Translational Science in Drug Development: Surrogate Endpoints, Biomarkers, and More

Duke-Margolis Center for Health Policy | Virtual Meeting

May 24-25, 2022

Duke | MARGOLIS CENTER *for* Health Policy

Welcome and Overview | Day 1

Mark McClellan

Director, Duke-Margolis Center for Health Policy

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Meeting Agenda (Day 1)

12:00 pm Welcome and Opening Remarks

12:20 pm Session 1: Enhancing Clinical Development Programs by Leveraging Translational Science Throughout the Drug Development Lifecycle

1:45 pm Break

2:00 pm Session 2: Identification and Development of Novel Surrogate Endpoints for Use in Clinical Development Programs

3:35 pm Concluding Remarks

3:45 pm Adjournment

Meeting Agenda (Day 2)

12:00 pm Welcome and Overview

12:10 pm Session 3: Clinical Validation and Regulatory Acceptance of Biomarkers as Surrogate Endpoints

1:50 pm Break

2:05 pm Session 4: Beyond Surrogate Endpoints: Other Ways Translational Science Can Support Drug Development

3:30 pm Session 5: Opportunities and Challenges for Incorporation of Translational Science in Clinical Development Programs

4:15 pm Closing Remarks

4:25 pm Adjournment

All times listed in EDT

Opening Remarks from FDA

Peter Stein

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Session 1: Enhancing Clinical Development Programs by Leveraging Translational Science Throughout the Drug Development Lifecycle

12:20 pm – 1:45 pm EST

Peter Stein

Director of the Office of New Drugs

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

U.S. FOOD & DRUG ADMINISTRATION

Translational Medicine: A Regulatory Perspective

Peter P. Stein, MD
Director, Office of New Drugs
CDER/FDA

Duke-Margolis Meeting: Translational Science in Drug Development: Surrogate Endpoints, Biomarkers, and More

Introduction

- Translational science – translational biomarkers – play key roles throughout drug development – *and* in supporting regulatory decision-making
- Translational work, e.g., biomarkers, may not fulfill its potential in drug development unless the discovery phase is followed by adequate analytic and clinical validation
- Partnering with drug developers, consortia can allow translational science discoveries to fulfill their potential in drug development

BEST Resource: Biomarkers, EndpointS, and other Tools

- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- Created by the NIH-FDA Biomarker Working Group
- Publicly available a: http://www.ncbi.nlm.nih.gov/books/NBK326791/
- BEST harmonizes terms and definitions and addresses nuances of usage and interpretation among various stakeholders, including:

- Biomedical scientists
- Translational and clinical researchers
- Medical product developers
- Patient/disease advocacy groups
- Government officials
- Clinicians

BEST (Biomarkers, EndpointS, and other Tools) Classification: range of biomarker types

- Susceptibility / risk biomarker
- Diagnostic biomarker
- Prognostic biomarker
- Monitoring biomarker

Measures of disease presence and status

- Predictive biomarker
- Pharmacodynamic/Response biomarker – including surrogate endpoints
- Safety biomarker

Measure aspects of response to treatment

Potential "regulatory" roles of translational medicine

Some key roles in early clinical development

- Demonstrating human target engagement
- Dose selection / E-R / supporting MIDD
- Initial PoC with PD endpoints
- Safety evaluation
- Study population selection
- Study enrichment

Some key roles in late clinical development

- Study population selection for target disease: (diagnostic BMs)
- Study enrichment: prognostic or predictive BMs
- Safety biomarkers
- PD BM response to correlate with effectiveness endpoints
- Surrogate endpoints

Some key roles in supporting regulatory decision-making

- Defining indicated population where benefit outweighs risk for PI
- Surrogate endpoints to support accelerated or traditional approval
- Providing confirmatory evidence to support substantial evidence of effectiveness
- Providing supportive evidence
- BM supporting biosimilar approval

Substantial evidence - a statutory standard for approval: role of confirmatory evidence

- *As defined in Section 505(d), substantial evidence is*:
  - "evidence consisting of **adequate and well-controlled investigations**, including clinical investigations, by **experts qualified by scientific training and experience to evaluate the effectiveness** of the drug involved, on the basis of which it could **fairly and responsibly be concluded** by such experts that the drug will have the effect it purports or is represented to have **under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."**

- The FDA *standard* requirement for *two* A&WC studies
- Replication as scientific standard approach: reduces risk of false positive findings, bias or confounding in a single trial

- FDAMA (1997) added *flexibility*: one A&WC trial and ***confirmatory evidence***, if considered appropriate

Single trial plus confirmatory evidence: types of evidence

Single A&WC clinical trial supported by:

- **Results from trials in a related indication**
  - **Two or more completed A&WC trials demonstrating efficacy in an indication** – FDA may accept one trial in a related indication (i.e., similar drug MOA in producing clinical benefit)
- **Compelling mechanistic information from earlier *clinical* or *non-clinical* studies**
  - Reliance on pharmacodynamic endpoint with well-established relationship to clinical endpoint
  - Reliance on well-established, translatable animal model
- **Well described natural history of disease**
  - Evidence clearly describing natural history of disease: may be natural history study, registry, compelling case series
- **Adequate and well controlled trials from other members of same drug class**
  - Same pharmacological target

The limitations of surrogate endpoints

- Not a direct measure of how a patient ***feels, functions*** *or* ***survives***
- Intended to reflect and predict clinical benefit not measure the outcome
- With a surrogate endpoint, the benefit to risk balance based on *assumptions regarding benefit*
  - Challenges of translating from **indirect measure** to **extent of clinical benefit**
  - Often more limited trial safety exposure with surrogate endpoint – so less precision on "risk"
  - **However**, can still estimate "quantum" of benefit vs harm, *even if more challenging*
- And biomarkers may *fail* to predict clinical benefit – *residual risk that strength (or presence) of relationship to clinical endpoint is not valid*
  - Many examples of "sure thing" biomarkers that failed – e.g., NSVT and death

Using confirmatory evidence to meet substantial evidence of effectiveness

- Pharmacodynamic or mechanistic information providing confirmatory evidence must be robust, using biomarkers that are well understood
- *However*, sponsors often focus on the AWC trial – especially in rare diseases where only one such trial may be feasible
  - Common to have detailed discussions of AWC trial design – and little discussion of confirmatory evidence
- Approval based upon a "single" AWC trial requires highly persuasive evidence (essentially comparable to two positive trials) – a high bar
- Essential to **plan confirmatory evidence early in program** – not after the fact (i.e., when the single trial does not provide highly persuasive evidence)
- Work to enhance analytic and clinical support for proposed biomarker or other mechanistic evidence – **must start early and requires meaningful resource investment**
- Importance of meetings with FDA divisions to discuss / support planning

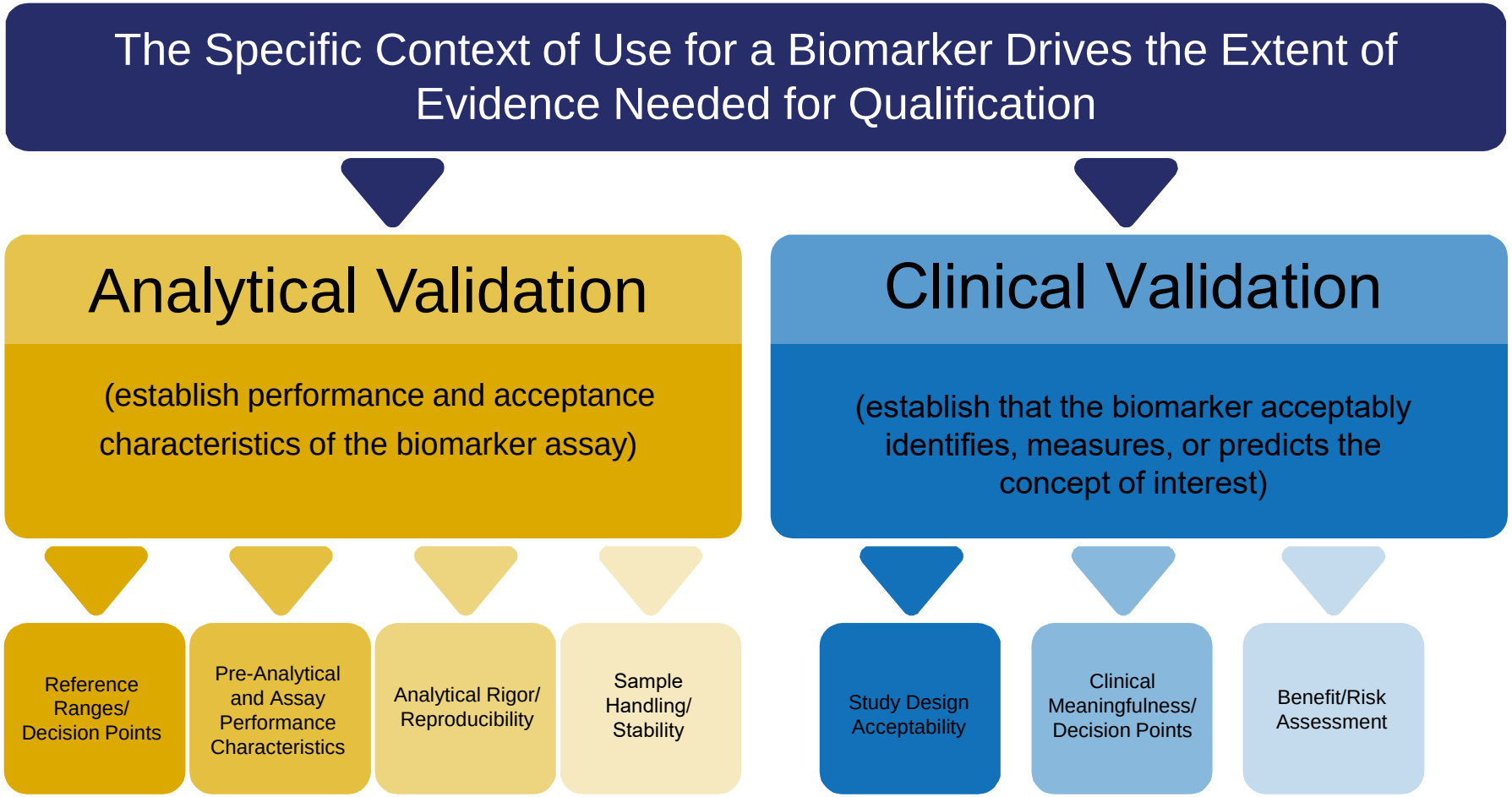
The challenges of biomarker development

- **Disease characteristics that challenge biomarker development**:
  - Slowly progressive, or rare, disorder impeding biomarker validation: long course to outcomes
  - Diseases that are genetically and phenotypically heterogeneous, especially with differences in pathogenetic mechanisms: multiple subtypes
  - Lack of widely accepted "gold standard" for diagnosis – creating "noise" for qualification of biomarker
- **Limited understanding of disease pathogenesis**
  - Many changes in proteomic, lipidomic, gene expression profile, changes in imaging etc – but limitations in separating pathogenic vs epiphenomenon ("downstream" of disease, or unrelated)
- Biomarker development *is a* **long and resource-intensive process**
  - Biomarker *discovery*: biased or unbiased screening in animal, clinical, epidemiological datasets
  - Early animal *translational* models
  - Clinical or epidemiology observational studies
  - *Analytic validation* efforts: assure accuracy / reproducibility of measure
  - Interventional studies with "gold standard" endpoints compared to candidate – with multiple different treatments (different MOAs) to show that BM works across drug classes

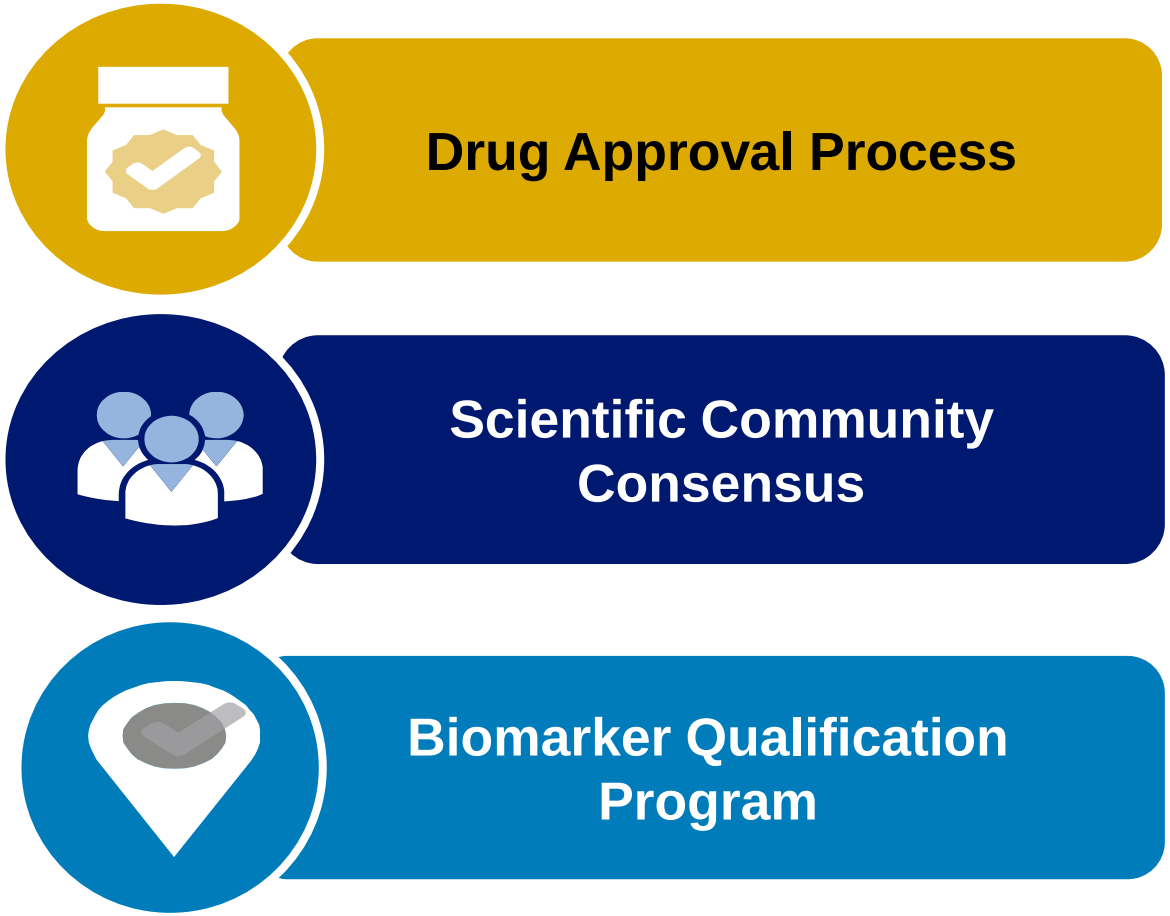
The challenges of biomarker development (cont.)

- **Many stakeholders** in the mix – with potential for **competing interests**
  - Academic investigators at multiple institutions, US and ex-US
  - Often several academic societies in disease area with different viewpoints and membership
  - Different companies – both drug and device-focused may be working in the area
  - May be different patient stakeholder organizations
- **Development program-related**
  - Lack of clarity on biomarker *purpose* – biomarker development program aimed too broadly, seeking to validate multiple COUs – ***lack of focus***
  - Lack of **adequate analytic validation** efforts early – unreliable assays undermining observations
  - **Lack of cohesive planning** – focused purpose, focused program
- **Lack of infrastructure** to align varying interests into cohesive development program
- **The challenge**: how to ***prioritize*** biomarker needs, ***focus*** resources, and ***integrate*** efforts across stakeholders

Analytical Assay and Clinical Validation Considerations in Biomarker Qualification



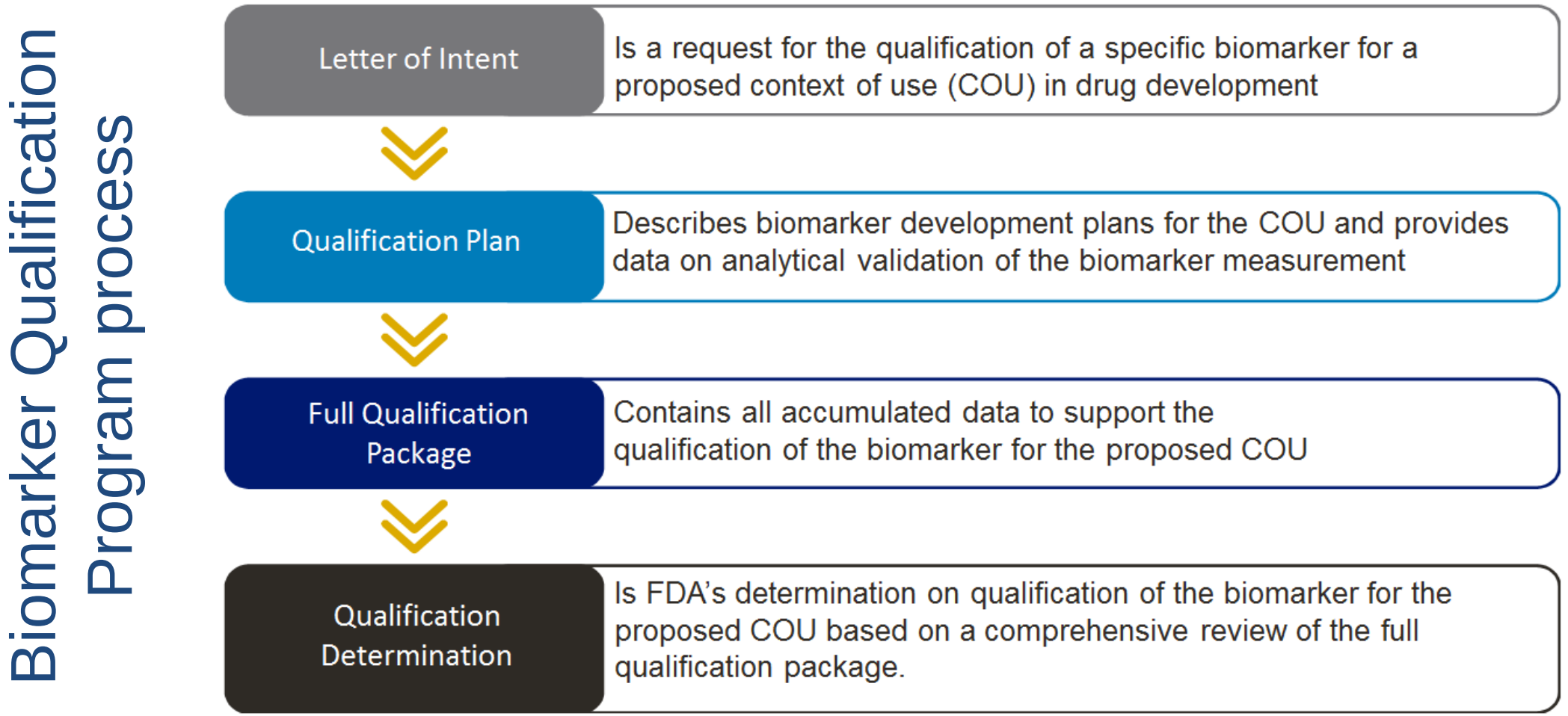
Biomarker Integration into Drug Development



Note: These pathways do not exist in isolation and many times parallel efforts are underway within or between pathways. All share common core concepts, are data-driven, and involve regulatory assessment and outcomes based on the available data.

Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration; Published June 2016, Duke-Margolis Center for Health Policy

Biomarker Qualification and 21st Century Cures DDT Legislation



Importance of Partnerships

- Qualification of biomarkers is a resource-intensive process
- Academic groups may not have funds or necessary data to qualify biomarkers for regulatory decision-making
- The challenge: how to *prioritize* biomarker needs, *focus* resources, and *integrate* efforts across stakeholders
- Public-private partnerships like FNIH, Critical Path Institute can play important role
  - Intermediary between patient groups, industry, academia, regulators to develop novel DDT's
  - Key role is to collect trial data, share biosamples, integrate datasets, analyze and share data
  - Public workshops offer opportunity for all stakeholders to share views
- Biomarker developers may want to seek partnership with drug developers to assist in analytic validation/clinical validation and incorporating the candidate biomarker in prospective clinical trials

New CDER Program: Accelerating Rare disease Cures (ARC) program

Vision: Speeding and increasing the development of effective and safe treatment options addressing the unmet needs of patients with rare diseases.

Mission: CDER's Accelerating Rare disease Cures (ARC) Program drives scientific and regulatory innovation and engagement to accelerate the availability of treatments for patients with rare diseases.

Learn more at: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cders-arc-program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Joni Rutter

Acting Director

National Center for Advancing Translational Sciences

National Institutes of Health

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Enhancing Clinical Development Programs by Leveraging Translational Science Throughout the Drug Development Lifecycle

Duke-Margolis Center for Health Policy and the U.S. Food & Drug Administration
May 24, 2022

Joni L Rutter, Ph.D.

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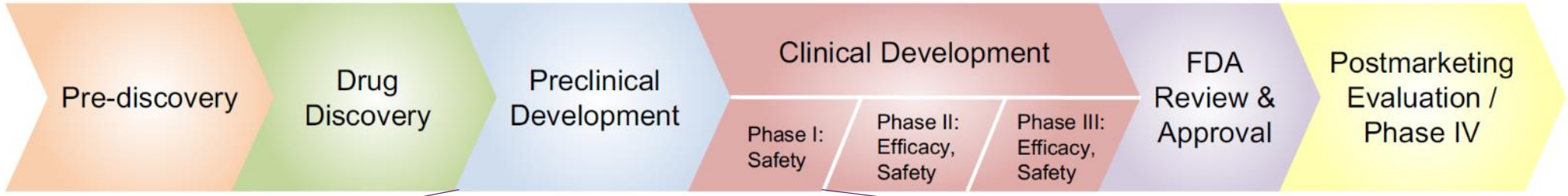
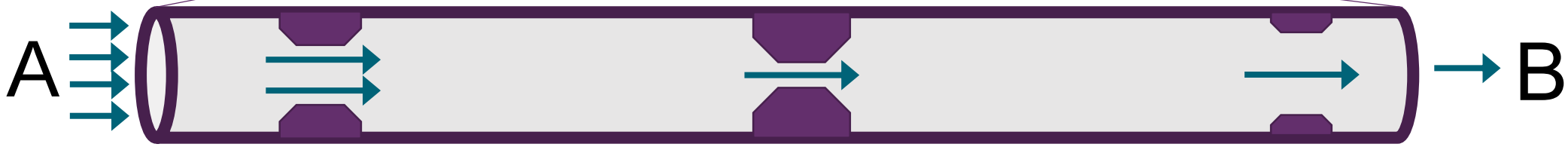
National Center for Advancing Translational Sciences

NCATS: Radically Re-engineering the Translational Pipeline Flow Rate

1. Translational Research (**Evolutionary**)





2. Translational Science (**Revolutionary**)

Translational Science

The **field of investigation** focused on understanding the **scientific and operational principles** underlying each step of the translational process.

Requires:

- Understanding common challenges or roadblocks to translation
- Determining the scientific and operational principles that can be utilized to remove the roadblocks
- Developing solutions that employ these principles and will be applicable to many research areas, diseases, and conditions.

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Pre-clinical

Human Physiologically-relevant Models

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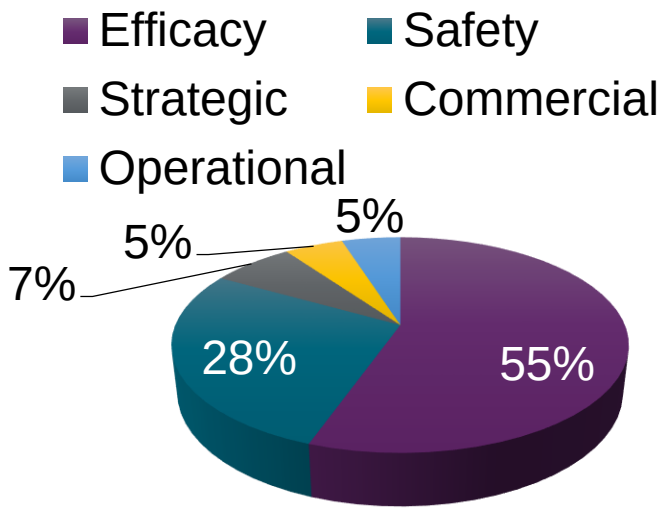
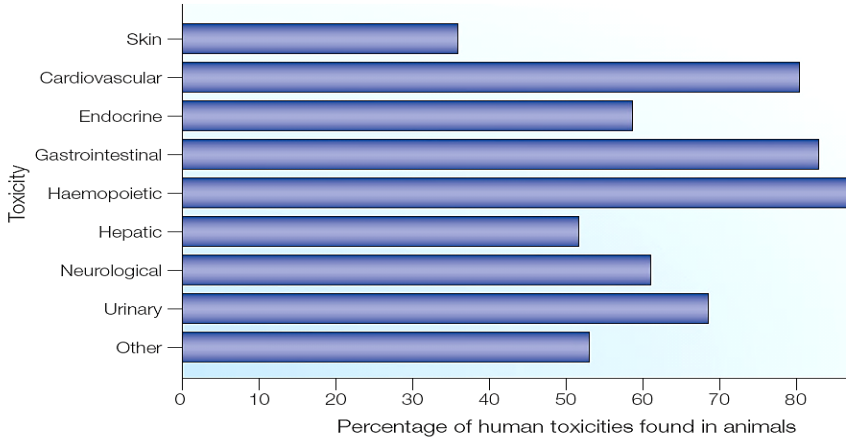
Translational Problems in Drug Development

- The percentage of drugs entering clinical trials resulting in an approved medicine is less than 12%
  - 55% fail due to lack of efficacy
  - 28% fail due to toxic effects in humans
- Average time to develop a drug takes 10-15 years
- Average cost to develop a drug to market, including cost of failures is $2.6 billion
- Current tools used for drug development involving 2-D cell culture and animal models do not always predict human response
- “One size fits all” approach

Drug Failure Modes



Concordance of Toxicities



Arrowsmith and Miller, Nature Reviews Drug Discovery, Volume 12, 569 (2013)

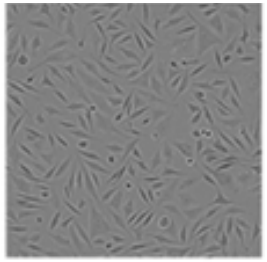
Cook et al., Nature Reviews Drug Discovery, Volume 13, 419 (2014)

NIH National Center for Advancing Translational Sciences

Mired in Old Drug Development Approaches

*(**PhRMA**, Biopharmaceutical Research Industry Profile, 2016)*

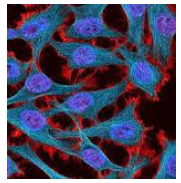
2D Cell Lines

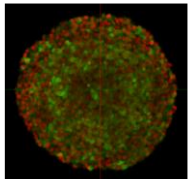


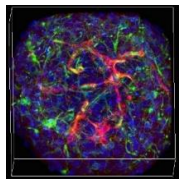
Mouse

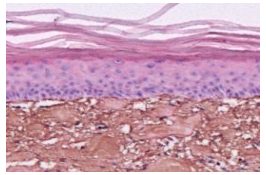
Human

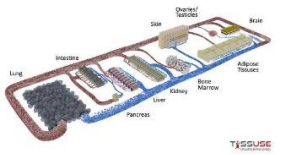
2D	Spheroids	Organoids	Printed Tissues	Organ-on-a-chip

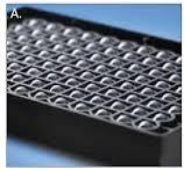


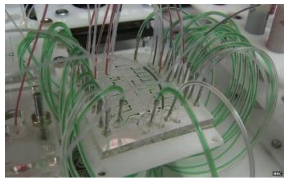












Need for new technologies and better predictive tools across the translational pipeline

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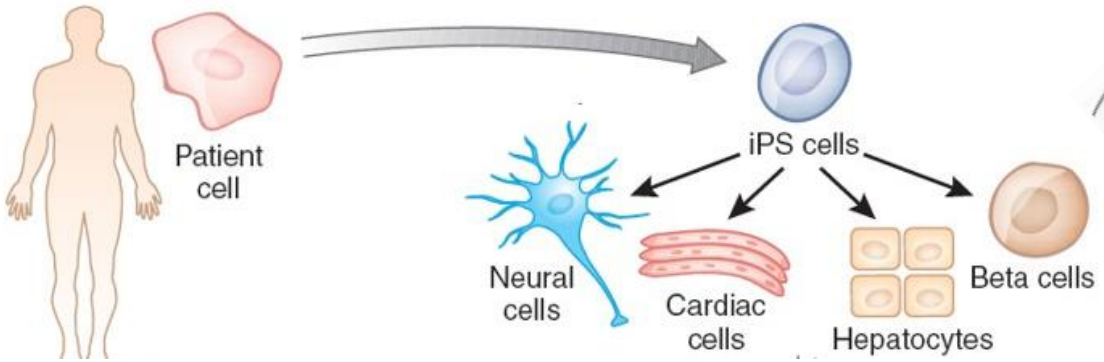
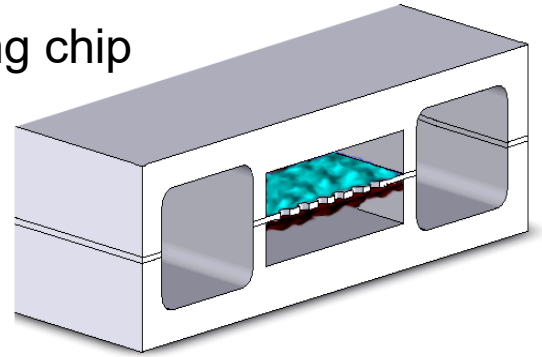
Better predictive models

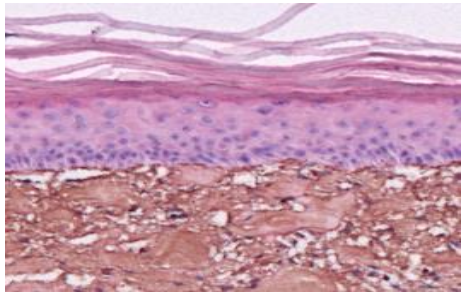


Lung chip

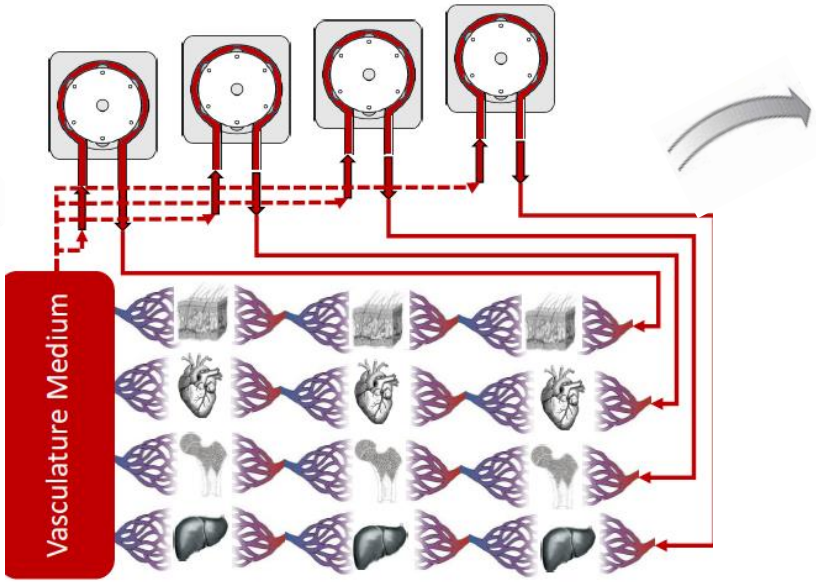


Precision Medicine
You-on-a-chip

- Identify & test biomarkers
- Reduce trial risk
- Hone patient selection
- Explain variable treatment response



3D Bioprinted skin tissue



Multi-organ chip

Courtesy of Marc Ferrer, NCATS, Dan Tagle, NCATS, and Gordana Vunjak-Novakovic, Columbia

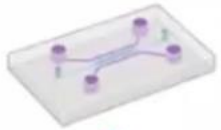
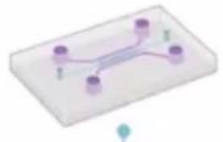
National Center for Advancing Translational Sciences

Tissue Chip Applications and Impact in Drug Development

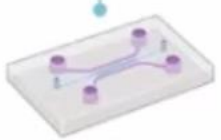
In 2019, R&D spending in the pharmaceutical industry totaled $182 billion globally and predict an annual investment of $213 billion by 2024

- Provide insight where simple models fail
- Potential to reduce animal studies
- Disease models can evaluate disease-associated risk factors

- Human-follow up of clinical findings

Target identification & validation → Lead Identification → Lead Optimisation → Preclinical Safety → Clinical Assessment

- Target validation and biomarker identification using disease models
- Assess safety of a chemical class (on/off target toxicity)

- Improve *in vivo* study design and/or reduce the number of *in vivo* studies
- Identify species-specific responses
- Aid species selection

A recent survey of 15 pharmaceutical experts forecast that within 5 years, tissue chips would save between 10% and 26% of drug development R&D cost
Drug Discovery Today 24:1720–1724 (2019)

Adapted from Nature Reviews Drug Discovery, Low et al. 2020

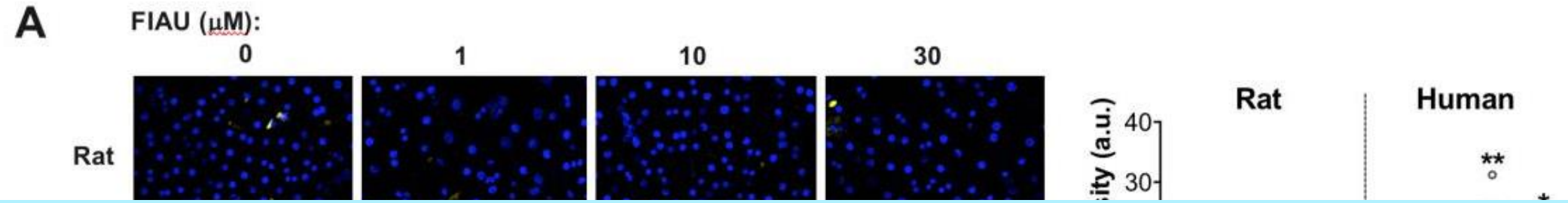
Tissue Chips Addressing Translational Gaps in Safety Pharmacology & ADME Research (2012 – 2016)

- Having relevant models for cardiovascular, hepatic, neuronal, renal, GI and immune toxicities
- Assessing toxicity where no physiologically and pharmacologically relevant models are available

Rare Diseases/rare cancers	Neurodevelopmental	Pregnancy
Pediatric Diseases	Neurological	Lactation

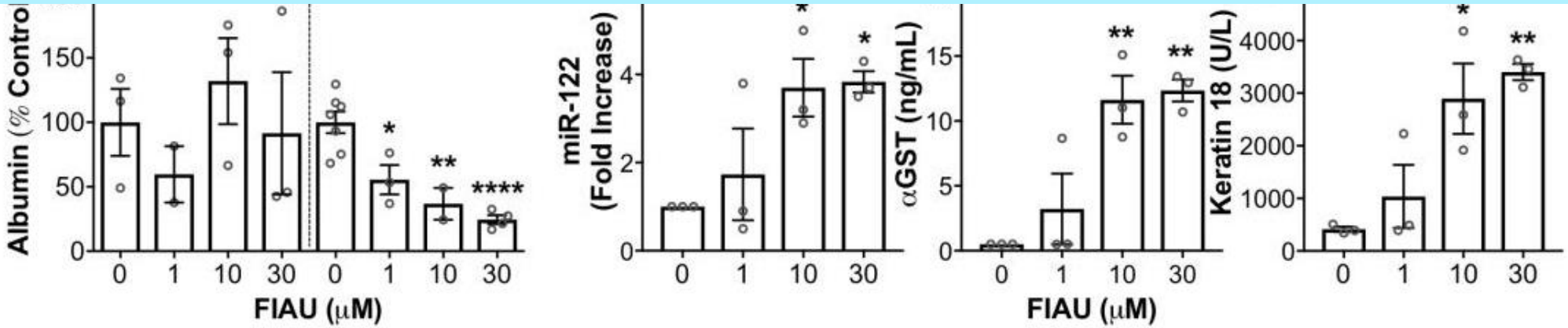
- Identifying rare or idiosyncratic toxicity of investigational drugs
- Representing disease and population heterogeneity
- Understanding human relevance of toxicity in animal studies (Comparative Medicines Research)

Differences in Steatosis (Fat Deposits) in Rat and Human Liver Chips following Fialuridine (FIAU) Treatment



Follow up blinded study to predict DILI caused by 22 compounds with known hepatotoxic (was advanced to human use based on previous preclinical data but was withdrawn due to toxicities which collectively are responsible for more than 200 patient deaths and 10 liver transplants, and (5) non-hepatotoxic compounds – liver chips showed an 87% sensitivity and 100% specificity in predicting drug toxicity, far outperforming liver spheroids (a common preclinical model) which showed a sensitivity of only 47%.

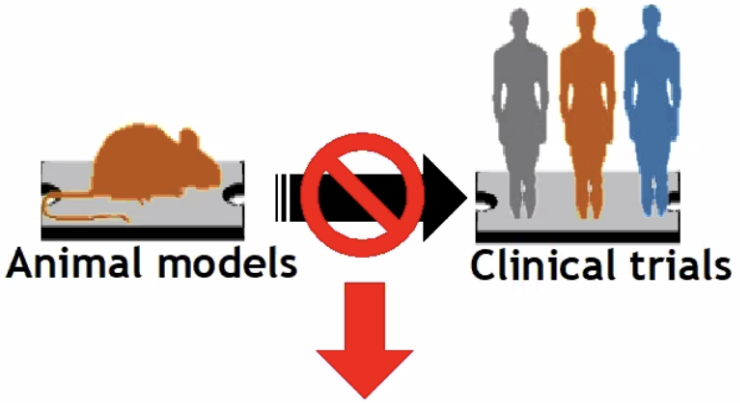
BioRxiv 2022, doi: https://doi.org/10.1101/2021.12.14.472674

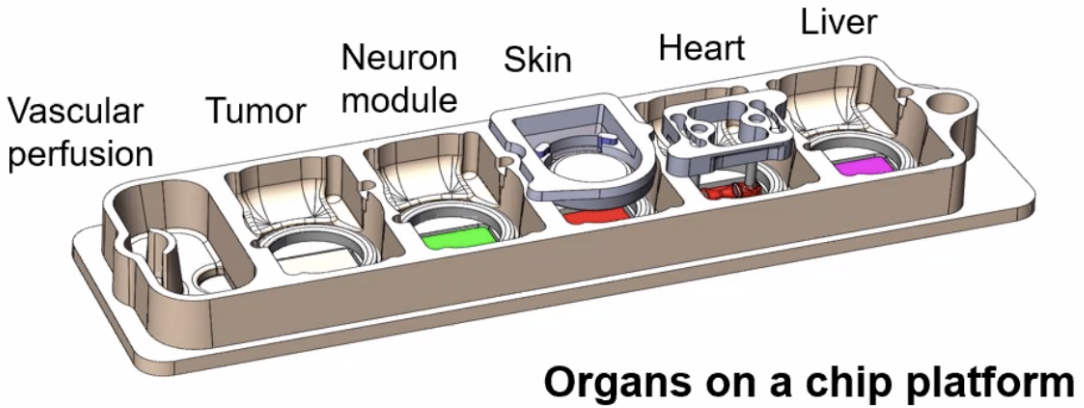


Science Translational Medicine, 11: 2019

National Center for Advancing Translational Sciences

Tissue Chips 2.0 for Disease Modeling and Efficacy Testing 2017-2022





Organs on a chip platform

Translational Needs:

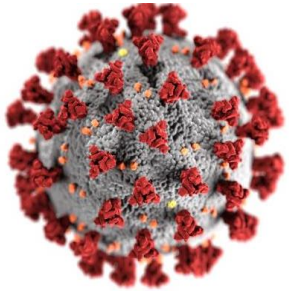
- Able to recapitulate in vivo functions and responses in both normal and disease states
- Capture the pathophysiology, mutation spectrum and phenotypic diversity of human diseases
- Stable tissue phenotype over weeks and months
- Reflect the multi-organ pathology and organ crosstalk
- Real-time functional readout and surrogate markers

Ronaldson-Bouchard et al, ***Cell Stem Cell*** *(2018); Tavakol et al* ***Cell Stem Cell*** *(2021);*

Responding to National Health Emergencies

- **Opioid** crisis
  - **HEAL** awards issued in 2019 for program ‘Tissue Chips to Model Nociception, Addiction and Overdose’
    - Sensory/pain circuitry; reward pathways
    - Blood-brain barrier (BBB) and respiratory control for overdose studies
    - Develop novel drug screening platforms for pain, opioid use disorder (OUD) and/or overdose

- **COVID-19** pandemic
  - Through **CARES Act Congressional supplemental funding**, Emergency Awards issued in 2020 for administrative supplements and competitive revisions to:
    - Develop tissue chip models for COVID-19
    - Understand multiple tissue/organ pathologies
    - Model infection
    - Test candidate drugs and vaccines
    - Understand immune responses
    - Model complications from vulnerable and at-risk patient groups



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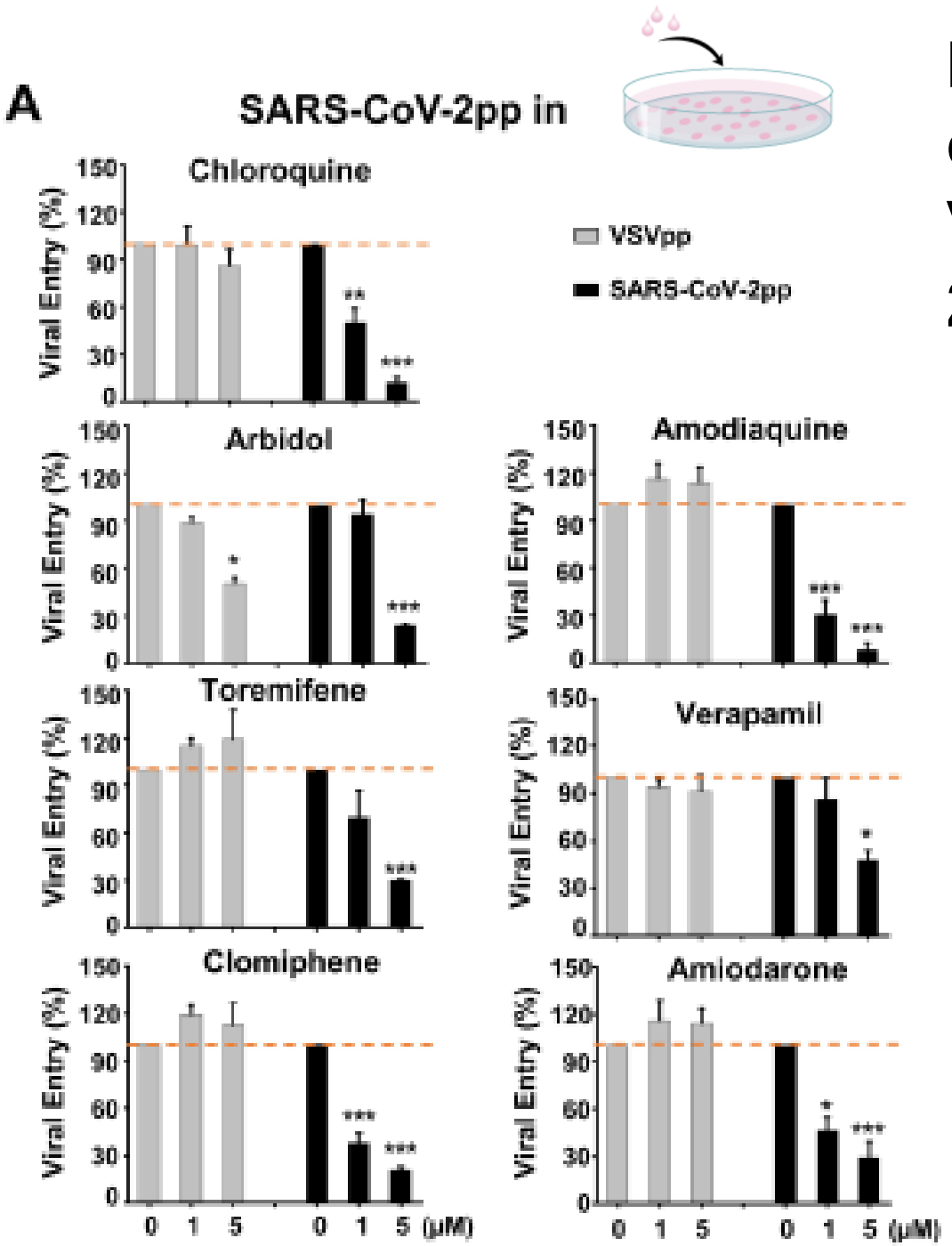
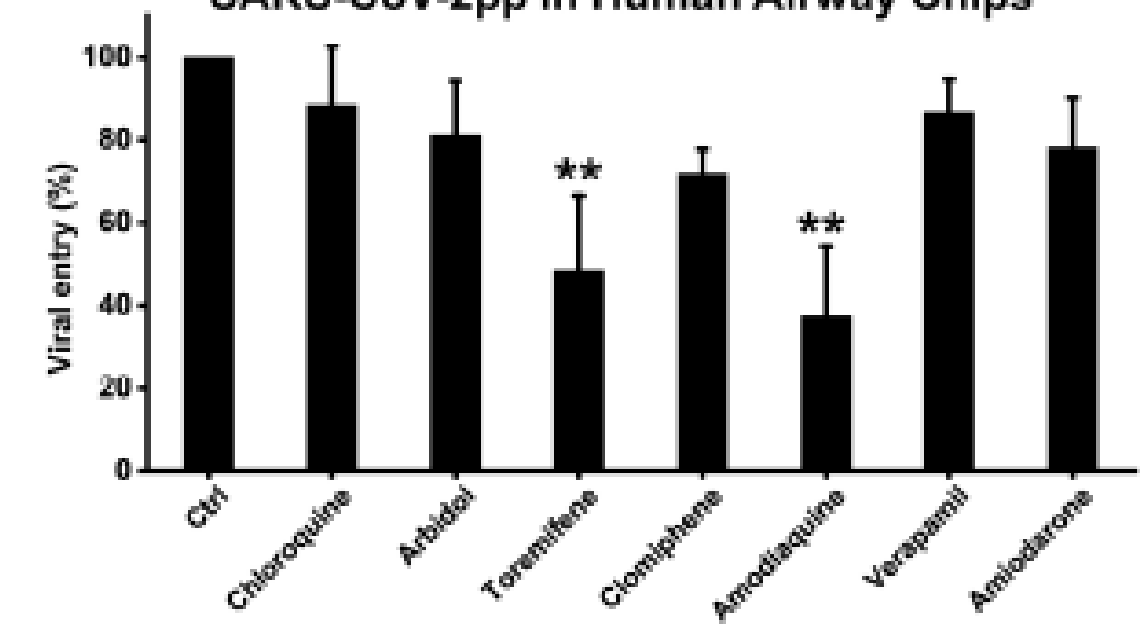
Effects of FDA-approved Drugs on Pseudotyped SARS-CoV-2 Viral Entry in Epithelial Cells in 2D vs. 3D Human Airway Chips





Nature Biomedical Engineering 2021, 5:815-829

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MPS already being used for internal portfolio decision-making by pharma

MPS-based Organ/Tissue model	Nr. of cases	Area of usage (drug development phase)	MPS-Supplier	End user	Reference (if available)
Blood Vessel, Vasculature	5	Target identification, validation and compound selection	AIST	Daiichi-Sankyo	Satoh et al., 2016
		Discovery (scleroderma)	Mimetas	Galapagos	-
		Systems toxicology for consumer products	Mimetas	Philip Morris	Poussin et al., 2019
		Pharmacokinetics and pharmacology	Mimetas	undisclosed	-
		Target identification and validation	Mimetas	NovoNordisk	-
Bone Marrow	4	Preclinical safety	TissUse	AstraZeneca	Sieber et al., 2018
		Preclinical safety	Emulate	AstraZeneca	Chou et al., bioRxiv 2018
		Preclinical safety	TissUse	Roche	-
		Preclinical safety	TissUse	Bayer	-
Gut Epithelium	4	Discovery (inflammatory bowel disease)	Mimetas	Galapagos	Beaurivage et al., 2019
		Discovery	Mimetas	Roche	-
		Clinical development	Mimetas	Roche	-
		Preclinical Safety	Emulate	Roche	-
Lung	3	Discovery (alveolus)	Wyss	undisclosed	Huh et al., 2012
		Drug efficacy (epithelium)	Wyss	Pfizer, Merck USA	Benam et al., 2016b
		Preclinical safety	Emulate	Roche	-
Liver	2	Pharmacological and toxicological effects	Emulate	AstraZeneca	Foster et al., 2019
		Preclinical safety – assessment of species (Rat, Dog, Human)	Emulate	J&J, AstraZeneca	Jang et al., 2019
Ocular compartment	1	Discovery	Fh IGB / EKUT	Roche	Achberger et al., 2019
Kidney Epithelium	1	Pharmacokinetics and pharmacology	Mimetas	undisclosed	Vormann et al., 2018
Liver-Pancreas	1	Target validation / identification	TissUse	AstraZeneca	Bauer et al., 2017
Liver-Thyroid	1	Preclinical safety – assessment of species-specificity (Rat and Human)	TissUse	Bayer	Kuehnlenz et al., 2019
Skin-Tumor	1	Preclinical safety & efficacy	TissUse	Bayer	Huebner et al., 2019

Abbreviation: Wyss – Wyss Institute at Harvard Boston, MA, USA; AIST – National Institute of Advanced Industrial Sciences, Tokyo, Japan; Fh IGB – Fraunhofer Institute Fraunhofer Institute for Interfacial Engineering and Biotechnology, Germany; EKUT - Eberhard Karls University Tübingen, Germany;

Target Identification

Lead Optimization

Preclinical Safety

Preclinical Efficacy

PK/TK

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NCATS

COLLABORATE. INNOVATE. ACCELERATE.

Clinical

Human Physiologically-relevant Models

National Center for Advancing Translational Sciences

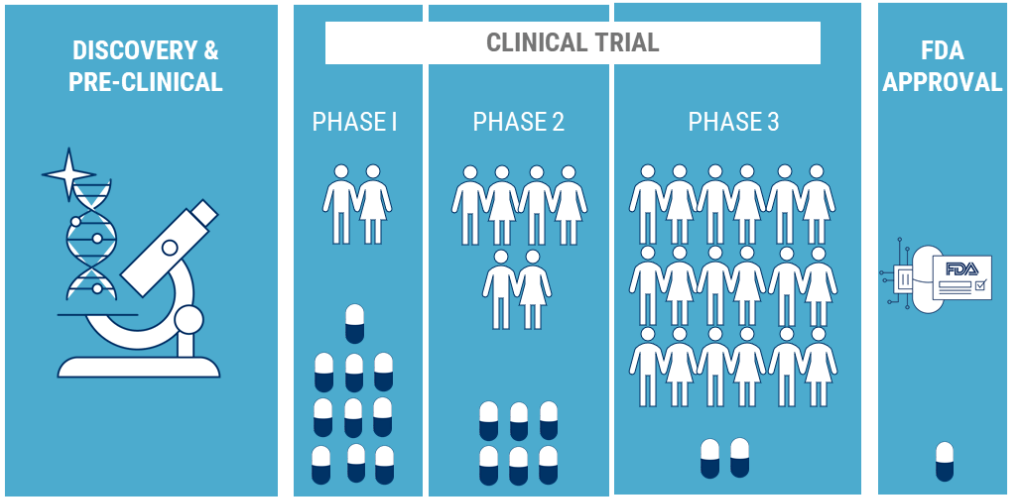
"Clinical Trials" on a Chip to Inform Clinical Trial Design and Implementation in Precision Medicine (2021 – 2025)

National Center for Advancing Translational Sciences

NATIONAL CANCER INSTITUTE

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institute of Arthritis and Musculoskeletal and Skin Diseases

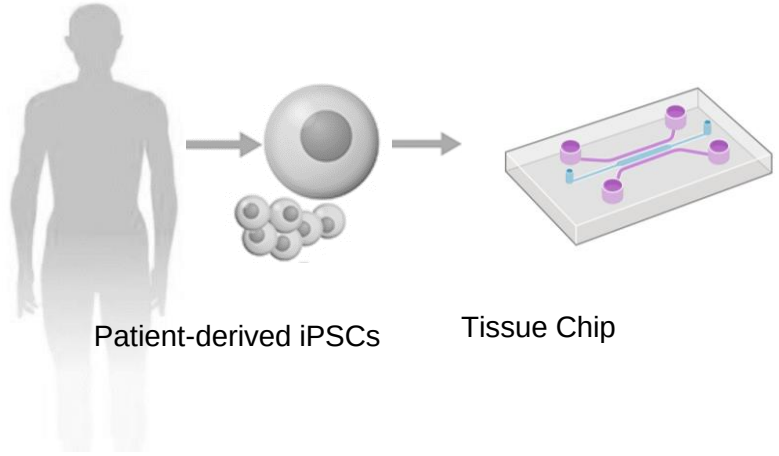


Source: cbinsights.com

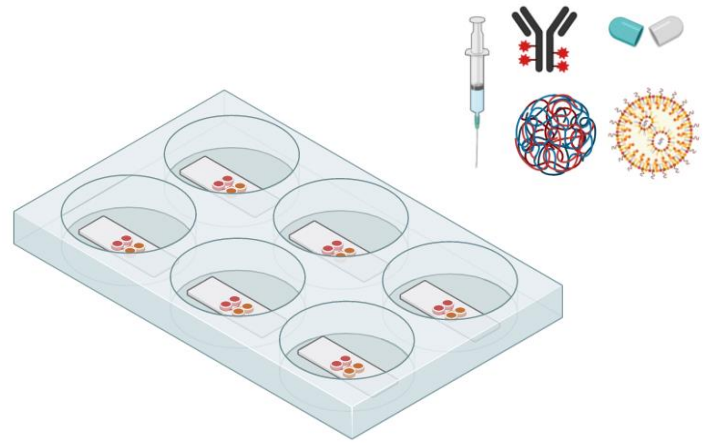
Goal → Inform clinical trial design and execution

1. **Establish recruitment criteria**
2. **Patient stratification**
3. **Develop clinically relevant biomarkers**

Phase 1: Develop and validate rare, pediatric and common disease models containing patient-derived cells representing diversity in patient cohorts



Phase 2: Test potential drugs for efficacy and safety assessments in clinical trials



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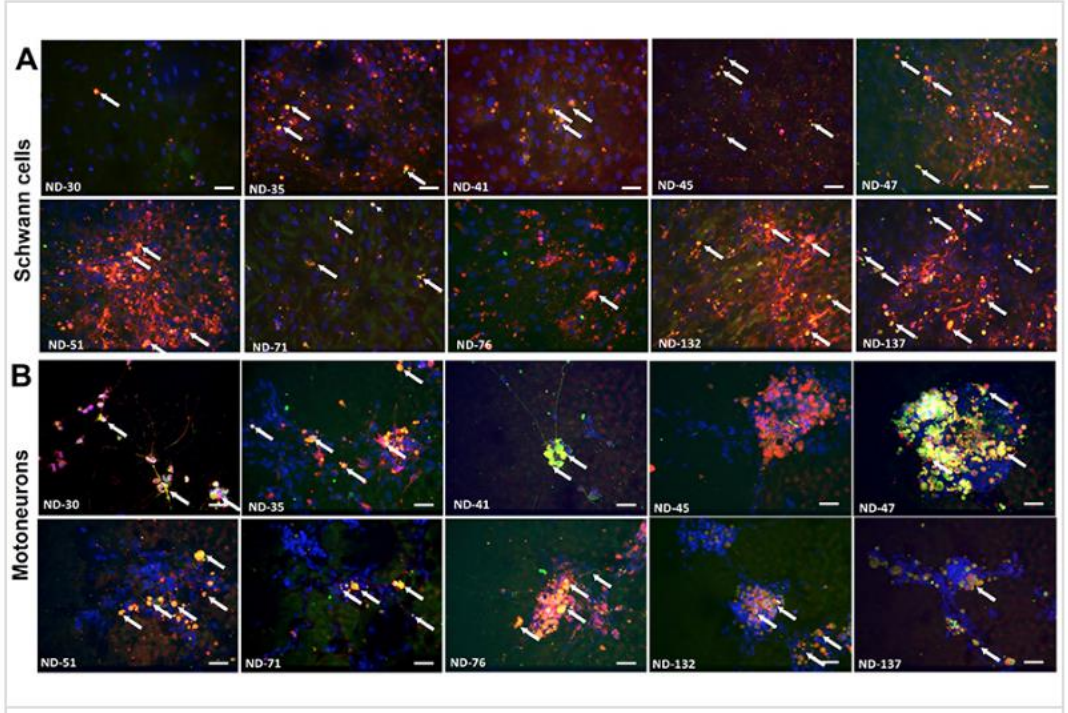
Researchers Create 3-D Model for Rare Neuromuscular Disorders, Setting Stage for Clinical Trial

April 19, 2022

Tissue chip platform shows potential uses for developing treatments for rare diseases

A scientific team supported by the National Institutes of Health has created a tiny, bioengineered 3-D model that mimics the biology of **chronic inflammatory demyelinating polyneuropathy** and **multifocal motor neuropathy**, a pair of rare, devastating neuromuscular diseases. The researchers used the organ-on-a-chip, or "tissue chip," model to show how a drug could potentially treat the diseases. They provided key preclinical data for a drug company to submit to the U.S. Food and Drug Administration to get authorization for testing in a clinical trial.



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Biomarker Development in Rare Disease

Clinical Trial Readiness for Rare Diseases, Disorders and Syndromes

Clinical trials are critical to developing and evaluating new treatments for rare diseases. Scientists, however, often do not have enough information about the symptoms and biology of rare diseases to design clinical trials. NCATS, working with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, created the Clinical Trial Readiness for Rare Diseases, Disorders and Syndromes grants to address some of the obstacles scientists face. These obstacles include, among other issues, gaps in our understanding of a rare disease's natural history and a lack of suitable biomarkers or clinical outcome measures.

Through these grants, NCATS seeks to facilitate rare disease research by enabling efficient and effective movement of candidate therapies or diagnostics toward clinical trials and to increase their likelihood of success. These grants are modeled after a grant program at the National Institute of Neurological Disorders and Stroke.

Contact: **Alice Chen Grady, M.D.**

Current Funding Opportunities

Clinical Trial Readiness for Rare Diseases, Disorders, and Syndromes (R03 Clinical Trial Not Allowed)
PAR-22-100 · **Posted Date:** 02/03/2022

Clinical Trial Readiness for Rare Diseases, Disorders, and Syndromes (R21 Clinical Trial Not Allowed)
PAR-22-101 · **Posted Date:** 02/03/2022

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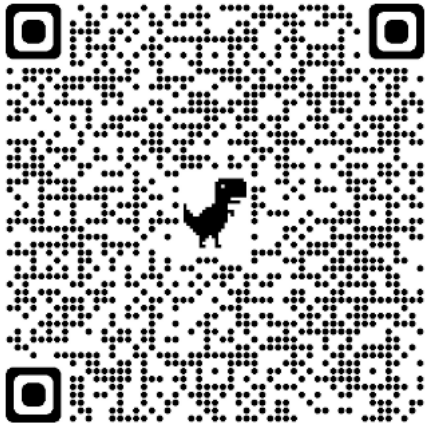
NCATS Clinical Trial Readiness Program

- Emphasizes clinical validation of the biomarkers
- Encourages applicants to seek advice from the FDA about the Drug Development Tool Qualification Programs early in the process

Assessing readiness to initiate the qualification process?

- Requestors may ask for a meeting with the relevant DDT qualification program at any time to discuss the qualification pathway for their specific DDT and COU
- Early interaction with FDA before formal submission provides advantages, including identification of a drug development need, alignment on an appropriate drug development COU, and identification of a pathway for the development of the supporting evidence for qualification



VIRTUAL

FDA CDER & NIH NCATS Regulatory Fitness in Rare Disease Clinical Trials Workshop

MAY 16 - 17, 2022

More Meetings, Conferences, and Workshops

On This Page

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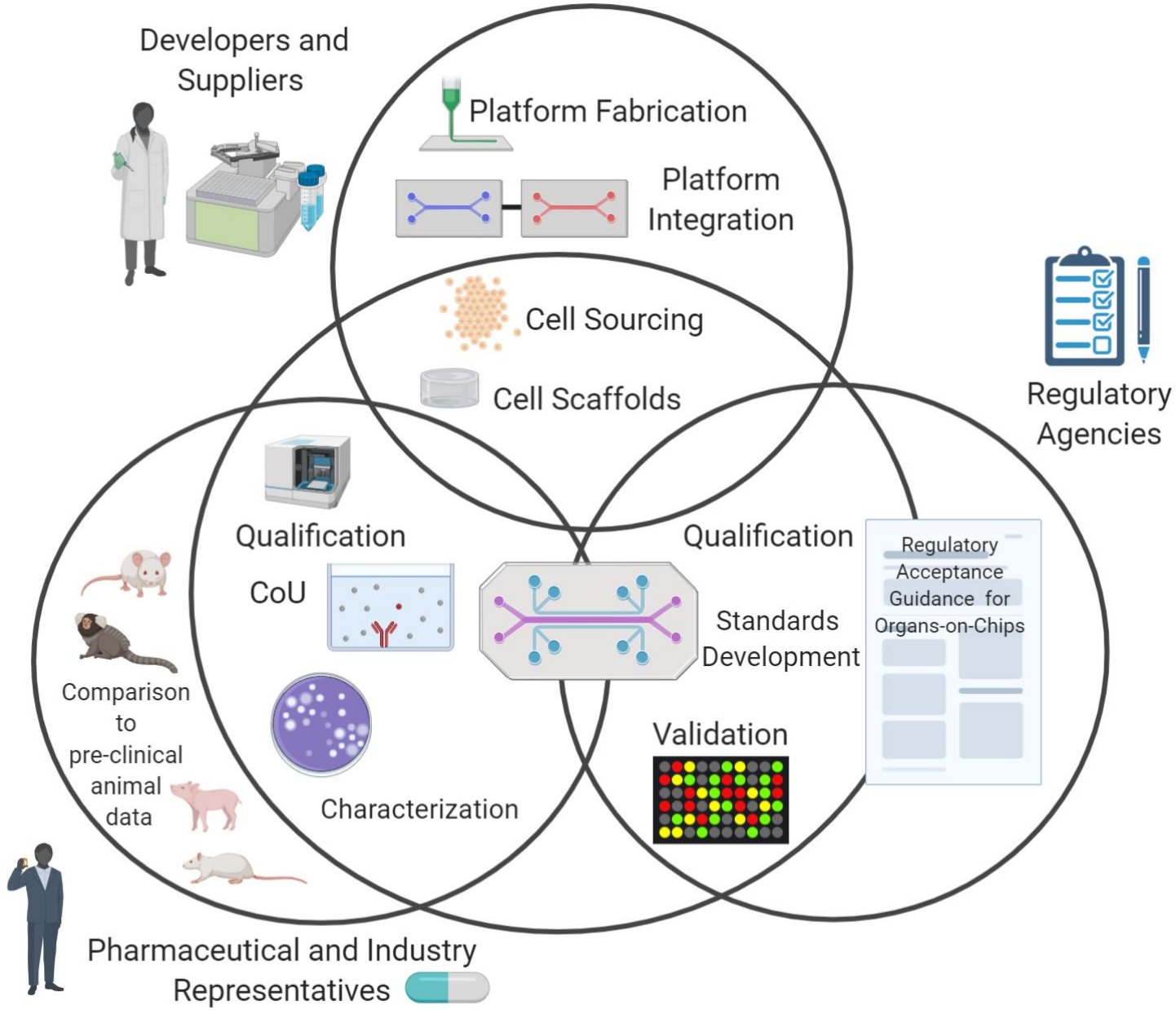
Challenges and Future Vision



Future Goals:

- Sustain and increase utilities and adoption of TC
- Work towards global harmonization of regulatory use and standardization of platforms
- Train next generation of MPS/TC scientists and practitioners

National Center for Advancing Translational Sciences

John Wagner

Chief Medical Officer

Koneksa Health

Enhancing Clinical Development Programs by Leveraging Translational Science: Industry Perspectives and Approaches

John Wagner | john@koneksahealth.com

May 2022

koneksa

Disclosures

- Employee – Koneksa Health
- Editor-in-Chief – *Clinical and Translational Science*
- Executive Committee – FNIH Biomarkers Consortium
- Consultant – Various

Leveraging Translational Science in Industry: Agenda

- General biomarker introduction and approaches
- Digging deeper with vignettes
  - Biomarkers and surrogate endpoints
  - Mechanism of action
  - Digital biomarkers
  - Translational clinical models
  - Reverse translation
- Challenges and potential solutions

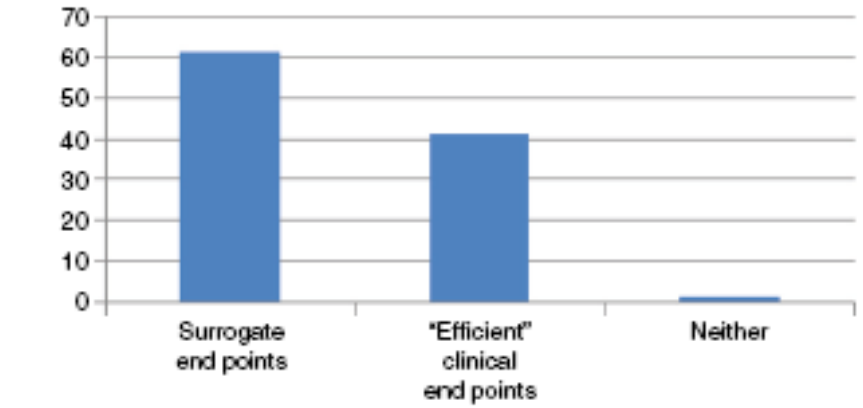
- Notes
  - The focus of this presentation is on late clinical development to integrate with workshop objectives
  - Translational science is heavily leveraged across drug development, particularly discovery and early clinical development

1

General biomarker introduction and high level approaches

koneksa

Biomarkers enable, accelerate and increase efficiency of drug development



- Surrogate endpoints increase drug approvals
  - Surrogate endpoints associated with higher numbers of new drugs when compared with similar conditions for which they do not exist
- Biomarkers increase probability of success

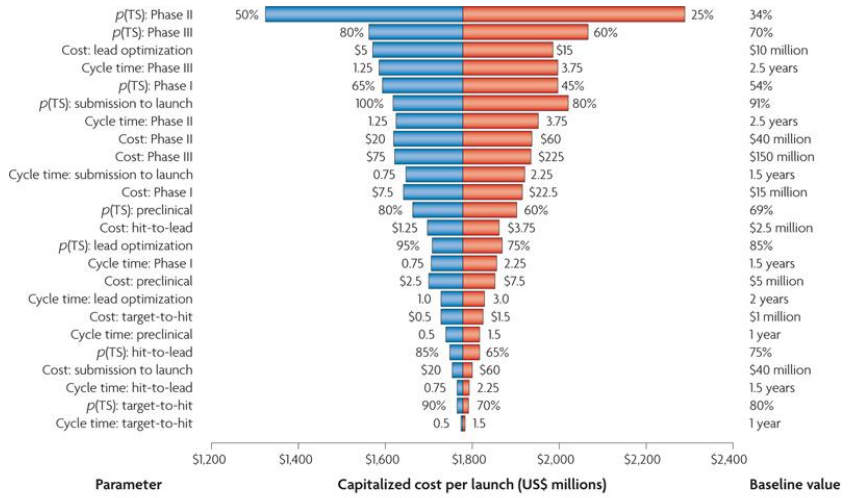
Therapeutic Area	Drug approvals per 100 Candidates [1]		Biomarker POS Multiple
	With biomarker	without biomarker	
Cardiovascular	83	10	8.3
Anti-infectives	29	10	2.9
Immunomodulators	12	6	2.0
Oncology	11	2	5.5
Gastro-intestinal	10	6	1.7
Haematology	10	6	1.7
Respiratory	10	6	1.7
CNS	9	6	1.5

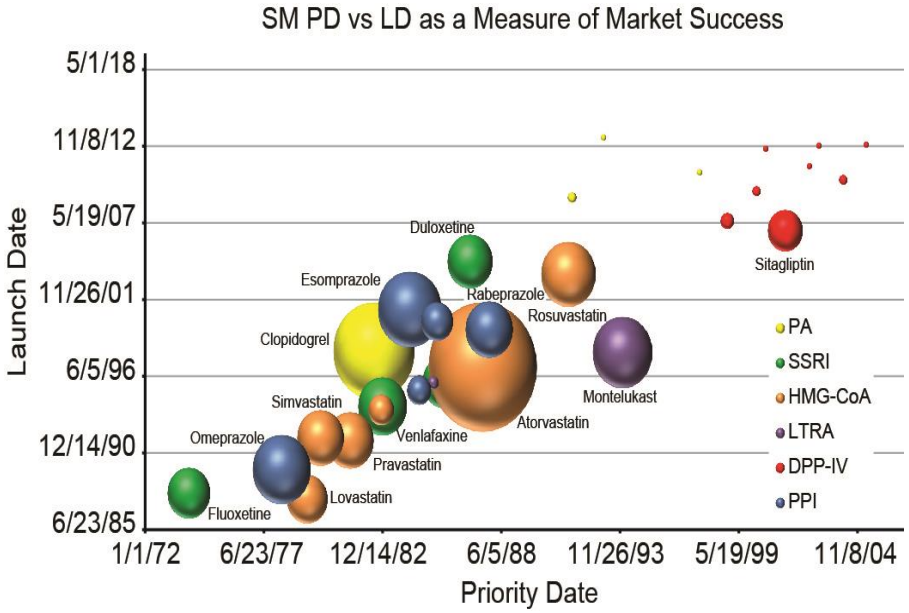
Lathia et al. CPT 86:32-43, 2009 PMID: 19474783

Wong et al. Biostatistics 20(2): 273-286, 2019 PMID: 30445524

koneksa

Value of Translational Science: Quality and Operational Excellence Matters





- Quality matters
  - High quality, compelling early decisions will increase PTS
  - Prioritize the winners
  - Opportunity costs
- Speed and operational excellence matter
  - Biomarker, surrogate endpoint, and translational strategies require rigor and operational excellence
  - First-to-patent does not equal market success
  - Corollary: industry competes on the basis of execution

Paul et al. NRDD 9, 203-214, 2010 PMID: 20168317

Roland, Xu, Wagner. CPT, 97(1):19-21., 2015 PMID: 25670379

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Leveraging Translational Science in Industry: Approaches

- Problem statement: Drug development is expensive, inefficient and slow - most new drug candidates fail
- Biomarkers and translational strategies enable, accelerate and increase efficiency of drug development
  - Biomarker strategies are numerous
    - Biomarkers and surrogate endpoints are mainstays
    - Digital biomarkers and multi-component biomarkers are enjoying increased usage
  - Translational mechanism of action provides
    - Confirmatory evidence
    - Label support (eg clinical pharmacology section)
    - Go-No Go decisions
  - Translational clinical models
    - Go-No Go decisions
    - Label support
    - Possibly confirmatory evidence
  - Biomarker, surrogate endpoint, and translational strategies require rigor and operational excellence

Leveraging Translational Science in Industry: Preview the challenges

Challenge
Validation and qualification are slow, laborious, and uncertain: “Get better playing in the sandbox”
Definitional and other ambiguities abound, including eCOA vs biomarker: “Biomarker tower of Babel”
Multi-component biomarkers present unique challenges: ”When is enough, enough?”
Discovery of new biomarkers often prioritized over biomarker development: “Pursuing the next shiny object”
Pre-specified goalposts are not uniformly defined: “Can't play football without a goal post”
Operational challenges can disrupt: "Nothing's for certain. It can always go wrong.”

2

Digging deeper with vignettes

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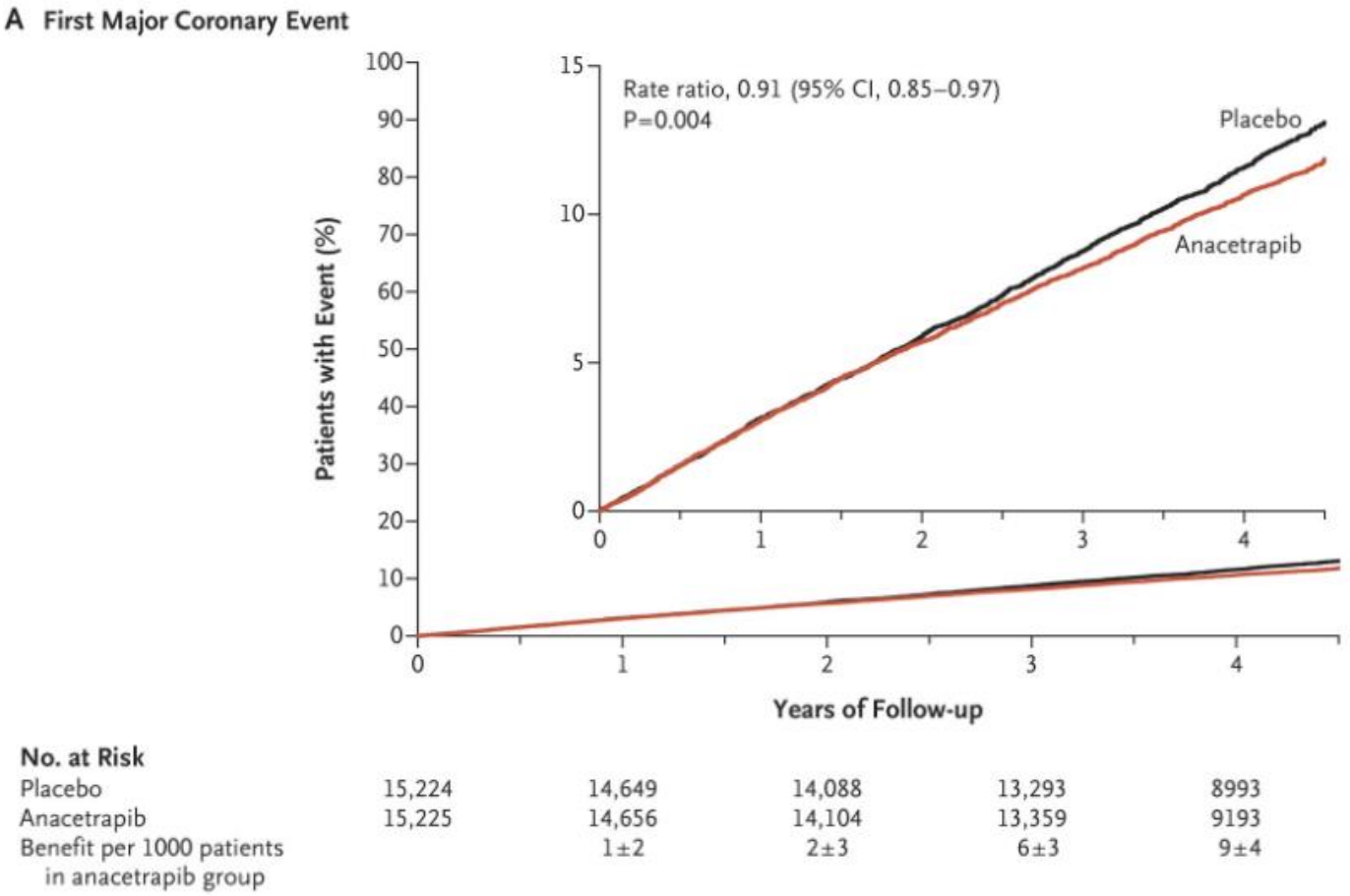
Surrogate endpoint: LDL-c

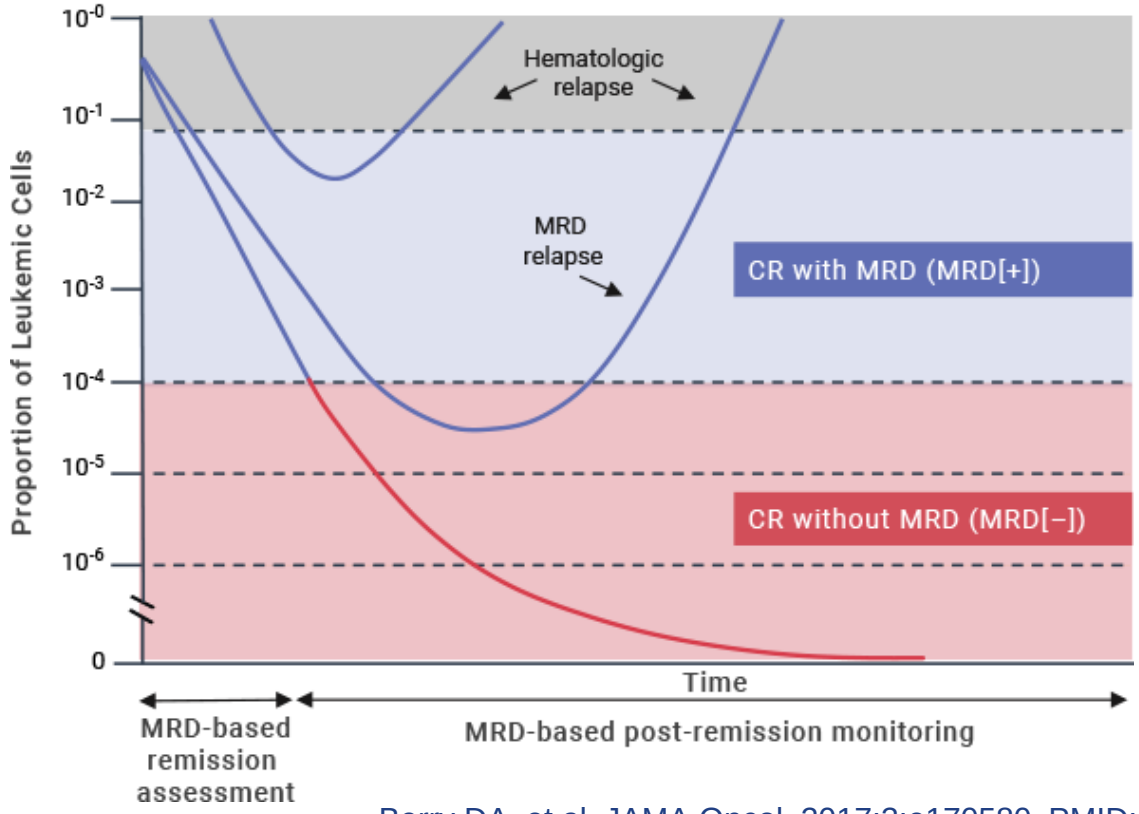
- LDL-c is a surrogate endpoint for CHD events in patients
- One of best qualified surrogate endpoints based on prodigious amounts of rigorous epidemiologic and interventional data
- First approvals of several cholesterol lowing agents based on LDL-C lowering including PCSK-9 antibodies and siRNA
- Newer developments include at home testing
- And yet… questions remain including generalizability to all classes of cholesterol lowering agents

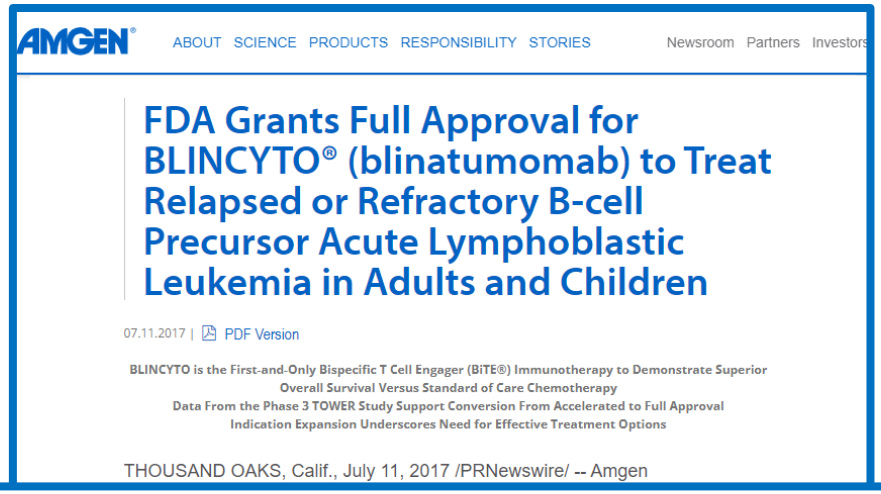


HPS3/TIMI55–REVEAL Collaborative Group. NEJM 377:1217-1227, 2017 PMID: 28847206

Surrogate endpoint / prognostic biomarker: Measurable residual disease

- MRD contributed to regulatory approvals in ALL
- MRD rapidly extending to AML, multiple myeloma and Monoclonal Gammopathy of Undetermined Significance
- Slide courtesy of Joe Menetski and Steve Hoffmann, FNIH



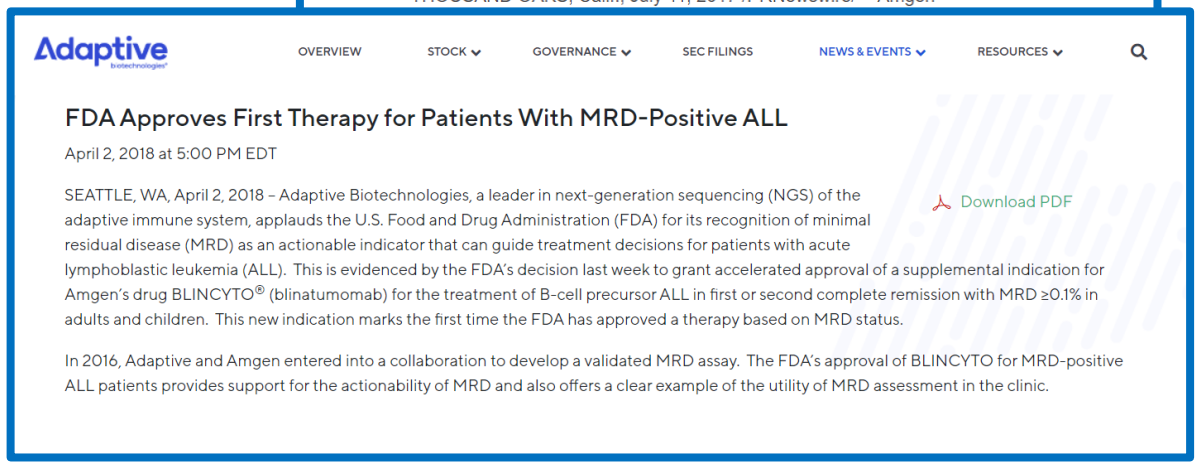

AMGEN ABOUT SCIENCE PRODUCTS RESPONSIBILITY STORIES Newsroom Partners Investors

FDA Grants Full Approval for BLINCYTO® (blinatumomab) to Treat Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukemia in Adults and Children

07.11.2017 | PDF Version

BLINCYTO is the First-and-Only Bispecific T Cell Engager (BiTE®) Immunotherapy to Demonstrate Superior Overall Survival Versus Standard of Care Chemotherapy
Data From the Phase 3 TOWER Study Support Conversion From Accelerated to Full Approval
Indication Expansion Underscores Need for Effective Treatment Options

THOUSAND OAKS, Calif., July 11, 2017 /PRNewswire/ -- Amgen


Adaptive OVERVIEW STOCK GOVERNANCE SEC FILINGS NEWS & EVENTS RESOURCES

FDA Approves First Therapy for Patients With MRD-Positive ALL

April 2, 2018 at 5:00 PM EDT

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SEATTLE, WA, April 2, 2018 – Adaptive Biotechnologies, a leader in next-generation sequencing (NGS) of the adaptive immune system, applauds the U.S. Food and Drug Administration (FDA) for its recognition of minimal residual disease (MRD) as an actionable indicator that can guide treatment decisions for patients with acute lymphoblastic leukemia (ALL). This is evidenced by the FDA's decision last week to grant accelerated approval of a supplemental indication for Amgen's drug BLINCYTO® (blinatumomab) for the treatment of B-cell precursor ALL in first or second complete remission with MRD ≥0.1% in adults and children. This new indication marks the first time the FDA has approved a therapy based on MRD status.

In 2016, Adaptive and Amgen entered into a collaboration to develop a validated MRD assay. The FDA's approval of BLINCYTO for MRD-positive ALL patients provides support for the actionability of MRD and also offers a clear example of the utility of MRD assessment in the clinic.

Berry DA, et al. JAMA Oncol. 2017;3:e170580. PMID: 28494052

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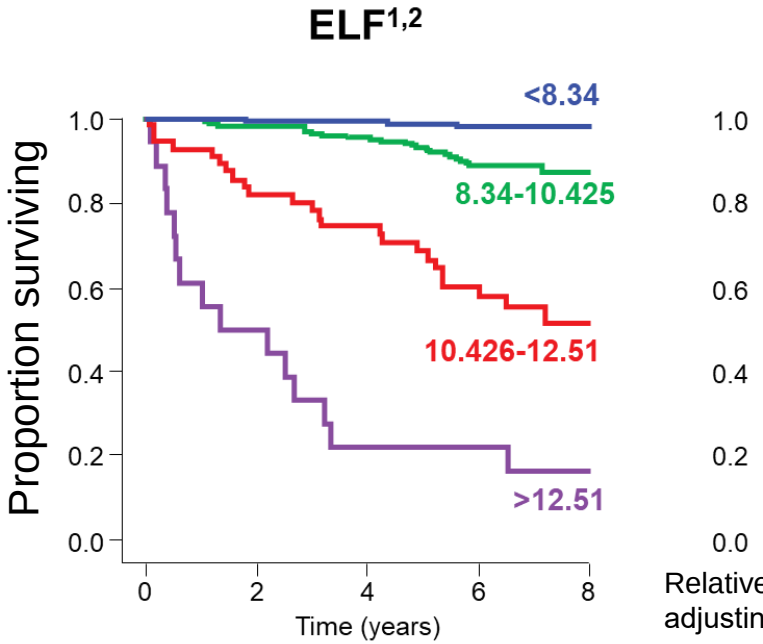
BIOMARKERS CONSORTIUM

FNIH

Biomarker: Multi-component biomarker as NASH prognostic biomarker



"ADVIA Centaur Enhanced Liver Fibrosis Test (ELF™) is indicated as a prognostic marker in conjunction with other laboratory findings and clinical assessments in patients with advanced fibrosis (F3 or F4) due to non-alcoholic steatohepatitis (NASH), to assess the likelihood of progression to cirrhosis or liver related events."

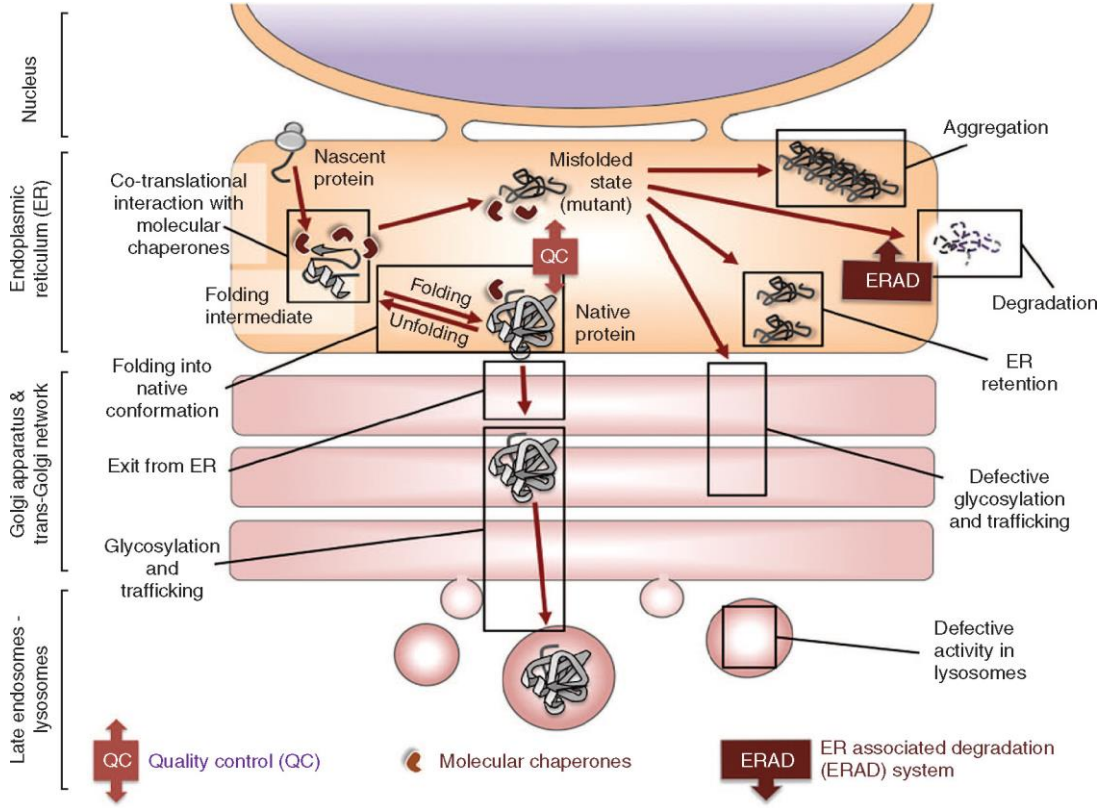
- Enrolling NASH trials via a non-invasive prognostic multi-component biomarker is feasible
- Slide courtesy of Andrew Billin, Mark Dresser and Scott Paterson, Gilead

Relative Risk (calculated hazard ratio using Cox proportional hazard ratio model after adjusting for age and sex, relative to ELF ≤9.8) for Liver Related Outcomes at 5 years.

Tactics	Result	Issues	Solutions
Biopsy driven study but NIT is an inclusion criterion.	Highly enriched in subjects with desired NIT score. NIT/biopsy concordance should reduce PBO rate.	What to do with discordant NIT/biopsy subjects?	• Exclude from study • Keep as a sub-study • Stratify across groups
NIT based enrollment only and endpoint.	Highly enriched in subjects with desired NIT scores.	Exclude subjects who fail NIT criteria?	• Exclude from study • Keep as a sub-study • Stratify across groups

1. Parkes J et al. Gut 2010;59:1245-51 PMID: 20675693
2. Sanyal AJ et al. Hepatology 2019; Apr 16. PMID: 30993748

Translational mechanism of action: Confirmatory evidence in Fabry disease



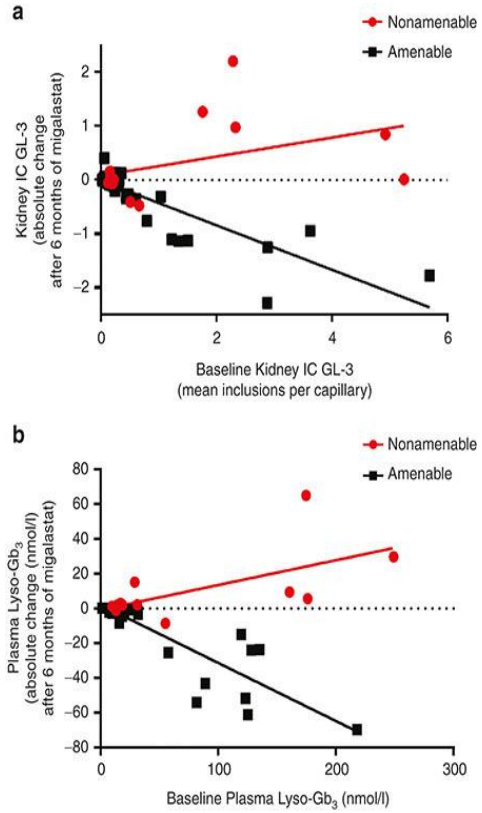


Table 3: Changes from Baseline to Month 6 in Average Number of GL-3 Inclusions per KIC in Adults with Fabry Disease with Amenable *GLA* Variants in Study 1 (N = 45)

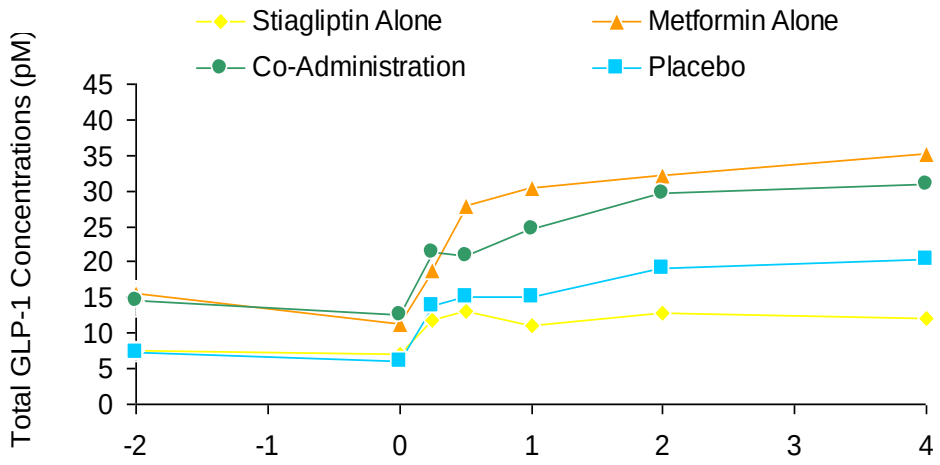
	GALAFOLD n/N (%) with ≥ 50% reduction Median change from baseline (range)	Placebo n/N (%) with ≥ 50% reduction Median change from baseline (range)
All patients (N = 45)	13/25 (52%) -0.04 (-1.94, 0.26)	9/20 (45%) -0.03 (-1.00, 1.69)
Females (N = 29)	8/18 (44%) -0.02 (-0.46, 0.26)	5/11 (46%) -0.03 (-0.35, 0.10)
Males (N = 16)	5/7 (71%) -1.10 (-1.94, -0.02)	4/9 (44%) -0.03 (-1.00, 1.69)
Patients with baseline GL-3 ≥ 0.3 (N = 17; 9 males, 8 females)	7/9 (78%) -0.91 (-1.94, 0.19)	2/8 (25%) -0.02 (-1.00, 1.69)
Patients with baseline GL-3 < 0.3 (N = 28; 7 males, 21 females)	6/16 (38%) -0.02 (-0.10, 0.26)	7/12 (58%) -0.05 (-0.16, 0.14)

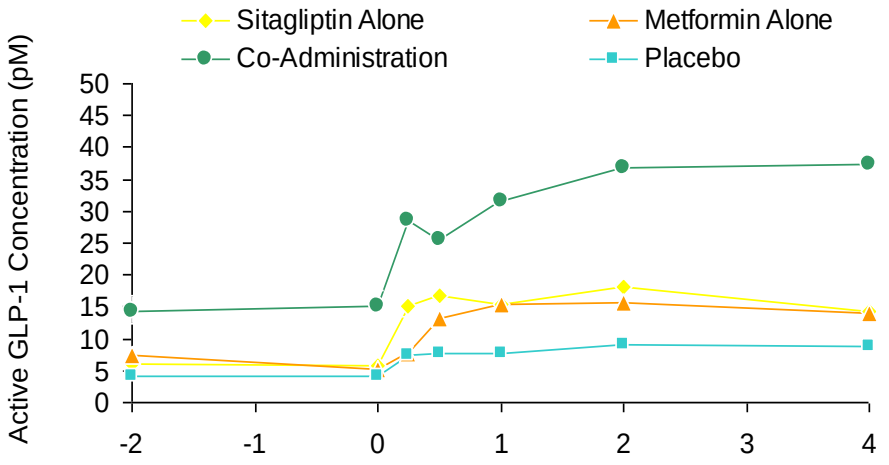
- Accelerated approval of migalastat in patients with Fabry disease
  - Surrogate endpoint: Reduction of GL-3 inclusions in biopsied renal peritubular capillaries
  - Mechanism of action evidence: amenable GLA gene variants

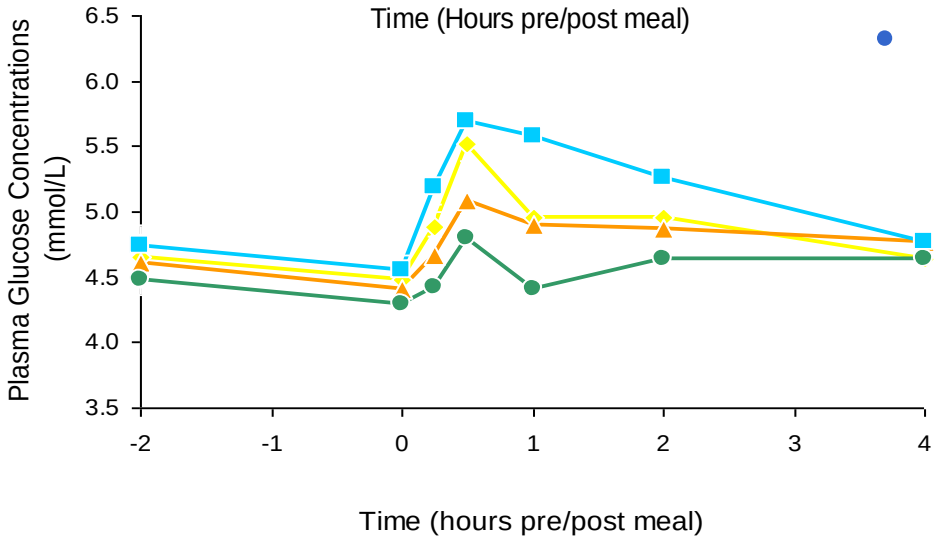
Parenti et al. Mol Ther 23(7):1138-1148, 2015 PMID: 25881001

Benjamin et al. Genet Med 19(4):430-438, 2017 PMID: 27657681

Translational mechanism of action: Label







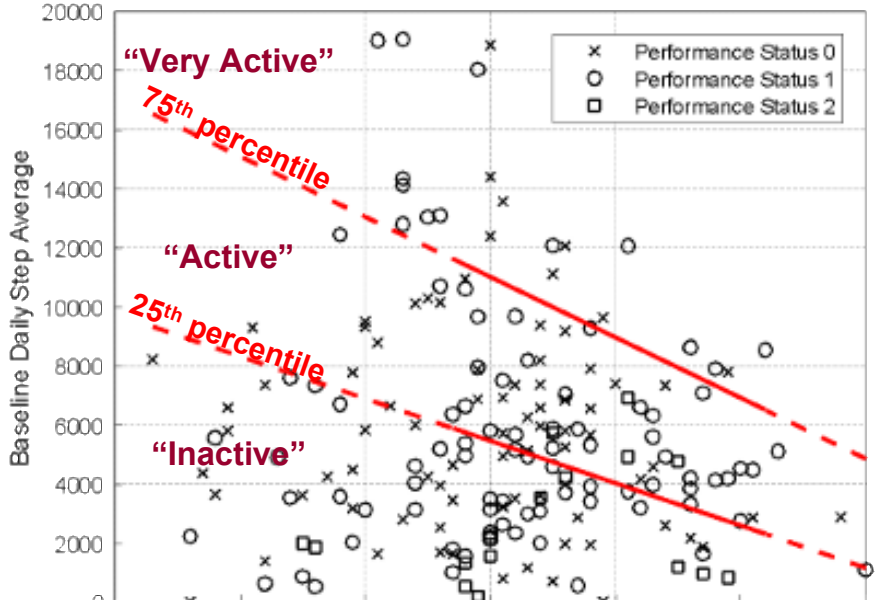
Label

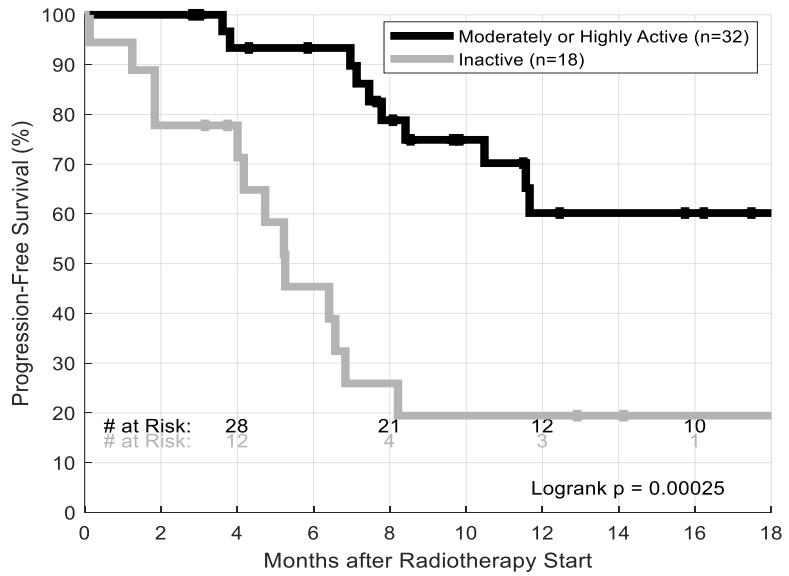
- Sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Coadministration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations

Migoya et al. CPT 88(6):801-8, 2010 PMID: 21048706

Digital biomarkers and digital health technologies: Functional status

- Functional status
  - Conventional performance status is poor reflection of digitally measured activity
  - Activity may better predict PFS
- Digital biomarkers and DHTs
  - Augment drug development tools by providing an opportunity to objectively measure how patients function, feel and behave
  - DHT-based measures may combine characteristics of biomarkers and eCOA
  - Validation characteristics are not well defined and continue evolving
  - Recognition of an acute need for data standards





Ohri et al. Int J Radiat Oncol Biol Phys 105(4):745-751, 2019 PMID: 31398385

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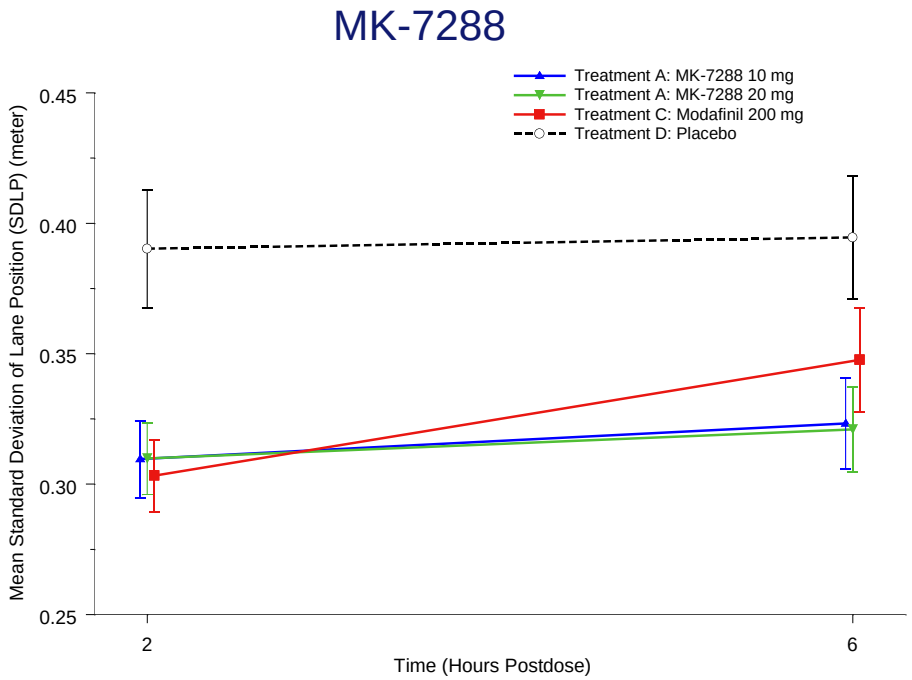
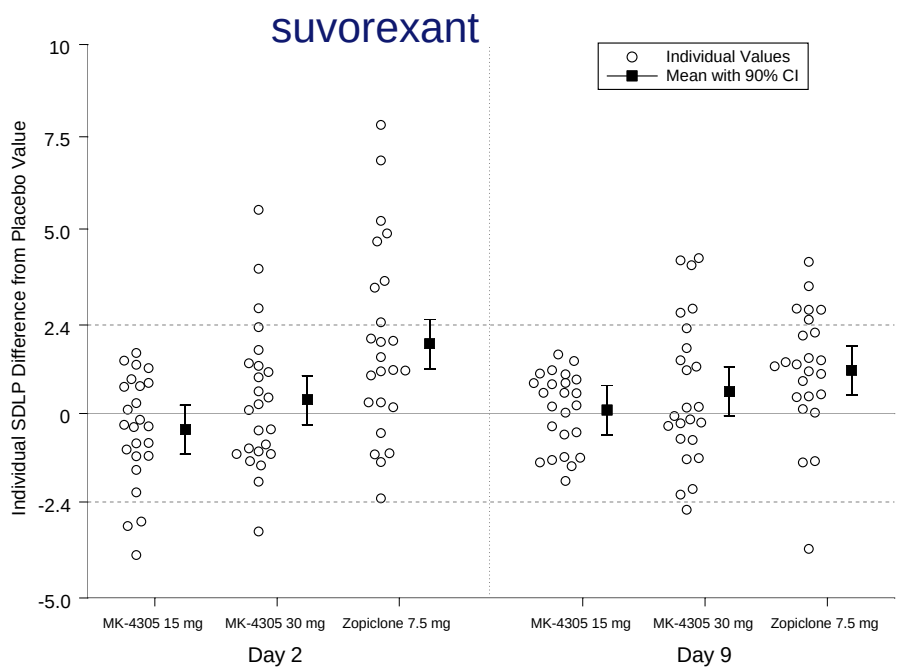
Translational clinical models: Roles in drug development

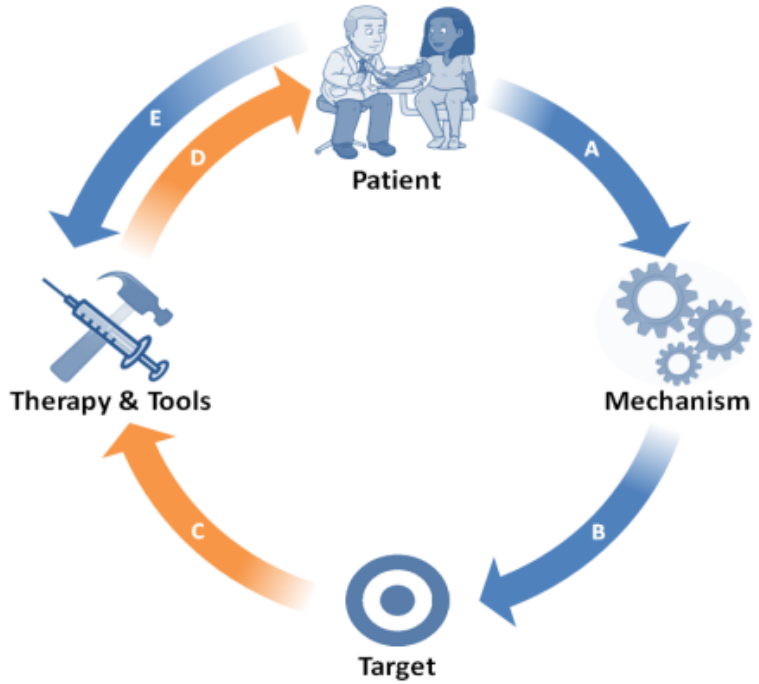




- Translational clinical models are pharmacologic or other perturbations designed to provoke a measurable clinical state
- Examples include driving simulation, dental impaction, and scopolamine
- Translational clinical models serve for Go-No Go decisions and label support
- In addition, may provide confirmatory evidence

Sun et al. JCP 53(12):1294-302, 2013 PMID: 24122944
Vermeeren et al. Sleep. 38(11):1803-13, 2015 PMID: 26039969

Role of reverse translation and other innovative approaches in development



- Reverse translation informs
  - Drug targets e.g. PCSK9
  - Biomarkers
  - Precision medicine
  - Animal models

- And many other innovative translational approaches
  - Patient centricity
  - Precision medicine
  - Real world data / trials / big data
  - Decentralized clinical trials
  - Clinical trial designs e.g. adaptive, informational, basket
  - Analyses e.g. prospective-retrospective, Bayesian
  - Model-informed drug development
  - Machine learning / artificial intelligence

Wagner JA. CPT, 103(2):168-170, 2018. PMID: 29210055

3

Challenges and potential solutions

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Leveraging Translational Science in Industry: Challenges and solutions

Challenge	Potential solutions
Validation and qualification are slow, laborious, and uncertain: “Get better playing in the sandbox”	• Precompetitive work - Drug developers compete on drug assets not tools • Share the risks • Avoid siloed development and validation
Definitional and other ambiguities abound, including eCOA vs biomarker: “Biomarker tower of Babel”	• Continue updating FDA / NIH BEST Glossary • Frequent public workshops to discuss evolving definitions and adjust to emerging use cases
Multi-component biomarkers present unique challenges: ”When is enough, enough?”	• Collaboration via public-private partnerships • Frequent updates and public transparency
Discovery of new biomarkers often prioritized over biomarker development: “Pursuing the next shiny object”	• Multi-stakeholder collaborations, particularly NIH • Learning from real-life examples
Pre-specified goalposts are not uniformly defined: “Can't play football without a goal post”	• Industry
Operational challenges can disrupt: "Nothing's for certain. It can always go wrong.”	• Industry

Acknowledgments

Thanks to colleagues across .com .edu .gov and .org

- In particular
  - Chris Austin, Vesalius Therapeutics
  - Chris Benko, Koneksa Health
  - Andrew Billin, Gilead Sciences, Inc.
  - Mark Dresser, Gilead Sciences, Inc.
  - Robert Ellis, Koneksa Health
  - Steve Hoffmann, FNIH
  - Elena Izmailova, Koneksa Health
  - Joe Menetski, FNIH
  - Chris Morabito, Fulcrum Therapeutics
  - Scott Patterson, Gilead Sciences, Inc.
  - Jeffrey Siegel, FDA

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Peter Marks

Director

Center for Biologics Evaluation and Research

U.S. Food and Drug Administration

Efficacy Outcomes in Rare Disease Gene Therapy Clinical Development

Peter Marks, MD, PhD

Translational Science in Drug Development: Surrogate Endpoints, Biomarkers, and More

May 24, 2021

Biologics License Application (BLA)

- Biologics are licensed under section 351 of the Public Health Service Act
- Product must be safe, pure, potent
- FDA considers evidence from adequate and well-controlled clinical trials
  - Substantial evidence of effectiveness

https://www.fda.gov/media/133660/download

Types of BLA Approvals

- Traditional (full)
- Accelerated approval
  - Approval based on effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit
- Animal rule approval
  - Safety in humans, efficacy in validated animal model
  - Field study for confirmation of clinical benefit

Clinical Endpoints

- Direct Endpoints (Traditional Approval)
  - How patients feel, function, or survive
- Surrogate Endpoints
  - Well-validated or for Accelerated Approval
    - Biomarkers
    - Intermediate clinical endpoints

Individualized medicine

Creating the right drug to treat the patient

Customized Products

Same indication

Same mode of action

Example:
Personalized vaccine for pancreatic cancer using dendritic cells pulsed with an individualized peptide mixture

Created Products

Different indication

Different mode of action

Example:
Gene therapies for two different hemoglobin mutations using same vector back bone

Clinical Endpoint Challenges

- How to appropriately document the natural history of disease or collect baseline data?
- Determination of efficacy in very small populations can be challenging

Clinical Endpoint Solutions

- How to appropriately document the natural history of disease or collect baseline data?
- Determination of efficacy in very small populations can be challenging
- Potential solutions: templates for collecting baseline data and Bayesian clinical trial designs

Potential for Surrogate Endpoints

- Development of animal models of disease
- Correction of defects with gene therapy associated with measurable levels of gene expression (protein expression or activity)
- Bridge animal model findings to human clinical trials for accelerated approval

Regenerative Medicine Advanced Therapy Designation (RMAT)

- Products must be intended for serious or life-threatening diseases or conditions
- Preliminary clinical evidence must indicate potential to address unmet medical needs
- Designated products are eligible as appropriate for priority review and accelerated approval
- Expanded range of options for fulfilling post approval requirements of accelerated approval

INTERACT Program

INitial Targeted Engagement for Regulatory Advice on CBER producTs

- To further encourage early interaction with sponsors and replace the pre-pre-IND meeting process across the Center regarding preclinical, manufacturing and, clinical development plans

https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm

Summary

- FDA is committed to advancing the development of gene therapy for populations of all sizes
  - Helping to individualize product development
  - Providing input and collaboration on novel endpoints
  - Encouraging innovative clinical trial designs


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Session 1: Enhancing Clinical Development Programs by Leveraging Translational Science Throughout the Drug Development Lifecycle

Moderator:

- Peter Stein, US Food and Drug Administration

Panelists:

- Joni L. Rutter, National Center for Advancing Translational Sciences
- John Wagner, Koneksa Health
- Peter Marks, US Food and Drug Administration

Session 1: Enhancing Clinical Development Programs by Leveraging Translational Science Throughout the Drug Development Lifecycle

Discussion Questions:

1. What are key decision points and challenges of incorporating biomarkers in clinical development programs?
2. How can the incorporation of biomarkers and other translational approaches help promote trial efficiency?
3. How do developers identify internal or external candidate biomarkers for inclusion in clinical trials? What are the risks when including candidate biomarkers and how are they mitigated?
4. What more can be done to promote the use of translational science in drug development programs?

Break

We will be back momentarily.

The next panel will begin at 2:00 p.m. (U.S. Eastern Time)

Session 2: Identification and Development of Novel Surrogate Endpoints for Use in Clinical Development Programs

2:00 pm – 3:35 pm EST

Charles Venditti & Oleg Shchelochkov

Investigators

National Human Genome Research Institute

National Institutes of Health

Development of Response Biomarkers in Rare Disease Datasets: Application to Organic Acidemias

Oleg Shchelochkov, MD
Charles Venditti, MD/PhD
NHGRI/MGMGB
Venditti Lab

NIH
NHGRI

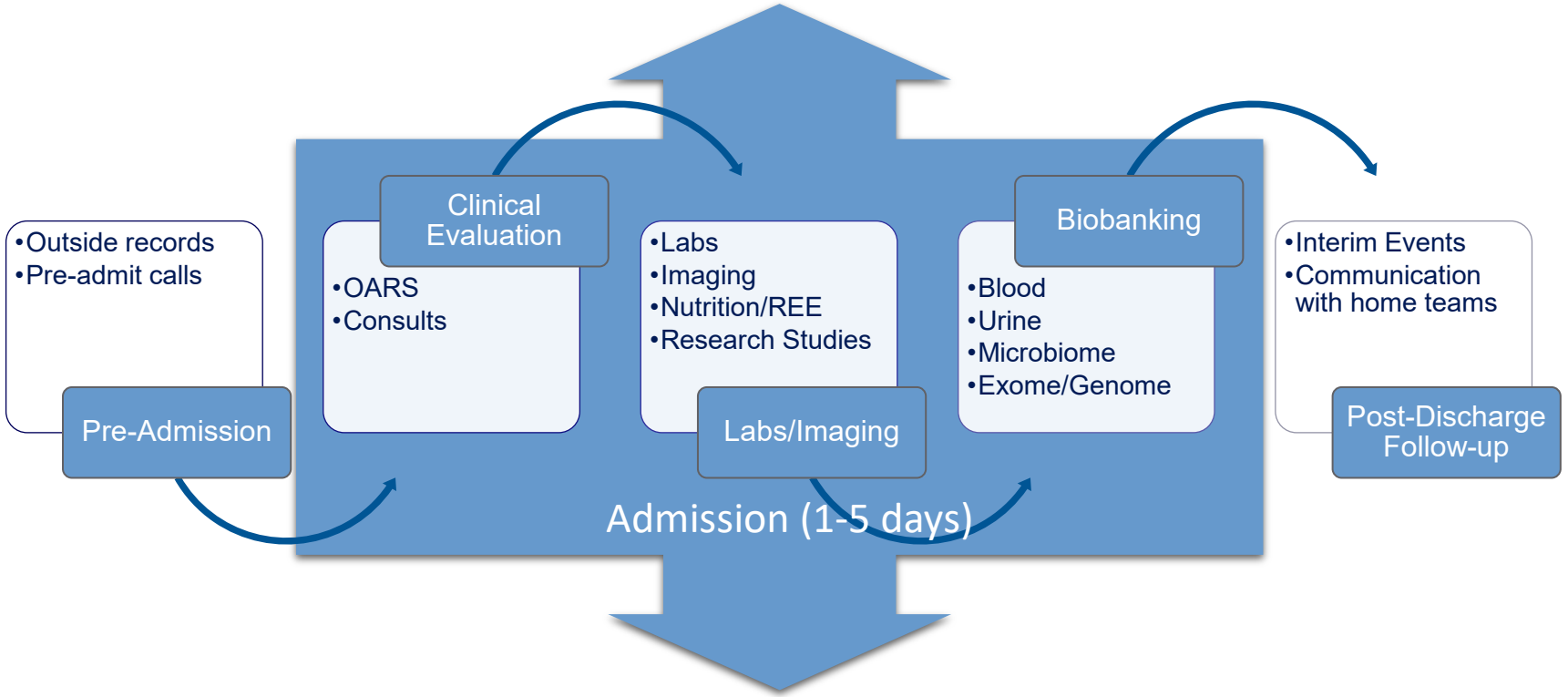
Acknowledgements

- **Organic Acid Research Section (NHGRI)**
  - **PI:** Charles P. Venditti, MD/PhD
  - **Associate Investigator**: Irini Manoli, MD/PhD
  - Members of the Venditti Lab
- **Patients and their families**
- **Referring physicians, NIH consultants, genetic counselors and dietitians**

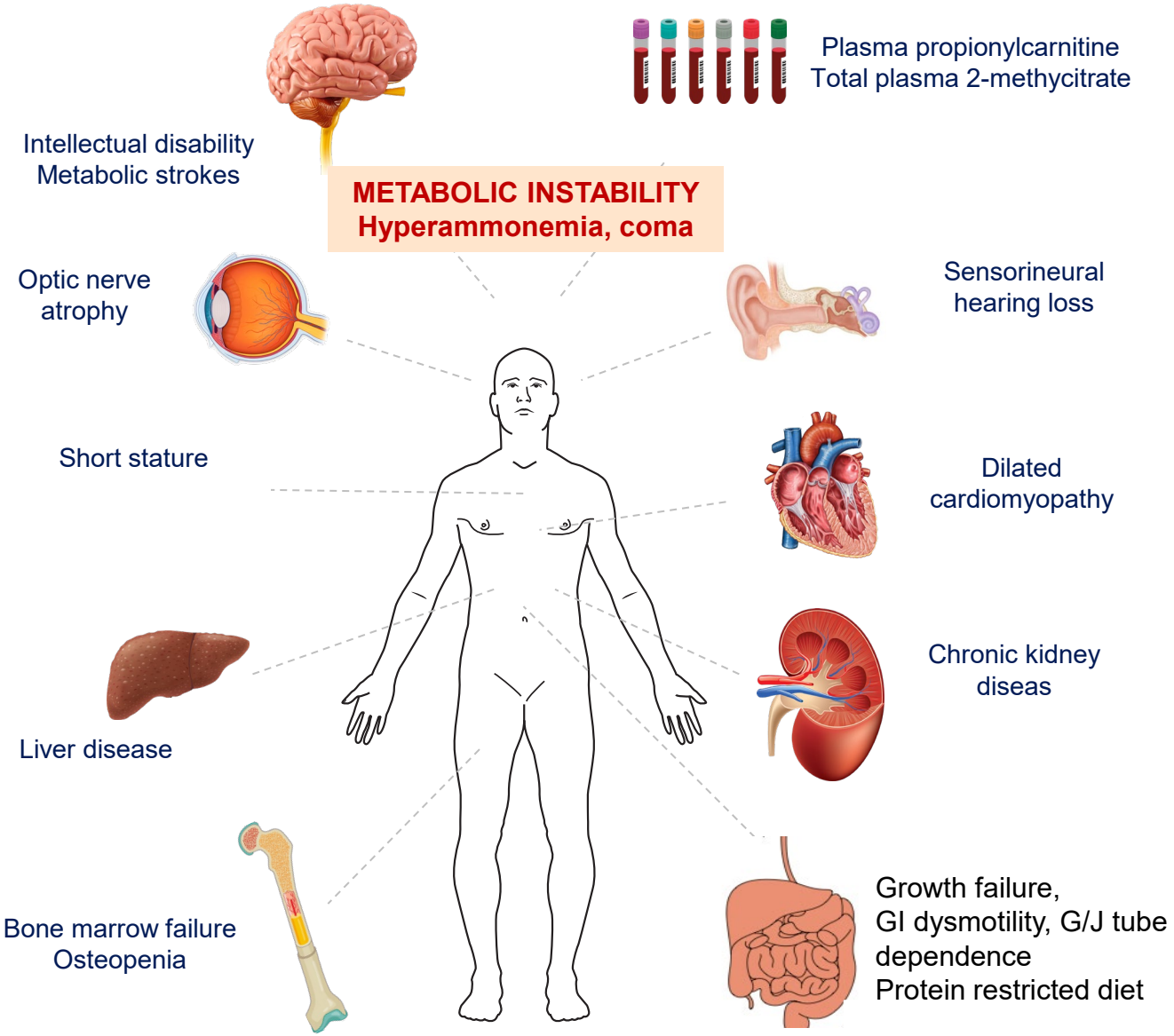
NIH NHGRI

National Institutes of Health
Clinical Center

Internal MMA and PA Datasets



Staged Release of Data Linked to Publications



Multisystemic Manifestations of Organic Acidemias

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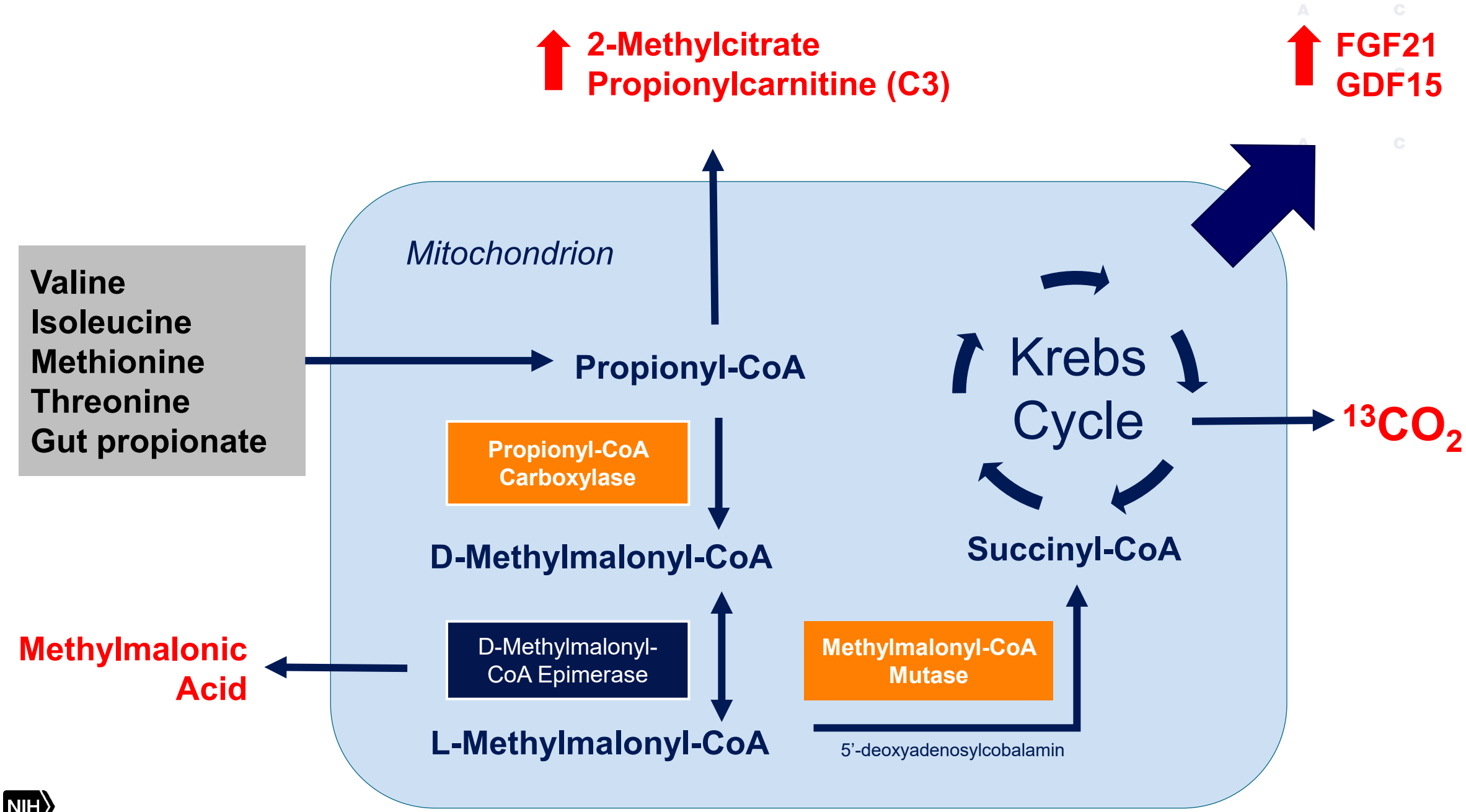
2-Methylcitrate
Propionylcarnitine (C3)
FGF21
GDF15
Mitochondrion
Valine
Isoleucine
Methionine
Threonine
Gut propionate
Propionyl-CoA
Propionyl-CoA Carboxylase
D-Methylmalonyl-CoA
Krebs Cycle
Succinyl-CoA
$^{13}CO_2$
Methylmalonic Acid
D-Methylmalonyl-CoA Epimerase
Methylmalonyl-CoA Mutase
L-Methylmalonyl-CoA
5'-deoxyadenosylcobalamin

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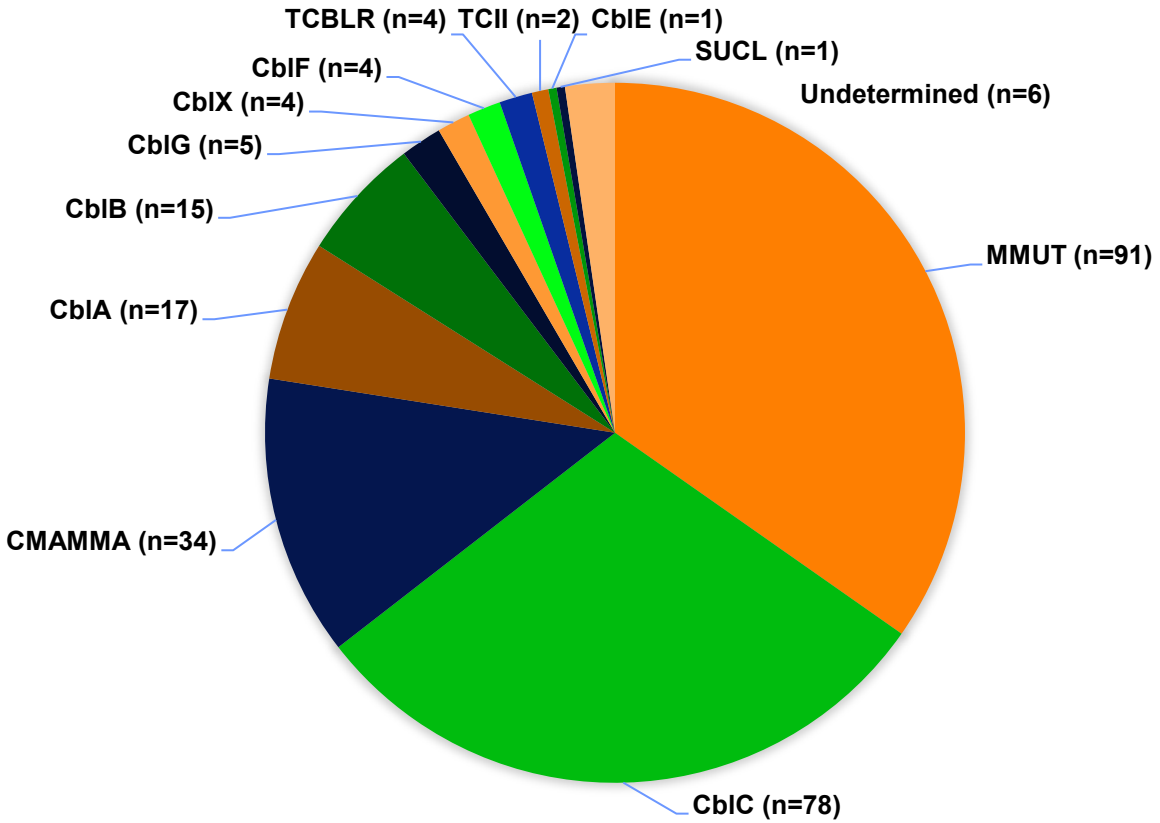
NIH Methylmalonic Acidemia Protocol

- Clinical and Laboratory Study of Methylmalonic Acidemia (ClinicalTrials.gov Identifier: NCT00078078)



- 2004-2022: 262 Subjects with MMA-related syndromes
- > 1250 Visits at NIH

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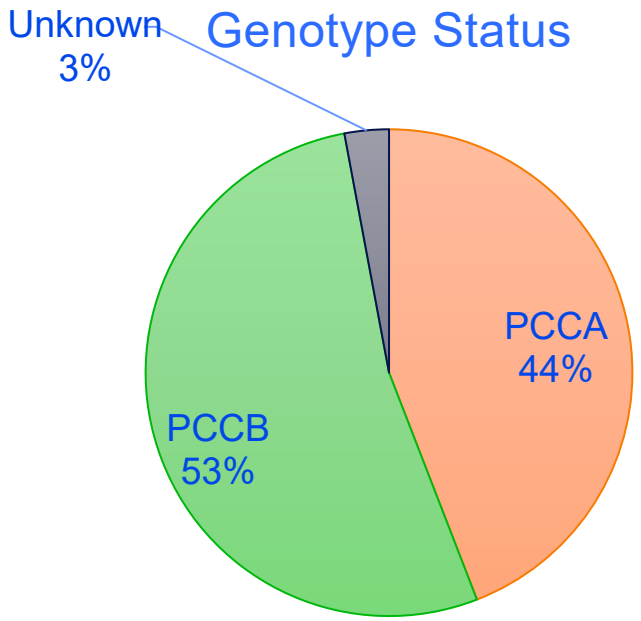
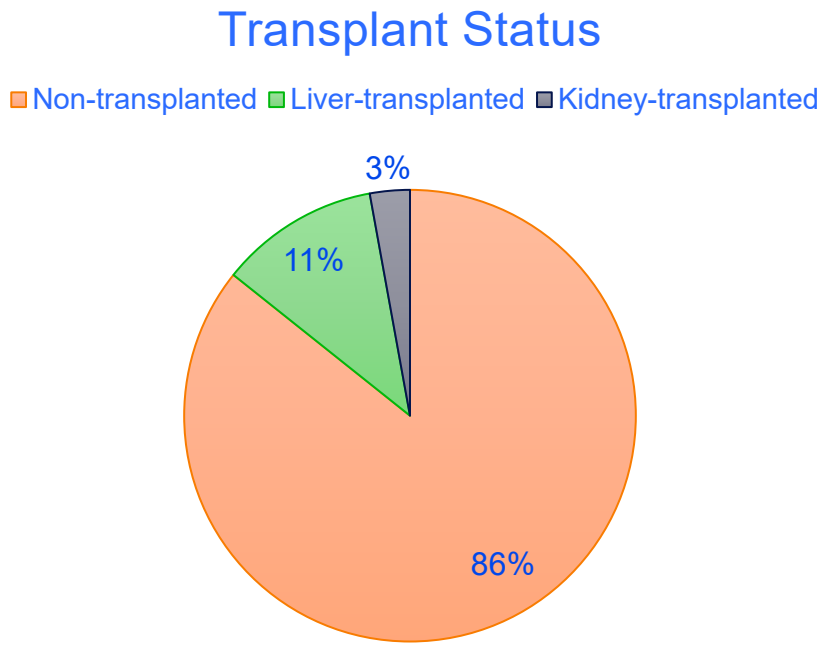
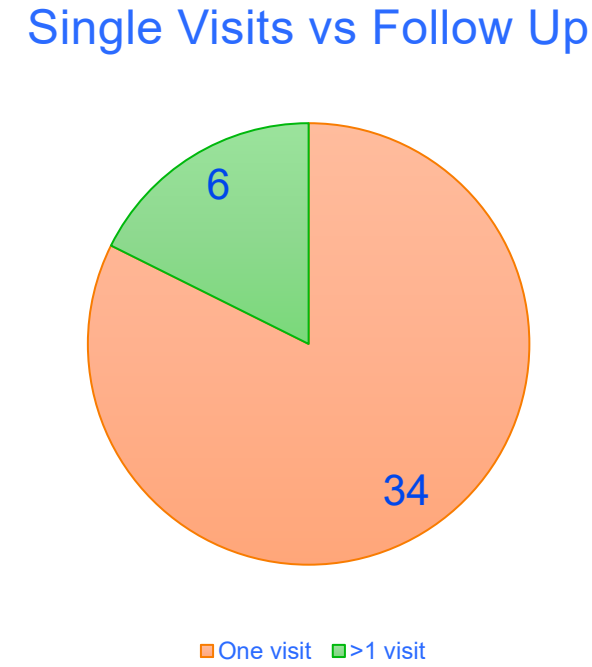
NIH Propionic Acidemia Protocol

- Natural History, Physiology, Microbiome and Biochemistry Studies of Propionic Acidemia (ClinicalTrials.gov Identifier: NCT02890342)







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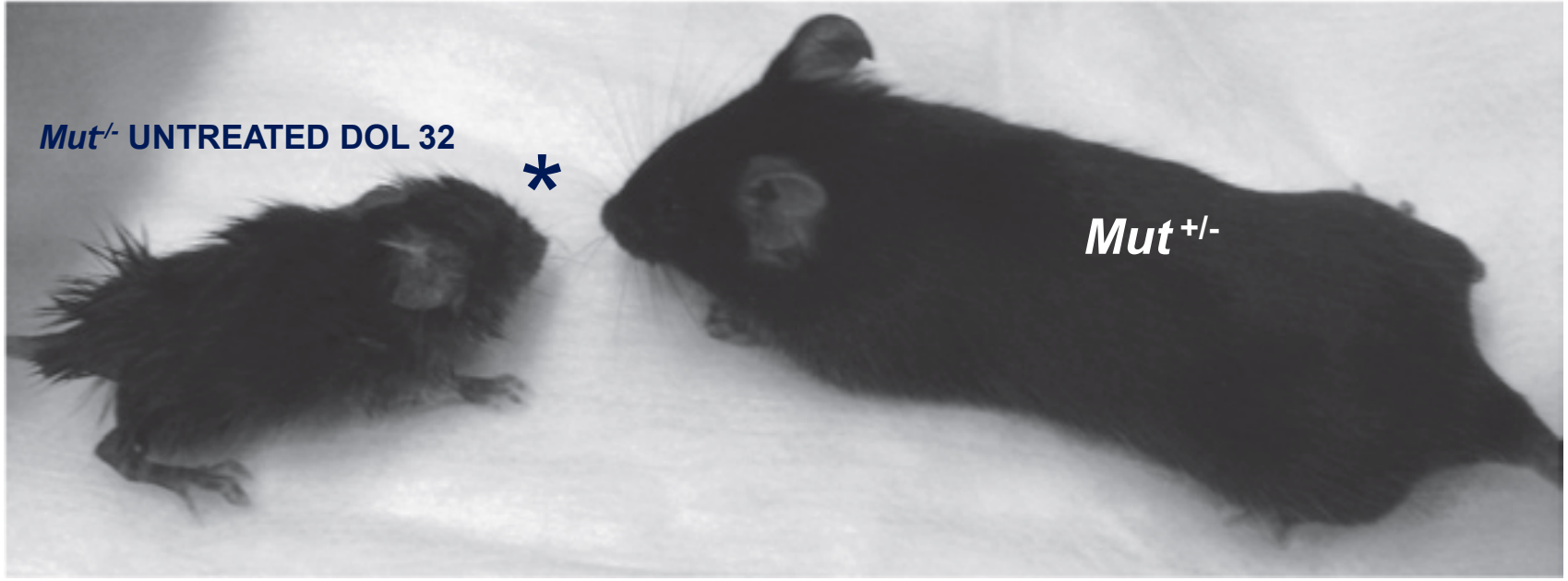
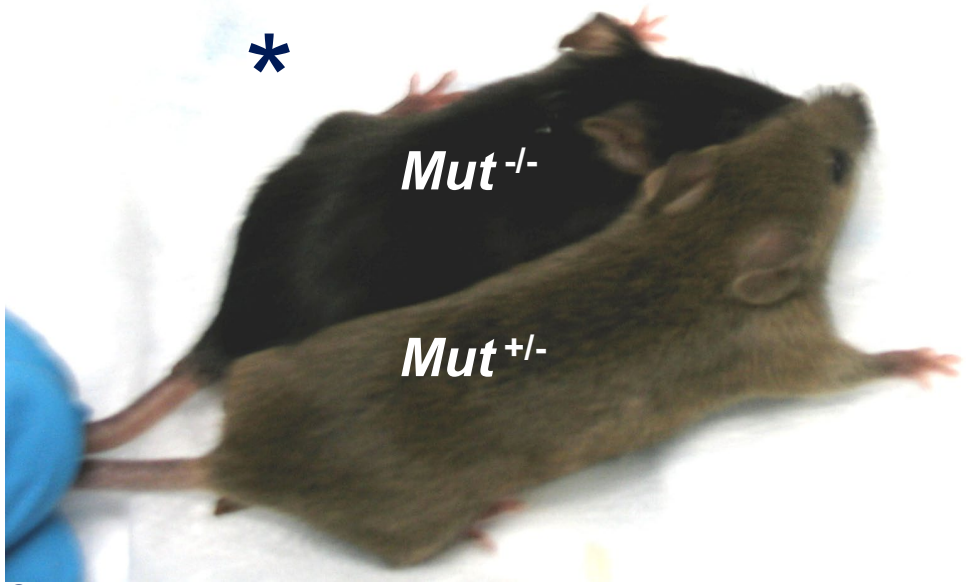
Our Motivation: No FDA-Approved Response Biomarkers for Organic Acidemia

- Significant gene therapy development efforts are in progress
- There are no FDA approved response or surrogate biomarkers
- Diagnostic biomarkers are the obvious candidates
  - Methylmalonic acid for MMA
  - Propionylcarnitine (C3) for PA
  - 2-Methycitrate (2MC) for PA

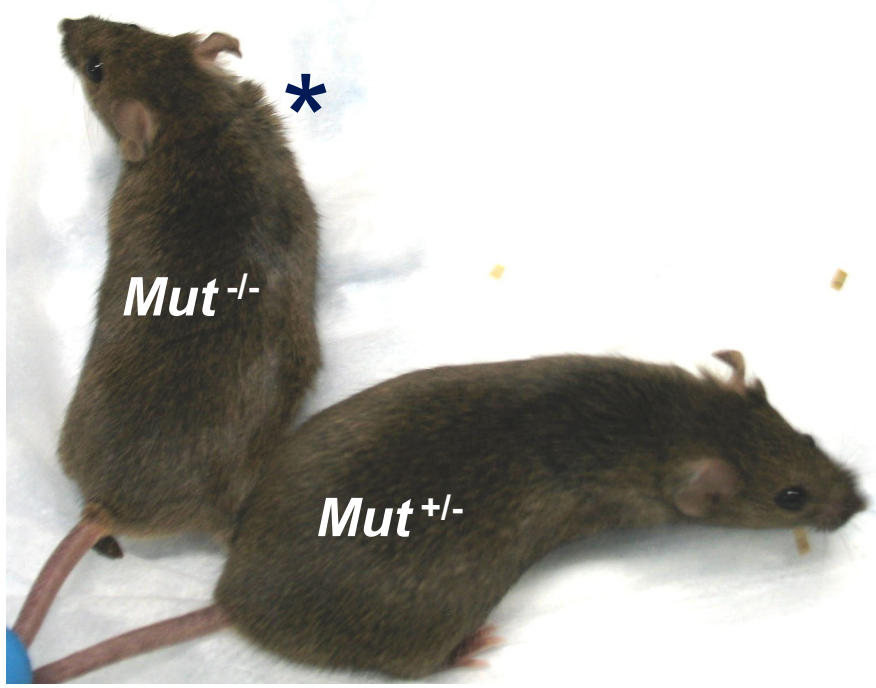


Mut-/- TREATED WITH rAAV8 DOL 124



Chandler and Venditti
(2010) Mol Ther 18:11

Mut-/- TREATED WITH rAAV8 DOL 259



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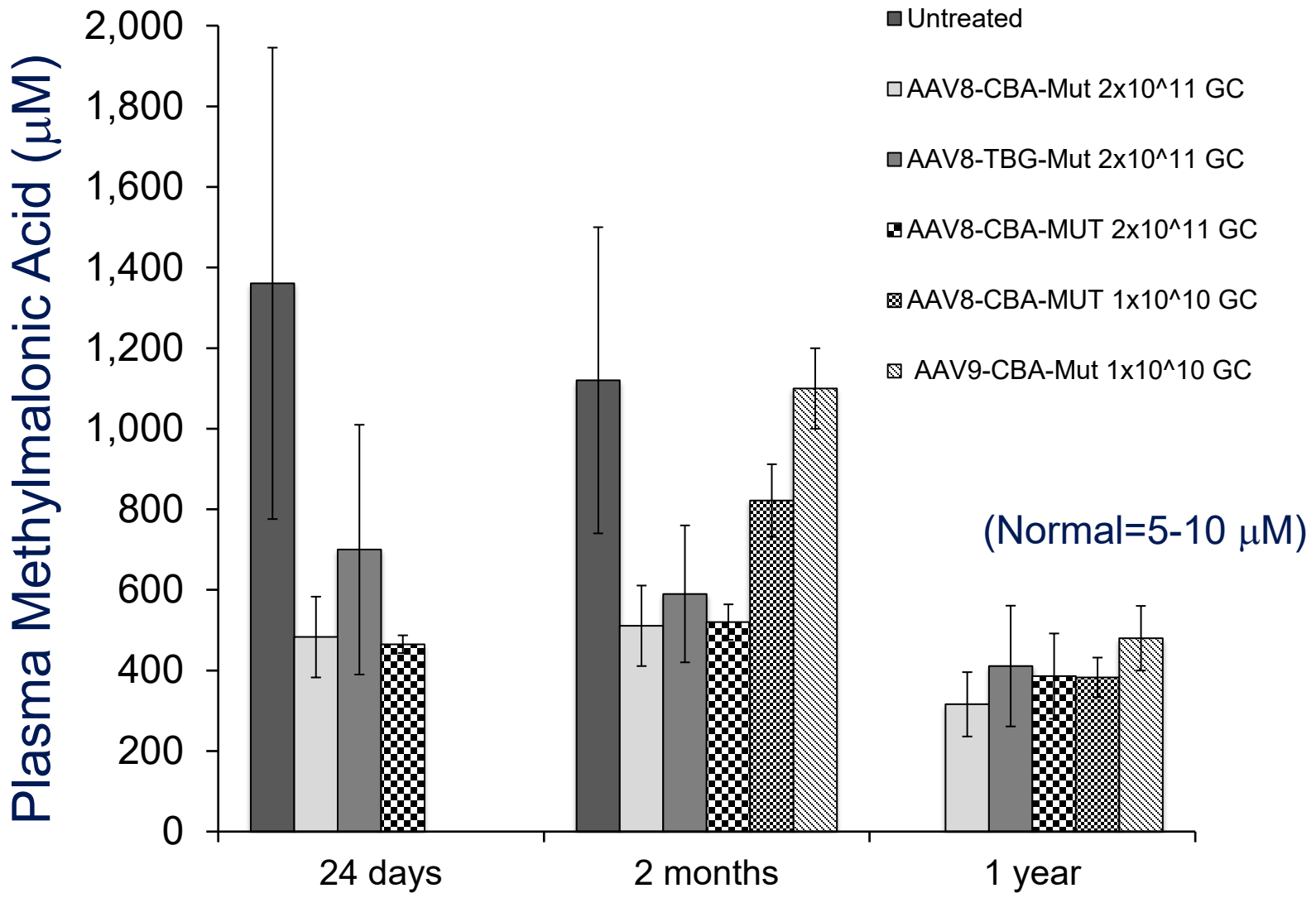
Metabolic Correction After AAV Gene Therapy



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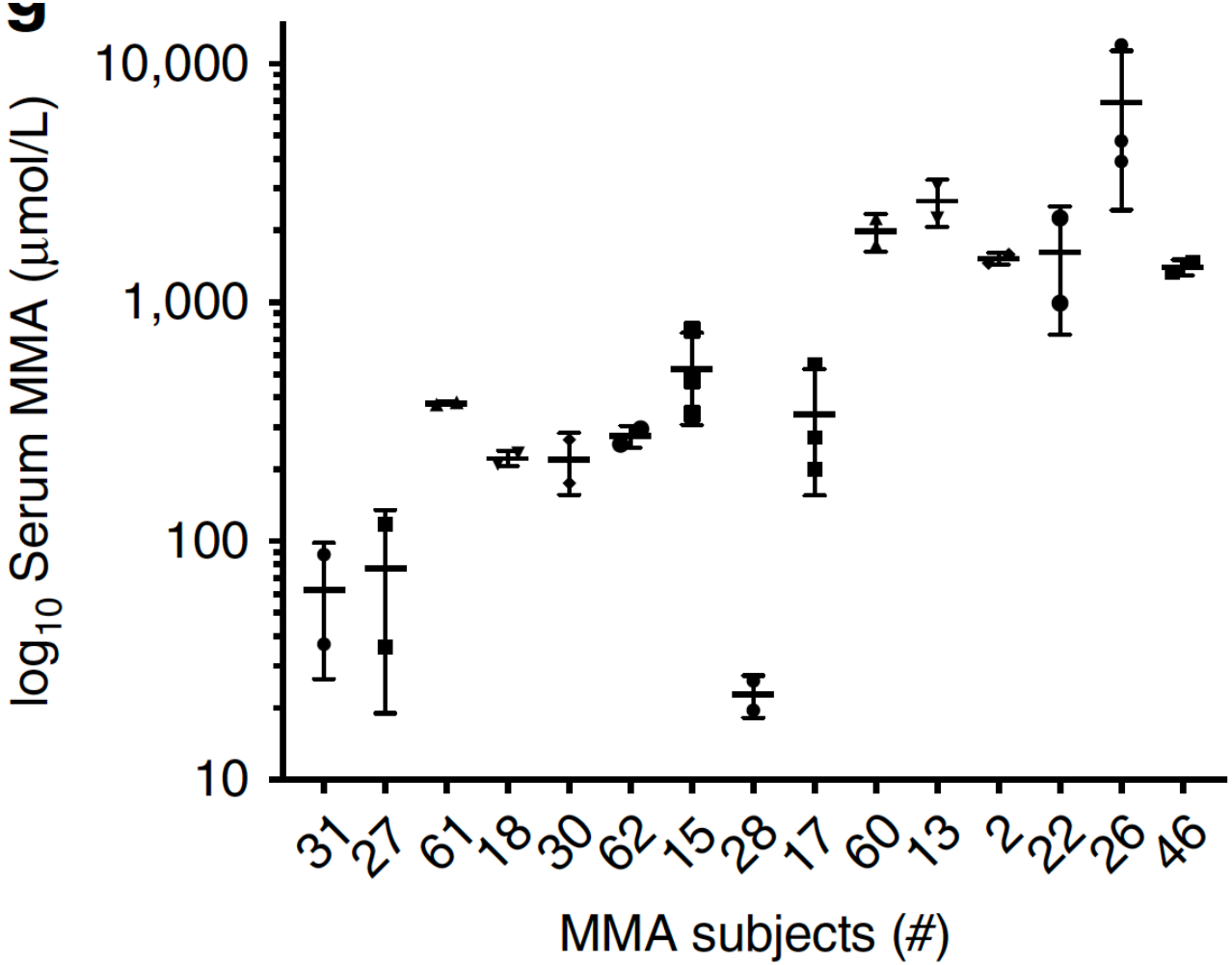
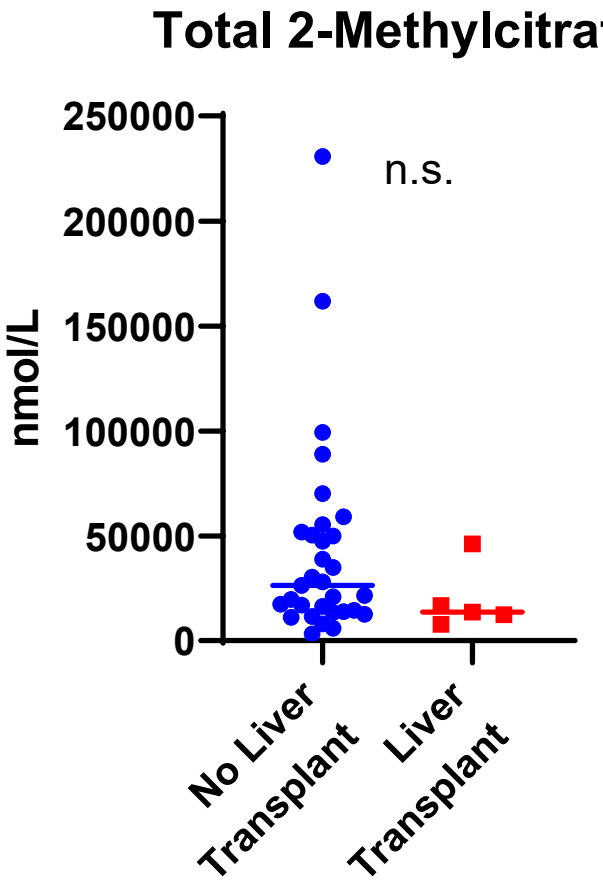
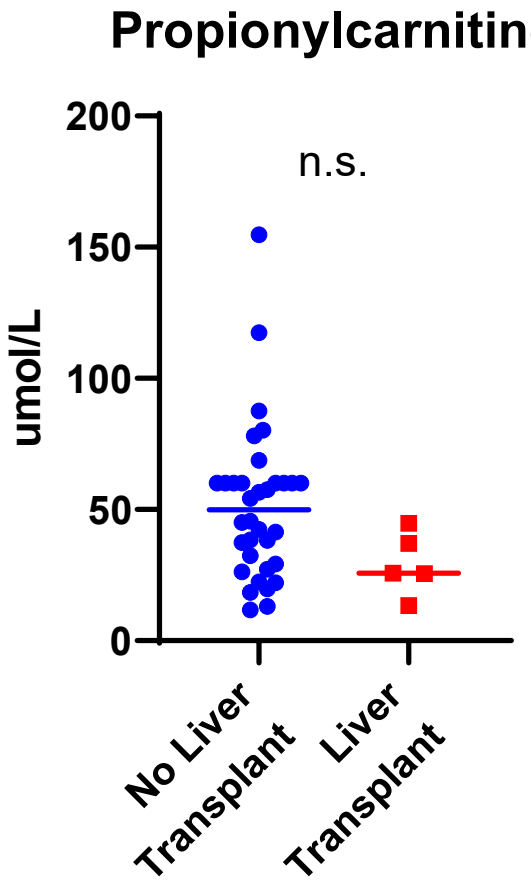
Plasma MMA Shows High Intrasubject Variability in MMA



Manoli I. et al., Genetics in Medicine, 2021

Diagnostic Biomarkers Can Also Fail To Detect the Effect of Liver Transplantation





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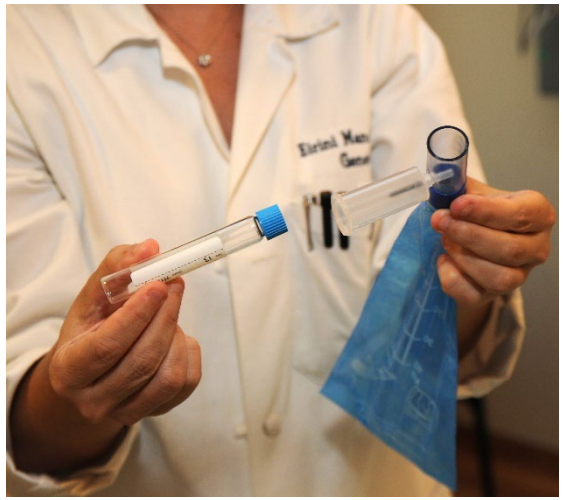
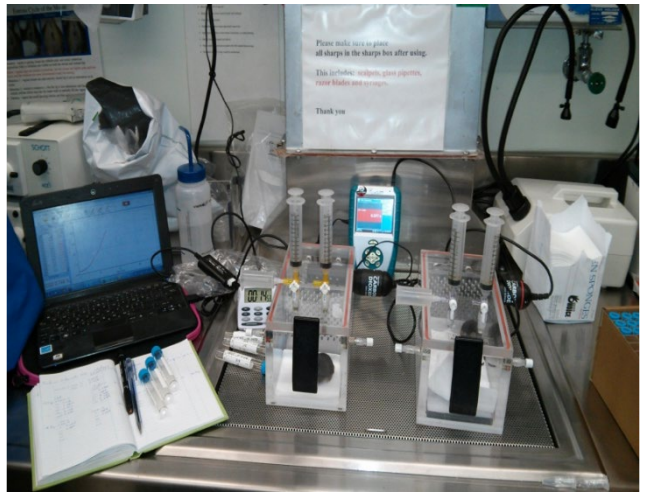
Shchelochkov et al, Genetics in Medicine, 23, pages 1534–1542 (2021)

A Promising Lead: Labelled Propionate Oxidation Studies





1-^{13}C Propionate (tracer)

↓ **LIVER, RAPID**

Propionyl-CoA

↓

↓

L-methylmalonyl-CoA

↓ **Methylmalonyl-CoA mutase**

Succinyl-CoA

↓

Krebs/TCA Cycle → **$^{13}CO_2$ (IRMS)** and **V_{CO_2}**

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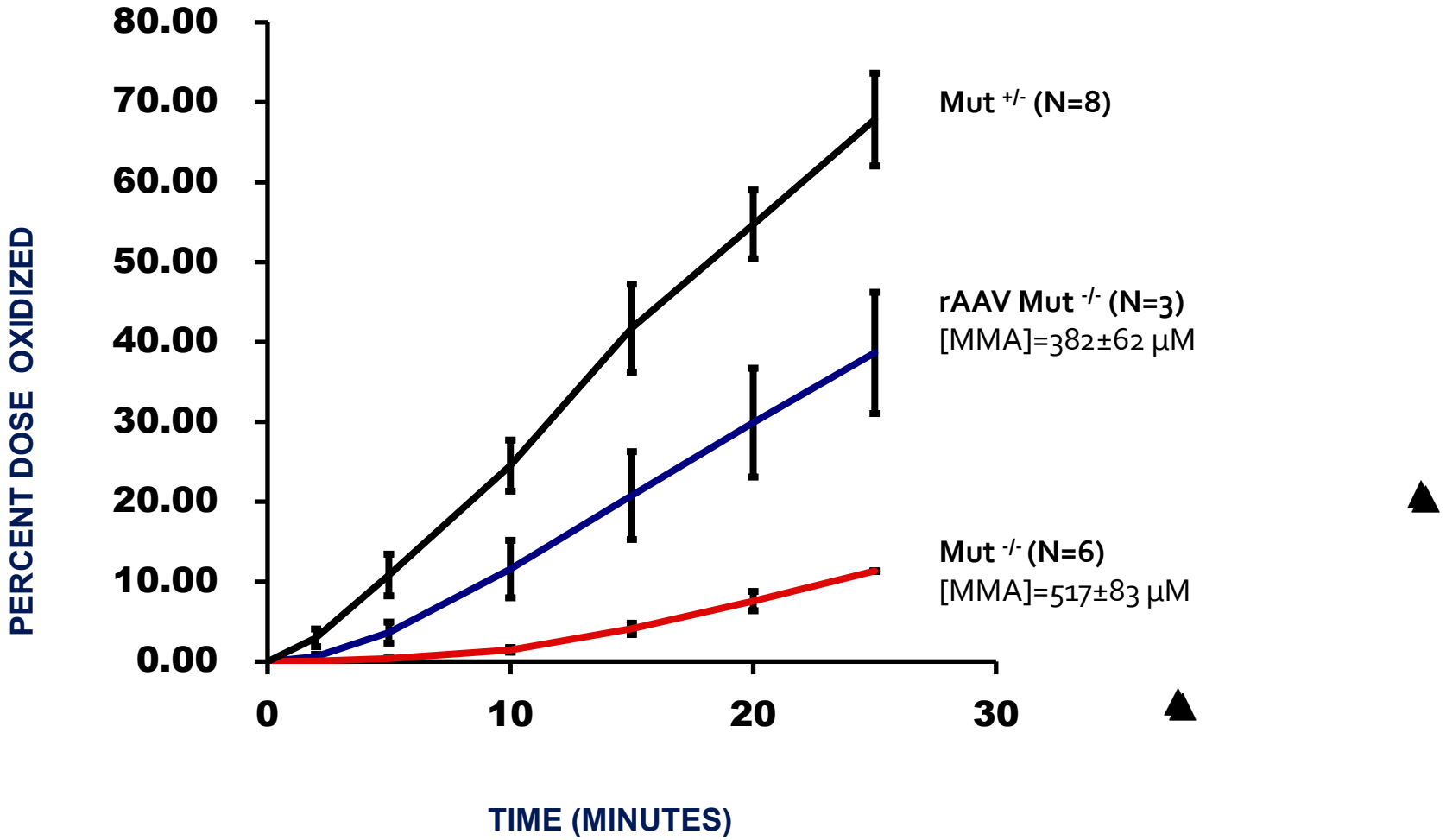
1-^{13}C Propionate Oxidation 1 year after Neonatal Gene Therapy with rAAV



Chandler and Venditti (2010) Mol Ther 18:11

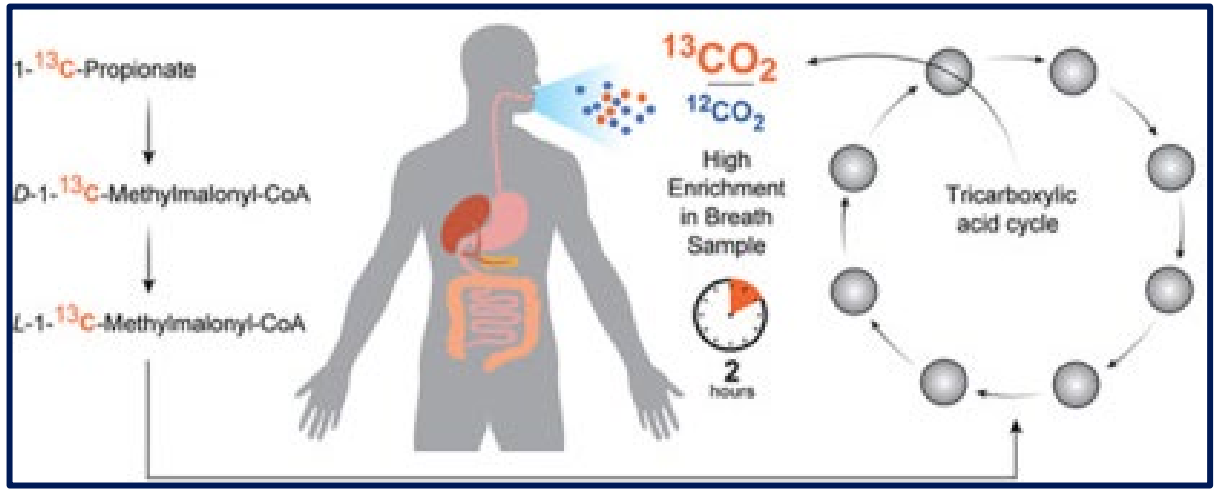
1-^{13}C Propionate Oxidation Is Restored In MMA Patients After L(K)T Despite Significant MMAemia

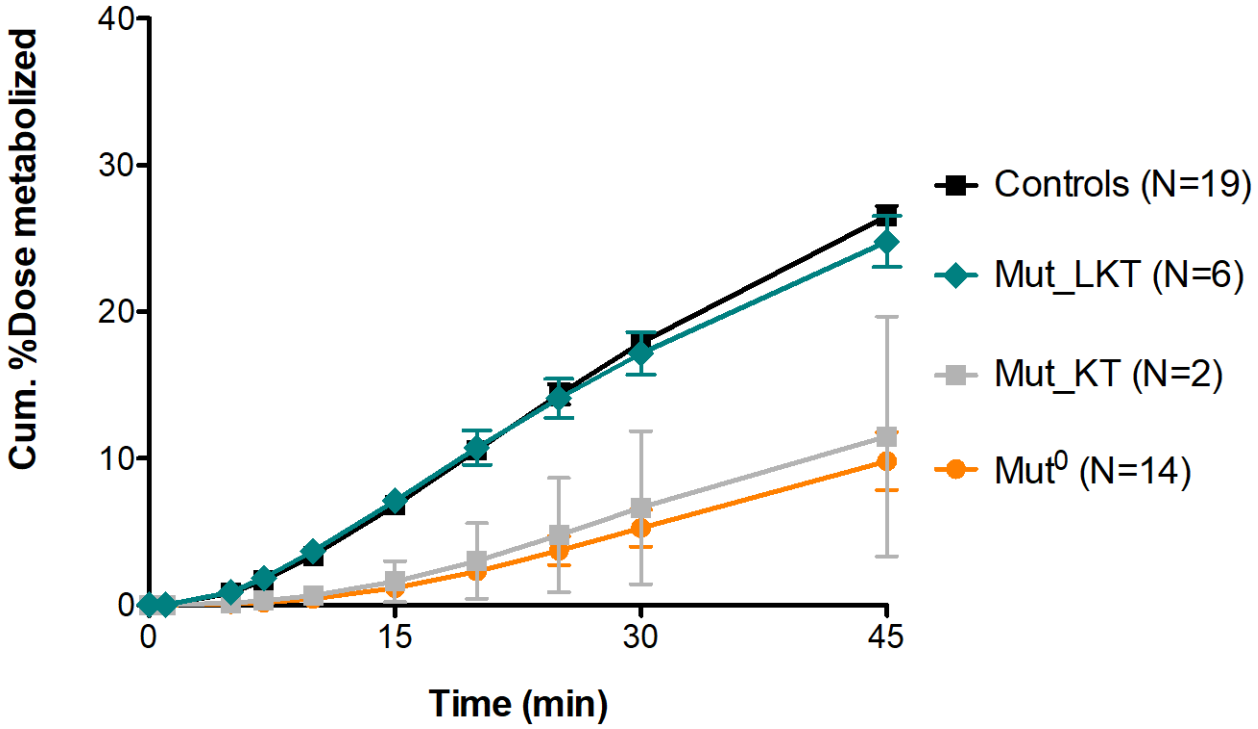
ARTICLE

1-^{13}C-propionate breath testing as a surrogate endpoint to assess efficacy of liver-directed therapies in methylmalonic acidemia (MMA)

Irini Manoli[1], Alexandra R. Pass[1], Elizabeth A. Harrington[1], Jennifer L. Sloan[1], Jack Gagné[1], Samantha McCoy[1], Sarah L. Bell[2], Jacob D. Hattenbach[2], Brooks P. Leitner[2], Courtney J. Duckworth[2], Laura A. Fletcher[2], Thomas M. Cassimatis[2], Carolina I. Galarreta[1], Audrey Thurm[3], Joseph Snow[4], Carol Van Ryzin[1], Susan Ferry[1], Nicholas Ah Mew[5], Oleg A. Shchelochkov[1], Kong Y. Chen[2] and Charles P. Venditti[1]✉

Genet Med. 2021 PMCID: PMC8354855





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Scaling Up Unbiased Screening of Biomarkers

nature > genetics in medicine > articles > article

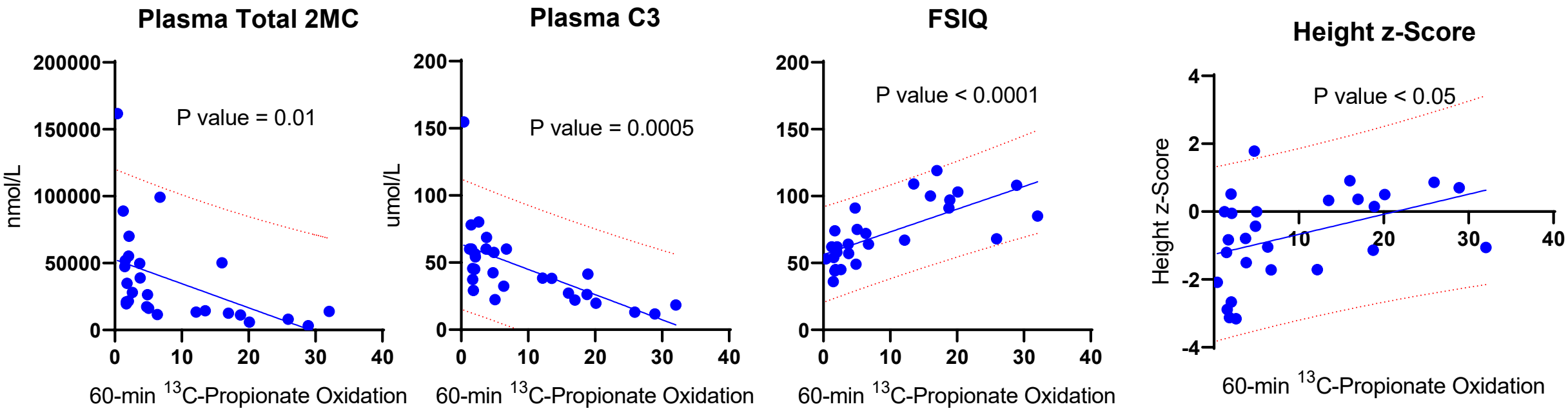
Article | Open Access | Published: 18 May 2021

Severity modeling of propionic acidemia using clinical and laboratory biomarkers

Oleg A. Shchelochkov, Irini Manoli, Paul Juneau, Jennifer L. Sloan, Susan Ferry, Jennifer Myles, Megan Schoenfeld, Alexandra Pass, Samantha McCoy, Carol Van Ryzin, Olivia Wenger, Mark Levin, Wadih Zein, Laryssa Huryn, Joseph Snow, Colby Chlebowski, Audrey Thurm, Jeffrey B. Kopp, Kong Y. Chen & Charles P. Venditti

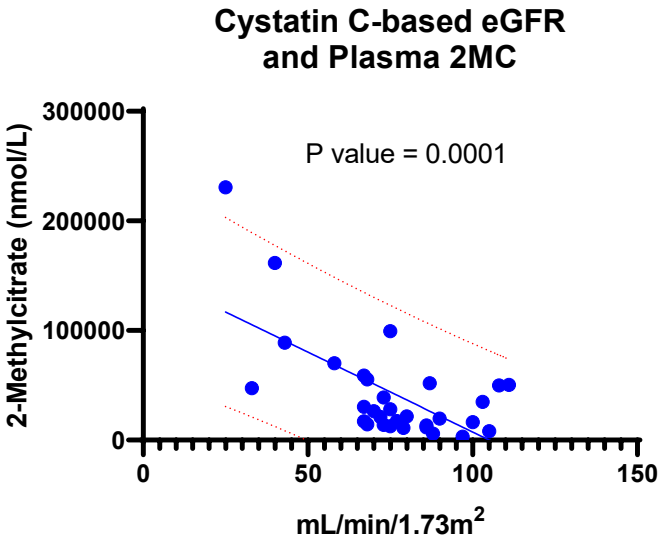
Genetics in Medicine **23**, 1534–1542 (2021) | Cite this article

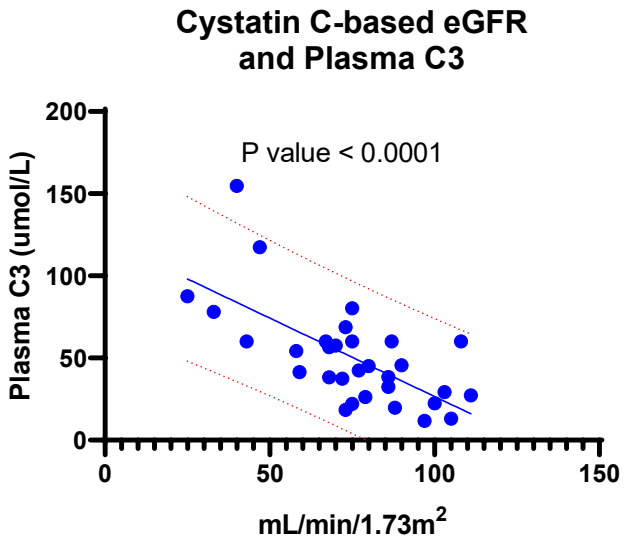
In vivo Propionate Oxidation Correlates with Diagnostic Biomarkers and Clinical Parameters

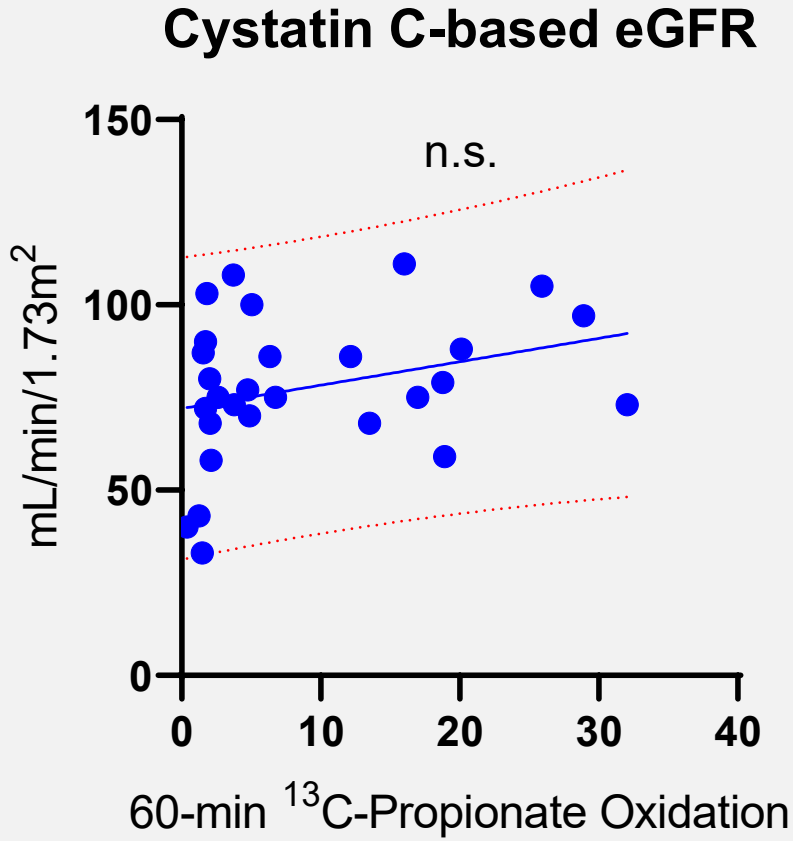


Shchelochkov et al, Genetics in Medicine, 23, pages 1534–1542 (2021)

1-^{13}C-Propionate Oxidation Remains Stable under Various Renal Conditions

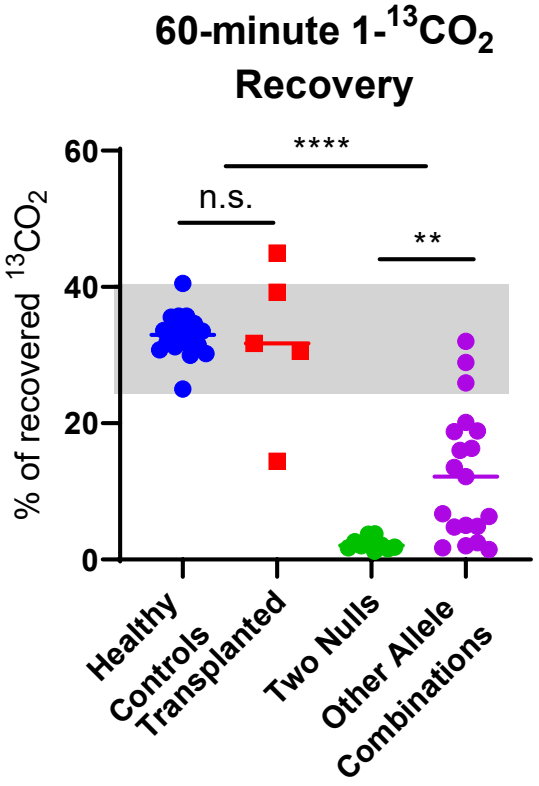


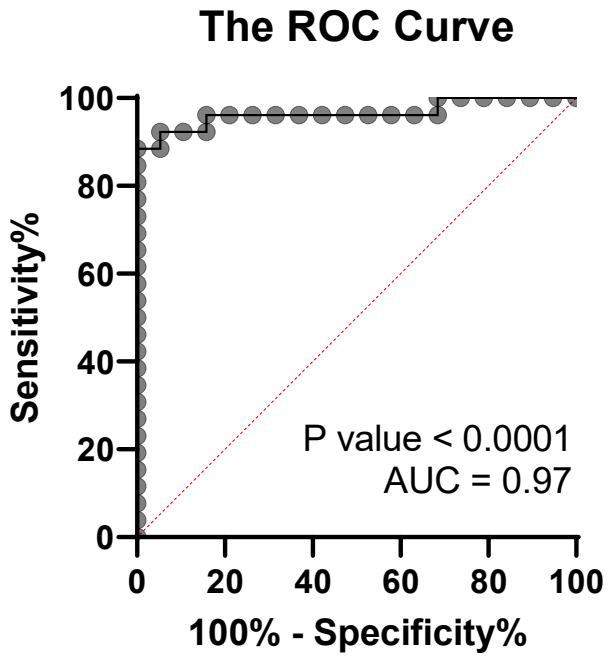


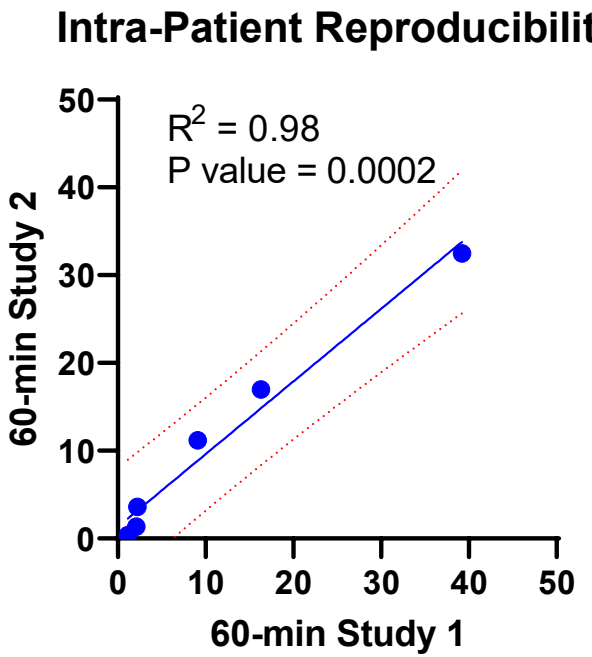


Shchelochkov et al, Genetics in Medicine, 23, pages 1534–1542 (2021)

Validity and Reproducibility

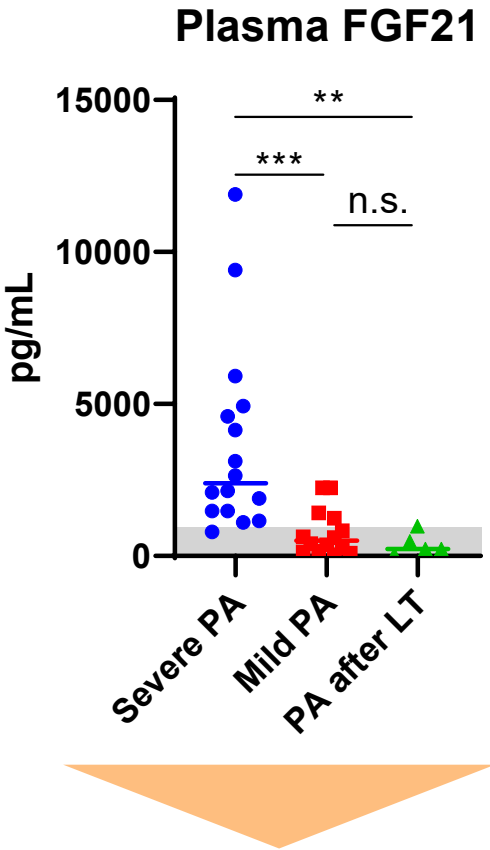


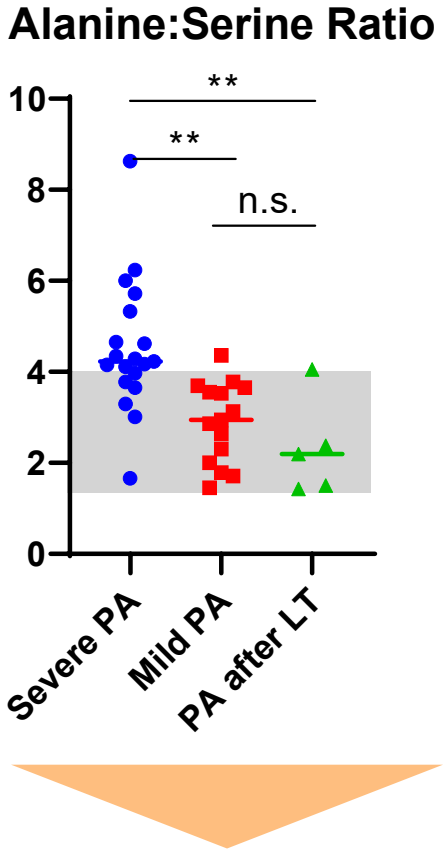


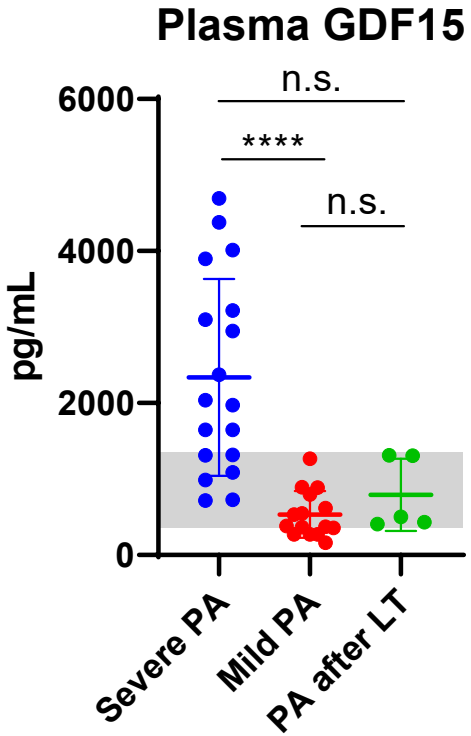


Shchelochkov et al, Genetics in Medicine, 23, pages 1534–1542 (2021)

Machine Learning Algorithm Prioritized Novel PA Biomarkers







Molema F et al, J Inherit Metab Dis. 2018 Nov;41(6):1179-1187.

Maines E, et al. *J Inherit Metab Dis*. 2020;**43**(6):1173-1185.

Schumann, A, et al. J Inherit Metab Dis. 2021; 44(6): 1330- 1342.

NIH NHGRI

Summary

- Combining data from OA natural history studies and mouse work helps understand strengths and limitations of conventional biomarkers
- Data from liver-transplanted study OA participants is an opportunity to validate candidate response biomarkers and surrogate endpoints for future gene replacement strategies
- *In vivo* oxidation of labelled propionate is a resilient candidate response biomarker
- Supervised ML approach provides a scalable and unbiased framework to extract biomarkers


The Forefront
of Genomics®

Issam Awad

The John Harper Seeley Professor of Neurological Sciences

University of Chicago Medicine

QUANTITATIVE SUSCEPTIBILITY MAPPING ON MAGNETIC RESONANCE IMAGING (QSM MRI) AS A BIOMARKER OF REBLEEDING IN CAVERNOUS ANGIOMAS WITH SYMPTOMATIC HEMORRHAGE (CASH)

Issam A. Awad, MD, MSc, FACS

University of Chicago Medicine and Biological Sciences

On behalf of NIH/NINDS funded Atorvastatin Treatment for CASH Exploratory Proof of Concept Phase I-IIA Trial (AT CASH EPOC;clinicaltrials.gov NCT 02R01NS107887)

and CASH Trial Readiness for Rare Diseases (CASH TR; U01 NS104157)

What is a Biomarker?

- A relevant biomarker is an imaging or molecular signature reflecting chronic disease activity over the patient's lifetime, recent acute clinical activity or predict future events (Amur et al., *Biomarkers Medicine* 2015).

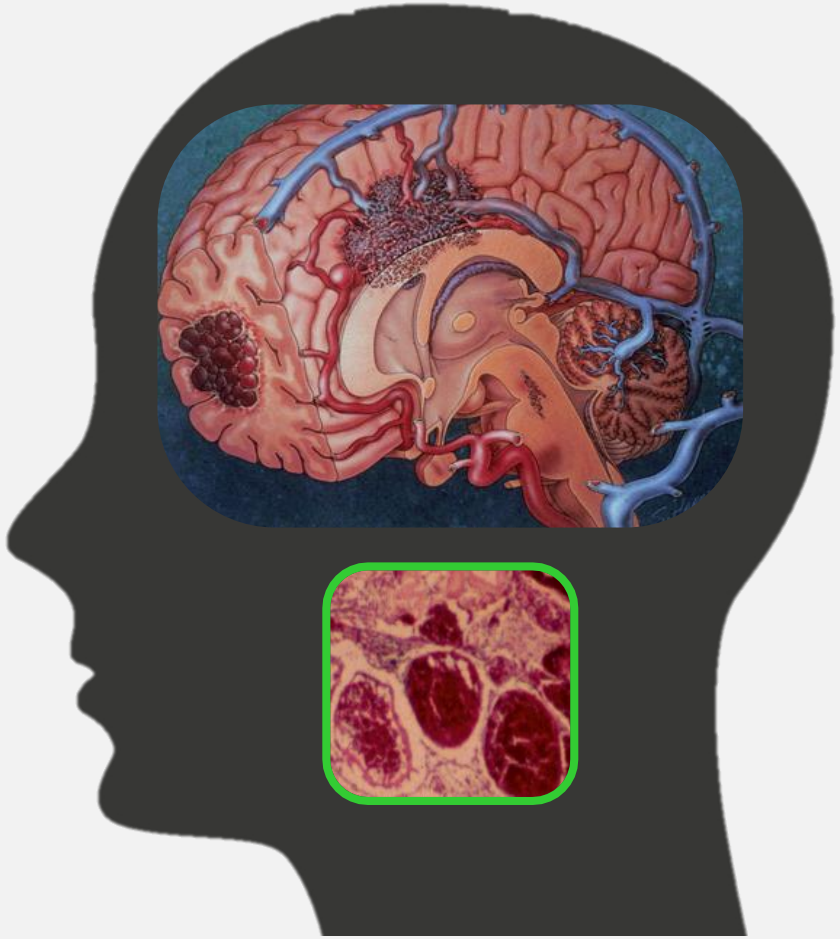
- Categories of biomarkers (https://www.ncbi.nlm.nih.gov/books/NBK326791)
  - ✓ **Diagnostic:** distinguish patients with a particular disease.
  - ✓ **Prognostic:** provide information on the likely natural course of disease.
  - ✓ **Predictive:** provide a forecast of the potential responses (favorable or unfavorable) to one or more specific treatments.
  - ✓ **Response/Monitoring:** dynamic assessments of a biological response after a therapeutic intervention, including:
    - ➢ **Safety** indicating biological adverse effects in response to treatment.
    - ➢ **Efficacy-response or surrogate endpoints** predicting disease-related clinical outcome.

TYPE OF BIOMARKER AND PROPOSED CONTEXT OF USE

- Mean lesional QSM on MRI (ppm) as a monitoring biomarker of cavernous angioma hemorrhage
- To assess the effects of drug treatment on bleeding in a cavernous angioma that had caused a symptomatic hemorrhage in the prior year
- Drug effect *DECREASING* QSM change during one-year epoch is a signal of drug benefit (effectiveness)
- Drug effect *INCREASING* QSM change during one-year epoch is a signal of safety concern (risk)
- Current use in single site Phase I-IIA proof of concept trial of repurposed drug (Atorvastatin) with FDA IND exemption
- Ongoing validation of biomarker in multisite use
- Consideration of potential use as a surrogate outcome in Phase IIB or Phase III trials for approval of drug indication in rare disease

Background
Cavernous Angioma

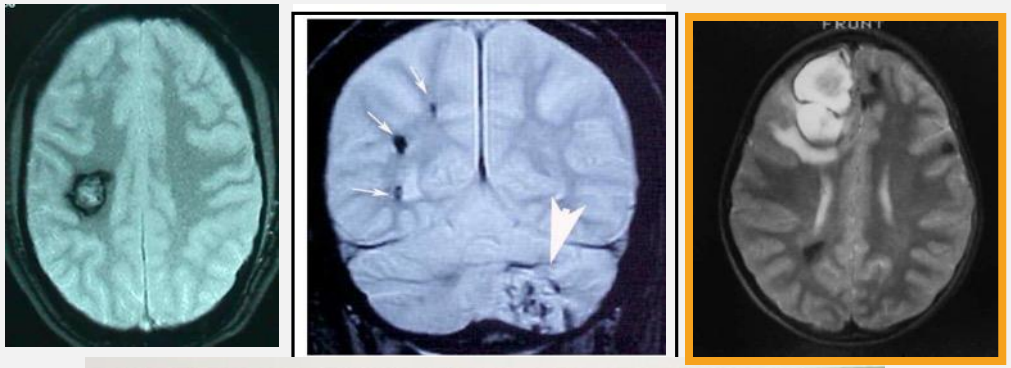
Cerebral cavernous angioma (CA), also known as cerebral cavernous malformation (CCM)

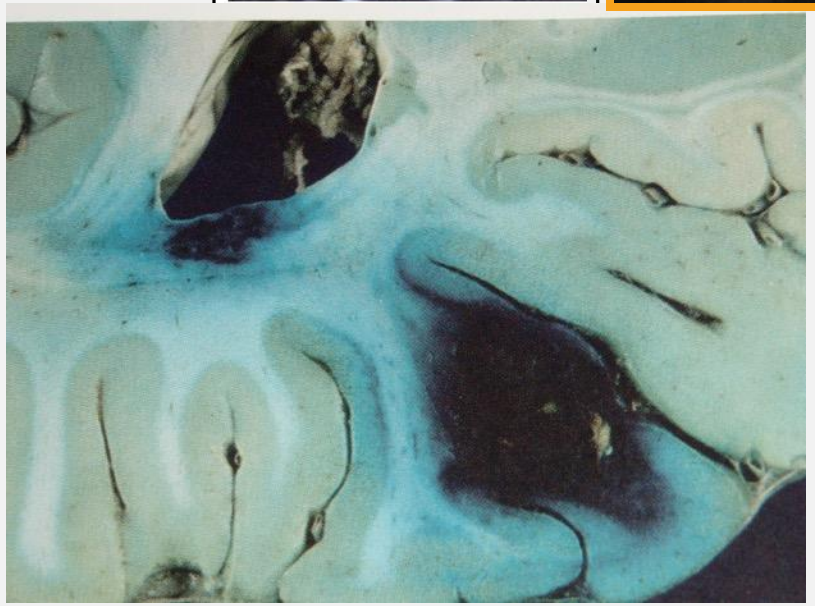


Endothelial lined, clustered, blood-filled capillary spaces (“caverns”), separated by an amorphous matrix lacking mature vessel wall elements

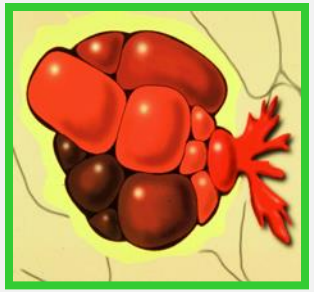
- Sporadic and Familial forms
- Same genetic aberrations in sporadic and familial lesions

HEMORRHAGE AS A DEFINING FEATURE OF THE CA PHENOTYPE

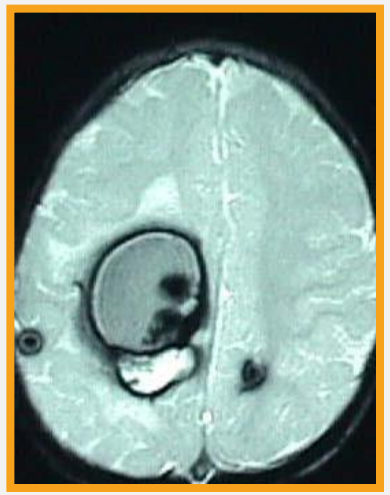


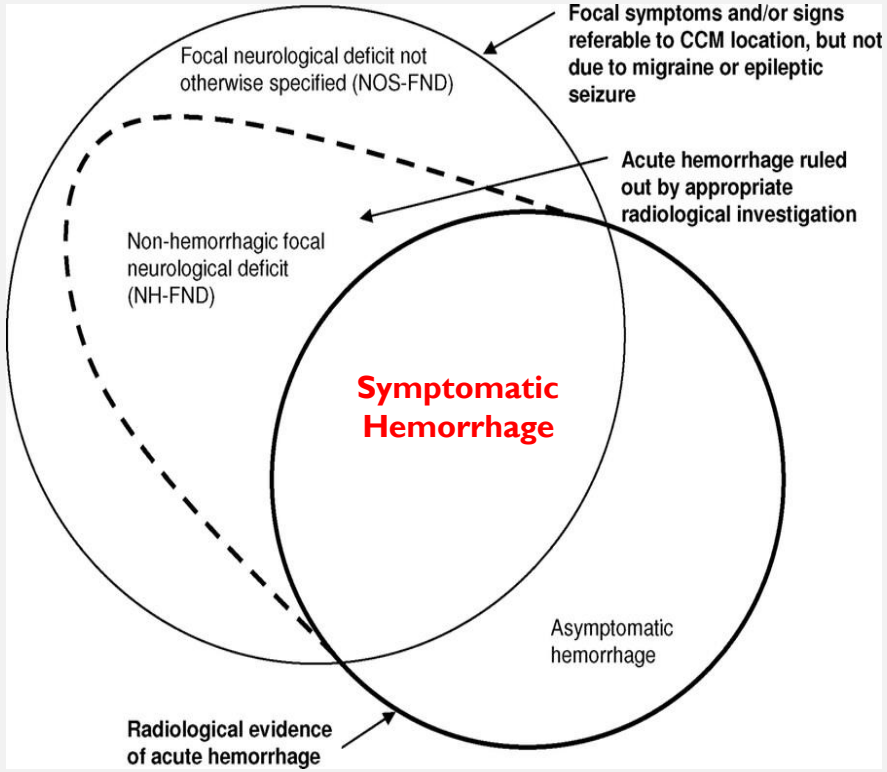


- Hemorrhage
  - Sine qua non of every CA lesion
  - Thrombus at different stages of organization in bubble-like caverns
  - Chronic blood products in perilesional brain in every case
  - Acute symptomatic hemorrhage



SYMPTOMATIC HEMORRHAGE AS A CLINICALLY RELEVANT DISEASE FEATURE





IMAGING

- Acute/subacute blood within the lesion **(hemorrhagic expansion)**
- Acute/subacute blood outside the lesion **(perilesional hemorrhage)**
- Hemorrhagic lesion proliferation (**hemorrhagic growth**)

AND ATTRIBUTABLE SYMPTOMS

Hemorrhage From Cavernous Malformations of the Brain: Definition and Reporting Standards

Rustam Al-Shahi Salman, FRCP, Edin; Michel J. Berg, MD; Leslie Morrison, MD; Issam A. Awad, MD; on behalf of the Angioma Alliance Scientific Advisory Board

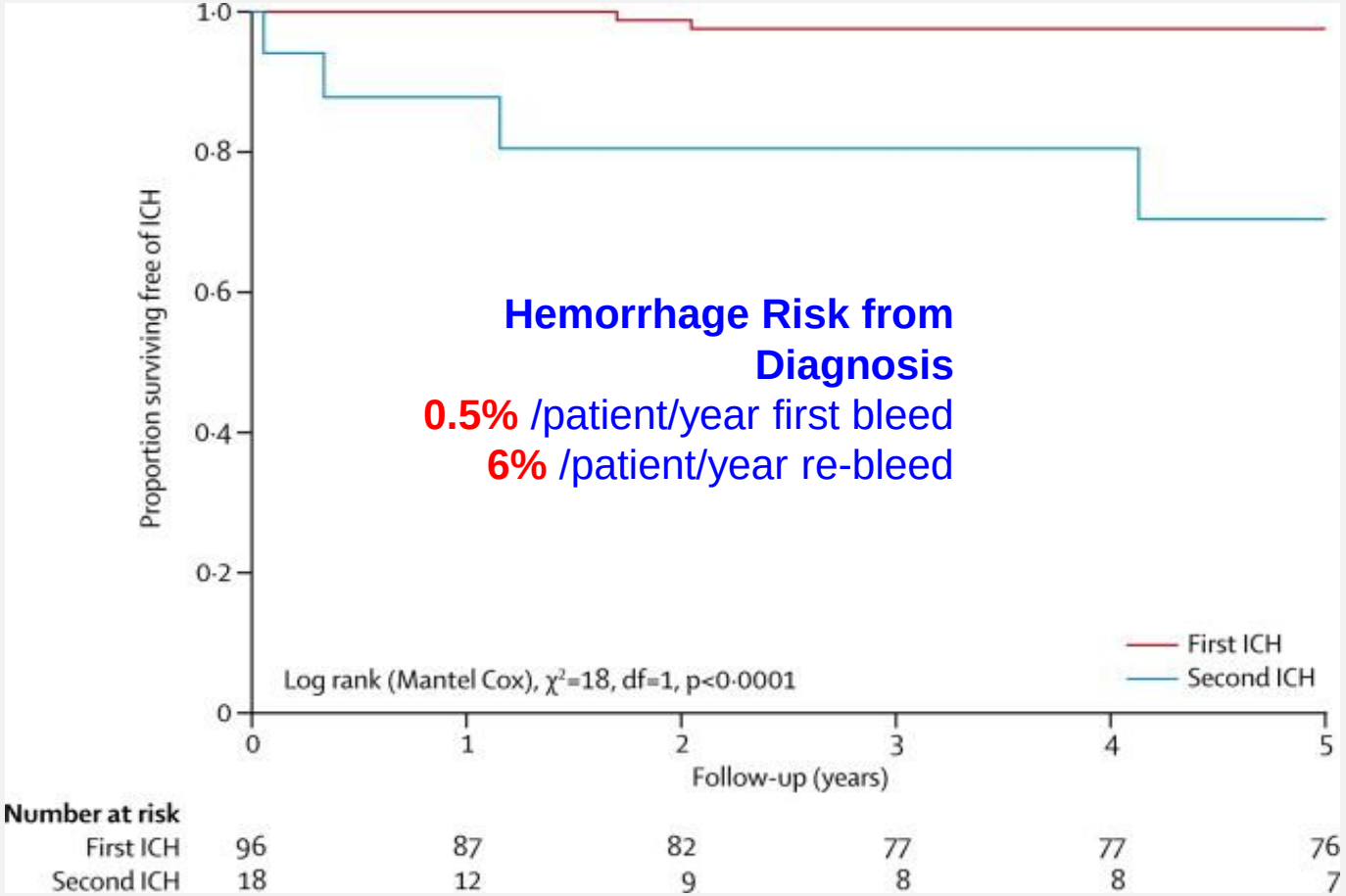
Stroke 2008

RISK OF FIRST BLEED VS RE-BLEED

CA is a common lesion (> 1 million carry the lesion in the U.S.

Cavernous angioma with symptomatic hemorrhage (CASH) is more likely [OR > 10X] to re-bleed

CASH is a rare disease and target of therapies (< 200,000 in the US)



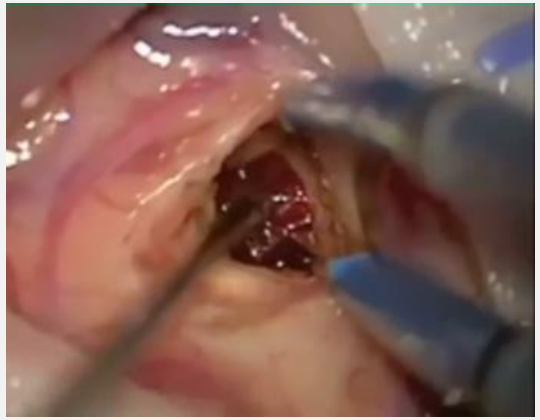
"Population based" Salman R et al. **Lancet Neurol 2012**

THE GOAL OF PREVENTING BLEEDING IN CA

- Of more than a million CAs in the US today, < 200,000 have had a recent SH. More than a third of these would rebleed again within 5 years.

- Those with brainstem and deep brain lesion locations are more likely than other CAs to bleed, rebleed and cause severe disability.

- With clinical equipoise and candidate therapeutics aimed at preventing re-bleeding it would be desirable to develop a drug that stabilizes CASH and prevents recurrent bleeding, avoid risks of surgery in brainstem and deep brain locations.



LIMITATION OF CONVENTIONAL IMAGING AND CLINICAL SYMPTOMS AS ENDPOINTS OF CLINICAL TRIALS AND THE CASE FOR A SURROGATE BLEEDING MEASURE

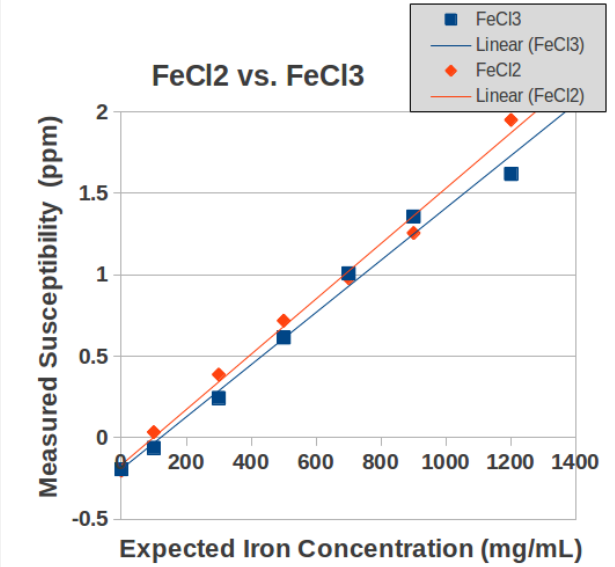
- Clinical events confirmed with imaging rebleed are uncommon, a challenge in rare disease clinical trials
- Subclinical rebleeds and asymptomatic lesion growth occur more often than clinical events, and subsequently herald clinically overt rebleeds (*Carrion-Penagos, et al. J Neurosurg 2020*)
- Novel biomarker would be useful if it is more sensitive to bleeding in lesions than clinical events or asymptomatic change with conventional imaging
- Novel biomarker changes over a time epoch (ie one year) would be useful if it detects cumulative impact of bleeding in lesions throughout the epoch

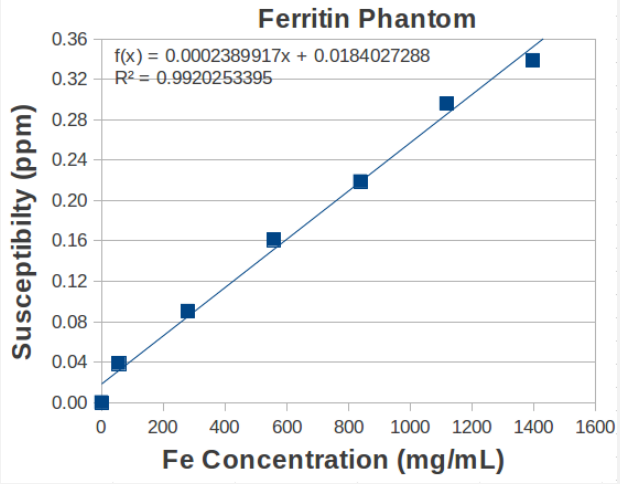
CANDIDATE THERAPEUTIC TARGETS

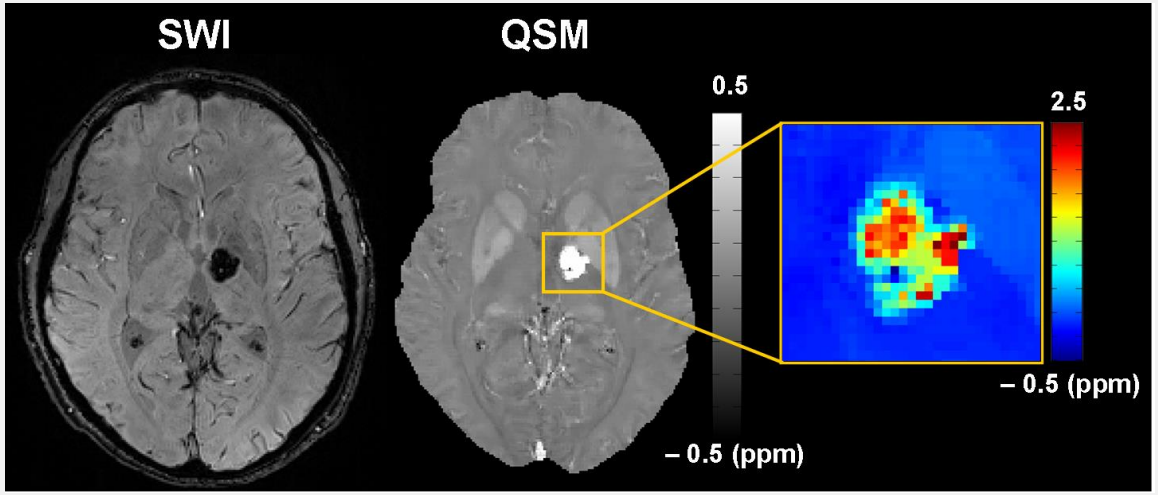
Mechanisms of disease	Plasma circulating biomarkers	Validating preclinical models	Candidate therapeutics	Lesion pathogenesis	Development status
MAPK signaling, PI3K-mTOR signaling, microbiome mechanisms[27,43,51,52,71,89,90,103,138]	ADAMTS4	Murine/human	BIX02189 (anti-MEK5)	Lesion burden	Preclinical
	ADAMTS5		XMD17-109 (anti-ERK5)	Bleeding	
	TLR4		Rapamycin (mTOR inhibitor)		
	LPB (LPS)		TLR4 inhibitors		
	CD14				
Angiogenesis[106,138,162,163]	VEGF	Murine/human	Bevacizumab	Lesion growth	Preclinical
	Angiopoietin 1-2		Semaxanib	Bleeding	
	ROBO4		TSP1 replacement		
	Thrombospondin 1				
Inflammatory processes, autophagy, focused immune response[138,159,163–166]	25-OH vitamin D	Murine/human	Vitamin D3	Lesion burden	Preclinical
	CRP		Tempol	Bleeding	
	Endoglin		Anti-BR3 antibody		
	IL-1β				
	IL-10				
Coagulation domains and thrombin-endothelial interactions[104,121,162]	Thrombomodulin	Murine/human	Potential biomarker	Bleeding	Preclinical
Rheological mechanisms[97,121]	Blood pressure pro-thrombotic states	Zebrafish/murine/human	Propranolol	Lesion growth	Preclinical
			β1-receptor antagonists		Phase I-IIA
Endothelial-mesenchymal transition[97]	TGF-β	Murine	Exisulind	Lesion burden	Preclinical
			Propranolol		
Endothelial permeability (RhoA/ROCK)[167–170]	pMLC	Murine/human	Fasudil	Lesion burden	Preclinical
	pMBS		BA1049	Bleeding	Phase I-IIA
	Leukocytes		Atorvastatin		

Snellings, et al.
Circ Res 2021

QUANTIFYING THE IRON LEAK IN HUMAN LESIONS: QUANTITATIVE SUSCEPTIBILITY MAPS (QSM)







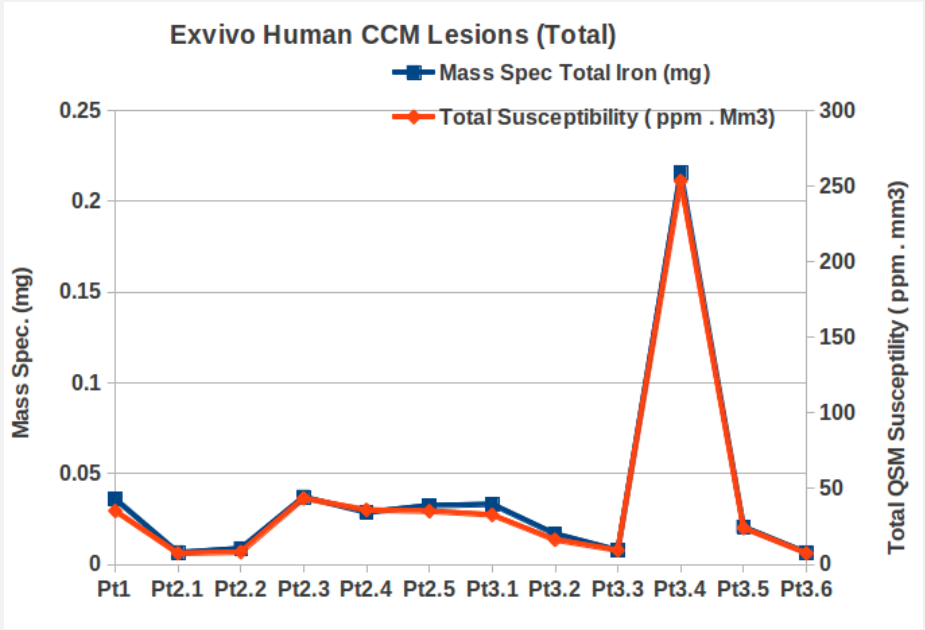
A Biomarker of Lesion Progression and Therapeutic modification…

Validation of mouse lesion histology, iron vs QSM
Validation in vivo and ex vivo lesion QSM vs iron concentration

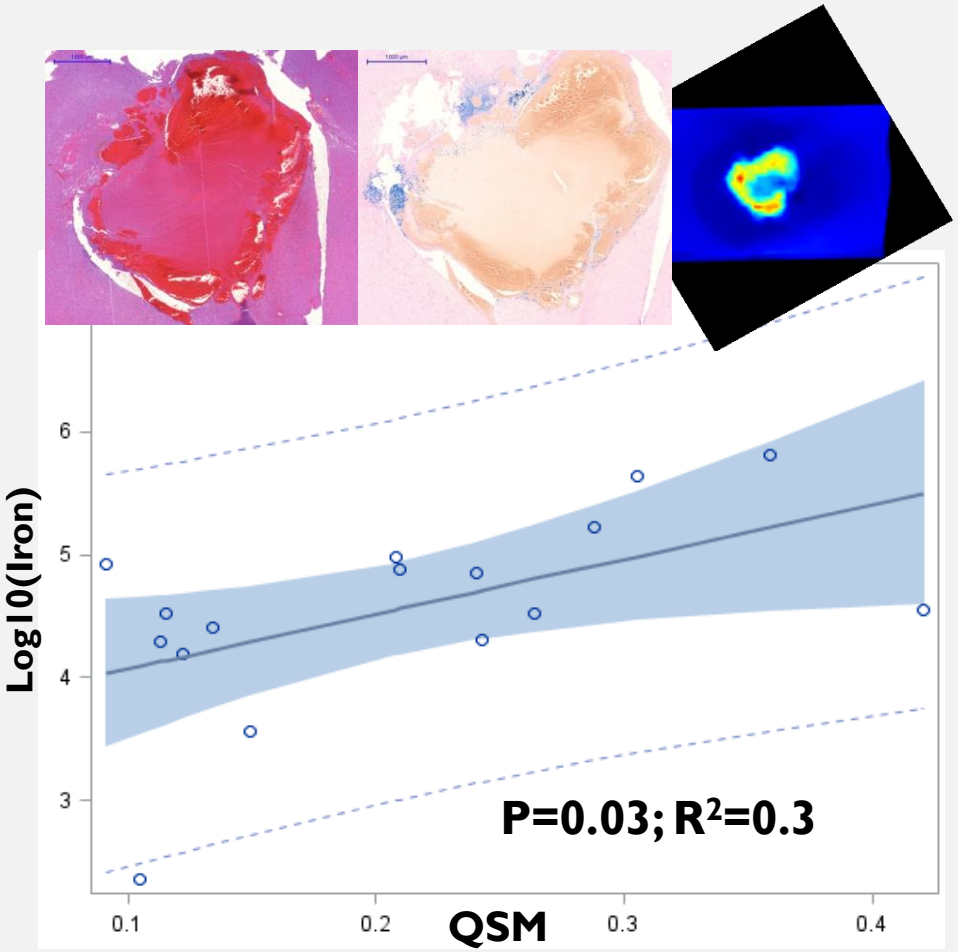
CTSA *ULI TR000430*

Tan et al. Investigative Radiology, 2014

VALIDATING QSM VS LESIONAL IRON IN HUMAN AND MOUSE CAS



Total QSM of human CCM lesion sample *ex vivo* versus lesional Fe content by mass spectrometry

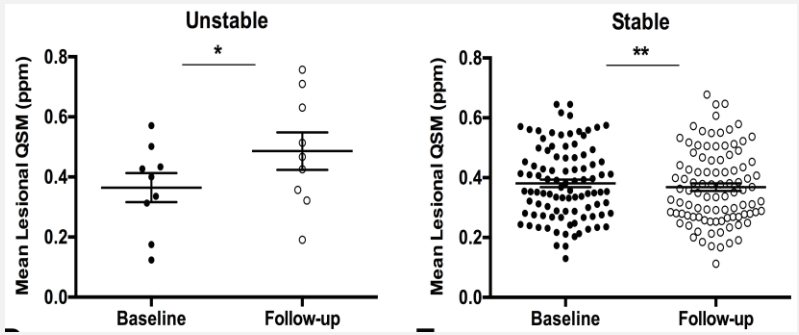


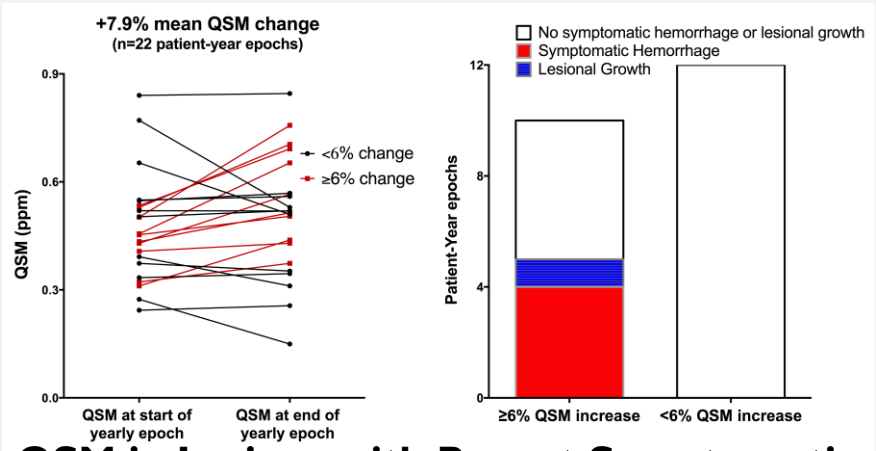
QSM in Mouse CCM lesion versus non-heme Iron (Perl stain) and histology

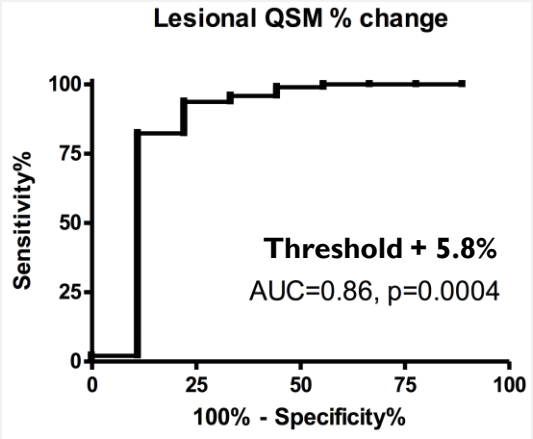
CTSA *ULI TR000430*

Tan et al. Investigative Radiology, 2014

> 6% QSM CHANGE IS SENSITIVE AND SPECIFIC TO SYMPTOMATIC HEMORRHAGE IN CA
QSM MORE SENSITIVE THAN CLINICAL IMAGING TO DETECT BLEEDING IN FOLLOW-UP OF LESIONS WITH RECENT HEMORRHAGE CASH







QSM in Lesions with Recent Symptomatic Hemorrhage During Follow-up

- Lesions which bleed exhibit sensitive and specific increase in mean lesional QSM (threshold +5.8%)
- About half of unresected lesions with recent hemorrhage have a threshold increase in QSM/patient-year epoch during follow-up; half of these are symptomatic
- No symptomatic rebleed occurs without a threshold increase in QSM

Tan, et al. *AJNR 2016*
Girard, et al. *J Neurosurg 2016*
Zeineddine et al. *J MRI 2017*

Biomarkers and CA Clinical Trial Models

SYMPTOMATIC REBLEED (PHASE III TRIALS)

2-tailed	3 years Follow-Up		5 years Follow-Up	
Genotype	All	CCM3	All	CCM3
Effect assumption	50% decrease	50% decrease	50% decrease	50% decrease
Sample size / group	299	108	190	76
Significance level	0.05	0.05	0.05	0.05
Power	80%	80%	80%	80%

QSM Biomarker Modification (Proof of Concept Phase I-II Trials with Smaller # of Cases)

2-tailed	QSM 2 years f/u (safety and efficacy POC)
Genotype	All
Effect assumption	Percent QSM change observed in CASH lesions; or therapeutic effect in mice
Sample size / group	20-25
Significance level	0.1
Power	90%

Zeineddine et al. *J MRI 2017*

STABILIZE THE UNRESECTED CAVERNOUS ANGIOMA WITH RECENT SYMPTOMATIC HEMORRHAGE (CASH)

Critical Gap: Trial Readiness

(U01 PAR-16-020)

U Chicago (PI), UCSF, Mayo, Johns Hopkins, UNM, Utah, Barrow

- **Prevalence and enrollment rates of non-excised CASH, baseline characteristics (age/sex, lesion location, functional/disability status, QOL)**
- **Biomarker validation at multiple sites (feasibility, accuracy, precision, reproducibility)**
- **Rebleed rates, functional outcome/QOL, biomarker changes over time (during prospective follow-up)**

Polster, et al. CASH TR *Neurosurgery* 2018

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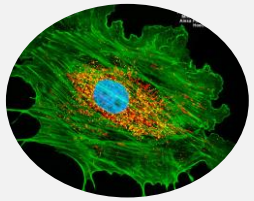
NIH National Institute of Neurological Disorders and Stroke

Biologic Premise of the Proposed Therapy
Mechanistic Rationale, Preclinical Studies



Defective Endothelial Barrier and Bleeding as Hallmarks of CA

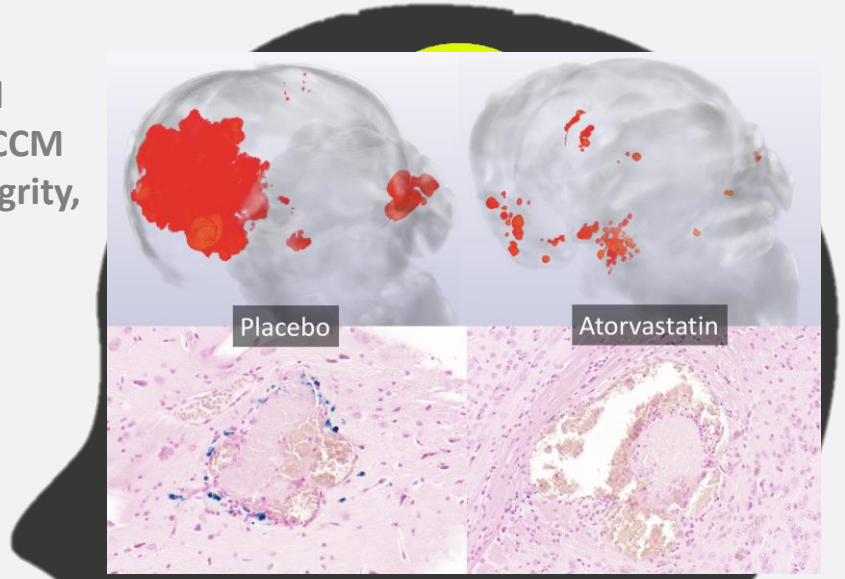
Hemosiderin deposition as a result of chronic hemorrhage from "leaky" and defective endothelial barrier. Loss of CCM results in disruption of junctional integrity, resulting in increased endothelial permeability in vitro and in vivo.

Wong, et al. 2000; McDonald, et al. 2011

Mediated by RhoA/ROCK

CCM loss in ECs activates the GTPase protein RhoA, and results in increased actin stress fiber, decreased EC lumen formation, and increased permeability. ROCK activation was demonstrated in surgically excised human CA lesion specimens from sporadic and all 3 familial genotypes.

Stockton, et al. 2010; Zhou, et al. 2016



Atorvastatin 80 mg/kg/day decreases lesion burden and non-heme iron in mouse models compared with placebo

Block ROCK

ROCK Inhibition Reverses CCM-Related Cellular Phenotypes. ECs from $Ccm^{+/-}$ mice exhibit a generalized vascular leakage in vitro and in vivo that is reversed by fasudil, a specific ROCK inhibitor.

McDonald, et al. 2012; Shenkar, et al. 2017

Atorvastatin

Atorvastatin inhibits ROCK activity (pleiotropic effect) at high dose in humans. It recapitulates the benefits of Fasudil in recent experiments, with no hint of increased hemorrhage or attrition

There is currently no pathway for the approval of fasudil for chronic use in man. A pharma pipeline for a safer or more effective chronic ROCK inhibitor will require several years before potential Investigational New Drug (IND) and clinical trials begin in man.

Atorvastatin Treatment in Cavernous Angiomas with Symptomatic Hemorrhage Exploratory Proof of Concept Trial (AT CASH EPOC)

Phase I-IIa Randomized, Placebo-Controlled, Double-Blinded, Single-Site Clinical Trial

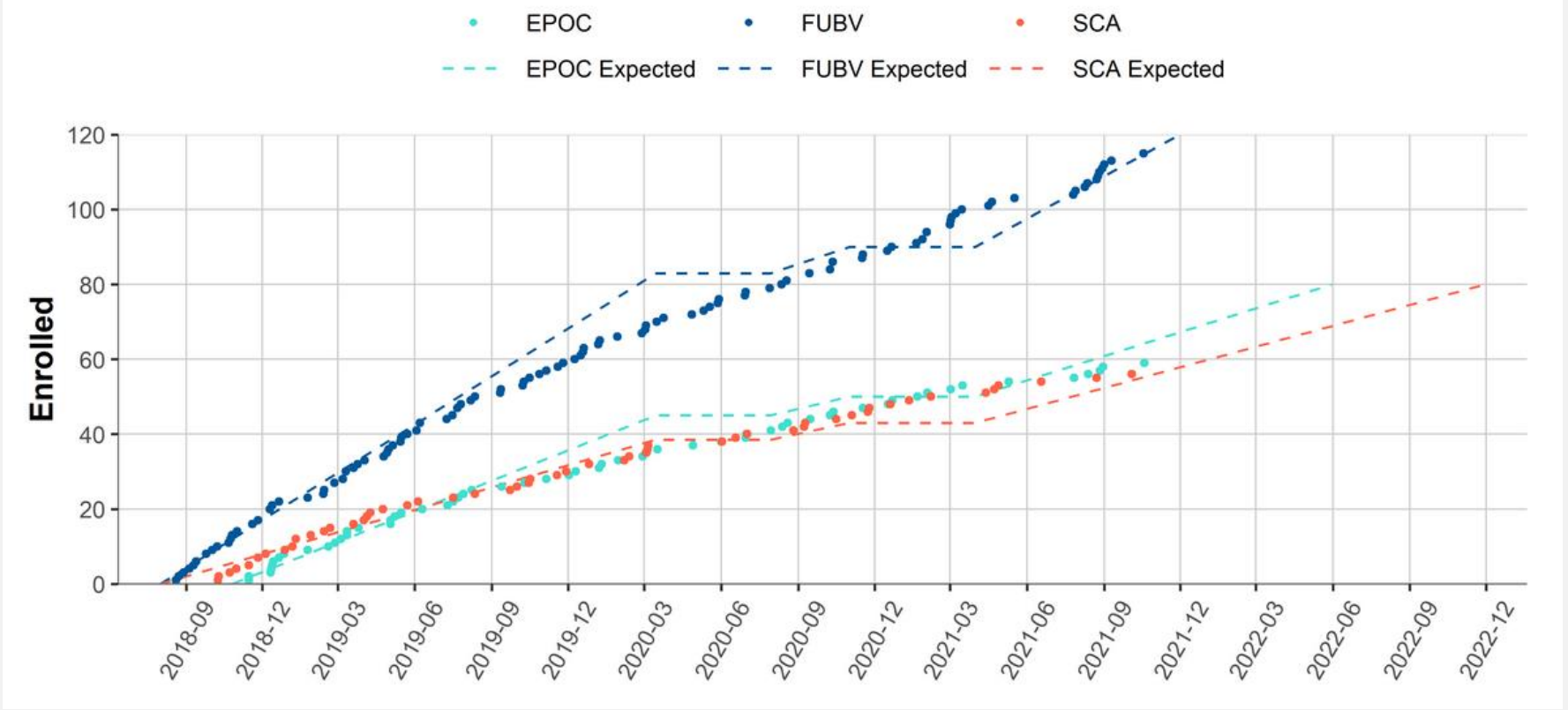
Intervention impacts QSM biomarker activity with a 20% change score during 2 time epochs (years 1 and 2)

Two tailed: – change (benefit); + change (risk)

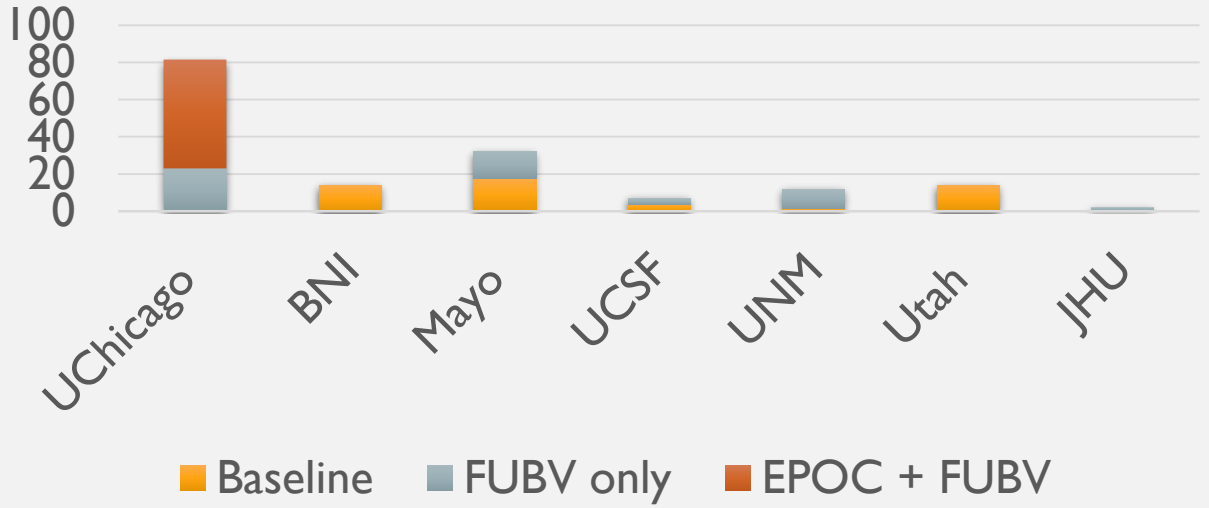
ClinicalTrials.Gov NCT02603328

NIH/NINDS (R01NS107887) 2018-2023

Polster, et al. AT CASH EPOC *Neurosurgery* 2019



10-15% CASH Enrollment Among Screened CAs



CASH Projects Enrollments on Track
All milestones met !

SAMPLE SIZES BASED ON POSTULATED EFFECTS OF QSM

Actual changes in QSM during follow-up of CASH cases must be known, including standard deviation and within person correlations during each year of follow-up. These can greatly impact sample size needed to detect changes in hemorrhage based on QSM effect size

				Postulated Effect Sizes					
				20%		15%		25%	
STD	Rho	Var of Mean	STD of Mean	N per group	N inflated	N per group	N inflated	N per group	N inflated
28	-0.5	196	14.00	12	19	20	32	8	13
28	0	392	19.80	22	35	38	61	15	24
28	0.5	588	24.25	33	53	56	90	21	34
30	-0.5	225	15.00	13	21	23	37	9	14
30	0	450	21.21	**25**	**40**	44	70	17	27
30	0.5	675	25.98	37	59	65	104	48	77
32	-0.5	256	16.00	15	24	25	40	10	16
32	0	512	22	28	45		78	19	30
32	0.5	768		42	67	73	117	27	43

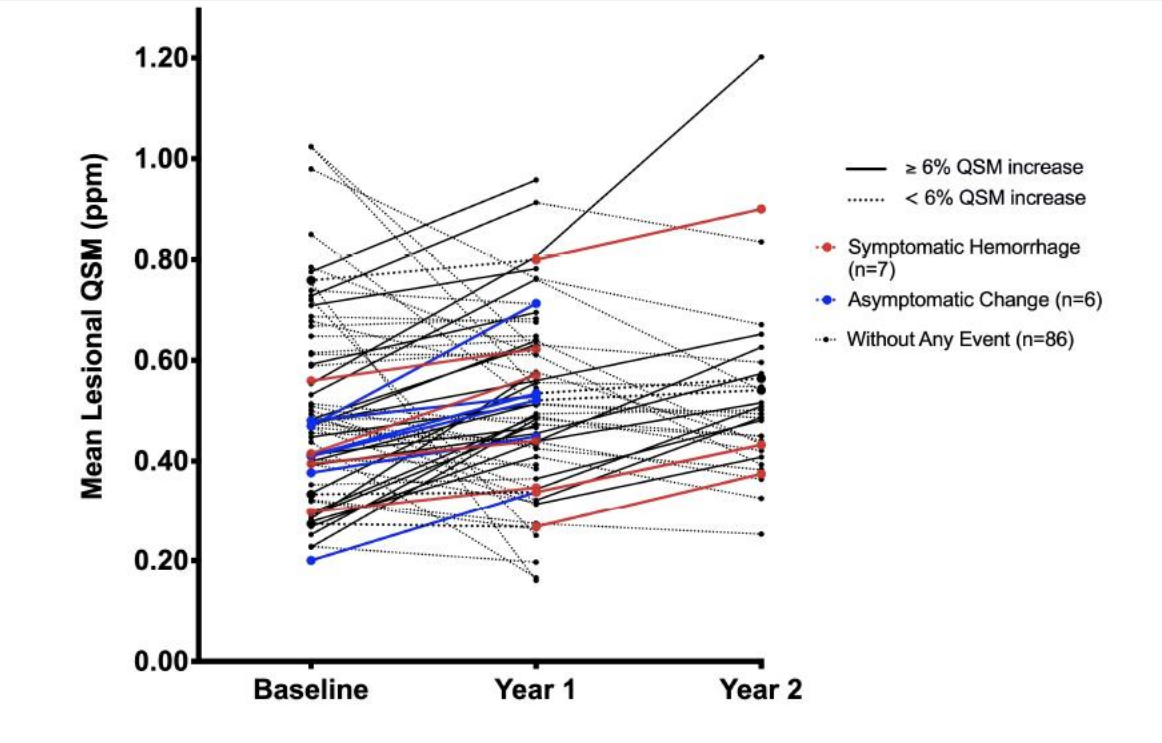
Range of sample sizes based on slight variations of the within person correlation.

20% effect size clinically meaningful (> 3X the change detected with a new SH in previously stable lesion)

Hence with these conservative assumptions, in order to detect a 20% difference in the mean change score, would require 25 patients

Further inflated if we assume 37.5% estimated missing data

ACTUAL PERFORMANCE OF QSM IN AT CASH EPOC AND IN CASH TR (INTERIM ANALYSES 2021)



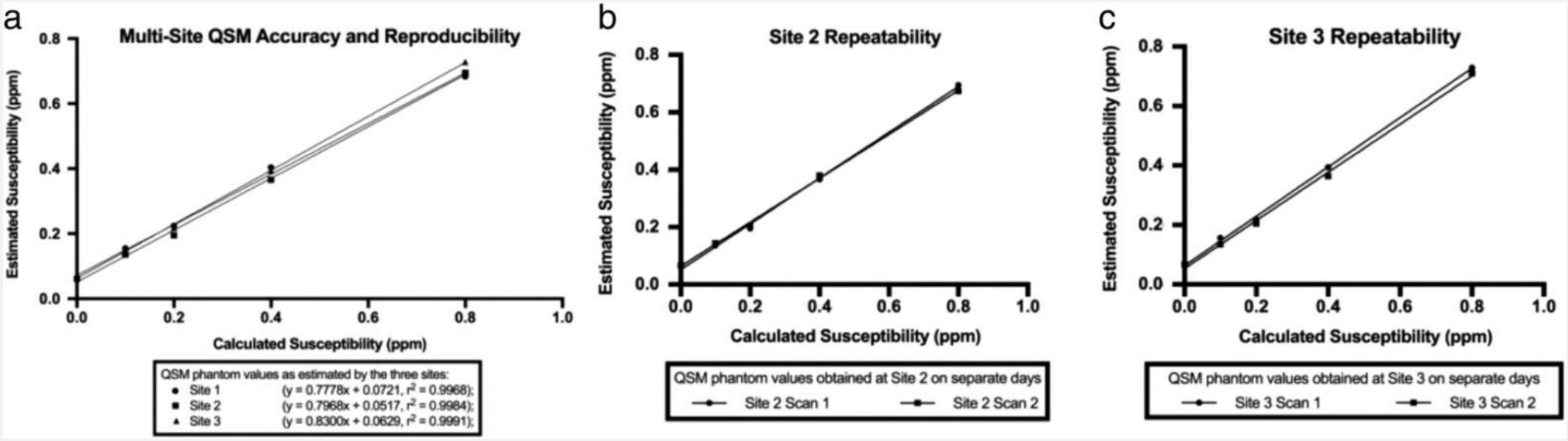
- Satisfactory biomarker acquisition in > 95% of cases with hybrid clinical/research chaperoned MRI study (postulated 80%), less data missingness than projected
- STD and Rho as projected (or better)
- All cases with SH or with demonstrated asymptomatic change during the 1-year epoch had QSM> 6%
- > 6% QSM change 4X more common than SH
- Favorable multisite validation

ORIGINAL RESEARCH

Hobson et al *J MRI* 201

Phantom Validation of Quantitative Susceptibility and Dynamic Contrast-Enhanced Permeability MR Sequences Across Instruments and Sites

Nicholas Hobson, MS,[1] Sean P. Polster, MD,[1] Ying Cao, MS,[1] Kelly Flemming, MD,[2] Yunhong Shu, PhD,[3] John Huston, MD,[3] Chandra Y. Gerrard, MPH, BS,[4] Reed Selwyn, PhD,[4] Marc Mabray, MD,[4] Atif Zafar, MD,[5] Romuald Girard, PhD,[1] Julián Carrión-Penagos, MD,[1] Yu Fen Chen, PhD,[6] Todd Parrish, PhD,[6] Xiaohong Joe Zhou, PhD,[7] James I. Koenig, PhD,[8] Robert Shenkar, PhD,[1] Agnieszka Stadnik, MS,[1] Janne Koskimäki, MD, PhD,[1] Alexey Dimov, PhD,[9] Dallas Turley, PhD,[9] Timothy Carroll, PhD,[9] and Issam A. Awad, MD[1*]



NEXT STEPS WITH QSM IN CASH TRIALS

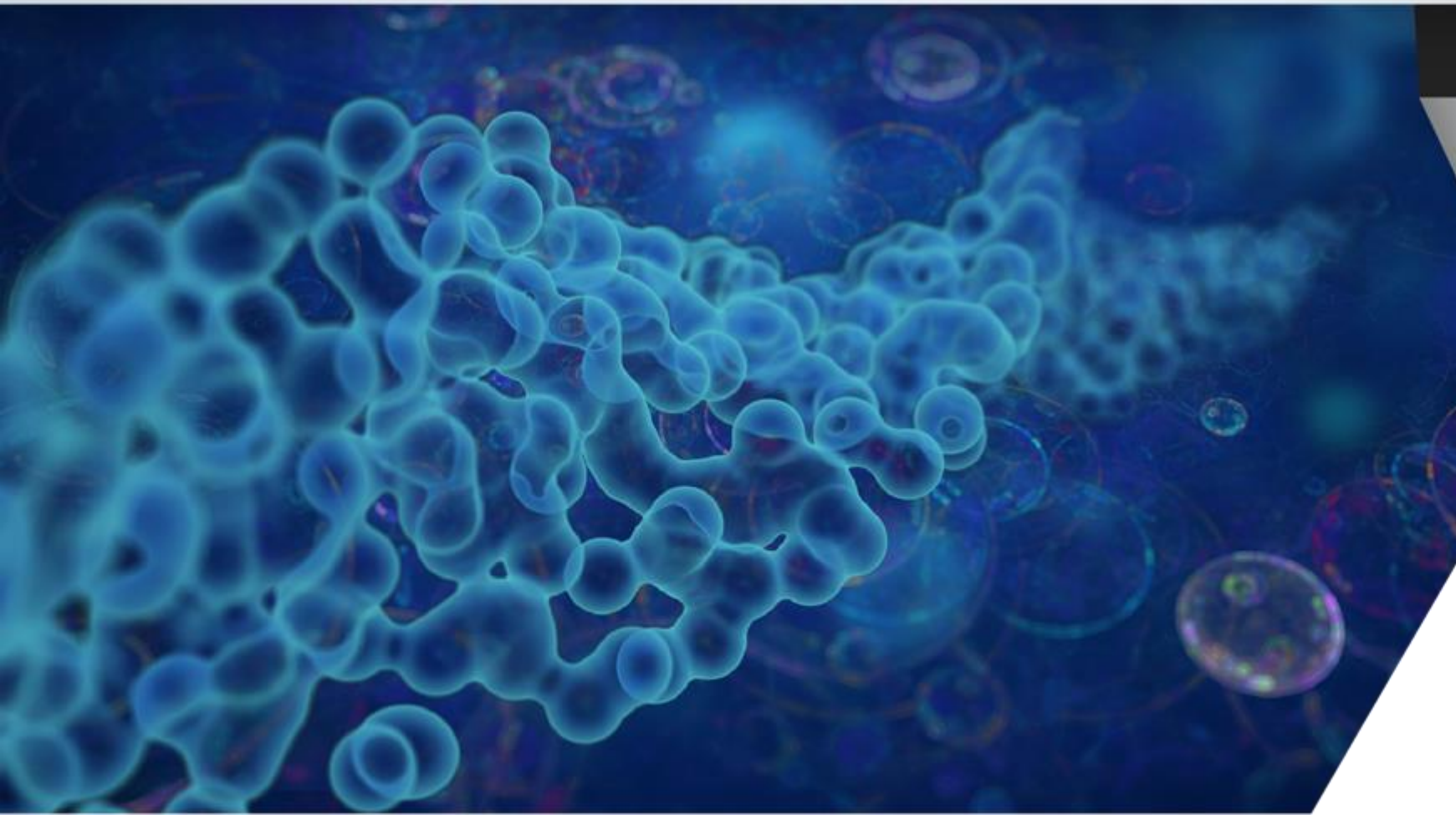
- If AT CASH EPOC is favorable, need Phase IIB or Phase III multisite trial aimed toward new atorvastatin approved indication.
- Other repurposed drugs are in the pipeline, awaiting Phase I-IIA results (Propranolol Italy) or potential Phase I-IIA testing (low dose Rapamycin), both with other FDA approved indications, or ROCK2 inhibitor (NRL-1049 under development for human use).
- Can we qualify QSM in those trials? FDA application in progress

Steve Williams

Chief Medical Officer

SomaLogic

Proteomic Prediction of Cardiovascular (CV) Risk, Sensitive to Change in Outcomes



Stephen A Williams

Translational Science in Drug Development Workshop

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somalogic

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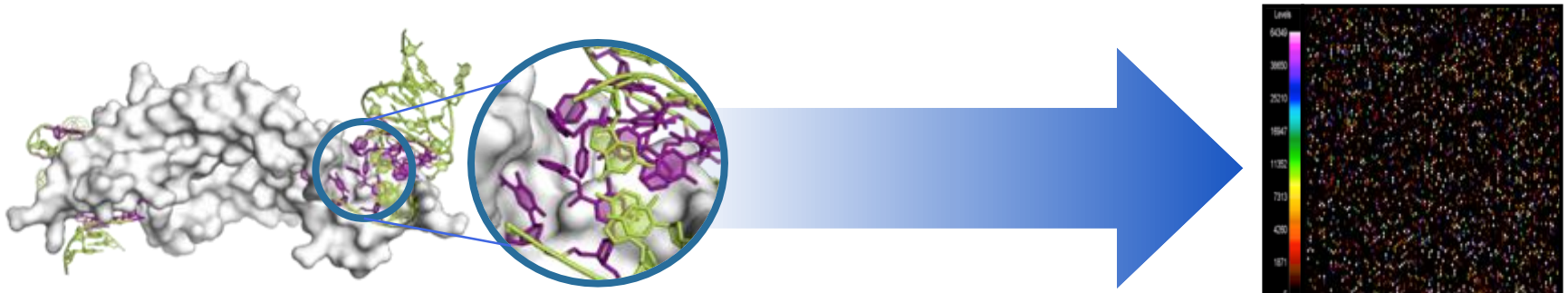
The SomaScan protein measurement assay

Slow Off-rate Modified Aptamers (SOMAmers): Next generation protein binders

Synthetic single-stranded DNA structures, with hydrophobic modifications

The SomaScan Assay multiplexes SOMAmer reagents to measure 5,000 analytes in each 55 µL biological sample



Platelet-derived growth factor and specific SOMAmer reagent

Custom array measuring 5K SOMAmer reagents

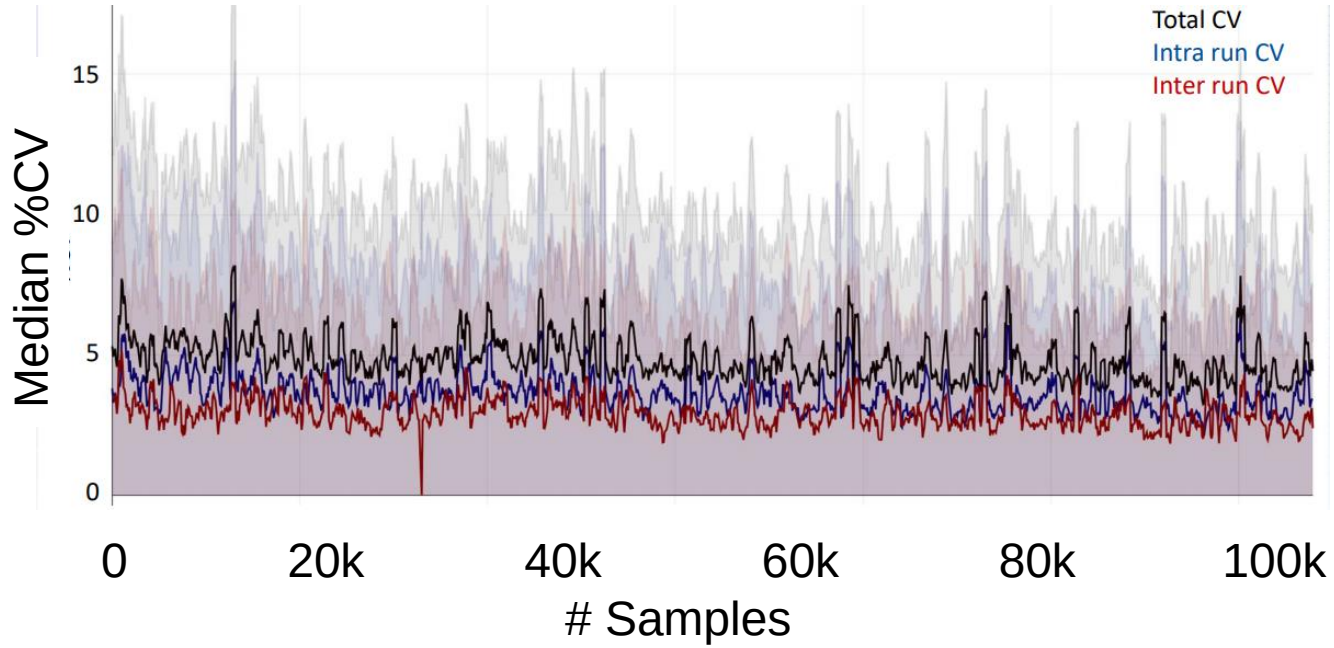
SomaScan Assay: Precision at Scale

~7,000 proteins analyzed in each sample

10-log dynamic range from fM to **µM**

5% median CV for plasma

55 µL Serum or plasma



Cardiovascular (CV) Risk

Needs statement

- **New drug mechanisms can impact cardiovascular outcomes independently of BP and LDL**
  - GLP-1 receptor agonists in diabetes (protective)
  - SGLT2 antagonists in diabetes (protective)
  - Canakinumab, anti-inflammatory (protective)
  - Torcetrapib (adverse)
  - Other CETP inhibitors (falures despite beneficial effects on lipids)
- **These effects are only detected during clinical outcomes trials (typically 10,000 participants or more, taking >5 years)**
  - And unexpected benefits manifest late, with delay to approval of those benefits (GLP1 and SGLT2)
  - People have to die and have events to demonstrate lack of efficacy or unexpected adverse safety effects
- **Therefore:**
  - An accurate prognostic can enable smaller/shorter trials through enrichment
  - A faithful monitor of change in outcomes could identify adverse and beneficial effects earlier in a program

Program design

- 5,000 proteins were measured in each of ~40,000 plasma samples from ~30,000 participants in 12 clinical studies using the SomaScan aptamer-based platform
- Machine learning was used to derive a 27-protein prognostic model in people with known cardiovascular disease
  - Predicts four-year likelihood of death, hospitalization for heart failure, myocardial infarction or stroke
- The model was then:
  - Validated in various multi-morbid populations with higher than typical risks
  - Evaluated in paired samples for sensitivity to longitudinal change concordant with changes in observed outcomes (adverse, neutral and beneficial)
  - Tested for “universality” as a detector of multiple epidemiologically observed risk elevations from different mechanisms

CARDIOVASCULAR DISEASE

A proteomic surrogate for cardiovascular outcomes that is sensitive to multiple mechanisms of change in risk

Stephen A. Williams[1]*†, Rachel Ostroff[1], Michael A. Hinterberg[1], Josef Coresh[2], Christie M. Ballantyne[3], Kunihiro Matsushita[2], Christian E. Mueller[4], Joan Walter[4,5], Christian Jonasson[6], Rury R. Holman[7], Svati H. Shah[8], Naveed Sattar[9], Roy Taylor[10], Michael E. Lean[11], Shintaro Kato[12], Hiroaki Shimokawa[13,14], Yasuhiko Sakata[13], Kotaro Nochioka[13], Chirag R. Parikh[2], Steven G. Coca[15], Torbjørn Omland[16], Jessica Chadwick[1], David Astling[1], Yolanda Hagar[1], Natasha Kureshi[1], Kelsey Loupy[1], Clare Paterson[1], Jeremy Primus[1], Missy Simpson[1], Nelson P. Trujillo[17], Peter Ganz[18]†

A reliable, individualized, and dynamic surrogate of cardiovascular risk, synoptic for key biologic mechanisms, could shorten the path for drug development, enhance drug cost-effectiveness and improve patient outcomes. We used highly multiplexed proteomics to address these objectives, measuring about 5000 proteins in each of 32,130 archived plasma samples from 22,849 participants in nine clinical studies. We used machine learning to derive a 27-protein model predicting 4-year likelihood of myocardial infarction, stroke, heart failure, or death. The 27 proteins encompassed 10 biologic systems, and 12 were associated with relevant causal genetic traits. We independently validated results in 11,609 participants. Compared to a clinical model, the ratio of observed events in quintile 5 to quintile 1 was 6.7 for proteins versus 2.9 for the clinical model, AUCs (95% CI) were 0.73 (0.72 to 0.74) versus 0.64 (0.62 to 0.65), *c*-statistics were 0.71 (0.69 to 0.72) versus 0.62 (0.60 to 0.63), and the net reclassification index was +0.43. Adding the clinical model to the proteins only improved discrimination metrics by 0.01 to 0.02. Event rates in four predefined protein risk categories were 5.6, 11.2, 20.0, and 43.4% within 4 years; median time to event was 1.71 years. Protein predictions were directionally concordant with changed outcomes. Adverse risks were predicted for aging, approaching an event, anthracycline chemotherapy, diabetes, smoking, rheumatoid arthritis, cancer history, cardiovascular disease, high systolic blood pressure, and lipids. Reduced risks were predicted for weight loss and exenatide. The 27-protein model has potential as a "universal" surrogate end point for cardiovascular risk.

Biomarker Qualification for CV risk; Evidence Sources

The existing weight of evidence (dark blue) and new components (light blue) being sourced

Prognosis
in outcomes prediction studies

n~27,000

ARIC
ACCORD
BASEL VIII
CRIC
CHART 2
EXSCEL
HUNT3

Placebo in SGLT2 and GLP-1 pivotal trials

Measurement of change in risk
In longitudinal studies and paired samples

n~10,000
Ageing
Approaching events
Acute COVID
Anthracycline tox.
COVID recovery
Caloric restriction
Diabetic control
GLP-1 efficacy
Exercise stress

SGLT2 efficacy
GLP-1 efficacy #2

Universality
across multiple risk mechanisms

Blood Pressure
Acute COVID-19
Chemotherapy
Cancer survivors
Heart failure
Diabetes
Diet
Undiagnosed lipids
Myocarditis
Rheumatoid A.
Smoking

Biologic plausibility of 27 proteins

- **Thematic grouping of at least 10 different biological processes represented in the model:**
  - Blood volume and natriuresis [NTproBNP, ANP], vesicle biogenesis [ARL11], matrix/tissue modeling, growth, angiogenesis or adhesion [ANTR2, CILP-2, CA125*, GOLM1, spondin-1*, SVEP1*, PTRPJ, ITI heavy-chain 2*, NELL1, GDF11/8*], cellular immunity [MMP12*, ERBB3, NCAM-120*], calcium channel modulation [CA2D3*], glomerular filtration rate [TFF3], immunoglobulins [IGDC4, JAM-B, sTREM1*], metabolism & lipids [SIRT2, PPR1A, LRP11*], inflammation [suPAR*, NDST1] and coagulation [ATS13*].

- **Causality component:**
  - Mendelian randomization analysis available for 989 proteins in the PheWAS database[1]
  - Sixteen of the 27 model proteins were included in the database, 12 of which (75%) were significantly associated with at least one cardiovascular disease-related trait, denoted by the asterisks in the list above

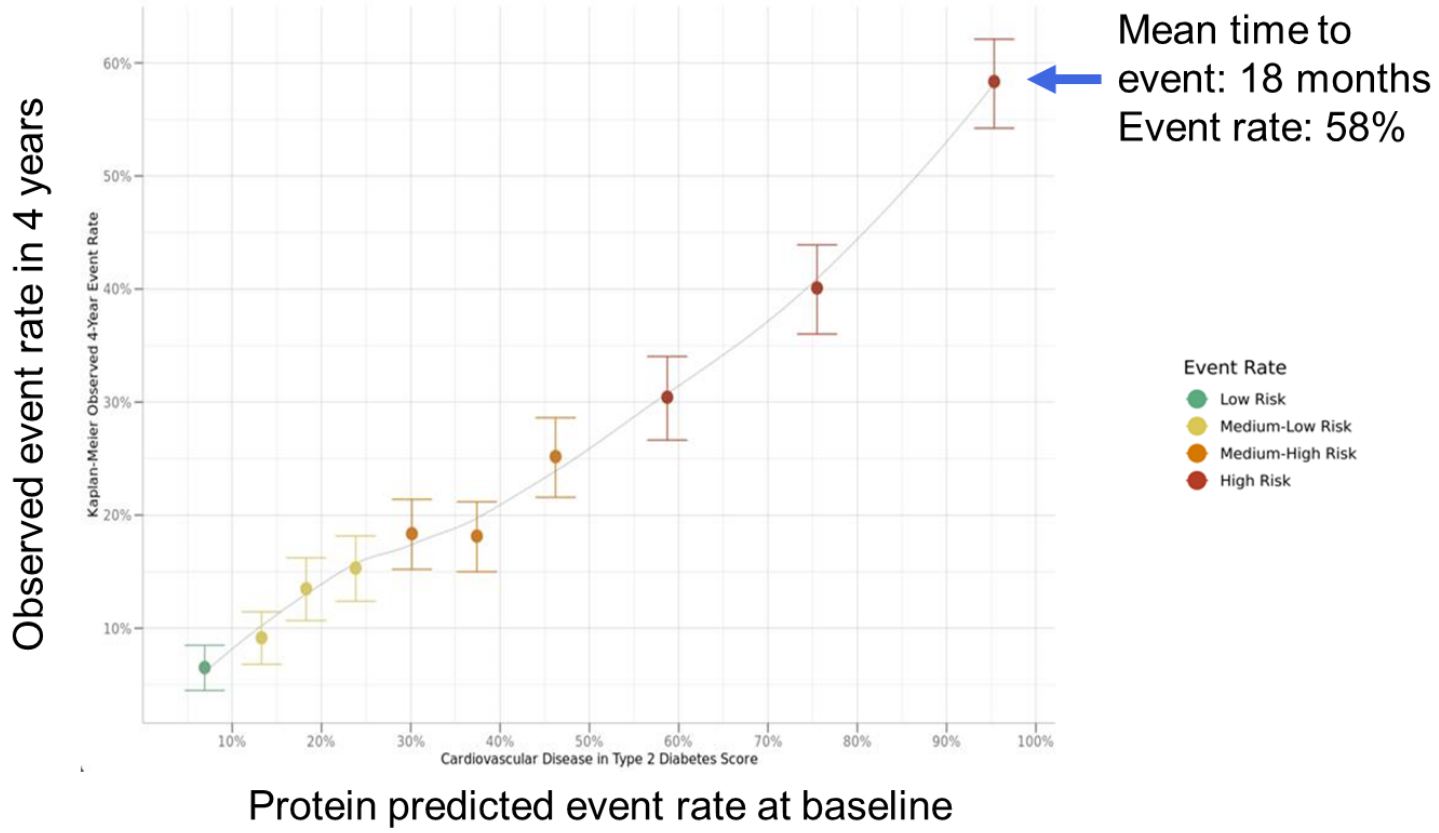
- **The equation for a fully quantitative accelerated failure time model (likelihood of an event):**
  - $\hat{\theta} = \exp\{-(2.83 + -0.09*TFF3 + -0.23*BNP + -0.05*SVEP1+0.01*"GDF-11/8 "+-0.02*"sTREM-" 1+ 0.09*IGDC4 + -0.03*NELL1 + -0.14*"MMP-12" + 0.02*ATS13 + -0.03*suPAR + 0.13*CILP2 + 0.02*NDST1 + -0.01*"Spondin-1 "+ 0.14*ANTR2 + 0.04*PTPRJ + -0.07*LRP11 + -0.07*ANP + -0.07*"JAM-B" + 0.08*SIRT2 + -0.11*CA125 + 0.1*CA2D3 + 0.03*ITI heavy chain H2 + 0.11*ERBB3 + -0.1*GOLM1 + -0.08*PPR1A + 0.22*ARL11 + 0.1*"NCAM-120")\},$

Context of Use, Risk Assessment and Evidentiary Requirements

- **Proposed contexts of use (COU) with sufficient validation:**
  - As a prognostic biomarker to predict the four-year risk of cardiovascular outcomes (myocardial infarction (MI), stroke, hospitalization for heart failure (HF), or death).
    - Used for enrichment and stratification in clinical trials, and/or to assess the presence of adverse or beneficial change (or lack of change) due to treatment
- **Risk assessment:**
  - Benefit of true positive or negative results – high (acceleration to pivotal trials, earlier termination for adverse impacts)
  - Consequence of false negative or positive results – medium (these will be discovered during subsequent pivotal trials)
- **Weight of evidence requirement:**
  - Medium (High benefits, medium consequences)
- **Nature of evidence requirement for a potential path to surrogacy:**
  - Biologic plausibility
  - Prognostic performance for all types of adverse cardiovascular event in varying populations
  - Within-participant sensitivity to change in risk
  - Detection of risks from multiple biologic mechanisms (universality)
  - Relation of predicted risks to observed risks and capture of a substantial proportion of risk (proportionality)

Validation results (1); Prognosis

- The 27-protein model was highly prognostic and robust to variation in ethnicity, race, geography and morbidity
- The stratification of event rates across quintiles for proteins was 8.4 vs. 2.9 for risk factors (independent validation results)
- Observed event rates in four predefined predicted risk categories were 5.6%, 11.2%, 20.0% and 43.4%
- Net reclassification index for proteins is +0.43 vs clinical factors
- Discrimination statistics were superior to clinical factors: AUC 0.74 for proteins vs. 0.63 for risk factors (independent validation results)



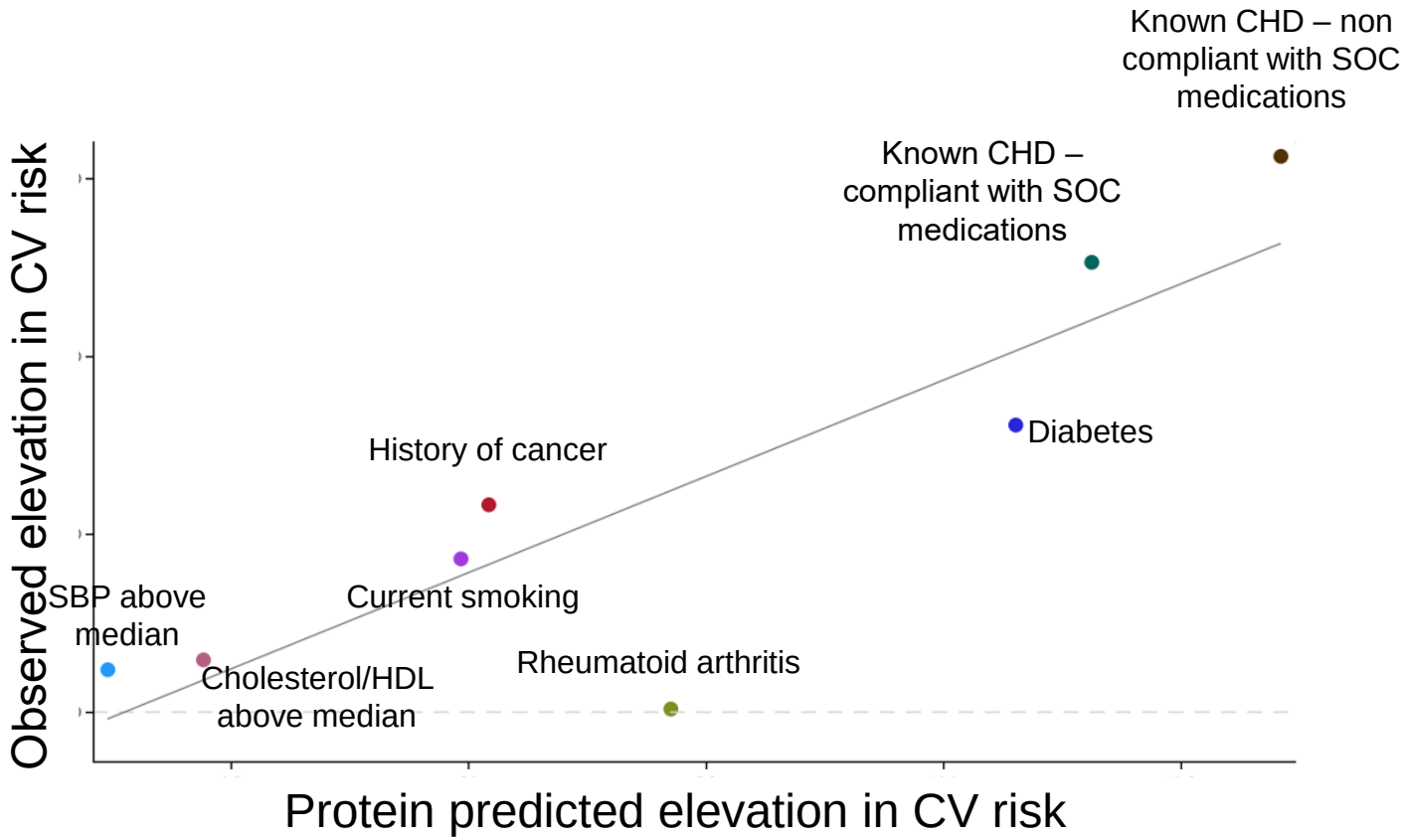
Validation results (2): Longitudinal change within participants

- Paired samples from the same participants were used to evaluate the concordance of the protein model with changes in outcomes in ~10,000 participants
  - In each case, proteins were consistent with directional changes in outcomes
- The directional consistency of protein model predictions was compared with commonly used protein biomarkers
  - No individual conventional biomarker was as sensitive and directionally consistent across mechanisms as the 27-protein model

Responsiveness to change: Inter-group change in protein predictions and common biomarkers in paired samples *Bold/colored symbols are p<0.01 corrected for multiple comparisons*		**27 Proteins, absolute change in risk**		**CRP**	**Cystatin-C**	**GDF-15**	**Myelo-peroxidase**	**NTproBNP**	**Troponin**
Expected Adverse Change	Approaching an event, 1-year change vs. no event (EXSCEL)	**+2.9%**	↑	↑				↑	↑
	Approaching an event, 2-year change vs. no event (ACCORD)	**+6.0%**	↑						
	Anthracycline chemotherapy, 3 month within-subject change (PRADA)	**+6.2%**	↑		↑	↑	↑		
Expected Neutral Change	Intensified oral hypoglycemic treatment, vs. standard therapy (ACCORD)			↑	↑		↑		
	Angiotensin receptor blocker in chemotherapy vs. placebo (PRADA)								
	Beta blocker in chemotherapy vs. placebo (PRADA)				↓	↓			
Expected Beneficial Change	Exenatide, within-subject change vs. placebo (EXSCEL)	**-1.5%**	↓	↓		↓		↓	
	Dietary weight loss in diabetics in one year vs. standard diet (DiRECT)	**-6.7%**	↓	↓		↓		↑	

Validation results (3): “Proportionality” and “Universality

- A further analysis of ARIC visit 3, n=11,301
- Comparison of case-control differences for conditions with epidemiologically observed elevated CV event rates
- 8 Different biologic mechanisms of risk were evaluated
- Predicted differences are significantly related to observed differences (r=0.83 p<0.04)
- Proteins were reflective of observed event elevations except for RA where proteins predicted increased risk that was not observed in this study (but n=39)



Summary/Conclusions

- A predictor of near-term cardiovascular outcomes that is also reliably sensitive to change in risk would be useful in drug development and medical practice
- In a large proteomic study, a 27-protein model was derived and validated to predict death, hospitalization for heart failure, myocardial infarction or stroke, with a median time to event of 1.7 years
  - This was robust across demographic, ethnic, racial and geographic differences and morbidities
- The protein model had greater dynamic range, improved discrimination, superior risk classification and more consistent response to therapeutic interventions than clinical risk factors or common biomarkers
- Multivariate protein models may also be more “universal” to different mechanisms of risk and/or intervention, and more responsive to change than other approaches
- Further research is aimed at expanding testing of concordance between predictions and outcomes changes for different drug mechanisms

Terina Martinez

Executive Director

Duchenne Regulatory Science Consortium and the Critical Path to Therapeutics for the Ataxias

Critical Path Institute

Neurofilament Light Chain in Neurodegenerative Diseases – Status Update

Translational Science in Drug Development: Surrogate Endpoints, Biomarkers, and More | May 24, 2022

NEUROSCIENCE PROGRAM

Terina N. Martinez, PhD
Executive Director, D-RSC & CPTA

CRITICAL PATH INSTITUTE

Advancing Science Through Cross-Disciplinary Collaboration

Critical Path Institute, founded in 2005 in Tucson, Arizona, is an independent, non-profit organization dedicated to bringing scientists from the FDA, industry, and academia together to collaborate and improve the drug development and regulatory process for medical products.

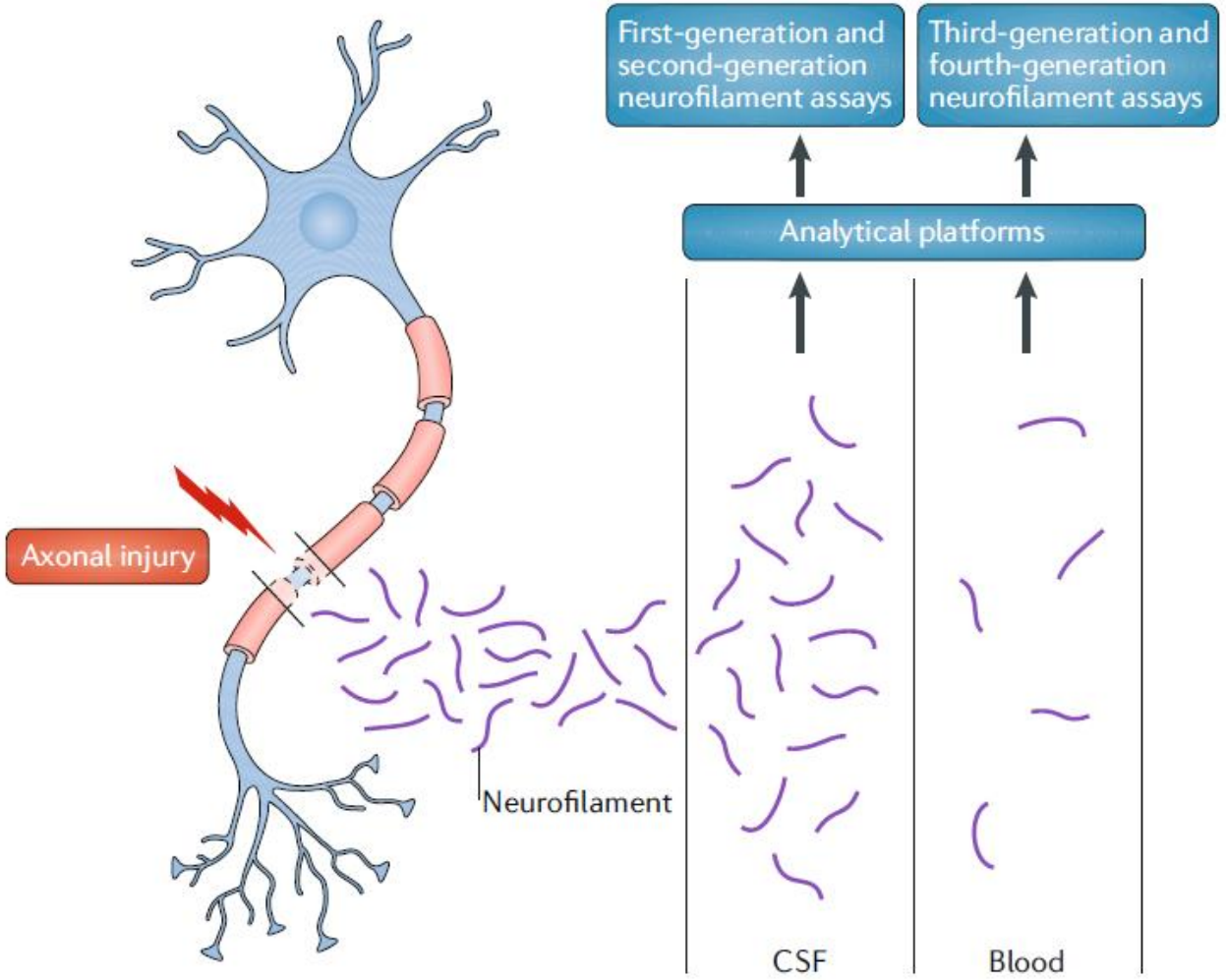
Create Consensus **Define Paths** **Improve Health**

Thematic Outline

- Neurofilament light chain (NfL) overview: molecular mechanism and biological significance as a biomarker
- Considerations for NfL biomarker potential across diverse neurodegenerative diseases – case study for multiple sclerosis
- Current challenges and knowledge gaps for developing NfL as a clinical trial-ready biomarker
- Best practices for advancing NfL as a fluid biomarker for neurodegenerative diseases in a manner that is maximized for regulatory success
- Lead-in to the panel discussion

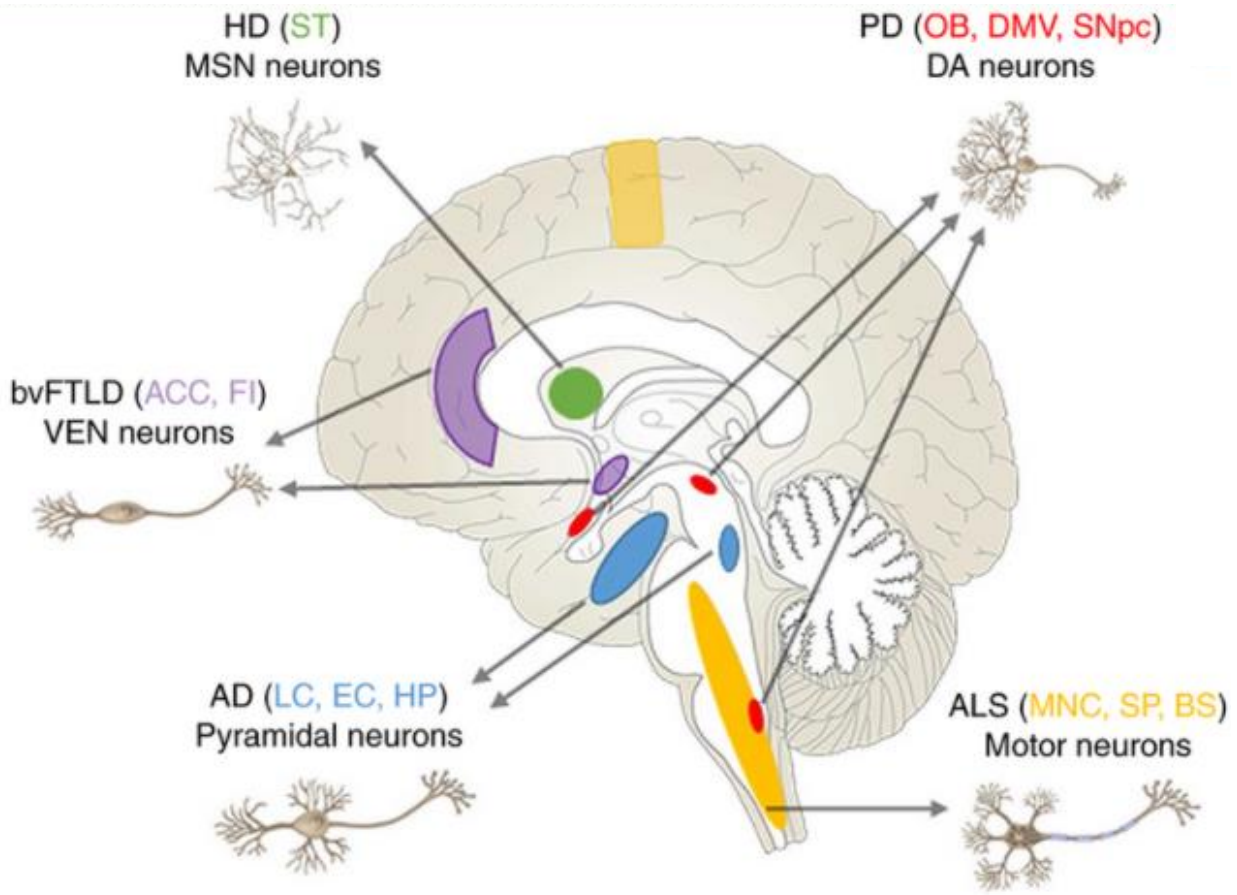
NfL Biology and Mechanism Overview

- Neurofilaments are abundant neuronal scaffolding proteins
- Neurofilament light chain (NfL) is the subunit of focus for biomarker applications
- Highly specific for neuroaxonal damage
- Agnostic to primary neuronal damage trigger
- Detectable in cerebral spinal fluid (CSF) and blood



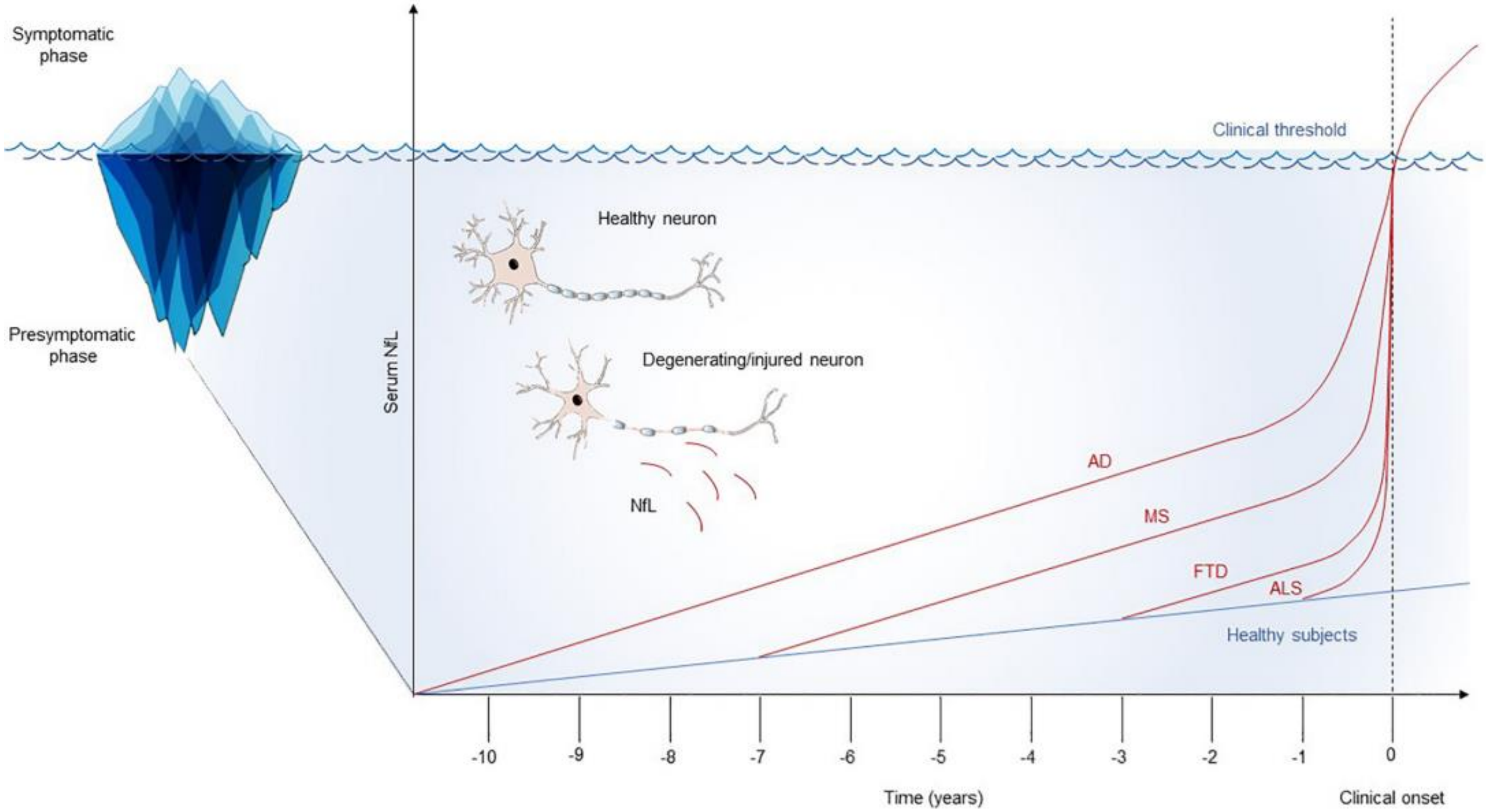
Ref.: Khalil M. et al., *Nat Rev Neurol.* 2018. PMID: 30171200

Divergent Vs. Conserved NfL Mechanisms



- Selective neuronal vulnerability, brain region specificity, and progressive pathology underly the complex etiology of neurodegenerative diseases
- Clinical manifestation reflects the brain region and specific cell population affected
- NfL is not disease specific, but it can be leveraged as a biomarker across neurodegenerative diseases

Ref.: Hongjun F. et al., *Nat Neurosci.* Review 2018. PMID: 30250262



NEUROSCIENCE PROGRAM

Ref.: Gaetani, L. et al., *Front in Neurosci.* 2021. PMID: 34108859

Considerations for NfL Biomarker Validity

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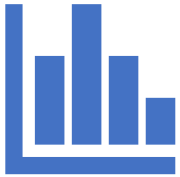
Translational Validity

High translational value for NfL

- Disease progression in mouse models for ALS, AD, and GD
- No progression in a PD model
- Ref.: PMID: 32595447



Analytical Validity

Assay performance for NfL

- Pre-analytical considerations
- Assay standardization
- Data analysis / reporting
- Breakthrough designation for RRMS

Clinical Validity

NfL performance as a surrogate of disease-related clinical outcomes of interest

- Biological rationale
- Supporting data

NfL demonstrates good translational and analytical validity in CSF, plasma, serum; in April 2022, the Quanterix Simoa assay receive Breakthrough Device designation by the FDA as a prognostic aid in relapsing-remitting multiple sclerosis (RRMS).
Clinical validity for NfL is growing but variable across different neurodegenerative diseases.

NfL: Differential / Prognostic for PD, HD, AD, SCA

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- Differential diagnostic biomarker in Parkinson's disease (PD); Hansson et al., *Neurology* 2017. PMID: 28179466
  - Showed NfL can discriminate between PD and atypical parkinsonian disorders
- Prognostic biomarker in Huntington's disease (HD); Byrne et al., *Sci Trans Med* 2018. PMID: 30209243
  - NfL levels in parallel with clinical evaluation and MRI in premanifest HD mutation carriers
- Prognostic biomarker in Alzheimer's disease (AD); Preische et al., *Nat Med* 2018. PMID: 30664784
  - Longitudinal within-subject analysis of NfL vs baseline correlated with MRI for cortical thickness and cognitive performance and discriminated mutation carriers and non-mutation carriers
- Prognostic marker in spinocerebellar ataxia (SCA3); Wilke et al., *EMBO Mol Med* 2020. PMID: 32510847
  - NfL levels correlated with CAG repeat length and with worsening ataxia symptoms via clinical scale (SARA score)

NfL: Prognostic / Prediction in ALS, FTD, MS

- Prognostic marker in frontal temporal dementia (FTD) spectrum; Grendon et al., *Cell Rep Med* 2022. PMID: 35492244
  - NfL was elevated across all FTD syndromes (even mild cases) and in presymptomatic FTD mutation carriers; NfL levels increased in mutation carriers prior to phenoconversion and associated with indicators of disease severity
- Prognostic marker in ALS; Huang et al., *Ann Clin Transl Neurol* 2020. PMID: 32515902
  - Longitudinal evaluation of NfL and other markers relative to the ALS Functional Rating Scale-Revised change rate; NfL had prognostic value for fast progressing patients
  - Caveat: plasma phosphorylated neurofilament heavy chain (pNF-H) as exploratory secondary biomarker in the recent Amylyx clinical trial for AMX0035 in ALS – no significant differences between drug and placebo groups were observed for rate of change from baseline
- Prognostic and prediction marker in multiple sclerosis (MS); Thebault et al., *Sci Rep* 2020. PMID: 32587320
  - NfL predicts long-term clinical outcomes in MS; baseline NfL was a sensitive predictive marker to rule out progression, highest NfL levels progressed most rapidly

Case Study: NfL in Clinical Trials for MS

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Serum neurofilament light as a biomarker in progressive multiple sclerosis

Neurology 2020; PMID: 32675076

Raju Kapoor [1], Kathryn E Smith [1], Mark Allegretta [1], Douglas L Arnold [1], William Carroll [1], Manuel Comabella [1], Roberto Furlan [1], Christopher Harp [1], Jens Kuhle [1], David Leppert [1], Tatiana Plavina [1], Finn Sellebjerg [1], Caroline Sincock [1], Charlotte E Teunissen [1], Ilir Topalli [1], Florian von Raison [1], Elizabeth Walker [1], Robert J Fox [2]

- Demonstrated analytical validity as well as clinical validity in relation to imaging and disability measures & responsiveness to Tx
- Discussed limitations of NfL – technical challenges, nonspecificity, impact of comorbidities

Table 1 Associations between baseline NfL concentrations and activity of progressive MS

Trial name	Progressive MS subtype and number of subjects	Study design	Correlations between baseline NfL and baseline imaging measures	Correlations between baseline NfL and baseline clinical measures	Correlations between baseline NfL and imaging outcomes	Correlations between baseline NfL and clinical outcomes	Comments
EXPAND and INFORMS[39]	SPMS (n = 1,452) and PPMS (n = 378)	Combined data from phase 3 RCTs (EXPAND and INFORMS)	Gd+ lesion count; T2 lesion volume	EDSS	Brain volume loss after 12 and 24 mo	1. EDSS worsening	Combined treatment and placebo subjects
						2. SDMT worsening (EXPAND study only[53])	
ASCEND[40]	SPMS (n = 365)	Phase 3 RCT	Gd+ lesion count; T2 lesion volume	T25FW, 9HPT	Brain volume loss after 96 wk	Not reported	Placebo data only
ORATORIO	PPMS (n = 516)	Phase 3 RCT	Gd+ lesion count	Not reported	Not reported	EDSS; T25FW; 9HPT	Combined treatment and placebo subjects

Abbreviations: EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; NfL = neurofilament light chain; RCT = randomized controlled trial; SDMT = Symbol Digit Modalities Test; T25FW = Timed 25-Foot Walk time; 9HPT = 9-Hole Peg Test time.

Table 2 Response of neurofilament light concentrations to treatment in progressive MS Kapoor, R. et al., *Neurology.* 2020. PMID: 32675076

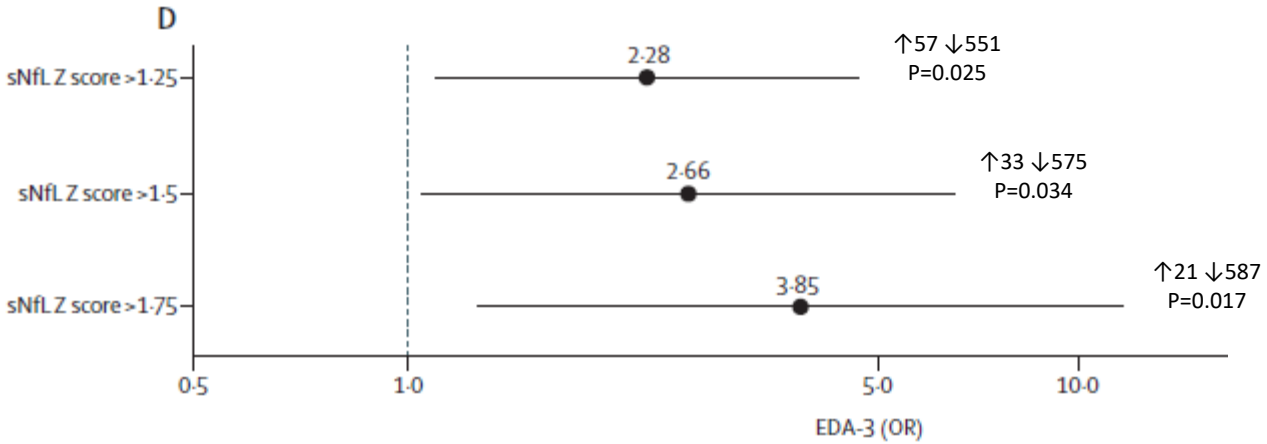
Study reference	MS phenotype	Study design (treatment duration)	Treatment	Subjects for NfL analysis	NfL biofluid (assay used)	Change in NfL concentration	Comments
Axelsson et al.[45]	SPMS and PPMS	Observational phase 2A, with age-matched controls (12–24 mo)	Rituximab (n = 5) or mitoxantrone (n = 30)	30 SPMS, 5 PPMS, and 14 healthy controls	CSF (Uman Diagnostics NF-light ELISA)[14]	Mean NFL concentration was reduced 51%, from 1,780 ng/L to 870 ng/L ($p = 0.007$) irrespective of MS phenotype or treatment	1. NfL concentration was only reduced in either previously untreated patients or those with enhancing lesions at baseline.
							2. There was no correlation between NfL concentrations at different time points and pre- and posttreatment EDSS or MSSS
Romme Christensen et al.[46]	SPMS and PPMS	Phase 2A single-arm (60 wk)	Natalizumab	7 SPMS and 10 PPMS	CSF (Uman Diagnostics NF-light ELISA)[14]	Mean NfL concentration was reduced by 37%, from 657 ng/mL to 414 ng/mL ($p = 0.03$)	1. Changes in NfL concentrations correlated with changes in MTR in NAWM and GM. 2. Combined data from this trial and a phase 2A trial of methylprednisolone in SPMS and PPMS[54] found a correlation between CSF NfL and changes in the MS Impact Scale
Ratzer et al.[48]	SPMS and PPMS	Phase 2A single-arm (60 wk)	Methylprednisolone	14 SPMS and 11 PPMS	CSF (Uman Diagnostics NF-light ELISA)[14]	Mean NfL concentration not reduced by treatment (baseline 827 pg/mL vs final 434 pg/mL, $p = 0.067$)	Treatment-associated changes in EDSS, MSFC, 9HPT, T25FW, MSIS, MTR, and DTI measures
INFORMS	PPMS	Phase 3 randomized trial (24 mo)	Fingolimod or placebo	170 fingolimod and 119 placebo	EDTA plasma (Quanterix Simoa NF-light® Advantage Kit)[19]	NfL levels lower in fingolimod-treated patients than placebo at mo 24 ($p = 0.0012$)	No significant difference between groups at mo 12
EXPAND[49]	SPMS	Phase 3 randomized trial (>21 mo)	Siponimod or placebo	380 siponimod and 145 placebo	EDTA plasma (Quanterix Simoa NF-light® Advantage Kit)[19]	Plasma NfL levels increased by 9.2% with placebo and decreased by 5.7% with siponimod ($p = 0.0004$)	
ASCEND[40]	SPMS	Phase 3 randomized trial (96 wk)	Natalizumab or placebo	379 natalizumab and 365 placebo	Serum (Quanterix Simoa NF-light® Advantage Kit)[19]	sNfL at wk 48 and 96 was lower in natalizumab vs placebo (ratios: 0.84, $p < 0.001$, and 0.80, $p < 0.001$, respectively)	1. Week 96 sNfL was higher in those with progression on the multicomponent disability endpoint. 2. Differences in sNfL were observed in those with and without Gd+ lesions at baseline, relapses in 2 y before study and on-study inflammatory activity (Gd+ lesions, new T2 lesions, or relapse).
SPRINT[52]	SPMS and PPMS	Phase 2 randomized trial (96 wk)	Ibudilast or placebo	Serum: 119 ibudilast and 120 placebo. CSF: 30 ibudilast and 28 placebo	CSF and serum (Quanterix Simoa NF-light® Advantage Kit)[19]	No between-group differences in change in NfL in either serum or CSF	Concurrent anti-inflammatory therapy was only injectibles or none; ongoing focal inflammatory activity may have confounded assessment of ibudilast's effect on NfL
ORATORIO[50]	PPMS	Phase 3 randomized trial (96 wk)	Ocrelizumab or placebo	347 ocrelizumab 169 placebo	Serum (Quanterix Simoa NF-light® Advantage Kit)[19]	NfL was 15.7% lower with ocrelizumab vs 0.2% lower with placebo ($p < 0.001$)	For patients with BL NfL above 90th percentile of healthy controls, a higher proportion decreased into normal range with ocrelizumab (40.4%) vs placebo (16.6%) ($p < 0.001$)

Abbreviations: DTI = Diffusion Tensor Imaging; GM = Gray Matter; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MSIS = Multiple Sclerosis Impact Scale; MSSS = Multiple Sclerosis Severity Score; MTR = Magnetization Transfer Ratio; NAWM = Normal Appearing White Matter; NfL = neurofilament light chain; PPMS = Primary Progressive Multiple Sclerosis; Simoa = single molecule array; sNfL = serum NfL; SPMS = Secondary Progressive Multiple Sclerosis; T25FW = Timed 25-Foot Walk time; 9HPT = 9-Hole Peg Test time.

NfL: Prediction and Response Marker in MS

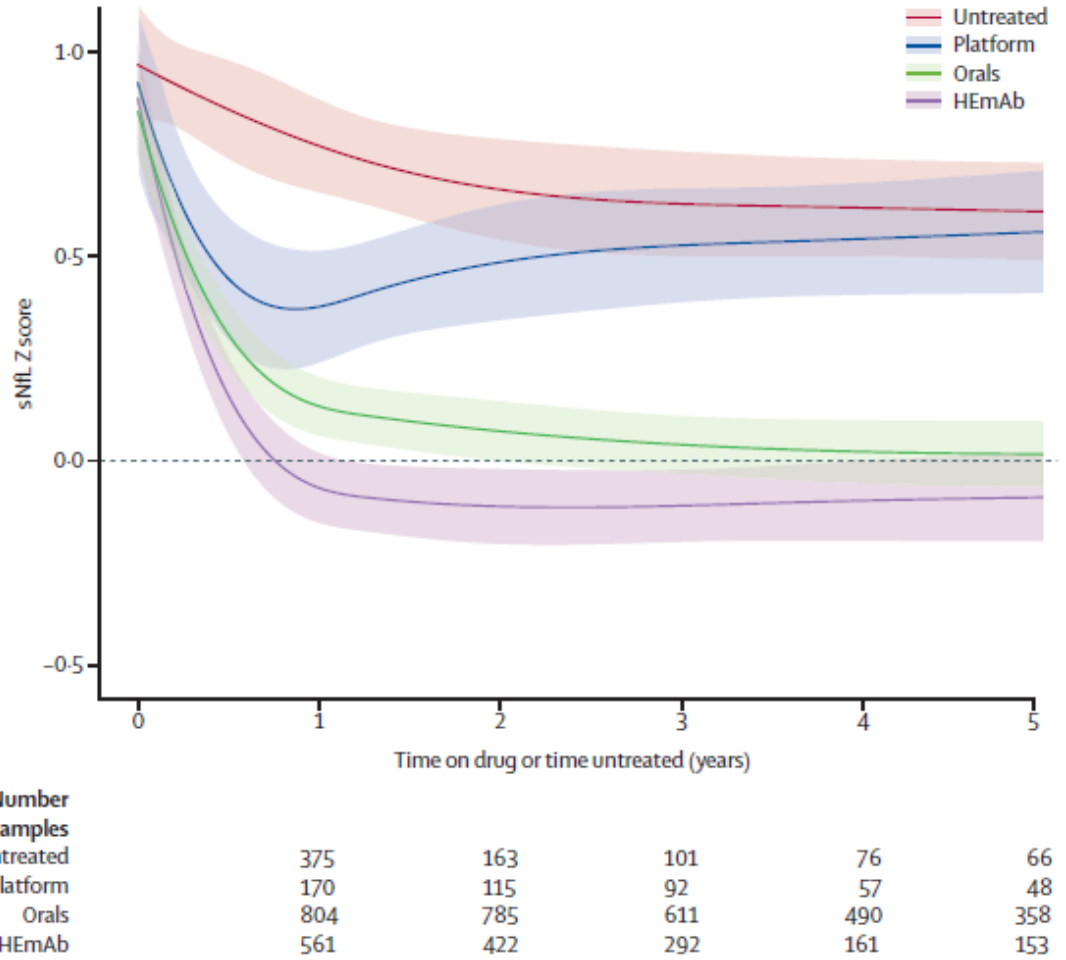
- NfL signal in MS evaluated as a marker of acute disease activity (e.g., lesion formation and relapses), long-term outcomes, and treatment response
- Compared NfL levels between MS patients and reference control database
- Elevated NfL Z scores were associated with increased risk of future disease activity (relapse)
- NfL Z scores in longitudinal samples can be used to compare the long-term effectiveness of disease-modifying therapies in a real-world setting

Probability of Relapse Occurrence in People with No Evidence of Disease Activity



EDA = evidence of disease activity

Temporal Evolution of NfL Z Scores Under Treatment



Number of samples					
Untreated	375	163	101	76	66
Platform	170	115	92	57	48
Orals	804	785	611	490	358
HEmAb	561	422	292	161	153

Ref.: Benkert et al., *Lancet Neurology.* March 2022. PMID: 35182510

Biomarker Considerations for Regulatory Science

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Biomarkers can integrate into the drug development process in many ways

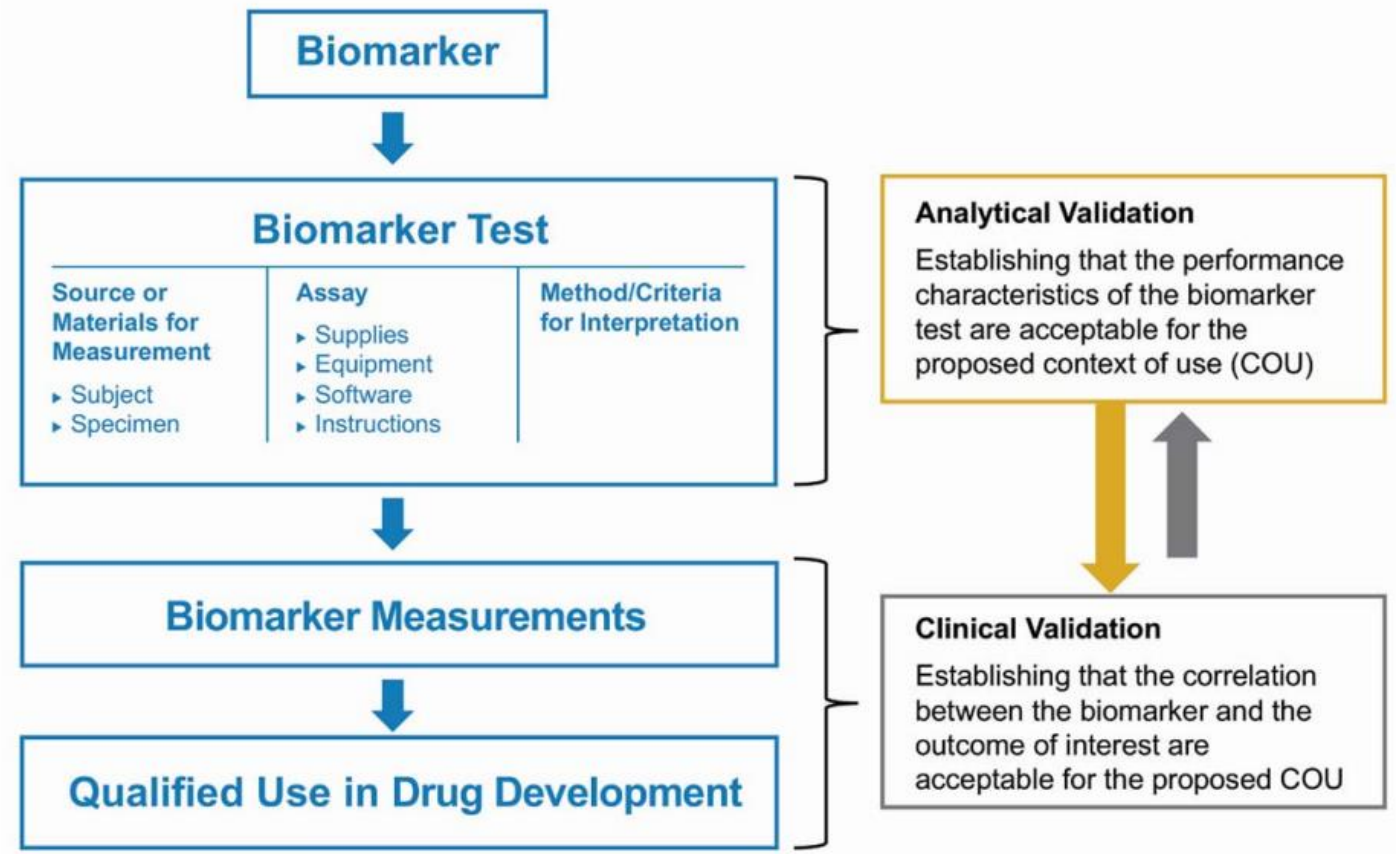

Image Ref.: Biomarker Qualification Evidentiary Framework Guidance for Industry and FDA Staff. 2018. https://www.fda.gov/media/119271/download

- Investigational new drug (IND) pathway in the context of a specific drug development program
- Scientifically-supported community implementation whereby a broadly used biomarker with appropriate scientific support, is generally accepted by experts in the field
- FDA's biomarker qualification program
- As a covariate within a clinical trial simulation model submitted via FDA's Drug Development Tools: Fit-for-Purpose (FFP) Initiative

NfL "Readiness" as a Surrogate Biomarker

To show surrogacy, NfL would need to sensitively track disease progression along with a clinical metric and also capture treatment effects at a mechanistic level.

Based on existing data, what is the quantitative link between NfL and at least one clinically meaningful outcome measure of disease? What confirmatory evidence is lacking?

Can NfL be linked to disease-specific features? Is NfL a continuous or categorical metric? What aspect of the given disease continuum does NfL represent across different neuro-degenerative diseases?

How can we reliably anchor NfL measurements to clinically meaningful metrics of disease such that both are amenable to application in clinical trials in neurodegeneration?

NfL represents an exciting candidate fluid biomarker being evaluated for its potential as a prognostic, susceptibility/risk, diagnostic (complimentary), and pharmacodynamic/response biomarker across diverse neurodegenerative diseases

NfL Strategic Advancement in Neuro Diseases

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Challenges	Potential Solutions
• Standardize sample collection and assay methods to align across multiple testing sites	• Evaluate SOPs, standardize/define collection & storage, standards, calibrators; compare assay methods
• Lack of standardized, accessible normative database of [NfL] in healthy and diseased subjects	• Establish necessary inclusion/exclusion parameters; identify appropriate control groups
• Knowledge gaps for predictive value of NfL for progression and/or severity across neurodegenerative diseases	• Cross-sectional validation in early and advanced disease; longitudinal studies in disease cohorts
• Fragmented data sharing/repository ecosystem	• Harmonize data integration and access to maximize utility

C-Path is working to evaluate and develop NfL and other candidate biomarkers, along with COAs and quantitative drug development tools, across all neuroscience consortia as well as building out infrastructure for non-consortium neuro diseases within the expanded Neuroscience Program

NEUROSCIENCE PROGRAM

Session 2: Identification and Development of Novel Surrogate Endpoints for Use in Clinical Development Programs

Moderator:

- Kerry Jo Lee, US Food and Drug Administration

Panelists:

- Oleg Shchelochkov, National Institutes of Health
- Charles Venditti, National Institutes of Health
- Issam Awad, University of Chicago
- Steve Williams, SomaLogic
- Terina Martinez, Critical Path Institute
- Patrick Archdeacon, US Food and Drug Administration

Session 2: Identification and Development of Novel Surrogate Endpoints for Use in Clinical Development Programs

Discussion Questions:

1. How do cross-sector partnerships play a role in identification of novel surrogate endpoints? How can cross-sector partnerships lead to innovation in this space?
2. What are important considerations for the future of biomarker development in clinical development programs?
3. What are the key considerations for biomarker development to ensure successful implementation in clinical trials?

Closing Remarks | Day 1

Mark McClellan

Director, Duke-Margolis Center for Health Policy

Thank You!

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