Moving from RLSE to a Validated Surrogate Endpoint for MASH trials

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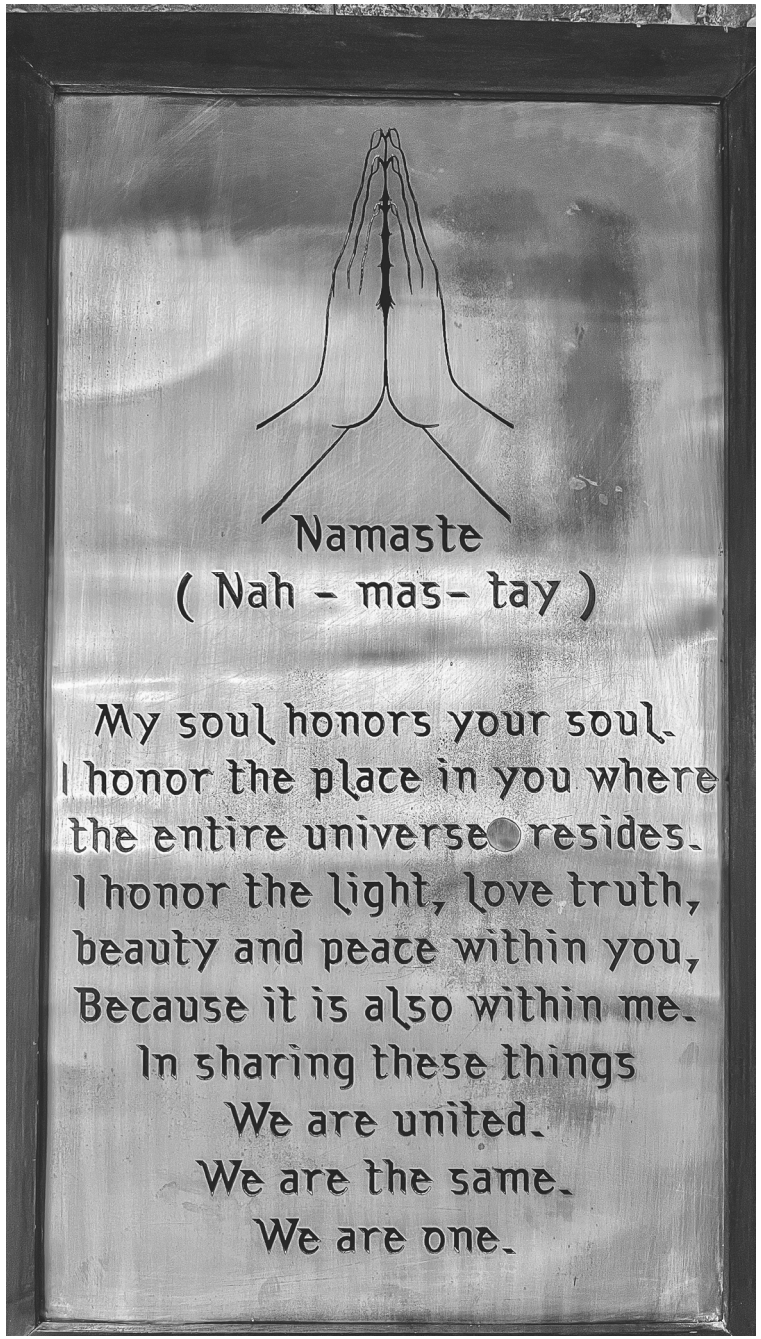

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- Ownership interests: Durect, Tiziana, Genfit, Exhalenz, Northsea, Rivus, Inversago
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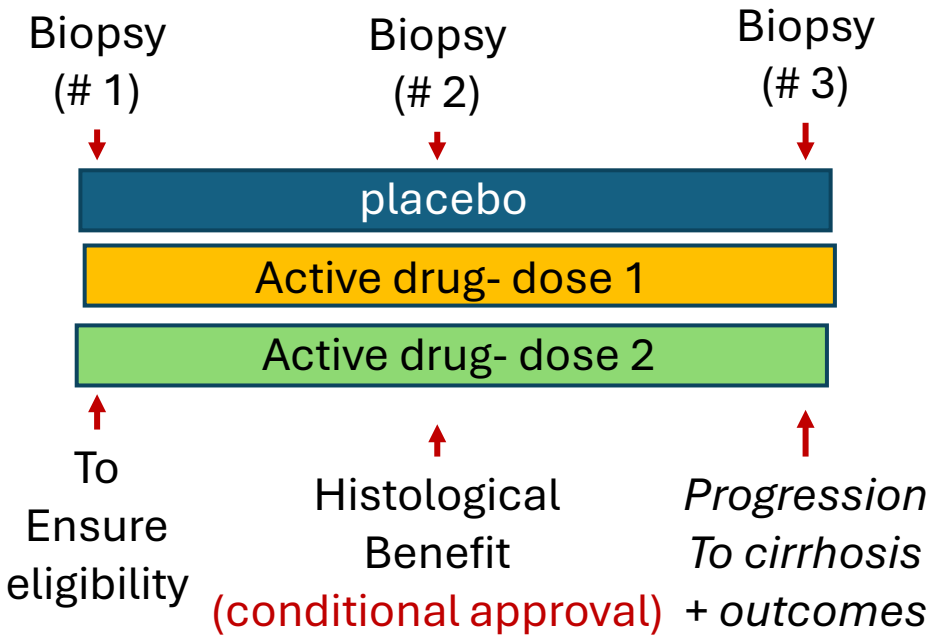
Current approach



- If we start with Stage 2-3 disease, progression to cirrhosis is the principal outcome we see within 5 year time frame

Sanyal et al, Hepatology 2015
FDA draft guidance 2018

Scenario 1: A NIT surrogate to capture progression to cirrhosis

The FDA strongly encourages ongoing work to characterize NIT thresholds that can identify progression to cirrhosis with high sensitivity and specificity – FDA MS Hepatology 2025- Anania et al

What is cirrhosis?

cirrhosis is defined as a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules.

- Features of cirrhosis:
  - Parenchymal nodules separated by fibrous septa
  - Differences in liver cell size and appearance
  - Fibrous septa with abnormal lobular architecture
  - Altered architecture and vascular relationships without septum formation (thrombosis, recanalization of veins)

Anthony et al, Bull WHO, 1977; 55:521-540

"The precise point at which pre-cirrhotic changes become established cirrhosis cannot always be determined".

Anthony et al, Bull WHO, 1977; 55:521-540

- Fibrosis stage is not synchronized and covers a spectrum of both fibrosis severity and distribution
- 20% + of stage 3 may have stage 4 disease

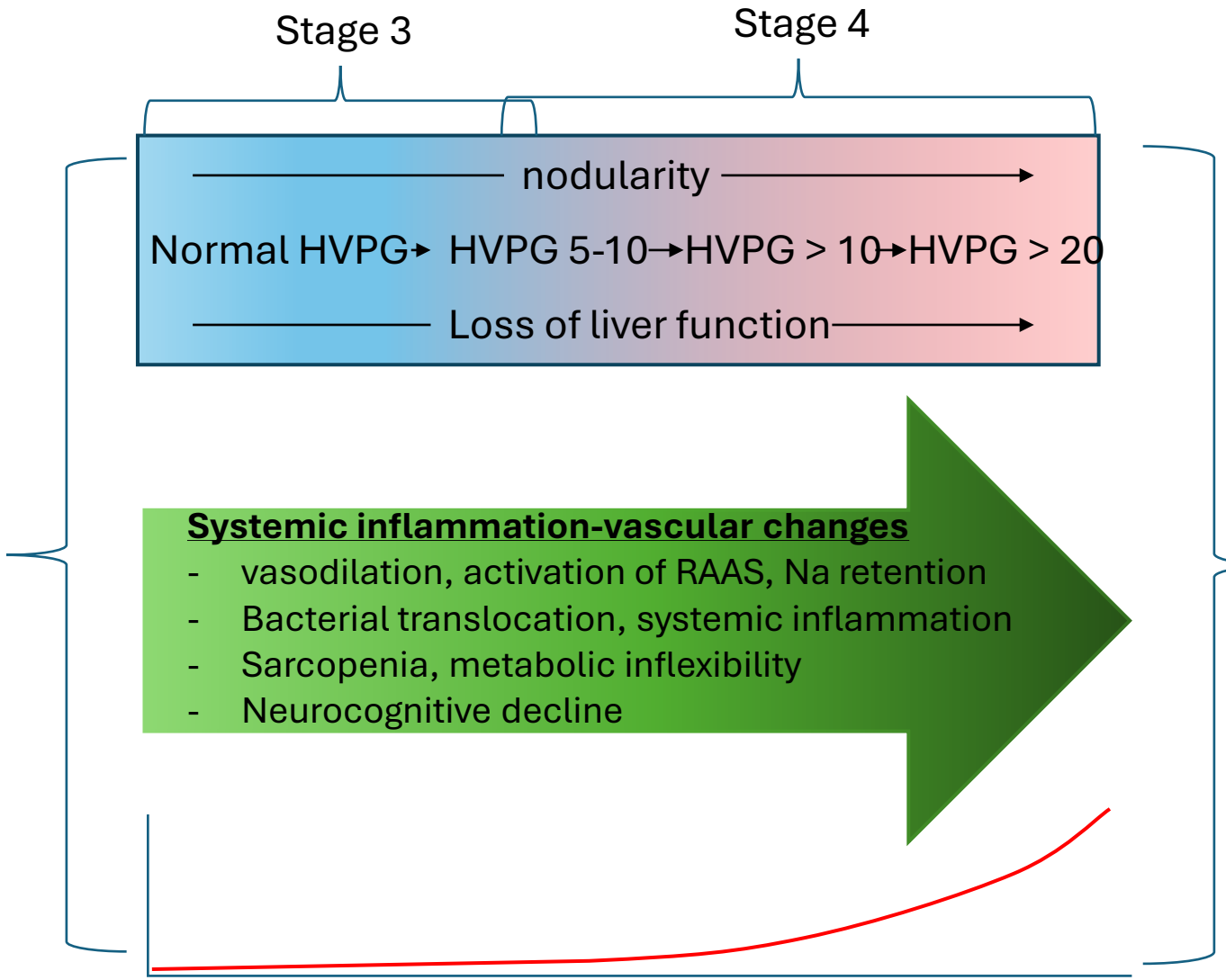
The evidence burden needed to consider a biomarker as a surrogate outcome endpoint needs to be met

Elastography
Measures of fibrosis or fibrogenesis
Measures of liver function/health
Imaging for nodularity and altered blood flow

An opportunity to combine measures to develop a composite

An endpoint supported by a **clear mechanistic rationale** and **clinical data** providing strong evidence that an **effect on the surrogate endpoint predicts** a **specific clinical benefit**.

Tipping point hypothesis



Current systems do not capture the full picture resulting in heterogeneity in populations

Biology of decompensation events vary

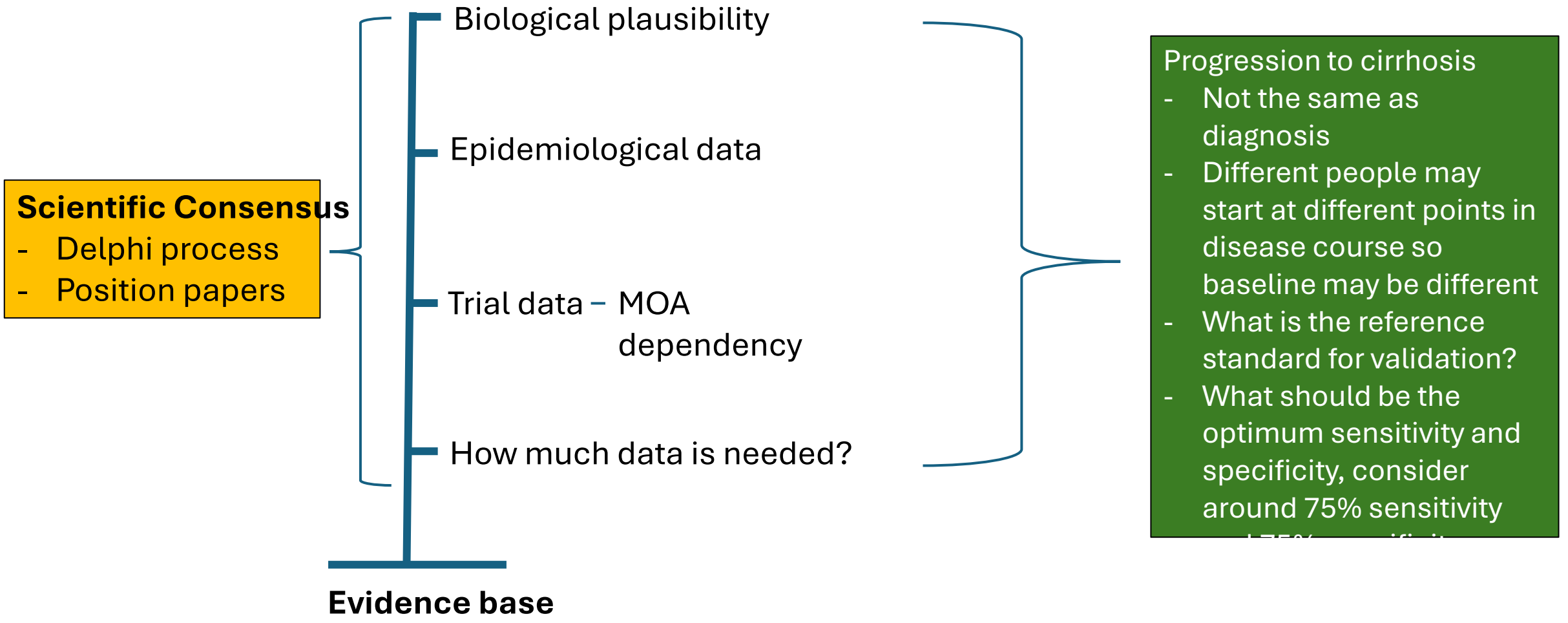
The toolkit available to capture progression to cirrhosis

Characteristics that change	Measures with large bodies of data to support Prognostic and disease monitoring COUs	Potential additional approaches- need more data
Fibrosis	• Histology • NIT reflective largely of fibro-inflammation (LSM, ELF etc.)	• Hot and cold fibrosis related endotypes
Structure	-	• nodularity
Vascular	• HVPG	• Collaterals-EUS based measures • Spleen size/pulsatility • Spleen stiffness
Functional	• Synthetic dysfunction • MELD	• Breath tests • Gadoxetate clearance

Some challenges

- False negatives an issue with high specificity cutoffs
- Cirrhosis may exist at LSM range 10-20 Kpa
- Platelet change takes time and may occur after progression to cirrhosis
- Imaging findings of portal hypertension occur after cirrhosis develops

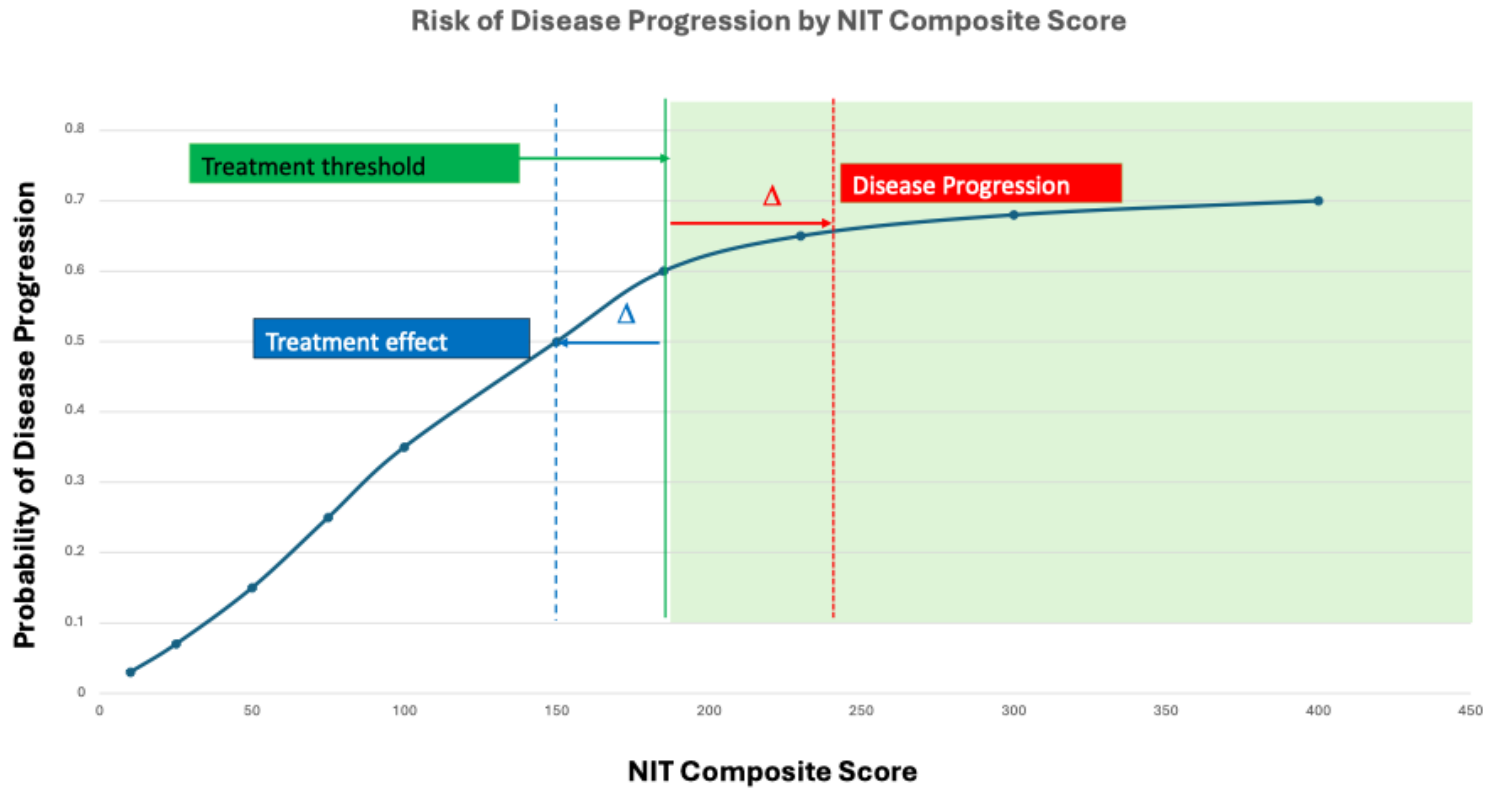
Issues related to validated surrogate endpoint



Scenario 2: Link NIT to clinical outcomes and demonstrate change in NIT predicts change in outcome profile

Hypothetical model of NIT trajectory related to disease progression

NIT changes in absence of treatment (red Δ) predicts increased probability of disease progression, while treatment induced changes in NIT (blue Δ) associated with a reduction in disease progression



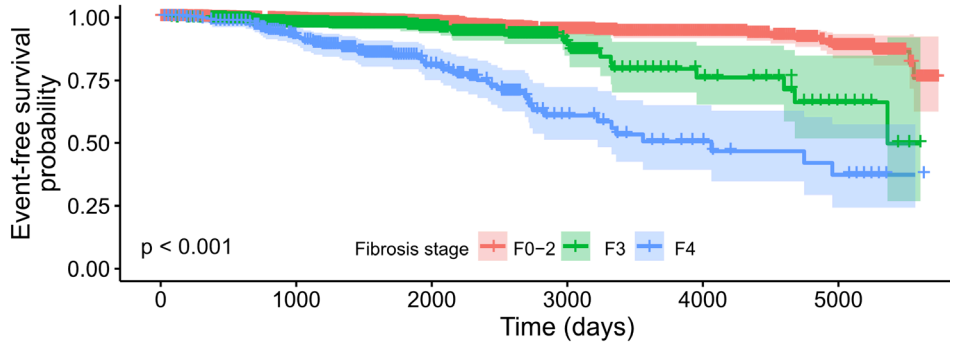
How to develop a validated surrogate

- Is a non-invasive profile or **<u>linkage to outcomes</u>** acceptable?
- Slope of change vs absolute or % change

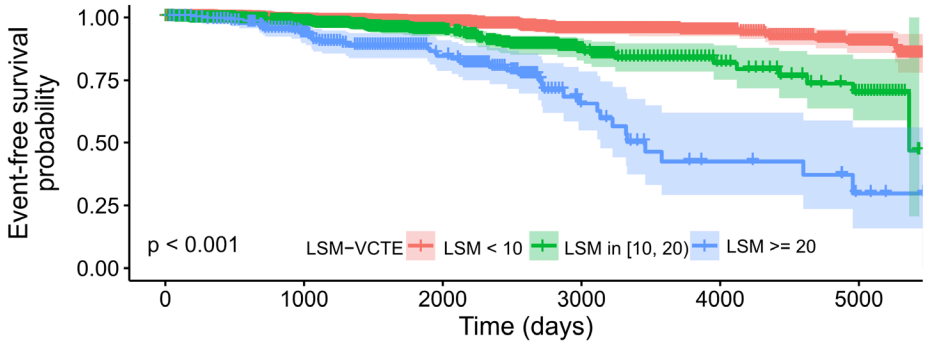
Measuring change- VCTE LSM

IPDMA 2,518 patients from 25 studies, median follow-up of 57 months.
145 (5·8%) all-cause mortality/LRE outcomes.

Histology

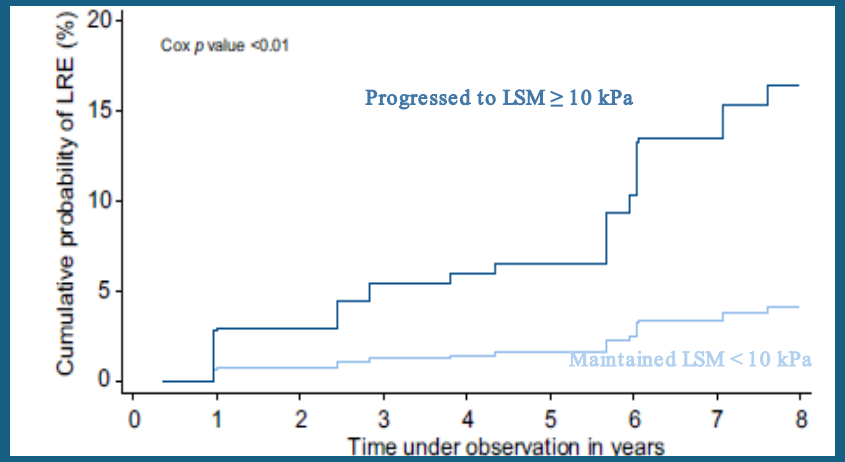


LSM-VCTE
LSM: <10 vs 10 to <20 vs ≥20 kPa

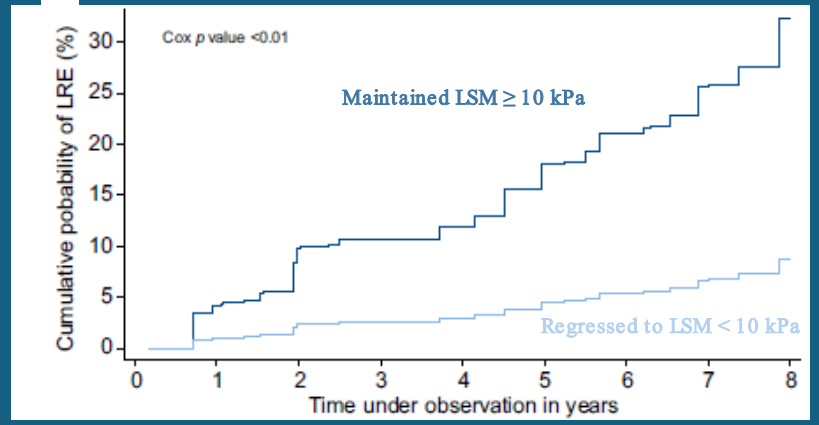


[1] Mozes et al.. Lancet Gastroenterol Hepatol 2023;8:704-713.

Progressors - Baseline LSM < 10 kPa (N=918)

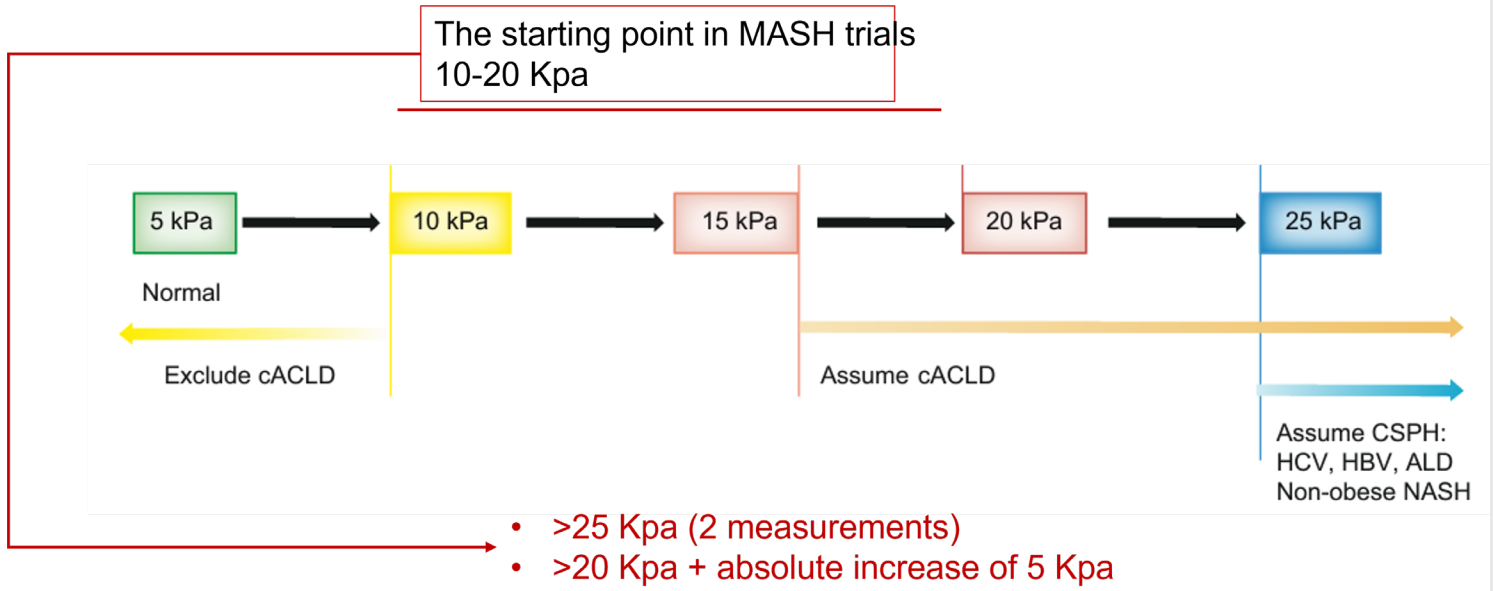


Regressors - Baseline LSM ≥ 10 kPa (N=485)



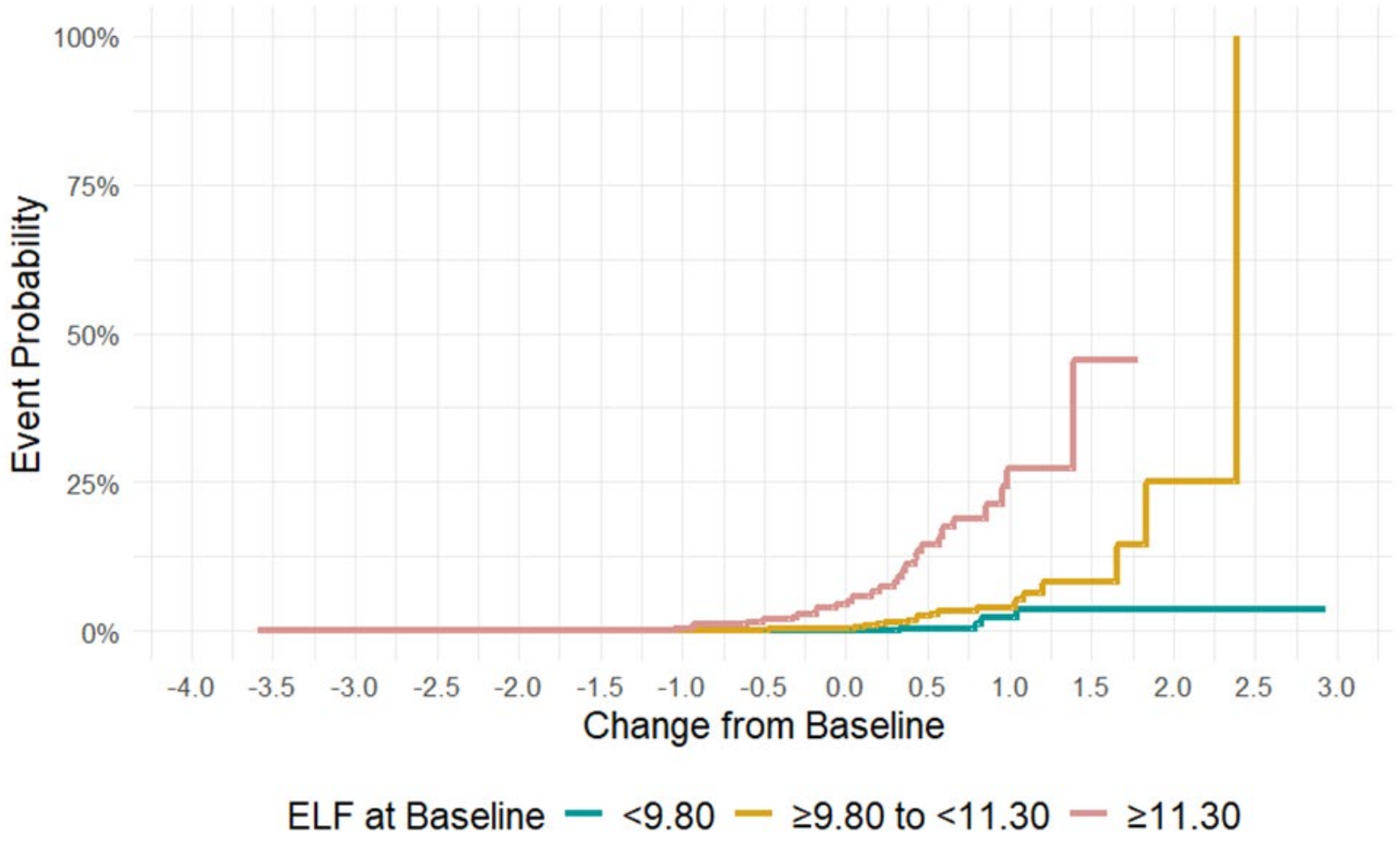
[1] Gawrieh et al. J Hepatol 2024.

A proposal for LSM based surrogate endpoint- applicable for RLSE and VSE



- Assume distribution at baseline is similar (10-20 Kpa)
- Endpoint validation Hypothesis: A left shift in distribution over time indicates less risk of outcome
- Hypothesis to be tested in phase 3-4: The distribution will become left shifted with active treatment
- Alternate hypothesis in trials: less proportion of people progressing to a high risk status

Change in ELF score is associated with differential LRE risk



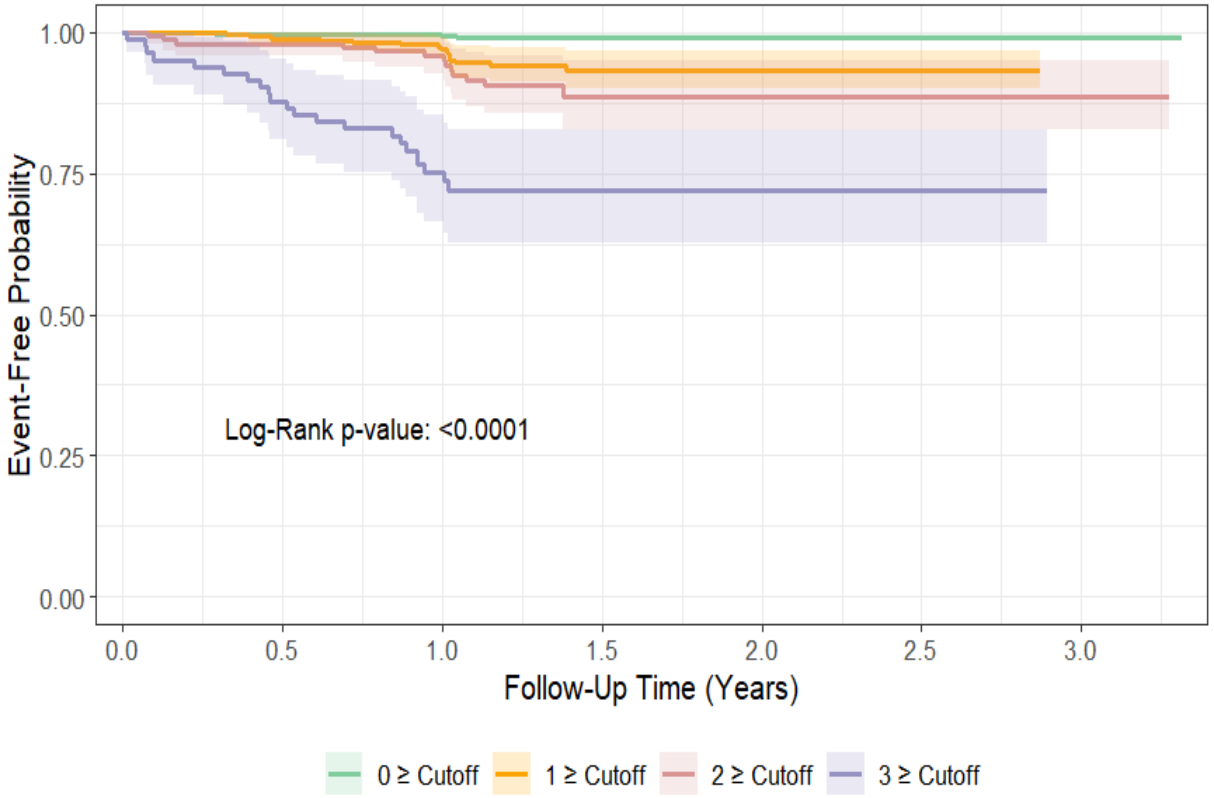
2071 Patients with F3-F4 MASH
with ELF measurement at baseline and 1 year

Large changes in ELF are unlikely to significantly increase LRE risk if baseline ELF score is low.

Conversely, LRE risk is sensitive to small changes in ELF score if baseline ELF is high.

Courtesy- Matthew Gee

NIT concordance increases prognostic performance



Group	At Risk (Events)						
0	988 (0)	964 (2)	858 (5)	296 (7)	48 (7)	24 (7)	6 (7)
1	291 (0)	282 (3)	213 (8)	77 (15)	7 (15)	3 (15)	0 (15)
2	152 (0)	147 (3)	108 (6)	37 (13)	4 (13)	1 (13)	1 (13)
3	84 (0)	72 (10)	48 (20)	11 (22)	3 (22)	3 (22)	0 (22)

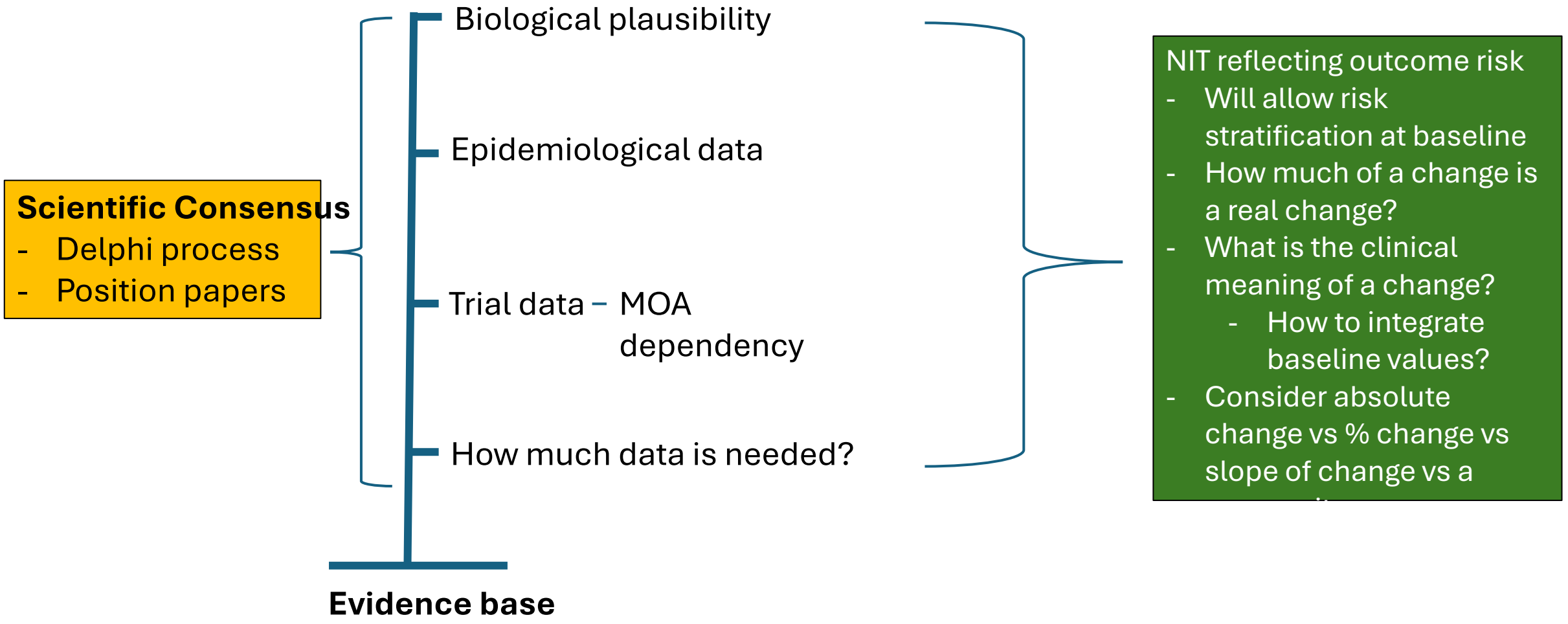
Fig. 2. Kaplan-Meier curves for event-free probability of liver-related outcomes. Risk stratification based on the number of NITs at or above cutoffs of ELF ≥11.30, VCTE ≥30.0 kPa and FIB-4 ≥3.48. Group 0 (Green): All 3 NITs below cutoffs; Group 1 (Orange): 1 NIT at or above cutoff; Group 2 (Red): 2 NITs at or above cutoffs; Group 3 (Purple): All 3 NITs at or above cutoffs

NIT criteria for enrollment:

- Evidence of MASLD- MRI-PDFF > 5% or CAP > 280 db/m
- 3 NIT concordant for being above cutoff
  - FIB-4: > 1-2.6
  - LSM by VCTE: 9-20 Kpa
  - ELF: 9- 10.5 Kpa

Gee, Sanyal et al- MS under review, presented at AASLD 2024

Issues related to validated surrogate endpoint



Constructing the endpoint- learning from anti-obesity medication drug-development

New generation anti-obesity medications should have the ability[1]:

- To safely produce an average of >10% placebo-subtracted weight loss in randomized clinical trials (i.e. over that attributable to lifestyle interventions) in the majority of patients ***or***
- To safely produce a ≥15% weight loss in over half the patients as an adjunct to lifestyle

Having a wide range of therapeutic options enables treatments to be tailored to individual needs

AOM, anti-obesity medication. 1. Garvey. J Clin Endocrinol Metab 2022;107:e1339.

	Entry level	Endpoints	Road map for future
FIB-4	1-2.6	% change	Slope of change similar to that for eGFR
VCTE-LSM	9 or 10-20	30% change 30% + 5 Kpa 30% + proportion < 10 Kpa	Proportion with 30% change vs individual change vs mean change across groups and placebo corrected change (> some threshold), Slope of change
ELF	9-10.5	0.5 or 0.75 absolute change % change	Slope of change

Opportunities exist to develop hierarchical endpoints based on rank ordered ordinal measures linked to risk of clinically meaningful outcome

Scenario 3: Be disruptive and measure clinically meaningful benefit in innovative manner!

Consider an ordinal outcome for compensated cirrhosis

- Alive with cirrhosis regression and no events without CSPH
- Alive with cirrhosis but without events or CSPH
- Alive with cirrhosis but without events but CSPH present
- Alive with cirrhosis and MELD > 15 from < 12
- Alive with one sentinel event (ascites, encephalopathy, bleeding)
- Alive with multiple events (can we include CVS, cancer, eGFR here)
- Dead

NIT based progression to cirrhosis can be captured operationally

- NITs to be used for progression to cirrhosis must be scalable and feasible (access- affordability-practicality) for wide spread implementation
- Ability of NITS to capture progression to cirrhosis:
  - Capture disease elements central to its biology that is targeted by therapeutics
  - Broad concordance with histological progression
  - Progression criteria will capture worsened outcome profile
  - Sensitivity to change

Thank you for your attention

When in doubt keep climbing