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

All times listed in EDT
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
Translational Medicine: A Regulatory Perspective

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

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


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

**Measures of disease presence and status**

**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

FIH to Phase 2  Phase 3 development  NDA / BLA
Substantial evidence - a statutory standard for approval: role of confirmatory evidence

• As defined in Section 505(d), substantial evidence is:
  
  o “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.”

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

• 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
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
  – Intervenational 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
The Specific Context of Use for a Biomarker Drives the Extent of Evidence Needed for Qualification

Analytical Validation

(establish performance and acceptance characteristics of the biomarker assay)

Reference Ranges/Decision Points
Pre-Analytical and Assay Performance Characteristics
Analytical Rigor/Reproducibility
Sample Handling/Stability

Clinical Validation

(establish that the biomarker acceptably identifies, measures, or predicts the concept of interest)

Study Design Acceptability
Clinical Meaningfulness/Decision Points
Benefit/Risk Assessment
Biomarker Integration into Drug Development

Drug Approval Process

Scientific Community Consensus

Biomarker Qualification Program

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.
Biomarker Qualification and 21st Century Cures
DDT Legislation

Biomarker Qualification Program process

- **Letter of Intent**: Is a request for the qualification of a specific biomarker for a proposed context of use (COU) in drug development.
- **Qualification Plan**: Describes biomarker development plans for the COU and provides data on analytical validation of the biomarker measurement.
- **Full Qualification Package**: Contains all accumulated data to support the qualification of the biomarker for the proposed COU.
- **Qualification Determination**: Is FDA’s determination on qualification of the biomarker for the proposed COU based on a comprehensive review of the full qualification package.
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](https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cders-arc-program)
Joni Rutter
Acting Director
National Center for Advancing Translational Sciences
National Institutes of Health
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.
Acting Director, National Center for Advancing Translational Sciences
NCATS, NIH

@jonirutter  joni.rutter@nih.gov
NCATS: Radically Re-engineering the Translational Pipeline Flow Rate

1. Translational Research (Evolutionary)
   - Pre-discovery
   - Drug Discovery
   - Preclinical Development
   - Clinical Development
   - FDA Review & Approval
   - Postmarketing Evaluation / Phase IV

   Operational
   Financial/ Administrative
   Scientific

   A → B

2. Translational Science (Revolutionary)
   - Efficient - Predictive - Transformative - Revolutionary

   A → B
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.
Pre-clinical

Human Physiologically-relevant Models
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

- Efficacy
- Safety
- Strategic
- Operational
- Commercial

Concordance of Toxicities

- Skin
- Cardiovascular
- Endocrine
- Gastrointestinal
- Hemopoietic
- Hepatic
- Neurological
- Urinary
- Other

Arrowsmith and Miller, Nature Reviews Drug Discovery, Volume 12, 569 (2013)
Cook et al., Nature Reviews Drug Discovery, Volume 13, 419 (2014)
**Mired in Old Drug Development Approaches**

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

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

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

Lung chip

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

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. 

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

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

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

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

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

<table>
<thead>
<tr>
<th>MPS-based Organ/Tissue model</th>
<th>Nr. of cases</th>
<th>Area of usage (drug development phase)</th>
<th>MPS-Supplier</th>
<th>End user</th>
<th>Reference (if available)</th>
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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;
Clinical

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

**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

Exp Biol Med. 2020, 245:1155-1162
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.
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., Ph.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
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

On This Page

- Meeting Information
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
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
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
General biomarker introduction and high level approaches
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

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<th>Therapeutic Area</th>
<th>Drug approvals per 100 Candidates [1]</th>
<th>Biomarker POS Multiple</th>
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Lathia et al. CPT 86:32-43, 2009 PMID: 19474783
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

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
<table>
<thead>
<tr>
<th>Challenge</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Validation and qualification are slow, laborious, and uncertain: “Get better playing in the sandbox”</td>
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<td>Operational challenges can disrupt: &quot;Nothing's for certain. It can always go wrong.”</td>
<td></td>
</tr>
</tbody>
</table>
2

Digging deeper with vignettes
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 lowering 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

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

Biomarker: Multi-component biomarker as NASH prognostic biomarker

---

**Tactics**

<table>
<thead>
<tr>
<th>Biopsy driven study but NIT is an inclusion criterion.</th>
<th>NIT based enrollment only and endpoint.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy driven study but NIT is an inclusion criterion.</td>
<td>NIT based enrollment only and endpoint.</td>
</tr>
</tbody>
</table>

**Result**

- Highly enriched in subjects with desired NIT score.
- NIT/biopsy concordance should reduce PBO rate.

**Issues**

- What to do with discordant NIT/biopsy subjects?
- Exclude subjects who fail NIT criteria?

**Solutions**

- Exclude from study
- Keep as a sub-study
- Stratify across groups

---

**ELF**

![Graph showing proportion surviving over time](graph.png)

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.

---

"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

---

Translational mechanism of action: Confirmatory evidence in Fabry disease

- 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

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)

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

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

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Day 2</th>
<th>Day 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK-4305 15 mg</td>
<td>0</td>
<td>2.4</td>
</tr>
<tr>
<td>MK-4305 30 mg</td>
<td>0</td>
<td>2.4</td>
</tr>
<tr>
<td>Zopiclone 7.5 mg</td>
<td>0</td>
<td>2.4</td>
</tr>
<tr>
<td>MK-4305 15 mg</td>
<td>0</td>
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<td>0</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Sun et al. JCP 53(12):1294-302, 2013 PMID: 24122944
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
Challenges and potential solutions
## Leveraging Translational Science in Industry: Challenges and solutions

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

---

The table above outlines the challenges faced in leveraging translational science in industry and potential solutions to address these challenges. Challenges include slow, laborious, and uncertain validation and qualification processes, definitional and other ambiguities, multi-component biomarkers, prioritization of new biomarkers over development, pre-specified goalposts, and operational disruptions. Solutions range from precompetitive work and sharing risks to updating definitions and adjusting to emerging use cases, collaboration via public-private partnerships, and multi-stakeholder collaborations.
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
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

www.fda.gov
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
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
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**
Internal MMA and PA Datasets

Staged Release of Data Linked to Publications

- Outside records
- Pre-admit calls

Pre-Admission

- OARS
- Consults

Clinical Evaluation

- Labs
- Imaging
- Nutrition/REE
- Research Studies

Labs/Imaging

- Blood
- Urine
- Microbiome
- Exome/Genome

Biobanking

- Interim Events
- Communication with home teams

Post-Discharge Follow-up

Admission (1-5 days)
Multisystemic Manifestations of Organic Acidemias

- Intellectual disability
- Metabolic strokes
- Optic nerve atrophy
- Short stature
- Liver disease
- Bone marrow failure
- Osteopenia
- Growth failure, GI dysmotility, G/J tube dependence
- Protein restricted diet
- Plasma propionylcarnitine
- Total plasma 2-methycitrate
- Sensorineural hearing loss
- Dilated cardiomyopathy
- Chronic kidney disease

**METABOLIC INSTABILITY**

- Hyperammonemia
- Coma

**Growth failure, GI dysmotility, G/J tube dependence, Protein restricted diet**
Valine
Isoleucine
Methionine
Threonine
Gut propionate

2-Methylcitrate
Propionylcarnitine (C3)

Mitochondrion

Propionyl-CoA

D-Methylmalonyl-CoA

Propionyl-CoA Carboxylase

D-Methylmalonyl-CoA Epimerase

L-Methylmalonyl-CoA

Methylmalonic Acid

Methylmalonyl-CoA

Methylmalonyl-CoA Mutase

5'-deoxyadenosylcobalamin

Krebs Cycle

Succinyl-CoA

2-Methylcitrate

13CO2

FGF21
GDF15
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
NIH Propionic Acidemia Protocol

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

Transplant Status
- Non-transplanted
- Liver-transplanted
- Kidney-transplanted

Genotype Status
- PCCB 53%
- PCCA 44%
- Unknown 3%

Single Visits vs Follow Up
- One visit
- >1 visit
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
Metabolic Correction After AAV Gene Therapy

![Graph showing plasma methylmalonic acid levels over time after different AAV gene therapies.](image)

- Untreated
- AAV8-CBA-Mut 2x10^11 GC
- AAV8-TBG-Mut 2x10^11 GC
- AAV8-CBA-MUT 2x10^11 GC
- AAV8-CBA-MUT 1x10^10 GC
- AAV9-CBA-Mut 1x10^10 GC

Plasma Methylmalonic Acid (µM)

(Normal=5-10 µM)
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

Shchelochkov et al, Genetics in Medicine, 23, pages 1534–1542 (2021)
A Promising Lead: Labelled Propionate Oxidation Studies

1-\textsuperscript{13}C Propionate (tracer) \rightarrow \text{LIVER, RAPID}

- Propionyl-CoA
- L-methylmalonyl-CoA
- \text{Methylmalonyl-CoA mutase}
- Succinyl-CoA
- \text{Krebs/TCA Cycle}

\textsuperscript{13}CO_2 (IRMS) and \text{V}_{CO_2}
1-\(^{13}\)C Propionate Oxidation 1 year after Neonatal Gene Therapy with rAAV

1-\textsuperscript{13}C Propionate Oxidation Is Restored In MMA Patients After L(K)T Despite Significant MMAemia
Scaling Up Unbiased Screening of Biomarkers

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 Chlebowsk, Audrey Thurm, Jeffrey B. Kopp, Kong Y. Chen & Charles P. Venditti

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

1835 Accesses | 5 Citations | 17 Altmetric | Metrics
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

60-minute 1-\(^{13}\)CO\(_2\) Recovery

- Healthy Controls
- Transplanted
- Two Nulls
- Other Allele Combinations

% of recovered \(^{13}\)CO\(_2\)

The ROC Curve

- Sensitivity%
- 100% - Specificity%
- P value < 0.0001
- AUC = 0.97

Intra-Patient Reproducibility

- R\(^2\) = 0.98
- P value = 0.0002

Shchelochkov et al, Genetics in Medicine, 23, pages 1534–1542 (2021)
Machine Learning Algorithm Prioritized Novel PA Biomarkers

Plasma FGF21

<table>
<thead>
<tr>
<th>Condition</th>
<th>Severe PA</th>
<th>Mild PA</th>
<th>PA after LT</th>
</tr>
</thead>
<tbody>
<tr>
<td>pg/mL</td>
<td>15000</td>
<td>10000</td>
<td>5000</td>
</tr>
</tbody>
</table>

Alanine:Serine Ratio

<table>
<thead>
<tr>
<th>Condition</th>
<th>Severe PA</th>
<th>Mild PA</th>
<th>PA after LT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
<td>8</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Plasma GDF15

<table>
<thead>
<tr>
<th>Condition</th>
<th>Severe PA</th>
<th>Mild PA</th>
<th>PA after LT</th>
</tr>
</thead>
<tbody>
<tr>
<td>pg/mL</td>
<td>n.s.</td>
<td>****</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

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
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).

  - **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.
• 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

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

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
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)

Hemorrhage Risk from Diagnosis
0.5% /patient/year first bleed
6% /patient/year re-bleed

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

<table>
<thead>
<tr>
<th>Mechanisms of disease</th>
<th>Plasma circulating biomarkers</th>
<th>Validating preclinical models</th>
<th>Candidate therapeutic</th>
<th>Lesion pathogenesis</th>
<th>Development status</th>
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<tr>
<td>MAPK signaling, PI3K-mTOR signaling, microbiome mechanisms</td>
<td>ADAMTS4</td>
<td>Murine/human</td>
<td>BIX02189 (anti- MEK5)</td>
<td>Lesion burden</td>
<td>Preclinical</td>
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<td></td>
<td>ADAMTS6</td>
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<td>XMD17-106 (anti- ERK5)</td>
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<td>TLR4</td>
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<td>Rapamycin (mTOR inhibitor)</td>
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<td>LPB (LPS)</td>
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<td>TLR4 inhibitors</td>
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<td>CD14</td>
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<td>Angiogenesis</td>
<td>VEGF</td>
<td>Murine/human</td>
<td>Bevacizumab</td>
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<td>Angiopoietin 1-2</td>
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<td>ROBO4</td>
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<td>TSP1 replacement</td>
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<td>Thrombospondin 1</td>
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<td>Inflammatory processes, autophagy, focused immune response</td>
<td>25-OH vitamin D</td>
<td>Murine/human</td>
<td>Vitamin D3</td>
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<td>Tempol</td>
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<td>Endoglin</td>
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<td>Anti-Br3 antibody</td>
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<td>IL-1β</td>
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<td>IL-10</td>
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<td>Coagulation domains and thrombin-endothelial interactions</td>
<td>Thrombomodulin</td>
<td>Murine/human</td>
<td>Potential biomarker</td>
<td>Bleeding</td>
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<td>Rheological mechanisms</td>
<td>Blood pressure pro-thrombotic states</td>
<td>Murine</td>
<td>Enoxaparin</td>
<td>Lesion growth</td>
<td>Preclinical</td>
</tr>
<tr>
<td></td>
<td>Zebrafish/murine/human</td>
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<td></td>
<td>Propranolol</td>
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<td></td>
<td>β1-receptor antagonists</td>
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<tr>
<td>Endothelial-mesenchymal transition</td>
<td>TGF-β</td>
<td>Murine</td>
<td>Enoxaparin</td>
<td>Lesion burden</td>
<td>Preclinical</td>
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<td>Propranolol</td>
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<td>Endothelial permeability (RhoA/ROCK)</td>
<td>pMLC</td>
<td>Murine/human</td>
<td>Fasudil</td>
<td>Lesion burden</td>
<td>Preclinical</td>
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<td></td>
<td>pMS</td>
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<td></td>
<td>Leukocytes</td>
<td></td>
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</tbody>
</table>

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

Validation of mouse lesion histology, iron vs QSM
Validation in vivo and ex vivo lesion QSM vs iron concentration
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 UL1 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

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
Zeineddine et al. J MRI 2017
### SYMPTOMATIC REBLEED (PHASE III TRIALS)

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

#### 2-tailed

<table>
<thead>
<tr>
<th></th>
<th>3 years Follow-Up</th>
<th>5 years Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genotype</strong></td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td><strong>Effect assumption</strong></td>
<td>50% decrease</td>
<td>50% decrease</td>
</tr>
<tr>
<td><strong>Sample size / group</strong></td>
<td>299</td>
<td>108</td>
</tr>
<tr>
<td><strong>Significance level</strong></td>
<td>0.05</td>
<td>0.05</td>
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<tr>
<td><strong>Power</strong></td>
<td>80%</td>
<td>80%</td>
</tr>
</tbody>
</table>

#### QSM 2 years f/u (safety and efficacy POC)

<table>
<thead>
<tr>
<th></th>
<th>QSM 2 years f/u (safety and efficacy POC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genotype</strong></td>
<td>All</td>
</tr>
<tr>
<td><strong>Effect assumption</strong></td>
<td>Percent QSM change observed in CASH lesions; or therapeutic effect in mice</td>
</tr>
<tr>
<td><strong>Sample size / group</strong></td>
<td>20-25</td>
</tr>
<tr>
<td><strong>Significance level</strong></td>
<td>0.1</td>
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<tr>
<td><strong>Power</strong></td>
<td>90%</td>
</tr>
</tbody>
</table>

Zeineddine et al. *JMRI* 2017
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
**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.


**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.


**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 80 mg/kg/day decreases lesion burden and non-heme iron in mouse models compared with placebo**
Atorvastatin Treatment in Cavernous Angiomas with Symptomatic Hemorrhage Exploratory Proof of Concept Trial (AT CASH EPOC)

Phase I-Ila 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!
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. 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)

---

**Postulated Effect Sizes**

<table>
<thead>
<tr>
<th>STD</th>
<th>Rho</th>
<th>Var of Mean</th>
<th>STD of Mean</th>
<th>N per group</th>
<th>N inflated</th>
<th>N per group</th>
<th>N inflated</th>
<th>N per group</th>
<th>N inflated</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>-0.5</td>
<td>196</td>
<td>14.00</td>
<td>12</td>
<td>19</td>
<td>20</td>
<td>32</td>
<td>8</td>
<td>13</td>
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<tr>
<td>28</td>
<td>0</td>
<td>392</td>
<td>19.80</td>
<td>22</td>
<td>35</td>
<td>38</td>
<td>61</td>
<td>15</td>
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<td>28</td>
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<td>588</td>
<td>24.25</td>
<td>33</td>
<td>53</td>
<td>56</td>
<td>90</td>
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<td>34</td>
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<tr>
<td>30</td>
<td>-0.5</td>
<td>225</td>
<td>15.00</td>
<td>13</td>
<td>21</td>
<td>23</td>
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<td>9</td>
<td>14</td>
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<tr>
<td>30</td>
<td>0</td>
<td>450</td>
<td>21.21</td>
<td><strong>25</strong></td>
<td><strong>40</strong></td>
<td>44</td>
<td>70</td>
<td><strong>17</strong></td>
<td><strong>27</strong></td>
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<td>30</td>
<td>0.5</td>
<td>675</td>
<td>25.98</td>
<td>37</td>
<td>59</td>
<td>65</td>
<td>104</td>
<td>48</td>
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<td>256</td>
<td>16.00</td>
<td>15</td>
<td>24</td>
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<td>512</td>
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<td>32</td>
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<td>768</td>
<td>24.66</td>
<td>42</td>
<td>67</td>
<td>73</td>
<td>117</td>
<td>27</td>
<td>43</td>
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</table>

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.
- 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
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,7 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,6 Robert Shenkar, PhD,1 Agnieszka Stadnik, MS,1 Janne Koskimäki, MD, PhD,1 Alexey Dimov, PhD,9 Dallas Turley, PhD,7 Timothy Carroll, PhD,7 and Issam A. Awad, MD1*
NEXT STEPS WITH QSM IN CASH TRIALS

• If AT CASH EPOC is favorable, need Phase IIIB 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
May 2022
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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
- 5/23/2022
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 (failures 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
A proteomic surrogate for cardiovascular outcomes that is sensitive to multiple mechanisms of change in risk

Stephen A. Williams14,†, Rachel Ostroff1, Michael A. Hinterberg1, Josef Coresh2, Christie M. Ballantyne3, Kunihiro Matsushita4, Christian E. Mueller4, Joan Walter4,5, Christian Jonasson6, Ruy R. Holman7, Svatì H. Shah8, Naveed Sattar9, Roy Taylor10, Michael E. Lean11, Shinhtar Kato12, Hiroaki Shimokawa13,14, Yasuhiko Sakata13, Kotaro Nochik5a13, Chirag R. Parikh9, Steven G. Coca15, Torbjorn Omland16, Jessica Chadwick1, David Astling1, Yolanda Hagar1, Natasha Kureshi1, Kelsey Loupy1, Clare Paterson1, Jeremy Primus1, Missy Simpson1, Nelson P. Trujillo17, Peter Ganz18,†

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 1.76 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

**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*, PTPRJ, 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
  • 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-" + 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"\},
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

<table>
<thead>
<tr>
<th>Responsiveness to change: Inter-group change in protein predictions and common biomarkers in paired samples</th>
<th>27 Proteins, absolute change in risk</th>
<th>CRP</th>
<th>Cystatin-C</th>
<th>GDF-15</th>
<th>Myeloperoxidase</th>
<th>NTproBNP</th>
<th>Troponin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Expected Adverse Change</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approaching an event, 1-year change vs. no event (EXSCEL)</td>
<td>+2.9%</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Approaching an event, 2-year change vs. no event (ACCORD)</td>
<td>+6.0%</td>
<td>↑</td>
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<tr>
<td>Anthracycline chemotherapy, 3 month within-subject change (PRADA)</td>
<td>+6.2%</td>
<td>↑</td>
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<tr>
<td><strong>Expected Neutral Change</strong></td>
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<tr>
<td>Intensified oral hypoglycemic treatment, vs. standard therapy (ACCORD)</td>
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<tr>
<td>Angiotensin receptor blocker in chemotherapy vs. placebo (PRADA)</td>
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<tr>
<td>Beta blocker in chemotherapy vs. placebo (PRADA)</td>
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<tr>
<td><strong>Expected Beneficial Change</strong></td>
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<tr>
<td>Exenatide, within-subject change vs. placebo (EXSCEL)</td>
<td>-1.5%</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<td>↓</td>
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<tr>
<td>Dietary weight loss in diabetics in one year vs. standard diet (DIRECT)</td>
<td>-6.7%</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<td>↑</td>
</tr>
</tbody>
</table>

Bold/colored symbols are p<0.01 corrected for multiple comparisons
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

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

Symptomatic phase

Presymptomatic phase

Serum NL

Healthy neuron

Degenerating/injured neuron

NfL

AD

MS

FTD

ALS

Healthy subjects

Time (years)

Clinical threshold

Clinical onset

Considerations for NfL Biomarker Validity

**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

• 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

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

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Progressive MS subtype and number of subjects</th>
<th>Study design</th>
<th>Correlations between baseline NfL and baseline imaging measures</th>
<th>Correlations between baseline NfL and baseline clinical measures</th>
<th>Correlations between baseline NfL and imaging outcomes</th>
<th>Correlations between baseline NfL and clinical outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXPAND and INFORMS 90</td>
<td>SPMS (n = 1,452) and PPMS (n = 378)</td>
<td>Combined data from phase 3 RCTs (EXPAND and INFORMS)</td>
<td>Gd+ lesion count; T2 lesion volume</td>
<td>EDSS</td>
<td>Brain volume loss after 12 and 24 mo</td>
<td>1. EDSS worsening</td>
<td>Combined treatment and placebo subjects</td>
</tr>
<tr>
<td>ASCEND 40</td>
<td>SPMS (n = 365)</td>
<td>Phase 3 RCT</td>
<td>Gd+ lesion count; T2 lesion volume</td>
<td>T25FW, 9HPT</td>
<td>Brain volume loss after 96 wk</td>
<td>Not reported</td>
<td>Placebo data only</td>
</tr>
<tr>
<td>ORATORIO</td>
<td>PPMS (n = 516)</td>
<td>Phase 3 RCT</td>
<td>Gd+ lesion count</td>
<td>Not reported</td>
<td>Not reported</td>
<td>EDSS; T25FW; 9HPT</td>
<td>Combined treatment and placebo subjects</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Study reference</th>
<th>MS phenotype</th>
<th>Study design (treatment duration)</th>
<th>Treatment</th>
<th>Subjects for NFL analysis</th>
<th>NFL biofluid (assay used)</th>
<th>Change in NFL concentration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axelsson et al.</td>
<td>SPMS and PPMS</td>
<td>Observational phase 2A, with age-matched controls (12-24 mo)</td>
<td>Rituximab (n = 5) or mitoxantrone (n = 39)</td>
<td>30 SPMS, 5 PPMS, and 14 healthy controls</td>
<td>CSF (Uman Diagnostics), NFL-light ELISA</td>
<td>Mean NFL concentration was reduced 51% from 1,780 ng/mL to 870 ng/mL (p = 0.007) irrespective of MS phenotype or treatment</td>
<td>1. NFL concentration was only reduced in either previously untreated patients or those with enhancing lesions at baseline.</td>
</tr>
<tr>
<td>Romme Christensen et al.</td>
<td>SPMS and PPMS</td>
<td>Phase 2A single-arm (60 wk)</td>
<td>Natalizumab</td>
<td>7 SPMS and 10 PPMS</td>
<td>CSF (Uman Diagnostics), NFL-light ELISA</td>
<td>Mean NFL concentration was reduced by 37%, from 657 ng/mL to 414 ng/mL (p = 0.03)</td>
<td>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 found a correlation between CSF NFL and changes in the MS Impact Scale.</td>
</tr>
<tr>
<td>Ratzer et al.</td>
<td>SPMS and PPMS</td>
<td>Phase 2A single-arm (60 wk)</td>
<td>Methylprednisolone</td>
<td>14 SPMS and 11 PPMS</td>
<td>CSF (Uman Diagnostics), NFL-light ELISA</td>
<td>Mean NFL concentration not reduced by treatment baseline 287 pg/mL vs final 343 pg/mL (p = 0.067)</td>
<td>Treatment-associated changes in EDSS, SMC, SHPT, T25FW, NMS, MRT, and DTI measures.</td>
</tr>
<tr>
<td>INFORMS</td>
<td>PPMS</td>
<td>Phase 3 randomized trial (24 mo)</td>
<td>Fingolimod or placebo</td>
<td>170 fingolimod and 119 placebo</td>
<td>EDTA plasma (Quanterix Simoa NFL-light® Advantage K15)</td>
<td>NFL levels lower in fingolimod-treated patients than placebo at mo 24 (p = 0.0012)</td>
<td>No significant difference between groups at mo 12</td>
</tr>
<tr>
<td>EXPAND</td>
<td>SPMS</td>
<td>Phase 3 randomized trial (&gt;21 mo)</td>
<td>Siponimod or placebo</td>
<td>380 siponimod and 145 placebo</td>
<td>EDTA plasma (Quanterix Simoa NFL-light® Advantage K15)</td>
<td>Plasma NFL levels increased by 9.2% with placebo and decreased by 5.7% with siponimod (p = 0.0004)</td>
<td></td>
</tr>
<tr>
<td>ASCEND</td>
<td>SPMS</td>
<td>Phase 3 randomized trial (96 wk)</td>
<td>Natalizumab or placebo</td>
<td>379 natalizumab and 365 placebo</td>
<td>Serum (Quanterix Simoa NFL-light® Advantage K15)</td>
<td>sNfL at wk 48 and 96 was lower in natalizumab vs placebo (ratios: 0.84, p &lt; 0.001, and 0.80, p &lt; 0.001, respectively)</td>
<td>1. Week 96 sNfL was higher in those with progression on the multicompartment 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).</td>
</tr>
<tr>
<td>SPRINT</td>
<td>SPMS and PPMS</td>
<td>Phase 2 randomized trial (96 wk)</td>
<td>Ibudilast or placebo</td>
<td>Serum: 119 ibudilast and 120 placebo. CSF: 30 ibudilast and 28 placebo</td>
<td>CSF and serum (Quanterix Simoa NFL-light® Advantage K15)</td>
<td>No between-group differences in change in NFL in either serum or CSF</td>
<td>Concurrent anti-inflammatory therapy was only injectables or none; ongoing focal inflammatory activity may have confounded assessment of ibudilast’s effect on NFL.</td>
</tr>
<tr>
<td>ORATORIO</td>
<td>PPMS</td>
<td>Phase 3 randomized trial (96 wk)</td>
<td>Ocrelizumab or placebo</td>
<td>347 ocrelizumab and 169 placebo</td>
<td>Serum (Quanterix Simoa NFL-light® Advantage K15)</td>
<td>NFL was 15.7% lower with ocrelizumab vs 0.2% lower with placebo (p = 0.001)</td>
<td>For patients with BI, NFL above 90th percentile of healthy controls, a higher proportion decreased into normal range with ocrelizumab (40.4%) vs placebo (16.6%) (p &lt; 0.001)</td>
</tr>
</tbody>
</table>
**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

**Temporal Evolution of NfL Z Scores Under Treatment**

Biomarker Considerations for Regulatory Science

Biomarkers can integrate into the drug development process in many ways

- 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 neurodegenerative 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.
Challenges

- Standardize sample collection and assay methods to align across multiple testing sites
- Lack of standardized, accessible normative database of [NfL] in healthy and diseased subjects
- Knowledge gaps for predictive value of NfL for progression and/or severity across neurodegenerative diseases
- Fragmented data sharing/repository ecosystem

Potential Solutions

- Evaluate SOPs, standardize/define collection & storage, standards, calibrators; compare assay methods
- Establish necessary inclusion/exclusion parameters; identify appropriate control groups
- Cross-sectional validation in early and advanced disease; longitudinal studies in disease cohorts
- 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
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!

Contact Us

healthpolicy.duke.edu

Subscribe to our monthly newsletter at dukemargolis@duke.edu

1201 Pennsylvania Avenue, NW, Suite 500
Washington, DC 20004

DC office: 202-621-2800
Durham office: 919-419-2504

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