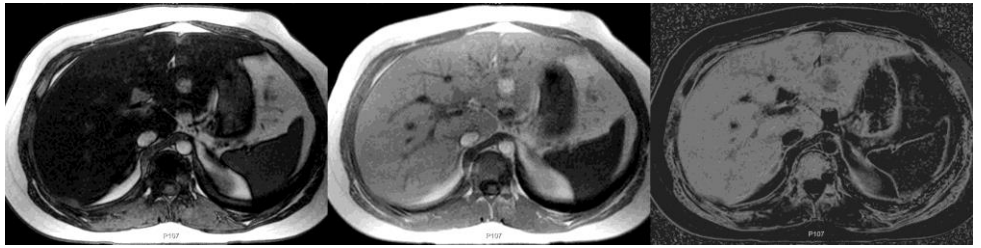
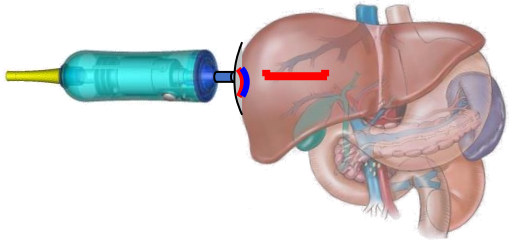
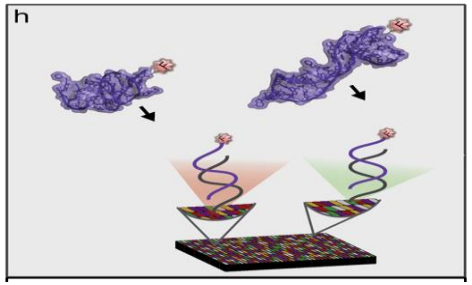
Treatment response in MASH: are we ready for NITs?







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Disclosures

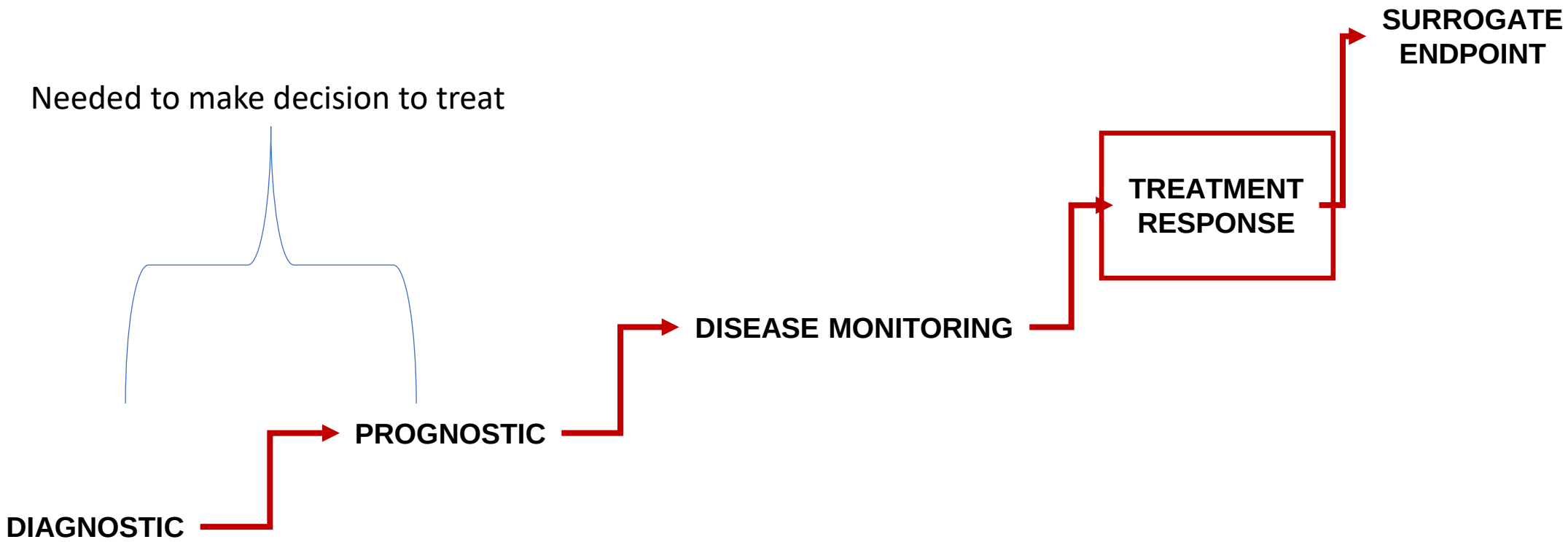
[Arun J. Sanyal]

I disclose the following financial relationship(s) with a commercial interest:

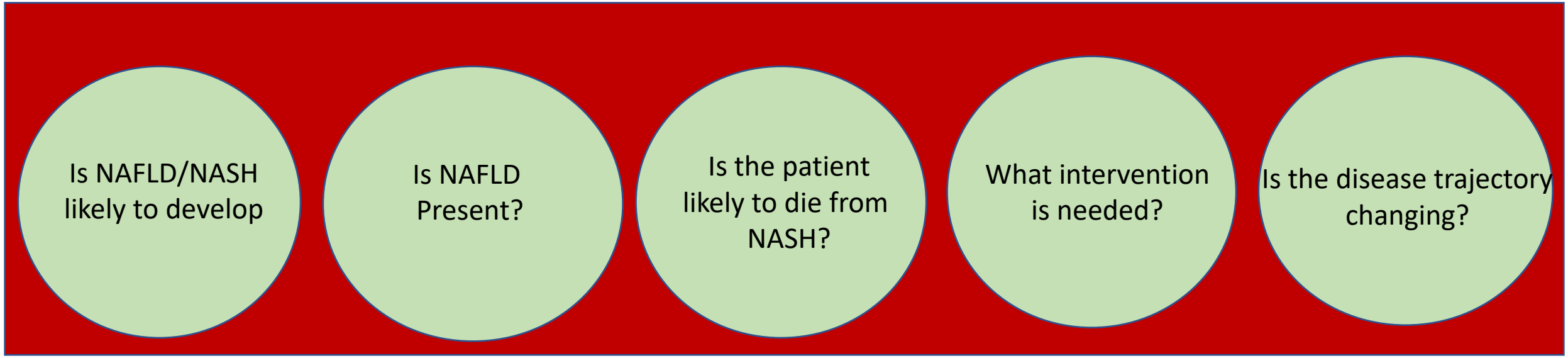
- Ownership interests: Durect, Tiziana, Genfit, Exhalenz, Rivus, Inversago, Northsea
- Consultant: Gilead, Intercept, Novartis, Novo Nordisk, Inventiva, Merck, Pfizer, Boehringer Ingelhiem, Bristol Myers Squibb, Eli Lilly, Genentech, Amgen, Alnylam, Regeneron, Thera Technologies, Madrigal, Salix, Malinckrodt, Gatehouse, Rivus, Siemens, Lipocine, 89 Bio, Astra Zeneca, Akero, Histoindex,PathAI, Mitopower, Takeda
- Grant support to school: Gilead, Intercept, Novartis, Novo Nordisk, Inventiva, Eli Lilly, Genentech, Boehringer Ingelhiem, Bristol Myers Squibb, Avant Sante, Astra Zeneca, Merck, Takeda

Wish I was there

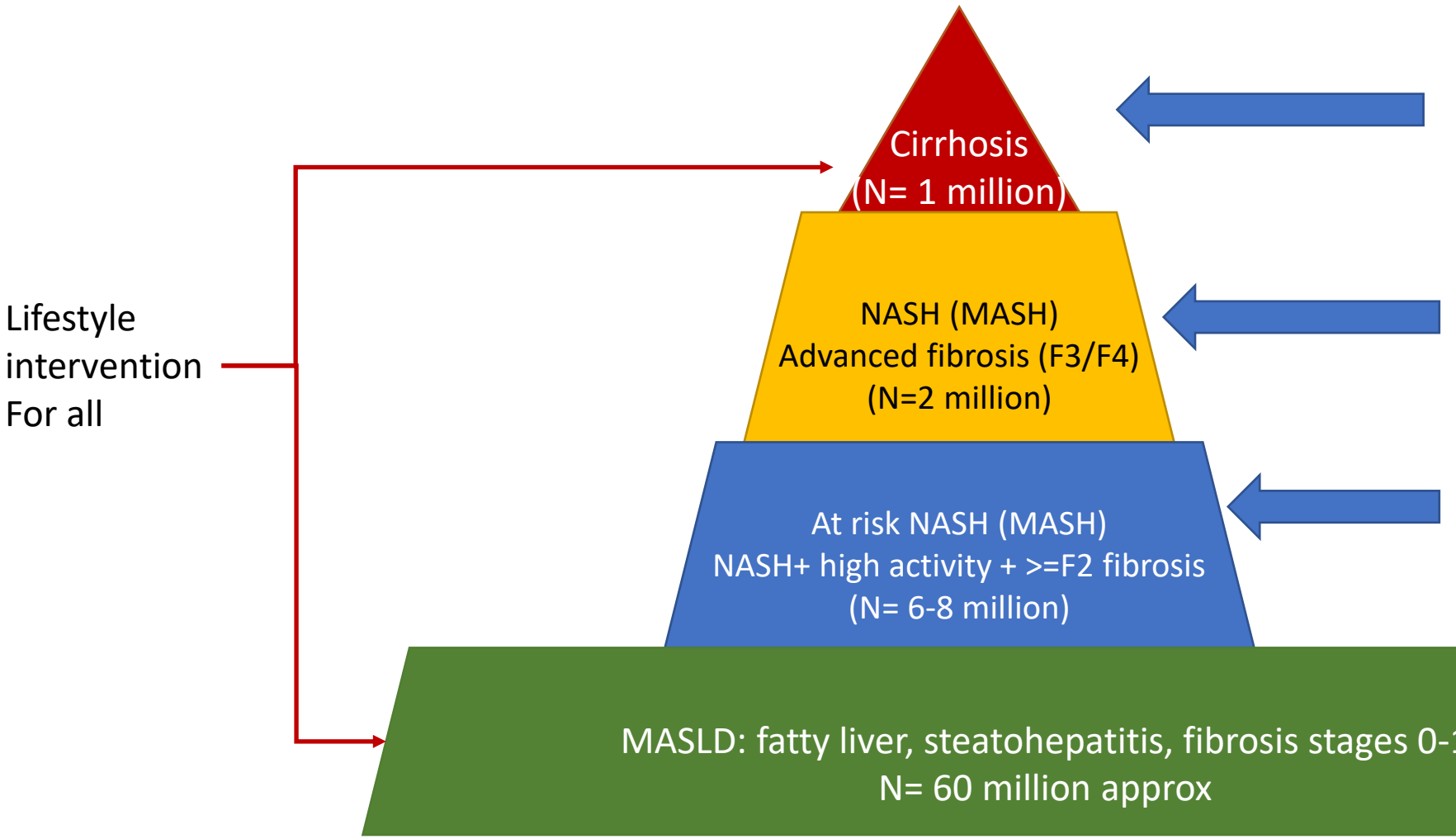
There is a hierarchy of biomarker use



It all starts by framing “fit for purpose” biomarker use in a “relevant” clinical question



Taking down the MASLD pyramid



Top down Rx

- Prevent decompensation/death
- Reverse cirrhosis
  - Rifaximin
  - Carvedilol
  - Minimize insulin
  - Nutrition-sarcopenia
- Stop progression to cirrhosis
  - Resmetirom
  - FGF21
  - Semaglutide/tirzepatide/ Survodutide
- Rx NASH and reduce fibrosis

Bottom up Rx

Wipe out NAFLD before it progresses

GLP-1 analogs

There is an extensive and growing tool kit for assessment of liver disease

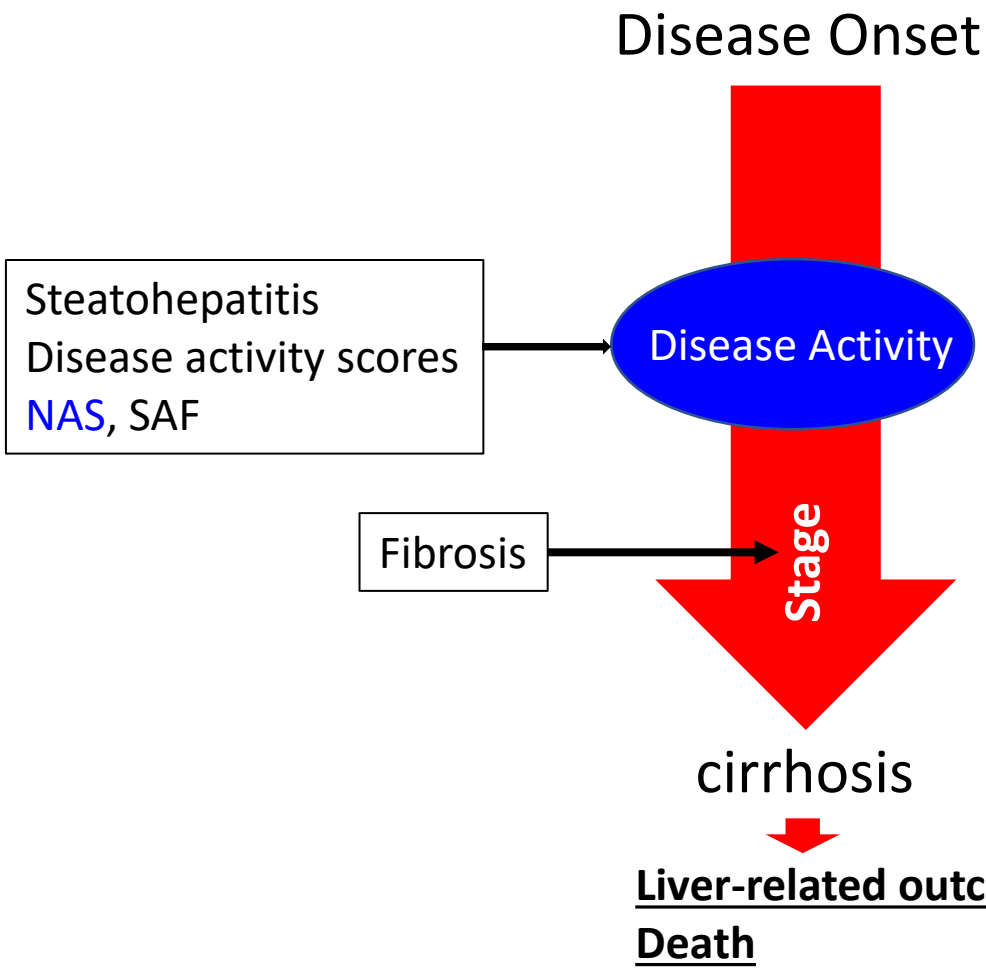
Established biomarkers

- Fibroscan
- Enhanced liver fibrosis (ELF) test
- 2D-MRE

In development

- Blood based:
  - NIS2
  - ProC3-ADAPT score
  - Proteomic profile
  - Fibrometer
- Imaging:
  - Corrected T1 map (MRI)
  - 3D-MRE

Measuring success in MASH treatment



In the long term: reduce clinical Outcomes

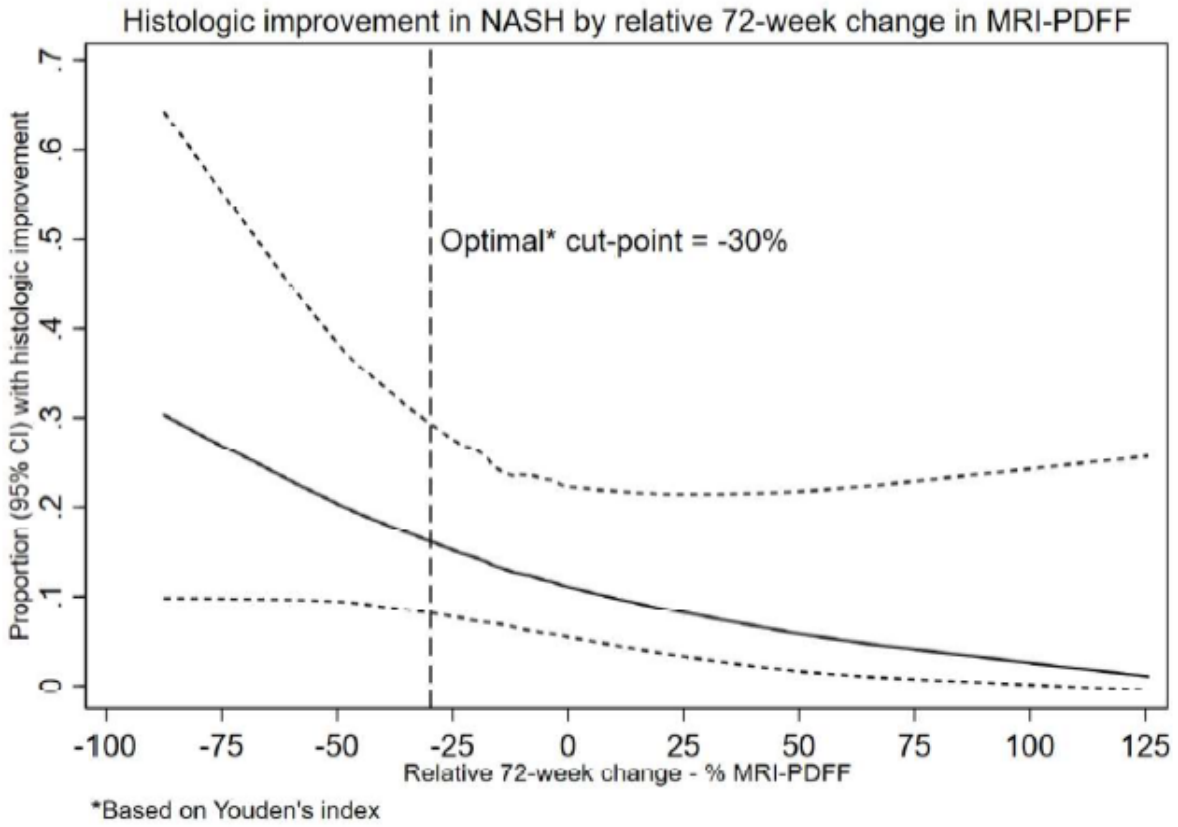
In the short term: improve histology

A surrogate outcome

NIT Surrogates:

- Markers of activity
- Markers of fibrosis

MRI-PDFF and histological improvement

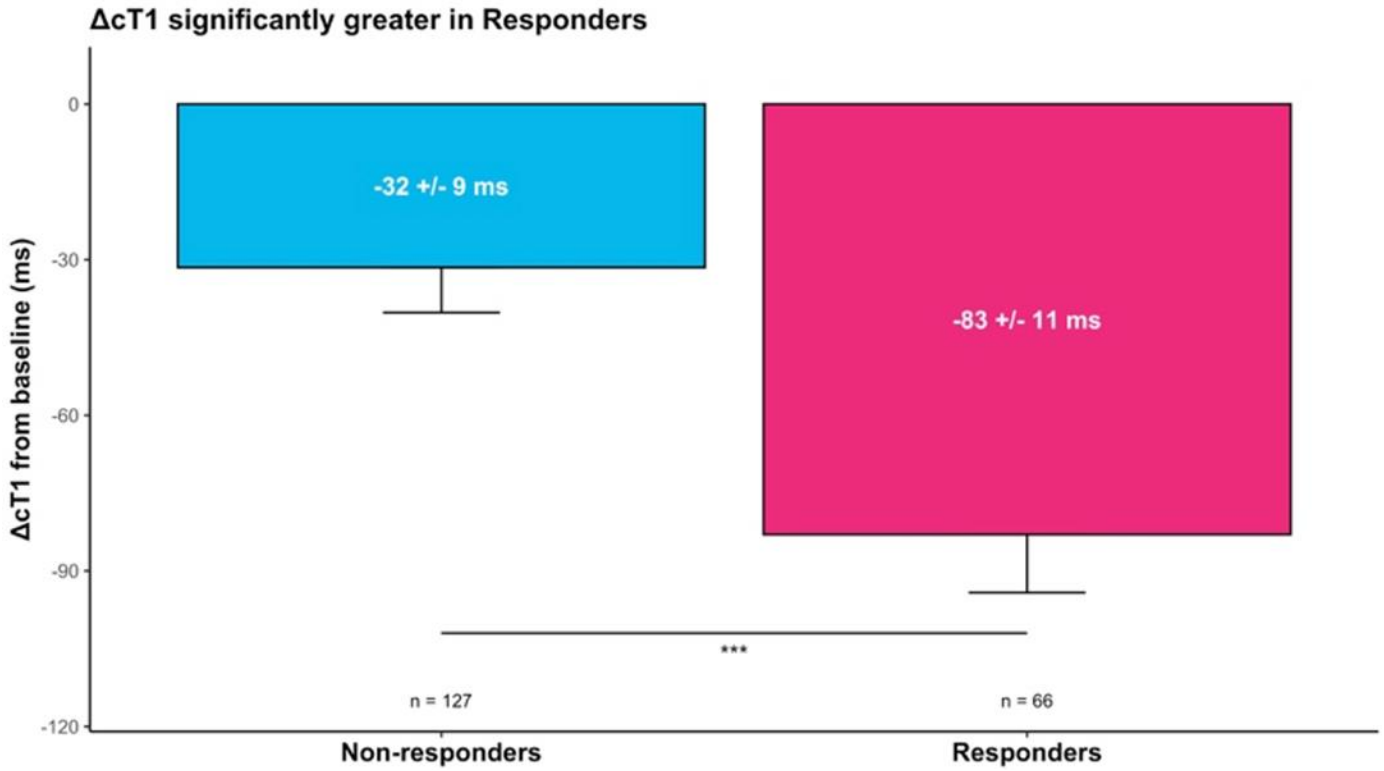


Title: Histologic response in NASH increases as relative decline in MRI-PDFF increases

Middleton et al, gastroenterology 2019

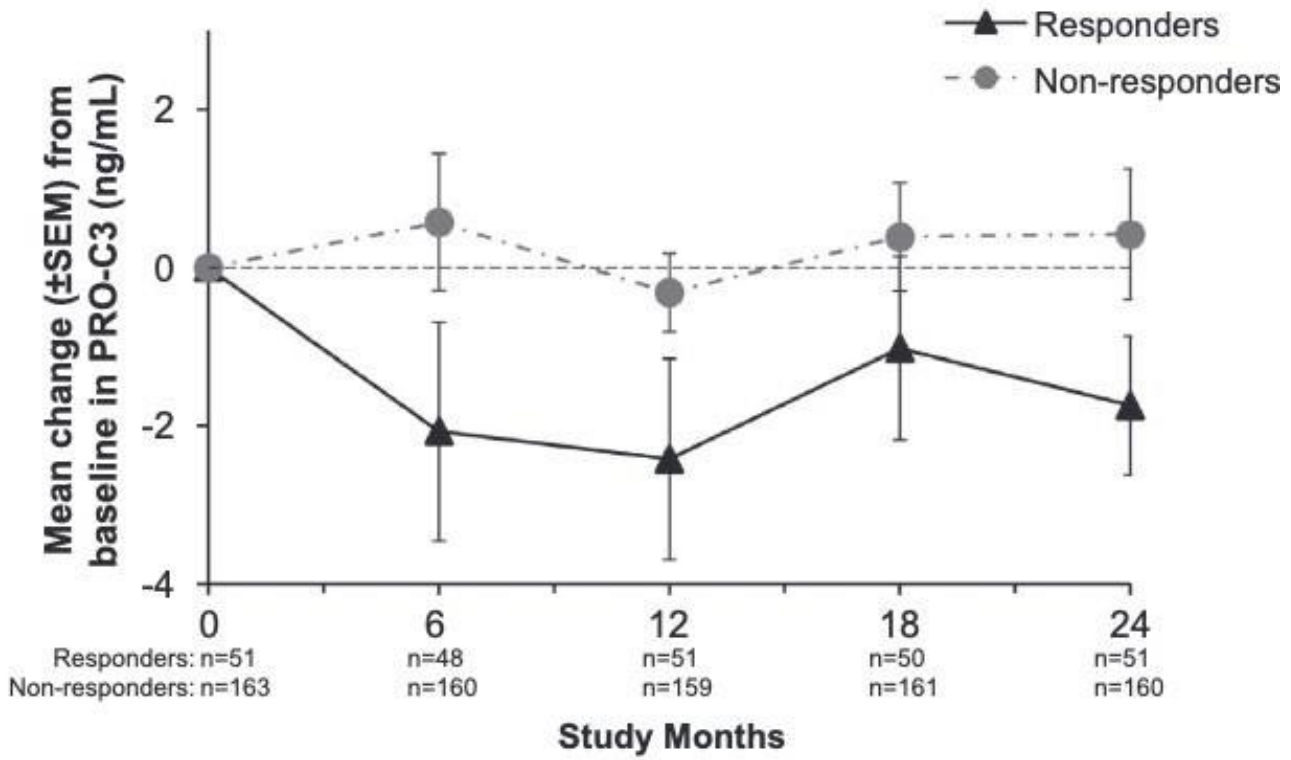
cT1 accurately reflect histological improvement
A multi-center pooled cohort analysis

- N=193 (from 3 interventional NASH studies)
- MRI and biopsy at baseline and 22-52 weeks following intervention.
- Participants were characterized as responders (NAS decrease ≥2 with no worsening of fibrosis), or non-responders.



Dennis A, et al. Frontiers in Endocrinology 2021; International Liver Meeting 2021, abstract presentation

ProC3 to Monitor Response to Therapy – CENTAUR trial



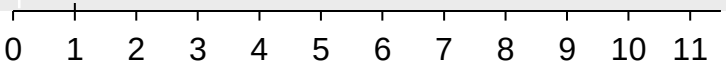
Responders: ≥1-stage fibrosis

Ratziu V Cenicriviroc Treatment for Adults With Nonalcoholic Steatohepatitis and Fibrosis: Final Analysis of the Phase 2b CENTAUR Study. Hepatology. 2020 Sep;72(3):892-905

NITs for monitoring progression

Cirrhosis

	Hazard Ratio *	95% CI	p-value
Ishak stage 5 vs 6 (baseline)	**1.25**	0.68, 2.29	0.48
No improvement vs improvement	**9.63**	1.33, 69.81	0.025
Hepatic collagen (baseline), per 5%	**1.39**	1.15, 1.69	<0.001
Change from baseline, per 5%	**1.20**	1.03, 1.39	0.017
ELF (baseline)	**2.37**	1.69, 3.31	<0.001
Change from baseline	**1.54**	1.10, 2.15	0.002



* Separate multivariate models run with baseline and change from baseline for each variable.

- Increased risk of clinical events with:
  - Higher baseline hepatic collagen content and ELF
  - Worsening of fibrosis (by Ishak stage, collagen content, ELF)

Sanyal et al, Hepatology, 2019

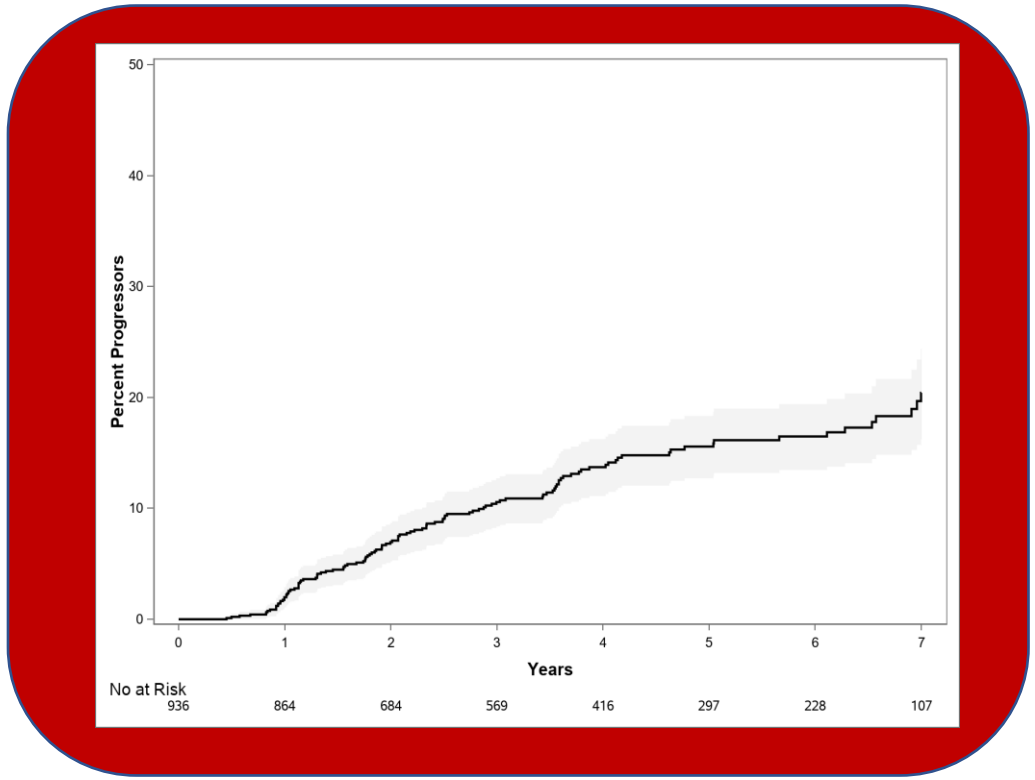
VCTE Reproducibility and Repeatability

	# subjects	# obs	Mean of Median SWS (m/s)	$RDC_{diff\text{-}day,\ diff\text{-}oper}$	Upper 95% confidence bound
Fibroscan/VCTE	39	39	1.641	35.6%	43.9%

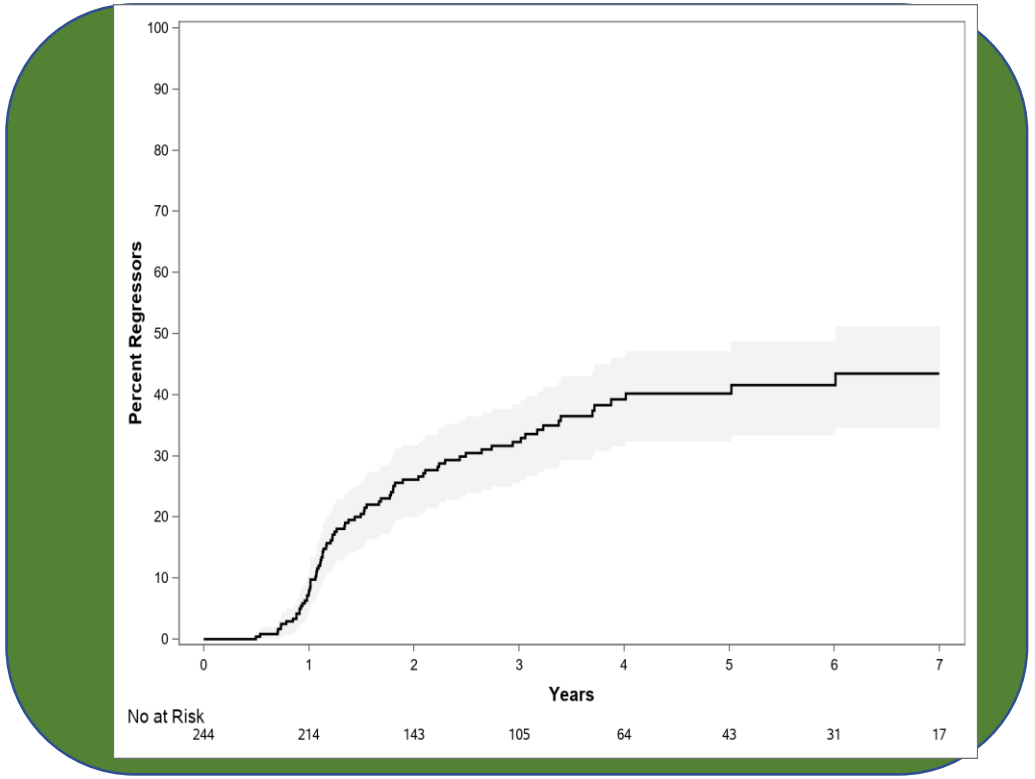
Key Takeaway: Changes in shear wave speed as evaluated by VCTE **>35.6%** can be considered true change (with 95% confidence).

Data from NIMBLE- MS under review

MASLD progression and regression assessed by liver stiffness measurement by VCTE



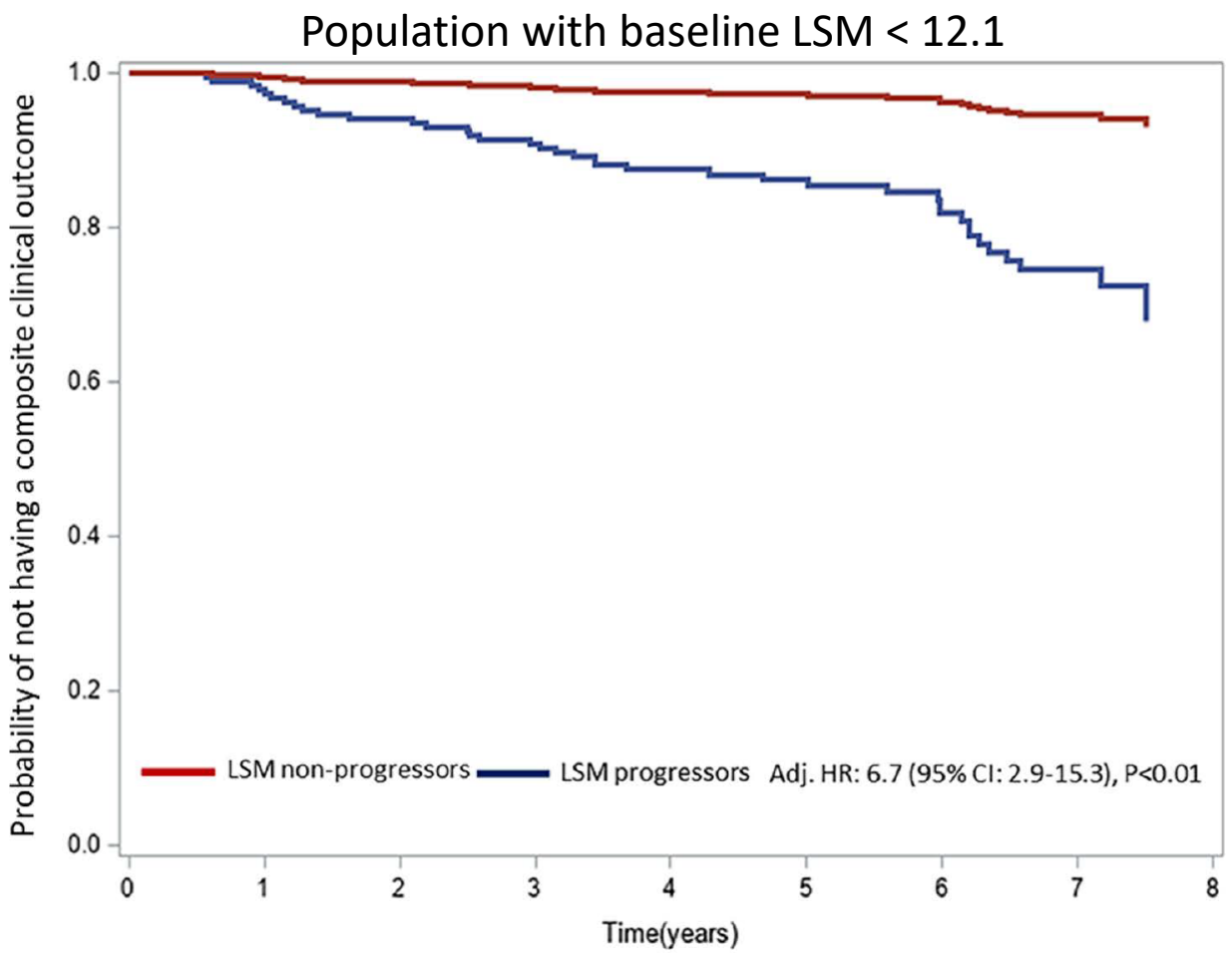
From LSM < 12.1 to > 14.9



From LSM > 14.9 to < 12.1

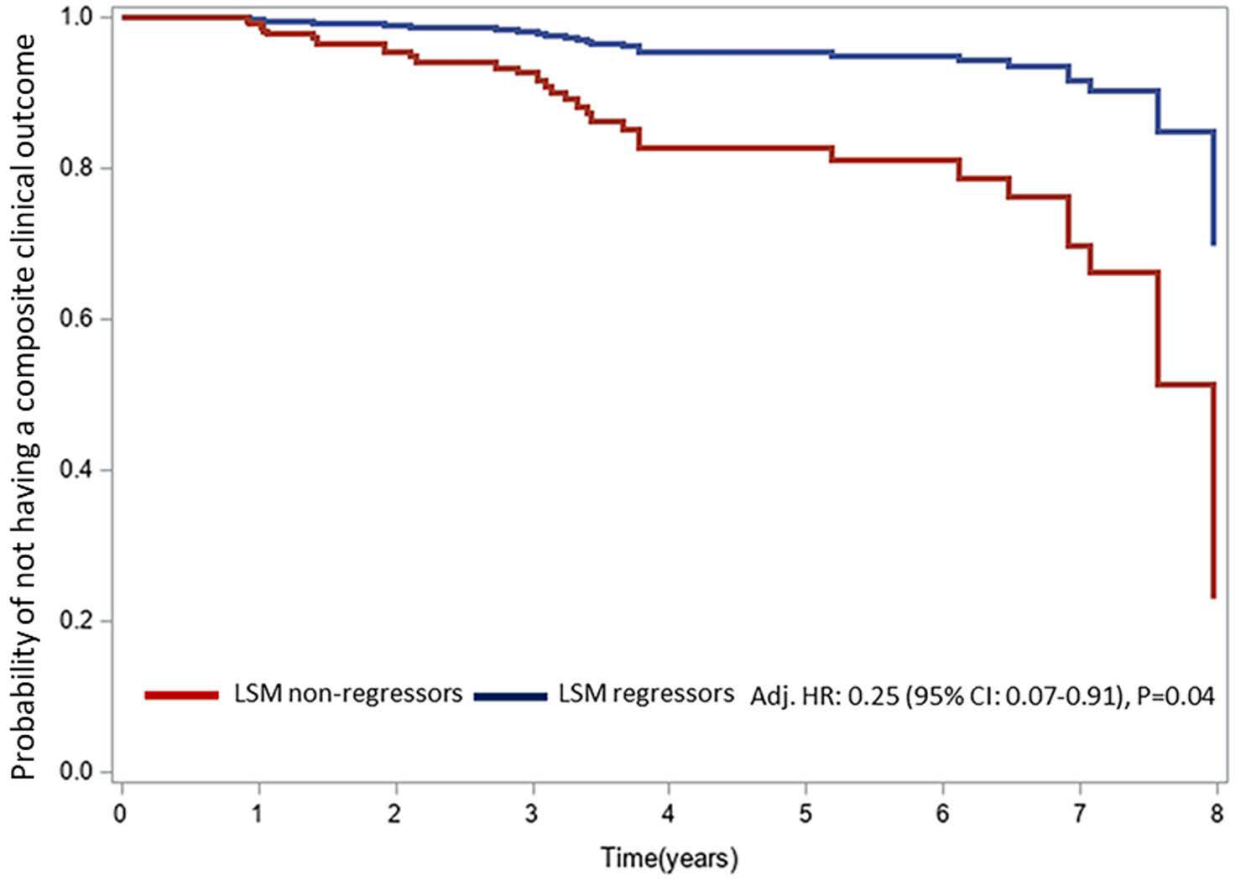
Gawrieh et al, AASLD 2022, Under review for publication 2023

Clinical outcomes seen almost entirely in progressors



Gawrieh et al, AASLD 2022, Under review for publication 2023

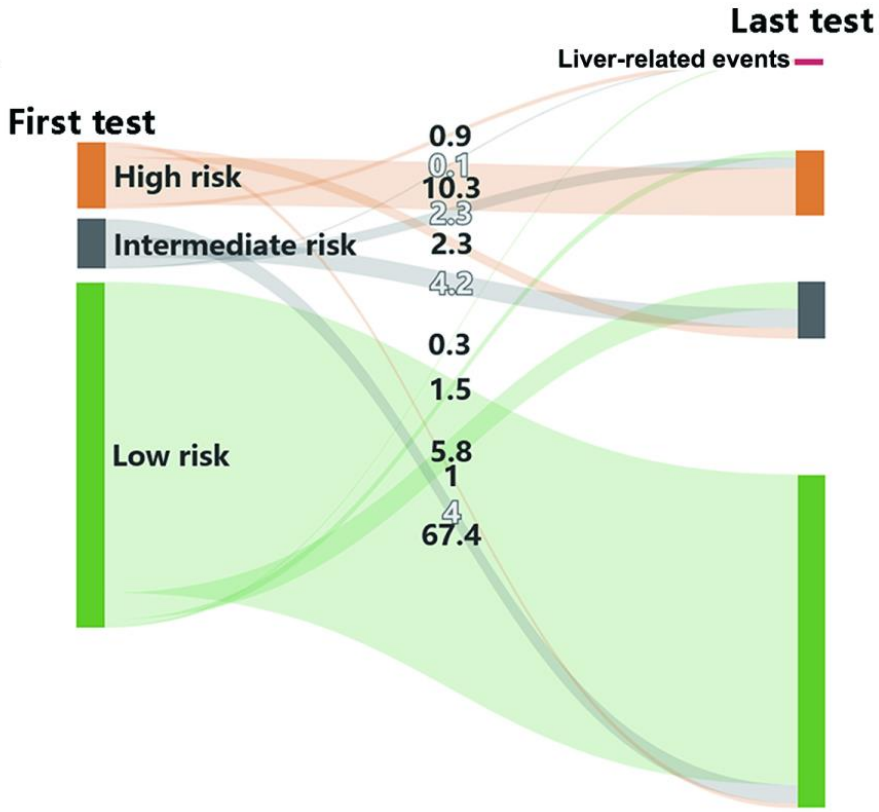
Conversely regressors were protected from outcomes



Gawrieh et al, AASLD 2022, Under review for publication 2023

NIT changes over time predict risk of outcomes

A

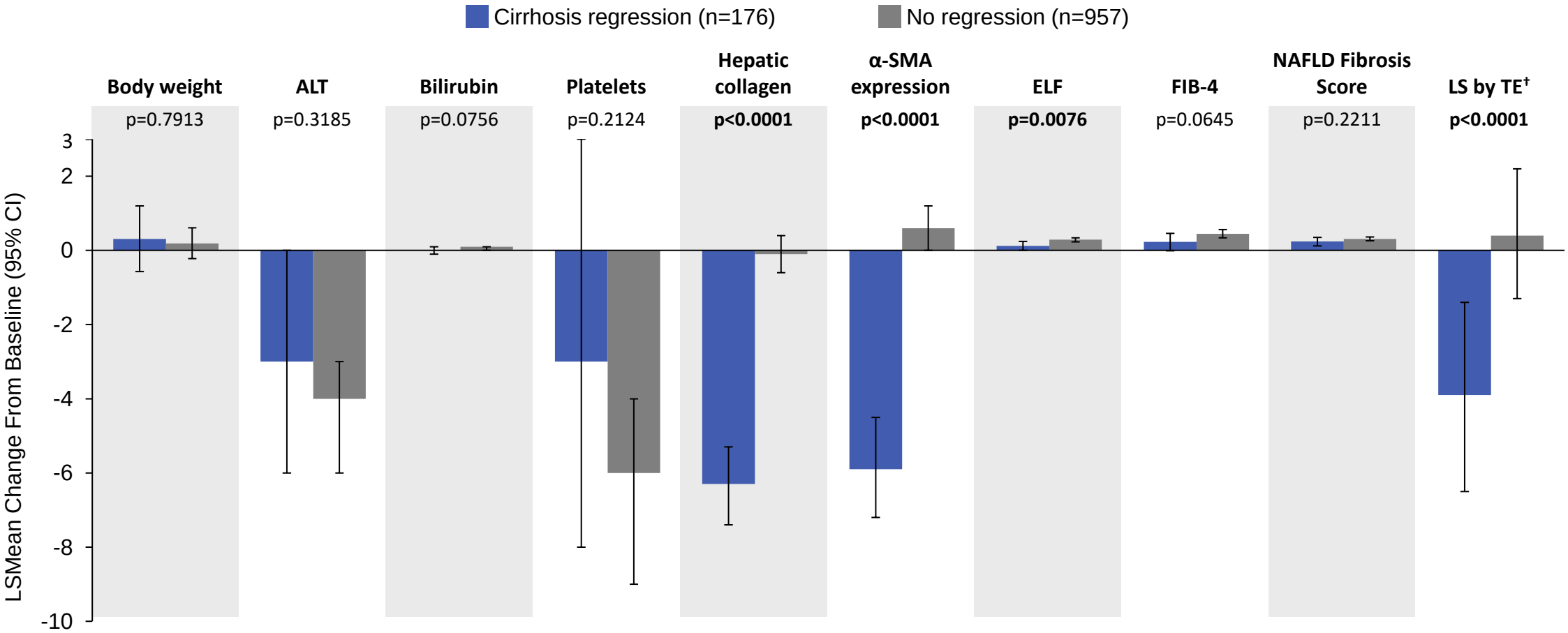


B

First test	Relative change 10%	N (%)	5-year LRE (%)	Relative change 20%	N (%)	5-year LRE (%)	Relative change 30%	N (%)	5-year LRE (%)
High risk	Decreasing >10%	403 (4.6)	1.8 (0.7-3.9)	Decreasing >20%	263 (3.0)	0.5 (0.1-2.7)	Decreasing >30%	162 (1.8)	-
	Stable	665 (7.6)	14.1 (10.2-18.6)	Stable	888 (10.2)	12.2 (9.0-15.9)	Stable	1 029 (11.8)	11.9 (8.9-15.4)
	Increasing ≥10%	129 (1.4)	19.7 (7.9-35.3)	Increasing ≥20%	46 (0.5)	31.0 (7.6-58.6)	Increasing ≥30%	6 (0.1)	33.3 (-)
Intermediate risk	Decreasing >10%	437 (5.0)	0.3 (0.1-1.5)	Decreasing >20%	341 (3.9)	0.4 (0.1-1.9)	Decreasing >30%	246 (2.8)	0.5 (0.1-2.7)
	Stable	195 (2.2)	0.6 (0.1-2.9)	Stable	366 (4.2)	0.6 (0.1-2.1)	Stable	528 (6.0)	0.4 (0.1-1.5)
	Increasing ≥10%	291 (3.3)	0.9 (0.2-3.9)	Increasing ≥20%	216 (2.4)	0.6 (0.1-3.0)	Increasing ≥30%	149 (1.7)	0.9 (0.1-4.3)
Low risk	Decreasing >10%	2 179 (25.0)	0.3 (0.1-1.0)	Decreasing >20%	1 763 (20.2)	0.4 (0.1-1.3)	Decreasing >30%	1 359 (15.6)	0.1 (0.1-0.5)
	Stable	698 (8.0)	-	Stable	1 463 (16.8)	0.3 (0.1-0.9)	Stable	2 194 (25.2)	0.4 (0.1-1.1)
	Increasing ≥10%	3 703 (42.5)	0.4 (0.2-0.8)	Increasing ≥20%	3 354 (38.5)	0.4 (0.1-0.8)	Increasing ≥30%	3 027 (34.7)	0.4 (0.2-0.9)

Lin et al, JAMA 2024, in press

Patient Characteristics According to Cirrhosis Regression Change from Baseline*

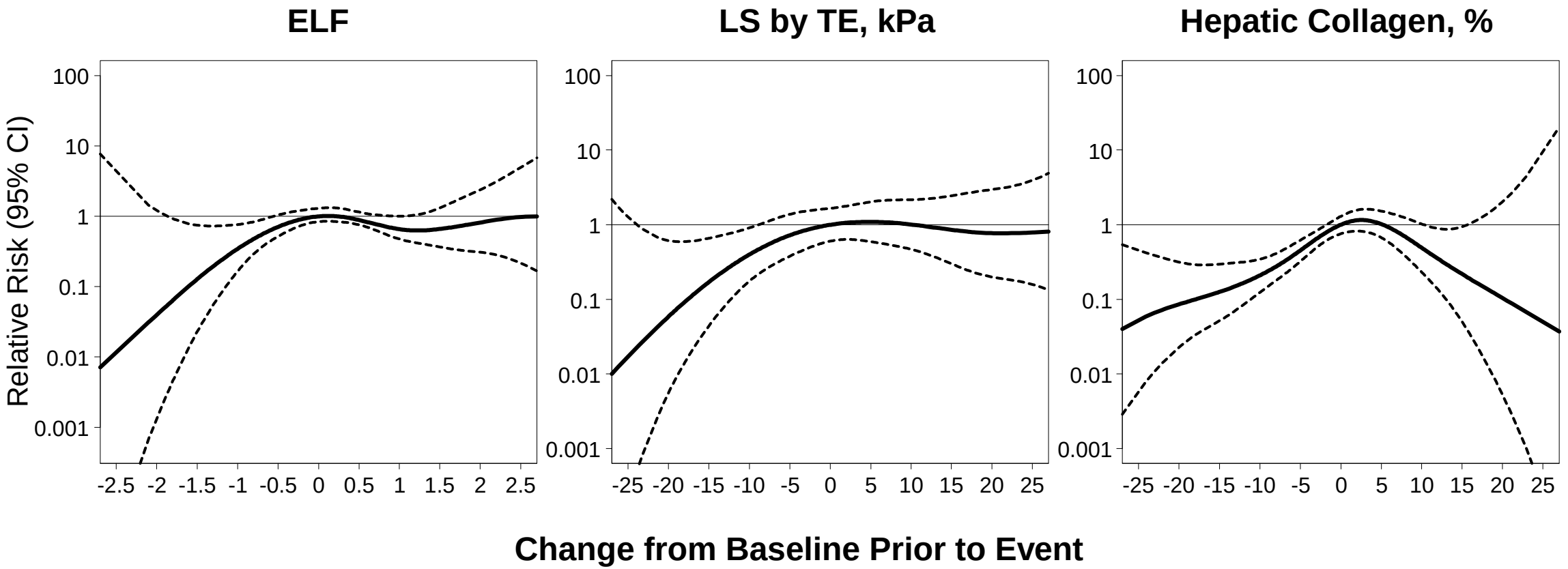


- Patients with cirrhosis regression had greater reductions in hepatic collagen and α-SMA expression, ELF, and LS by TE

LSMeans and p-values by ANCOVA with adjustment for baseline value and study. * Change from baseline up to clinical event.
† Available in 40 patients in SIM study and 694 patients in STELLAR-4.

Sanyal et al, Hepatology 2021

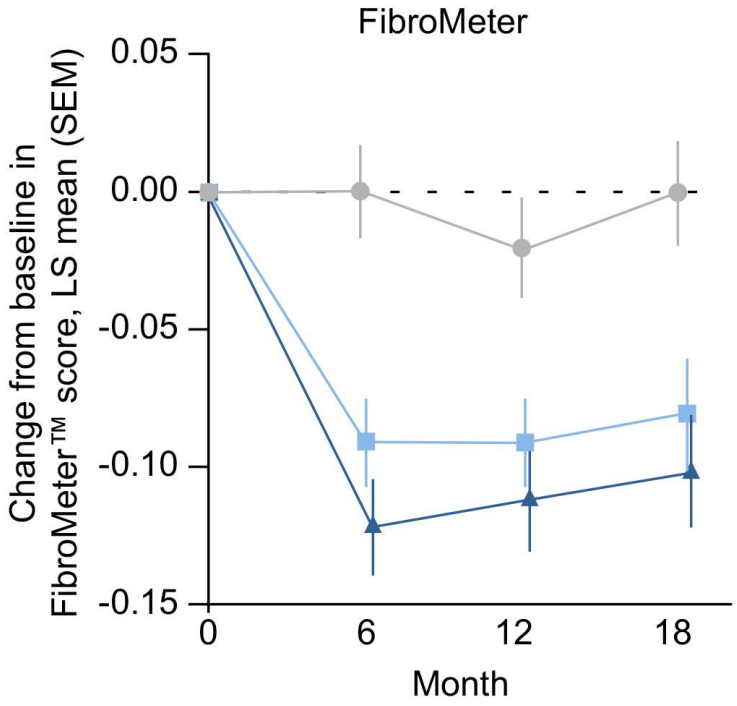
Relationship Between Changes in NITs and Hepatic Collagen with Clinical Events



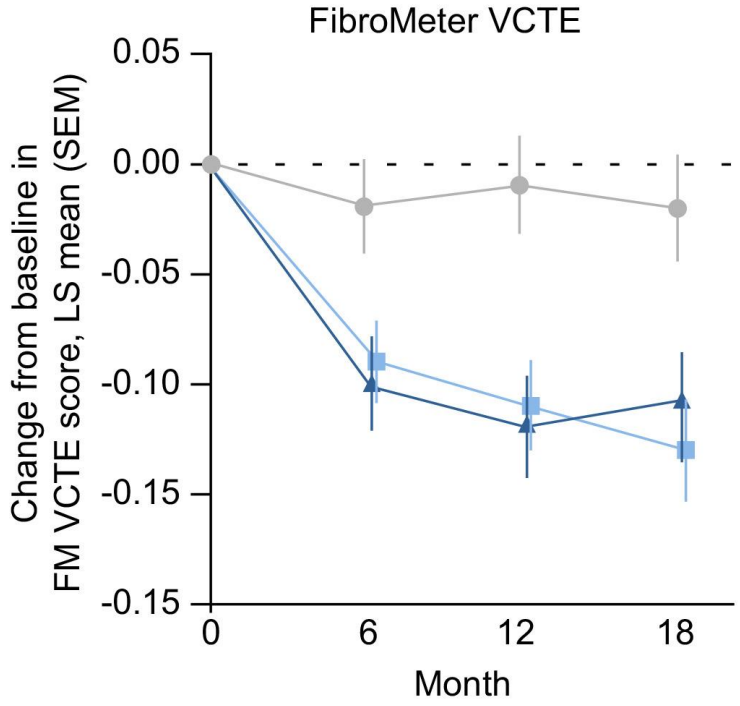
- Reductions in ELF, LS by TE, and hepatic collagen content associated with a reduced risk of clinical events

Figures generated using Cox models adjusted for baseline value (linear) and change from baseline (smoothing spline). Relative risk of clinical events vs a reference of no change from baseline.

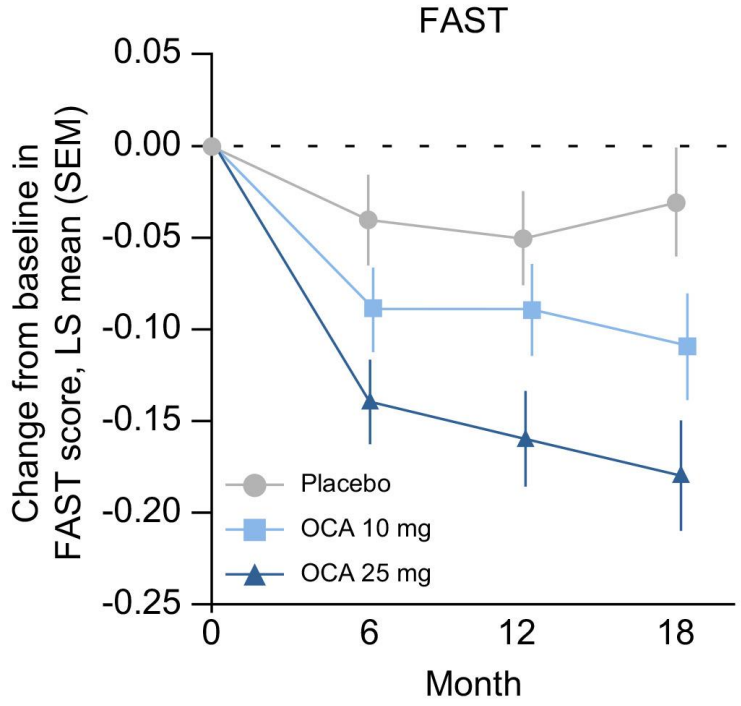
NITs to assess treatment response



Placebo	131	106	103	91
OCA 10 mg	166	134	136	111
OCA 25 mg	133	110	95	86



Placebo	129	104	102	89
OCA 10 mg	155	134	134	111
OCA 25 mg	131	109	93	85



Placebo	100	83	80	68
OCA 10 mg	107	92	86	73
OCA 25 mg	103	90	76	61

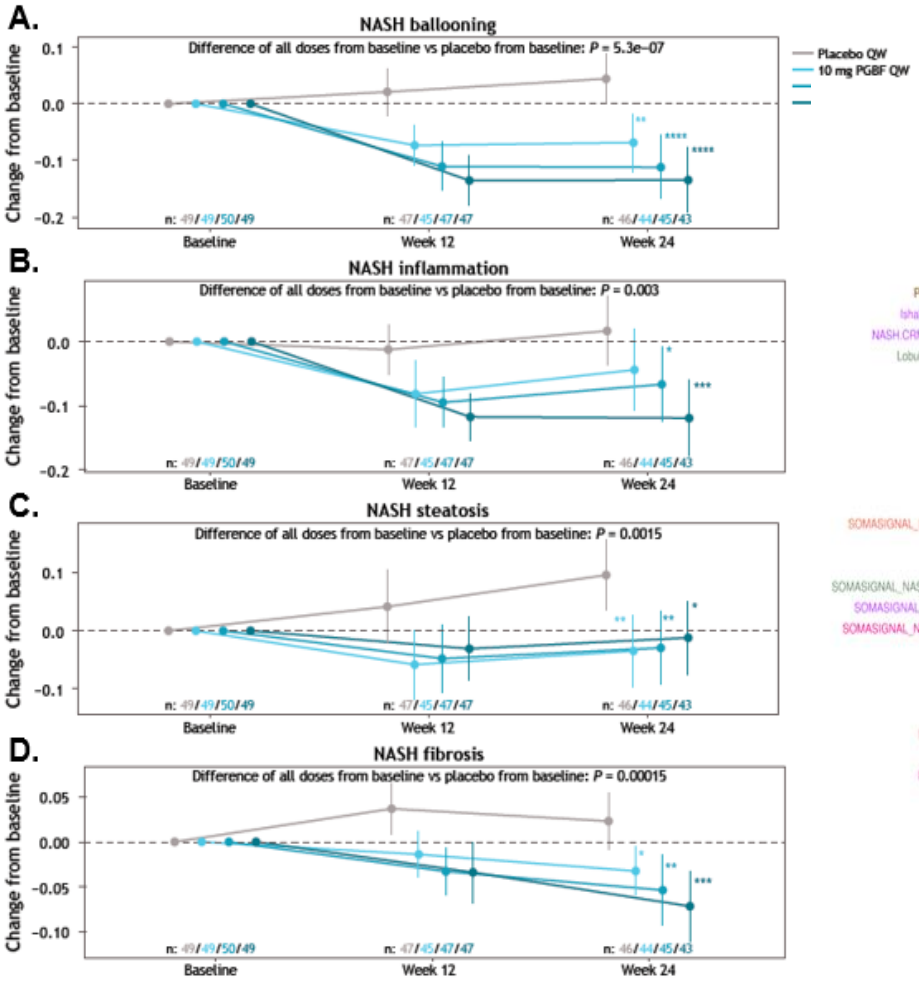
Rinella et al, J Hepatology, 2022, 76: 536-548

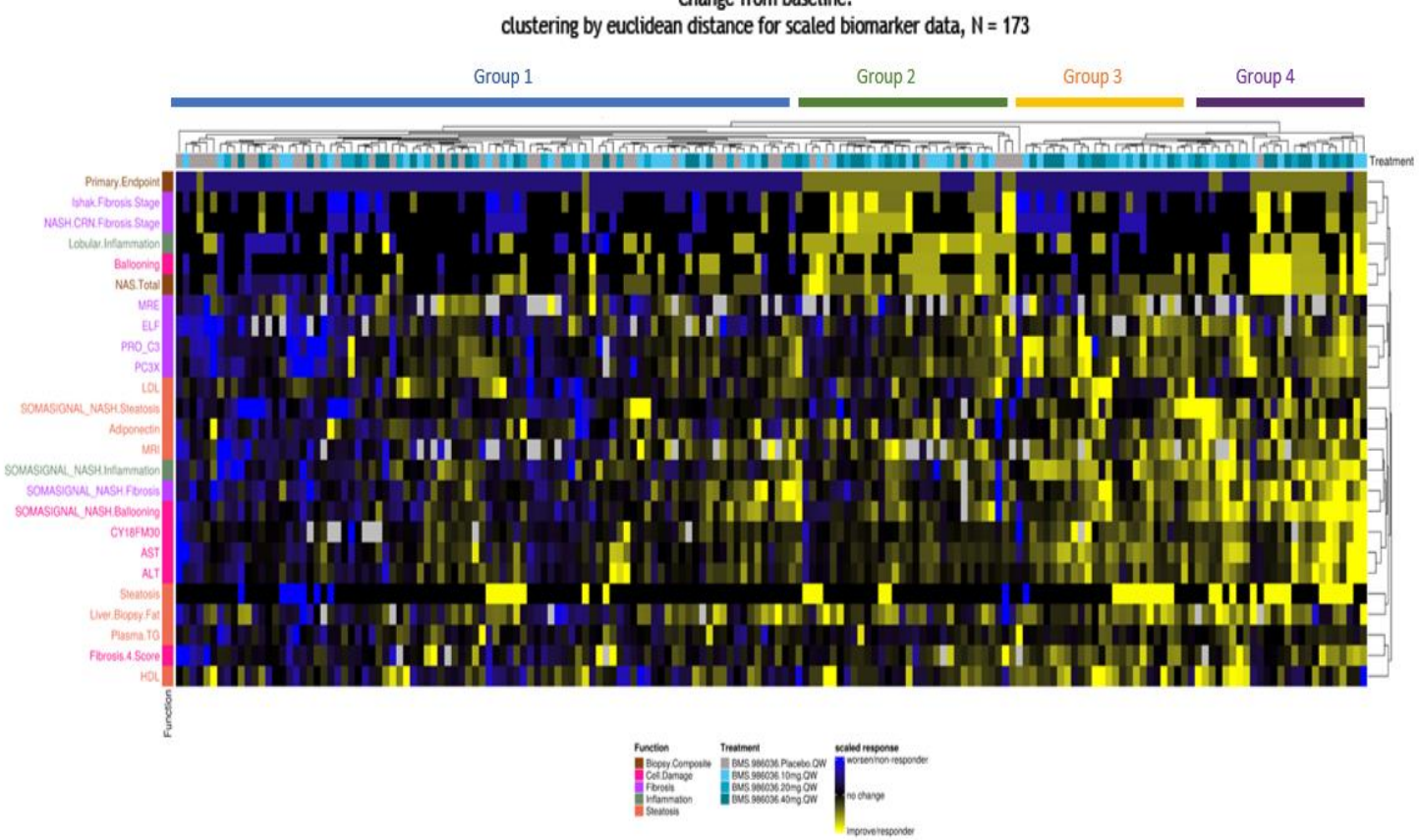
VCTE to Monitor Response to Therapy

Drug	Study Duration	Treatment groups	Fibrosis Improvement	VCTE change from baseline
Pegozafermin	24 weeks	15 mg	22%	-1.4
		30 mg	26%	-3.1
		44 mg	27%	-2.4
		Placebo	7%	0.8
Selonsertib	48 weeks	6 mg	14%	-0.3
		18 mg	13%	-1.3
		Placebo	17%	-0.7
Efruxifermin	24 weeks	28 mg	39%	-4.3
		50 mg	41%	-2.6
		Placebo	20%	-0.7

Integrated assessment of treatment response in trials provide greater certainty

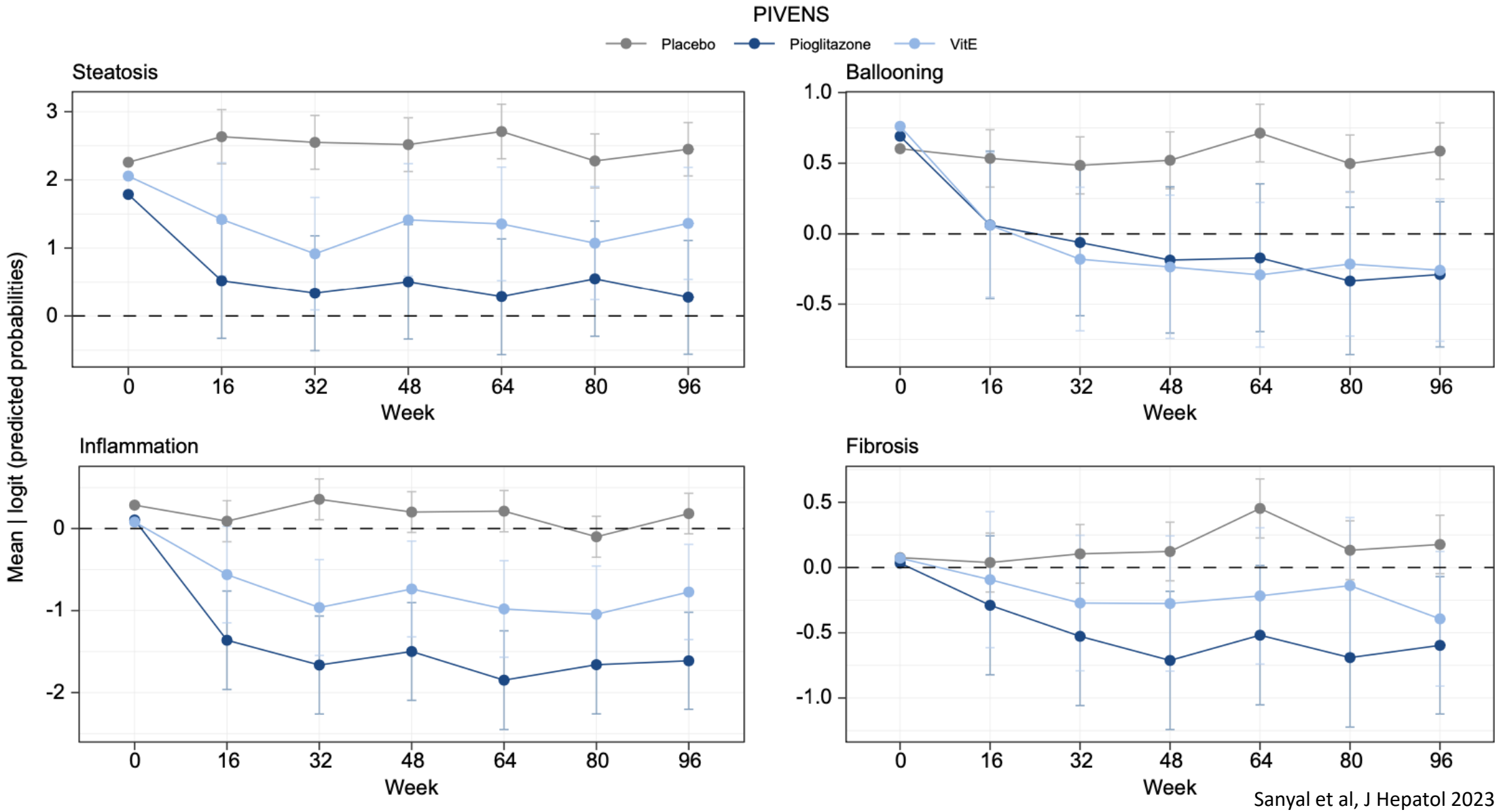
Somascan panel





Brown et al, J Hep Rep 2023; 5:100661

Disease monitoring and treatment response contexts of use: Predictions of protein models in longitudinal serum samples

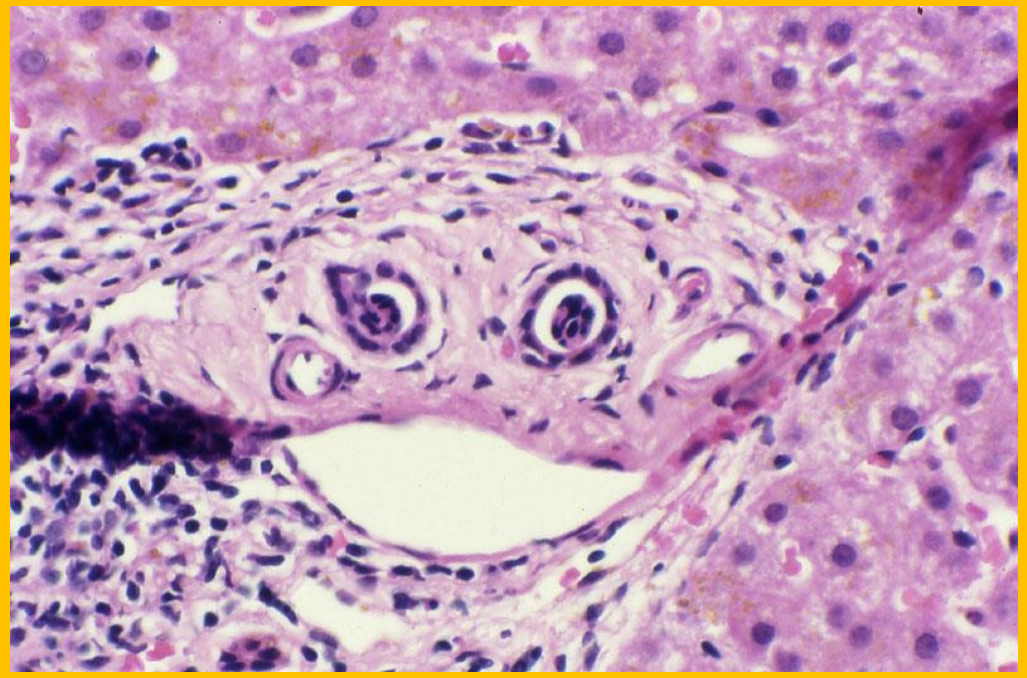


Sanyal et al, J Hepatol 2023

Summary

- There have been substantial advances in the development of NITs for the management of MASLD
- The greatest advances have been in the diagnostic and prognostic assessment of MASLD
- Emerging data indicate that several NITs are particularly suitable for monitoring treatment response
- Elastography is emerging as a leading approach to monitor and assess treatment response
- New label language for resmetirom, approved by FDA, does not mandate a biopsy to either identify who to treat or to monitor response

THANK YOU



Stravitz-Sanyal Institute for Liver Disease and Metabolic Health
VCU