NASH PDB WG Update

Manal Abdelmalek, Mayo Clinic

Michael Cooreman, Inventiva Pharmaceuticals

The Liver Forum Welcomes:

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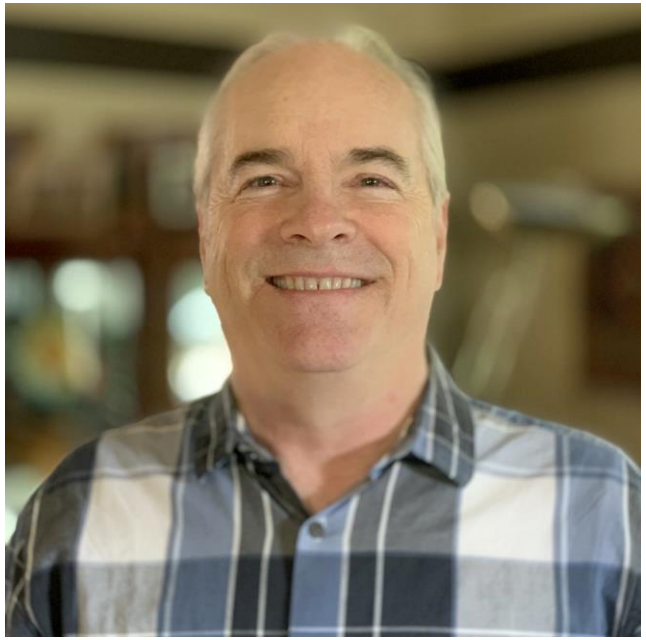
For Collaborative Research℠

Chris Hoffman, PhD

IT & Operational Director



- Experience leading a set of research computing services and projects designed to facilitate research across the Berkeley campus.

- Expertise with complex challenges related to research involving highly sensitive data; campus-wide Research Data Management Programs; IRB; and Information Systems.

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Zachary Rooney, MSCS

Research Associate

• Experience in Java, Python, C, Swift, MIPS, and in programming biomedical devices and in storing health data for patient and health care providers' use.

• Knowledge of programming languages, computer systems, and computer networking building a diverse portfolio with data structures, algorithms, and computer systems examples.

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Margot Yann, PhD, M.Eng

Senior Computational and Data Science Research Specialist

- Experience in research and applications using Deep Neural Networks, Bayesian Networks, Multiagent Learning, and Game Theory—and processes at the forefront of artificial intelligence.
- Hands-on big-data experience in Natural Language Processing (NLP), Computer Vision, and Electronic Health Records (EHR) both in industry and academia.
- Wide background and expertise in AI & ML in healthcare.

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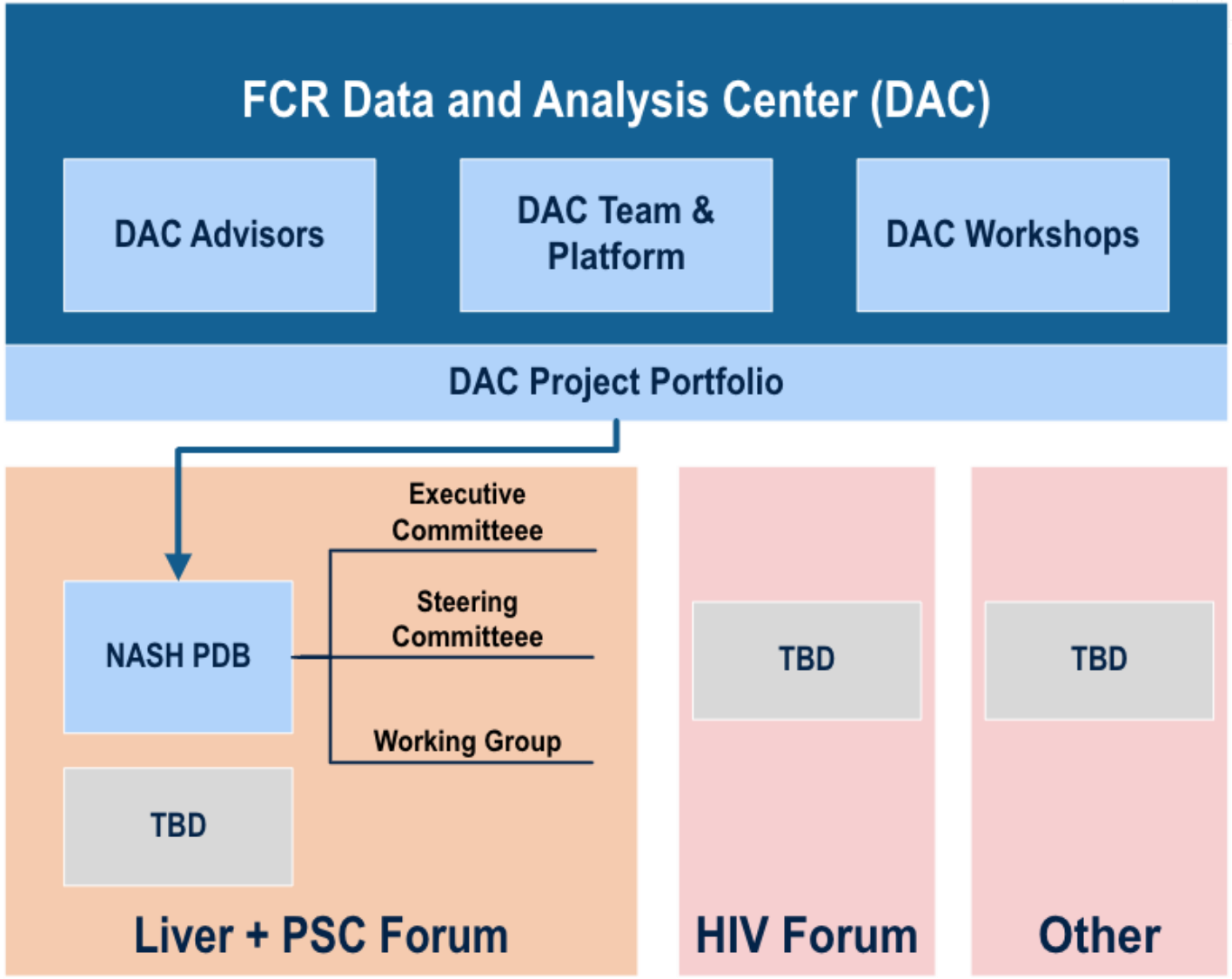
Samantha Berman, MSc, BSc

Research Data Analyst

- Expertise in mathematical modeling and longitudinal public health studies.

- Experience integrating national health datasets, dozens of longitudinal health-related studies, and other social and environmental dataset.

DAC Organization Model



Importance & Value of Data Sharing

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- Develop better tools to stratify patient populations/assess treatment benefits
- Promote development of biomarkers, simulation tools to improve clinical trial design; improve likelihood of success
- Reduce risk/increase confidence
- Reduce time, size and cost of phase 3 trials through optimization

Galson et al. *Failure to fail smartly*. Nat Rev Drug Disc 2021
Thompson & Parekh. *Value of data sharing to advance drug development: a regulatory perspective*. TIRS 2021

Liver Forum Placebo Arm DB Project

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Neutral venue for data sharing and analysis that aims to facilitate responsible use of data through collaboration to honor patient contributions to clinical research.

- **Aim:** To combine the power of a PDB and novel analytics to advance regulatory science and increase the quality, efficiency and output of clinical trials to accelerate drug development
- **Strategy:** pooling placebo arms from all completed Phase 2 and Phase 3 NASH studies

Themes/questions NASH PDB Project

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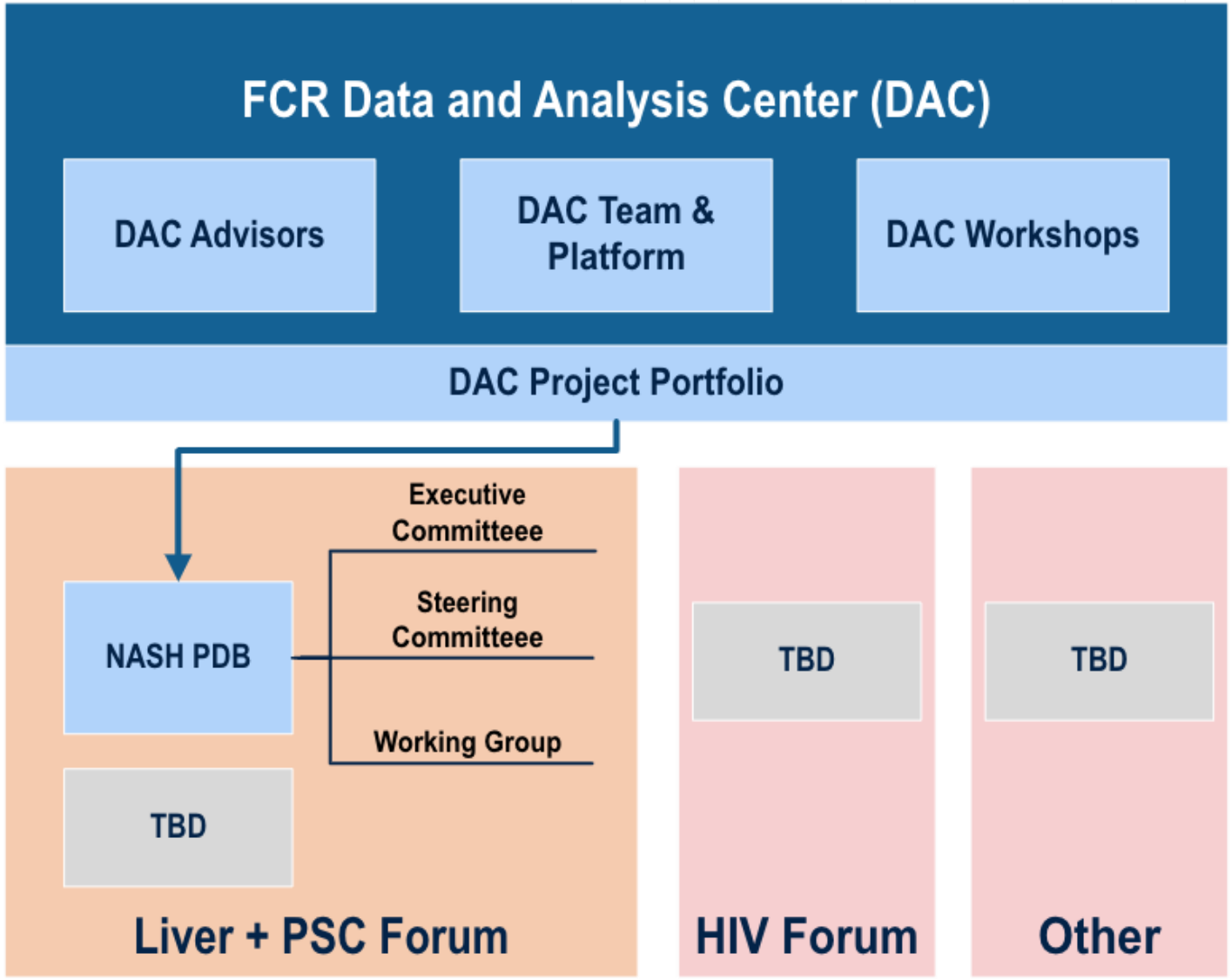
- Natural history of NASH in untreated trial patients
- Comparability of RCT patients to “real world” patients
- Predictors of disease improvement, stability, worsening
- Fluctuation in safety parameters in untreated patients
- Screen failures
- Application of AI/ML to paired biopsies
- Comparison of causal inference statistical methods
- Shared placebo arm in future trials
- Others?

NASH PDB Project Governance

- Executive Committee
- Steering Committee
- Working Group
  - subgroups



Questions about data: Principles & Access to the database

- Support the Forum's projects by maximizing the impact of each data point, reduce drug development failure rate, and potentially decrease R&D costs
- Protect subject privacy
- Protect partner data
- Comply with relevant laws and policies
- Be transparent with Forum partners and stakeholders
- **Direct Access to the database is restricted to:**
  - FCR-DAC team
  - Regulatory authorities by invitation

Statistics sub-Working Group

- Open to statisticians from industry, regulatory agencies, academia
  - Assess the importance of baseline and time-varying factors in predicting spontaneous resolution vs. NASH progression
  - Identify novel baseline patient stratifications for these outcomes
  - Develop individualized machine learning predictive algorithms for these outcomes
  - Plan annual liver-specific statistical workshops

Outputs

- Published peer-reviewed papers
- Sponsor-specific requested analyses
- Potential placebo-arm patient contribution to new RCTs

NASH Placebo Arm Database

- Challenges:
  - Informed consent forms around data sharing
  - Inclusion and exclusion criteria
  - Proportional balance of data contribution per sponsor
  - Country specific requirements and restrictions
  - Protocol differences in terms of timing data – periodicity of data
  - Harmonization of data across clinical trials (C-DISC)

NASH Placebo Arm Database

- Opportunities:
  - Data driven clinical trial design for future trials
  - Cost savings – reduce the number of placebo patients needed in future trials
  - Standardization of clinical trials
  - Placebo sharing in future trials
  - Understand:
    - Why the placebo groups differ so much?
    - Understanding rare events

NASH RCT Placebo Data Base
Guidance for discussion

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- The project
  - What are the next steps to build the database?
    - Commitment; clarity of scope
  - It is not easy, but once achieved invaluable
  - Many pros; any cons?
- A trove on information relevant for patients, healthcare providers, Health Authorities and drug developers
  - Understanding of the condition by patients, conversations with their physicians
  - Improve efficiency of clinical studies
    - External placebo data - matched
    - Response to placebo in defined patient population as a known (a statistical prior)

NASH RCT Placebo Data Base
Guidance for discussion

- Information - knowledge
  - (natural) course of NAFLD/NASH
    - In a controlled environment – Hawthorne effect
    - As a metabolic-immune liver disease
    - Symptoms, quality of life… is NASH really asymptomatic?
  - What influences effects in placebo arms?
    - Patient background
    - Setting of healthcare facility
    - Duration of treatment
    - Geography
    - History, duration of disease
    - Histological response: reader variability?
    - …
  - Scientific-medical progress benefits society