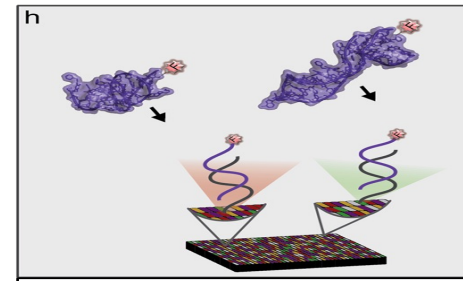
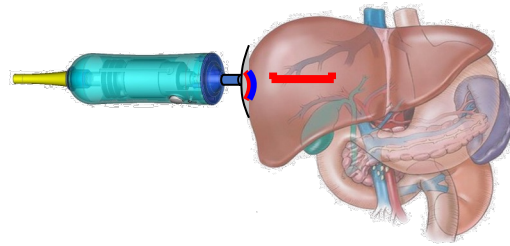




UNMET NEEDS IN NON-INVASIVE TEST DEVELOPMENT FOR NASH- FOCUS ON CIRRHOSIS



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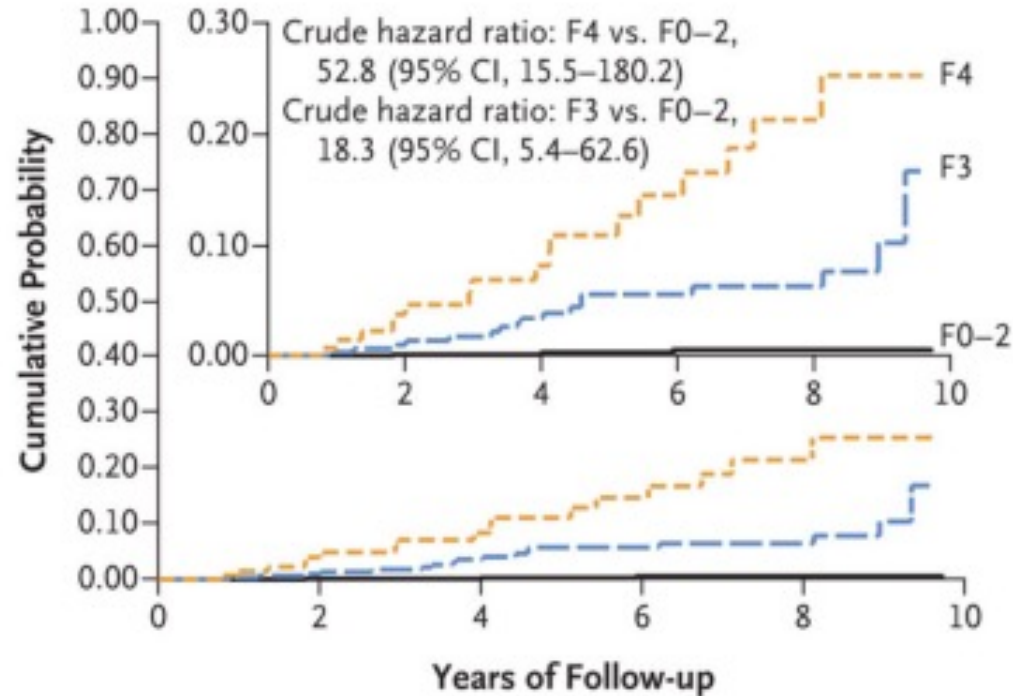
Disclosures

Arun J. Sanyal

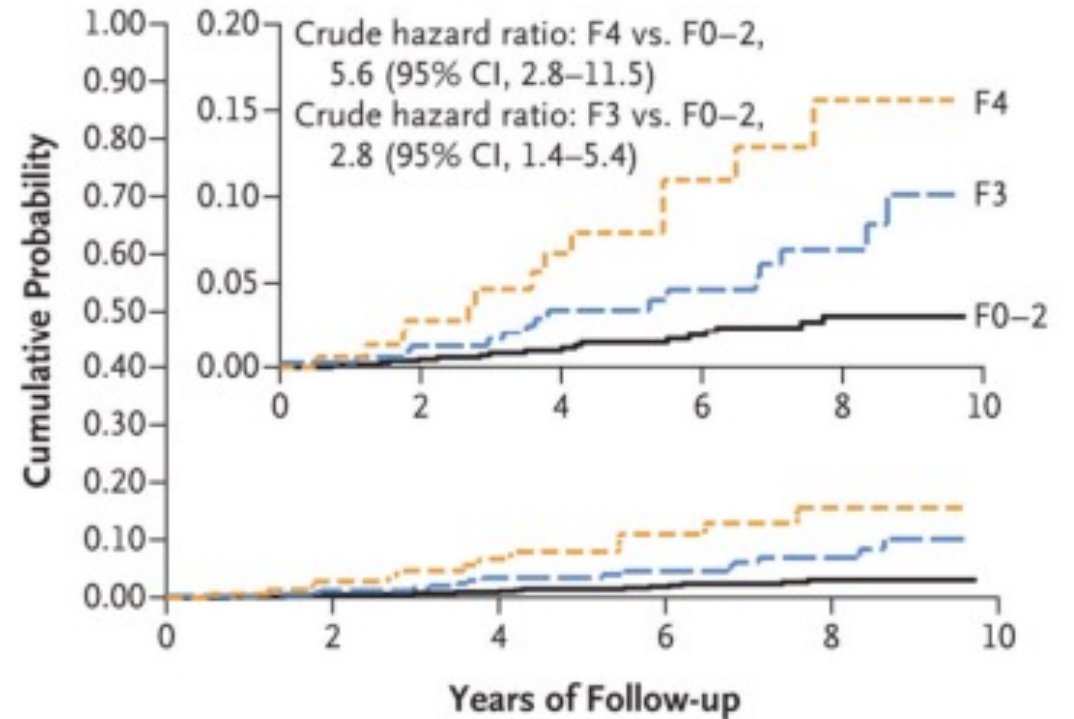
- I disclose the following financial relationship(s) with a commercial interest:
- Stock options for Genfit, Tiziana, Indalo, Durect, Exhalenz, Galmed
- Consultant- Gilead, Intercept, Allergan, Lilly, Novo Nordisk, Astra Zeneca-Medimmune, Novartis, Pfizer, Genentech, Merck, Bristol Myers, Boehringer Ingelhiem, Immuron, Siemens, Echosense, GE, Birdrock, Tern, Sundise, IFMO, Lipocine, Innovate, Zydus, AMRA, Hemoshear,
- Grant support: Bristol Myers, Intercept, Gilead, Allergan, Merck, Echosense, Novartis, Boehringer Ingelhiem, Viking, Novo Nordisk, Pfizer, Merck, Lilly

Both the incidence of hepatic and nonhepatic outcomes increase with increasing fibrosis stage

Hepatic Decompensation Events

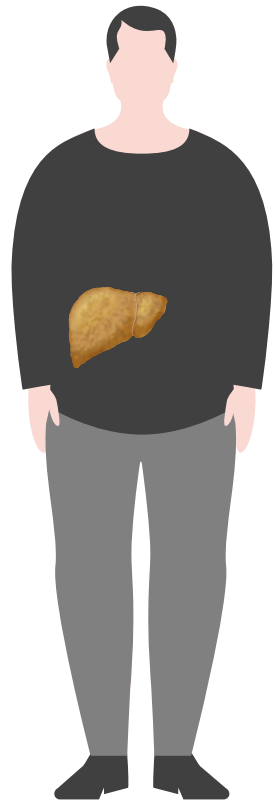


Death from Any Cause

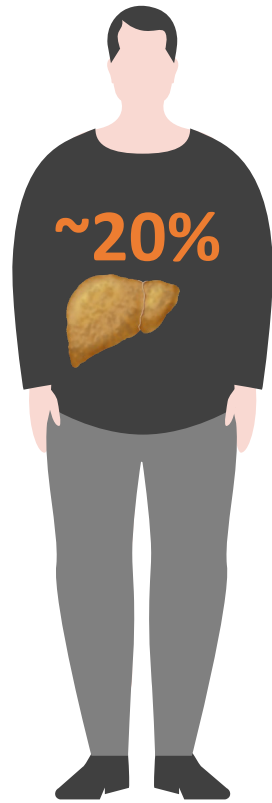


Mortality in stages 0-2 are not liver related

Defining the need for a diagnostic/prognostic test for NASH



NAFLD
~90M (2021)



NASH
~18M (2021)

~20–30% advanced
fibrosis/cirrhosis in hepatology
clinics

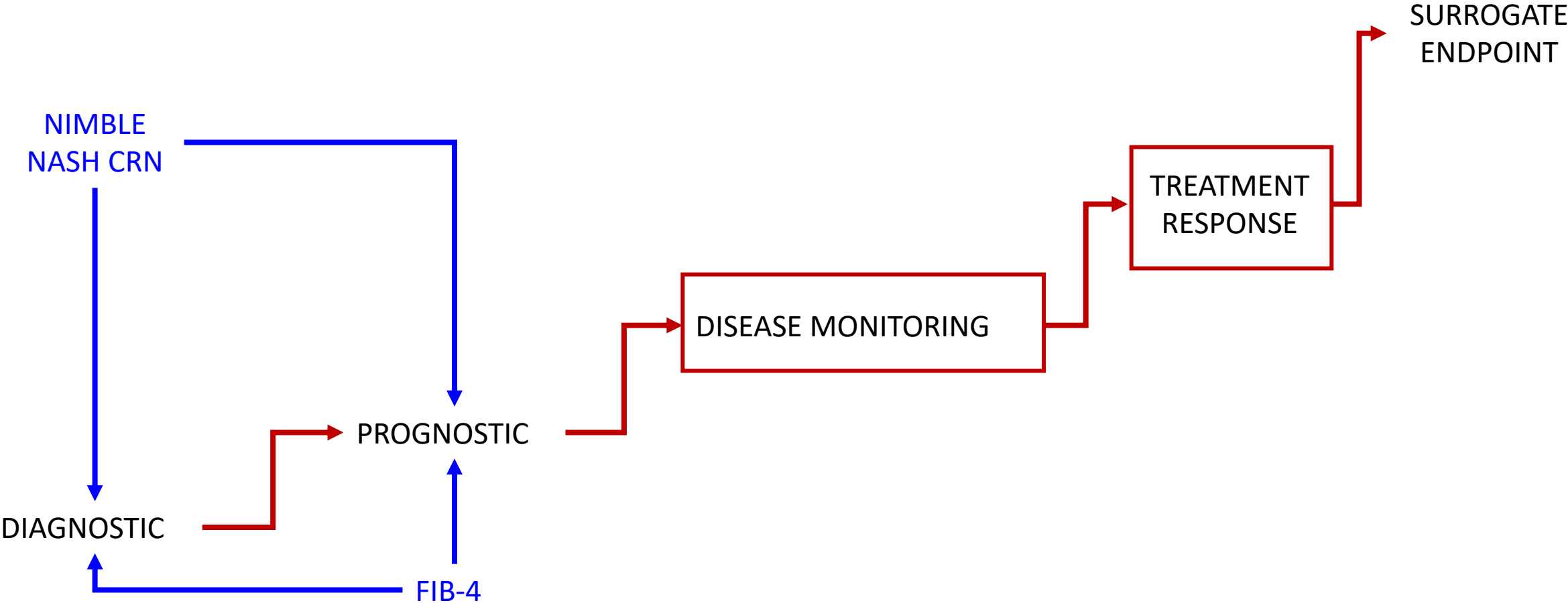
An illustration of three healthcare providers (two men and one woman) standing behind a light blue text box. The text box contains statistics about hepatologists and advanced fibrosis patients.

~824 Hepatologists:
~4,369 – 7,281 Advanced
fibrosis patients/provider

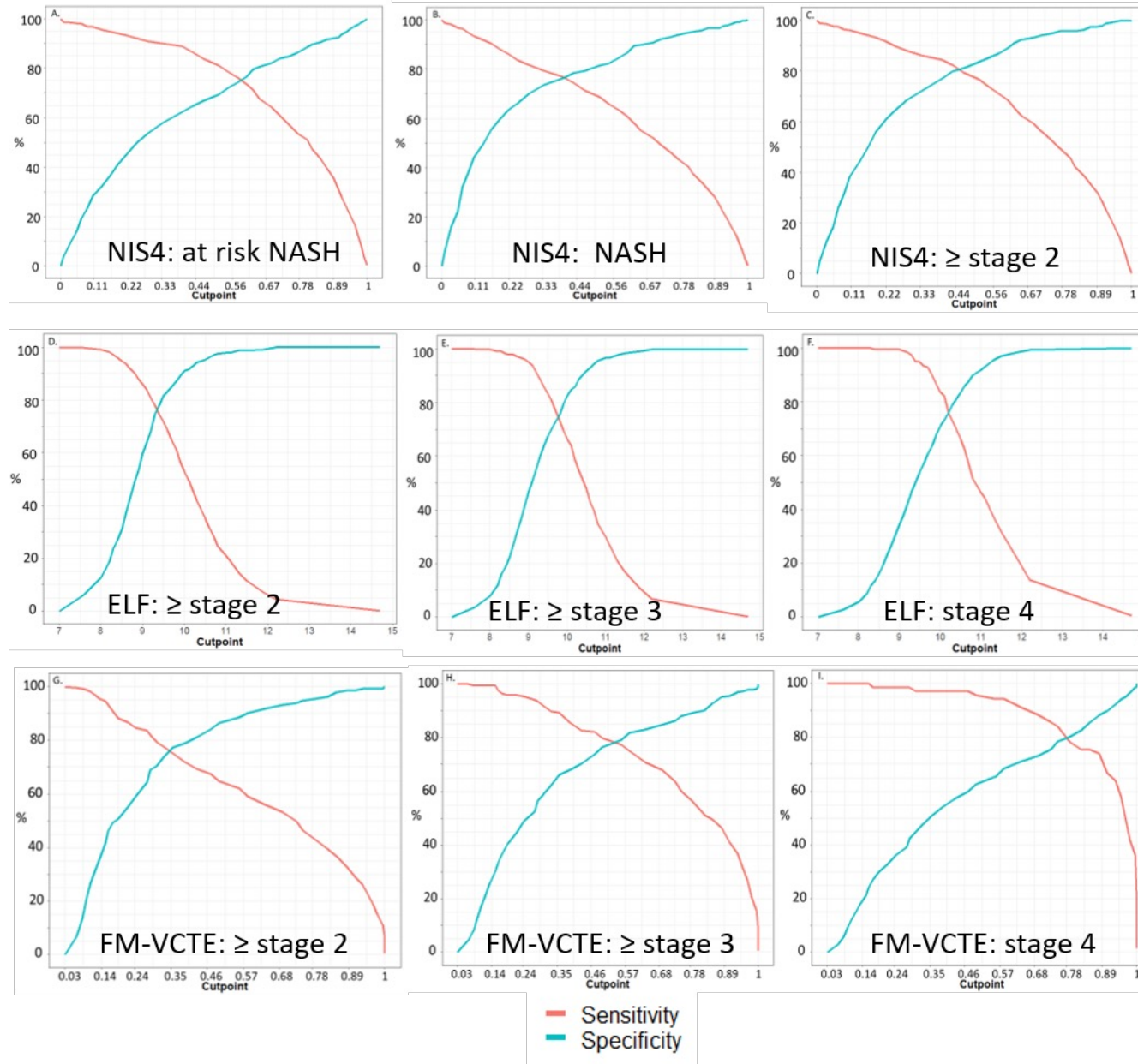
How do you identify those
requiring prognostic assessment?

- Sanyal AJ, et al. Hepatol. 2019;70(6):1913-27; Russo MW, et al. Hepatology 2020;72(4):1444-54.

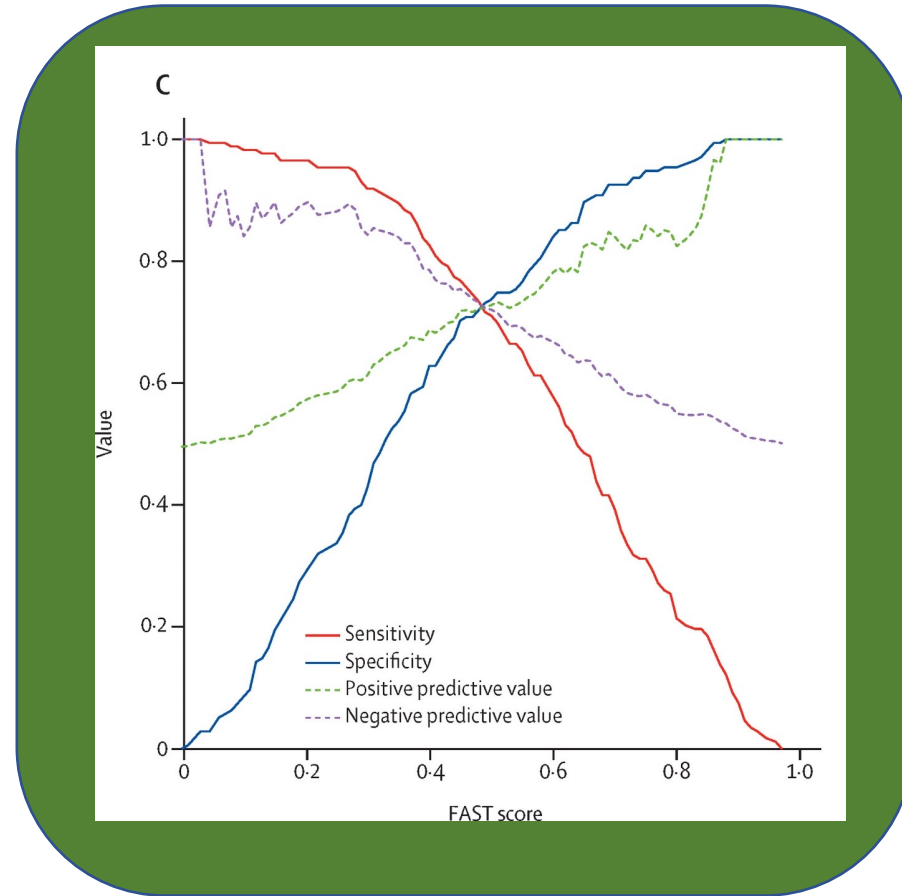
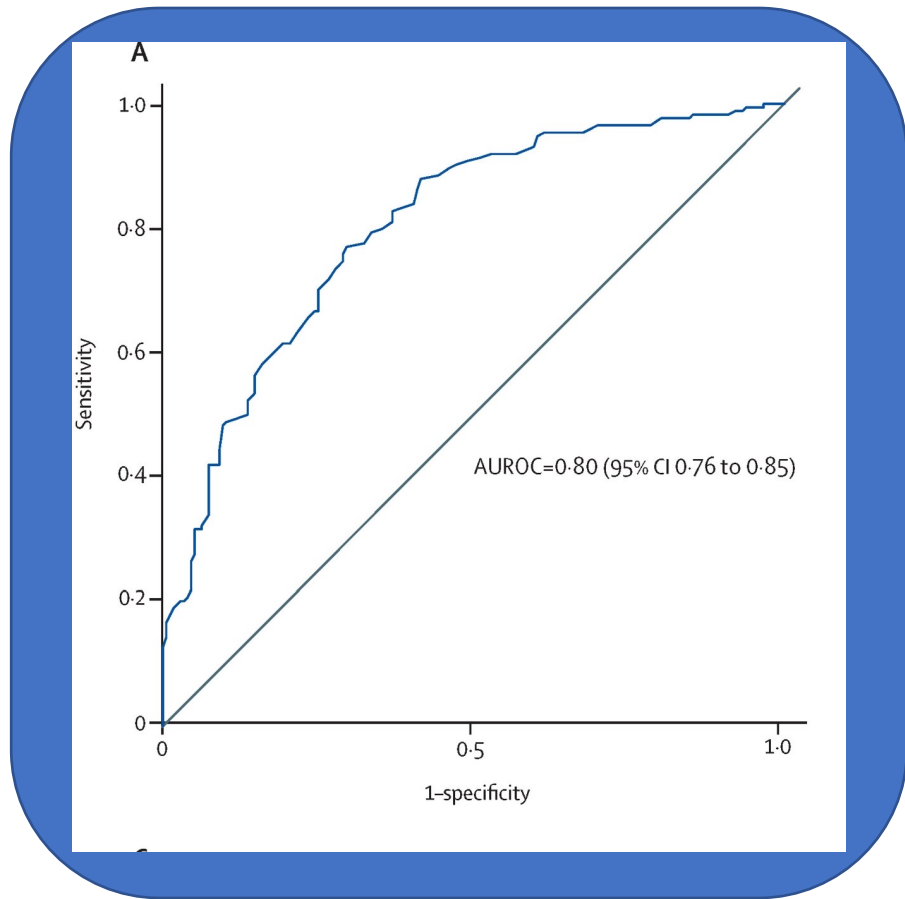
NONINVASIVE TEST DEVELOPMENT FOR NASH



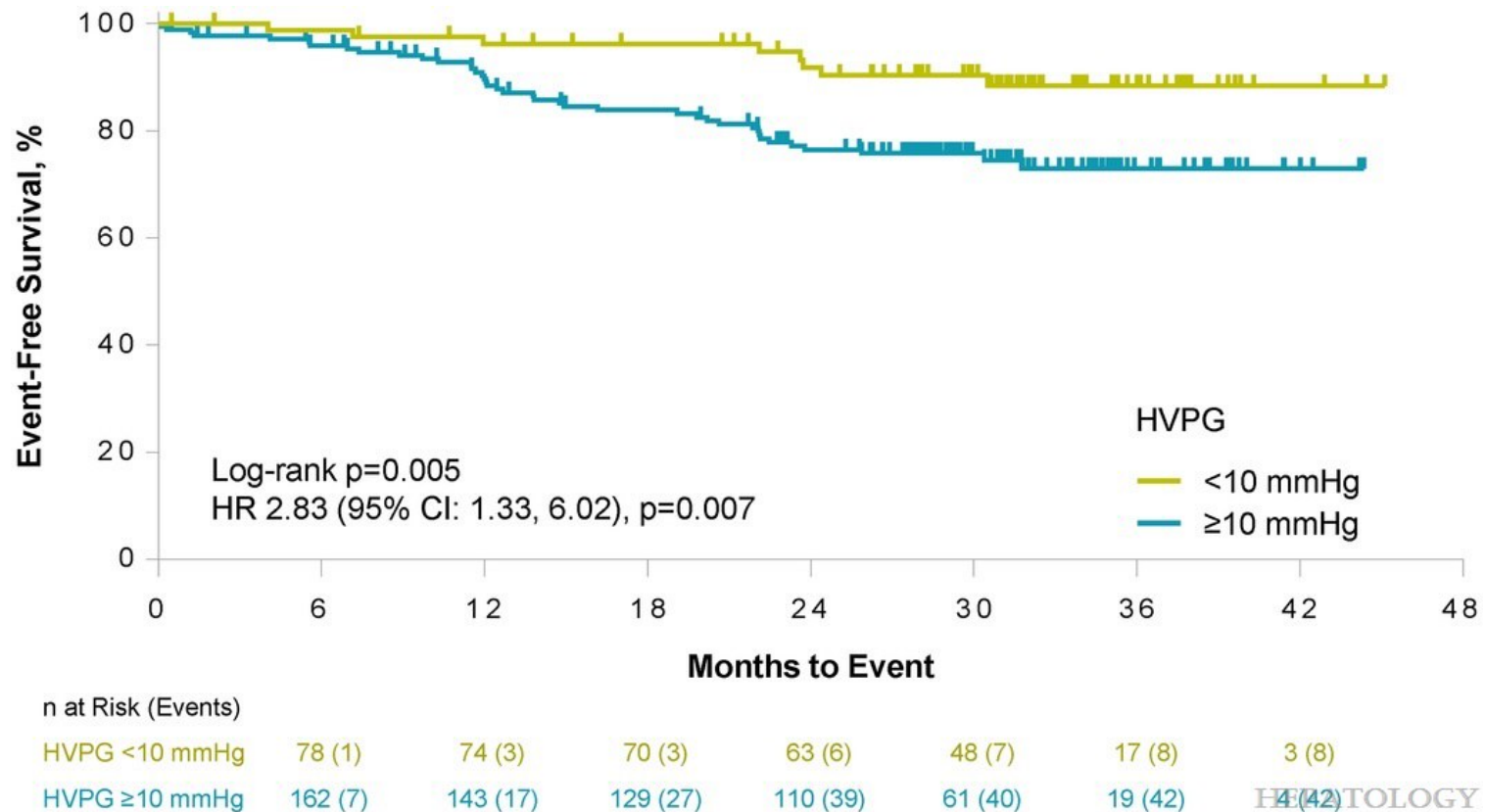
NIMBLE- performance of biomarkers for NASH



Fibroscan-AST score for at risk NASH



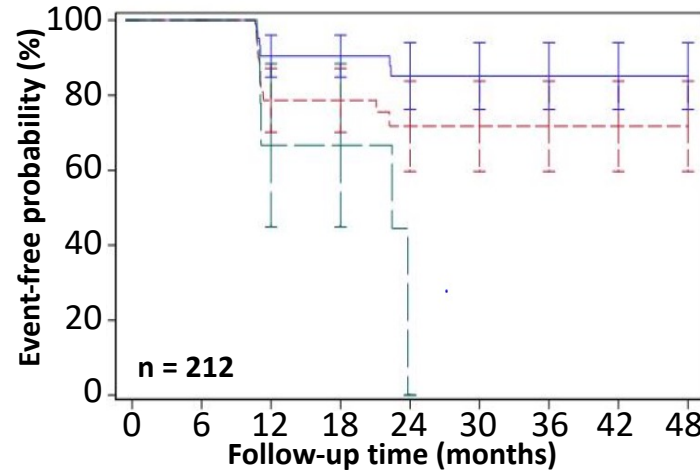
HVPG- a critical determinant of outcomes in NASH



ELF Test: Clinical performance claims in label

F3 (Bridging Fibrosis)

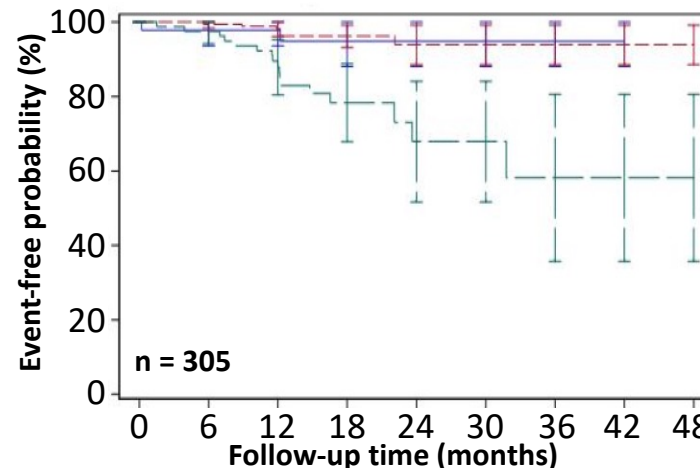
Progression to Cirrhosis				
Score	n	Events	Risk	Hazard Ratio
<9.80	105	12	11.4%	1.00
≥9.80 to <11.30	89	21	23.6%	2.30
≥11.30	18	8	44.4%	4.58



Data pooled from placebo arms of 2 clinical trials (SIM F3, STELLAR-3)

F4 (Compensated Cirrhosis)

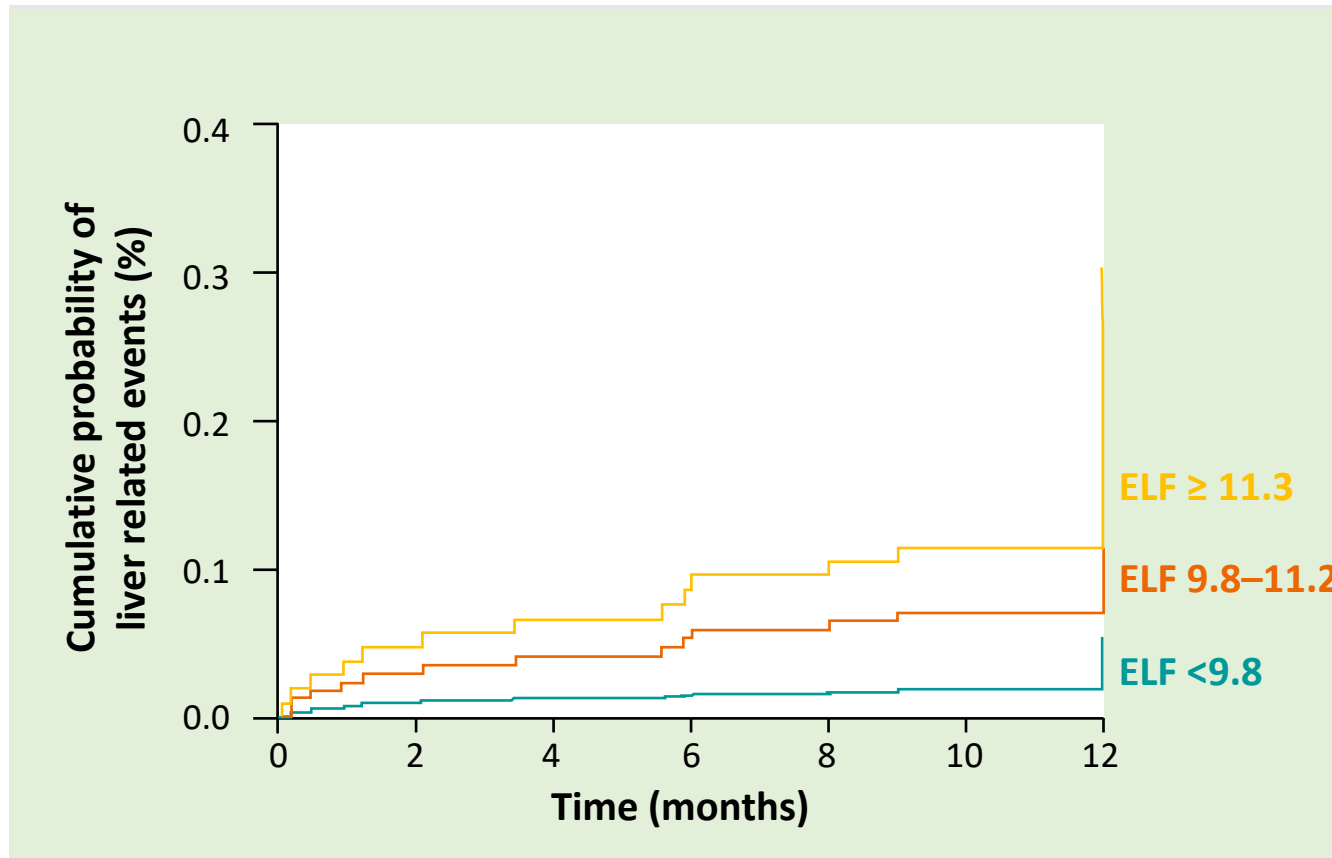
Progression to Liver Related Events				
Score	n	Events	Risk	Hazard Ratio
<9.80	47	2	4.3%	1.00
≥9.80 to <11.30	177	7	4.0%	0.93
≥11.30	81	17	21.0%	5.84



Data pooled from placebo arms of 3 clinical trials (SIM F4, STELLAR-4, NASH-CX)

Patient impact analysis (II)- ELF test predicts liver events

ELF at baseline



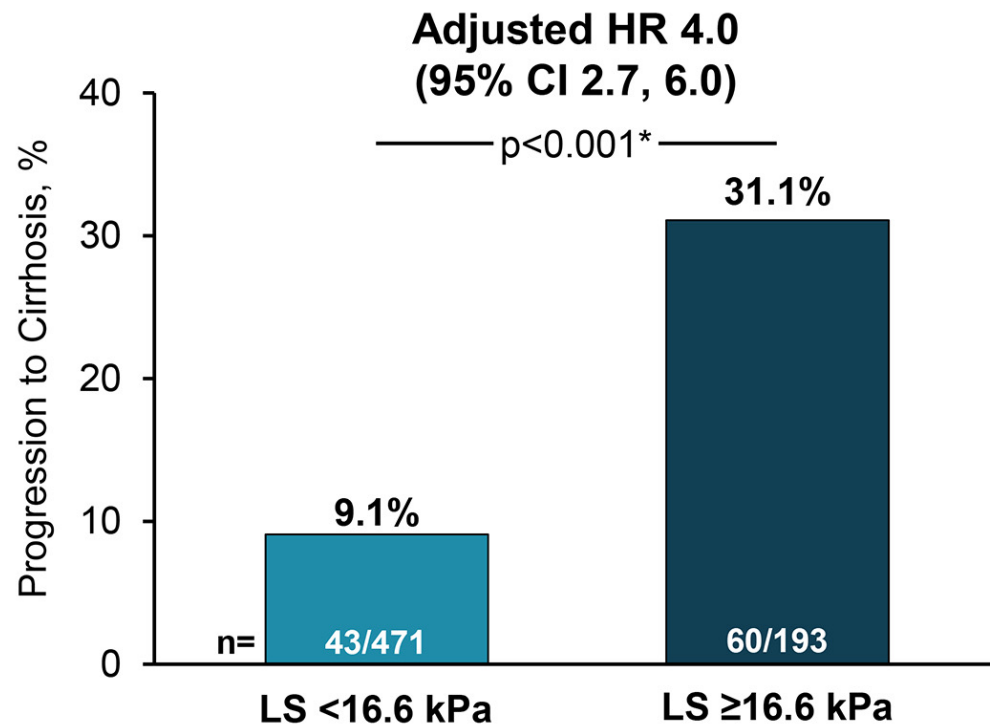
ELF can indicate near-term risk!

ELF score	Absolute risk	Likelihood ratio	Hazard ratio
≥ 11.3	32.7	1.88	4.81
9.8–11.2	16.9	0.79	1.46
< 9.8	10.5	0.46	1.00

• Are VS, et al. Clin Gastro Hepatol. 2021;19:1292-3 e3.
4/1/23

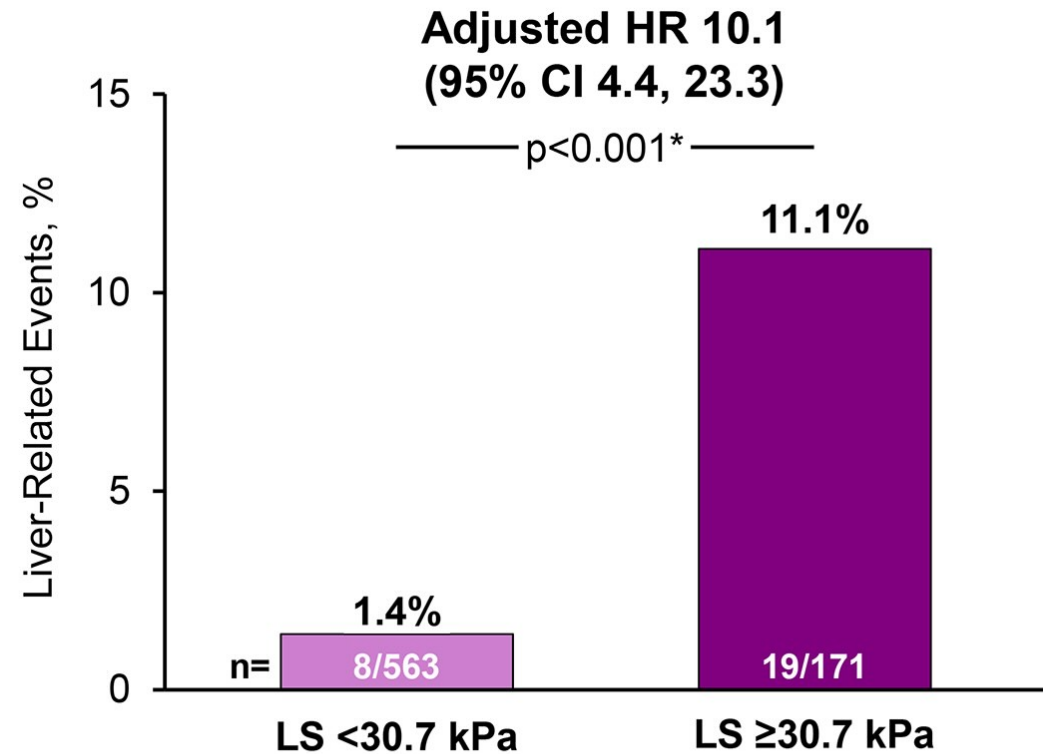
• Data from the placebo arm of this study are included in the pooled study analysis in the U.S. Instructions for Use.

Liver stiffness has prognostic value in NASH



*Fisher exact test.

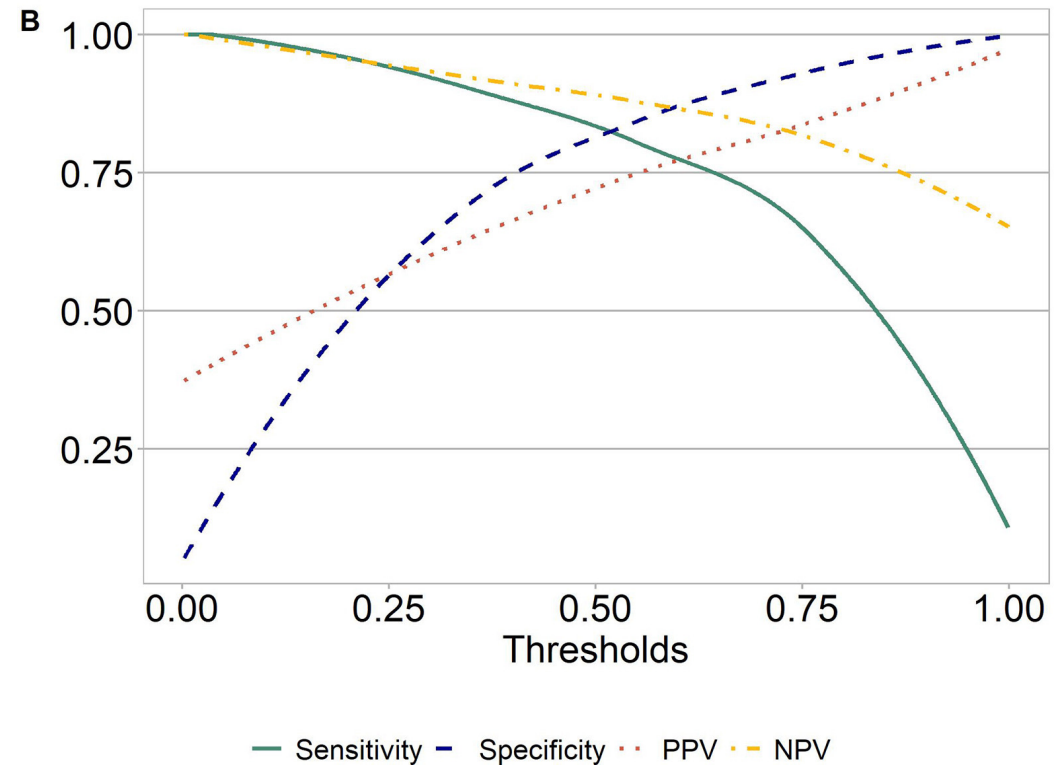
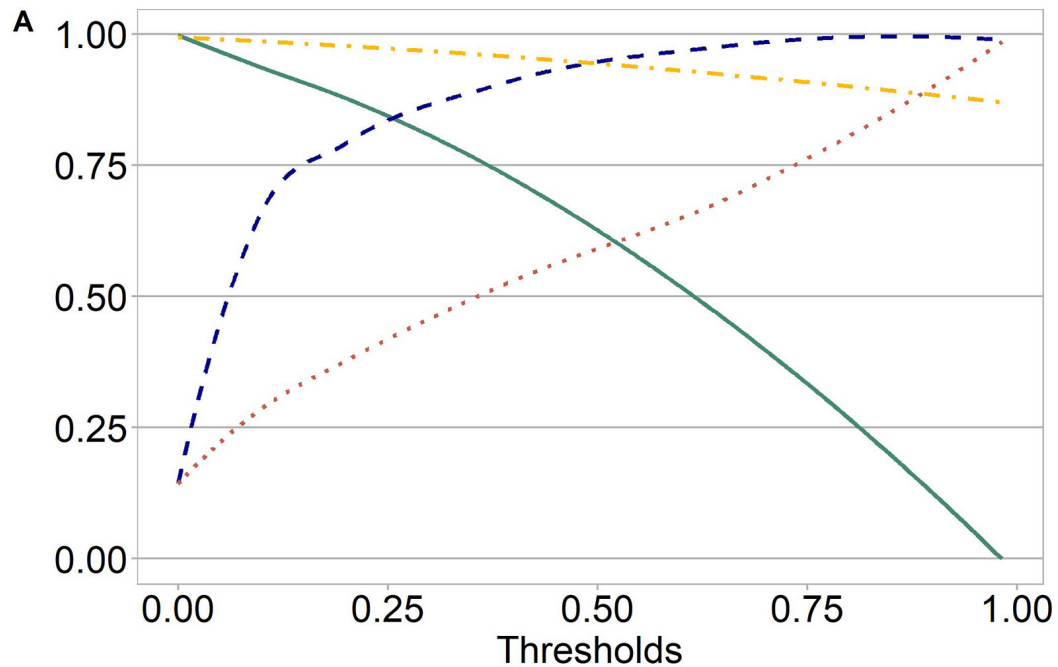
Baseline bridging fibrosis



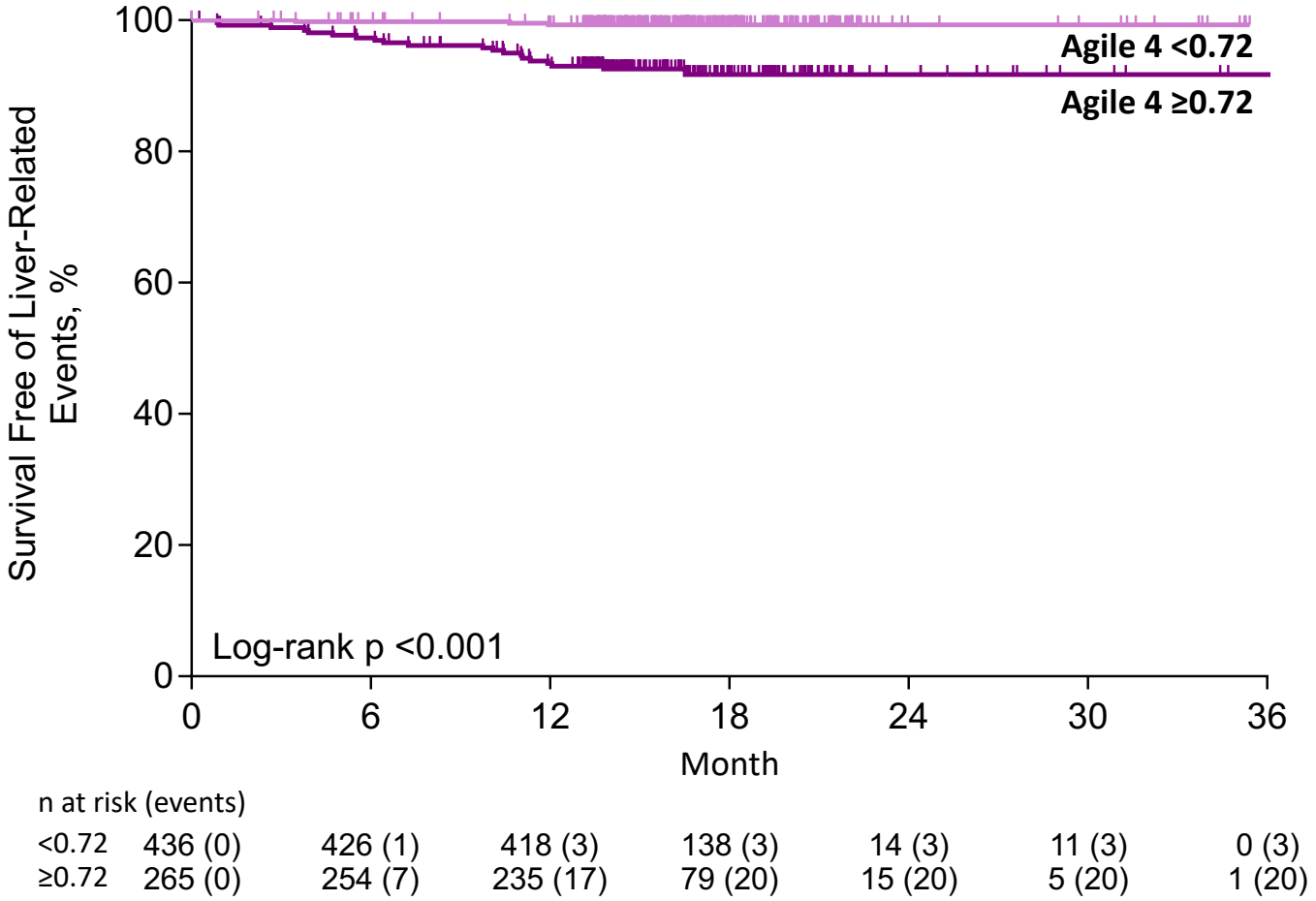
*Fisher exact test.

Baseline cirrhosis

Agile 4 score for the diagnosis of cirrhosis

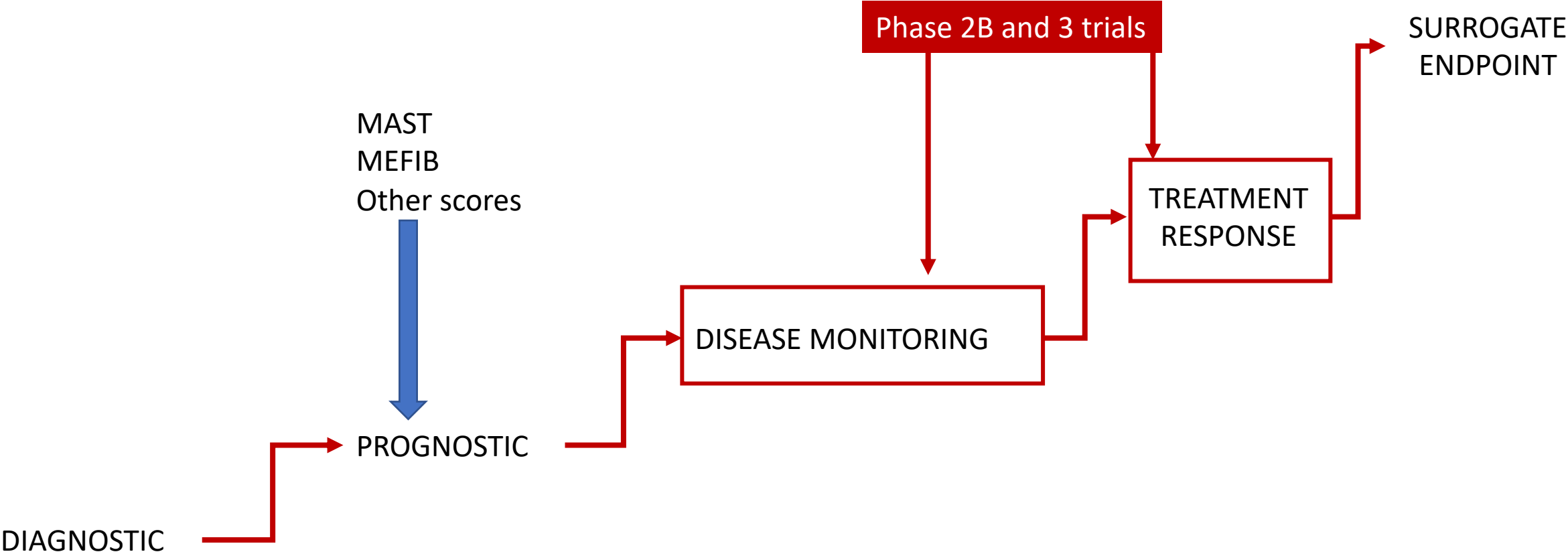


Survival Free of Liver-Related Events: Agile 4 Score



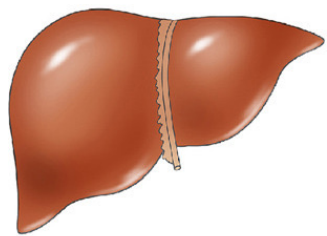
Diagnostic Performance of BL Agile 4 to Predict Liver-Related Events	
Optimal threshold	≥0.72
Sensitivity, % (n/n)	87 (20/23)
Specificity, % (n/n)	64 (433/678)
PPV, % (n/n)	8 (20/265)
NPV, % (n/n)	99 (433/436)

UNMET NEEDS IN NONINVASIVE TEST DEVELOPMENT

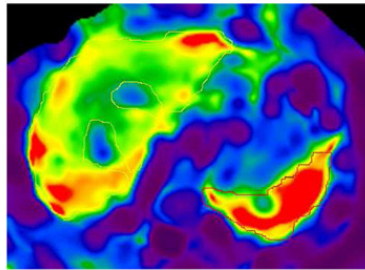


MR elastography can predict future decompensation and mortality risk

Liver Stiffness by Magnetic Resonance Elastography Predicts Future Cirrhosis, Decompensation and Death in NAFLD

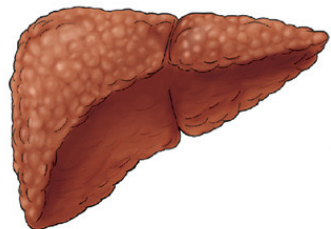
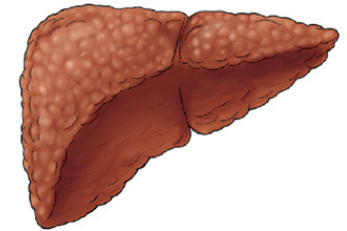


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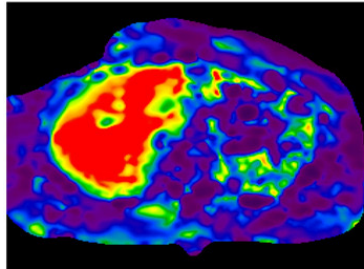


For each 1 kPa increase in liver stiffness by MRE, non-cirrhotic NAFLD subjects are 3 times more likely to develop cirrhosis in the future.

Adjusted HR=2.93 (95% CI, 1.86-4.62, p<0.0001) per 1 kPa

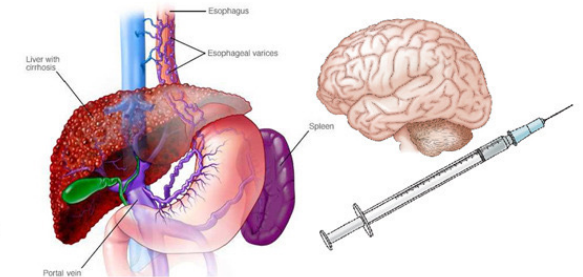


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For each 1 kPa increase in liver stiffness by MRE, subjects with NASH cirrhosis are 32% more likely to develop decompensation and/or die in 5 years.

Adjusted HR for age, sex and MELD-Na =1.32 (95%CI 1.13-1.56, p=0.0007)



Clinical Gastroenterology and Hepatology

LiverMultiScan for identification of at-risk NASH

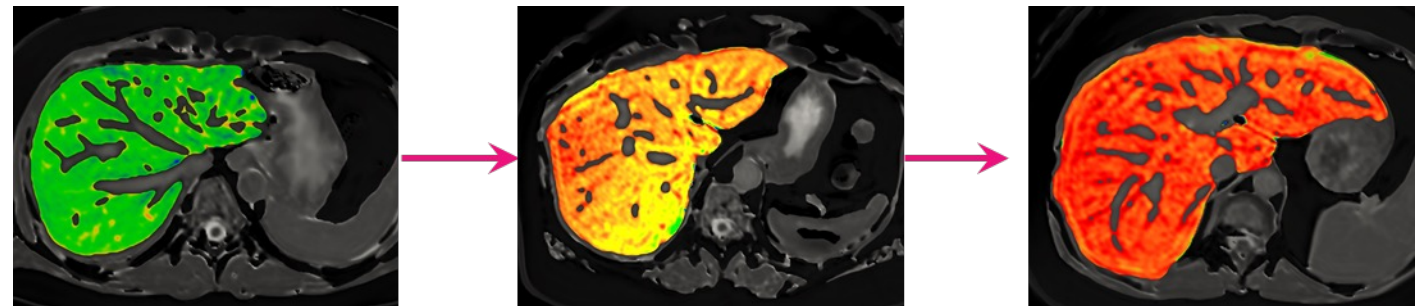
cT1 < 800ms
Not indicative of
NASH

cT1=800 to 875ms
Indicative of
NASH

cT1 ≥ 875ms
Indicative of NASH with
high risk of progression

Study population

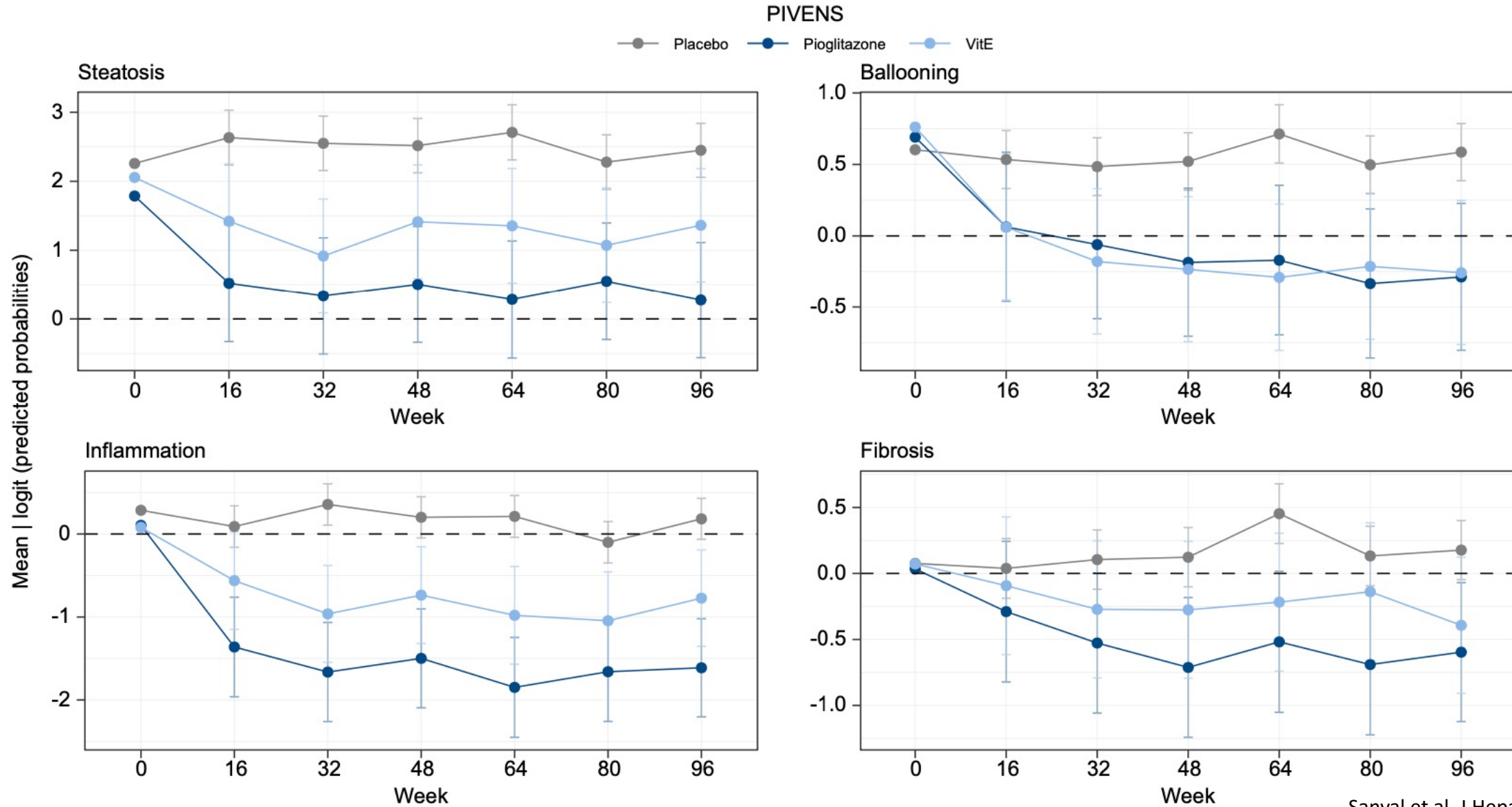
- n=543 NAFLD
- n=100 healthy
- Biopsy - NAS CRN



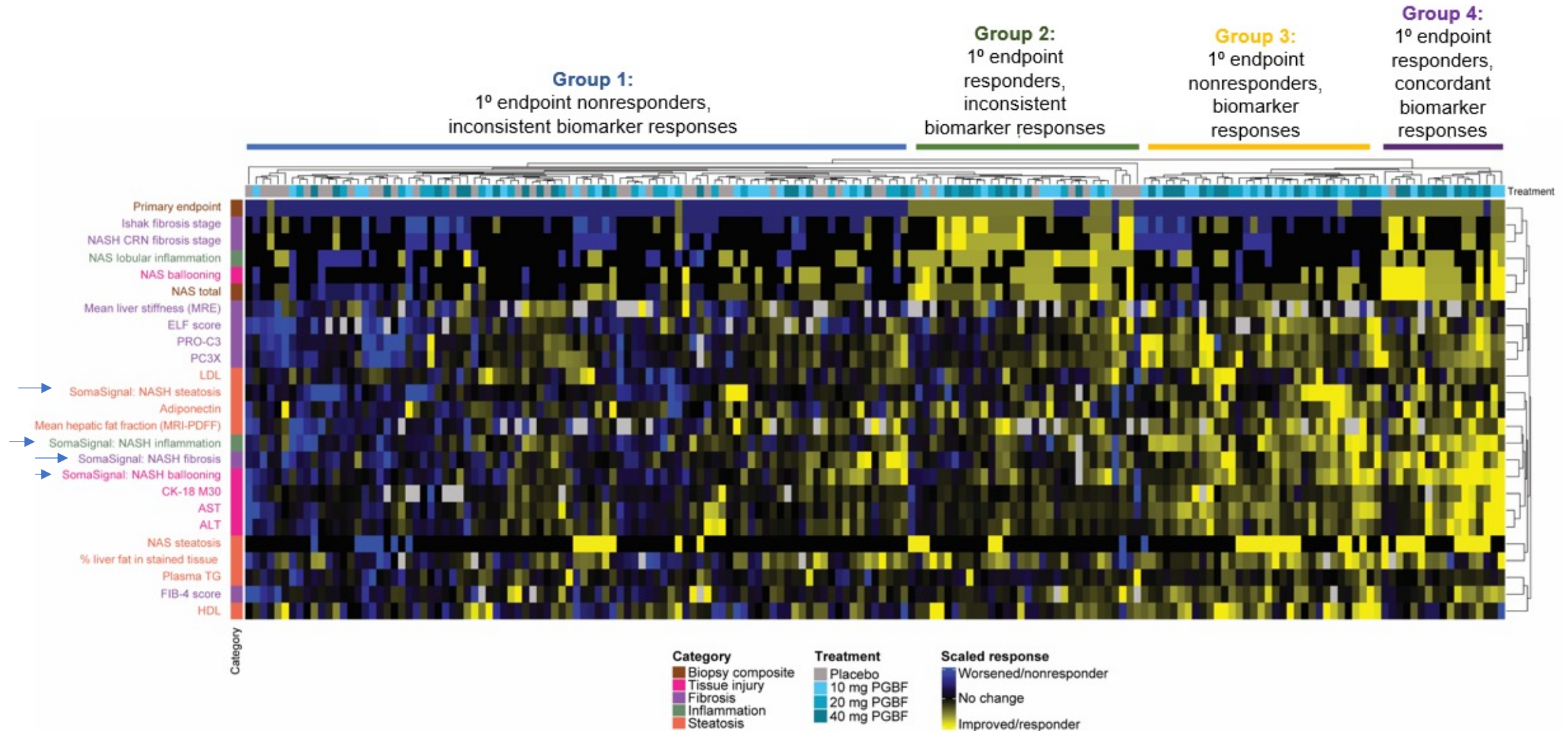
Study comprising the largest cohort of patients so far who had Liver*MultiScan* paired with biopsy showed that cT1 could accurately identify NASH patients at high risk of disease progression (AUC=0.78) and eligible for clinical trials.

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

DIVENS



Effect of pegbelfermin on noninvasive NASH and fibrosis biomarkers and correlation with histological response: a post hoc analysis of the FALCON 1 trial



SUMMARY

- NIT development is a very active area of research
- Multiple biomarker panels are moving towards qualification for diagnostic enrichment/diagnostic:
 - NIS4; NIS2
 - ADAPT
 - FAST
 - ELF
- ELF is approved as prognostic NIT
- Additional NITs show prognostic utility and early data support use of NITs for disease monitoring and treatment response
- These data can be used to further refine risk strata in those with compensated cirrhosis and potentially used to develop novel treatment paradigms