NAIL-NIT CONSORTIUM

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NAIL-NIT: Background & Objective

NAIL-NIT Consortium

NASH Consortium for the **A**ssessment of Non-Invasive Testing in Monitoring **I**nterventions and Treatment Response and Major **L**iver Related Outcomes

OUR VISION

A FUTURE WHERE BIOPSY IS NO LONGER NEEDED

NAIL-NIT Consortium Objective

To close the current gaps in the non-invasive tests (NIT) field especially in the longitudinal assessment for response to treatment as well as correlation with Major Liver Related Outcomes (MALO). This will lead to the replacement of liver biopsy in late-stage clinical trials and clinical practice guidance.

NAIL-NIT: Background & Objective

Key Issues about Liver Biopsy

High Intra- & Inter-Observers Variability - Sampling variability

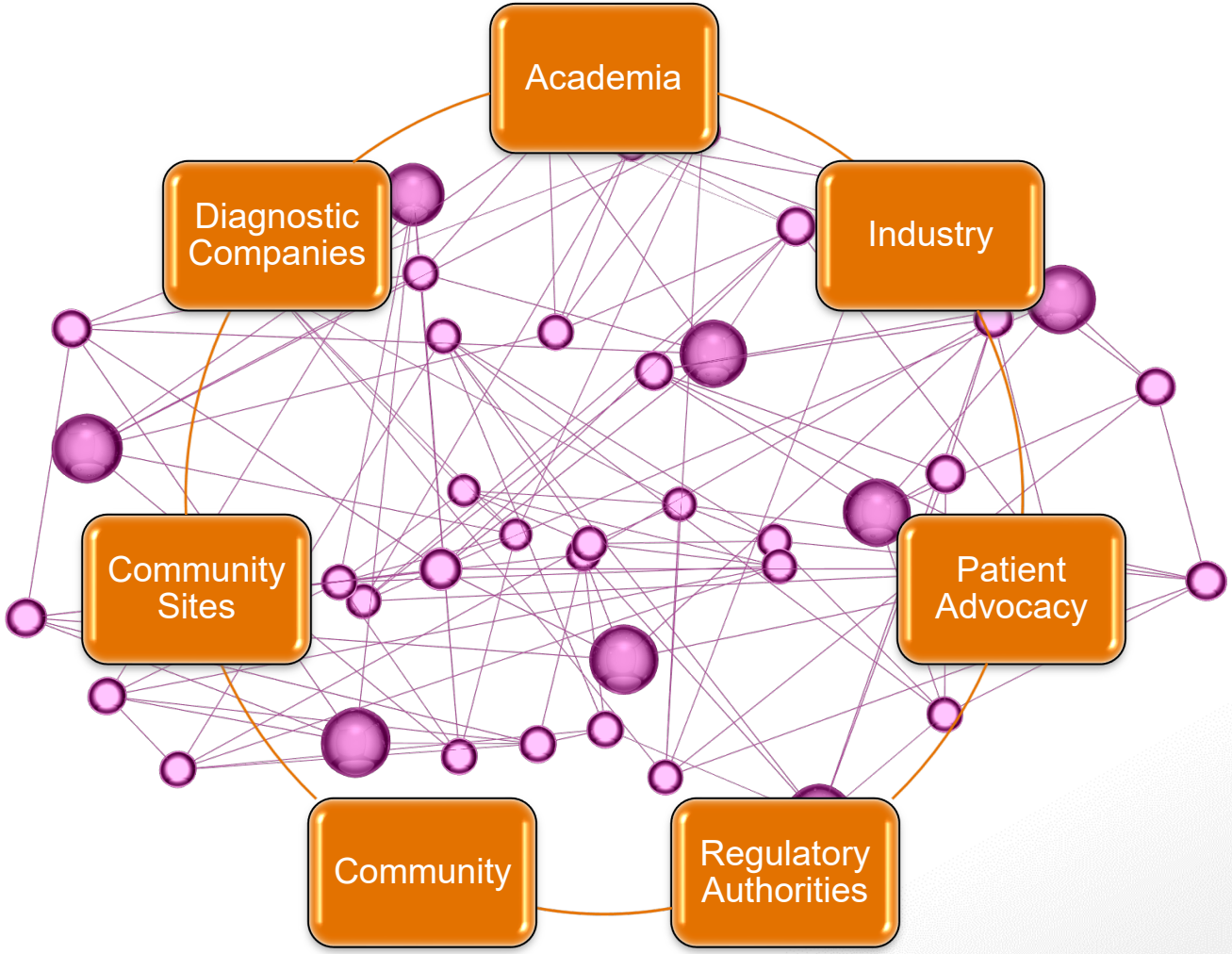
Various central reading processes and different scoring systems across programs

Placebo Effect

High Screen Failure Rate Up to 65%

NAIL-NIT: Background & Objective

The Structure of the Consortium



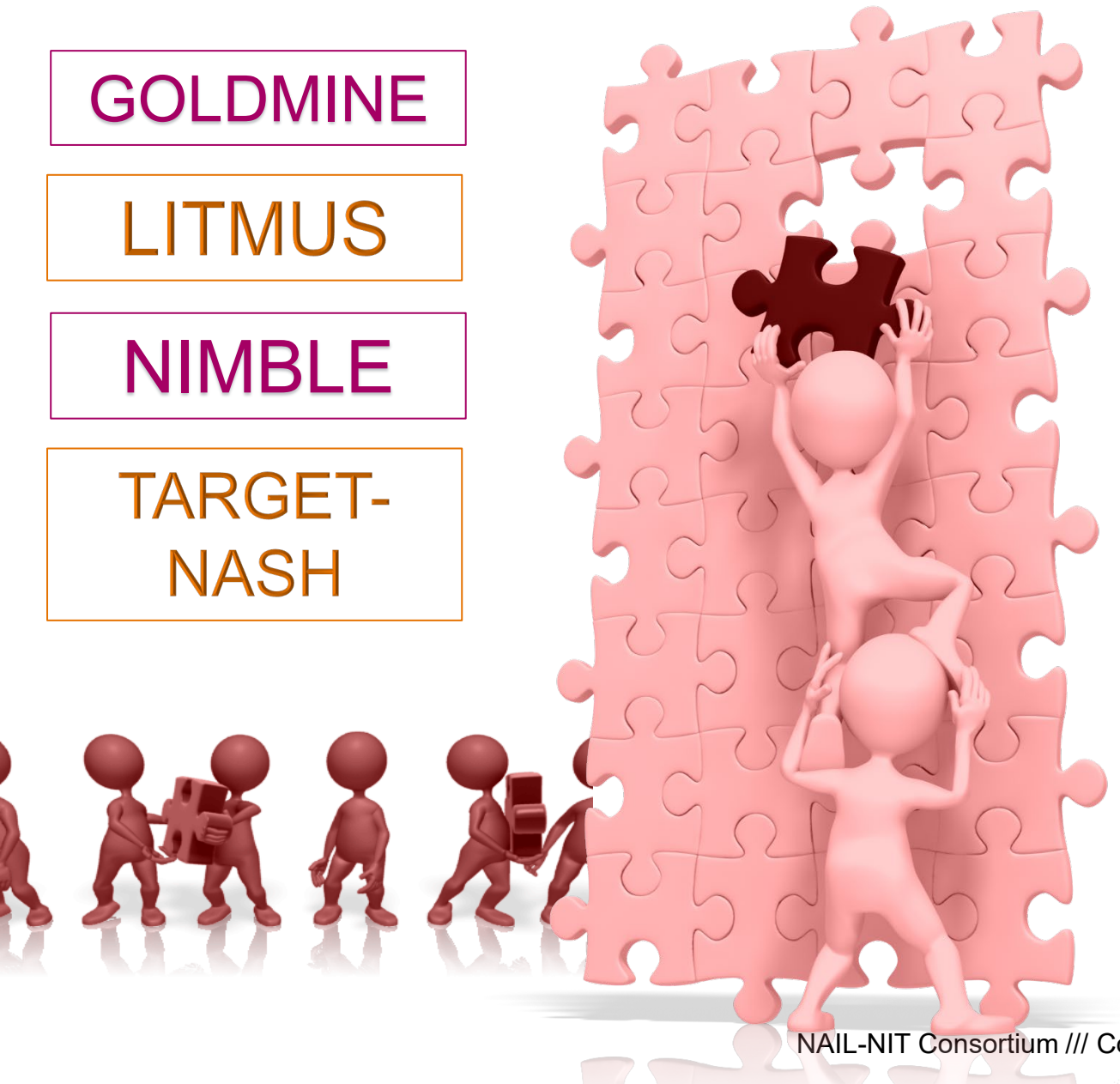
NAIL-NIT: Background & Objective

Key Points

- Multiple publications that will lead to changing future guidelines favoring implementing NITs in long term follow up of patient and monitoring treatment response
- Will lead to changing clinical practice
- Pool NITs collected to date to assess for biomarker efficacy as it pertains to:
  - Diagnosis of at-risk NASH patients (NASH with F2 or greater fibrosis)
  - Monitoring for therapeutic response
- Funded by private industry
- Clinical sites that have a track record of enrolling large number of patients in NASH clinical trials
- Driven by pharmaceutical and diagnostic companies in a non-biased design
- Discussion with FDA prior to initiation of prospective study

NAIL-NIT: Supporting the field & Scientific Society

- GOLDMINE
- LITMUS
- NIMBLE
- TARGET-NASH



Complimentary

to the effort of other initiatives where NAIL-NIT will focus on the longitudinal and outcome component of NITs

NAIL-NIT: Background & Objective

Retrospective analysis

- Data collection from ongoing and completed NASH trials
- Value contribution for Industry
  - ✓ Decrease of Screen Failure rates
  - ✓ Decrease screening costs
  - ✓ Decrease studies timelines
  - ✓ Identification of NIT to enhance enrollment and monitor MALOs for future trial designs
  - ✓ Identification of NIT to enrich study population for future trials

Prospective Study

- Clinical Trial Initiation in agreement with health authorities
- Value contribution for Industry
  - ✓ Identification of NIT/combination of NITs which correlate to MALOs
  - ✓ Identification of NITs to replace liver biopsy for phase 2b/3 trials which lead to:
    - Shorter trials duration
    - Less screening failure
    - Major cost saving
  - ✓ Meetings with FDA to approve NITs to diagnose at risk patients and monitor disease/therapeutic response
  - ✓ Goal to perform future phase 3 without liver biopsy endpoint and to change the guidelines to endorse using NITs in identifying patients qualified for treatment and using NITs to monitor response

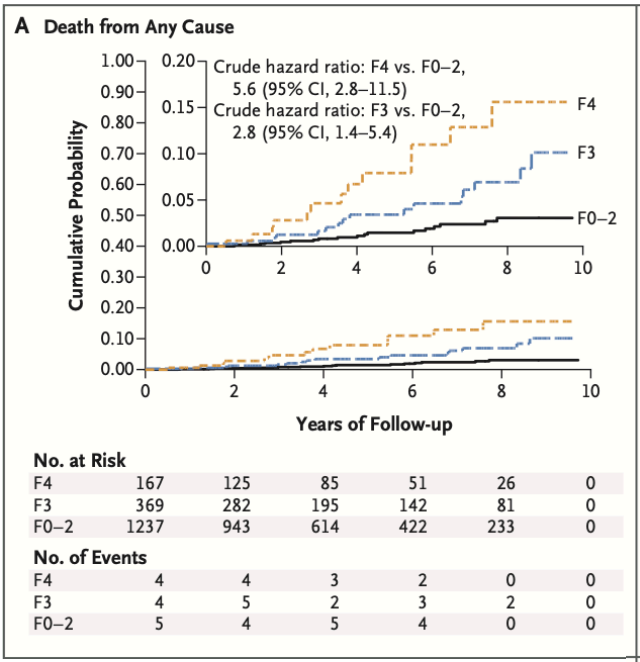
NAIL-NIT: Major Adverse Liver Outcomes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

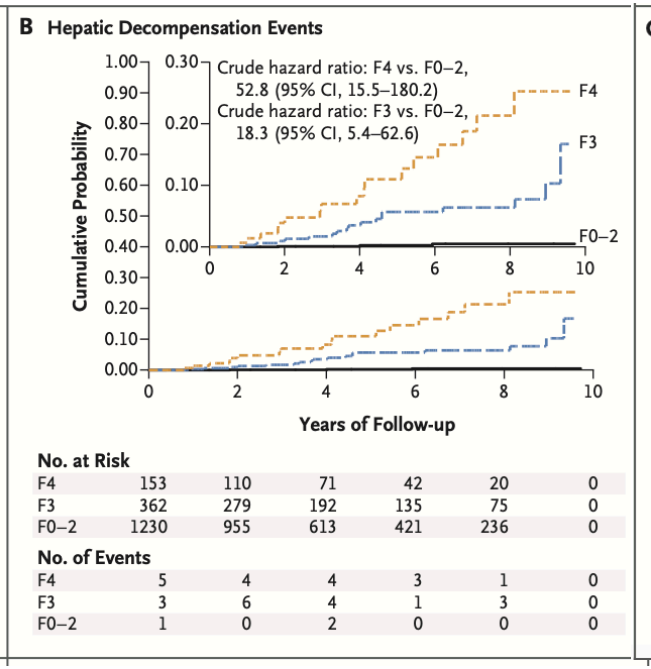
Prospective Study of Outcomes in Adults with Nonalcoholic Fatty Liver Disease

Arun J. Sanyal, M.D., Mark L. Van Natta, M.H.S., Jeanne Clark, M.D., M.P.H., Brent A. Neuschwander-Tetri, M.D., AnnaMae Diehl, M.D., Srinivasan Dasarathy, M.D., Rohit Loomba, M.D., M.H.Sc., Naga Chalasani, M.D., Kris Kowdley, M.D., Bilal Hameed, M.D., Laura A. Wilson, Sc.M., Katherine P. Yates, Sc.M., Patricia Belt, B.S., Mariana Lazo, M.D., Ph.D., David E. Kleiner, M.D., Ph.D., Cynthia Behling, M.D., Ph.D., and James Tonascia, Ph.D., for the NASH Clinical Research Network (CRN)*



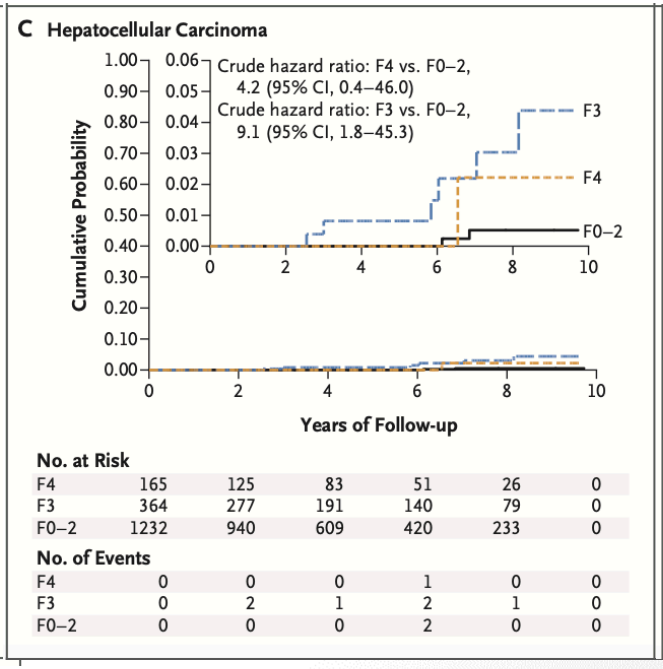
No. at Risk						
F4	167	125	85	51	26	0
F3	369	282	195	142	81	0
F0–2	1237	943	614	422	233	0

No. of Events						
F4	4	4	3	2	0	0
F3	4	5	2	3	2	0
F0–2	5	4	5	4	0	0



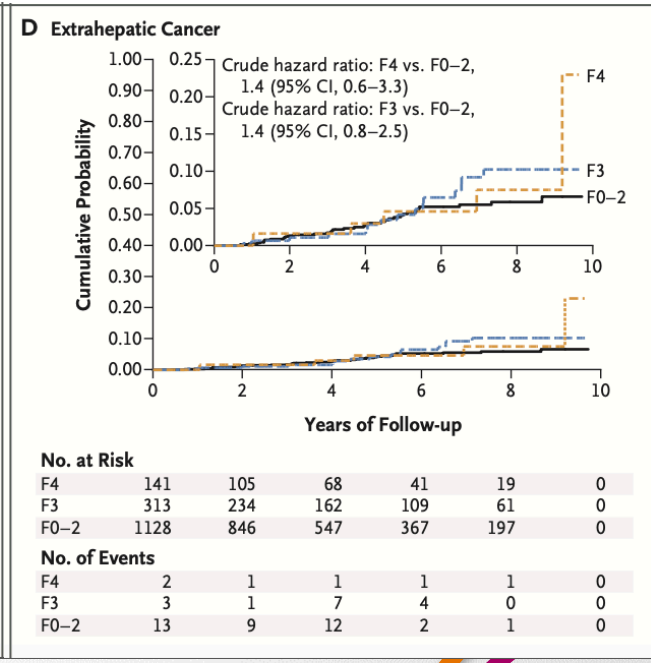
No. at Risk						
F4	153	110	71	42	20	0
F3	362	279	192	135	75	0
F0–2	1230	955	613	421	236	0

No. of Events						
F4	5	4	4	3	1	0
F3	3	6	4	1	3	0
F0–2	1	0	2	0	0	0



No. at Risk						
F4	165	125	83	51	26	0
F3	364	277	191	140	79	0
F0–2	1232	940	609	420	233	0

No. of Events						
F4	0	0	0	1	0	0
F3	0	2	1	2	1	0
F0–2	0	0	0	2	0	0



No. at Risk						
F4	141	105	68	41	19	0
F3	313	234	162	109	61	0
F0–2	1128	846	547	367	197	0

No. of Events						
F4	2	1	1	1	1	0
F3	3	1	7	4	0	0
F0–2	13	9	12	2	1	0

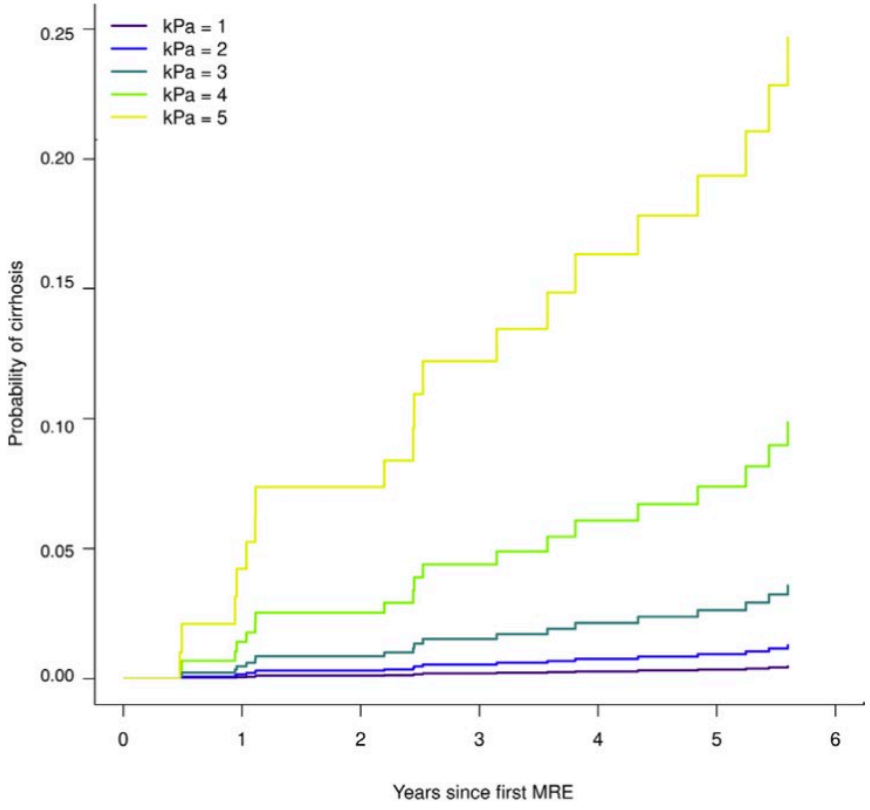
NAIL-NIT: Major Adverse Liver Outcomes

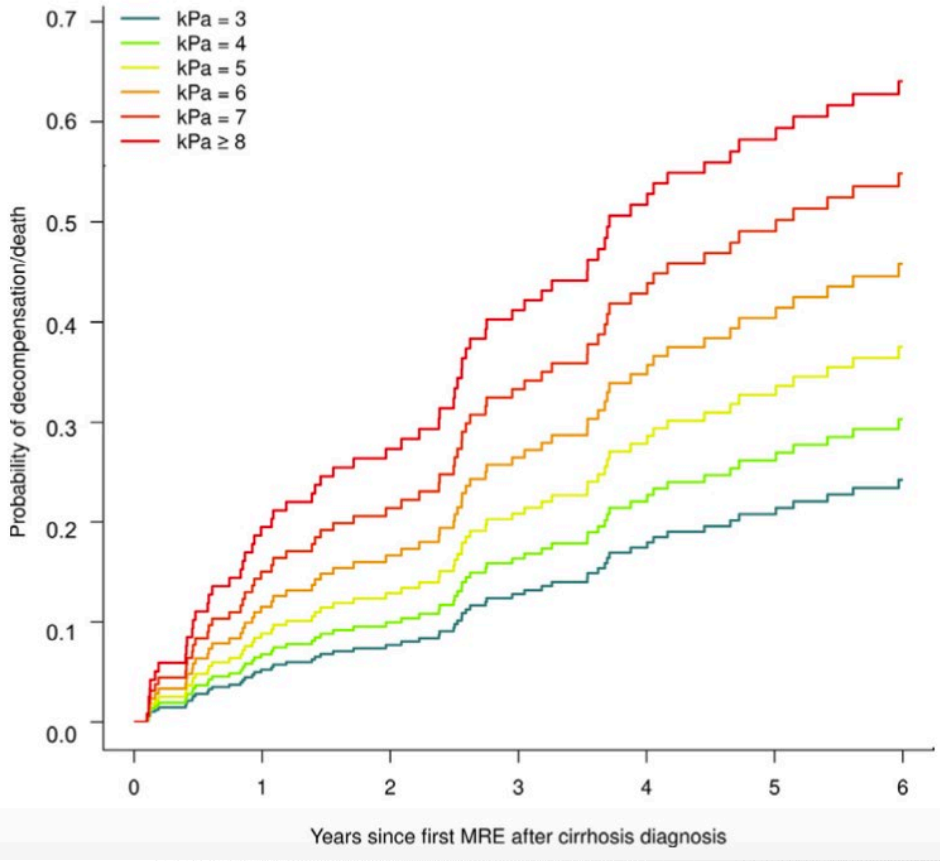
Clinical Gastroenterology and Hepatology 2021;19:1915–1924

Liver Stiffness by Magnetic Resonance Elastography Predicts Future Cirrhosis, Decompensation, and Death in NAFLD

Tolga Gidener,* Omar T. Ahmed,* Joseph J. Larson,‡ Kristin C. Mara,‡ Terry M. Therneau,‡ Sudhakar K. Venkatesh,§ Richard L. Ehman,§ Meng Yin,§ and Alina M. Allen*

*Division of Gastroenterology and Hepatology, Mayo Clinic, F… Informatics, Mayo Clinic, Rochester, Minnesota; and §Departı…



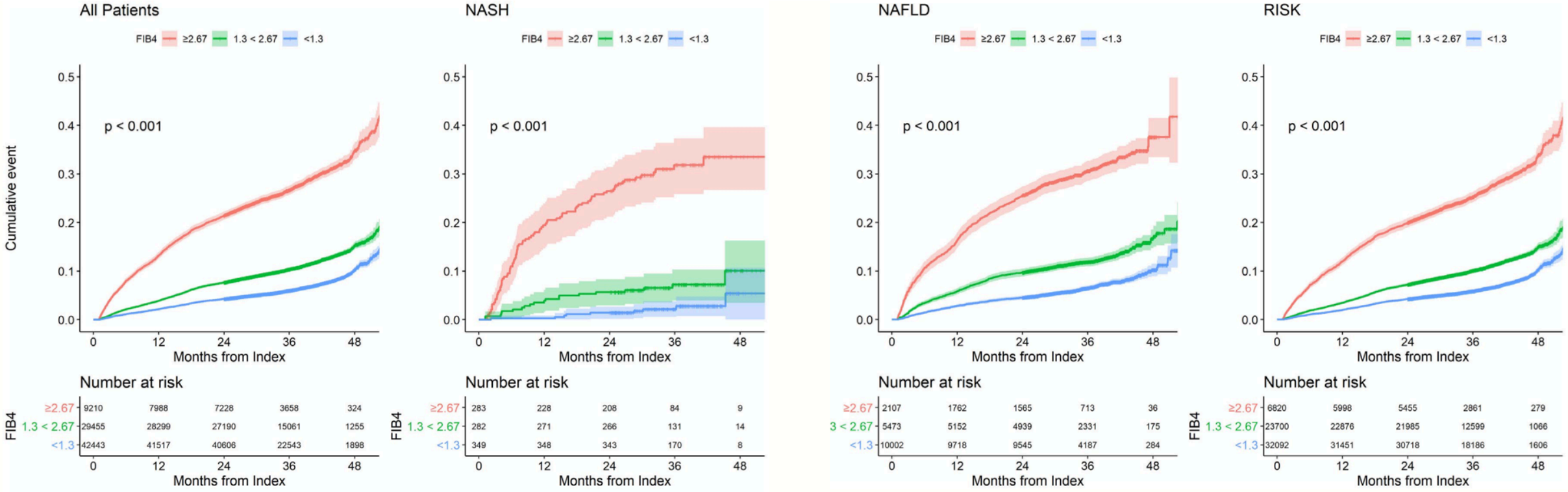


NAIL-NIT: Major Adverse Liver Outcomes

HEPATOLOGY COMMUNICATIONS, VOL. 6, NO. 4, 2022

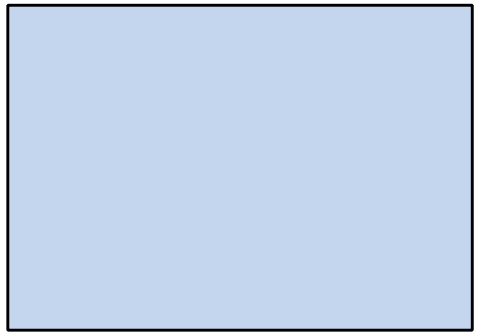
Fibrosis-4 Index as an Independent Predictor of Mortality and Liver-Related Outcomes in NAFLD

Joana Vieira Barbosa,[1,2] Scott Milligan,[3] Andrew Frick,[3] Jeremy Broestl,[3] Zobair Younossi ,[4,5] Nezam H. Afdhal,[1] and Michelle Lai[1]



NAIL-NIT: Major Adverse Liver Outcomes

- Meta-analysis of 11 studies
- ELF test had a sensitivity of >0.90 for excluding fibrosis at a threshold of 7.7
- To achieve a specificity of 0.90 for advanced and significant fibrosis, thresholds of 10.18 (sensitivity: 0.57) and 9.86 (sensitivity: 0.55) were required, respectively



FDA Grants Marketing Authorization to Siemens Healthineers ELF Test for NASH Prognostic Assessment

Tarrytown, NY | 08/24/2021

- **The Enhanced Liver Fibrosis (ELF) is the first prognostic tool for patients with advanced fibrosis (F3 or F4) due to non-alcoholic steatohepatitis (NASH) to be granted De Novo marketing authorization.**
- **The blood test, for use in patients with advanced fibrosis due to NASH, helps assess the likelihood of progressing to cirrhosis and liver-related clinical events.**
- **There is a clinical need for a simple noninvasive test that is convenient, objective, reproducible, accurate, and widely accessible.**
- **This milestone follows the Breakthrough Device Designation FDA granted for the test in November 2018.**

Siemens Healthineers announced today that its Enhanced Liver Fibrosis (ELF™) Test was granted marketing authorization under the De Novo review pathway.[1] The ELF Test, for use with the ADVIA Centaur® XP Immunoassay System, provides a simple numeric score that is automatically generated via an algorithm and is used to improve patient care by assessing the likelihood of progression to cirrhosis and liver-related clinical events in patients with advanced fibrosis (F3 or F4) due to non-alcoholic steatohepatitis (NASH).

NAIL-NIT: Prospective Trial Design

Inclusion criteria will be enriched with those who will develop MALO within 2-3 years

- 6 year and more FU
- Biobanking of samples
- AI technologies

- **Collection of MALOs**
- **NITs assessments**

NAIL-NIT: Status Update

- **Industry Partners**
  - Data Sharing Agreement
  - Consortium Agreement
  - Initial Funding

- **Retrospective Committee**
  - First Meeting – April 2022
  - Ongoing SAP to define analyses

- **Prospective Committee**
  - Ongoing definition of sample size & study design

The ultimate goal of NAIL-NIT consortium is to identify the best clinical prediction model, using existing NITs, to replace liver biopsy in clinical trials and standard of care

NAIL NIT