Liver Forum- FNIH Collaborations

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LIVER FORUM

Development of Non-invasive Biomarkers for Non-alcoholic Steatohepatitis (NASH)/Non-alcoholic Fatty Liver Disease (NAFLD)

FNIH Biomarkers Consortium

A Public-Private Partnership

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FNIH
Foundation for the National Institutes of Health

THE biomarkers CONSORTIUM

FNIH Biomarkers Consortium is well prepared to take on this project

Specific aspects that increase likelihood of success

- **Scientific Leadership**:
  - Multidisciplinary
  - Clinical-technical-analytic-strategic expertise
- **Industry partners and their deep level of engagement**
- **Regulatory science- FDA and Liver Forum (includes EMA)**
- **Work plan development**:
  - Multiple weekly teleconferences
  - Face-to-Face meetings and workshop
  - Engagement with FDA, NIDDK, Liver Forum, QIBA
  - Identification and inclusion of growing number of industry partners

Work plans

The FNIH works closely with FDA to ensure that study design and endpoints meet requirements for biomarker qualification

- **Phase 1: Establish infrastructure:**
  - establish collaborative partnerships
  - make sure working groups have the right mix of scientific expertise
  - complete literature analysis to determine short list of candidates for further validation
- **Phase 2: Retrospective-prospective validation studies:**
  - develop and complete standardization of methods that can be translated in to routine practice
  - analysis of existing data sets of cross-sectional and longitudinal cohorts with associated samples
- **Phase 3: Prospective cross-sectional validation:**
  - Study design to be finalized in phase 2 and samples collected prospectively with all of the data elements needed for biomarker qualification
- **Phase 4: FUTURE longitudinal validation studies** (outside of initial project scope)

Approach

Substantial progress in establishing the infrastructure for the studies has already been made

- Initial formation of working groups
- Identification of priorities in biomarker development
- Focusing the question
- Review of literature
- Identification of biomarkers with sufficiently mature science to support qualification studies
- Initial identification of potential cohorts and existing sample sets for retrospective and prospective cross-sectional analyses.
- Initial identification of partners to provide access to such cohorts or to provide technologies needed to perform the studies
- Integrated approach to circulating and imaging markers aiming to generate a quality data package suitable for biomarker qualification in proper context of use (keep regulatory requirements for biomarker qualification in mind as a guide)

Retrospective analysis of samples and prospective cross sectional validation study

- **RETROSPECTIVE ANALYSIS OF EXISTING DATA SETS**
  - Literature review and meta-analysis (where possible)
  - Selection of lead candidates
  - Establishing standards for sample collection, analysis, interpretation and reporting
  - Establishing collaborations to gain access to existing sample sets

- **PROSPECTIVE ANALYSIS OF A SELECT CONFIRMATORY DATA SET**
  - Validation of select candidate-biomarkers in retrospective sample set
  - Identification of biomarker candidates for prospective cross sectional study
  - Advancing collaboration and design of a prospective cross sectional study
  - Execute cross sectional study for circulating and imaging biomarkers informed by retrospective analyses and anchored on present (however imperfect) “gold-standard” of liver biopsy
  - Development of algorithms to aid in clinical diagnosis and optimize use of biomarkers
  - Seamless integration with longitudinal assessments also likely

Quantitative Biomarkers

Benchmarks for selecting biomarkers:

- **Complementarity** – address a range of histologic abnormalities relevant to NASH
- Biological **plausibility**
- Can be measured using **standardized methodology**
- Can be reported using **standardized terminology**
- Demonstrated **feasibility** in clinical trials

Gaps in qualification remain, which this proposal addresses (subproject I and II)

Critical Steps in qualification of circulating biomarkers

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

- Methodological issues (to be standardized by working group with the appropriate breadth and depth of expertise):
  - sample collection
  - storage and transport
  - analysis
  - quantification and internal/external controls
  - data reporting
- Study Design (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

    assessment of disease activity

Quantitative biomarkers for Imaging

1. Identify key gaps for each candidate biomarker's qualification with respect to

- **Accuracy**
  - for diagnosing NAFLD, NASH, advanced fibrosis
  - for predicting and monitoring treatment response
- **Measurement precision**
  - Repeatability
  - Reproducibility across key conditions
- **Temporal and physiological variability**
- **Complementarity with other data**

2. Design and conduct efficient studies to address key gaps

Deliverables

- **Key data on biomarkers to support a non-invasive case definition** for subject inclusion in clinical trials for 2 populations:
  - NASH with NAS ≥ 4 and fibrosis stage 2-3
  - Cirrhosis due to NASH
- **Algorithm** incorporating clinical aids, circulating biomarkers and imaging to provide a known disease classification performance at each sequential testing stage.
- **Key data towards biomarker qualification**
- **Key data for imaging to assess suitability for large scale application** (to inform future project 2)
- Data to be rigorously reviewed and disseminated through **peer-reviewed publications and white papers**
- Data to be made available in publically-accessible forum

Metrics of Success

Metrics Measurable in Real Time

- Achievement of the project specific aims
- Generation and publication of scientific findings
- Incorporation of the qualified biomarkers in clinical trials

Long Term Impact – Difficult to Measure in Real Time

- Incorporation into clinical trials as an eligibility criterion and as an endpoint- collaboration with Liver Forum
- Incorporation in clinical practice- practice guidelines