2024

DESERT LIVER CONFERENCE

PHOENIX, ARIZONA

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DESERT LIVER CONFERENCE
PHOENIX, ARIZONA

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A few “housekeeping” items……

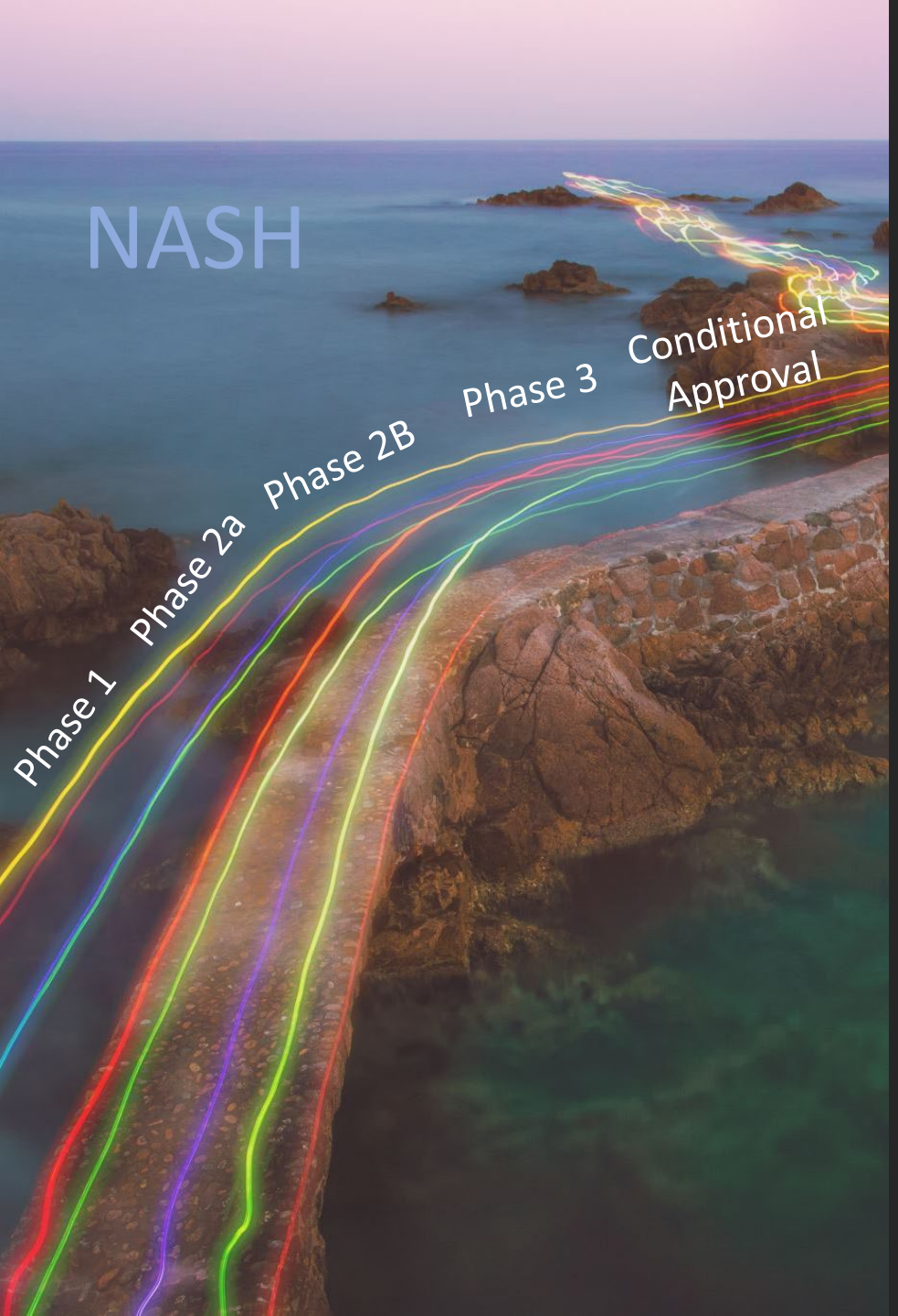
- Breaks will take place in the exhibit spaces.
- The link to claim your CME/ABIM MOC (10.25 credits) is in your mobile app and flyer in your bag.
- This meeting is being recorded and we have attendees who are logged in virtually. Please use the aisle microphones or raise your hand for a microphone for the Q&A to be captured for the virtual audience.
- Conference information can be found on the Cvent Meeting App. Please visit the helpdesk for assistance with the app.
- Please visit the helpdesk to address any questions, emergencies, accommodations, or needs during the conference.
- Restrooms are in the foyer area. Please follow the signage or visit the helpdesk for directions.
- Please place all mobile devices in silent/airplane mode.
- Parking lot gates will be open during morning and meeting ending times. For valet tickets, please visit the conference helpdesk.

Friday Opening Remarks

Thank you to our sponsors. Please interact with them during the breaks and the NIT Demonstration Session

Please download the MDCalc App and MyFibroscan App for the interactive session

Signed copies of the new MASLD textbook are available for purchase



Non-Invasive Imaging Tests for MASH

Mazen Noureddin, MD, MHSc
Professor of Medicine
Sherrie & Alan Conover Center for Liver Disease & Transplantation
Houston Methodist Hospital

Director Houston Research Institute
Director Houston Liver Institute
CSO Summit Clinical Research
Houston, Texas

Strategies to Identify at Risk NASH:

1st Generation

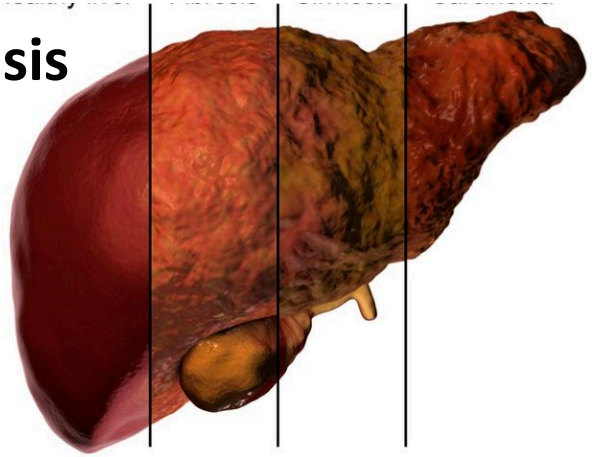
Prior to 2019

2nd Generation

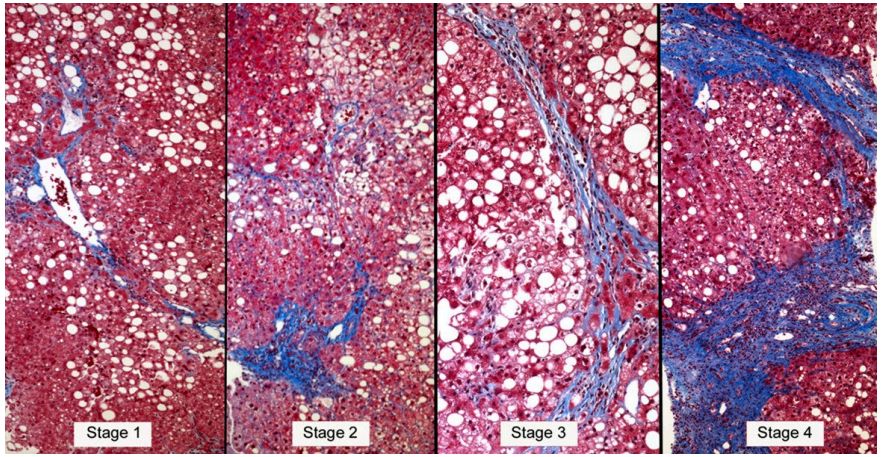
2019

Keep an Eye on The outcomes

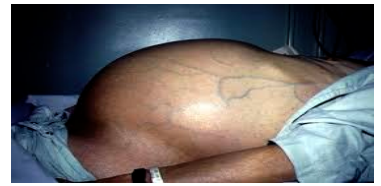
Fibrosis

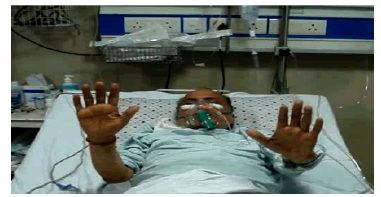


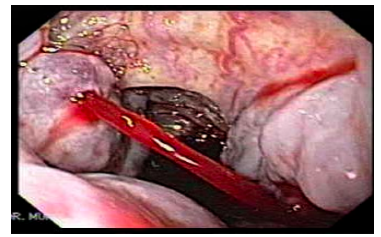
NASH with NAS ≥ 4 + ≥ F2



Major Clinical Liver Events (MALO)



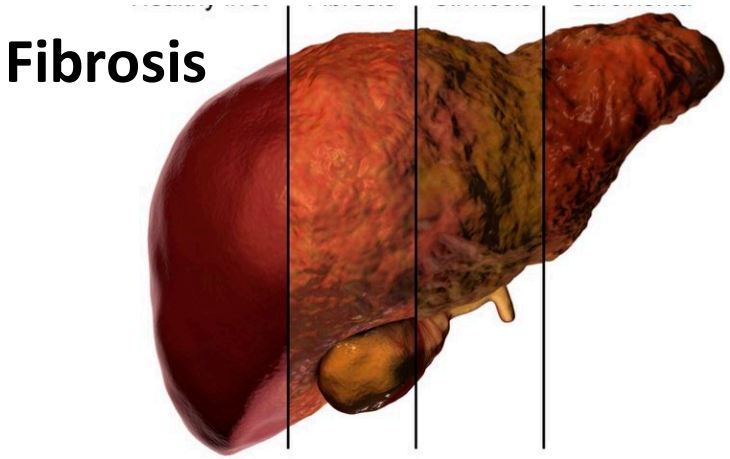




Strategies:

1st Generation

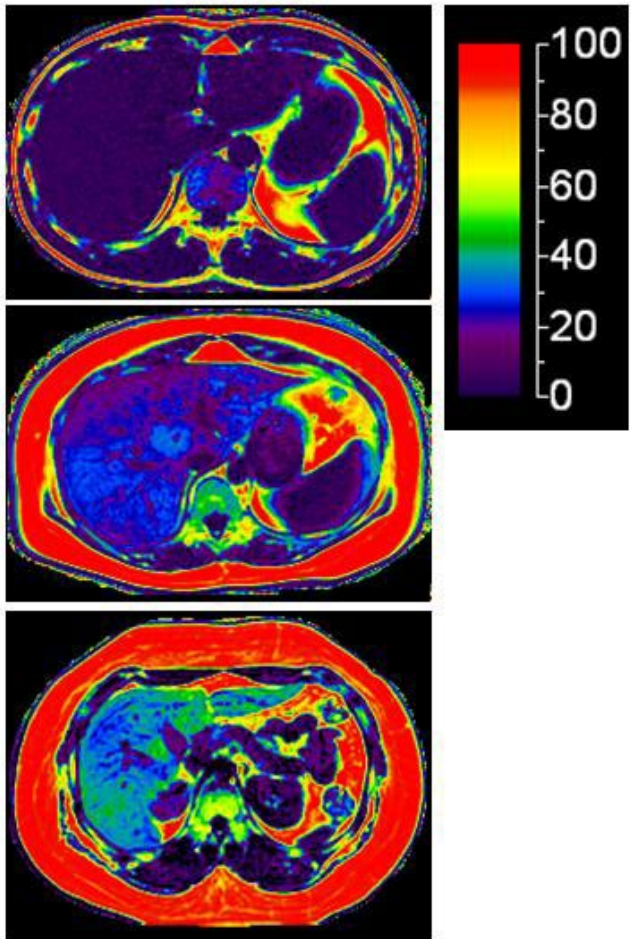
Prior to 2019

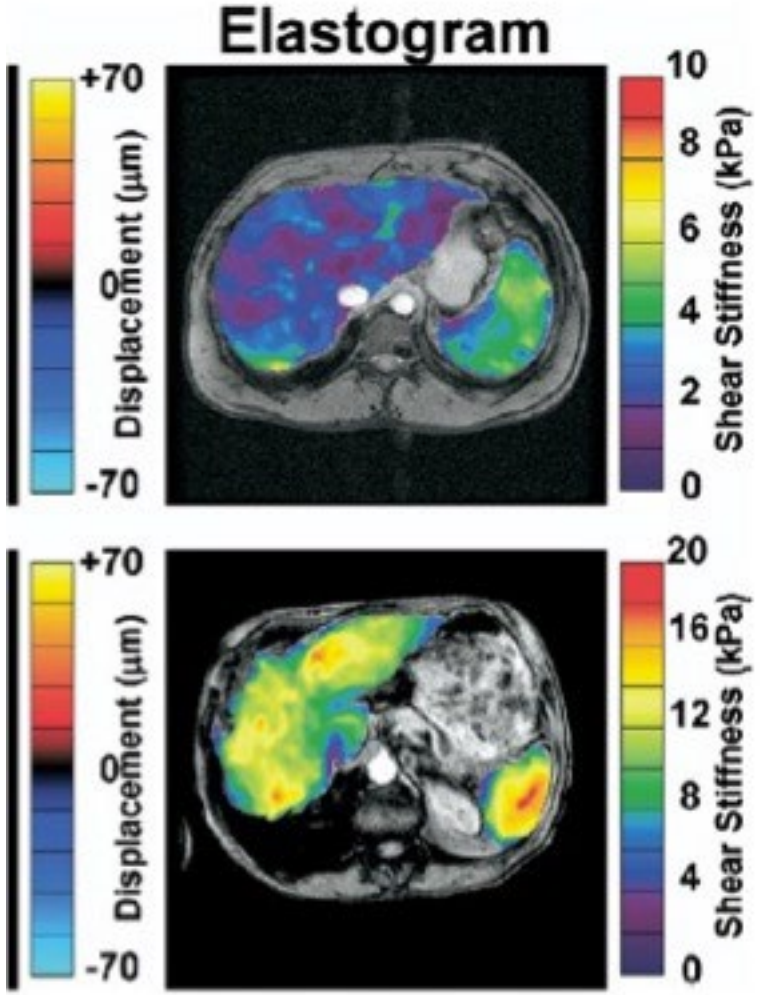


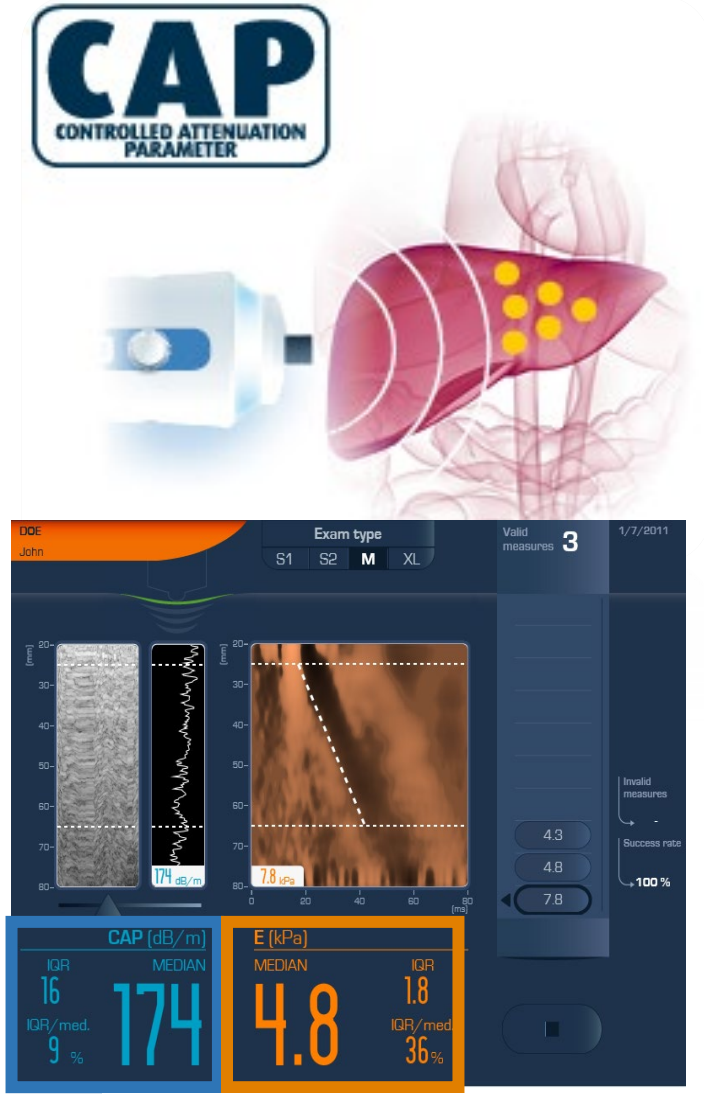
FIB-4
ELF
VCTE
MRE

AST

VCTE and MRE Assess Fibrosis Stages and Correlate with MALO







MRI_PDFF

MRE

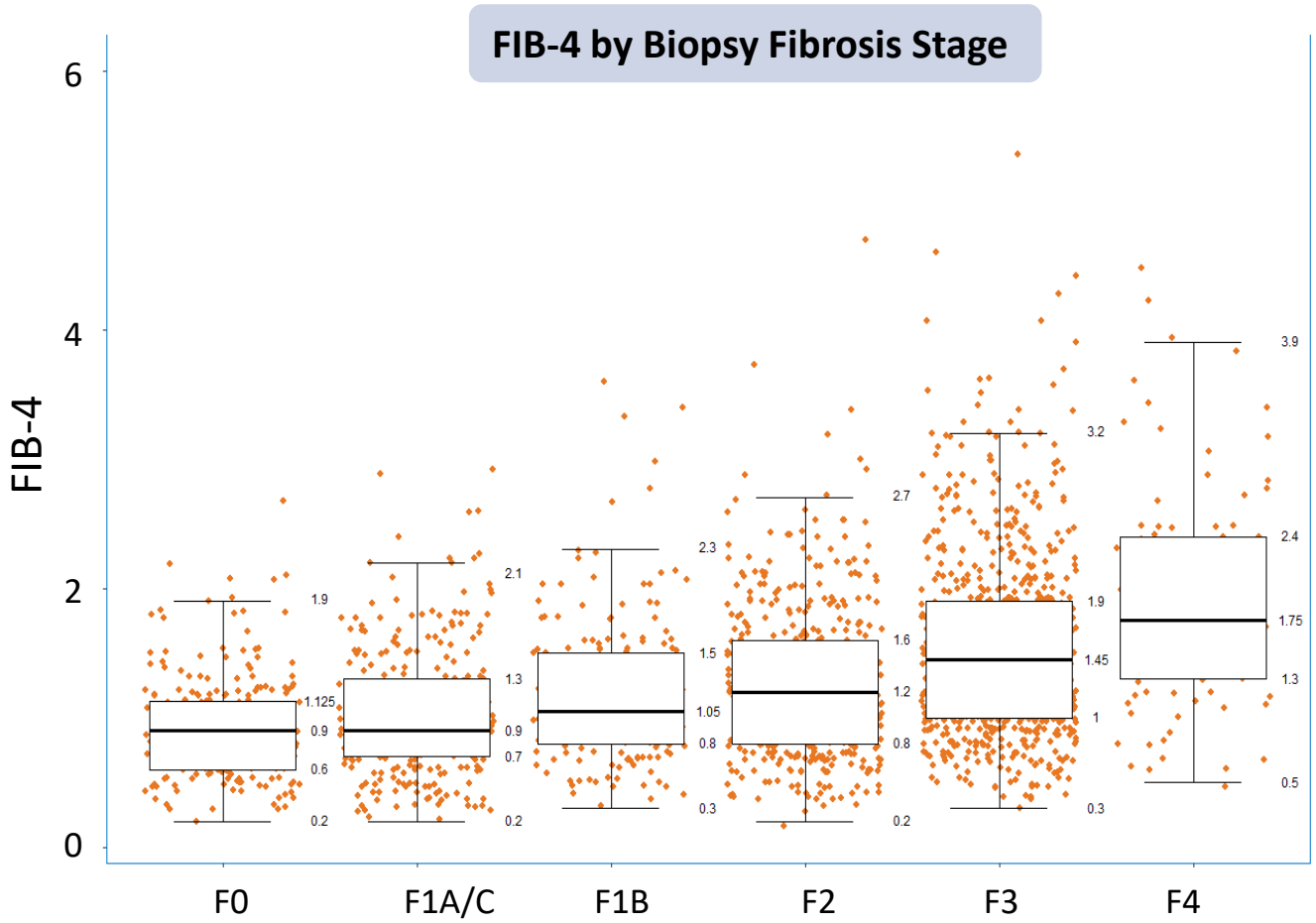
Can be coupled with MRE

Loomba et al. Hepatology. 2014;
Noureddin et al; Hepatology 2014
Wong VW et al; Gut 2019

Comparison of Diagnostic Accuracy of Noninvasive Imaging in NASH

Noninvasive Imaging	Patient Groups	AUROC for ≥F2 Fibrosis
FIB-4	F0-F4	0.68
FibroScan VCTE (LSM)	F0-F4	0.66
FAST	F0-F4	0.72
MAST	F0-F4	0.79
MRE	F0-F4	0.79

- The "prevalence" of biopsy-confirmed NASH with significant fibrosis ≥F2 in this population was 74%
- FIB-4 AUROC was 0.68
- AUROC of MRE, MAST, FAST for fibrosis stage & NASH were >0.7

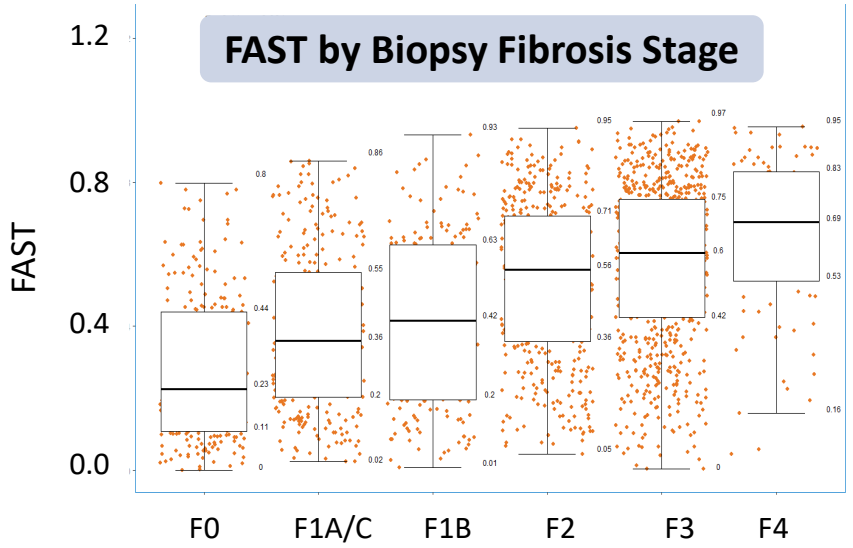


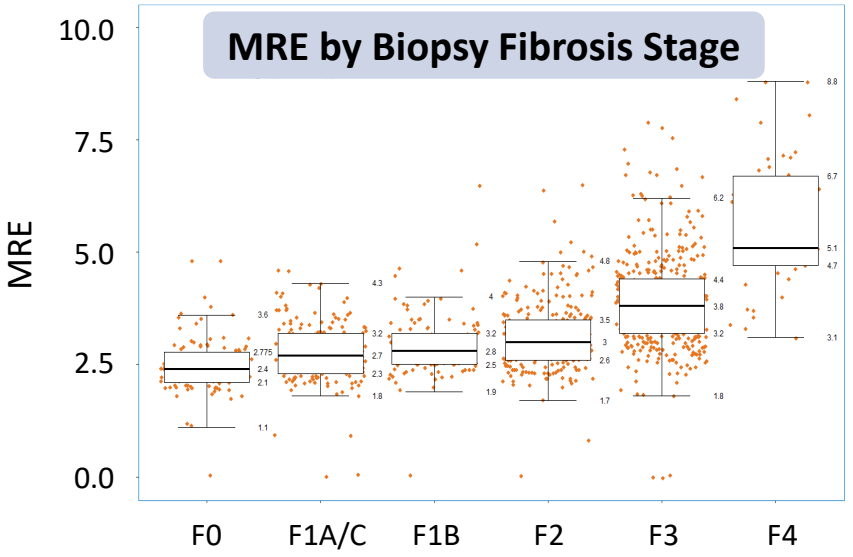
***FAST** = CAP + LSM + AST; **MAST** = MRI-PDFF + MRE + AST; **MEFIB** = MRE ≥3.3 + FIB-4 ≥1.6*

AUROC, area under the receiver operating characteristic curve; FAST, FibroScan-aspartate aminotransferase; FIB-4, fibrosis-4; LSM, liver stiffness measurement; MAST, magnetic resonance imaging-aspartate aminotransferase; MEFIB, MRE combined with FIB-4; MRE, magnetic resonance elastography; NASH, nonalcoholic steatohepatitis; VCTE, vibration-controlled transient elastography.

Assessment of Imaging Modalities For Detecting ≥F2 Fibrosis in Liver Biopsy

	AUROC	Sensitivity	Specificity	Optimal Value
Fibrosis (F2-F4)				
FIB-4	0.68	61%	64%	1.1
FibroScan VCTE (LSM)	0.66	NA	62%	10.6 kPa
FAST	0.72	58%	73%	0.52
MRE	0.79	70%	73%	2.9 kPa
MAST	0.79	70%	73%	0.10
MEFIB	0.78	33% (F3)	>90% (≥F2)	NA





- Lower than reported thresholds for MAST, FAST showed optimal sensitivity & specificity (PPV & NPV) in this highly enriched NASH fibrosis population
  - PPV of 88% & 92% for MAST ≥0.1 & ≥0.165, respectively; NPV 44% & 38%
  - PPV of 86% for FAST of 0.52; NPV 38%
- MEFIB showed PPV of 93% & NPV of 33% due to low FIB-4 in this population

AUROC, area under the receiver operating characteristic curve; FAST, FibroScan-aspartate aminotransferase; FIB-4, fibrosis-4; LSM, liver stiffness measurement; MAST, magnetic resonance imaging-aspartate aminotransferase; MEFIB, MRE combined with FIB-4; MRE, magnetic resonance elastography; NASH, nonalcoholic steatohepatitis; NPV, negative predictive value; PPV, positive predictive value; VCTE, vibration-controlled transient elastography.

Authors' Conclusions

- Based on a large Phase 3 data set of biopsy-confirmed patients with NASH, FIB-4 ≥1.3 lacks the sensitivity to accurately identify patients with at-risk (F2/F3) fibrosis
- The influence of age on FIB-4 may require an adjustment to ensure younger patients are not removed from consideration for therapy
- Additional tests such as FAST, MAST, or MEFIB may improve at-risk patient enrichment
- MAST & MRE showed the best sensitivity & specificity in this cohort
- Learnings from MAESTRO-NASH provide insight on the utility of FIB-4 & other noninvasive tests/imaging modalities for identification of at-risk NASH

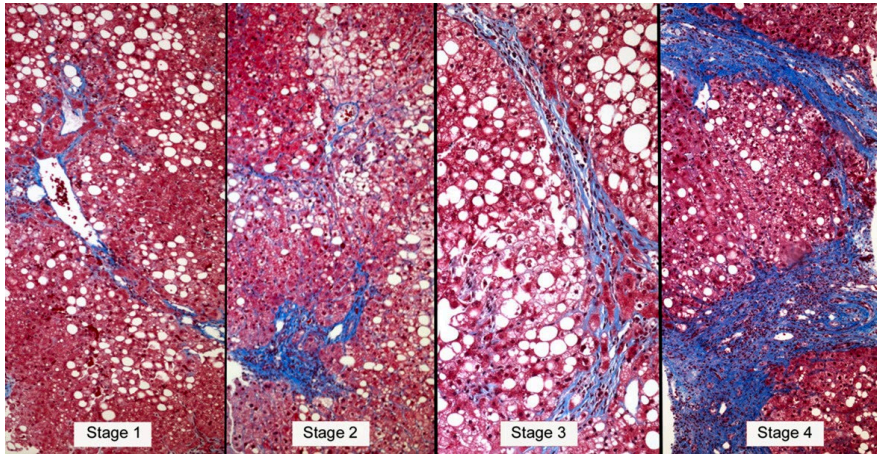
FAST, FibroScan-aspartate aminotransferase; FIB-4, fibrosis-4; MAST, magnetic resonance imaging-aspartate aminotransferase; MRE, magnetic resonance elastography; NASH, nonalcoholic steatohepatitis.

Strategies:

2nd Generation

2019

NASH with NAS ≥ 4 + ≥ F2



FAST
Agile 3+
Agile 4
cT1
MEFIB
MAST

FAST: VCTE-Based to Identify at Risk NASH

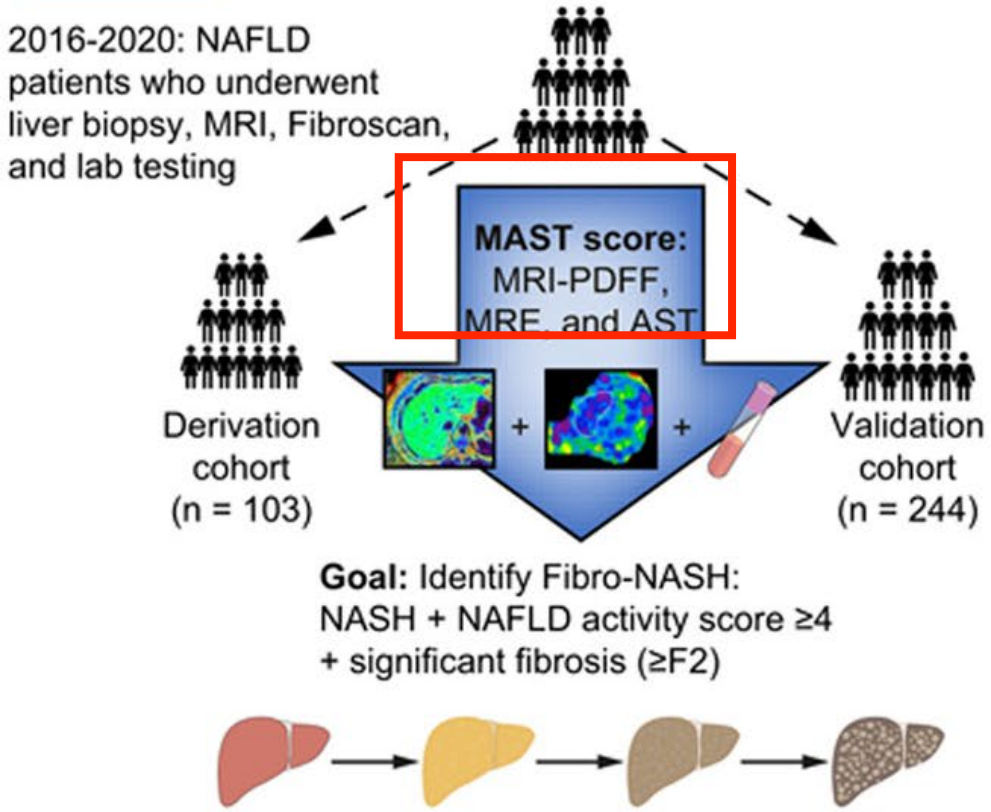
	AUROC (95% CI)	n	Prevalence of NASH + NAS ≥ 4 + F ≥ 2	Rule-out zone (FAST ≤0·35)				Grey zone (FAST 0·35–0·67), n (%)	Rule-in zone (FAST ≥0·67)			
				n (%)	Sensitivity	Specificity	NPV		n (%)	Specificity	Sensitivity	PPV
Derivation cohort	0·80 (0·76–0·85)	350	174 (50%)	113 (32%)	0·90 (157/174)	0·53 (93/176)	0·85 (93/110)	136 (39%)	101 (29%)	0·90 (159/176)	0·48 (84/174)	0·83 (84/101)
French bariatric surgery cohort	0·95 (0·91–0·99)	110	16 (15%)	69 (63%)	1·00 (16/16)	0·73 (69/94)	1·00 (69/69)	22 (20%)	19 (17%)	0·93 (87/94)	0·75 (12/16)	0·63 (12/19)
USA screening cohort	0·86 (0·80–0·93)	242	28 (12%)	194 (80%)	0·64 (18/28)	0·86 (183/214)	0·95 (183/193)	39 (16%)	9 (4%)	0·99 (212/214)	0·25 (7/28)	0·78 (7/9)
China Hong-Kong NAFLD cohort	0·85 (0·76–0·93)	83	36 (43%)	28 (34%)	0·94 (34/36)	0·55 (26/47)	0·93 (26/28)	29 (35%)	26 (31%)	0·89 (42/47)	0·58 (21/36)	0·81 (21/26)
China Wenzhou NAFLD cohort	0·84 (0·73–0·95)	104	9 (9%)	55 (53%)	0·89 (8/9)	0·56 (53/95)	0·98 (58/67)	37 (36%)	12 (11%)	0·92 (87/95)	0·44 (4/9)	0·33 (4/12)
French NAFLD cohort	0·80 (0·73–0·86)	182	78 (43%)	67 (37%)	0·88 (69/78)	0·56 (58/104)	0·87 (58/67)	69 (38%)	46 (24%)	0·89 (93/104)	0·45 (35/78)	0·76 (35/46)
Malaysian NAFLD cohort	0·85 (0·78–0·91)	176	36 (20%)	78 (44%)	0·94 (34/36)	0·54 (75/140)	0·97 (75/77)	59 (34%)	39 (22%)	0·87 (122/140)	0·58 (21/36)	0·54 (21/39)
Turkish NAFLD cohort	0·74 (0·65–0·82)	129	74 (57%)	26 (20%)	0·91 (67/74)	0·35 (19/55)	0·73 (19/26)	57 (44%)	46 (36%)	0·82 (45/55)	0·49 (36/74)	0·78 (36/46)
Pooled external patients cohort	0·85 (0·83–0·87)	1026	277 (27%)	517 (51%)	0·89 (246/277)	0·64 (483/749)	0·94 (483/514)	312 (30%)	197 (19%)	0·92 (688/749)	0·49 (136/277)	0·69 (136/197)

FAST: CAP+LSM+AST

Newsome et al; Lancet Gastro Hep 2020
Noureddin N et al; Hepatology 2020

MAST score: MRI-Based to Identify at Risk NASH

Methods



Findings

Score	Sample	ROC area	Sensitivity	Specificity	PPV	NPV
MAST	Derivation	0.858	94.4%	72.9%	42.5%	98.4%
MAST	Validation	0.929	89.3%	73.1%	30.1%	98.1%
FAST	Validation	0.868	93.1%	64.1%	25.0%	98.6%
NAFLD (NFS)	Derivation	0.748	100.0%	52.9%	30.5%	100.0%
NAFLD (NFS)	Validation	0.689	58.6%	66.6%	18.7%	92.5%
Fib-4	Derivation	0.891	88.9%	74.7%	42.1%	97.0%
Fib-4	Validation	0.711	20.7%	95.5%	37.5%	90.2%

Noureddin et al, J Hep 2021

Conclusions

The MAST score is an accurate, MRI-serum-based score that outperforms the NAFLD fibrosis (NFS), Fib-4, and FAST scores in non-invasively identifying patients at higher risk of Fibro-NASH.

MEFIB Score:

UCSD-NAFLD Cohort
(N=238)

MRE ≥ 3.3kPa
PPV: 86.9

+

FIB-4 ≥ 1.6
PPV: 61.5

MRE ≥ 3.3kPa + FIB-4 ≥ 1.6
PPV: 97.1

Japan-NAFLD Cohort
(N=222)

MRE ≥ 3.3kPa + FIB-4 ≥ 1.6
PPV: 91.0

Jung et al. GUT 2020

Combination of imaging and serum markers (MRE≥3.3kPa and FIB-4≥1.6) yielded a high positive predictive value(97.1) for a clinician to rule in clinically significant disease that needs pharmacologic treatment in NAFLD.

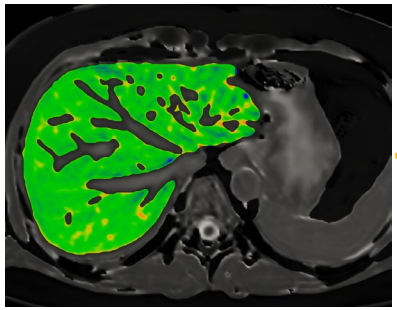
LiverMultiScan cT1 accurately identifies NASH patients at Risk

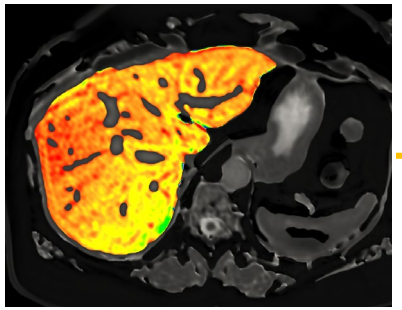
n=543 NAFLD
n=100 Healthy
cT1 and PDFF
Biopsy - NAS

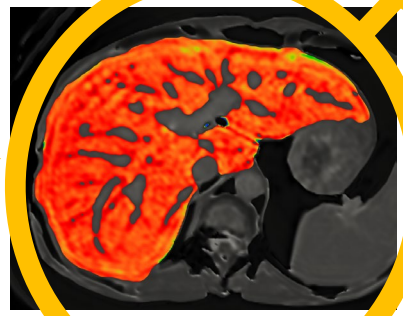
Low likelihood of having NASH
cT1 <800ms

Evidence of NASH
cT1 800-875ms

High likelihood of having "High-risk" NASH
cT1 >875ms







AUROC=0.78

Andersson et al CGH 2021

Predictive performances of diagnostic models for significant fibrosis or “at risk” NASH
For MAST vs MEFIB vs FAST

Models	For “at risk” NASH	
	AUC (95% CI)	*p* value
Entire cohort		
MAST score	0.719 (0.671–0.766)	0.011
FAST score	0.687 (0.640–0.733)	<0.001
MEFIB	0.768 (0.728–0.808)	Reference
UCSD cohort		
MAST score	0.701 (0.613–0.789)	<0.001
FAST score	0.716 (0.638–0.794)	0.006
MEFIB	0.832 (0.770–0.895)	Reference
Yokohama City University cohort		
MAST score	0.696 (0.636–0.756)	0.776
FAST score	0.662 (0.601–0.723)	0.389
MEFIB	0.689 (0.631–0.747)	Reference

Kim et al; J Hep 2022

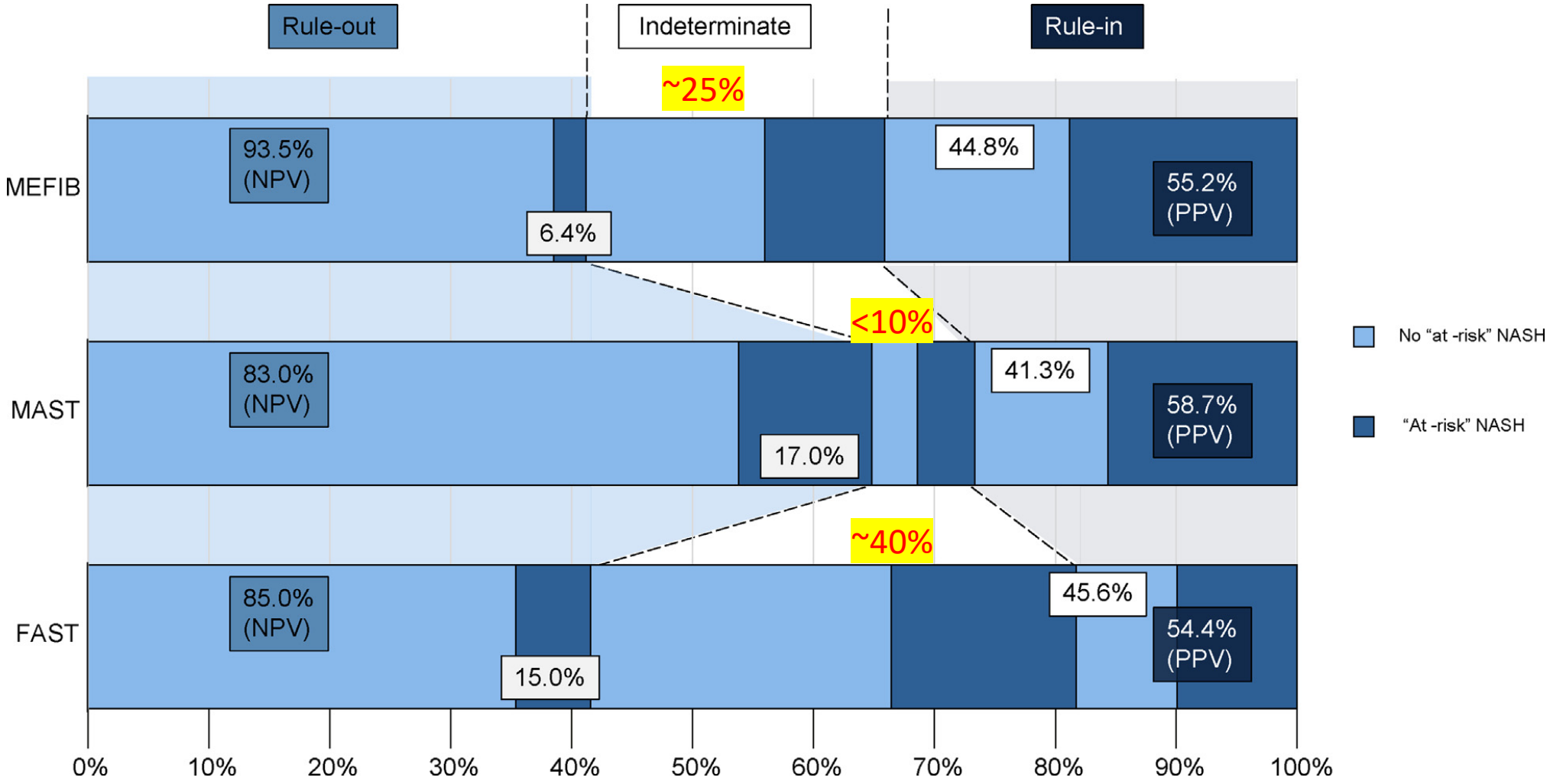
Predictive performances of diagnostic models for significant fibrosis or “at risk” NASH
For MAST vs MEFIB vs FAST

Models	For “at risk” NASH					
	No. of patients	Sensitivity	Specificity	NPV	PPV	*p* value
Entire cohort						
MAST score	88	49.7%	83.9%	78.5%	**58.7%**	0.522
FAST score	56	31.6%	87.8%	73.7%	**54.4%**	0.890
MEFIB	106	59.9%	77.7%	80.9%	**55.2%**	Reference
UCSD cohort						
MAST score	20	37.7%	91.3%	84.4%	**54.1%**	0.429
FAST score	18	34.0%	89.8%	83.4%	**47.4%**	0.163
MEFIB	27	50.9%	91.8%	87.4%	**62.8%**	Reference
Yokohama City University cohort						
MAST score	68	54.8%	76.3%	72.1%	**60.2%**	0.248
FAST score	38	30.6%	85.8%	65.5%	**58.5%**	0.462
MEFIB	79	63.7%	63.2%	72.7%	**53.0%**	Reference

p values by Chi-square test indicates they hold fort

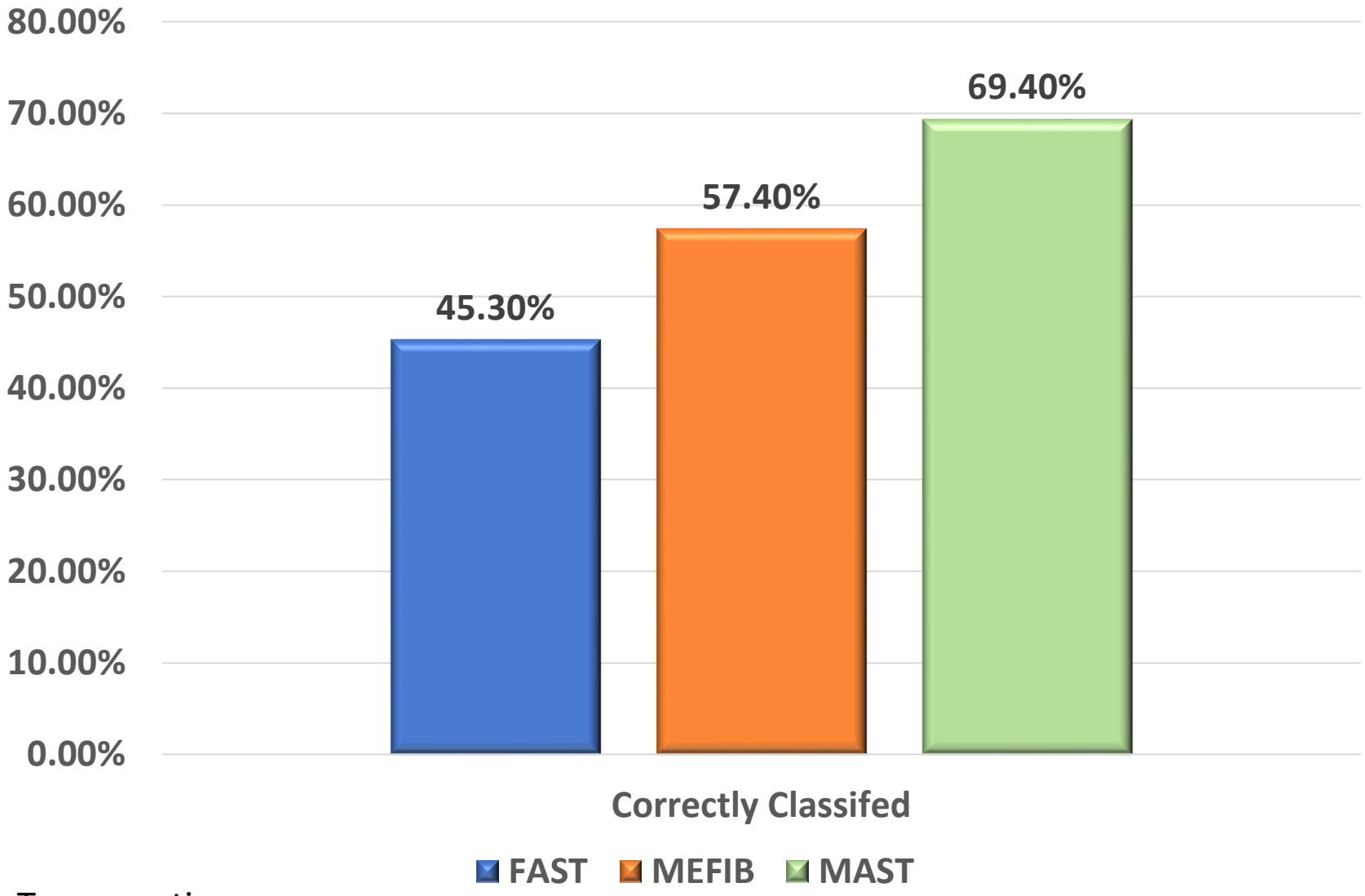
Kim et al; J Hep 2022

Predictive performances of diagnostic models for significant fibrosis or “at risk” NASH
For MAST vs MEFIB vs FAST



Kim et al; J Hep 2022

Correctly Classified Cases of NASH F2,F3 and F4, MAST vs MEFIB vs FAST



True Positive + Ture negative

_____

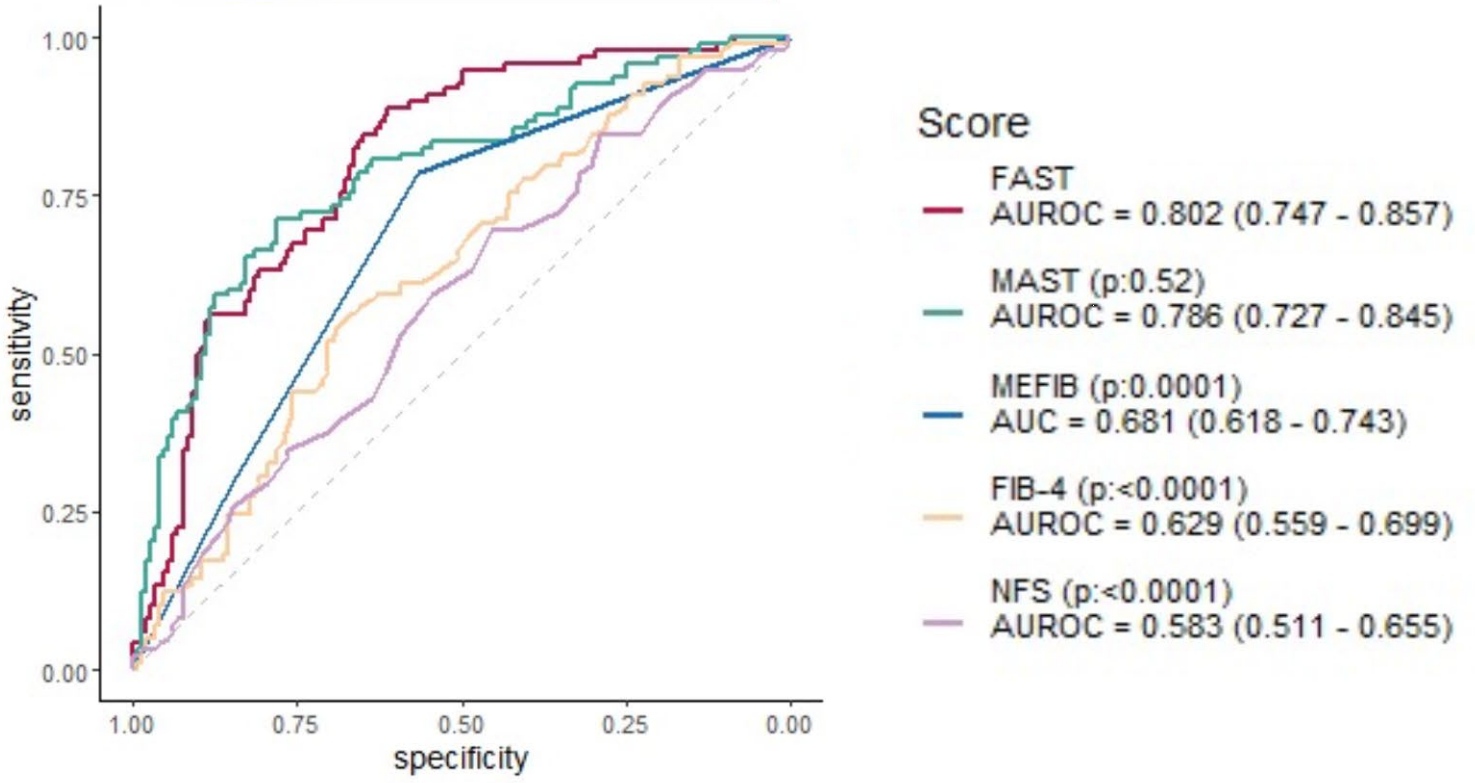
Overall

Noureddin, Harrison and Alkhouri J Hep 2022

Comparison of FAST, MAST, MEFIB, FIB-4 and NFS

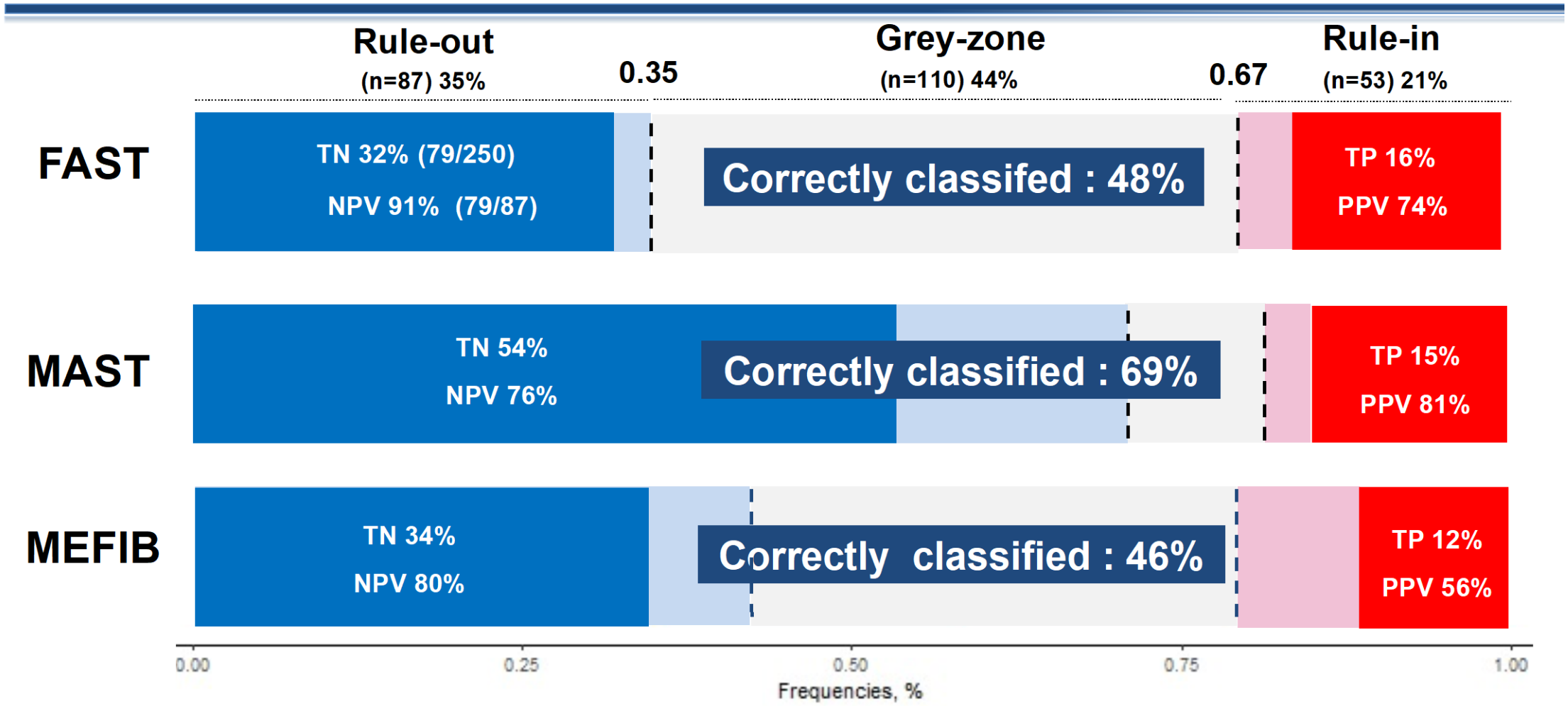
Prospective multicenter study (October 2018 to March 2021) 713 T2D patients with suspected NAFLD seen in 4 Diabetes clinics
of whom 360 underwent a liver biopsy

At risk NASH



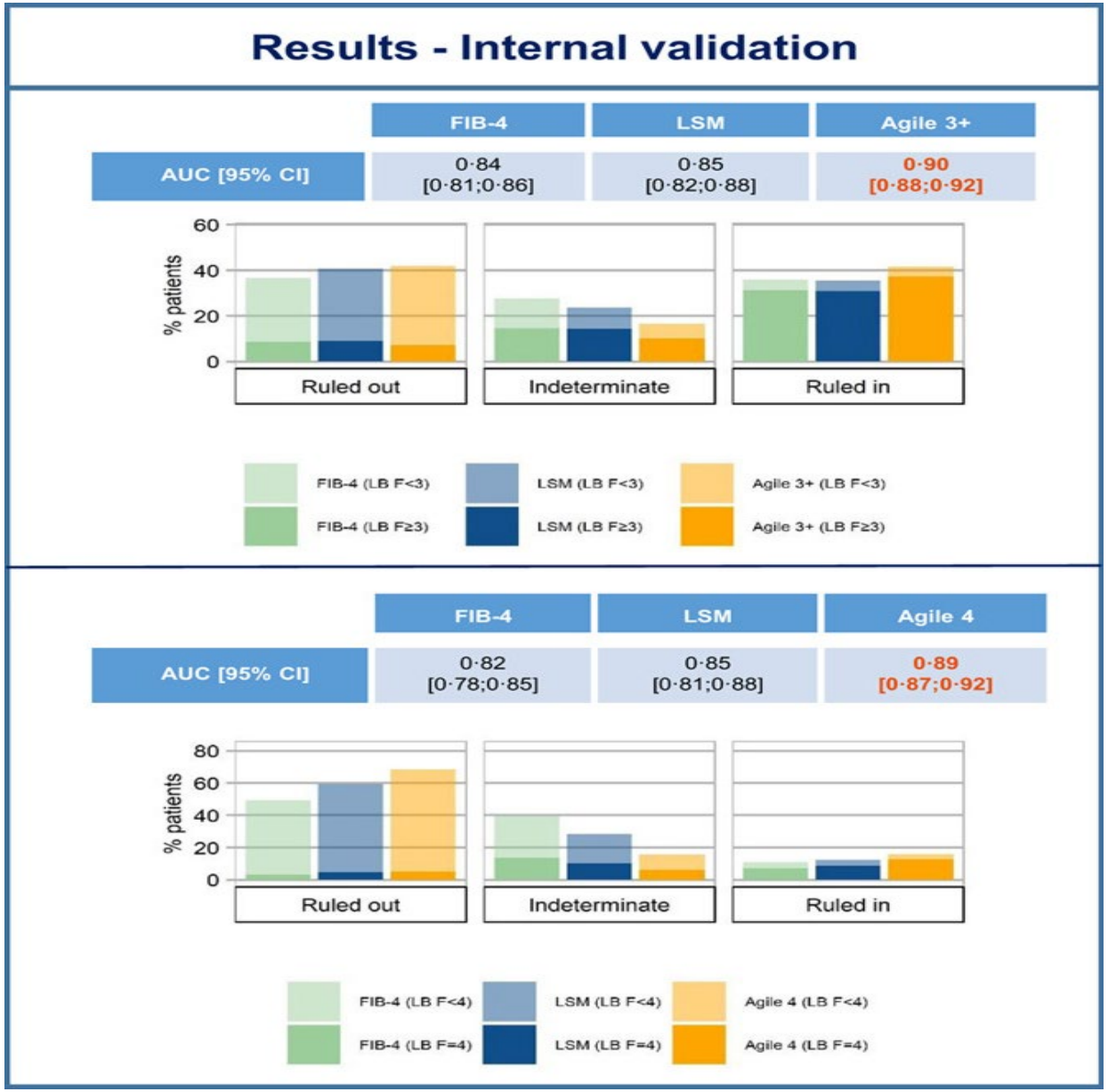
Castera et al; AASLD 2022

Proportions of spared liver biopsies: at risk NASH



Castera et al; AASLD 2022

Agile 3+ and Agile 4

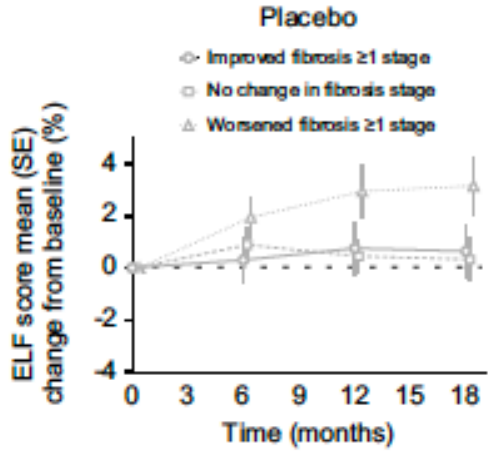


Sanyal et al; J Hep 2022

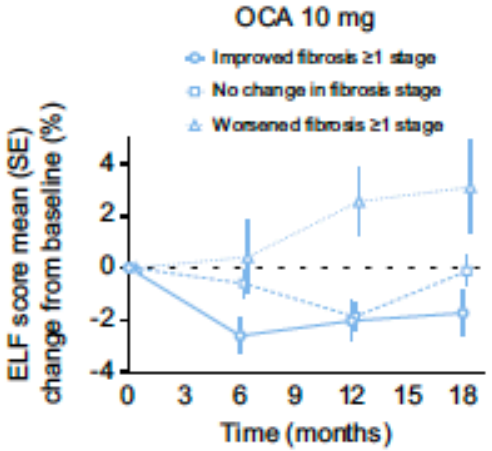
How do I monitor response?

B

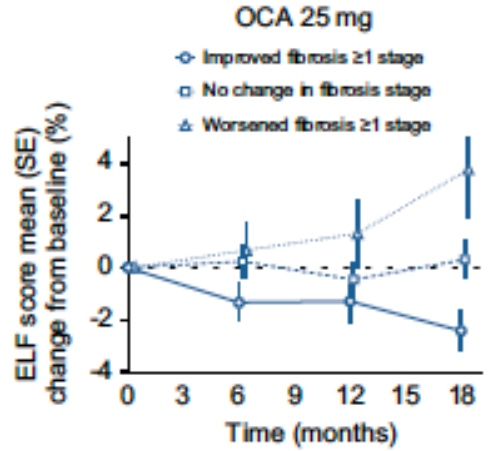
ELF



Improved, n =	60	59	57	58
No change, n =	137	137	134	127
Worsened, n =	52	52	53	50



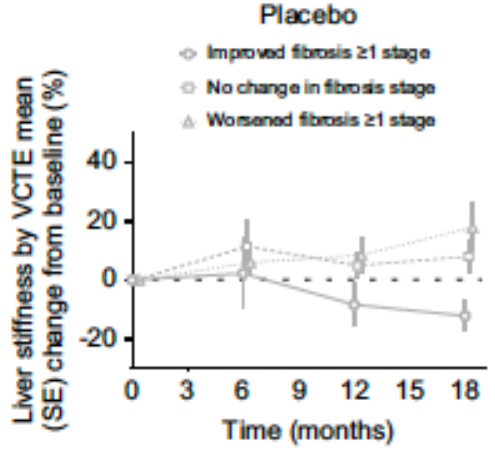
Improved, n =	70	70	70	64
No change, n =	142	139	139	134
Worsened, n =	40	40	40	41



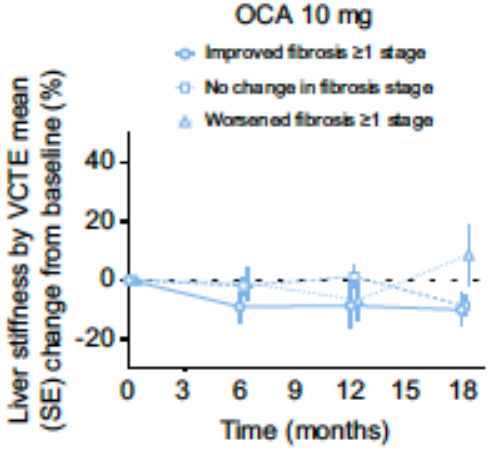
Improved, n =	89	88	88	86
No change, n =	118	117	117	114
Worsened, n =	32	33	33	31

C

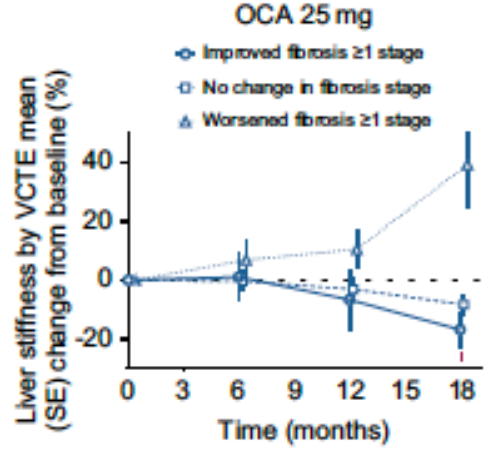
Liver Stiffness by VCTE



Improved, n =	40	38	38	37
No change, n =	111	100	104	100
Worsened, n =	42	41	40	39



Improved, n =	53	53	50	49
No change, n =	104	100	101	95
Worsened, n =	32	30	29	29

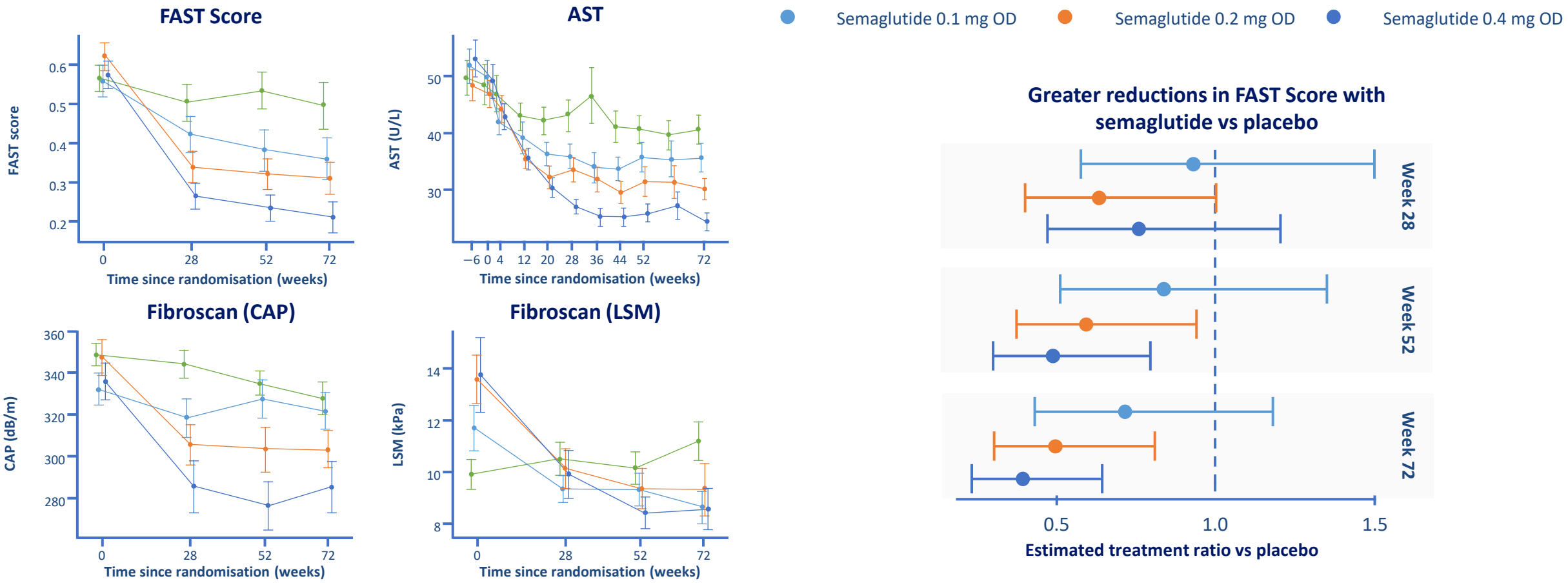


Improved, n =	66	63	59	57
No change, n =	92	90	87	82
Worsened, n =	26	25	26	25

Rinella et al; J Hep 2022

Changes in FAST score during semaglutide treatment

BASELINE TO WEEK 72 – SUBSET ANALYSIS (N=161)



香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

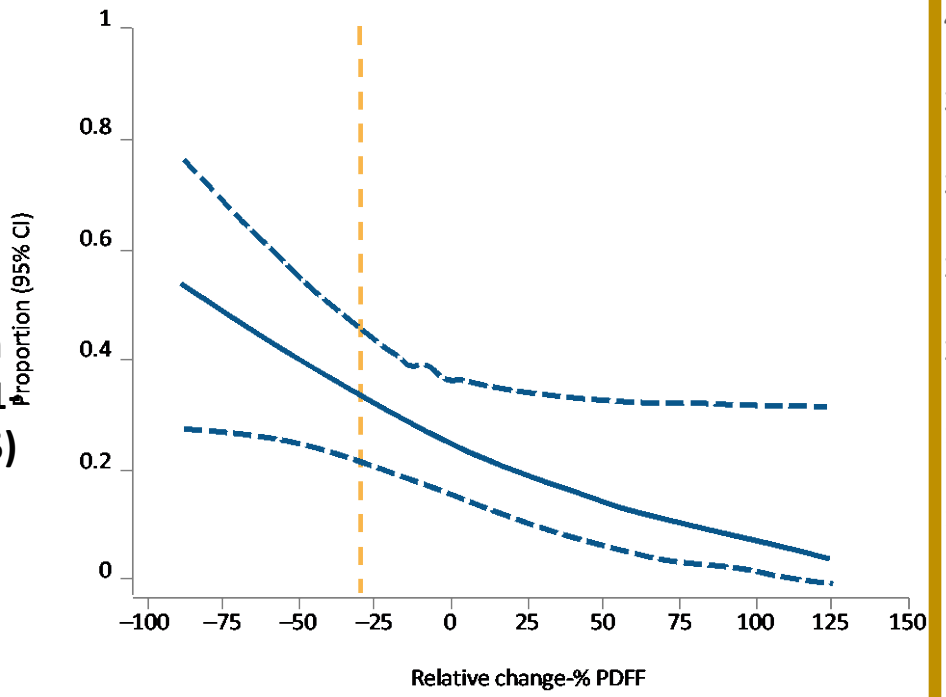
AST, FibroScan CAP and FibroScan LSM are the individual components of the FAST score. Data are for patients with FAST scores at baseline during the on-treatment period. Line plots are observed mean (±SEM). AST, aspartate aminotransferase; CAP, controlled attenuation parameter; FAST, FibroScan aspartate aminotransferase; LSM, liver stiffness measurement; OD, once-daily; SEM, standard error of the mean.

Wong VW et al. EASL 2021 (OS-1556)

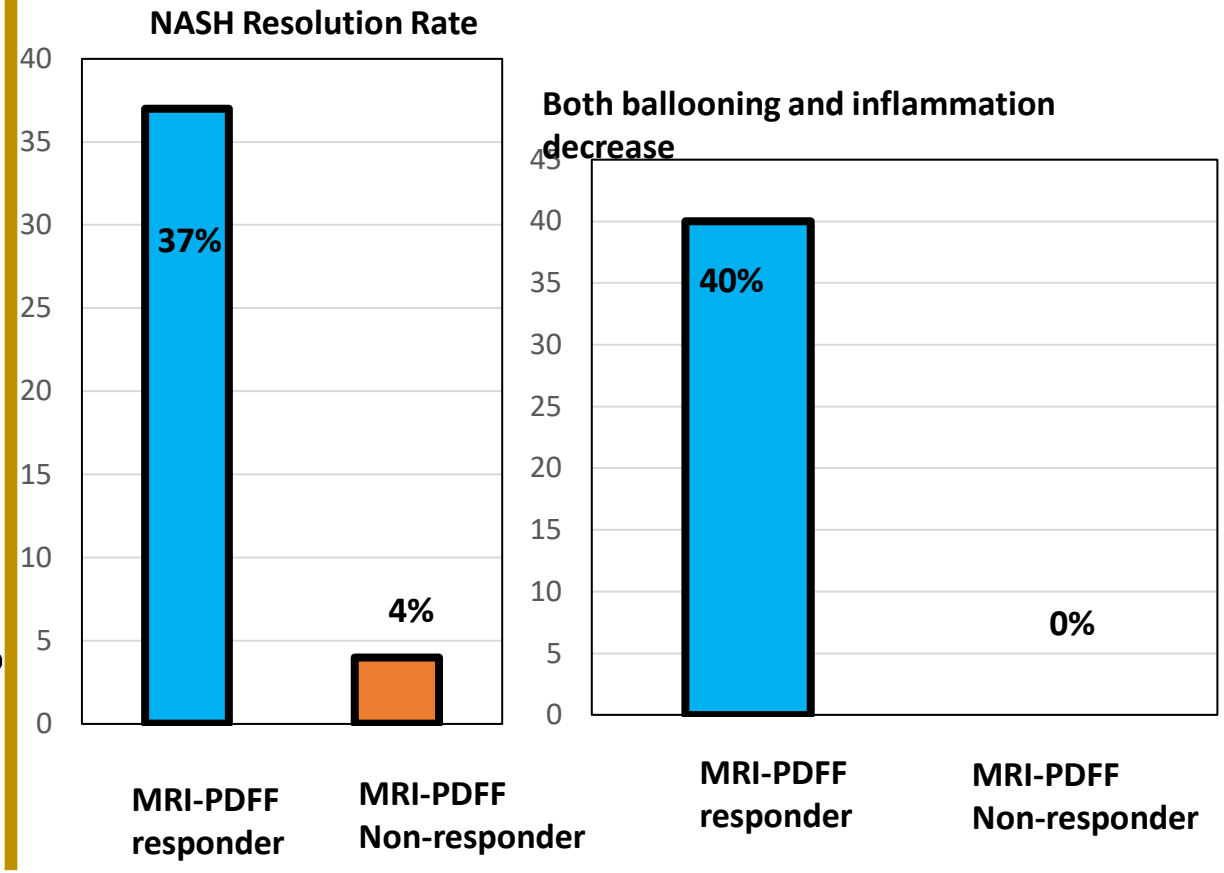
PDFF-Changes in Recent Trials

MRI-PDFF responders had significantly higher odds of histologic response , ballooning with OR 2.9 (95% CI, 1-8.2, p-value 0.05)

Flint Trial



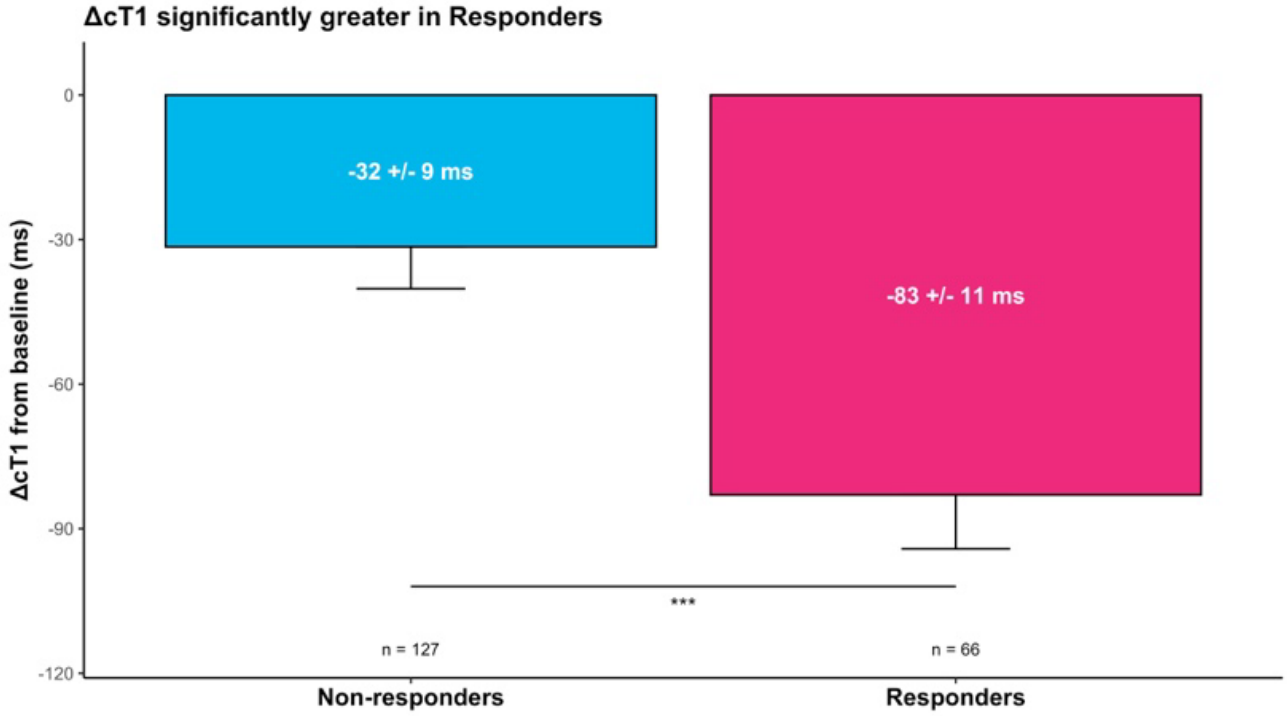
Resmetirom Trial



Patel et al. Advances in Gastro 2016
Loomba EASL 2020
Loomba et al. Hepatology 2020
Harrison et al. Lancet 2019

A Decrease in cT1 Accurately reflects Histological Improvements

- 193 patients 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.**



Decrease in cT1 of ≥ 80ms predicted a decrease in NAS by 2 points or more on histology

Internal Perspectum's data

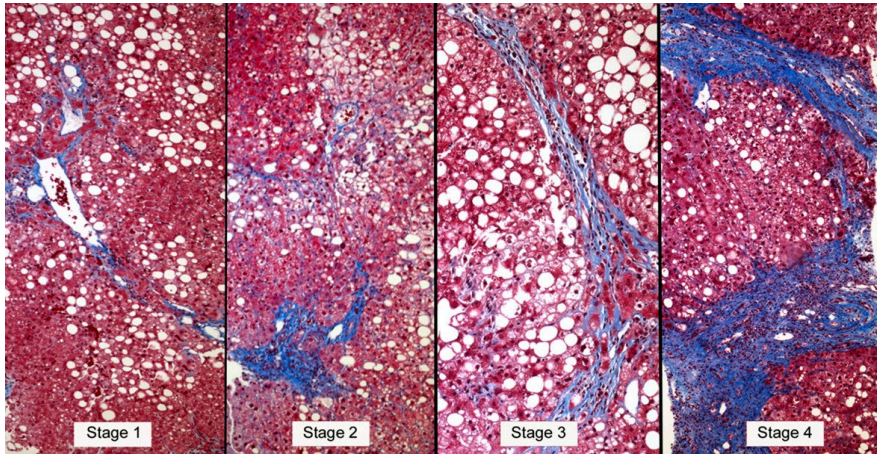
Strategies to Identify at Risk NASH:

2nd Generation

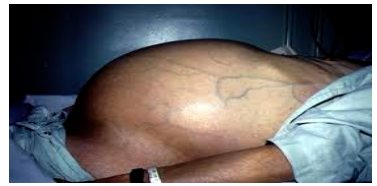
2019

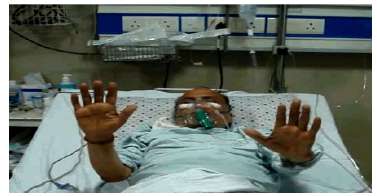
Keep an Eye on The outcomes

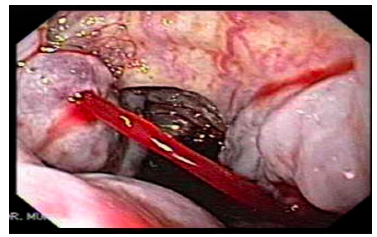
NASH with NAS ≥ 4 + ≥ F2



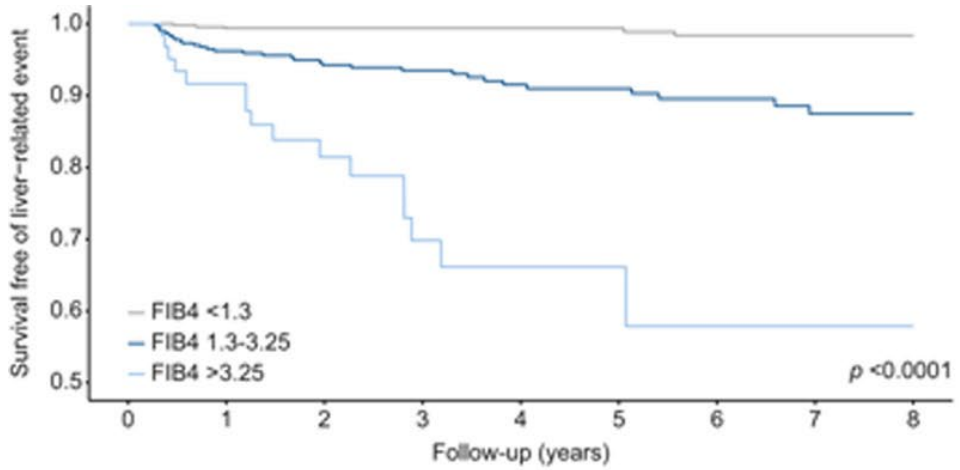
Major Clinical Liver Events (MALO)

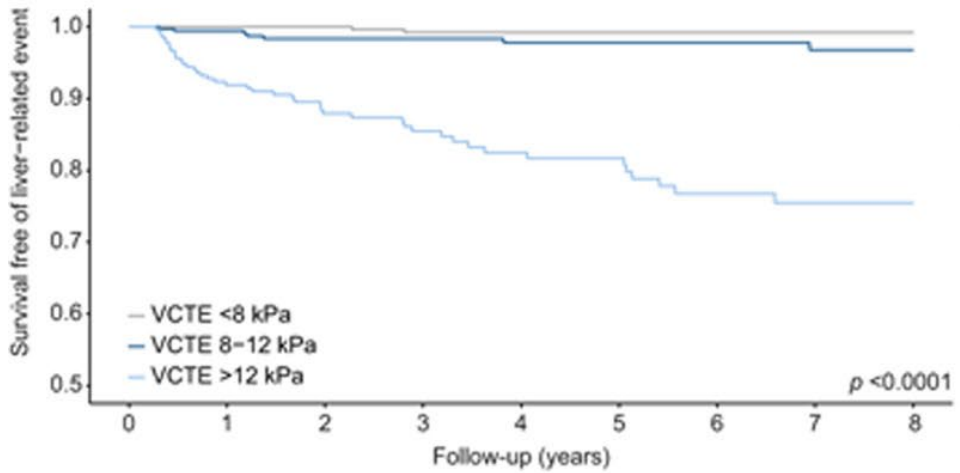


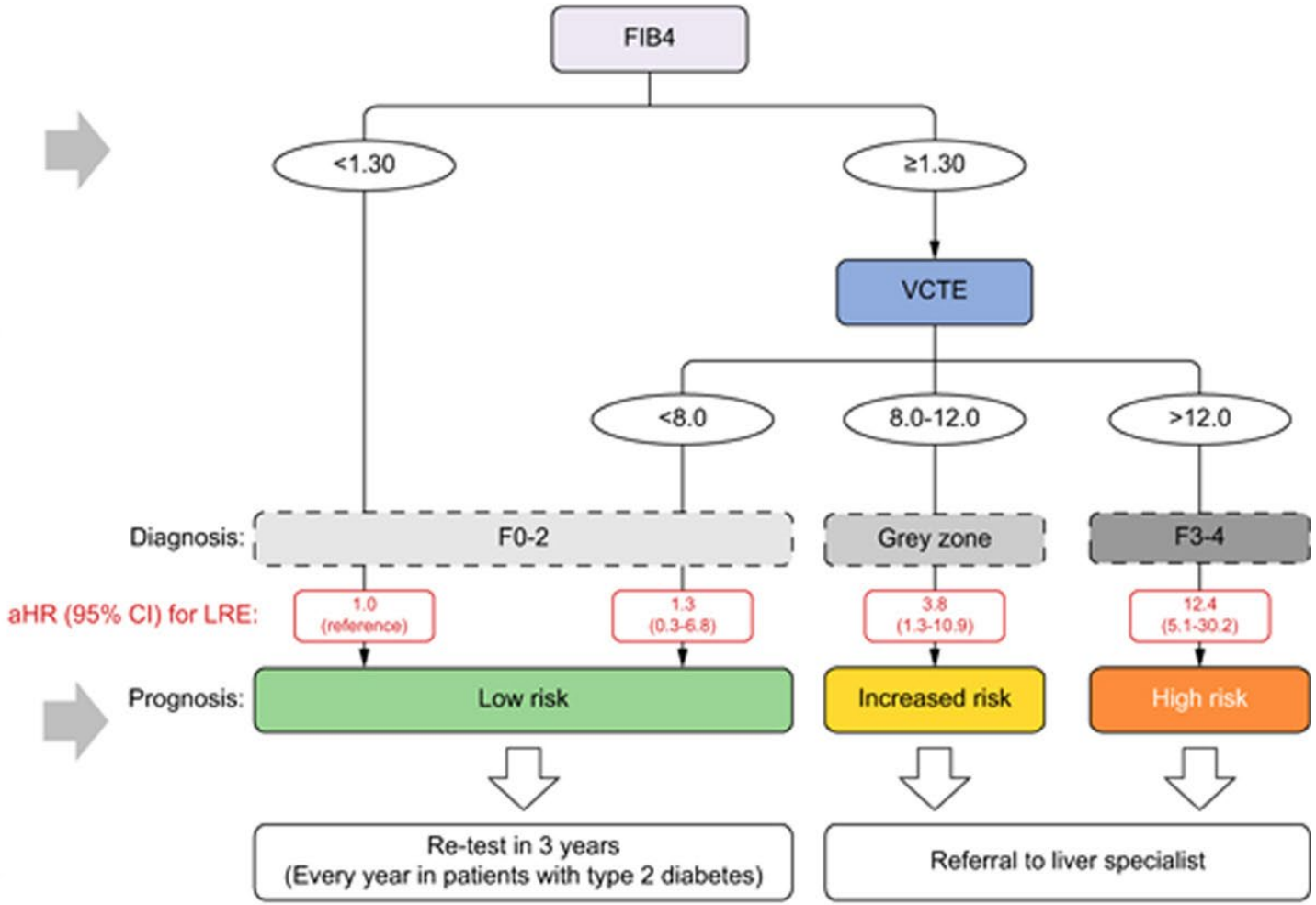




VCTE Predicts Clinical Events





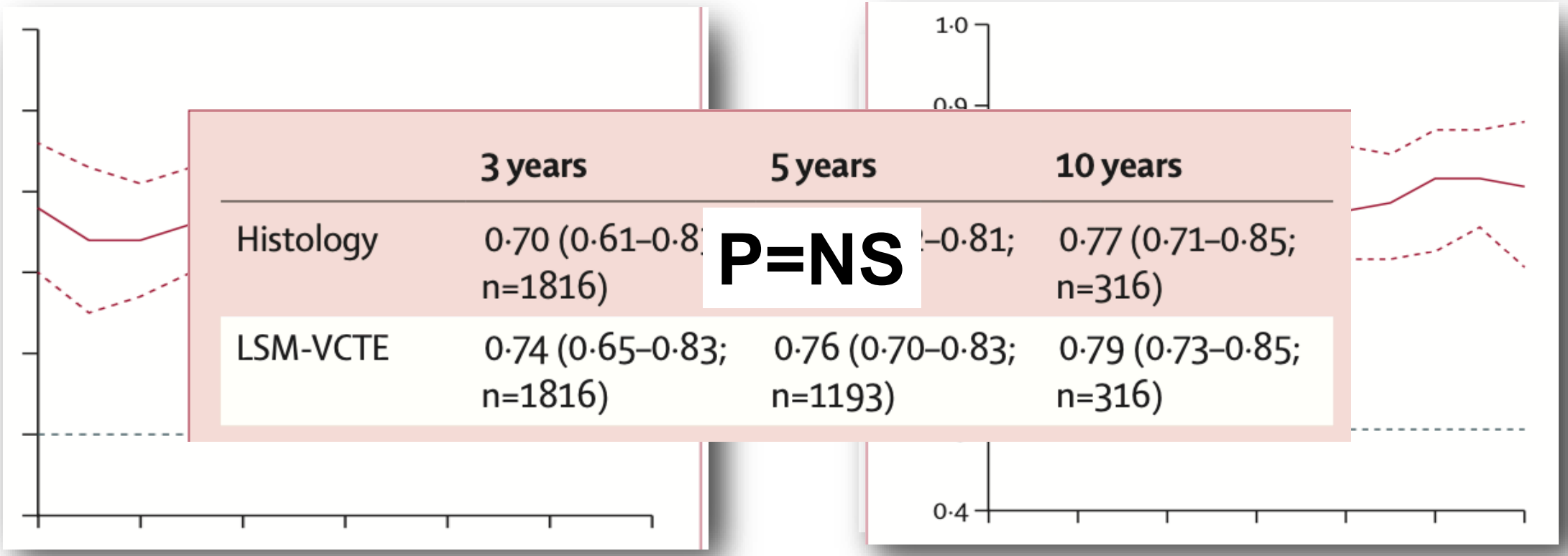


Bousier J et al J Hep 2022

Baseline LSM (VCTE) Predicts Clinical Outcomes as well as liver biopsy in NAFLD

Baseline LSM

Liver biopsy



	3 years	5 years	10 years
Histology	0·70 (0·61–0·8 n=1816)	–0·81;	0·77 (0·71–0·85; n=316)
LSM-VCTE	0·74 (0·65–0·83; n=1816)	0·76 (0·70–0·83; n=1193)	0·79 (0·73–0·85; n=316)

P=NS

IPD Meta-analysis N= 25 studies ; N= 2518 NAFLD patients; median f-up 57 mo

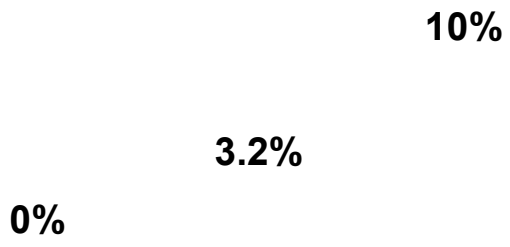
Courtesy of L. Castera

Mozes FE et al. Lancet GH 2023; 8: 704-13

Changes (>20%) in LSM (VCTE) Predict Outcomes in F3-F4

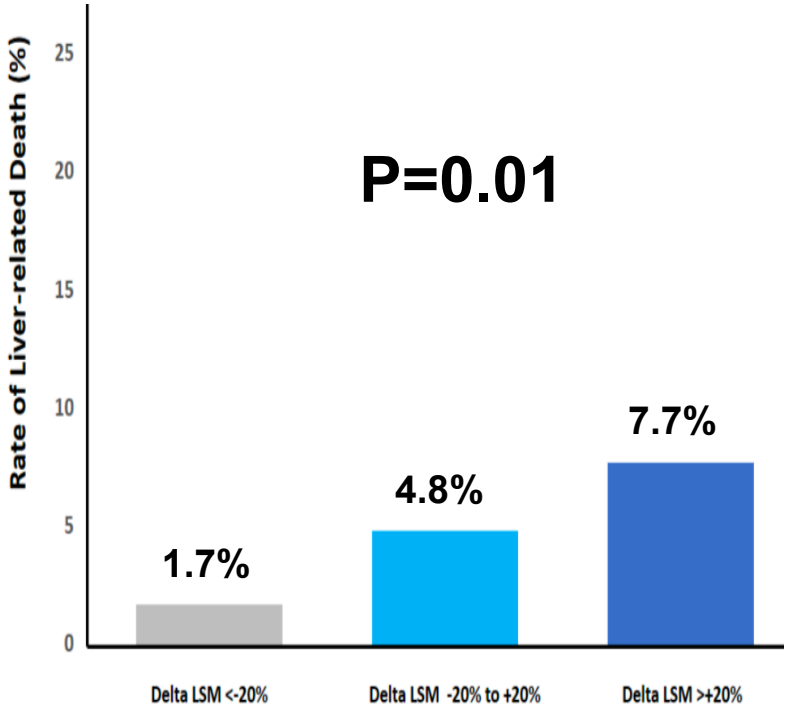
Liver-related events

P=0.001



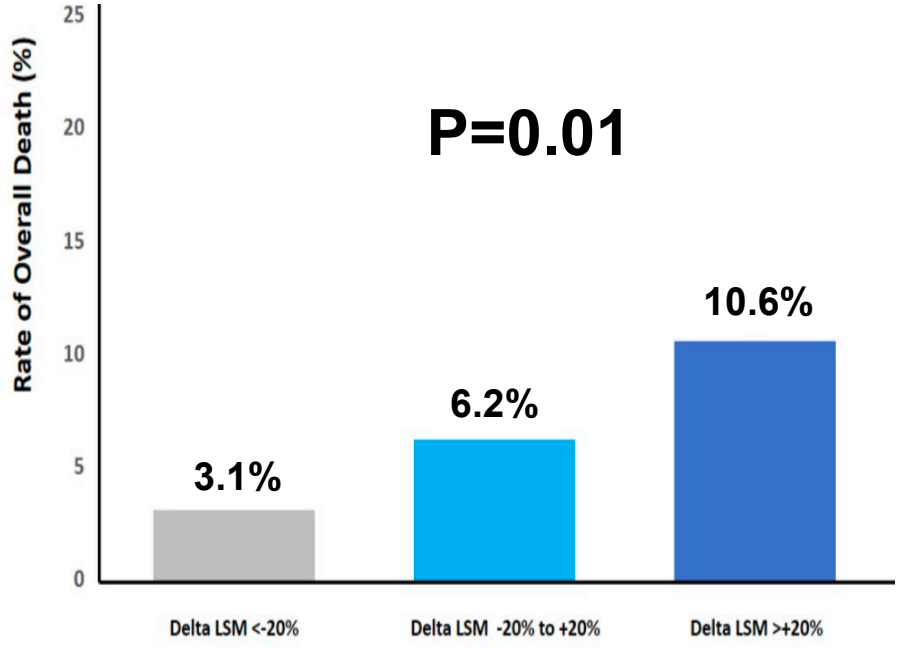
Liver-related mortality

P=0.01



Overall mortality

P=0.01



N= 563 NAFLD patients with LSM >10 kPa and repeated LSM; median f-up 35 months

Petta et al. Clinical Gastroenterol Hepatol 2021; 19:806-15

What magnitude of LSM (VCTE) Decline is Relevant ?

20%

Petta et al. CGH 2021

de Franchis et al. J Hepatol 2022

Courtesy of L. Castera

25%

Harrison et al. J Hepatol 2020

30%?

Aim Conservatively

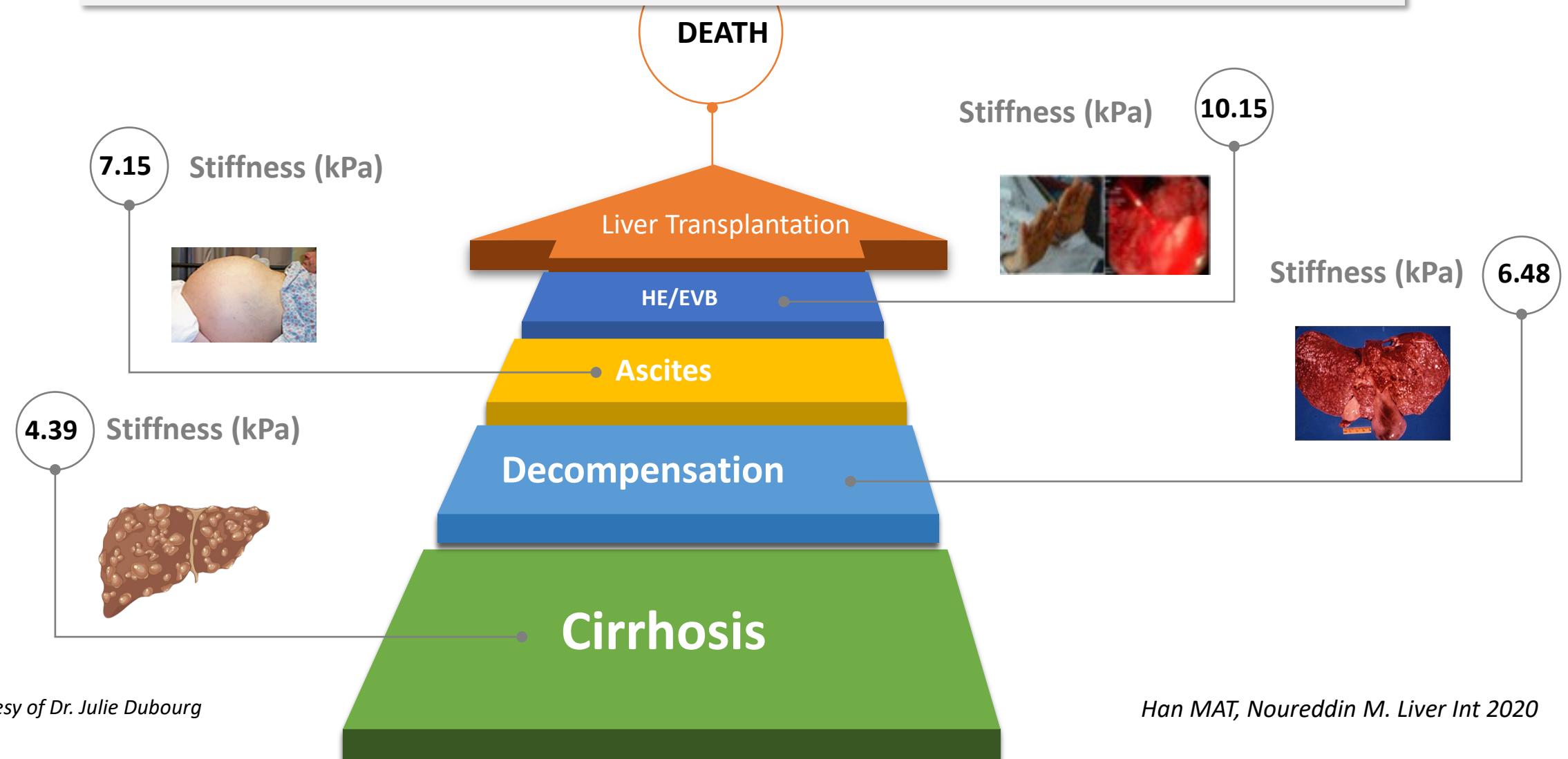
BAVENO 7: Algorithm for the non-invasive determination of Clinically Significant Portal Hypertension (CSPH)

- Although the concept of CSPH is HVPG-driven concept, non-invasive tests are sufficient for septimating CSPH in clinical practice
- VCTE >25----------CSPH
- VCTE 20-25+ PLT <150-------CSPH
- VCTE 15-20 +PLT <110-------CSPH

Franchis et al; J Hep 2022

MRE Predicts Liver Outcomes

Odds of Decompensation increase as liver stiffness increase (OR 3.28)

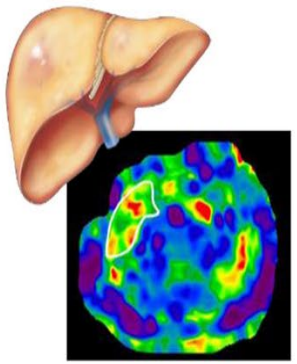


Slide courtesy of Dr. Julie Dubourg

Han MAT, Noureddin M. Liver Int 2020

MRE is Predicts Liver Outcomes

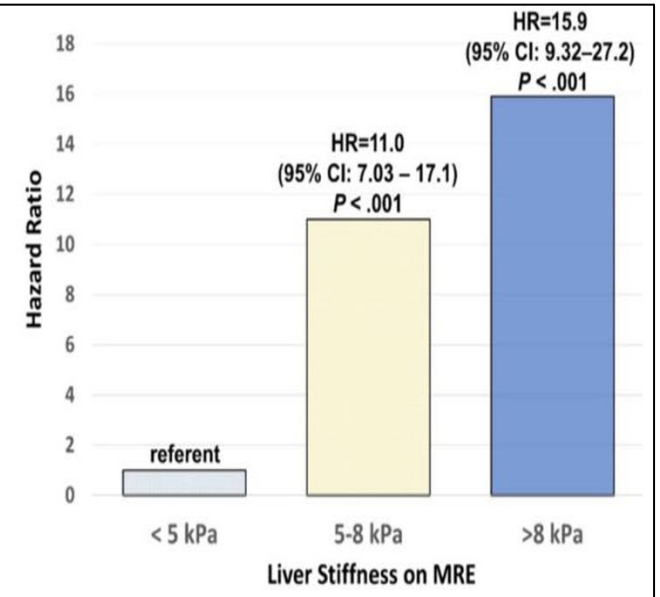
Underwent magnetic resonance elastography

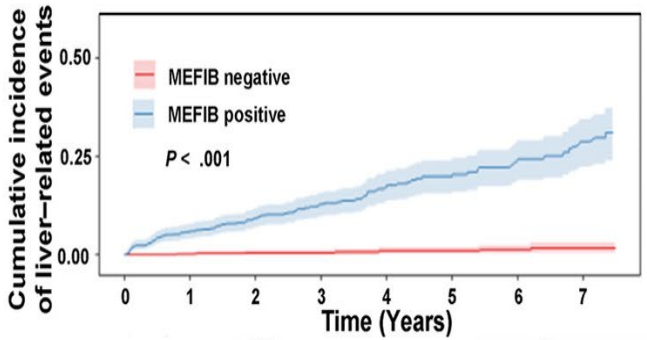


Liver stiffness assessed by MRE is associated with development of ascites, hepatic encephalopathy and varices needing treatment

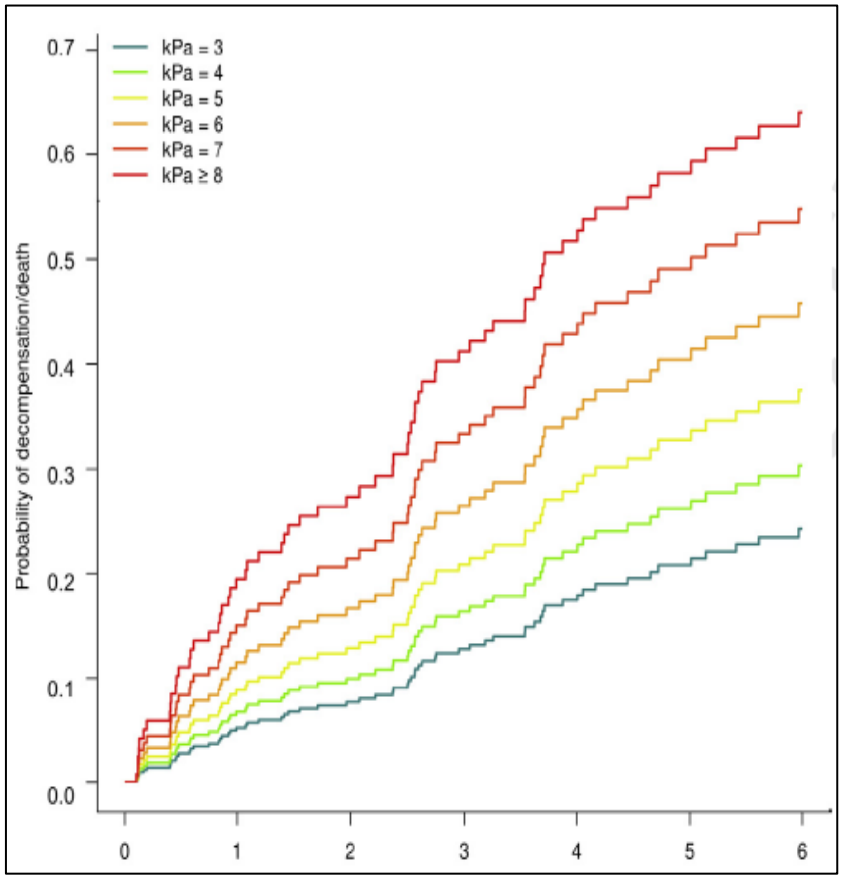
The MEFIB combination of MRE and FIB-4 (defined as positive when MRE ≥ 3.3kPa and FIB-4 ≥ 1.6) has excellent negative predictive value for hepatic decompensation.

Ajmera et al; Gastro 2022



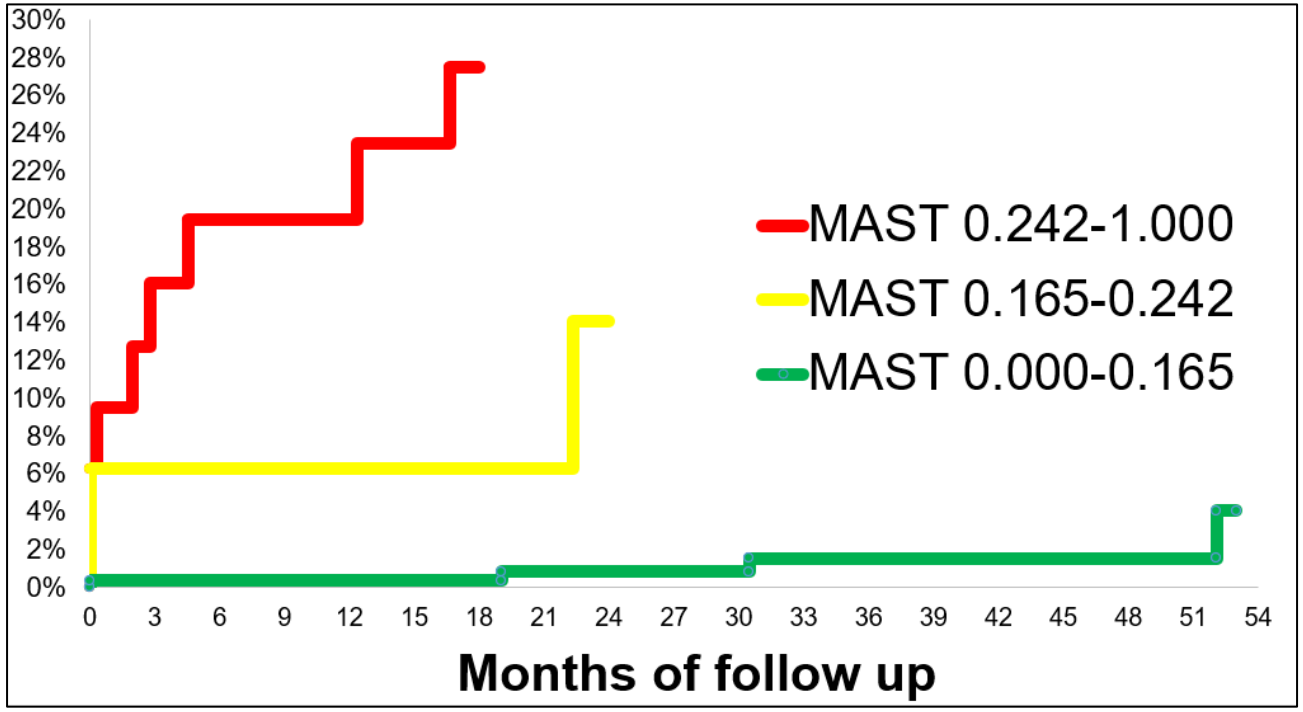


Gastroenterology



Gindener T…Allen A; CGH 2021

The MAST Score is Accurate in Predicting Major Adverse Liver Outcome (MALO), Hepatocellular Carcinoma, Liver Transplant, and Liver-Related Death



- MAST score accurately:
  - Identifies NASH patients at highest risk for disease progression
  - Predicts up to 22-fold increased risk of adverse outcomes (MALO, liver transplant, HCC, and liver-related death)
  - **C statistic of prediction: 0.92**

Troung E; ..Noureddin M; CGH 2023

Conclusions

- Multiple strategies can be placed to identify ”at risk NASH”
- First generation tests assessed mainly fibrosis (with AST added for activity/fibrosis)
- 2nd generation tests/scores include the disease activity and/or optimize fibrosis stage assessment (e.g., Agile 3+ and Agile 4)
- More data are coming to assess longitudinal changes
- Keep an eye on the association with outcomes!!..... The Future is Bright

Serologic Non-Invasive Tests for Hepatic Fibrosis (NITs)

Diagnostic Performance and Limitations

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Desert Liver Conference
March 1, 2024

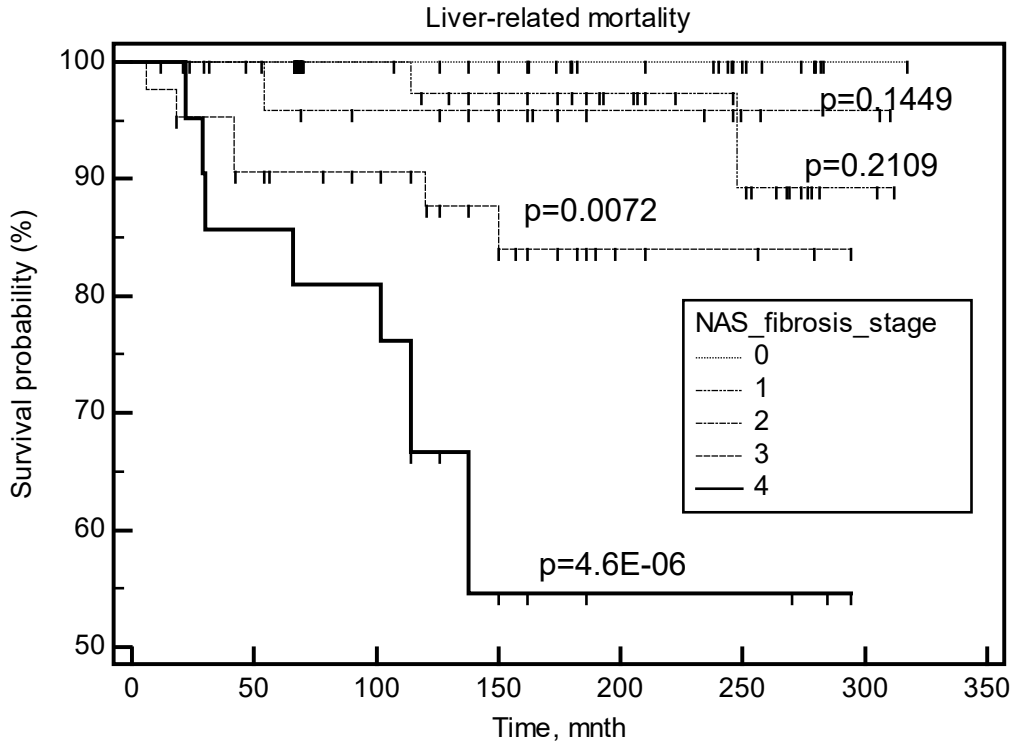
Disclosures

- Grant Support: NIH, CDC/NIOSH, Pfizer, The Kinetix Group, Histoindex
- Consultant/Advisory Board: Madrigal, Theratechnologies, NOVO Nordisk, Intercept, The Kinetix Group, Fibronostics, Merck, GSK

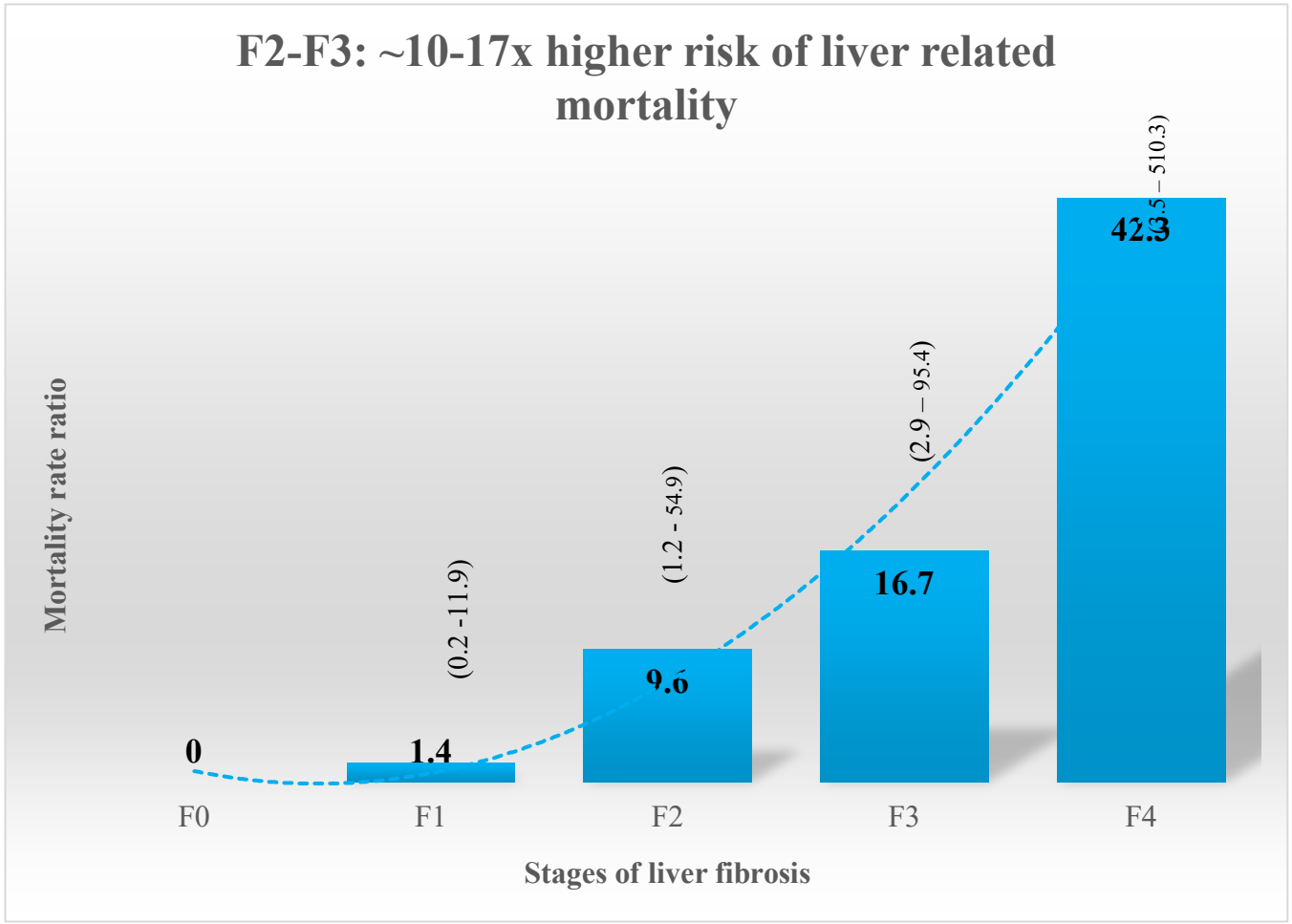
Agenda

- Conceptual framework of NITs
  - Fibrosis Matters
- Population Based Screening in High-Risk Groups
- Identifying “At-Risk” NASH/MASH
  - Target population for clinical trials and FDA-approved treatments
- Monitoring Response to Treatment
- Progression to Cirrhosis
- Predicting Clinical Outcomes
- Fibrosis Progression
  - Longitudinal vs. Cross-Sectional View

Fibrosis Matters

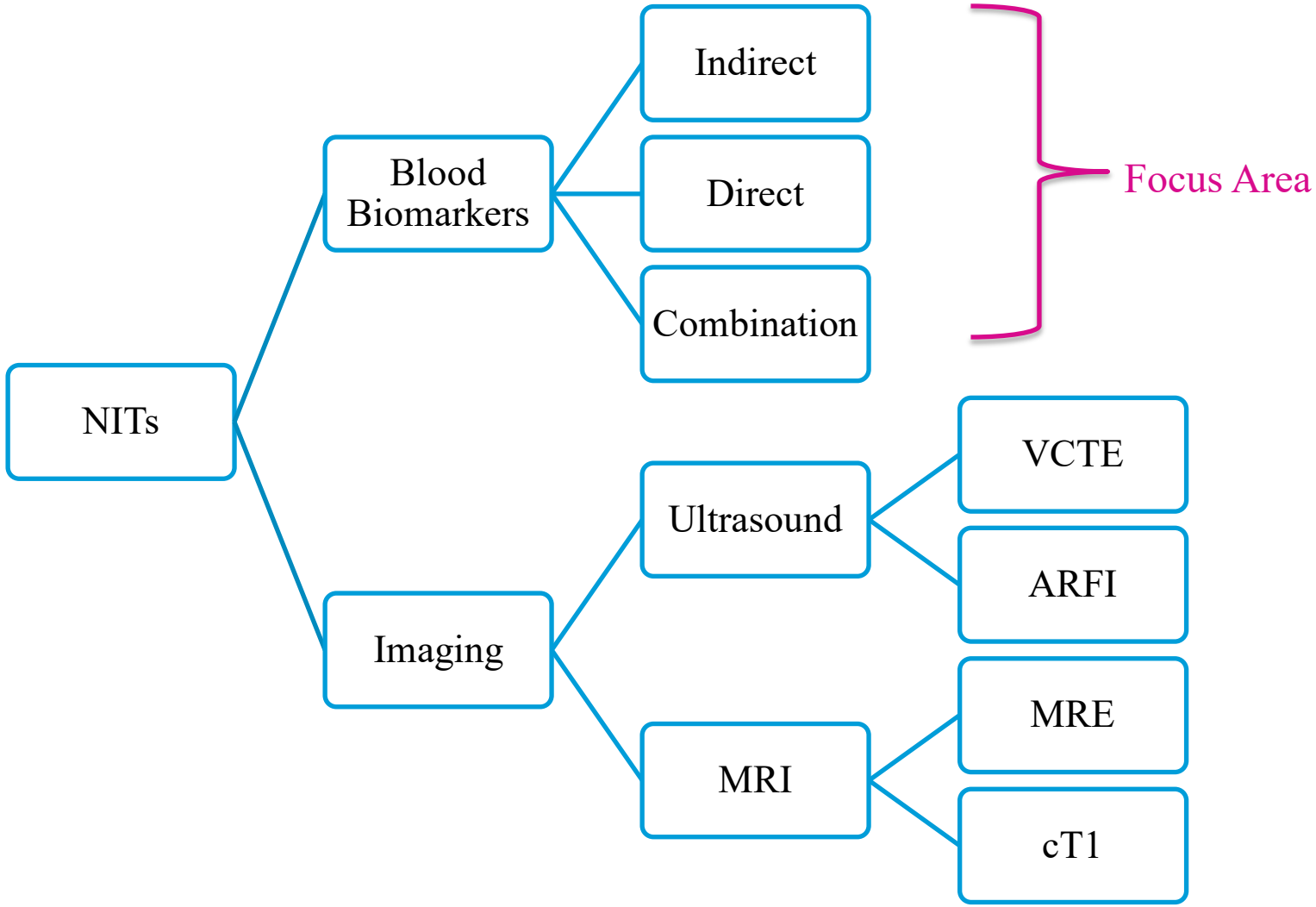


Younossi Z et al., Hepatology, 2011

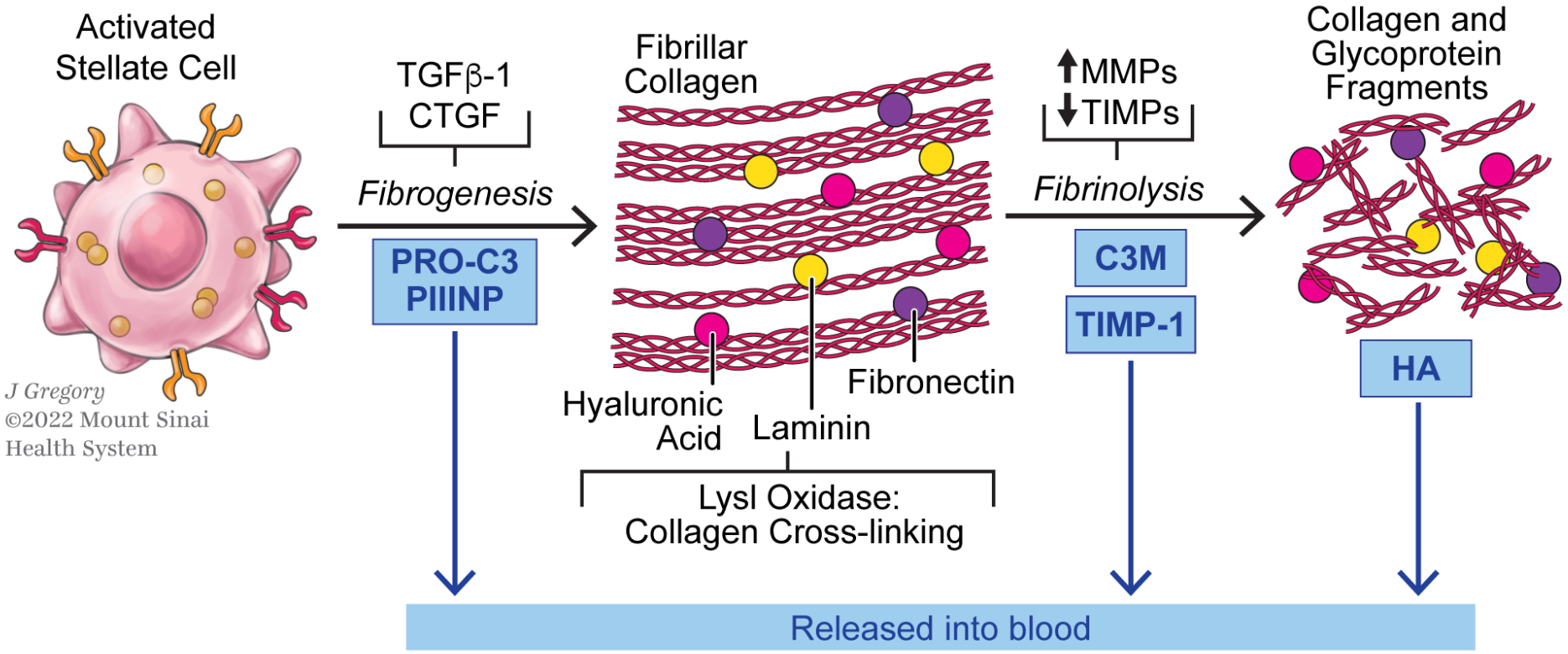


Dulai et al., Hepatology, 2017

Classification of NITs



Direct Biomarkers: Tracking Fibrogenesis and Fibrinolysis

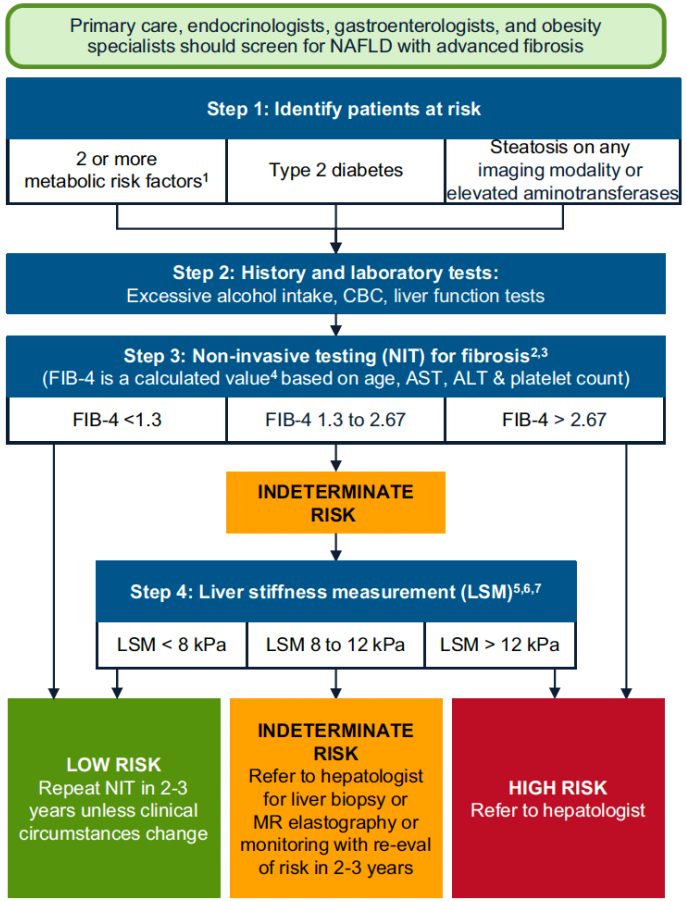


ELF=PIIINP, HA, TIMP-1

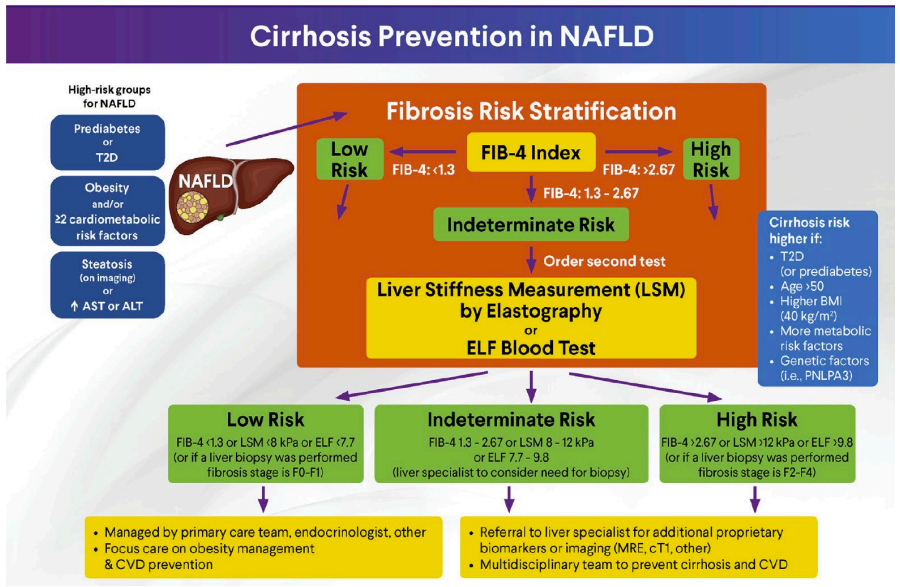
Bansal MB, Hepatic Fibrogenesis, INEDSYS submitted

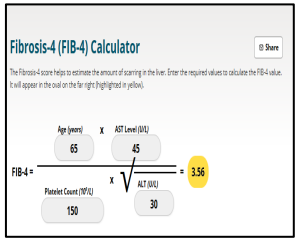
Screening in High-Risk Populations:
The Rule-Out Approach

AGA pathway



AACE pathway





If age > 65
- Can use FIB-4>2.0 as cut off

If age <35
- Can use FIB-4 >1.0 as cut off

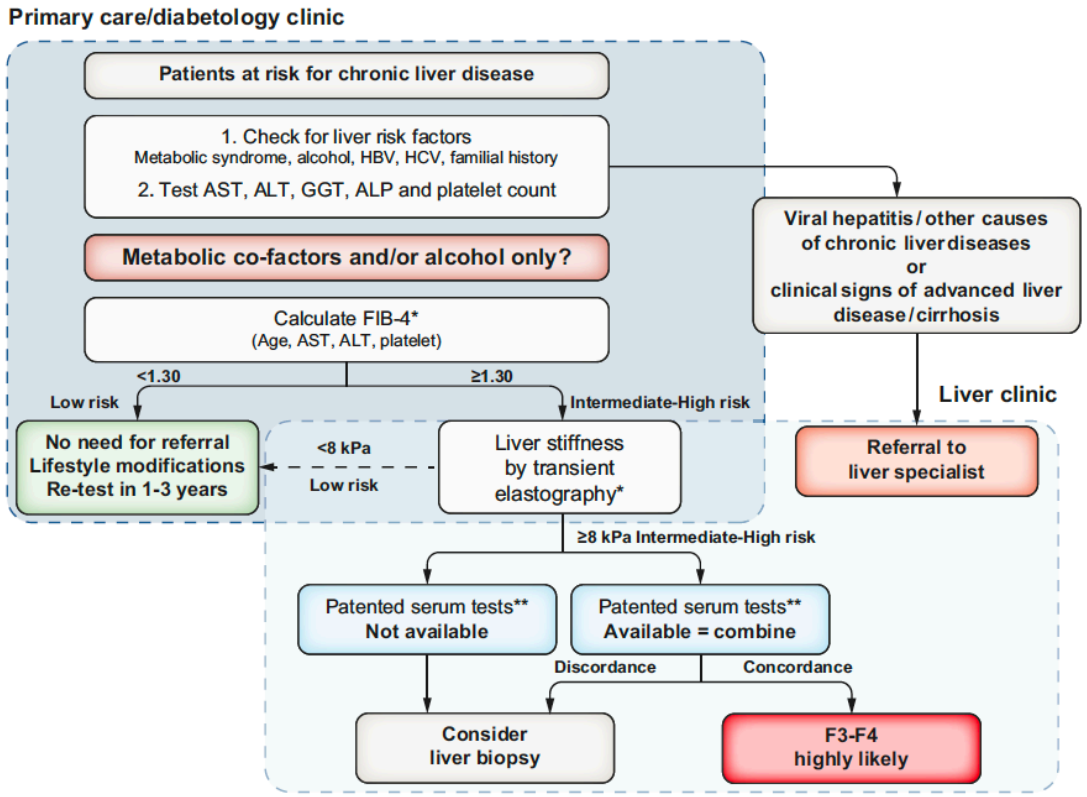
Metabolic Risk Factors
- Central Obesity
- High Triglycerides
- Low HDL
- Hypertension
- Pre-Diabetes/Insulin Resistance

Kanwal F et al, Gastroenterology, 2021

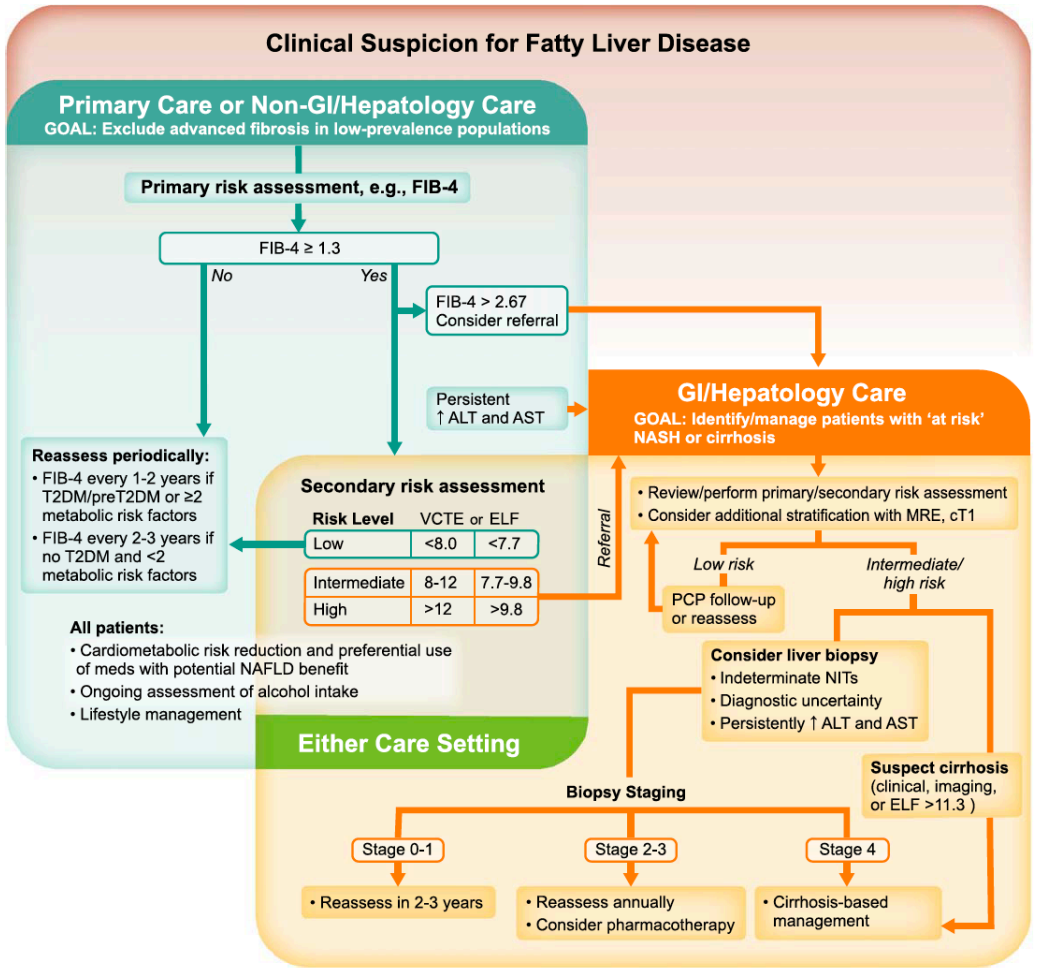
Cusi K et al, Endocrine Practice, 2022

Screening in High-Risk Populations:
The Rule out approach

EASL



AASLD



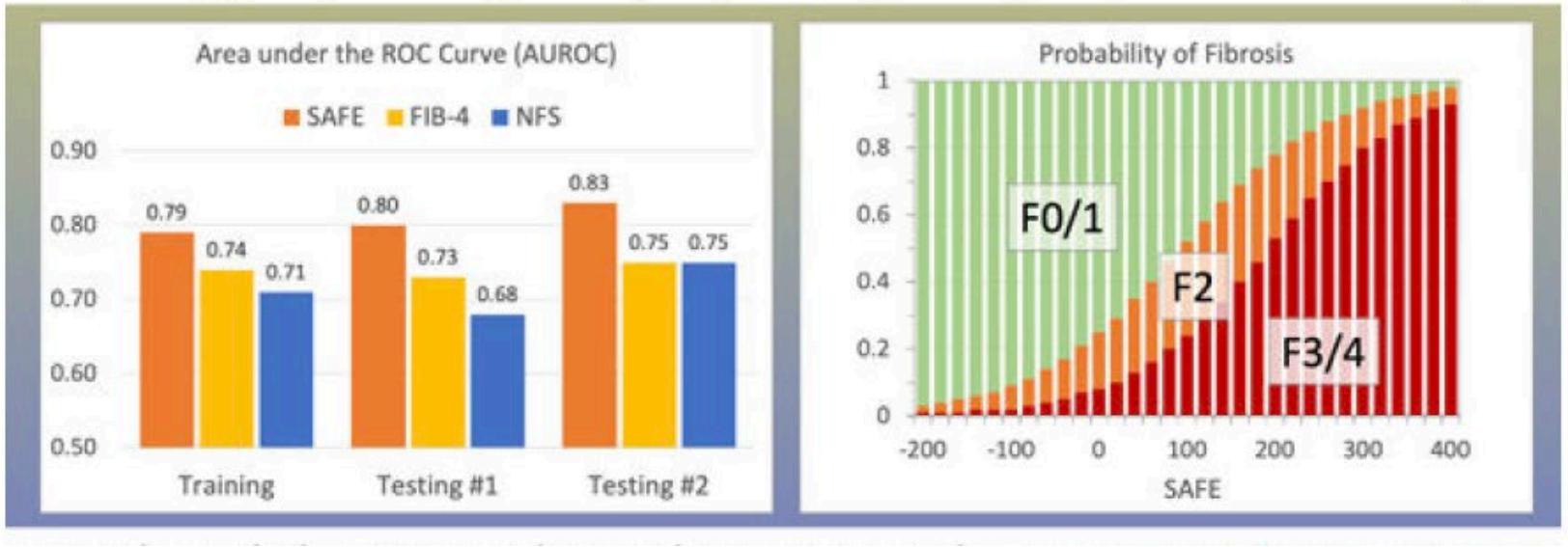
EASL, J Hep, 2022

Rinella M et al, Hepatology, 2022

SAFE Score: Increasing Scores correlate with shorter survival

The Steatosis-Associated Fibrosis Estimator (SAFE) Score

- Developed to distinguish clinically significant fibrosis (F2+) versus minimal fibrosis (F0/1).
- Includes age, BMI, diabetes, platelets, AST, ALT and globulins (total protein minus albumin).



NASH CRN N=676

FLINT trial N=280

Stanford Cohort N=130

NHANES III n=11,954

- 54.0% had low- probability (n=2,324),
- 14.4% high-probability (n=620)
- 31.6% intermediate-probability (n=1,362) of ≥F2

After a median follow-up of 22.4 years 20-yr survival

- 86.8% for MASLD with a low-risk score (SAFE<0)
- 60.5% for those at intermediate risk (SAFE 0–100)
- 37.2% for those at high risk (SAFE≥100).

Increasing SAFE scores correlated with shorter overall survival (not with liver-specific outcomes) with an adjusted HR of 1.53 ($p < 0.01$) for subjects with SAFE > 100

Sripongpun et al, Hepatology, 2023

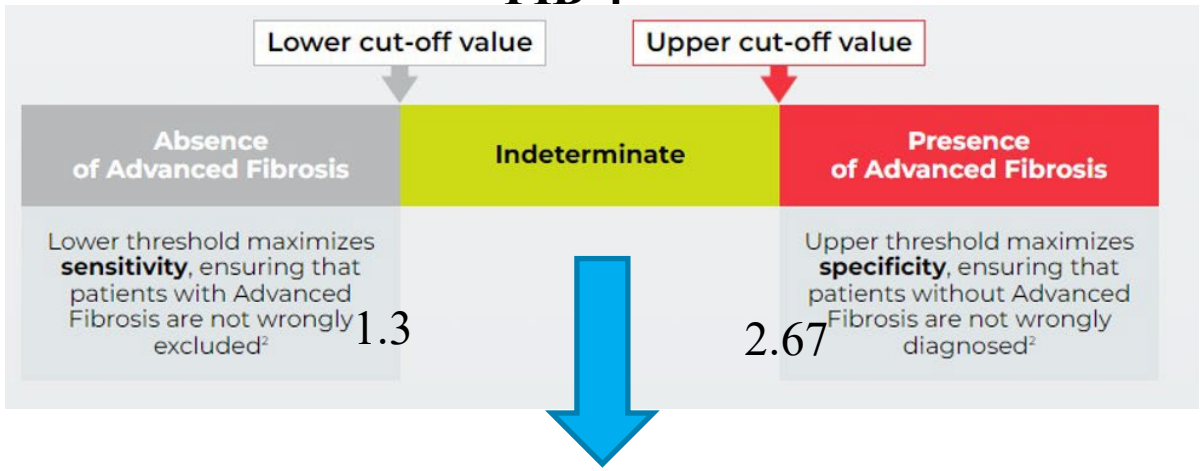
Identifying "At Risk MASH" The Rule In Approach

Identifying "At Risk" MASH
- NAS ≥ 4
- F2 fibrosis

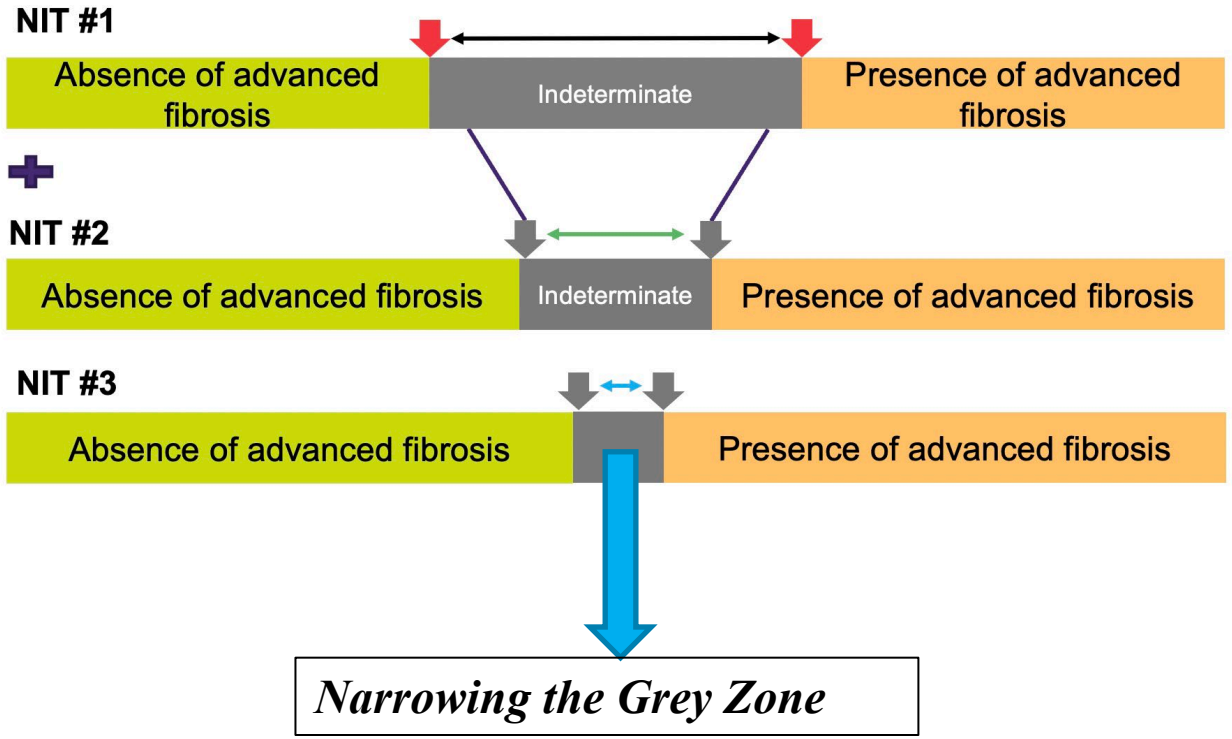
Patient Population
- Clinical Trials
- FDA-approved therapies

- Sequential or Combination Testing
  - Better detection of advanced fibrosis and cirrhosis, especially when patients fall into the indeterminate zone

FIB-4



The Infamous GREY ZONE



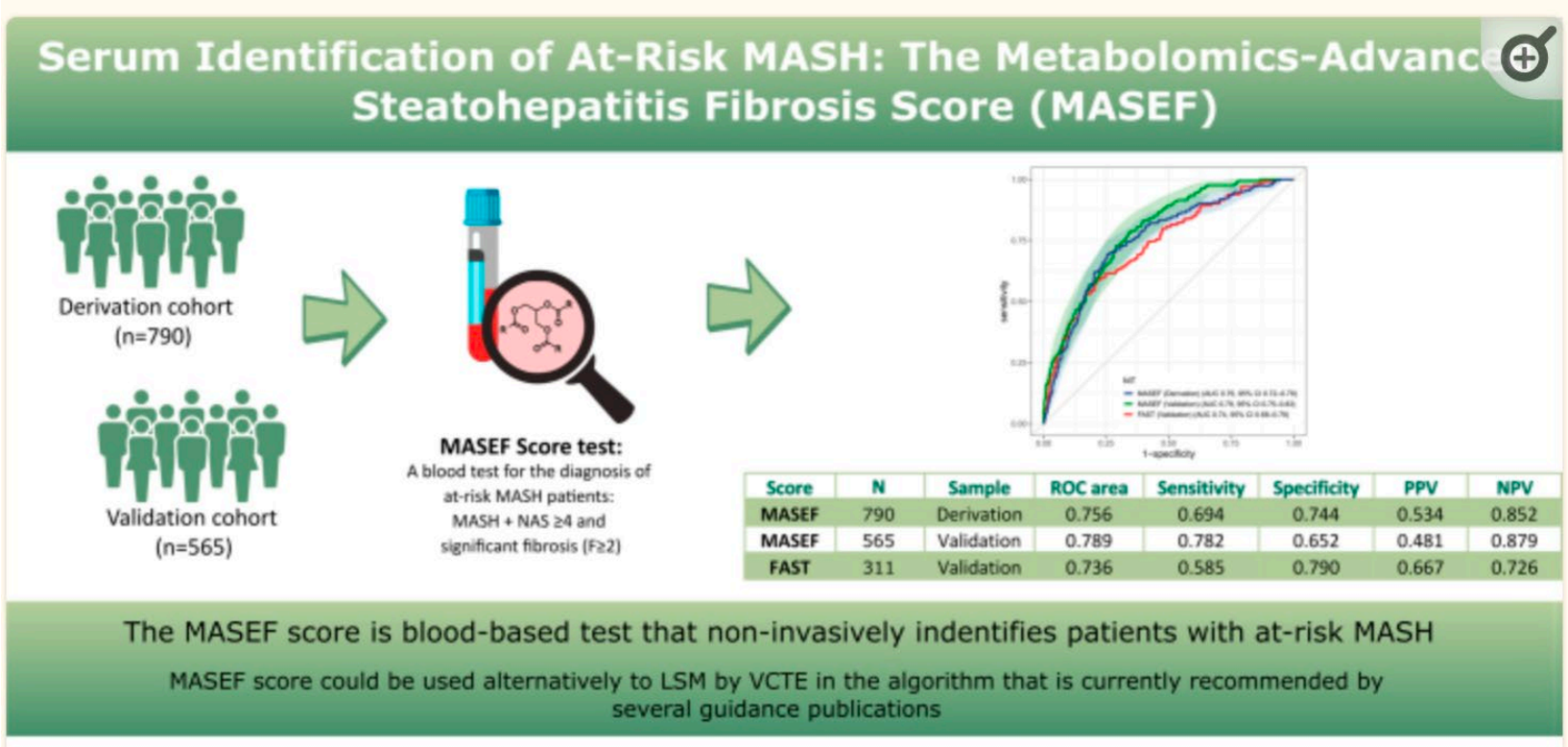
Anstee et al; Hepatology 2019

Alphabet Soup: Serologic Tests NITS Studied to Identify At-Risk MASH/Significant Fibrosis

- APRI (AST/ALT ratio)
- FIB-4
- Fibrotest
- NAFLD Fibrosis Score
- Pro-C3/C3M
- ADAPT
- FIBC3
- ABC3D
- MACK-3
- ELF™
- NIS-4/NIS-2™
- MASEF Score
- LIVERFASt™
- MASML™

MASEF Score: Identifying At-Risk MASH/Alternate to LSM in AGA/AASLD Guidelines

- **Metabolomics:** Measures lipids, carbohydrates, amino acids, and other metabolites
- Probability Score (0-1) for at-risk MASH
- Machine learning models
- Final MASEF score includes 12 lipids, BMI, AST, and ALT
- MASEF score <0.258=Low risk
- MASEF score >0.513=At-risk MASH

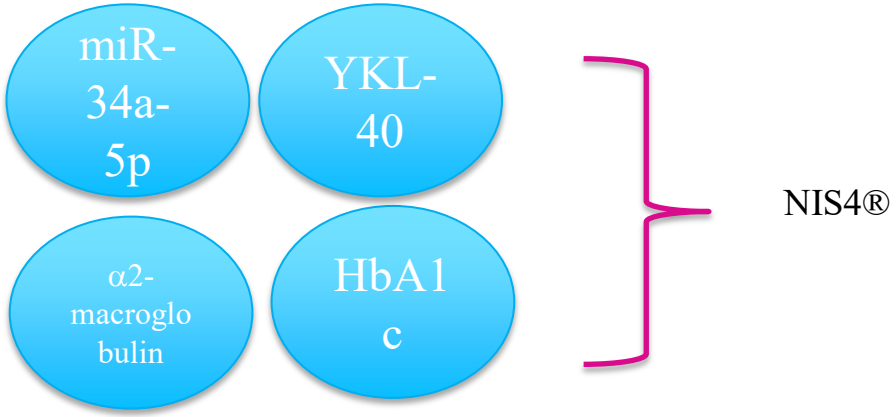


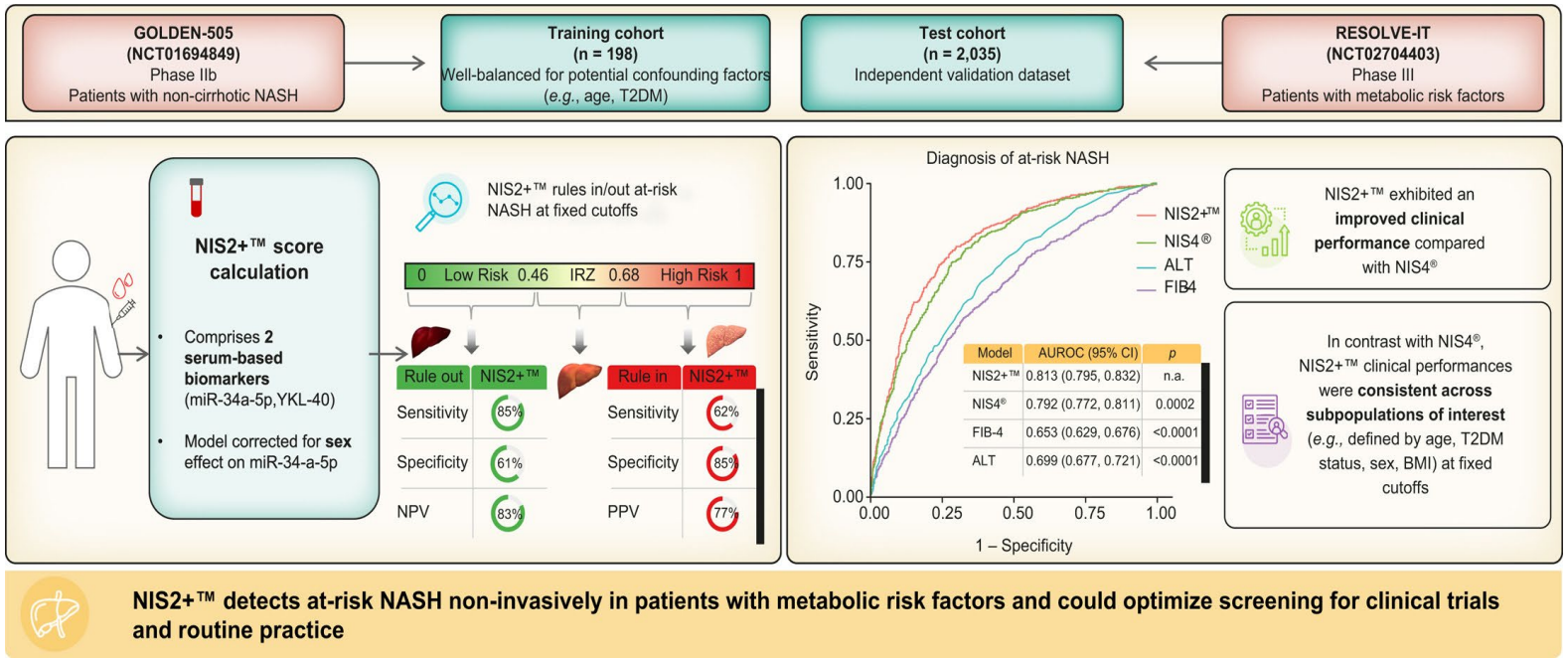
Score	N	Sample	ROC area	Sensitivity	Specificity	PPV	NPV
MASEF	790	Derivation	0.756	0.694	0.744	0.534	0.852
MASEF	565	Validation	0.789	0.782	0.652	0.481	0.879
FAST	311	Validation	0.736	0.585	0.790	0.667	0.726

Overall performance of Fib-4+MASEF, slightly higher but not statistically different than Fib-4 +LSM

Nourredin et al, Hepatology, 2024

NIS-2+: Blood based biomarker to detect at-risk NASH in those age>65





- Patients ≥65 (n = 410)
- NIS2+™ highest AUROC (0.83) compared to NIS4® (0.78), FIB-4 (0.68), NFS (0.58), ELF™(0.69), and ALT (0.74) all p ≤ 0.0009)
- With fixed cut off of <0.46 for ruling out at-risk NASH: NPV=86%
- Fixed cut-off of >0.68 for ruling in At-risk NASH: PPV=76%

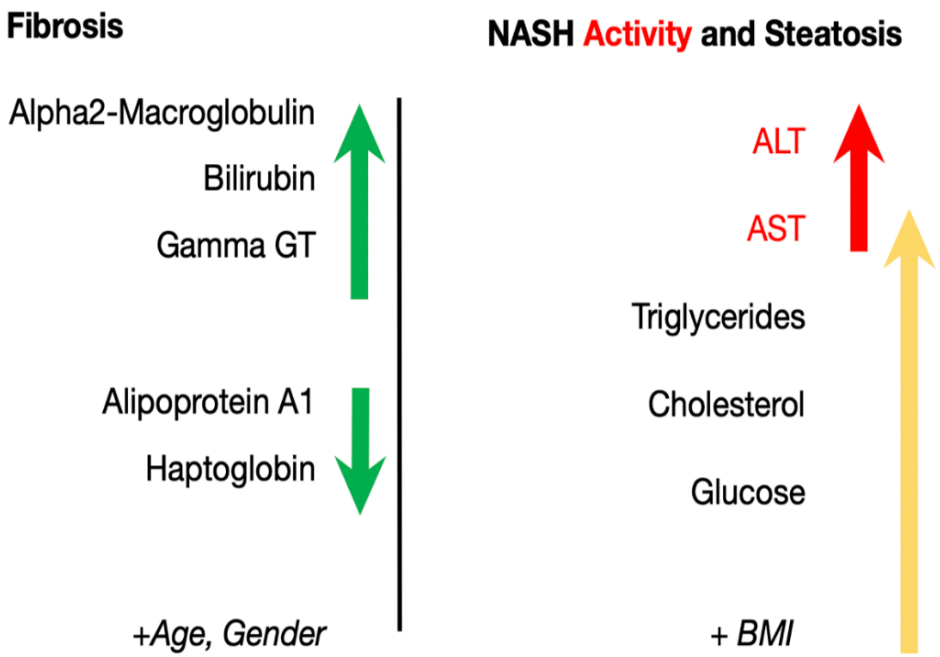
Harrison SA, J Hep, 2023

Sanyal A et al, Hepatology Communications, 2023

LIVERFASt

LIVERFASt™ Biomarkers

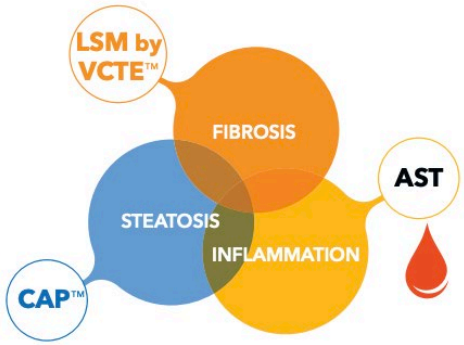
		Liver Injury		
		Fibrosis	Activity	Steatosis
	Age	✓	✓	✓
	Gender	✓	✓	✓
	BMI	✓	✓	✓
BIOMARKERS	α2-macroglobulin	✓	✓	✓
	Haptoglobin	✓	✓	✓
	Apolipoprotein A1	✓	✓	✓
	Total bilirubin	✓	✓	✓
	GGT	✓	✓	✓
	ALT *with pyridoxal phosphate*		✓	✓
	AST *with pyridoxal phosphate*			✓
	Fasting Glucose			✓
	Triglycerides			✓
	Total Cholesterol			✓



Courtesy of Dr. Naim Alkhouri

Combining Serologic NITs with Liver Stiffness Assessments To Identify At-Risk NASH

FAST Score to detect At-Risk NASH/MASH



	AUROC (95% CI)	n	Prevalence of NASH + NAS ≥ 4 + F ≥ 2	Rule-out zone (FAST ≤0·35)				Grey zone (FAST 0·35–0·67), n (%)	Rule-in zone (FAST ≥0·67)			
				n (%)	Sensitivity	Specificity	NPV		n (%)	Specificity	Sensitivity	PPV
Derivation cohort	0·80 (0·76–0·85)	350	174 (50%)	113 (32%)	0·90 (157/174)	0·53 (93/176)	0·85 (93/110)	136 (39%)	101 (29%)	0·90 (159/176)	0·48 (84/174)	0·83 (84/101)
French bariatric surgery cohort	0·95 (0·91–0·99)	110	16 (15%)	69 (63%)	1·00 (16/16)	0·73 (69/94)	1·00 (69/69)	22 (20%)	19 (17%)	0·93 (87/94)	0·75 (12/16)	0·63 (12/19)
USA screening cohort	0·86 (0·80–0·93)	242	28 (12%)	194 (80%)	0·64 (18/28)	0·86 (183/214)	0·95 (183/193)	39 (16%)	9 (4%)	0·99 (212/214)	0·25 (7/28)	0·78 (7/9)
China Hong-Kong NAFLD cohort	0·85 (0·76–0·93)	83	36 (43%)	28 (34%)	0·94 (34/36)	0·55 (26/47)	0·93 (26/28)	29 (35%)	26 (31%)	0·89 (42/47)	0·58 (21/36)	0·81 (21/26)
China Wenzhou NAFLD cohort	0·84 (0·73–0·95)	104	9 (9%)	55 (53%)	0·89 (8/9)	0·56 (53/95)	0·98 (58/67)	37 (36%)	12 (11%)	0·92 (87/95)	0·44 (4/9)	0·33 (4/12)
French NAFLD cohort	0·80 (0·73–0·86)	182	78 (43%)	67 (37%)	0·88 (69/78)	0·56 (58/104)	0·87 (58/67)	69 (38%)	46 (24%)	0·89 (93/104)	0·45 (35/78)	0·76 (35/46)
Malaysian NAFLD cohort	0·85 (0·78–0·91)	176	36 (20%)	78 (44%)	0·94 (34/36)	0·54 (75/140)	0·97 (75/77)	59 (34%)	39 (22%)	0·87 (122/140)	0·58 (21/36)	0·54 (21/39)
Turkish NAFLD cohort	0·74 (0·65–0·82)	129	74 (57%)	26 (20%)	0·91 (67/74)	0·35 (19/55)	0·73 (19/26)	57 (44%)	46 (36%)	0·82 (45/55)	0·49 (36/74)	0·78 (36/46)
Pooled external patients cohort	0·85 (0·83–0·87)	1026	277 (27%)	517 (51%)	0·89 (246/277)	0·64 (483/749)	0·94 (483/514)	312 (30%)	197 (19%)	0·92 (688/749)	0·49 (136/277)	0·69 (136/197)

- Available AUROC = 0.74 – 0.95
- PPV = up to 0.83 for FAST≥ 0.67
- NPV = 0.73 to 1 for FAST≤ 0.35
- Poor performance in Low Prevalence settings
- Gray Zone 16-44%
- NASH CRN data
  - -AUROC=0.81
  - -NPV 0.90
  - -PPV 0.69
  - -Better performance in non-whites vs. whites (0.91 vs. 0.78; p=0.001), normal BMI vs. BMI>35 (0.94 vs 0.78; p=0.008)

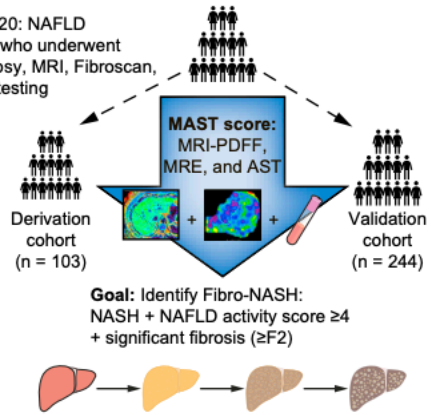
Newsome et al, Lancet Gastroenterol and Hepatol, 2020
Noureddin N et al; Hepatology 2020
Woreta TA et al., PLOS One, 2022

MAST score to detect At-risk NASH/MASH

MAST score: MRI-Based Score to Identify Patients with NASH and Significant Fibrosis

Methods

2016-2020: NAFLD patients who underwent liver biopsy, MRI, Fibroscan, and lab testing



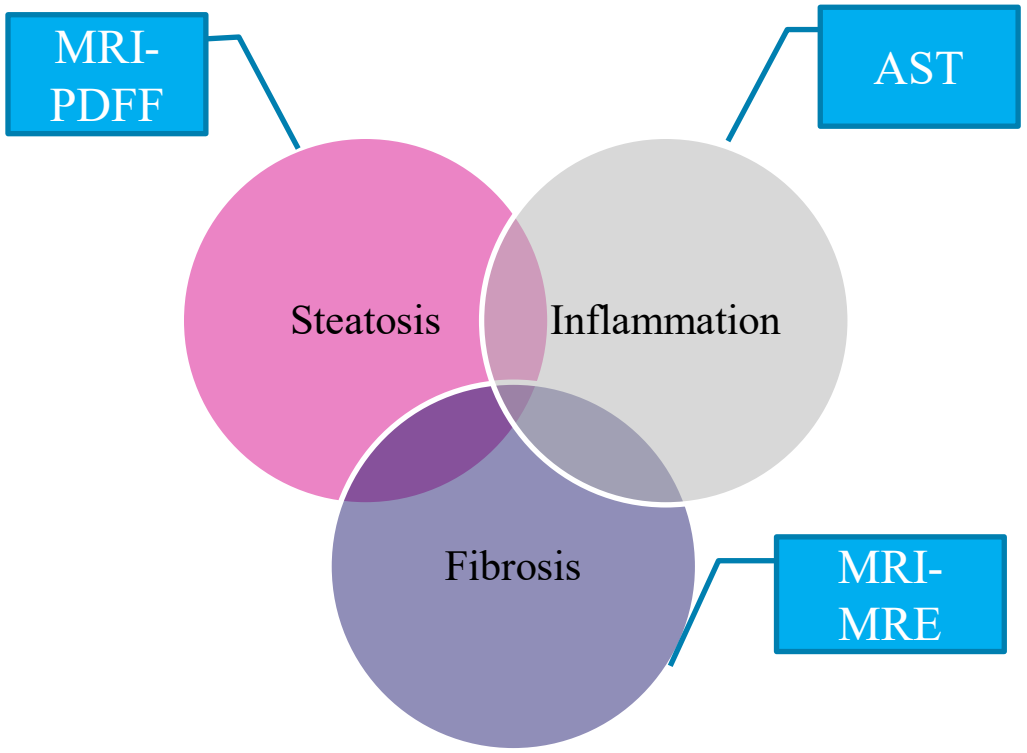
Goal: Identify Fibro-NASH: NASH + NAFLD activity score ≥4 + significant fibrosis (≥F2)

Findings

Score	Sample	ROC area	Sensitivity	Specificity	PPV	NPV
MAST	Derivation	0.858	94.4%	72.9%	42.5%	98.4%
MAST	Validation	0.929	89.3%	73.1%	30.1%	98.1%
FAST	Validation	0.868	93.1%	64.1%	25.0%	98.6%
NAFLD (NFS)	Derivation	0.748	100.0%	52.9%	30.5%	100.0%
NAFLD (NFS)	Validation	0.689	58.6%	66.6%	18.7%	92.5%
Fib-4	Derivation	0.891	88.9%	74.7%	42.1%	97.0%
Fib-4	Validation	0.711	20.7%	95.5%	37.5%	90.2%

Conclusions

The MAST score is an accurate, MRI-serum-based score that outperforms the NAFLD fibrosis (NFS), Fib-4, and FAST scores in non-invasively identifying patients at higher risk of Fibro-NASH.



Compared to NFS and FIB-4, MAST resulted in fewer patients having indeterminate scores and an overall higher AUC
Compared to FAST, MAST exhibited a higher AUC and overall better discrimination

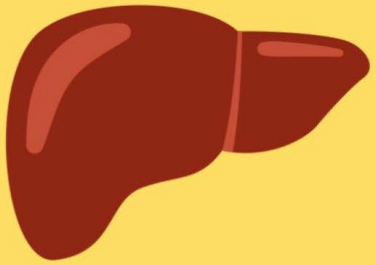
Noureddin et.al, J Hepatol, 2022

ME-FIB detects At-Risk NASH/MASH

Identifying Patients with a High Positive Predictive Value (PPV) for Detection of Patients with Stage 2 Fibrosis or Higher

Gut

Study Population



Prospective cohort of patients with biopsy-proven NAFLD

(N=238, UCSD-Cohort;
N=222, Japan-Cohort)

Jung J, Loomba RR et al. Gut 2020; doi:10.1136/gutjnl-2020-322976

MEFIB Index

MRE ≥ 3.3kPa
and
FIB-4 ≥ 1.6

MRE: Magnetic Resonance Elastography
FIB-4 includes AST, ALT, age, platelet count

Outcome

PPV: 97.1%
for detection of
≥ stage 2 fibrosis

In UCSD cohort
PPV: 91% in Japanese Cohort

Going Head-to-Head for Identification of At-Risk NASH/MASH

Study population
This prospective study included 563 biopsy proven NAFLD patients from two cohorts in the United States and Japan.

Endpoints: Diagnostic models for detecting ***significant fibrosis*** and ***"at risk" NASH*** defined NAS ≥4 and fibrosis stage ≥2

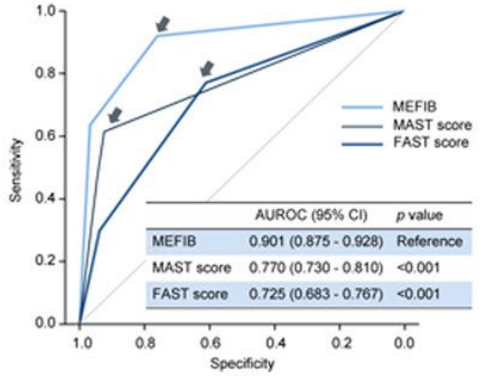
Procedures performed

2D MRE
MRI-PDFF
VCTE
CAP
FIB-4
Liver histology

Models assessed

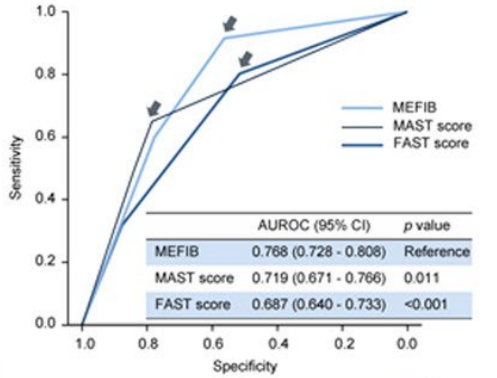
MEFIB (includes MRE and FIB-4)
Rule-in: ≥3.3 kPa and FIB-4 ≥1.6
Rule-out: MRE <3.3 kPa and FIB-4 <1.6
vs.
MAST (includes MRI-PDFF, MRE and AST)
Rule-in: >0.242
Rule-out: <0.165
vs.
FAST (includes CAP, LSM by VCTE and AST)
Rule-in: ≥0.67
Rule-out: ≤0.35

MEFIB is superior to **MAST** or **FAST** or the detection of ***significant fibrosis***



	AUROC (95% CI)	*p* value
MEFIB	0.901 (0.875 - 0.928)	Reference
MAST score	0.770 (0.730 - 0.810)	<0.001
FAST score	0.725 (0.683 - 0.767)	<0.001

MEFIB is superior to **MAST** or **FAST** for the detection of ***"at risk" NASH***

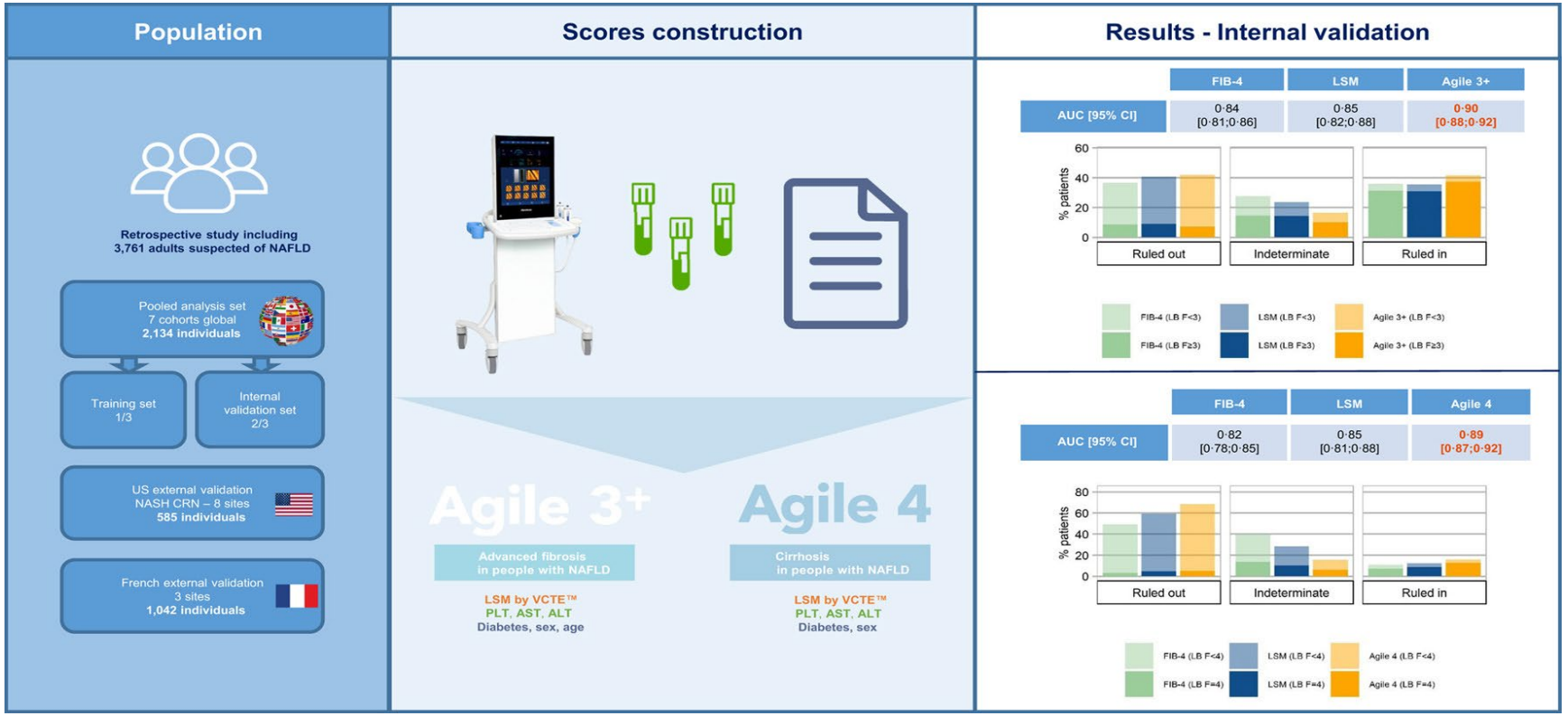


	AUROC (95% CI)	*p* value
MEFIB	0.768 (0.728 - 0.808)	Reference
MAST score	0.719 (0.671 - 0.766)	0.011
FAST score	0.687 (0.640 - 0.733)	<0.001

MEFIB has a high PPV (95%) and a high NPV (90%) to detect significant fibrosis and may be used as a two-step strategy

Kim B, J Hep, 2022

Ruling In Advanced Fibrosis (F3) and Cirrhosis: AGILE 3+ and AGILE 4



- Italian Cohort of 520 patients with biopsy-proven NASH
- AUROC for LSM and Agile 3+ (0.88) comparable for advanced fibrosis
- Agile 3+: Gray zone 8.3% compared to 13% for LSM and 25% for FIB-4

Sanyal A, J Hep 2023

Pennisi et al, CGH, 2023

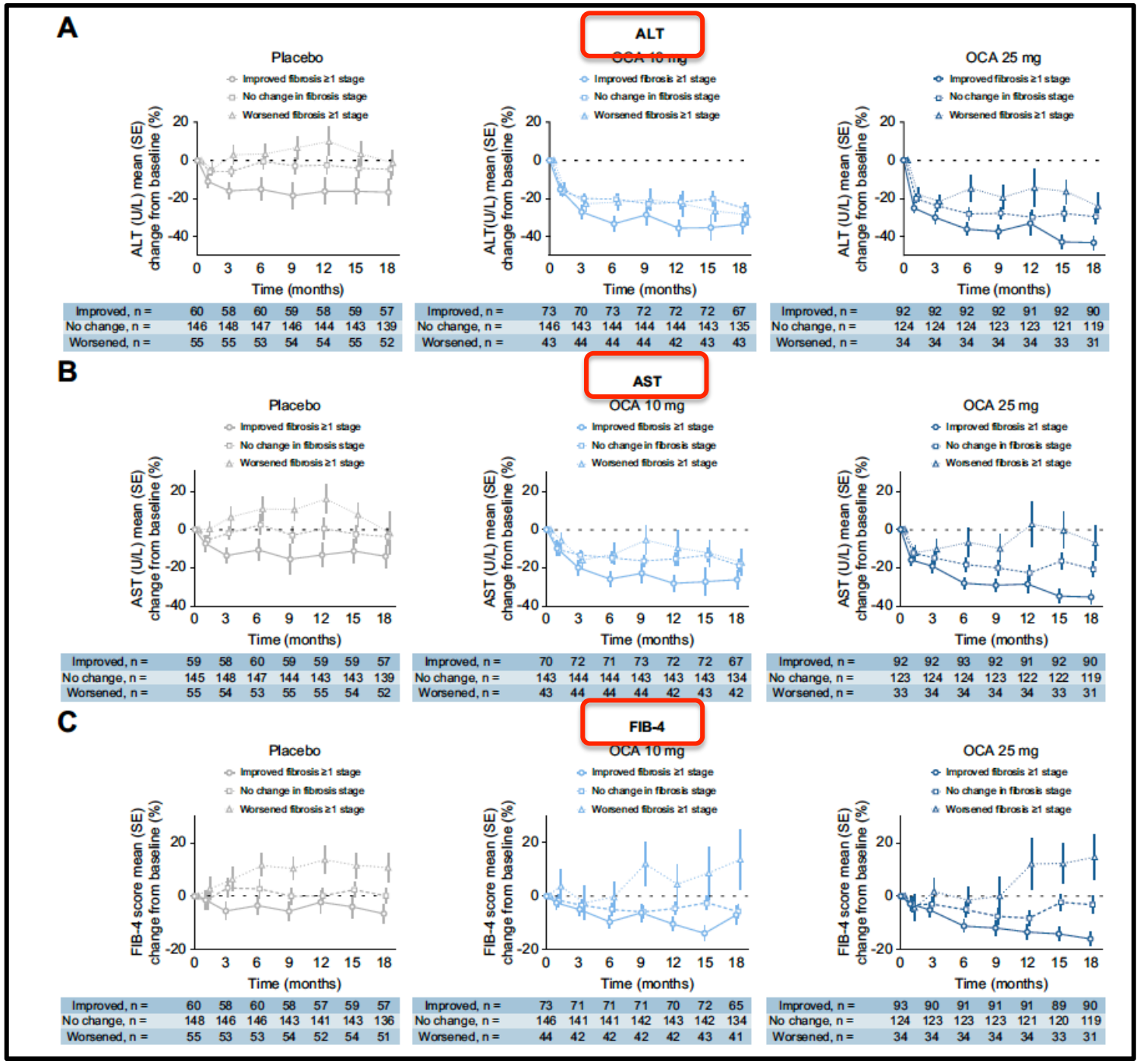
Predicting Response to Treatment *Lessons from Clinical Trials*

- **Predicting Histologic Response (NASH Resolution or Fibrosis)**
  - OCA
  - Resmetirom

- **Caveat:** Can you apply response in the context of clinical trials to real world experience?

Longitudinal Assessment of NITs from the REGENERATE study

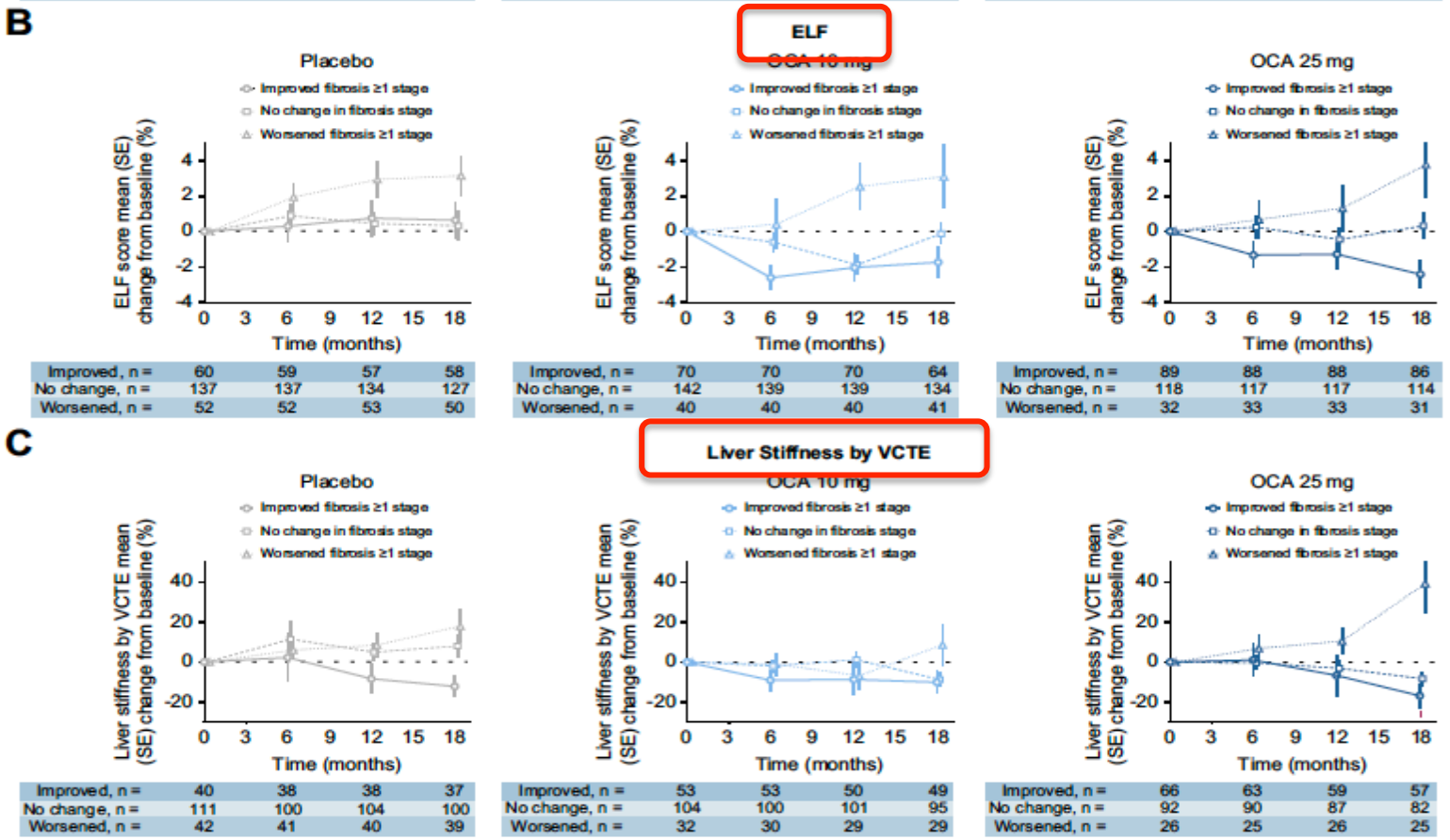
- At month 18, patients with ≥1 stage fibrosis improvement had the greatest improvement in NITs, while patients with ≥1-stage fibrosis worsening typically showed no NIT improvement.
- AUROC values for each of these were suggestive of only weak association



Rinella et al; J Hep 2022

Longitudinal Assessment of NITs from the REGENERATE study

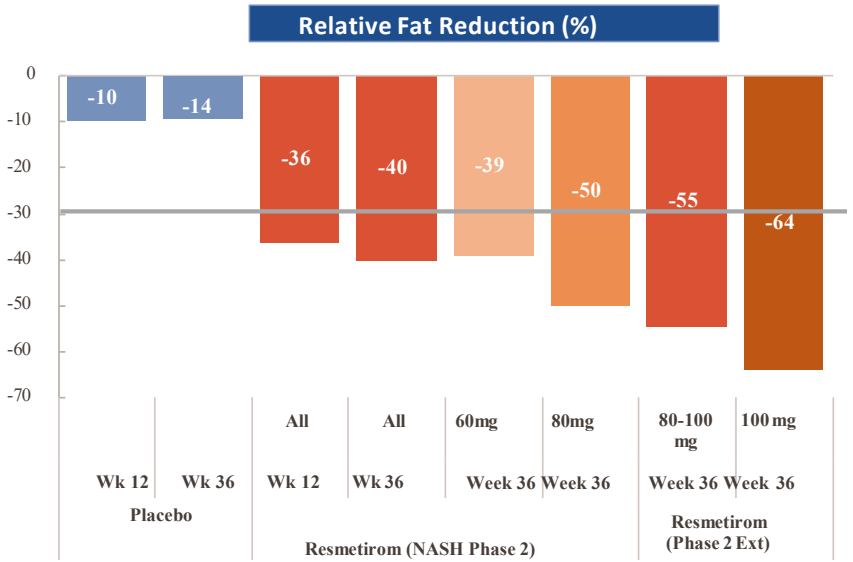
- Individual NIT changes are not likely to be effective univariate clinical predictors of fibrosis improvement
- Taken together, NITs could be used as indicators of therapeutic efficacy in clinical practice



Rinella et al; J Hep 2022

Predictors of response to Resmetirom

Can early PDFF response predict NASH Resolution and Potential Anti-Fibrotic Effect?

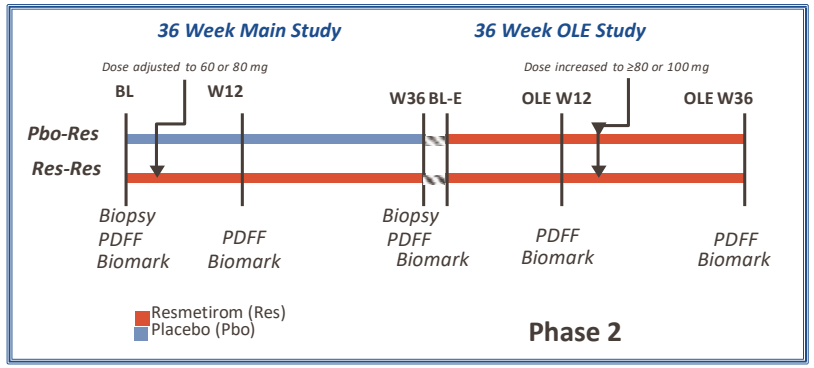


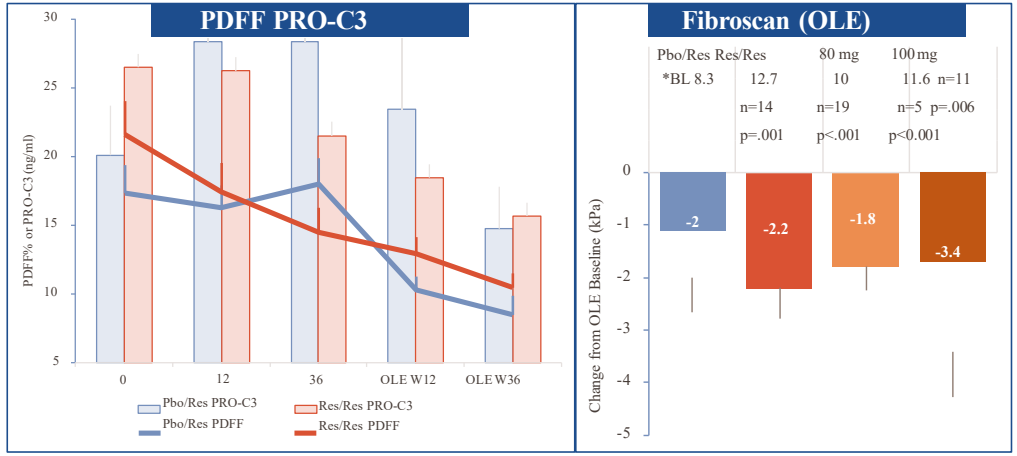
- Primary endpoint achieved, relative reduction in hepatic fat on MRI-PDFF at Week 12
  - Dose dependent 50% reduction of hepatic fat at 80 mg dose
- Key secondary and exploratory endpoints achieved
  - Statistically significant reduction and resolution of NASH as compared with placebo
  - Statistically significant reduction in fibrosis biomarkers
  - Statistically significant reduction in liver enzymes
  - Statistically significant reduction in LDL-cholesterol, apolipoprotein B, triglycerides and lipoprotein(a)
- Safety
  - No change in Grade 2 or higher AEs
  - No safety signals related to mechanism of action

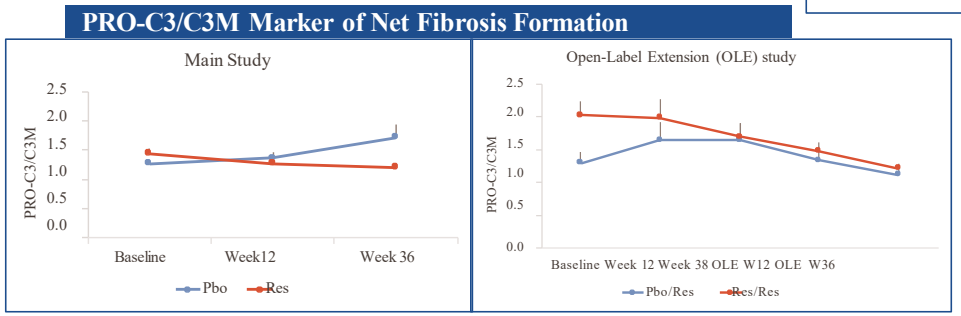
Resmetirom responders with 30% PDFF reduction at Week 12 had higher rates of NASH resolution (37%) on Week 36 liver biopsy compared to non-responders (4%)

Harrison S, Lancet, 2019

Non-invasive Biomarkers and Imaging Follows Patient Response to Resmetirom



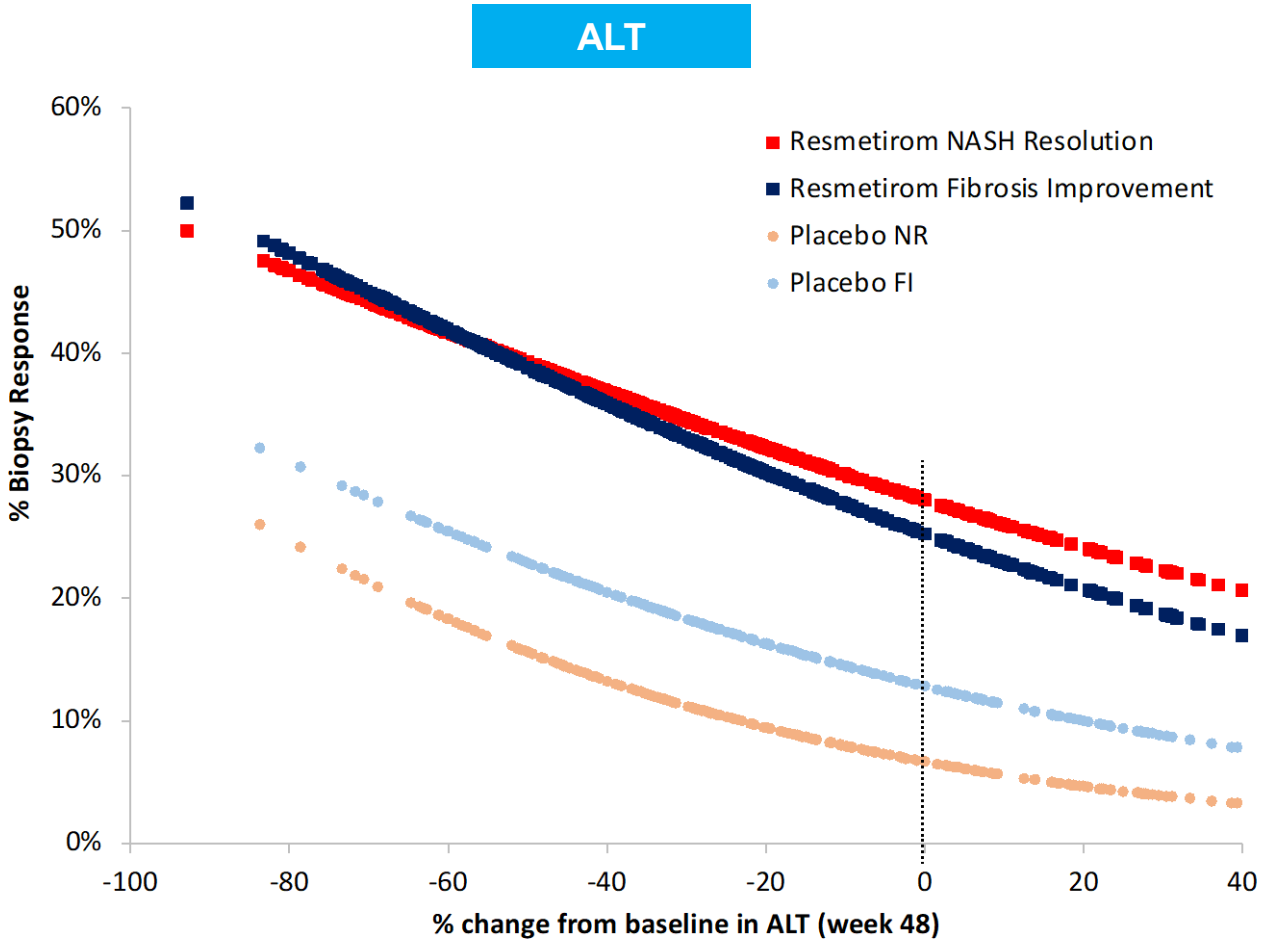




In addition to routine assessments like liver enzymes, other non-invasive tests such as MRI-PDFF (liver fat), fibroscan (liver stiffness/fibrosis stage) and fibrosis biomarkers (e.g PRO-C3 and PRO-C3/C3M) may be used to monitor resmetirom response over time in individual NASH patients

Harrison S, Lancet, 2019

ALT as a Marker of Biopsy Response to Resmetirom

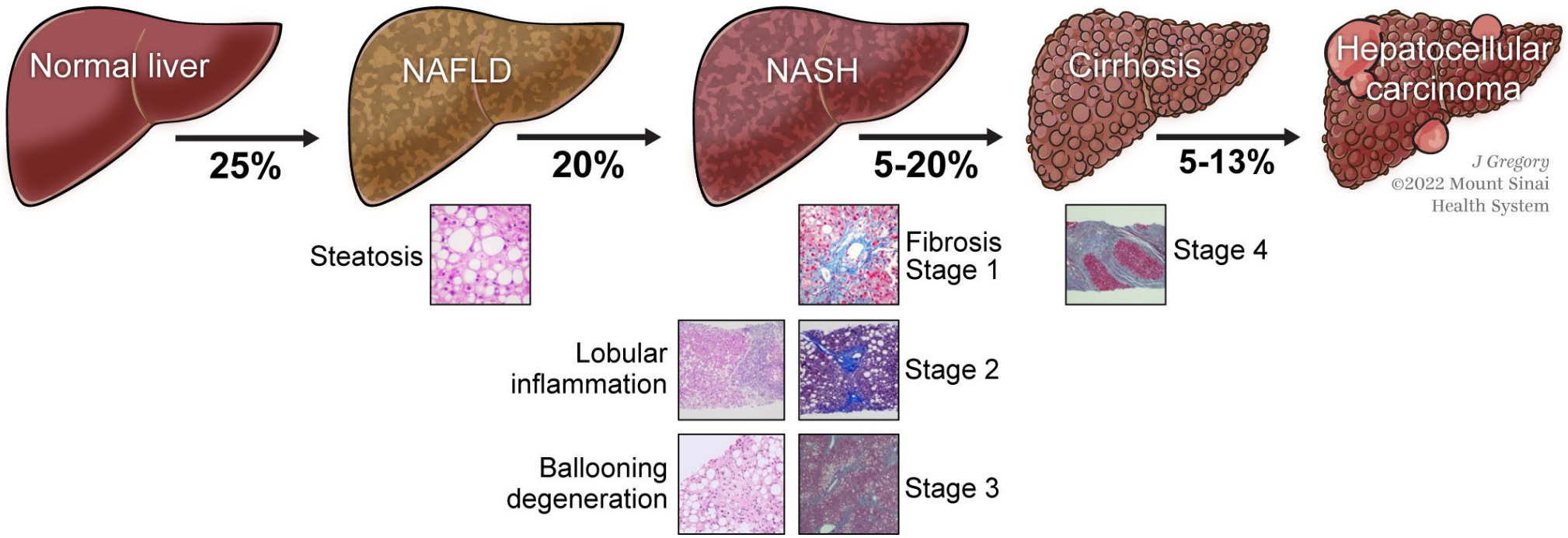


- Both doses of resmetirom significantly reduced ALT approximately 30% relative to placebo
- In resmetirom treated patients, higher % reductions in ALT were associated with slightly higher NASH resolution and Fibrosis improvement on biopsy
- For resmetirom treated patients without a reduction in ALT, the NASH resolution and fibrosis improvement responses were predicted to be higher than the mean placebo biopsy responses

All resmetirom treated patients (80 mg and 100 mg combined)

Loomba R et al, AASLD 2023

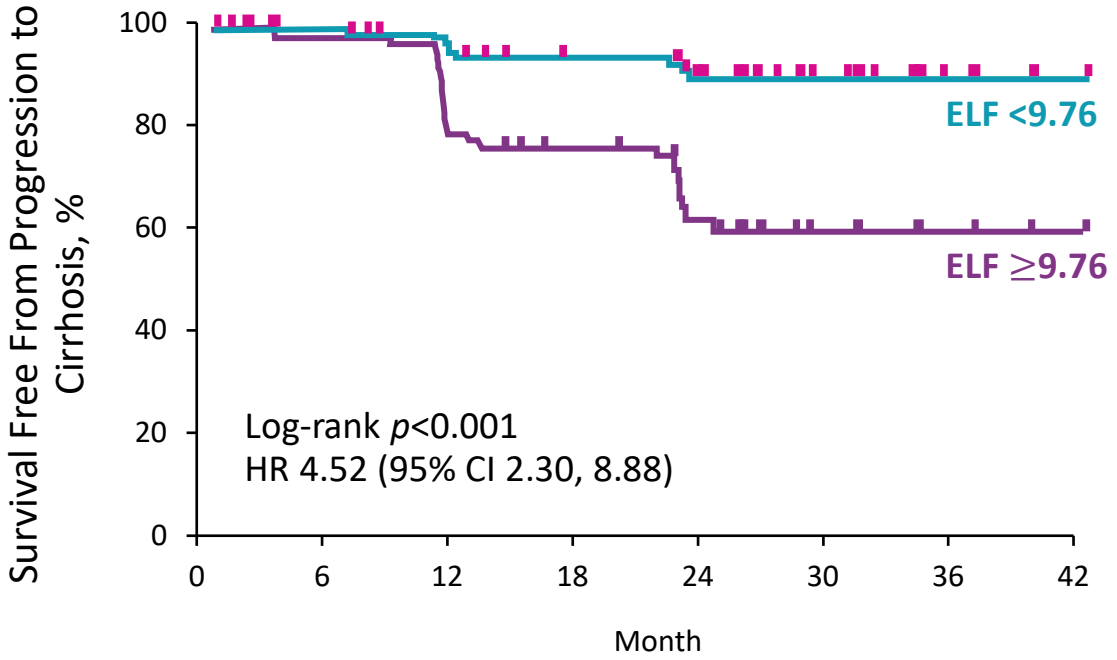
Progression to Cirrhosis



Karim and Bansal, TOUCHReviews Endocrinlogy, 2023

ELF predicts progression to Cirrhosis

Progression to Cirrhosis According to Baseline ELF



Predictors of progression to cirrhosis

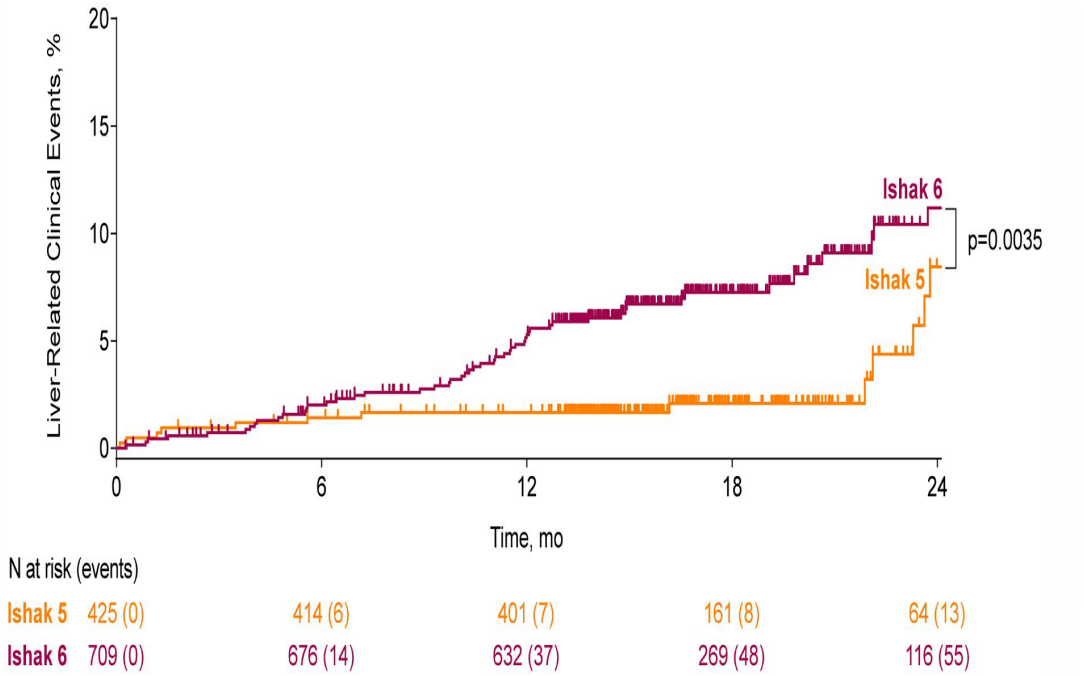
Parameter	Adjusted HR (95% CI)	*p*-value
Baseline ELF	3.20 (2.33, 4.39)	<0.001
Change in ELF	1.60 (1.19, 2.16)	<0.01
Ishak stage 4 vs 3	0.87 (0.47, 1.59)	0.64

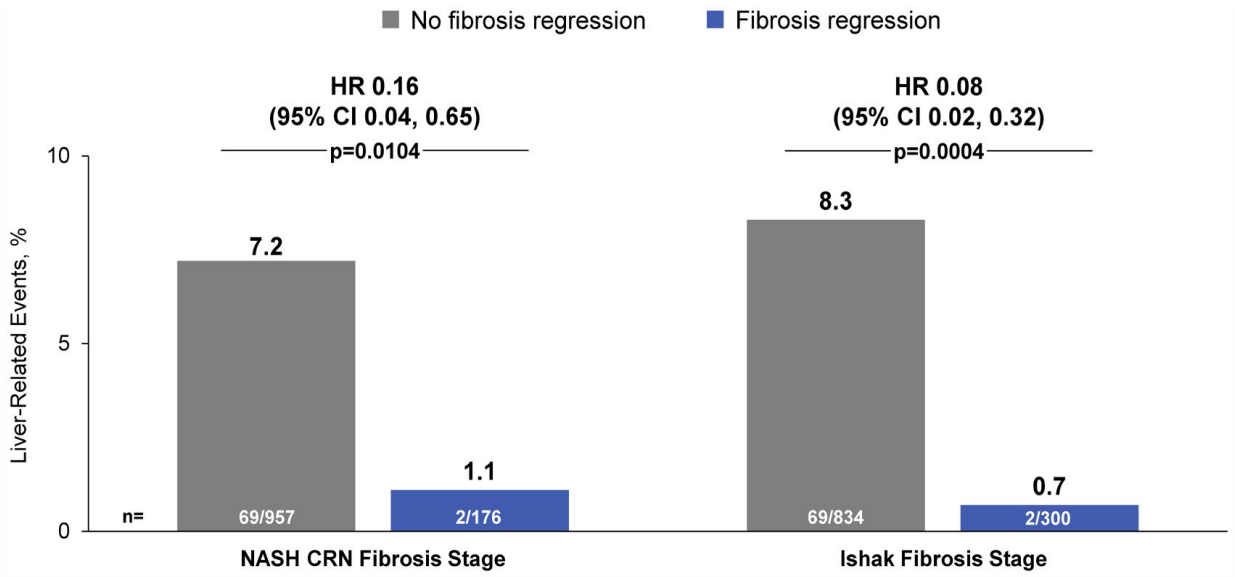
Optimal threshold of baseline ELF: 9.76
(sensitivity 77%, specificity 66%)

Higher baseline ELF and greater change in ELF were associated with increased risk of progression to cirrhosis

Sanyal A et al, Hepatology, 2019

Cirrhosis regression is associated with improved clinical outcomes in patients with NASH



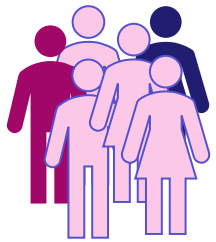


Sanyal et al., Hepatology 2022

Predicting Clinical Outcomes

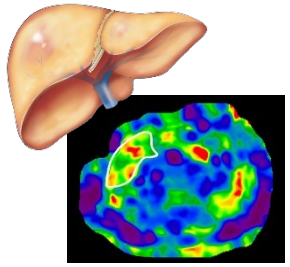
MRE and the MEFIB Index and Liver-Related Outcomes in NAFLD:
A Systematic Review and Meta-Analysis of Individual Participants

Six international cohorts with nonalcoholic fatty liver disease



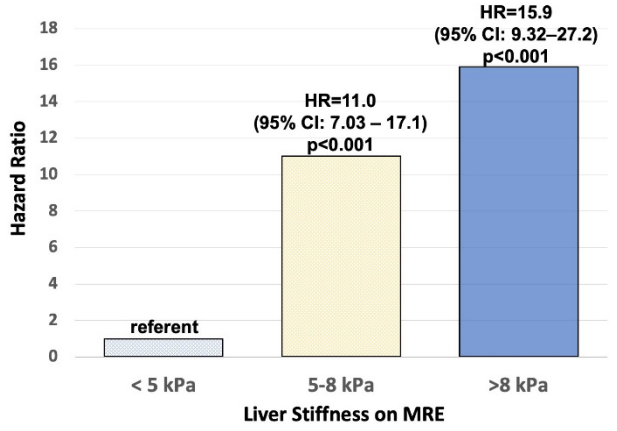
n=2018

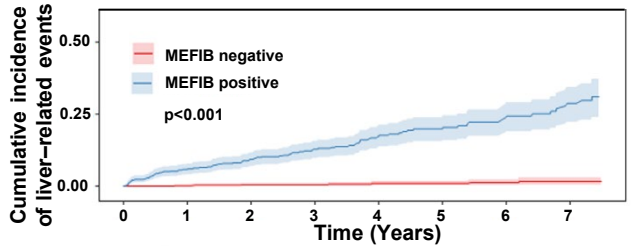
Underwent magnetic resonance elastography



Liver stiffness assessed by Baseline MRE is associated with development of ascites, hepatic encephalopathy and varices needing treatment

The MEFIB combination of MRE and FIB-4 (defined as positive when MRE ≥ 3.3kPa and FIB-4 ≥ 1.6) has excellent negative predictive value for hepatic decompensation.



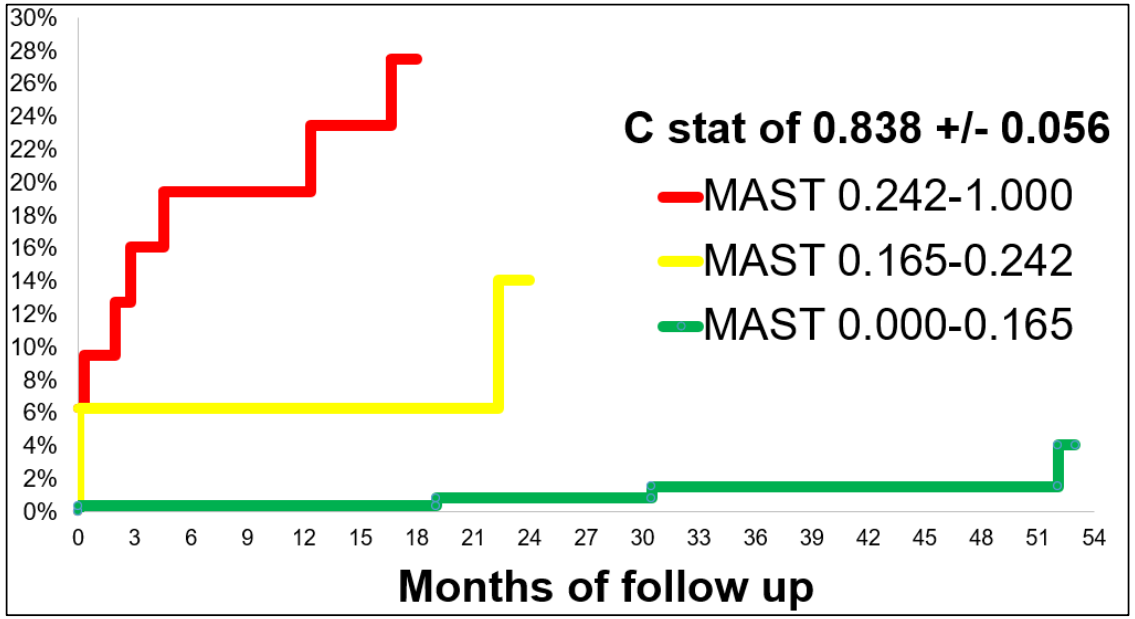


Negative MEFIB index was associated with a <1% liver related outcome at 3 years

Ajmera et al., Gastro 2022

MAST Score predicts Major Adverse Liver Outcomes

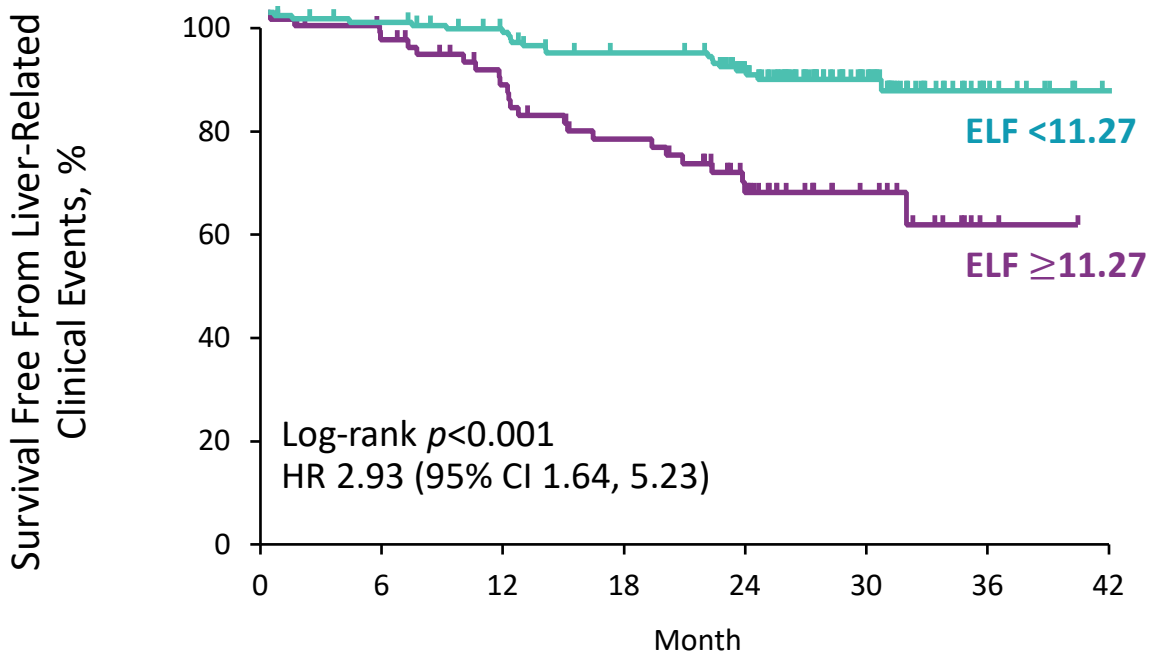
- Retrospective Cohort of 346 patients with MRI between 2013-2022
- MAST between 0.245-1.000 predicted 22-fold increased risk of adverse outcomes (MALO, liver transplant, HCC, and liver-related death)
- MAST between 0.165-0.242 associated with increased HR=7.75



Troung E et al, CGH, 2023

ELF predicts Liver-Related Clinical Events

Liver-Related Clinical Events According to Baseline ELF



Predictors of liver-related clinical events

Parameter	Adjusted HR (95% CI)	*p*-value
Baseline ELF	2.40 (1.70, 3.38)	<0.001
Change in ELF	1.53 (1.09, 2.14)	0.01
Ishak stage 6 vs 5	0.89 (0.47, 1.68)	0.71

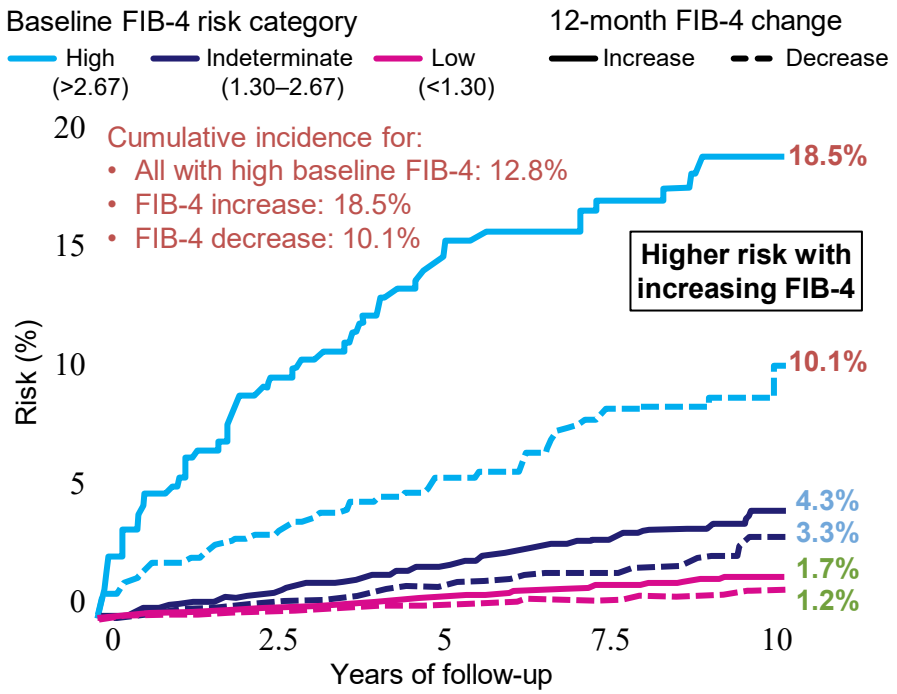
Optimal threshold of baseline ELF: 9.76
(sensitivity 77%, specificity 66%)

Higher baseline ELF and greater change in ELF were associated with liver-related clinical events

Sanyal A et al, Hepatology, 2019

Association between FIB-4 changes over time and subsequent risk of liver events in patients with obesity and/or type 2 diabetes

Cumulative incidence over 10 years for liver events according to 12-month increase or decrease in FIB-4 by baseline FIB-4



HR of liver events for 12-month changes in FIB-4 compared with no change in the low baseline FIB-4 group

vs no change in low baseline FIB-4	HR	95% CI
High baseline FIB-4 and 1 unit FIB-4 ↑	24.27	16.98, 34.68
High baseline FIB-4 and 1 unit FIB-4 ↓	10.90	7.90, 15.05
Indeterminate baseline FIB-4 and 1 unit FIB-4 ↑	4.48	3.36, 5.98
Indeterminate baseline FIB-4 and 1 unit ↓	1.67	1.22, 2.29
Low baseline FIB-4 and 1 unit FIB-4 ↑	2.48	2.04, 3.02
Low baseline FIB-4 and 1 unit FIB-4 ↓	0.40	0.33, 0.49

- Real-world data showing change in FIB-4 have significant predictive value for clinical use
- Further sequential data are critical

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

Conclusions

- **Screening High Risk-Populations**
  - Fib-4=FIRST LINE of DEFENSE (version 1.0)
  - SAFE Score
  - Sequential or Combination testing to address the Grey Zone
- **Identification of At-Risk NASH-Combo best**
  - FAST, MAST, ME-FIB
  - Agile 3+ (F3 fibrosis)
  - Machine Learning Algorithms
- **Response to Resmetirom**
  - 30% reduction in MRI-PDFF
  - Pro-C3/C3M ratio
  - ALT in those with elevation at baseline
  - VCTE
  - Everything moving in the right direction
- **Progression to Cirrhosis**
  - VCTE>16.6kPa
  - ELF> 9.75
- **Predicting MALO**
  - ELF>11.27
  - VCTE >30.7kPa
  - MAST >0.24
  - ME-FIB+ (MRE≥3.3 and FIB-4 ≥1.6)
- **Longitudinal changes over time more important than single cross-sectional view**
  - FIB-4
  - VCTE
  - MRE

Serum or Combo NITs

Thank you!!

Meena.bansal@mssm.edu

2024

DESERT LIVER CONFERENCE

PHOENIX, ARIZONA

Selecting Patients for Treatment & Monitoring Response

Stephen A. Harrison, MD, COL (Ret.), FAASLD

Visiting Professor of Hepatology

Radcliffe Department of Medicine, University of Oxford

Chairman and Founder, Pinnacle Clinical Research

Chairman and Co-Founder, Summit Clinical Research

AGA 2021 Guidance

Step 1: Identify patients at Risk
2 or more metabolic risk factors, Type 2 diabetes, Steatosis on any imaging modality of elevated aminotransferases

Step 2: History and laboratory Tests
Excessive alcohol intake, CBC, liver function tests

Step 3: Non-Invasive testing for Fibrosis => FIB-4

FIB-4 < 1.3

LSM < 8 kPa

LOW RISK

Repeat NIT in 2-3 years unless clinical circumstances changes

FIB-4 1.3 to 2.67

Step 4: Liver Stiffness Measurement (LSM)

LSM 8 to 12 kPa

INDETERMINATE RISK

Refer to hepatologist for liver biopsy or MRE or monitoring with re-eval of risk in 2-3 years

FIB-4 > 2.67

LSM > 12 kPa

HIGH RISK

Refer to hepatologist

AACE 2022 Guidance

High-risk groups for MASLD:
Prediabetes or T2D Obesity and/or ≥ 2 cardiometabolic risk factors Steatosis (on imaging) or increase AST or ALT

FIB-4 < 1.3
Low Risk

FIB-4 1.3 to 2.67
Indeterminate Risk

FIB-4 > 2.67
High Risk

Liver Stiffness Measurement (LSM)
or ELF

Low Risk
FIB-4 < 1.3
or LSM < 8 kPa
or ELF < 7.7
or Fibrosis F0-F1

Indeterminate Risk
FIB-4 1.3 - 2.67
or LSM 8 -12 kPa
or ELF 7.7 – 9.8
Consider liver specialist to consider need for biopsy

High Risk
FIB-4 > 2.67
or LSM > 12 kPa
or ELF > 9.8
or Fibrosis F2-F4

Managed by primary Care team, endocrinologist, other
Focus care on obesity management & CVD prevention

Referral to liver specialist for additional proprietary biomarkers or imaging (MRE, cT1, other)
Multidisciplinary team to prevent cirrhosis and VCD

AASLD 2023 Guidance

Primary Care of Non-GI/Hepatology Care
GOAL: Exclude advanced fibrosis in low-prevalence populations

Primary risk assessment, e.g. FIB-4

FIB-4 ≥ 1.3

No

Reassess periodically:
- FIB-4 every 1-2 years if TD2M/preT2DM or ≥ 2 metabolic risk factors
- FIB-4 every 2-3 years if no T2DM and < 2 metabolic risk factors

Yes

FIB-4 ≥ 2.67
Consider referral

Persistent ↑ ALT & AST

Secondary risk assessment

Risk Level	VCTE	ELF
Low	<8.0	<7.7
Intermediate	8-12	7.7-9.8
High	>12	>9.8

Either Care Setting

All patients
- Cardiometabolic risk reduction and preferential use of meds with potential NAFLD benefit
- Ongoing assessment of alcohol intake
- Lifestyle Management

GI/Hepatology Care
GOAL: Identify/manage patients with "at risk" NASH or cirrhosis

Review/Perform primary/secondary risk assessment
Consider additional stratification with MRE, cT1

Low risk

PCP follow-up or reassess

Intermediate/ high risk

Consider liver biopsy
Indeterminate NITs
Diagnostic uncertainty
Persistently ↑ ALT & AST

Biopsy Staging

Stage 0-1

Reassess in 2-3 years

Stage 2-3

Reassess annually
Consider pharmacotherapy

Stage 4

Cirrhosis-based management

Suspect cirrhosis
(clinical, imaging, or ELF >11.3)

Rinella ME. Hepatology. 2023 Mar 17
doi: 10.1097/HEP.0000000000000323

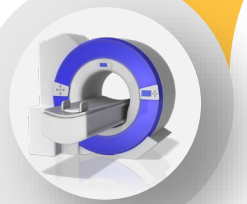
Summit Clinical Research Database

COLLABORATION
Pharma companies
Academia
Summit

6,558 patients

8 Randomized Therapeutic Clinicals Trials

5,514 patients with lab data



Imaging data
2,514 FibroScan
2,385 MRI-PDFF
563 MRI-cT1

2,277 patients with liver histology data

Predictors of At-Risk MASH

	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

Data are mean (SD) or % ; Excluding 104 F4 patients

Predictors of At-Risk MASH

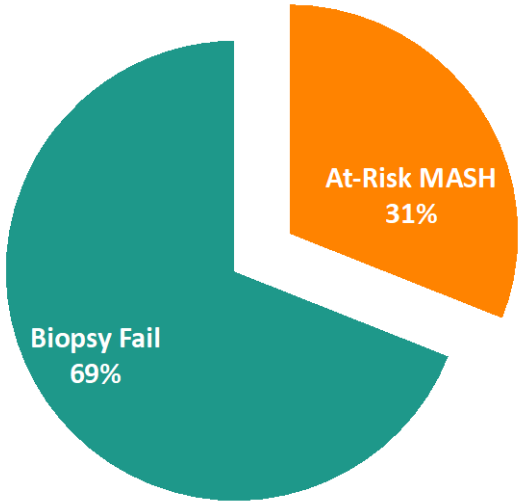
	Failed Biopsy N=1,261	At-Risk MASH NASH - NAS ≥ 4 Fibrosis 2 or 3 N=912	p-value
Lipid Parameters			
LDL, mg/dL	106 (39)	100 (37)	<0.001
HDL, mg/dL	45 (14)	44 (12)	0.136
Triglyceride, mg/dL	160 (86)	166 (82)	0.146
Transient Elastography			
Liver Stiffness Measurement, kPa	11.9 (6.0)	13.6 (6.5)	<0.001
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

Data are mean (SD) or % ; Excluding 104 F4 patients

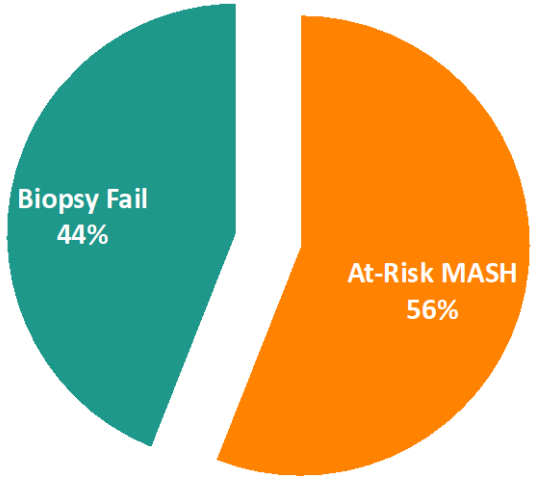
Predictors of At-Risk MASH: FIB-4

Proportion of At-Risk NASH by FIB-4 Range

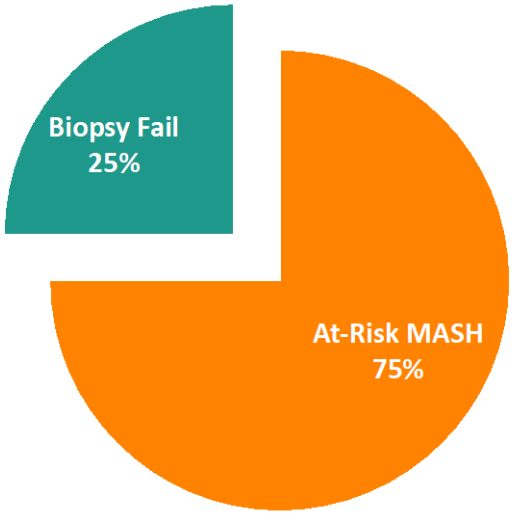
FIB-4 < 1.3



FIB-4 1.3 – 2.67



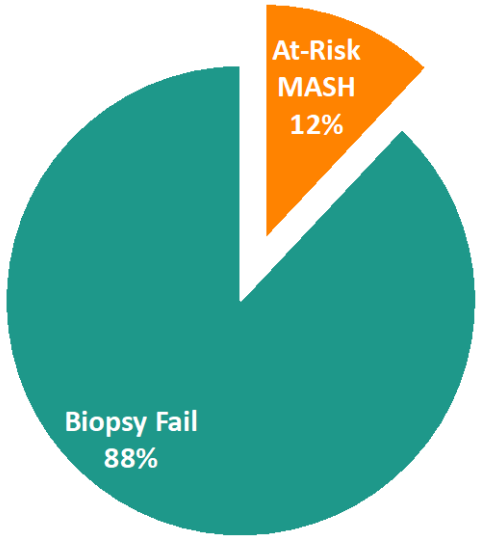
FIB-4 ≥ 2.67



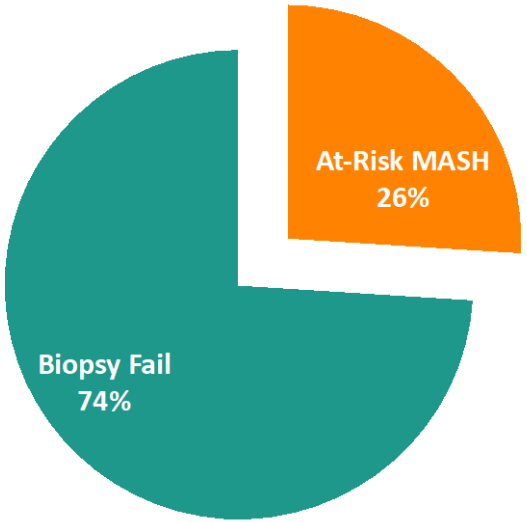
Liver enzymes as a Simple Tool

Proportion of At-Risk MASH by AST Range

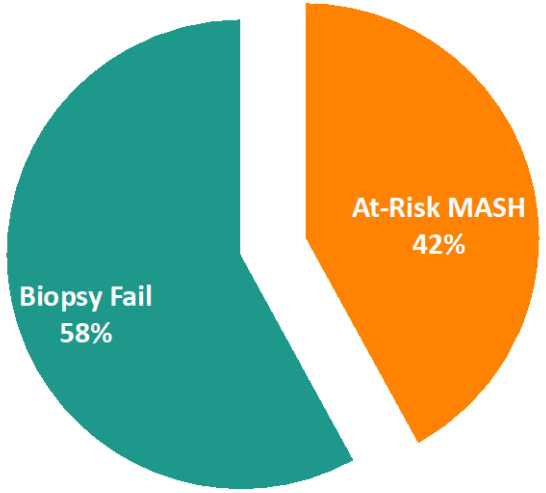
AST < 20



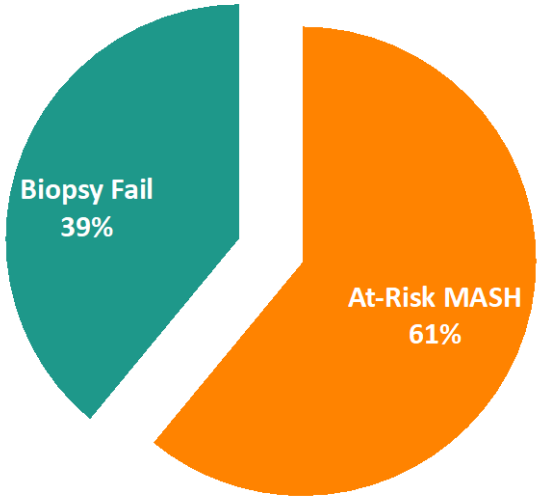
AST 20 - 30



AST 31 - 40



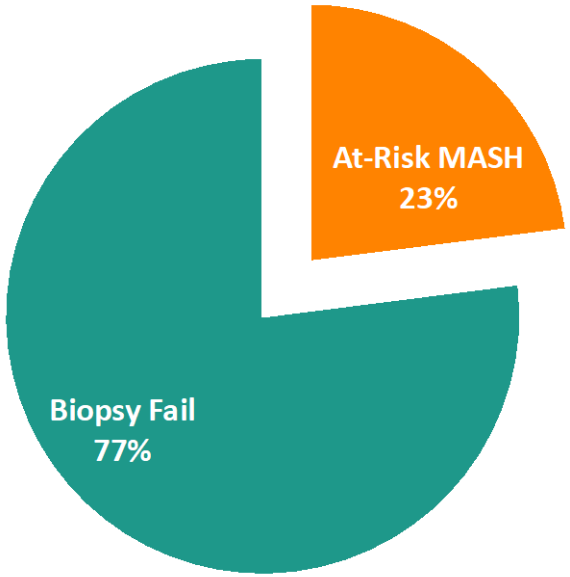
AST ≥ 40



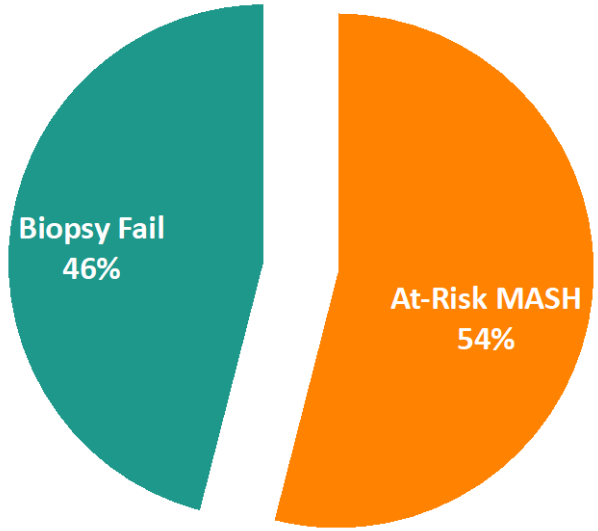
Liver enzymes as a Simple Tool

Proportion of At-Risk MASH by AST Range

AST < 30

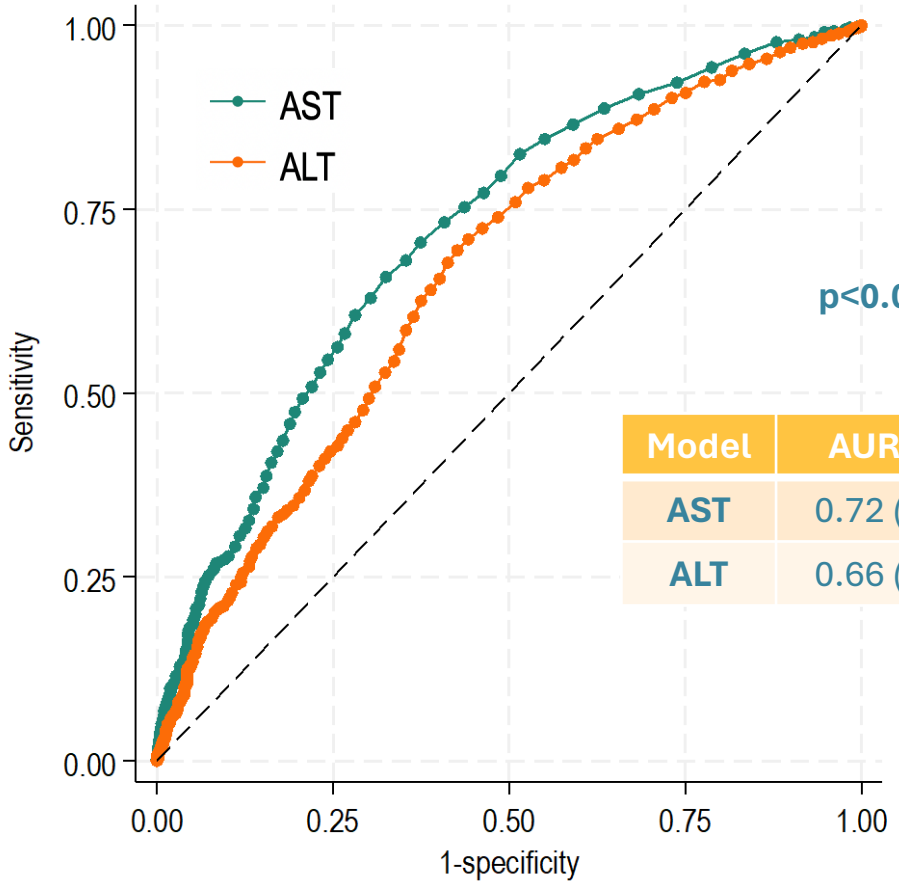


AST ≥ 30



Liver enzymes as a Simple Tool

AST versus ALT for the identification of At-Risk MASH



p<0.001

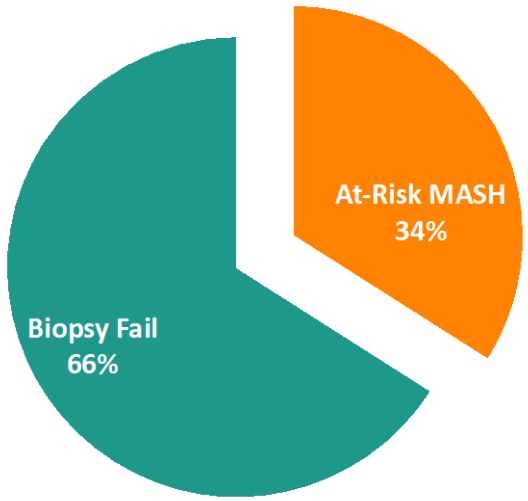
Model	AUROC (95% CI)
AST	0.72 (0.695, 0.739)
ALT	0.66 (0.639, 0.685)

- AST is a better predictor of at-risk MASH

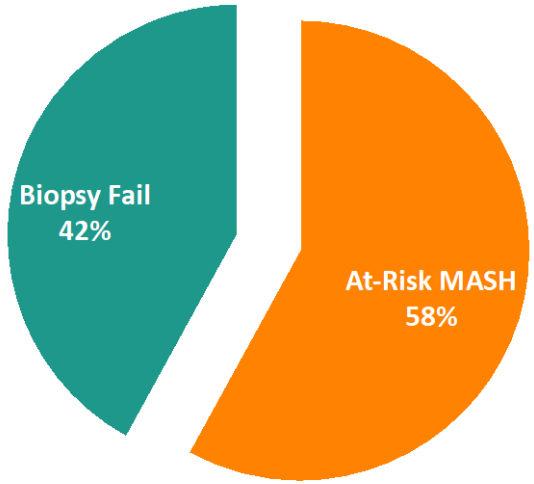
Combination of FibroScan & AST: FAST

Proportion of At-Risk MASH by FAST Range

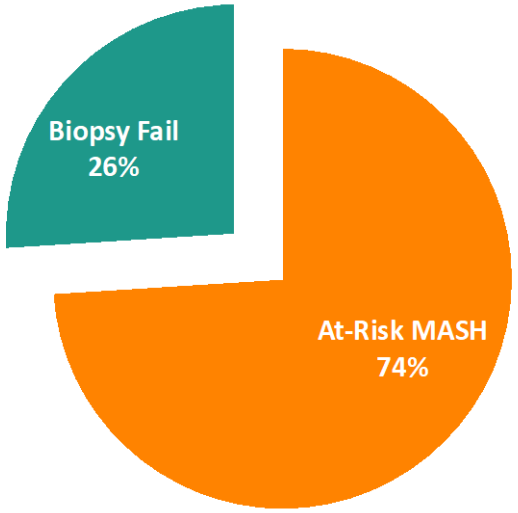
FAST < 0.35



FAST 0.35 – 0.50



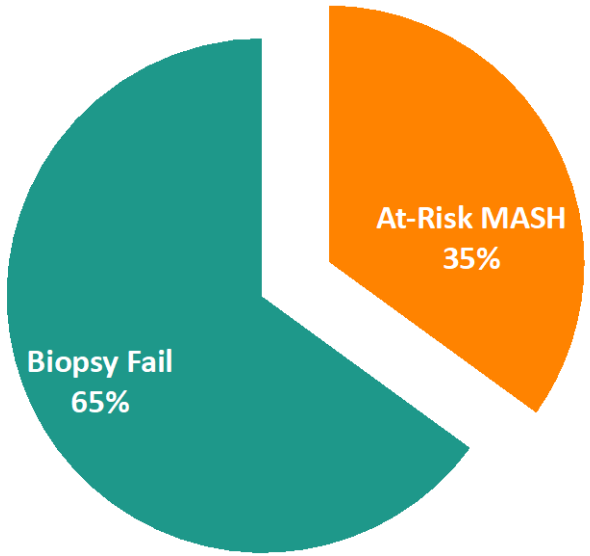
FAST ≥ 0.67



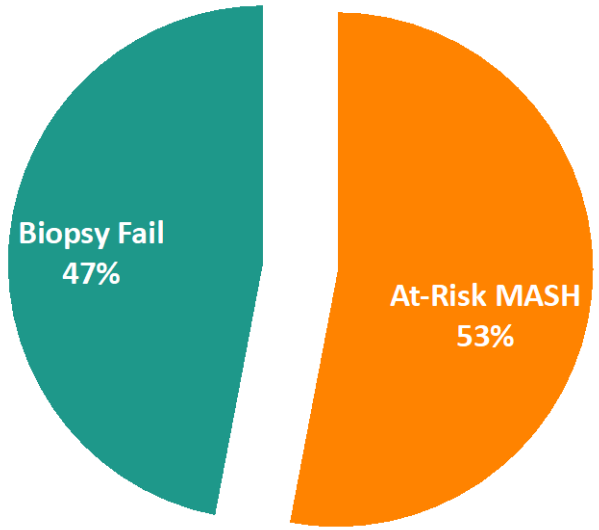
Glycemic Control as an Additional Predictor

Proportion of At-Risk MASH by HbA1c Range

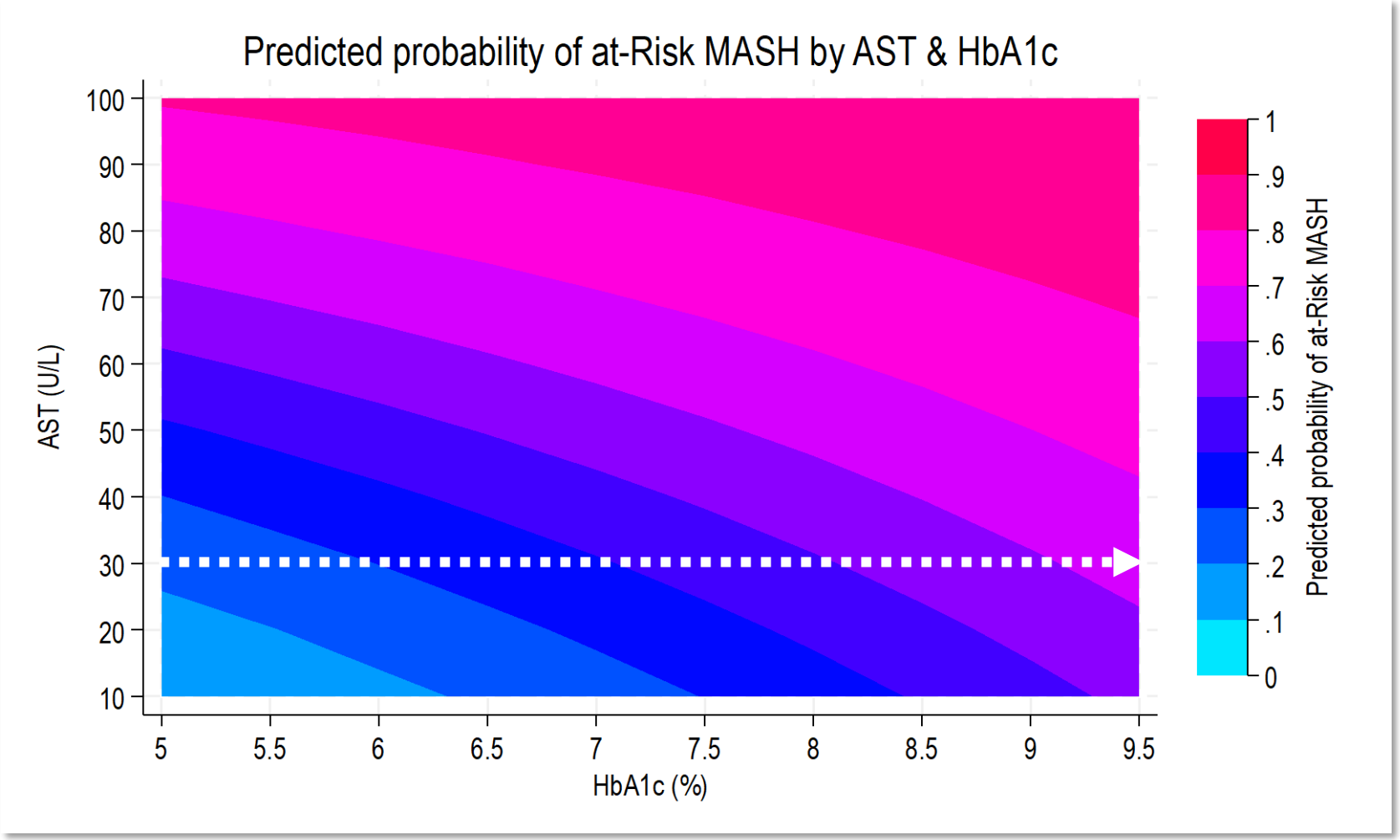
HbA1c < 6.5 %



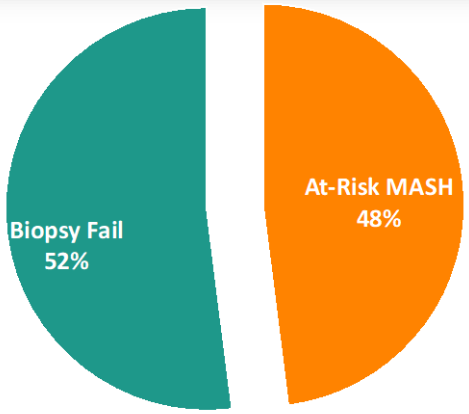
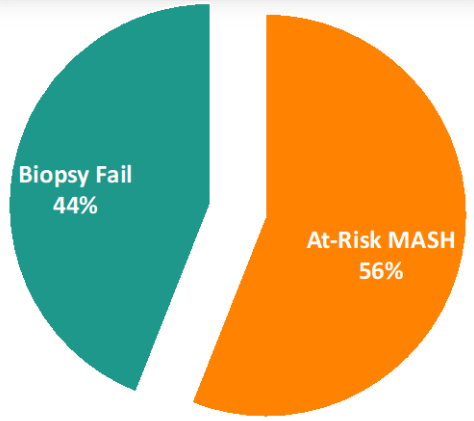
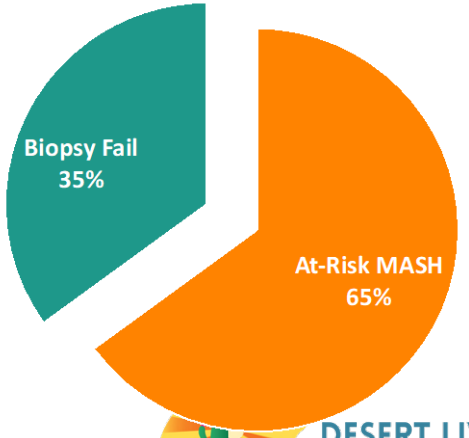
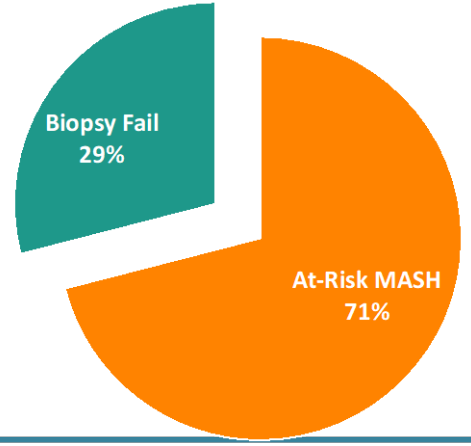
HbA1c ≥ 6.5 %



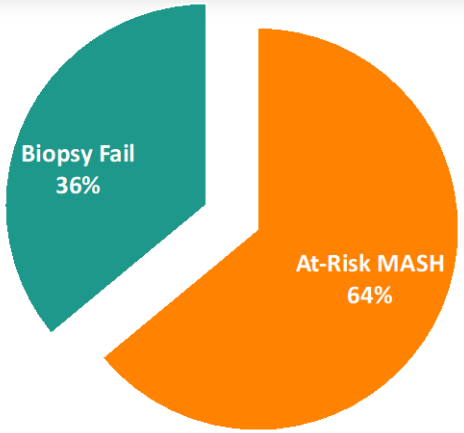
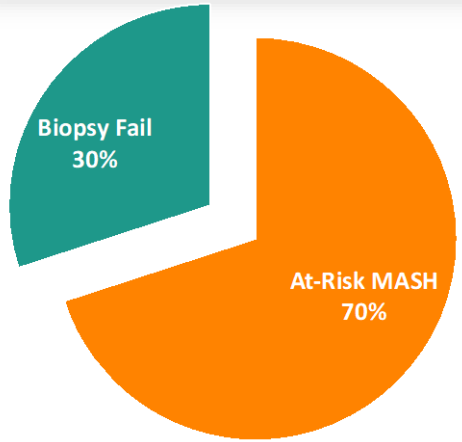
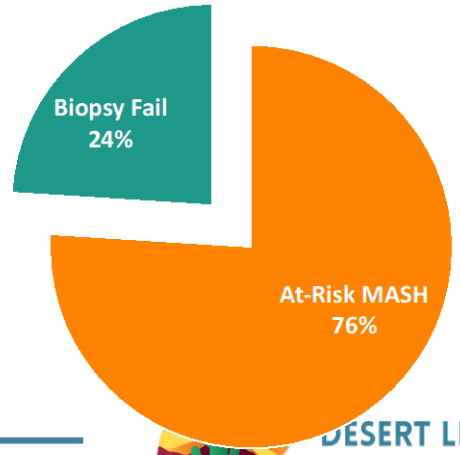
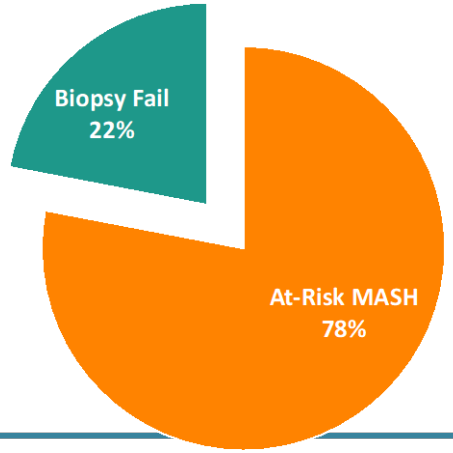
Glycemic Control as an Additional Predictor



Combination of Glycemic Control & AST

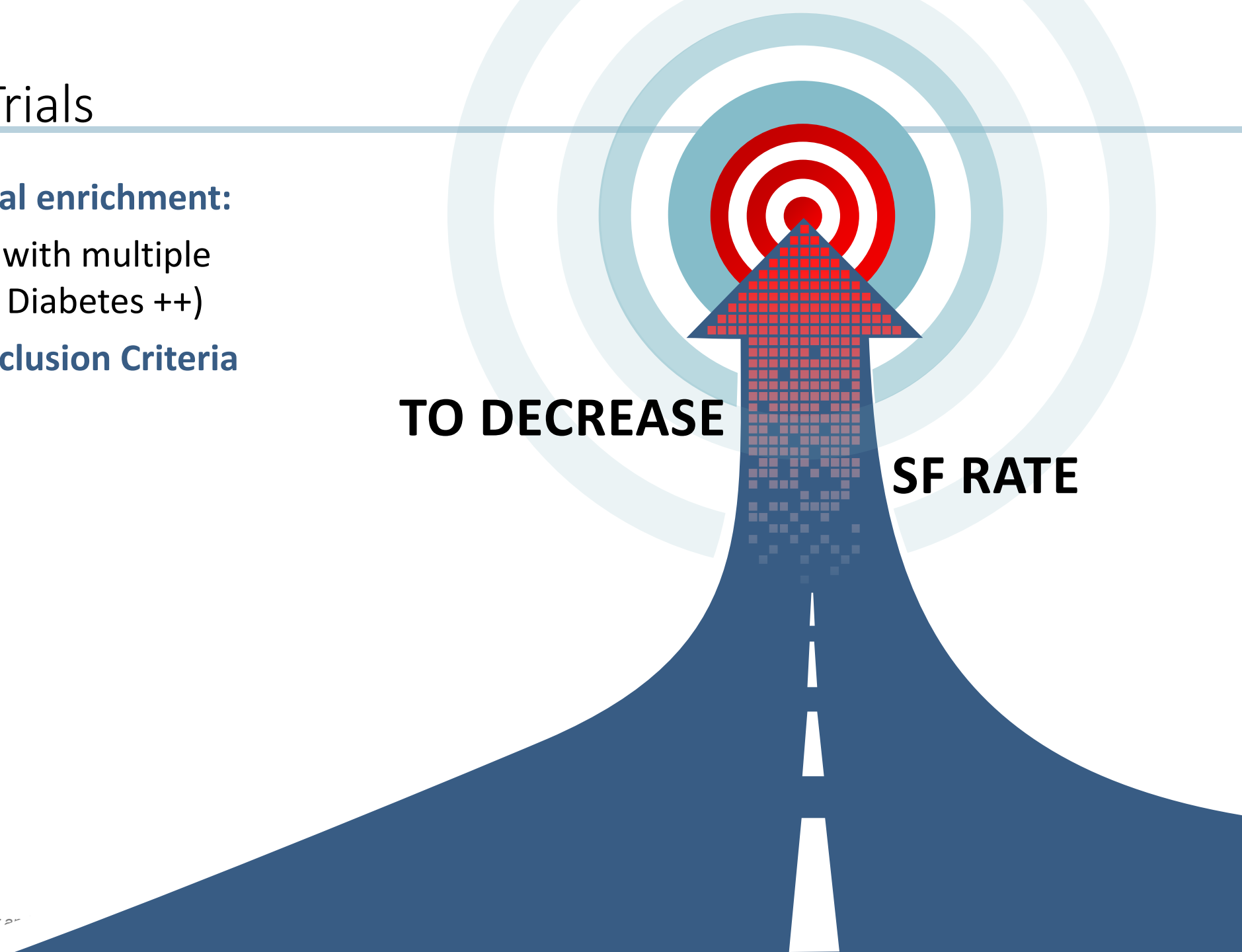
	AST ≥ 30	AST ≥ 40
HbA1c < 6.5 %		
HbA1c ≥ 6.5 %		

Combination of Glycemic Control & FAST

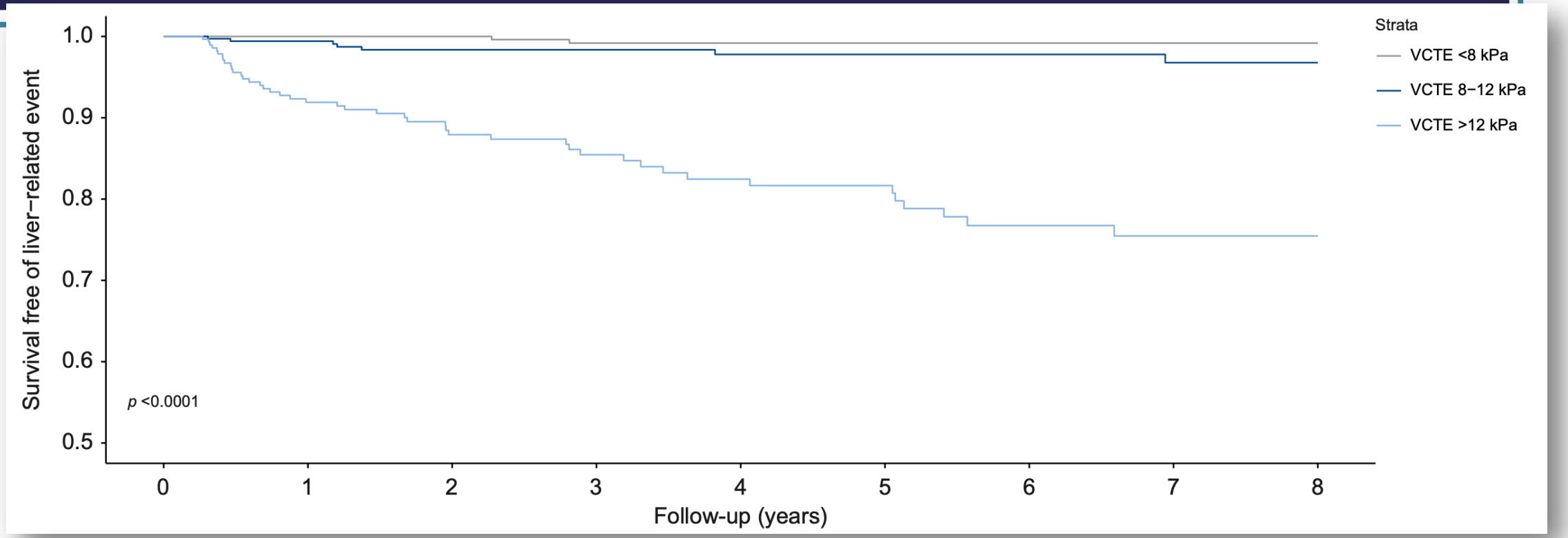
	FAST ≥ 0.50	FAST ≥ 0.67
HbA1c < 6.5 %		
HbA1c ≥ 6.5 %		

Key Takeaways
for Non-Cirrhotic Trials

- **Ideal population for trial enrichment:**
  - Middle-aged patients with multiple comorbidities (Type 2 Diabetes ++)
- **Recommended Trial Exclusion Criteria**
  - FibroScan < 8.5 kPa
  - AST < 20
- **Target NITs:**
  - if HbA1c < 6.5%
    - AST ≥ 40
    - FAST ≥ 0.67
  - if HbA1c ≥ 6.5%
    - AST ≥ 30
    - FAST ≥ 0.50



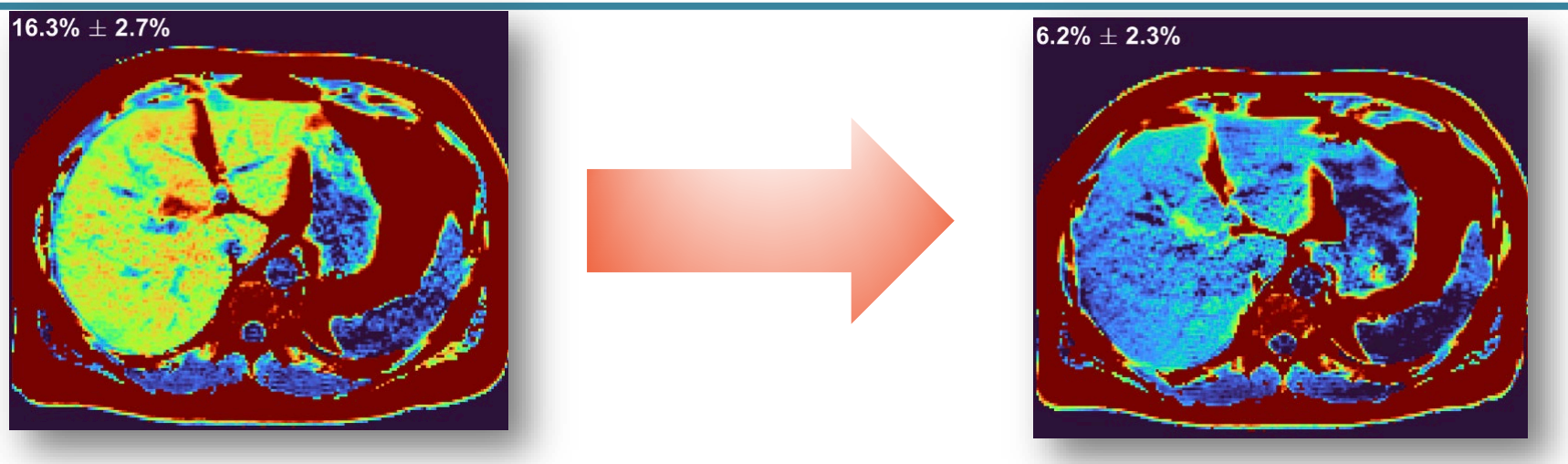
VCTE to Predict Major Adverse Liver Outcomes



- Multicenter Cohort, N=1,057
- VCTE > 12 kPa associated with a 21-fold increased risk of MALOs

Boursier J. et al. J Hep. 2022;76:1013-1020

MRI-PDFF to Monitor Treatment-Response

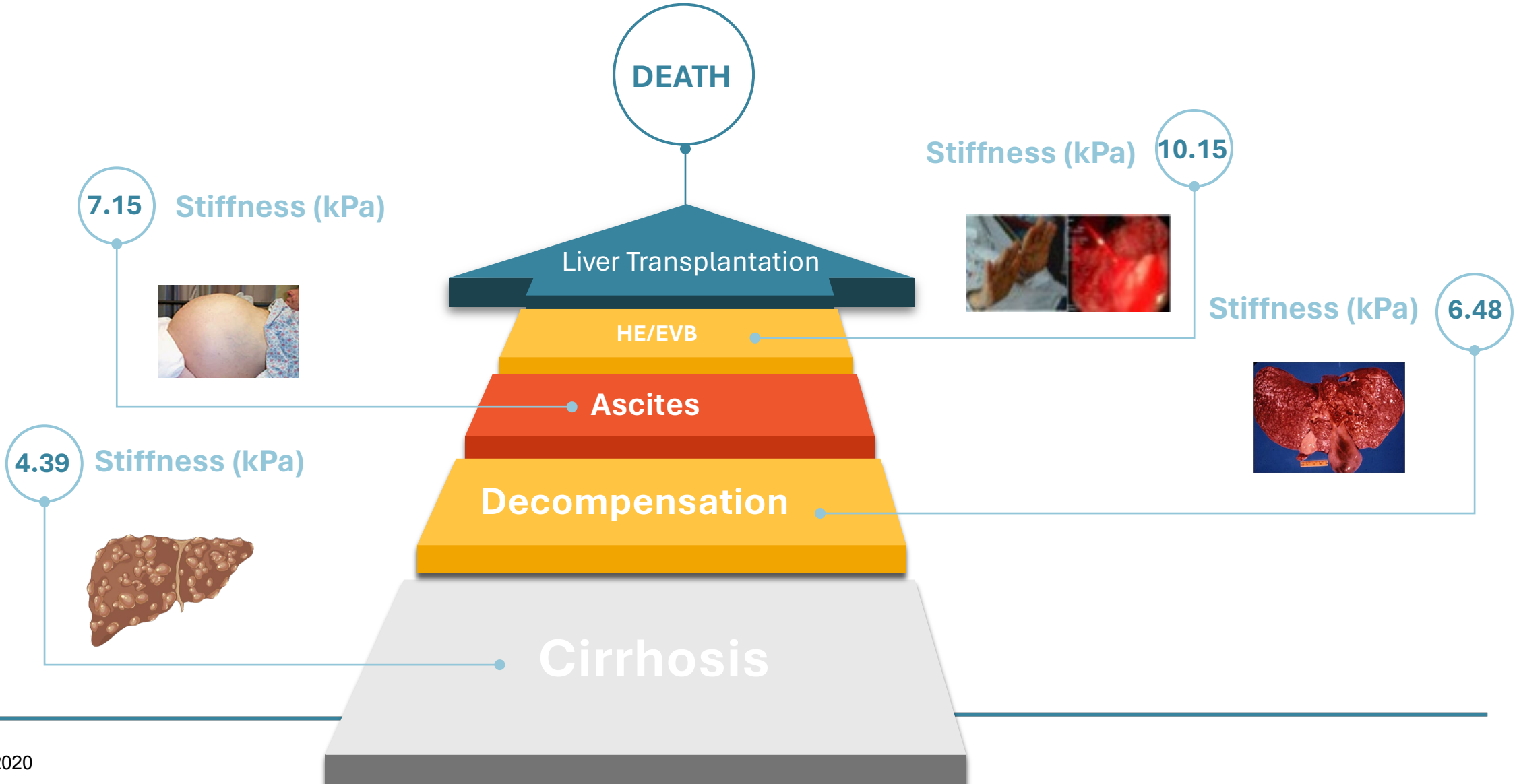


Meta-analysis, 7 studies, 346 patients

MRI-PDFF responders were significantly more likely to
- Have a histologic response (51% vs 14%)
- NASH resolution (41% vs 7%)

a. Stine J. Clinical Liver Disease. 2022;20:198-201. b. Stine J et al. Clin Gastroenterol Hepatol. 2021;19:2274-2283.e5

MRE is Associated with Liver Outcomes

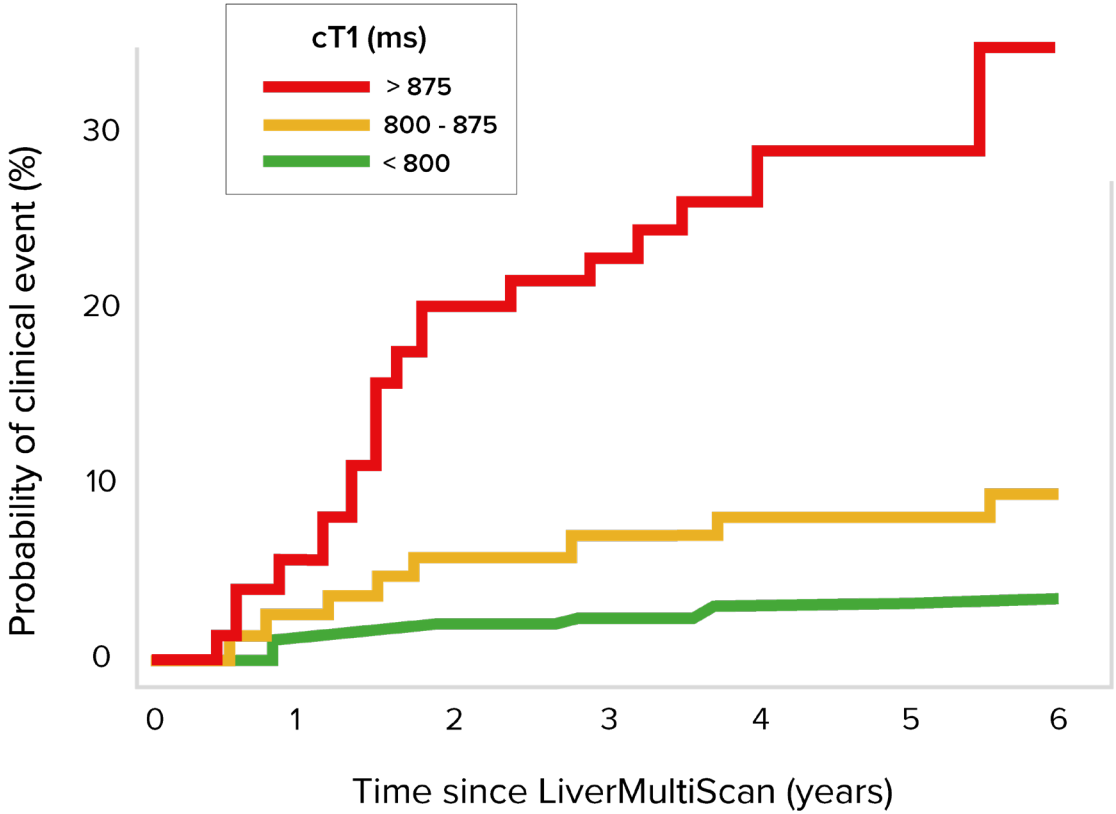


Han MAT. Liver Int 2020

MRI-cT1 to Predict Major Adverse Liver Outcomes

In 182 patients, (54% with MASLD) followed up over 620 person-years, an increase in cT1 of 100 ms corresponded to a 91% increase in the risk of a clinical event (HR = 1.91)

Patients with cT1 > 875 ms had a higher cumulative probability of clinical events than patients with intermediate (800 – 875 ms) and low (< 800 ms) cT1



cT1 > 875 ms identified high-risk MASH patients and predicted who is at a higher risk for clinical events

Cirrhosis, Ascites, Variceal bleeding, Encephalopathy, HCC Transplantation, Mortality

Alkhouri et al. J Hep 2022; 77:S453

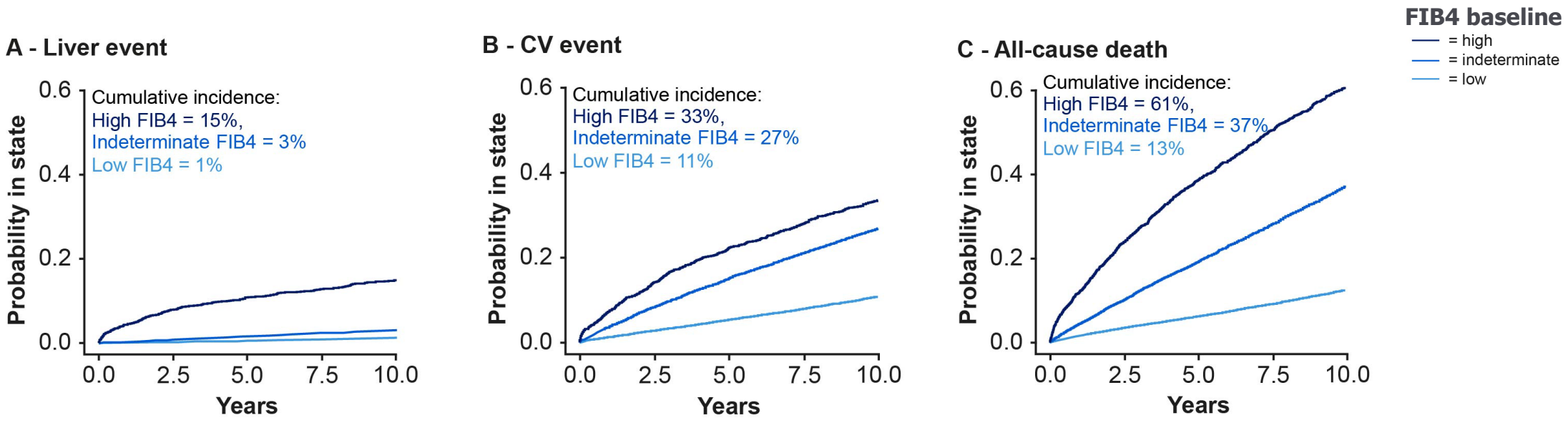
FIB-4 Predicts Long-Term Outcomes

Longitudinal Non-Interventional Observational Cohort Study Based in UK Primary Care – N= 44.481

Study period: 2001–2020

Endpoints

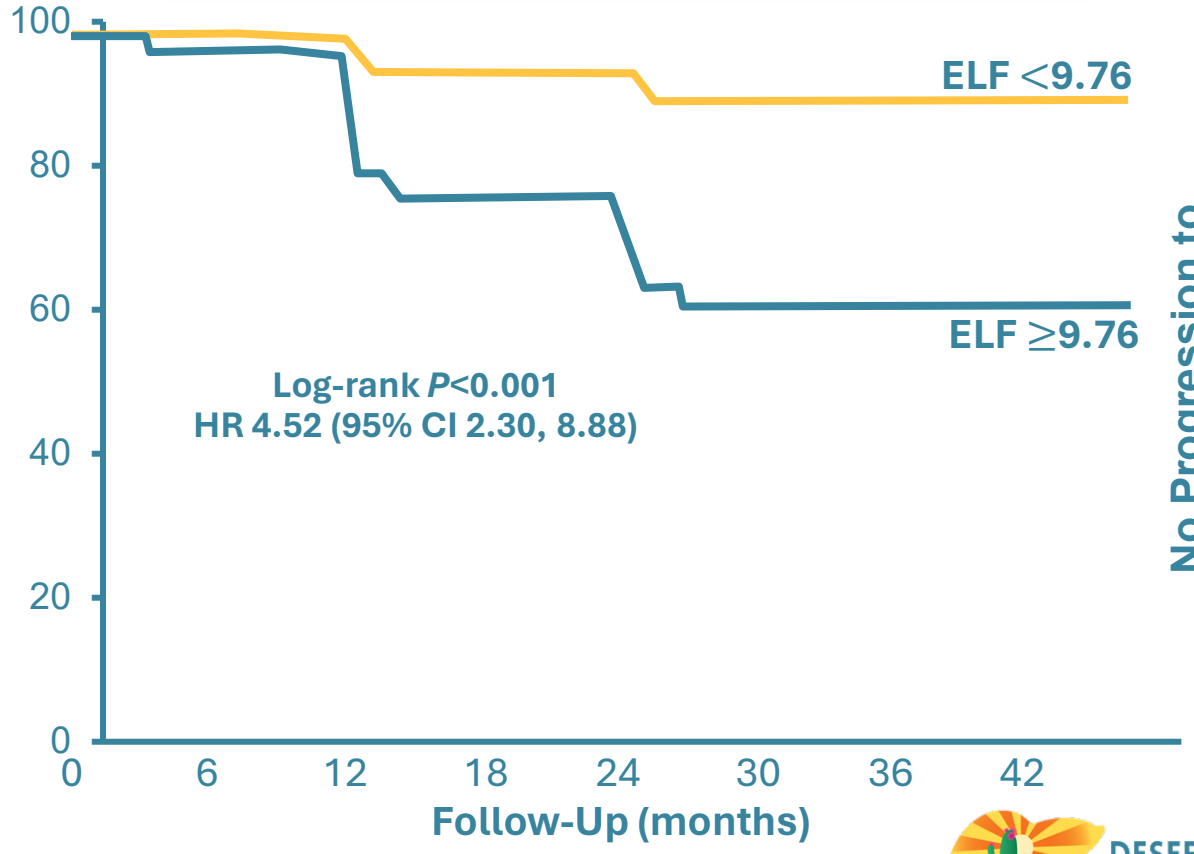
- Time to first **liver event** (liver-related hospitalisation or death)
- Time to first **CV event** (CV-related hospitalisation or death)
- Time to **death** of any cause



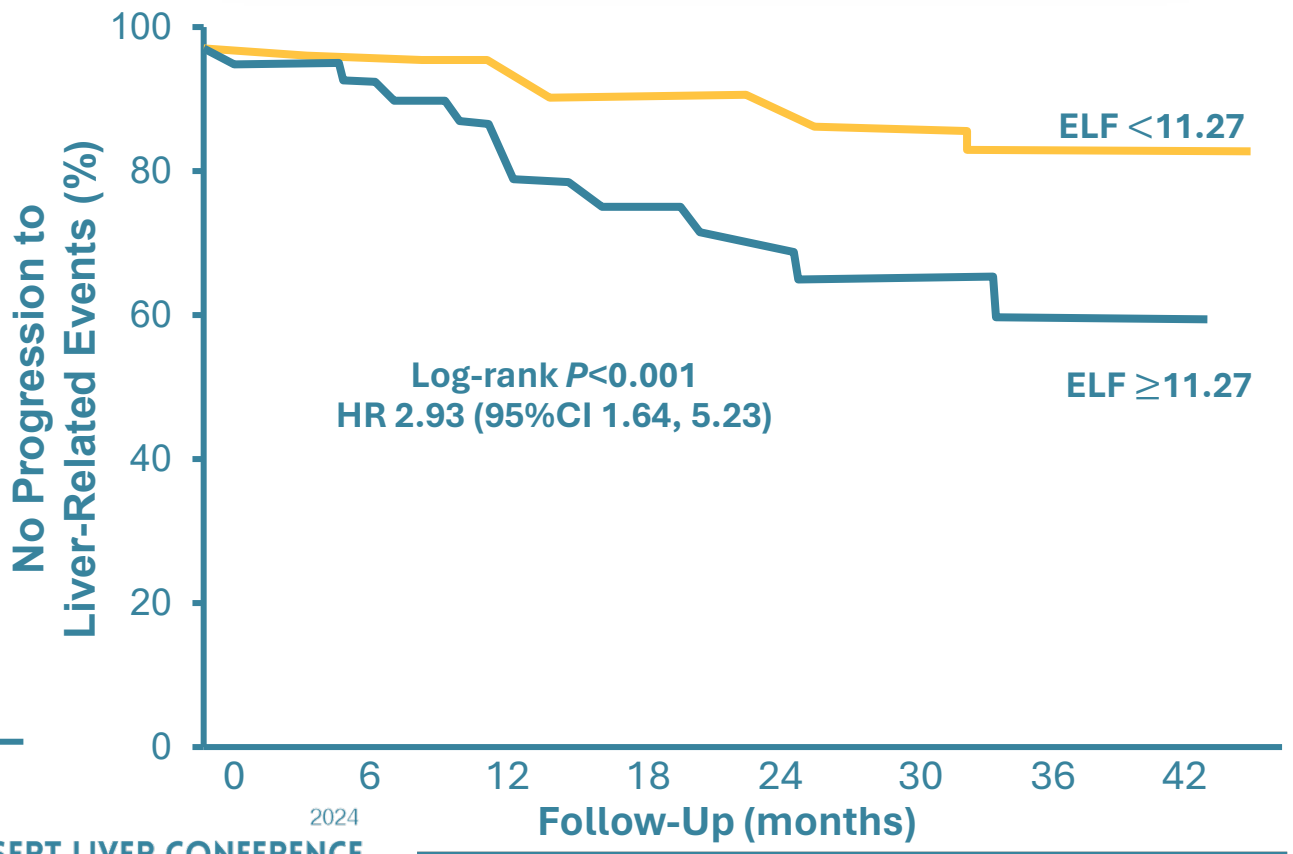
Anstee Q, et al. EASL 2022. Abstract OS025.

ELF Predicts Progression to Cirrhosis and MALOs

Progression to Cirrhosis by Baseline ELF score

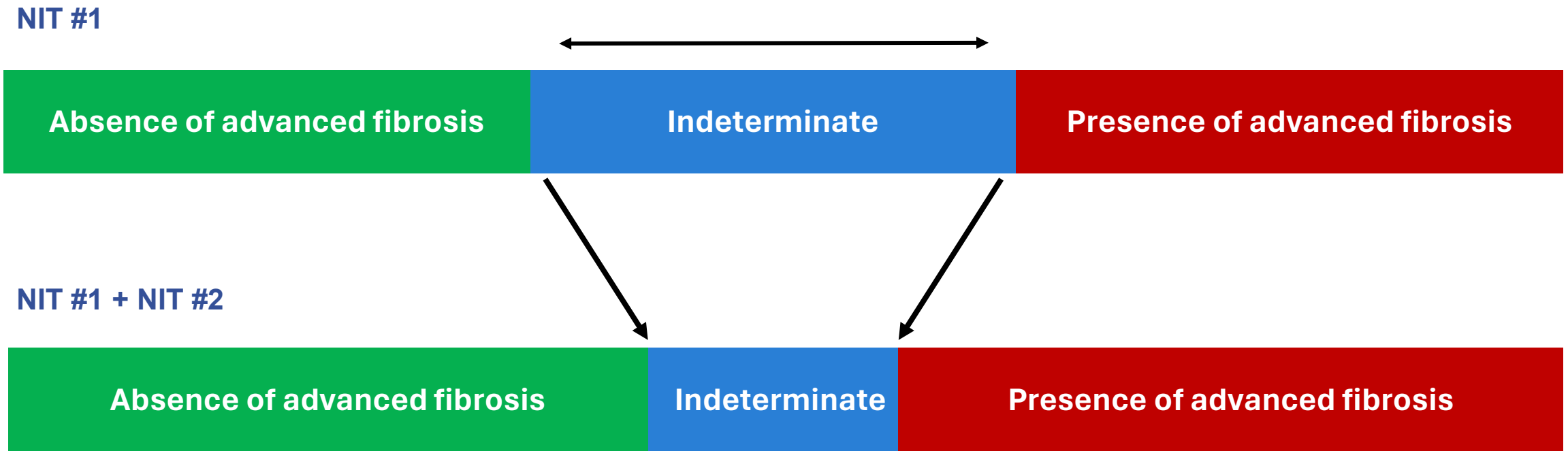


Progression to MALOs by Baseline ELF score



Harrison et al Hepatology 2017; 66 (Suppl S1 Abstract 2122) *Simtuzumab trial * Galectin Trial

Use of Sequential Non-Invasive Tests



The sequential use of NITs maintains sensitivity and specificity while enabling the classification of a larger proportion of patients

Younossi. AASLD 2018. Abstr LB-10.

Summary

Non-Invasive Test	Monitoring Therapeutic Intervention	Predicting MALOs
FIB-4	✓	✓ > 2.67
FibroScan VCTE	✓	✓ ≥ 12 kPa
ELF	✓	✓ ≥ 11.3 kPa
ProC3	✓ ≥ 20% reduction	
MRI-PDFF	✓ ≥ 30% relative reduction in LFC	
MRI-cT1	✓ ≥ 80 ms reduction	✓ ≥ 875 ms
MRE	✓ ≥ 20% reduction	✓ ≥ 6.48 kPa

Harrison SA et al. Nature Med. 2023 Mar;29(3):562-573; Boursier J. et al. J Hep. 2022;76:1013-1020; Harrison et al Hepatology 2017; 66

2024
DESERT LIVER CONFERENCE
PHOENIX, ARIZONA

Selecting Patients for Treatment and Monitoring Response

- **Naim Alkhouri, MD**
- Chief Medical Officer
- Director of the Steatotic Liver Program
- Arizona Liver Health (ALH)
- Chandler, AZ

ARIZONA LIVER HEALTH™

Objectives

- Demonstrate the use of NITs in clinical practice to select patients that will likely benefit from pharmacologic treatment for at-risk MASH without cirrhosis (resmetirom and semaglutide).
- Discuss how NITs will be used to monitor response to pharmacologic treatment.
- This is an interactive session, let’s have fun☺
- @AlkhouriNaim 

Get You Phones Out and Open the MDCalc App → Search for FIB4

- Mrs. Bilirubina is a 61-year-old Hispanic female with T2DM, obesity, and dyslipidemia.
- What's her pre-test probability of having at-risk MASH?
- Let's calculate her FIB4: AST 72, ALT 65, Platelets 188.

FIB4= 2.90 (High > 2.67) → Refer to a specialist

Open the MyFibroscan App → Interpretation

- Fibroscan: CAP 389 and LSM 10.5 kPa

Fibroscan Interpretation: S3 and F3

MyFibroscan App → Scores → FAST

- To calculate FAST, you need LSM/ CAP/ AST (10.5, 389, 72).

FAST = 0.83 → High probability for at-risk MASH

Is This Patient a Good Candidate for Pharmacologic Treatment for at-Risk MASH?

- Absolutely, the patient has T2DM and MetS with NITs indicating at-risk MASH.
- How can you rule out the presence of cirrhosis?

FIB4 < 3.48
LSM < 20 kPa
Platelets > 150k/uL
Obtain US: smooth liver surface and no splenomegaly

Mr. Tequina

- 49-year-old with no significant PMHx presents for elevated liver enzymes (AST 112, ALT 79, Platelets 178, Albumin 3.4, Hb 11.9, MCV 108, Bilirubin 1.2).
- BMI is 31.2 Kg/m2 and his HbA1C is 6.1%.
- He denies excessive alcohol intake but admits to drinking 2-3 beers socially especially during football season.
- What's your next step?

PETH testing, labs suggestive of ALD→ PETH is back at 200 indicating heavy alcohol use

Mrs. H

- 51-year-old Caucasian female with PMHx of HTN and obesity (BMI of 41 kg/m2) who presents for incidental finding of steatotic liver on US done for RUQ pain.
- ALT 23, AST 18, Platelets 312.
- Let's calculate the FIB4.

FIB4= 0.61 (Low < 1.3) → keep in primary care
Consider semaglutide 2.4 mg/week for obesity
Repeat FIB4 in 2-3 years

Mr. J

- 63-year-old Hispanic male with PMHx of diabetes for 20 years, dyslipidemia, and CAD who presents for elevated FIB4 that was calculated by his PCP.
- AST 54, ALT 47, Platelets 134.
- Let’s calculate the FIB4.

FIB4 3.70 (Risk for cirrhosis > 3.48)
Fibroscan LSM 22 kPa (Risk for cirrhosis > 20)

MyFibroscan App → Scores → AGILE4

- To calculate the AGILE4 score, you need LSM/ AST/ ALT/ Platelets/ Diabetes/ Gender (22/ 54/ 47/ 134/ Yes/ M).

AGILE4 = 0.74 → High probability for cirrhosis
US shows nodular liver with splenomegaly (16.6 cm)

Is This Patient a Good Candidate for Pharmacologic Treatment for at-Risk MASH? ?

- Absolutely NOT, the patient is cirrhotic and will not be a candidate for resmetirom until the results of MAESTRO NASH Outcomes demonstrate good safety and efficacy.
- Semaglutide was not associated with fibrosis regression in a small trial in patients with MASH cirrhosis. No plans for trials with semaglutide monotherapy in patients with MASH cirrhosis.

Biomarkers to Assess Treatment Response

Liver Fat Fraction (MRI-PDFF)

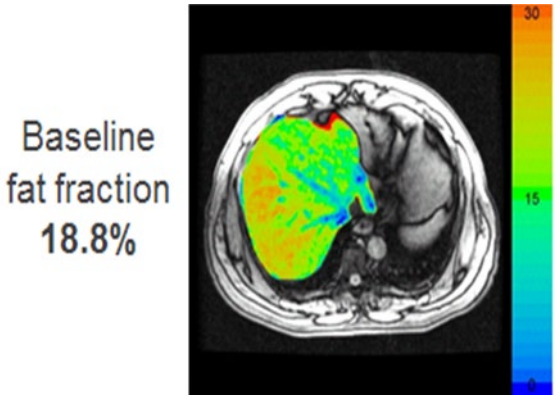
- ≥ 5% absolute/ ≥ 30% relative reduction associated with improvement in NAS

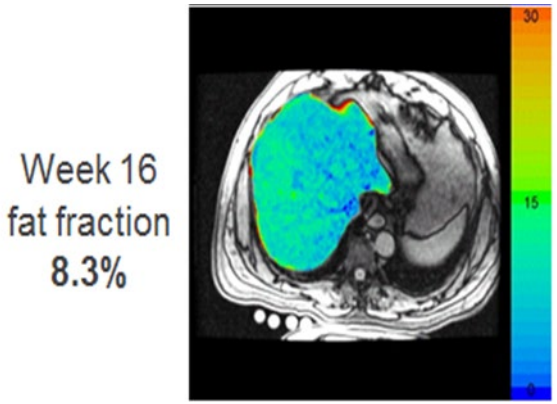
ALT/ AST

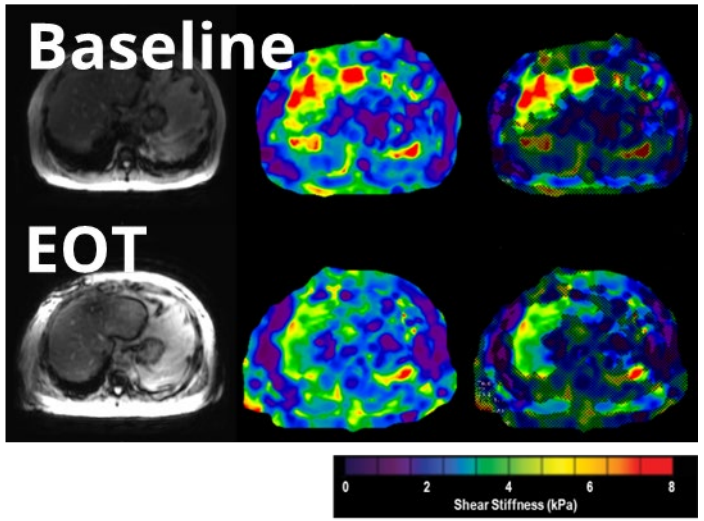
- ≥ 17 U/L reduction predicts histologic response

ELF/ cT1/ LSM

- ELF reduction by 0.5 from BL
- cT1: > 80 ms reduction from BL or change in category
- LSM decrease by 25-30% from BL



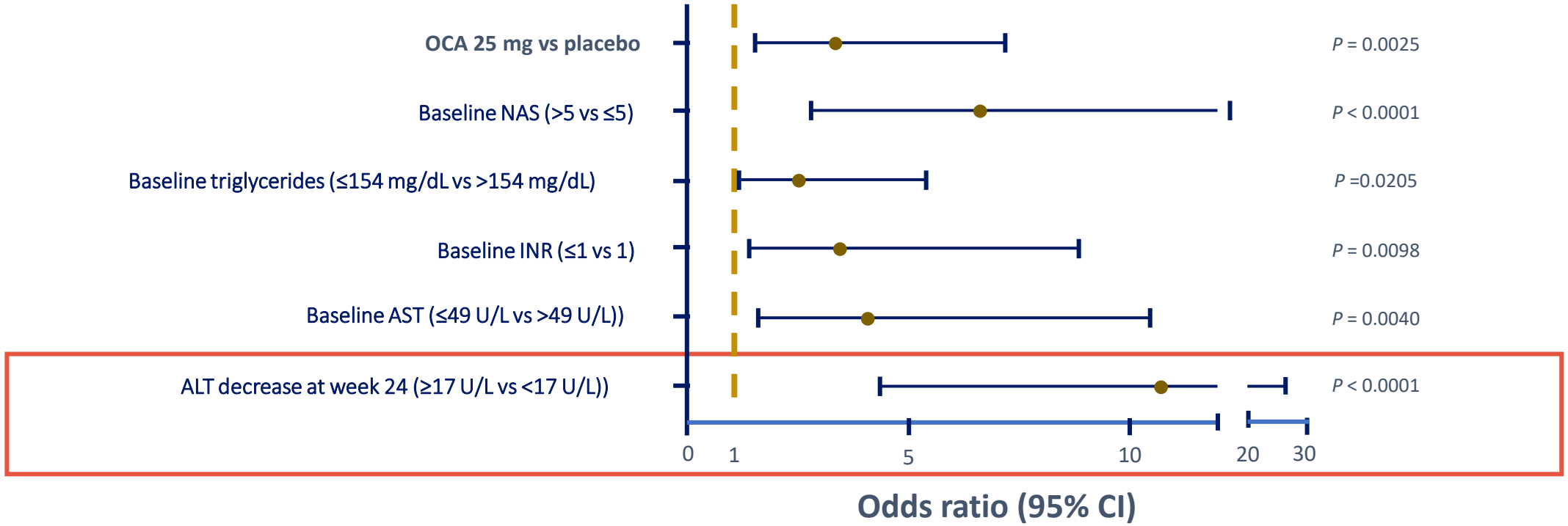




Loomba R et al. Gastroenterol. 2019;156(1):88-95.e5; Patel J et al. Therap Adv Gastroenterol. 2016 Sep;9(5):692-701.

Predictor(s) of histologic improvement

ALT levels



Decrease in ALT level at week 24 by 17 U/L or more is significantly associated with histologic response

Loomba R et al. Gastroenterol. 2019;156(1):88-95.e5

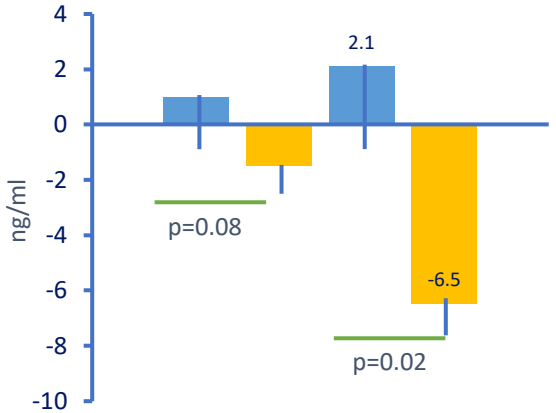
Predictor(s) of histologic improvement

Pro-C3 and ELF

MGL-3196 (THR-β agonist)[1]

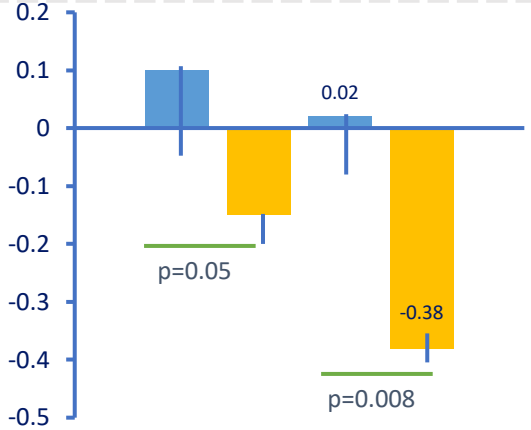
Pro-C3

All		Elevated BL Pro-C3 (≥17·5 ng/mL)	
Placebo	MGL-3196	Placebo	MGL-3196
n=38 p=NS	n=78 0.057	n=12 p=NS	n=29 0.0019

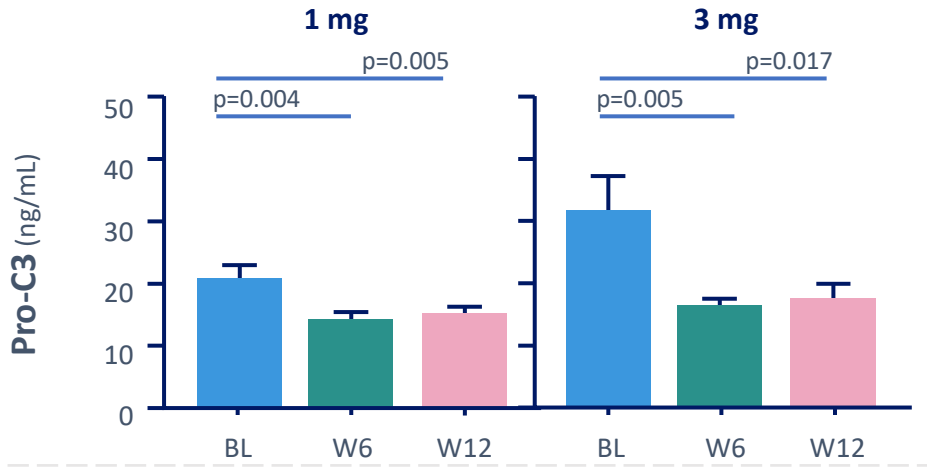


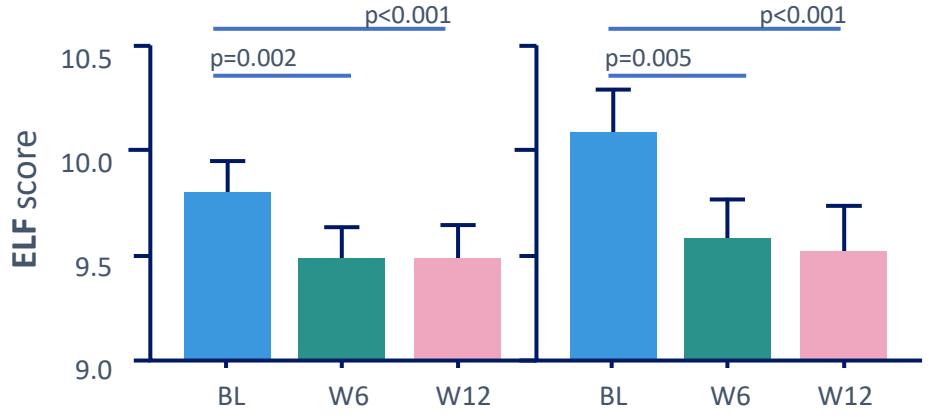
ELF

All		Elevated BL ELF ((≥9.0)	
Placebo	MGL-3196	Placebo	MGL-3196
n=32 p=NS	n=64 p=0.12	n=21 p=NS	n=40 p<0.0001



NGM282 (FGF 19 analogue)[2]





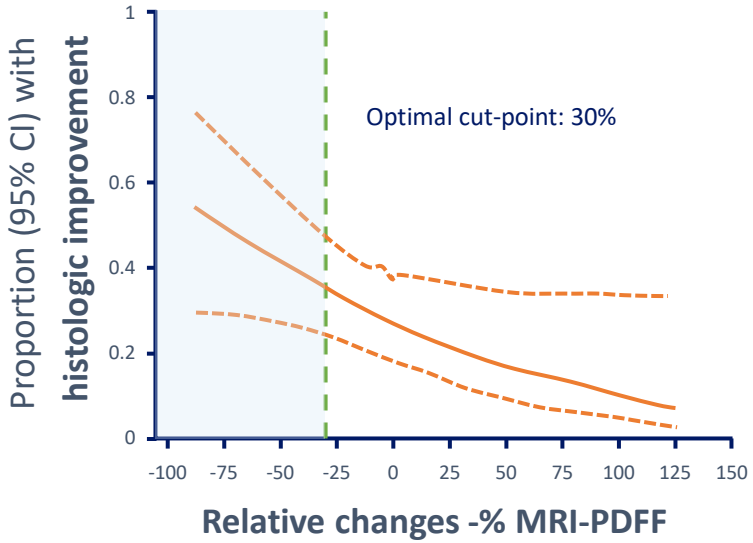
BL, baseline; ELF, enhanced liver fibrosis; FGF19, fibroblast growth factor-19; LDL-C, low-density lipoprotein cholesterol; mITT, modified intention-to-treat; NAS, nonalcoholic fatty liver disease activity score; Pro-C3, neoepitope-specific N-terminal propeptide of type III collagen; SD, standard deviation; W, week. Shown are mean ± SEM; P values by one-sample t test

1. Harrison SA et al. Lancet. 2019;394(10213):2012-2024.; 2. Harrison SA et al. Hepatol. 2020;71(4):1198-1212

Measuring treatment responders and non-responders

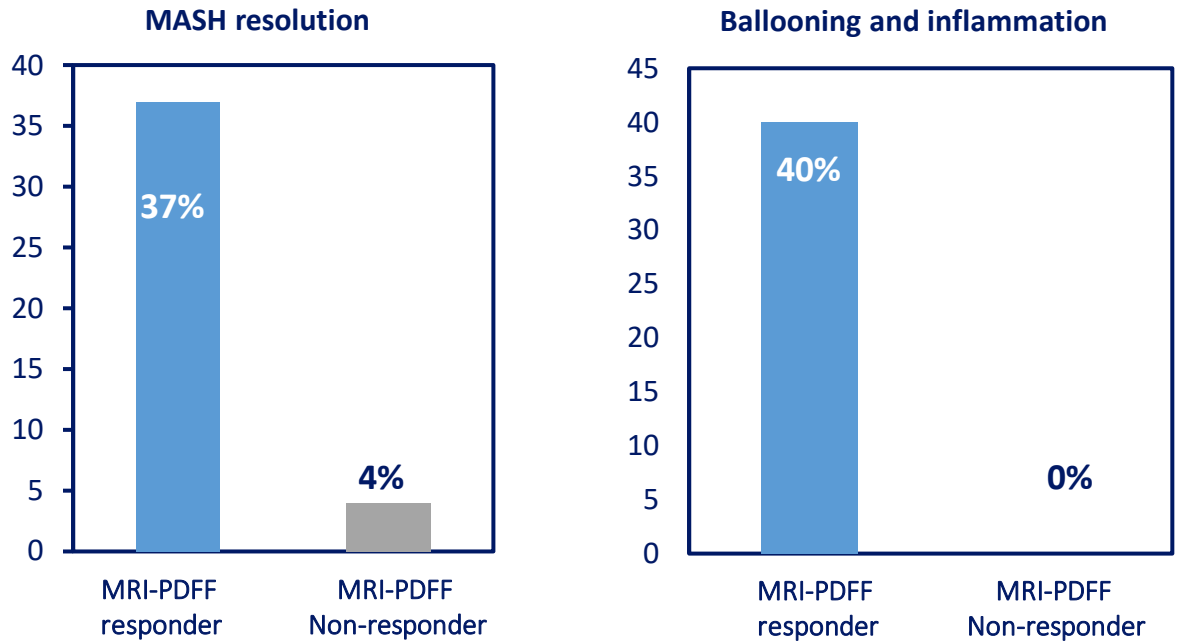
MRI-PDFF*

FLINT Trial[1]



MRI-PDFF responders demonstrate significantly higher odds **4.86** (95% CI, 1.4-12.8, P < 0.009) of histologic response

Resmetirom Trial[2]



MRI-PDFF responders demonstrate improved histologic response in MASH resolution

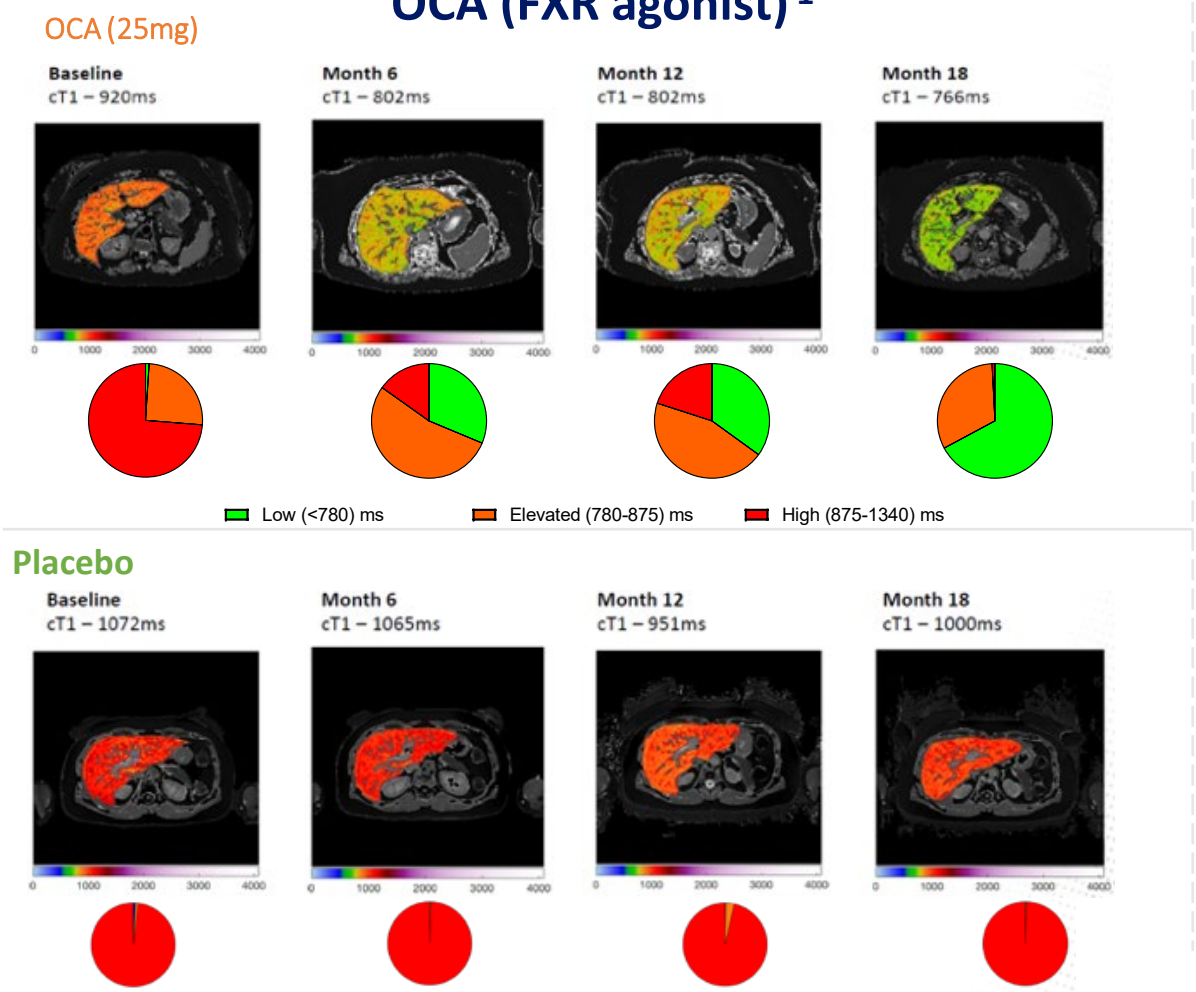
**MRI-PDFF response defined as 30% or more relative fat reduction at week 12. CI, confidence interval; FLINT, farnesoid X receptor ligand obeticholic acid in NASH trial; MASH, metabolic dysfunction-associated steatohepatitis; MRI-PDFF, magnetic resonance imaging-proton density fat fraction*

1. Loomba R et al. Hepatol. 2020;72(4):1219-1229; 2. Harrison et al. Lancet. 2019;394(10213):2012-2024

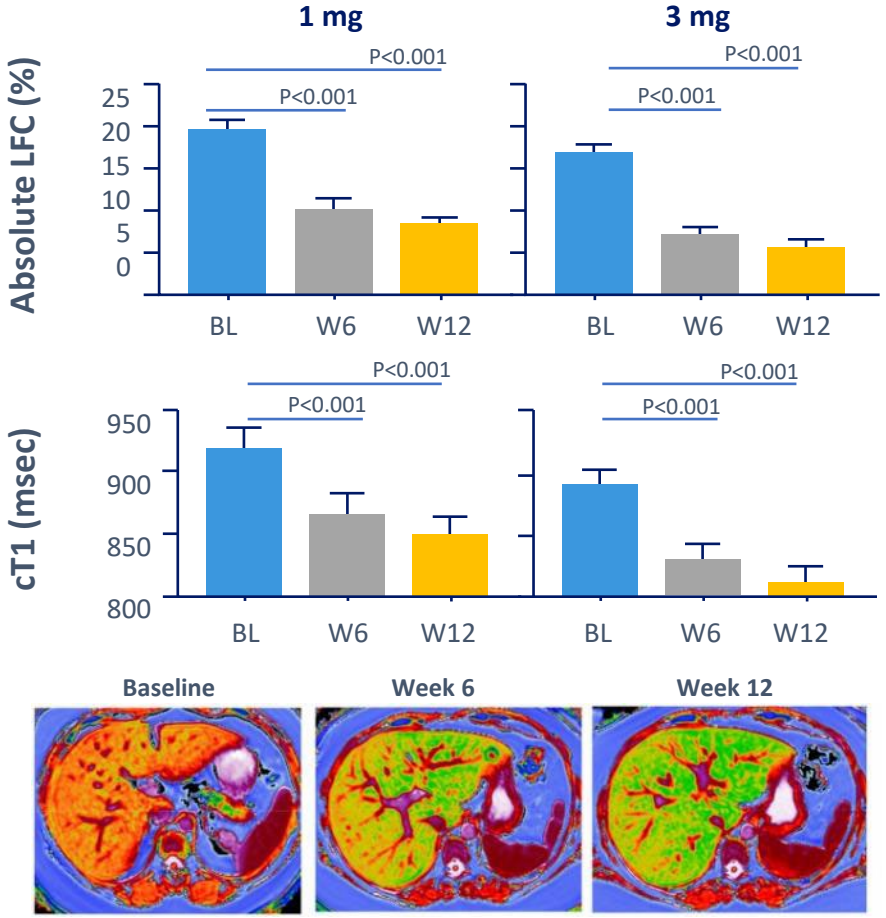
Measuring histological response

cT1

OCA (FXR agonist) [1]



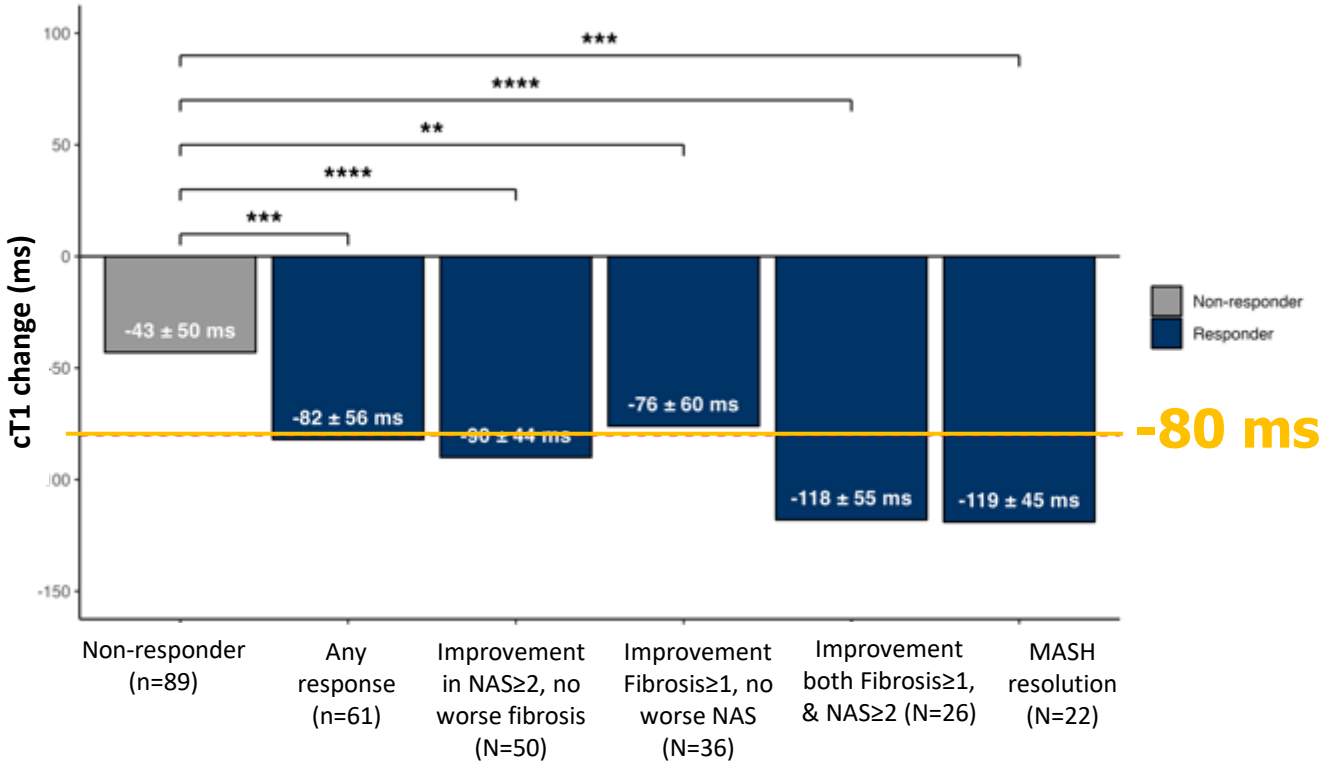
NGM282 (FGF 19 analogue)[2]

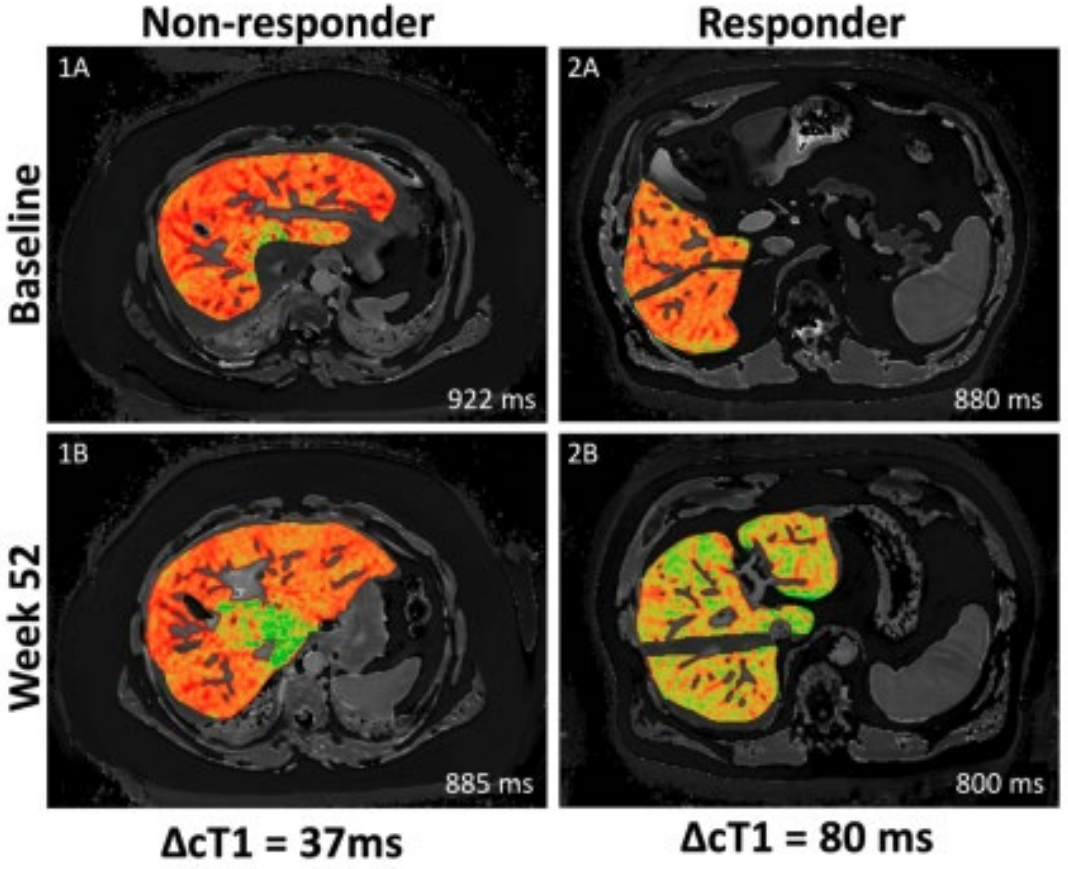


BL, baseline; cT1, corrected T1; FGF 19, fibroblast growth factor 19; FXR, farnesoid X receptor; LFC, liver fat content; OCA, Obeticholic acid; W, week

1. Loomba R et al. EASL 2020; 2. Harrison SA et al. Hepatol. 2020;71(4):1198-1212

Using cT1 to Determine Meaningful Change in MASH





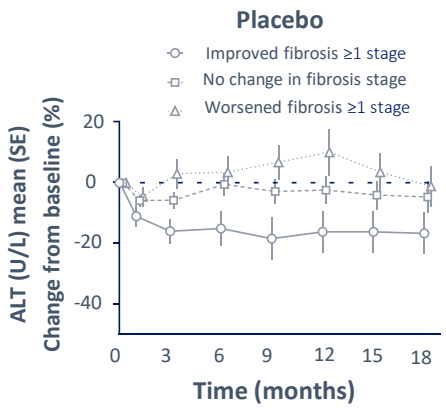
An absolute decrease of >80 ms in cT1 was found to distinguish responders from non-responders.

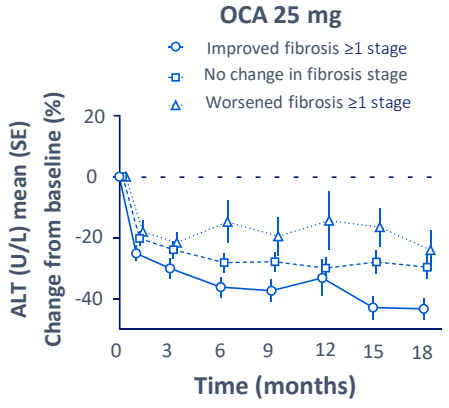
Monitoring change in fibrosis with NITs: ALT and AST

Phase 3, obeticholic acid, REGENERATE–18 months

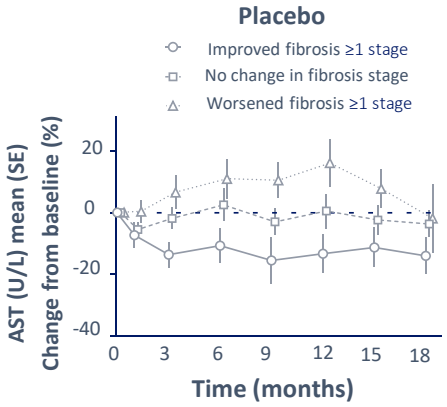
Change from baseline in NITs over time by treatment group and histological fibrosis improvement status

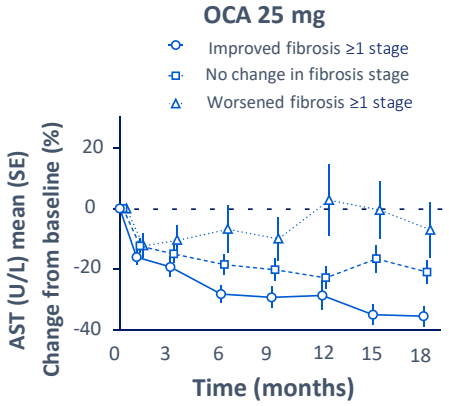
ALT





AST





- In both PBO and OCA 25 mg arms, ALT and AST:
  - Decreases in patients with improvement of fibrosis by histology
- Among patient with stable fibrosis by histology, both ALT and AST reduced in patients receiving OCA 25 mg vs PBO

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NITs, noninvasive tests; OCA, obeticholic acid; PBO, placebo; SE, standard error. Rinella ME et al. J Hepatol. 2022;76(3):536-548.

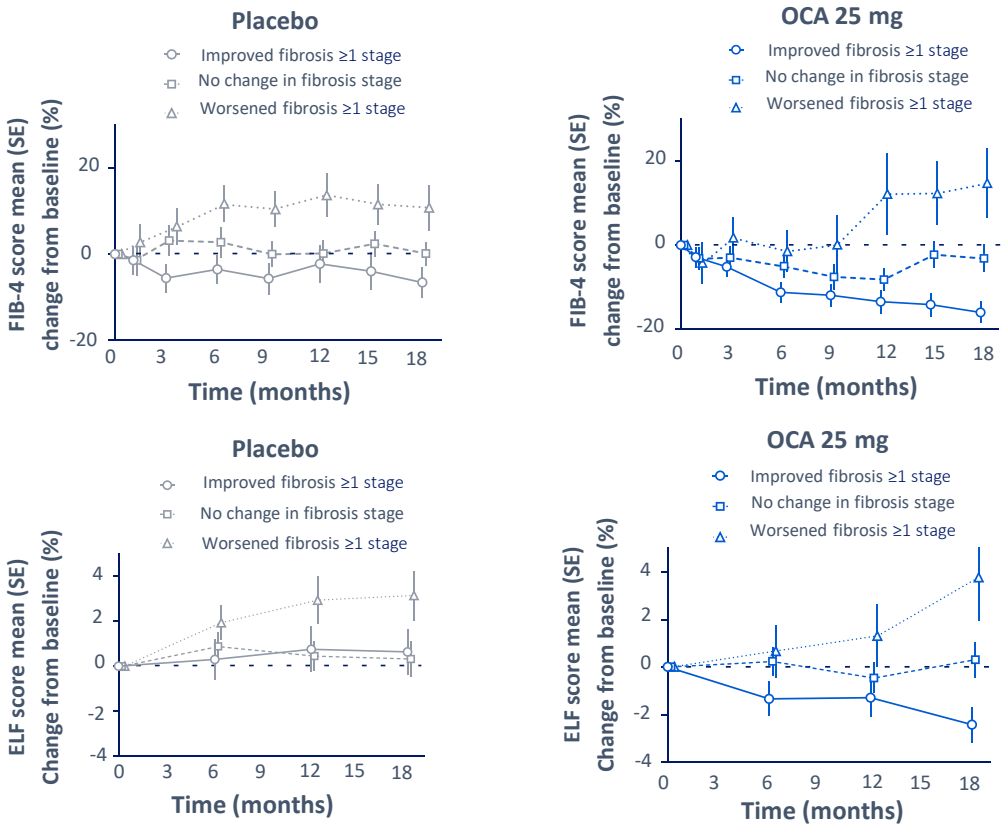
Monitoring change in fibrosis with NITs: FIB-4 and ELF

Phase 3, obeticholic acid, REGNERATE–18 months

Change from baseline in NITs over time by treatment group and histological fibrosis improvement status

FIB-4

ELF



- In both PBO and OCA 25 mg arms, FIB-4 score
  - Improves with a ≥ 1-stage improvement in histologic fibrosis, but was most pronounced in patients treated with OCA 25mg
- In patients with stable fibrosis, mean FIB-4 values remained near baseline in all groups
- Patients in the OCA treatment groups with ≥ 1-stage fibrosis improvement had improved ELF scores over time

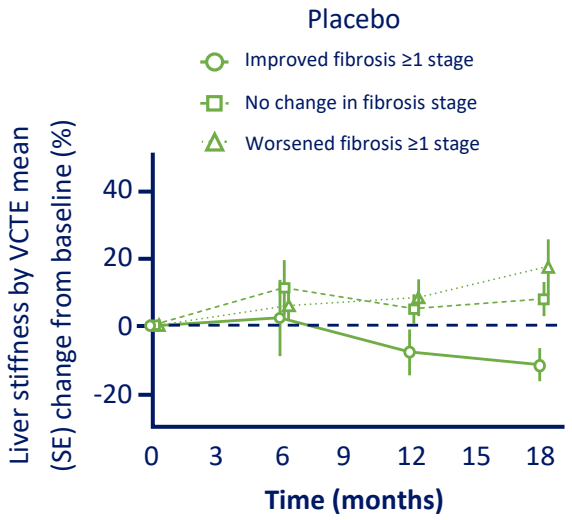
OCA, obeticholic acid; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4 index for liver fibrosis; PBO, placebo; SE, standard error.
Rinella ME et al. J Hepatol. 2022;76(3):536-548.

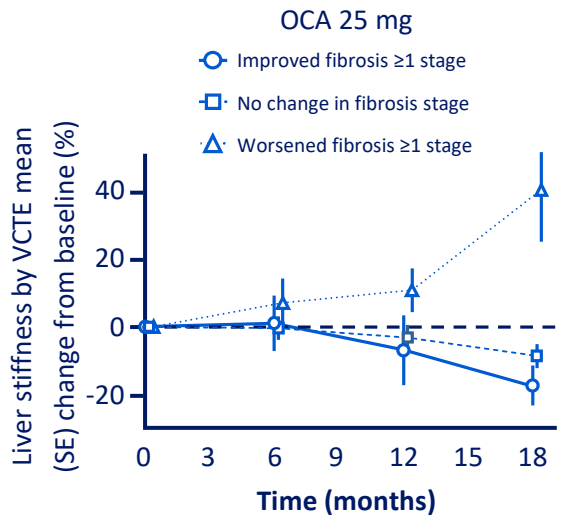
Monitoring change in fibrosis: LSM by VCTE

Phase 3, obeticholic acid, REGENERATE–18 months

Change from baseline in NITs over time by treatment group and histological fibrosis improvement status

FibroScan





- In both PBO and OCA 25 mg arms, LSM by VCTE :
  - Increases in patients with worsening of fibrosis by histology
  - Decreases in patients with improvement of fibrosis by histology
- Among patient with stable fibrosis by histology, LSM by VCTE improved in patients receiving OCA 25 mg vs PBO

Individual NITs are not enough for treatment monitoring

LSM, liver stiffness measurement; NIT, non-invasive test; OCA, obeticholic acid; PBO, placebo; SE, standard error; VCTE, vibration-controlled transient elastography. Rinella ME et al. J Hepatol. 2022;76(3):536-548.

#149: Relationship of Non-Invasive Measures With histological Response in Patients with MASH And Fibrosis: 52-Week Data From the Phase 3 MAESTRO-NASH Trial

Loomba et al; University of California San Diego

KEY ELIGIBILITY CRITERIA

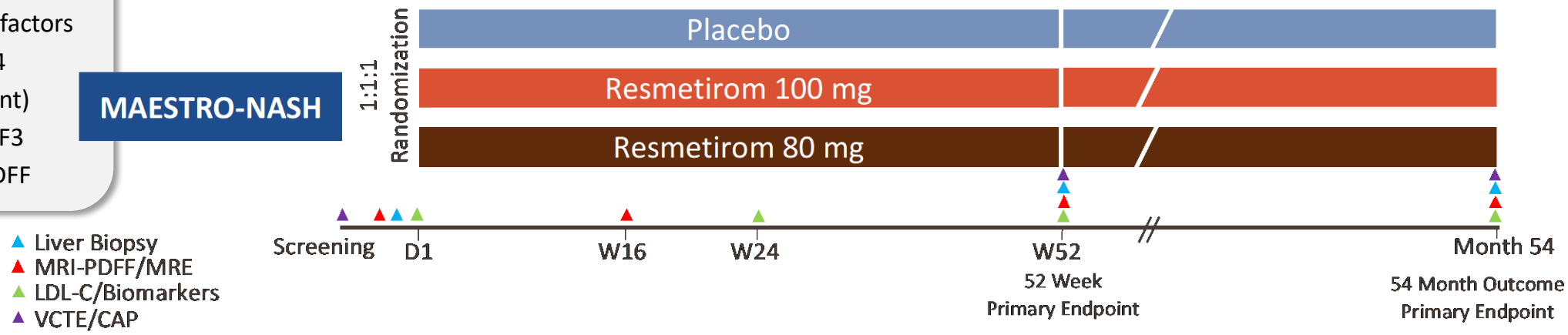
Presence of ≥3 metabolic risk factors

NASH on biopsy: NAS ≥4
(with ≥1 in each component)

Fibrosis stage F1B, F2, or F3

≥8% hepatic fat by MRI-PDFF

MAESTRO-NASH

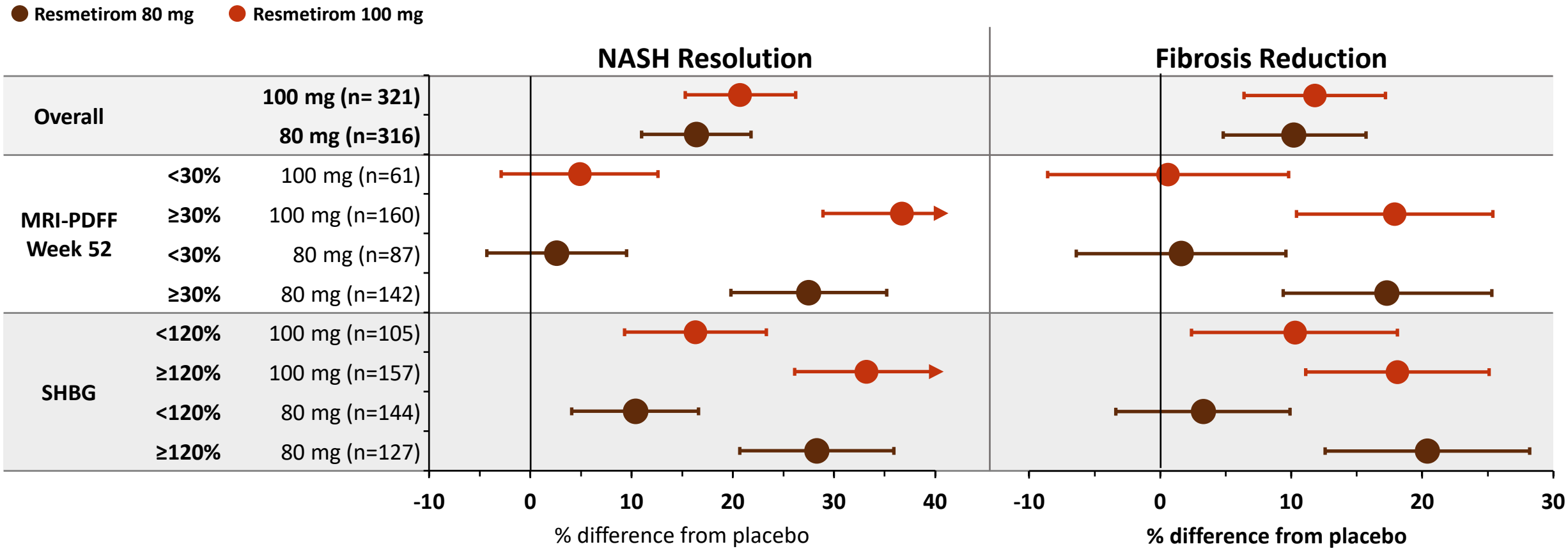


DUAL PRIMARY ENDPOINT AT WEEK 52

NASH resolution (ballooning score=0, inflammation score=0/1, & ≥2-point reduction in NAS) with no worsening of fibrosis

≥1-stage improvement in fibrosis with no worsening of NAS

Resmetirom Response Analysis, Continued



- Median reduction in MRI-PDFF was 42% and 52% in the paired biopsy population at resmetirom 80 mg and 100mg and ¾ of patients achieved at least this reduction at 100 mg
- Among patients treated with resmetirom 80 mg or 100 mg who achieved a ≥30% reduction from baseline in MRI-PDFF, NASH resolution was observed in 28% and 38% and fibrosis improvement in 17% and 18% more patients than placebo.

MRI-PDFF, Magnetic Resonance Imaging Proton Density Fat Fraction; SHBG = sex hormone binding globulin

Are kinetics of NIT change over time associated with therapeutic response strength?

Kinetics of NIT change over time

Early change:

<12

weeks after treatment initiation

Mid-range change:

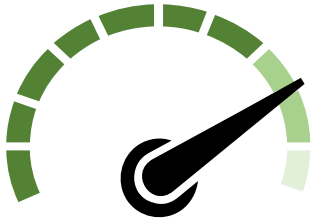
12–24

weeks after treatment initiation

Late change:

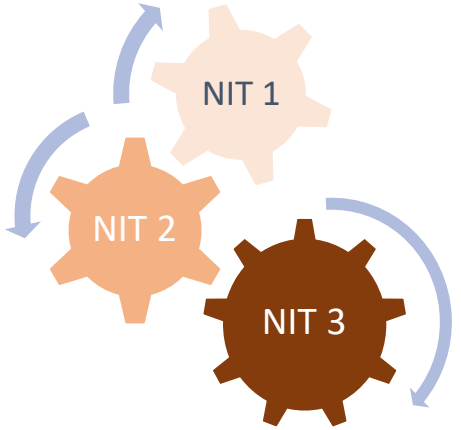
>24

weeks after treatment initiation



Monitoring therapeutic response

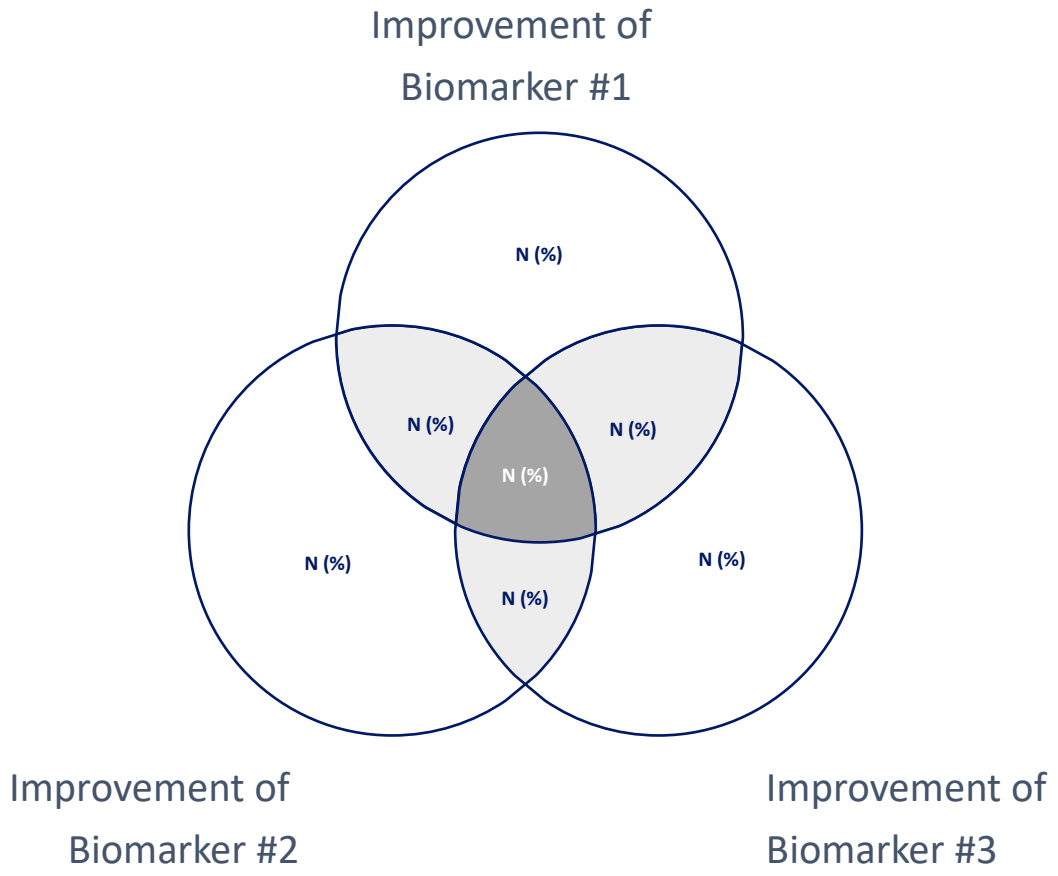
- The use of combined NITs increases the diagnostic accuracy of at-risk MASH patient
- Is that true for therapeutic response monitoring?
- If yes, how many and which ones are needed?



MASH, metabolic dysfunction-associated steatohepatitis; NIT, non-invasive test.

Combination NITs to assess treatment response

Assessment of consistency of NIT changes at the *per patient* level



Assessment of drug efficacy should include consistency of NIT change at the patient level, using combination of NITs

Take home message

01 NITs are progressively being used to capture the course of **disease progression** and **treatment response** to therapies

02 NITs have their own prognostic value independent of histologic severity and may help predict liver related events

03 **Combination NITs** are increasingly being developed and explored as **options for diagnosis** and can identify patients **at-risk of MASH and advanced fibrosis/cirrhosis**

04 Biomarkers can be **combined and selected depending on patient characteristics** to inform clinicians on the next steps and follow-up testing

Break

2:50 PM – 3:10 PM

NITs Demonstration

- Aegle Medical Solutions
- Echosens
- E-Scopics
- SonicIncytes

3:10 PM – 4:30 PM

Panel Discussion

Naim Alkhouri, MD, FAASLD, ABOM

Meena Bansal, MD

Stephen Harrison, MD, FACP, FAASLD

Mazen Noureddin, MD, MHSc

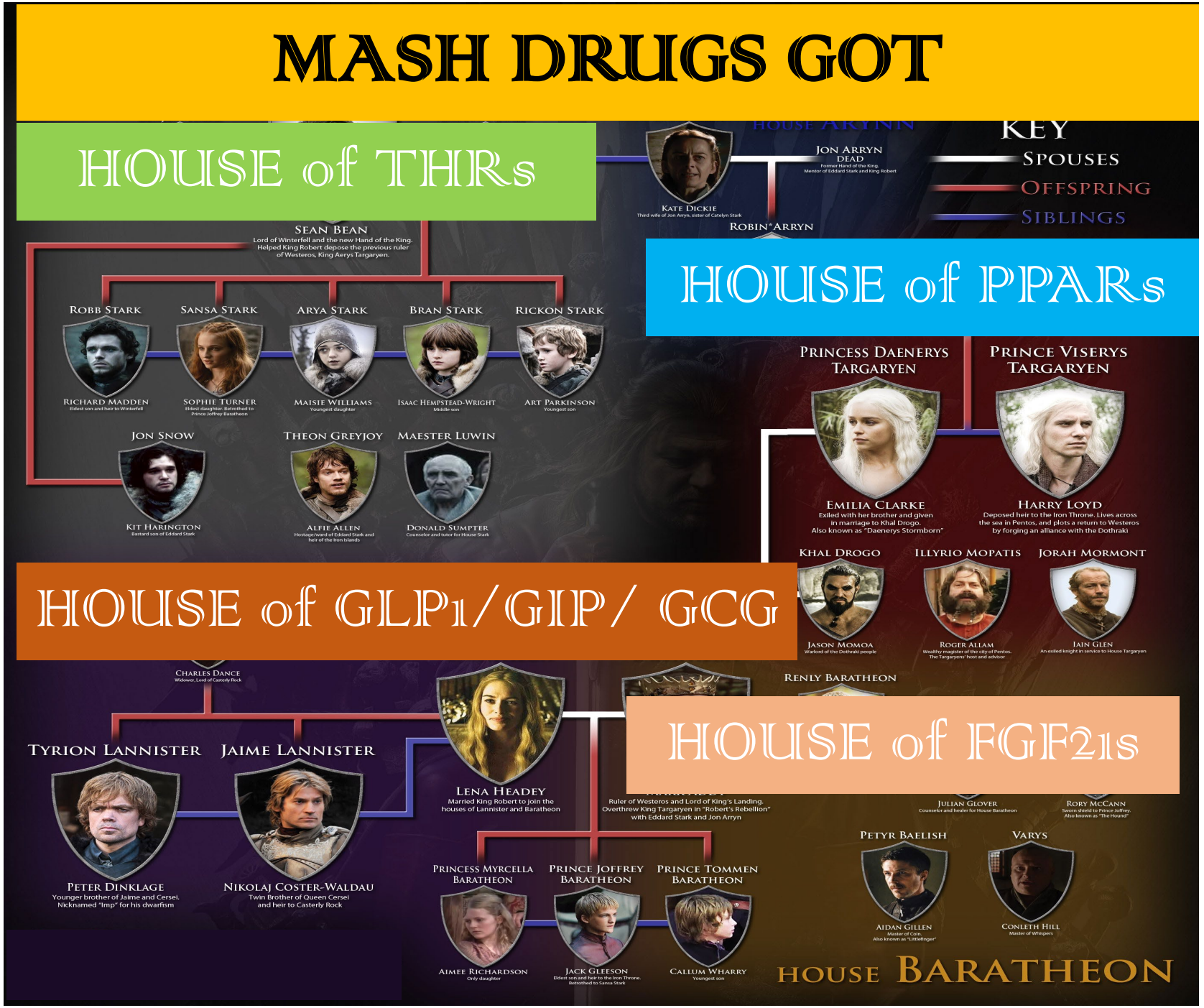
2024
DESERT LIVER CONFERENCE
PHOENIX, ARIZONA

Panel Discussion on the Future of MASH Therapeutics

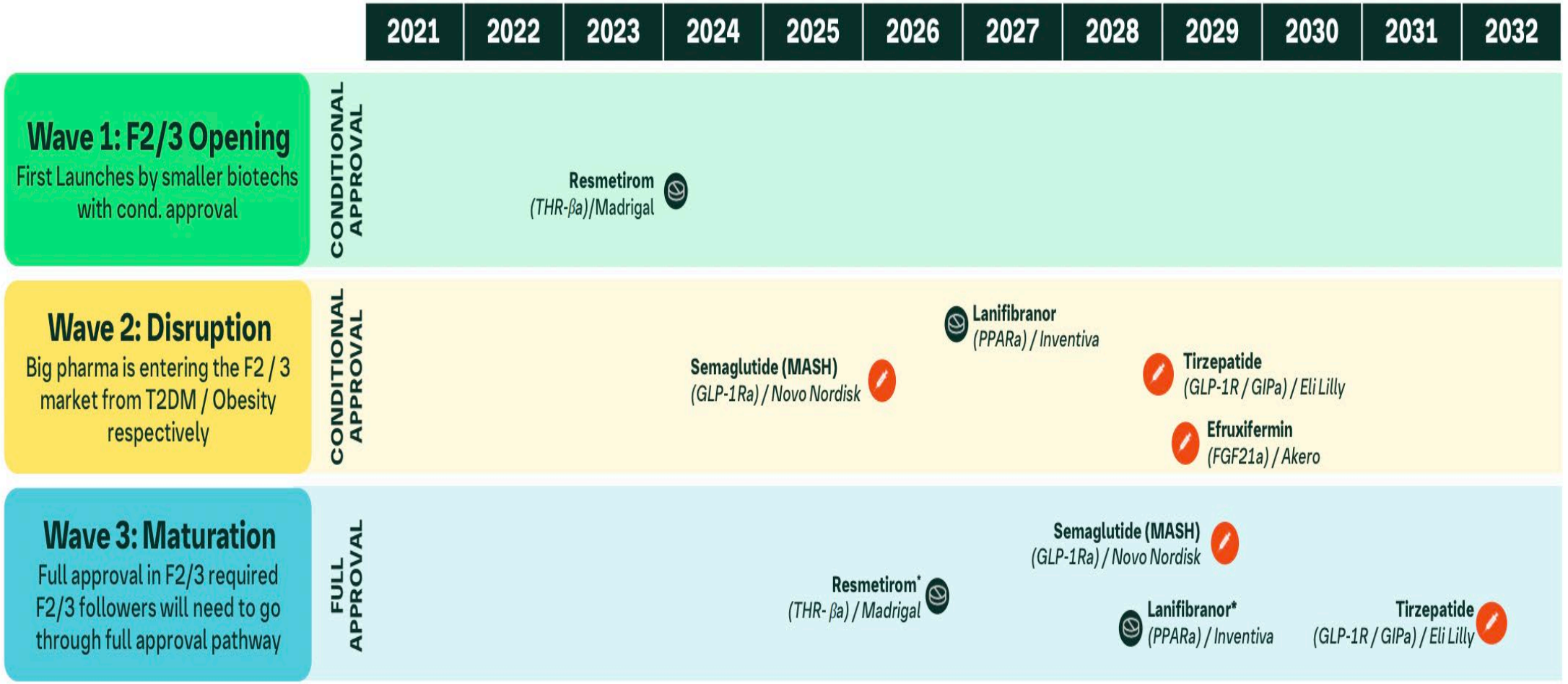
- **Naim Alkhouri, MD**
- Chief Medical Officer
- Director of the Steatotic Liver Program
- Arizona Liver Health (ALH)
- Chandler, AZ

ARIZONA LIVER HEALTH™

MASH DRUGS GOT



The Evolution of MASH Drugs



Case 1

- 58 y.o. with PMHx of T2DM and dyslipidemia for 10 years who has been on Dulaglutide (Trulicity) for the past 6 years.
- BMI is 28.9 and HbA1C is at 6.3%.
- ALT 50, AST 45, platelets 195.
- Fibroscan: LSM 11.3 kPa c/w F3 fibrosis and CAP of 362 dB/M c/w S3 steatosis.
- What medication would you pick to treat this patient in 2025 if both resmetirom and semaglutide are FDA approved for at-risk MASH?

How Would You Monitor for Response?

- What’s an adequate response?
- How to determine futility?
- How to decide on adding other medications?

Case 2

- 52 y.o. male with PMHx of HTN, OSA and obesity (BMI 41.2) presents with incidental finding of hepatosplenomegaly on US.
- ALT 40, AST 33, Platelets 289.
- Fibroscan: LSM 8.6 kPa c/w F2 fibrosis and CAP of 371 dB/M c/w S3 steatosis.
- What medication would you pick to treat this patient in 2025 if both resmetirom and semaglutide are FDA approved for at-risk MASH?

Case 3

- 48 y.o. Female with type 2 diabetes on metformin with HbA1C of 8.7%, obesity BMI 44.3 kg/m2, and dyslipidemia on high-dose atorvastatin LDL of 134 mg/dL presents with elevated liver enzymes.
- ALT of 99, AST, 87, Platelets at 187.
- Fibroscan LSM 12.6 kPa c/w F3 fibrosis and CAP of 400 dB/M c/w S3 steatosis.
- Would consider combination therapy with semaglutide + resmetirom?

Case 4

- 62 y.o. Female with type 2 diabetes and obesity presents with elevated liver enzymes and enlarged spleen found on imaging (15.6 cm).
- ALT 68, AST 87, Platelets 141 → FIB4
- Fibroscan LSM 22.4 kPa c/w F4 fibrosis and CAP of 282 dB/M c/w S1 steatosis.
- How would you manage this patient today?
- What's on the horizon for MASH cirrhosis?

Attendee Meeting Survey

Sponsor Meeting Survey

thank you

Saturday Agenda