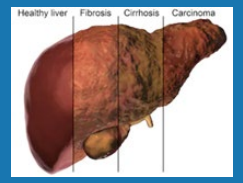
NIMBLE Project



BIOMARKERS CONSORTIUM FNIH

NIMBLE Leadership Team

Arun J Sanyal MD
Virginia Commonwealth University
Academic Co-Chair NIMBLE

Sudha Shankar, MD
AstraZeneca
Industry Co-Chair NIMBLE

Roberto Calle, MD,
Pfizer
Industry Co-Chair NIMBLE/MDSC Co-Chair

Tania Kamphaus, PhD
Scientific Program Manager

Overall Goals for the Project and for Today's Presentation

- **Overarching Project Goal**: to leverage state of the art contemporary scientific tools to qualify strategically relevant biomarkers to enable timely development of NASH therapeutics

- **Today's Discussion**:
  - Update on evolving NIMBLE organization
  - The scientific approach to develop a stepwise plan to qualify select non-invasive biomarkers to enable accelerated drug development and increased access to care for patients with NASH
  - What has been accomplished so far
  - Next steps- analysis of barriers and solutions

NIMBLE Program Team Structure

NIMBLE Program Leadership Team
Project Co-chairs: Arun Sanyal, Sudha Shankar, Roberto Calle
Members: Claude Sirlin, Anthony Samir, Rohit Loomba, Sarah Sherlock
Scientific Program Manager: Tania Kamphaus

Circulating & Functional Markers Work Stream

Rohit Loomba (UCSD) – Co-chair
Sudha Shankar (Astra Zeneca) – Co-chair
Roberto Calle (Pfizer)
Academic collaborators

Pathology Expert Team

Cynthia Guy (DCRI)
Melissa Contos (VCU)
Others TBD

Data Analysis & Modeling Expert Team

Nancy Obuchowski (Cleveland Clinic)
Santos Carvajal-Gonzalez (Pfizer)
Statistical CRO

Imaging Markers Work Stream

Claude Sirlin (UCSD)– Co-chair
Anthony Samir (Harvard/MGH) – Co-chair
Sarah Sherlock (Pfizer) – Co-Chair
Academic collaborators

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NIMBLE PROJECT TEAM

12 Funding Companies

9 Academic Centers

FDA, NIH

Biomarker Companies

Allergan
AstraZeneca
MedImmune
Boehringer Ingelheim
Bristol-Myers Squibb
ECHOSENS
GE Healthcare
Genentech
A Member of the Roche Group
GILEAD
Intercept
novo nordisk
Pfizer
Takeda

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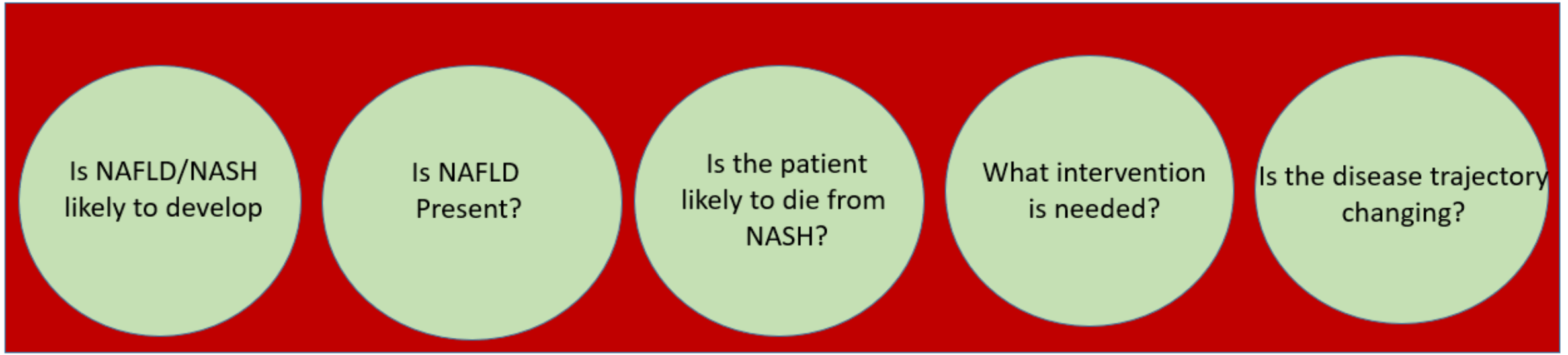
FNIH

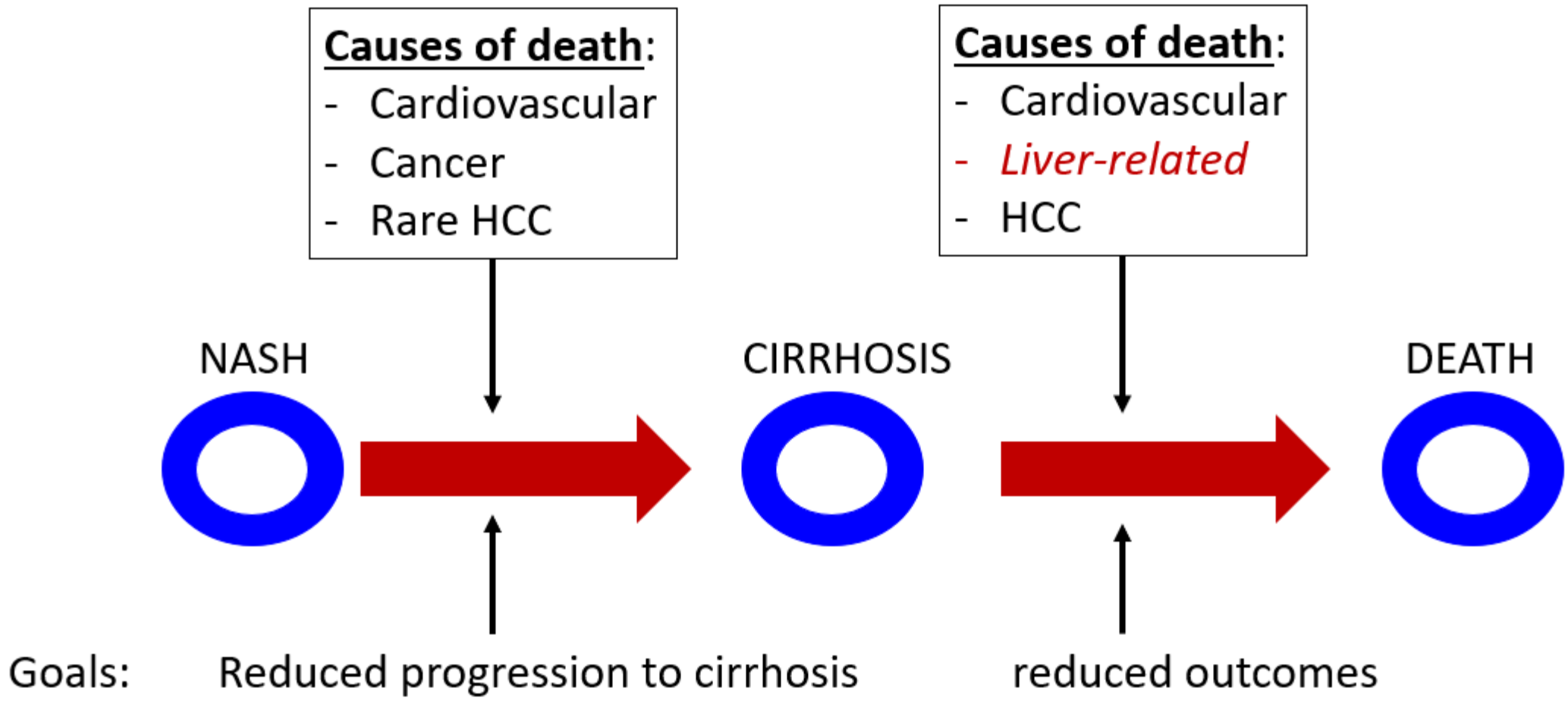
Columbia University Irving Medical Center
Duke University
U.S. Food & Drug Administration
Indiana University School of Medicine
Massachusetts General Hospital
National Institutes of Health
Turning Discovery Into Health
Saint Louis University
Swedish
UC San Diego
VCU Health
Mayo Clinic

Rationale For Approach Being Taken

Key Biomarker related Questions in NASH: A Clinician's Perspective



The Development of Cirrhosis is a Key Milestone in the Course of Cirrhosis



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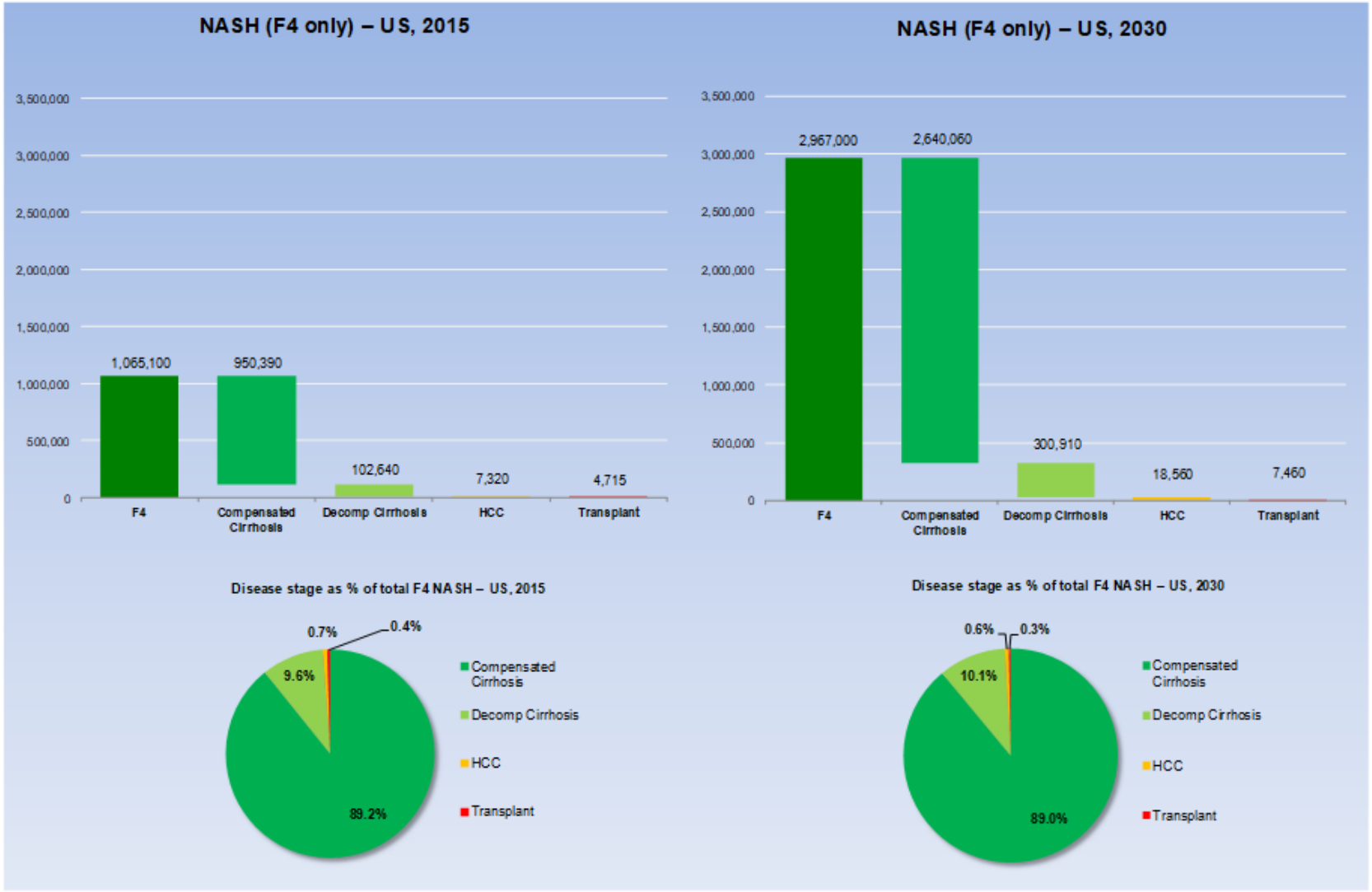
NASH (F4) – Prevalence by disease state – 2015 & 2030 (US)



Estes et al, Hepatology. 2018 Jan;67(1):123-133

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Priorities in Biomarker Development for NIMBLE- based on Biggest Impact on Patients Life and Field

Biomarker "fit for purpose" use	Impact	Rank order
Susceptibility	Low due to knowledge gaps and genetics based therapeutics	5
Is NAFLD present?	Low, can be easily predicted from clinical risk factor profile, does not correlate well with outcomes	4
What is the risk of liver outcome?	Very high- critical to determine who requires drug/surgical/endoscopic intervention	1
Can we match drug to patient?	Intermediate- more work needed to validate molecular classification	3
Is disease trajectory changing (with or without intervention)	High- needed to determine when to intervene, assess disease progression/regression and impact of therapy	2

Administrative Update

Tania Kamphaus PhD
Helen Heymann PhD
Joe Menetski PhD

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NIMBLE- SOME KEY MILESTONES – Since Launch Q4 2018 and Q2 2019

Contracting

- Academic Centers Key Collaborators
- CROs and Vendors
- Sample Cohorts

Protocol and Study Design

- Draft SAP Design
- Draft Protocol Design
- Updating Imaging Study Design

Regulatory

- LOI for circulating BMx
- Planning submission to EMA

Governance

- New NIMBLE PM
- COI policies signed
- Engaging Patient Representatives

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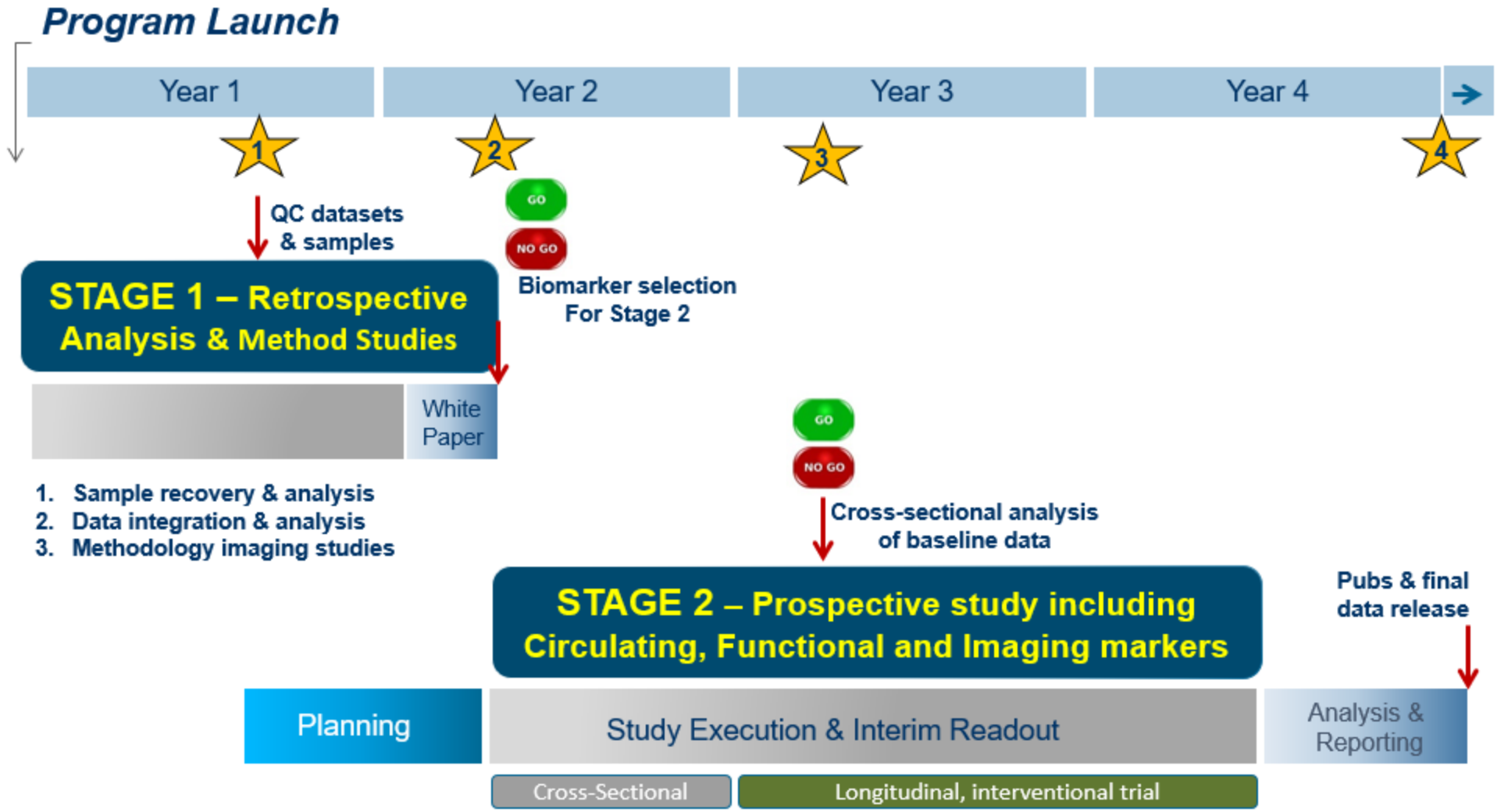
NIMBLE Approved Project Plan



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Project Milestones

Conflict of Interest Policy

- ***COI document has been previously circulated to all project team members and signed by members***
- *Levels of COI:*
  - *Academic investigators: low, intermediate and high levels of COI defined*
  - *Industry investigators: low and high levels*
  - *All key collaborators are considered to have a high level of COI*

Engaging Patient Representatives and FDA

- NIMBLE has invited **Global Liver Institute** to participate in and provide feedback at a steering level
- Drs. Lara Dimick and Veronica Pei will serve as **FDA representatives** and provide guidance for regulatory submissions and study design

Contracting

Academic Centers

- **VCU** (Arun Sanyal)
- **UCSD** (Rohit Loomba & Claude Sirlin)
- **MGH** (Anthony Samir)
- **Case Western** (Nancy Obuchowski)

Contractors and CROs

- **AG MedNet**
- **CRC Pharma** (CRO)
- **Celerion** (CRO)
- Statistical CRO (SAP planning)

Imaging Work Stream Update

Dr. Claude Sirlin, MD
Dr. Anthony Samir, MD
Dr. Sarah Sherlock, PhD

BIOMARKERS CONSORTIUM FNIH

Imaging work stream update (Oct 2018-current)

- Imaging Protocol **draft** ☑
- Imaging service identified and contracting underway ☑
- Quality control documents developed ☑
- Chain of custody of data established ☑
- Statistical analysis subgroup established with inclusion of Dr. NANCY OBUCHOWSKI ☑
- Site selection RFP for stage 1.1 and 1.2 ☑
- Study design and sample size for stage 1.1 and 1.2 ☑

- *Establishment of SAP and ICF*
- *Site finalization* ☑
- *Registration of study*

Imaging Study Updates

Initial Proposal 1.1

- Test-retest repeatability (US and MRI)
- Temporal reproducibility (US and MRI)
- Scanner reproducibility (US)

Initial Proposal 1.2

- Scanner reproducibility (MRI)

Updated Proposal 1.1 – Ultrasound Only

- Test-retest repeatability (US)
- Temporal reproducibility (US)
- Scanner reproducibility (US)

Updated Proposal 1.2 – MRI Only

- Scanner reproducibility (MRI)
- Test-retest repeatability (MRI)
- Temporal reproducibility (MRI)

Proposed updates will simplify the study design and should have favorable impacts on subject recruitment, study timelines and cost.

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Proposed Activities in the next 6 Months

- Imaging Biomarkers:
  a. Finalization of protocol with SAP (underway)
  b. Contract between participating sites and FNIH (underway)
  c. ICF approval
  d. Patient recruitment

Circulating Markers Work Stream Update

Dr. Arun Sanyal, MD
Dr. Sudha Shankar, MD
Dr. Roberto Calle, MD
Dr. Rohit Loomba, MD

BIOMARKERS CONSORTIUM FNIH

Circulating Biomarkers Work Stream Update (Oct 2018-current)

- Circulating biomarkers (applications received after project plan approval) flagged for review and inclusion based on thorough literature review ☑
- Protocol Drafted ☑
- Statistical CROs finalized ☑
- Biomarker vendors identified, under contracting ☑
- Operations CROs identified (pending contracts) ☑
- Quality control documents under development ☑
- Chain of custody of data under developments ☑
- Identification of cohorts with "intended use" populations in different clinical settings and establishing collaborative contracts – near finalization ☑
- **Submission of draft LOI to FDA** ☑

Next Steps (Q3-4 2019)

- *Biosample repositories ideal for protocol: discussions ongoing between academic PI and cohort leads*
- *Protocol finalization WITH SAP*
- *Contracting with sample cohorts*
- *Contracting with Key Collaborators*

Sample and Data Chain of Custody

Cohort

Contract and MTA

VCU

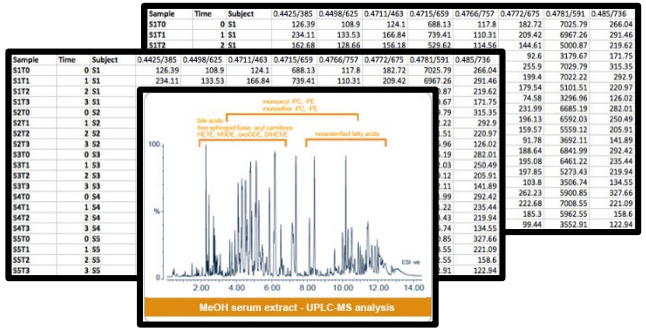
MTA

1

Lab 1 | Lab 2 | Lab 3 | Lab4

2

Analysis



Raw and Primary Data

3

Statistical CRO

4

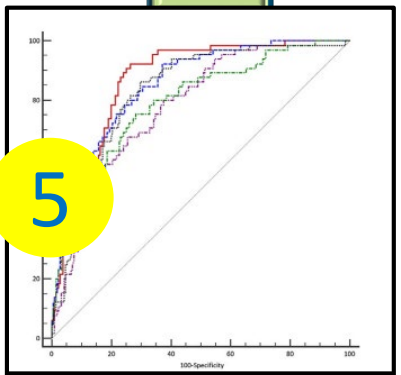
Clinical data

Clinical cohort DCC

Independent Statistical Analysis Plan

CRO +
NIMBLE Team +
Cohort Leadership +

5



Comprehensive Primary Data

6

NIMBLE-Cohort Joint Review

7

NIMBLE manuscript; Stage 2 Go/no go decision

CONSORTIUM

Critical Steps in Qualification of Circulating Biomarkers-II

<u>Methodological issues</u> (being standardized and aligned by working group):

- Sample collection
- Storage and transport
- Analysis
- Quantification and internal/external controls
- Data reporting

<u>Study Design</u> (retrospective data will inform prospective study):

- Populations to be interrogated
- Standardization of collection of meta-data
- Analytic issues:
  - determination of disease activity
  - separation from F0 or F1 vs higher stages
  - separation of F4 from lower stages

Critical Steps in Qualification of Circulating Biomarkers-I

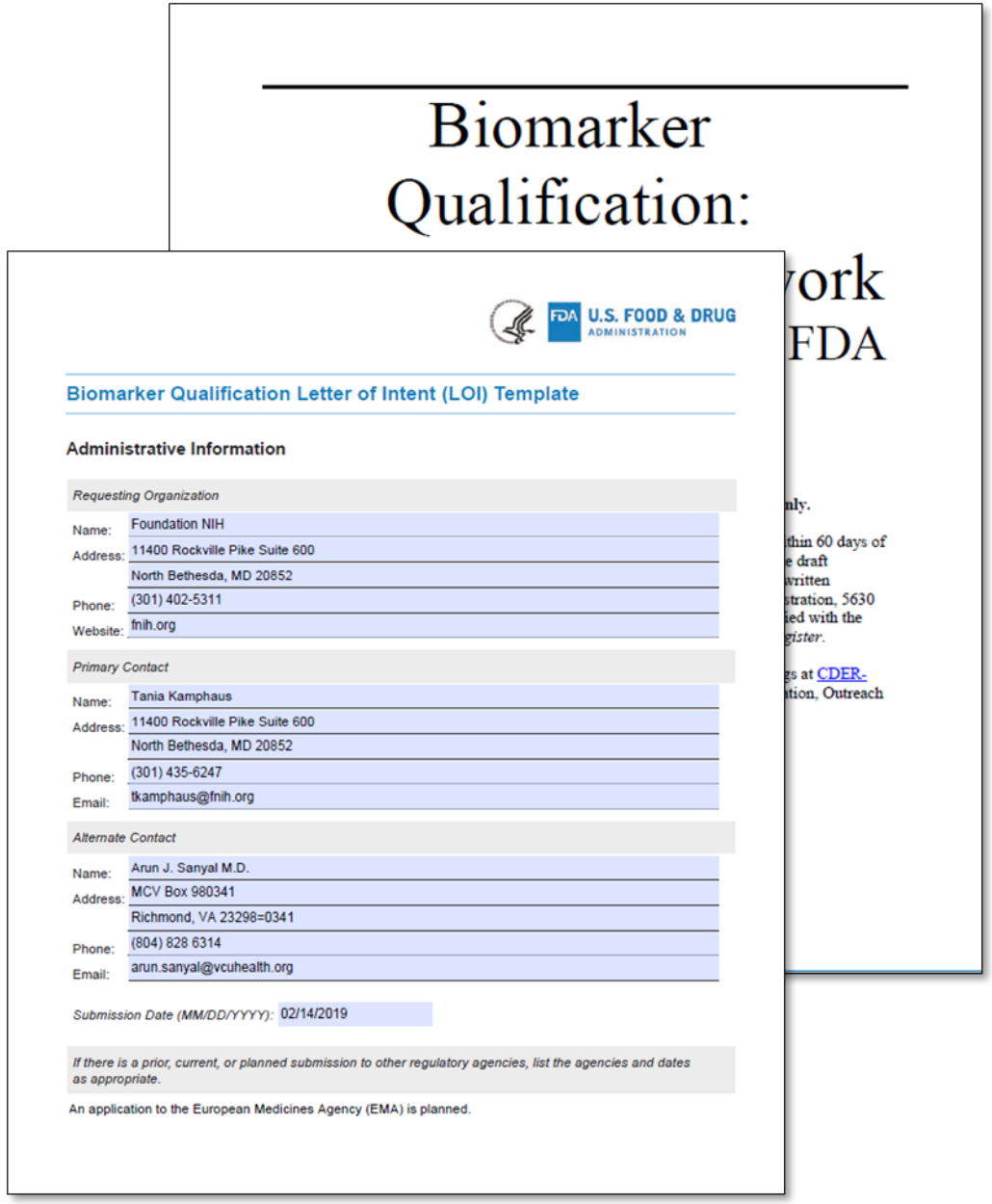
Identification of NASH with NAS ≥ 4 and Fibrosis stage 2-3, Cirrhosis due to NASH

Criteria used to pick which sample sets will be interrogated for circulating biomarkers:

- time from sample collection to liver biopsy
- amount of meta-data collected
- data on storage conditions available
- cross-sectional vs longitudinal data available with accompanying biopsy
- availability of biopsy for scan and re-read

FDA LOI Update

- **NIMBLE Letter of Intent (LOI) -**
  - Submitted: 02-26-2019
  - Confirmation of Receipt: 02-26-2019
  - Initial Feedback: April 2019
  - Revision of LOI ongoing – due to be submitted this week
- **LOI markers -**
  - NIS4
  - Nordic Panel: Pro-C3-C6
  - OWL Liver Test
  - ELF



Biomarker Qualification:

U.S. FOOD & DRUG ADMINISTRATION

Biomarker Qualification Letter of Intent (LOI) Template

Administrative Information

Requesting Organization

Name: Foundation NIH
Address: 11400 Rockville Pike Suite 600
North Bethesda, MD 20852
Phone: (301) 402-5311
Website: fnih.org

Primary Contact

Name: Tania Kamphaus
Address: 11400 Rockville Pike Suite 600
North Bethesda, MD 20852
Phone: (301) 435-6247
Email: tkamphaus@fnih.org

Alternate Contact

Name: Arun J. Sanyal M.D.
Address: MCV Box 980341
Richmond, VA 23298=0341
Phone: (804) 828 6314
Email: arun.sanyal@vcuhealth.org

Submission Date (MM/DD/YYYY): 02/14/2019

If there is a prior, current, or planned submission to other regulatory agencies, list the agencies and dates as appropriate.

An application to the European Medicines Agency (EMA) is planned.

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Proposed Activities in the next 3 Months

- Circulating Biomarkers:
  - a. Finalization of protocol with initial SAP
  - b. Establish contract between biosample cohorts and VCU
  - d. Finalizing contract between vendors and FNIH

STRENGTHS

- Many tools available
- Disease biology increasingly well understood
- Large clinical cohorts available

WEAKNESSES

- Paucity of longitudinal data sets
- “concrete” thinking with respect to fibrosis implications
- Suboptimal therapeutics

OPPORTUNITIES

- Active drug development space
- Growing consensus on endpoints and case-definitions
- Integrated approaches to get read out for liver and other end organs

THREATS

- Challenges in histological assessment
- Bidirectional natural course
- Primary care MDs overwhelmed with work
- Burden of diagnostics for patient

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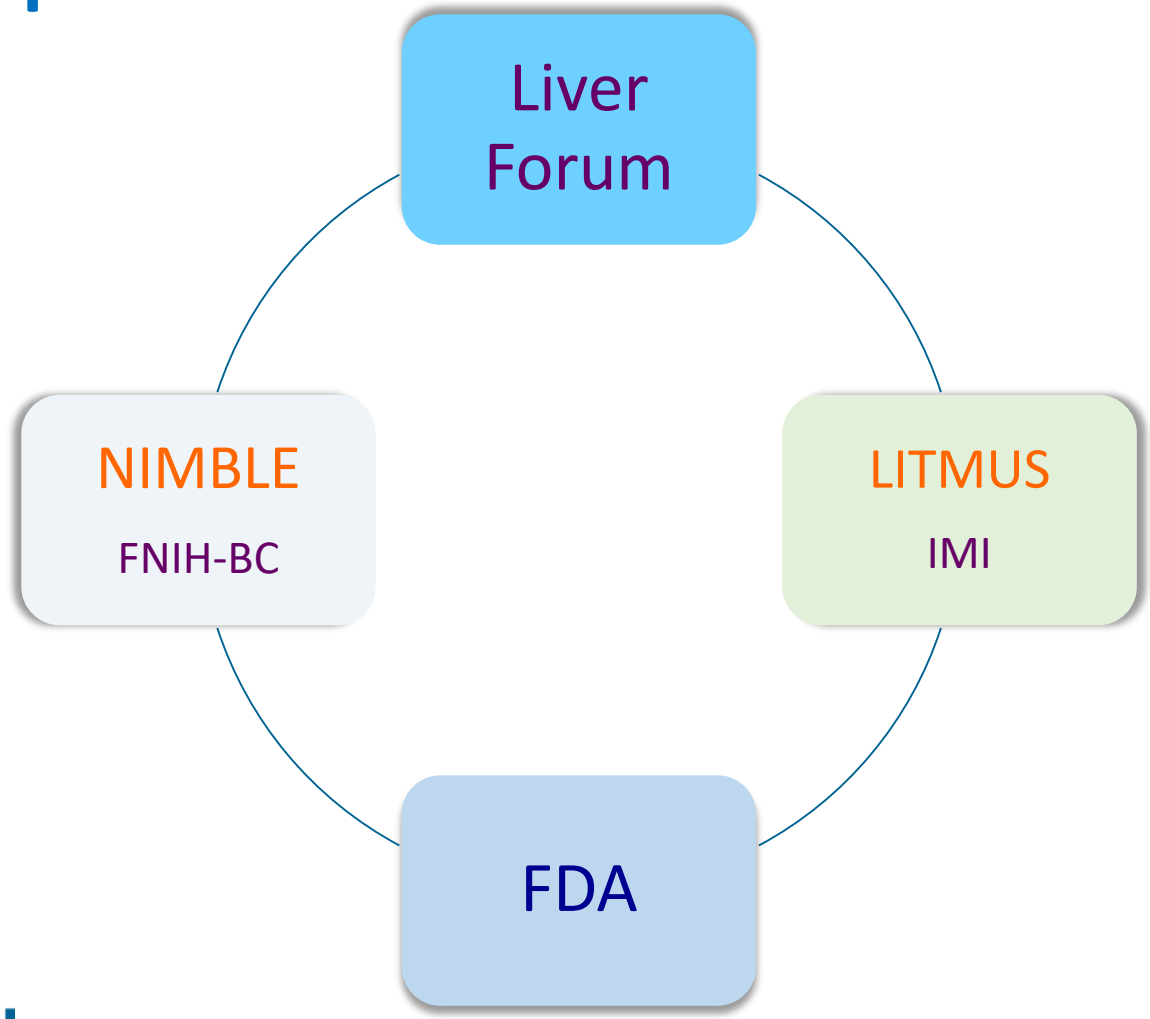
NIMBLE and LITMUS are Collaborative Activities that Build Synergy and are Working in Concert with Regulators to Accelerate Biomarker Development



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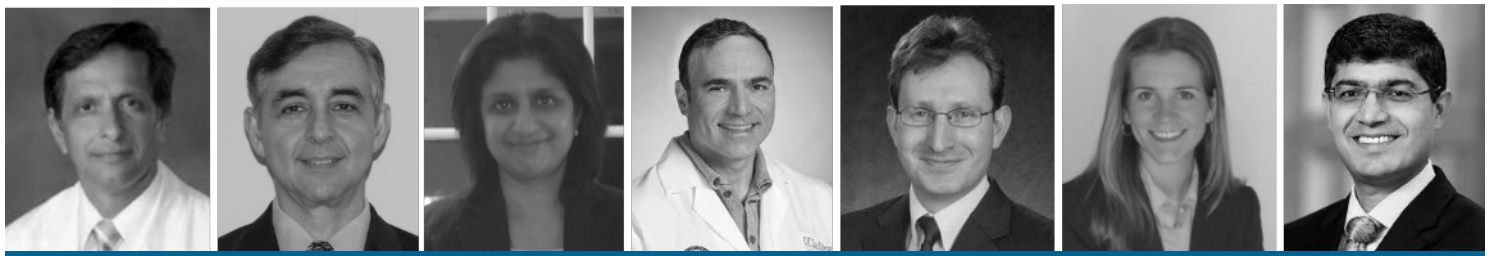
NIMBLE: A True Public - Private Partnership



NIMBLE Co-chairs

BIOMARKERS CONSORTIUM

FNIH