CAMD Digital Biomarker Conference:
Assessment of Cognition & Function in Neurodegenerative Diseases
March 31, 2016
Stephen P Arneric, PhD
Executive Director, Coalition Against Major Diseases
Digital Biomarkers Conference –
Goals & Desired Outcomes

• View the current landscape of approaches to use biosensor technologies to assess changes in patient function across neurodegenerative diseases with impaired cognition.

• Understand the current gaps & barriers that impede the advancement of regulatory science progress for these technology platforms.

• Prioritize which gaps & barriers that would have the highest impact across more than one disease to advance regulatory science.

• Formalize the output of the meeting by publishing a manuscript detailing the findings and recommendations of the participants.
C-Path: A Public Private Partnership

- Act as a trusted, neutral, non-profit entity
- Convene scientific consortia of industry, academia, and government for sharing of data/expertise
  - The best science
  - The broadest experience
  - Active consensus building
  - Shared risk and costs
- Enable iterative FDA/EMA participation in developing new methods to assess the safety and efficacy of medical products
- Official regulatory endorsement of novel methodologies and drug development tools
C-Path Consortia

Twelve global consortia collaborating with 1,300+ scientists and 61 companies

- Coalition Against Major Diseases
  Focusing on diseases of the brain

- Coalition For Accelerating Standards and Therapies
  Data standards

- Critical Path for Parkinson’s Consortium
  Enabling clinical trials in Parkinson’s Disease

- Critical Path to TB Drug Regimens
  Accelerating the development of TB drug regimens and diagnostics

- Duchenne Regulatory Science Consortium
  Duchenne Muscular Dystrophy

- International Neonatal Consortium
  Neonatal clinical trials

- Multiple Sclerosis Outcome Assessments Consortium
  Drug Effectiveness in MS

- Polycystic Kidney Disease Outcomes Consortium
  New imaging biomarker for PKD

- Patient-Reported Outcome Consortium
  Assessing treatment benefit

- Electronic Patient-Reported Outcome Consortium
  Electronic capture of treatment benefit

- Predictive Safety Testing Consortium
  Drug safety

- Pediatric Trials Consortium
  Developing effective therapies for children

✔ Biomarkers
✔ Clinical outcome assessment instruments
✔ Clinical trial simulation tools
✔ Data standards
✔ In vitro tools
CAMD as a Consortium

CAMD is aimed at developing drug development tools that advance regulatory science, and accelerate the delivery of innovative treatments for Alzheimer’s disease and related neurodegenerative diseases that have impaired cognition and function.
## CAMD’s 2016 Regulatory Pipeline

<table>
<thead>
<tr>
<th>Disease or Target</th>
<th>Drug Development Tool</th>
<th>Feasibility</th>
<th>Scoping</th>
<th>Research</th>
<th>Submitted</th>
<th>Qualified</th>
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<tbody>
<tr>
<td>Alzheimer's disease (AD)</td>
<td>Hippocampal vMRI Biomarker</td>
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<td>Disease model of mild and moderate AD</td>
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<td>Disease model of MCI/aMCI leading to AD</td>
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<td>Function &amp; Cognition in Dementias</td>
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<td>Digital Biomarker</td>
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C-Path CAMD Alzheimer’s Disease Modeling & Simulation Tool

Mized Legacy Data

CDISC ‘Standardized Data’

Integrated Data

Clinical Data Contributed to C-Path: Strong Foundation for Neurodegenerative Diseases

Clinical Data Studies: 78
Subjects: 41,114

Nonclinical studies: 118
Subjects: 5,458

- Kidney healthy volunteer study
- Polycystic kidney disease
- Multiple sclerosis
- Tuberculosis
- Parkinson's disease
- Alzheimer's disease

Not in database.....
Alzheimer’s Disease (AD) Stages: The dilemma of what to measure & when?

Unless different outcomes are validated, approvals will require patients to reach this stage of disease progression!

• Current outcomes insensitive
• Patient enrichment is critical
• Current outcomes focused on aMCI to Moderate AD
• Current outcomes unreliable

Pre-Dementia  ➔  Dementia

Memory complaints  ➔  Cognitive Impairment  ➔  Cognitive, Functional & Behavioral deficits

Pre-Symptomatic  ➔  MCI / Prodromal AD  ➔  Mild, Moderate, Severe

No apparent symptoms  ➔  Symptoms  ➔  Current diagnosis & treatment

Johan Luthman (Eisai)
Using accepted outcome measures...

2014 CAMD Annual Meeting
- Richard Mohs (Lilly)

Symptomatic Treatment Effects on Cognition Appear Before Effects on Function - Donepezil

Figure Legend: Least squares mean (± SEM) change from baseline in the Alzheimer’s Disease Assessment Scale--Cognitive Subscale (ADAS-cog) scores for patients with mild to moderately severe Alzheimer disease receiving 5 mg/d and 10 mg/d of donepezil hydrochloride and placebo. Of the 468 patients randomized to receive treatment, 457 were included in the intention-to-treat analysis at end point.

Figure 2. Kaplan–Meier survival estimates of time to clinically evident functional decline (by investigator, intent-to-treat population).

Well Recognized Diseases/Disorders with Co-morbid Dementia

- Alzheimer’s Disease
- Parkinson’s Disease
- Multiple Sclerosis
- Frontal Lobe Dementia
- Lewy Body Dementia
- Traumatic Brain Injury
- Down’s Syndrome
- Gaucher’s Disease
- Vascular Dementia
- Dravet’s Syndrome
- Huntington’s Disease
- Congestive Heart Failure
Concordance of Symptoms & Functional Impact

**Functional Impact:**
- Social Life and Social Participation
- Work/Life
- Relationships and Family
- Independence

### Alzheimer’s Disease
- Cognitive Impairments
- Speech Problems
- Depression
- Sleeping Changes
- Gait slowed
- Dizziness/Vertigo
- Swallowing (advanced stages)
- Pain

### Parkinson’s Disease
- Tremor
- Walking & Gait Impairment
- Spasticity
- Pain
- Depression
- Bowel/Bladder Problems
- Fatigue
- Sleeping Impaired
- Dizziness/Vertigo
- Cognitive Impairments
- Speech Problems

### Multiple Sclerosis
- Depression
- Pain
- Numbness/Tingling
- Sexual Dysfunction
- Fatigue
- Spasticity
- Lower & Upper Extremity Impairments
- Walking Impairment
- Bowel/Bladder Problems
- Dizziness/Vertigo
- Cognitive Impairments
- Speech Problems
- Sleeping Impaired

### Huntington’s Disease
- Irritability
- Depression
- Pain
- Fatigue
- Sleeping Problems
- Spasticity
- Walking Impairment
- Upper & Lower Extremity Impairments
- Dizziness/Vertigo
- Cognitive Impairments
- Speech Problems
Dementia & other symptoms are co-morbid across many neurodegenerative diseases

Which drugs [molecular target] ?

.....in which patients?
Our Current Scope: What we are not doing!

- **Electronic Health Records**: X

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**Biosensor/Device Measures**

**Mobile/Remote Health Measures**
- Cognitive measures
- Blood glucose monitor
- EEG monitor
- Heart monitor
- Wearables (fall monitors; Fitbit™; AppleWatch™)
- ResearchKit™

"Biosensor Measurements"

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**Patient-Focused Healthcare**

**Telemedicine**
- Periodic Diagnosis/Counseling
- Daily mobile counseling based on wearable devices and patient reported feedback

"Mobileceuticals"

The What:
Data (signal output) collected from a biosensor that measures a biological recognition element

The How:
Continuous physiological monitoring with devices (wearables/smart phones, clothing, implants/ingestibles, remote biosensors)

The Why:
Improve our understanding of real-time changes in FUNCTION during the progression of life in health & disease
Cognition & “Instrumental Activities of Daily Living”

Premise:
Cognition is a key lens through which we see ‘view’ the world, and how we can focus/functionally organize our “instrumental activities of daily living”.

Hypothesis:
Changes or increased variance in the key functional domains of “activities of daily living” should reflect current, and potentially future, changes in cognitive function.
Digital Biomarkers: Potential to measure all domains of function comprising instrumental activities of daily living (IADLS)

**Mental Function**
- working memory
- attention
- wakefulness/sleep
- long-term memory

**Physical Function**
- mobility
- frailty
- homeostatic physiology
- drug disposition/metabolism

**Health Maintenance**
- injury & sickness
- surgery
- disease

**Social Networking**
- friends/family
- mood
- social engagement/employment

*Arneric et al., 2014 Drug Discovery Today [focus on chronic pain]*
Fig. 3 – Attributes of outcome assessments. A specific outcome assessment is selected or created to operationalize measurement of the concept of interest. Outcome assessments are of two major types: clinical outcome assessments and biomarkers. Clinical outcome assessments have an attribute identifying the type of person whose judgment can influence the reported measurement. Clinical outcome assessments may be influenced by the judgment of the patient, clinician, or a nonclinician observer; they may also be a nonjudged recording of a task performed by the patient (performance outcome). Clinical outcome assessments may be directly reporting the meaningful feelings or functions selected as the potential treatment benefit, or may be reporting measurements that are thought to be indirectly informative regarding those feelings or functions (see Fig. 1). Biomarkers can only indirectly measure the meaningful aspect of health.

**Biosensor Observed Measures**
- Less “observer specific bias”
- No need for “observer training”
- Potential for lower cross-site variance of measures
- Reduced clinical fees
Can biosensor measurements ‘observe’ functionally meaningful changes before accepted outcome measures?

- Pain relievers must show at least a 1 point change in NRS before being considered clinically meaningful
- Clinical trials typically will require a pain score of >4.0 as an inclusion criterion
Digital Biomarkers enable a paradigm shift in assessing IADLs

**SUBJECTIVE**
Current Practice
In Drug Development

- **Efficacy**
  - “IADLs”
  - Challenges: Patient reported, subjective, memory-dependent, non-verifiable, not used in label claims
- **Safety**

**OBJECTIVE**
Digital Biomarkers
In Drug Development

- **Efficacy**
  - “IADLs”
  - Objective, verifiable, patient-independent outcomes for potential use in label claims; ‘Surrogate for QoL’
- **Safety**
Digital Biomarkers: Potential Roles in Filling Regulatory Science Gaps

BARRIERS

Lack of qualified biomarkers for decision making

No effective therapy for modifying disease progression

High risk and increasing costs for drug development

GAP

Highly variable subpopulations recruited into randomized clinical trials

Inadequate outcome measures for assessing functional efficacy of drugs in early presymptomatic stages

Huge uncertainty in design of clinical trials

CAMD Approach

Regulatory biomarker qualification for enrichment in randomized clinical trials

Innovative/sensitive clinical outcome assessments for efficacy of novel drug candidates

Regulatory endorsed AD clinical trial simulation tool
Thank You!

www.c-path.org
Poll Everywhere

Live Audience Participation
Poll Everywhere lets you engage your audience or class in real time

Create your first poll
Watch our 2 min video

What's your favorite animal?

Text a KEYWORD to 22333

LION 50%
TURTLE 33%
GRANDPA 17%

Message and data rates may apply
Poll Everywhere Log-In

- Please download the Poll Everywhere App on your smartphone
- Please select “I’m Participating”
- Please input the user name “CAMD” and click “Join”
- Answer questions after each presentation
# Agenda

**March 31, 2016**

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
<th>Duration</th>
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<tbody>
<tr>
<td>8:00 a.m.</td>
<td>Breakfast</td>
<td>All</td>
<td>30 minutes</td>
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<tr>
<td>8:30 a.m.</td>
<td>Welcome &amp; Objectives of the Meeting</td>
<td>Stephen Arnerić, PhD, Executive Director, CAMD, C-Path</td>
<td>15 minutes</td>
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<td>Unmet Needs</td>
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<td><strong>Health Measurements</strong></td>
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<td>8:45 a.m.</td>
<td>Digital Biomarkers: Life Kinetics as Outcomes in Clinical Trials</td>
<td>Jeffrey Kaye, MD, Director, NIA - Layton Aging &amp; Alzheimer's Disease Center; Director, NIA - ORCATECH - Oregon Center for Aging &amp; Technology; Professor of Neurology and Biomedical Engineering</td>
<td>45 minutes</td>
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<td>9:30 a.m.</td>
<td>Repurposing Consumer Technology for Digital Biomarkers</td>
<td>Max Little, PhD, Associate Professor, Aston University; TED Fellow, Visiting Associate Professor, MIT</td>
<td>20 minutes</td>
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<td>9:50 a.m.</td>
<td>Health Measurements Panel Discussion</td>
<td>All</td>
<td>20 minutes</td>
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<td>10:10 a.m.</td>
<td>Break</td>
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<td>15 minutes</td>
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<td><strong>Regulatory Considerations</strong></td>
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<td>10:25 a.m.</td>
<td>Why do Standards Matter?</td>
<td>Rebecca D. Kush, PhD, President &amp; CEO, CDISC</td>
<td>20 minutes</td>
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<td>10:45 a.m.</td>
<td>Informed Consent</td>
<td>John Wilbanks, BA, Senior Fellow, FasterCures; Chief Commons Officer, Sage Bionetworks</td>
<td>20 minutes</td>
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<td>11:05 a.m.</td>
<td>Information Exchange and Data Transformation (INFORMED) Initiative</td>
<td>Sean Khoozin, MD, MPH, Senior Medical Officer, FDA, Project Lead of Information Exchange and Data Transformation (INFORMED)</td>
<td>20 minutes</td>
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<tr>
<td>11:25 a.m.</td>
<td>Regulatory Considerations Panel Discussion</td>
<td>All</td>
<td>20 minutes</td>
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<td><strong>Multiple Sclerosis</strong></td>
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<td>11:45 a.m.</td>
<td>Advances Towards Remote Assessment of Disease and Relapse in MS patients</td>
<td>Jane Rhodes, MBA, PhD, Senior Director of New Initiatives for the Value Based Medicine team in the Biogen innovation hub</td>
<td>20 minutes</td>
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<tr>
<td>12:05 p.m.</td>
<td>Multiple Sclerosis Discussion</td>
<td>All</td>
<td>10 minutes</td>
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## Agenda (continued)

<table>
<thead>
<tr>
<th>Time</th>
<th>Session Description</th>
<th>Speaker(s)</th>
<th>Duration</th>
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<tr>
<td>12:15 p.m.</td>
<td>Lunch</td>
<td>All</td>
<td>60 minutes</td>
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<tr>
<td><strong>Alzheimer’s Disease</strong></td>
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| 1:15 p.m. | Use of internet based assessment for tracking the course of early Alzheimer’s disease with potential for determining response to treatment | Paul Maruff, PhD  
Chief Science Officer, CogState, Ltd. | 20 minutes |
| 1:35 p.m. | Cognitive Assessment in the Digital Era                  | Rhoda Au, MBA, PhD  
Prof. of Neurology, Director of Neuropsychology for the Framingham Heart Study (FHS) and serves to facilitate the collaboration between FHS and the Boston University Alzheimer’s Disease Center | 20 minutes |
| 1:55 p.m. | Real-world Digital Biomarkers from Symptomatic Community Population with Cognitive Impairment | John Hall, PhD  
SVP, Commercial Operations IXICO  
Ken Tubman, PhD  
VP, Healthcare Technology IXICO | 20 minutes |
| 2:15 p.m. | Alzheimer’s Disease Panel Discussion                     | All                                                                       | 20 minutes |
| **Parkinson’s Disease** | | | |
| 2:35 p.m. | Musings on Measuring Movement                            | Jesse M. Cedarbaum, MD  
Vice President, Movement and Neuromuscular Disorders Clinical Development, Biogen | 20 minutes |
| 2:55 p.m. | Digital Biomarkers in Neurology                          | Ray Dorsey, MD, MBA  
David M. Levy Professor in Neurology, Director, CHET | 20 minutes |
| 3:15 p.m. | Parkinson’s Disease Panel Discussion                     | All                                                                       | 20 minutes |
| 3:35 p.m. | Break                                                    | All                                                                       | 15 minutes |
| **Huntington’s Disease** | | | |
| 3:50 p.m. | Digital Biomarkers for Huntington’s Disease: Promises and Challenges | Ottavio Vitolo, MD, MMS  
Senior Director, Head of Neuromuscular Clinical Research, Rare Disease Research Unit, Research Project Lead in Huntington’s disease, Pfizer Inc. | 20 minutes |
| 4:10 p.m. | Challenges & Promises of digital biomarkers in the quantification of motor function | Spyros Papapetropoulos, MD, PhD  
Vice President, Global Development Head, Neurodegenerative Diseases at Teva Pharmaceuticals | 20 minutes |
| 4:30 p.m. | Huntington’s Disease Panel Discussion                    | All                                                                       | 20 minutes |
| 4:50 p.m. | Conclusion                                               | Stephen Amerić, PhD  
Executive Director, CAMD, C-Path | 10 minutes |