The NASH-TARGET Approach for Non-Invasive Diagnosis and Risk Stratification

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Disclosures

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- Steering and publication committee member, Target –NASH study

- Consultant for Target-RWE

Roadmap

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- What is Target-NASH?
- Disease severity assessment is important
- How is severity assessed in real world clinical practice?
- Are real world assessments meaningful?

TARGET–RWE and TARGET-NASH

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Target RWE – Company Overview

Target RWE Health Evidence Solutions

WHO IS TARGET RWE?

Target RWE is a leading provider of real-world data, analytics and evidence solutions

COMPANY HISTORY

Target RWE was founded in 2015 based on the success of HCV-TARGET, a case study of the Target RWE observational study model in Hepatitis C

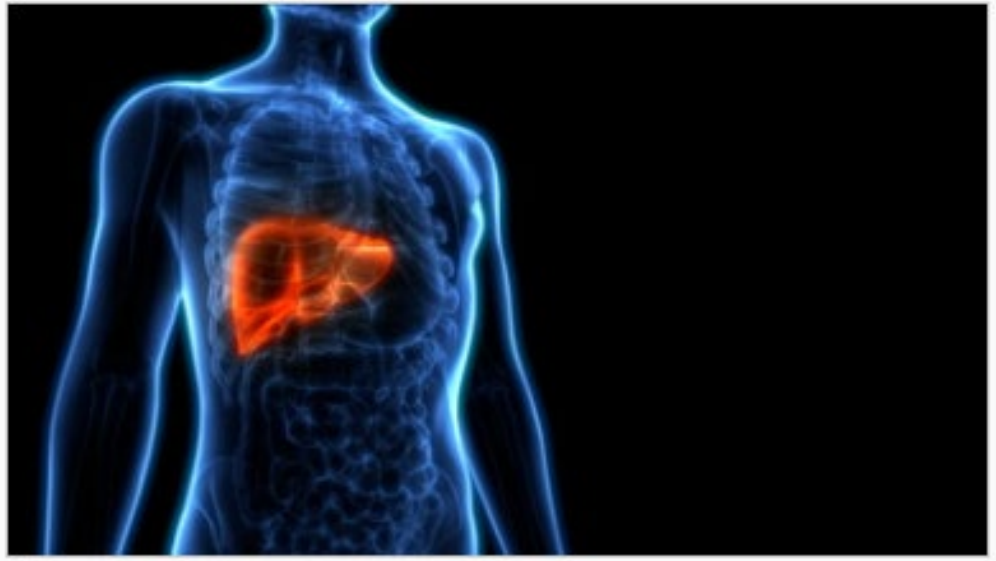
TARGET RWE SOLUTIONS

The Real-World Evidence marketplace is rapidly evolving, and TARGET RWE will work with partners to customize a fit-for-purpose solution

8 different study cohorts covering liver diseases, lung diseases, infectious disease and dermatologic conditions

TARGET-NASH LAUNCHED

JUL 2016



As the company's first observational longitudinal study, TARGET-NASH is launched to produce real-world data and insights for nonalcoholic steatohepatitis (NASH).

8 publications, 30+ meeting presentations

TARGET-NASH disease state definitions

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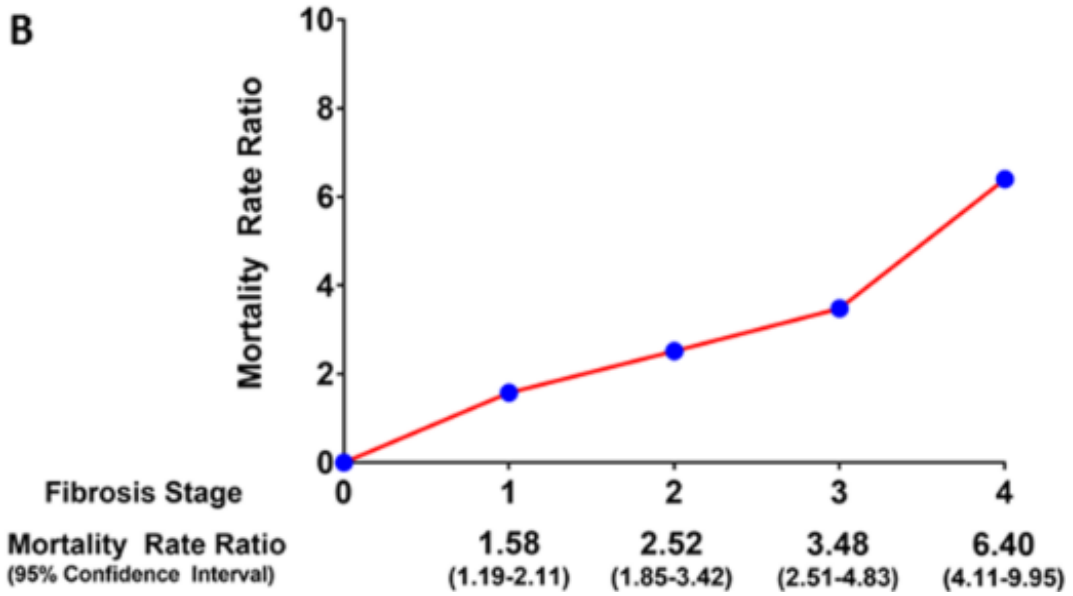
- >7000 study subjects to date
- Patients are enrolled in TARGET-NASH based on a diagnosis of NAFLD by their treating provider
  - Academic and community
  - GI/hepatology/endocrinology
  - US and Europe
- Post-enrollment, patients are stratified to NAFL, NASH or Cirrhosis

- Pragmatic Clinical Definitions
  - Cirrhosis
    - Liver biopsy with fibrosis stage = 4, or
    - Liver biopsy with fibrosis stage = 3 and at least one 2* indicator, or
    - Two or more 2* indicators, or
    - VCTE stiffness result 12.5-15.9 kPa and at least one 2* indicator, or
    - VCTE stiffness result ≥ 16 kPa.
  - NASH
    - Biopsy proven NASH or
    - Elevated ALT
    - Hepatic steatosis on imaging
    - At least one MetS risk factor.
  - NAFL
    - Simple steatosis on biopsy or
    - Not meeting above criteria

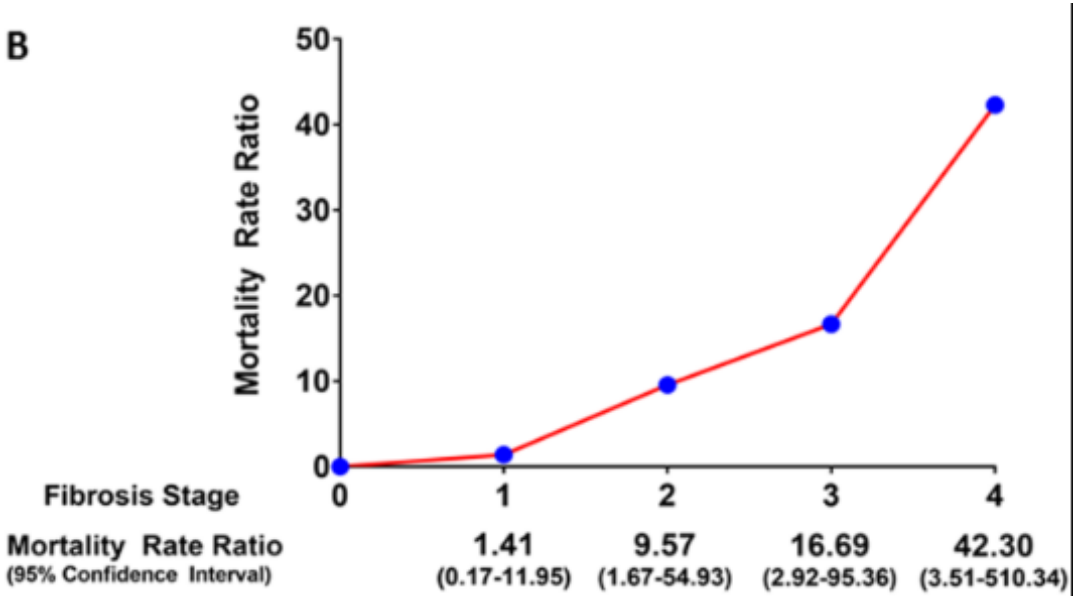
*portal hypertension complications

Barritt et al Contemp Clin Trials 2017

Fibrosis progression is associated with increased mortality



All cause mortality



Liver related mortality

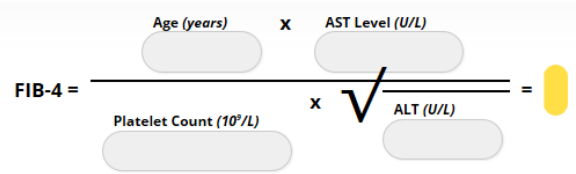
Dulai et al Hepatology 2017

Non invasive assessment of disease

- Several clinical prediction scores for assessing severity of disease
  - NAFLD fibrosis score (NFS)

    = 1.675+ (0.037*age) + (0.094*BMI) + (1.13 if DM) + (0.99* AST/ALT)- (0.013*plt) – (0.66*alb)

  - FIB-4

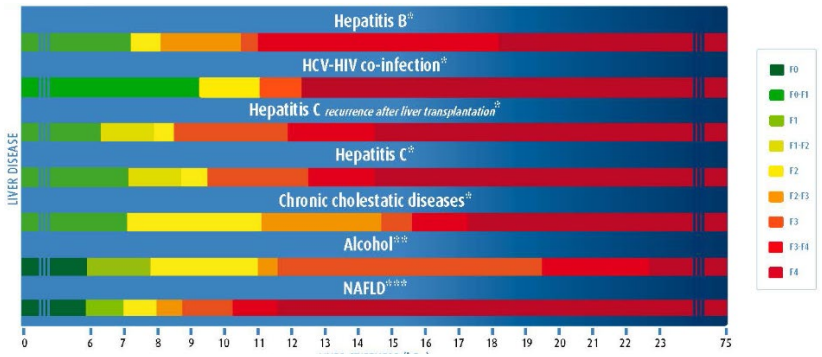


- Both are reasonable to use.
  - Comparable AUROC scores
    - NFS 0.81, FIB-4 0.82
  - Inexpensive
  - On hand held devices
  - Many others with similar accuracy

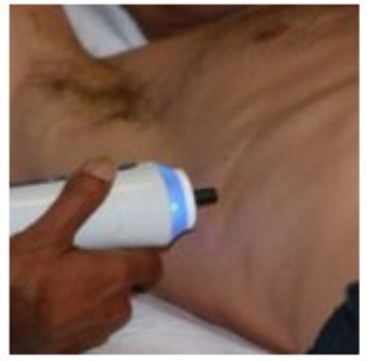
Sterling, Hepatol 2006, Angulo, Hepatol 2007, Angulo, Hepatol 2010, Kim, Radiology 2013

Non-invasive imaging

- Vibration Controlled Transient Elastography (VCTE)
  - Liver stiffness measured in kilopascals and correlated with fibrosis stage, F0-F4
    - Must know disease etiology to interpret score
  - AUROC for F3 or higher disease 0.93 in NAFLD



- Controlled Attenuation Parameter (CAP)
  - Steatosis measured in dB/m and correlated with steatosis grade, S0-S3
  - AUROC score for S1 and greater 0.86



Wong, Hepatol 2010, Karlas, J Hepatol 2017

Magnetic Resonance Imaging Technology

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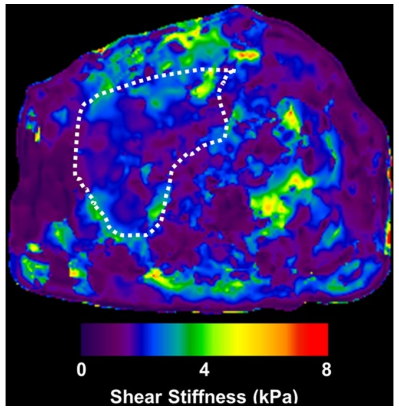
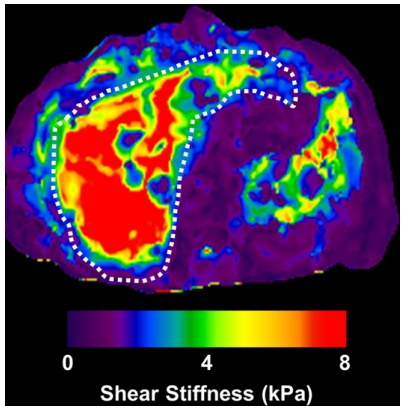
- MR-Elastography (MRE) for Fibrosis
  - 2D and 3D MRE have AUROC >0.92
  - Multiple single center trials show MRE>VCTE

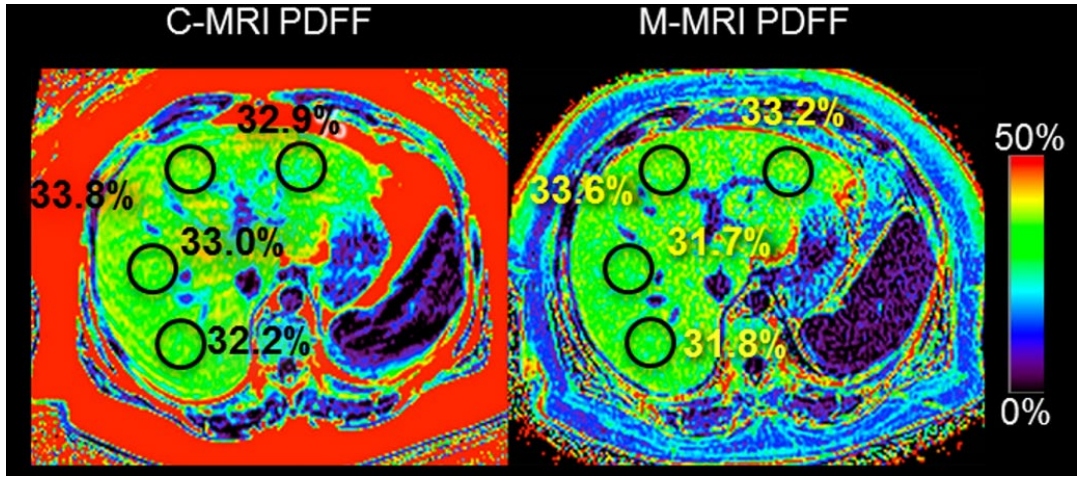


No fibrosis



Advanced fibrosis

- MR-Proton density fat fraction for steatosis (MR-PDFF)
  - MR-PDFF>CAP for fat quantification



Kim, Radiology 2013, Caussy, Hepatology 2018, Hsu, Clin Gastroenterol Hepatol 2018

How often are these tools used in practice?

- Adult Target-NASH population
  - Clinical prediction scores ~ 100%*
  - VCTE (Fibroscan) 32% CAP 25%
    - Cirrhosis 32% CAP 23%
    - NASH 43% CAP 33%
    - NAFL 19% CAP 16%
  - Elastography 4%
    - Cirrhosis 3%
    - NASH 6%
    - NAFL 2%
- Liver Biopsy ~31%
  - Cirrhosis 48%
  - NASH 37%
  - NAFL 4%

*Data to calculate CPS (FIB-4, NFS, API) are nearly universally available to TARGET – the extent to which providers use these in clinical practice is unclear

Clinical practice is very different from clinical trials

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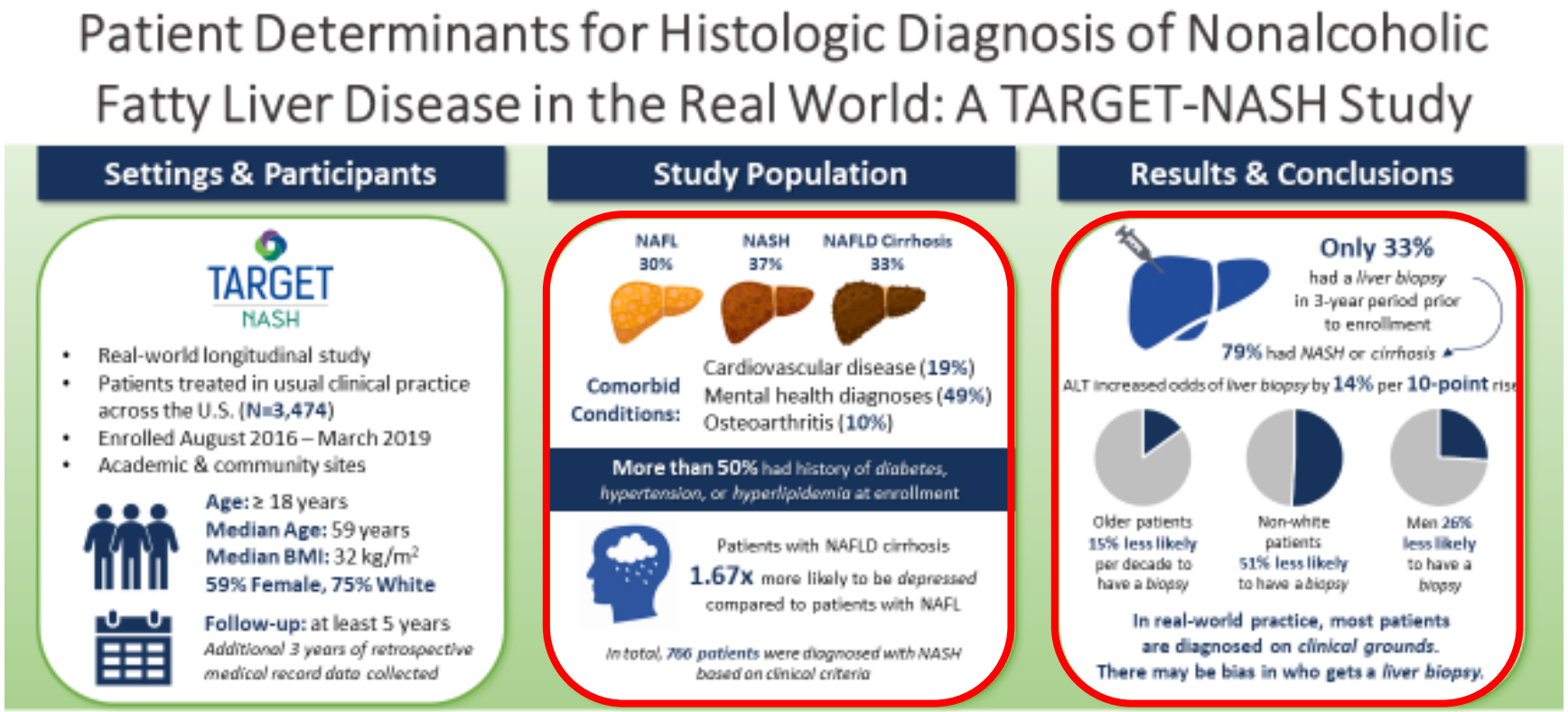
- We treat patients differently in clinical trials than we do in routine clinical practice
  - 1/3 have diagnosis confirmed with liver biopsy
    - Bias in who we choose to biopsy
    - Older, non-white, male patients all less likely to have biopsy
- Significant comorbid conditions
  - Depression
  - Polypharmacy



Barritt, et al. *Hepatol Commun. 2021*

HEPATOLOGY COMMUNICATIONS Open Access

Barritt et al Hep Comm 2021

Practical application of liver biopsy ?

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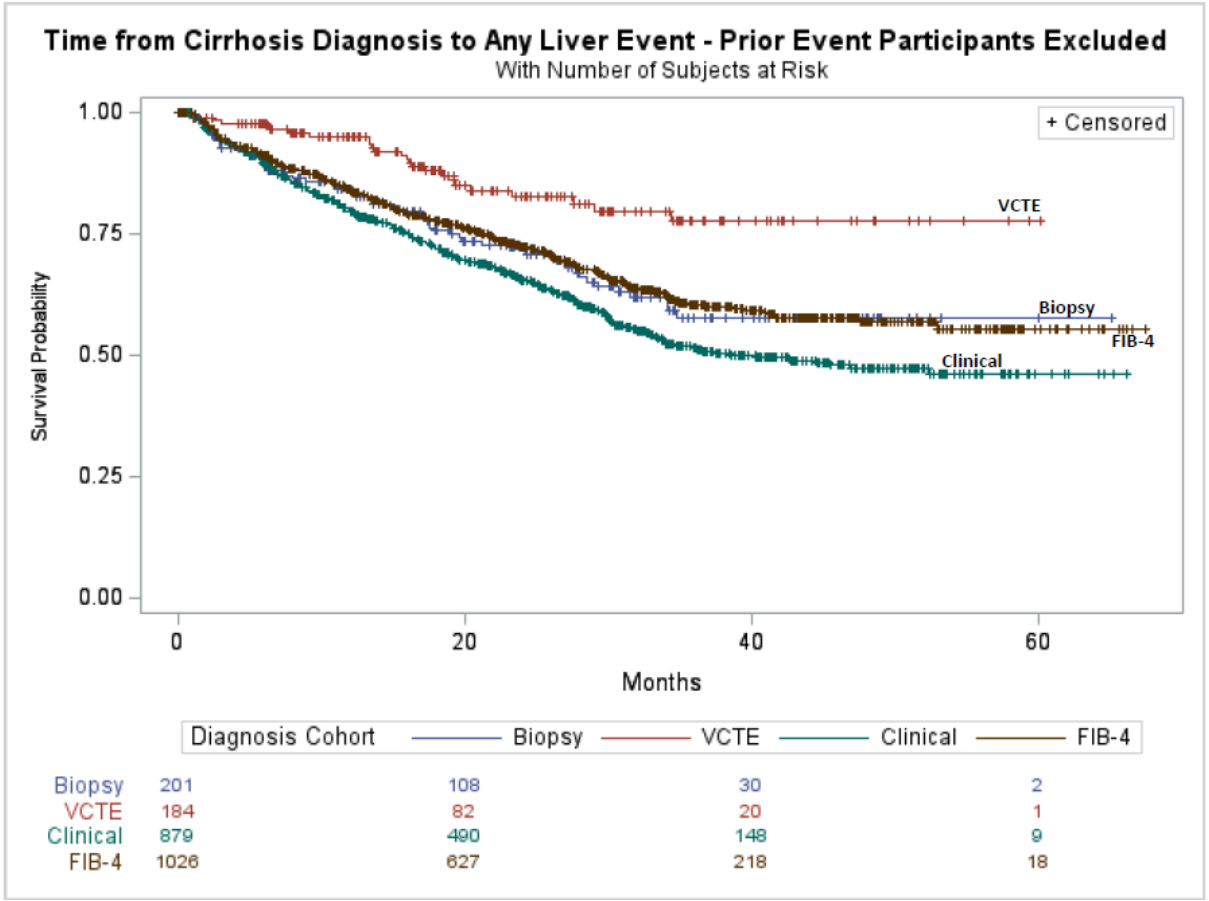
- Liver biopsy is the referent standard for assessing NASH
  - How reliable is the application of this standard in real world practice?
- Reviewed how NASH biopsies were reported in academic and community centers and assessed agreement with a centralized pathologist
  - 21-40% of biopsy reports missing key descriptors of NASH disease activity
- 75-91% concordance between the expert central pathologist diagnosis and TARGET-NASH clinical definition for NASH
  - Concordance for advanced fibrosis/cirrhosis was >0.61 (substantial)

Histological Characteristic	Number of Pathology Reports Compared	Weighted Kappa Statistic (95% CI)	Concordance Interpretation
Steatosis	57	0.364 (0.2029, 0.5242)	**Fair**
Lobular Inflammation	29	-0.081 (-0.1847, 0.0220)	**Poor**
Portal Inflammation	31	0.210 (-0.0376, 0.4580)	**Fair**
Hepatocyte Ballooning	26	0.117 (-0.0708, 0.3038)	**Slight**
Fibrosis Stage	69	0.575 (0.4603, 0.6894)	**Moderate**
Scoring System			
NAFLD Activity Score	38	0.237 (0.0591, 0.4150)	**Fair**
Brunt Grade (Inflammation)	26	0.384 (0.1591, 0.6082)	**Fair**
Brunt Stage (Fibrosis)	69	0.590 (0.4775, 0.7019)	**Moderate**

Kim et al APT 2021

How useful are real world NITs?

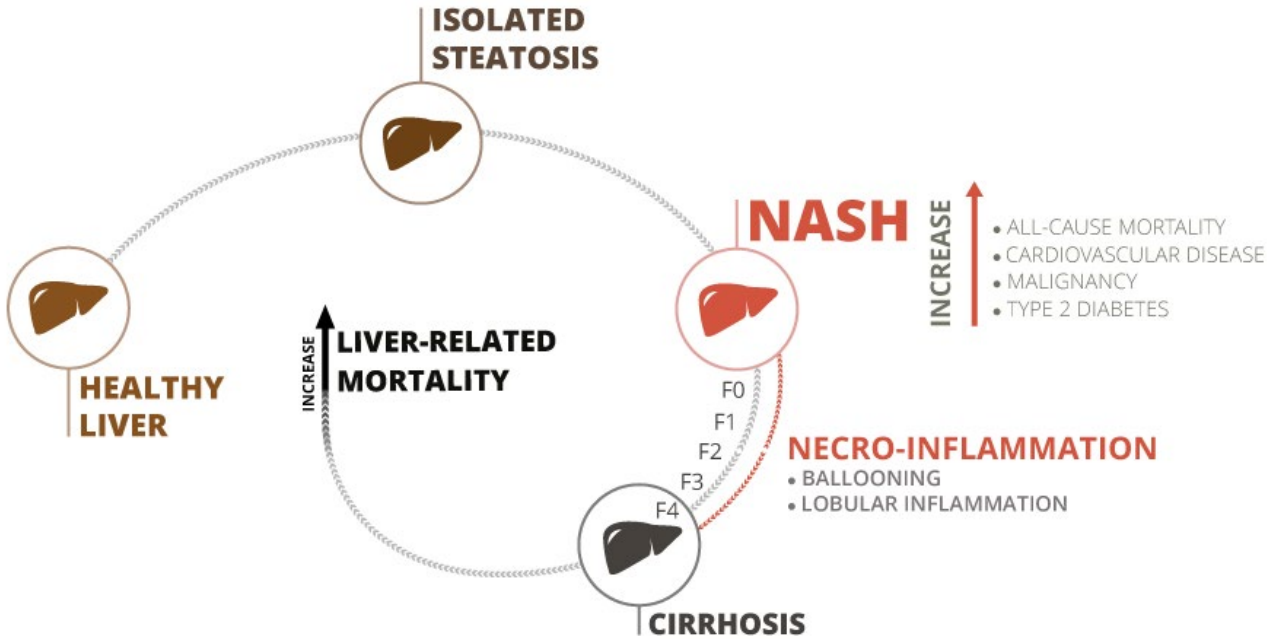
- Cirrhosis may be diagnosed on clinical/NIT criteria or by biopsy
  - How well does an NIT diagnosis predict events compared to biopsy?
  - FIB-4 diagnosis of advanced fibrosis/cirrhosis was equal to biopsy for predicting LACE



Barritt et al AASLD 2020

Can NITs predict risk for other events?

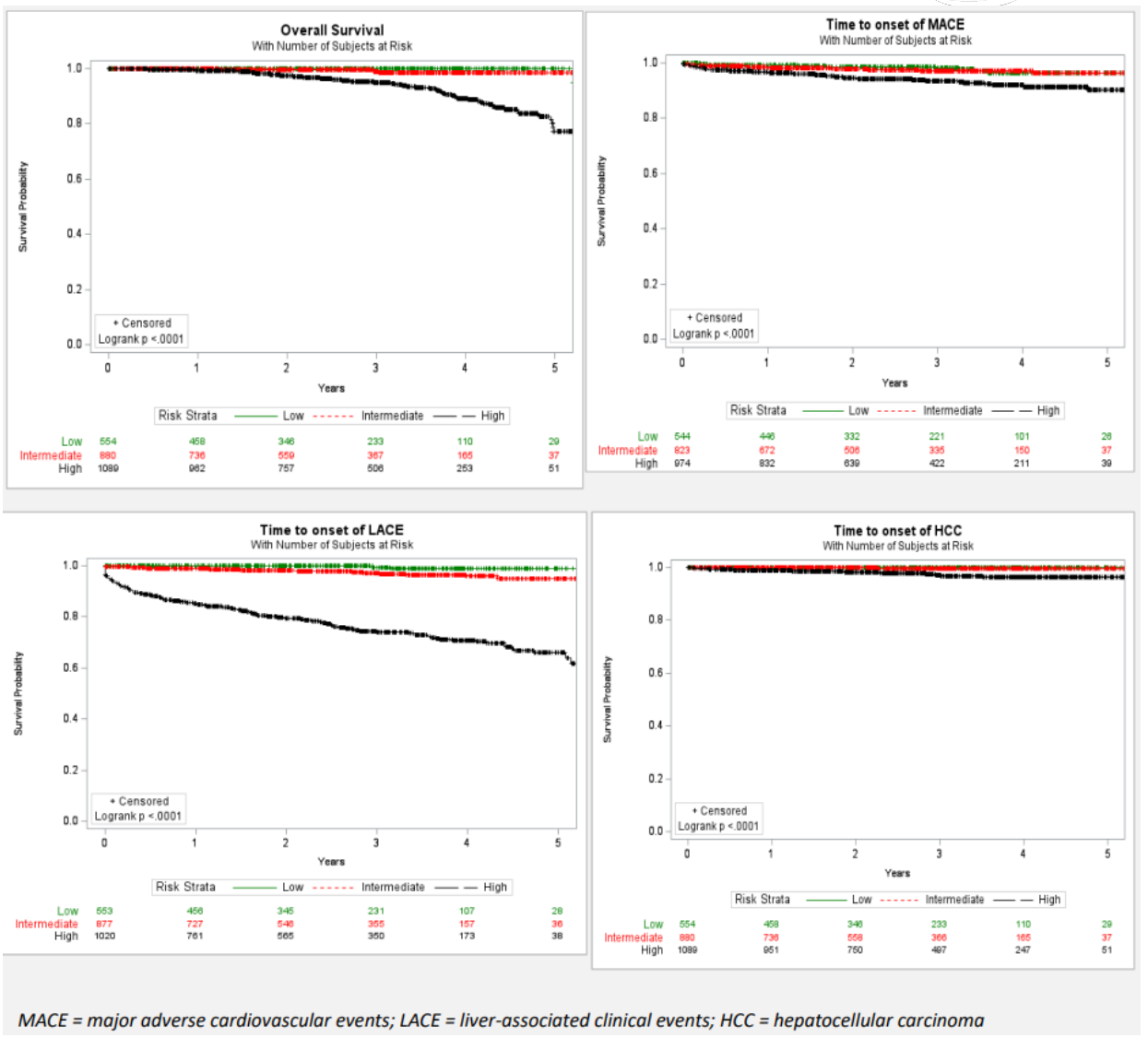
- Patients with NASH are at risk for MACE and depending on fibrosis stage, may also be at risk for liver events and HCC.
- Validated a prognostic system, derived from previously described profiles (Nature Reviews, 2016), using widely available measures to predict incident outcomes in those with NAFLD



Rinella et al Nat Rev 2016
Sanyal et al AASLD 2021

NITs can predict outcome across all NALFD

- Patients stratified into low, intermediate and high risk based on NITs
- FIB-4/LSM criteria:
  - Low- Class A was defined by having either a FIB-4 ≤1.3 or a liver stiffness measurement (LSM) ≤8 kPa by Fibroscan.
  - Intermediate- Class B was defined by FIB-4 1.3-2.6 kPa or LSM 8.1-12.5 kPa.
  - High- Class C was defined by FIB-4 >2.6 or LSM >12.5.
- There was a significant stepwise increase in the mortality and incidence rate of liver and cardiac events from class A to B to C (p< 0.0001 for trend)



MACE = major adverse cardiovascular events; LACE = liver-associated clinical events; HCC = hepatocellular carcinoma

Sanyal et al AASLD 2021

Are NITs reliable to determine treatment thresholds?

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- Liver biopsy may be impractical for treatment decisions
- Some NITs have been studied to identify advanced fibrosis (≥F3), there is limited evidence on the ability of NITs to discriminate significant liver fibrosis (≥F2) in real-world cohorts.

Table 1: Thresholds and Test Characteristics for Non-Invasive Tests for Determining Significant Fibrosis

NIT	Fibrosis	Threshold	Sensitivity	Specificity	PPV	NPV	AUROC
FIB-4	Stage ≥ F2	≥ 2.43	49%	90%	87%	56%	0.79
	F0 - F1	≤ 0.95	90%	41%	68%	75%	
APRI	Stage ≥ F2	≥ 1.07	36%	90%	83%	51%	0.72
	F0 - F1	≤ 0.32	90%	36%	66%	72%	

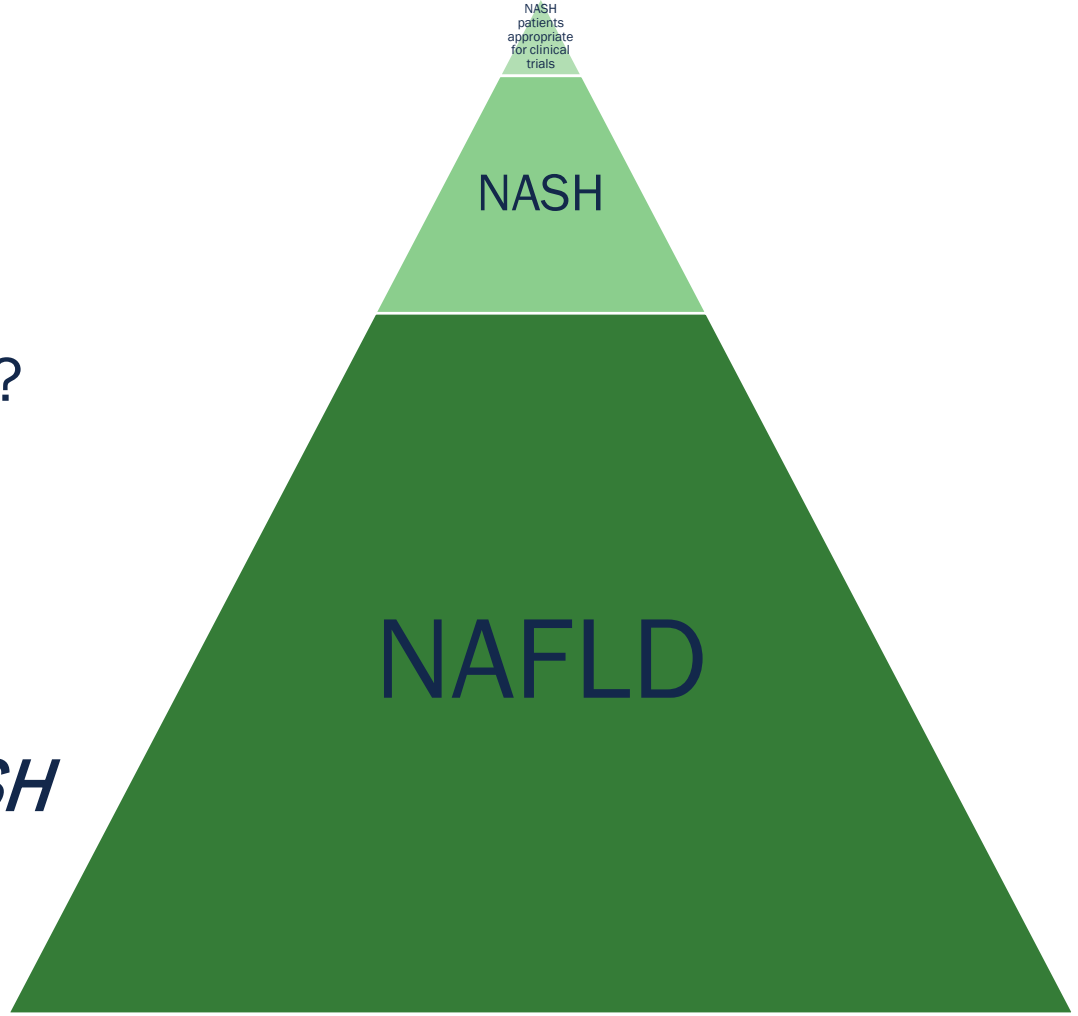
Conclusion

FIB-4 at a threshold ≥2.43 and APRI ≥1.07 of can be used to potentially identify significant fibrosis among real-world NASH patients with an acceptable level of accuracy.

Barritt et al Paris NASH 2021

The challenge to treat NASH will continue

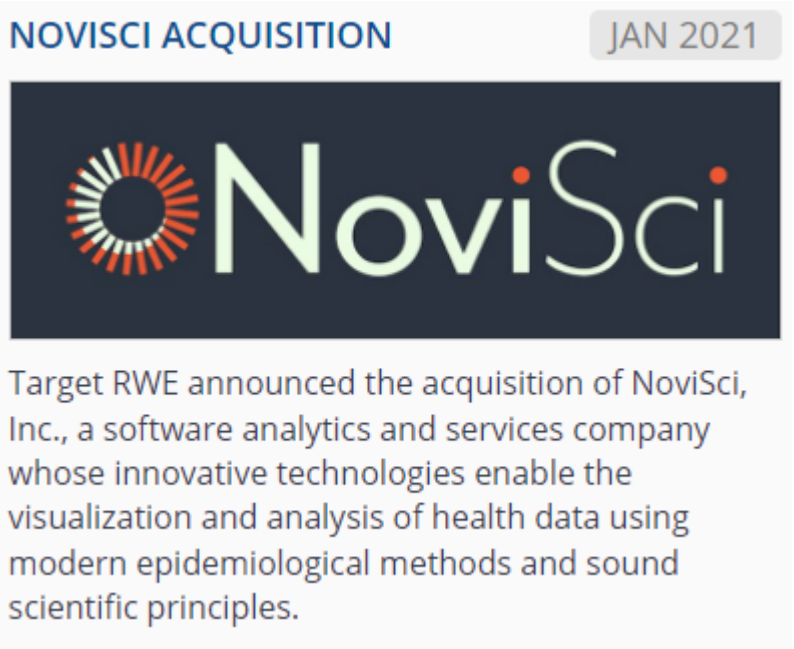
- When there are FDA approved interventions for NASH, questions and challenges will remain
  - Are these lifetime drugs?
  - Are medications interventions to pause disease while patients fix lifestyle problems?
  - Are there adverse liver events?
  - What is the CV risk/benefit?
  - What is the cancer risk/reduction?
  - Clinical trial ***efficacy*** vs. ***real world effectiveness***
- ***NITs will be essential for monitoring NASH in routine clinical practice***



Barritt, AASLD Postgraduate Course 2018

Next steps

- Expansion in Europe
- Continuing to accrue longitudinal NIT metrics and LACE/MACE/cancer outcomes
  - TARGET-NASH disease progression/regression working group
- Sophisticated analytic capabilities to analyze real world data
  - Acquisition of NoviSci 2021
- Use of NITs for post marketing surveillance of new NASH therapies.



Thank you!

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