



**PARIS
MASH
MEETING**

10th edition

**Organized by
Arun Sanyal & Lawrence Serfaty**



**September 5 & 6 2024
Institut Pasteur, Paris**



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Liver Forum Updates

September 6, 2024

Veronica Miller, PhD

Director, Forum for Collaborative Research

Adjunct Professor

UC Berkeley School of Public Health

Disclosures

- Liver Forum receives funding from multiple companies
 - Next slide

Liver Forum Sponsors



THE FORUM

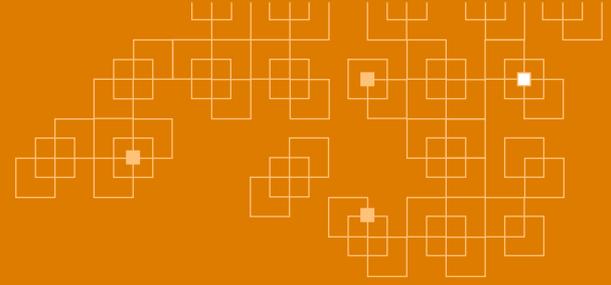
For Collaborative ResearchSM

Berkeley's Hub for Regulatory Science



EA Pharma Co., Ltd.

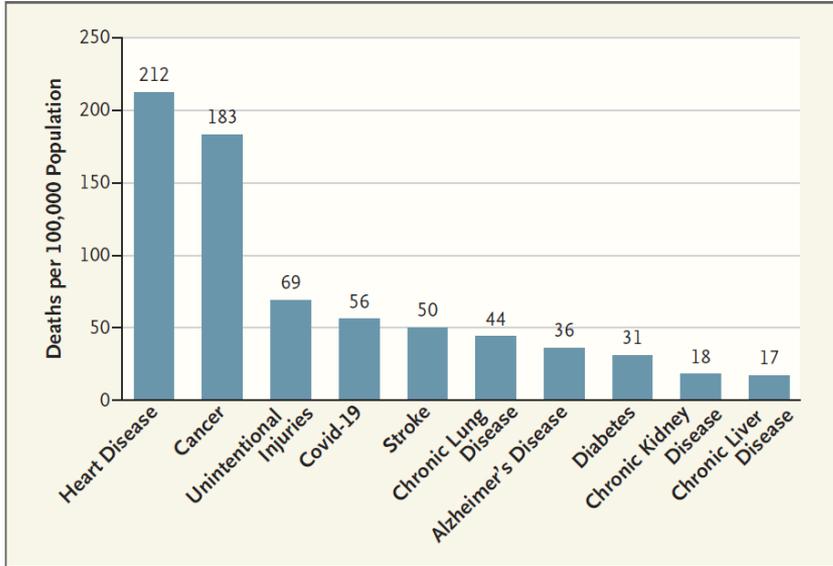




Liver Forum 2024 Theme: *Building a broad coalition*

Addressing the Challenge of Common Chronic Diseases — A View from the FDA

Haider J. Warraich, M.D., Hilary D. Marston, M.D., M.P.H., and Robert M. Califf, M.D.



Crude Mortality for the 10 Leading Causes of Death in the United States, 2022.

Preliminary data are from the Centers for Disease Control and Prevention's WONDER database.

N ENGL J MED 390;6 NEJM.ORG FEBRUARY 8, 2024

- Wide disparities in prevalence and outcomes
- FDA: regulatory, scientific, and public health agency
 - Support development of effective and accessible interventions
 - Improve the way evidence is generated
 - Collaboration among stakeholders

Strategies:

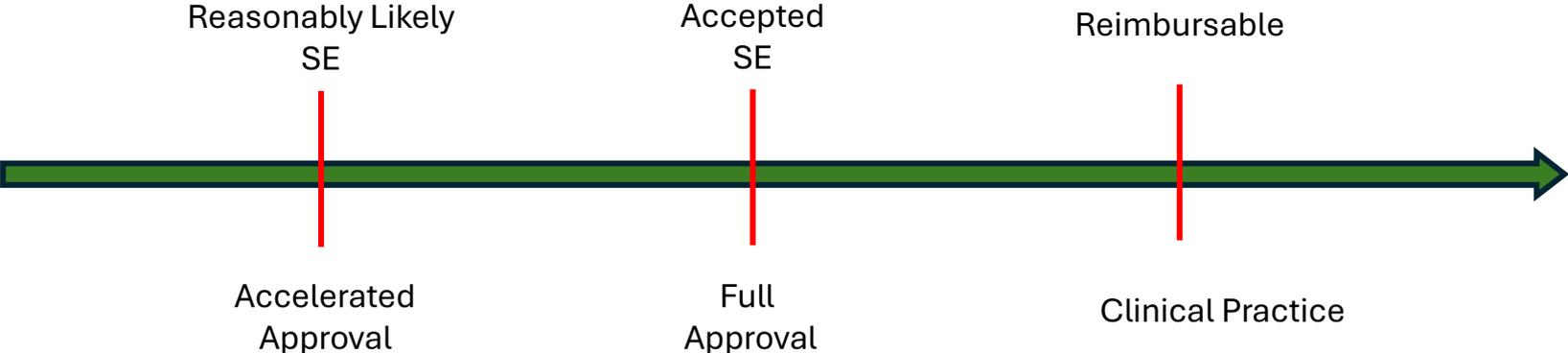
- Transform evidence-generating methods
- Make better use of technology
- Develop coherent approaches to issues across chronic diseases
- Foster patient-centered innovation

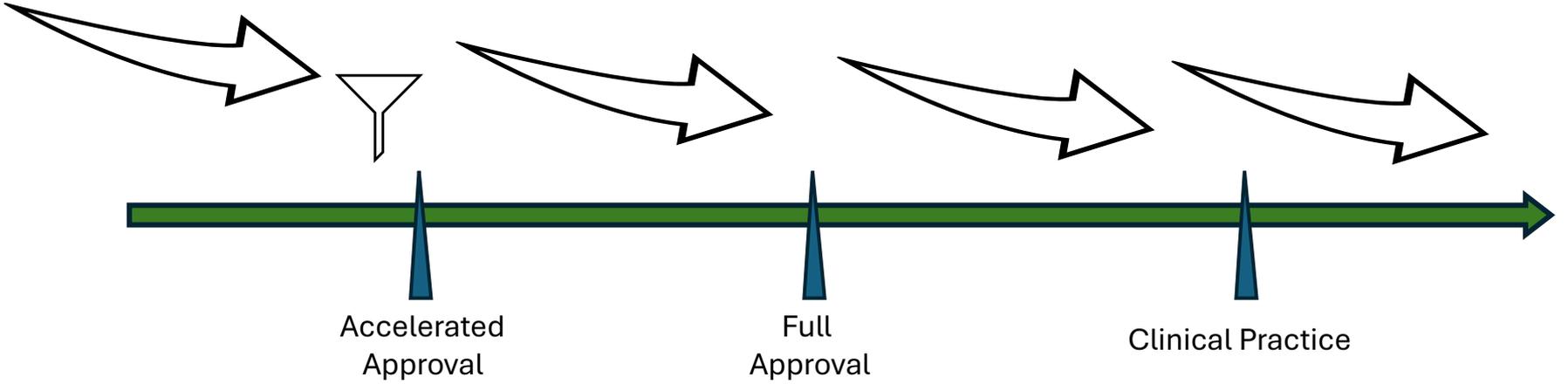
“There is an urgent need for a research environment that facilitates prospective development and evaluation of reliable biomarkers and surrogate end points for outcomes of interest to overcome the challenge that many candidate therapeutics with promising results in phase 2 trials aren't found to effective in phase 3 trials”

“Requires a broad coalition”

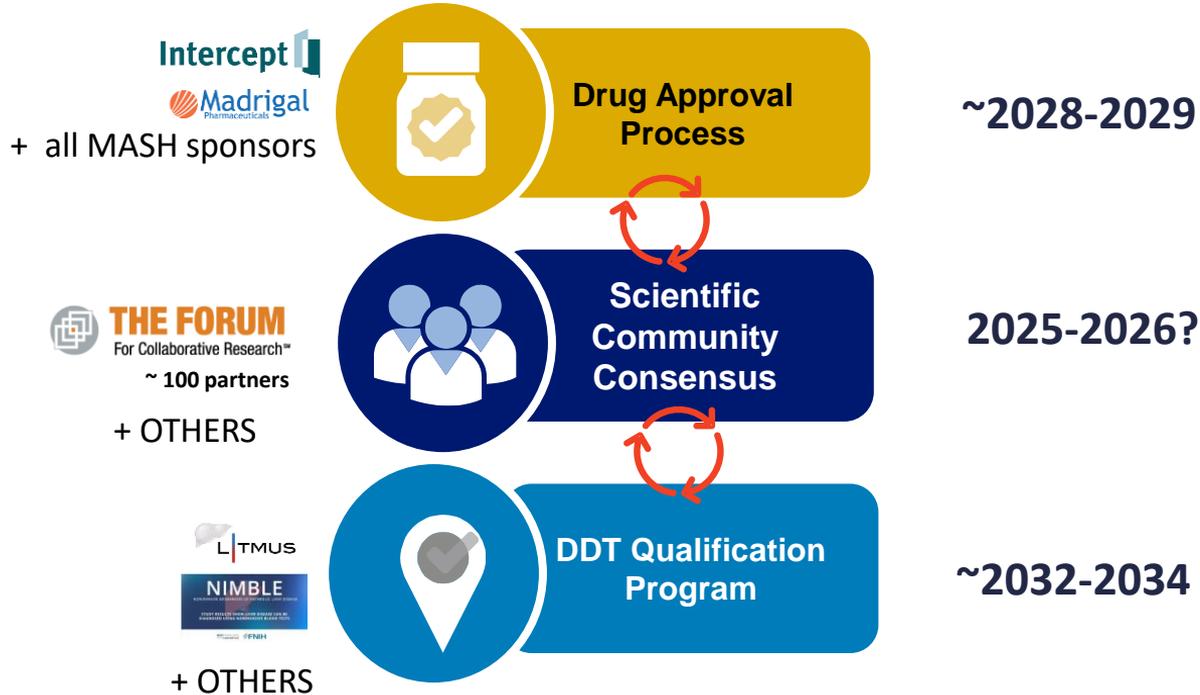


**Putting
patients
front and
center**





Three pathways to biomarker validation: a long-term endeavor



Can the scientific community come to consensus?

Liver Forum Proposal:

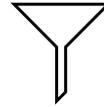
Facilitate scientific community consensus on RLSE* NITs

New Working Group

*Reasonably Likely Surrogate Endpoints

LF Consensus: NIT- based RSLE

NIT Properties & Measurements



- Pathophysiological properties *expected* to correlate w clinical benefit
 - Physical (liver stiffness)
 - Biological (fibrosis/inflammation)

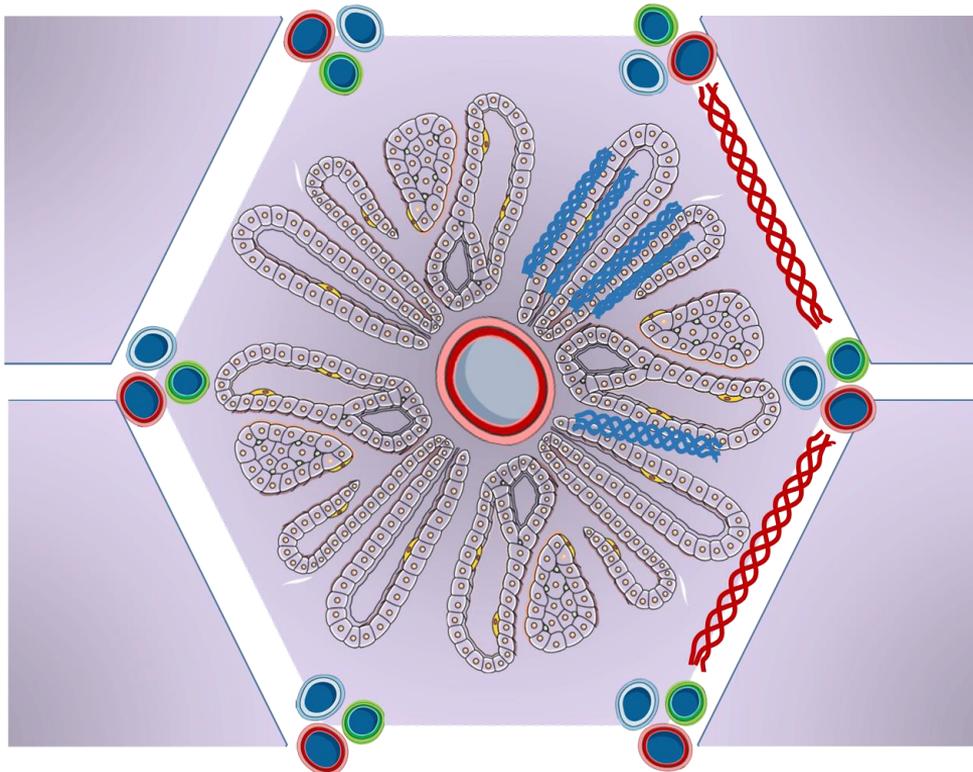


Fibrosis is not just fibrosis!

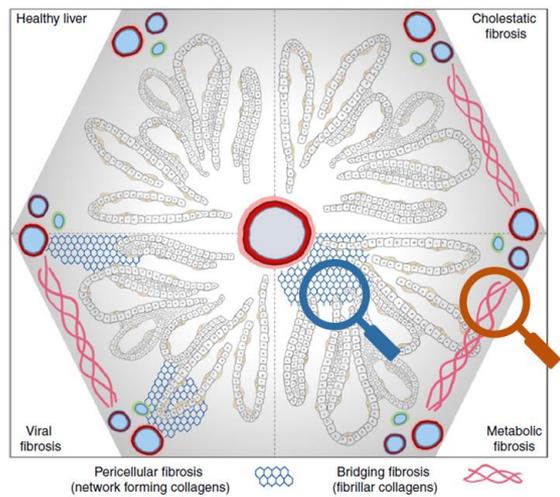
Pericellular basement membrane versus fibrillar collagens in the bridging fibrosis

Healthy Liver Lobule

Fibrotic Liver Lobule



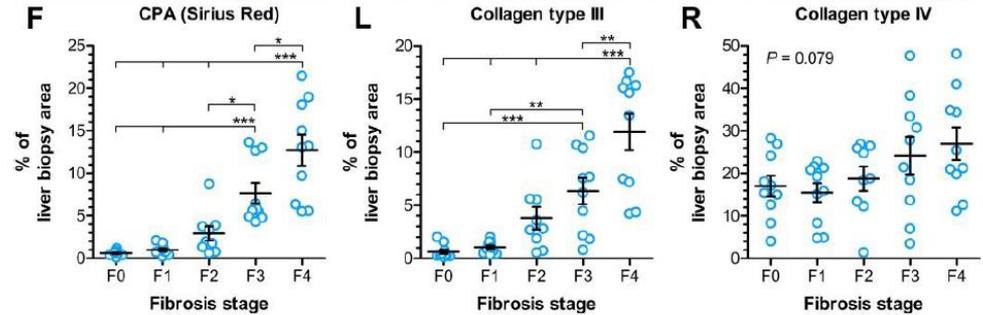
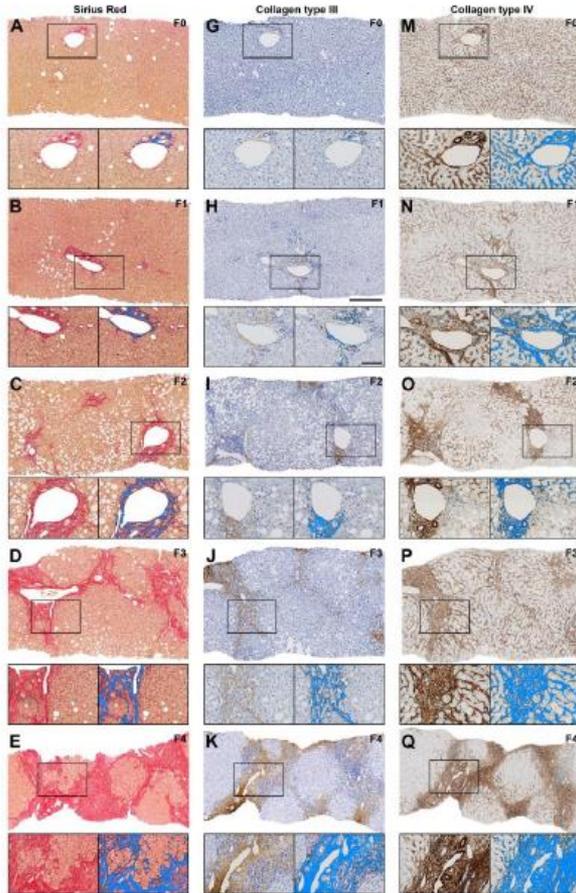
— Pericellular fibrosis (Network forming collagens) — Bridging fibrosis (Fibrillar collagens)



Basement membrane formation ➔ Reparative response

Interstitial matrix ➔ Dense matrix indicative of late stage disease

Type IV changes location, not amount !



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Stage-dependent expression of fibrogenic markers in alcohol-related liver disease

Mia Dahl Sørensen^{a,b}, Maja Thiele^{b,c}, Aleksander Krag^{b,c}, Samuel Joseph Daniels^d,
Diana Julie Leeming^d, Morten Karsdal^{d,e}, Sönke Detlefsen^{a,b,*}

^a Department of Pathology, Odense University Hospital, Odense, Denmark

^b Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark

^c Fibrosis, Fatty Liver and Steatohepatitis Research Centre Odense (FLASH), Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark

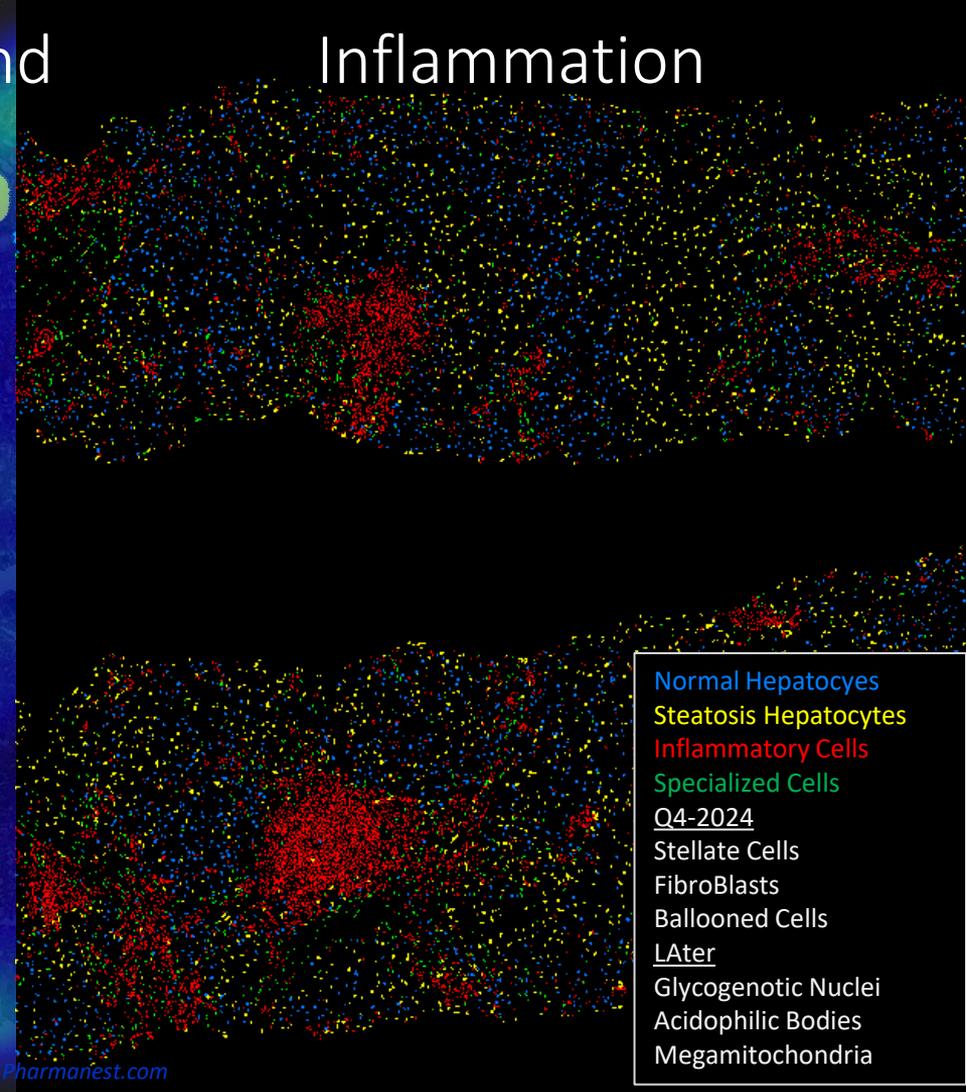
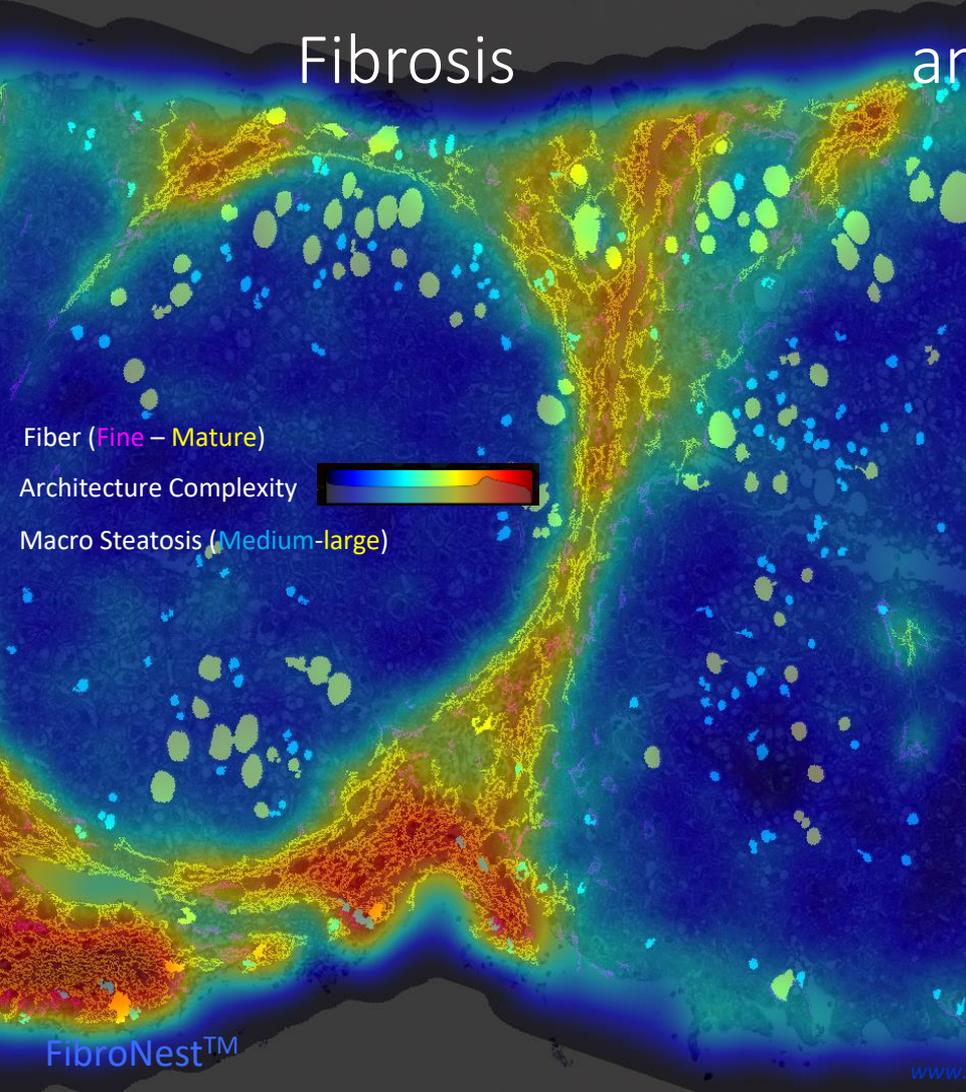
^d Nordic Bioscience A/S, Herlev Hovedgade, Herlev, Denmark

^e Department of Molecular Medicine, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark

Fibrosis

and

Inflammation

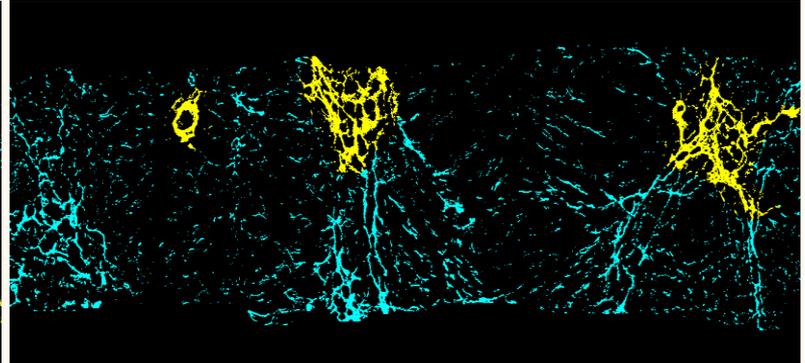
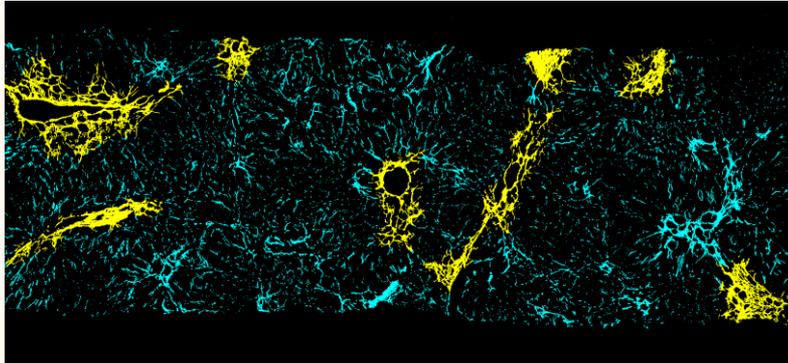


Closer Look at the Collagen Fibrosis

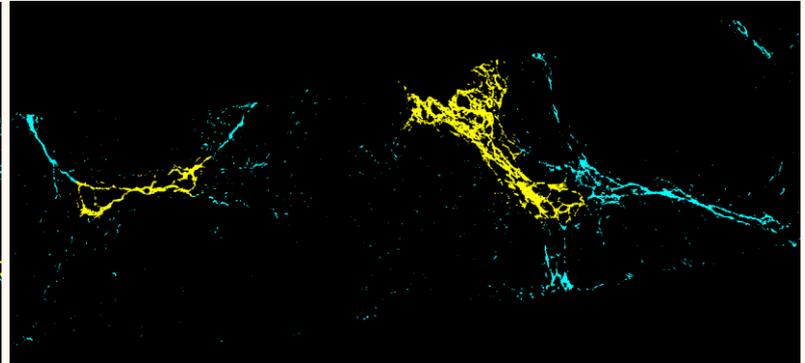
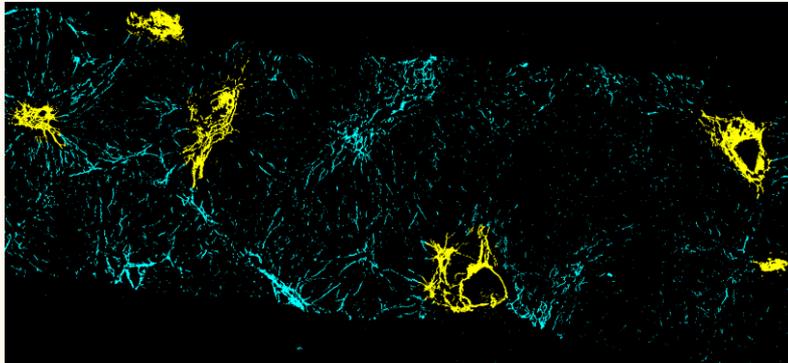
Baseline F2 → End of Treatment F2

Baseline F3 → End of Treatment F3

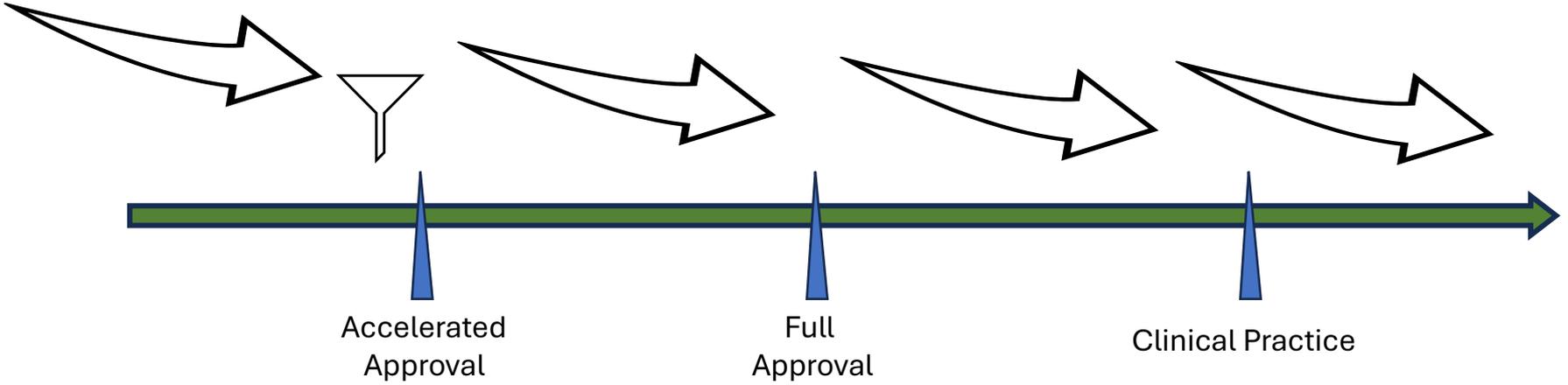
Before
Treatment

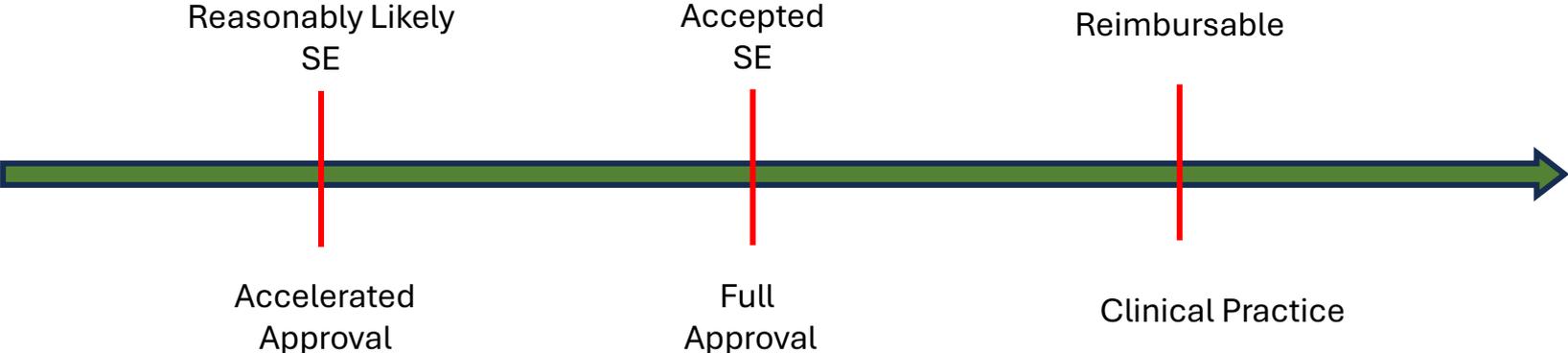


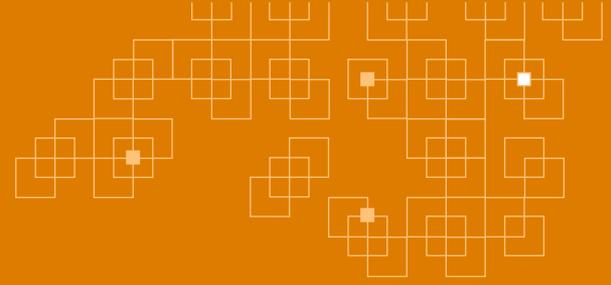
End of
Treatment



 PT/CV collagen
 PS collagen







All hands on deck

Data sources to consider

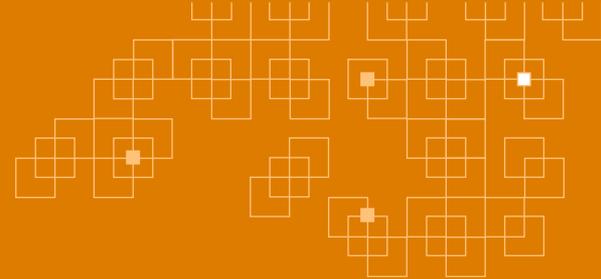
Potential sources of data to support a RL surrogate

- Randomized clinical trial **treatment-group level** data evaluating relationship between change in surrogate and change in clinical endpoint
- **Individual patient-level** data from intervention trials
 - May or may not be a correlation; interpretation and limitations if present or not present
- **Observational data**
 - *Natural history study / cohort data (e.g., registry)*
 - *Epidemiological data*
- **Mechanistic data** showing the role of proposed surrogate in disease pathogenesis
- **Human drug pharmacodynamic studies** showing changes in surrogate leading to modulation of putative causative pathways
- **Human genetic data**
- **Translational animal models**

Usually
more
limited
Information

Primary
Source

*Reasonably
likely
surrogate /
rare disease*



Liver Forum MASH Placebo Database

MASH PDB – Potential Research Questions

- **Natural history of MASH in untreated trial patients**
- Comparability of RCT patients to “real world” patients
- Predictors of disease improvement, stability, worsening
- Fluctuation in safety parameters in untreated patients
- Analysis and prediction of screen failures
- Application of AI/ML to paired biopsies
- Comparison of causal inference and other analytical methods
- **Shared placebo arm for future trials**
- Others?



**Maximizing
Data Potential**



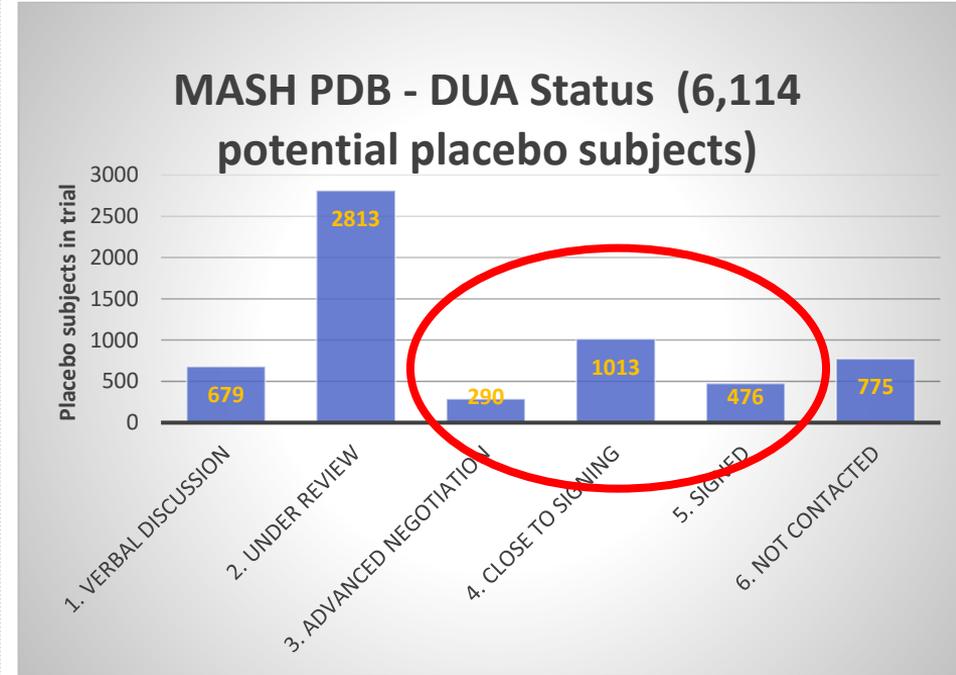
**Data-Driven
Questions &
Solutions**

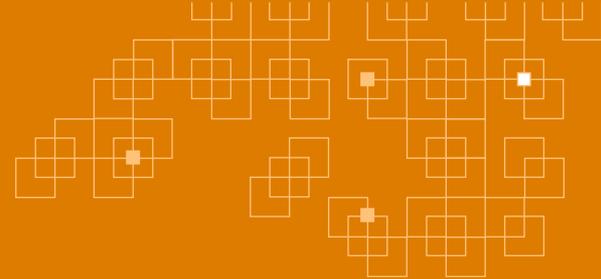
Data Sources & Data Availability

As of 30-August-2024



- Invited to participate
 - All completed phase 2 and phase 3 studies
- Potential # of placebo patients: >6K
 - Signed / data received: 476 (2 companies plus five clinical trials from NIH NIDDK)
 - Close to signing – 1,013 (4 companies)
 - Advanced negotiations – 290 (1 company)
 - Under review / strong commitment: 2,813 (10 companies)
 - Verbal discussion – 679 (5 companies)
 - Declined to share data: 1



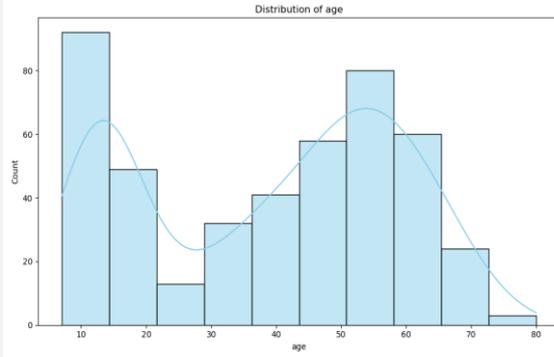


MASH Placebo Data – Data merging and initial analysis

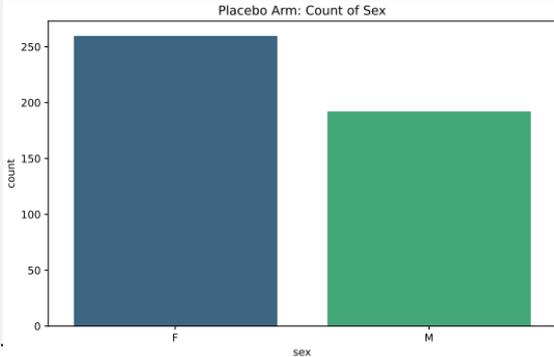
Patient Data Distribution

- Demographics

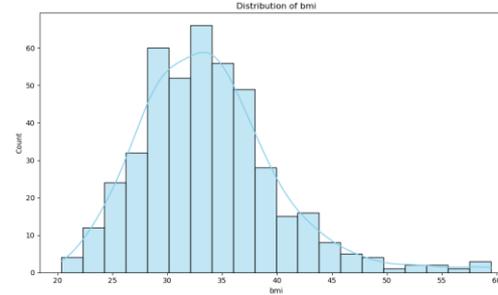
Age



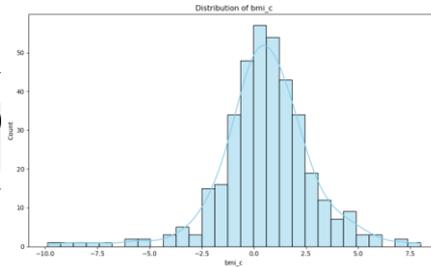
Gender



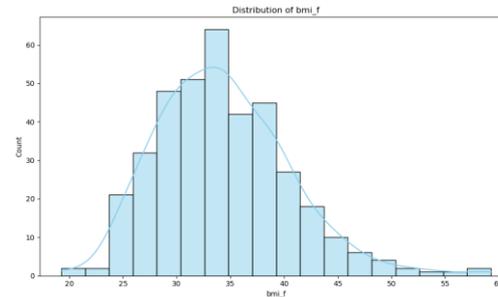
BMI - baseline



BMI - changes:



BMI - endpoint follo



Routine Laboratory Biomarkers

- Baseline

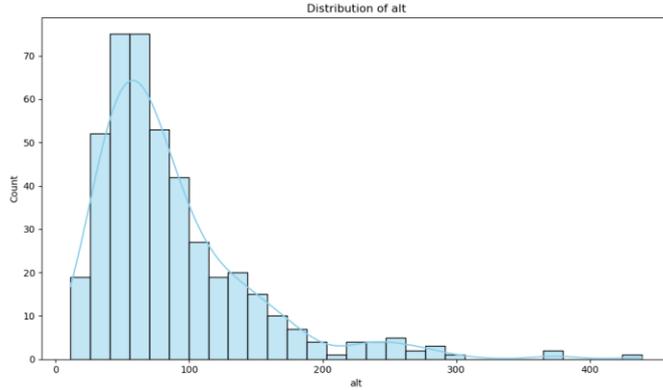


THE FORUM

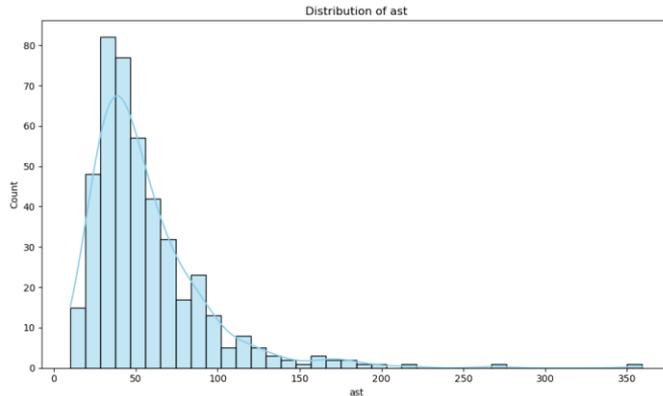
For Collaborative ResearchSM

Berkeley's Hub for Regulatory

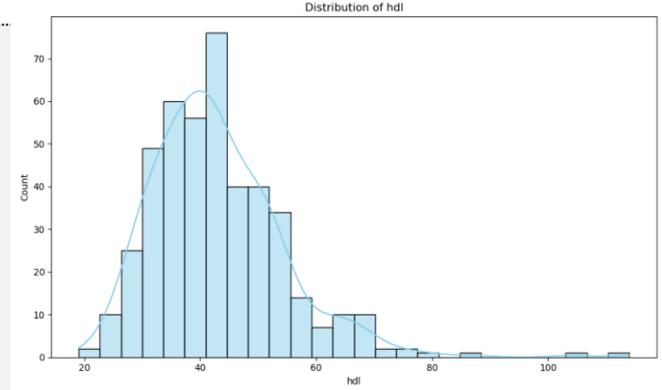
■ ALT



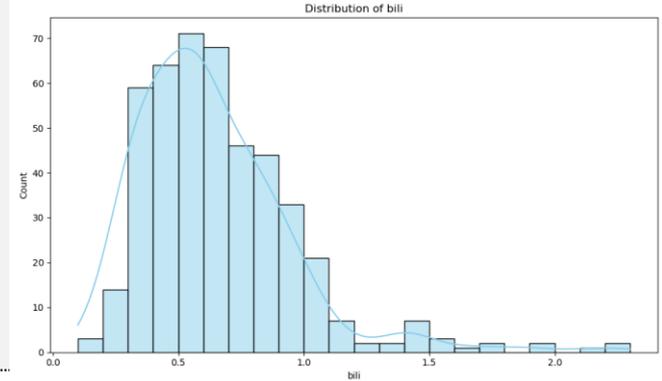
■ AST



■ HDL



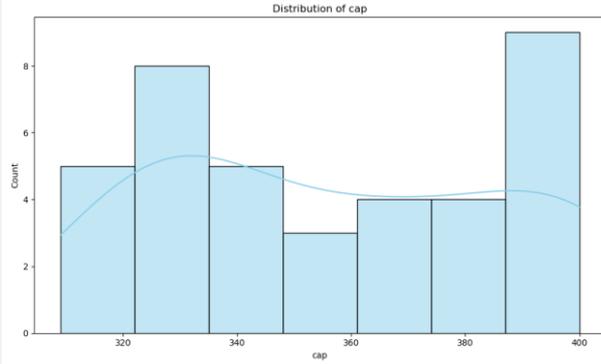
■ Bilirubin



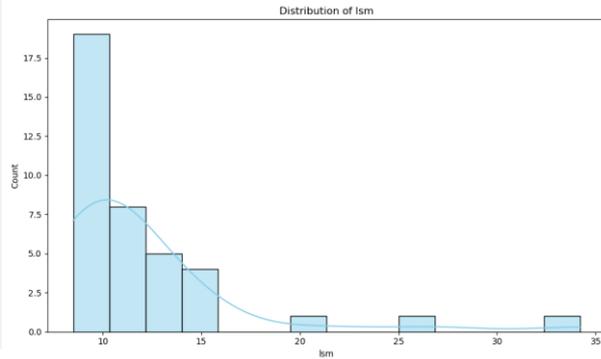
NITs

- Baseline

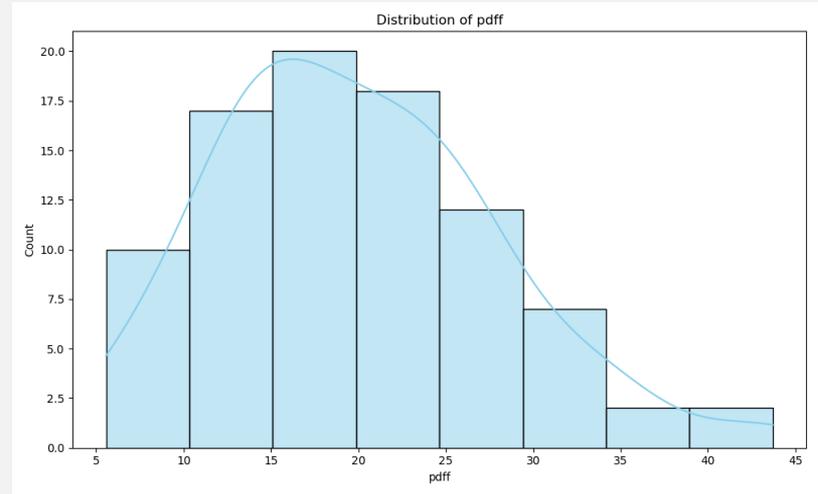
■ CAP



■ LSM



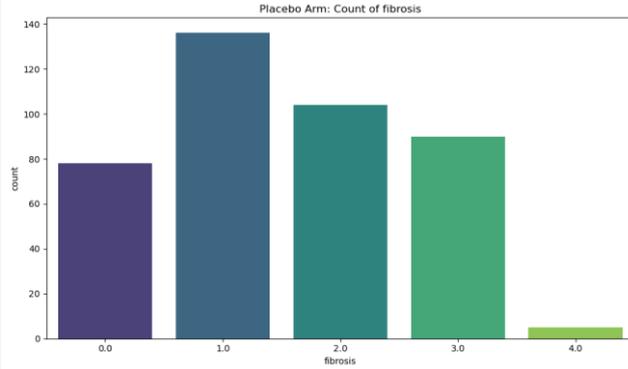
■ MRI-PDFF



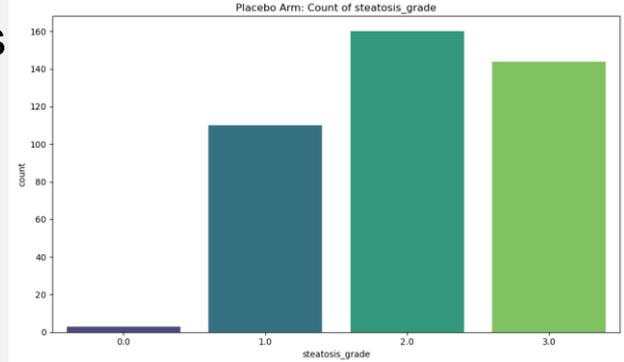
Liver Histology

- Baseline

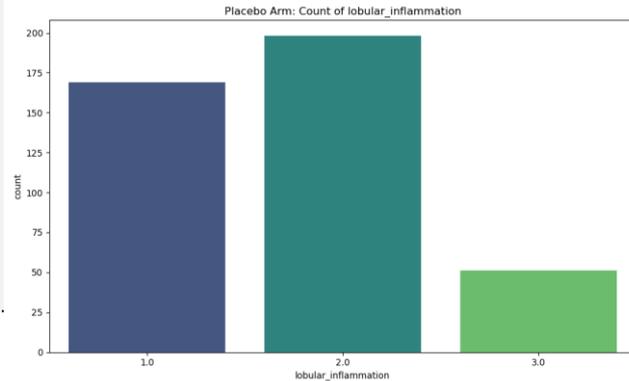
Fibrosis



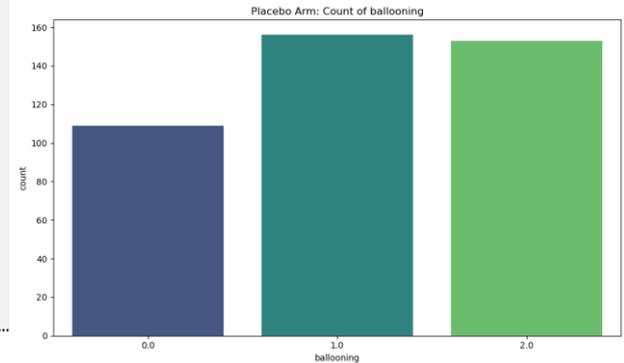
Steatosis



Lobular Inflammation



Ballooning



Exploratory Analysis

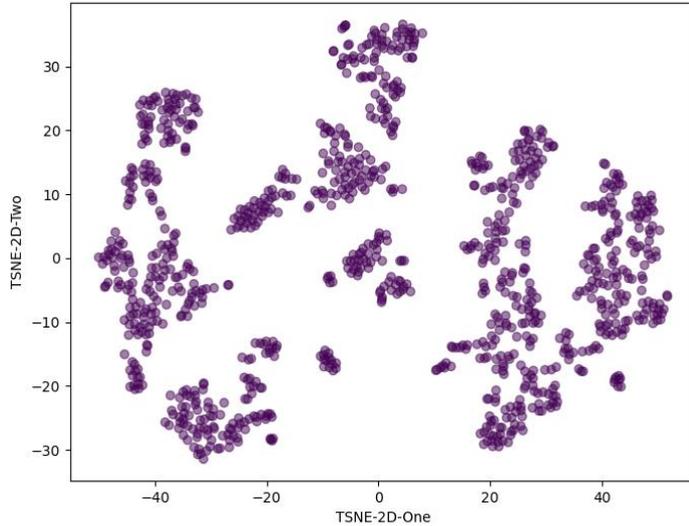
t-SNE (t-distributed Stochastic Neighbor Embedding)

- t-SNE effectively reduces high dimensions non-linear relationships to 2D or 3D while preserving the local structure of the data, making it easier to visualize complex relationships.
- To identify groups of patients with similar conditions, responses to treatments, or other relevant medical characteristics.
- Data exploration:
 - understand the underlying structure of the data without making strong assumptions
 - discovering new patterns

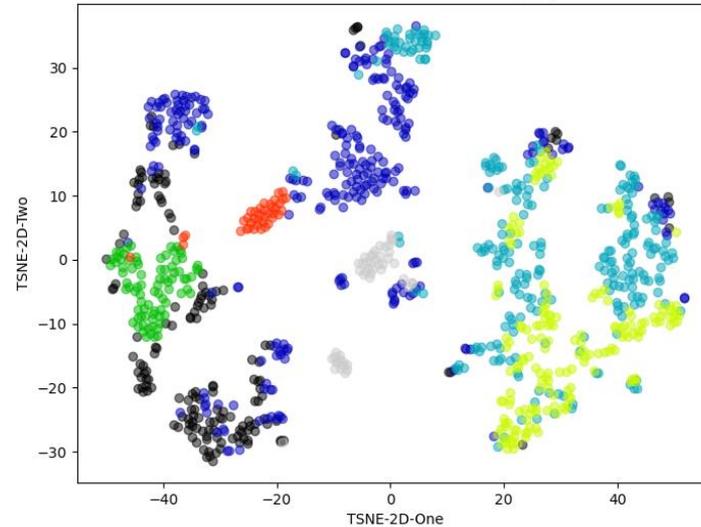
Preliminary Analysis

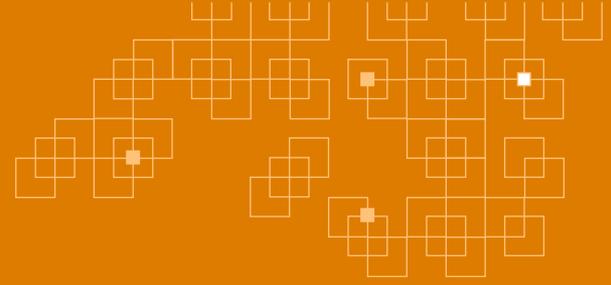
■ 2D

t-SNE visualization of Patient Groups



2D t-SNE Visualization of Patient Groups by Trial





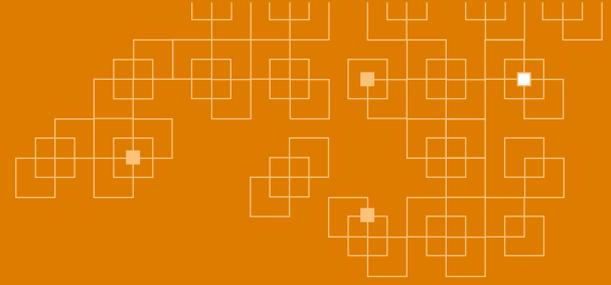
Expanding Vision

"A life science database for all hepatic indications"

Michael Cooreman



- Growing need & interest for data aggregation and analysis
 - Digital AI/ML Histology Working Group
 - Image analysis
 - NIT for RLSE Working Group
 - Radiology Working Group
 - Genetic and –omics data
 - PSC and PBC interest
 - Beyond placebo data: treatment data, baseline data ...
 - Beyond clinical trial data: Real-world data and evidence (RWD/RWE)



Next generation data science at the intersection of regulatory science and public health

Thank you!

- Slides
 - Margot Yann and Chris Hoffman
 - Forum DAC
 - Dean Tai
 - Mathieu Petitjean
- Liver Forum team!!





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