Developing a digital eco-system for disease understanding, insightful drug development tools, and innovative treatments require a standardized, actionable database

Critical Path for Alzheimer's Disease Consortium

Stephen P. Arnerić, PhD, Executive Director

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Harnessing Mobile Technology to Predict, Diagnose, Monitor, and Develop Treatments for Nervous System Disorders

CPAD

CRITICAL PATH FOR ALZHEIMER'S DISEASE

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ADVANCING SCIENCE THROUGH CROSS-DISCIPLINARY COLLABORATION

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Mission

Critical Path Institute is a catalyst in the development of new approaches to advance medical innovation and regulatory science. We achieve this by leading teams that share data, knowledge, and expertise, resulting in sound, consensus-based science (https://c-path.org/about/).

Who We Are

Critical Path Institute (C-Path) is a nonprofit, public-private partnership with the Food and Drug Administration (FDA) created under the auspices of the FDA's Critical Path Initiative program in 2005.

C-Path's aim is to accelerate the pace and reduce the costs of medical product development through the creation of new data standards, measurement standards, and methods standards that aid in the scientific evaluation of the efficacy and safety of new therapies.

CRITICAL PATH INSTITUTE

Fifteen global consortia collaborating with 1,450+ scientists and 84 organizations

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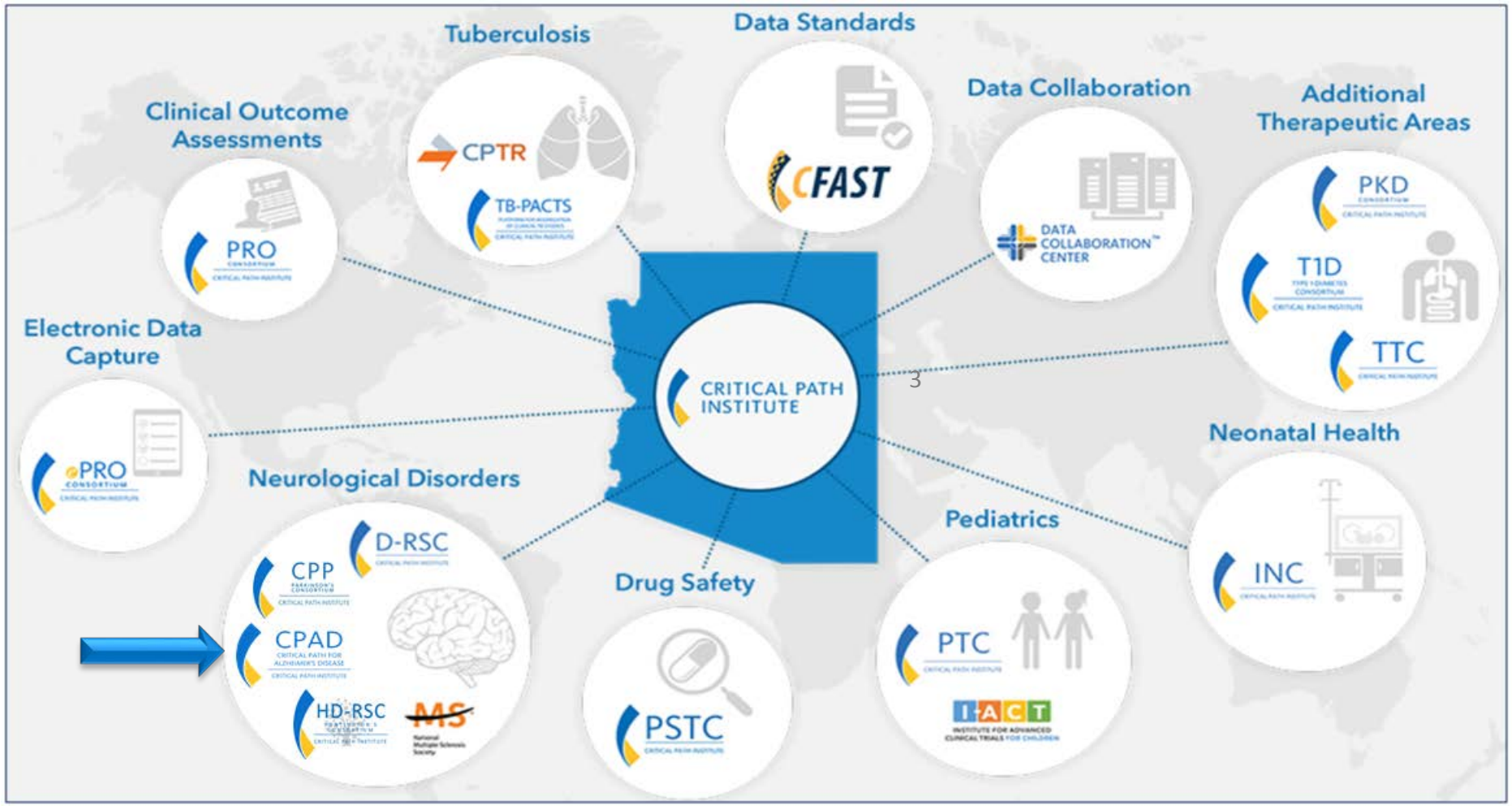

FOCUS: Data standards; clinical trial simulation tools from actionable data, disease progression models; biomarkers; clinical outcome assessment instruments

C-PATH CLINICAL DATA

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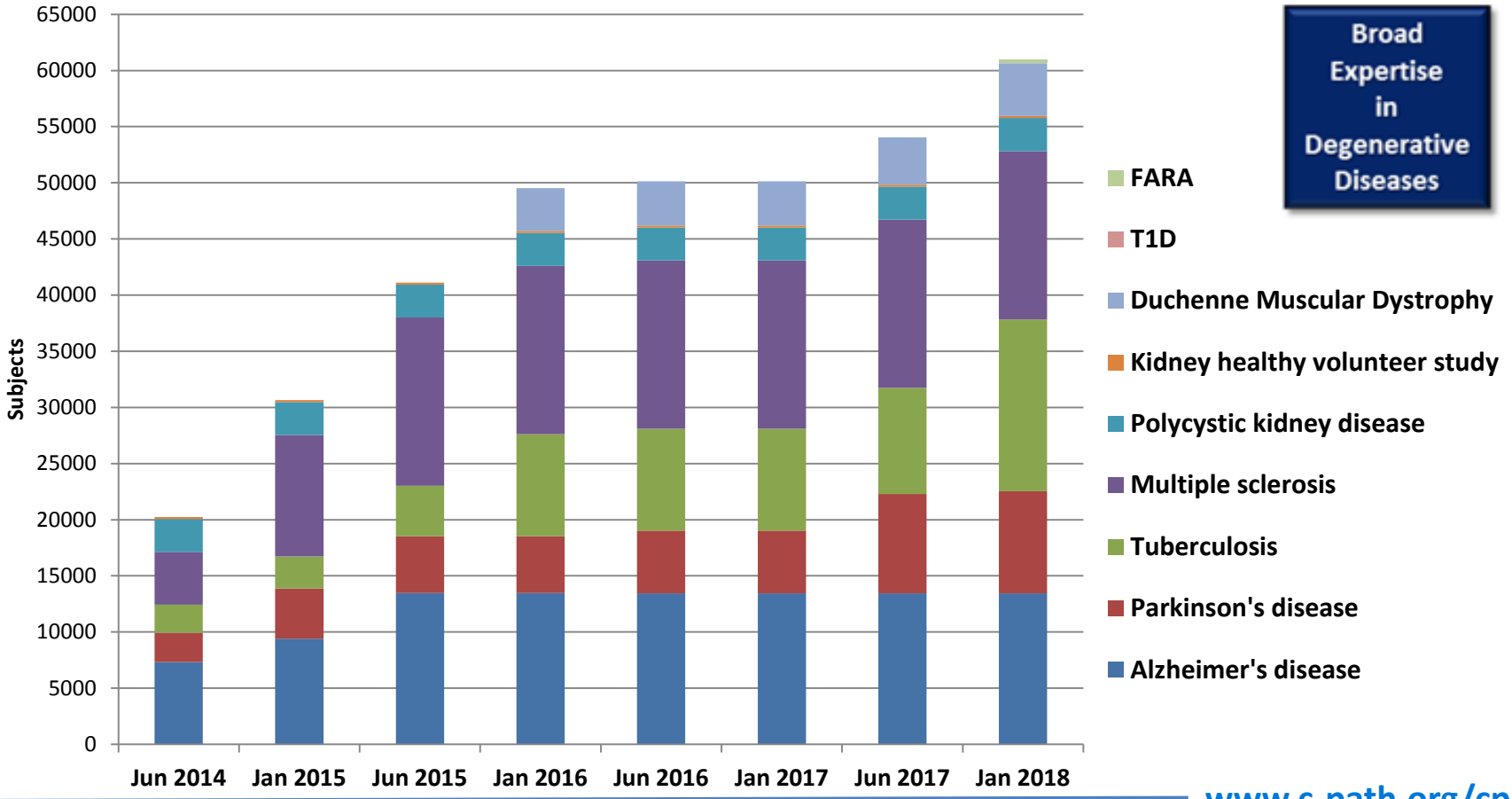
Clinical data: 107 studies
60,642 subjects

Note: nonclinical 119 studies. 6296 subjects.
ReSeqTB: 7835 Individual Isolates

Clinical data contributed to C-Path



CPAD QUALIFIES DRUG DEVELOPMENT TOOLS FOR CLINICAL DRUG TRIALS TREATING DEMENTIA

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Why? / What?

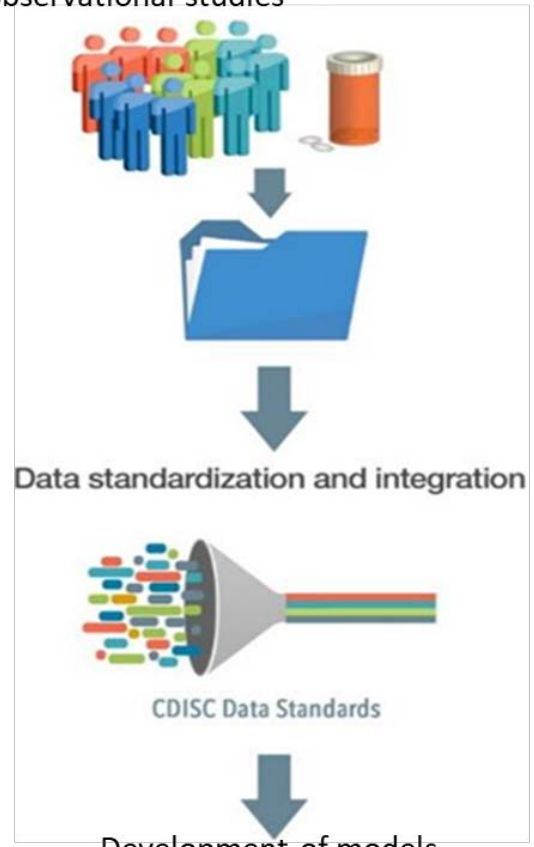
- To understand disease progression rates and responses to treatments, as these can vary significantly across different patients
- Advance Drug Development Tools

Who?

Key stakeholders: Patients, Pharma Companies, Regulators, Patient-Advocacy Organizations, Academics, Government Agencies

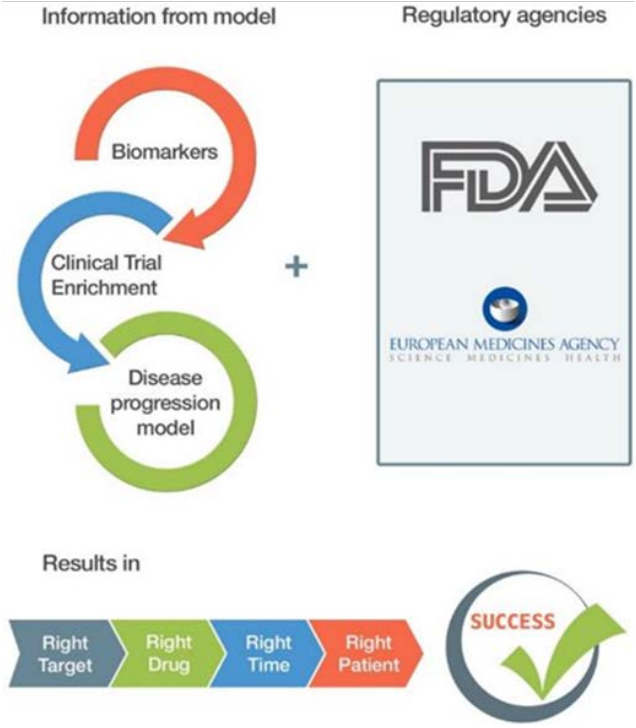
How?

Integrate anonymized patient-level data from past clinical trials and longitudinal observational studies



IMPACT

- **Actionable data/models to inform optimal trial design**
- **Improved trial efficiency, and accelerated delivery of innovative treatments to the right patients**



KEY ACHIEVEMENTS FOR CPAD
(previously CAMD)

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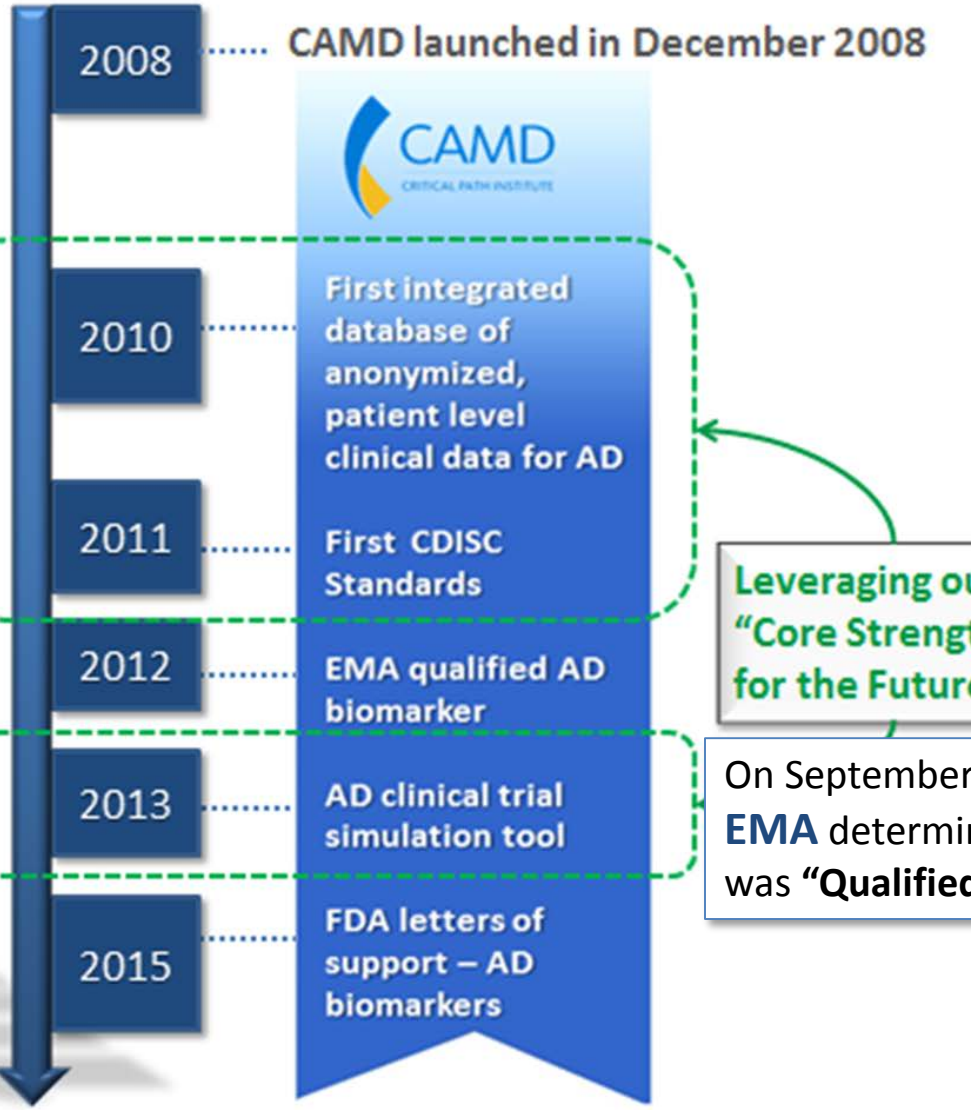

Leveraging our "Core Strengths for the Future"

On June 12, 2013 the **FDA** determined the CTS tool was **"Fit for Purpose."**

On September 19, 2013 the **EMA** determined the CTS tool was **"Qualified for Use."**

VALUE, HISTORY, & FUTURE OF CDISC (Clinical Data Interchange Standards Consortium) STANDARDS FOR AD

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Value Proposition:

- A reproducible research framework with controlled terminology which accelerates our understanding of AD across trials trials using a uniform format.
- Improves our ability to detect signals in new compounds; maximizes learnings from successes and failures.

Historical Perspective (CPAD/CDISC partnership):

Version 1.0 (2011) –

- First user guide for AD CDISC standards (did not include biomarkers) focused on key demographic, genetic and clinical outcome assessments (COAs).

Version 2.0 (2016) –

- Added global consensus data standards for key ***CSF AD biomarkers, vMRI imaging and PET ligands.***

Future:

Version 3.0 (~2019) –

- Focus on promising ***exploratory biomarkers and biometric assessments***.

FDA REQUIREMENT
(as of December 2016)
All clinical data from registration trials must be in CDISC format

Concepts covered by the Alzheimer's CDISC User Guide
ApoE Genotype
Family History of AD
Volumetric MRI
PET, PET/CT (FDG, Florbetapir, PiB)
CSF Biomarkers and Sampling
Outcome Assessment Scales
ADAS-COG
CDR
AVLT
FAQ
Modified Hachinski
DAD
ADCS-ADL MCI
NPI
CGI
GDS

OVERVIEW OF CPAD'S AD PATIENT CHARACTERISTICS

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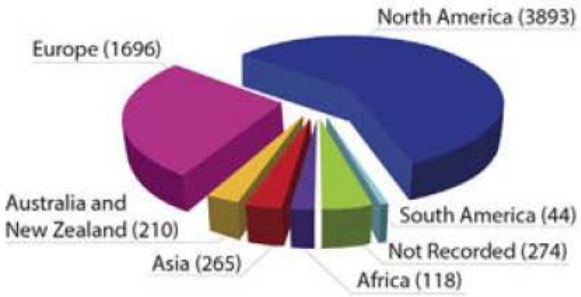
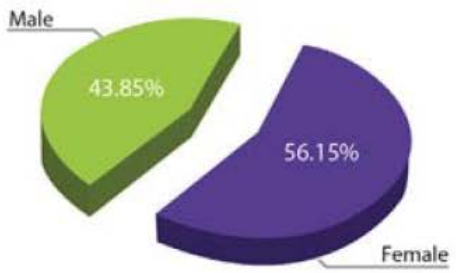
J. Neville et al. / Alzheimer's & Dementia 11 (2015) 1212-1221

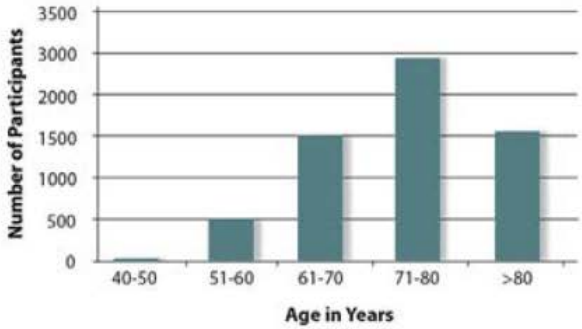
A **Number of Patients By Region**



B **Gender Distribution**

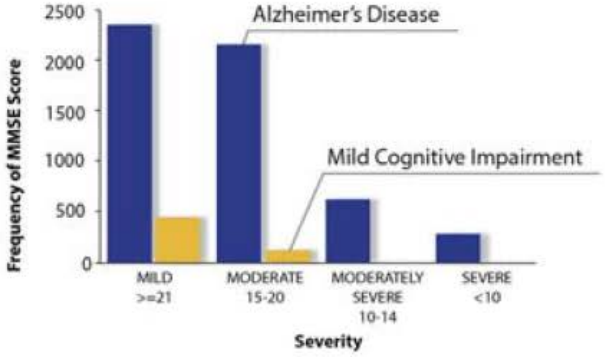


C **Age Range of Participants**

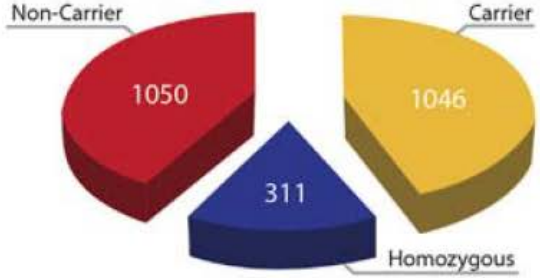


D **Patients with Alzheimer's disease or Mild Cognitive Impairment**

E **MMSE Baseline Score for Patients with Alzheimer's disease and Mild Cognitive Impairment**



F ***APOE* Genotype**



DEMONSTRATED UTILITY OF THE CLINICAL TRIAL SIMULATION TOOL

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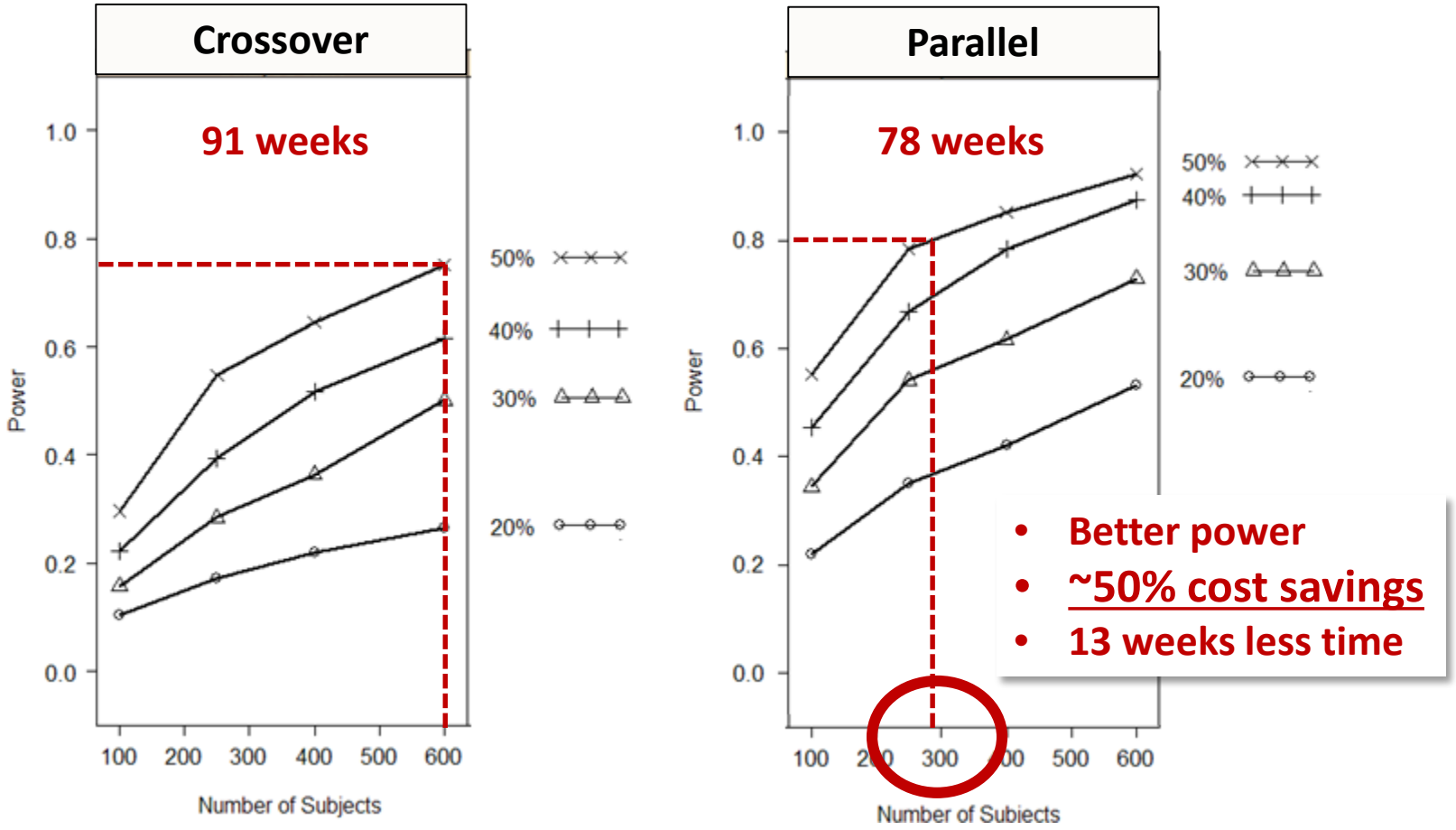
Balancing power, sample size, and duration, given varying effect magnitudes



CPAD DATABASE UTILIZATION (as of 4/30/2018)

550 Total Applicants

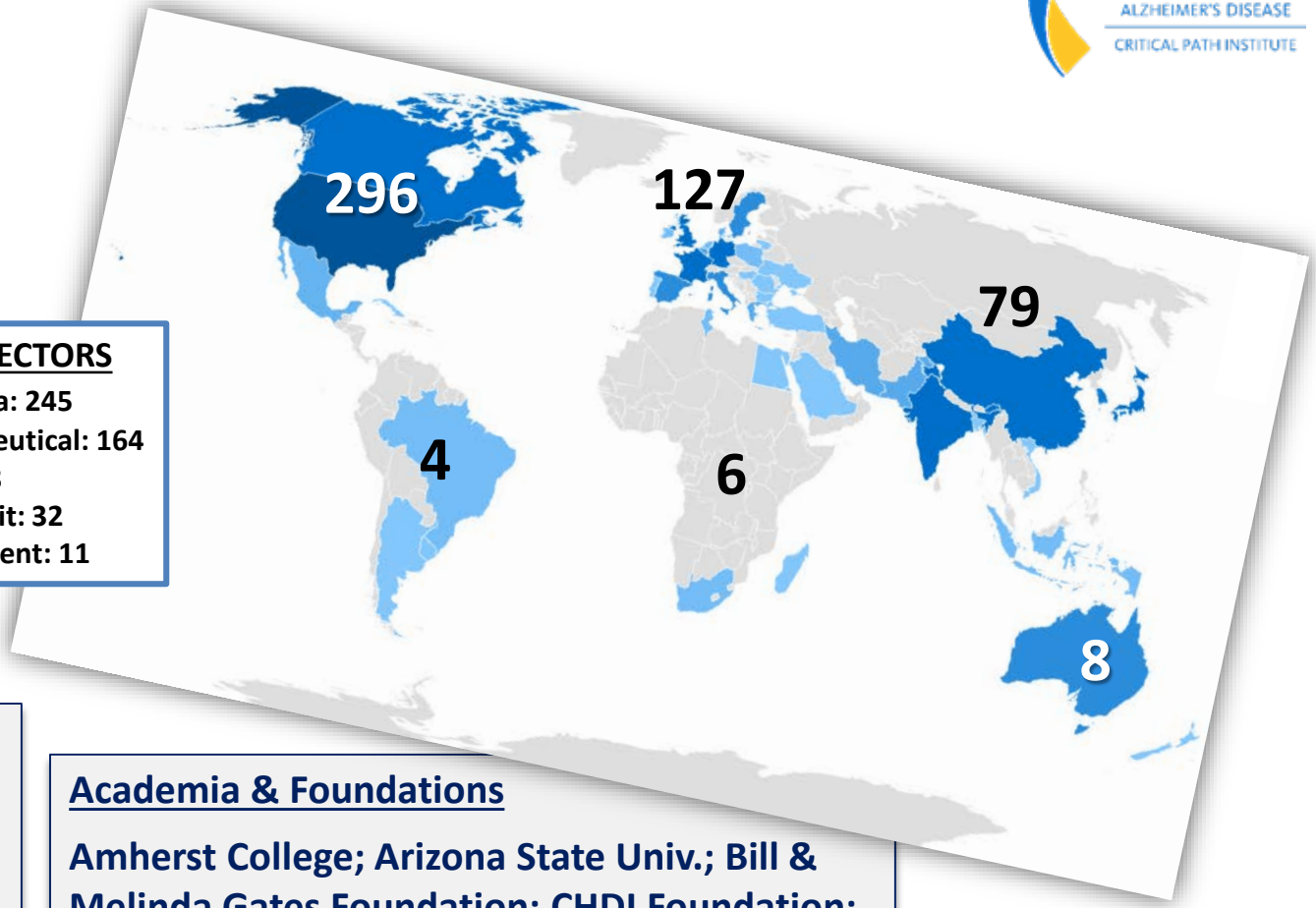
from

338 Distinct Institutions

GAAIN alzheimer's association Data Partner

USE BY SECTORS

- Academia: 245
- Pharmaceutical: 164
- Other: 68
- Non-profit: 32
- Government: 11



Industry

Abbvie; Allergan; AstraZeneca; Biogen; Biomarkable; CoreLab; Daewong; Eisai; GE Healthcare; IBM; Johnson & Johnson; Lundbeck; Merck; NeuroCog; Novartis; Pentara; Pfizer; Siemens; SAS

Academia & Foundations

Amherst College; Arizona State Univ.; Bill & Melinda Gates Foundation; CHDI Foundation; Duke Univ.; Fraunhofer Institute; Goethe Univ.; Harvard Univ.; Karolinska Institute; King's College London; Michael J Fox Foundation; Rockefeller Univ.; Seoul National Univ.; Univ. of Oxford; Yale Univ.

Government & Other

NIH; Neurology Today; Gigatrust

CREATE AN INTEGRATED DATA SHARING APPROACH TO FRAME QUESTIONS ADDRESSING UNMET NEEDS

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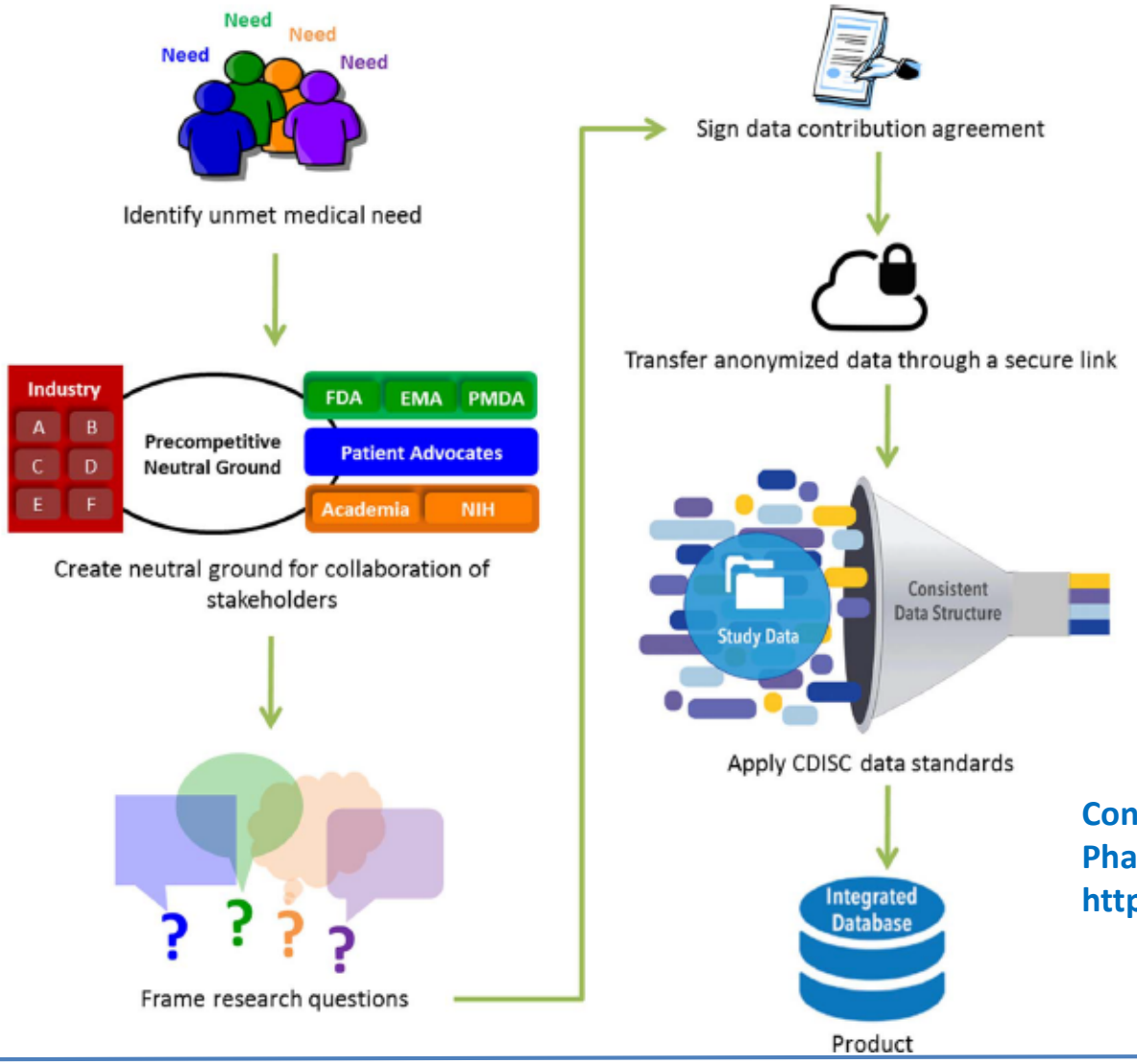

What changes can be seen in the pre-symptomatic stages of the disease?

Conrado, D.J., European Journal of Pharmaceutical Sciences (2017) http://dx.doi.org/10.2016/j.ejps.2017.06.035

KEY DATA PRINCIPLES

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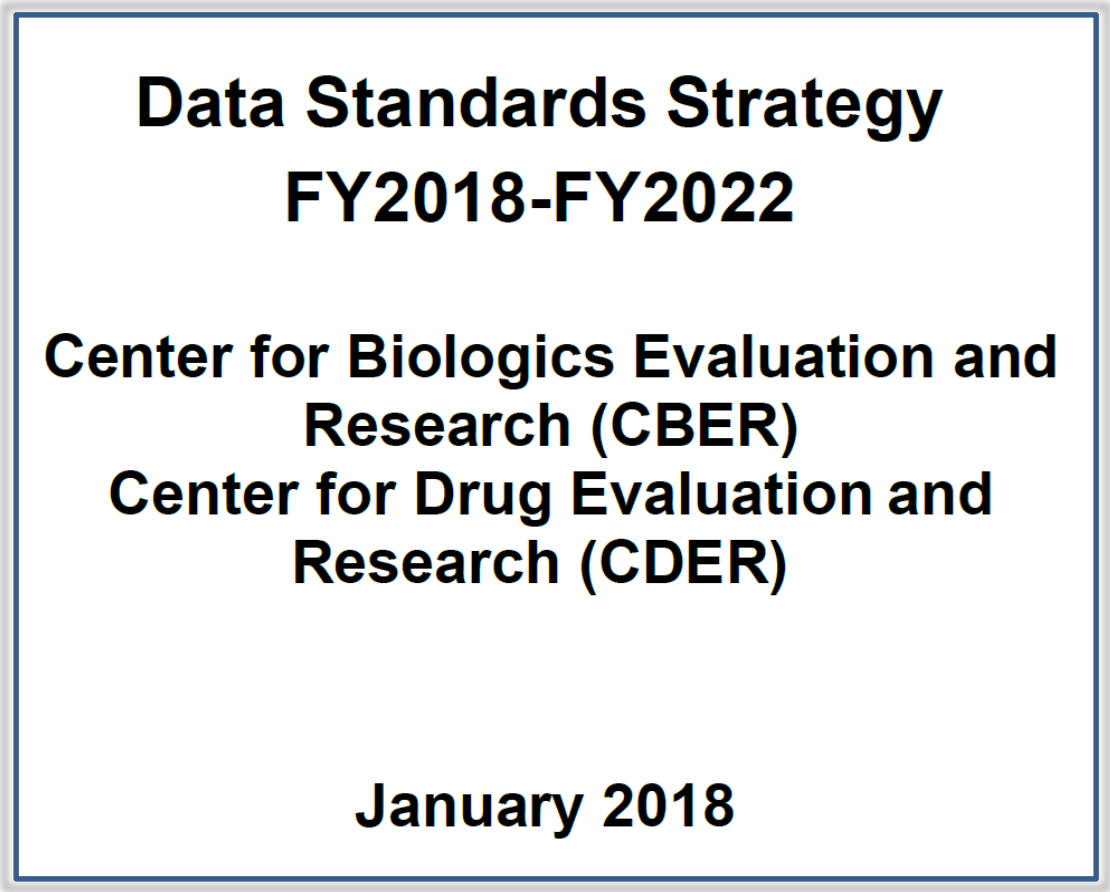
"F-A-I-R"

- Findable
- Accessible
- Interoperable
- Reusable



Link includes a video with Janet Woodcock:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm249979.htm?utm_campaign=CDER%20New%202%2F6&utm_medium=email&utm_source=Eloqua&elqTrackId=6fe706eedc0640aab77d7fca9e9a9277&elq=895d2651f88e431ca0cb8644f26cb542&elqaid=2342&elqat=1&elqCampaignId=1658

ACCELERATE DATA SHARING

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- Data sharing – especially from prevention trials [Informed Consent]
- Understanding of what matters most to patients and caregivers
- Data sharing from pilot Biometric Monitoring Device (BMD) studies

A proposed framework

Alzheimer's & Dementia 12 (2016) 631-632

Alzheimer's & Dementia

Collaboration for Alzheimer's Prevention: Principles to guide data and sample sharing in preclinical Alzheimer's disease trials

Stacie Weninger[a,*], Maria C. Carrillo[b,**], Billy Dunn[c], Paul S. Aisen[d], Randall J. Bateman[e], Joanne D. Kotz[a], Jessica B. Langbaum[f], Susan L. Mills[e], Eric M. Reiman[f], Reisa Sperling[g], Anna M. Santacruz[e], Pierre N. Tariot[f], Kathleen A. Welsh-Bohmer[h]

Collaboration for Alzheimer's Prevention

Facilitating data sharing as early **as possible**

- Where possible, standardized data acquisition techniques and assessments should be included to enhance the ability to compare data between trials.
- Measurement of multiple potential biomarkers should be included in trial designs to facilitate the identification of biomarkers of disease evolution and treatment response that could be used in future trials.
- Screening and prerandomization baseline data should be made available to the scientific community within 12 months of enrollment completion.
- **All study data should be made available to the scientific community after the earlier of either regulatory approval of the tested treatment or 18 months after the completion or early termination of the trial.**

Sharing of Data After Trial Completion

Trial	Data After Trial Completion	
	Analyses and sharing with collaborators	General availability (through approved data request)
DIAN-TU		
Sola	2019+ (timing may change w/ open label extension)	2020+ (timing may change w/ open label extension)
Gant	2019+ (timing may change w/ open label extension)	2020+ (timing may change w/ open label extension)
NexGen	Agree to adhere to principles	Agree to adhere to principles
API ADAD Colombia	Agree to adhere to principles (~2023+)	Data will be shared following the earlier of (a) approval by the FDA for commercialization of the Study Drug for any indication or (b) 18 months following completion or early termination of the Study.
API Generation (APOE4 HM) Study	Agree to adhere to principles (~2024+)	Data will be shared following the earlier of: (a) a Joint Publication, (b) the FDA has approved for commercialization the Study Drug to which the proposed presentation or publication relates, or (c) eighteen (18) months have elapsed following the completion or early termination of the Study.

INFORMED CONSENT IS CRITICAL

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Alzheimer's & Dementia: Translational Research & Clinical Interventions 3 (2017) 536-541

Alzheimer's & Dementia

Perspective

Concise informed consent to increase data and biospecimen access may accelerate innovative Alzheimer's disease treatments

Ann M. Hake[a], Penny A. Dacks[b], Stephen P. Arnerić[c,*], CAMD ICF working group[1]

[a]*Eli Lilly and Company, Indianapolis, IN, USA*
[b]*Alzheimer Drug Discovery Foundation, New York City, NY, USA*
[c]*Coalition Against Major Diseases (CAMD), Tucson, AZ, USA*

TYPES OF BIOMARKERS & DRUG DEVELOPMENT TOOLS

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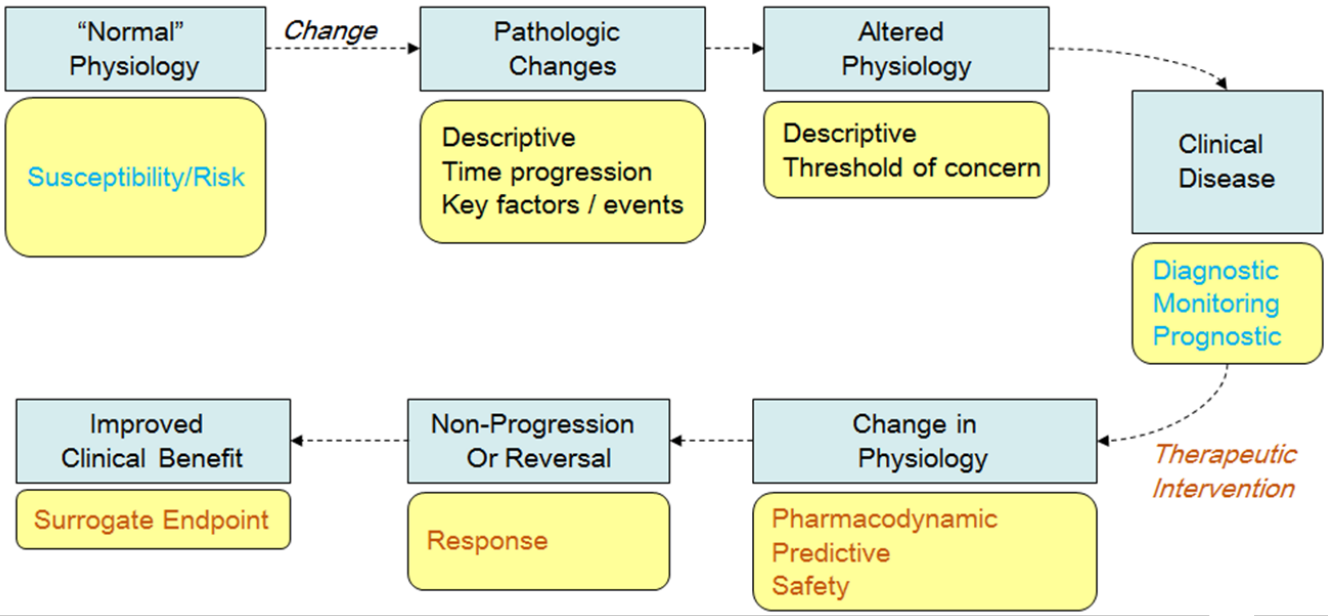
"Fit for Purpose": BEST Biomarker Classes in Perspective

FDA



NCBI NLM NIH. BEST (Biomarkers, EndpointS, and other Tools) Resource. NCBI Bookshelf, 2016 *Available from*: https://www.ncbi.nlm.nih.gov/books/NBK338448

NEUROFILAMENT LIGHT (NfL) AND BIOMETRIC MONITORING DEVICES: POTENTIAL SURROGATE ENDPOINTS?

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BIOMARKER TERMINOLOGY: SPEAKING THE SAME LANGUAGE

Shashi Amur, Ph.D.
Scientific Lead, Biomarker Qualification Program, Office of Translational Sciences, Center for Drug Evaluation and Research, FDA

FDA

SURROGATE ENDPOINT

An endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives.

Validated Surrogate Endpoint	
Supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate predicts a clinical benefit; therefore, such endpoints can be used to support traditional approval without the need for additional efficacy information.	**Example: Hemoglobin A1C reduction in diabetes clinical trials**

Reasonably Likely Surrogate Endpoint	
Supported by clear mechanistic and/or epidemiologic rationale but with insufficient clinical data to show that it is a validated surrogate endpoint; such endpoints can be used for accelerated approval for drugs or expedited access for medical devices.	**Example: Radiographic evidence of tumor shrinkage in some cancer types**

Candidate Surrogate Endpoint
A surrogate under evaluation for its ability to predict clinical benefit.

WHAT ARE THE COMMON AND DIFFERENTIATING FEATURES?

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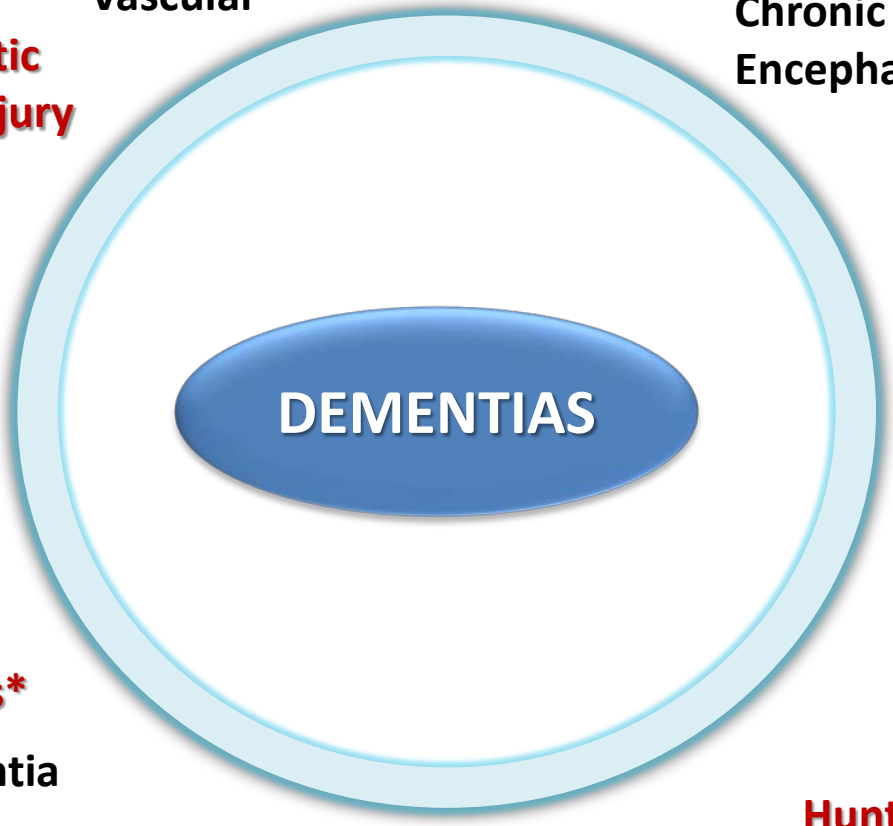
NfL Studies:



Alzheimer Disease
Vascular
Chronic Traumatic Encephalopathy (CTE)
Traumatic Brain Injury
Creutzfeldt-Jakob Disease
Schizophrenia
Parkinson Disease
Depression
Posterior Cortical Atrophy
Down Syndrome
Normal Pressure Hydrocephalus
Epilepsy
Multiple Sclerosis*
Frontal Temporal Dementia
Mixed Dementia
Huntington Disease
Mild Cognitive Impairment
Korsakoff Syndrome
Lewy Body Dementia

http://www.alz.org/dementia/types-of-dementia.asp

DIGITAL DRUG DEVELOPMENT TOOLS

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Qualifying Biometric Monitoring Devices (BMDs) for spec

Data (s
collected
that meas
r

FDA approves pill with sensor that digitally tracks if patients have ingested their medication

New tool for patients taking Abilify

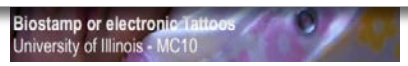
f SHARE TWEET in

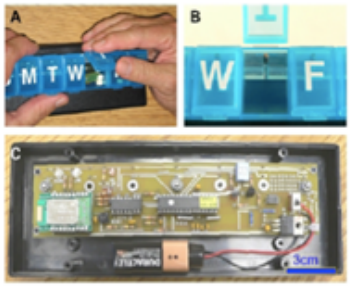
For Immediate Release

Summary

Release

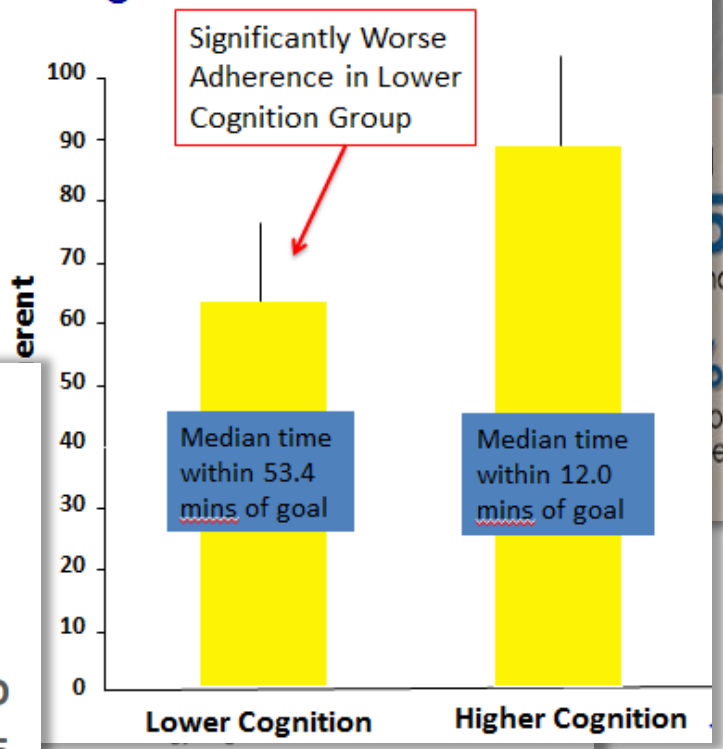
THE FUTURE OF SENSORS





- Adherence assessed continuously x 5 wks with MedTracker taking a

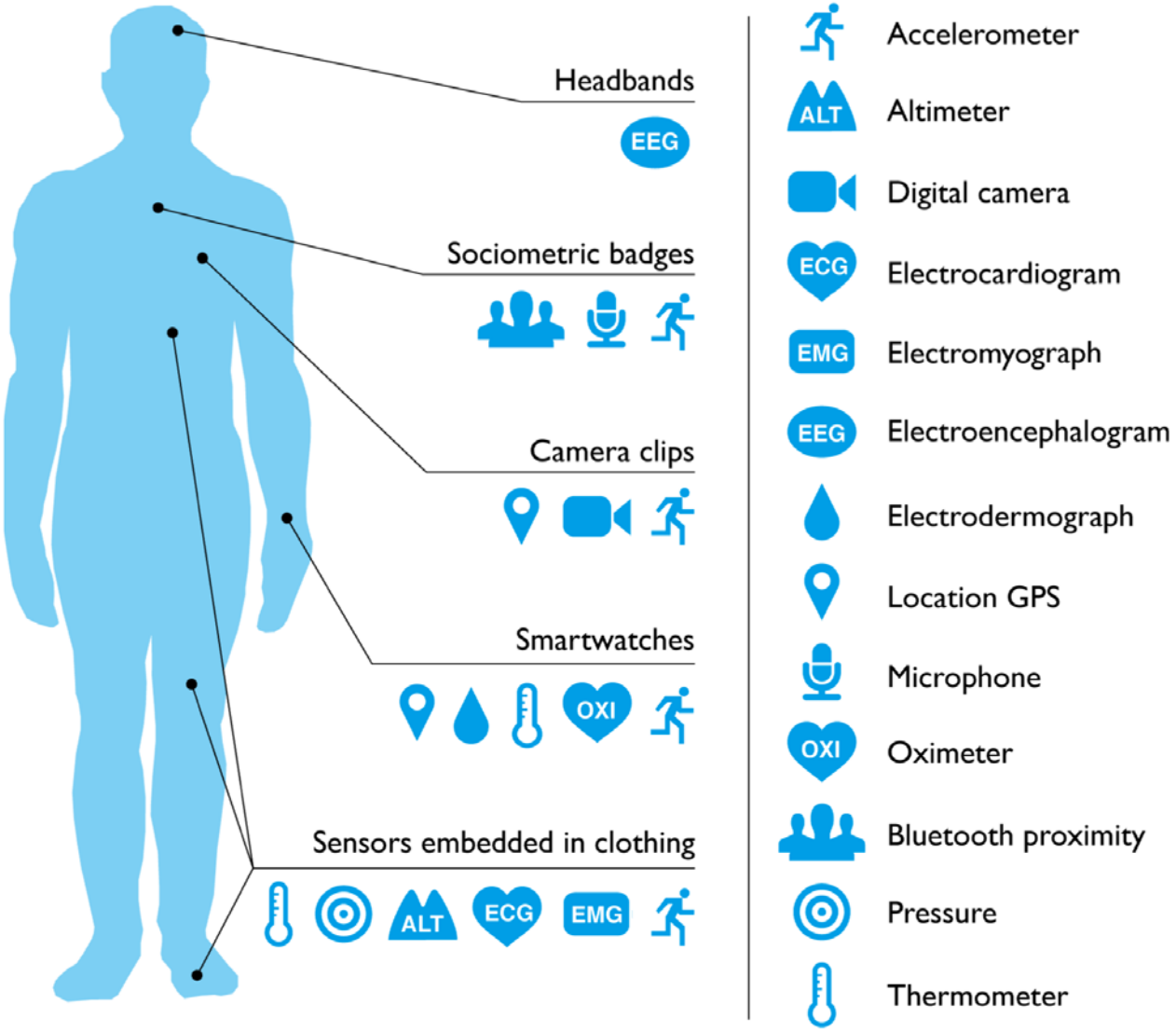
Every Day Cognition:
Medication adherence as a measure of cognitive function



'Drugs don't work in patients who don't take them'

\- C. Everett Koop, MD
Former US Surgeon General, 1985

COLLECTING REAL WORLD DATA



The Rise of Consumer Health Wearables: Promises and Barriers.
Piwek L, Ellis DA, Andrews S, Joinson A
PLoS Med 13(2): e1001953. pmed.1001953, Feb 2016

Careful data standardization, aggregation, and quantitative modeling will be required to transform RWD to RWE

WHY CONTINOUS MEASUREMENT IS RELEVANT AND CRITICAL!

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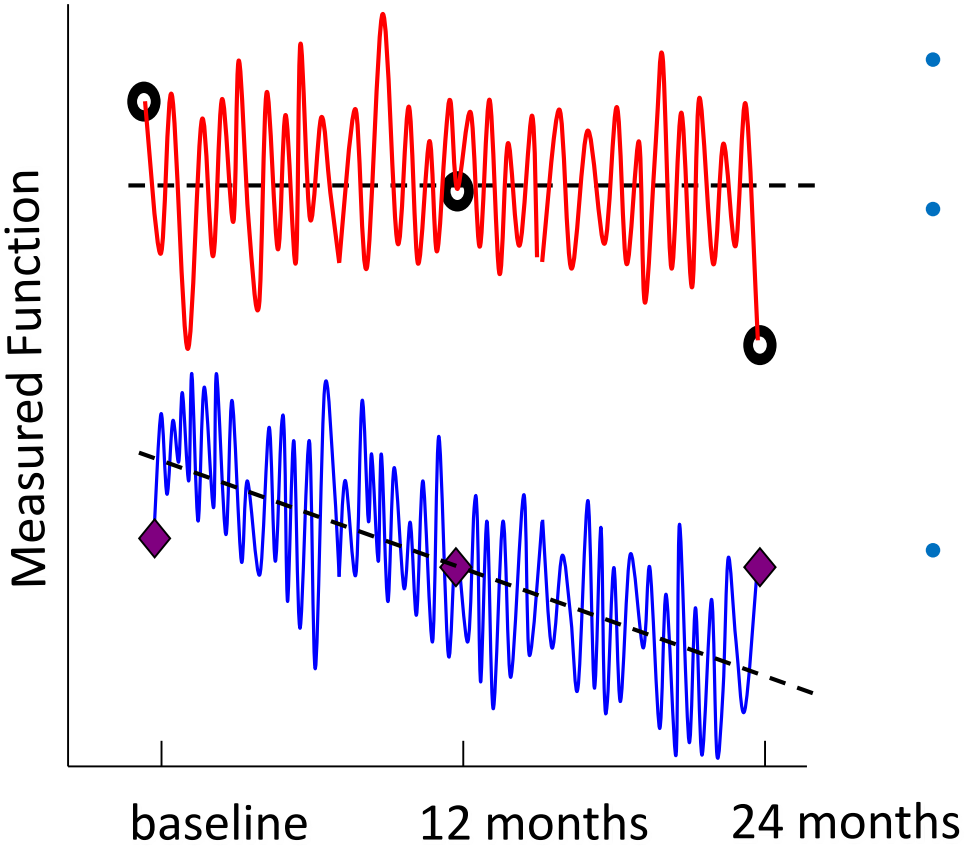
Which patient is rapidly declining?



- These data highlight the challenge of infrequent cross-sectional assessments
- Understanding vector trends in individual continuous performance would be more reflective of true long-term trends in performance/health maintenance
- Infrequent 'snapshots' of day-to-day performance of people, like the stock market, can be misleading

Courtesy of Dr. Jeff Kaye

OHSU ORCATECH

BIOMETRIC MONITORING DEVICES (BMDs)

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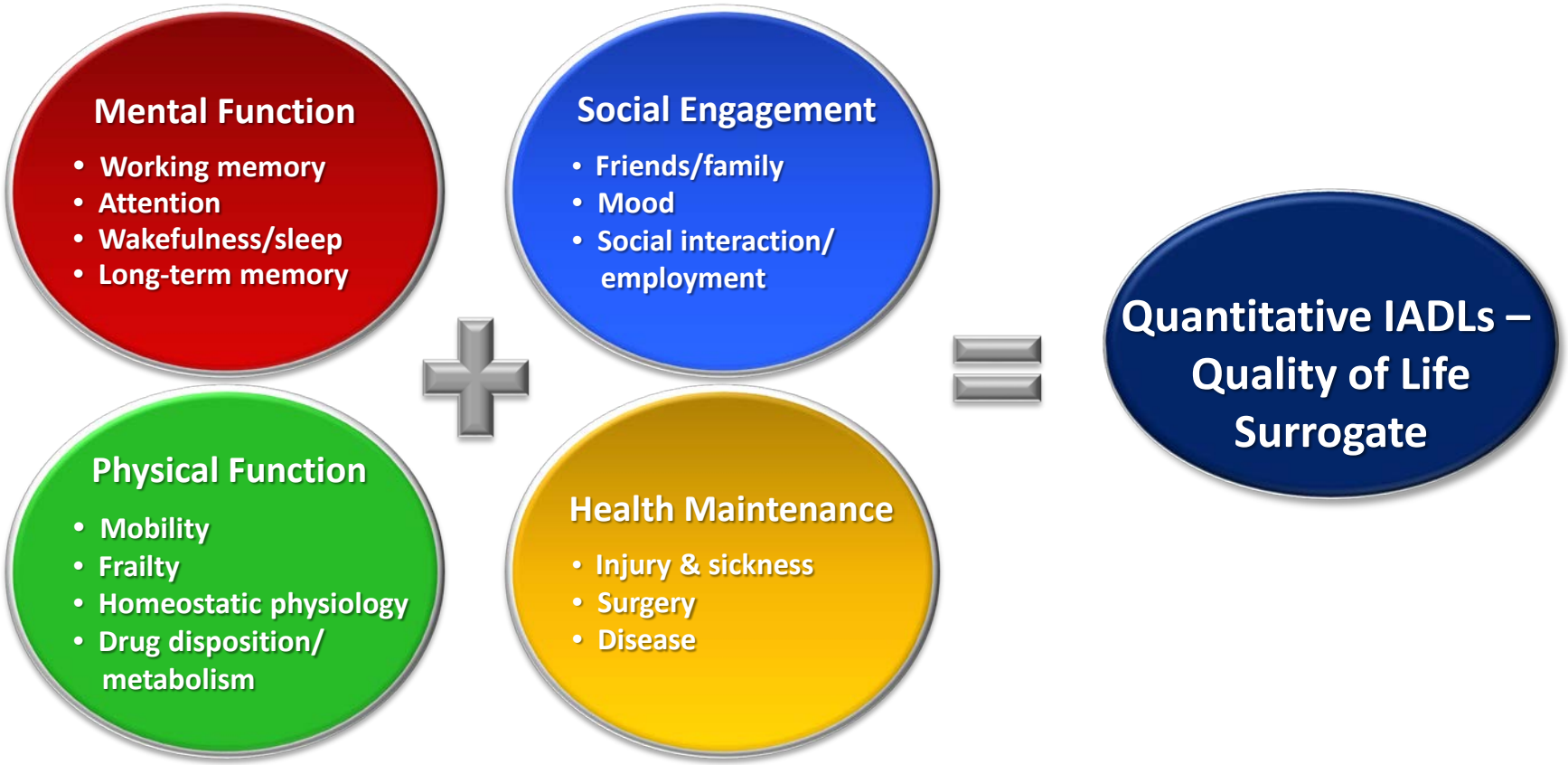
Measuring 'Signs' Related to Instrumental Activities of daily Living

BMDs have the potential to measure signs related to all domains of function comprising what is viewed as Instrumental Activities of Daily Living (IADL)



TRANSFORMING CLINICAL TRIALS WITH HIGH FREQUENCY, OBJECTIVE, CONTINUOUS DATA

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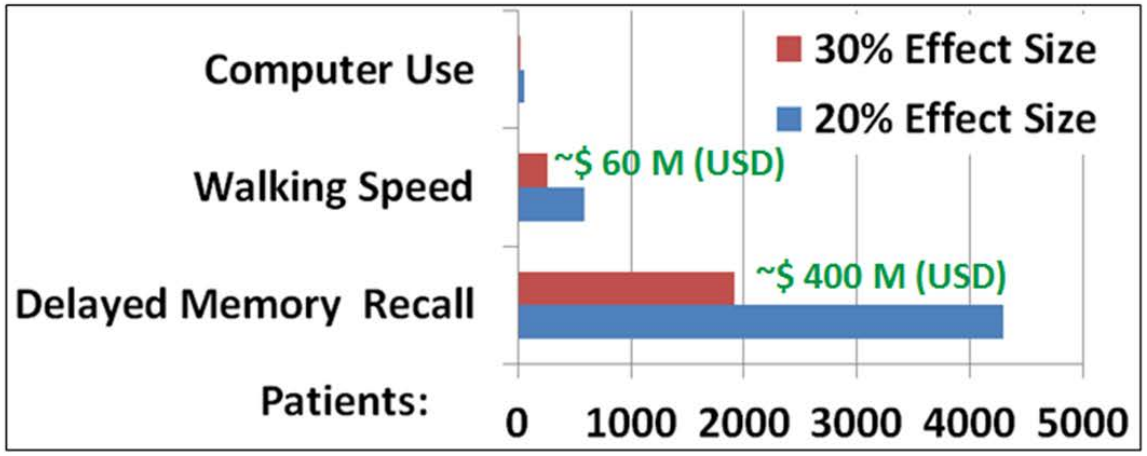

TRIAL COSTS
(3 yr. Prevention Study)
- ~$ 1 M/5 patients

Dodge *et al.*, PLoS One, 2015

ORCATECH

MCI Prevention Trial – sample size estimates

- Reduces required sample size and/or time to identify meaningful change
- Reduces exposure to harm (fewer needed/fewer exposed)
- Provides the opportunity to substantially improve efficiency and inform go/no-go decisions of trials
- **Dramatically reduces recruitment time and costs**
- **>80% Cost Savings of current approaches**

WE MUST WORK COLLECTIVELY TO BUILD A SUSTAINABLE ECOSYSTEM

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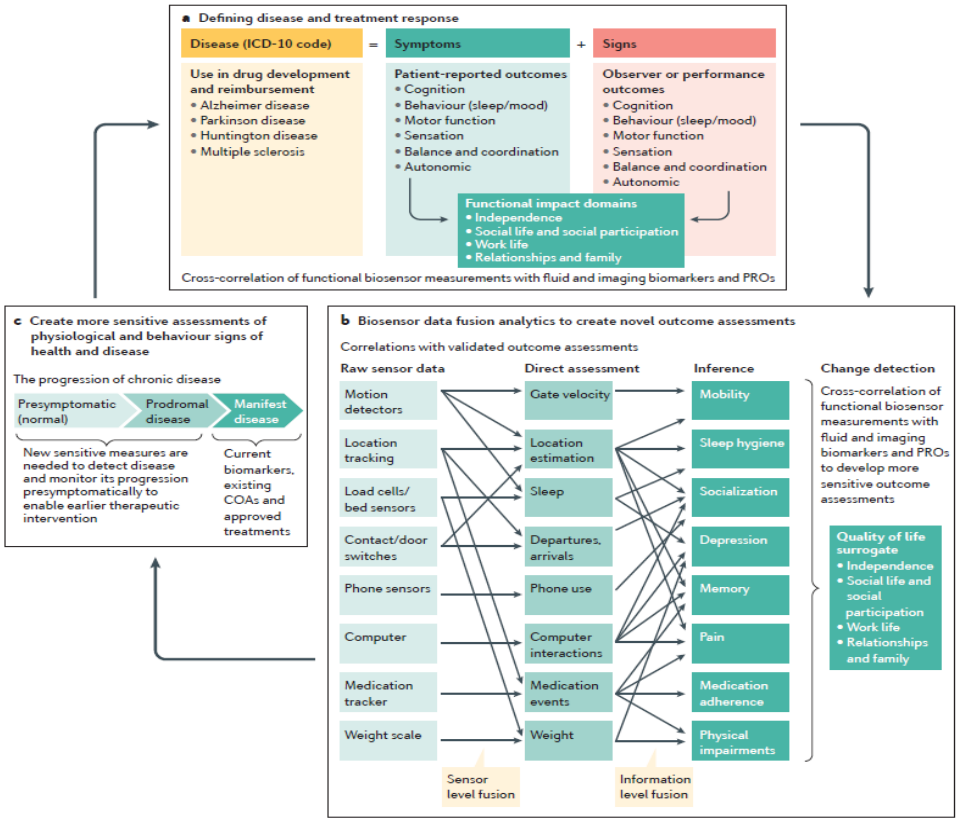
CORRESPONDENCE

Biometric monitoring devices for assessing end points in clinical trials: developing an ecosystem

Stephen P. Arnerić, Jesse M. Cedarbaum, Sean Khozin, Spyros Papapetropoulos, Derek L. Hill, Michael Ropacki, Jane Rhodes, Penny A. Dacks, Lynn D. Hudson, Mark Forrest Gordon, Volker D. Kern, Klaus Romero, George Vradenburg, Rhoda Au, Daniel R. Karlin, Maurizio F. Facheris, Cheryl J. Fitzer-Attas, Ottavio V. Vitolo, Jian Wang, Bradley M. Miller and Jeffrey A. Kaye

Nature Reviews Drug Discovery (online September 22, 2017)

http://rdcu.be/v5bS



VISION TO EXPAND A GLOBAL AD DATA REPOSITORY

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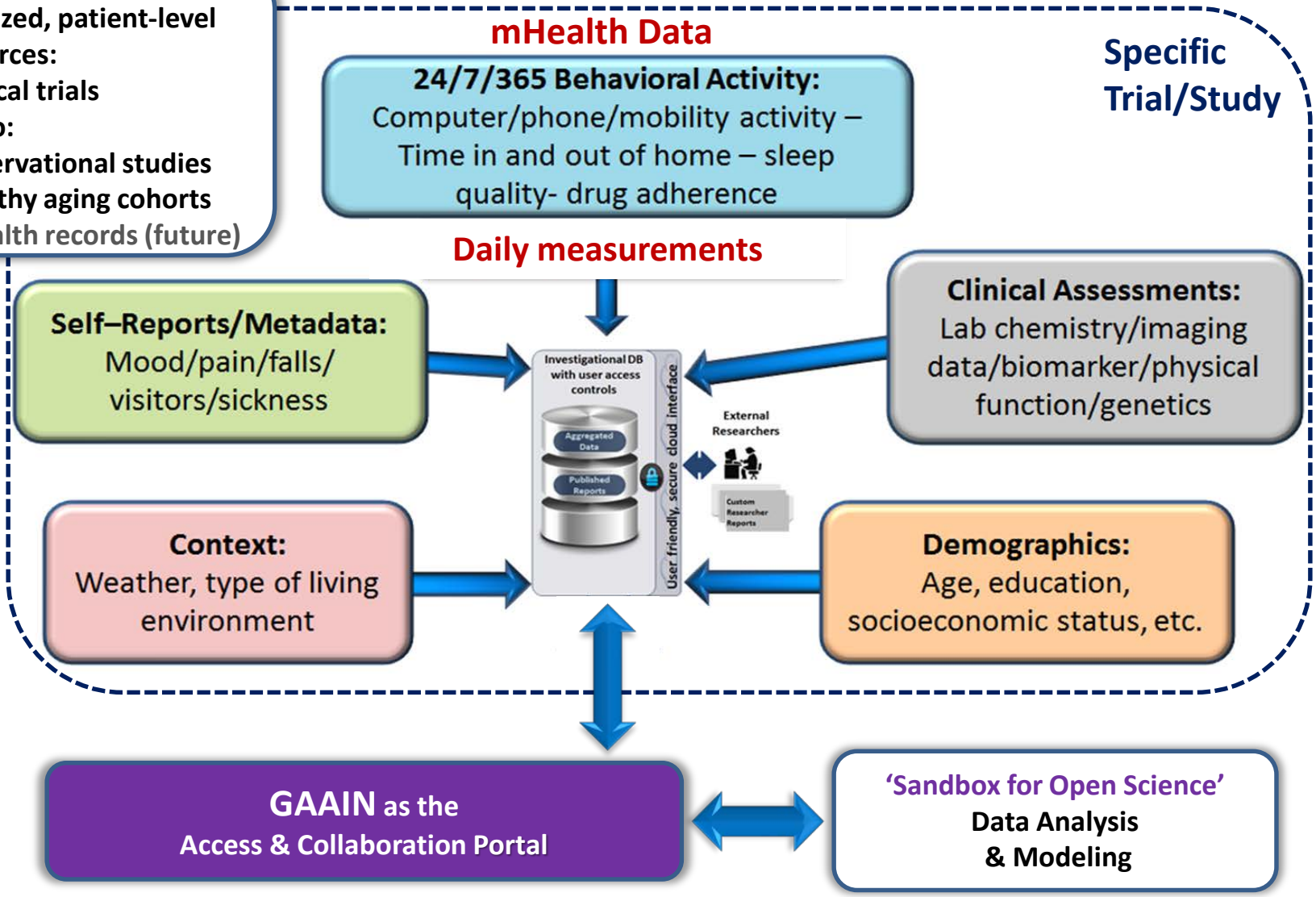
Actionable, standardized, anonymized, patient-level data sources:
- **Clinical trials**

Linked to:
- **Observational studies**
- **Healthy aging cohorts**
- **eHealth records (future)**



CPAD MEMBERS & CONTRIBUTORS

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Pharmaceutical Industry

- AbbVie Inc.
- Biogen
- Boehringer Ingelheim Pharmaceuticals, Inc.
- Eisai
- Eli Lilly and Company
- Roche/ Genentech
- Johnson & Johnson Pharmaceutical Research & Development, LLC
- Merck, Sharp & Dohme Corp.
- Novartis Pharmaceutical
- Pfizer, Inc.
- Takeda

Government and Regulatory Agencies

- European Medicines Agency (EMA)
- National Institute of Neurological Disorders and Stroke (NINDS)
- National Institute on Aging (NIA)
- U.S. Food and Drug Administration (FDA)
- National Institutes of Health (NIH)

Non-profit Research Organizations

- Alzheimer's Association
- UsAgainstAlzheimer's Network
- Alzheimer's Research UK
- Alzheimer's Drug Discovery Foundation
- CHDI Foundation
- ARIZONA ALZHEIMER'S CONSORTIUM

Grant number 1U18FD005320 from the U.S. Food and Drug Administration's Critical Path Public Private Partnerships Grant

C-Path Staff Advancing CPAD

Stephen P Arnerić
Executive Director

Volker D Kern
Senior Project Manager

Nicky Kuhl
Project Coordinator

Klaus Romero
Director of Clinical Pharmacology and Quantitative Medicine

Daniela Conrado
Associate Director of Quantitative Medicine

Jackson Burton
Associate Program Director, Quantitative Medicine

Robert Stafford
Senior Data Specialist, Data Programming Team Lead

All other C-Path Support Staff.....

GLOBAL AD DATA REPOSITORY

CPAD
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Actionable, standardized, anonymized, patient-level data sources:

- **Clinical trials**
- **Observational studies**
- **Healthy aging cohorts**
- **eHealth records**

mHealth Data

Specific Trial/Study

24/7/365 Behavioral Activity:
Computer/phone/mobility activity – Time in and out of home – sleep quality- drug adherence

49,992,645 observations

Self–Reports/Metadata:
Mood/pain/falls/ visitors/sickness

Clinical Assessments:
Lab chemistry/imaging data/biomarker/physical function/genetics

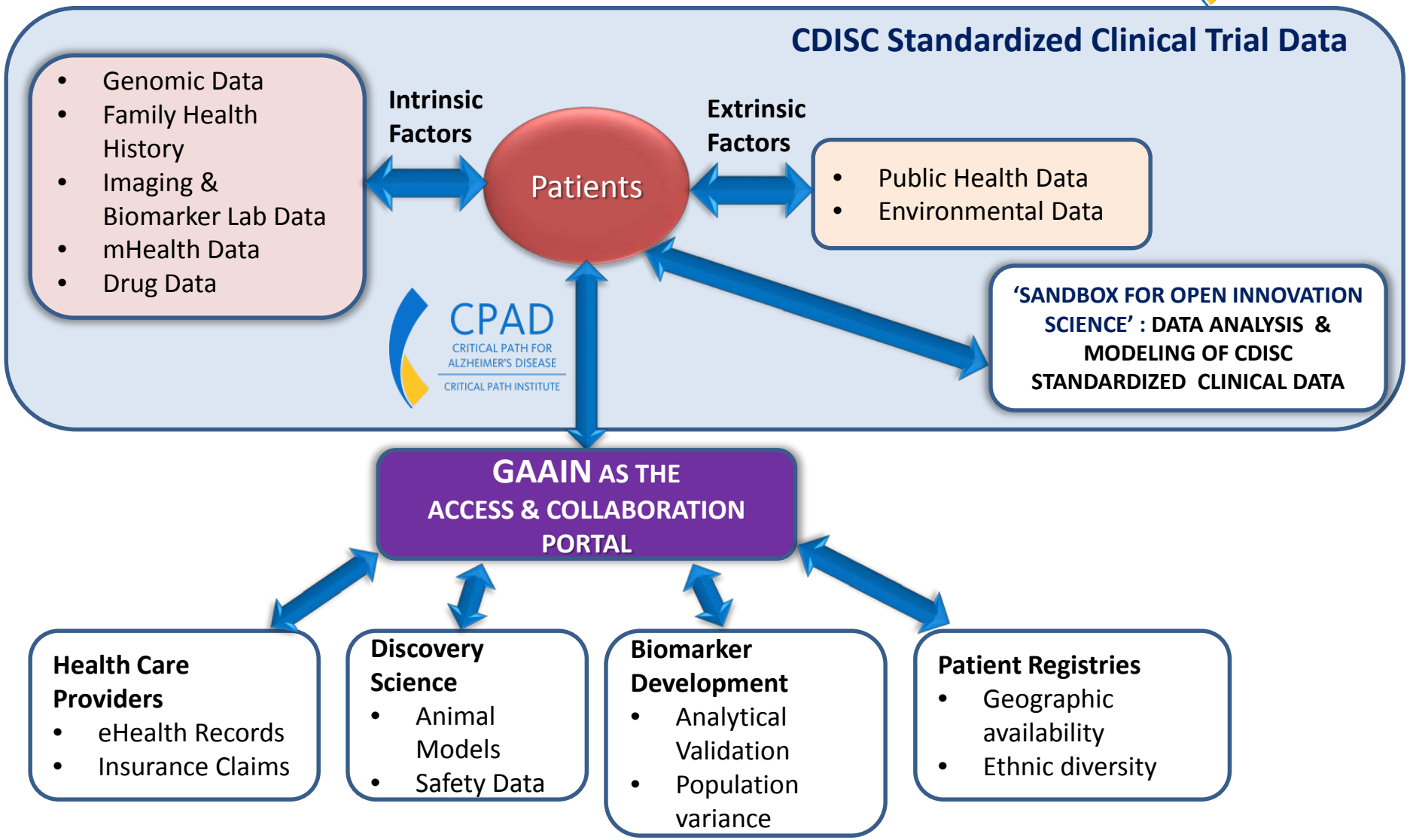
Context:
Weather, type of living environment

Demographics:
Age, education, socioeconomic status, etc.

GAAIN AS THE ACCESS & COLLABORATION PORTAL

'SANDBOX FOR OPEN SCIENCE' DATA ANALYSIS & MODELING

CREATING AN OPEN INNOVATION ECO-SYSTEM



THE VISION:
END-TO-END MODEL OF ALZHEIMER DISEASE

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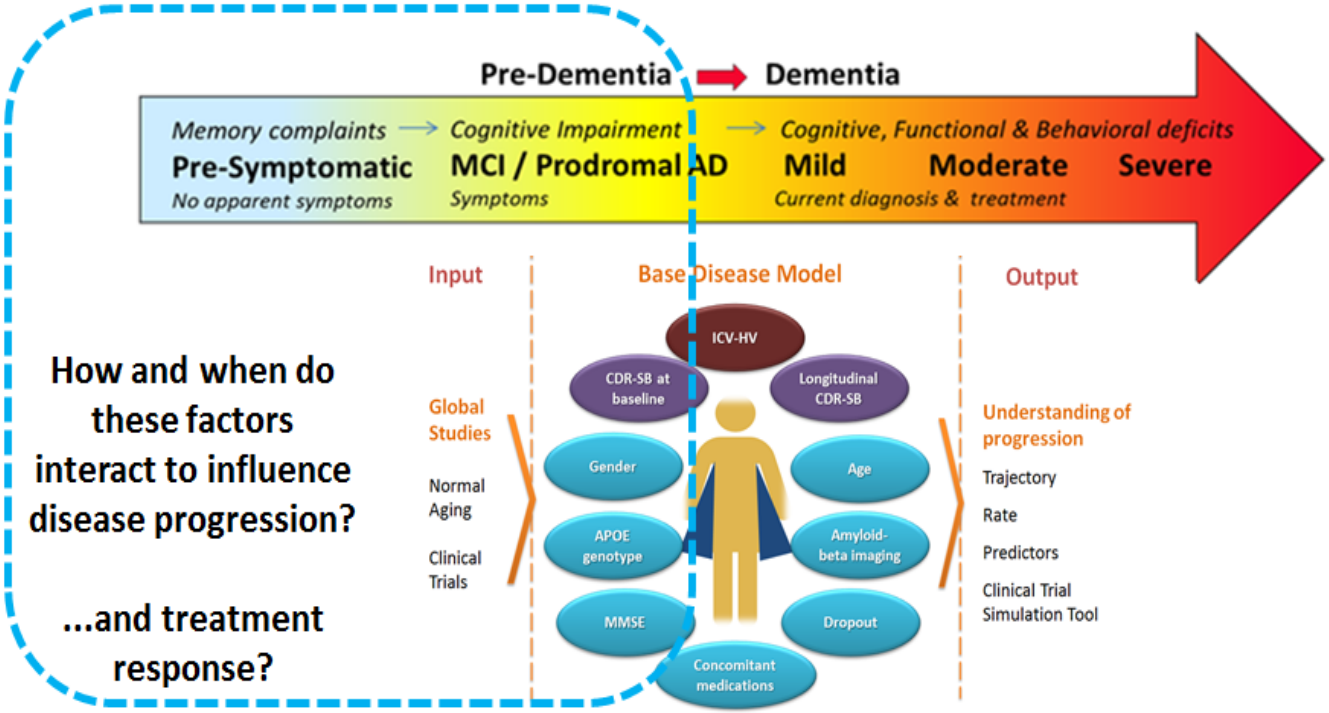
CRITICAL PATH INSTITUTE



Other Relevant Sources of Variability to Evaluate

Genetics	Life Events	Co-Morbid Infections [active /latent]	Co-Morbid Disease	Biomarkers	Outcome Assessments
• Protective • Promoting • Race/ Ethnicity	• Trauma • Surgery • Nutrition • Education	• Bacterial • Viral • Parasites • Fungal	• Depression • Diabetes • Cardiovascular • Cancer • Inflammation • Etc.	• Fluid • PET Imaging • EEG • Evoked responses • Etc.	• PROs • Digital/ wearables • IADLs • Etc.

IMPAIRED FUNCTION & COGNITION IS PROMINENT ACROSS NEURODEGERATIVE DISEASES

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Functional Impact:

- Social life and social participation
- Work/life
- Relationships and family
- Independence

Alzheimer disease	Parkinson disease	Multiple Sclerosis	Huntington disease
Symptoms & Signs	**Symptoms & Signs**	**Symptoms & Signs**	**Symptoms & Signs**
• Gait slowed	• Walking and gait impairment	• Walking impairment	• Walking impairment
• Sleeping changes	• Sleeping impaired	• Sleeping impaired	• Sleeping problems
• Cognitive impairments	• Cognitive impairments	• Cognitive impairments	• Cognitive impairments
• Dizziness/vertigo	• Dizziness/vertigo	• Dizziness/vertigo	• Dizziness/vertigo
• Depression	• Depression	• Depression	• Depression
• Speech problems	• Spasticity	• Pain	• Irritability
• Swallowing (advanced stages)	• Tremor	• Sexual dysfunction	• Pain
• Pain	• Pain	• Fatigue	• Fatigue
	• Bowel/bladder problems	• Spasticity	• Spasticity
	• Fatigue	• Lower and upper extremity impairments	• Upper and lower extremity impairments
	• Speech problems	• Speech problems	• Speech problems

THREE KINDS OF CLINICAL STUDIES

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- Meets all pre-specified criterion of success → **Positive Study** leads to Product Approval
- Does not meet pre-specified criterion of success → **Negative Study** does not support Product Approval – but data shared to augment disease understanding
- Does not meet pre-specified criterion of success → **Failed Study** does not support Product Approval – data not shared to augment disease understanding

‘It takes a village to advance science and healthcare’ - Janet Woodcock, Director, CDER, FDA

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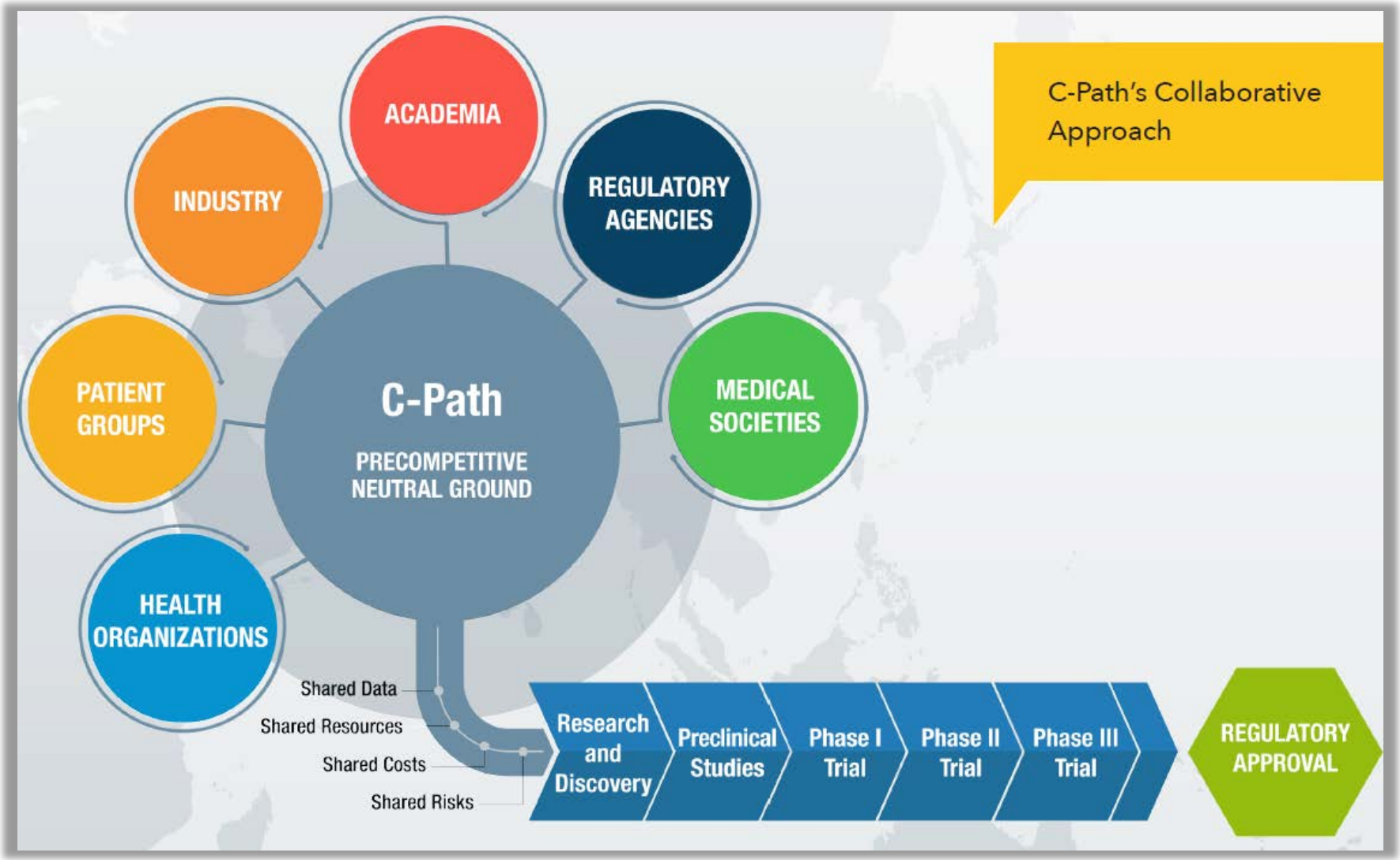
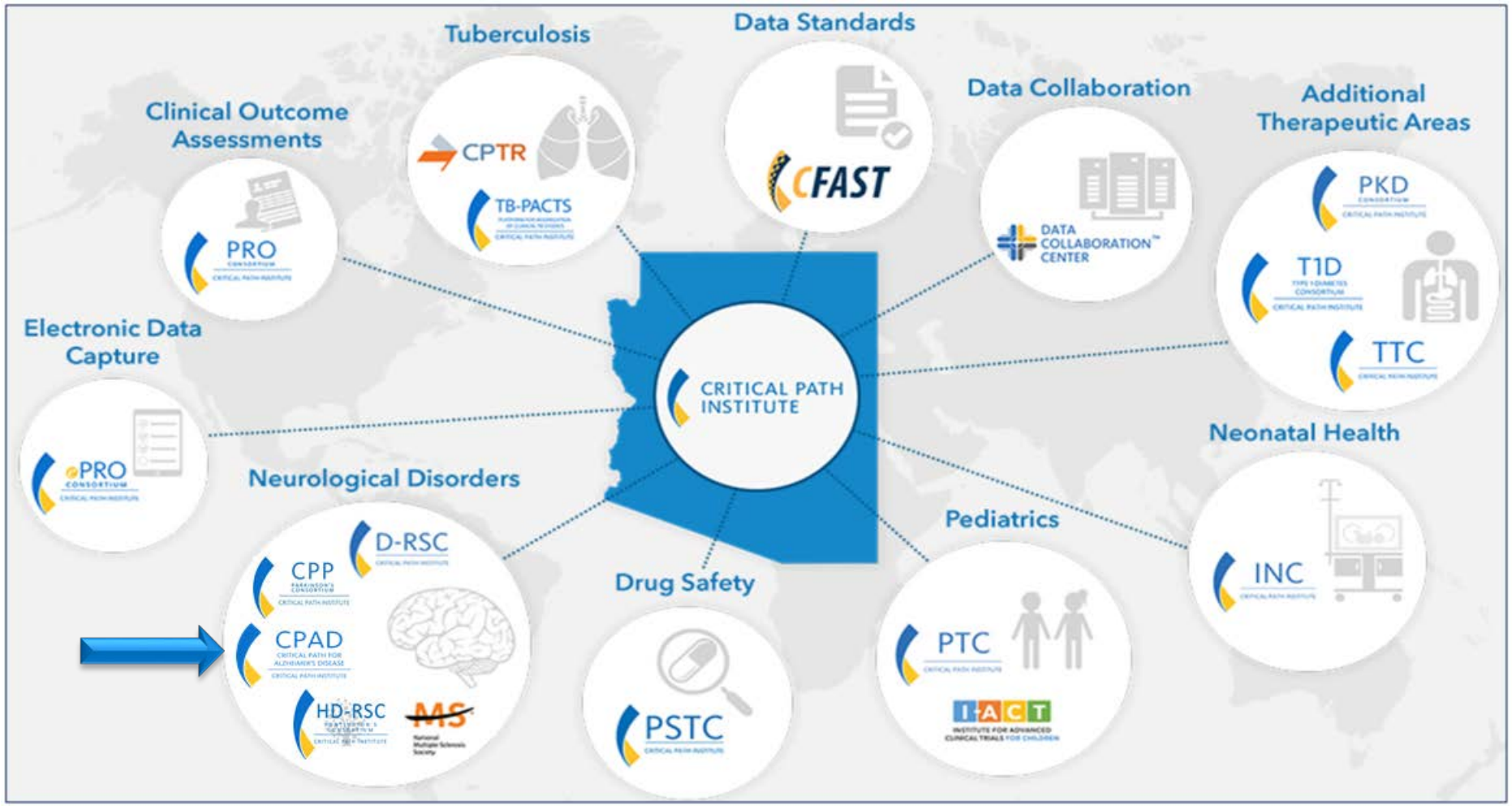


CRITICAL PATH INSTITUTE

Fifteen global consortia collaborating with 1,450+ scientists and 84 organizations

CRITICAL PATH INSTITUTE
collaborate · innovate · accelerate



FOCUS: Data standards; clinical trial simulation tools from actionable data, disease progression models; biomarkers; clinical outcome assessment instruments

C-PATH ONLINE DATA REPOSITORY (CODR) DATABASES

CRITICAL PATH INSTITUTE
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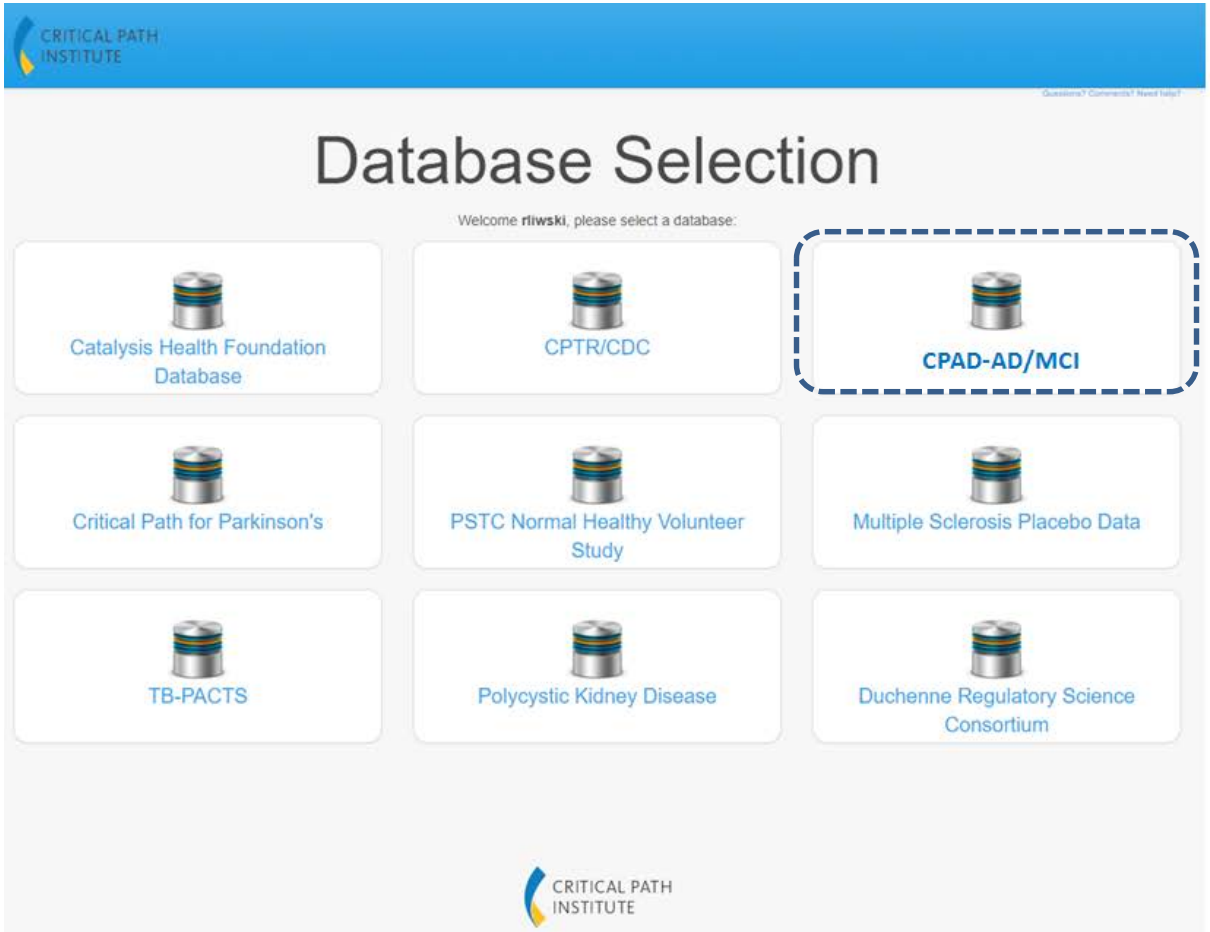

- ✓ Enterprise Class Data Platform
- ✓ CDISC-Based DB Schema
- ✓ Curated, Anonymized, Aggregated Data
- ✓ Data Source Anonymity
- ✓ Secure, Multi-Tiered Access Control
- ✓ Fully ACID Compliant
  - ✓ Atomicity
  - ✓ Consistency
  - ✓ Isolation
  - ✓ Durability

C-PATH CLINICAL DATABASE: NUMBER OF EXTERNALLY-SHARED AD STUDIES

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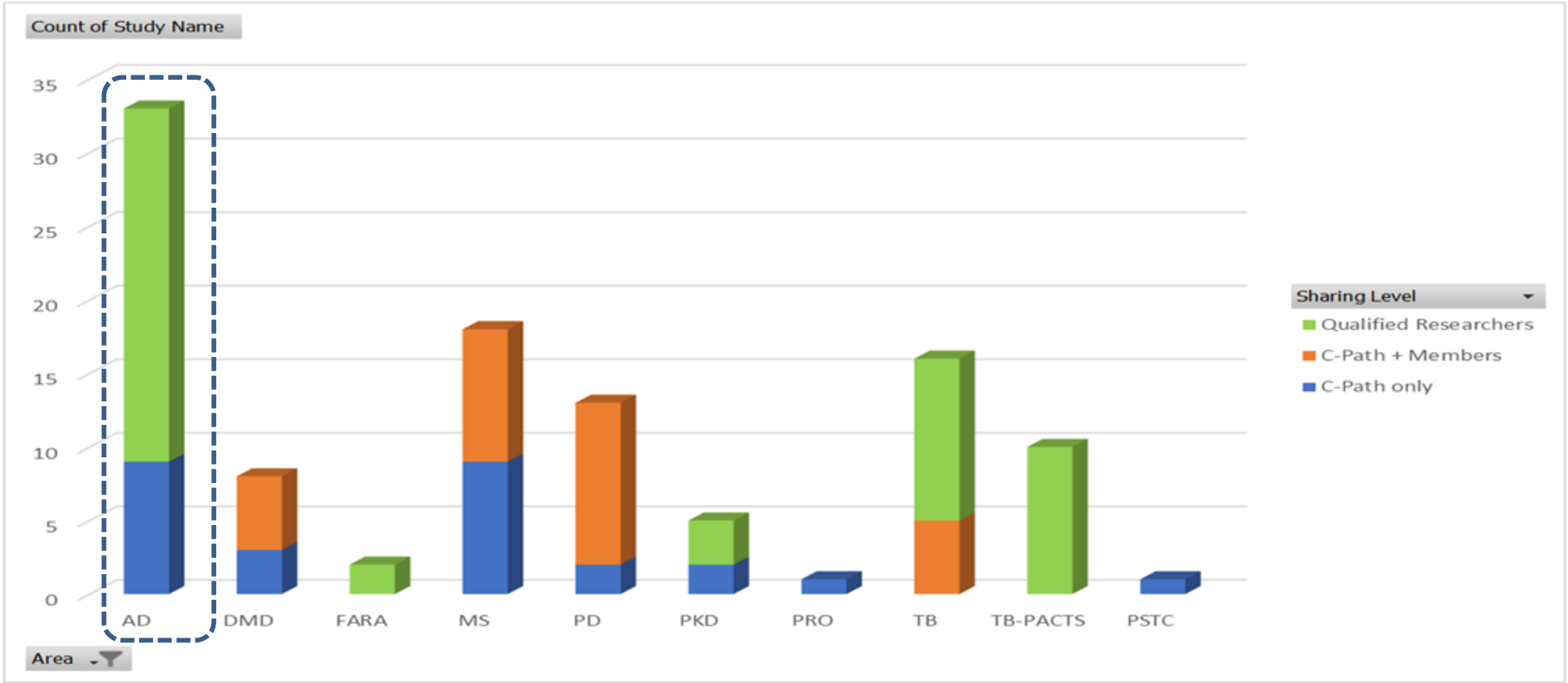

Sharing Scope	# Studies by Database										
	AD	DMD	FARA	MS	PD	PKD	PRO	TB	TB-PACTS	PSTC	**Grand Total**
C-Path Internal Use Only	9	3		9	2	2	1			1	27
C-Path + Consortia Members		5		9	11			5			30
External	24		2			3		11	10		50
SubTotal	**33**	**8**	**2**	**18**	**13**	**5**	**1**	**16**	**10**	**1**	**107**

CPAD DEVELOPS REGULATORY-ENDORSED TOOLS TO OPTIMIZE DRUG DEVELOPMENT IN AD

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Why? / What?

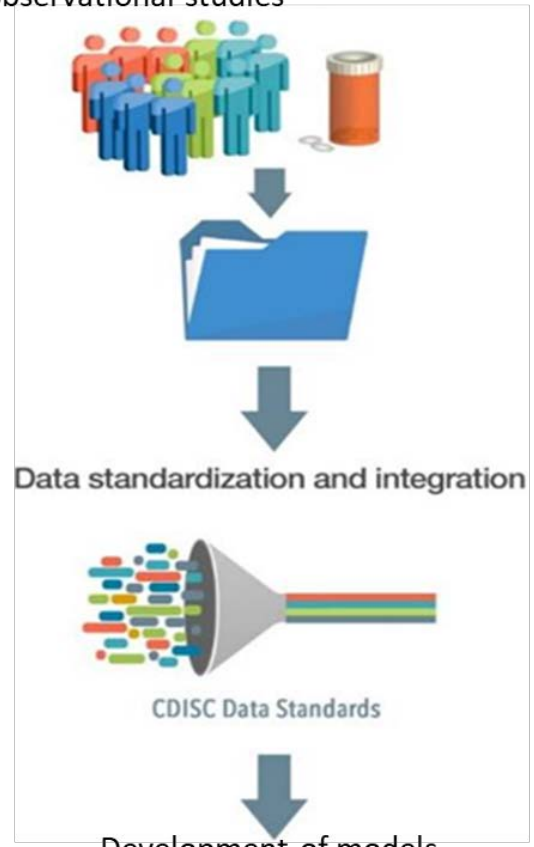
- To understand disease progression rates and responses to treatments, as these can vary significantly across different patients
- Advance Drug Development Tools

Who?

Key stakeholders: Patients, Pharma Companies, Regulators, Patient-Advocacy Organizations, Academics, Government Agencies

How?

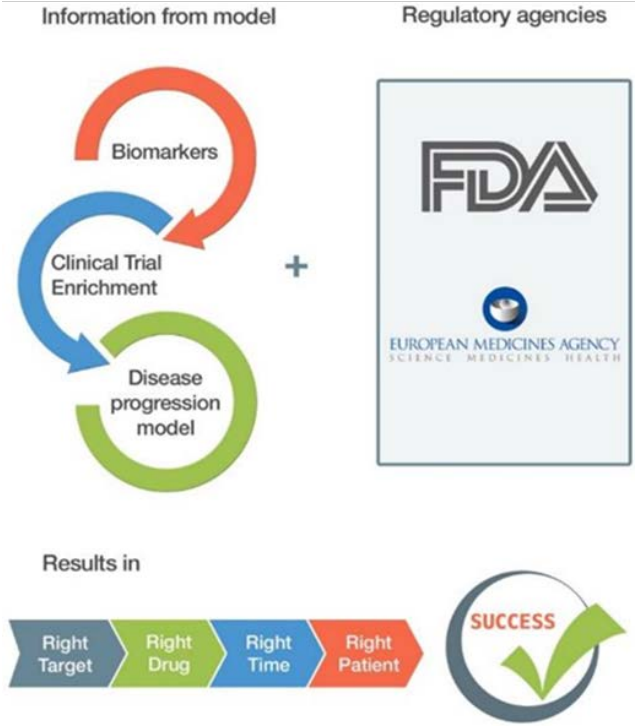
Integrate anonymized patient-level data from past clinical trials and longitudinal observational studies



Development of models relating key covariates over time

IMPACT

- **Actionable data/models to inform optimal trial design**
- **Improved trial efficiency, and accelerated delivery of innovative treatments to the right patients**



CPAD's KEY MILESTONES
[previously known as Coalition Against Major Diseases]

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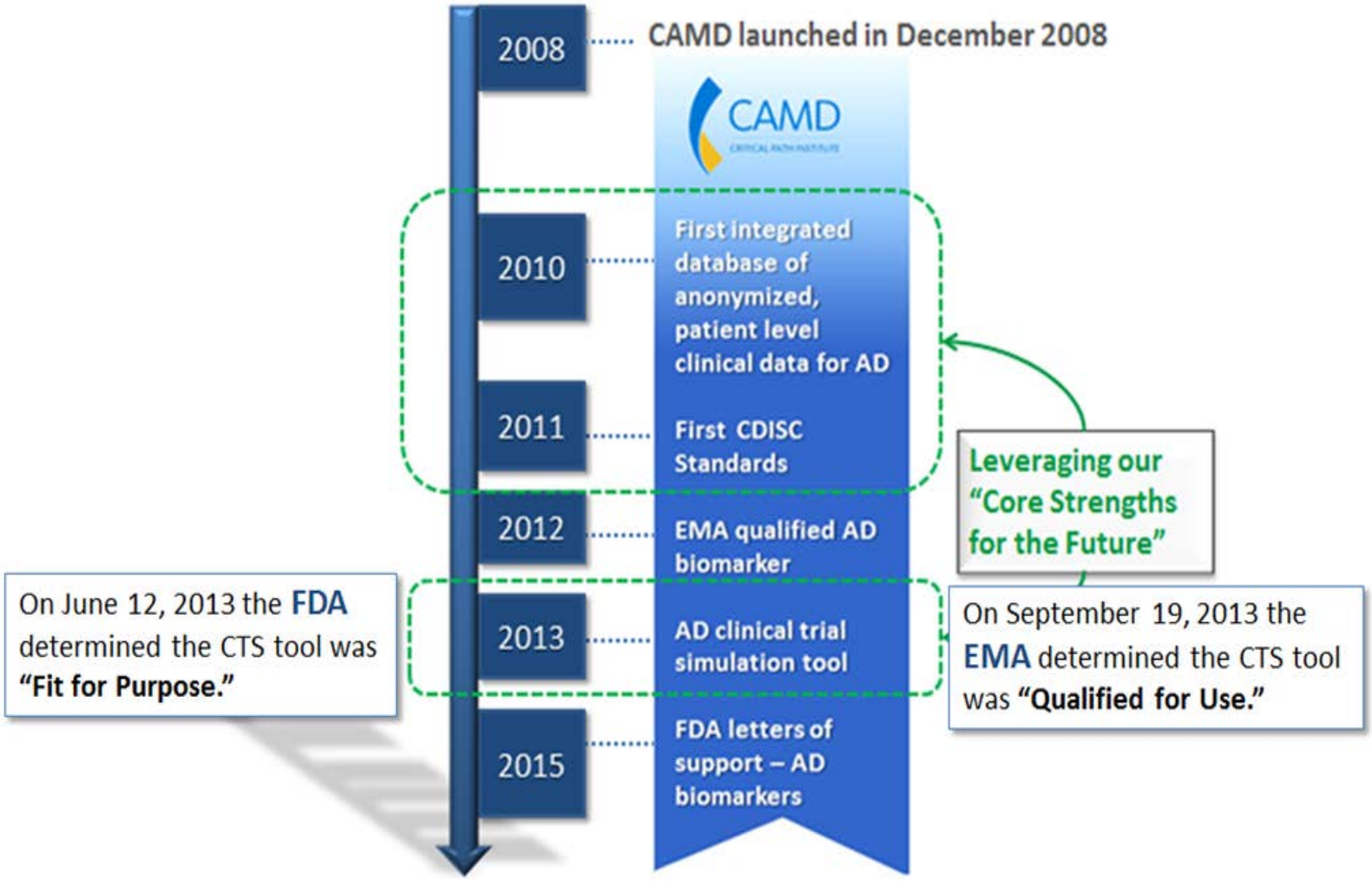
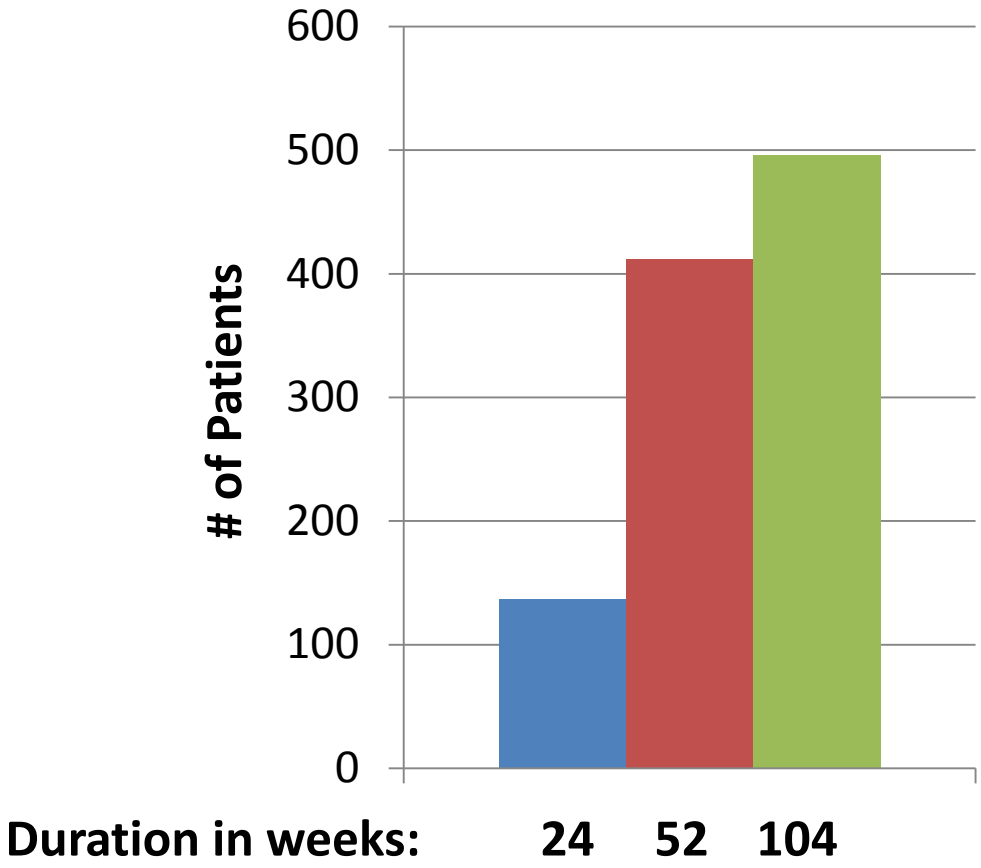


MCI STUDIES IN SHARED CPAD DATABASE



MILD-TO-MODERATE STUDIES IN SHARED CPAD DATABASE

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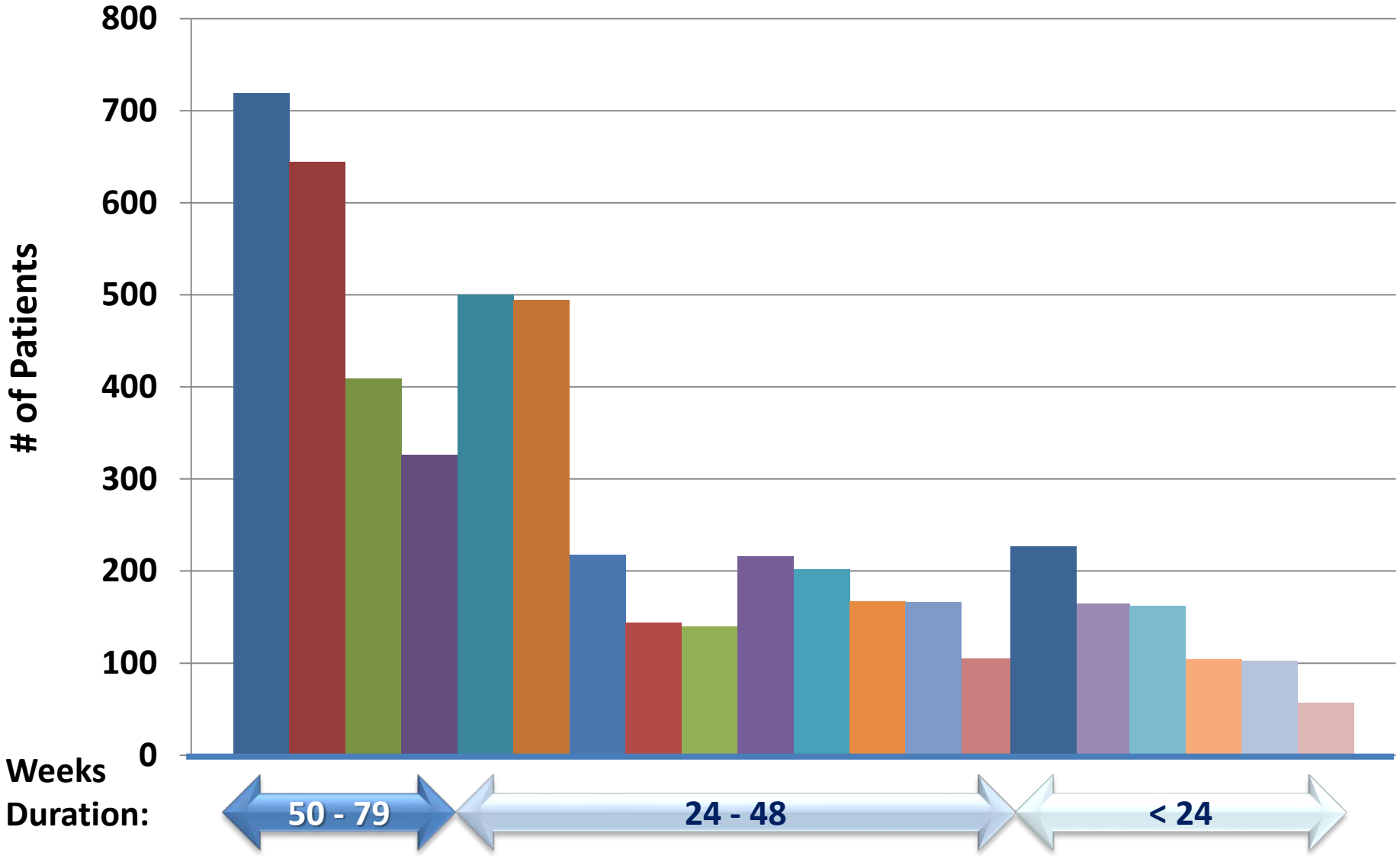
CRITICAL PATH INSTITUTE



AD/COGNITION LANDSCAPE:

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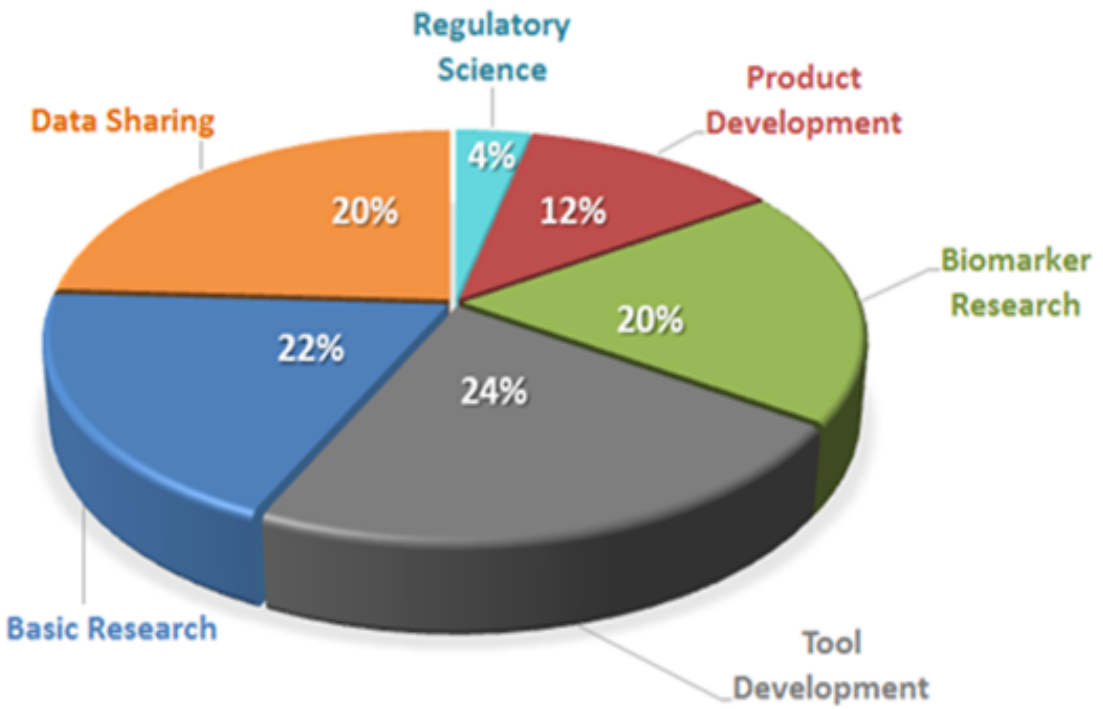
FasterCure's Consortia-pedia (34 organizations)

CHALLENGES

- 80% of consortia choose not to invest in data sharing; of the 20% that do, not all make data available outside the consortium
- **4% focus on advancing regulatory sciences (i.e., Critical Path Institute)**

SPECIFIC AREAS OF FOCUS:



WHAT CAN YOU SEE?

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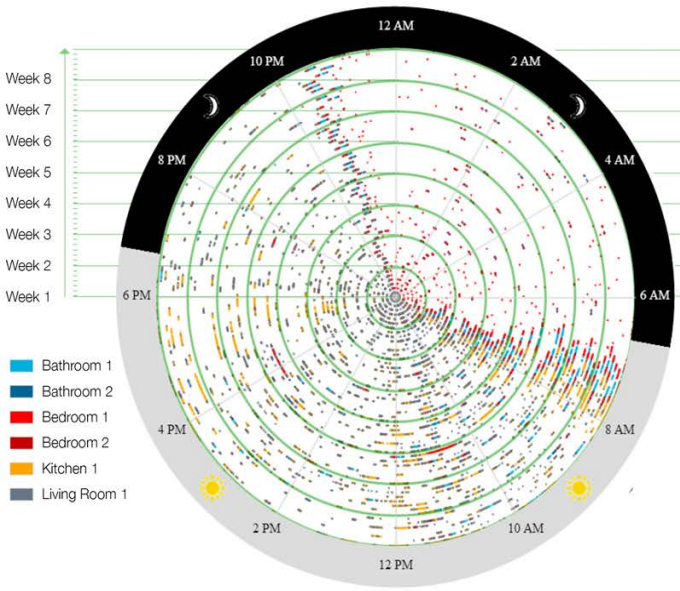
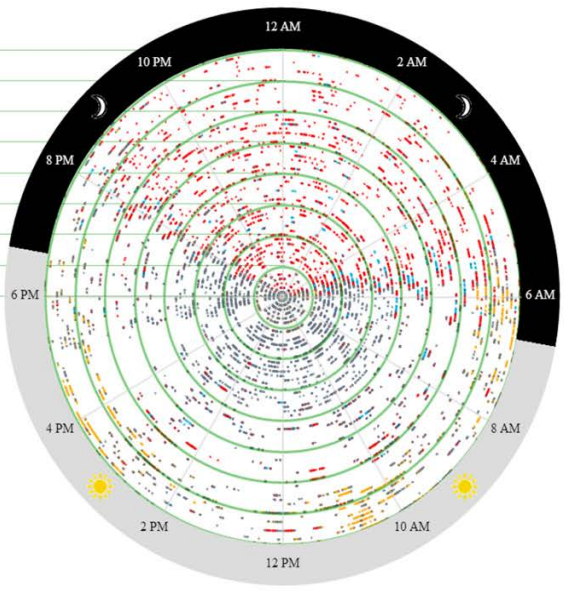
FEB-MAR 2011



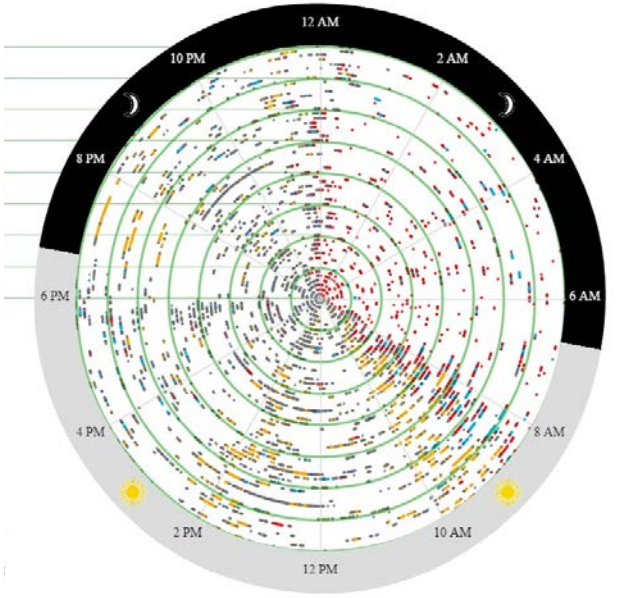
Healthy

SEPT-OCT 2012



Diagnosed with Parkinson disease

SEPT-OCT 2013



Treatment with Sinemet

Courtesy of Dr. Jeff Kaye

ORCATECH SENSING LIFE KINETICS

OREGON HEALTH & SCIENCE UNIVERSITY OHSU

DIFFERENTIATING AD & FTD

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Using the Disease State Fingerprint Tool for Differential Diagnosis of Frontotemporal Dementia and Alzheimer's Disease

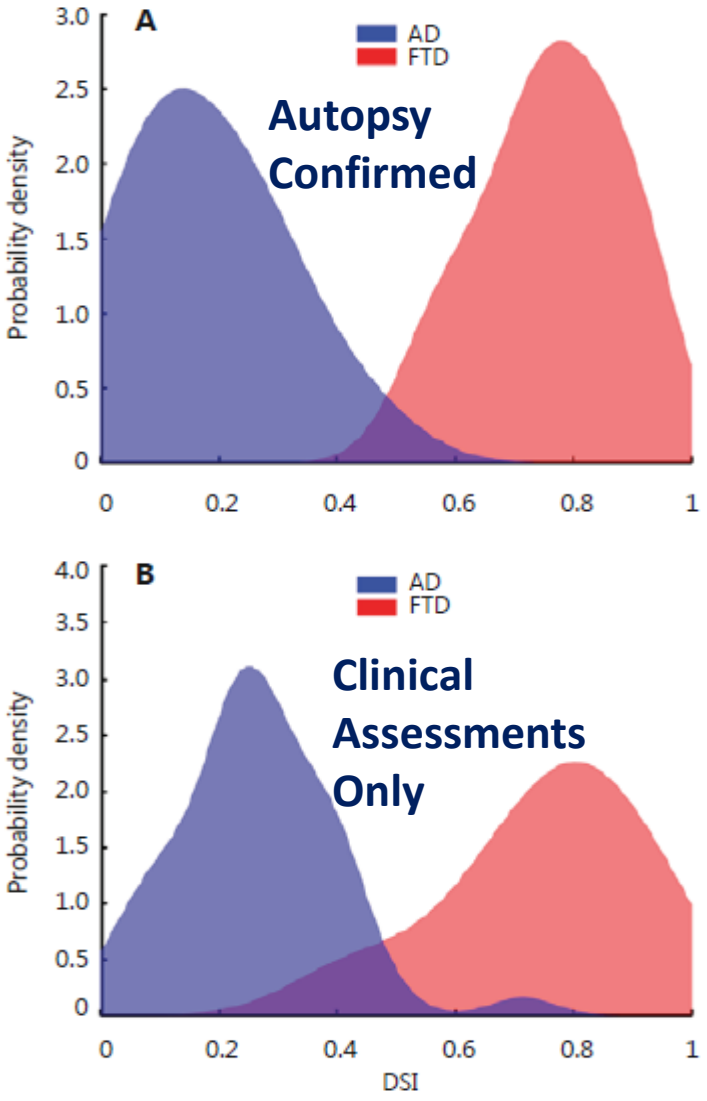
Miguel Ángel Muñoz-Ruiz[a] Anette Hall[a] Jussi Mattila[d]
Juha Koikkalainen[d] Sanna-Kaisa Herukka[a, b] Minna Husso[c]
Tuomo Hänninen[b] Ritva Vanninen[c] Yawu Liu[a, c] Merja Hallikainen[a]
Jyrki Lötjönen[d] Anne M. Remes[a, b] Irina Alafuzoff[e, f] Hilkka Soininen[a, b]
Päivi Hartikainen[a, b]

Dement Geriatr Cogn Disord Extra 2016;6:313–329
DOI: 10.1159/000447122
Published online: July 22, 2016

Table 3. The classification results for the DSI calculated by using bootstrapping for each case separately, excluding the case being tested from the randomized training sets

	C vs. FTD	C vs. AD	AD vs. FTD all	AD vs. FTD autopsy	AD vs. FTD clinical
AUC	0.99±0.01	1.00±0.00	0.89±0.01	0.97±0.02	0.94±0.02
Accuracy	0.95±0.02	0.98±0.01	0.83±0.02	0.91±0.04	0.89±0.03
Sensitivity	0.92±0.03	0.98±0.01	0.81±0.03	0.92±0.05	0.81±0.05
Specificity	0.99±0.02	1.00±0.01	0.83±0.03	0.90±0.06	0.93±0.03

The means and standard deviations are calculated from each round of bootstrapping (n = 100) for all tested cases. DSI classification results calculated with bootstrapping. Values are expressed as mean ± standard deviation.



DATABASE UTILIZATION (as of 1/31/2018)

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410 Total Applicants

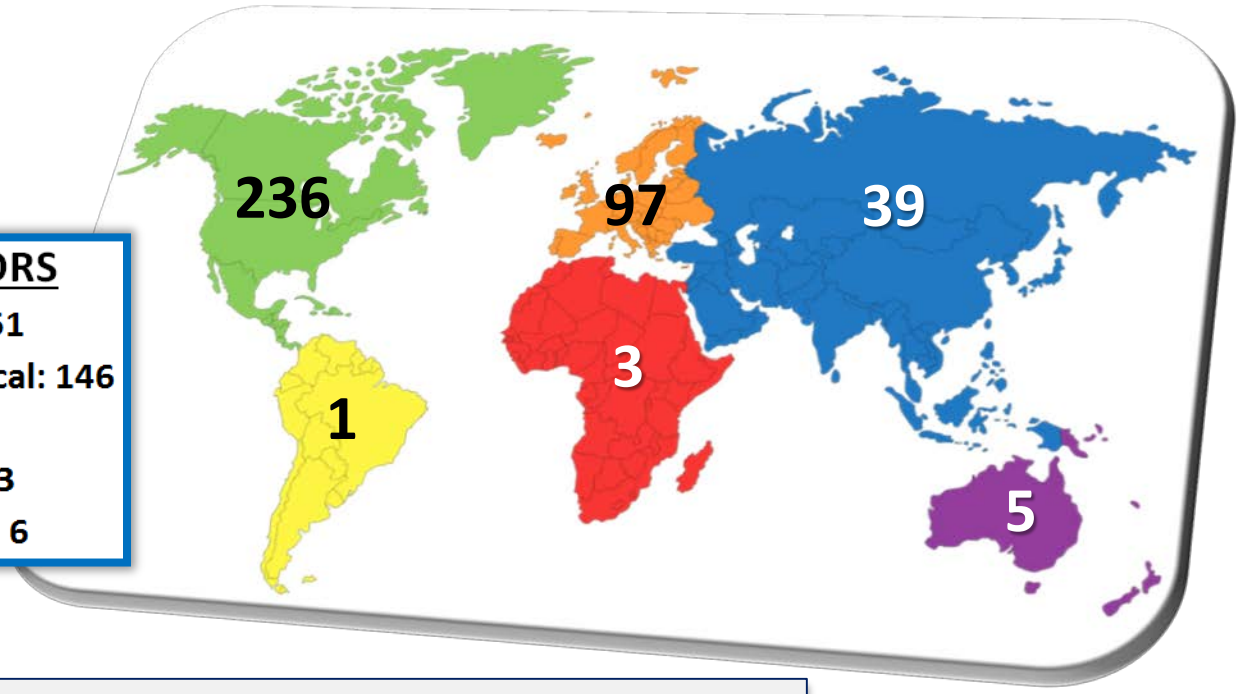
from

327 Distinct Institutions

GAAIN
alzheimer's association
Data Partner

USE BY SECTORS

- Academia: 151
- Pharmaceutical: 146
- Other: 55
- Non-profit: 23
- Government: 6



Industry

Abbvie; Allergan; AstraZeneca; Biogen; Biomarkable; CoreLab; Daewong; Eisai; GE Healthcare; IBM; Johnson & Johnson; Lundbeck; Merck; NeuroCog; Novartis; Pentara; Pfizer; Siemens; SAS

Academia & Foundations

Amherst College; Arizona State Univ.; Bill & Melinda Gates Foundation; CHDI Foundation; Duke Univ.; Fraunhofer Institute; Goethe Univ.; Harvard Univ.; Karolinska Institute; King's College London; Michael J Fox Foundation; Rockefeller Univ.; Seoul National Univ.; Univ. of Oxford; Yale Univ.

Government & Other

NIH; Neurology Today; Gigatrust

DRUG DISEASE TRIAL MODEL OF MILD-to-MODERATE AD: THE REGULATORY PATH

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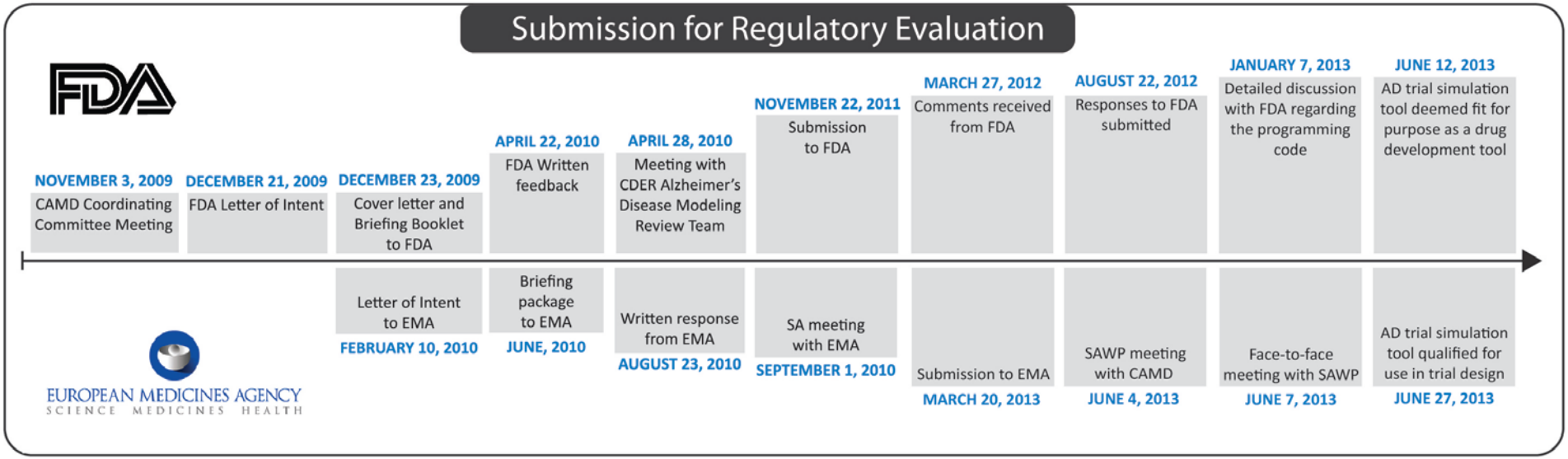
The total journey took 1,317 days (3 years, 7 months and 9 days)

- On June 12, 2013 the **FDA** determined the CTS tool was **"Fit for Purpose."**

- On September 19, 2013 the **EMA** determined the CTS tool was **"Qualified for Use."**



THE PATIENT CONNECTED TO THE 'INTERNET OF THINGS (IOT)'

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Aptar Pharma Image

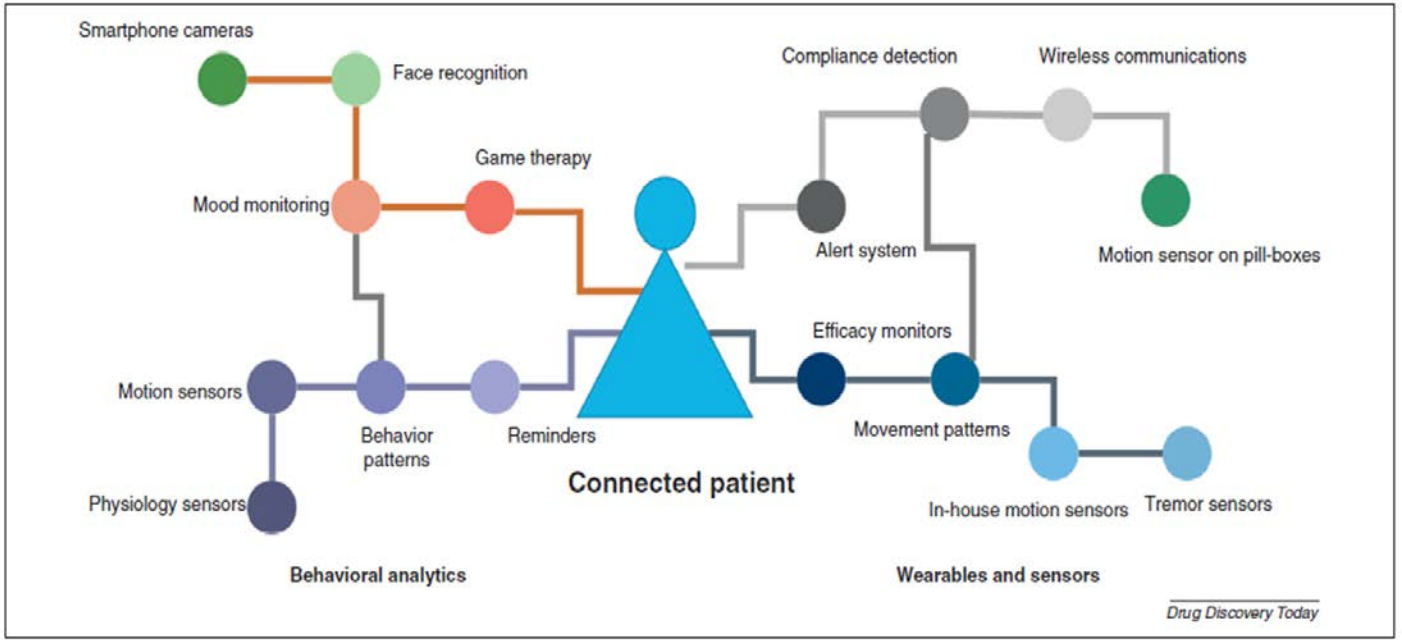

FIGURE 2

Connected patient. With a side variety of sensors, wearable devices and personal health monitors becoming readily available, it is becoming increasingly important to connect these diverse devices and data to provide benefit to patients in a holistic manner.

CONSENSUS SCIENCE MUST INCLUDE REGULATORY CONSIDERATIONS

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EPAD
European Prevention of Alzheimer's Dementia Consortium

Consensus Statement

Alzheimer's & Dementia 13 (2017) 186-195

Perspective

Recommended cognitive outcomes in preclinical Alzheimer's disease: Consensus statement from the European Prevention of Alzheimer's Dementia project

Karen Ritchie[a,b,j,l,*], Michael Ropacki[c,l], Bruce Albala[d], John Harrison[e,f], Jeffrey Kaye[g], Joel Kramer[h], Christopher Randolph[i], Craig W. Ritchie[j]

RBANS:

Repeatable **B**attery for the **A**ssessment of **N**europsychological **S**tatus

CONSIDERATION

This Clinical Outcome Assessment does not have CDISC standards

CONSEQUENCE

Data not suitable for FDA registration submission (potential 18-months delay