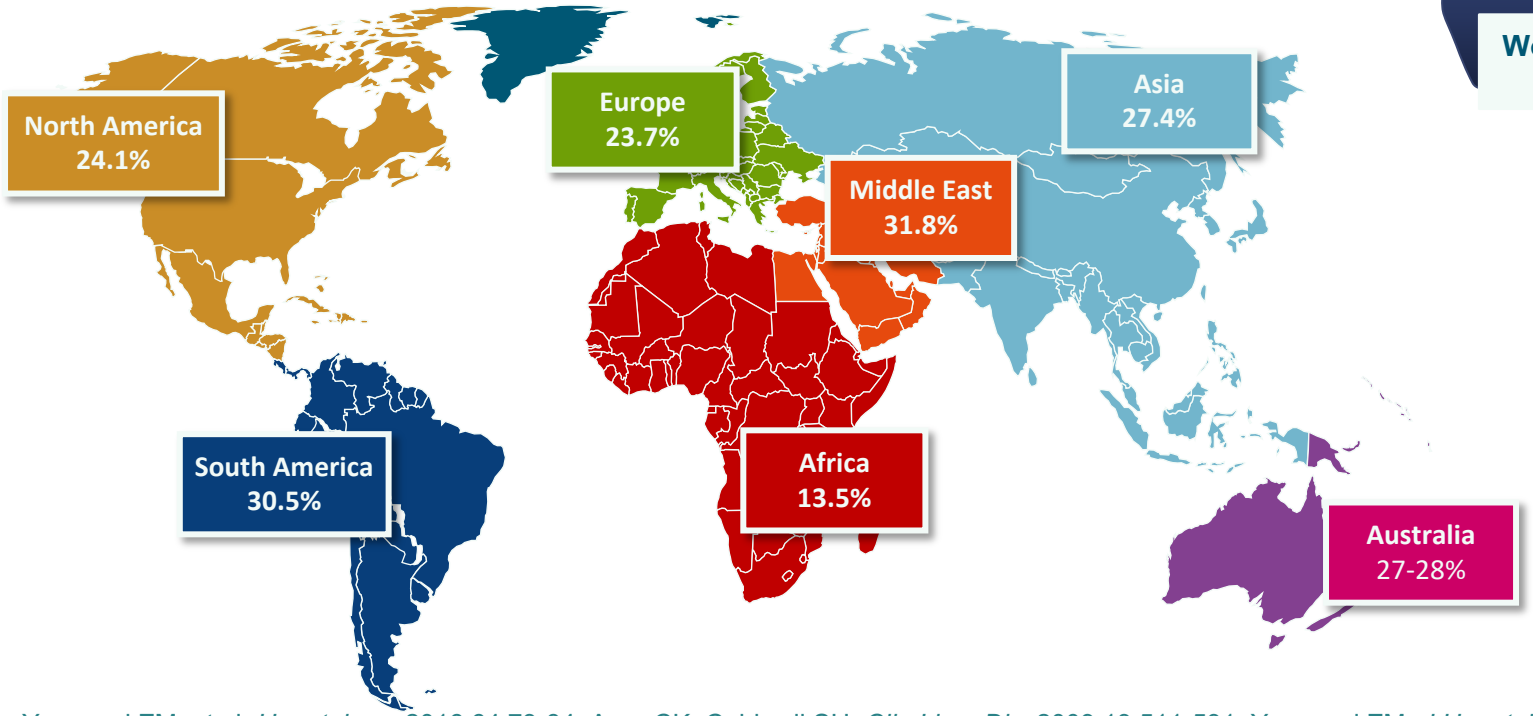
Prevalence of NAFLD and NASH



Worldwide prevalence of NAFLD is 25%

Younossi ZM, et al. *Hepatology*. 2016;64:73-84; Argo CK, Caldwell SH. *Clin Liver Dis.* 2009;13:511-531; Younossi ZM. *J Hepatol*. 2019;70:531-544. Alkassabany YM, et al. *Arab J Gastroenterol*. 2014;15(2):76-81; Song P, et al. *Int J Environ Res Public Health*. 2017;14(5):465; Adams L, et al. *J Gastroenterol Hepatol*. 2020;35(9):1628-1635.

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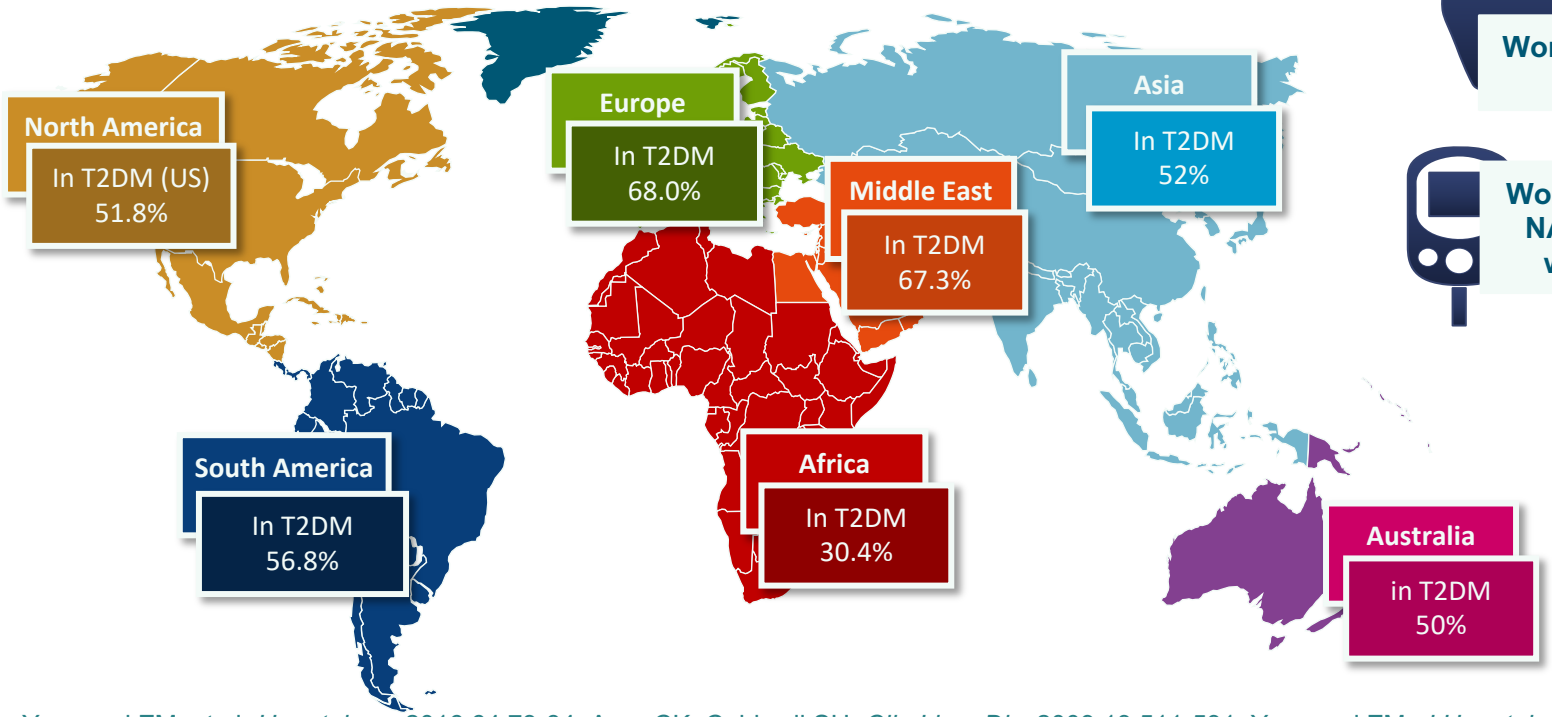
Prevalence of NAFLD and NASH



Worldwide prevalence of NAFLD is 25%

Worldwide prevalence of NAFLD among people with T2DM is 55.5%

Younossi ZM, et al. *Hepatology*. 2016;64:73-84; Argo CK, Caldwell SH. *Clin Liver Dis.* 2009;13:511-531; Younossi ZM. *J Hepatol.* 2019;70:531-544. Alkassabany YM, et al. *Arab J Gastroenterol*. 2014;15(2):76-81; Song P, et al. *Int J Environ Res Public Health*. 2017;14(5):465; Adams L, et al. *J Gastroenterol Hepatol*. 2020;35(9):1628-1635.

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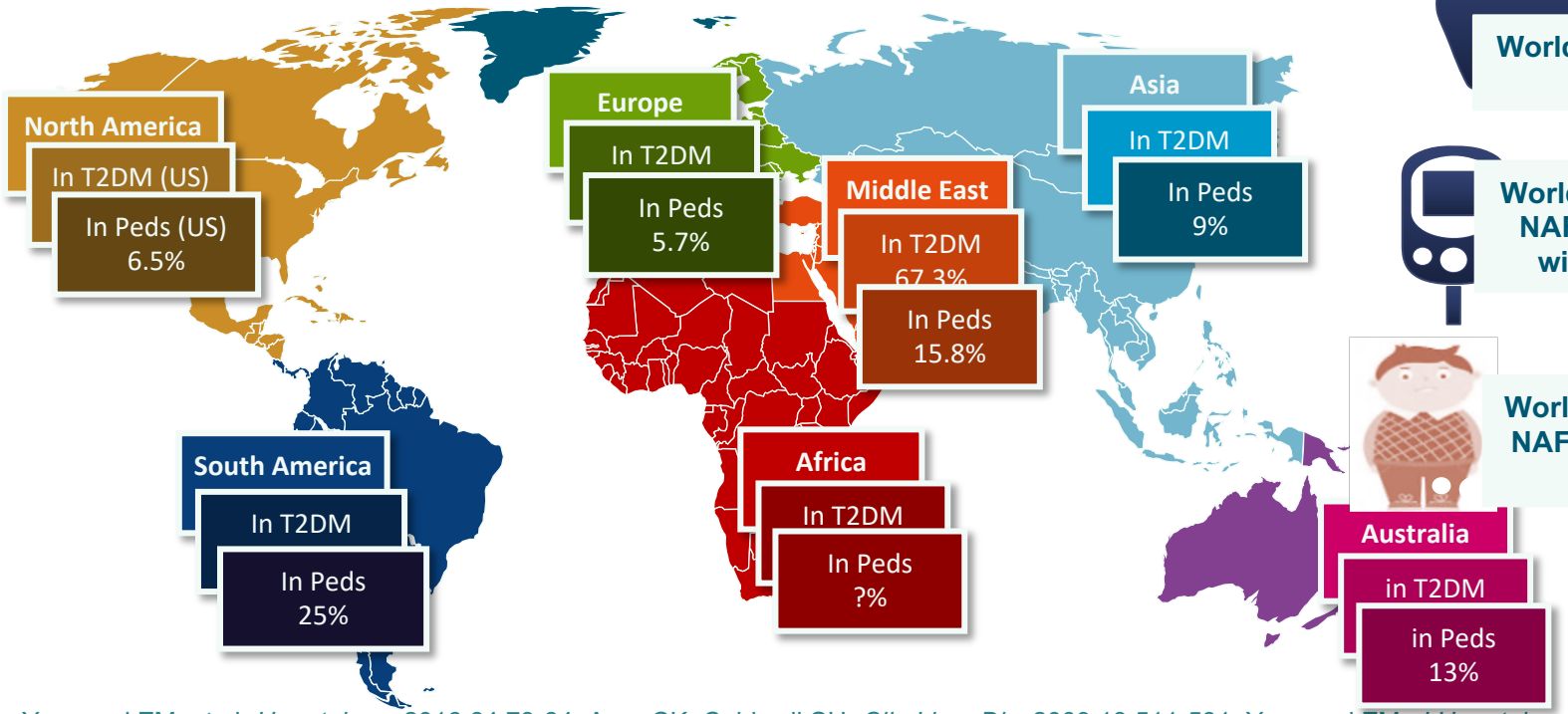
Prevalence of NAFLD and NASH



Worldwide prevalence of NAFLD is 25%

Worldwide prevalence of NAFLD among people with T2DM is 55.5%

Worldwide prevalence of NAFLD among Children is 7.6%

Younossi ZM, et al. *Hepatology*. 2016;64:73-84; Argo CK, Caldwell SH. *Clin Liver Dis.* 2009;13:511-531; Younossi ZM. *J Hepatol.* 2019;70:531-544. Alkassabany YM, et al. *Arab J Gastroenterol*. 2014;15(2):76-81; Song P, et al. *Int J Environ Res Public Health*. 2017;14(5):465; Adams L, et al. *J Gastroenterol Hepatol*. 2020;35(9):1628-1635.

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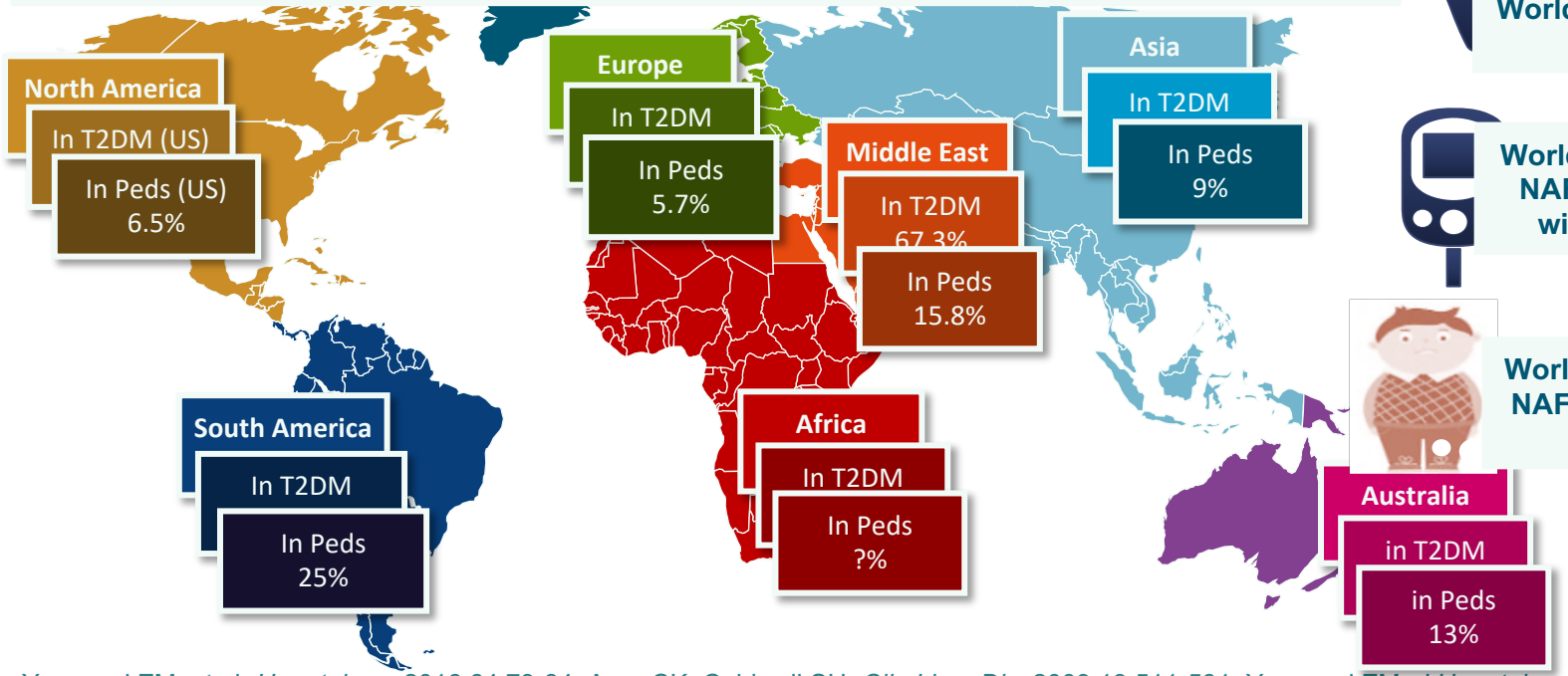
Prevalence of NAFLD and NASH

- Prevalence of NASH in general population is between 1.5–6.5%
- Prevalence of NASH among T2DM is 37.3% (24.7-50.0%)



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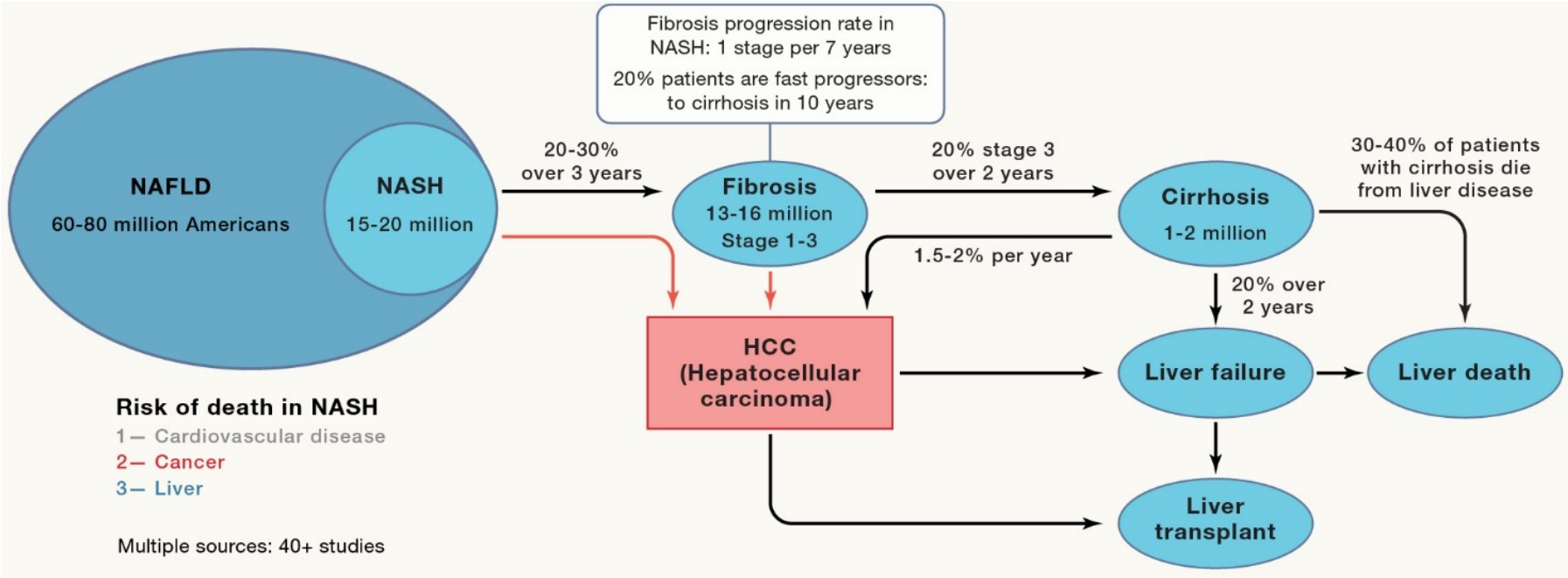
Younossi ZM, et al. *Hepatology*. 2016;64:73-84; Argo CK, Caldwell SH. *Clin Liver Dis.* 2009;13:511-531; Younossi ZM. *J Hepatol.* 2019;70:531-544. Alkassabany YM, et al. *Arab J Gastroenterol*. 2014;15(2):76-81; Song P, et al. *Int J Environ Res Public Health*. 2017;14(5):465; Adams L, et al. *J Gastroenterol Hepatol*. 2020;35(9):1628-1635.

CME OUTFITTERS

NAFLD/NASH: Prevalence and Natural History

Global prevalence of NAFLD is ~25%; among people with T2DM: ~56%)
Global prevalence of NASH is between 1.5% and 6.5%; among people with T2DM: ~37%

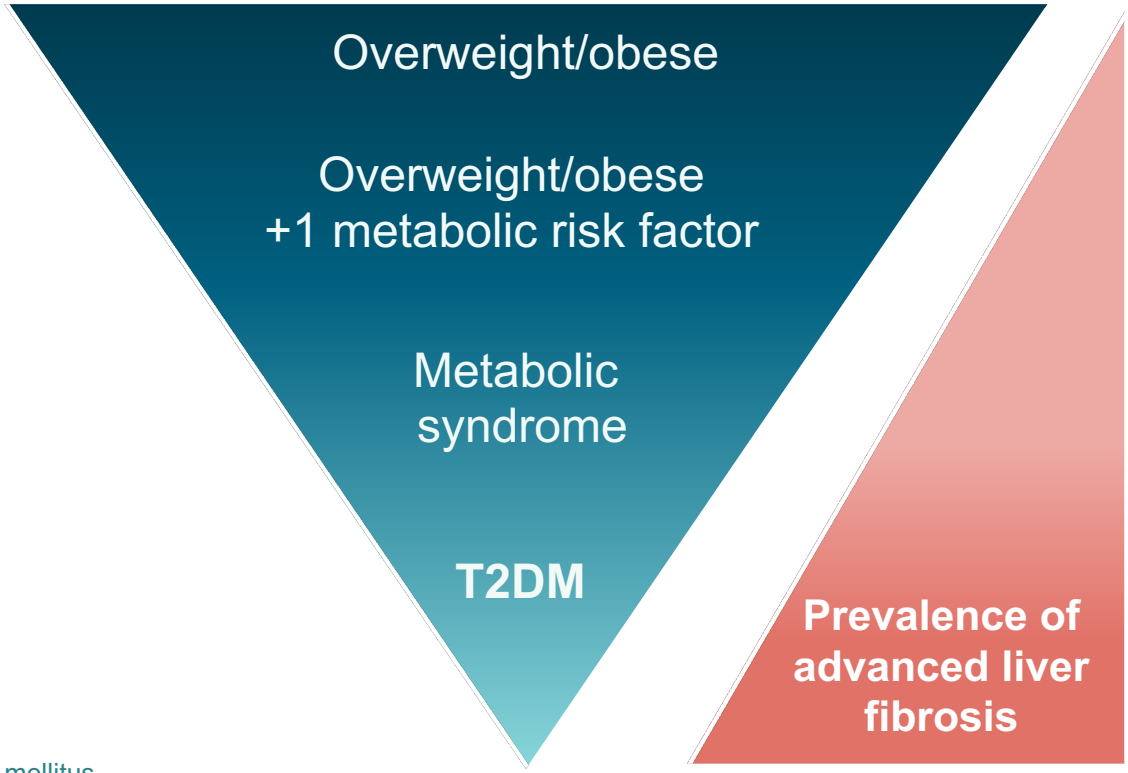


T2DM = type 2 diabetes mellitus

Loomba R, Friedman SL, Shulman GI. *Cell.* 2021;184(10):2537-2564.

CME OUTFITTERS

Populations at Risk of NAFLD-Related Liver Outcomes



T2DM = type 2 diabetes mellitus

Boursier J, Tsochatzis EA. *JHEP Rep.* 2020;3(2):100219.

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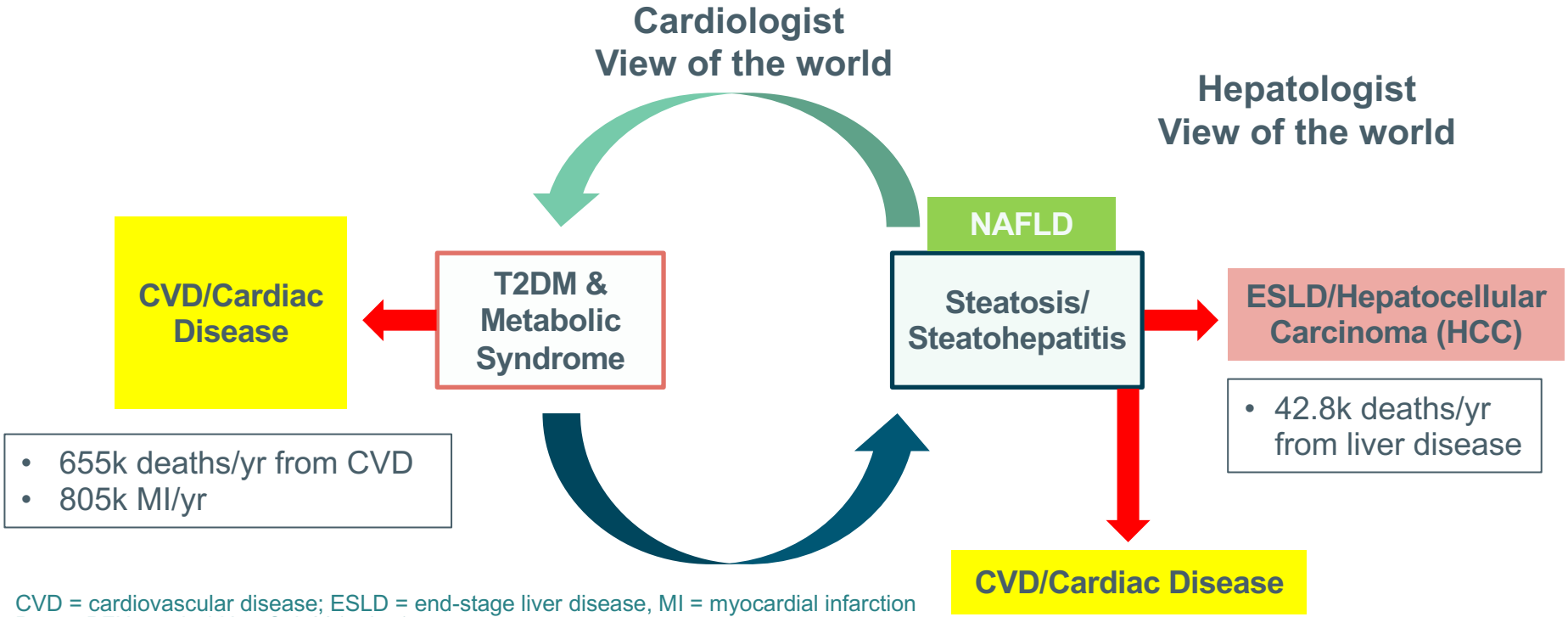
NAFLD & Metabolic Syndrome: Reciprocal Risk Factors



CVD = cardiovascular disease; ESLD = end-stage liver disease, MI = myocardial infarction

Peters PFH, et al. *J Nutr Sci.* 2017;6:e15;
CDC. Heart Disease Facts. https://www.cdc.gov/heartdisease/facts.htm. Accessed November 10, 2021;
CDC. Chronic Liver Disease and Cirrhosis. 2018. https://www.cdc.gov/nchs/fastats/liver-disease.htm. Accessed November 10, 2021.

CME OUTFITTERS

PANEL DISCUSSION
Why is there low awareness of NASH? What can be done to increase awareness?

Despite the Enormous and Growing Worldwide Burden of NASH, Awareness is Very Limited

- **Patient level:**[1] Using NHANES data, only 4.4% of NAFLD patients were aware of having liver disease vs. 37.8% with viral hepatitis

1. Alqahtani SA, et al. *Hepatol Commun*. 2021;5(11):1833-1847.

CME OUTFITTERS

Despite the Enormous and Growing Worldwide Burden of NASH, Awareness is Very Limited

- **Patient level:**[1] Using NHANES data, only 4.4% of NAFLD patients were aware of having liver disease vs. 37.8% with viral hepatitis

- **Health system level:**[2] Using EHR of patients who were considered to have NAFLD (n = 251) from a VA facility:
  - Only 22% had a documented diagnosis of NAFLD
  - 15% received lifestyle modification recommendations
  - 10% were referred to a specialist (only 3% of those with possible advanced fibrosis)

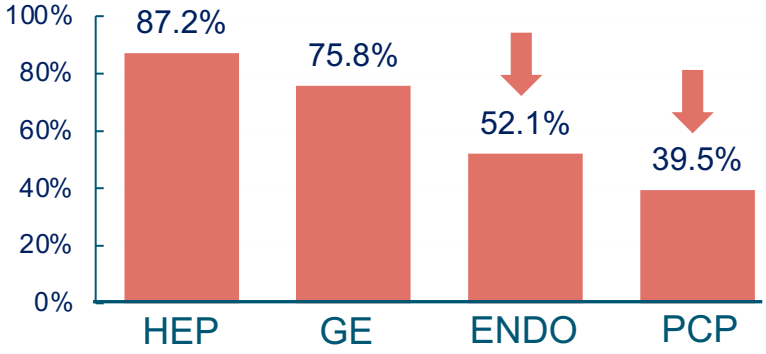
1. Alqahtani SA, et al. *Hepatol Commun*. 2021;5(11):1833-1847; 2. Blais P, et al. *Am J Gastroenterol.* 2015;110(1):10-14.

CME OUTFITTERS

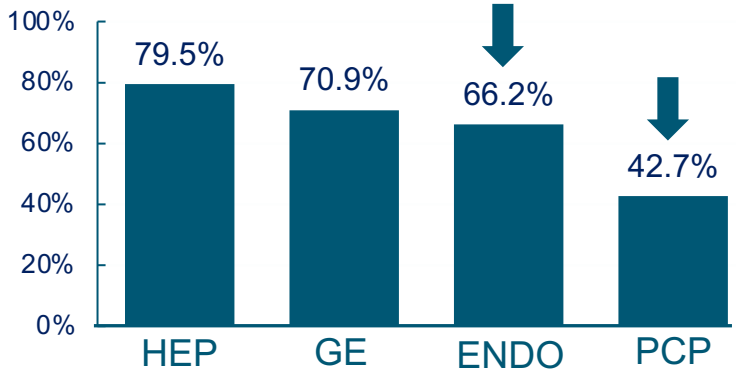
Despite the Enormous and Growing Worldwide Burden of NASH, Awareness is Very Limited

- **Provider level:**[3] Survey (54 and 59 questions) of 2202 clinicians (hepatologists [HEP], gastroenterologists [GE], endocrinologists [ENDO], and primary care physicians [PCP] from 40 countries

Correctly identified the most common cause of death in NAFLD



Correctly identified pathologic criteria for NASH



3. Younossi Z, et al. *Clin Gastroenterol Hepatol*. 2021;3:S1542-3565(21)00719-9.

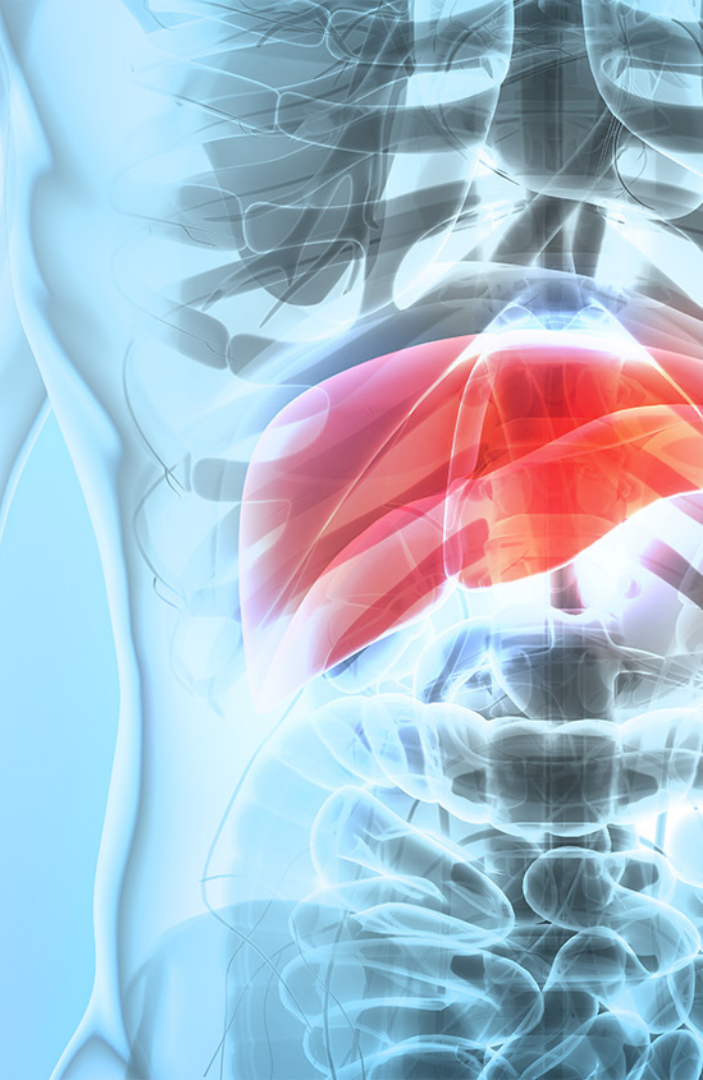
CME OUTFITTERS

Current Treatment Strategies

Mazen Noureddin, MD, MHSc

Incorporate currently recommended therapies and interventions for preventing serious or fatal complications of disease/comorbidities into the plan of care for patients with NAFLD/NASH.

LEARNING OBJECTIVE 1



Owen, 61-year-old attorney

- T2DM, dyslipidemia, hypertension
- Central adiposity (BMI = 32.7 kg/m^2)
- High carb diet; 5-7 alcoholic drinks/week
- Complains of abdominal discomfort (upper right quadrant)
- Currently takes metformin for T2DM; irbesartan for hypertension

CME OUTFITTERS

Owen's Lab Results

Laboratory Values

- ALT: 60 U/L
- AST: 65 U/L
- Total bilirubin: 0.8 mg/dL
- Albumin: 4.0 g/dL
- Platelets: 180,000/µL
- LDL: 130 mg/DL
- HDL: 36 mg/dL
- TG: 235 mg/dL
- A1C: 7.1%

ALT = alanine aminotransferase test; AST = aspartate aminotransferase test; HDL = high-density lipoproteins; LDL = low-density lipoproteins; TG = triglycerides

CME OUTFITTERS

Audience Response

Owen is diagnosed with NASH and is concerned about further weight gain (his BMI is 32.7 kg/m$^{2)}$. Which one of the following would you NOT recommend for him?

A. Exercise
B. Optimize his metformin dose
C. Pioglitazone
D. Vitamin E
E. I'm not sure

CME OUTFITTERS

Treatment Potentially Improves Patient Outcomes

- Currently no FDA-approved NASH-specific therapies
  - Certain treatments can optimize metabolic risk factors and may improve NASH histology
- Treatment Goal: 7%-10% weight loss
  - Weight loss of 3%-5% improves steatosis, but 7%-10% weight loss is needed to improve most histologic features of NASH including fibrosis
  - Combination of Mediterranean diet and moderate exercise has improved visceral fat as well as hepatic fat

Chalasani N, et al. *Hepatology* 2018;67:328-357; Plaz Torres MC, et al. *Nutrients*. 2019;11(12):2971; Salman MA, et al. *Obes Surg*. 2020;30(1):87-95

CME OUTFITTERS

NASH Improvement Correlates With Weight Loss

≥ 10% Weight Loss

Improvement in fibrosis stage (45% of patients)
NASH resolution (64% - 90% of patients)

7% to 10% Weight Loss

Improvement in NASH Activity Score
Ballooning/Inflammation
(41% - 100% of patients)

5% Weight Loss

Improvement in liver fat and liver stiffness [steatosis]
(35 – 100% of patients)

Patel NS, et al. *Clin Gastroenterol Hepatol.* 2017;15:463-464; Promrat K, et al. *Hepatology.* 2010;51:121-129; Vilar-Gomez E, et al. *Gastroenterol.* 2015:149: 367-378.

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Approaches to Current Treatment: AASLD Guidelines

- Lifestyle modifications (dietary change, weight loss, structured exercise)
  - GLP-1 RAs, SGLT2i for weight loss; bariatric surgery when indicated
- Vitamin E: In nondiabetic patients with biopsy-proven NASH (800 IU/day)
- Pioglitazone: In patients with and without T2DM and biopsy-proven NASH
- Metformin: Not recommended
- Statin: For use in dyslipidemia (not NASH); does not confer higher risk for serious liver injury
- Ursodeoxycholic acid (UDCA): Not recommended
- Omega-3 Fatty Acids: For use in hypertriglyceridemia (not specific NAFLD treatment)
- Obeticholic acid (awaiting further data)
- GLP-1 RAs (awaiting further data)

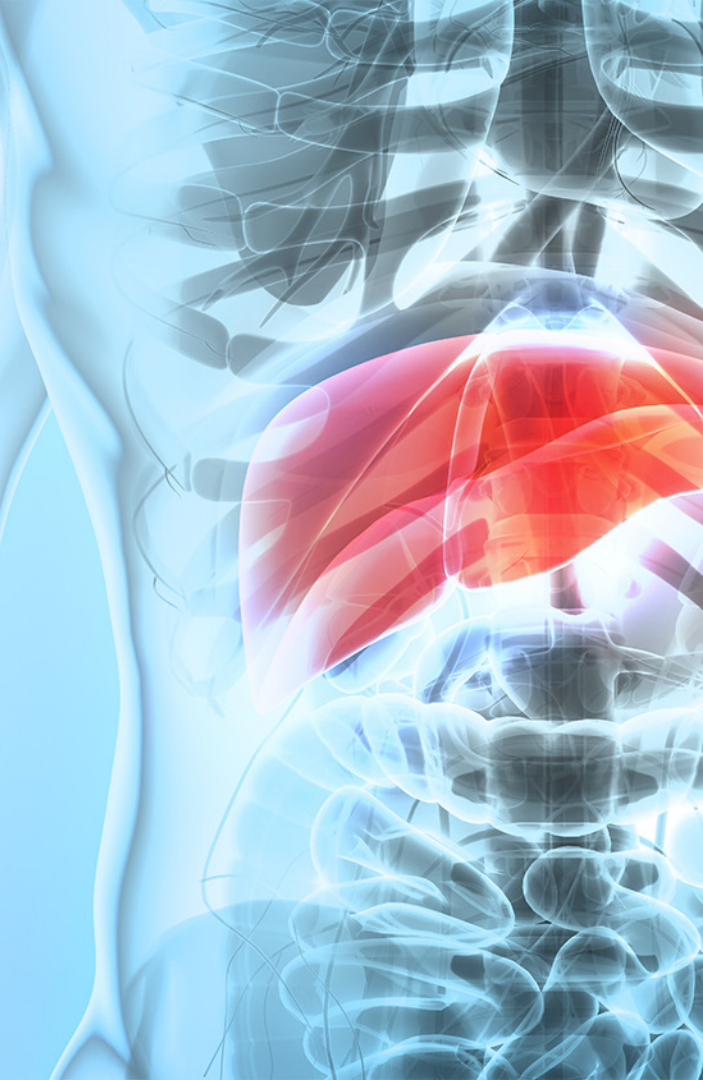
GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT2i = sodium-glucose cotransporter-2 inhibitor

Chalasani N, et al. *Hepatology.* 2018;67(1):328-357.

CME OUTFITTERS

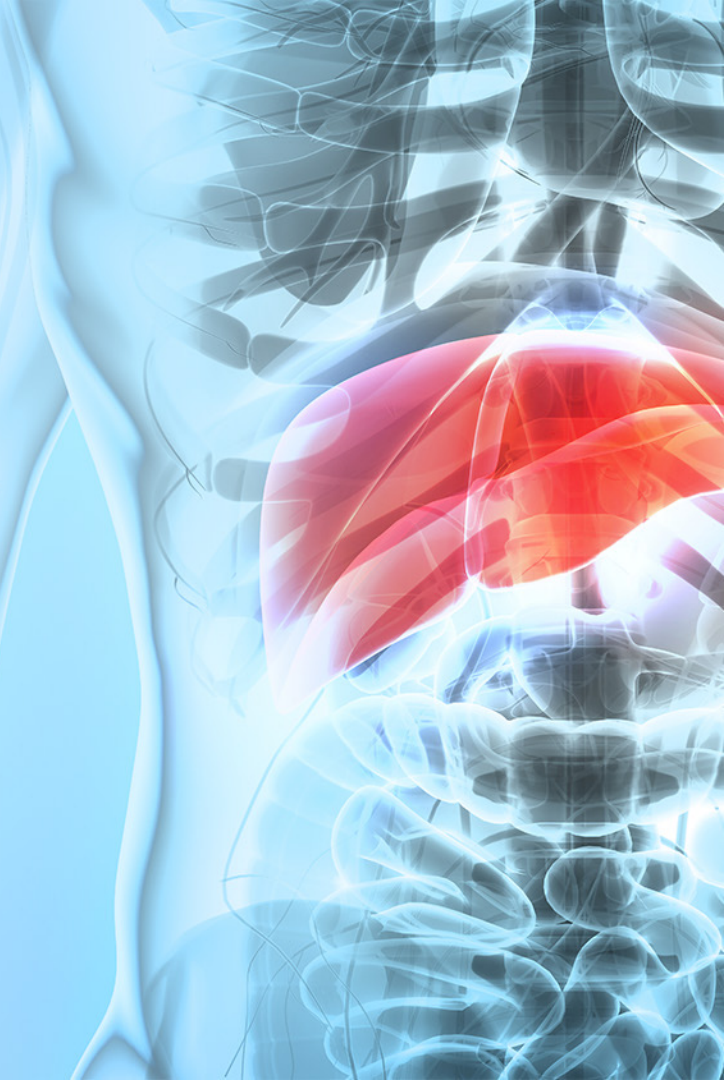
New Therapies: How Close Are We?

Mazen Noureddin, MD, MHSc



Identify the molecular basis of pharmacologic agents in late-stage clinical trials for the treatment of NASH.

LEARNING OBJECTIVE 2



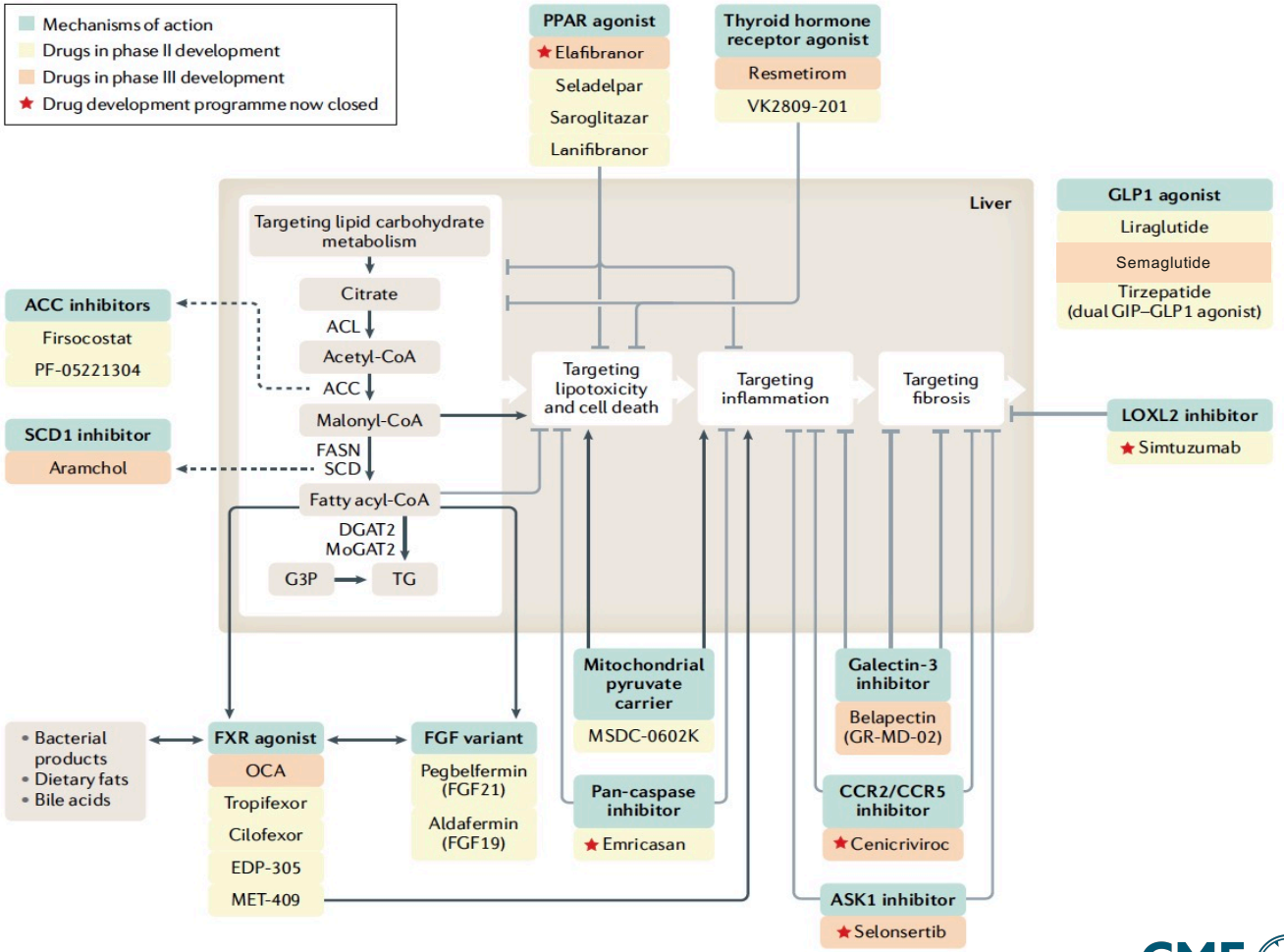
Audience Response

Which of the following agents in development can improve glycemic control and promote weight loss in addition to its potential histopathologic benefit?

A. Aramchol
B. Elafibinor
C. FXR agonists
D. GLP-1 receptor agonists
E. I'm not sure

CME OUTFITTERS

Emerging Therapies for NASH

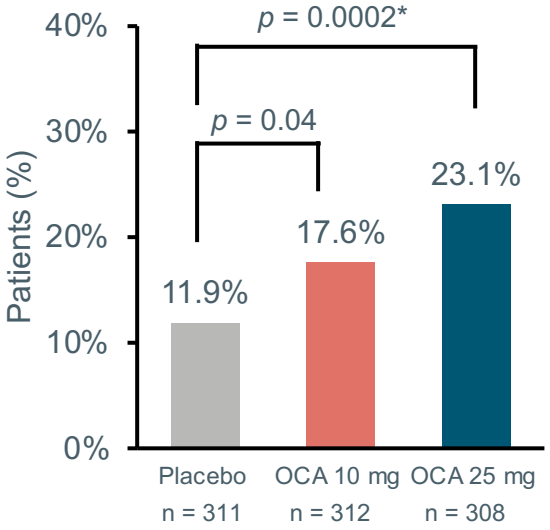


Adapted from Vuppalanchi R, et al. *Nat Rev Gastroenterol Hepatol.* 2021;18(6):373-392.

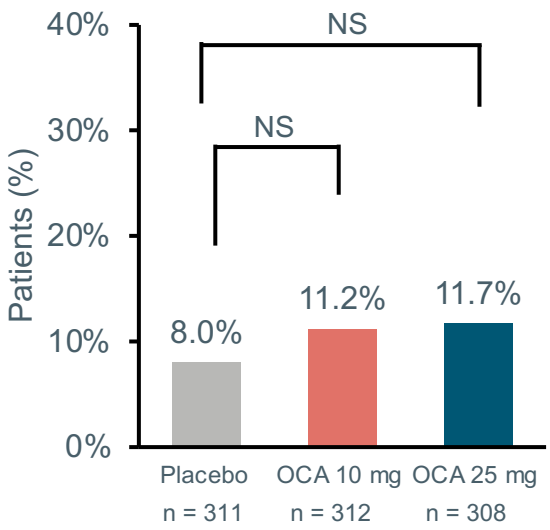
CME OUTFITTERS

Obeticholic Acid: REGENERATE Trial

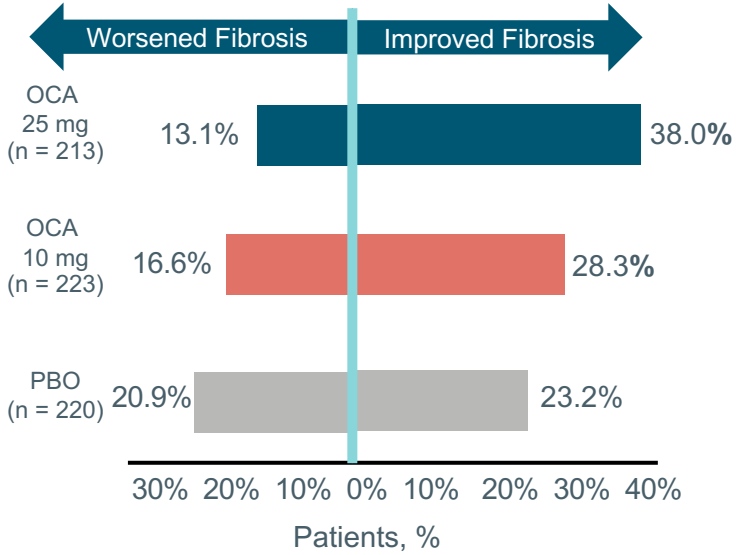
Primary Endpoint (ITT): Fibrosis Improvement by ≥ 1 Stage With No Worsening of NASH



NASH Resolution With No Worsening of Liver Fibrosis



Regression or Progression of Fibrosis by ≥ 1 Stage in the per-protocol population



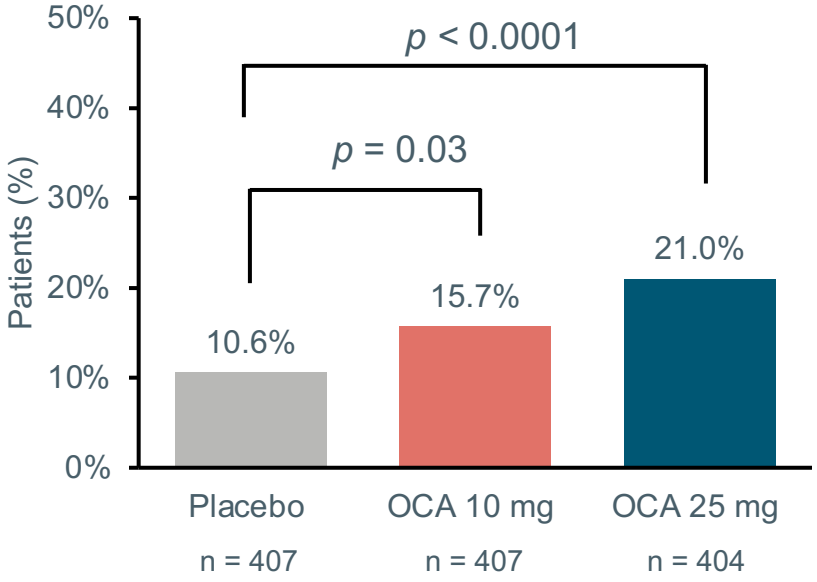
*Statistically significant in accordance with the statistical analysis plan agreed with the FDA

Younossi Z, et al. *Lancet.* 2019;394:2184-2196; Ratziu V, et al. *Contemp Clin Trials*. 2019;84:105803.

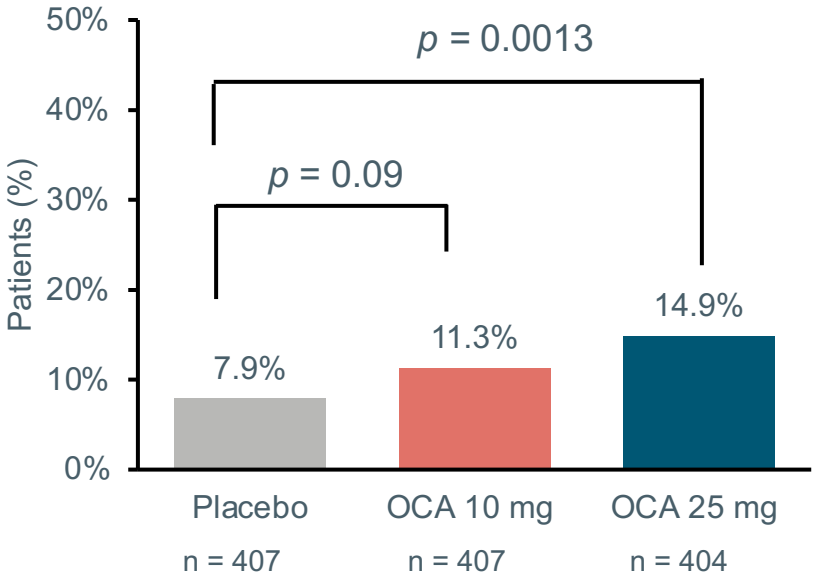
CME OUTFITTERS

OCA: REGENERATE
Expanded Intent to Treat (ITT) Population

Fibrosis Improvement ≥ 1 Stage With No Worsening of NASH



NASH Resolution With No Worsening of Fibrosis

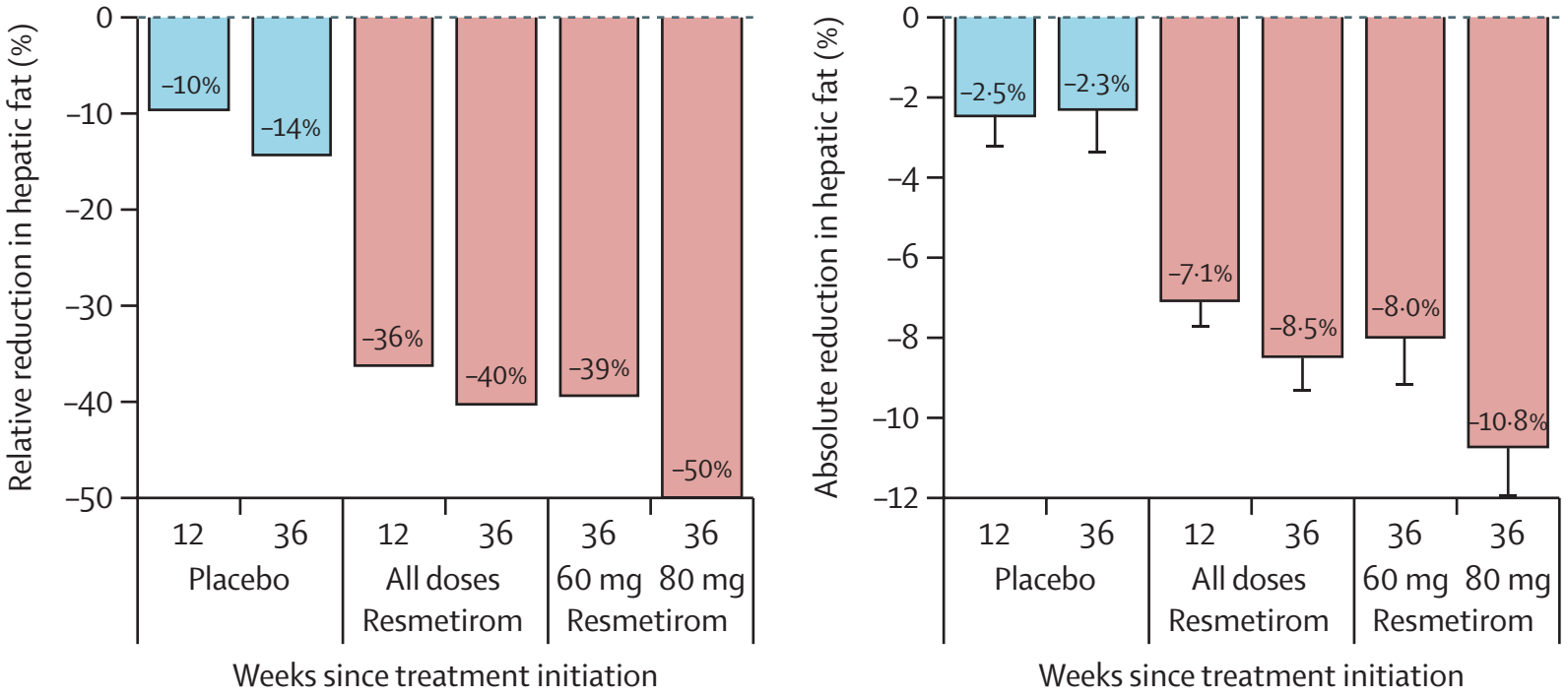


Sanyal A, et al. AASLD; 2019. Abstract No. 34.

CME OUTFITTERS

Resmetirom for NASH: Phase 2 Trial

Primary Endpoint: Relative change in hepatic fat fraction assessed by MRI-PDFF 12 Weeks (N = 348)



Harrison S, et al, *Lancet*. 2019;394(10213):2012-2024.

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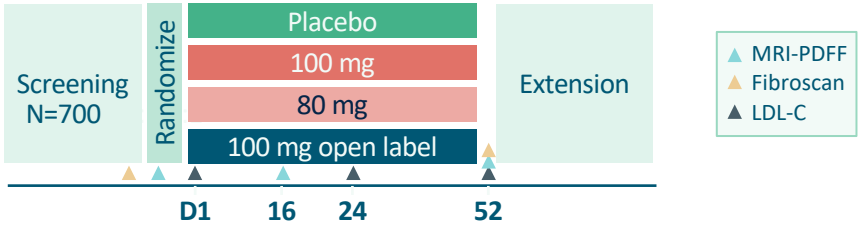
Resmetirom for NASH: Phase 2 Trial

	n	Placebo, n (%)	n	Resmetirom, n (%)	Odds ratio	p value
≥2-point NAS reduction	34	11 (32·4%)	73	41 (56·2%)	2·7 (1·1–6·3)	0·024
High exposure group	..	..	43	28 (65·1%)	3·9 (1·5–10·1)	0·0059
Low exposure group	..	..	30	13 (43·3%)	1·6 (0·6–4·4)	0·44
High SHBG group	..	..	44	28 (63·6%)	3·7 (1·4–9·4)	0·012
Low SHBG group	..	..	29	13 (44·8%)	1·7 (0·6–4·7)	0·44
MRI-PDFF responder	..	..	46	32 (69·6%)	4·8 (1·8–12·4)	0·0014
<5% weight loss group	27	5 (18·5%)	61	30 (49·2%)	4·3 (1·4–12·7)	0·0090
NASH resolution (without fibrosis worsening)	31	6 (6·5%)	73	18 (24·7%)	4·75 (1·03–21·9)	0·032
MRI-PDFF responder	..	..	46	17 (37·0%)	8·50 (1·80–40·2)	0·0026
Including weight loss >9·5%	34	5 (14·7%)	73	18 (24·7%)	1·9 (0·64–5·6)	0·32
MRI-PDFF responder (including weight loss >9·5%)	..	..	46	17 (37·0%)	3·4 (1·1–10·4)	0·042
Fibrosis responder	34	8 (23·5%)	73	21 (28·8%)	1·3 (0·51–3·36)	0·65
MRI-PDFF responder	..	..	46	15 (32·6%)	1·6 (0·58–4·29)	0·46
NASH resolution responder	..	..	18	11 (61·1%)	5·1(1·5–17·6)	0·014

Harrison S, et al, *Lancet*. 2019;394(10213):2012-2024.

CME OUTFITTERS

Resmetirom: Phase 3 MAESTRO-NAFLD-1



- 1:1:1:1 resmetirom 80mg, 100mg, placebo, open label 100 mg
- Primary endpoints: % change from baseline in LDL-C, ApoB, hepatic fat fraction by MRI-PDFF, triglycerides, PRO-C3
- Inclusion criteria: ≥ 3 metabolic risk factors; Fibroscan kPa ≥ F1; CAP ≥ 280; 8% liver fat on MRI-PDFF

Week 16 Changes from Baseline	All	SHBG (high)
MRI-PDFF (%)		
Baseline (%)	17.6	17.9
Relative % change	-53%	-62%
p-value	<0.0001	<0.0001
MRE (kPa)		
Baseline (>2.9, F1-F3)	3.5	3.5
Absolute change	-0.34	-0.46
p-value	0.003	0.003

Hepatic and inflammatory biomarker effects →

Biomarker*	Baseline	SD	Post-Baseline*	SD	CFB	P value
ALT (BL >34 U/L)	58.3	47.4	38.9	16.1	-17.7	<0.0001
AST (BL >26 U/L)	39.3	12.2	31.8	11.3	-6.9	0.0060
GGT (BL >30 U/L)	70.2	58.3	54.6	47.8	-16.2	0.0015
Adiponectin (ug/mL)	5.0	3.5	5.9	1.6	0.9	<0.0001
Reverse T3 (ng/dL)	17.7	5.4	12.4	4.8	-5.3	<0.0001
PRO-C3 (BL ≥14) (ng/L)	19.2	4.9	16.0	3.5	-3.4	0.019
hsCRP (mg/L)	4.9	(1.9-8.4)	3.3	(1.5-6.2)	-1.1	0.027

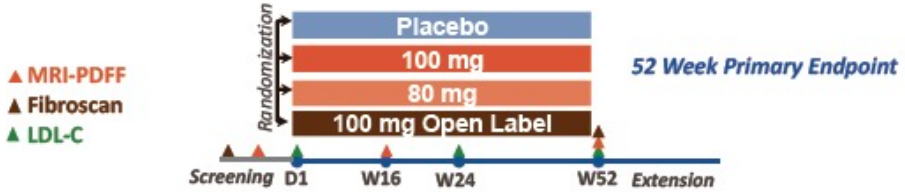
*Biomarkers were assessed at weeks 12 or 24; LE at week 20; median is shown for hsCRP.

Harrison S, et al, *Lancet*. 2019;394(10213):2012-2024. Harrison SA, et al. *Hepatology*. 2018;68(1 suppl):9A; Harrison S, et al. AASLD TLMdx 2020;1707.

CME OUTFITTERS

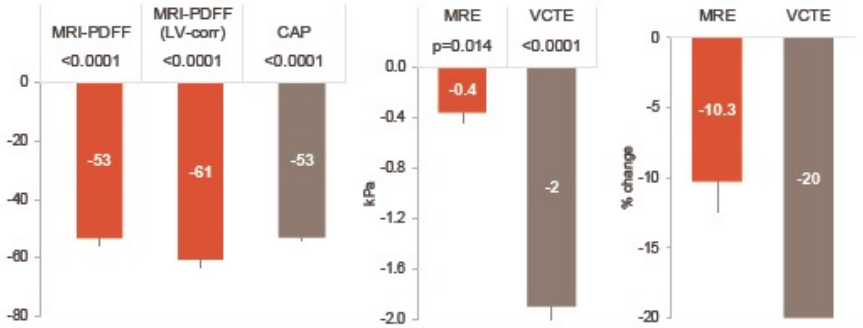
Resmetirom: Phase 3 MAESTRO-NAFLD-1 52 Week Data

Study Design

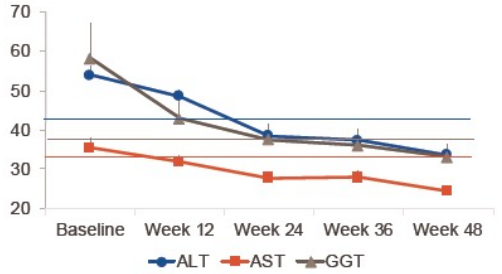


- ~1200 NASH patients enrolled

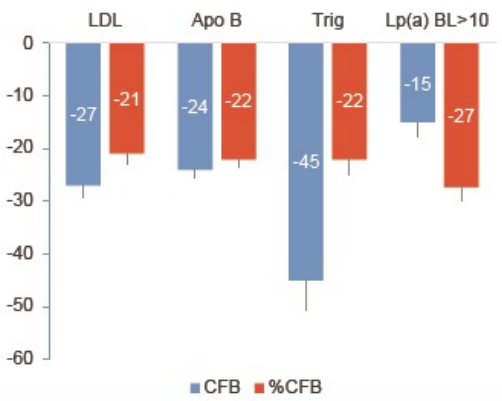
Week 52 MRE and FibroScan (kPa)



Liver Enzymes



Lipids



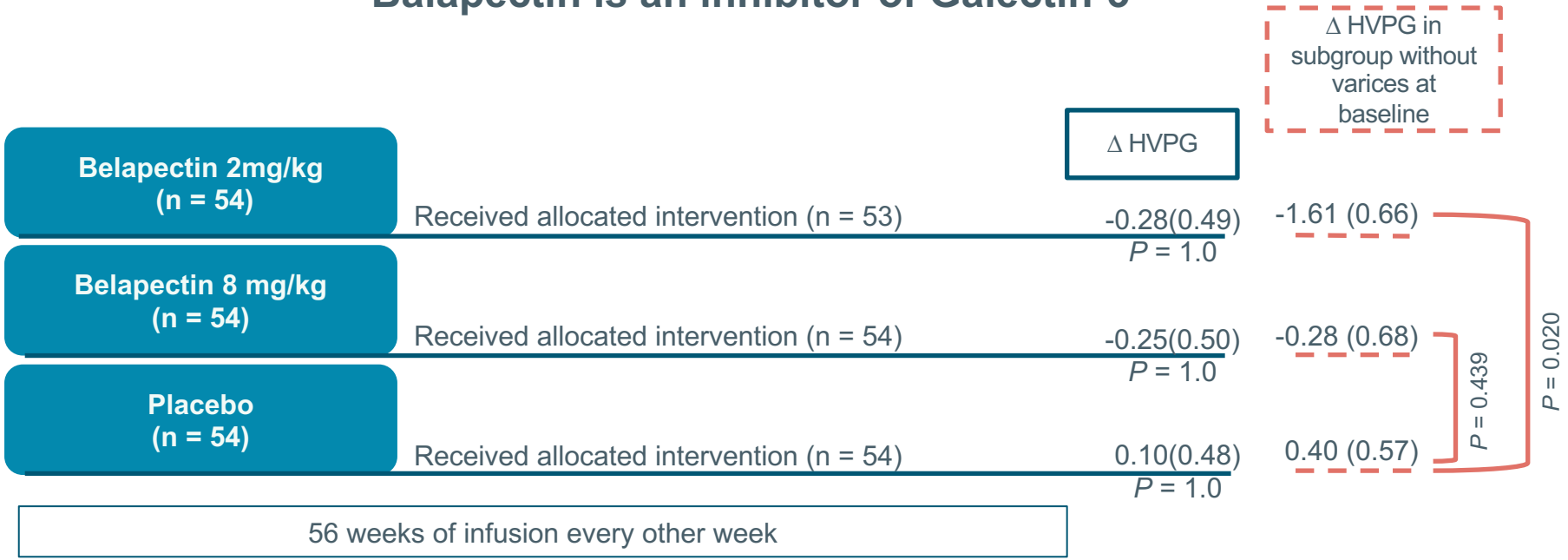
CFB = change from baseline

Harrison SA, et al. Biomarkers, imaging and safety in resmetirom 52-week non-cirrhotic NASH phase 3 clinical trial, completed open-label arm of MAESTRO-NAFLD-1. Adapted from poster presentation. AASLD 2021.

CME OUTFITTERS

Effects of Balapectin in Patients With NASH With Cirrhosis and Portal Hypertension

Balapectin is an inhibitor of Galectin-3

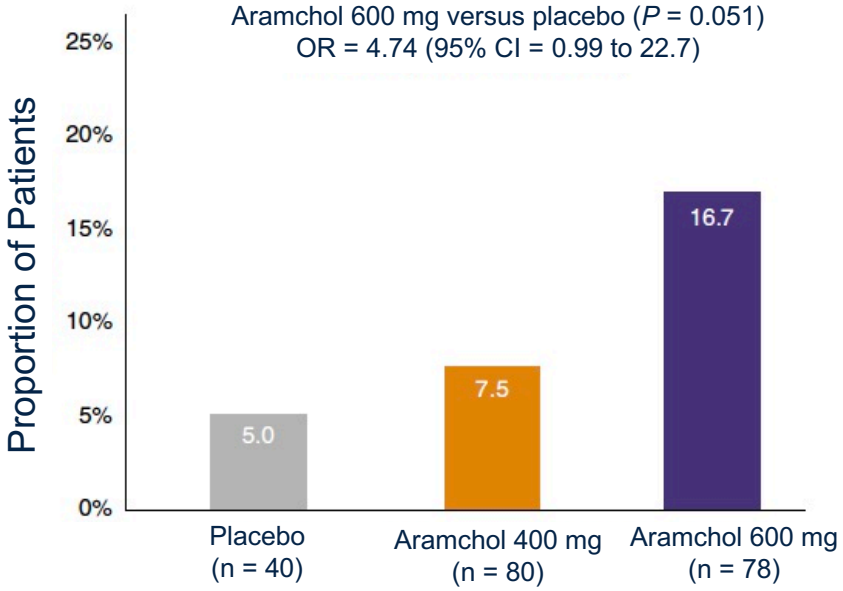


HVPG = hepatic venous pressure gradient

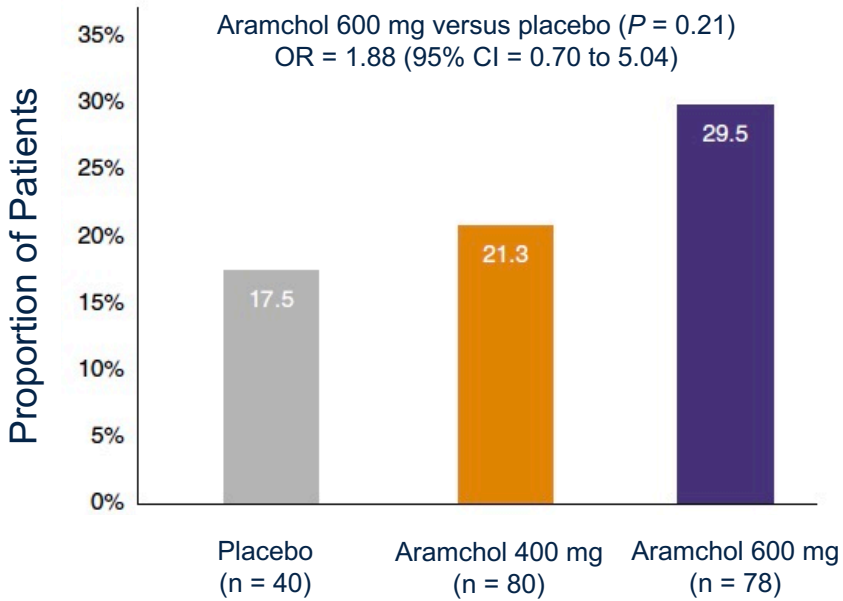
Chalasani N, et al. *Gastroenterology*. 2020;158(5):1334-1345.E5.

CME OUTFITTERS

Aramchol in Patients With NASH: Double-Blind, Placebo-Controlled Phase 2b Trial



Proportion of patients with NASH resolution without worsening fibrosis



Proportion of patients with fibrosis improvement without worsening NASH

Ratziu V, et al for the ARREST Study Group. *Nat Med.* 2021;27(10):1825-1835.

CME OUTFITTERS

Aramchol (cont'd)

Change in MRS and histology-based end points after 52 weeks of treatment

				Difference when compared to placebo		OR and 95% CI	
	Placebo	Aramchol 400 mg	Aramchol 600 mg	Aramchol 400 mg	Aramchol 600 mg	Aramchol 400 mg	Aramchol 600 mg
Primary outcome							
Number of patients with paired MRI evaluations	41	90	83				
Absolute percentage change from baseline in mean liver fat	−0.09 ± 1.38%	−3.41 ± 0.96%	−3.18 ± 1.01%	−3.32 ± 1.65% $P = 0.045$	−3.09 ± 1.67% $P = 0.066$		
Percentage of MRS responders[a]	24.4	36.7	47.0			2.20 (0.89 to 5.46) $P = 0.088$	2.77 (1.12 to 6.89) $P = 0.028$
Changes in histopathological parameters from baseline							
Number of patients with paired biopsies	40	80	78				
NASH resolution without worsening of fibrosis, %	5.0	7.5	16.7			1.79 (0.33 to 9.62) $P = 0.50$	4.74 (0.99 to 22.66) $P = 0.051$
Fibrosis improvement without worsening of NASH, %	17.5	21.3	29.5			1.11 (0.40 to 3.05) $P = 0.84$	1.88 (0.7 to 5.04) $P = 0.21$
Two or more points improvement in NAS contributed by at least two of: steatosis, inflammation, ballooning without worsening of fibrosis, %	17.5	20.0	25.6			1.36 (0.49 to 3.80) $P = 0.56$	1.68 (0.62 to 4.57) $P = 0.31$
Two or more points improvement in SAF activity score without worsening of fibrosis, %	25.0	25.0	35.9			1.08 (0.44 to 2.63) $P = 0.86$	1.84 (0.78 to 4.35) $P = 0.16$

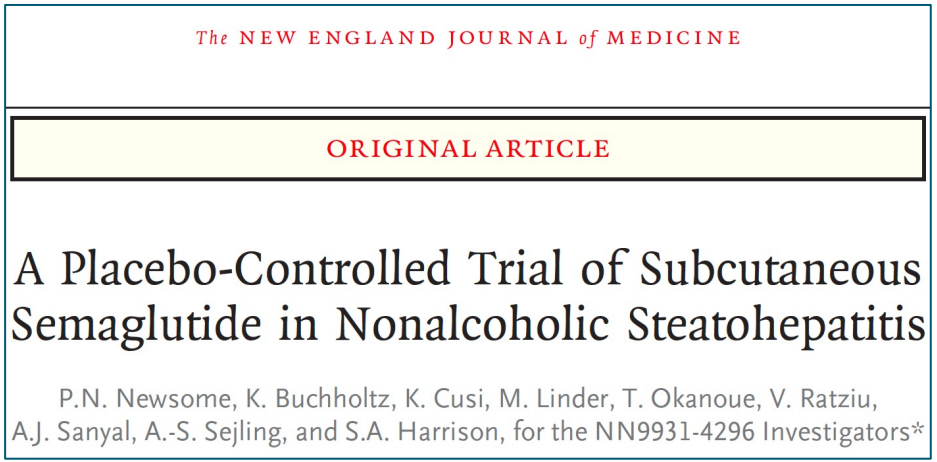
MRS = magnetic resonance spectroscopy

Ratziu V, et al for the ARREST Study Group. *Nat Med.* 2021;27(10):1825-1835.

CME OUTFITTERS

Semaglutide in NASH

- Glucagon-like peptide-1 (GLP-1) receptor agonist
  - Stimulates insulin secretion
  - Delays gastric emptying
  - Inhibits the production of glucagon
- Approved for the treatment of type 2 diabetes
- Reduces cardiovascular risk among patients with type 2 diabetes
- Approved for weight management

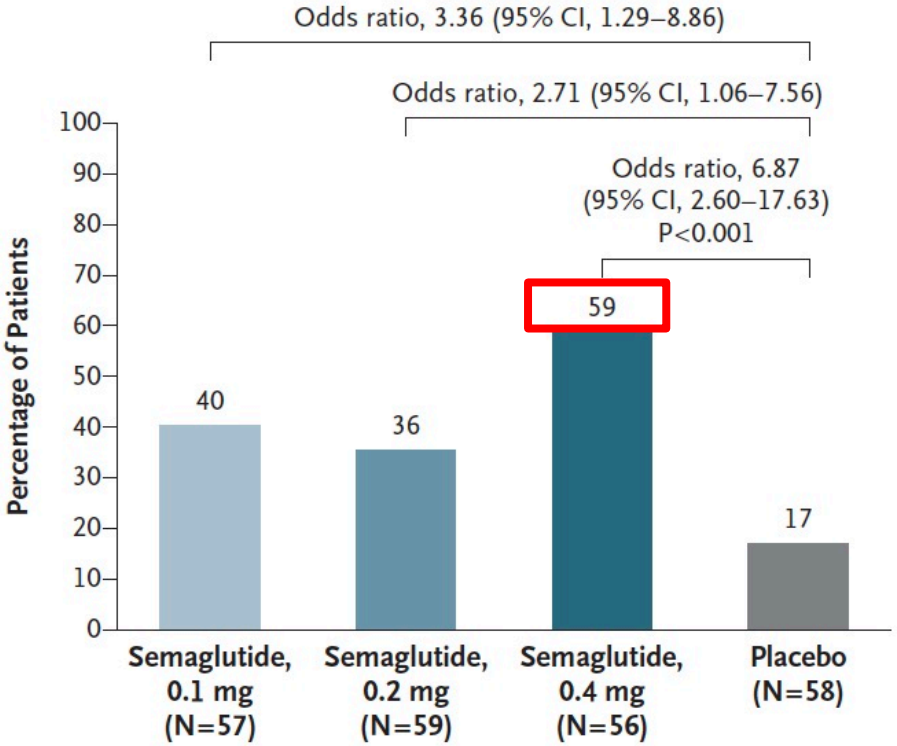


Newsome PN, et al. *N Engl J Med*. 2021;384:1113-1124.

CME OUTFITTERS

Semaglutide in NASH: Primary End Point (F2 and F3)

- Primary End Point: resolution of NASH with no worsening of liver fibrosis

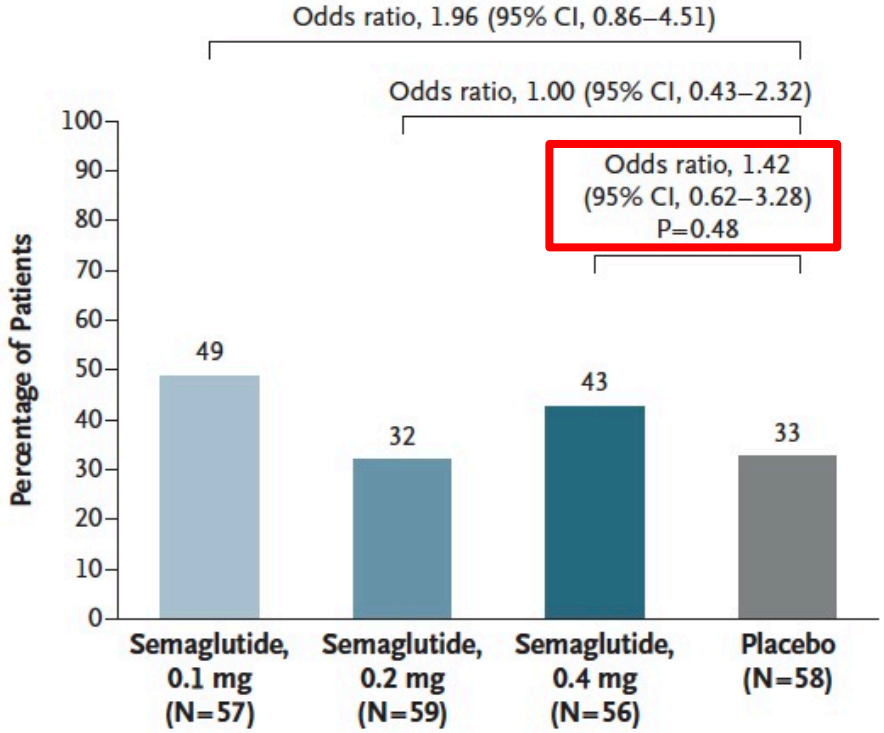


Newsome PN, et al. *N Engl J Med*. 2021;384:1113-1124.

CME OUTFITTERS

Semaglutide in NASH: Secondary End Point (F2 and F3)

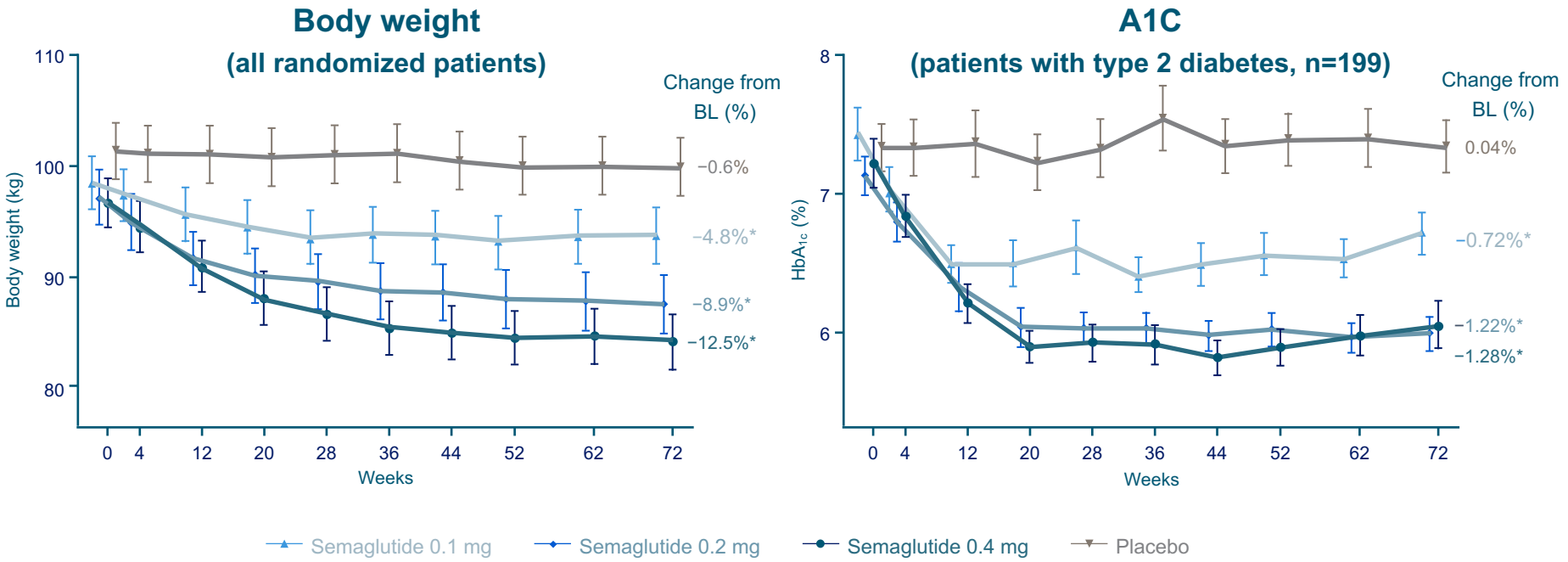
- Confirmatory Secondary End Point: improvement in liver fibrosis stage with no worsening of NASH



Newsome PN, et al. *N Engl J Med*. 2021;384:1113-1124.

CME OUTFITTERS

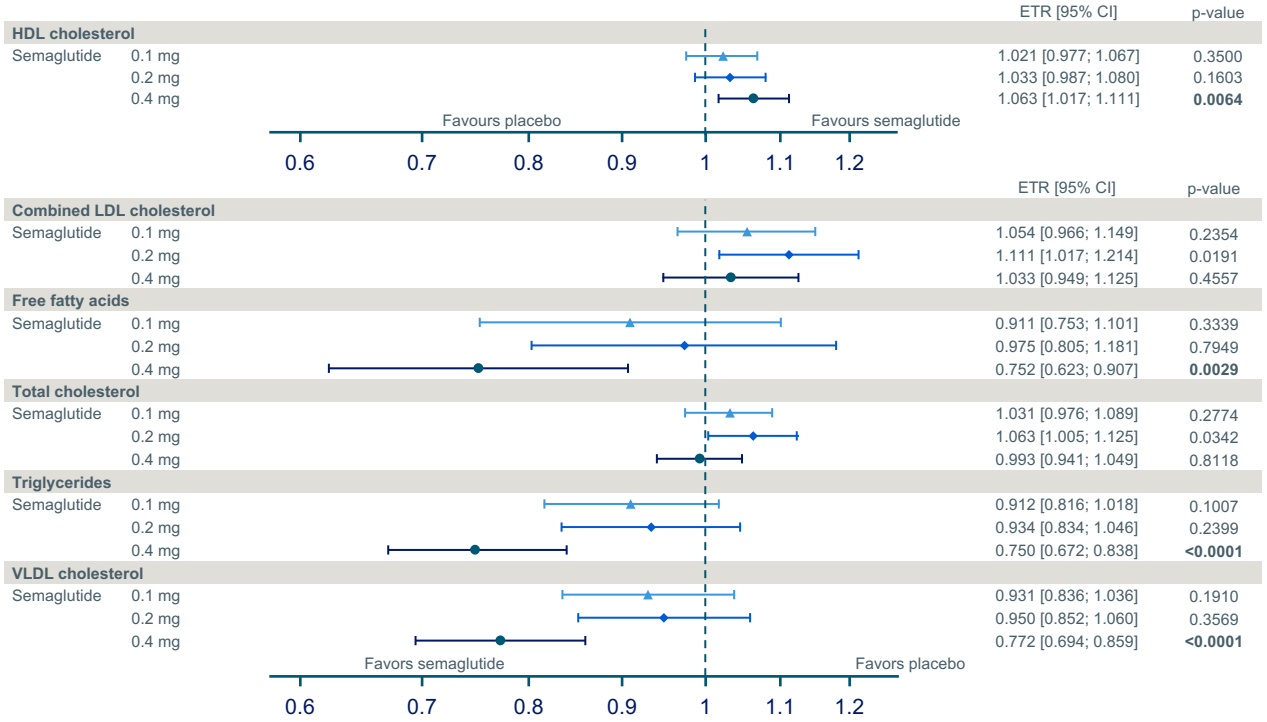
Semaglutide in NASH: Changes in Body Weight and A1C



In-trial data. Data are observed means with standard error of the mean. Change from baseline values are estimated means.
BL = baseline. *$P < 0.05$ for estimated treatment difference versus placebo.
Newsome PN, et al. *N Engl J Med*. 2021;384:1113-1124.

CME OUTFITTERS

Semaglutide: Changes in Lipids



Semaglutide 0.4 mg versus placebo

↑ HDL cholesterol

↓ free fatty acids triglycerides and VLDL cholesterol

VLDL = very-low density lipoprotein

Newsome PN, et al. *N Engl J Med*. 2021;384:1113-1124.

CME OUTFITTERS

Semaglutide: Adverse Events

Event	Semaglutide 0.1-mg Group (N=80)	Semaglutide 0.2-mg Group (N=78)	Semaglutide 0.4-mg Group (N=81)	Placebo Group (N=80)
	number of patients (percent)			
Any adverse event	72 (90)	76 (97)	76 (94)	67 (84)
Adverse events from gastrointestinal disorders system organ class	51 (64)	60 (77)	55 (68)	36 (45)
Adverse events from any system organ class, according to preferred term†				
Nausea	24 (30)	29 (37)	34 (42)	9 (11)
Constipation	13 (16)	17 (22)	18 (22)	10 (12)
Decreased appetite	16 (20)	18 (23)	18 (22)	4 (5)
Diarrhea	23 (29)	22 (28)	16 (20)	11 (14)
Vomiting	14 (18)	17 (22)	12 (15)	2 (2)
Back pain	7 (9)	5 (6)	10 (12)	7 (9)
Headache	7 (9)	10 (13)	10 (12)	8 (10)
Nasopharyngitis	11 (14)	15 (19)	10 (12)	12 (15)
Arthralgia	0	4 (5)	9 (11)	7 (9)
Fatigue	7 (9)	8 (10)	7 (9)	7 (9)
Abdominal pain	9 (11)	8 (10)	6 (7)	3 (4)
Abdominal distension	1 (1)	8 (10)	4 (5)	4 (5)
Dyspepsia	4 (5)	9 (12)	4 (5)	5 (6)

Event	Semaglutide 0.1-mg Group (N=80)	Semaglutide 0.2-mg Group (N=78)	Semaglutide 0.4-mg Group (N=81)	Placebo Group (N=80)
	number of patients (percent)			
Adverse events that resulted in premature discontinuation of treatment				
All adverse events	3 (4)	10 (13)	4 (5)	4 (5)
Gastrointestinal disorders	1 (1)	6 (8)	2 (2)	0
Serious adverse events				
Any serious adverse event	12 (15)	15 (19)	12 (15)	8 (10)
Gastrointestinal disorders	2 (2)	2 (3)	4 (5)	0
Musculoskeletal and connective-tissue disorders	0	1 (1)	3 (4)	1 (1)
Infections and infestations	2 (2)	2 (3)	2 (2)	1 (1)
Neoplasms, including benign, malignant, and unspecified	0	4 (5)	1 (1)	0
Nervous-system disorders	0	3 (4)	1 (1)	0
Metabolism and nutrition disorders	2 (2)	1 (1)	0	1 (1)
Neoplasms‡	10 (12)	11 (14)	14 (17)	6 (8)
Malignant neoplasms	1 (1)	2 (3)	0	0
Polyp in large intestine§	1 (1)	4 (5)	3 (4)	0
Renal cyst§	3 (4)	1 (1)	0	1 (1)
Fatal events	0	1 (1)¶	0	0

CME OUTFITTERS

Lanifibranor in NASH

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 21, 2021 VOL. 385 NO. 17

A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH

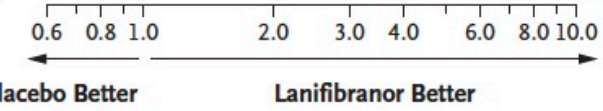
S.M. Francque, P. Bedossa, V. Ratziu, Q.M. Anstee, E. Bugianesi, A.J. Sanyal, R. Loomba, S.A. Harrison, R. Balabanska, L. Mateva, N. Lanthier, N. Alkhouri, C. Moreno, J.M. Schattenberg, D. Stefanova-Petrova, L. Vonghia, R. Rouzier, M. Guillaume, A. Hodge, M. Romero-Gómez, P. Huot-Marchand, M. Baudin, M.-P. Richard, J.-L. Abitbol, P. Broqua, J.-L. Junien, and M.F. Abdelmalek, for the NATIVE Study Group*

Francque SM, et al. *N Engl J Med*. 2021;385:1547-1558.

CME OUTFITTERS

Lanifibranor in NASH: Primary and Secondary End Points

End Point	Placebo	Lanifibranor	Risk Ratio (95% CI)	P Value
	percent of patients with response			
Primary end point: reduction of ≥2 points in SAF-A score and no worsening of fibrosis				
Lanifibranor, 800 mg	33	48	1.45 (1.00–2.10)	0.07
Lanifibranor, 1200 mg	33	55	1.69 (1.22–2.34)	0.007
Secondary end point: resolution of NASH without worsening of fibrosis				
Lanifibranor, 800 mg	22	39	1.70 (1.07–2.71)	
Lanifibranor, 1200 mg	22	49	2.20 (1.49–3.26)	
Secondary end point: improvement in fibrosis stage of ≥1 without worsening of NASH				
Lanifibranor, 800 mg	29	34	1.15 (0.72–1.85)	
Lanifibranor, 1200 mg	29	48	1.68 (1.15–2.46)	
Composite secondary end point: resolution of NASH and improvement in fibrosis stage of ≥1				
Lanifibranor, 800 mg	9	25	2.57 (1.20–5.51)	
Lanifibranor, 1200 mg	9	35	3.95 (2.03–7.66)	



Francque SM, et al. *N Engl J Med*. 2021;385:1547-1558

CME OUTFITTERS

Combination Therapies in NASH

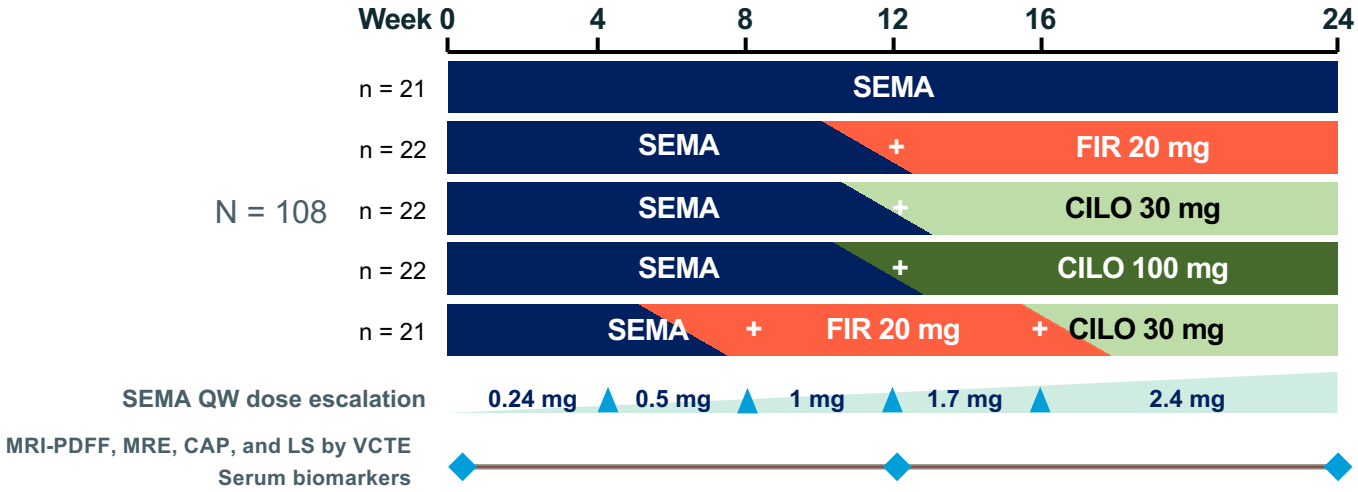
Safety and Efficacy of Combination Therapies Including Semaglutide, Cilofexor, and Firsocostat in Patients with NASH

Naim Alkhouri, Robert Herring, Heidi Kabler, Zeid Kayali, Tarek Hassanein, Anita Kohli, Ryan Huss, Yanni Zhu, Jun Xu, Lars Holm Damgaard, Kristine Buchholtz, Mette Skalshøi Kjær, Clare Balendran, Robert P. Myers, Rohit Loomba, Mazen Noureddin

The Liver Meeting, 13-16 November 2020: Abstr LO2

CME OUTFITTERS

Combination Therapies in NASH: Study Design



- Key inclusion criteria
  - Histologically confirmed NASH with NASH CRN F2–F3 fibrosis (or equivalent), **or**
  - Clinical diagnosis of NAFLD, MRI-PDFF ≥ 10%, LS by VCTE ≥7.0 kPa, and FibroTest <0.75
- Randomization stratified by diabetes mellitus (1:1:1:1:1); open label

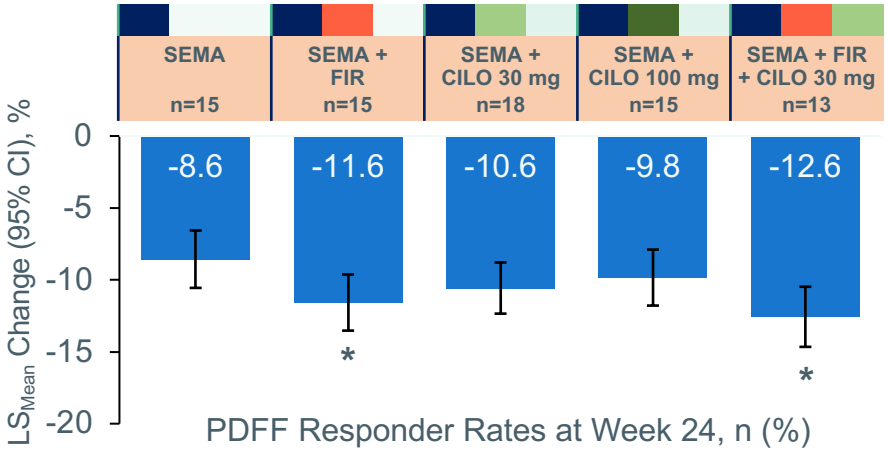
CAP = Controlled Attenuation Parameter; CILO = cilofexor; CRN = Clinical Research Network; FIR = firsocostat; LS = liver stiffness; QW = once weekly; SEMA = semaglutide; VCTE = vibration-controlled transient elastography

Alkhouri N, et al. The Liver Meeting. 2020; Abstract No. LO2.

CME OUTFITTERS

MRI-PDFF: Greater Improvements With Combinations

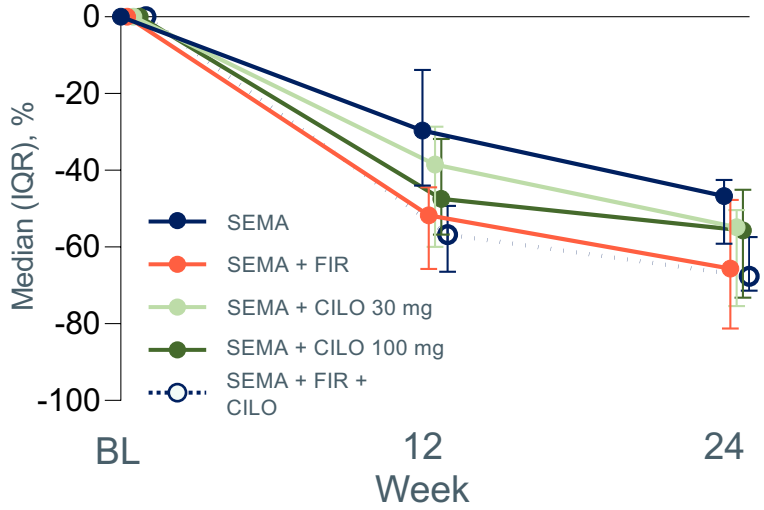
Absolute Change at Week 24



PDFF Responder Rates at Week 24, n (%)

≥30% ↓	12 (80)	14 (93)	17 (94)	13 (87)	12 (92)
≥50% ↓	6 (40)	10 (67)	14 (78)	8 (53)	11 (85)
≥70% ↓	1 (7)	4 (27)	6 (33)	5 (33)	4 (31)

Relative Change from Baseline



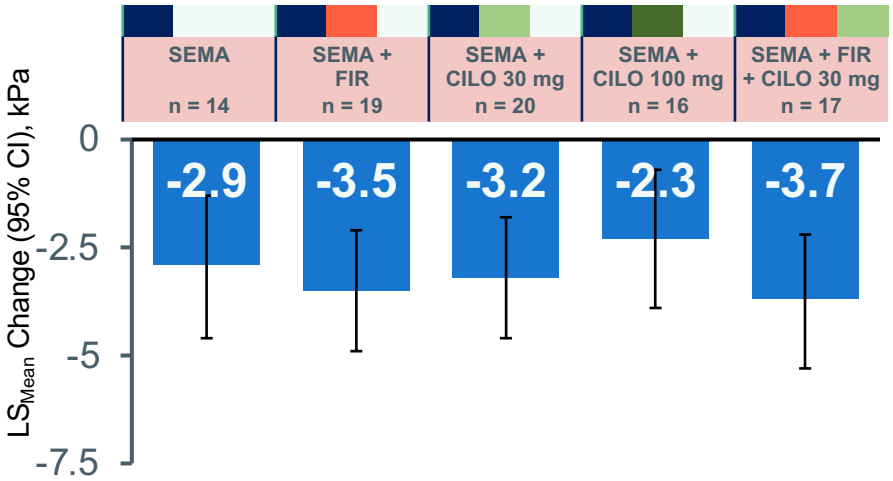
- Greatest reductions in PDFF in FIR groups
- Similar findings observed with CAP

Data collected beyond 30 days after last dose of any study drug excluded from analysis.
Changes in PDFF based on ANCOVA models adjusted for BL and diabetes status. * $p < 0.05$ vs SEMA alone.
ANCOVA = analysis of covariance; BL = baseline; CAP = Controlled Attenuation Parameter; CI = confidence interval; IQR = interquartile range; LS mean = least squares mean; PDFF = proton density fat fraction

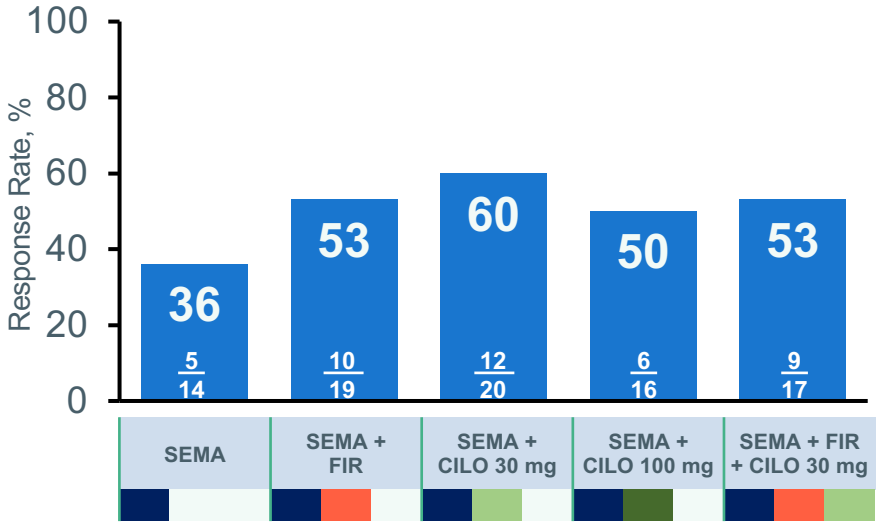
CME OUTFITTERS

Reductions in Liver Stiffness by VCTE in All Groups

Absolute Change at Week 24



≥ 25% Reduction at Week 24



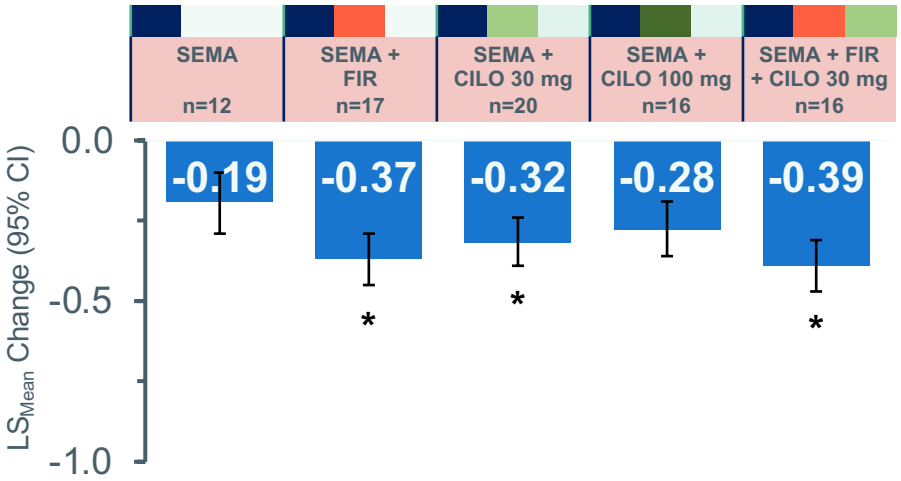
- Similar reductions in LS by VCTE between treatment groups
- No differences in changes in LS by MRE

Changes in LS by VCTE based on ANCOVA models adjusted for BL and diabetes status.
Harrison SA, et al. *J Hepatol.* 2020;73:26-39.

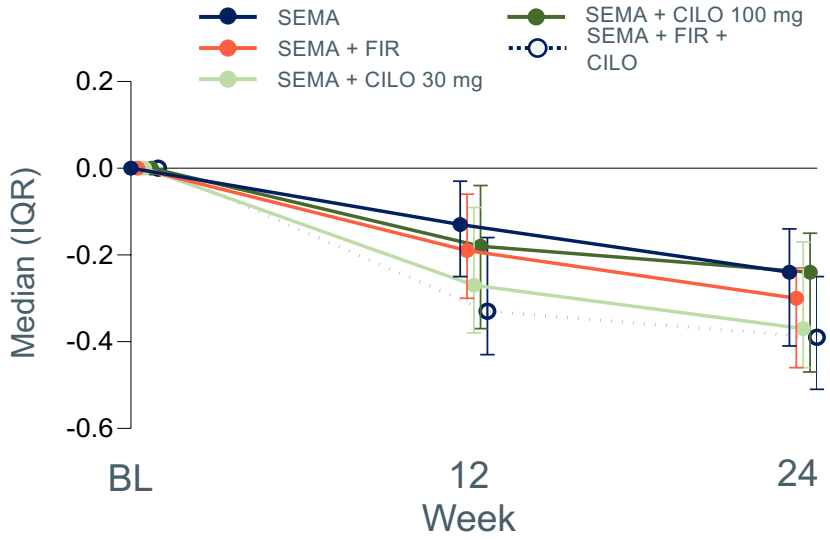
CME OUTFITTERS

FAST Score: Greater Improvements with Combinations

Change at Week 24



Change from Baseline



- All combinations, except CILO + FIR 100 mg, led to significantly greater improvements in FAST score vs. SEMA alone

Changes in FAST score based on ANCOVA models adjusted for BL and diabetes status. * p<0.05 vs SEMA alone.
Newsome PN, et al. *Lancet Gastroenterol Hepatol.* 2020;5:362-373.

CME OUTFITTERS

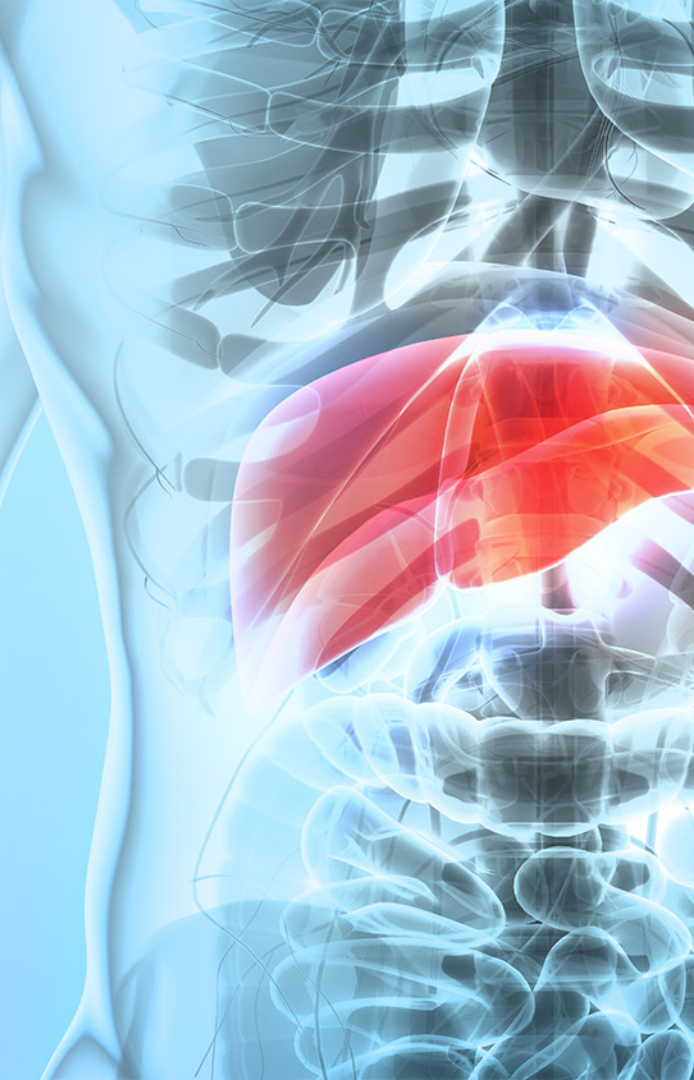
PANEL DISCUSSION
Benefits of NASH resolution, fibrosis improvement

Non-Invasive Testing

Rohit Loomba, MD, MHSc

Select appropriate noninvasive diagnostic tests to stratify risk in patients with NAFLD/NASH.

LEARNING OBJECTIVE 3



Owen Revisited: 61-year-old attorney

- T2DM, dyslipidemia, hypertension
- Central adiposity (BMI = 32.7 kg/m^2)
- High carb diet; 5-7 alcoholic drinks/week
- Complains of abdominal discomfort (upper right quadrant)
- Currently takes metformin for T2DM; irbesartan for hypertension

CME OUTFITTERS

Owen's Lab Results

Laboratory Values

- ALT: 60 U/L
- AST: 65 U/L
- Total bilirubin: 0.8 mg/dL
- Albumin: 4.0 g/dL
- Platelets: 180,000/µL
- LDL: 130 mg/DL
- HDL: 36 mg/dL
- TG: 235 mg/dL
- A1C: 7.1%

ALT = alanine aminotransferase test; AST = aspartate aminotransferase test; HDL = high-density lipoproteins; LDL = low-density lipoproteins; TG = triglycerides

CME OUTFITTERS

Audience Response

You and Owen agree to screen him for high-risk NAFLD. Which of the following is the next step for risk stratification?

A. Liver biopsy

B. FIB-4

C. MRE

D. Transient elastography (e.g., FibroScan)

E. I am not sure

CME OUTFITTERS

Noninvasive Tests Available* for NAFLD

Clinical or Lab Tests/Scores

- **Enhanced liver fibrosis test (ELF)**
- **FibroScan AST Score (FAST)**
- **Fibrosis-4 (FIB-4)**
- **FIBROSpect**
- ADAPT/Pro-C3
- AST/platelet ratio index
- BARD Score
- Fatty liver index
- *FibroSure*
- Hepascore
- NAFLD fibrosis score (NFS)
- NIS4
- Agile Score

Imaging (Elastography)

- **Magnetic resonance elastography (MRE)**
- **Transient elastography (TE) *[FibroScan]***
- 2D shear wave elastography (2D-SWE)
- Acoustic radiation force impulse (ARFI)
- Controlled attenuation parameter (CAP)
- Computer tomography (CT)
- Corrected T1 (*Liver MultiScan*)
- MRI proton density fat fraction (MRI-PDFF)
- Quantitative ultrasound (QUS)

*List of available tests/scores/imaging includes some that are not currently validated or endorsed by guidelines. **Bold red type** indicates validated tests most often used by today's faculty.

Loomba R, Adams LA. *Gut*. 2020;69(7):1343-1352; Papagianni M, et al. *World J Hepatol*. 2015;7:638-648; Golabi P, et al. *Expert Rev Gastroenterol Hepatol*. 2016;10:63-71; Castera L, et al. *Gastroenterology*. 2019;156(5):1264-1281.

CME OUTFITTERS

Exploring Noninvasive Tests: Fibrosis-4 (FIB-4) Index and NAFLD Fibrosis Score (NFS)

FIB-4

- Predicts advanced fibrosis in the liver
  - Age (years)
  - ALT (U/L)
  - AST (U/L)
  - Platelet count (x10^9/L)

Understanding the FIB-4 Score

Score < 1.3 Rules out advanced fibrosis Sn: 74%; Sp: 71%	Indeterminate	**Score > 2.67** Predicts advanced fibrosis Sn: 33%; Sp: 98%

NFS

- Predicts liver fibrosis in patients with NAFLD
  - Age (years)
  - ALT (U/L)
  - AST (U/L)
  - BMI (kg/m2)
  - Hyperglycemia
  - Platelet count (x10^9/L)

Understanding the NFS Score

Score < -1.455 Rules out fibrosis Sn: 82%; Sp: 77%	Indeterminate	**Score > 0.66** Predicts fibrosis Sn: 51%; Sp: 98%

Shah AG, et al. *Clin Gastroenterol Hepatol*. 2009;7:1104-1112; Angulo P, et al. *Hepatology*. 2007;45:846-854.

CME OUTFITTERS

Exploring Noninvasive Tests: Enhanced Liver Fibrosis (ELF) Score

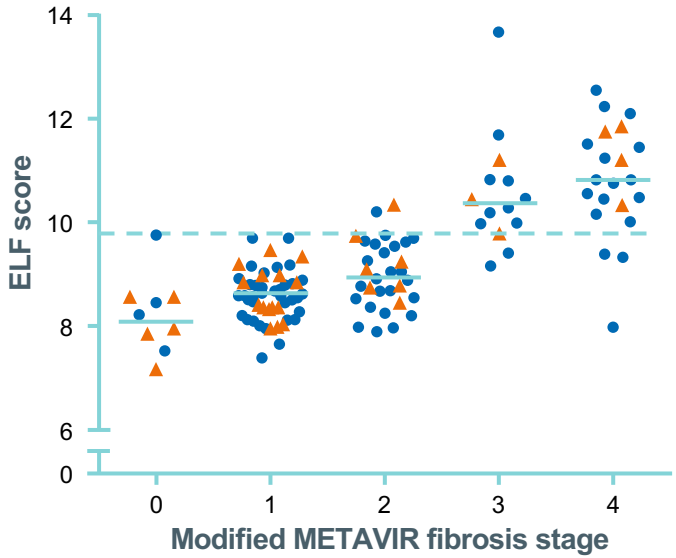
Proprietary blood test delivers information on liver fibrosis severity

Algorithm incorporates 3 common serum biomarkers:

- HA (hyaluronic acid)
- PIIINP (amino-terminal propeptide of type III procollagen)
- TIMP-1 (tissue inhibitor of metalloproteinase-1)

Understanding the ELF Score

Score 7.7	Score 9.8	Score 11.3
Rules out fibrosis	Predicts fibrosis	Predicts cirrhosis
Sn: 97%	Sn: 69%	Sn: 83%
Sp: 33%	Sp: 98%	Sp: 97%



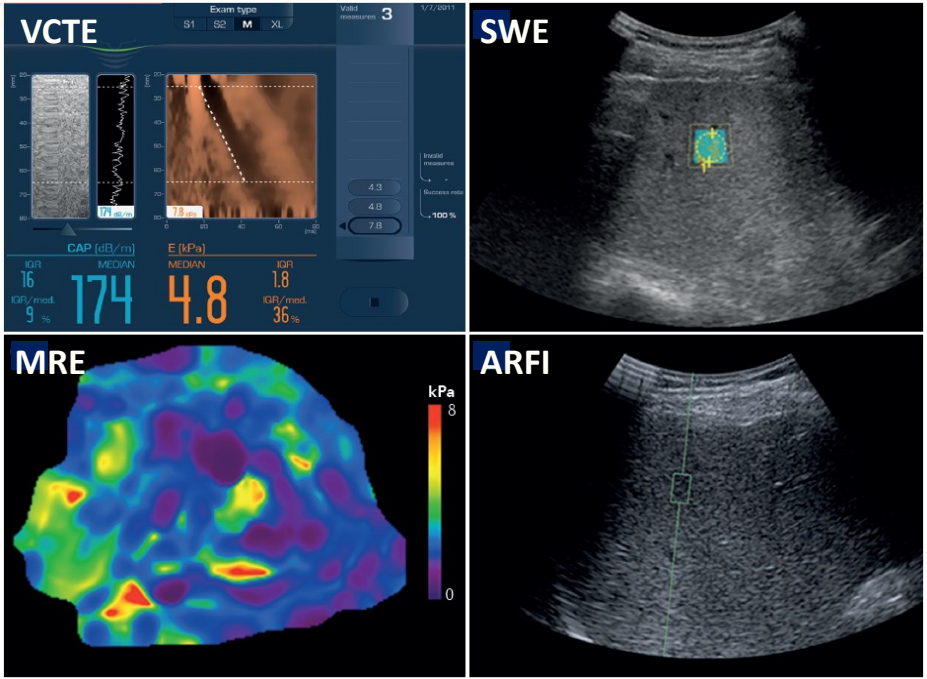
ELF ≥ 9.8 is associated with advanced fibrosis

Lichtinghagen R, et al. *J Hepatol.* 2013;59(2):236-242; Fagan KJ, et al. *Liver Int.* 2015;35(6):1673-1681.

CME OUTFITTERS

Elastography-Based Methods to Estimate Liver Stiffness

- VCTE (FibroScan) most widely used
  - ≥ 10 images are required
  - Accurate for stages F3-F4
  - Can estimate steatosis when used with CAP
- SWE/ARFI can be used to measure stiffness in a single region of interest
- MRE measures stiffness across multiple regions of interest



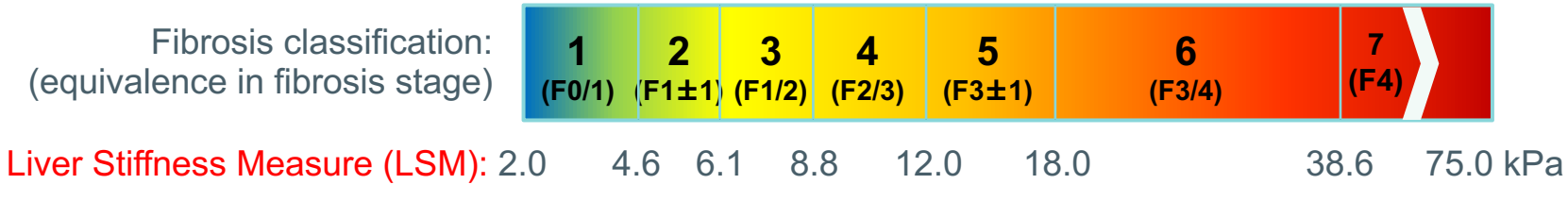
SWE = shear wave elastography; VCTE = vibration-controlled transient elastography

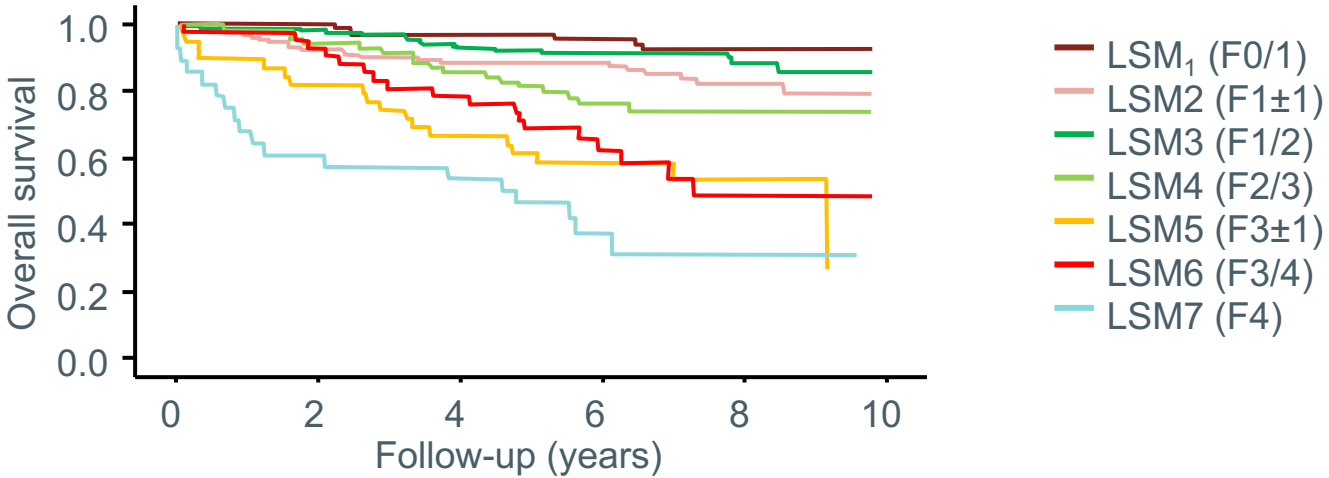
Tapper EB, Loomba R. *Nat Rev Gastroenterol Hepatol*. 2018;15(5):274-282.

CME OUTFITTERS

Liver Stiffness As a Non-Invasive Biomarker of Fibrosis

A cross-sectional study of 452 patients with liver biopsy

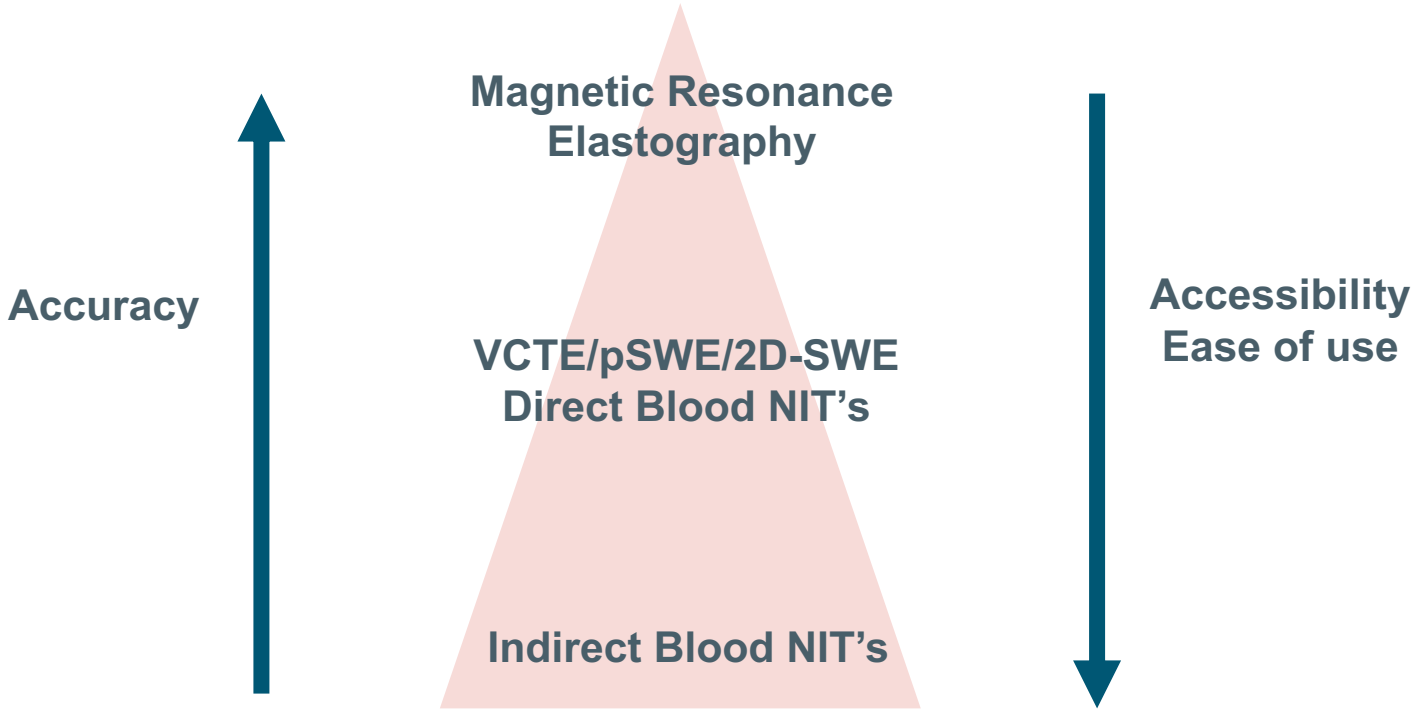




Boursier J, et al. *J Hepatol*. 2016;65(3):570-578.

CME OUTFITTERS

Comparative Accuracy and Accessibility of NITs



NITs = non-invasive fibrosis tests; pSWE = pulse shear wave elastography

Loomba R, Adams LA. *Gut.* 2020;69(7):1343-1352.

CME OUTFITTERS

Audience Response

Owen's FIB-4 score is 2.2 which puts him in the "indeterminate" zone. What would be the most efficient next step to risk stratify Owen?

A. Attempt lifestyle modifications only (exercise, nutrition)

B. Use a second non-elastographic NIT to potentially narrow the indeterminate zone

C. Rule out/in advanced fibrosis with transient elastography or MRE

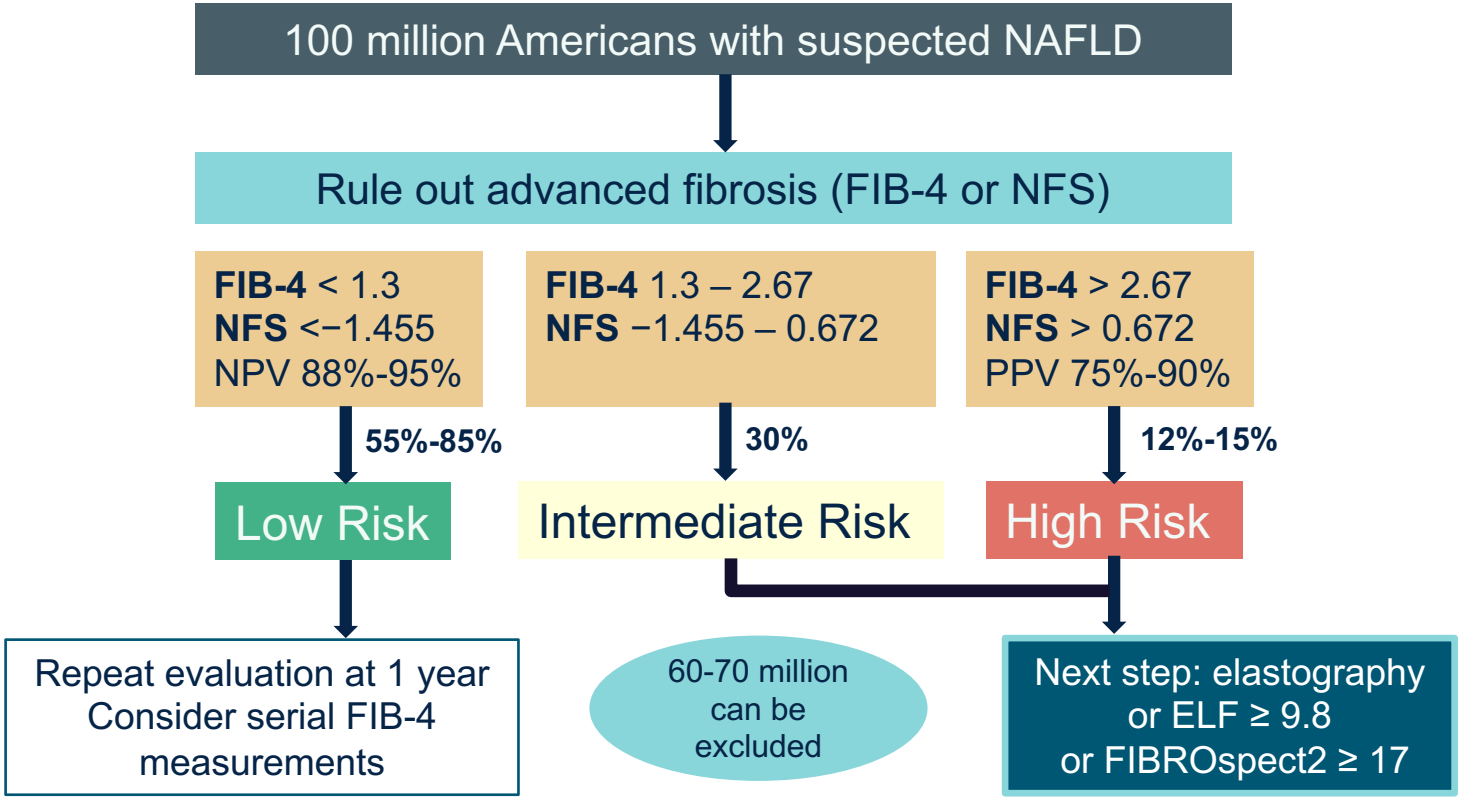
D. Liver biopsy

E. B or C

F. I am not sure

CME OUTFITTERS

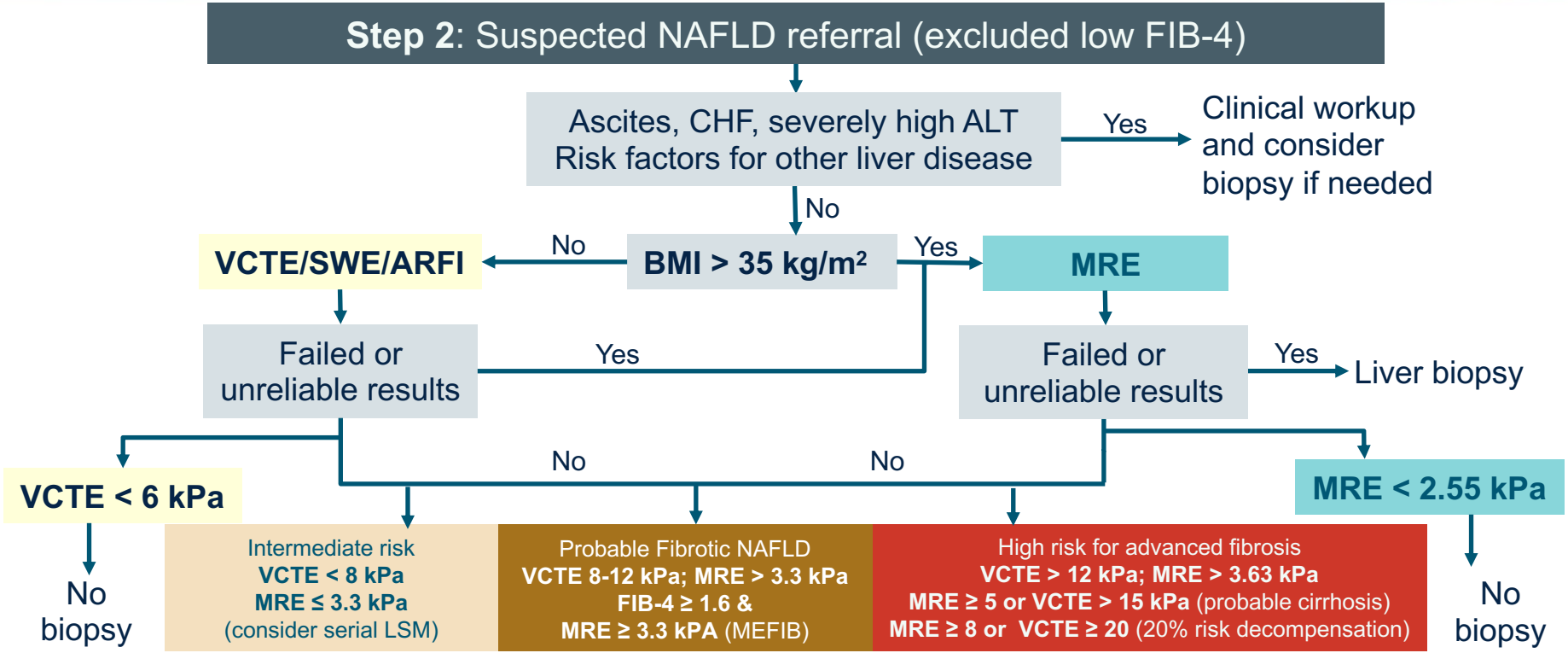
Optimizing Risk Management



ELF = enhanced liver fibrosis; NFS = NAFLD fibrosis score; NPV = negative predictive value; PPV = positive predictive value
Adapted from Castera L, Friedrich-Rush M, Loomba R. *Gastroenterology.* 2019;156(5):1264-1281.

CME OUTFITTERS

Elastography in Assessing Advanced Fibrosis

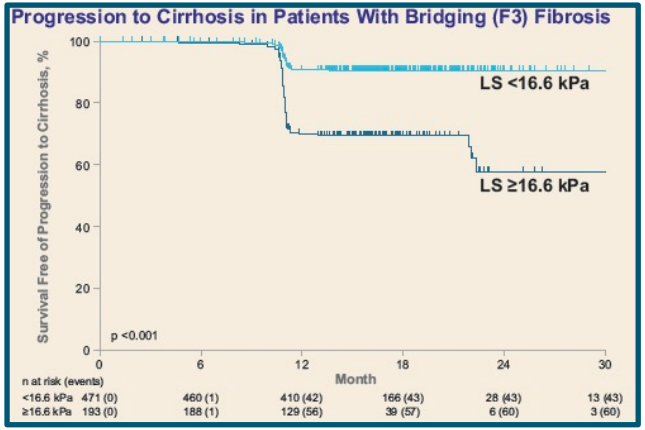


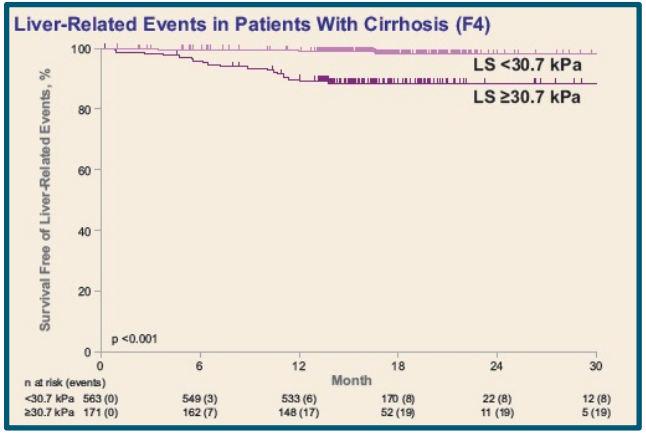
ARFI = acoustic radiation force impulse; ALT = alanine aminotransferase; BMI = body mass index; CHF = congestive heart failure; kPa = kilopascals; MRE = magnetic resonance elastography; SWE = shear-wave elastography; VCTE = vibration-controlled transient elastography.

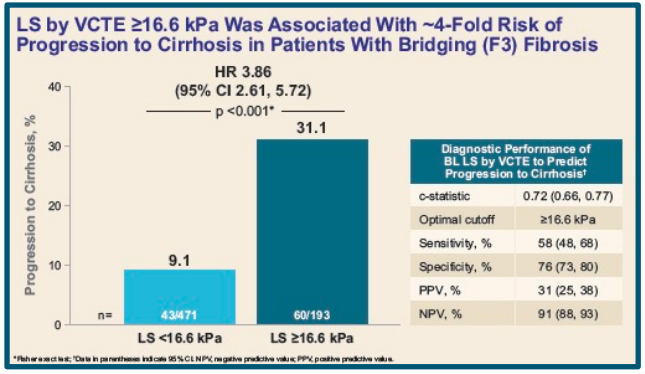
Adapted from Tapper EB, Loomba R. *Nat Rev Gastroenterol Hepatol*. 2018;15:274-282; Natarajan Y, Loomba R. *J Clin Transl Hepatol*. 2021. In press; Ajmera V, Loomba R. *Mol Metab.* 2021;50:101167.

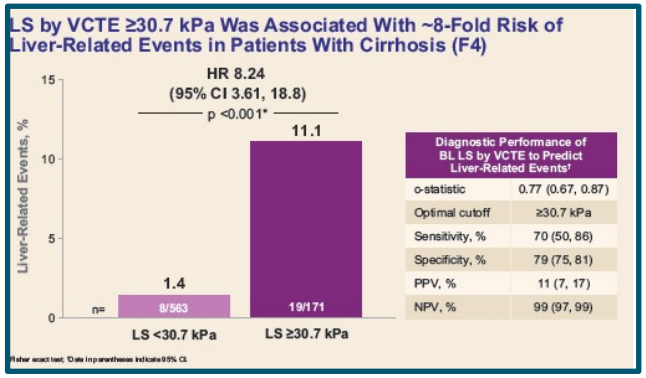
CME OUTFITTERS

FibroScan Cut Points for Progression to Cirrhosis and for Those With Cirrhosis at Risk for Decompensation









Objective

To establish thresholds of LS by VCTE that predict clinical outcomes in patients with bridging fibrosis and cirrhosis due to NASH.

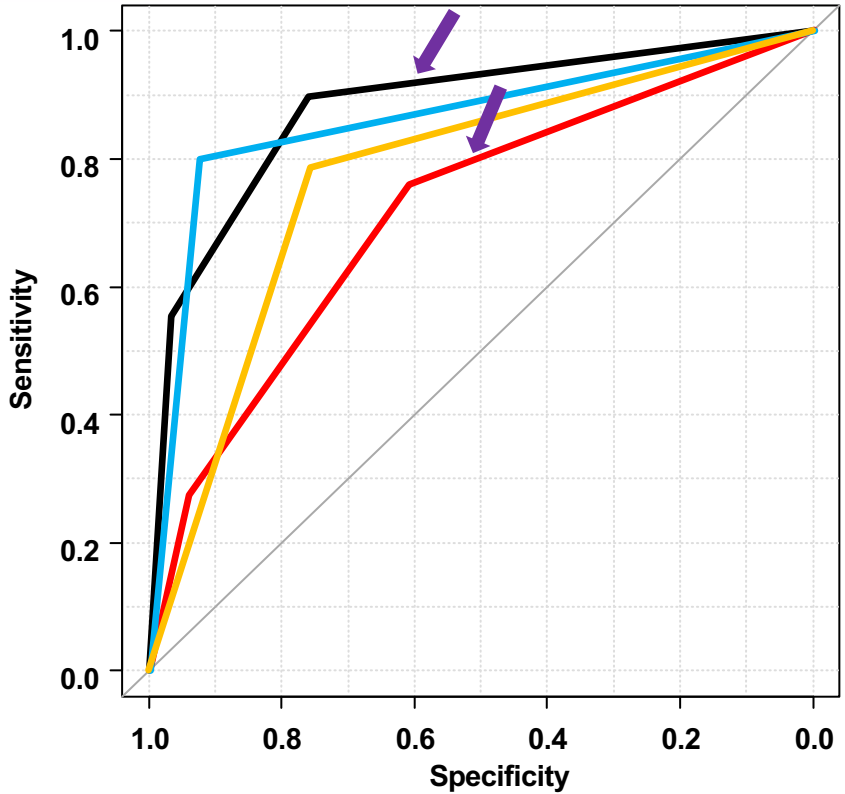
LS = liver stiffness

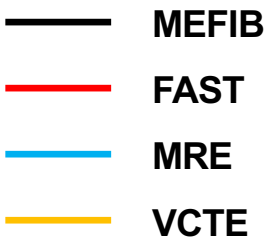
Loomba R, et al. Presented at International Liver Congress 2021, 23-26 June.

CME OUTFITTERS

PANEL DISCUSSION
Over the past year, what's new in identifying who needs to be treated?

MEFIB Superior to FAST in Detection of "At Risk" NASH Patients Among Those With Biopsy-Proven NAFLD





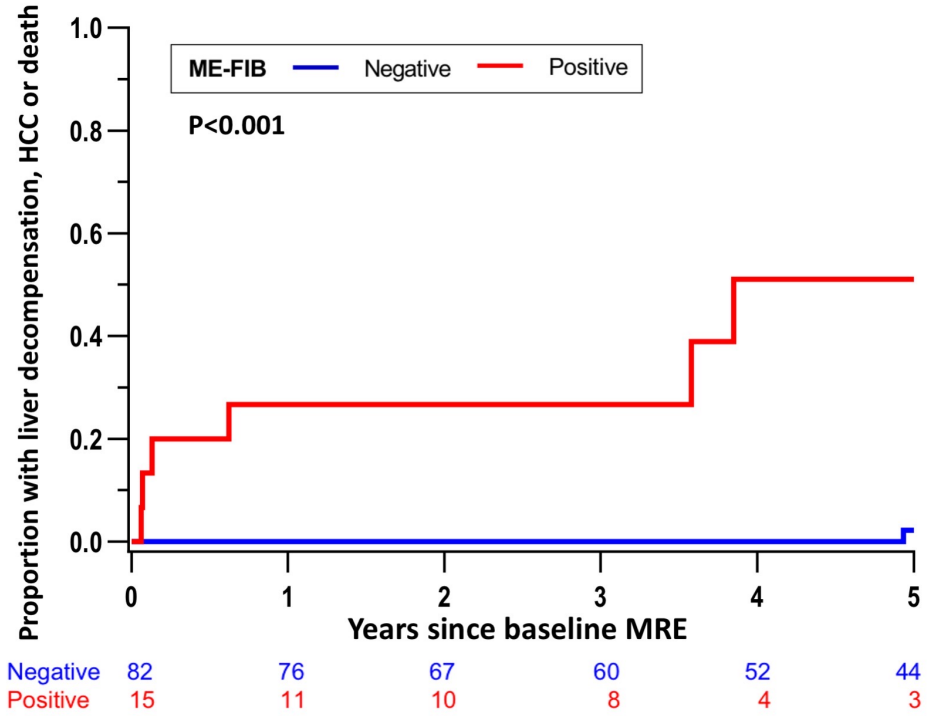
	AUROC (95% CI)	P value
MEFIB	0.880 (0.85–0.91)	Ref
FAST	0.715 (0.67–0.76)	< 0.001
MRE	0.863 (0.83–0.89)	0.06
VCTE	0.771 (0.73–0.81)	< 0.001

MEFIB = MRE combined with FIB-4; FAST = FibroScan AST Score; MRE = Magnetic resonance elastography; VCTE = vibration-controlled transient elastography.

Tamaki N, Loomba R. AASLD 2021. https://doi.org/10.1002/hep.32145.

CME OUTFITTERS

5-Year Cumulative Incidence of Hepatic Decompensation, Hepatocellular Carcinoma, or Death by MEFIB Score



- A positive MEFIB score, defined as a combination of MRE ≥ 3.3 kPa and FIB-4 ≥ 1.6
- A negative MEFIB score was associated with a 98% negative predictive value for liver-related events or death

Ajmera V, et al. UCSD NAFLD Research Center. 2021.

CME OUTFITTERS

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Screen patients with T2DM for NASH
- Counsel patients with cardiometabolic disease, including T2DM, about nutrition and exercise to reduce hepatic risk
- Use non-invasive tests to stratify risk in patients with potential NASH
- Monitor patients for progression of NASH
- Keep current with safety and efficacy of emerging therapies, including those with extra-hepatic benefits such as improvement in glycemic control, lipid profile and weight loss

CME OUTFITTERS

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