Non-Invasive Biomarkers of Metabolic Liver DiseasE
NIMBLE: Stage 2.0 - Research Design

FNIH Foundation for the National Institutes of Health

BIOMARKERS CONSORTIUM
IMPROVING HEALTH THROUGH MEANINGFUL MEASUREMENTS

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BACKGROUND

- Alternative biomarkers are needed to replace liver biopsy for diagnosis and staging of MASH with fibrosis, which affects 30% of the population.
- Liver biopsy is the reference standard for MASH risk assessment but is invasive, variable, and carries procedural risk.
- The NIMBLE project was commissioned by the Biomarkers Consortium of the FNIH to qualify non-invasive tests (NITs) for MASH. It represents a collaborative effort involving the FNIH, Food and Drug Administration, academic, industry partners, and patient advocates.
- The NIMBLE project plan was designed to occur across two stages, generating data on NITs to support seeking regulatory qualification of one or more biomarker(s) for **the diagnostic enrichment of MASH**.

PRIMARY OBJECTIVES

1. Detection of At-Risk MASH: Evaluate the diagnostic performance of individual and combined biomarkers for identifying at-risk MASH (MASLD + NAS ≥4 + fibrosis stage ≥2).

2. Fibrosis Staging: Assess blood-based, imaging, and composite biomarkers for detecting clinically significant fibrosis (≥2), advanced fibrosis (≥3), and fibrosis stage 4 (cirrhosis, histologically defined).

3. Liver Fat Content Assessment: Evaluate imaging-based biomarkers by assessing hepatic steatosis.

4. Diagnostic Enrichment: Identify biomarkers that enhance participant selection for clinical trials, focusing on populations with at-risk MASH, specific fibrosis stages, or steatosis**.**

5. Exploratory Biomarkers: Investigate exploratory biomarkers (e.g., AI-based histological scoring or quantitative characterization, sequential testing strategies) for novel diagnostic workflows.

STUDY DESIGN, POPULATION, AND PROCEDURES

Study Overview

- **Design.** Prospective, multicenter, observational, cross-sectional.
- **Sites.** ERG-managed clinical network; 4 sites across the USA (San Antonio, TX; Houston, TX; Miami, FL; Columbus, OH).
- **Target enrollment.** >400 participants; >1600 screened.
- **Study duration per participant.** ~21 weeks

Key Inclusion and Exclusion Criteria

- **Adults aged 18–74 years**, male or female.
- **Evidence of metabolic dysregulation**, defined as **either**: type 2 diabetes or at least 2 metabolic risk factors.
- **Evidence of increased fibrosis risk**, defined by **FIB-4 >1.3** (age <65 years) or **>2.0** (age ≥65 years).
- **Stable medication regimen** for at least **3–6 months** prior to screening (depending on therapy), with no recent changes expected to affect liver fat, inflammation, or fibrosis.
- An Alcohol Use Disorders Identification Test (**AUDIT**) score of 7 or higher and / or a **PEth test** score of ≥ 20ng/ml.

METABOLIC SYNDROME CRITERIA
- Waist circumference / obesity
- BMI / weight
- Triglycerides
- HDL cholesterol
- Blood pressure
- Fasting glucose / diabetes

Study Visit Schedule

SCREENING PART 1
Phone Screen (No >1600 Participants)
- Demographics
- Medical History (MetS, T2DM, dyslipidemia, phenotypic risk for MAFLD).

SCREENING PART 2
In-Person Visit (No >450 Participants)
-28 to Day -1
- Informed Consent
- Anthropometry
- Demographics
- Medical History
- Vital Signs
- Physical Exam
- Lab Tests (to confirm eligibility)

VISIT 2
Days 1-89
Procedures may occur on one or more days.
- Sampling for blood-based biomarkers
- FibroScan
- Ultrasound and MR imaging procedures

VISIT 3
After Visit 2 up to Day 90
- Liver Biopsy

VISIT 4
After Visit 3 up to Day 121
- Abbreviated physical exam
- Subject counseling on findings

BIOMARKERS

BLOOD-BASED BIOMARKERS
- ELF (Siemens)
- NIS2+ (Labcorp, GenFit)
- ADAPT, PRO-C3, PRO-C6 (Nordic Biosciences)
- OWLiver Test (Rubio Metabolomics)

IMAGING-BASED BIOMARKERS
- LSM by VCTE, CAP, ADAPT*, AGILE3+*, AGILE4* (Echosens)
- Liver and Spleen Volume, MRI-PDFF, 2D- & 3D-MRE Ultrasound SWE, Fat Quantification^
- *Hybrid Biomarkers
- ^Through collaboration with Antaros, Resoundant, and Calimetrix.

AI-POWERED DIGITAL PATHOLOGY BIOMARKERS
- LiverExplore‡ quantitative histology features (PathAI)
- qFibrosis (HistoIndex)

HISTOPATHOLOGY
- Manual Pathology performed by 3 independent pathologists

‡For Research Use Only. Not for use in diagnostic procedures.

STATISTICAL APPROACH

For advanced biomarkers, test if specificity is >0.75 and sensitivity is >0.60 using pre-defined cutpoints (one-tailed tests, each @ 0.025), assuming 30% baseline prevalence. Biopsy will serve as the reference standard. This aligns with reducing the screen failure rate to <50% (PPV≥50%).

For each of the biomarkers, or combination of biomarkers, test if the area under the ROC curve >0.7 for discriminating MASH vs non-MASH, MASH and MAS≥4 and F≥2 vs other, MAS≥4 vs MAS<4, F≥2 vs F<2, F≥3 vs F<3, F=4 vs F<4, and S≥1 vs S0 (one-tailed tests @ 0.025).

Estimate sensitivity and specificity of biomarkers, along with their 95% CIs, using pre-defined cutpoints, as well as derived best-fit cutpoints.

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EXPECTED IMPACT

MASH-TAG CONFERENCE 2026

NIMBLE 2.0 will generate the data to support **approved** letters of intent (LOI; DDT000084, DDT000112) for **qualification of noninvasive biomarkers** as diagnostic enrichment for MASH.

Biomarker qualification will rapidly **accelerate therapeutic development** in MASH, by **reducing diagnostic failures** and **screen failure rates** based on liver biopsy-based histology.

This will substantially **reduce the number of participants** undergoing unnecessary liver biopsies, **improving morbidity and mortality risk** for patients / study participants and **reducing** clinical and clinical research **resource investment**.

NIMBLE 2.0 Webpage