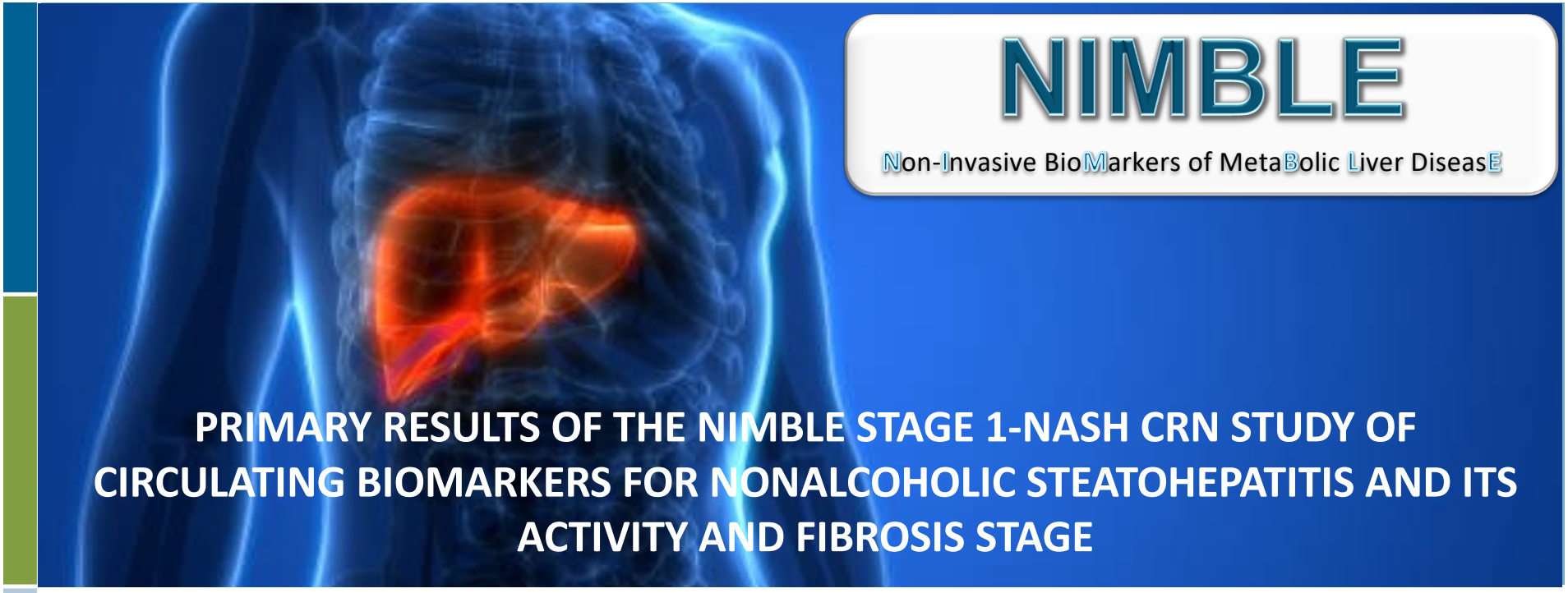

NIMBLE

Non-Invasive BioMarkers of MetaBolic Liver DiseasE

PRIMARY RESULTS OF THE NIMBLE STAGE 1-NASH CRN STUDY OF CIRCULATING BIOMARKERS FOR NONALCOHOLIC STEATOHEPATITIS AND ITS ACTIVITY AND FIBROSIS STAGE

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BIOMARKERS CONSORTIUM
IMPROVING HEALTH THROUGH MEANINGFUL MEASUREMENTS

FNIH Foundation for the National Institutes of Health

NIH National Institute of Diabetes and Digestive and Kidney Diseases

NASH CRN

VCU Health System

**co-primary authors*
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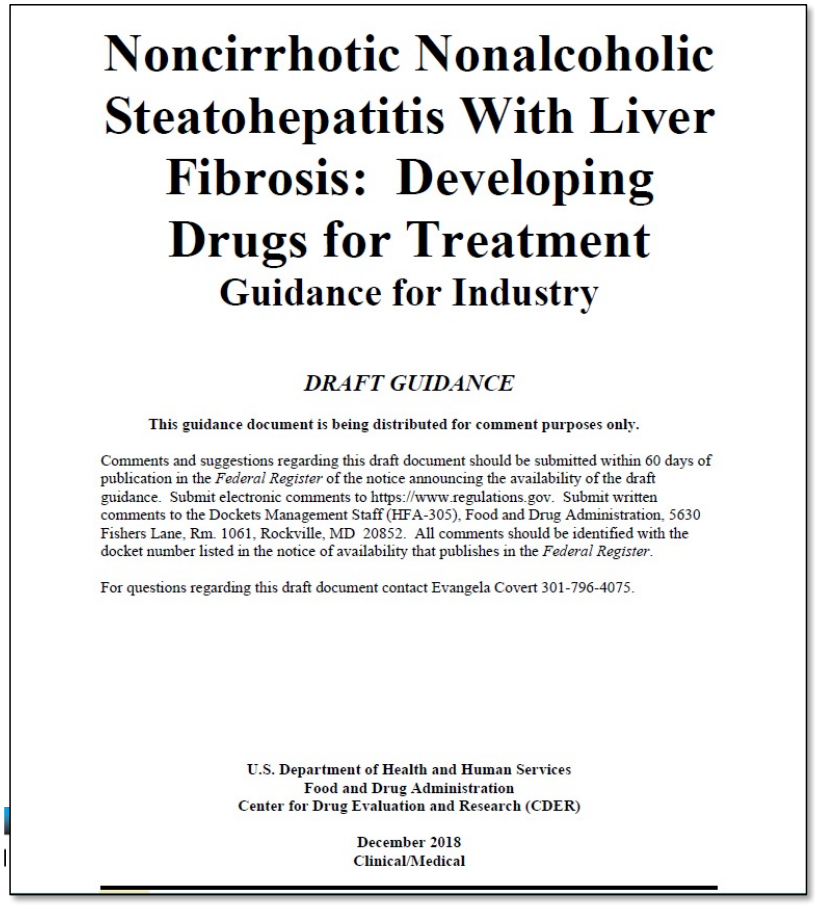
Disclosures

Employee of Astra Zeneca

NIMBLE goals align with FDA guidance on biomarker qualification and needs in NASH



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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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"

BEST Definitions

FDA-NIH Biomarker Working Group BEST (Biomarkers, EndpointS, and other Tools) Resource[1]

- ***Biomarker***: "A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention"[1]
- ***Contexts of Use:*** Diagnostic, monitoring, response, predictive, prognostic, safety, ***surrogate***[1]
- ***Diagnostic Biomarker***: "A diagnostic biomarker detects or confirms the presence of a disease or condition of interest, or identifies an individual with a subtype of the disease"[1]

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[1]*Califf RM. Experimental Biology and Medicine 2018; 243: 213–221*

NIMBLE Circulating Biomarker Context of Use per accepted LOI

In patients with NAFLD, to ***diagnose***:

- those with NASH and high activity (NAS ≥ 4)
- those with clinically significant fibrosis (fibrosis stage 2 or higher)
- those with “at-risk” NASH (steatohepatitis + NAFLD activity score ≥ 4 + fibrosis stage ≥ 2)
- those with advanced fibrosis (fibrosis stage 3 or 4)
- those with cirrhosis (stage 4)

FNIH NIMBLE Stage 1

Collaboration between NIMBLE and NIDDK NASH Clinical Research Network

AIM: To perform a comparative assessment against histology of the performance of 5 blood-based biomarker panels selected by the NIMBLE team for their respective intended uses, by rigorously establishing the sensitivity/specificity at the Youden's cutoff in a cross-sectional analysis of a large multi-center US cohort of patients with NAFLD/NASH

Primary hypothesis: The biomarkers selected will have a diagnostic accuracy, as defined by an AUROC of 0.7 or higher and be significantly superior to an AUROC of 0.5 for their specific "fit for purpose" use (diagnosis of NASH, NAS, fibrosis stage etc.). Sensitivity. Specificity, Predictive values and Youden index to be computed.

Secondary hypothesis: Biomarkers for NASH and NAS will be superior to ALT and biomarkers for fibrosis will be superior to FIB-4

DESIGN:

- All tests run on different aliquots of the same blood sample obtained within 90 days of a liver biopsy
- All biopsies read by the NASH CRN pathology committee using a pre-specified protocol and masked to any clinical data

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Biomarker Panel Evaluation for Specific Intended Use

Panels were selected based on prior rigorous analytical validation and promising clinical data

	NASH	NAS ≥ 4	Clinically significant fibrosis (stage ≥ 2)	Advanced fibrosis (stage 3-4)	Cirrhosis	At risk NASH
NIS-4	+	+	+	+	+	+
ELF test			+	+	+	+
Fibrometer-VCTE			+	+	+	+
PRO-C3			+	+	+	+
OWL panel	+	+				

Non-invasive Score-4/NIS-4 (GENFIT SA): mir34a + alpha2 macroglobulin + HBA1c + YKL40- ***score 0-1***
Extended Liver Fibrosis/ELF test (Siemens): hyaluronic acid + procollagen 3 n terminal peptide + TIMP1- ***numerical score***
Fibrometer-VCTE (Echosens): platelets +AST +ALT + ferritin + glucose + alpha2 macroglobulin- ***score 0-1***
Procollagen-3/PRO-C3 (Nordic Biosciences): collagen fragments – ***score µg/ml***
One-Way Liver (OWL Metabolomics): 16 lipids- ***probability score or yes/no score***

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Primary Results of the FNIH NIMBLE Stage 1-NASH CRN Study of Circulating Biomarkers for Non-Alcoholic Steatohepatitis (NASH) and its Activity and Fibrosis Stages

UNMET NEED: Gaps in extant literature on noninvasive tests (NITs) for NASH are currently a barrier to their development as diagnostic and prognostic tools.

HYPOTHESES: (1) Biomarker AUROC at least 0.7 and superior to unit line, and (2) superior to ALT for diagnosis of NASH or disease activity, and FIB4 for fibrosis.

MAIN FINDINGS: Multiple biomarkers met criteria for success in diagnosis of NASH, high NAS, fibrosis stages ≥ 2, ≥ 3, 4 and diagnosis of "at risk" NASH (NASH + NAS ≥4 + fibrosis stage ≥ 2.

CONCLUSIONS:

- Data from Stage 1 of NIMBLE, provide robust sensitivity and specificity metrics for various intended use for selected biomarkers

AT RISK NASH	NIS-4	FIB-4
AUROC	0.81*^	0.72*

AT RISK NASH	SENSITIVITY	SPECIFICITY
OWL	63.3	75.4

FIBROSIS stage diagnosis	≥ STAGE 2	≥ STAGE 3	CIRRHOSIS
FIB-4	0.80*	0.79*	0.81*
ELF Test	0.82*^	0.83*^	0.85*^
Pro-C3	0.80*	0.76*	0.72*
Fibrometer-VCTE	0.84*^	0.86*^	0.90*^

AUROC rounded off to 2 decimals
**p significantly superior (<0.05) to AUROC of 0.5*
^p for AUROC significantly superior (<0.05) to AUROC for FIB4

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Summary

- **NIS-4** met *a priori* criteria for:
  - Diagnosis of NASH
  - Diagnosis of NAS ≥ 4
  - Fibrosis stage 2 or higher
- **ELF Test** and **Fibrometer-VCTE** met *a priori* criteria for:
  - Clinically significant fibrosis (≥ stage 2)
  - Advanced fibrosis (stage 3 or 4)
  - Cirrhosis (stage 4)
- **PRO-C3** superior to unit line but not superior to FIB-4 for fibrosis endpoints
- **OWL** able to identify "at risk" NASH with sensitivity of 63.3% and specificity of 75.4%
- **FIB-4** had robust diagnostic characteristics for fibrosis endpoints
- Data from NIMBLE Stage 1 met prespecified Go-No-Go criteria for initiation of Stage 2 (*prospective interventional paradigm)*

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Multifold Impact for Patient Benefit

	CURRENT UNMET NEED	NIMBLE-BASED SOLUTION
Clinical Care	No reliable non-invasive tool for diagnosis, disease staging	Soluble biomarkers for diagnosis and disease staging
Drug Development	Diagnostic tools for population enrichment, reducing on-study biopsy procedures	***Reliable soluble biomarkers*** 1. Population enrichment 2. Resource-sparing strategy 3. Enhanced clinical trial efficiency 4. Getting new drugs to patients faster
Scientific Contributions	Standardized yet novel paradigms for NAFLD biomarker development	Novel reliable yet feasible paradigms for NAFLD biomarker identification and development

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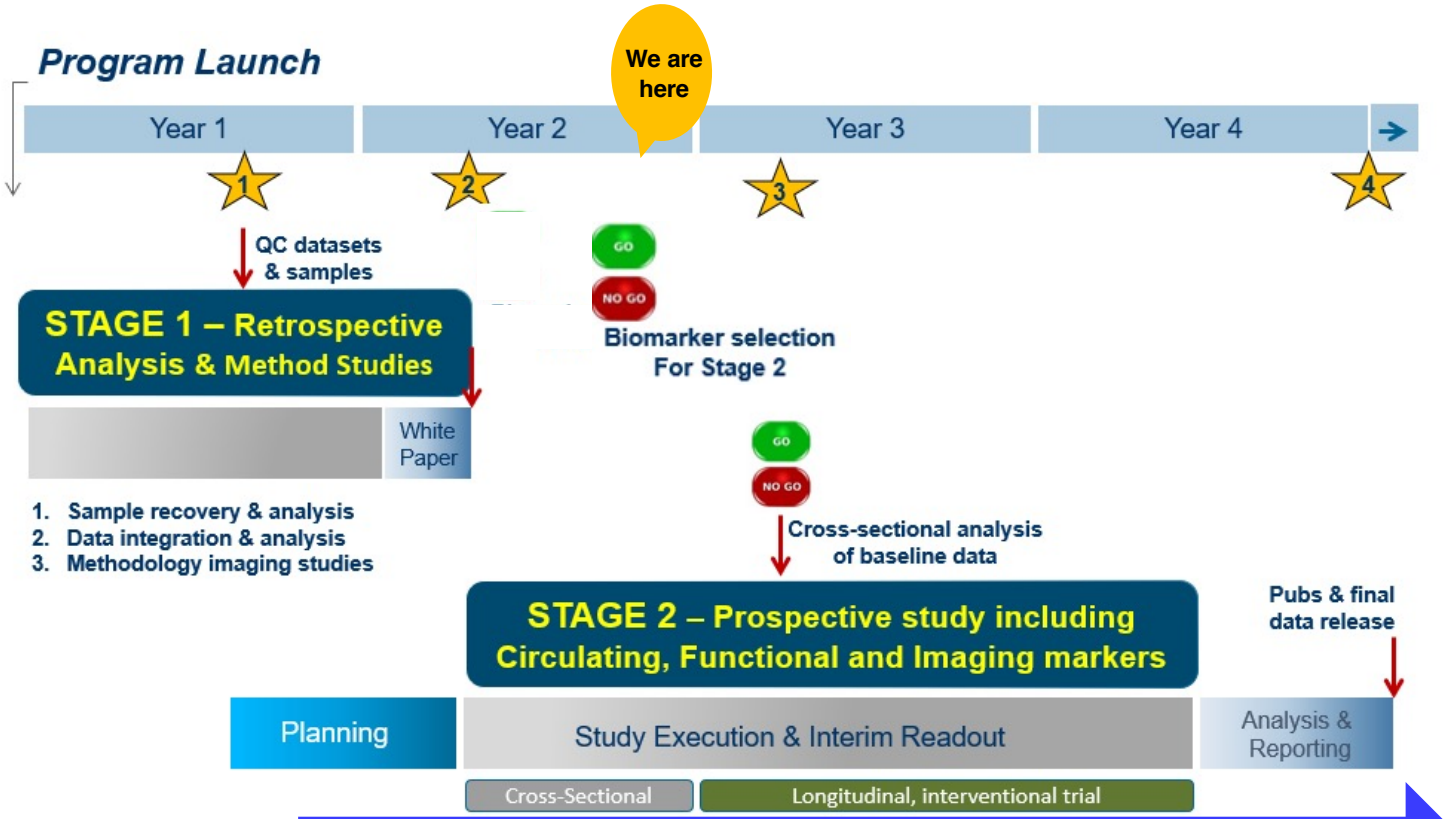
NIMBLE Approved Project Plan



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ALL THE PATIENTS WHO PROVIDED THEIR TIME, BLOOD AND LIVER TISSUE FOR THE ADVANCEMENT OF SCIENCE

NASH CRN:

Clinical Site Investigators: Anna Mae Diehl (Duke), Manal Abdelmalek (Duke), Mohammad Siddiqui (VCU), Velimir Luketic (VCU), Srinivasan Dasarathy (CCF), Arthur McCullough (CCF), Naga Chalasani (IU), Norah Terrault (USC), Bilal Hameed (UCSF)

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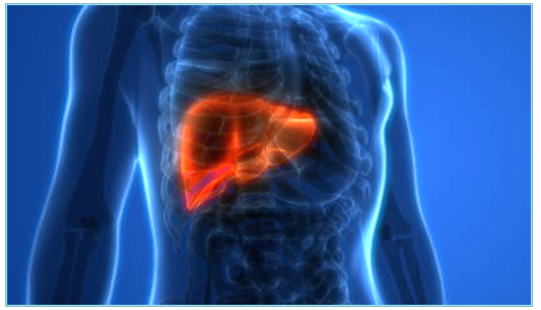
NIDDK: Jay Hoofnagle, Edward Doo, Averell Sherker



NIMBLE Team:

FNIH: Joseph Menetski, Steve Hoffman, Tania Kamphaus, Helen Heymann, Biomarkers Consortium Metabolic Disorders Steering Committee and all FNIH Biomarkers Consortium staff supporting NIMBLE

Project Team: AbbVie, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Echosens, GE Healthcare, Genentech, Inc., Gilead Sciences, Inc., Intercept Pharmaceuticals, Inc., Novo Nordisk A/S, Pfizer Inc, Takeda Development Center Americas Inc.

Key Lab collaborators: Genfit SA, Siemens Healthineers, One-Way Lipidomics, Nordic Biosciences, Echosens

U.S. FDA: Regulatory guidance and feedback through Biomarker Qualification Program

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