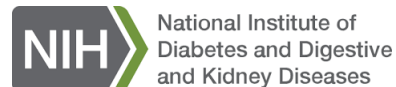


Efforts in Biomarker Qualification in MASH at the Foundation for NIH

- 1) *NIMBLE (Diagnostic enrichment biomarkers)*
- 2) *MASHTrack (Prognostic biomarkers)*
- 3) *Developing... Progression to Cirrhosis as a surrogate endpoint*



NIMBLE will generate evidence for regulatory qualification of diagnostic enrichment biomarkers

Current Status – Recruiting for Phase 2

NIMBLE Stage 1 (2019 – 2022)

A retrospective assessment of NITs in banked samples from NASH CRN to assess performance against biopsy, Fib4

Circulating work stream:

- Sensitivity/Specificity for at-risk MASH
- Sensitivity/Specificity for components
 - NIS2+
 - ELF test
 - FibroMeter-VCTE
 - MASEF
 - ADAPT

Imaging work stream:

- Different day different operator variance
 - Ultrasound-based methods (SWE, TE)
 - MR-based methods (PDFF, 2D MRE)

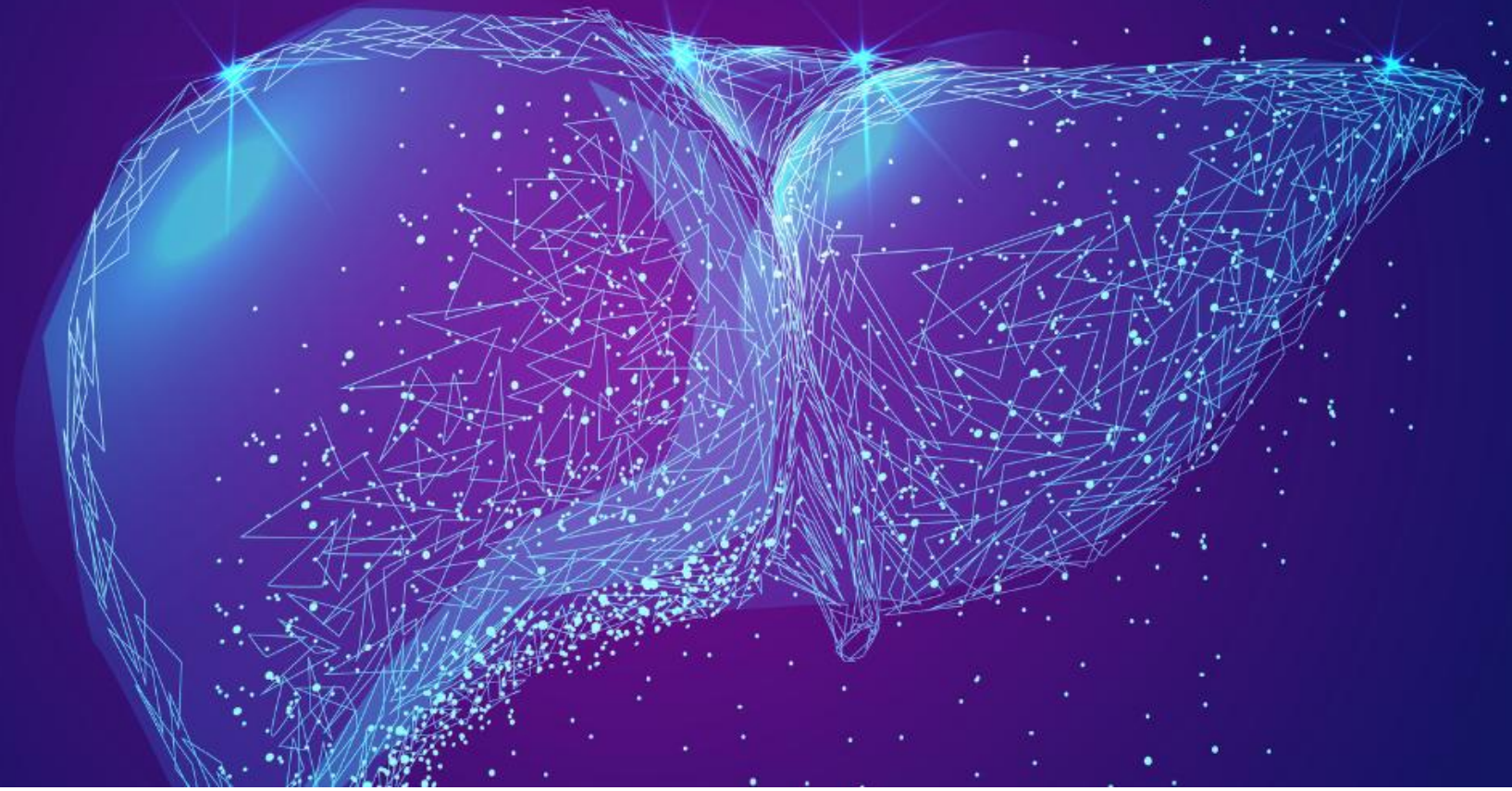
NIMBLE Stage 2 (2024 – 2027)

A prospective evaluation of the diagnostic utility of select NITs for their diagnostic enrichment COU

- NIS2+
- ELF test
- FibroMeter-VCTE
- LSM
- MASEF
- ADAPT
- MRI-PDFF
- 2D MRE
- SWE
- *Digital Pathology approaches will also be validated against pathology reads and NITs above*

**Tracking Liver Fibrosis and
Outcomes Through Non-
Invasive Prognostic
Biomarkers in Patients with
Metabolic Dysfunction-
Associated Steatohepatitis**

MASHtrack >>>



MASHtrack Launched on June 1, 2025

MASHtrack Co-Chairs

Academic Co-Chair



Arun Sanyal, MD

Professor

Director, Stravitz-Sanyal Institute for Liver Disease and Metabolic Health
School of Medicine, Internal Medicine, Virginia Commonwealth University

Industry Co-Chair



Michelle Long, MD, MS

International Medical Vice President, NASH, Medical & Science
Novo Nordisk

NASH CRN and MASHtrack WG members

MASHtrack Working Group

Primary Investigator	Patient Groups/Nonprofits	Academic Institutions	Pharmaceutical Companies	Biotechnology Companies
Arun Sanyal (VCU)	Donna Cryer (Global Liver Institute)	Nancy Obuchowski (Cleveland Clinic)	Armando Flor (AstraZeneca)	Alejo Llopart (CIMA Sciences)
NASH CRN	Jeff McIntyre (Global Liver Institute)	Rohit Loomba (UCSD)	Lars Hansen (AstraZeneca)	Rebeca Mayo (OWL Metabolomics)
Katherine Yates	CROs	Anthony Samir (Mass General)	Melissa Thomas (Eli Lilly)	Toni Felís Soto (OWL Metabolomics)
Brent Tetri	Jonah Chates (Cytel)	Theodore Pierce (Mass General)	Maria Wilson (Genentech)	Alexandre Akoulitchev (Oxford BioDynamics)
Raj Vuppalanchi	Scott Bergeron (Cytel)	Medical Device Companies	Jeremy Magnanensi (Genfit)	Ewan Hunter (Oxford BioDynamics)
Srinivasan Dasarathy	Clayton Dehn (Evolution Research Group)	Céline Fournier (Echosens)	Anyka Kauh (Merck)	Hanna Pulaski (PathAI)
Mohammad Siddiqui	Mark Delegge (IQVIA)	Greg Everson (Hepquant)	Daniel Rasmussen (Novo Nordisk)	Lara Murray (PathAI)
David Kleiner	Katherine Landschulz (Labcorp)	Joel Gogain (Somalogic)	Michelle Long (Novo Nordisk)	
Matthew Yeh	Marge Connelly (Labcorp)	Joel Wommak (Somalogic)	Sharat Varma (Novo Nordisk)	
James Tonascia	Casey Ustick (ProSciento)	FNIH Support	Sudha Shankar (Pfizer)	
	Federal Health Agencies	Alex Pasek	Roberto Calle (Regeneron)	
	Ashish Dhawan (FDA)	Melissa Jones Reyes	Thomas Norton (Regeneron)	
	Tim Morgan (VA)	Tré LaRosa	Xiping Cheng (Regeneron)	

Hypotheses for MASHtrack

Primary:

- Biomarkers will be significantly related to future development of clinical outcomes
- Biomarkers are superior to FIB-4 for future development of fibrosis related outcomes: ascites, encephalopathy, variceal hemorrhage, MELD increase from less or equal to 12 to 15 or higher

Secondary:

- Biomarkers reflective of disease activity and fibrosis will both be linked to risk of fibrosis progression in those with serial liver biopsies

MASHtrack Project Aims

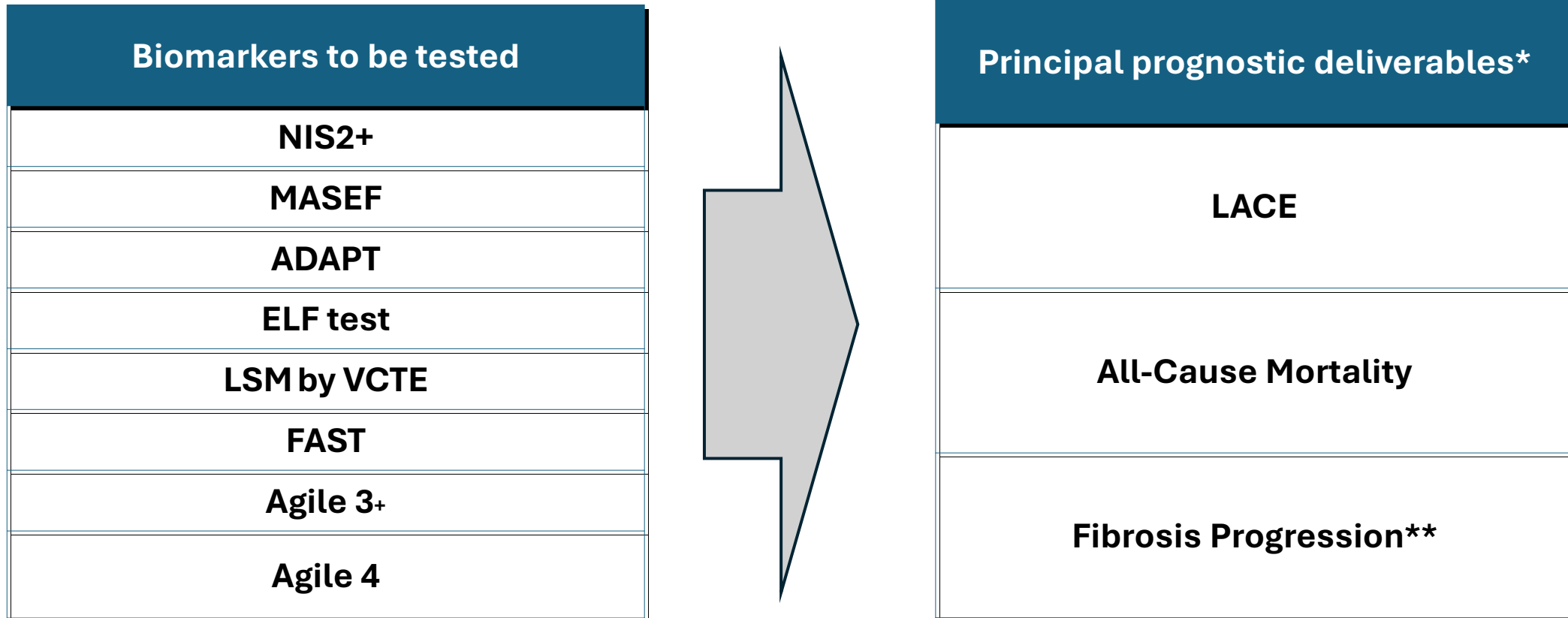
Aim 1

Assess the performance of each pre-identified, analytically robust, fit-for-purpose non-invasive, circulating biomarker to predict the likelihood of a liver-associated clinical event (LACE) in patients with MASLD and MASH.

Aim 2

Test whether the biomarkers being developed as diagnostic tools for fibrosis provide superior prognostic information over and above provided by existing clinical tools such as the FIB-4 score.

Biomarkers to be tested and their principal prognostic deliverables



**Nonhepatic outcomes (MACE, development of T2D, hypertension, and decline in eGFR) will also be evaluated but will be exploratory outcomes*

***Fibrosis progression will be assessed where 2 biopsies are available (NIS2+, MASEF, ADAPT, ELF, LSM, FAST, Agile 3+, Agile 4)*

NASH CRN Cohort Supported Key Data Generated in NIMBLE 1 and will be critical to MASHtrack's Success

- Large, deeply-phenotyped cohort with **more than 2000 participants**.
- Prospective follow up with adjudicated outcomes data (**median 5+ years**) already available.
- Substantial number of participants with advanced fibrosis: **10% of population has F4; 20% has F3**.
- Rigorously evaluated histological assessment of liver.
- Transient elastography available on most patients.
- **NIMBLE has already generated baseline data on approximately 1100 participants with several biomarkers (i.e., NIS4, PRO C3 (ADAPT), ELF test, and FibroMeter-VCTE).**
- No other cohort like this exists worldwide and generation of this type of data would take 10 years and cost many millions of dollars.

Partners

Funding

89bio
echosens

Lilly



REGENERON
science to medicine®

Donating Biomarker Tech



SIEMENS
Healthineers



NASH CRN



What Comes Next?

Public Private Partnerships: Role of the FNIH

The FNIH convenes the best minds around the world to tackle complex health problems through partnership and collaboration.

GOVERNANCE

Establish and manage a variety of structures appropriate to each partnership

POLICY MANAGEMENT

Provide safe harbor for interactions between companies, government, and academic entities

Policies support NIH ethical and policy standards

PROGRAM MANAGEMENT

Drive stakeholder consensus about appropriate scientific selection and execution of projects

FUNDRAISING & RELATIONSHIP MANAGEMENT

Directly solicit contributions
Steward and manage donor funds

PROJECT MANAGEMENT








Ensure projects meet established deliverables and “go/no go” milestones

INTELLECTUAL PROPERTY MANAGEMENT

Provide “pre-competitive” structures for handling intellectual property, if needed

Projects in Metabolic Disease That are Generating Relevant Data

Data Types Available Through Collaborations

Organ	FNIH Program	Disease State(s)	Persons in Study	Genetic/ Genomic	Clinical	Imaging	Biomarker Evaluation	Regulatory Strategy
	Pan-metabolic	AMP Common Metabolic Diseases	HF, Atherosclerosis, MASH/MASLD, Obesity, diabetes, CKD/DKD	Over 2 million	X	X		
	Heart	AMP Heart Failure	HFpEF, HFrEF	~30,000	X	X	X	X
	Liver	NIMBLE, MASHTrack	MASH/MASLD	~2400		X	X FDA U01 award	XXX 2 approved LOIs
	Placenta	Biomarkers for diagnosing Preeclampsia	Early-onset preeclampsia	~25,000		X	X	X
	Bone	SABRE	Osteoporosis	~150,000		X	X 3 FDA U01 awards	XXXX Surrogate endpoint qualification
	Pan-metabolic	Redefining Prediabetes	Prediabetes	TBD		X	X	
	Pan-metabolic	Redefining Obesity	Obesity	~300		X	X	

FNIH Collaborated with the FDA to Establish the Evidentiary Criteria for Surrogate Endpoints in 2019



Who We Are ▾

Our Programs ▾

Fighting Diseases ▾

Powering Science ▾

Patient Engagement ▾

Partner With Us

Biomarkers Consortium – Workshop: Defining an Evidentiary Criteria Framework for Surrogate Endpoint Qualification

Overview

The Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium, in partnership with the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research, hosted a public meeting entitled Framework for Defining

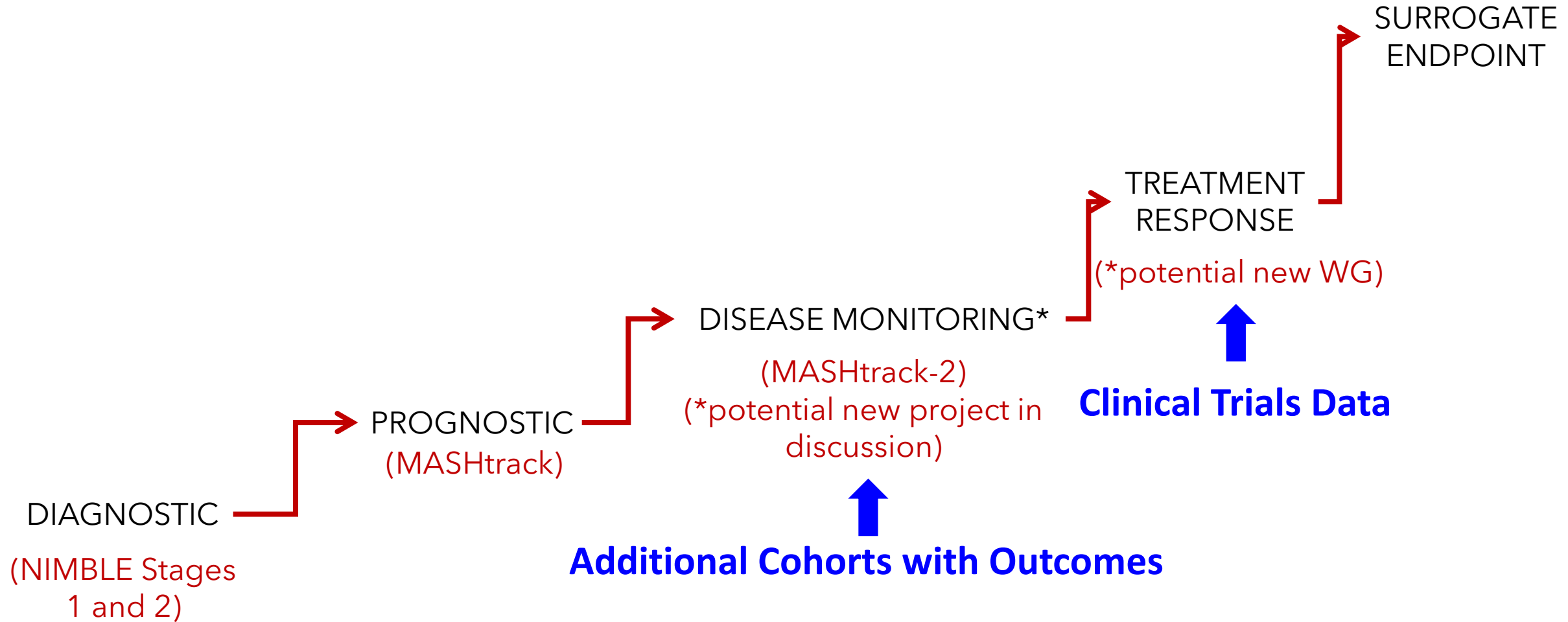
Partners

Children's Hospital of Philadelphia
Critical Path Institute
Dana-Farber Cancer Institute
Food and Drug Administration

**Engage FDA early
Bring Data**

<https://fnih.org/our-programs/biomarkers-consortium-workshop-defining-an-evidentiary-criteria-framework-for-surrogate-endpoint-qualification/>

Increasing Evidentiary Burden for Data Generation for Regulatory Submission



Prognostic and Disease Monitoring data - epidemiological data linking NIT to outcomes

- Many cohort studies to support prognostic and monitoring utility with respect to outcomes:
 - Liver Stiffness Measurement (over 40000 patient level data published)
 - ELF test (several thousand patient level data available)
- Treatment trials demonstrated LSM and ELF improvement linked to histological improvement
- **Proposal:**
 - MASH track expansion – NASH CRN samples have annual blood collection – could we generate a longitudinal study looking at change in NIT along the timepoints to outcomes?
 - May need to add additional cohorts with outcomes
 - Align with other ongoing efforts - liver forum, Delphi process for academic consensus

Suggested path to get to treatment response

- A large number of phase 2B treatment trials have been completed
- Several phase 3 trials have reached interim analysis time point:
 - OCA
 - Semaglutide
 - Elafibranor
 - Cenicrivaroc
- REGENERATE trial is the only trial to read out to 48 months.
- **Proposal:** to identify a dedicated FTE at FDA to analyze data available to FDA to further evaluate the utility of the NITs in the context of the phase 2B and 3 trials reported out to date

Path for Surrogate Endpoint

- White Paper on what is needed and a road map for greater community
 - Accepted LOI for LSM by VCTE for RLSE
 - Recent FDA publication on RLSE
 - Liver Forum RLSE Working Group
 - FNIH publishing guidance on statistical considerations for NITs for RLSEs (in final edits)
 - Ongoing discussions between FDA and FNIH on requirements for RLSE
- Publications summarizing evidence to support that relevant biomarkers are in the disease pathway and causal paths targeted by therapy- systematic reviews (collaboration with developers of relevant NITs)
- Data gap mapping – discussion with FDA to guide additional needed data generation-
 - Development of analytic questions, approach and review of data
 - Mechanism to revisit approach and add new endpoints based on new data generated
- Development of a guidance document on NIT-based inclusion into trials and NIT based outcome assessment

Thank You!