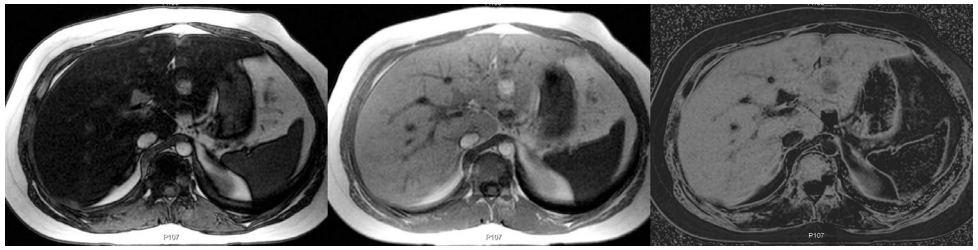
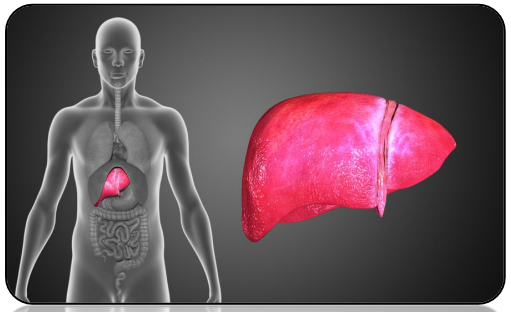
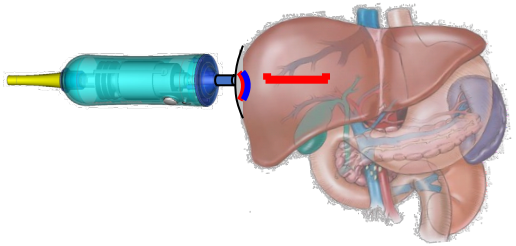
Making the case for NIT-based inclusion for NASH trials and assessment of progression to cirrhosis







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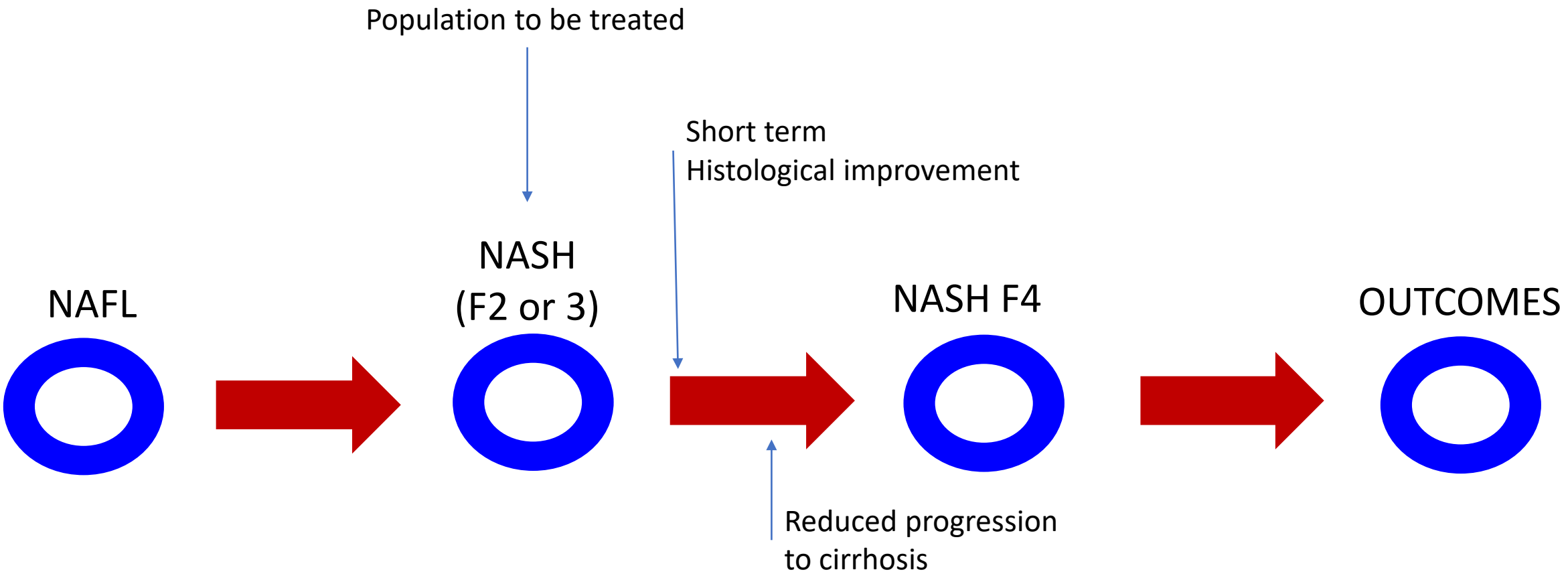
Disclosures

- Consultant- Gilead, Intercept, Novo Nordisk, Eli Lilly, Merck, Pfizer, Boehringer Ingelheim, Bristol Myers Squibb, Genfit, Genentech, Amgen, Regeneron, Galmed, Alnylam, Madrigal, Astra Zeneca, Avant Sante, Siemens, Blade, 89 Bio, Akero, NGM Bio, Rivus, Fortress, Foresite labs, Glympse, Hemoshear, Surrozen, Poxel, Tern, Fractyl, LG science, Zydus
- Grant support to institution: Gilead, Novo Nordisk, Pfizer, Merck, Galmed, Echosense, Siemens, Boehringer Ingelheim, Genentech, Akero, Hanmi, Intercept, Astra Zeneca, Fractyl, Madrigal, Zydus
- Stock options: Genfit, Exhalenz, Galmed, Tiziana, Durect

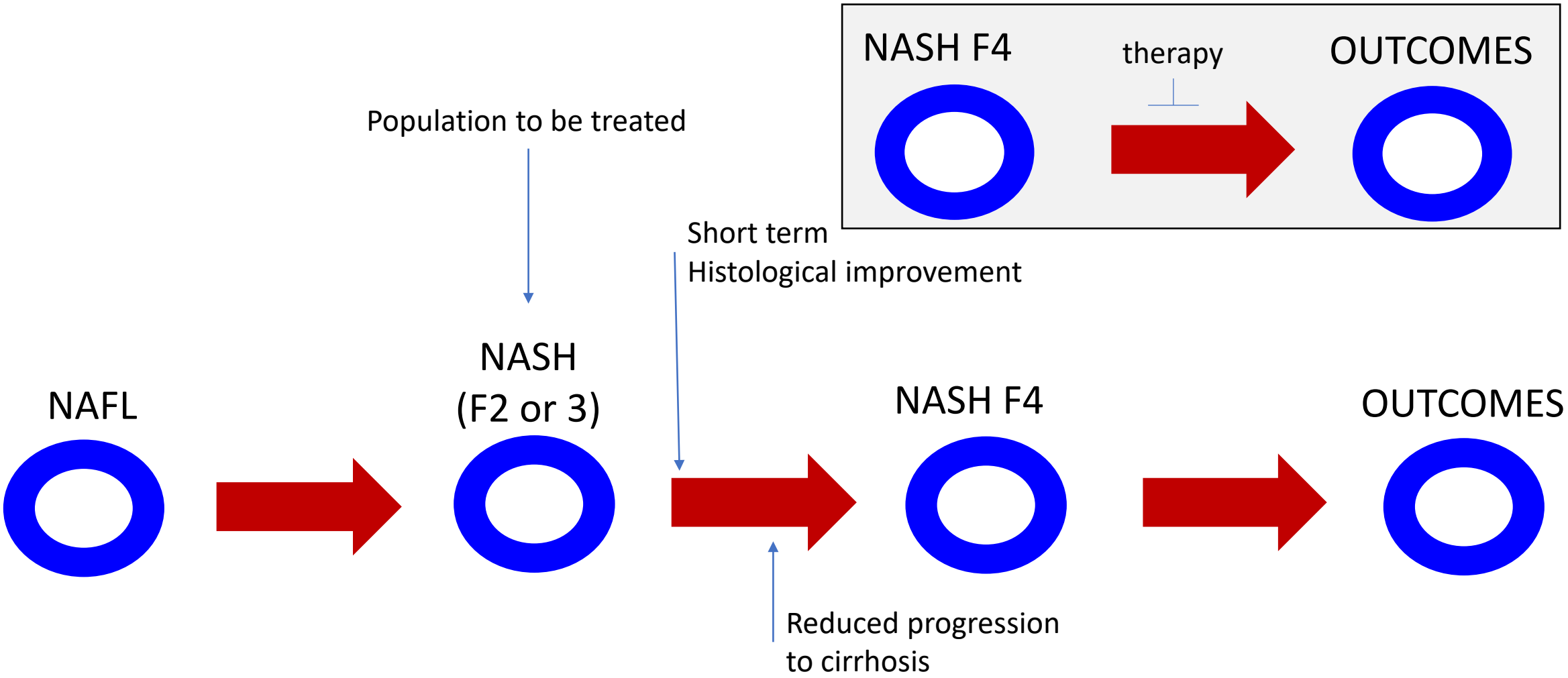
Current drug development pathway for NASH-subpart H



Long-term Goal: reduced outcomes

FDA draft guidance
EMA reflection document

Current drug development pathway for NASH- parallel development

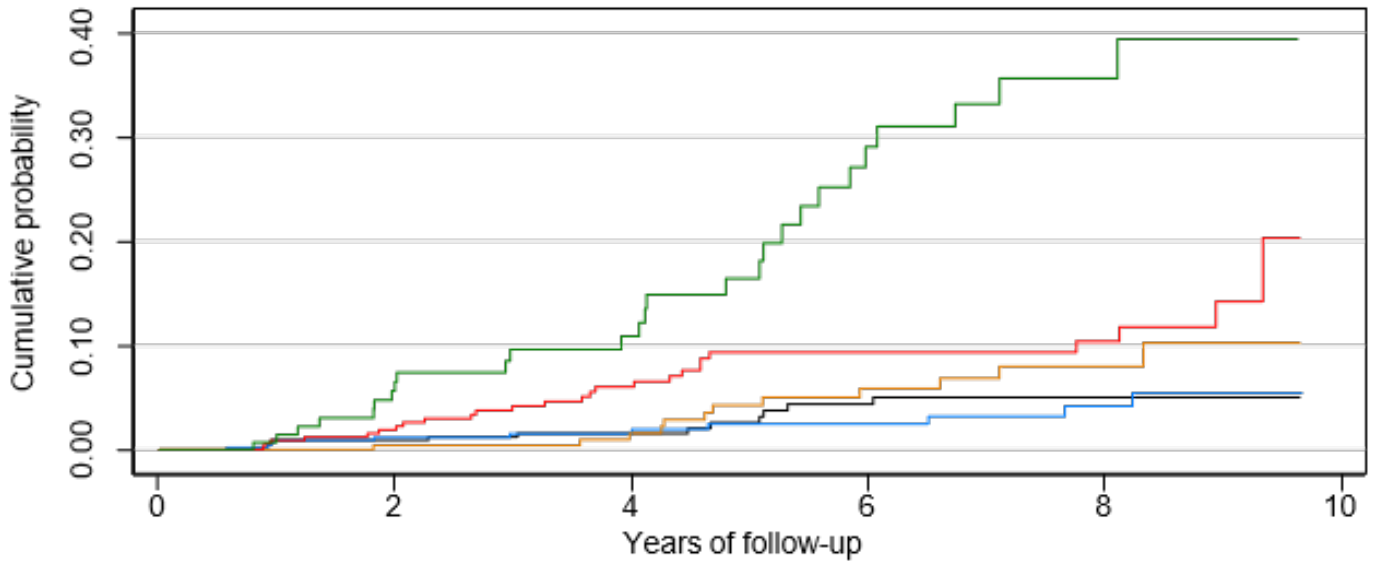


Long-term Goal: reduced outcomes

FDA draft guidance
EMA reflection document

Defining the population to treat

Advanced fibrosis (mainly cirrhosis) drives hepatic decompensation



No. at risk (Events)

F4	150	(7)	106	(5)	69	(11)	36	(3)	17	(1)	0
F3	359	(6)	274	(10)	185	(6)	127	(1)	70	(3)	0
F2	317	(1)	239	(2)	156	(6)	108	(2)	46	(1)	0
F1	448	(5)	346	(1)	223	(2)	146	(2)	82	(1)	0
F0	456	(4)	355	(2)	221	(5)	150	(1)	94	(0)	0

Crude RR(95% CI): F4 vs F0 = 8.1 (4.1, 15.9)
Crude RR(95% CI): F3 vs F0 = 2.7 (1.3, 5.3)
Crude RR(95% CI): F2 vs F0 = 1.5 (0.7, 2.1)
Crude RR(95% CI): F1 vs F0 = 0.9 (0.4, 2.1)

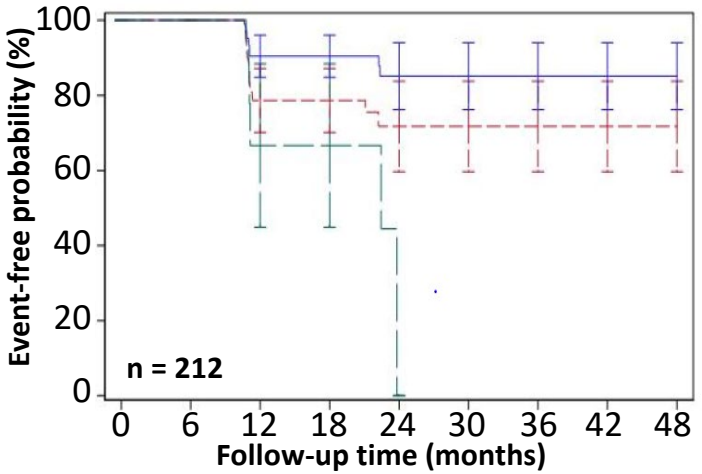
Sanyal et al, NEJM 2021

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

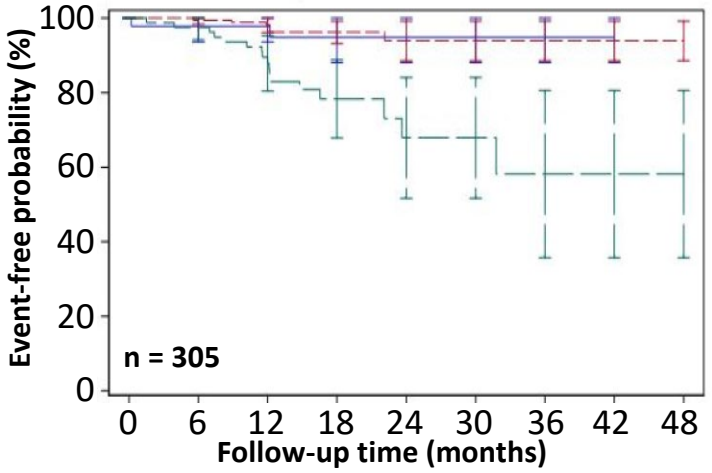


Data pooled from placebo arms of 2 clinical trials (SIM F3, STELLAR-3)

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



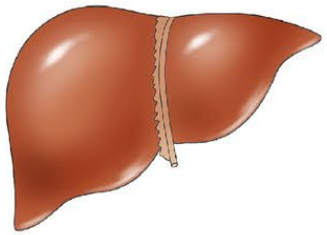
Data pooled from placebo arms of 3 clinical trials (SIM F4, STELLAR-4, NASH-CX)

ELF IFU 11205858_EN Rev. 01, 2021

See also: Sanyal AJ et al. Hepatology. 2019;70(6):1913–1927
Are VS et al. Clin Gastroenterol Hepatol. 2021;19(6):1292–1293.e3
Younossi ZM et al. Gastroenterology 2021;160:1608–1619.

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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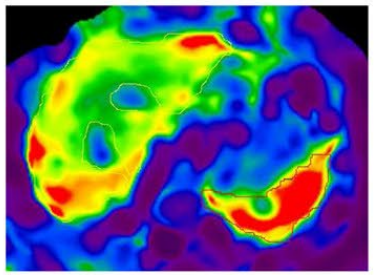
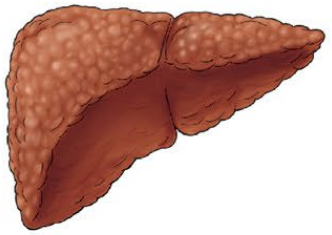
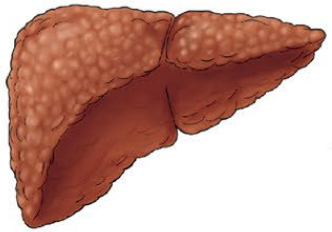


For each 1 kPa increase in liver stiffness by MRE, non-cirrhotic NAFLD subjects are 3 times more likely to develop cirrhosis in the future.

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





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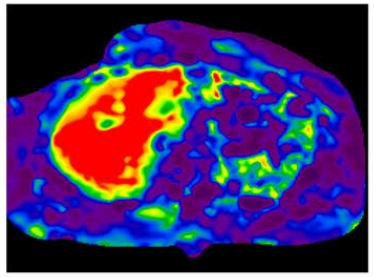
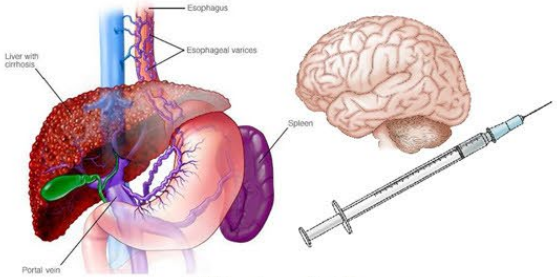


For each 1 kPa increase in liver stiffness by MRE, subjects with NASH cirrhosis are 32% more likely to develop decompensation and/or die in 5 years.

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



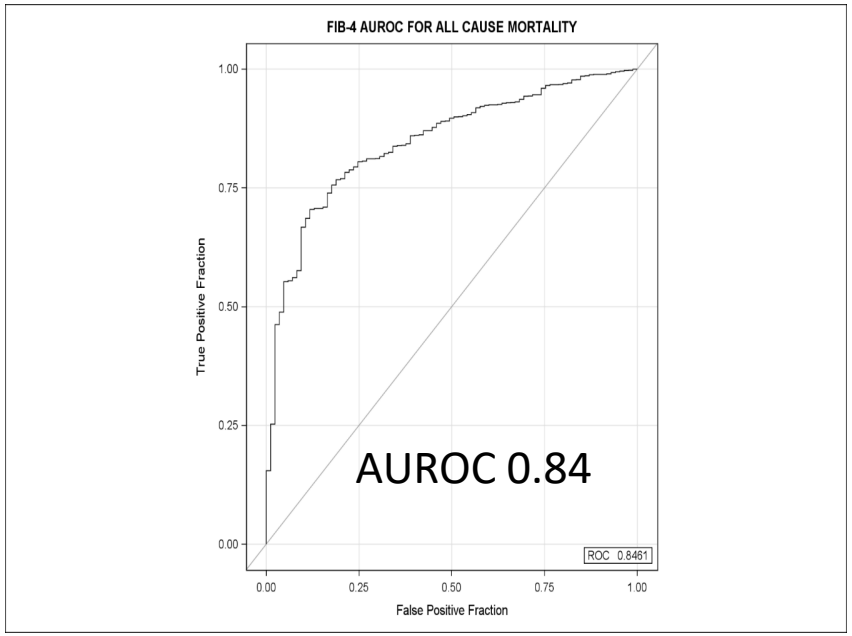
Clinical Gastroenterology and Hepatology

Gidener et al, CGH 2021 Sep;19(9):1915-1924.e6. doi: 10.1016/j.cgh.2020.09.044.

Prognosis can be identified by FIB4 test

Incidence rate (per 100 person years) by risk classification at baseline

	Included Using FIB4 and/or LSM Criteria		
Rate per 100 person yrs	Class A (n=554) Fib4<1.3	Class B (n=536) Fib4 1.31-2.6	Class C (n=846) Fib4 > 2.6
Deaths *	0.07	0.42	3.08
Liver events *	0.21	1.32	9.33
MACE *	0.83	1.60	2.54
HCC *	0	0.07	1.08



N= 2523 (median follow up 3 years)

Sanyal et al, AASLD 2020
MS under review

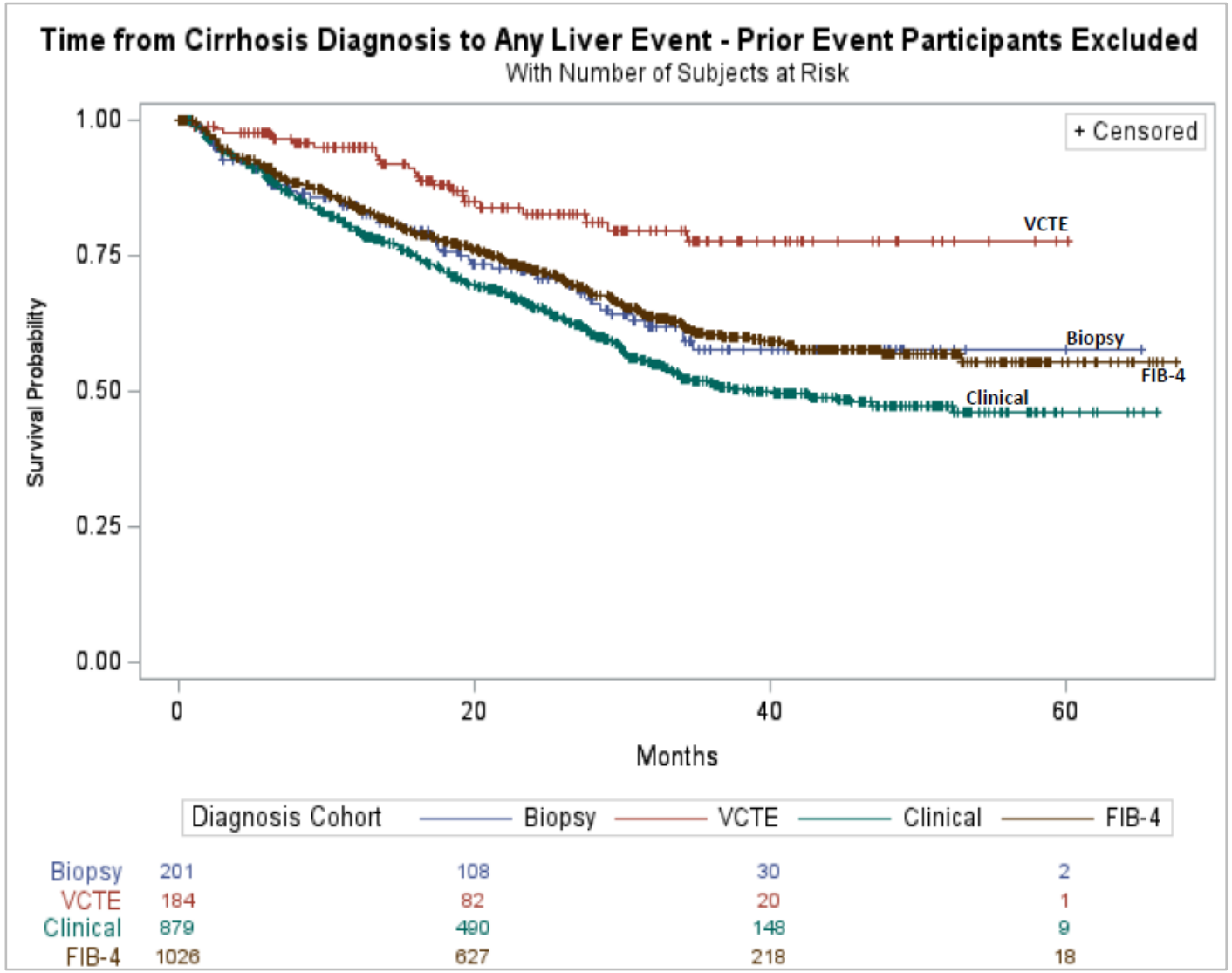
Fibrosis Assessed by Non-Invasive Tests is Similar to Liver Biopsy for Predicting Clinical Outcomes

Barritt et al. *AASLD Virtual Meeting. 2020*.

Adult patients enrolled in TARGET-NASH and diagnosed with cirrhosis by liver biopsy, FIB-4 ≥2.67, VCTE ≥16kPa, or a clinical algorithm* were included in the analysis.

Clinical outcomes:

→ Decompensation events (ascites, encephalopathy, variceal bleeding), hepatocellular carcinoma, liver transplantation, and death.



*Barritt et al. *Patient Determinants for Histologic Diagnosis of NAFLD in the Real World: A TARGET-NASH Study*. Hep Comm 2021; 5(6): 938-46

VCTE = vibration controlled transient elastography

NIS4 - utility for diagnosis of “at risk” NASH

Context of Use: to identify those with “at-risk” NASH i.e. *NASH + NAS ≥ 4* **+** *fibrosis stages ≥ 2* within a NAFLD population

At risk NASH	True+	True -	Total Subjects
NIS4 +	421	125	546
NIS4 -	118	349	467
Total	539	474	1013

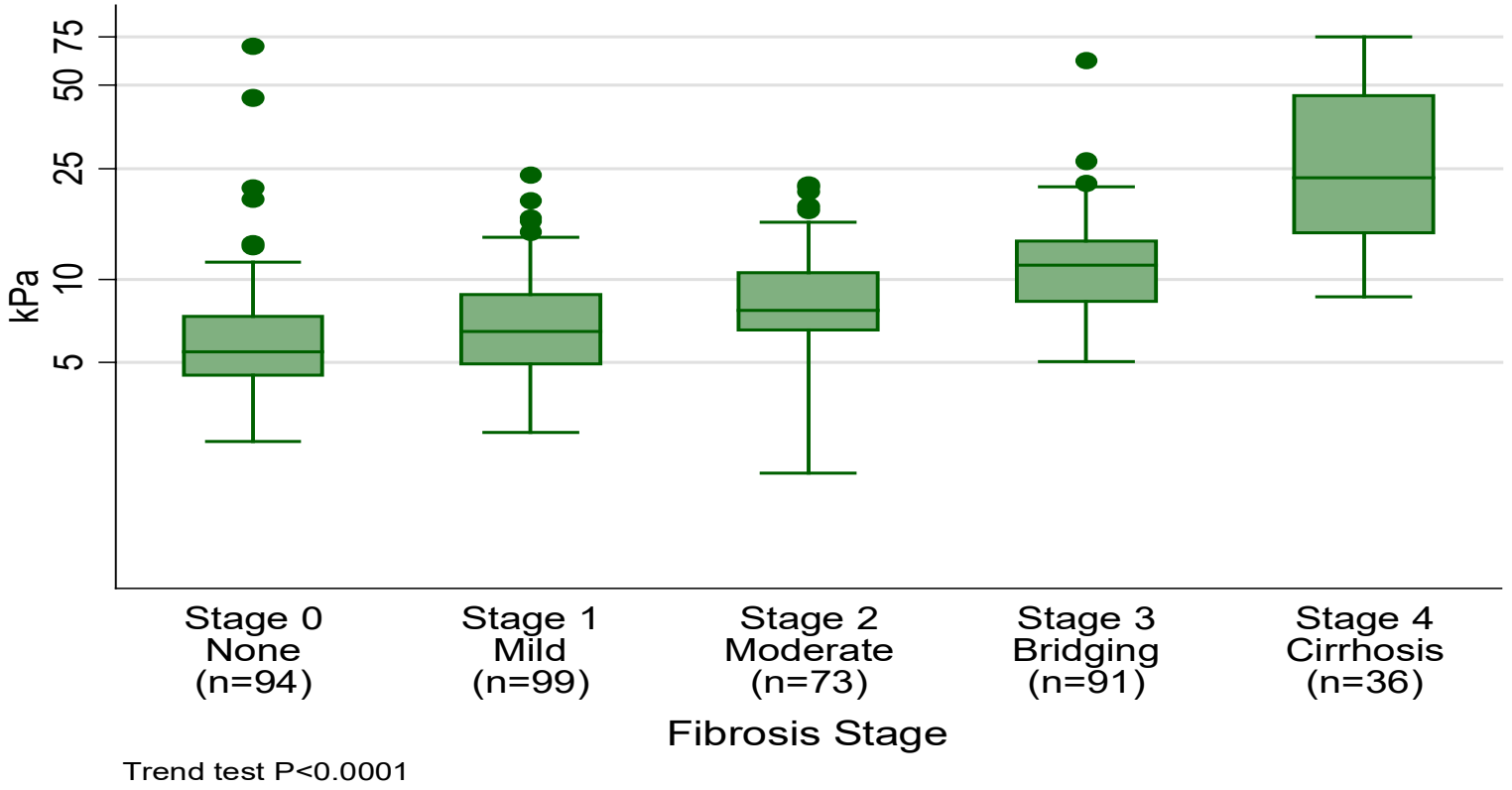
Youden Cutpoint: ≥ 0.6
Sensitivity: 78.1%
Specificity: 73.6%

Primary Hypothesis: AUROC > 0.7 and superior to 0.5
Secondary Hypothesis: AUROC superior to FIB-4

AUROC NIS4	P value vs unit line	AUROC FIB4	P value vs FIB4
0.815	<0.001	0.726	<0.001

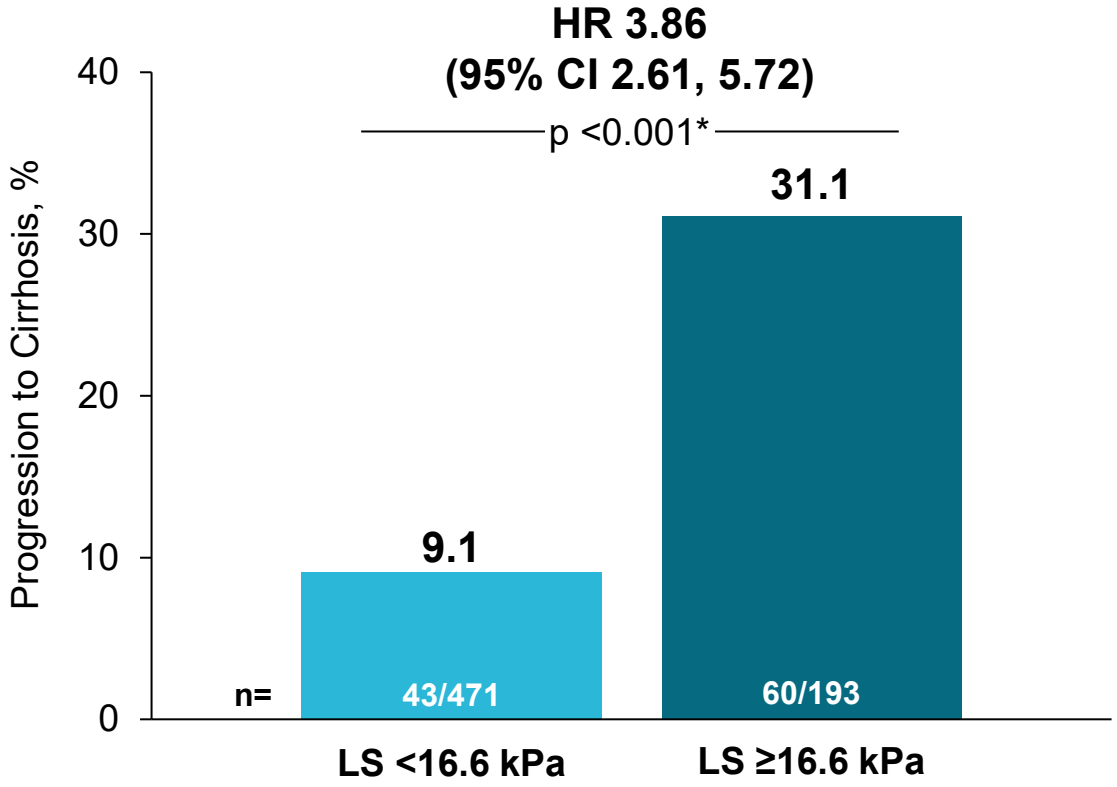
Sanyal et al, AASLD 2021

Liver stiffness as a measure of fibrosis



Siddiqui et al, Clinical Gastroenterol Hepatol 2018

LS by VCTE ≥16.6 kPa Was Associated With ~4-Fold Risk of Progression to Cirrhosis in Patients With Bridging (F3) Fibrosis



Diagnostic Performance of BL LS by VCTE to Predict Progression to Cirrhosis†	
c-statistic	0.72 (0.66, 0.77)
Optimal cutoff	≥16.6 kPa
Sensitivity	58% (48, 68)
Specificity	76% (73, 80)
PPV	31% (25, 38)
NPV	91% (88, 93)

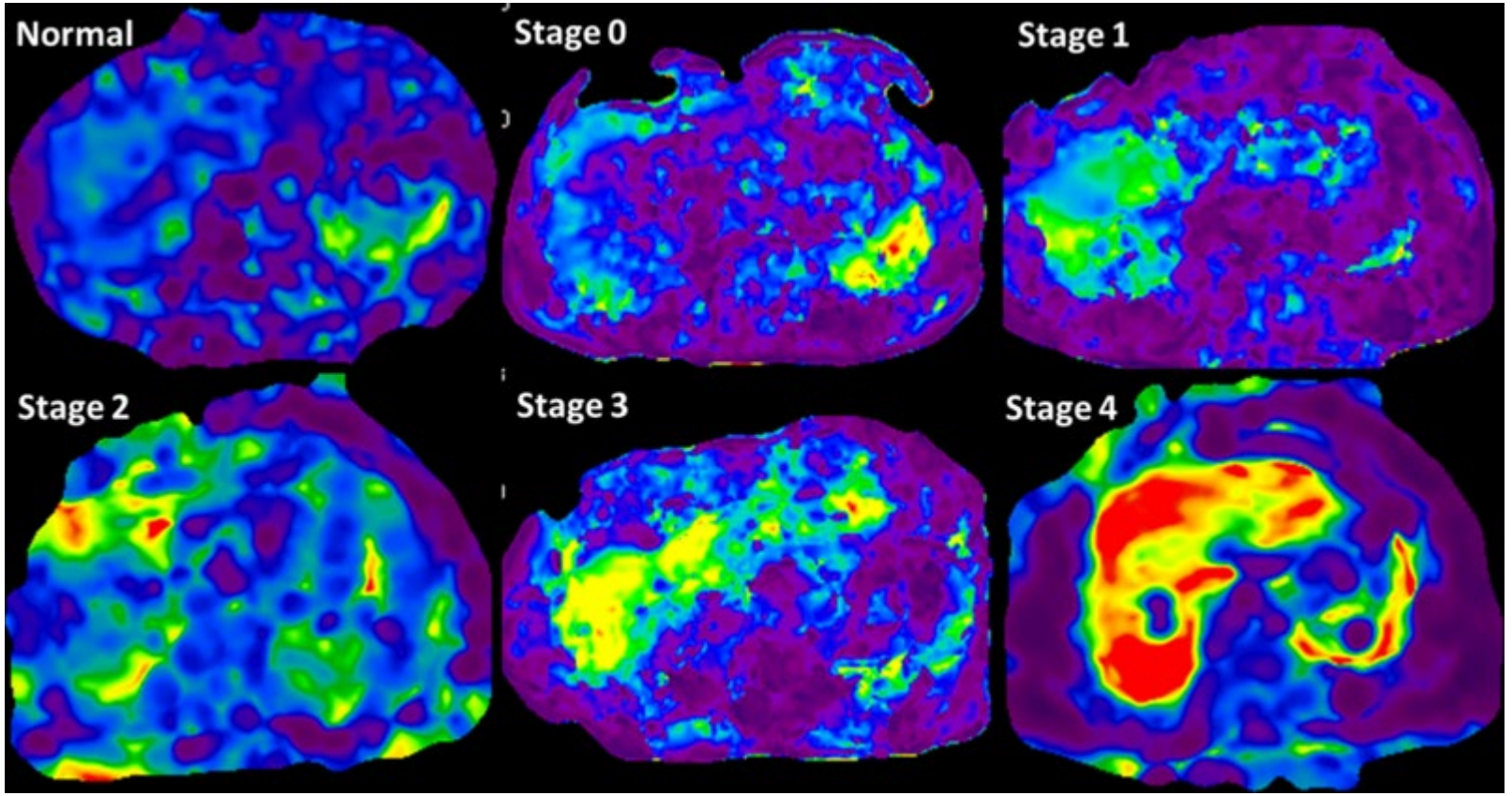
Loomba et al, AASLD 2021

*Fisher exact test; †data in parentheses indicate 95% CI. NPV, negative predictive value; PPV, positive predictive value.

Progression to cirrhosis- diagnosis of cirrhosis by NITs

2D MRE for detection of cirrhosis

Cirrhosis diagnosis with > 95% accuracy



LSM < 2.9 not clinically significant

LSM 2.93-3.5: Stage 1-2

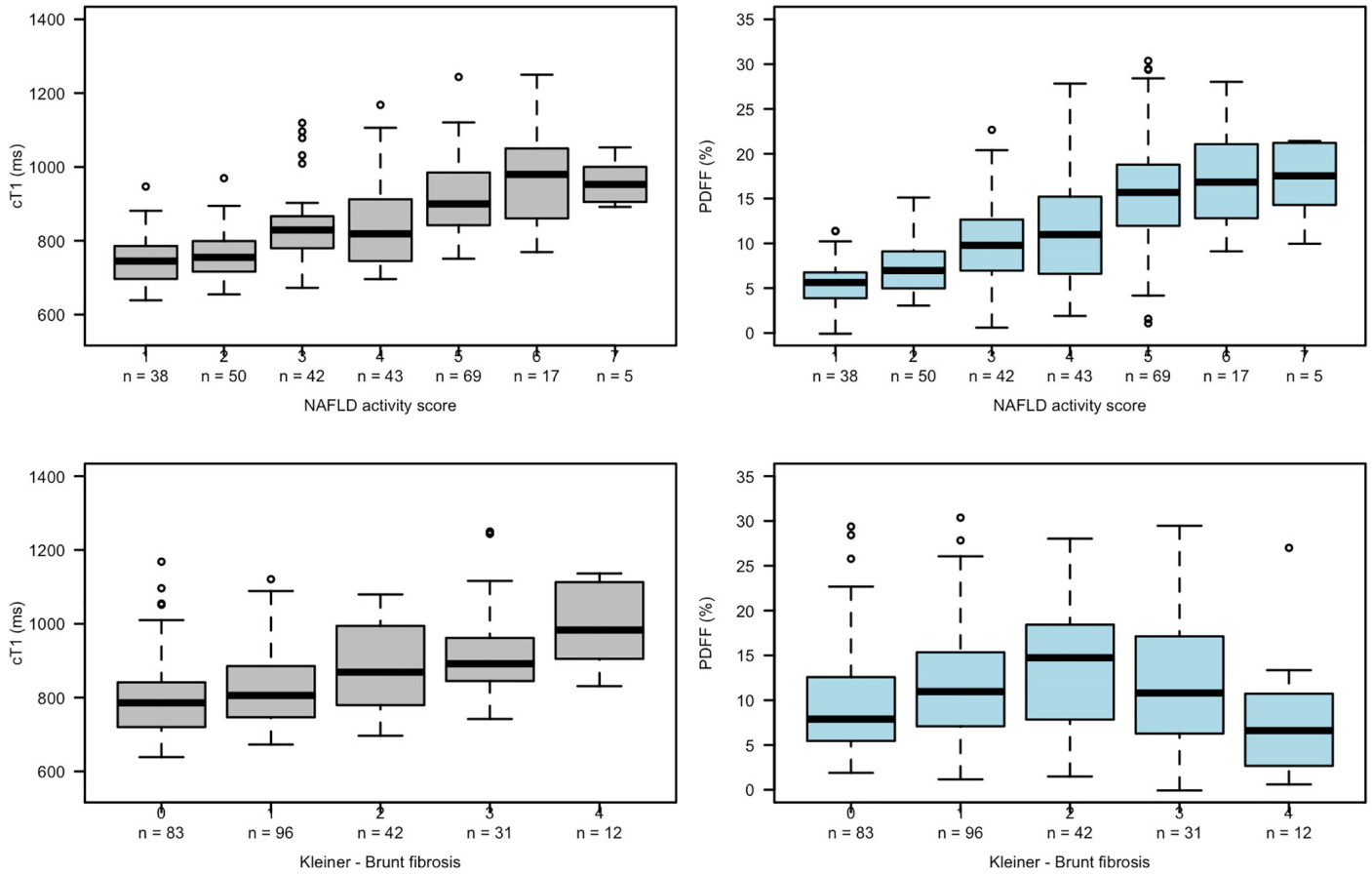
LSM 3.5-4: Stage 2-3

LSM 4-5: Stage 3-4

LSM > 5: cirrhosis

Hoodeshenaz et al, Top Magn Res Imaging, 2018; 27:319-333

Iron-corrected T1 (cT1) maps liver fibrosis



Dennis et al, Front Endocrinol, Jan 2021

Enhanced liver fibrosis (ELF) test- utility for diagnosis of clinically relevant fibrosis

Context of Use: to identify those with fibrosis in patients with NAFLD

Clinically significant fibrosis (stage 2 or higher), Advanced fibrosis (stage 3 or 4), Cirrhosis (stage 4)

	≥ Stage 2	Stage 3 or 4	Stage 4
AUROC (ELF test)	0.828	0.835	0.855
AUROC (FIB-4)	0.798	0.789	0.81
Is AUROC > 0.7 and superior to 0.5?	<0.001	<0.001	<0.001
Is AUROC superior to FIB4?	0.01	<0.001	<0.001
Performance statistics for ELF test			
Youden index cutoff	9.5	9.6	10.1
Sensitivity	71.8	80.8	82.1
Specificity	81.5	70.2	73.3

ELF performance improved progressively for diagnosis of progressively more advanced fibrosis

Sanyal et al, AASLD 2021

Fibrometer-VCTE: utility for diagnosis of clinically relevant fibrosis

Context of Use: to identify those with fibrosis in patients with NAFLD

Clinically significant fibrosis (stage 2 or higher), Advanced fibrosis (stage 3 or 4), Cirrhosis (stage 4)

Total n= 393 for this analysis	≥ Stage 2	Stage 3 or 4	Stage 4
AUROC (Fibrometer-VCTE)	0.841	0.858	0.897
AUROC (FIB-4)	0.763	0.779	0.839
Is AUROC > 0.7 and superior to 0.5?	<0.001	<0.001	<0.001
Is AUROC superior to FIB-4?	<0.001	<0.001	0.002
Performance statistics of Fibrometer-VCTE			
Youden index cutoff	≥ 0.5	≥ 0.6	≥ 0.6
Sensitivity	66.7	76.2	94.2
Specificity	86.4	81.3	70.4

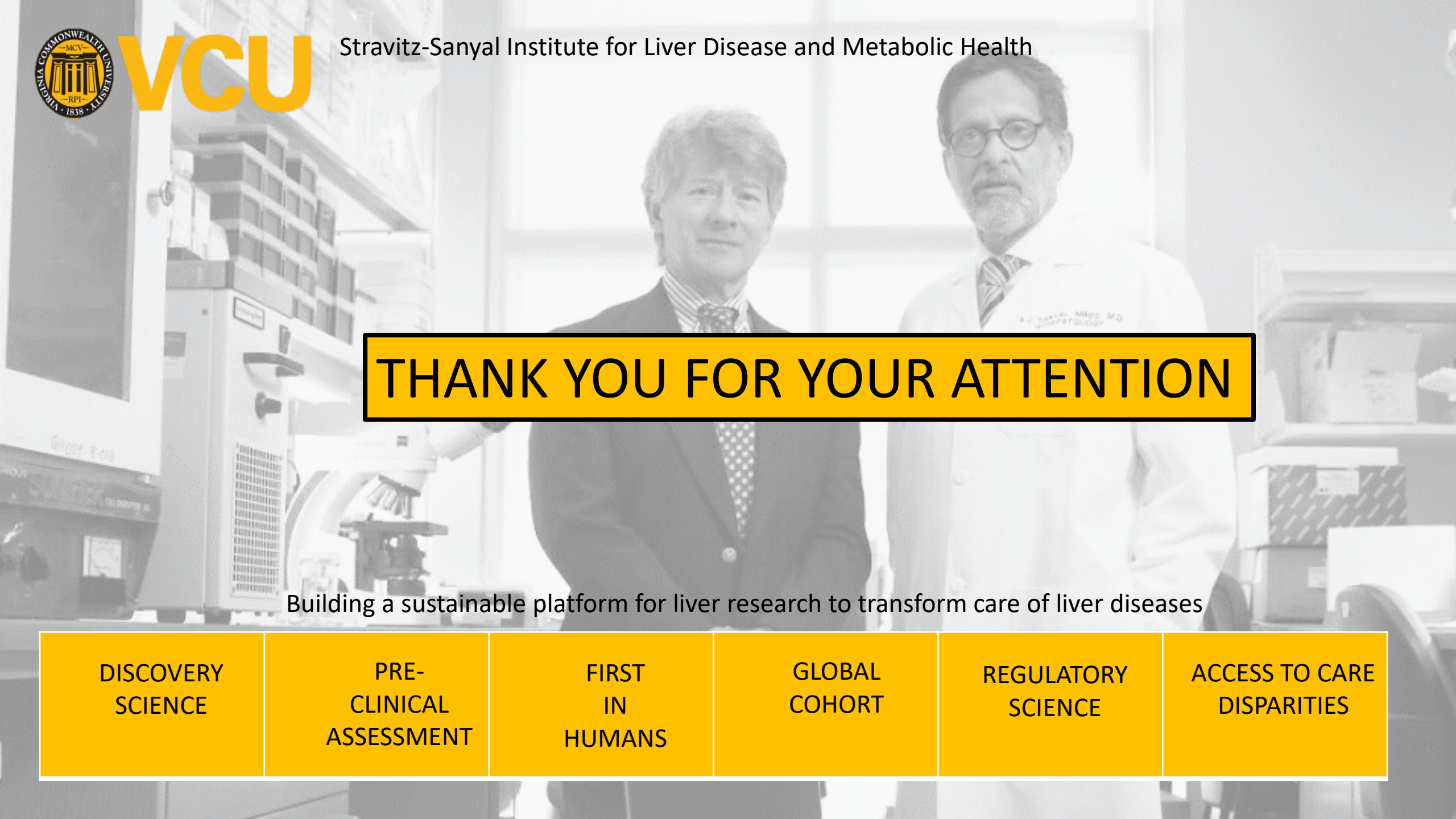
Fibrometer-VCTE performance improved progressively for diagnosis of progressively higher fibrosis stages

Sanyal et al, AASLD 2021

Summary

- Risk stratification in patients with NAFLD can be accomplished by:
  - Liver biopsy fibrosis stages
  - By FIB4
  - By LSM- measured by 2D MRE, in those with advanced fibrosis, LSM > 16.6 by VCTE is associated with higher risk of outcomes
- NASH with fibrosis stages 2 or higher can be diagnosed with relative accuracy by NIS4
- The presence of clinically significant fibrosis, advanced fibrosis or cirrhosis can be diagnosed with relative accuracy by multiple modalities
- These support the use of NITs to define the populations for clinical trials and to measure progression to cirrhosis. Qualification of NITs for the diagnosis of “at risk” NASH and varying fibrosis strata are a key priority for the field.

Stravitz-Sanyal Institute for Liver Disease and Metabolic Health



THANK YOU FOR YOUR ATTENTION

Building a sustainable platform for liver research to transform care of liver diseases

DISCOVERY SCIENCE	PRE-CLINICAL ASSESSMENT	FIRST IN HUMANS	GLOBAL COHORT	REGULATORY SCIENCE	ACCESS TO CARE DISPARITIES