Liver Forum 2024

Session III: Collaboration for Greater Efficiency – NIMBLE + MASHtrack collaboration

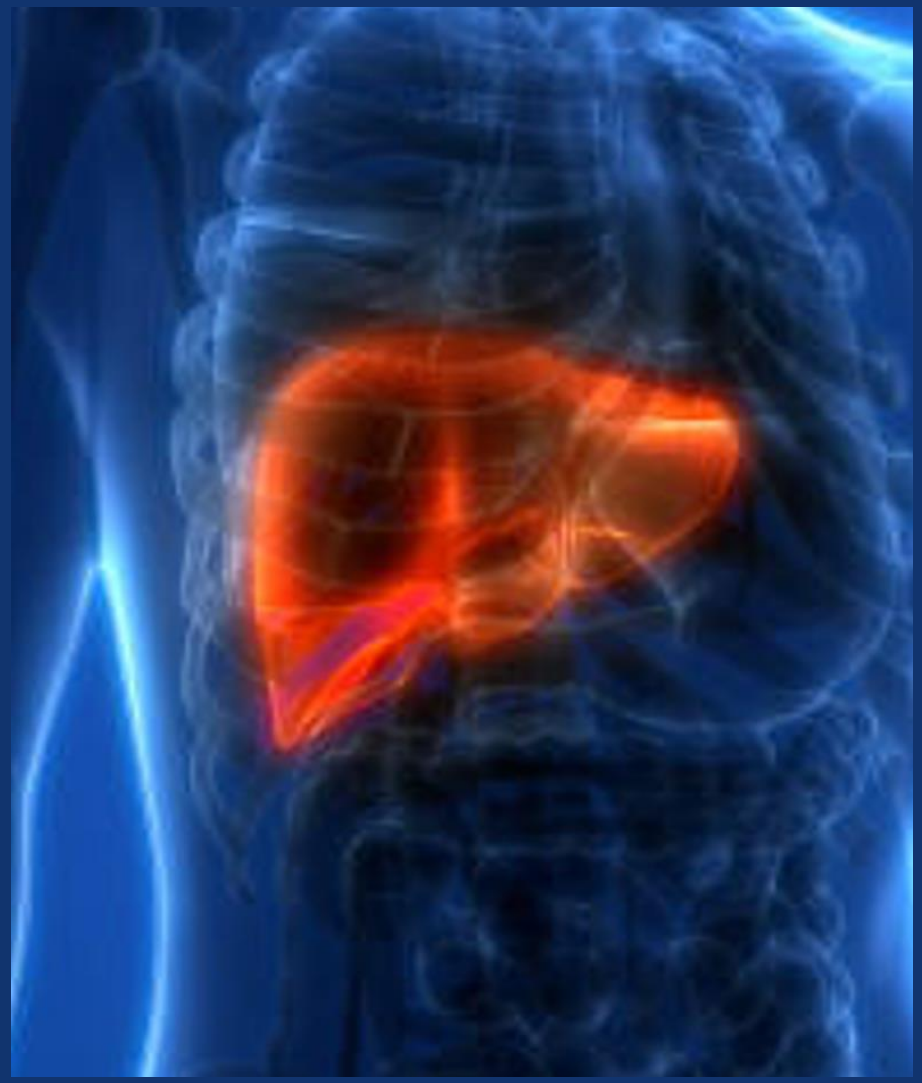
Foundation for the National Institutes of Health

March 2024

FNIH

Topics for our discussion

1. **About FNIH & Biomarkers Consortium**
2. **Unmet needs in MASH space**
3. **MASHtrack and NIMBLE projects**
4. **Future Studies**



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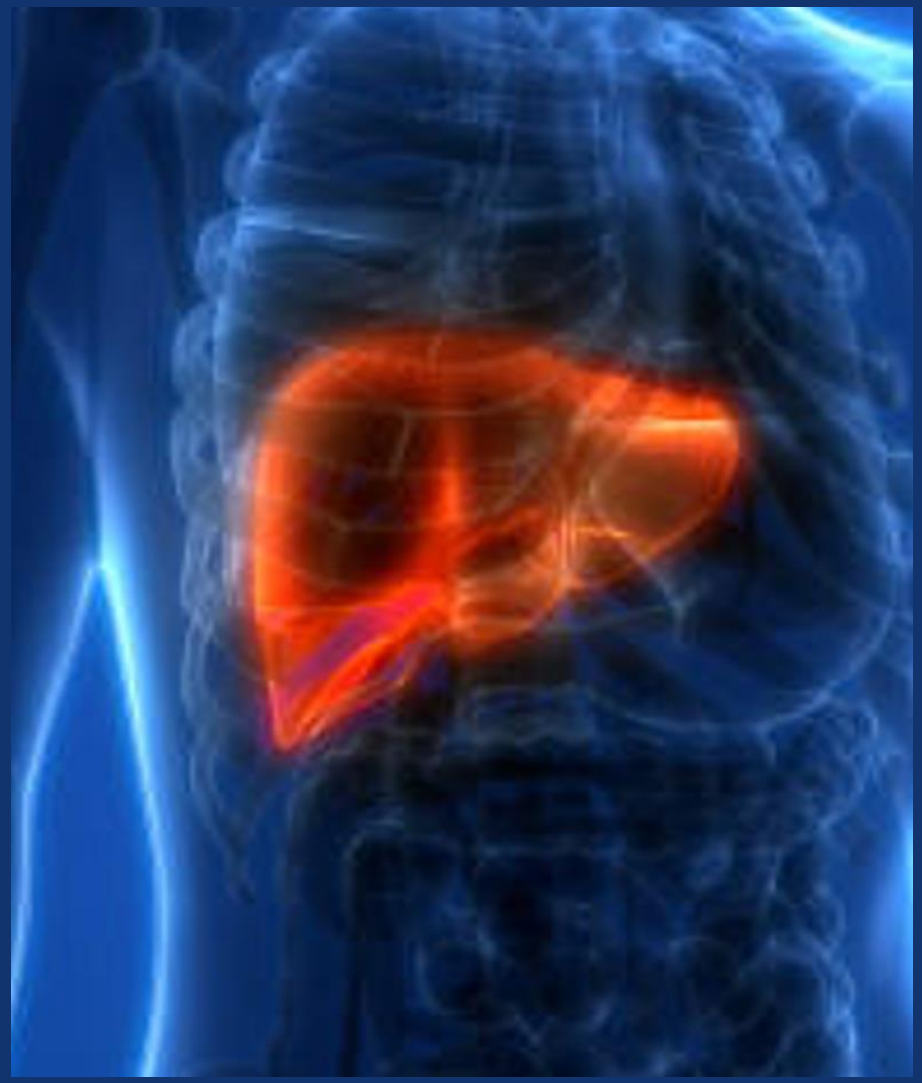
Section 1
About the FNIH and Biomarker Consortium



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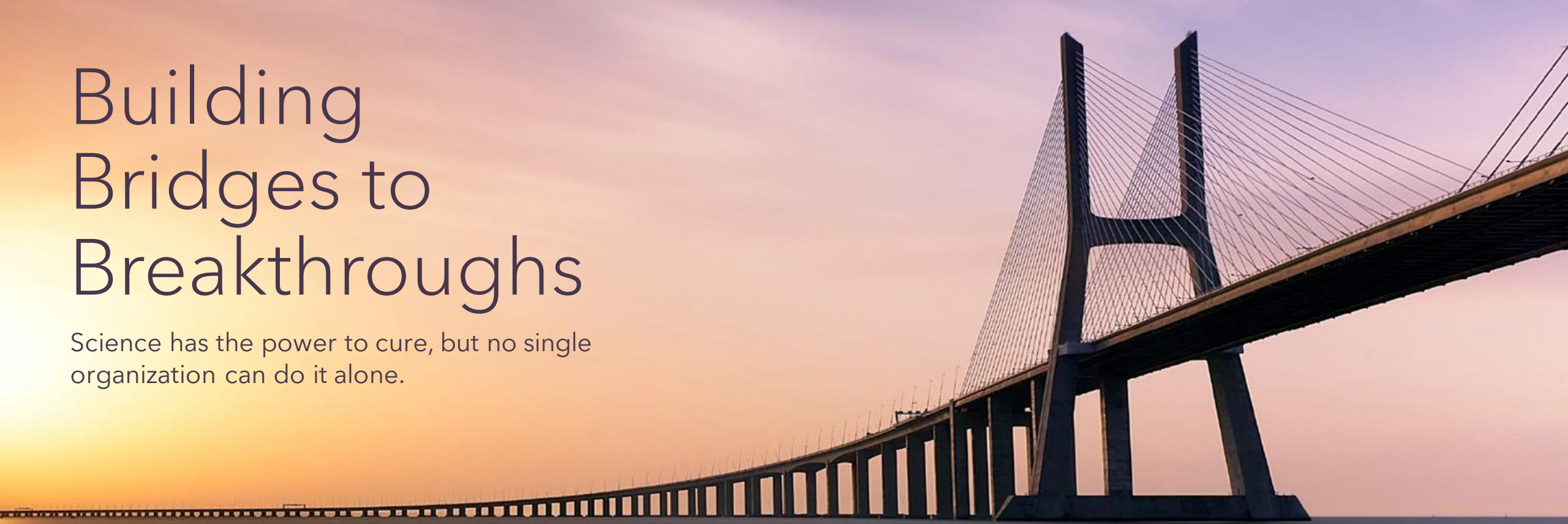
Building Bridges to Breakthroughs

Science has the power to cure, but no single organization can do it alone.



We connect world-leading NIH researchers with the ingenuity and expertise of public and private sector leaders to accelerate medical breakthroughs.

The FNIH is a non-profit organization charted by congress and launched in 1996 to support the mission of NIH.

FNIH

Partnering with world-class organizations to tackle the most pressing health challenges

PUBLIC

We support the mission of the nation's premier biomedical research agency, driving discoveries that improve health and save peoples' lives

BIOPHARMA

We collaborate with leading R&D organizations to advance research that will lead to new therapies, diagnostics, and potential cures

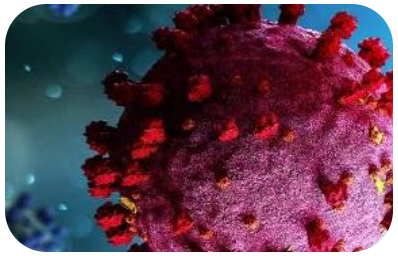
FOUNDATIONS

We work with foundations to address urgent issues in global health and accelerate biomedical innovation across a range of diseases

We accelerate prevention, new therapies, diagnostics and potential cures

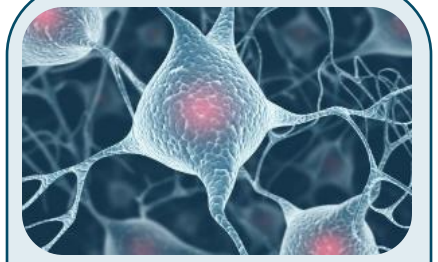
ACCELERATING MEDICINES PARTNERSHIP (AMP®)

Drug candidates & platforms for serious diseases, including Alzheimer's, type 2 diabetes, heart failure



ACCELERATING COVID-19 THERAPEUTIC INTERVENTIONS & VACCINES (ACTIV)

Accelerated clinical development of therapeutics and vaccines to address a global pandemic



BIOMARKERS CONSORTIUM

Uncovering novel biomarkers that unlock new development & regulatory pathways

BESPOKE GENE THERAPY CONSORTIUM (BGTC)

Faster development & delivery of bespoke gene therapies for rare diseases

PARTNERSHIP FOR ACCELERATING CANCER THERAPIES (PACT)

Robust biomarkers to advance new therapies that harness the immune system to attack cancer

BIOMARKERS CONSORTIUM

IMPROVING HEALTH THROUGH MEANINGFUL MEASUREMENTS

14 therapeutics advanced based on tools generated

9 clinical tools being used in drug development

5 FDA guidance documents supported

1 Clinical Safety Biomarker Qualification

Biomarker Evidence Criteria & Framework Guidance

$108M private funds raised

60+ active partnerships

FNIH

Biomarker Consortium projects operate in a pre-competitive manner releasing results to the public as early as possible.

Biomarker projects bridge the gap between basic research and the practical needs for advancing drug development and regulatory science.

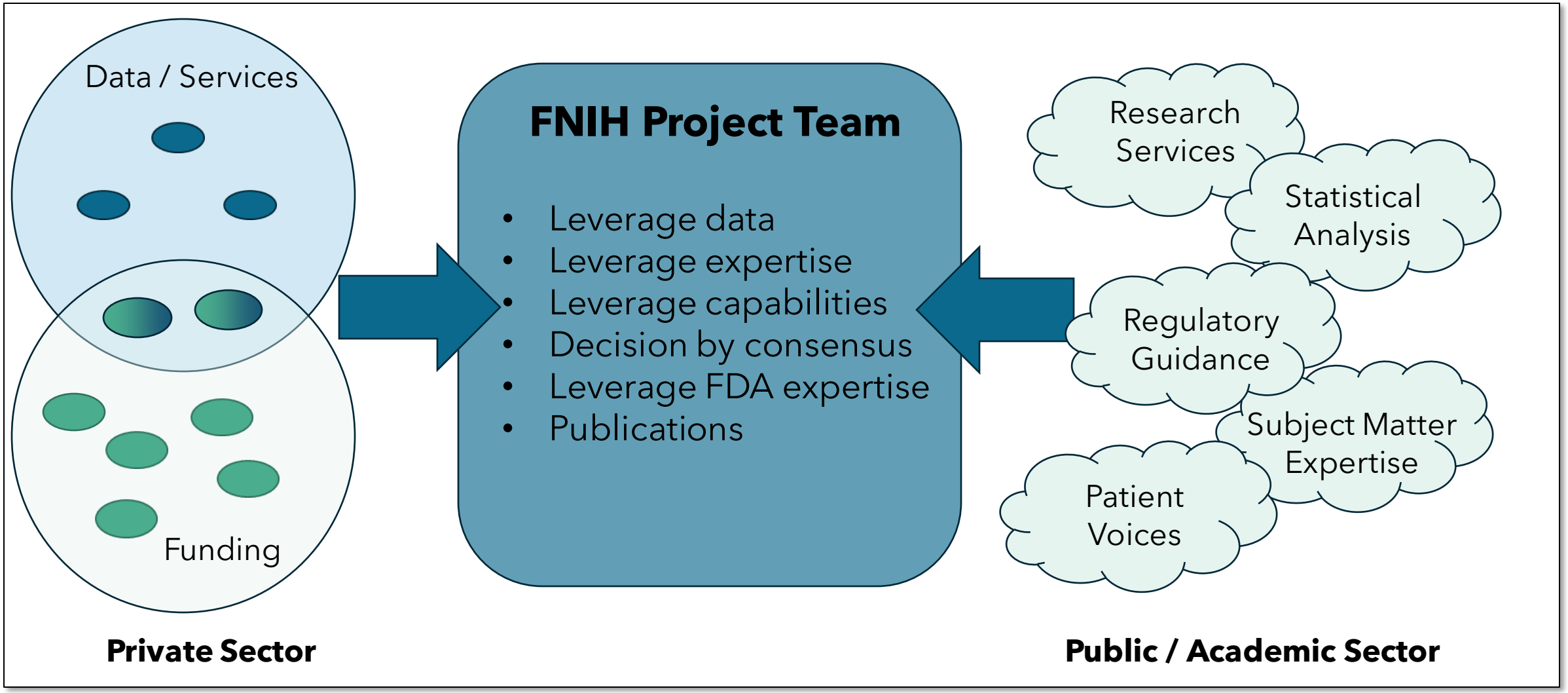
Projects are developed collaboratively with involvement from academic, government and industry stakeholders. Projects can be generated in any therapeutic area.

All projects have specific, well-defined goals and are milestone-driven, including interim scientific decision and funding gates.

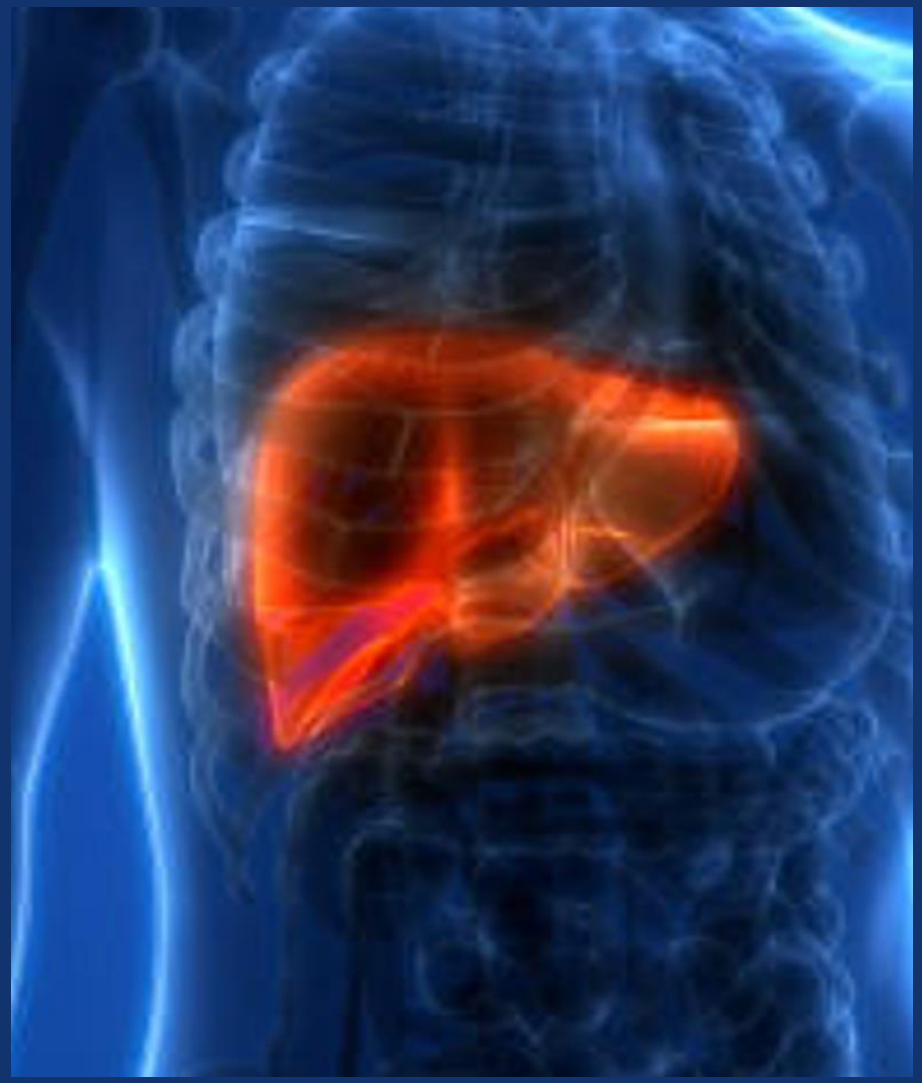
Biomarkers Consortium Private Sector Members *(as of February 27, 2024)*

Represent large and small companies, trade groups and not-for-profit organizations

Example of Public Private Partnership



Section 2
Unmet needs



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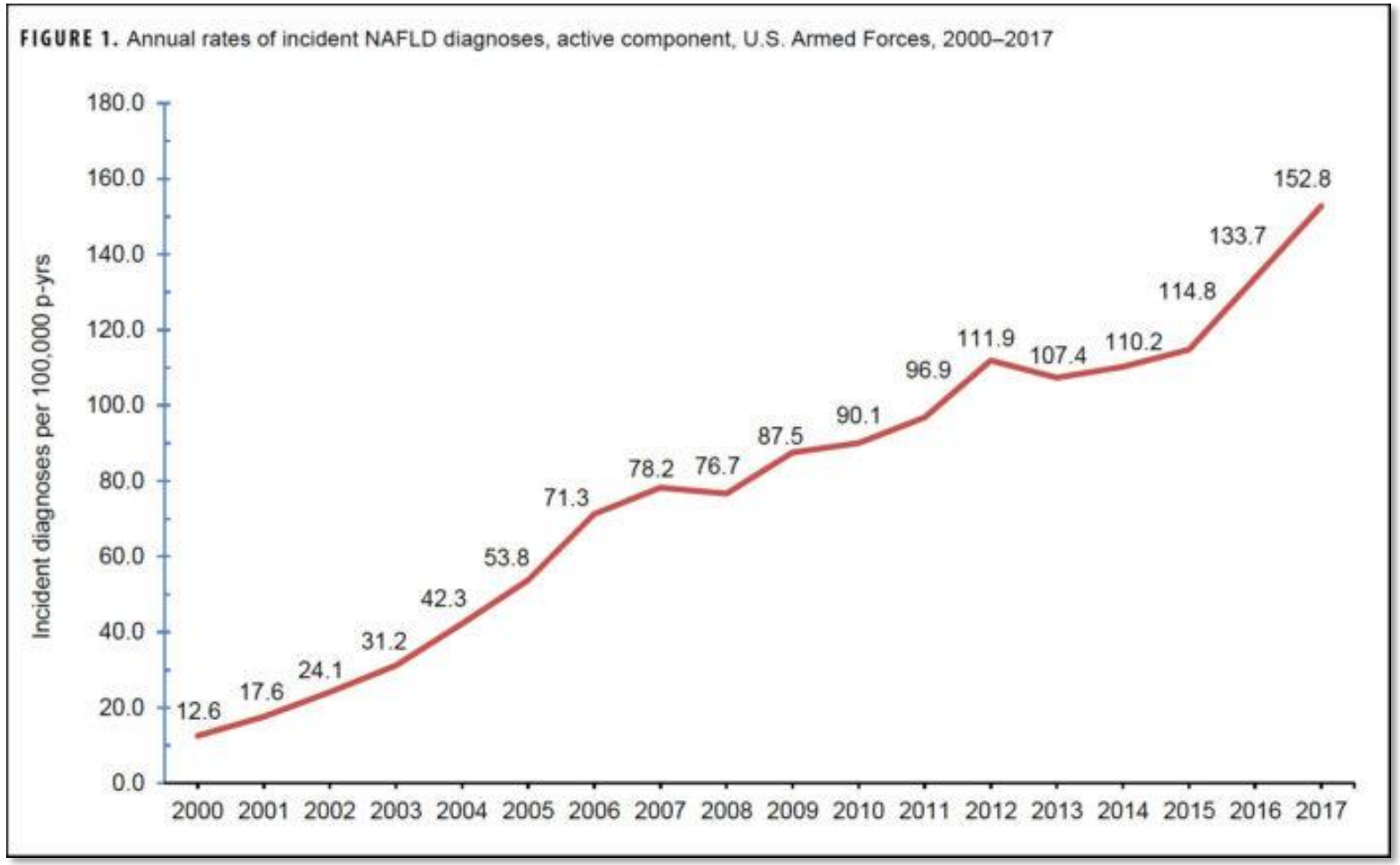
MAFLD continues to rise

(US Armed forces data[2])



Patient's view

Liver biopsy is invasive.

Liver biopsy is painful.

Risk of complications.

Feasibility

Liver biopsy provides a small sample.

Limited repeatability.

Limited accessibility.

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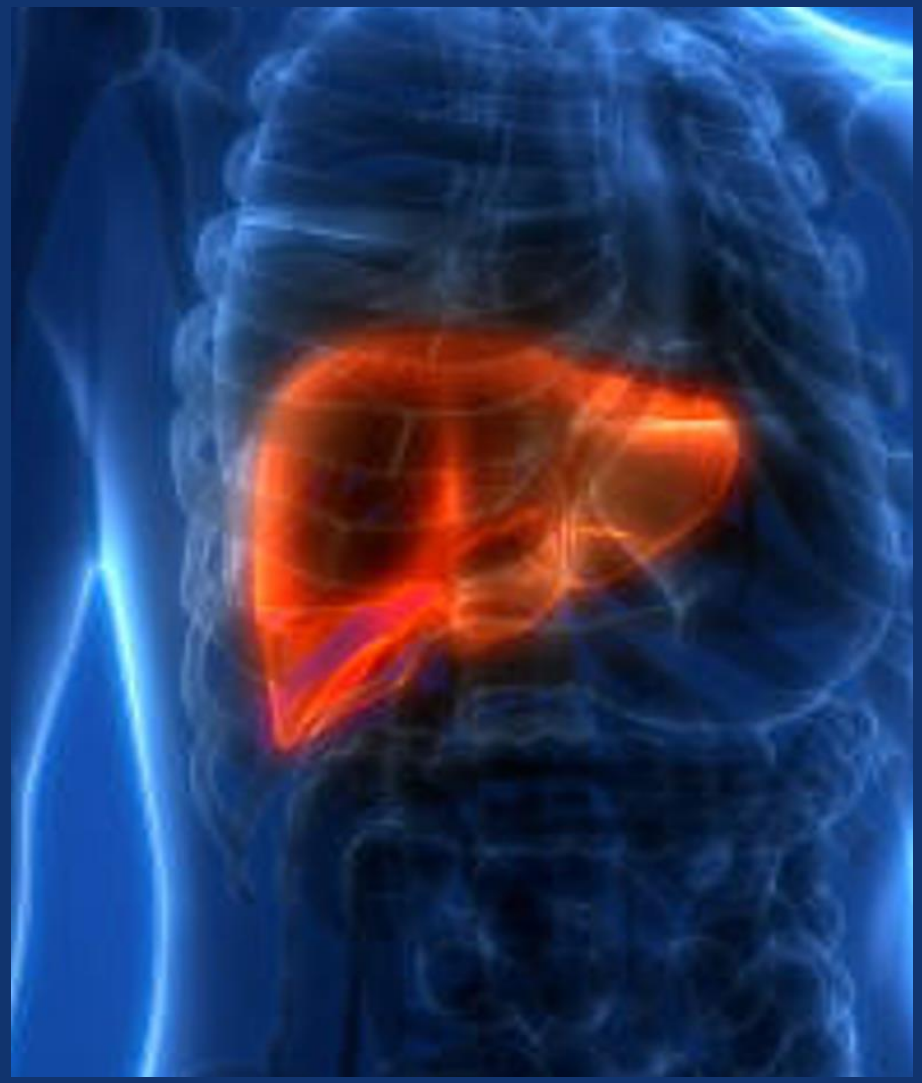
Section 3
MASHtrack and NIMBLE



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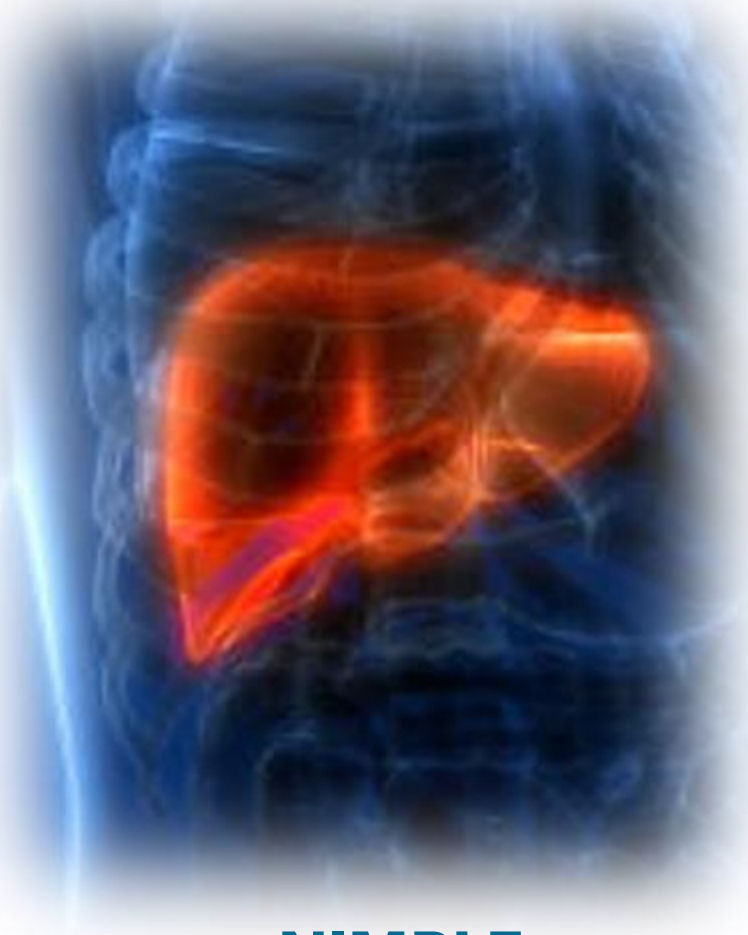
In development MASHtrack: Prognostic Study

Category	Description
Goal	▪ Assess performance of non-invasive biomarker panels to predict liver-related clinical events (LACE) in NAFLD patients; ▪ Not part of NIMBLE, but available through a partnership with NASH CRN
Data Generated	▪ Biomarker data for ELF, NIS4, PRO-C3, OWLiver, FM-VCTE on ~1100 of ~1800 patients in NASH CRN DB 2 cohort
Context of Use	▪ Prognosticate future clinical events or histological evolution in adults with NAFLD
Intended Use	▪ Risk stratification of MAFLD patients to inform clinical trial populations and clinical decision making
Population	▪ Full spectrum of MAFLD patients from NASH CRN, balanced with respect to fibrosis stages to avoid spectrum bias
Liver-related clinical events (LACE)	▪ Composite outcome including overt ascites, overt hepatic encephalopathy, variceal hemorrhage, or varices requiring therapy



NIMBLE

Non-**I**nvasive Bio**M**arkers for Meta**B**olic
Liver **D**iseas**E**

FNIH

Goals and Outcomes for NIMBLE:

Diagnostic standard for NASH is an invasive Liver Biopsy

- Lacks repeatability
- Limited accessibility
- Risks of complications

Industry Perspective

- Population enrichment for clinical trials
- Increased efficiencies in clinical trials
- Cost savings strategies for trial conduct

NIMBLE approaches qualification with a highly focused, two-staged approach

1. Identify, standardize, and advance qualification of a set of fit for purpose, non-invasive biomarkers (circulating and imaging) for the diagnosis and staging of NASH and identification of **individuals at risk of progression to cirrhosis and in need of pharmacological or non-pharmacologic intervention**.
2. Identify, standardize, and advance qualification of a set of fit-for-purpose, non-invasive biomarkers (circulating and imaging) **in subjects with various stages of NASH**

Stage 1: standardization and cross-sectional analysis of circulating and imaging biomarkers.

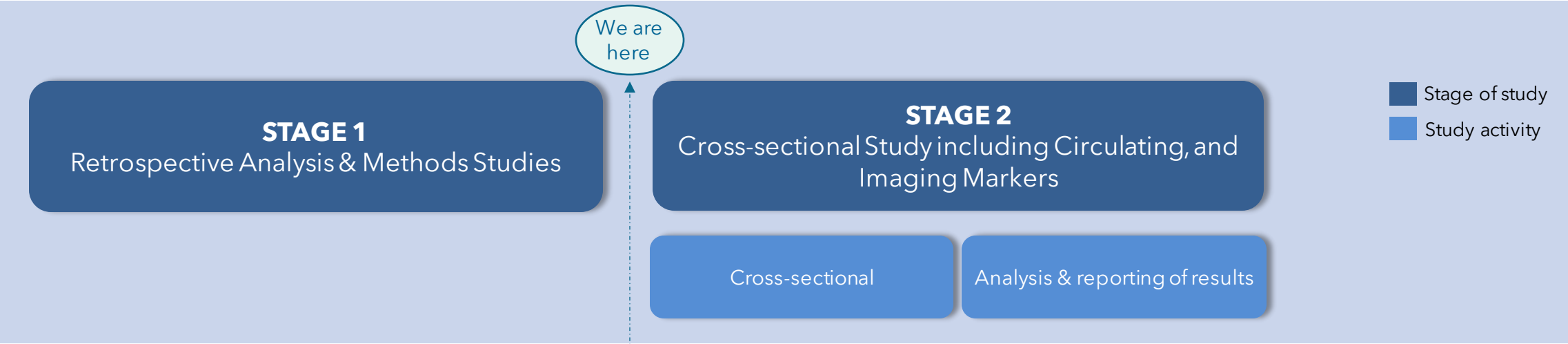
Stage 2: most promising candidate biomarkers identified in Stage 1 to be qualified in a study

NIMBLE Project Partners

PUBLIC SECTOR PARTNER	PROJECT TEAM	COMPANIES THAT PROVIDED IN-KIND ASSAYS AND SERVICE*	ACADEMIC PARTNERS
• U.S. Food and Drug Administration (FDA)	• AbbVie* • Amgen* • AstraZeneca* • Boehringer Ingelheim* • Bristol Myers Squibb* • Echosens* • GE Healthcare* • Genentech, a member of the Roche Group* • Gilead Sciences, Inc.* • Global Liver Institute • Intercept Pharmaceuticals, Inc.* • Novo Nordisk* • Pfizer Inc.* • Regeneron Pharmaceuticals Inc.* • Takeda*	• AMRA Medical • Canon Medical Systems USA, Inc. • Echosens • GENFIT SA • GE Healthcare • Nordic Bioscience • OWL Metabolomics • Philips Ultrasound, Inc. • P-Value, LLC Hologic • SuperSonic Imagine • Siemens Healthineers • Siemens Medical Solutions USA, Inc.	• Cleveland Clinic • Massachusetts General Hospital, an affiliated teaching hospital of Harvard Medical School • Mayo Clinic • University of California San Diego School of Medicine • Virginia Commonwealth University.

** Provided financial and/or in-kind support for this program*

Overall Project Structure



- **Rigorous assessment of sensitivity and specificity** within deeply phenotyped and curated cohort from NASH CRN
- **Methodology Studies for Imaging Modalities**
- **Selection of robust candidate biomarkers advancing to Stage 2:**
  - Assay robustness
  - Clinical performance and rigorous assessment of sensitivity/specificity

- **Cross-sectional Study for characterization of biomarker performance**
- **Individual qualification packages** may include validation in additional cohorts as well
- **At-risk NASH, cirrhosis, advanced fibrosis** are major priorities
- **UO1 with FDA to work on analytic plan** for qualification for imaging biomarkers

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Chain of Custody of Samples and Data

1. Sample Acquisition

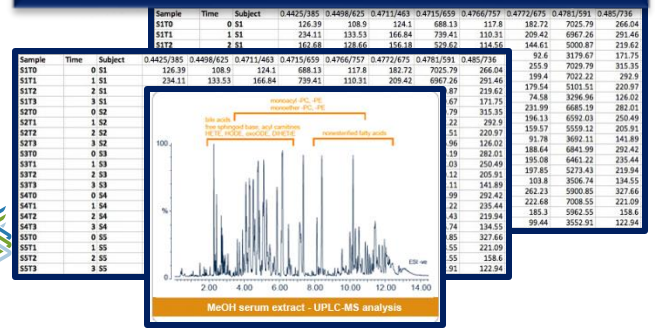
NASH CRN Cohorts >7000 samples, across disease spectrum (F1 – F4)

2. Sample Analysis (~1000 per company)

GENFIT | OWL | NORDIC | ELF | LabCorp

NIS4 | OWL-liver | PRO-C3 Panel | ELF score | Hepatic Panel

3. De-identified Raw and Primary Data



Biomarkers tested

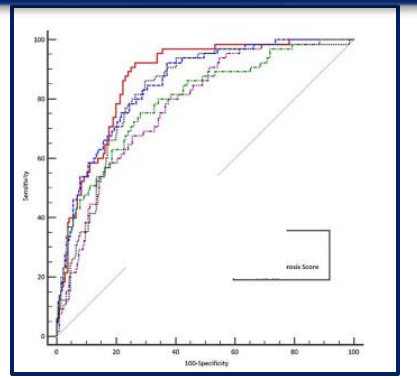
Echosens: Fibrometer - VCTE / Echosens

4. Independent Statistical Analysis

Statistical Analysis by Cytel per SAP generated *a priori* by NIMBLE team

Metadata from NASH CRN per SAP

5. Comprehensive Primary Data (Cytel)



6. NIMBLE CWS-CRN Data Review (Cytel)

7. NIMBLE PT Review (Cytel)

8. Manuscripts and Presentations

9. FDA Qualification Submission

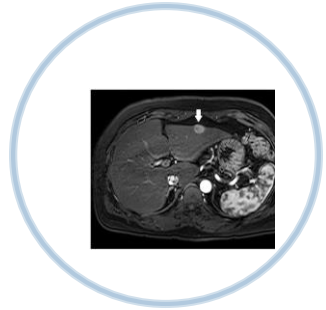
With FDA feedback, NIMBLE is advancing up to 10 biomarkers for qualification

4 blood-based

NIS-4 (GENFIT)
PRO-C3/ADAPT (NORDIC BIOSCIENCE)
ELF (SIEMENS)
Fibrometer-VCTE (ECHOSENS)

1 Ultrasound - based

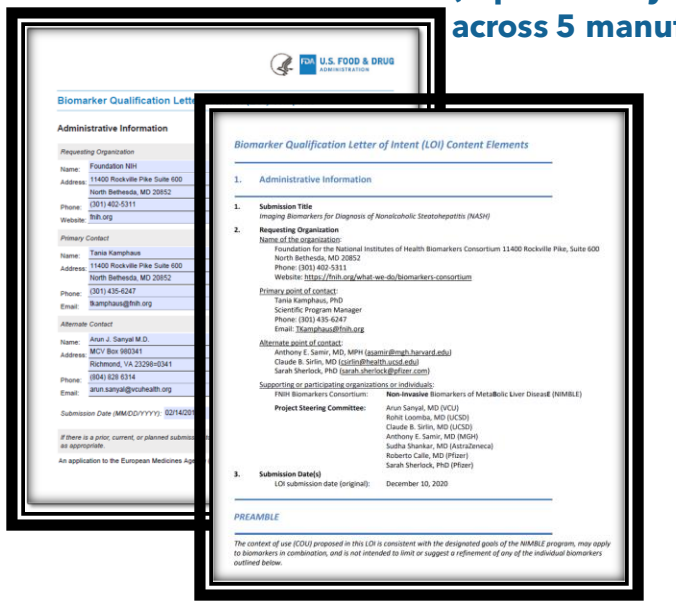
Sheer Wave Speed
(repeatability and reproducibility across 5 manufacturers)



5 MR - based

CSE-MRI, magnitude – PDFF,
CSE-MRI, complex – PDFF,
2D MRE – "stiffness",
3D MRE – magnitude of complex shear modulus, Whole-body imaging – VAT
(repeatability and reproducibility across 5 manufacturers)

Two accepted LOIs (DDTBQP000084, 000112)



Biomarker Qualification Letter of Intent (LOI) Content Elements

1. Administrative Information

1. Submission Title
Imaging Biomarkers for Diagnosis of Nonalcoholic Steatohepatitis (NASH)

2. Requesting Organization
Name of the organization:
Foundation for the National Institutes of Health Biomarkers Consortium 11400 Rockville Pike, Suite 600
North Bethesda, MD 20852
Phone: (301) 402-5311
Website: https://fnih.org/what-we-do/biomarkers-consortium

Primary point of contact:
Tania Kamphaus, PhD
Scientific Program Manager
Phone: (301) 435-6247
Email: TKamphaus@fnih.org

Alternate point of contact:
Anthony E. Samir, MD, MPH (asamir@mgh.harvard.edu)
Claude B. Sirlin, MD (csirlin@health.ucsd.edu)
Sarah Sherlock, PhD (sarah.sherlock@pfizer.com)

Supporting or participating organizations or individuals:
FNIH Biomarkers Consortium: Non-Invasive Biomarkers of Metabolic Liver Disease (NIMBLE)

Project Steering Committee: Arun Sanyal, MD (VCU)
Rohit Loomba, MD (UCSD)
Claude B. Sirlin, MD (UCSD)
Anthony E. Samir, MD (MGH)
Sudha Shankar, MD (AstraZeneca)
Roberto Calle, MD (Pfizer)
Sarah Sherlock, PhD (Pfizer)

3. Submission Date(s)
LOI submission date (original): December 10, 2020

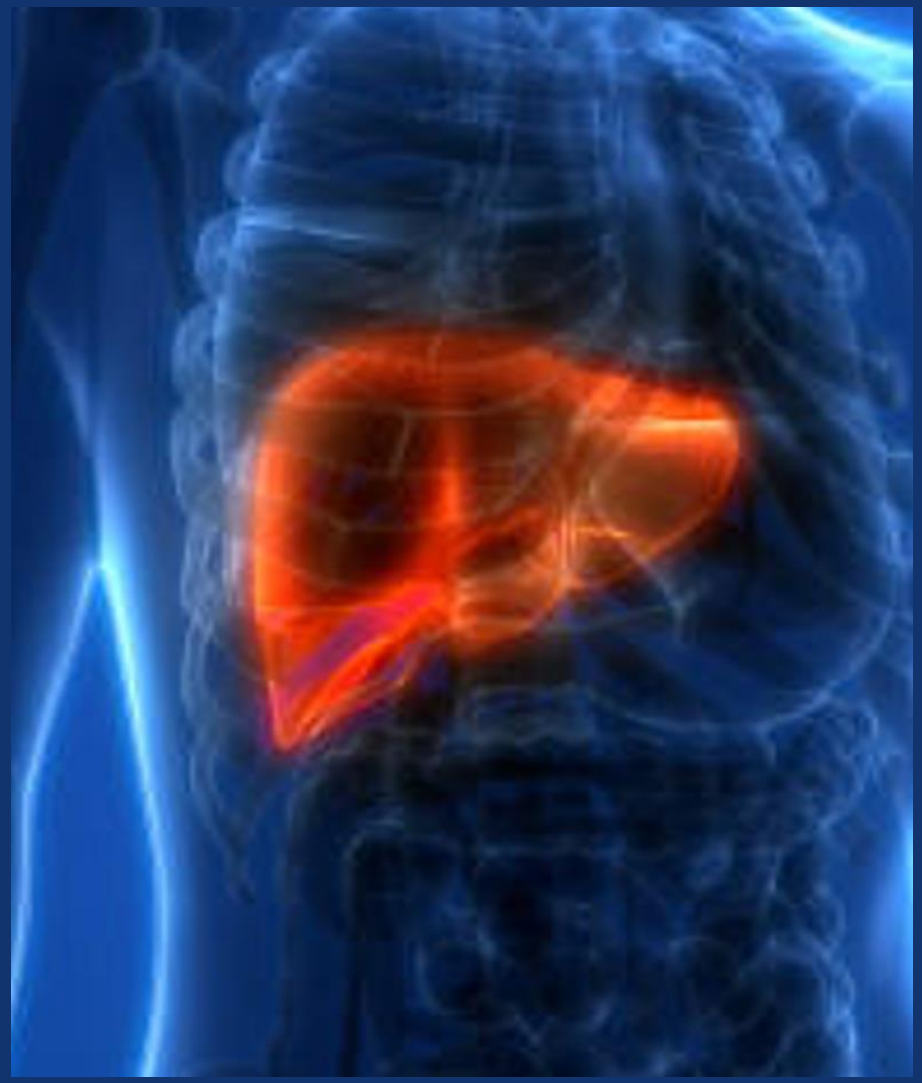
PREAMBLE

The context of use (COU) proposed in this LOI is consistent with the designated goals of the NIMBLE program, may apply to biomarkers in combination, and is not intended to limit or suggest a refinement of any of the individual biomarkers outlined below.

4-10 Qualification Plans to enable diagnosis of high-risk patients and ability to enrich the clinical trials population

https://www.fda.gov/drugs/biomarker-qualification-program/biomarker-qualification-submissions

Section 4
Future Studies



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NIMBLE Stage 2 in progress…

- Stage 2 will involve a **diagnostic enrichment-based biomarker study**
- Will look at **the circulating biomarkers, imaging biomarkers**
- Will include **digital pathology groups**
- Q2 2024 is the **expected launch timeline**

Thank You

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Project Manager, NIMBLE / MASHTrack
Alex Pasek, MD
apasek@FNIH.org

Sources

1 - Mooney, B. (2019, May 24). Incidence of Nonalcoholic Fatty Liver Disease Rises Quickly in U.S. Military. U.S. Medicine. Retrieved from https://www.usmedicine.com/uncategorized/incidence-of-nonalcoholic-fatty-liver-disease-rises-quickly-in-u-s-military/