
2023
SCSG
LIVER SYMPOSIUM
DECEMBER 9-10, 2023

MASLD/MASH Abstracts Update

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Disclosure

- Research grant from intercept, Madrigal, Gilead Sciences, and Zydus

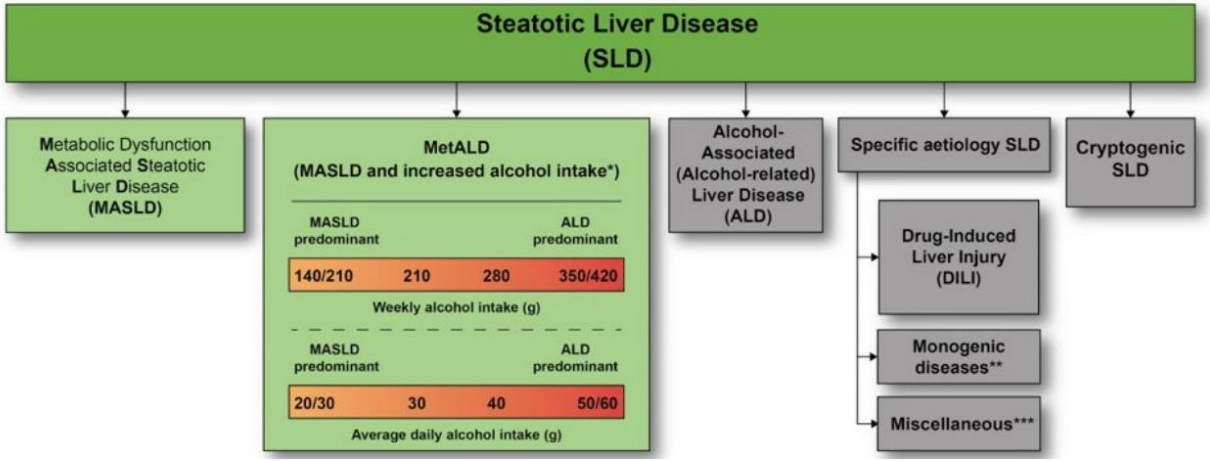
Changes in Nomenclature: MASLD

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
- ☐ 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

Steatotic Liver Disease Sub-classification



AASLD The Liver Meeting® Nov. 10-14, 2023

Economic and social burden of MASLD in the United States

Homie Razavi[1], Ivane Gamkrelidze[1], Chris Estes[1], Arun Sanyal[2]

[1] Center for Disease Analysis Foundation, Lafayette, CO, United States, 2 Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA

CDA FOUNDATION

- The updated forecast estimates a higher increase in MASLD population and larger number of MASH cases relative to our 2017 forecasts (Figure 1).
- In 2022, an estimate 26 million people had MASH in the U.S., forecasted to grow to **40 million by 2044**, and **2.5 million people** had cirrhosis due to MASH.
- MASLD is estimated to cost the U.S. health system $13.2B annually and increasing to **$16.8B** (Figure 2)

Figure 1. MASLD & MASH forecasts

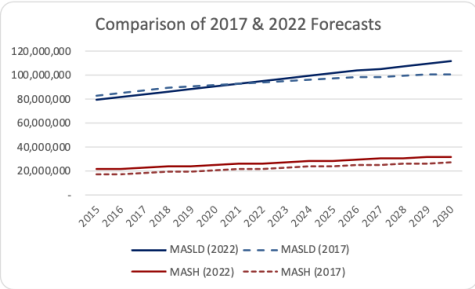


Figure 2. Cost of test & treat ≥F2 patients

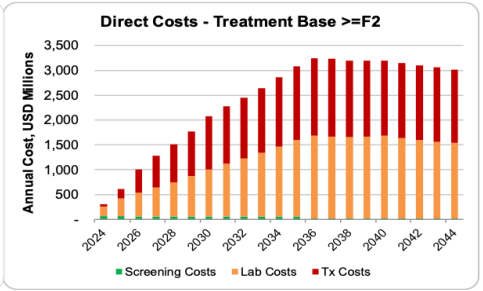
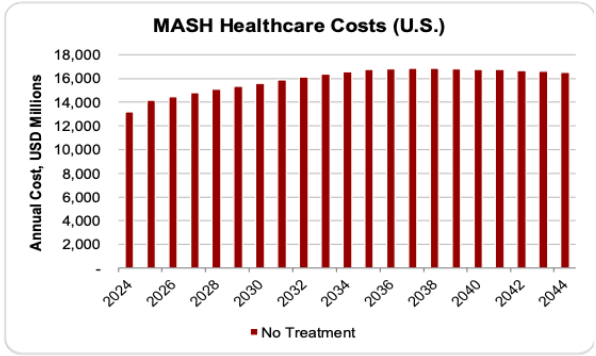
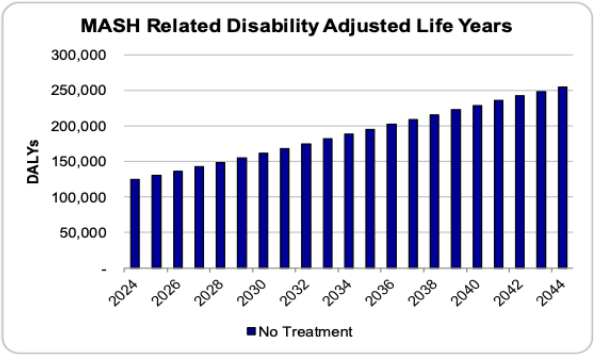


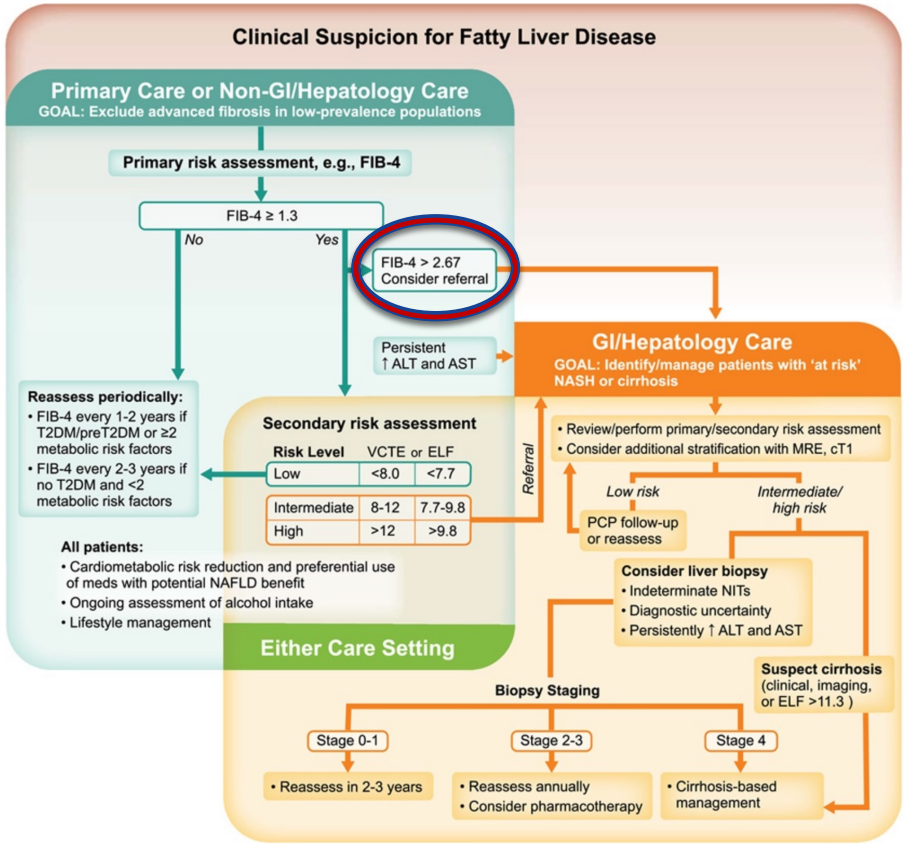
Figure 2. Total Healthcare costs & DALY





Screening, Awareness and Educations – Starting From Primary Care Clinic

AGA/AASLD Guideline



Cost-Effectiveness of Identifying High-risk Non-Alcoholic Fatty Liver Disease (NAFLD) Patients in the United States (U.S)

- A cost-utility model for patients seen at primary care or endocrinology practices consists of a decision tree and Markov model.
- If patients had type 2 diabetes (T2D), prediabetes (Pre-D), or ≥2 other components of metabolic syndrome (≥2-MS) without any other causes of liver diseases (viral hepatitis, alcoholic liver disease, excessive alcohol use), they entered a decision tree with 6 NIT screening strategies using first line FIB4 and second line NIT testing. Markov model was used to simulate the natural history of NAFLD/NASH
- Costs and health effects of 6 screening strategies were compared to no screening

Table. Per-patient costs and QALYs and cost-effectiveness of strategies for base case

	Projected Prevalence AF (%)	Average Diagnostic Pathway Costs	Average Staging Costs	Average Long-term Care Costs	Average Total cost	Average Total QALYs	Average Total Cost/Total QALY
No Screen	12.85%	$0.00	$818.07	$46,023.23	$46,841.31	9.437	$4,984.58
FIB4 (≥1.30)+VCTE	12.68%	$208.72	$670.82	$45,151.68	$45,822.50	9.499	$4,843.14
FIB4 (≥1.30)+ELF	12.67%	$193.35	$772.17	$45,124.40	$45,896.57	9.497	$4,852.19
FIB4 (1.30-2.67)+VCTE	12.66%	$135.65	$698.35	$45,056.08	$45,754.43	9.496	$4,837.44
FIB4 (1.30-2.67)+ELF	12.66%	$180.18	$904.02	$45,065.94	$45,969.96	9.488	$4,864.35
FIB4 (≥1.30)+VCTE +ELF	12.67%	$221.63	$778.87	$45,099.24	$45,878.11	9.498	$4,849.61
FIB4 (≥1.30)+ELF+VCTE	12.67%	$221.63	$945.20	$45,115.14	$46,060.34	9.494	$4,871.04
Scenario Analysis							
VCTE availability at primary care							
50%	12.66%	$235.98	$843.00	$45,046.68	$45,889.68	9.494	$4,852.54
0%	12.65%	$235.33	$927.93	$44,994.12	$45,922.05	9.488	$4,859.06

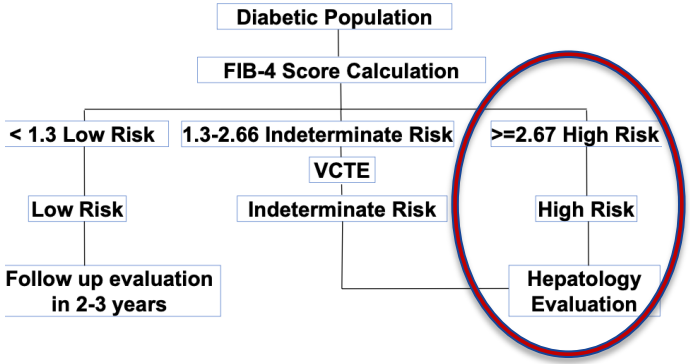
FIB4+any NIT is saving in long-term health cost than no screen

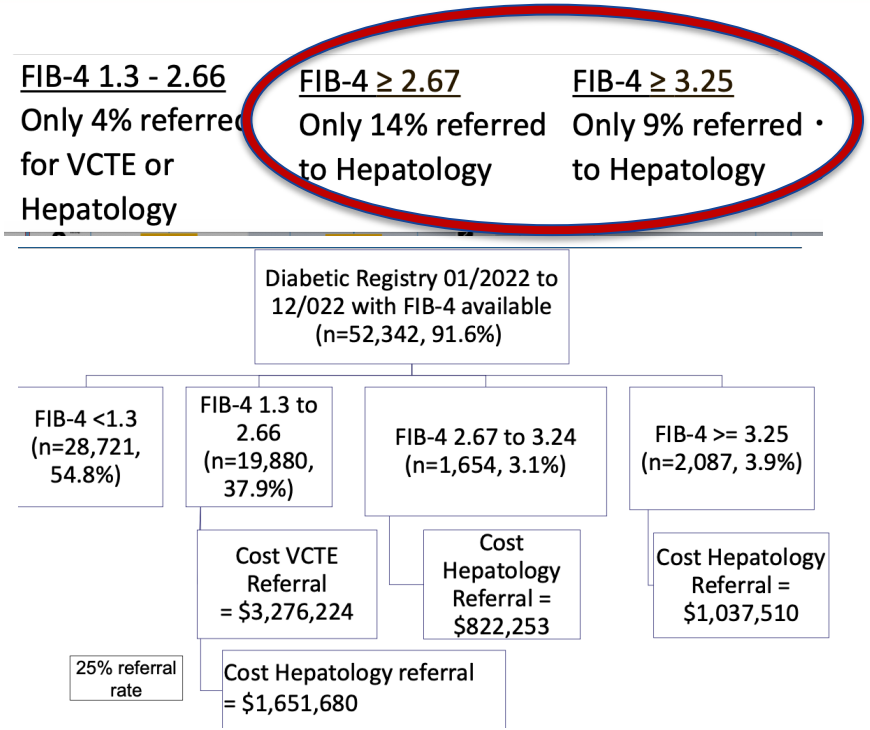
Zobair M. Younossi et al.

AASLD/AGA MASLD Practice Guidance for Screening Diabetics

Factors Associated With Advanced Fibrosis, Implications for Care Delivery, and Cost-Reduction Using Age-Adjusted FIB-4 Cut-offs

- Calculate FIB-4 scores in Mount Sinai's diverse urban DM population engaged in Primary Care





91% of cirrhotic may be undiagnosed

Rohit R. Nathani et al.

Improving Primary Care Provider Awareness and Use of FIB-4 Risk-Stratification for Metabolic-Dysfunction Associated Steatotic Liver Disease (MASLD)

Max L Goldman, MD[1,2]; Rena K Fox, MD[2]; Danielle Brandman, MD, MAS, FAASLD[3]; Delia Falliers[4]; Kendall Islam, BS[5]; Janet N Chu, MD, MPH, MAS[2]

1. Department of Gastroenterology, Kaiser Permanente, Northern California; 2. Division of General Internal Medicine, UCSF; 3. Weil Cornell Center for Liver Disease and Transplantation; 4. UCLA; 5. UCSF School of Medicine

SF CAN San Francisco Cancer Initiative

UCSF School of Medicine

KAISER PERMANENTE

Pre- Intervention Survey and Assessment

A pre-intervention PCP survey to ascertain MASLD knowledge and management patterns.

Intervention Implementation

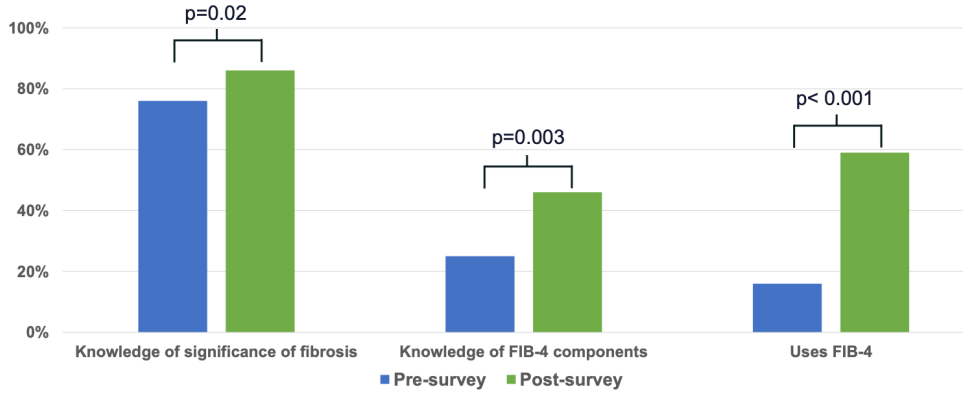
An 18-month intervention implementing the FIB-4 risk-stratification referral algorithm in primary care.

- Identified all adults with diabetes in PC, age < 75, excluding those with other common liver diseases.
- Over 18-months, PCPs received **an electronic medical record (EMR) notification** for each patient 18-75 years old with diabetes (DM) and either a:
- Low-risk Fib-4 (<1.3) Manage in primary care OR
- **High-risk Fib-4 (>2.67) Refer to hepatology**

Post-Intervention Survey After One Year

- A post-intervention PCP survey one year later.
- Pre-and post survey responses were compared using two-sample z-tests.

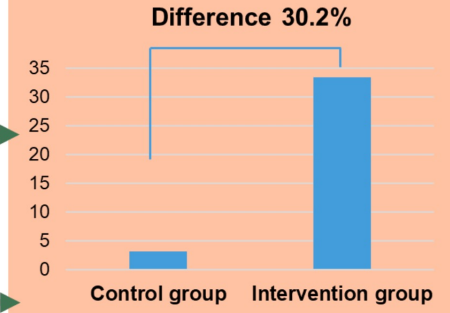
Figure 2. Difference in PCP knowledge and use of FIB-4 based risk stratification before and after implementation of the AASLD's a referral algorithm in primary care.



Implementing a FIB-4 risk stratification algorithm in primary care substantially impacted PCP management of MASLD.

How We Can Do Better: Electronic Reminder? RHM Alert?

Clinical care pathway to detect advanced liver disease in patients with type 2 diabetes through automated fibrosis score calculation and electronic reminder messages: a randomised controlled trial

Study Population		Intervention	Outcome
five general medical or diabetes clinics 1061 patients with type 2 diabetes were screened between 19 May 2020 and 14 October 2021	RANDOMIZATION	**Control (n=528)**: fibrosis score calculation + no electronic reminder messages **Intervention (n=533):** fibrosis score calculation + electronic reminder messages if abnormal fibrosis scores **Primary outcome:** Proportion of patients with high fibrosis scores who received hepatology care or further fibrosis assessment	 Automated fibrosis score calculation and electronic reminders increase referral of patients with type 2 diabetes and abnormal fibrosis scores at non-hepatology settings

Zhang X et al. *Gut*. 2023.

Clinical, Biological and Imaging Predictors of At-Risk MASH: Combined Data From Multiple Therapeutic Trials Including More than 6,000 Patients

- 8 therapeutic non-cirrhotic trial
- 6558 patients
- 2385 MRI-PDFF
- 2514 fibroscan
- 2277 liver bx
- 5514 lab data

Screen failure rate for biopsy proven NASH trial 75-85%

	Failed Biopsy N=1,261	At-Risk MASH NASH - NAS ≥ 4 Fibrosis 2 or 3 N=912	p-value
Lipid Parameters			
LDL, mg/dL	106 (39)	100 (37)	<0.001
HDL, mg/dL	45 (14)	44 (12)	0.136
Triglyceride, mg/dL	160 (86)	166 (82)	0.146
Transient Elastography			
Liver Stiffness Measurement, kPa	11.9 (6.0)	13.6 (6.5)	<0.001
Controlled Attenuation Parameter	342 (40)	345 (37)	0.206
MRI-PDFF			
LFC, %	18.5 (7.8)	18.0 (7.1)	0.238
Scores			
AST/ALT ratio	0.79 (0.27)	0.84 (0.37)	<0.001
FIB-4	1.09 (0.57)	1.47 (0.69)	<0.001
FAST	0.48 (0.22)	0.62 (0.20)	<0.001
AGILE3+	0.49 (0.24)	0.62 (0.25)	<0.001

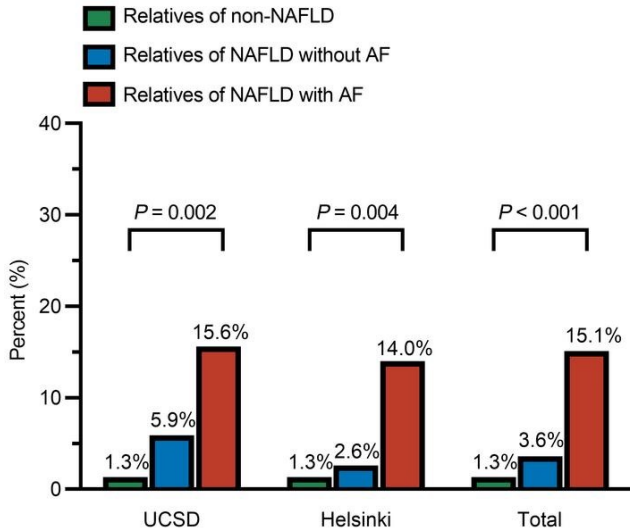
	Failed Biopsy N=1,261	At-Risk MASH NASH - NAS ≥ 4 Fibrosis 2 or 3 N=912	p-value
Demographics			
Age, years	53.2 (12.2)	55.0 (11.1)	<0.001
Female	56 %	62 %	0.007
Female > 50 years	37%	45%	<0.001
Hispanic	46%	42%	0.025
BMI, kg/m^2	37.7 (7.7)	36.9 (6.6)	0.113
Liver Enzymes			
AST, IU/L	34 (19)	50 (29)	<0.001
ALT, IU/L	47 (29)	64 (37)	<0.001
GGT, IU/L	51 (55)	74 (72)	<0.001
ALP, IU/L	83.1 (27.6)	82.7 (26.3)	0.704
Glycemic Parameters			
FPG, mg/dL	109 (35)	120 (35)	<0.001
HbA1c, %	6.2 (1.0)	6.6 (1.1)	<0.001
HbA1c ≥ 6.5%	31%	48%	<0.001

- **Middle aged patients with multiple comorbidities (type 2 DM); exclude: Fibroscan <8.5Kpa, AST<20**
- **If HbA1C<6.5%, AST>=40, FAST>=0.67**
- **If HbA1C>=6.5%, AST>=30, FAST>=0.50**

SA Harrison et al.

Development and Validation of the NAFLD (MASLD) Familial Risk Score to Detect Advanced Fibrosis: A Prospective, Multicenter Study

- First-degree relatives of NAFLD patients with advanced fibrosis are at higher risk of NAFLD with advanced fibrosis



Daniel Q Huang et al.

Total 87 probands with advanced fibrosis

Derivation of the Familial Risk Score

Variable	Regression coefficient	NAFLD Familial Risk Score
Age	1.22	< 50 years = 0 points
		≥ 50 years = 1 points
Obesity	1.86	Non obese = 0 points
		Obese = 2 points
DM	1.11	No diabetes = 0 points
		Diabetes = 1 points
Family History	2.01	Proband does not have advanced fibrosis = 0 points
		Proband has advanced fibrosis = 2 points

NAFLD Familial Risk Score

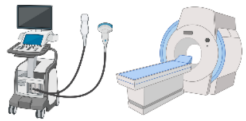
- **Age** ≥ 50 yrs = 1 point
- **T2DM** = 1 point
- **Obesity** = 2 points
- **Family history*** = 2 points

Proband evaluated for NAFLD/fibrosis

Apply NAFLD Familial Risk Score to first-degree relatives

- **Age** ≥ 50 yrs = 1 point
- **T2DM** = 1 point
- **Obesity** = 2 points
- **Family history*** = 2 points

NAFLD Familial Risk Score ≥ 4 points → **Fibrosis assessment** by non-invasive imaging



NAFLD Familial Risk Score < 4 points → Risk factor modification

*Family history of NAFLD with advanced fibrosis

Non-Invasive Testing and Artificial Intelligence

AASLD The Liver Meeting® Nov. 10-14, 2023

Head-to-head comparison of FAST, MAST, MEFIB and cT1 in identifying at-risk NASH patients in a low-prevalence population

Mazen Noureddin[1], Naim Alkhouri[2], Cassandra Chaldaureille[3], Julie Foucquier[3], Véronique Miette[3], Laurent Sandrin[3], Céline Fournier-Poizat[3], Stephen A. Harrison[4]
(1) Houston Liver Institute, (2) Arizona Liver Health, (3) Echosens, (4) University of Oxford

- 4 non-invasive tests (NIT) and associated cut-off values to rule-in and rule-out presence of “at-risk NASH”:

FAST (FibroScan-AST)

MAST (Magnetic Resonance Imaging based score)

MEFIB (Magnetic Resonance Elastography + FIB-4) 4

cT1 (Iron-corrected T1, Liver MultiScan)

170 patients (40.6% females; mean ± SD age 55.9 ± 6.0 years; mean ± SD BMI 33.1 ± 4.9 kg/m2) who underwent a prospective LB and had all four NITs available were included in this analysis with a prevalence of at-risk NASH patients at 11.8%

	FAST	MAST	MEFIB	cT1
AUC [95% CI]	0.86 [0.78;0.94]	0.91 [0.85;0.98]	0.52 [0.48;0.57]	0.77 [0.67;0.87]
Rule-out cut-off	**< 0.35**	**≤ 0.165**	**MRE < 3.3 kPa & FIB-4 < 1.6**	**< 825 ms**
Number of patients (%)	133 (78%)	168 (99%)	146 (86%)	114 (67%)
Se / Sp	0.65 / 0.84	0.1 / 1.0	0.45 / 0.9	0.70 / 0.72
NPV	0.95	0.89	0.92	0.95
Indeterminate zone				
Number of patients (%)	31 (18%)	0 (0%)	23 (14%)	35 (22%)
Rule-in cut-off	**≥ 0.67**	**≥ 0.242**	**MRE ≥ 3.3 kPa & FIB-4 ≥ 1.6**	**≥ 875 ms**
Number of patients (%)	6 (4%)	2 (1%)	1 (<1%)	21 (12%)
Se / Sp	0.25 / 0.99	0.1 / 1.0	0.05 / 1.0	0.3 / 0.90
PPV	0.83	1.0	1.0	0.29
Well-classified*	94%	89%	93%	84%

MAST and FAST have demonstrated superior performance in the identification of at-risk NASH

Machine Learning Score Improves Classification of Individuals With Indeterminate Non-Invasive Risk of Incident Cirrhosis into Low or High Risk Groups

- The prevalence of MASLD is >30% in the general population: FIB-4 Indeterminate range (25-40%)
- Machine learning algorithms >stratify risk of liver related events (LREs)
- Adults with MASLD diagnosed 2010-2020 (n=28,684) Case-control definition
  - Case = **incident cirrhosis** <10 years from index date
  - Control = **no cirrhosis**, >10 years of follow-up Predictors/features: age, sex, race/ethnicity, metabolic comorbidities, common laboratory values

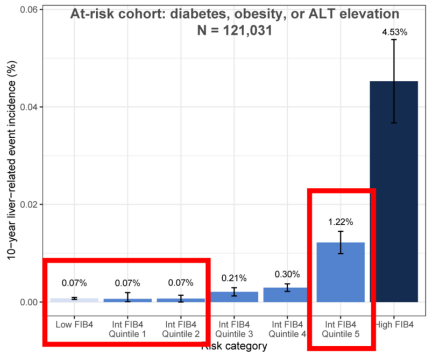
Combining ELM with FIB4 can reduce the indeterminate-risk population and decrease need for second-line testing --- readily-available values, implementation cost would be minimal

Model performance

Score	Overall cohort (n=355,418)		At-risk cohort: diabetes, obesity, or ALT elevation (n=121,031)		Elevated ALT (n=41,176)		Age > 60 years (n=138,560)	
	tAUC (95% CI)	Pval	tAUC (95% CI)	Pval	tAUC (95% CI)	Pval	tAUC (95% CI)	Pval
FIB4	0.810 (0.787-0.833)	Ref	0.821 (0.796-0.847)	Ref	0.825 (0.795-0.855)	Ref	0.784 (0.751-0.818)	
NFS	0.756 (0.731-0.780)	-	0.729 (0.699-0.758)	-	0.774 (0.740-0.808)	-	0.718 (0.683-0.753)	
Model 1	0.834 (0.815-0.854)	0.016	0.824 (0.802-0.846)	0.80	0.828 (0.801-0.855)	0.83	0.798 (0.768-0.829)	0.37
Model 2	0.837 (0.816-0.859)	0.0022	0.839 (0.816-0.862)	0.066	0.847 (0.821-0.873)	0.053	0.807 (0.774-0.840)	0.068
Model 3	0.827 (0.805-0.850)	0.12	0.821 (0.796-0.846)	0.96	0.813 (0.785-0.842)	0.43	0.807 (0.774-0.839)	0.16
Model 4	0.821 (0.799-0.843)	0.33	0.815 (0.790-0.840)	0.58	0.836 (0.808-0.864)	0.50	0.799 (0.768-0.830)	0.32

Model 2 = ELM score (estimator of LREs in MASLD)
Features: age, AST, ALP, PLT, T2DM, HTN

Disease heterogeneity in indeterminate-risk FIB4



Vincent Chen et al.

Pipelines of Clinical Trials for MASH Treatment

TRIPLE HORMONE RECEPTOR AGONIST RETATRUTIDE RESOLVES STEATOSIS IN >85 % OF SUBJECTS WITH MASLD AND OBESITY IN ASSOCIATION WITH IMPROVED METABOLIC HEALTH

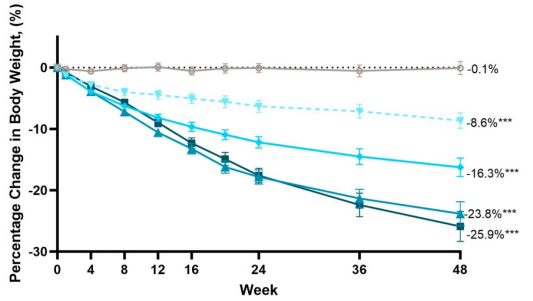
- Semaglutide (GLP-1a): WL 10–15%
- Tirzepatide (GIP/GLP-1a): WL ~20%
- Retatrutide (tri-agonists of the GIP, GLP-1, and glucagon (GCG) receptors)

- **Near-maximal liver fat reductions were achieved at ~20% reduction in body weight**
- **~40% reductions in both abdominal subcutaneous and visceral adipose tissue**

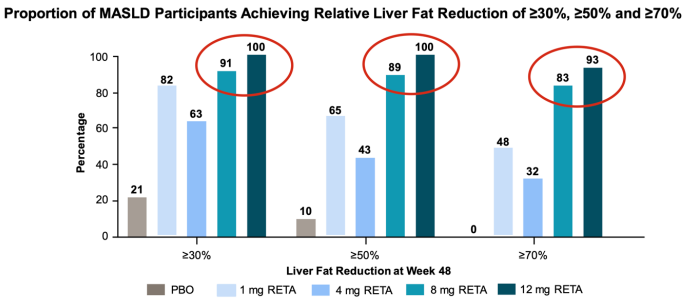
Results

Changes in Body Weight in MASLD Substudy

- Reductions in body weight relative to BL observed with all RETA doses
- Percent change similar to that observed in the full study population[1]



Relative Liver Fat Reduction of ≥30-70% at Week 48



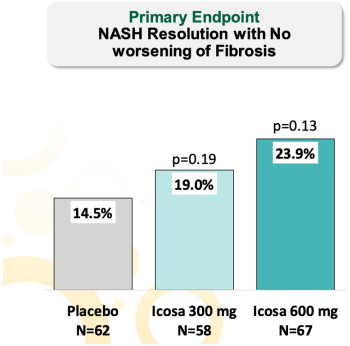
Arun J Sanyal et al.

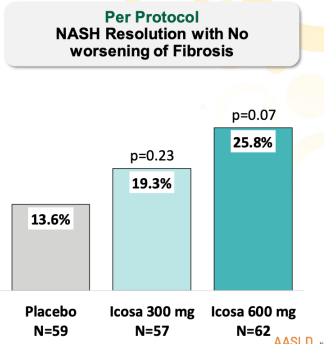
Icosabutate in NASH/MASH With Fibrosis: Results From a Randomized, Multicentre, Double-Blind, Placebo Controlled, Phase 2 b Trial (ICONA)

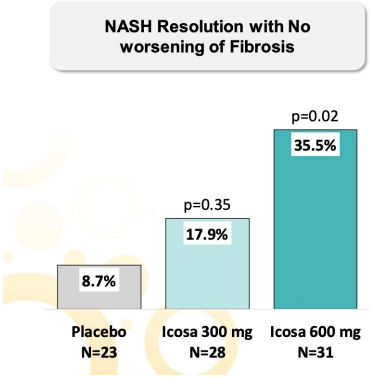
- **Icosabutate, dual FFAR1/FFAR4**
- Free-fatty acid receptor (FFAR)1
- FFAR4 (b-arrestin2)
- PPAR-a (partial agonist)

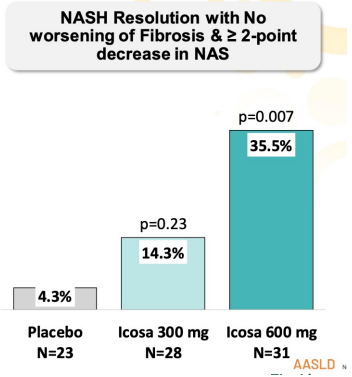
Targeting at Fatty acid metabolism and insulin resistance

Superior Effect in Type 2 Diabetes





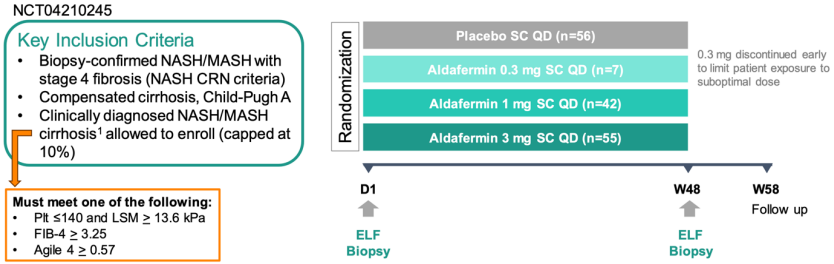


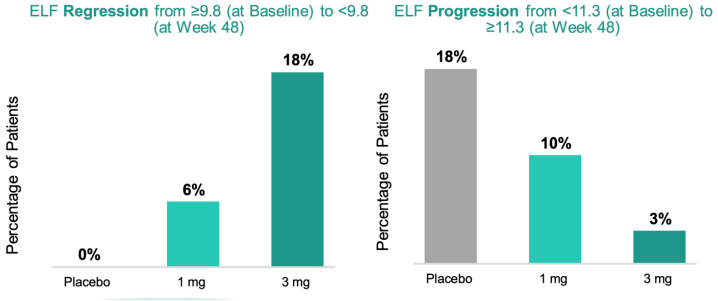


Harrison SA et al.

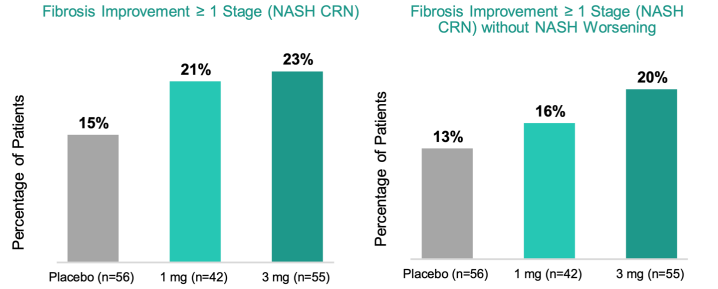
Positive Results From the ALPINE-4 study: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 2b Trial Evaluating Multiple Doses of the FGF19 Analogue Aldafermin in Patients With Compensated Cirrhosis Due to NASH/MASH

Aldafermin, an FGF19 Analog,
Improve insulin resistance
Reduce *De Novo* Lipogenesis





- **Significant in Enhanced Liver Fibrosis (ELF) score reduction**
- **Significant, dose-dependent improvements (Pro-C3, ALT, AST)**
- **Not significant in histology MASH fibrosis regression**



Mary E. Rinella et al.

Fibrosis Improvement With Pegozafermin Treatment in MASH Patients With F4 Fibrosis

FGF21 Analog

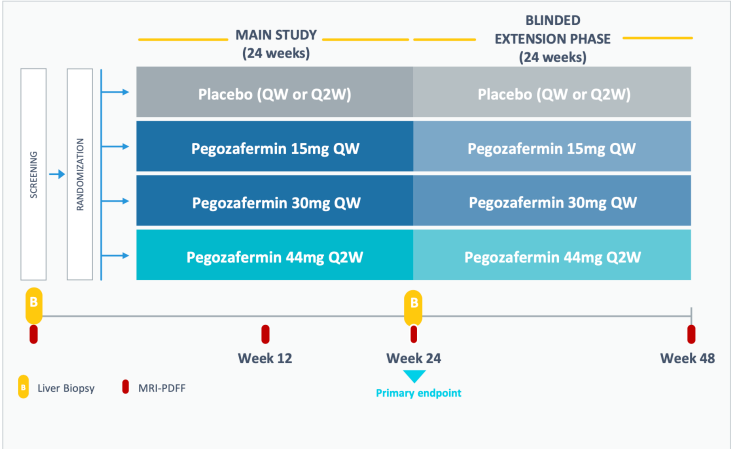
Direct effects on fibroblasts

Anti-inflammatory

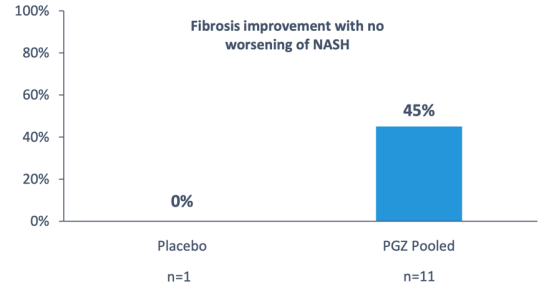
Regulate oxidative stress and apoptosis

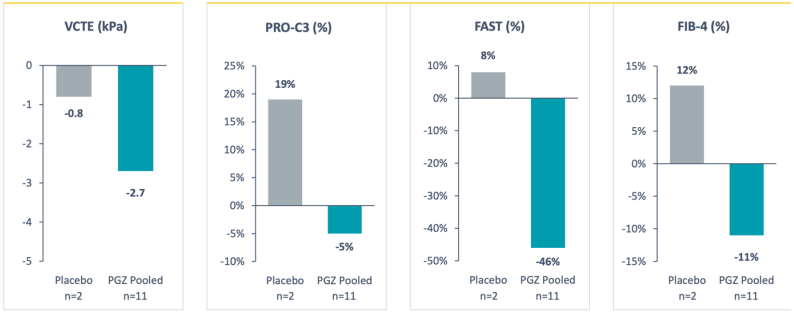
Reduce hepatic steatosis

glycoPegylation of FGF21 > Pegozafermin



Reclassify 14 patients from F2/3 to F4





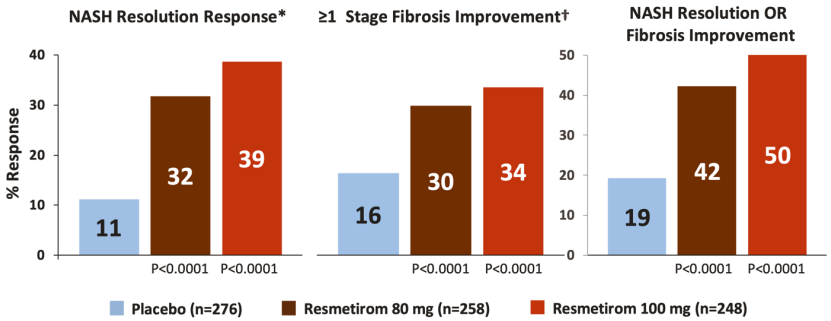
Need to be validated in a dedicated study of patients with compensated cirrhosis

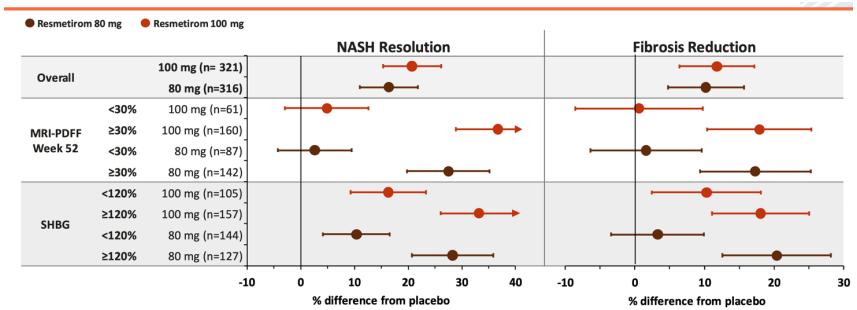
Rohit Loomba et al.

RELATIONSHIP OF NON-INVASIVE MEASURES WITH HISTOLOGICAL RESPONSE IN PATIENTS WITH NONALCOHOLIC STEATOHEPATITIS AND FIBROSIS: 52-WEEK DATA FROM THE PHASE 3 MAESTRO-NASH TRIAL

- Resmetirom is an oral, **liver-directed THR-β selective agonist** in development for NASH
- Two doses: 80mg, and 100mg
- Week-52 data
- NASH resolution with at least a 2-point reduction in NAS and no worsening of fibrosis
- AND ≥1 stage fibrosis improvement with no worsening of NAS

- **MRI-PDFF response was highly associated with both fibrosis improvement and NASH resolution; higher levels of PDFF reduction were associated with a greater biopsy response for both fibrosis and NASH resolution endpoints**
- **SHBG increase, was associated with a higher biopsy response**





Rohit Loomba et al.

Maximal the Available Treatments to Improve the Outcome Among Patients With MASLD

AN AGE-STATIN INTERPLAY IN PREVENTING THE DEVELOPMENT OF CIRRHOSIS IN A 10-YEAR COHORT OF PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

- Assess age-/sex-disparities in the association between statin use and the incidence of cirrhosis in patients with NAFLD
- **National Archives Veterans' Medical and Health Records 01/01/2007-12/31/2009**
- Eligible patients with NAFLD for 10-year follow-up N=344,975

- **Statin use at baseline was associated with reduced risk of incident cirrhosis**
- **Higher cumulative dose and longer duration of statin use associated with a stronger protective effect**

The association between incident cirrhosis and statin use at baseline

	* unadjusted	Adjusted 1	Adjusted 2	Adjusted 3	Adjusted 4
	HR [95%CI], p-value	HR [95%CI], p-value	HR [95%CI], p-value	HR [95%CI], p-value	HR [95%CI], p-value
Baseline Statin use	1.21 [1.15, 1.27], <0.001	1.01 [0.96, 1.06], 0.77	0.79 [0.74, 0.84], <0.001	0.72 [0.67, 0.76], <0.001	0.74 [0.70, 0.78], <0.001

Adjusted Model 1: age, sex, and race/ethnicity
Adjusted Model 2: 1 plus BMI, DM, HT, HL, CAD
Adjusted Model 3: 2 plus comedications
Adjusted Model 4: 3 plus FIB-4 score (full model)

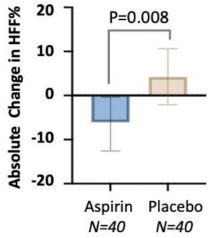
	Women ≤50 (N= 8,816)	Women >50 (N= 20,458)	Men ≤50 (N= 62,159)	Men >50 (N= 244,558)
	Adj.HR [95%CI], p-value	Adj.HR [95%CI], p-value	Adj.HR [95%CI], p-value	Adj.HR [95%CI], p-value
Baseline Statin use				
Unadjusted	1.52 [1.03, 2.24], 0.03	1.15 [0.91, 1.47], 0.24	1.38 [1.17, 1.62], <0.001	0.96 [0.91, 1.02], 0.16
Adjusted*	0.96 [0.63, 1.47], 0.84	0.79 [0.61, 1.02], 0.07	0.92 [0.77, 1.10], 0.35	0.80 [0.76, 0.85], <0.001

Georgia Sofia Karachaliou et al.

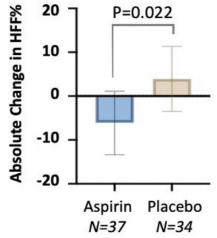
Daily Aspirin Therapy for the Treatment of Metabolic Dysfunction-Associated Steatotic Liver Disease: A Randomized Controlled Trial

- Aspirin (ASA) exerts anti-inflammatory and antitumor effects in liver
- Double blinded randomized single-center trial
- 40 ASA and 40 placebo, 6 month follow up.
- Change from baseline to month 6 in hepatic fat fraction (HFF) assessed by magnetic resonance spectroscopy (MRS)

A. Absolute Change in HFF from Baseline (Intention-to-Treat Population)



B. Absolute Change in HFF from Baseline (Per-Protocol Population)



Endpoints	Aspirin 81mg N=40	Placebo N=40	P-value
Primary Endpoint			
Absolute change in HFF by MRS, %	-6.1 (-12.6 to -0.4)	4.2 (-2.1 to 10.6)	0.008
Difference from placebo	-10.3 (-17.9 to -2.8)	--	0.009

ASA 81mg daily reduced liver fat content by MRS-HFF compared to placebo (10% mean absolute reduction)

Tracey G. Simon et al.

Vitamin E (300mg) versus Placebo in the Treatment of Nonalcoholic Steatohepatitis: a Multicenter, Randomized, Double-blind, Placebo-controlled Study

Yu Song [1*], MingHua Zheng [2*], Huiping Sheng [3*], Jing Wang [4*], Shilong Xie [5], YongFeng Yang [6], Xiaoling Chi [7], Jinjun Chen [8], Fangping He [9], Xiaotang Fan [9], Yuqiang Mi [10], Jing Zhang [11], Bingyuan Wang [12], Lang Bai [13], Wen Xie [14], Bihui Zhong [15], Yee Hui Yeo [16], Jie Li [17†], Shufei Zang [18†], Junping Shi [1†], on behalf of the Chinese NAFLD Clinical Research Network (CNAFLD CRN)

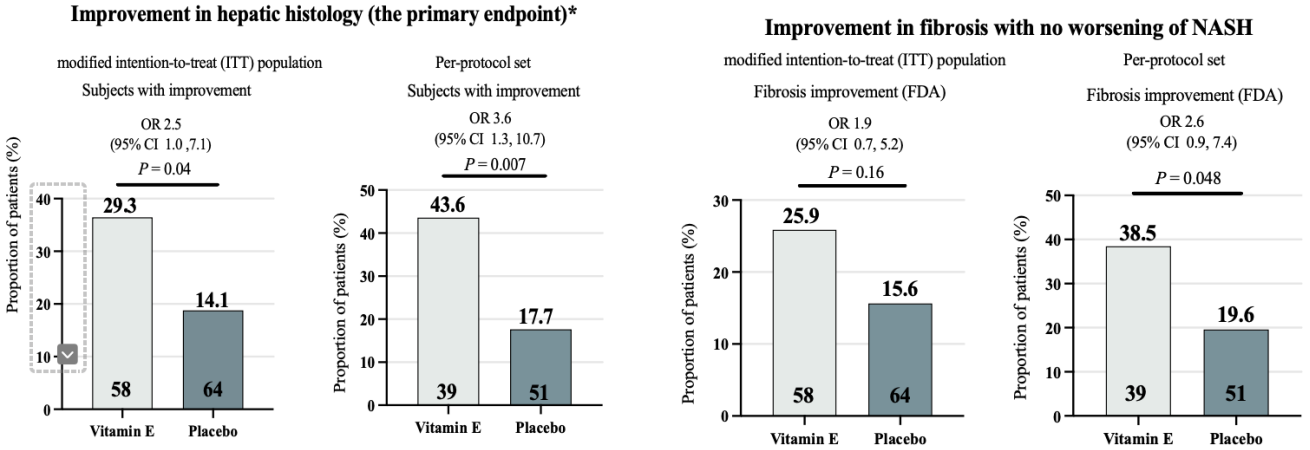
1.Department of Hepatology, Hangzhou Normal University Affiliated Hospital, Hangzhou, Zhejiang, China; 2.MAFLD Research Center, Department of Hepatology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China;

Patients were randomly assigned in a 1:1 ratio to receive oral vitamin E (300mg about 450 IU) or placebo.

Primary endpoint was improvement in hepatic histology after 96 weeks of treatment.

vitamin E (58 patients) or placebo (66 patients)

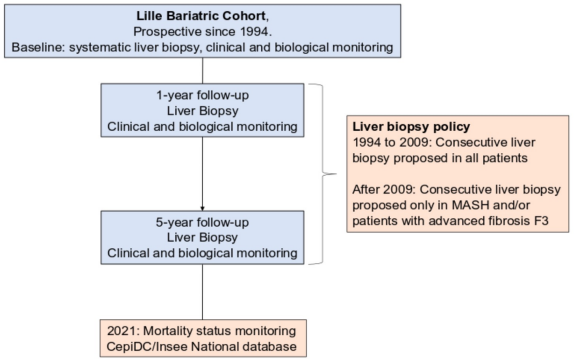
Histologic improvement: NAS score reduction

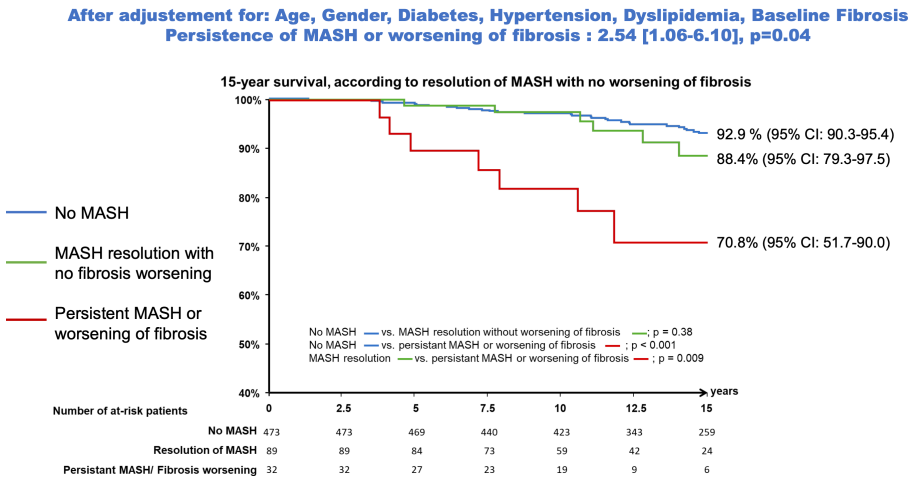


My Favorites – Bariatric Data, Lean MASH, Genetics

Resolution of MASH With No Worsening of Fibrosis After Bariatric Surgery Improves 15-Year Survival: A Prospective Cohort Study

- **Resolution of MASH without worsening of fibrosis** or **improvement in fibrosis** as acceptable **surrogate endpoints** to assess the prevention of cirrhosis and liver-related mortality
- **The study examined the effects of histological progression of MASH and fibrosis on long-term survival following bariatric surgery**





Resolution of MASH with no worsening of fibrosis is a reliable surrogate endpoint in the context of bariatric surgery.

Guillaume Lassailly et al.

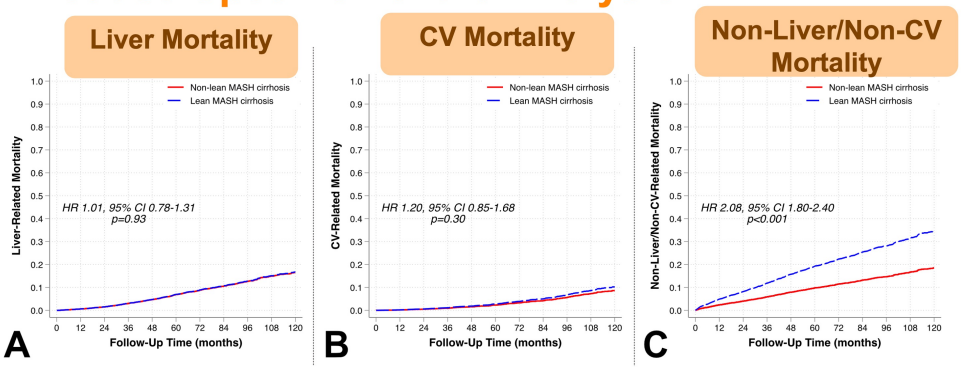
MORTALITY, HEPATIC DECOMPENSATION, AND CARDIOVASCULAR OUTCOMES IN LEAN VS. NON-LEAN MASH CIRRHOSIS: A VETERANS AFFAIRS COHORT STUDY

- Lean status in MASH on key adverse events: - Cardiovascular, hepatic decompensation, mortality
- Lean less likely to be screened

Study Method

- Design: retrospective cohort study using VOCAL cohort :*U.S. Veterans Affairs (VA) data:* Newly diagnosed compensated cirrhosis: 2008-2021
- Primary exposure: Lean status BMI (<25 or 23 Asians),12 months prior to cirrhosis diagnosis
- Primary outcome: Hepatic Decompensation (Ascites, HE, EVB, SBP)
- Secondary outcomes:
  - MACE (MI, A.fib, heart failure, stroke, cardiac arrest) - All-cause mortality

Cause-Specific Hazard Analysis



- Lean status is associated with **increased** all-cause mortality and **decreased** MASH cirrhosis decompensation
- Lean individuals at **equally high risk** of adverse CV events

Basile Njei et al.

Negative Impact of *PNPLA3* rs738409 C>G Is Significantly Modified by Dietary Factors, Caffeine and Non-Heavy Alcohol Consumption in the US Population

- Patatin-like phospholipase domain protein 3 (PNPLA3) polymorphism (rs738409 C>G) is a major genetic determinant of CLD and its complications
- Environmental/dietary factors may exacerbate or attenuate the effect.
- The study cohort comprised 39,695 persons aged ≥2 months enrolled in the Third National Examination and Nutritional Health Survey (NHANES III), a complex, multistage clustered probability sample that represents the US population from 1988 to 1994.
- 7,159 participants aged >12 years had DNA specimens available and were genotyped for *PNPLA3* rs738409.

Effect of *PNPLA3* G-allele on the risk of liver-related mortality at strata of exposure variables. *PNPLA3* CC genotype is the reference for risk estimates.

Environmental factors	Subhazard ratios (95% CI) [b]			
Light-to-moderate alcohol intake	Non-drinker			**Light-to-moderate drinker ***
G allele effect	1.9 (0.7-5.5)			**3.5 (1.9-6.4)**
* Light-to-moderate *vs* non-drinker, P <0.05				
BMI (kg/m²)	<25	25-29.9		**≥30 ****
G allele effect	2.7 (1.3-5.8)	2.5 (0.9-7.1)		**3.0 (1.5-6.3)**
** BMI ≥30 *vs* <25, P <0.05				
Saturated fat (%)	Q1	Q2	Q3	**Q4 *****
G allele effect	2.6 (1.5-4.6)	2.3 (0.6-9.2)	2.8 (0.8-9.3)	**3.9 (1.5-9.8)**
*** Saturate fat Q4 *vs* Q1, P <0.05				
Cholesterol (mg)	Q1	Q2	**Q3 ******	**Q4 ******
G allele effect	2.4 (1.2-5.2)	1.9 (0.5-7.8)	**3.3 (1.1-10.2)**	**3.7 (1.4-9.8)**
**** Cholesterol Q3/Q4 *vs* Q1, P <0.05				
Coffee/tea (cups/day) [a]	<1	≥1 to <2	≥ 2 to <3	**≥ 3 *******
G allele effect	3.1 (1.4-6.9)	3.3 (1.6-7.2)	2.7 (0.8-9.1)	**0.06 (0.006-0.59)**
***** ≥ 3 cups of coffee/tea *vs* <1, P <0.05				
MUFA *(%)* [a]	Q1	Q2	Q3	**Q4 ********
G allele effect	2.3 (0.9-5.9)	3.3 (1.7-6.8)	4.3 (2.2-8.4)	**0.4 (0.1-0.9)**

Joint deleterious effects

Joint protective effects

- *PNPLA3* rs738409 is associated with an increased risk of LRD in the US population.
- Light-to-moderate alcohol intake, BMI, and higher consumption of cholesterol are positively associated with LRD in the US population.
- Higher consumption coffee/tea (≥ 3 cups/day) and MUFA (%) (top quartile) were associated with lower risk of LRD.
- The risk of LRD due to *PNPLA3* rs738409 could be attenuated or exacerbated in the presence of certain environmental factors.

Eduardo Vilar-Gomez et al.

MACHINE LEARNING PREDICTS DIETARY PATTTERNS ASSOCIATED WITH FATTY LIVER DISEASE PROTECTION

- Large prospective cohort study conducted in UK : Around 500,000 participants ; Age 37 – 73 years: Recruited 2006 – 2010

Baseline assessments

Touchscreen questionnaires
Physical measures
Collection of biological samples

24h hour food recall

Very detailed food questionnaires at 5 time points
200 most commonly consumed foods and drinks
Mean nutrional values of all time points

Follow-up

via hospital inpatient reports and death registries
Additional MRI data for 50,000 participants

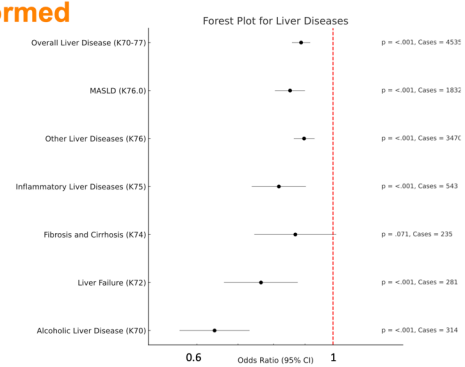
Food Rich in Mn
Nuts
Seeds
Dark Chocolates
Whole wheat bread
Crustaceans and Mollusks
Fruit and Vegetables (especially organic)

- Using a random forest classifier to find the strongest associations with steatosis (MRI fat>=5%) for 63 nutrients
- Manganese showed the strongest association

Manganese intake is associated with decrease of ICD10 coded diagnosis of liver disease diagnosed after the first questionnaire was performed

Manganese cohort study n=208,802

Covariates adjusted for:
- age
- sex
- BMI
- Townsend index for socio-economic status
- total kcal
- alcohol
- protein intake
- fat intake
- carbohydrate intake
- multiple testing



S. Schophaus et al.


Thank You!