Progression to Cirrhosis Non-invasive Models to Define F2/F3 versus F4 (compensated)

Becky Taub

Key requirements for non-invasive surrogates of transition from non-cirrhotic “F2-F3” to compensated F4

Must have:

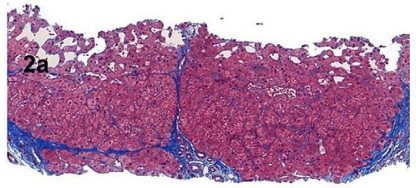
- Accurate non-biopsy based tests to confidently diagnose MASLD with F2-F3 stage fibrosis, clearly distinguishing F4
  - To demonstrate conversion to F4 in a reasonable time-frame **most enrolled patients should have baseline fibrosis stage consistent with F3 at baseline**
- Accurate, unconfounded tests that are specific for F4; sensitivity and accuracy may be aided by including multiple biomarker assessments, rather than a requirement for a change in one or two tests
- Ability to demonstrate a clear change from noncirrhotic to cirrhotic in an individual patient based on changes in and confirmation by a multitude of tests
  - **Unlikely to have a measurable, convincing transition to F4c in less than 2 years: requires long large trials to develop confidence in effect**

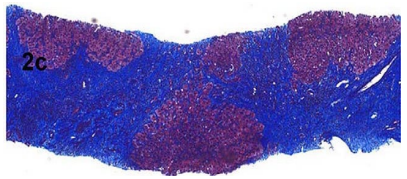
Risk in Chronic Liver Disease as a Continuum

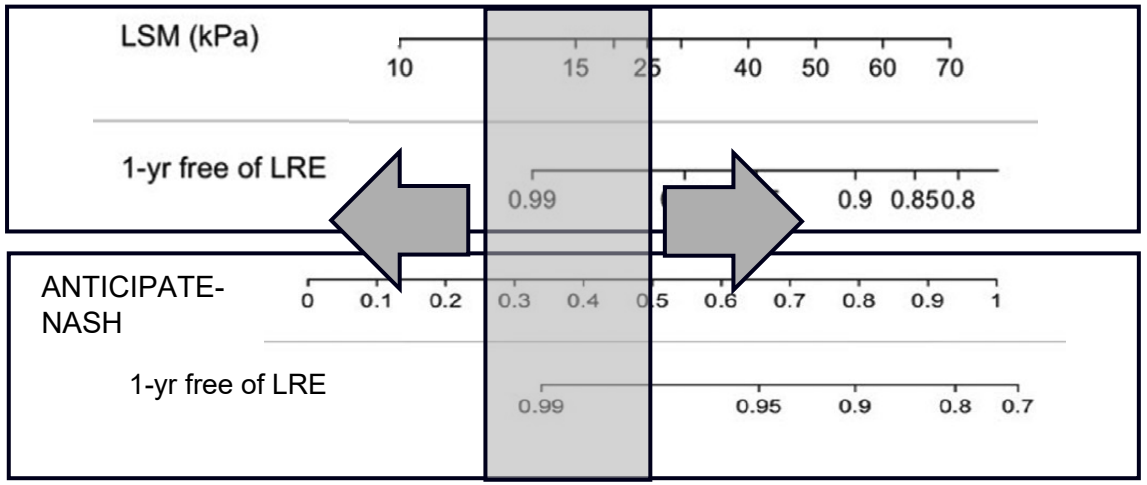
F3 **F4 Compensated** **F4 Decompensated**

Portal Hypertension

Hepatocyte







- Courtesy Juan Abraldes

Pons CGH 2024 / Aceituno 2026

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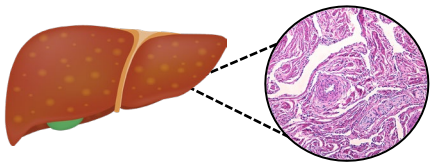
Machine Learning Models of Non-Invasive Tests to Predict Metabolic Dysfunction-Associated Steatohepatitis and Fibrosis Stage

1 BIOPSY-CONFIRMED MASH COHORT

1970 biopsy-confirmed patients

Retrospective analysis of patients screened for 2 phase 3 resmetirom trials



Fibrosis stage distribution

F0/F1	F2/F3	F4
556	1243	171
(28.2%)	(63.1%)	(8.7%)

1472 (74.7%) had NAS ≥4

2 MODEL INPUTS & OUTCOMES

Random forest models

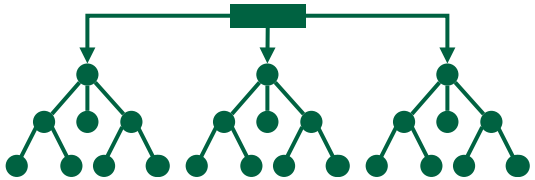
developed using various predictor biomarkers

- Clinical variables
- Laboratory tests
- Composite scores
- Imaging

Full model
37 predictors including MRE/MRI-derived variables

Lean models
≤25 predictors, most readily available in clinical practice

Predictive performance assessed by repeated 4-fold cross-validation



Outcomes Evaluated

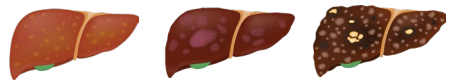
- Fibrosis stage (F0/F1 vs. F2/F3 vs. F4)
- MASH with F2/F3 fibrosis

***Additional individual and combination biomarkers and algorithmic scores were evaluated**

3 PREDICTIONS & PERFORMANCE

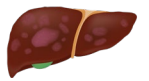
A. Fibrosis stage

(one-vs-rest AUC)



	F0/F1	F2/F3	F4
Lean Model 1	AUC 0.83	AUC 0.78	AUC 0.89
Full Model	0.76	0.75	0.94
FIB-4 + VCTE	0.74	0.67	0.87

B. MASH with F2/F3 (NAS ≥ 4)



Lean Model 1 AUC **0.79**

Full Model	0.75
FAST	0.68
SAFE	0.62
FIB-4+VCTE	0.58

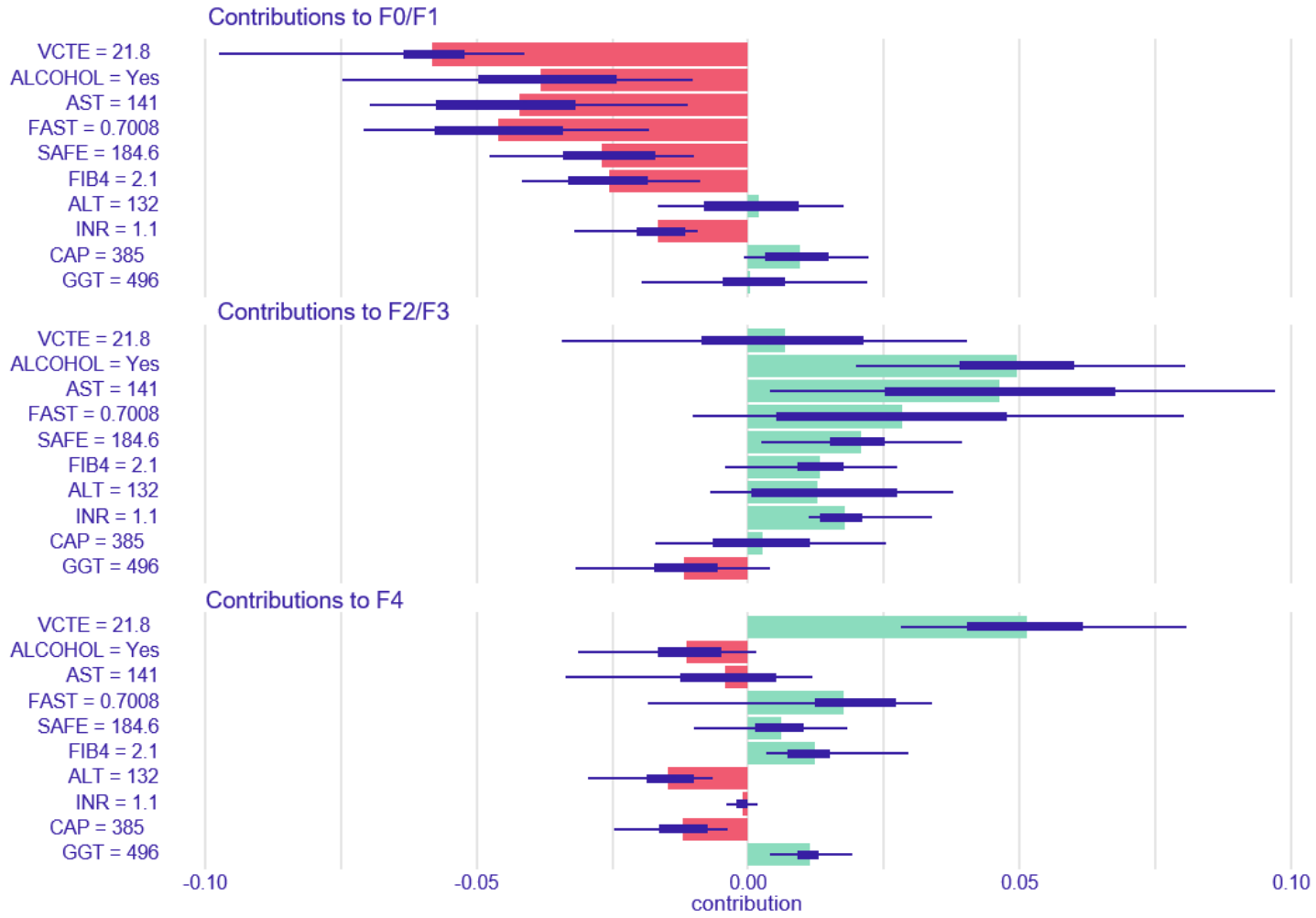
***Lean models* incorporating liver stiffness *outperformed* models limited to *blood-based biomarkers*. A *combination* of several readily available tests, including LSM, *outperformed* a *limited set* such as FIB-4 and LSM.**

Supports biopsy-sparing identification for clinical or trial-screening triage.

Next step External and prospective validation required before deployment

Potential use Patient selection for clinical trials or practice

Use of Shapley in Individual Patients to Diagnose and Show Change



- Based on sum of scores across multiple biomarker levels, individual patient is assigned a fibrosis stage

Comparative Baseline Phenotypes: Contemporary MASH-cirrhosis trials

Characteristic	Phase 2 Efruxifermin: SYMMETRY	Pegozafermin: ENLIGHTEN (partial)	Resmetirom: Biopsy F4	Resmetirom: NIT-confirmed F4	Belapectin: NAVIGATE
N	181	337	392	453	355
Selection gate	Biopsy-confirmed F4	Biopsy-confirmed F4	Biopsy F4	**≥2 positive NITs: VCTE >15 kPa, FIB-4 >3, MRE >4.2 kPa, ELF >10.25, platelets <140 ×10³/µL**	Portal hypertension required: any ONE of: Plat <150 ×10³/mm³; HVPG >6; ≥2 of [spleen ≥14 cm, abdominal collaterals, LSM ≥20 kPa, AST/ALT >1]
BMI (kg/m²)	35.8	35	34	35	34
Type 2 diabetes (%)	80%	75%	77%	65%	67%
VCTE / LSM mean (kPa)	24.4	19.4	23.0	27.6	25
Platelets (×10³/µL)	183.1	176	161.6	145.7	131
ELF	10.5	10.5	10.7	10.9	—
Est. ANTICIPATE-NASH	**0.37**	**0.29**	**0.43**	**0.59**	**0.58**
Interpretation	Highest platelets → regression significant only at wk 96	Broad compensated F4 continuum	Broader histologic F4 phenotype	More advanced PH phenotype	Most PH-enriched cohort

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- Courtesy Juan Abraldes

Sources: publicly available data, Liver Forum slides, EASL 2026 abstract book Publications

Diagnosis of Cirrhosis with Biomarkers

- Similar to the machine learning model a series of biomarkers may be used to diagnose F4 cirrhosis and develop certainty
- In MAESTRO-NASH Outcomes a combination of tests (FIB-4, ELF, MRE, VCTE, platelets) were used to identify >400 patients without liver biopsy. No one test was sufficient to make the diagnosis. Subsequent analyses have shown that ANTCIPATE-NASH scores(low platelets, high VCTE, corrected for BMI) predictive of CSPH are higher in this population than patients selected based primarily on F4 liver biopsy
- No one biomarker made the diagnosis in MAESTRO-NASH Outcomes. It will be possible to develop a robust model incorporating a series of important biomarkers using a machine learning model that provides the confidence (AUC) for a particular fibrosis stage (ie F3) in each enrolled patient at baseline and progression to F4 after >=2 years

Confounding issues

- Cirrhosis is a histologic not functional diagnosis; functional capacity decline that results in easily measured endpoints (platelets, bilirubin) ie portal hypertension unlikely in early “histologic” compensated cirrhosis
  - **F3-F4 transitional liver—When is the liver considered F4?**

Tips and Guidance for Use of Corporate PowerPoint Template

- **Editing & Formatting**
  - Slide titles should be title case, with the first word capitalized and all proper nouns capitalized
  - Capitalize the first letter of the first word in bullets
  - No period at end of bullets
  - All font should use Arial, including text, charts, etc.
  - All bullets should use orange
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  - When pasting content from a different deck, click “Reset,” located under “Layout” in the Home tool bar to match slide formatting to current layout
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Pam, patient advocate

Challenges and Opportunities in surrogate endpoint construction for MASH trials

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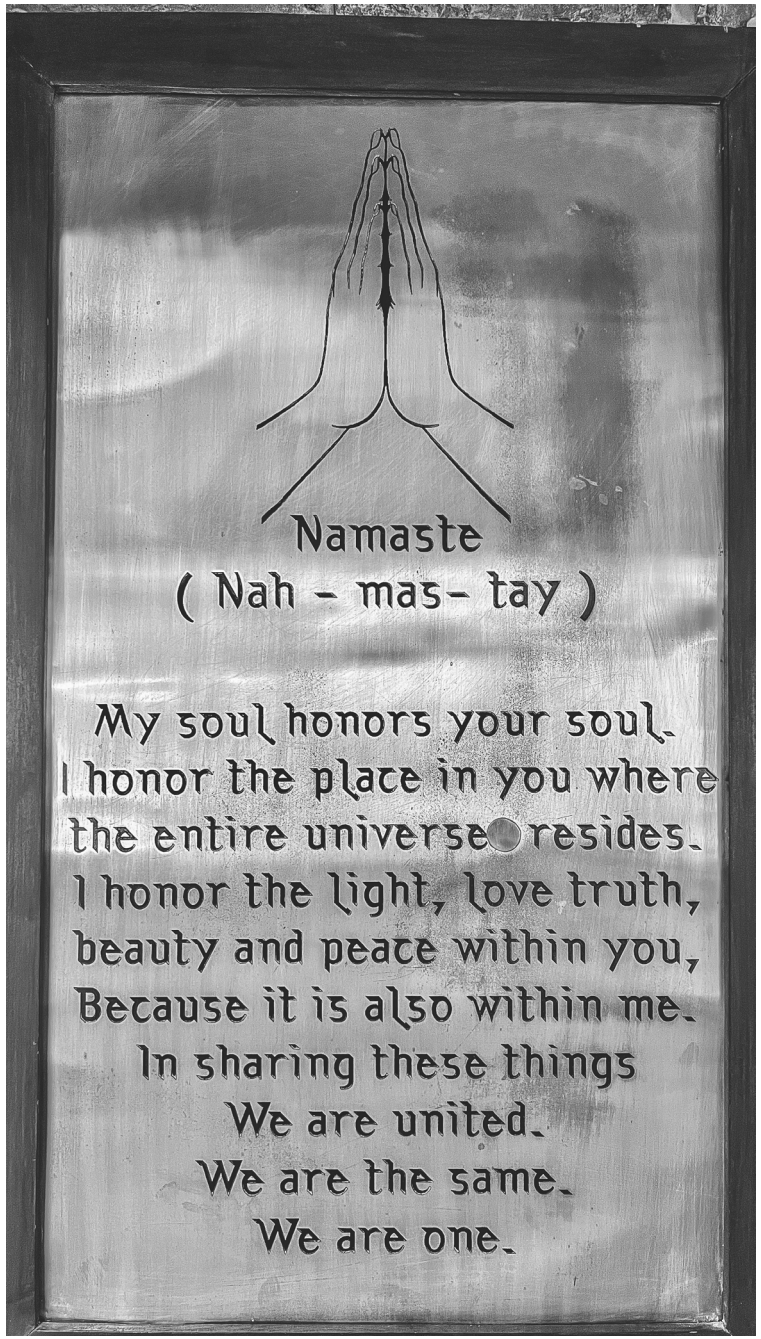

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- Grant support to school: Gilead, Intercept, Novartis, Novo Nordisk, Inventiva, Eli Lilly, Genentech, Boehringer Ingelhiem, Bristol Myers Squibb

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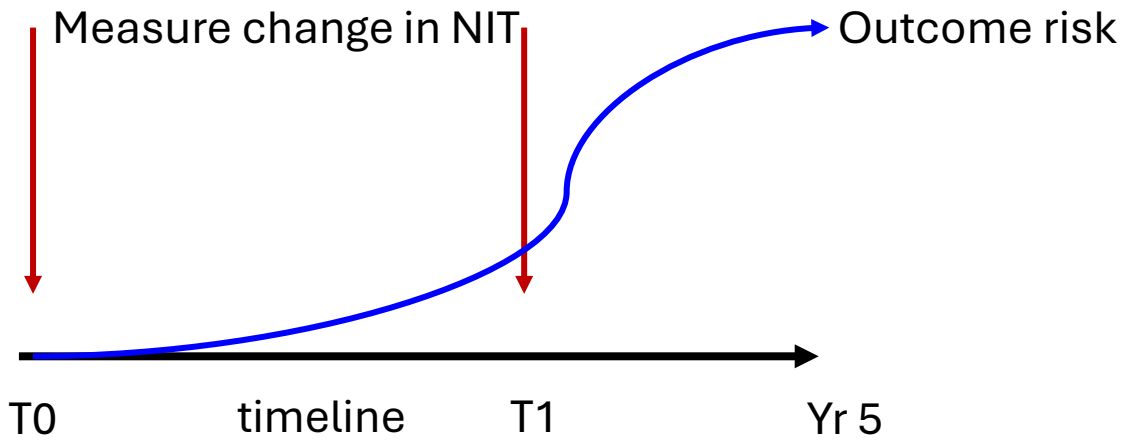
What is a reasonably likely surrogate endpoint (RLSE)?

An endpoint supported by strong mechanistic and/or epidemiologic rationale such that an effect on the *surrogate endpoint is expected to be correlated* with an **endpoint intended to assess clinical benefit in clinical trials**, but without sufficient clinical data to show that it is a validated surrogate endpoint.

- MECHANISTIC RATIONALE
- RELATIONSHIP OF NIT TO CLINICALLY MEANINGFUL OUTOCMES
- RELATIONSHIP OF CHANGE IN NIT TO CHANGE IN RISK OF OUTCOME
- LINKING THERAPEUTIC RESPONSE OF NIT TO CHANGE IN RISK OF CLINICALLY MEANINGFUL OUTCOMES

New Guidance recently accepted for Publication- Anania et al, Hepatology, DOI 10:1097, Aug 26, 2025

Establishing disease monitoring and Rx response utility



- Relate change in NIT to outcome risk
- Outcomes from T1 to yr 3-5

The greatest challenge is lack of well phenotyped longitudinal cohorts with carefully captured outcomes data obtained prospectively

An approach to data generation to support a RLSE for pre-cirrhotic MASH

Data in hand

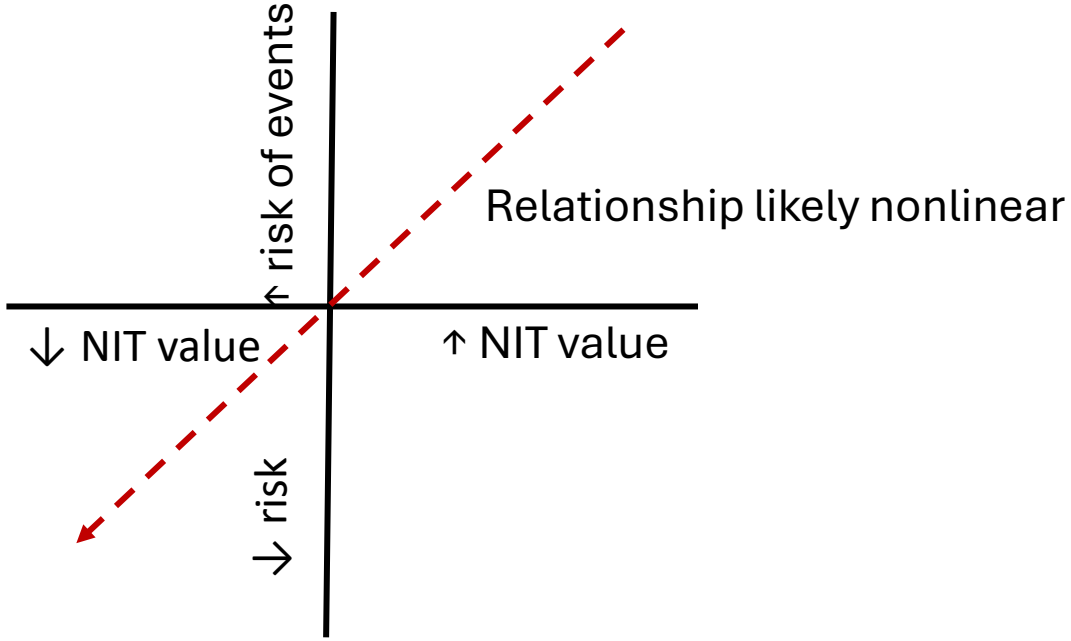
- Prognostic:
  - LSM by VCTE is linked to outcomes
  - ELF score is linked to outcomes
- Disease monitoring:
  - NASH CRN data and potential other data sets identify sensitivity to change with LSM and also disease monitoring utility for LSM and ELF

FNIH- Mashtrack + Surrogate endpoints workstream plan

- Prognostic:
  - NASH CRN baseline data from cohort study and relate to clinical outcomes- LSM by VCTE, Agile, ELF, NIS2+, ADAPT, MASEF scores
- Disease monitoring:
  - Identification of additional cohorts
  - Serial changes in NIT in NASH CRN and additional cohorts vs risk of outcome

Current approach to generate a RLSE for MASH

Pooled large observational cohort
Study population defined noninvasively
f/U exam at 12-18 M
Regulatory outcomes included only



Cox model- time dependent

- Set NIT change above technical performance limit
- Compute change in NIT and relate it to change in projected risk of outcome
- Endpoint construction-
  1. Statistically significant difference in the mean NIT change from baseline in active versus control arms
  2. Magnitude of difference between active and control arms is equal or

A key challenge is to capture clinically meaningful outcomes benefit within a reasonable time frame or a surrogate thereof in a very slowly progressive condition that affects a lot of people

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

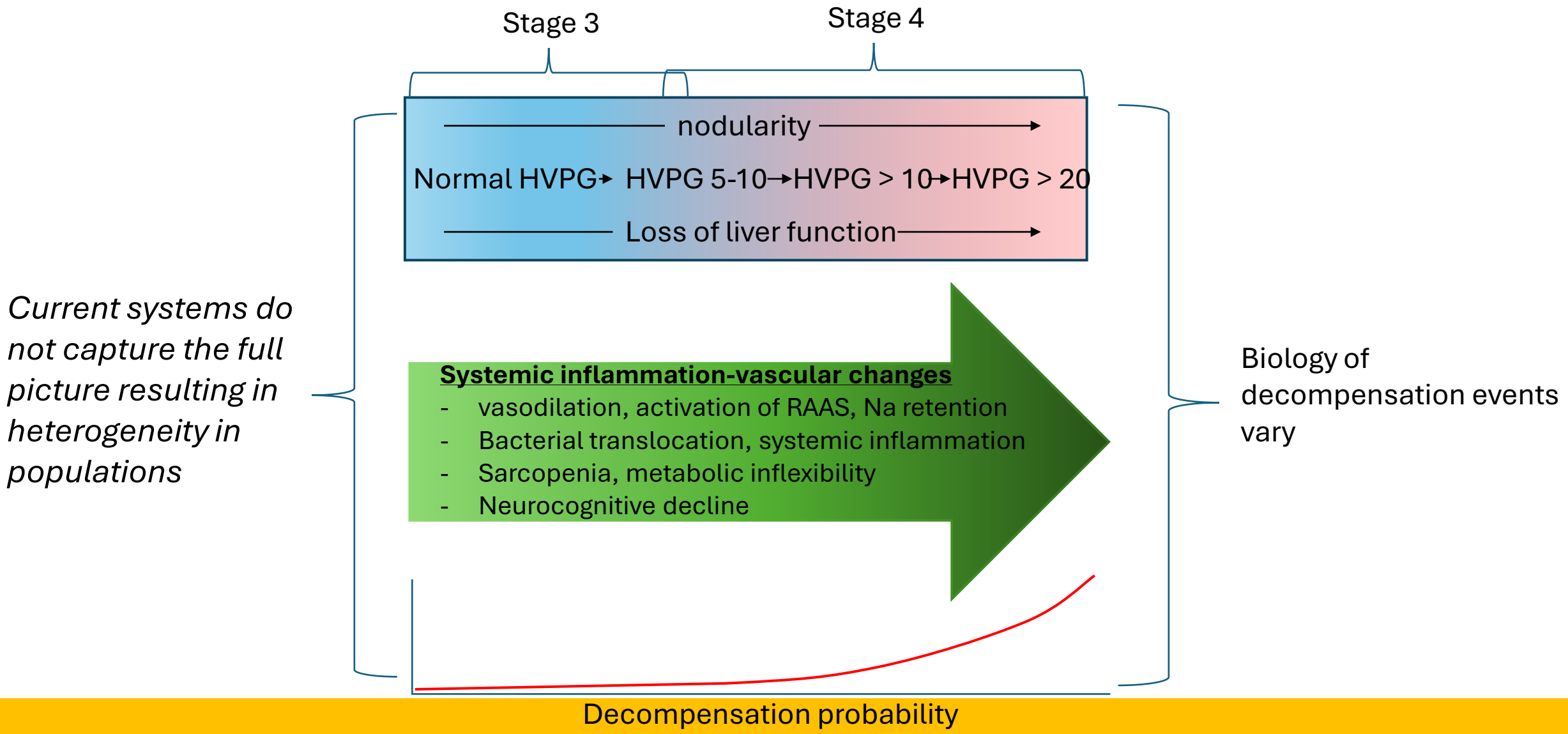
What is needed:

- Capture changes in morphology
- Capture changes in fibrosis burden
- Capture changes in blood flow
- Capture changes in liver function

↓

Link to outcomes

Tipping point hypothesis



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

Biology of decompensation events vary

Linking outcomes to create endpoints

- Heirarchical outcomes
- Steps:
  - Capture a series of clinical states
  - Establish the hierarchy of clinical states in terms of mortality and other clinically meaningful benefits
  - Evaluate the distribution of individuals across clinical states over a period of time with a common starting point
  - Evaluate differences in placebo versus active arms

Thank you for your attention

When in doubt keep climbing