NIMBLE – Non-Invasive BioMarkers for MetaBolic Liver DiseasE

Team Science: The Key to Non Invasive Biomarkers Development for NASH

BIOMARKERS CONSORTIUM
IMPROVING HEALTH THROUGH MEANINGFUL MEASUREMENTS

FNIH
Foundation for the National Institutes of Health

August 11, 2020
Tania Kamphaus, PhD
Scientific Program Manager
Foundation for NIH

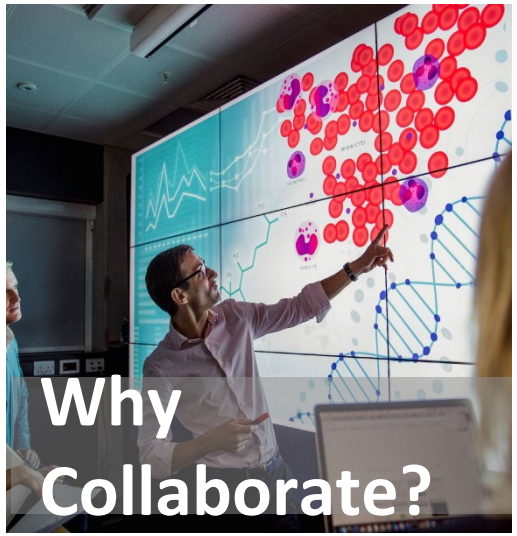
Foundation for the National Institutes of Health - FNIH

Mission

- The mission of the Foundation for the National Institutes of Health (FNIH) is to support the mission of the NIH. The FNIH creates and leads alliances and public-private partnerships that advance breakthrough biomedical discoveries and improve the quality of people's lives.

Founded by Congress

- The FNIH was created by Congress in 1990 as a not-for-profit charitable organization. The Foundation began its work in 1996 to facilitate groundbreaking research at the U.S. National Institutes of Health (NIH) and worldwide.



Why Collaborate?

- Attract and share resources
- Enable insight and innovation
- Establish standards
- Distribute expertise
- Create consensus
- Drive competitiveness in marketplace
- Disseminate knowledge
- Enhance credibility
- Reduce costs
- Support training & education
- Manage complexity

Accelerating Medicines Partnership
NIH (OD), NIA, NIAMS, NIDDK, NINDS, 12 companies, 10 not-for-profit organizations

Partnership for Accelerating Cancer Therapies
NCI, PhRMA, 12 pharmaceutical companies

Grand Challenges in Global Health (GCGH)
Bill & Melinda Gates Foundation

Alzheimer's Disease Neuroimaging Initiative (ADNI)
NIA, NIBIB, 25+ companies, 3 not-for-profit organizations

The Biomarkers Consortium
FDA, NIH, CMS, PhRMA, BIO, pharmaceutical and nutrition companies, not-for-profit organizations

Lung-MAP: Master Lung Protocol Trial
NCI (SWOG), FDA, Friends of Cancer Research, 5 companies to date

Helping End Addiction Long-Term (HEAL) Partnership Committee
NIH contract

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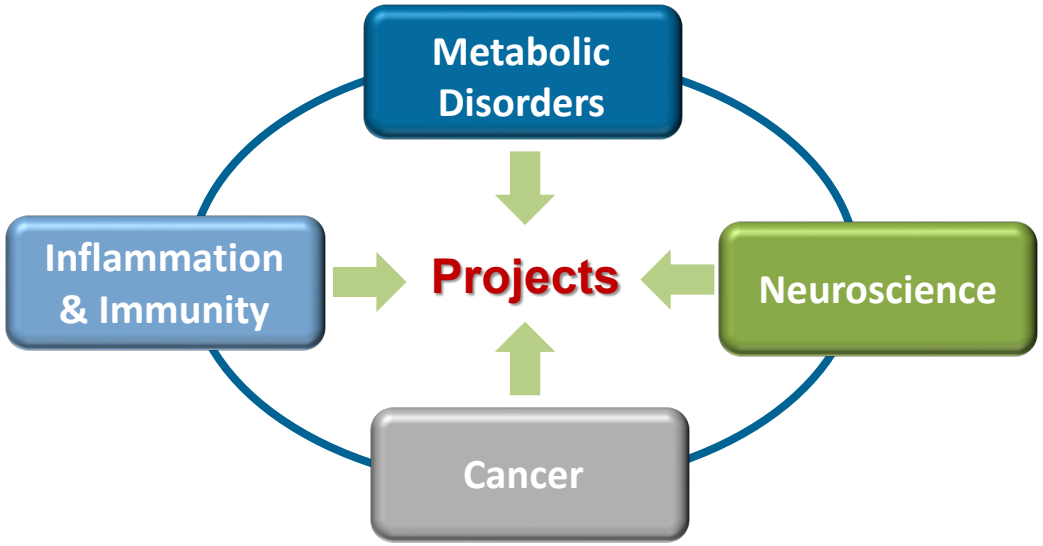
Biomarkers Consortium

13 years of collaboration, research and progress

TA Aligned Steering Committees



14 therapeutics advanced based on tools generated

9 clinical tools being used in drug development

5 FDA guidance documents supported by work of the BC

1 Clinical safety biomarker Qualification

>50 publications

800+ citations

59 member organizations

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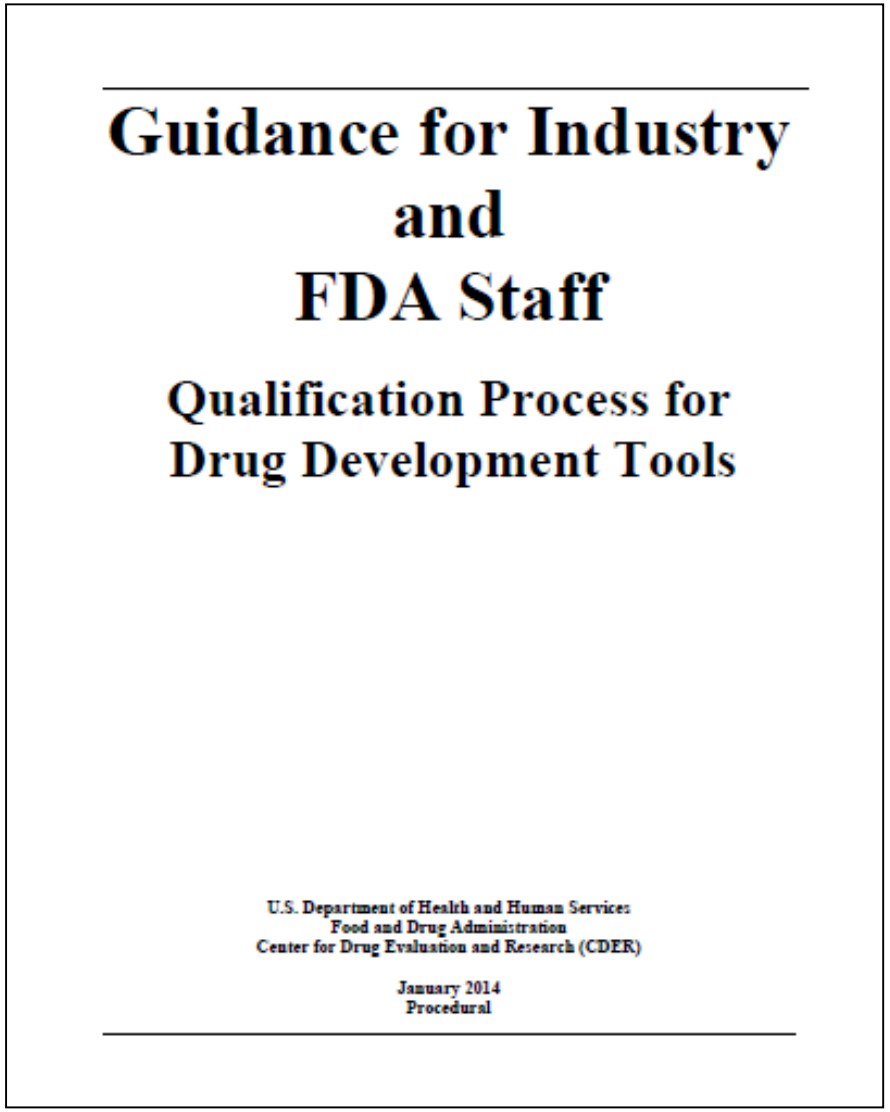
The consortium approach is encouraged by the FDA



Guidance for Industry
and
FDA Staff

Qualification Process for
Drug Development Tools

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2014
Procedural

"Because of the substantial work needed to achieve qualification, CDER [Center for Drug Evaluation and Research] encourages the formation of collaborative groups to undertake these tool-development programs… A variety of projects undertaken by consortia have demonstrated the usefulness of this approach."

Updated FDA Draft Guidance published January 2014

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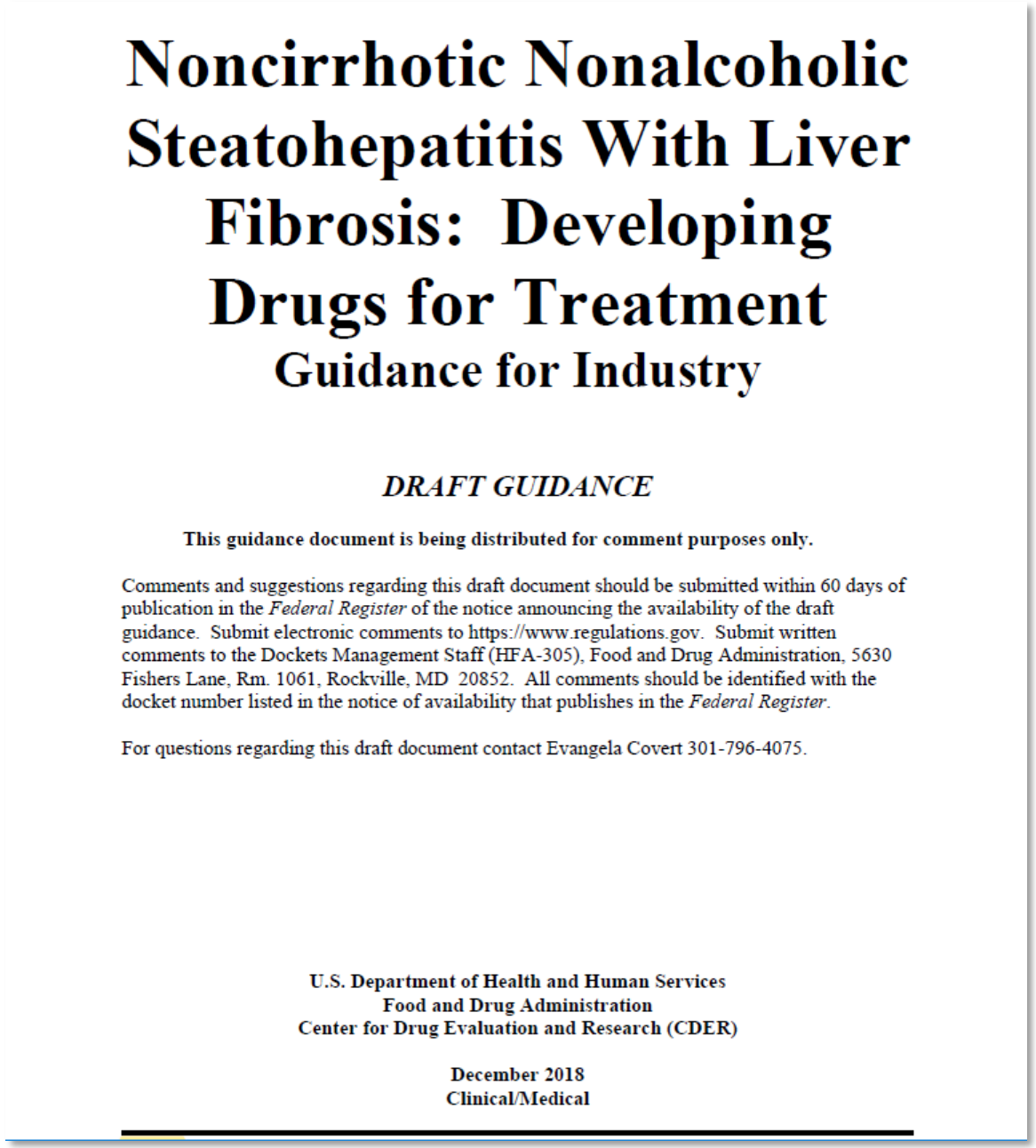

Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Evangela Covert 301-796-4075.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2018
Clinical/Medical

FDA Guidance

December 2018

"at this time, reliable diagnosis and staging of NASH can only be made by histopathological examination of the liver biopsy specimen. Liver biopsy, however, is an invasive procedure that can be associated with occasional morbidity, and in rare circumstances, mortality"

……"therefore noninvasive biomarkers are needed (including imaging biomarkers) to supplant liver biopsy and provide a comparable or superior ability to accurately diagnose and assess various grades of NASH and stages of liver fibrosis"

NIMBLE Approved Project Plan accounts for methodological elements needed to meet evidentiary standards

Stage 1

- Retrospective Analysis of Existing Datasets/Cohorts
- Methodology Studies for Imaging Modalities

Selection of robust candidate biomarkers advancing to Stage 2

Project Milestone

Stage 2

- Prospective Study for characterization of biomarker performance
- Circulating / Imaging / Others

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NIMBLE Cross-Stakeholder Team Science

NIMBLE Project Partners

Academic Institutions*

Pharmaceutical companies **

Diagnostic companies***

Patient Advocacy

NIMBLE Project Organization

NIMBLE Program Overall Leadership Team

Project Co-chairs: Arun Sanyal, Sudha Shankar, Roberto Calle
Members: Claude Sirlin, Anthony Samir, Rohit Loomba, Sarah Sherlock
Program Officer: Tania Kamphaus
Project Management: Helen Heymann, Emily Morgan, Sidra Iqbal
FDA liaison: Lara Dimick
Patient Advocacy: GLI (Donna Cryer)

Circulating & Functional Markers Work Stream

Co-chairs: Rohit Loomba, Sudha Shankar, Arun Sanyal

Imaging Markers Work Stream

Co-chairs: Claude Sirlin, Anthony Samir, Sarah Sherlock

Pathology Expert Team

Cynthia Guy
Melissa Contos
Others TBD

Data Analysis & Statistic Modeling Expert Team

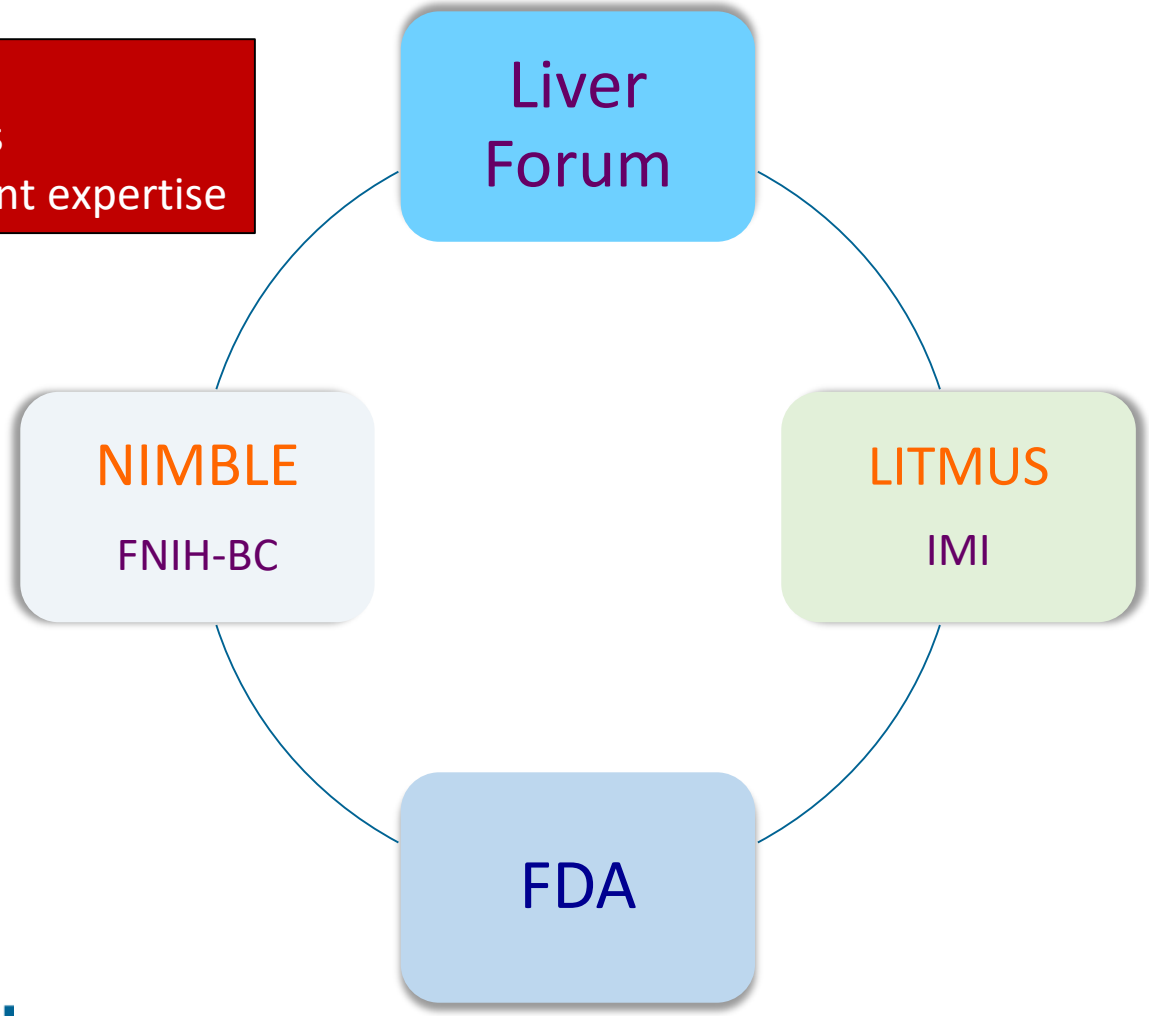
Nancy Obuchowski (Cleveland Clinic)
Santos Carvajal-Gonzalez (Pfizer)
Statistical CRO
Academic collaborators

Roles and Management

* Engage in project execution, steering of project. *FNIH manages research agreements and Conflict of Interest*
** Provide funding and actively involved in steering of project. *FNIH manages funding and deliverables*
*** Provide blinded assays only (all in kind). Not involved in steering. *FNIH manages sample and data chain of custody*

NIMBLE is working and collaborating with LITMUS and Working in Concert with Regulators to Accelerate Biomarker Development

Feedback on LOI application
Consensus on case definitions
Helping regulators gain content expertise



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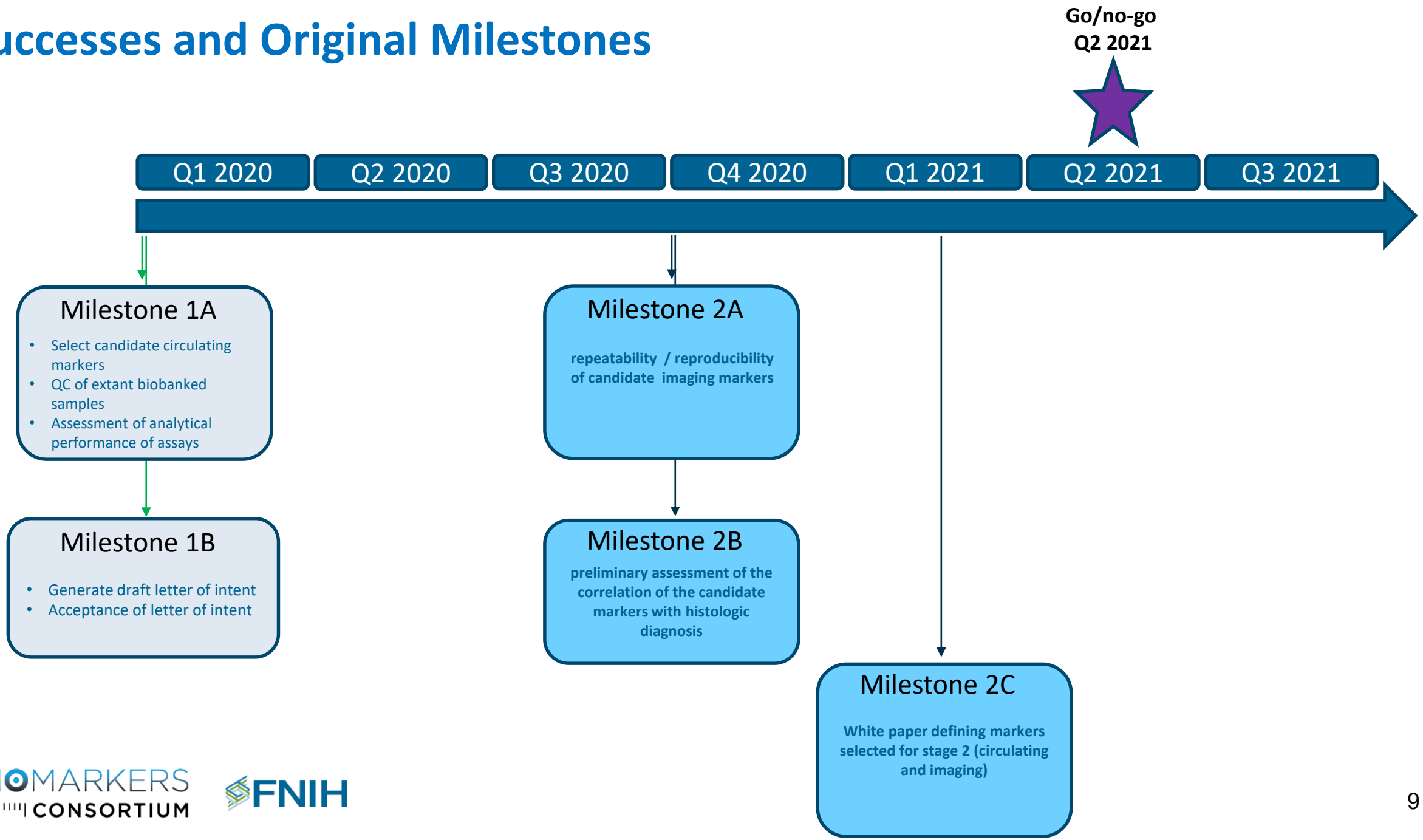
Successes and Original Milestones



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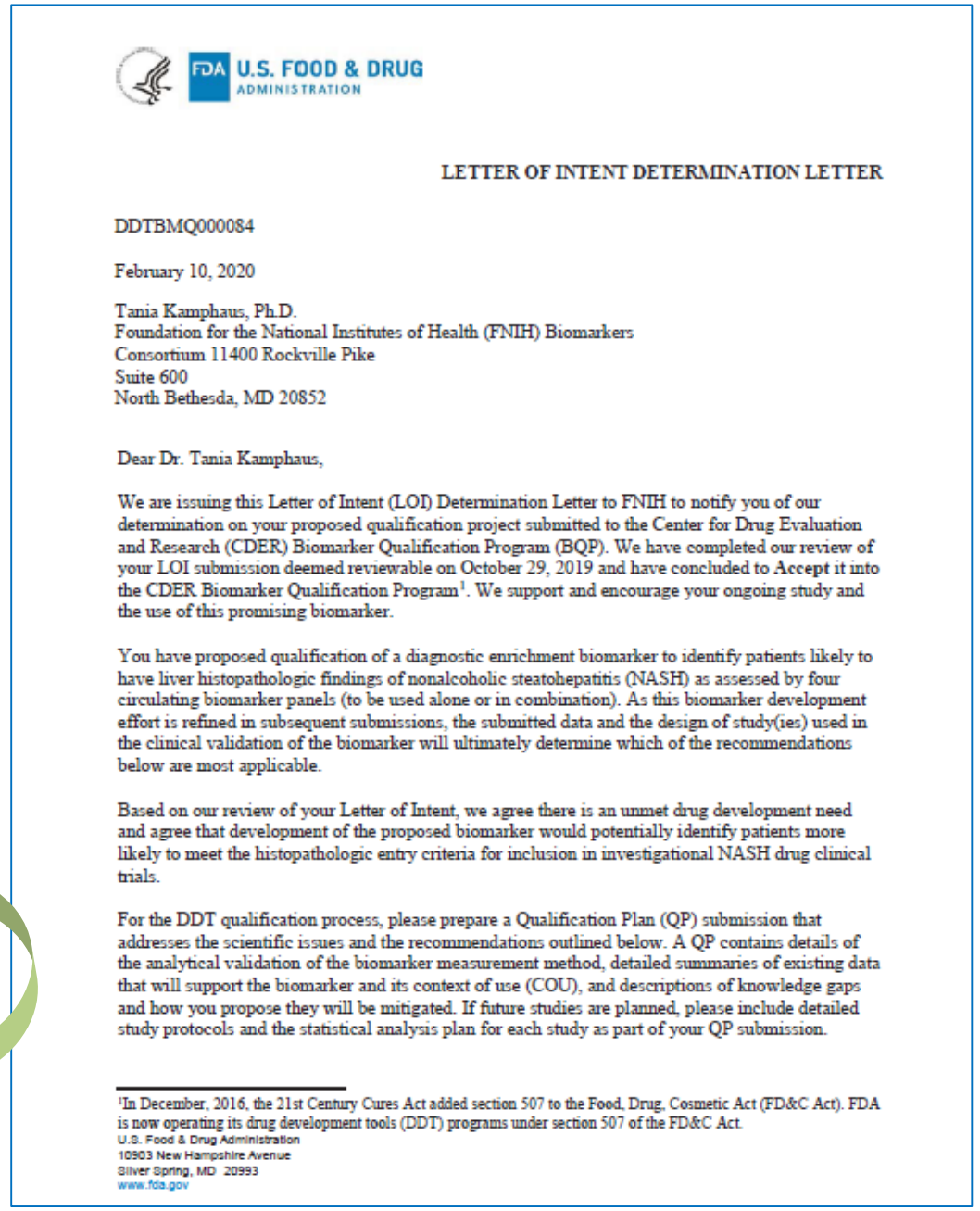
LOI accepted by FDA

- **NIMBLE Letter of Intent (LOI) -**
  - **Submitted: 02-26-2019**
  - **Confirmation of Receipt: 02-26-2019**
  - **Initial Feedback: April 2019**
  - **Revised LOI submitted October 15 2019**
  - **LOI accepted by FDA on February 20, 2020**

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



U.S. FOOD & DRUG ADMINISTRATION

LETTER OF INTENT DETERMINATION LETTER

DDTBMQ000084

February 10, 2020

Tania Kamphaus, Ph.D.
Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium 11400 Rockville Pike
Suite 600
North Bethesda, MD 20852

Dear Dr. Tania Kamphaus,

We are issuing this Letter of Intent (LOI) Determination Letter to FNIH to notify you of our determination on your proposed qualification project submitted to the Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (BQP). We have completed our review of your LOI submission deemed reviewable on October 29, 2019 and have concluded to **Accept** it into the CDER Biomarker Qualification Program[1]. We support and encourage your ongoing study and the use of this promising biomarker.

You have proposed qualification of a diagnostic enrichment biomarker to identify patients likely to have liver histopathologic findings of nonalcoholic steatohepatitis (NASH) as assessed by four circulating biomarker panels (to be used alone or in combination). As this biomarker development effort is refined in subsequent submissions, the submitted data and the design of study(ies) used in the clinical validation of the biomarker will ultimately determine which of the recommendations below are most applicable.

Based on our review of your Letter of Intent, we agree there is an unmet drug development need and agree that development of the proposed biomarker would potentially identify patients more likely to meet the histopathologic entry criteria for inclusion in investigational NASH drug clinical trials.

For the DDT qualification process, please prepare a Qualification Plan (QP) submission that addresses the scientific issues and the recommendations outlined below. A QP contains details of the analytical validation of the biomarker measurement method, detailed summaries of existing data that will support the biomarker and its context of use (COU), and descriptions of knowledge gaps and how you propose they will be mitigated. If future studies are planned, please include detailed study protocols and the statistical analysis plan for each study as part of your QP submission.

[1]In December, 2016, the 21st Century Cures Act added section 507 to the Food, Drug, Cosmetic Act (FD&C Act). FDA is now operating its drug development tools (DDT) programs under section 507 of the FD&C Act.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

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Coming up…

Q4 2020
- Early Read from Retrospective Study
- Submission of LOI 2 (Imaging)

Q1 2021
- Early reads from Imaging Studies
- 1.1 (US) & 1.2 (MR)

Q3 2021
- NIMBLE Proposal for go/no-go to Stage 2
- Qualification Plan

Q4 2021
- White Paper
- Prospective Study Initiated

Q1 2022
- Full Qualification Plan for FDA

Ongoing Conversations and Collaborations

- Steering committee updates
- Continuous FDA engagement
- Liver Forum and community updates
- Patient Groups engagement

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FNIH NIMBLE Contact Information

For further questions please contact:

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Scientific Project Manager
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Emily Morgan
Scientific Project Manager
emorgan@fnih.org

Dorcas Blue
Development Officer
dblue@fnih.org

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fnih.org/biomarkersconsortium

Backup Slides

Mitigation Factors to respond to Covid-19 delay

- Prioritize sample release from cohort/biorepository
- Align with labs and continuously monitor changing scenario – identify when labs can safely accept samples and able to process (e.g., potential backlog)
- Continue Statistical Planning, revising contracts, IRB, Protocols,
- Ongoing interactions of FNIH with Key Collaborator labs to keep posted on developments

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Biomarkers Consortium Private Sector Members (as of 10-10-19)

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

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