NASH

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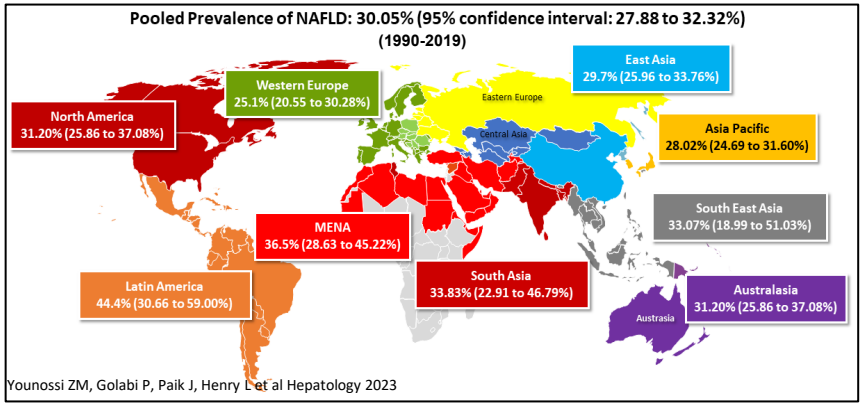
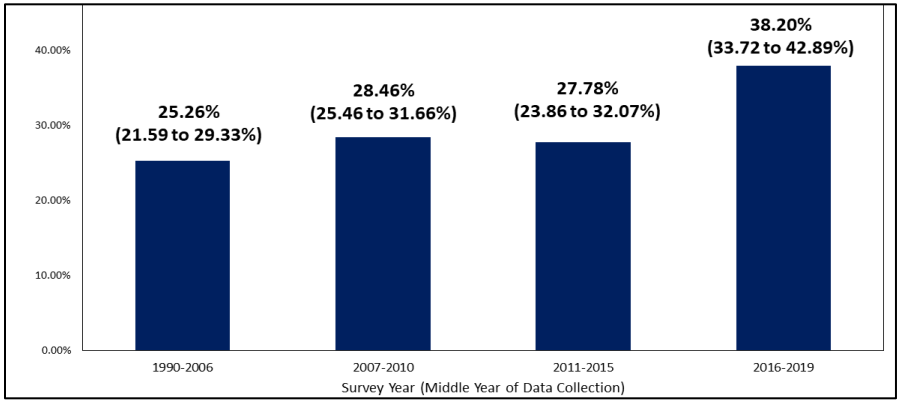
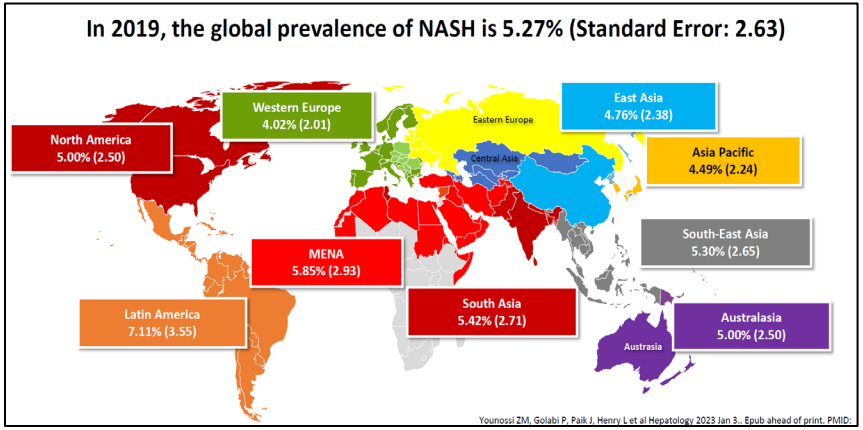
Disclosures

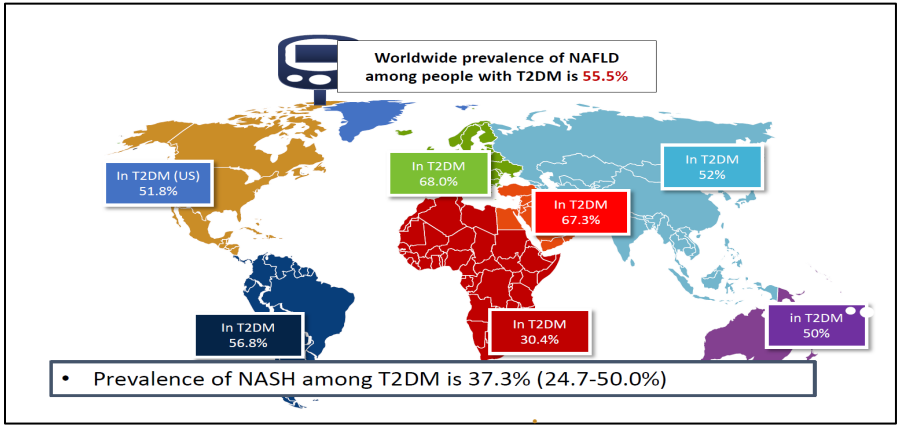
- ZMY has received research funding and/or serve as consultant to Intercept, Cymabay, Boehringer Ingelheim, BMS, GSK, NovoNordisk, AstraZeneca, Siemens, Madridgal, Merck, Abbott.

The Global Prevalence of NAFLD and NASH



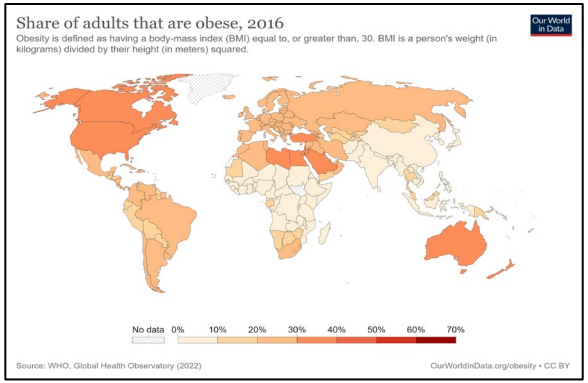


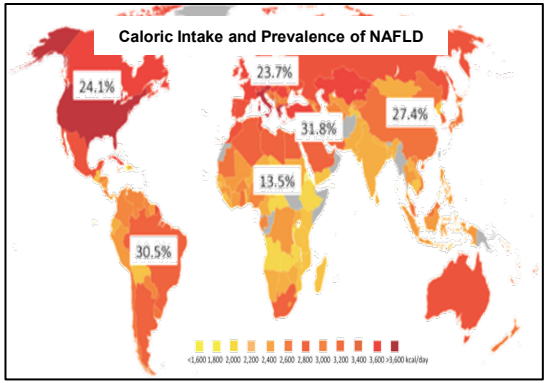




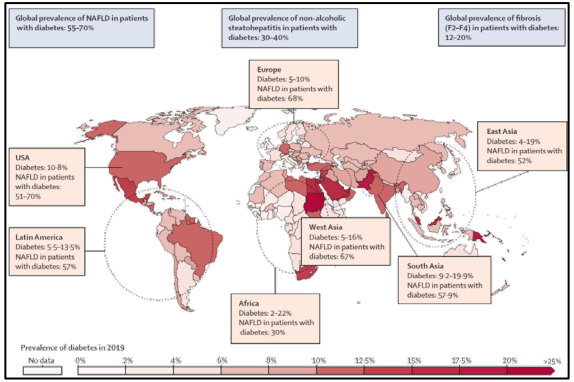
Younossi ZM. *J Hepatol*. 2019;70:531–544.

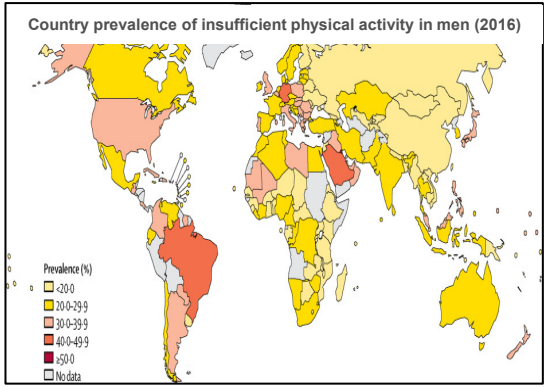
Drivers of NAFLD Epidemic: Obesity and T2D

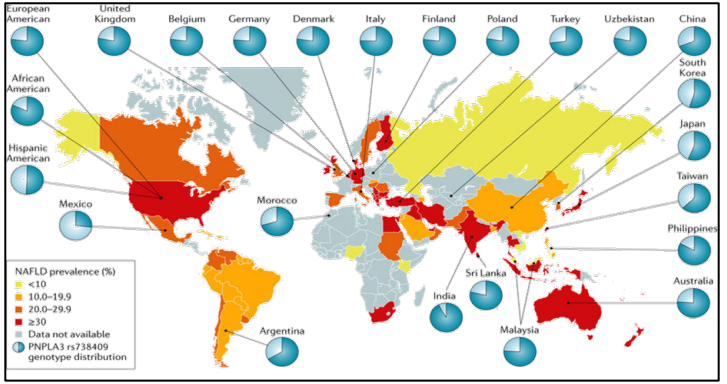




Gene	Variant	Effect size	Dir	Steatosis	NASH	Fibrosis	HCC	Mortality
PNPLA3	I148M	+++	↑	+	+	+	+	+
TM6SF2	E167K	+++	↑	+	+	+	+	
GCKR	P446L	+	↑	+				
MBOAT7	rs641738	+	↑	+		+	+	
HSD17B13	rs72613567	++	↓		+	+	+	
IL28B (IFNL3/4)	rs12979860	+	↓			+		
MERTK	rs4374383	+	↓			+		

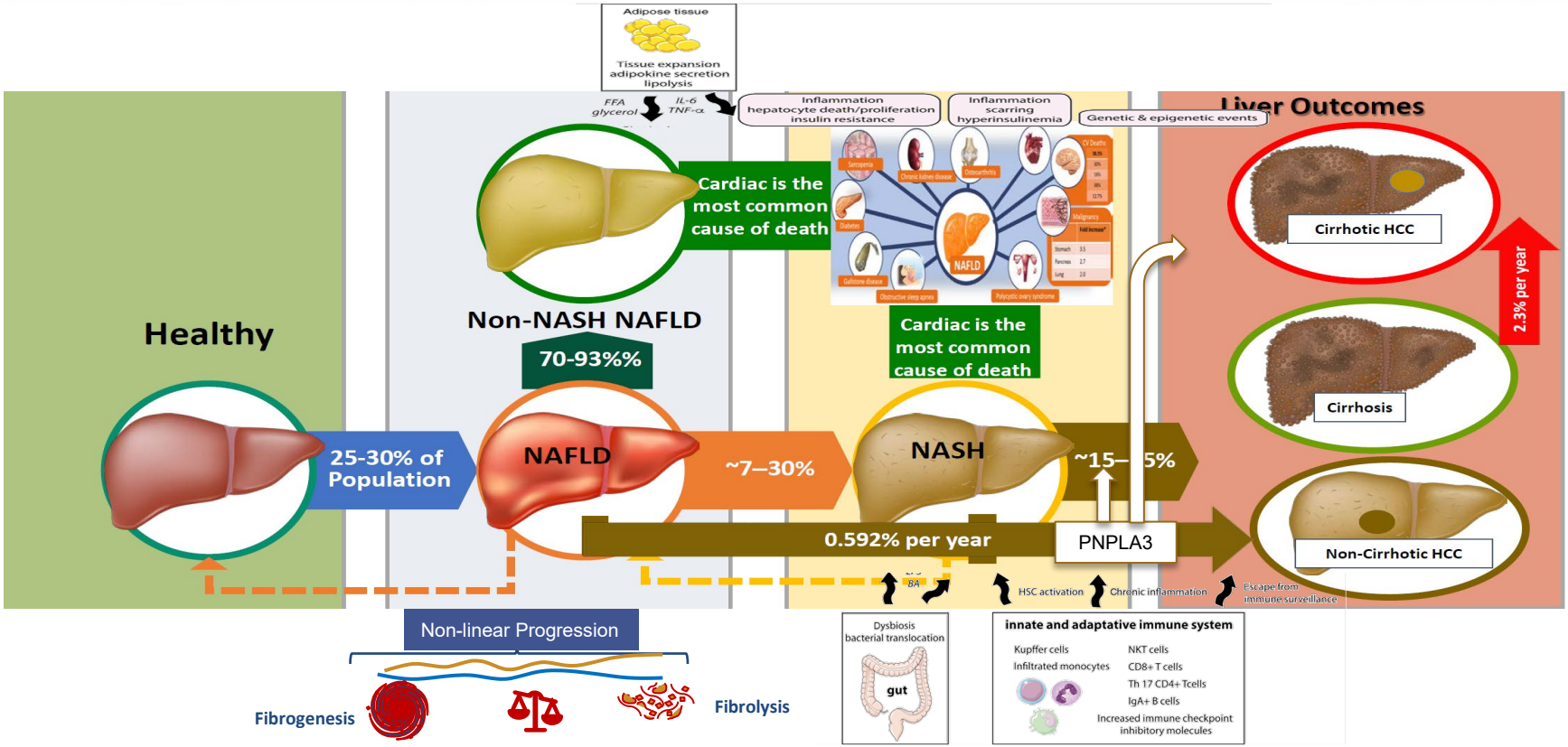






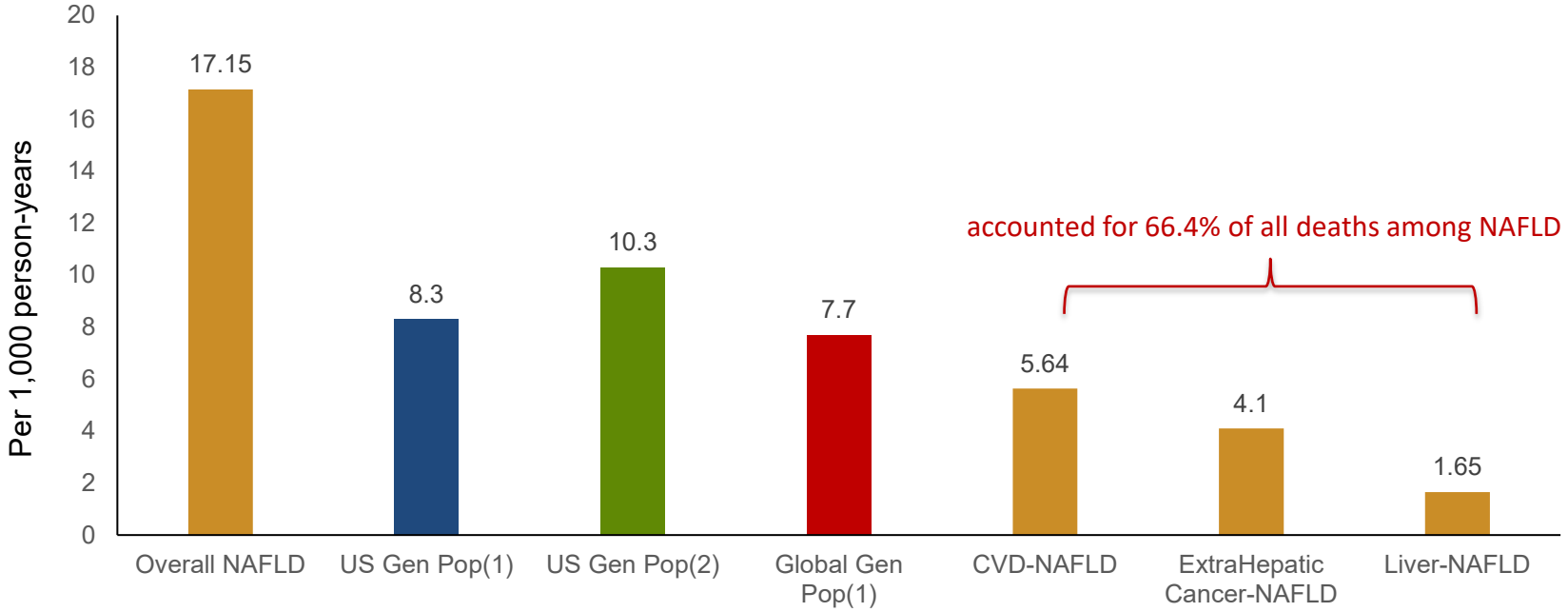
Stefan N, Cusi K. Lancet Diabetes Endocrinol. 2022 Apr;10(4):284-296, Younossi ZM et al. *Hepatology.* 2016;64:73–84; Younossi ZM. *J Hepatol*. 2019;70:531–544., Younossi ZM, et al. Gut. 2020 Mar;69(3):564-568, Arshad T, Paik J, Biswas R, Alqahtani S, Henry L, Younossi ZM. *Hepatology Communications*. 2021, Younossi, Z.,. *et al. Nat Rev Gastroenterol Hepatol* **15,** 11–20 (2018). , AISF_SIO_SID CPG NAFLD Dig Liv Dis. 2021; Manolio TA. Nat Rev Genet. 2013;14(8):549-558.

Natural History of NAFLD and NASH



Sayiner M, et al. *Clin Liver Dis*. 2016;20(2):205-214; Younossi ZM, et al. *Hepatology*. 2016; 64(5):1577-1586. Lequoy M, et al. Horm Mol Biol Clin Investig. 2020 Feb 29;41(1), Younossi Z et al. Hepatology 2018, Younossi Z J Hepatology 2019

Long Term Outcomes of NAFLD
Mortality



- The pooled mortality rate among NAFLD (N=7) was 17.2 per 1,000 PY (9.02-32.37).
- The top three leading causes of death, cardiovascular disease (5.64 per 1,000 PY [1.70-5.64]), extra-hepatic cancer (4.10 per 1,000 PY [0.97-4.10]), and liver complications (1.65 per 1,000 PY [0.00-1.65])

Younossi ZM, et al. Hepatology. 2023 Jan 3. doi: 10.1097/ Epub ahead of print. PMID: 36626630.

The Growing Global Burden of NAFLD

Trends in Mortality Rates (GBD 2012-2017)

	Liver Cancer						Cirrhosis					
	Liver cancer	Liver cancer due to HBV	Liver cancer due to HCV	Liver cancer due to Alcohol use	Liver cancer due to NASH	Liver cancer due to Other causes	Cirrhosis	Cirrhosis due to HBV	Cirrhosis due to HCV	Cirrhosis due to Alcohol use	Cirrhosis due to NASH	Cirrhosis due to Other causes
Global	0.51	0.00	0.00	0.53	1.41	0.86	-0.70	-1.43	-0.50	-0.44	0.29	-0.52
Australasia	1.55	0.00	1.28	0.00	0.00	0.00	1.63	1.07	1.43	1.27	1.61	0.92
High-income Asia Pacific	-2.88	-1.48	-3.25	-2.54	-2.02	-2.44	-1.51	0.00	-1.87	0.00	0.00	-1.21
High-income North America	0.64	0.46	0.52	0.00	0.51	0.52	0.00	0.00	0.00	0.00	0.00	1.11
Southern Latin America	0.00	-0.82	0.00	0.95	1.01	0.00	-0.18	-1.51	0.00	0.00	0.64	0.00
Western Europe	0.00	-0.66	-0.58	0.00	0.00	0.00	-1.08	-1.39	-1.24	-0.96	0.00	0.00
Central Asia	0.71	0.00	0.75	0.97	1.35	0.56	-0.91	-1.79	-0.65	-0.78	0.21	-0.58
Central Europe	0.00	-0.45	0.00	0.00	0.00	0.00	-1.87	-2.15	-1.86	-1.60	-1.12	-1.59
Eastern Europe	2.18	0.00	2.17	2.48	2.46	2.00	0.00	0.00	0.00	0.00	0.00	0.00
South Asia	1.40	0.94	1.44	1.59	1.94	1.46	0.00	-0.95	0.00	0.48	1.29	0.00
East Asia	0.68	0.00	1.21	1.68	1.84	0.94	-1.09	-2.37	0.00	0.00	1.12	0.00
Southeast Asia	0.00	0.00	0.00	0.00	0.71	-0.43	-1.33	-1.68	-1.36	-1.08	-0.46	-1.18
Oceania	-0.15	-0.31	-0.09	0.00	0.26	-0.23	-0.60	-0.77	-0.46	-0.58	-0.10	-0.60
Caribbean	1.48	1.24	1.38	1.60	1.88	1.33	0.74	0.00	0.63	0.81	1.23	0.46
Andean Latin America	0.00	-1.39	0.00	0.00	0.00	0.00	-1.74	-2.50	-1.91	-1.80	-0.87	-1.76
Central Latin America	0.47	0.00	0.00	0.90	0.96	0.45	-0.44	-0.99	-0.57	-0.39	0.00	-0.31
Tropical Latin America	1.44	1.38	1.29	1.54	2.31	1.34	0.00	0.00	0.00	0.00	0.00	0.00
North Africa and Middle East	-0.43	-0.69	-0.62	-0.67	0.95	-0.57	-1.27	-1.62	-1.31	-1.27	0.00	-1.48
Central Sub-Saharan Africa	-2.07	-2.96	-2.21	-1.01	-1.38	-2.10	-0.82	-1.95	-0.49	0.00	0.49	-0.45
Eastern Sub-Saharan Africa	-0.61	-1.30	-0.42	-0.35	-0.15	-0.69	-2.08	-3.10	-1.67	-1.86	-1.30	-1.62
Southern Sub-Saharan Africa	-1.24	-1.38	-1.33	-0.99	0.00	-1.63	-1.87	-2.43	-1.70	-1.63	0.00	-2.35
Western Sub-Saharan Africa	-1.27	-1.96	-0.98	-0.89	-0.38	-0.86	-2.83	-3.24	-2.32	-2.98	-1.76	-1.92
High SDI	-0.81	0.00	-1.28	-0.68	0.00	-0.28	-0.83	-1.14	-0.95	-0.92	-0.44	0.00
High-middle SDI	1.26	0.00	1.67	1.46	2.31	1.35	-1.15	-2.21	-0.75	-0.94	0.00	-1.05
Middle SDI	0.00	0.00	0.86	0.99	1.51	0.78	-0.71	-1.49	-0.70	0.00	0.00	-0.59
Low-middle SDI	0.29	-0.42	0.40	0.72	1.26	0.50	-0.84	-1.87	0.00	0.00	0.55	-0.60
Low SDI	-0.59	-1.20	-0.37	-0.30	0.00	-0.49	-0.90	-1.66	-0.66	-0.41	0.00	-0.71

Paike J and Younossi Z Hepatology 2020

Trends in Asia and MENA (GBD 2012-2019)

- Globally in 2019, 168,969 deaths were related to liver complications (LC)
- **Of the global incident and death cases related to LC-NAFLD, about half occurred in Asia and MENA,**
- In **Asia and MENA**, age-standardized DALY rate of LC-NAFLD was **associated dietary and metabolic risks**
- **In MENA, low physical activity** was also a risk

Figure 1. Changes in Incidence Rate of Liver Complications due to NAFLD from 2009 to 2019 : Data From Global Burden of Disease

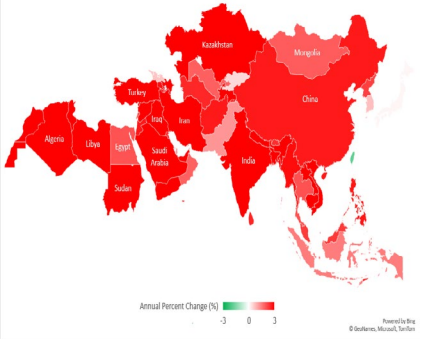
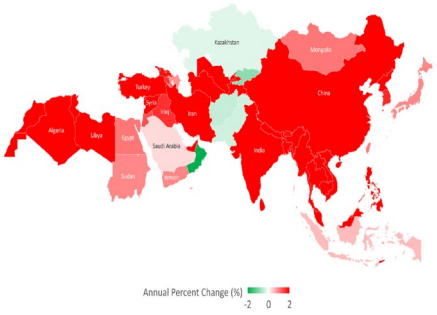
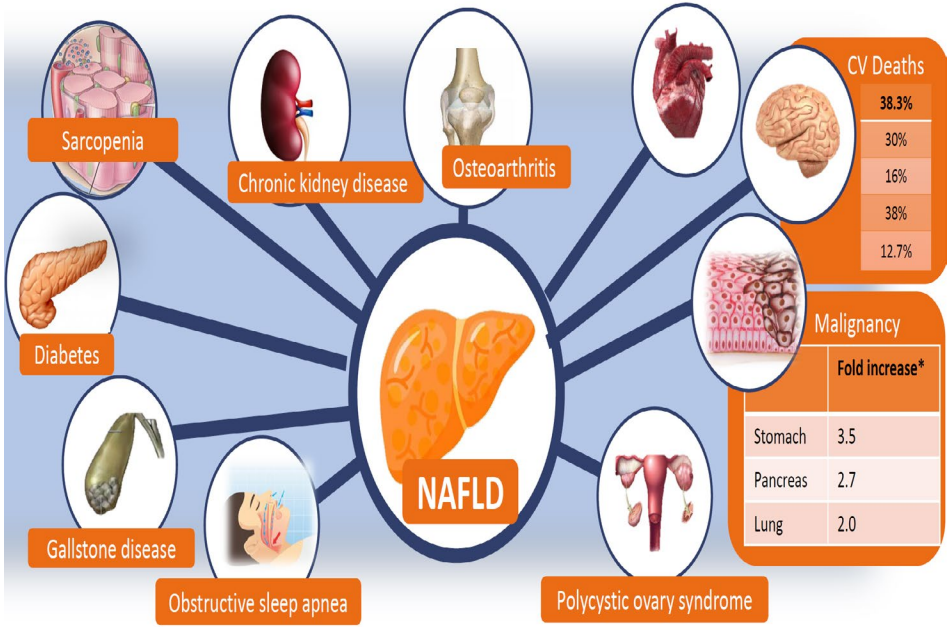


Figure 2. Changes in Death Rate of Liver Complications due to NAFLD from 2009 to 2019 : Data From Global Burden of Disease

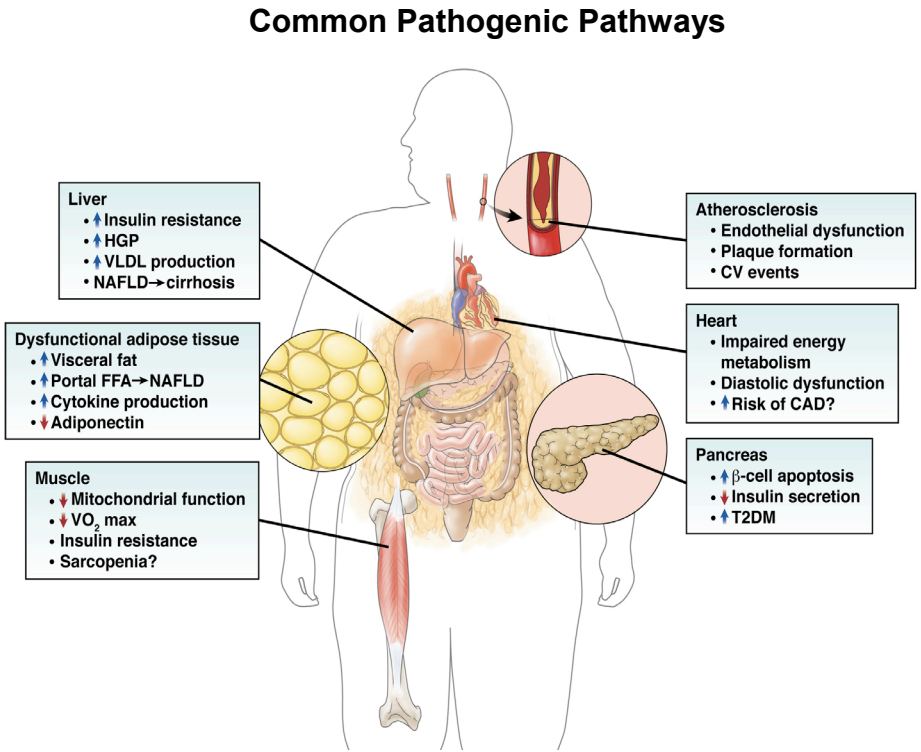


Golabi P, Paik J, AlQahtani S, Younossi Y, Tuncer G, Younossi ZM. J of Hep 2021

Common Extrahepatic Diseases Associated with NAFLD



Younossi Z et al 2020



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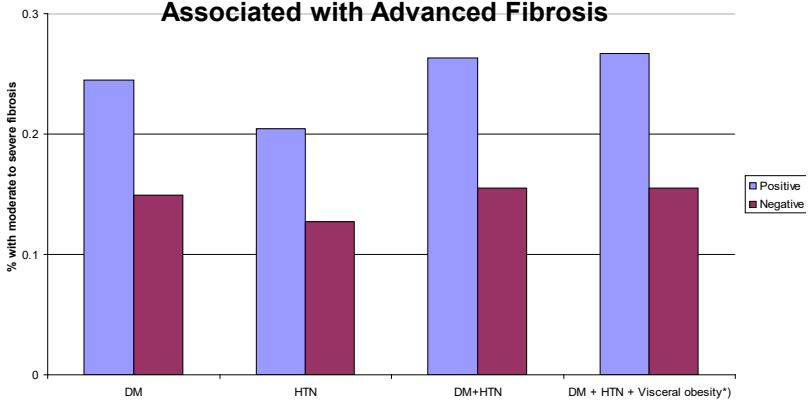
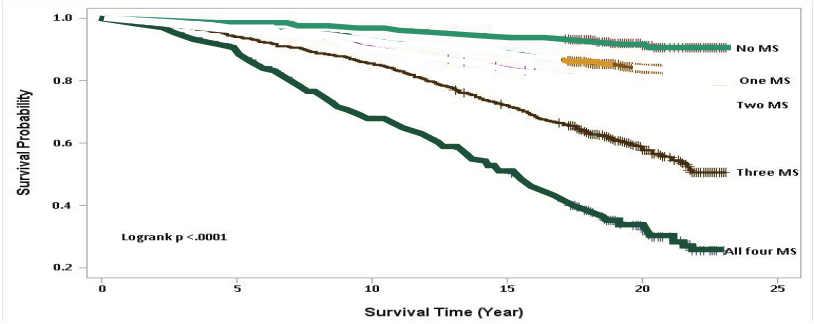
High Risk Groups
Clinical and Histologic Risks

Increasing Number of Metabolic Risks are Associated with Advanced Fibrosis



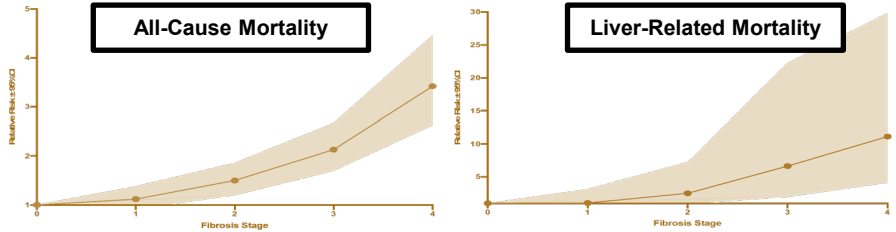
Hossain N, Younossi Z Gastro et al. Hepatology 2009;

Increasing Number of Metabolic Risks are Associated with Mortality



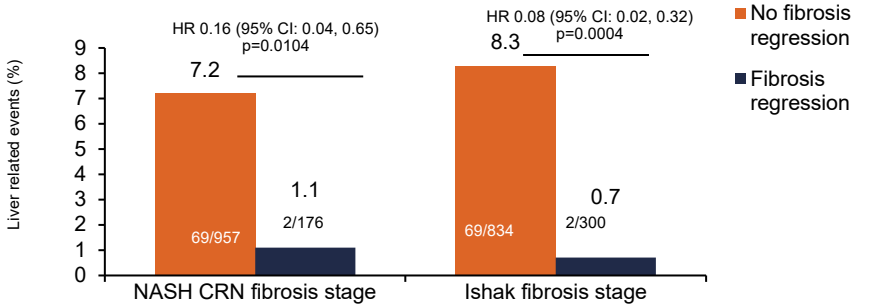
Golabi P, Younossi Z, et al. *Medicine* 2018;97(13):e0214;

Systematic review and meta-analysis of 13 studies 4,428 NAFLD patients (2,875 with histological NASH).



Taylor RS, Taylor RJ, Bayliss S, Hagström H, Nasr P, Schattenberg JM, Ishigami M, Toyoda H, Wai-Sun Wong V, Peleg N, Shlomai A, Sebastiani G, Seko Y, Bhala N, Younossi ZM, Anstee QM, McPherson S, Newsome PN. Gastroenterology. 2020May;158(6):1611-1625

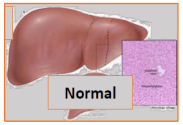
Fibrosis regression and liver-related events in NASH cirrhosis

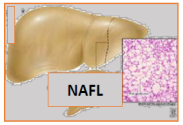


Sanyal A, et al. AASLD TLMdX2020. #90

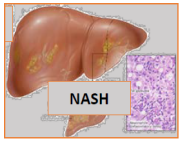
How to Identify High Risk NAFLD without Liver Biopsy?

Non-invasive Tests (NITs): Serum Biomarkers and Clinical Decision Tools

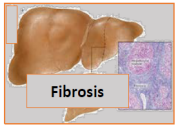




- Fatty Liver Index (FLI)
- Ultrasound
- FibroScan™ (CAP)
- MR-PDFF

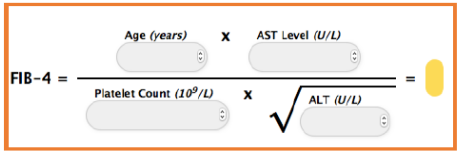


- Biopsy
- CK-18
- NIS4
- MR Liver MultiScan™

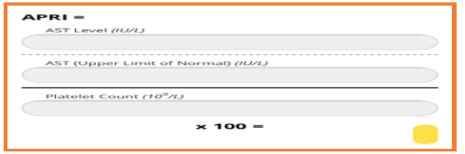


- Biopsy
- Algorithms (FIB-4, NFS, APRI)
- Serum biomarkers (ELF, NIS4)
- Imaging: (TE, MRE)

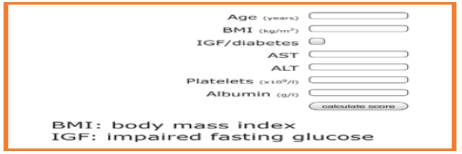
- **FIB-4 Index:**
  - Originally to predict advanced fibrosis in HIV/HCV coinfection
  - FIB-4<1.3 No significant fibrosis
  - FIB-4<1.45 F0–F2
  - FIB-4>3.25 F3–F4



- **APRI:**
  - The lower the APRI score (<0.5), the greater the NPV (ability to rule out cirrhosis) and the higher the value (>1.5) the greater PPV (ability to rule in cirrhosis).



- **NAFLD Fibrosis Score (NFS):**
  - Multivariate analysis (Age, hyperglycemia, BMI, platelet count, albumin, AST/ALT ratio) are independent predictors of advanced fibrosis
  - NFS<-1.455 F0–F2
  - NFS>0.676 F3–F4

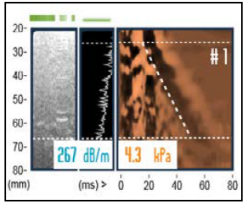
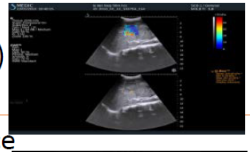
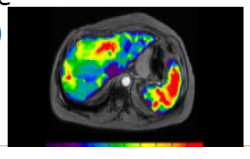


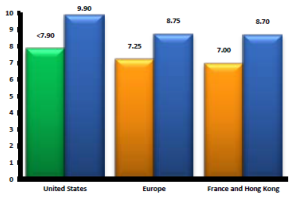
- **Enhanced Liver Fibrosis (ELF)**
  - Procollagen III N-terminal peptide (PIIINP)
  - Hyaluronic acid (HA)
  - Tissue inhibitor of metalloproteinase 1 (TIMP1)

Fibrosis	ELF	S (%)	Sp (%)	PPV (%)	NPV (%)
	9.93	57	90	88	64
Significant fibrosis ≥2	10.09	100	88	61	100
	10.18	**94**	**93**	**70**	**99**
	10.30	82	100	100	97
Advanced fibrosis ≥3	**10.51**	**100**	**98**	**80**	**100**
	10.78	50	99	80	96
	11.56	25	100	100	95

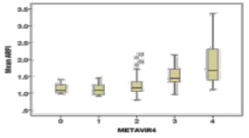
How to Identify High Risk NAFLD without Liver Biopsy?

Non-invasive Tests (NITs): Radiologic Tests

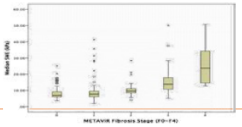
Technique		Visualize liver	
Transient elastography (TE) 		US	• Liver stiffness expressed in kPa; correlates with liver fibrosis stage • Controlled Attenuation Parameter (CAP™) expressed in dB/meter • Accurate in detecting advanced fibrosis • Predicts risk of decompensation • Correlates well with portal pressure • Most widely used
Acoustic radiation force impulse (ARFI)		US	• Employs high intensity acoustic beam to mechanically excite tissue and monitor tissue displacement response • No need for an external compression • Degree of displacement is interpreted into degree of lightness and darkness
Shear wave elastography (SWE)		US	• Shear waves are generated from acoustic pulses forced at five different tissue depth levels and SW velocity estimated by ultrafast Doppler-like acquisition of 5,000 frames/sec. • SW is converted to tissue stiffness as kilopascals
Magnetic resonance elastography (MRE)		MR	• Most accurate of the imaging modalities • Costly, no point-of-care access • MRI Methods to Estimate Proton Density Fat Fraction • MRI-PDFF shown to have high correlation to morphometric fat[3]



Fibrosis Severity	Median LSM (range)
Without F3-F4 fibrosis	6.6 kPa (5.3-8.9)
With F3-F4 fibrosis	14.4 kPa (12.1-24.3)

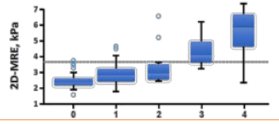


F1 – 1.24 m/s
F2 – 1.48 m/s
F3 – 1.61 m/s
F4 – 1.75 m/s



Median Values

F0 6.93 kPa
F1 7.7 kPa
F2 9.6 kPa
F3 13.95 kPa
F4 23.73 kPa



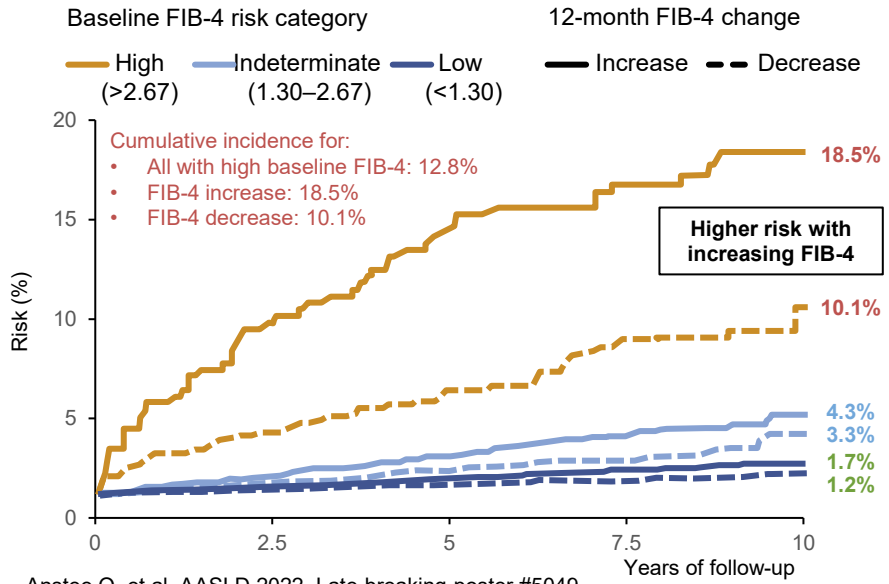
Stiffness cutoff: 3.63 kPa
- Sensitivity 0.86
- Specificity 0.91

AUC for advanced fibrosis: 0.924

NITs Predicting Outcomes

- Longitudinal cohort study of 20,433 patients to evaluate the association of 12-month changes in FIB-4 with risk of developing severe NASH-related clinical events
  - UK Clinical Practice Research Datalink linked with Hospital Episodes Statistics and Office for National Statistics data (2001–2020)

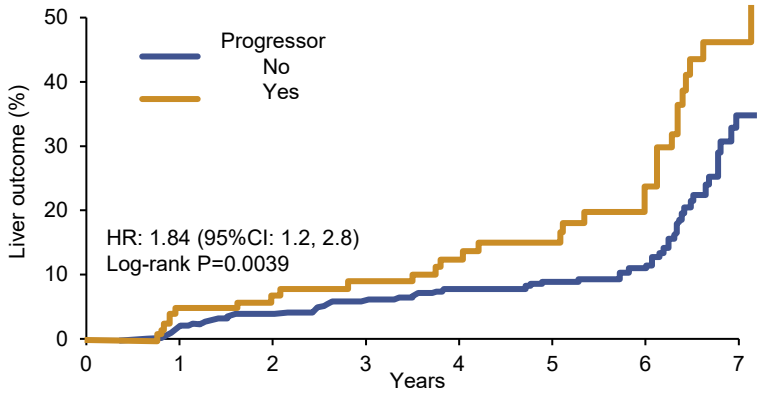
Change in FIB-4 calculated from baseline to 12 mts



Anstee Q, et al. AASLD 2022. Late-breaking poster #5049.

- 894 patients with biopsy-proven NAFLD in the NASH CRN NAFLD Database 2 and 3 studies with ≥2 LSM readings from 2014 to 2022 were included
- LSM cirrhosis: LSM >14.9 kPa in those without cirrhosis on initial VCTE
- Composite outcome, ≥1 of:
  1) Death 2) Decompensation 3) HCC 4) MELD >15

Time to composite clinical outcomes in progressors to LSM-defined cirrhosis vs non-progressors



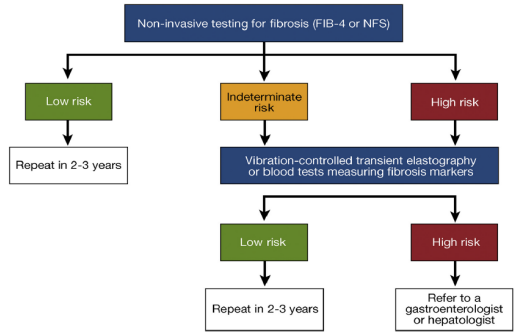
Gawrieh S, et al. AASLD 2022. Oral #72

Guidelines are Being Developed to Identify High Risk NAFLD

Preparing for the NASH Epidemic: A Call to Action

Fasiha Kanwal,[1] Jay H. Shubrook,[2] Zobair Younossi,[3] Yamini Natarajan,[4] Elisabetta Bugianesi,[5] Mary E. Rinella,[6] Stephen A. Harrison,[7] Christos Mantzoros,[8] Kim Pfotenhauer,[9] Samuel Klein,[10] Robert H. Eckel,[11] Davida Kruger,[12] Hashem El-Serag,[13] and Kenneth Cusi[14]

Gastroenterology, 2021



Algorithm for risk stratification in patients with NAFLD/NASH. FIB-4, Fibrosis-4 Index; NFS, NAFLD fib

- Algorithm to be included in the January 2023 American Diabetes Association Standards of Care

Diabetes Care Volume 44, February 2021 399

Advanced Liver Fibrosis Is Common in Patients With Type 2 Diabetes Followed in the Outpatient Setting: The Need for Systematic Screening

Romina Lomonaco,[1] Eddison Godinez Leiva,[1] Fernando Bril,[1] Sulav Shrestha,[1] Lydia Mansour,[1] Jeff Budd,[2] Jessica Portillo Romero,[2] Siegfried Schmidt,[3] Ku-Lang Chang,[3] George Samraj,[3] John Malaty,[3] Katherine Huber,[2] Pierre Bedossa,[4] Srilaxmi Kalavalapalli,[1] Jonathan Marte,[1] Diana Barb,[1] Danielle Poulton,[1] Nada Fanous,[1] and Kenneth Cusi[1,5]

Diabetes Care 2021;44:399–406 | https://doi.org/10.2337/dc20-1997

4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Medical Care in Diabetes—2019*

Diabetes Care 2019;42(Suppl. 1):S34–S45 | https://doi.org/10.2337/dc19-S004

Recommendation

4.14 Patients with type 2 diabetes or prediabetes and elevated liver enzymes (alanine aminotransferase) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. **C**

4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Medical Care in Diabetes—2022*

Diabetes Care 2022;45(Suppl. 1):S46–S59 | https://doi.org/10.2337/dc22-S004

Recommendation

4.14 Patients with type 2 diabetes or prediabetes and elevated liver enzymes (alanine aminotransferase) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. **C**

Clinical Practice Guidelines

EASL JOURNAL OF HEPATOLOGY

J Hepatol. 2016;64:1388–402.

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)

Endocrine Practice 28 (2022) 528–562

Contents lists available at ScienceDirect

AACE

Endocrine Practice

journal homepage: www.endocrinepractice.org

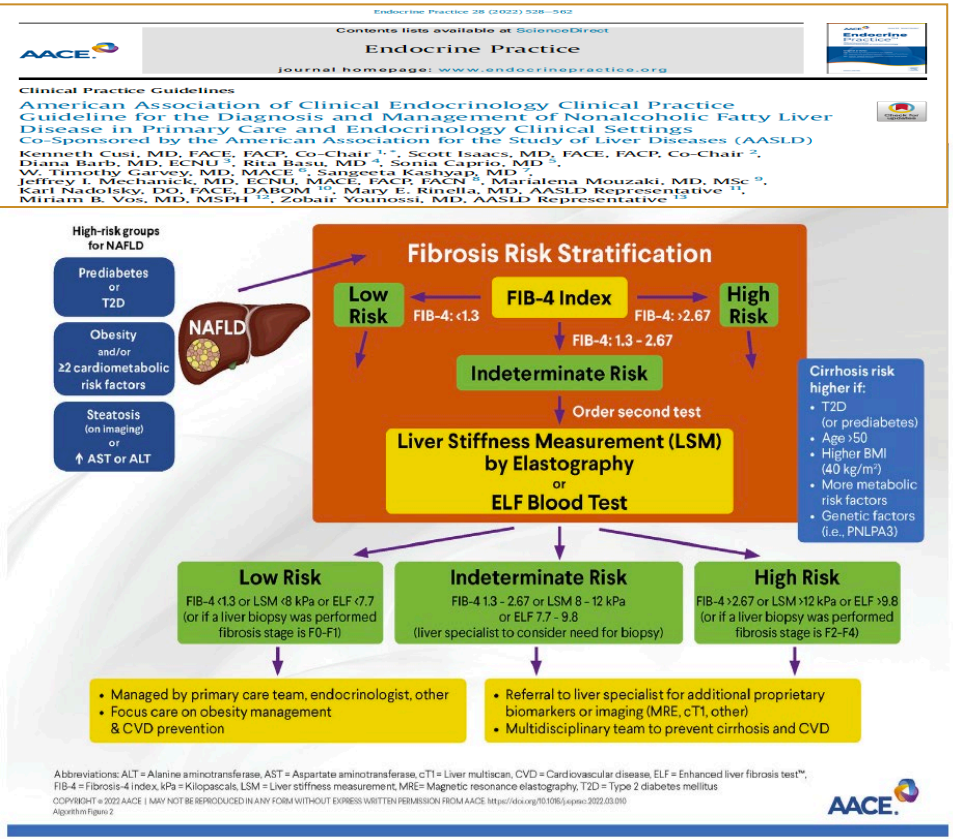
Clinical Practice Guidelines

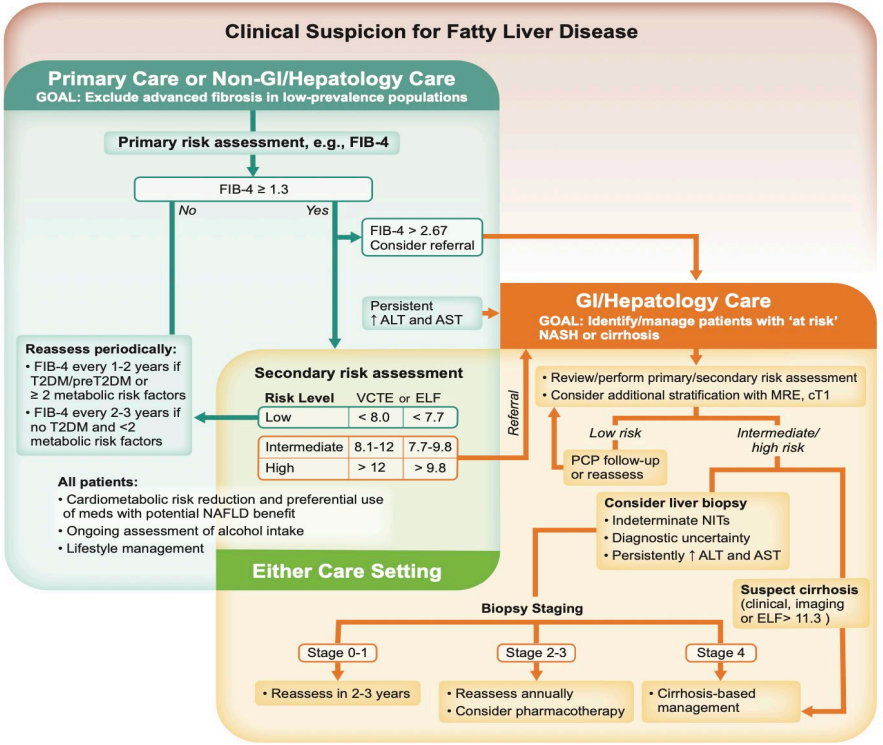
American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings

Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD)

Kenneth Cusi, MD, FACE, FACP, Co-Chair [1,*], Scott Isaacs, MD, FACE, FACP, Co-Chair [2], Diana Barb, MD, ECNU [3], Rita Basu, MD [4], Sonia Caprio, MD [5], W. Timothy Garvey, MD, MACE [6], Sangeeta Kashyap, MD [7], Jeffrey I. Mechanick, MD, ECNU, MACE, FACP, FACN [8], Marialena Mouzaki, MD, MSc [9], Karl Nadolsky, DO, FACE, DABOM [10], Mary E. Rinella, MD, AASLD Representative [11], Miriam B. Vos, MD, MSPH [12], Zobair Younossi, MD, AASLD Representative [13]

AACE (2022) and AASLD (2023) NAFLD Guidelines





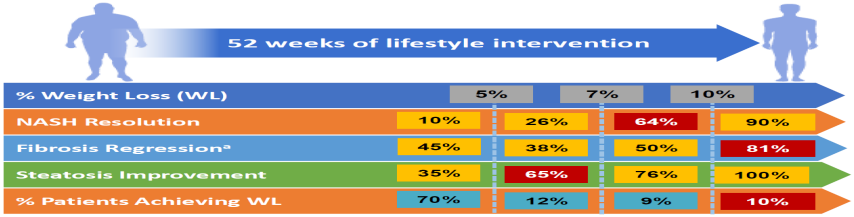
Rinella M et al. Hepatology, 77(5):p 1797-1835, May

Management: Addressing the Main Risks of NAFLD: Obesity and T2D

Managing Obesity Through Diet, Exercise and Bariatric Surgery

Weight Loss with Life Style Intervention

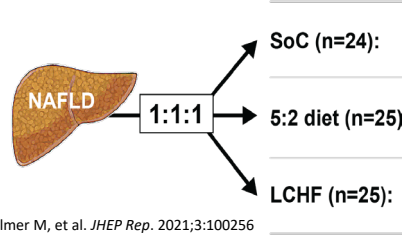
- N=293 NASH patients encouraged to adopt lifestyle changes for weight loss over 52



Vilar-Gomez E, et al. *Gastroenterology*. 2015;149(2):367-378.

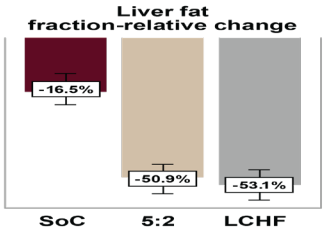
Intermittant Diet vs. LCHF Diet

- Open-label RCT in 74 subjects with NAFLD in 2 diet and SOC



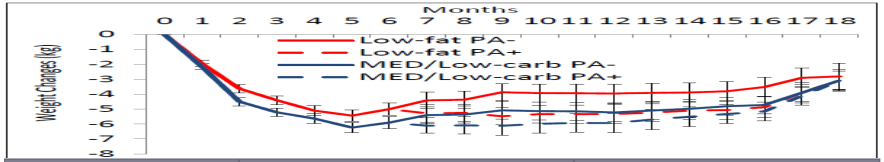
Holmer M, et al. *JHEP Rep*. 2021;3:100256

MRS



Diet and Exercise

- RCT of 278 sedentary adults with obesity (75%) or DYSL randomized to 18 wks of isocaloric low-fat or Mediterranean/low-carbohydrate diet+28 g walnuts/day ± moderate PA (80% aerobic).

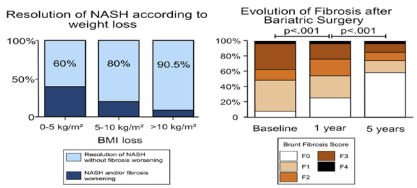


18-Month Changes	Low-Fat Diet		Mediterranean/Low-Carbohydrate Diet	
	PA– (Ref)	PA+	PA–	PA+
Visceral adipose tissue, cm²	–32.9±33.5	–48.9±43.0†	–31.1±32.7	–47.3±36.6*
Intrahepatic fat, %, absolute units	–3.72±7.12	–3.88±6.32	–3.67±6.51	–4.74±7.63

Gepner Y. *Circulation*. 2017

Weight Loss with Bariatric Surgery

- Severely obese patients with biopsy-proven NASH with 5 years of FU (N=180)



- Mortality risk of bariatric surgery in CC to be slightly higher than without cirrhosis (0.9% vs 0.3%) but significantly higher in DCC (16.3%)
- Alcohol use disorder may be an issue

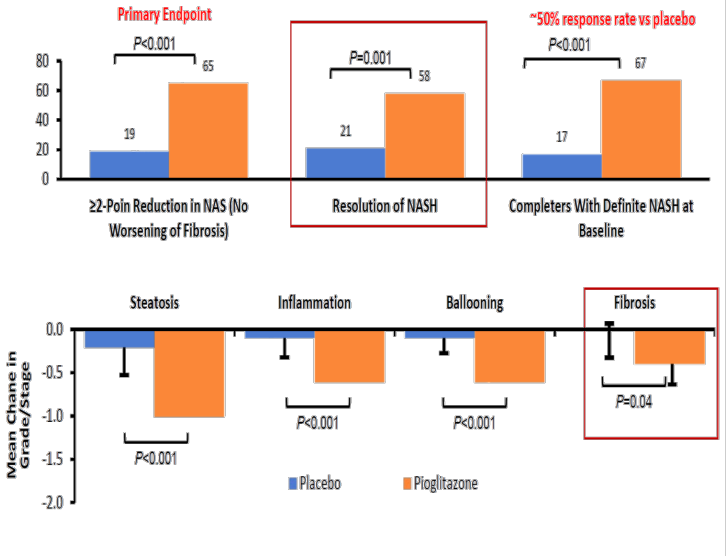
Hepatol. 2021Mar;19(3):436-445.

Lassailly G et al. Gastro 2020, Vol 159, p1193-1628

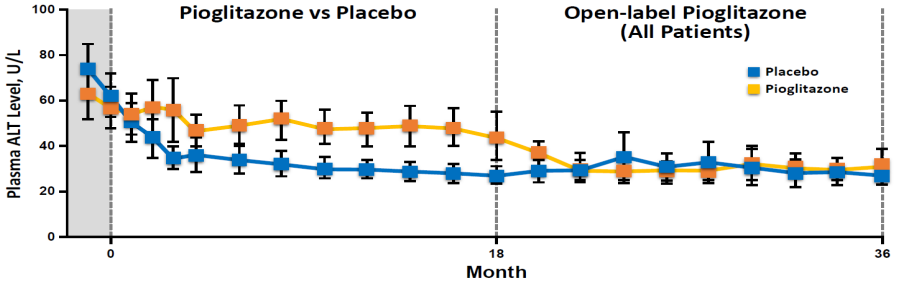
Addressing Risks Using Available Medications for NASH

Peroxisome Proliferator-Activated Receptors (PPARγ) Agonist (Pioglitazone)

- N=101 NASH with pre-DM or DM.
- All participants were placed on a 500 kcal/d deficit diet and randomized to placebo or pioglitazone 30 mg/day (titrated to 45 mg/d after 2 months) for 18 months.



Cusi K, et al. *Ann Intern Med*. 2016;165(5):305-315.



Cusi K, et al. *Ann Intern Med*. 2016;165(5):305-315.

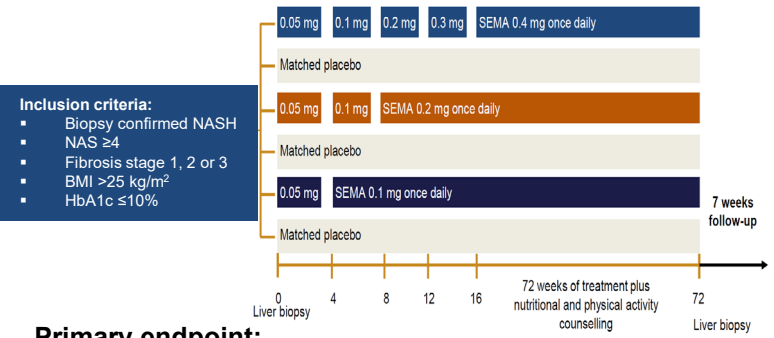
Study or Subgroup	Weight, %	Odds Ratio M-H, Random, 95% CI
Aithal et al, 2009	13.2	7.49 (0.37-151.50)
Belfort et al, 2006	14.0	16.54 (0.89-308.98)
Cusi et al, 2016	13.8	9.97 (0.52-190.16)
Sanyal et al, 2004	14.0	1.00 (0.05-18.57)
Sanyal et al, 2010	45.0	3.28 (0.64-16.78)
Total (95% CI)	100.0	4.53 (1.52-13.52)

0.01 0.1 1 10 100

Musso G, et al. *JAMA Intern Med*. 2017;177(5):633-640.

Addressing Risks Using Available Medications for NASH

GLP-1 Agonist in NASH (Semaglutide)

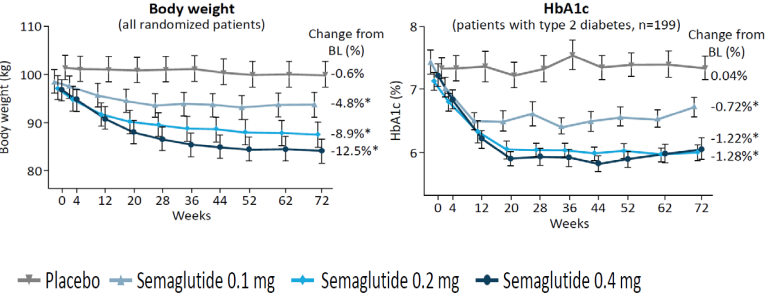


Primary endpoint:

- Resolution of steatohepatitis and no worsening in liver fibrosis

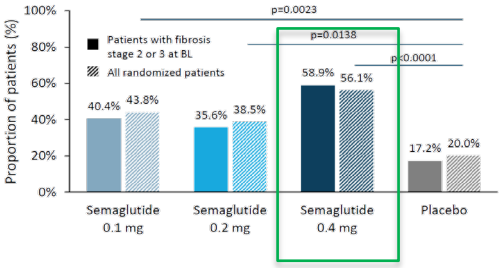
Confirmatory secondary endpoint:

- Improvement in liver fibrosis and no worsening in steatohepatitis

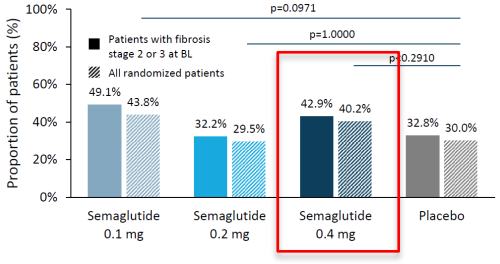


Newsome PN, et al. AASLD TLMdX2020. #10, Newsome et al. *NEJM.* 2020.

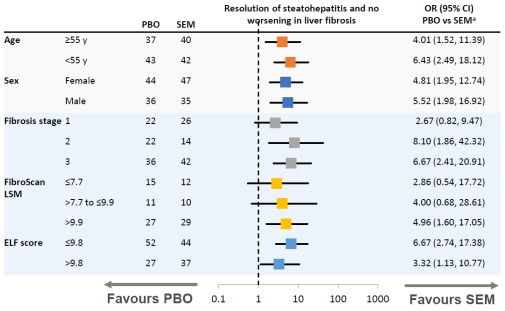
Resolution of steatohepatitis without worsening fibrosis

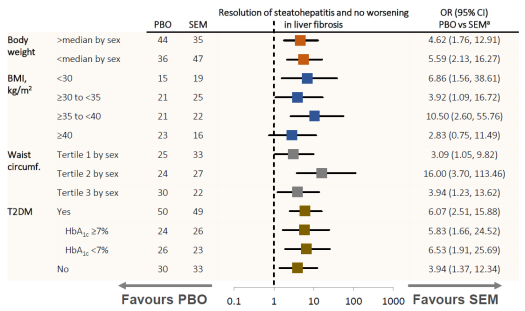


Improvement in liver fibrosis without worsening steatohepatitis



NASH resolution without fibrosis worsening with SEM 0.4 mg vs placebo, according to BL subgroups





- SEMA 0.4 mg resulted in increased HDL cholesterol and decreased free fatty acids, triglycerides and VLDL cholesterol versus placebo
- Overall AE profile excellent - major AEs were nausea, constipation, and vomiting, but these did not result in study drug discontinuation

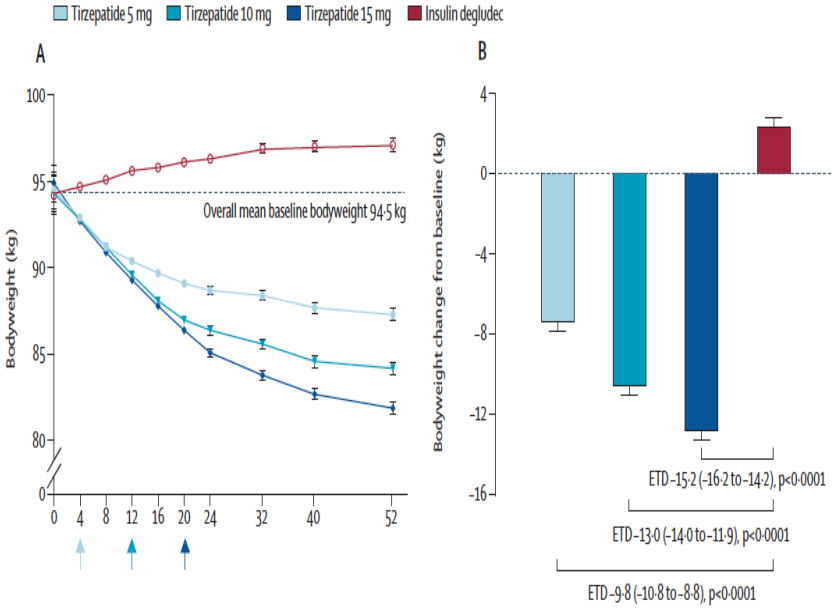
Addressing Risks Using Available Medications for NASH

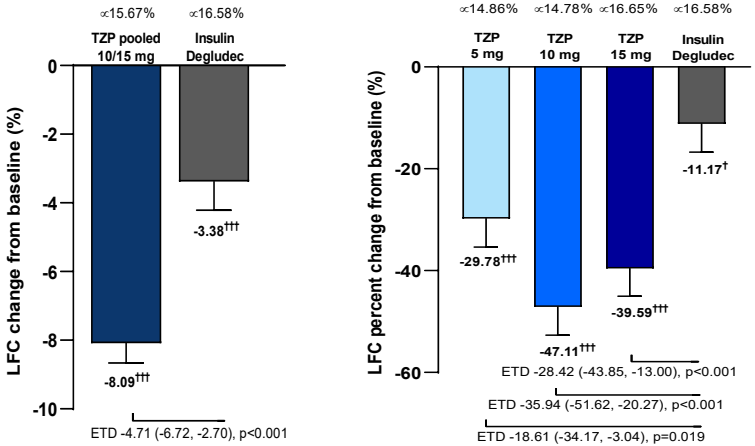
GIP receptor and GLP-1 receptor agonist (Tirzepatide)

Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial

Bernhard Ludvik, Francesco Giorgino, Esteban Jódar, Juan P Frias, Laura Fernández Landó, Katelyn Brown, Ross Bray, Ángel Rodríguez

- Weekly GIP (glucose-dependent insulinotropic polypeptide) receptor and GLP-1 (glucagon-like peptide-1) receptor agonist (Tirzepatide) for 52 weeks



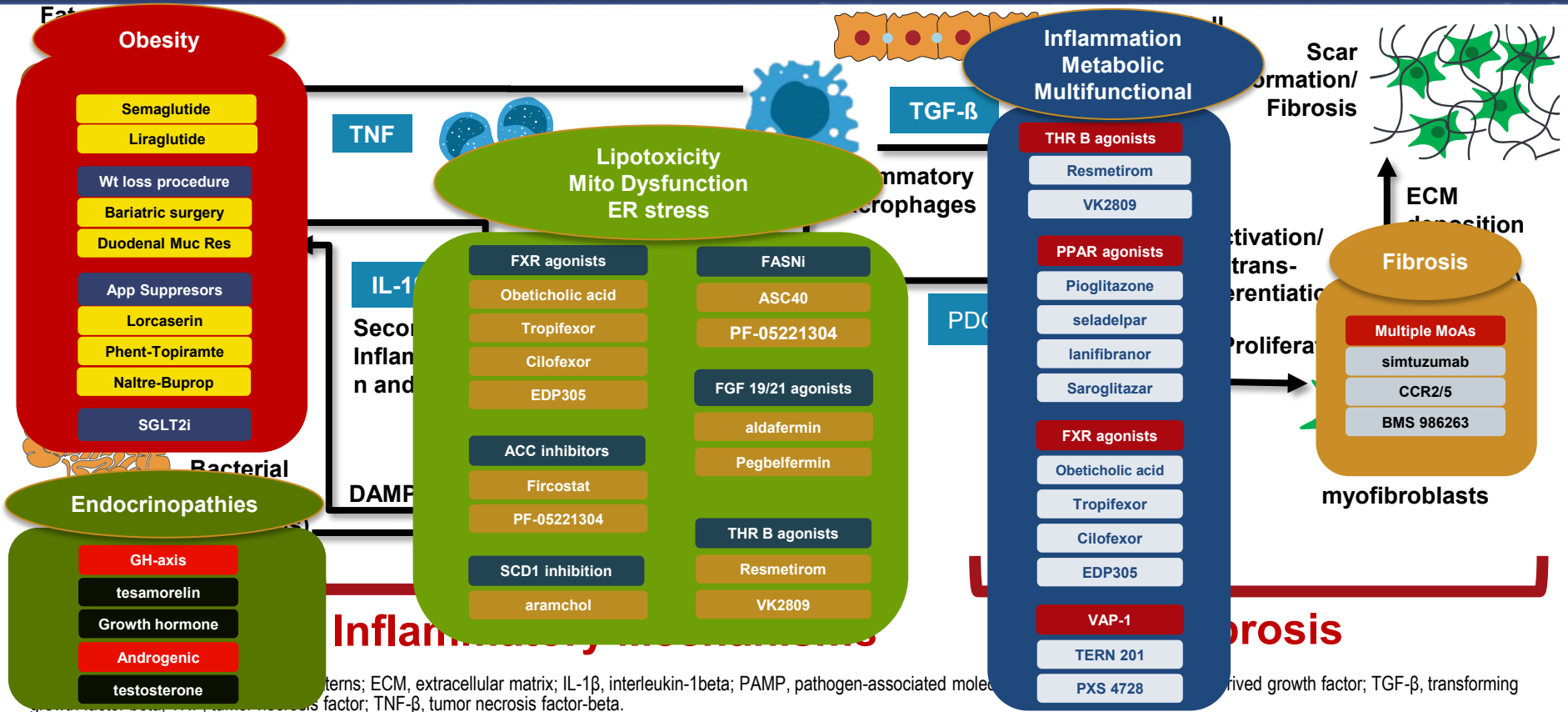


Data are LSM (SE) at 52 weeks. Estimated treatment differences (ETD) at 52 weeks are LSM (95% CI); mITT (MRI analysis set). ANCOVA analysis. † p<0.05; ††† p<0.001 vs. baseline within treatment group. ∝ represents the mean value at baseline for the respective group.

Ludvik B et al, Lancet 2021 Aug 14;398(10300):583-598. doi: 10.1016/S0140-6736(21)01443-4.

Gastaldelli, Cusi, Landó et al. Lancet Diabetes Endocrinol. 2022 June;10:393-406.

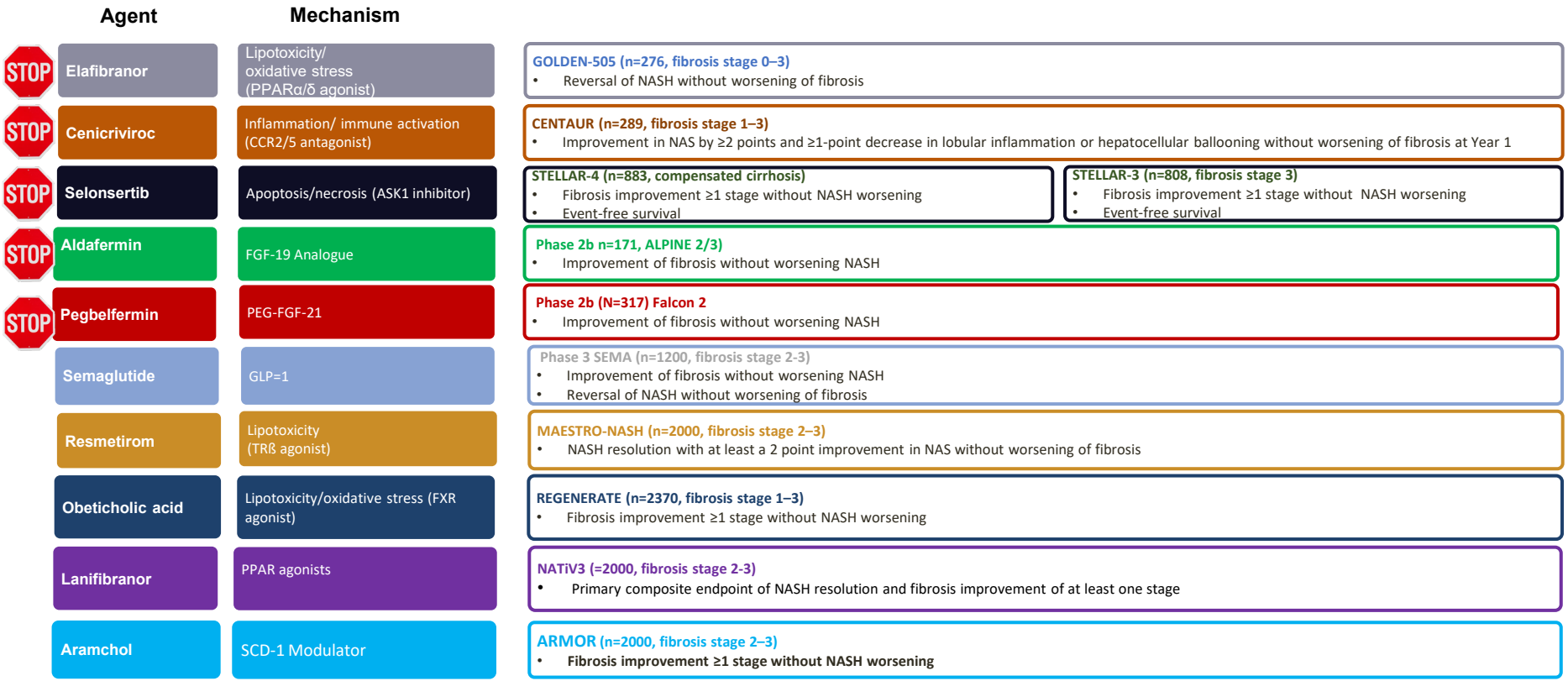
Future NASH Treatment: Potential Therapeutic Targets



terns; ECM, extracellular matrix; IL-1β, interleukin-1beta; PAMP, pathogen-associated mole… rived growth factor; TGF-β, transforming … factor; TNF-β, tumor necrosis factor-beta.

Benedict M, Zhang X. *World J Hepatol.* 2017;9(16):715-732; Bedossa P. *Liver Int.* 2017;37(suppl 1):85-89; Younossi ZM, et al. *Hepatology*. 2011;53(6):1874-1882.

New Regimens: Drugs in Phase 3



New Potential Regimen: PPAR Agonist in NASH (Lanifibranor)

PANPPAR (PPARa/d/g) agonist (N=247)

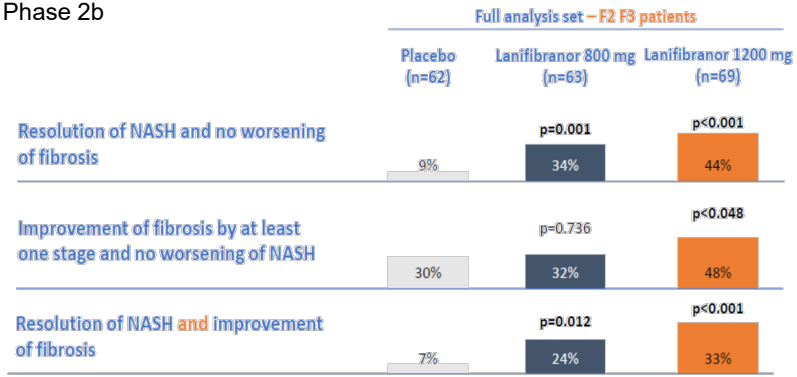
Screening
Liver biopsy

24-week treatment + 4-week follow-up
Double-blind, randomized, placebo-controlled

End of treatment
Liver biopsy

Randomization 1:1:1
Stratification on T2DM
Phase 2b

Once daily oral administration



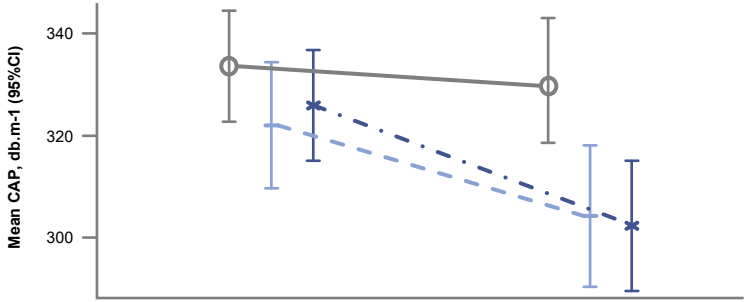
- increase in HDL-C at Week 4 and decrease in triglycerides at Week 14
- No change in LDL-cholesterol
- decrease of HbA1c

Francque SM, et al. AASLD TLMdX2020. #12

Mean ±SE (P-value vs PBO[a])	Lanifibranor 800 mg	Lanifibranor 1200 mg	Lanifibranor pooled	Placebo
APO-B/APO-A1	−0.09 ±0.02 (0.001)	−0.07 ±0.02 (0.01)	−0.08 ±0.01 (0.001)	0.01 ±0.02
Hs-CRP (mg/L)	−2.01 ±0.50 (0.02)	−1.00 ±0.52 (0.31)	−1.53 ±0.36 (0.053)	−0.23 ±0.55
MACK-3	−0.32 ±0.03 (<0.001)	−0.28 ±0.03 (<0.001)	−0.30 ±0.02 (<0.001)	−0.01 ±0.03
TIMP1/MMP2	−0.79 ±0.10 (<0.001)	−0.88 ±0.10 (<0.001)	−0.83 ±0.07 (<0.001)	−0.07 ±0.11

[a]From MMRM including absolute change from BL as endpoint, time, treatment, BL diabetic status, interaction treatment*time and BL value as fixed effects, time repeated effect within each subject

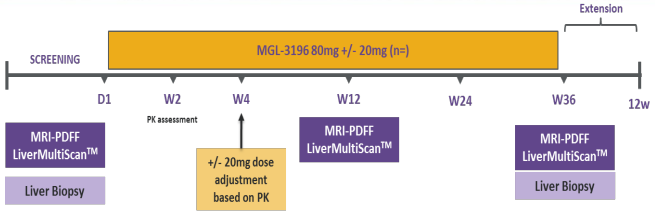
Francque S et al. EASL 2021

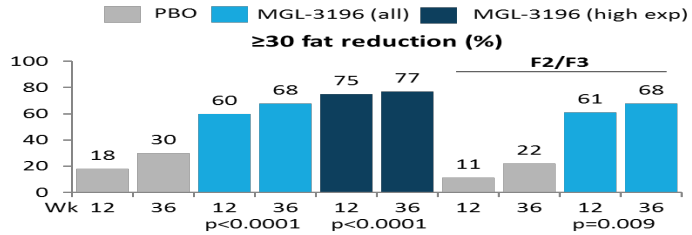


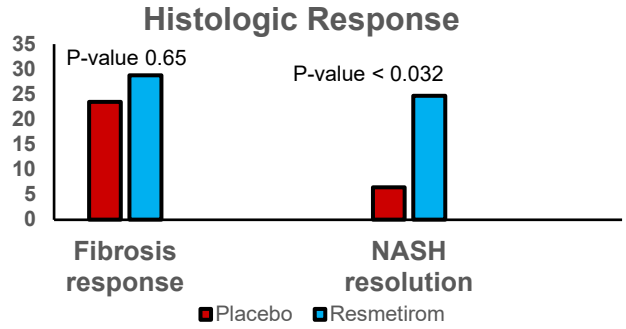
- Data suggest that LAN reduced hepatic steatosis, assessed using histologically and with CAP
- Fall in CAP correlated with HBA1c and TG drop

Cooreman MP, et al. AASLD 2021. #P1921

New Potential Regimen: Thyroid Receptor β Agonist in NASH (Resmetirom)

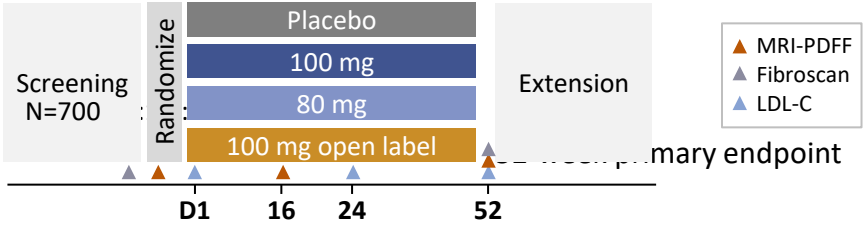






Harrison SA, et al Lancet. 2019 30;394(10213):2012-2024,Harrison SA, et al. *Hepatology*. 2018;68(1 suppl):9A..

Phase 3 MAESTRO-NAFLD-1 Study Design (F1–F3)



INCLUSION: 1) ≥3 metabolic risk factors 2)Fibroscan kPa ≥F1; CAP ≥280 3) MRI-PDFF ≥8%

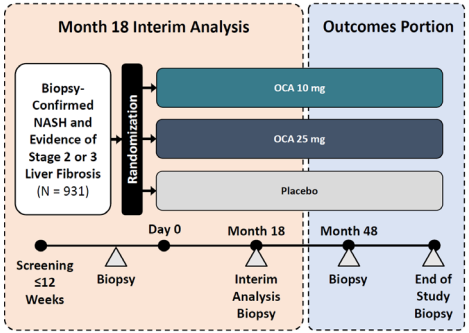
	All	SHBG (high)
MRI-PDFF (%)		
Baseline (%)	17.6	17.9
Relative % change	−53%	−62%
p-value	<0.0001	<0.0001
MRE		
Baseline (>2.9, F1–F3)	3.5	3.5
Absolute change	−0.34	−0.46
p-value	0.003	0.003

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(µg/mg)	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

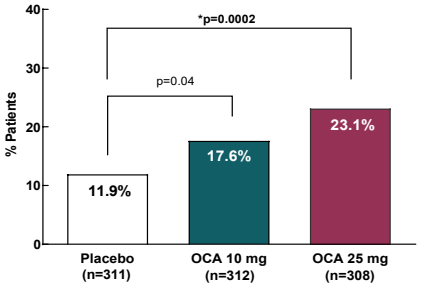
Harrison S, et al. AASLD TLMdX2020. #1707

New Potential Regimen: FXR Agonist in NASH (Obeticholic Acid)

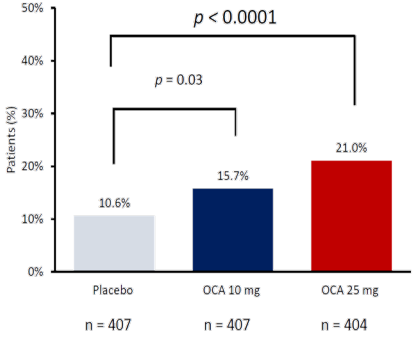


- End of Study analyses
  - Progression to cirrhosis
  - Complications secondary to cirrhosis
  - Liver transplant
  - All-cause mortality
- ~7.5 years in total study duration
  - Minimum 4 years follow-up

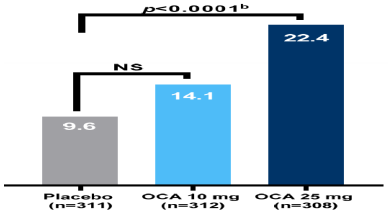
Primary Endpoint (ITT): Fibrosis Improvement by ≥1 Stage With No Worsening of NASH



Fibrosis Improvement ≥1 Stage With No Worsening of NASH: Expanded ITT Population

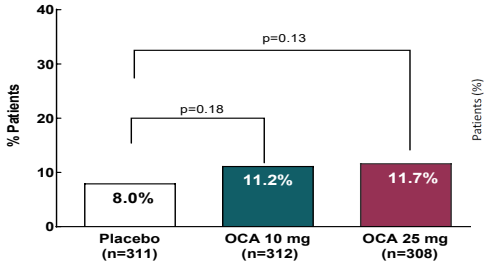


Primary Endpoint of Re-analysis Using Consensus Panel

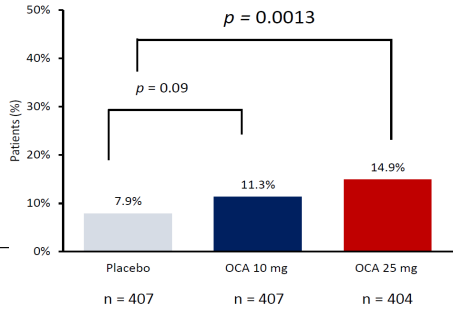


- Safety population, N=2477
  - 8000+ total pt yrs of exposure
  - ~1000 subjects received OCA for ≥4 years

Primary Endpoint (ITT): NASH Resolution With No Worsening of Fibrosis



NASH Resolution With No Worsening of NASH: Expanded ITT Population



	Placebo n=825	OCA 10 mg n=825	OCA 25 mg n=827
Deaths	8 (1.0)	9 (1.1)	10 (1.2)
TEAEs	766 (92.8)	795 (96.4)	807 (97.6)
Serious TEAEs	181 (21.9)	204 (12.4)	216 (26.1)
TEAEs leading to d/c of IP	93 (11.3)	102 (33.2)	179 (21.6)
Most frequent TEAE: pruritus	200 (24.2)	274 (33.2)	453 (54.8)
Most frequent TEAE leading to IP d/c	8 (1.0)	14 (1.7)	93 (11.2)
Neoplasms benign, malignant and unspecified	84 (10.2)	91 (11.0)	76 (9.2)

Younossi Z, et al. Lancet 2020

Sanyal A, et al AASLD 2019

Sanyal AJ, et al. AASLD 2022. Late-breaking oral #5008

Non-alcoholic Steatohepatitis Summary

- NASH and its complications are growing
- NASH+T2DM and those with stage≥2 are especially at high risk
- NIT algorithms can be used to risk stratify patients with NAFLD/NASH
- Management requires multidisciplinary team to address driver of progressive NAFLD (T2D and Obesity) through
  - Life style intervention for all (Diet & exercise)
  - Bariatric Experts (Endoscopic, Surg)
  - Medical Treatment of T2D and obesity
- A large number of drugs are in phase 2 with a few in phase 3 clinical trials
- Combination of regimens, Personalized Medicine and induction and maintenance may be the future

Development of Care Pathway