Need for Biomarker Development in Non-Alcoholic Fatty Liver Disease

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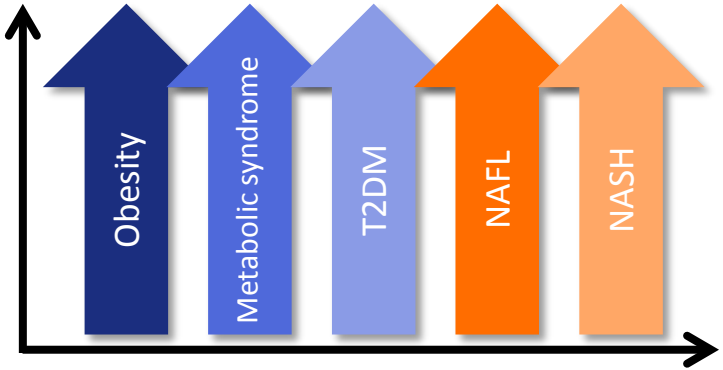
Disclosure

- Éric Lefebvre is an employee of Tobira Therapeutics, Inc.

Background

Prevalence of obesity, metabolic syndrome, and T2DM is **increasing rapidly**…



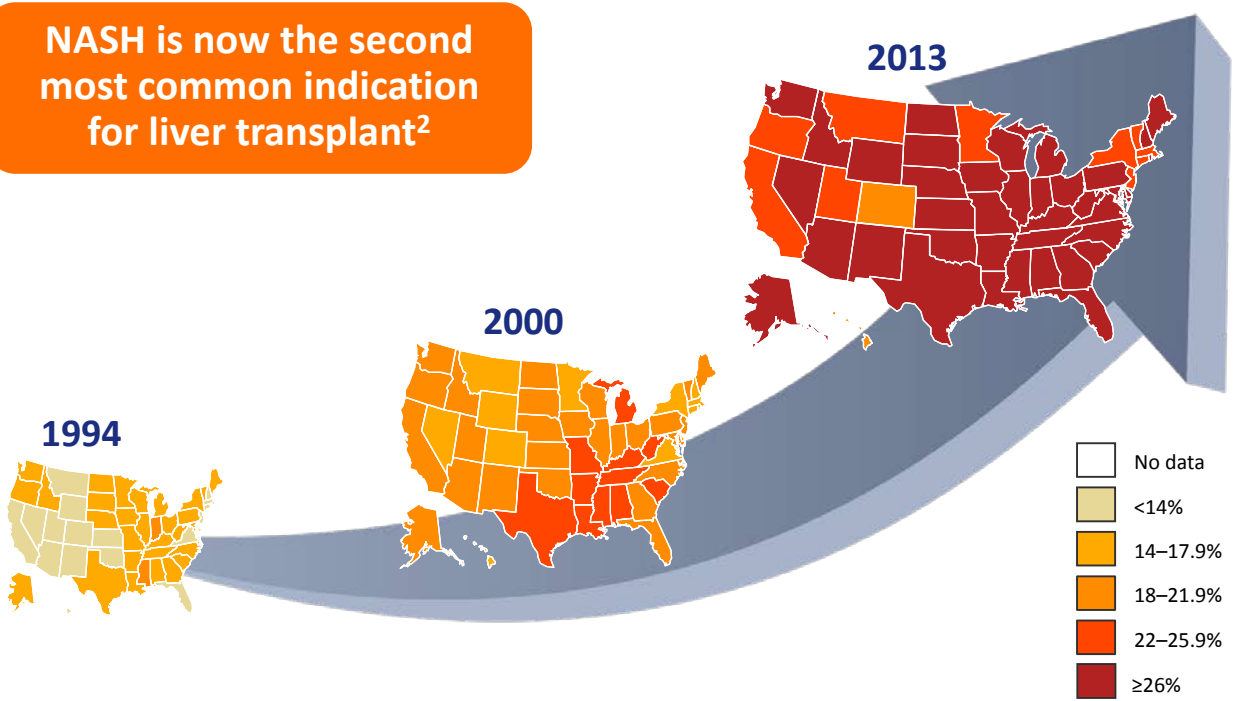
…**and is directly linked** to **NAFL** and **NASH**

- The definitive diagnosis of NASH currently relies on a **liver biopsy**, which is **not recommended** for routine screening

Non-invasive tools are urgently needed to identify patients with NAFLD and to determine which ones will require a liver biopsy

Obesity is Rapidly Increasing Among US Adults[1]

NASH is now the second most common indication for liver transplant[2]



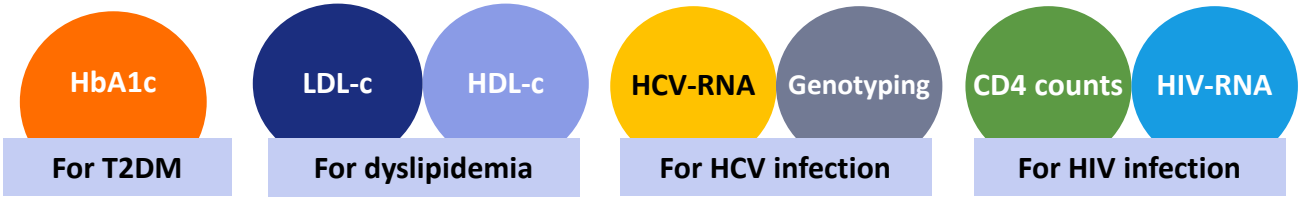
1. CDC, Behavioral Risk Factor Surveillance System (*BMI ≥30 kg/m², or about 30 lbs. overweight for 5'4" person*); 2. Wong *et al.* 2015

Biomarkers to Foster Clinical Development

- A biomarker is defined as:

> *"a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"*[1]

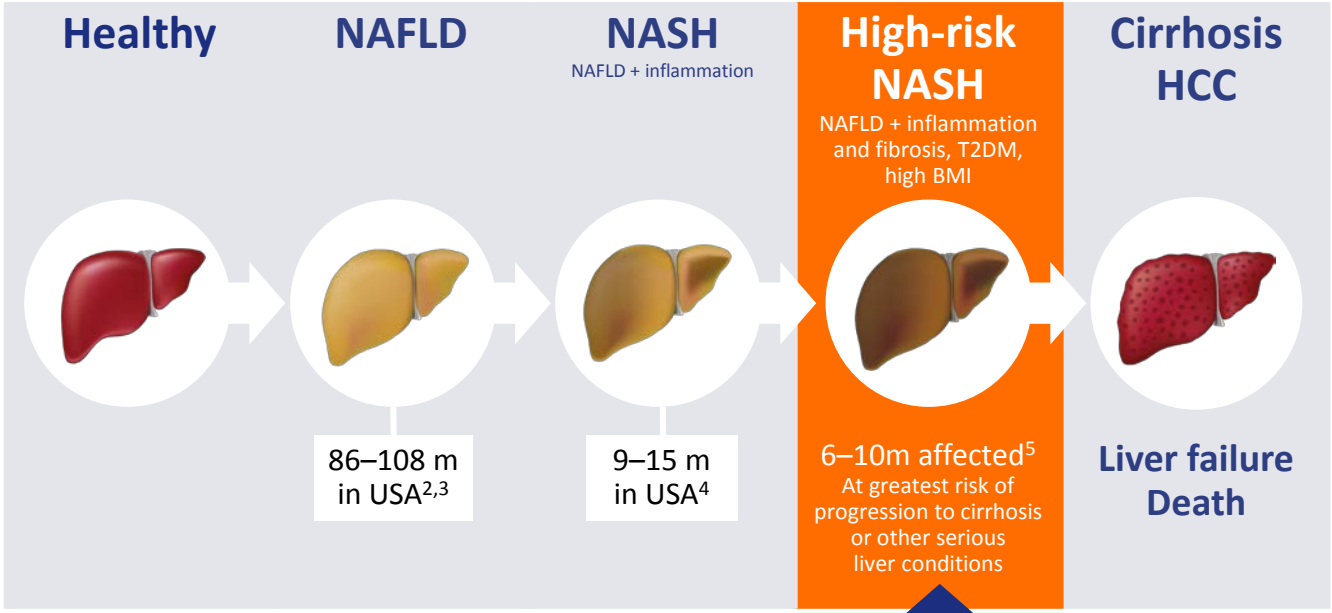
- Significant advances in biomarker development have improved the diagnosis and clinical management of life-threatening diseases



Validated NALFD biomarkers are needed to identify 'at-risk' patients and to evaluate new NASH therapies in randomized clinical trials

1 NIH Definitions Working Group. Biomarkers and Surrogate Endpoints. 2001

NASH: Severe, Progressive Form of Fatty Liver Disease[1]

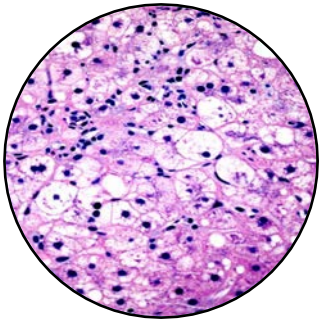


1. Matteoni *et al.* 1999; 2. Wree *et al. 2013*; 3. Vernon *et al.* 2011; 4. Schattenberg *et al.* 2011;
5. Angulo *et al. 1*999; 6. Friedman *et al.* 2016; 7. NCT02548351; 8. NCT02704403

Liver Biopsy: The Imperfect 'Gold-Standard'

Sampling error

Inter-operator variability



Low patient acceptance

High costs

Multiple staging systems

Procedural risks

Long intervals between serial biopsies
to monitor disease progression,
in practice and in clinical trials

Simply not practical or feasible in clinical practice at a global scale

Clinical Need for Biomarkers

Identification of patients with NAFLD

Distinction between steatosis (NAFL) and steatohepatitis (NASH)

Discrimination between stages of liver fibrosis

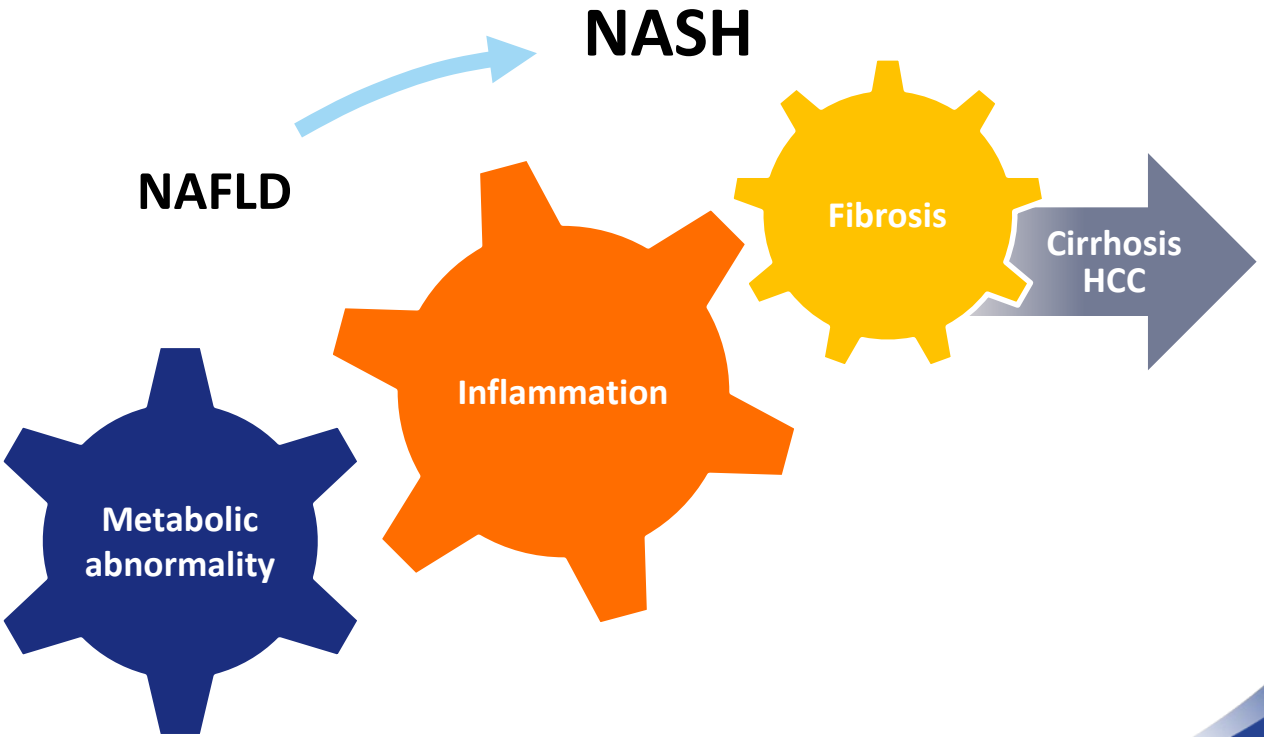
Sensitivity to change (progression + regression) and treatment effects

Correlation with clinical outcomes, including cirrhosis, CVD and cancer

Criteria for an Ideal Biomarker

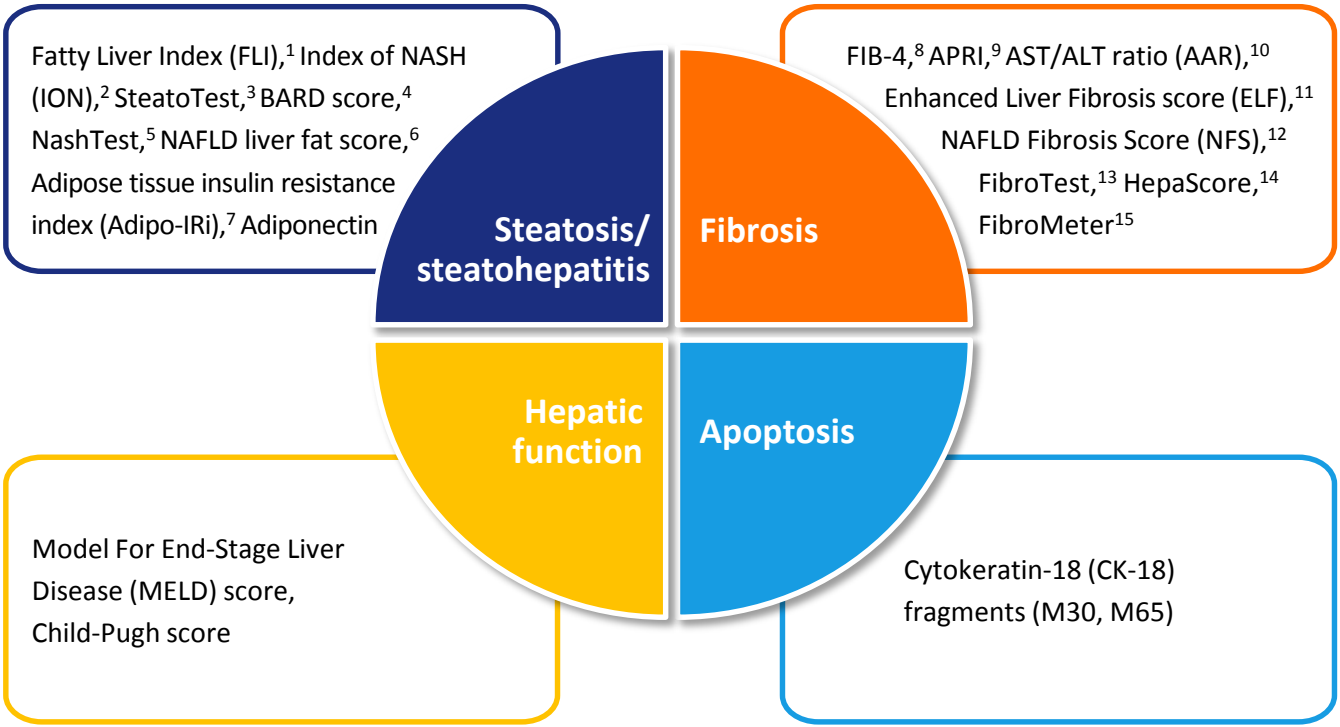
- Biologically plausible, accurate and reproducible
- Rapid, inexpensive, non-invasive, readily available
- Suitable for screening, diagnosis and monitoring
- Correlates with disease activity and fibrosis stage
- Capable of detecting treatment effects
- Predictive of clinical outcomes

The Molecular Engines that Drive NASH



Adapted from Arun Sanyal, NASH Symposium Paris June 2015

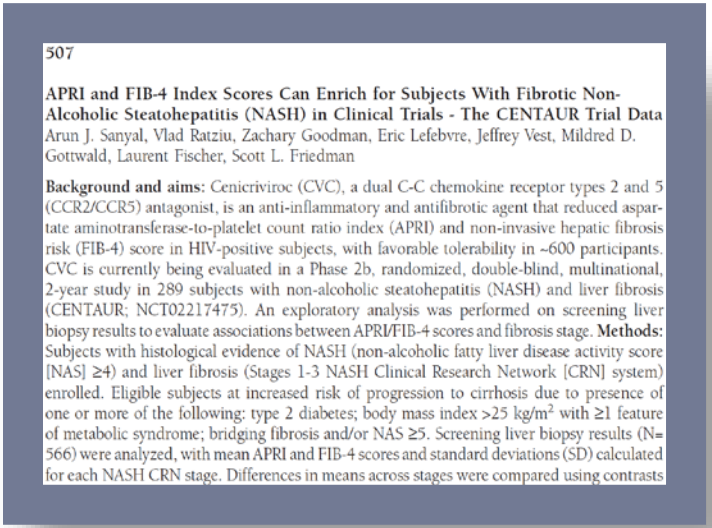
Currently Available Biomarkers



1. Bedogni *et al*. 2006; 2. Otgonsuren *et al.* 2014; 3. Poynard *et al.* 2005; 4. Harrison *et al.* 2008;
5. Poynard *et al.* 2006; 6. Kotronen *et al.* 2009; 7. Lomonaco *et al.* 2012; 8. Vallet-Prichard *et al.* 2007;
9. Wai *et al.* 2003; 10. Haukeland *et al.* 2008; 11. Guha *et al.* 2008; 12. Angulo *et al.* 2007;
13. Poynard *et al*. 2012; 14. Lackner *et al.* 2005; 15. Calès *et al.* 2010

Biomarkers to Enrich Trials for 'High-Risk' Patients

- High positive predictive values of APRI and FIB-4 in CENTAUR suggest that validated scores can aid in the selection of adults with fibrotic NASH and may be used to enrich studies while reducing the number of screening liver biopsies[1]



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APRI and FIB-4 Index Scores Can Enrich for Subjects With Fibrotic Non-Alcoholic Steatohepatitis (NASH) in Clinical Trials - The CENTAUR Trial Data

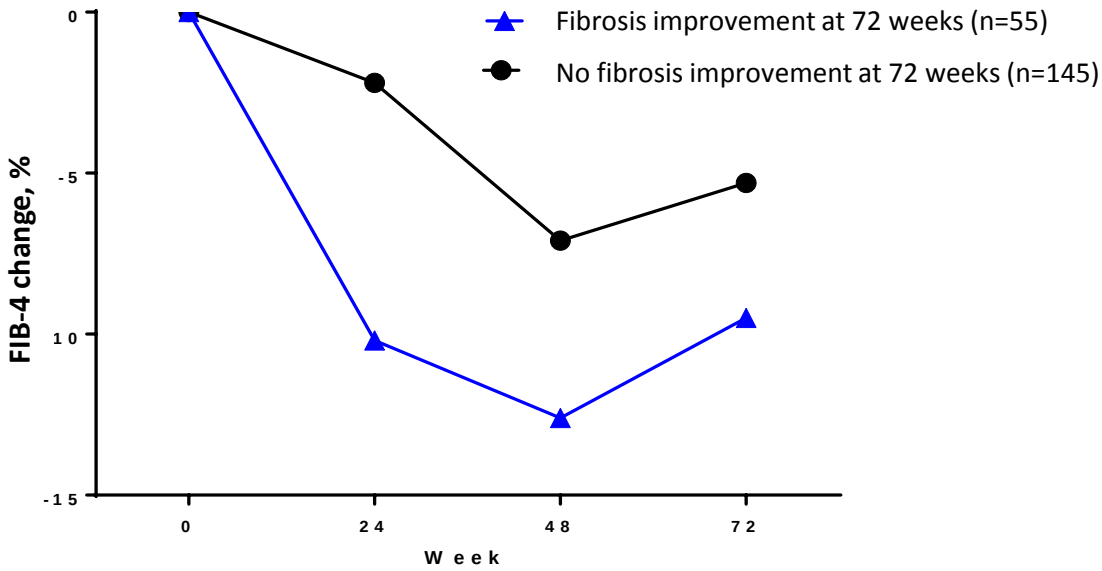
Arun J. Sanyal, Vlad Ratziu, Zachary Goodman, Eric Lefebvre, Jeffrey Vest, Mildred D. Gottwald, Laurent Fischer, Scott L. Friedman

Background and aims: Cenicriviroc (CVC), a dual C-C chemokine receptor types 2 and 5 (CCR2/CCR5) antagonist, is an anti-inflammatory and antifibrotic agent that reduced aspartate aminotransferase-to-platelet count ratio index (APRI) and non-invasive hepatic fibrosis risk (FIB-4) score in HIV-positive subjects, with favorable tolerability in ~600 participants. CVC is currently being evaluated in a Phase 2b, randomized, double-blind, multinational, 2-year study in 289 subjects with non-alcoholic steatohepatitis (NASH) and liver fibrosis (CENTAUR; NCT02217475). An exploratory analysis was performed on screening liver biopsy results to evaluate associations between APRI/FIB-4 scores and fibrosis stage. **Methods:** Subjects with histological evidence of NASH (non-alcoholic fatty liver disease activity score [NAS] ≥4) and liver fibrosis (Stages 1-3 NASH Clinical Research Network [CRN] system) enrolled. Eligible subjects at increased risk of progression to cirrhosis due to presence of one or more of the following: type 2 diabetes; body mass index >25 kg/m^2 with ≥1 feature of metabolic syndrome; bridging fibrosis and/or NAS ≥5. Screening liver biopsy results (N= 566) were analyzed, with mean APRI and FIB-4 scores and standard deviations (SD) calculated for each NASH CRN stage. Differences in means across stages were compared using contrasts

Sanyal *et al.* 2016

Biomarkers to Predict Treatment Effects in RCTs

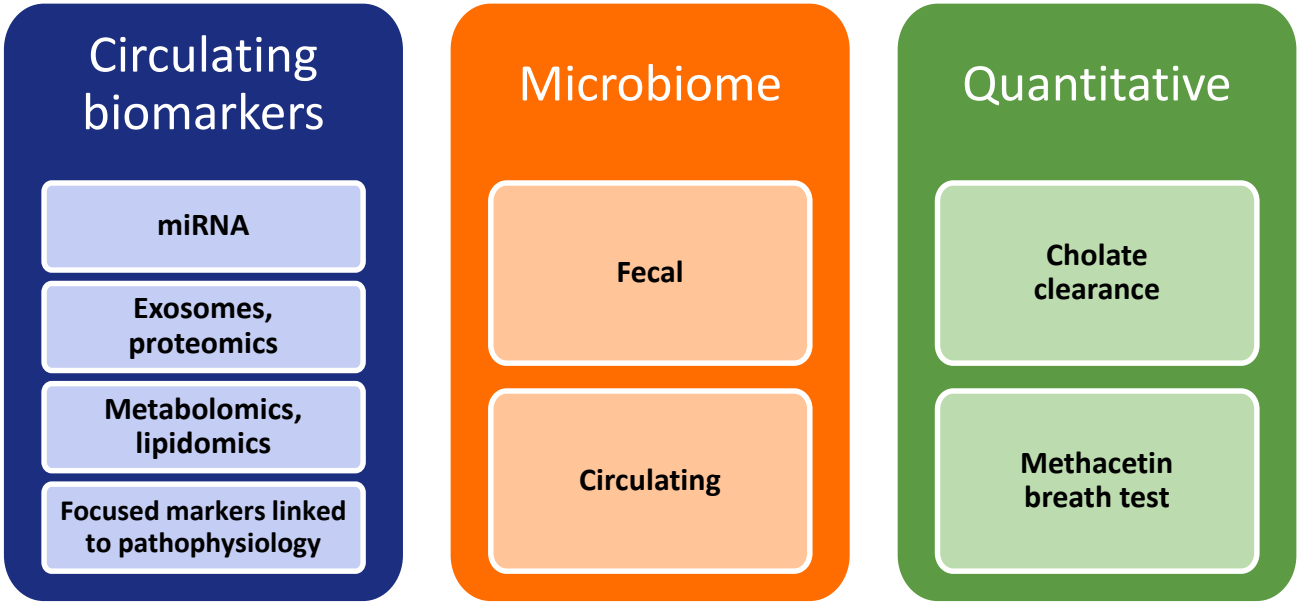
FLINT study analysis



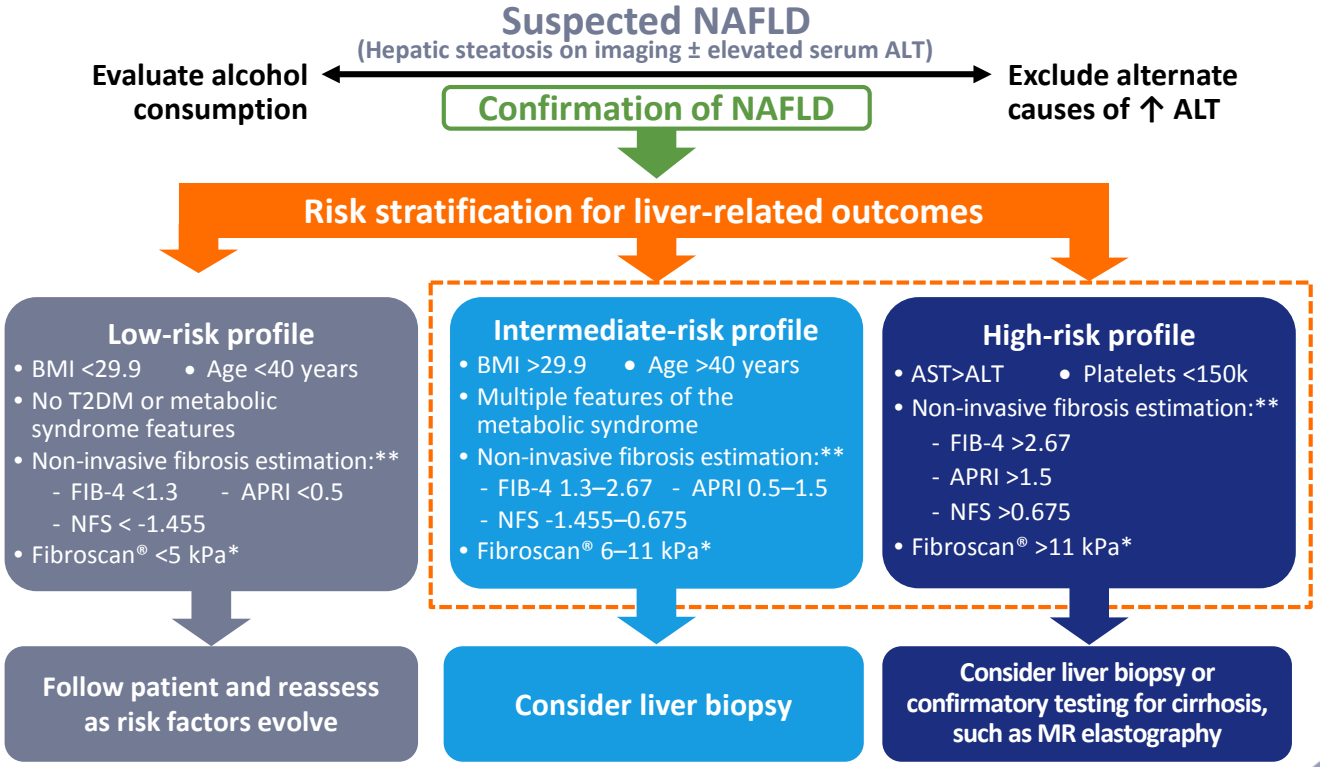
A Wilcoxon Rank Sum analysis showed that a 10% improvement in median FIB-4 values at 24 weeks is associated with a ≥1 stage improvement in fibrosis stage at 72 weeks (p=0.0448)

Sanyal *et al.* AASLD 2015

Biomarkers Under Development



Identification of 'High-Risk' Patients



*High-quality data for the use of Fibroscan® (Echosens, France) in patients with NASH are emerging and require confirmation
**Cut-off values reported by Angulo *et al.* 2013
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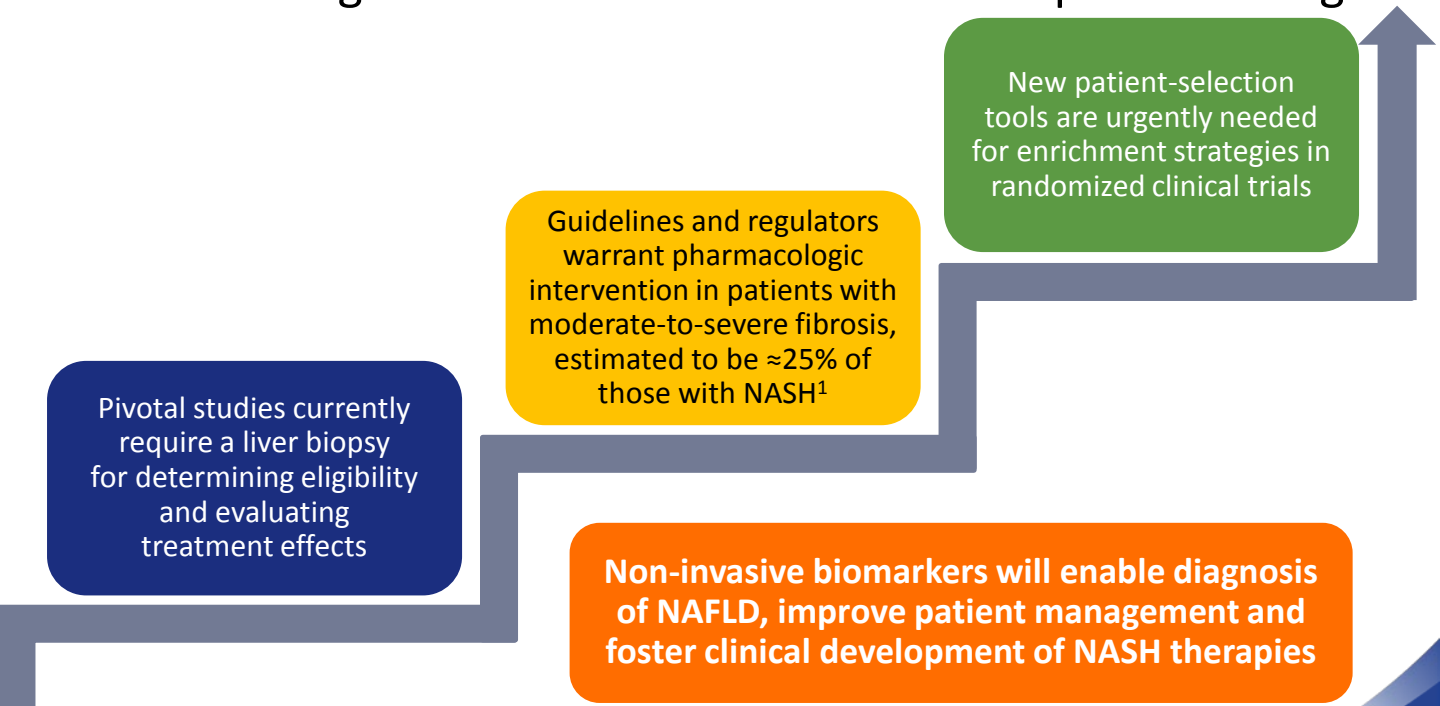
Rinella ME & Sanyal AJ. Management of NAFLD: a stage-based approach. 13:196–205, copyright 2016

Biomarkers in NAFLD Therapeutics

- The investigational NASH treatment landscape is evolving



Angulo *et al.* 2015

Call for Action

Raising awareness of NAFLD and improving diagnosis is critical

Non-invasive tests are needed for disease management and prognosis

Biomarkers must be evaluated and validated in NASH clinical trials

Collaboration between key stakeholders (e.g. The Liver Forum) on biomarker development will be essential to unlock the full potential of new NASH therapies and curb the impact of this looming health threat

Questions

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