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Non-Invasive Biomarkers of Nonalcoholic Steatohepatitis: the FNIH NIMBLE project

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Author contributions

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Competing interests

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To the Editor

Nonalcoholic fatty liver disease (NAFLD) affects approximately one-quarter of the global adult population[1]. A subset of affected individuals worldwide have nonalcoholic steatohepatitis (NASH), a more progressive form of the disease that has a higher risk of advancing to cirrhosis and end-stage liver disease (ESLD). Given the enormous number of afflicted patients, identification of the subset at risk of disease progression is critically important for efficient therapy allocation.

NASH patients with fibrosis stage 2 or higher have elevated all-cause and liver-related mortality[2], and those with high disease activity scores are at greater risk of fibrosis progression[3]. These at-risk NASH patients are the target population for therapeutic intervention beyond lifestyle improvement. Histopathological assessment is the current reference standard for diagnosis, risk stratification and therapeutic efficacy evaluation for NAFLD. Unfortunately, liver biopsy for histological assessment carries risks, including even rare mortality. Histopathological assessment is also susceptible to sampling error and intra- and inter-reader variability. These drawbacks of liver biopsy have limited biopsy-based assessment in routine practice and pose challenges in clinical trial design and interpretation. There is therefore a need for reliable non-invasive tools for the diagnosis, risk stratification and monitoring of the course of NAFLD.

The integration of non-invasive tools into routine practice and in trial design requires both acceptance by the scientific community and, ideally, regulatory endorsement. The latter is particularly relevant to the use of non-invasive tools for defining trial populations and monitoring the course of disease with or without therapeutic intervention. An important approval pathway for non-invasive tools by the US Food and Drug Administration (FDA) is the Biomarker Qualification Program (BQP)[4], which allows multiple stakeholders to come together to establish the utility of a non-invasive tool for its specific intended use. Substantial resources are needed for planning, data acquisition and analysis to meet the evidentiary burden for a full qualification package. This often requires a collaborative approach, and the likelihood of success can be maximized by pooling resources and expertise in a multi-stakeholder public–private partnership[4].

The NIMBLE (Non-invasive Biomarkers of Metabolic Liver Disease) consortium is a comprehensive, multi-year, pre-competitive public–private partnership collaboration conducted under the auspices of the Foundation for the NIH (FNIH) Biomarkers

Consortium. The Biomarkers Consortium brings together partners from academia, industry, regulatory bodies and nonprofit organizations to identify, develop and qualify potential biomarkers to improve drug development and regulatory decision-making[5]. The Metabolic Disorders Steering Committee and the Biomarker Consortium Executive Committee provide oversight for NIMBLE. NIMBLE is led by academic and industry co-chairs for the entire project and has two workstreams, for circulating biomarkers and for imaging biomarkers. NIMBLE is supported by a project team whose membership includes researchers from academia and industry and designated members from the FDA, who advise on project strategy without participating in the approval process for non-invasive tools. A central goal of NIMBLE is to systematically address and eliminate gaps in the existing scientific literature, thereby advancing FDA BQP qualification of one or more biomarkers for diagnosis and disease monitoring.

NIMBLE is structured as a two-stage project (Fig. 1). In stage 1, which is currently underway, the circulating biomarkers workstream will evaluate select biomarker panels for their ability to diagnose NASH and its activity, fibrosis stage or the presence of at-risk NASH (a composite including the presence of NASH with a NAFLD activity score of 4 or higher and fibrosis stage 2 or higher). The circulating workstream will evaluate the following biomarker panels for their specific intended use: NIS4 (Genfit) for at-risk NASH; OWLiver (one-way lipidomics) for diagnosis of NASH and for high disease activity (NAFLD activity score ≥ 4); PROC3 (Nordic Biosciences); the enhanced liver fibrosis (ELF) test (Siemens); and the FibroMeter test (Echosens) for fibrosis stages. For assessment of fibrosis, the ability to identify stage 2 or higher fibrosis, advanced fibrosis (stages 3 + 4) or cirrhosis (stage 4) will be evaluated. Work for the stage 1 circulating biomarkers workstream for blood-based biomarker panels is being conducted in collaboration with the NIDDK NASH Clinical Research Network and will simultaneously evaluate the performance of biomarker panels in the same serum sample. Samples are obtained within 90 days of a liver biopsy demonstrating NAFLD, in a cohort of appropriate size, with the full spectrum of disease.

In stage 1, the imaging biomarkers workstream will also fill important knowledge gaps by characterizing the test–retest repeatability and reproducibility of the leading imaging biomarkers across vendor platforms and across the spectrum of disease severity. Tests include ultrasound-based elastography measurements, magnetic resonance (MR)-based elastography measurements and MR-based measurements of liver fat content[6,7]. The imaging biomarkers workstream effort incorporates and builds upon rigorous methods developed by the Radiological Society of North America Quantitative Imaging Biomarker Alliance to collect technical performance data on the selected imaging biomarkers.

The first step in biomarker qualification via the FDA's BQP is the approval of a letter of intent describing the specific non-invasive tools proposed and their intended context of use. This letter of intent process provides a road map for subsequent biomarker qualification. Letters of intent for the circulating[8] and imaging[9] biomarkers have already been accepted by the FDA biomarker qualification program.

Based on the overall evidence from stage 1, a select group of non-invasive tools whose performance characteristics meet approved prespecified criteria will be advanced for further testing in stage 2 in patients with clinical risk factors for at-risk NASH in specific intended use populations. These criteria include the ability of selected biomarkers to outperform the alanine transaminase (ALT) level for the diagnosis of NASH and the fibrosis-4 (FIB4) score for assessment of fibrosis severity. Further, additional contexts of use may be included in stage 2, such as measurement of fibrogenesis and other dynamic measures of treatment response that can only be assessed prospectively. These studies and data will be part of the biomarker qualification plan for disease monitoring contexts of use and will also further support the qualification of non-invasive tests for diagnostic contexts of use.

It is critically important that data for biomarker qualification studies meet the highest standards for rigor and transparency of reporting. NIMBLE activities are governed by pre-established FNIH data sharing and conflict of interest policies. Furthermore, NIMBLE has established rigorous protocols and policies governing the chain of custody of both samples and data so that individual commercial entities that own biomarker technologies are appropriately firewalled from the data analyses and interpretation process. Data analyses are performed by an independent statistics center following stringent processes to maintain data integrity. Standards set by the FNIH Biomarkers Consortium mandate that data will be shared within the project team and results disseminated via peer-reviewed literature, or other data sharing mechanisms as determined by the project team and the FNIH.

The NIMBLE paradigm aims to qualify one or more non-invasive tools, singly or in combination, for NASH with increasing fibrosis, to allow the identification of patients who should be prioritized for therapeutic intervention and for the monitoring of treatment responses. These tools will facilitate selection of the right patients for clinical trials and increase identification of at-risk NASH and access to care in the clinical setting.

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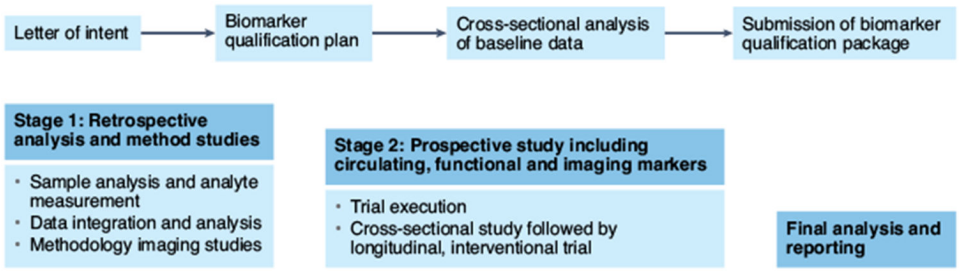

Fig. 1 |. The FNIH NIMBLE project plan.

The biomarker qualification process was initiated by approval of the letter of intent submitted by the NIMBLE consortium to the FDA. This will be complemented by cross-sectional studies of circulating biomarkers and methodological studies of MRI and ultrasound-based biomarkers in stage 1. After completion of stage 1, a full biomarker qualification plan will be submitted for review by the FDA. The results of stage 1 will also trigger stage 2, which will include a prospective evaluation of selected biomarkers for final and full qualification combining data from both stage 1 and stage 2.