Delving into the Role of Public Private Partnerships in Shaping the Landscape to Enable Precision Medicine for Neurodegeneration

Diane Stephenson, PhD, Executive Director, Critical Path for Parkinson's

February 20, 2019; World CNS Summit

CRITICAL PATH INSTITUTE
collaborate · innovate · accelerate

dstephenson@c-path.org

CPP
PARKINSON'S CONSORTIUM
CRITICAL PATH INSTITUTE

New Approaches are Needed to Tackling Drug Development Challenges

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Traditional Drug Development Approach

Reliance on limited information and experience based on:

- A small set of KOLs
- Small, possibly outdated, datasets
- Last paper bias

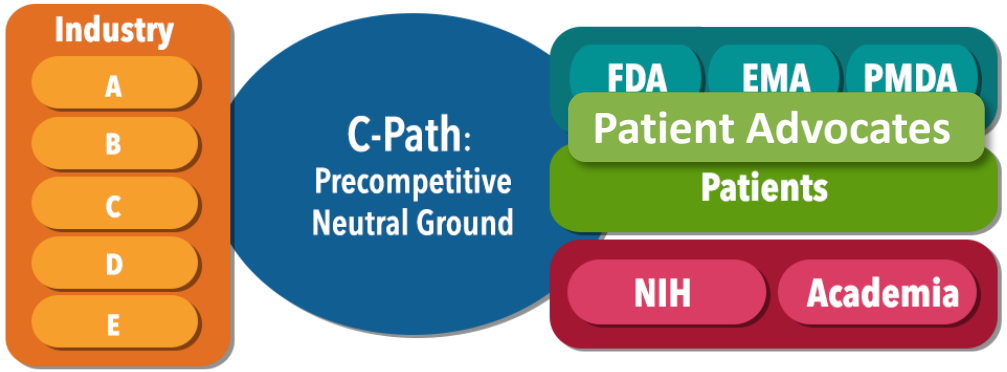
Data and Quantitative Model Based Drug Development Approach

A modern approach based on:

- Integrated global datasets including relevant populations and endpoints
- Quantitative models of disease progression, patient population and endpoint behavior

Critical Path Institute: A Public Private Partnership

- Act as a trusted, neutral third party
- 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 EMA/FDA/PMDA participation in developing new methods to assess the safety and efficacy of medical products

- Official regulatory endorsement of novel methodologies and drug development tools

Critical Path Institute Consortia

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

Critical Path for Alzheimer's Disease
Focusing on needs in AD clinical trials

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

Huntington's Disease Regulatory Science Consortium
Expediting approval of Huntington's therapeutics

International Neonatal Consortium
Neonatal clinical trials

Multiple Sclerosis Outcome Assessments Consortium
Drug Effectiveness in MS

Coalition For Accelerating Standards and Therapies
Data standards

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

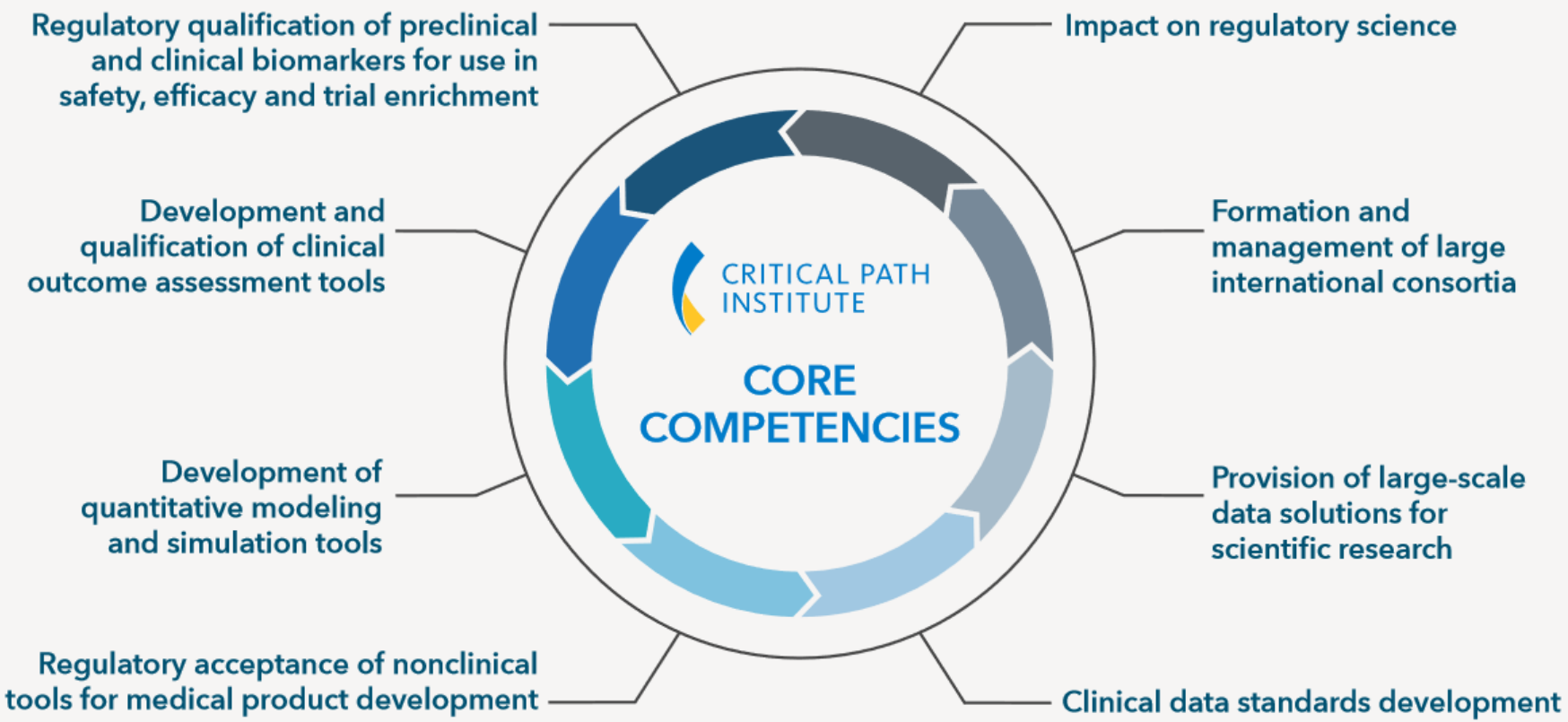
Type 1 Diabetes Consortium
Qualifying biomarkers for type 1 diabetes

Transplant Therapeutics Consortium
New drug development tools for transplantation

Pediatric Trials Consortium
Developing effective therapies for children

- Biomarkers
- Clinical outcome assessment instruments
- Clinical trial simulation tools
- Data standards
- In vitro tools

C-Path Core Competencies



Development of Open Access Global Consensus Data Standards

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Neuroscience Consortia Unified Databases Available to Qualified Researchers

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ELSEVIER

Alzheimer's & Dementia ■ (2015) 1-10

Alzheimer's & Dementia

Research Article

Data Shared from 28 Trials with 6995 patients

Development of a unified clinical trial database for Alzheimer's disease

Jon Neville[a], Steve Kopko[b], Steve Broadbent[a], Enrique Avilés[a], Robert Stafford[a], Christine M. Solinsky[c], Lisa J. Bain[d], Martin Cisneroz[a], Klaus Romero[a], Diane Stephenson[a,*], for the Coalition Against Maior Diseases

MULTIPLE SCLEROSIS JOURNAL | MSJ

Data Shared from 16 Trials with 14,430 patients

Original Research Paper

The MSOAC approach to developing performance outcomes to measure and monitor multiple sclerosis disability

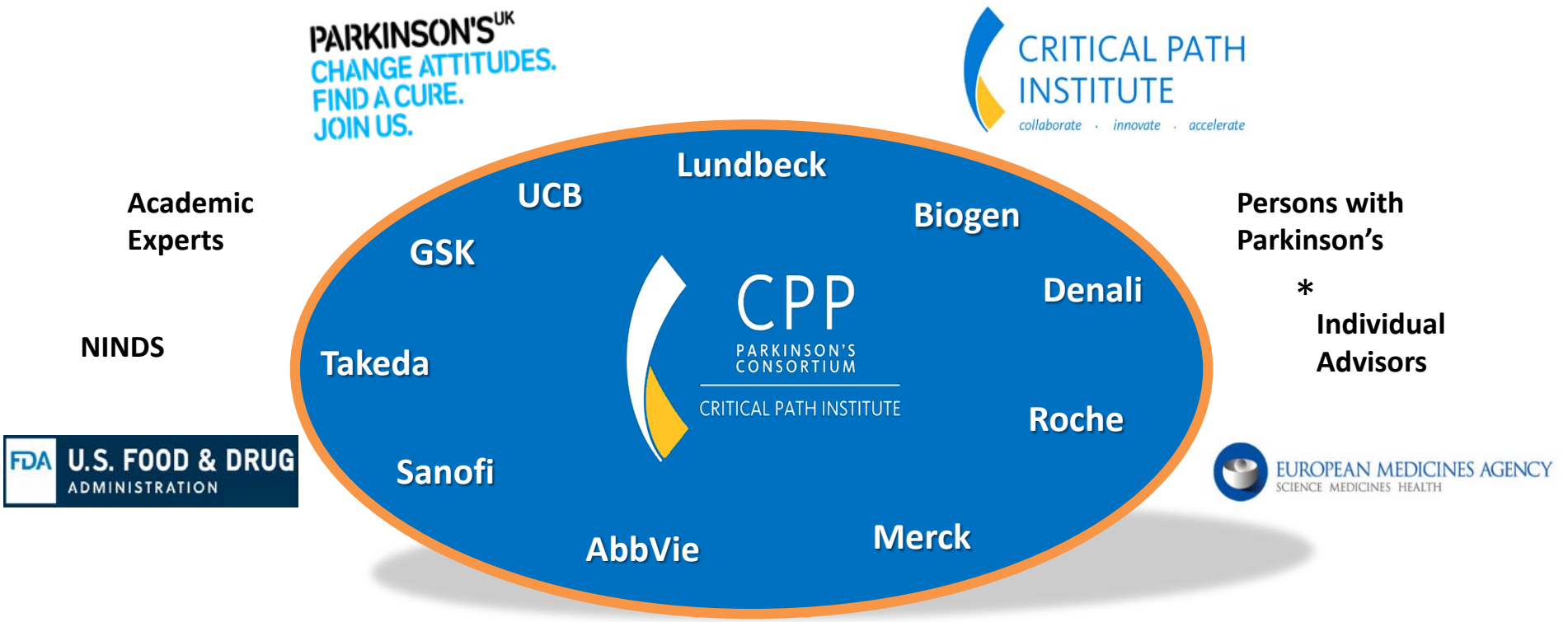
Nicholas G LaRocca, Lynn D Hudson, Richard Rudick, Dagmar Amtmann, Laura Balcer, Ralph Benedict, Robert Bermel, Ih Chang, Nancy D Chiaravalloti, Peter Chin, Jeffrey A Cohen, Gary R Cutter, Mat D Davis, John DeLuca, Peter Feys, Gordon Francis, Myla D Goldman, Emily Hartley, Raj Kapoor, Fred Lublin, Gary Lundstrom, Paul M Matthews, Nancy Mayo, Richard Meibach, Deborah M Miller, Robert W Motl, Ellen M Mowry, Rob Naismith, Jon Neville, Jennifer Panagoulias, Michael Panzara, Glenn Phillips, Ann Robbins, Matthew F Sidovar, Kathryn E Smith, Bjorn Sperling, Bernard MJ Uitdehaag and Jerry Weaver; for the Multiple Sclerosis Outcome Assessments Consortium (MSOAC)

Multiple Sclerosis Journal

1–16

DOI: 10.1177/1352458517723718

Critical Path for Parkinson's Consortium – *Accelerating therapies for PD*



Patient-Advocacy Organizations

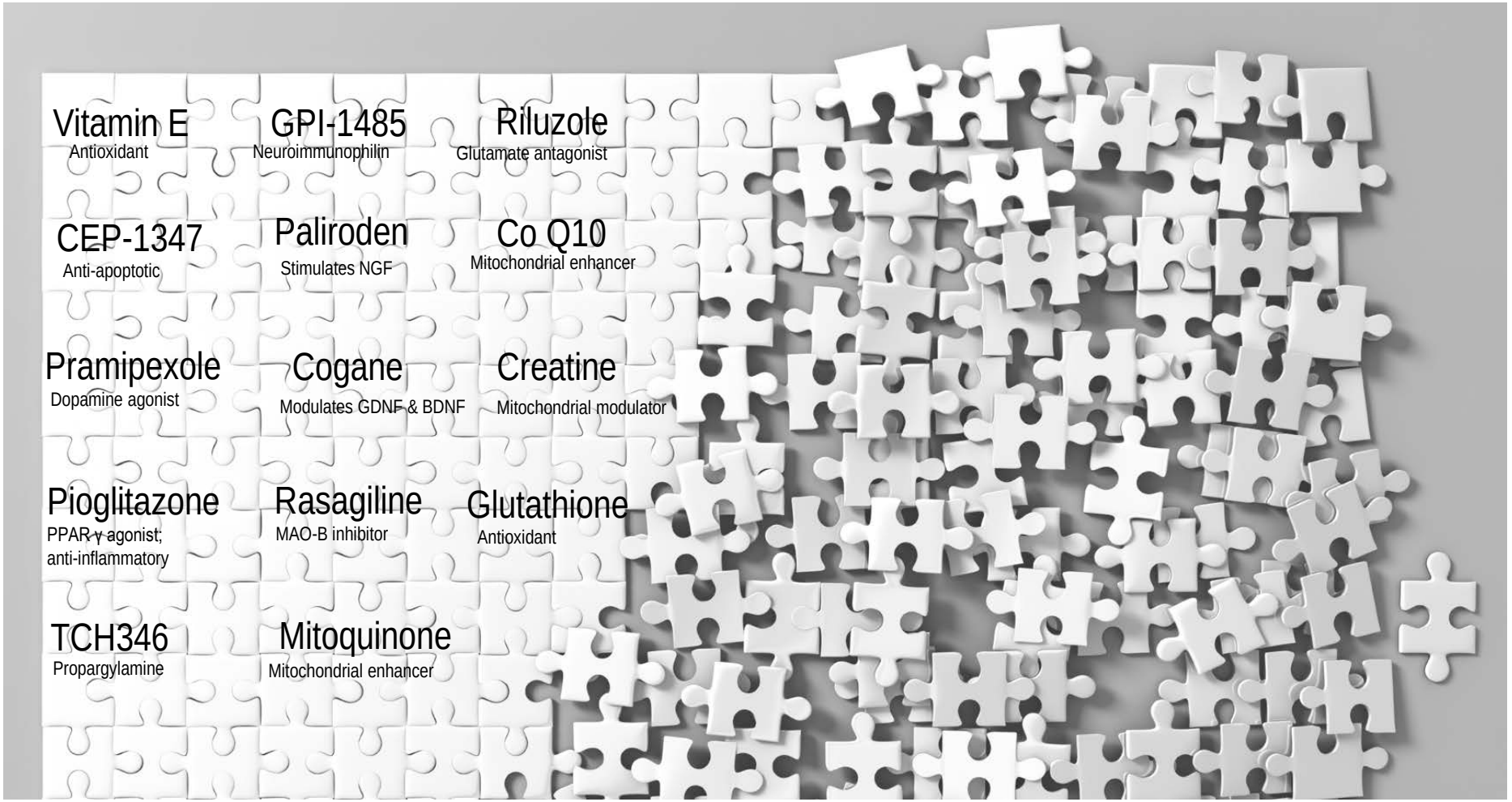
- Parkinson's Foundation
- Michael J. Fox Foundation
- Davis Phinney Foundation
- The Cure Parkinson's Trust

Academic Institutions

- University of Oxford
- University of Cambridge
- Newcastle University
- University of Glasgow
- Radboud University

*CPP Scientific Advisors: Ray Dorsey, Ken Marek, John Seibyl, Bas Bloem, Karl Kieburtz, Charles Venuto, Mark Gordon, David Russell, Brit Mollenhauer, Derek Hill, Glenn Stebbins, Spyros Papapetropoulos, Patrick Howson, Michael Schwarzchild

We can Learn from Past Clinical Trials?



‘Pre-competitive’ Collaboration

Working together to solve these problems and create tools that will benefit the whole community.

Many Promising New Therapies are in the Pipeline

VIEWPOINT

New Drugs for Parkinson's Disease: The Regulatory and Clinical Development Pathways in the United States

Karl Kieburtz, MD,[1,2] Russell Katz, MD,[1] and C. Warren Olanow, MD[1,3]*

TABLE 1. Selected promising therapies for PD that are in the pipeline[a]

Name	Sponsor	Mechanism/Indication	Stage	Regulatory Comments[b]
Short-term benefits or "Symptomatic"				
Opicapone	Bial	COMT inhibitor	III	Approved in Europe
Istradefylline	Kyowa-Kirin	A2A antagonist	III	Approved in Japan
Tozadenant	Acorda	A2A antagonist	III	505B1 pathway
CVT 301	Acorda	Inhaled L-dopa	III	505B2 pathway
APL130277	Sunovion	Sublingual apomorpine	III	Fast track
Amantadine ER	Adamas	NMDA antagonist for dysk	III	505B2 pathway
P2B001	Pharma2B	Low-dose prami/rasag combo	III	505B2 pathway
ND0612	Neuroderm	SC L-dopa/carbidopa	III	BE/505B2 pathway
Apo Infusion	USWM	Apomorphine infusion	III	505B2 pathway
Accordion pill	Intec	Long-acting L-dopa	III	505B2 pathway
PF-06649751	Pfizer	D1 agonist	IIB	505B1
LU-AE04621	Lundbeck	D1 agonist	IIB	505B1
SER-214	Serina	polymer-linked rotigotine	IIB	BE/505B2 pathway
AAV2-hAADC	Voyager	AAV2-gene delivery of AADC	II	Submitted through CBER
Light therapy	Photopharmics	Altered circadian rhythm	II	Device pathway
Dopafuse	Synagile	Continuous oral L-dopa delivery	II	Drug/device (505B2)
Disease modifying				
Isradipine	NIH	Ca+ + channel blocker	III	505B2
Inosine	NIH	Increase Urate as antioxidant	III	505B2
Nicotine Patch	Fox	Enhance nicotine levels	II	505B2
Affitope	Afferis	ImmunoRx target alpha syn	II	505B1 submitted through CDER
PRX002	Prothena	Monoclonal AB to alpha syn	IIa	505B1 submitted through CDER
BIIB054	Biogen	ImmunoRx target alpha syn	IIa	505B1 submitted through CDER
NPT 200-11	UCB	Antialpha syn aggregate	II	505B1
Nilotinib	Fox	CAbl kinase inhibitor	II	505B2 (approved in leukemia)
GZ/*SAR402671	Genzyme/Sanofie	GBA enhancer	II	505B1
Ambroxol	Weston Found	Enhances GCase activity	II	505B1
Exenatide	Cure PD Trust	Glucagon-like peptide 1	II	505B2
Deferiprone	APO Pharma	Iron chelator	II	505B2

Mov Disord. 2018 33(6):920-927.

"A better appreciation of regulatory pathways and requirements by scientists, clinical Investigators, and the pharmaceutical industry will likely help reduce the cost and time of Drug Development, and speed the approval process"

What Could We Do if We Had All the Data from Parkinson's Studies in One Place?

Data from clinical trials and cohorts

Standardization and integration

Researchers
Regulators
Industry

CPP has Gathered Data from 8100 people with Parkinson's From Around the World

Heinzel et al., JPD 7(3):423-432. *2017*

PARKINSON'S UK
CHANGE ATTITUDES.
FIND A CURE.
JOIN US.

OBSERVATIONAL

PPMI (n=1223)

CamPaIGN (n=142)

OPDC Discovery Cohort (n=877)

ICICLE (n=314)

Tracking Parkinson's (n=1998)

CLINICAL TRIALS

PRECEPT (n=806)

ADAGIO (n=1170)

DATATOP (n=800)

ELLDOPA (n=361)

FS-! (n=200)

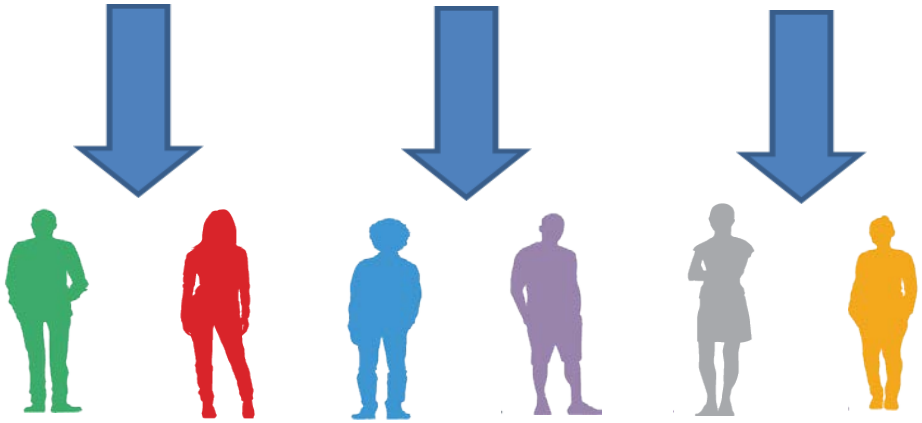
FS-Too (n=213)

TOTAL NUMBER OF SUBJECTS: 8104

Future Model of Parkinson's Therapies

Parkinson's -
Not all one flavor

Personalized Medicine
targeted treatments



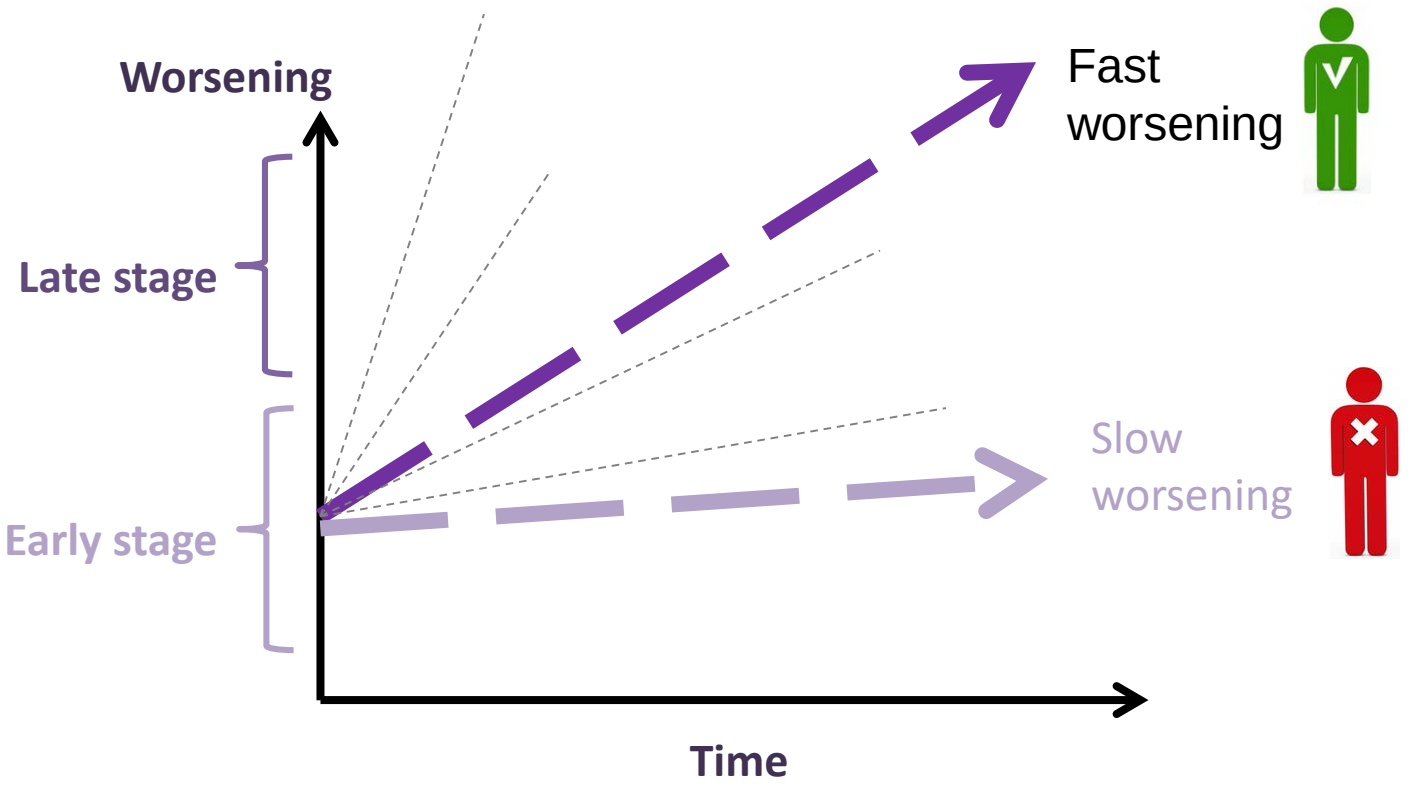
As modified from Alberto Espay

Up to 15% of People with Early Parkinson's who Take Part in Trials May Not Have the Disease

See :
Beach and Adler, Importance of low diagnostic Accuracy for early Parkinson's disease.
Mov Disord. 2018; 33(10):1551-1554

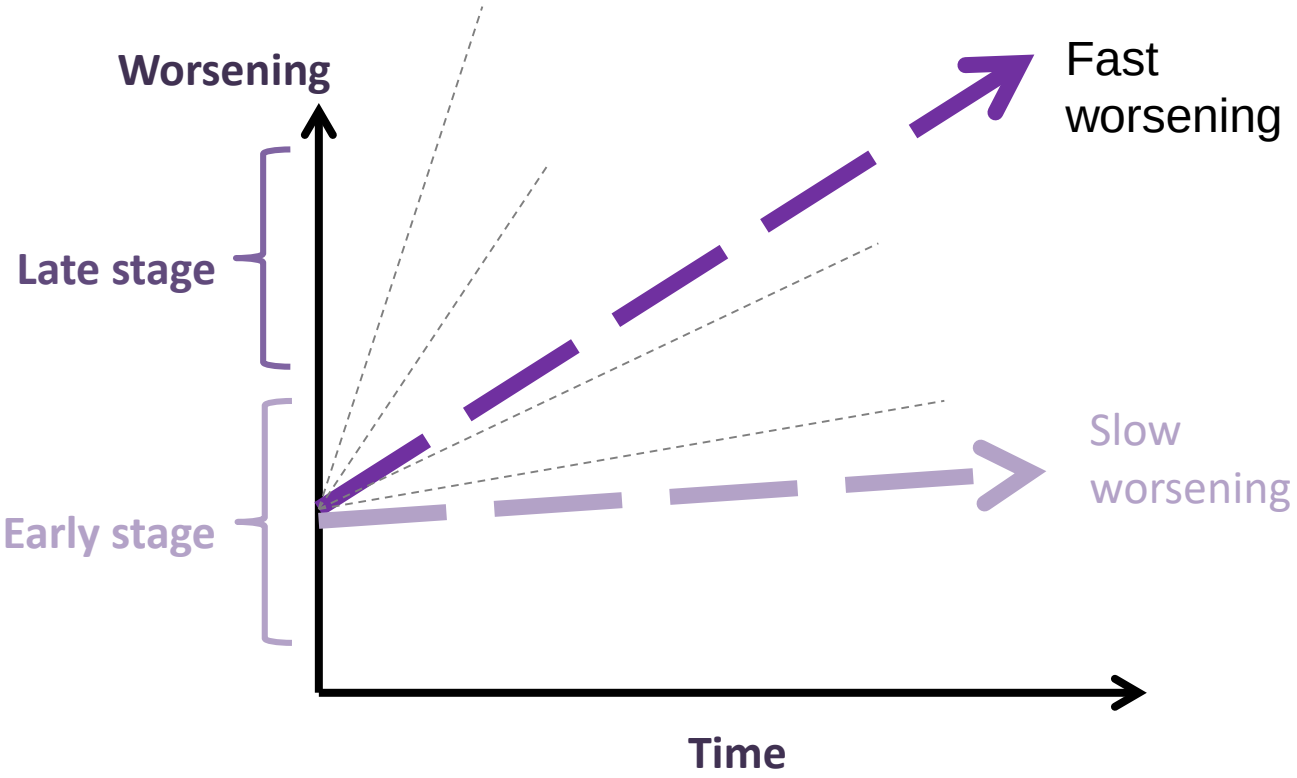
Beth Vernaleo, Parkinson's Disease Foundation

Rate of Disease Progression Varies…

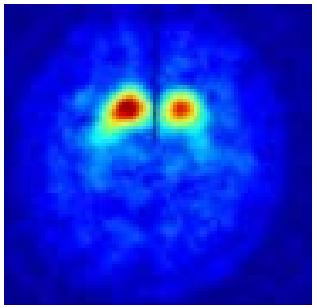


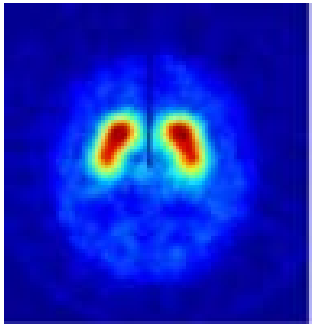
Can Biomarkers and Genetics help to determine rates of decline?

Using Imaging to Predict the Future



DAT deficiency





SWEDD (Scans without evidence of dopamine deficiency)

Enrichment Allows Meaningful Reduction of Trial Size

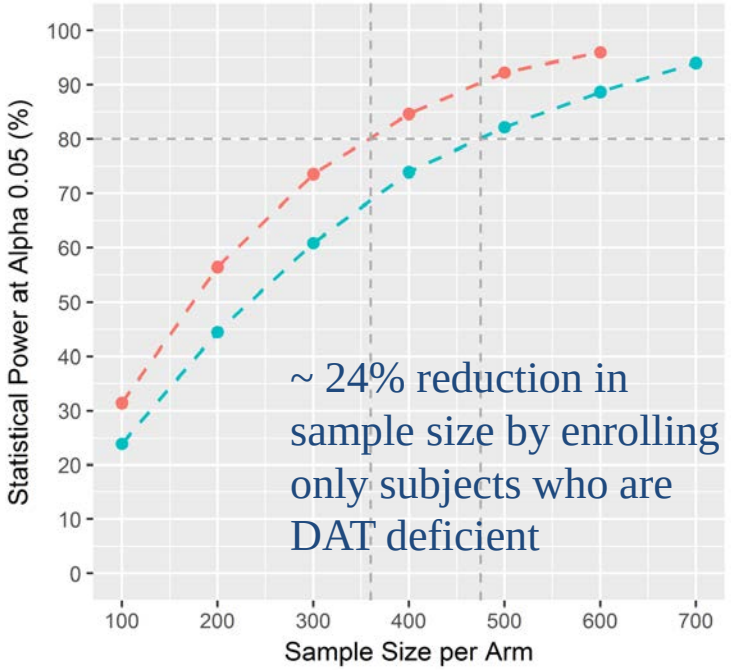
Citation: Clin Transl Sci (2017) 00, 1–8; doi:10.1111/cts.12492

ARTICLE

Dopamine Transporter Neuroimaging as an Enrichment Biomarker in Early Parkinson's Disease Clinical Trials: A Disease Progression Modeling Analysis

Daniela J. Conrado[1,*], Timothy Nicholas[2], Kuenhi Tsai[3], Sreeraj Macha[3], Vikram Sinha[3], Julie Stone[3], Brian Corrigan[2], Massimo Bani[4], Pierandrea Muglia[1], Ian A. Watson[5], Volker D. Kern[1], Elena Sheveleva[1,6], Kenneth Marek[7], Diane T. Stephenson[1] and Klaus Romero[1] on behalf of the Critical Path for Parkinson's (CPP) Parkinson's Disease Modeling and Simulation Working Group

Clin Transl Sci. 2018 Jan;11(1):63-70



Under these assumptions:

- 24-month placebo-controlled parallel group trial.
- Enriched trial had only subjects with DAT deficit, while non-enriched trial included 15% of SWEDD.
- Drug effect of 50% reduction in the progression rate.
- Power was calculated as the proportion of trials for which the effect of treatment on progression rate was beneficial with a two-tailed *P*-value < 0.05.

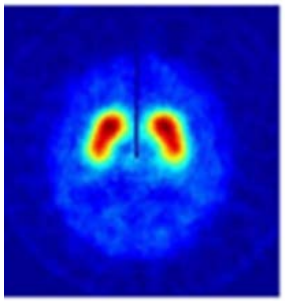
Using Imaging as an Enrichment Biomarker in Trials
Regulatory Endorsement by EMA and FDA

CPP PARKINSON'S CONSORTIUM CRITICAL PATH INSTITUTE

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

29 May 2018
EMA/CHMP/SAWP/765041/2017
Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion on dopamine transporter imaging as an enrichment biomarker for Parkinson's disease clinical trials in patients with early Parkinsonian symptoms



Normal brain scan (no dopamine deficiency)

DEPARTMENT OF HEALTH & HUMAN SERVICES — PUBLIC HEALTH SERVICE

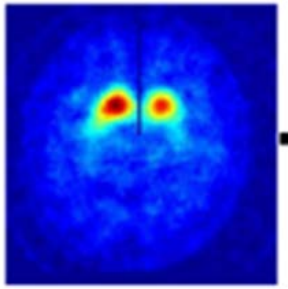
Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: March 16, 2015

ATTN: Diane Stephenson, Ph.D.
Executive Director, Coalition
Critical Path Institute
1730 E River Rd.
Tucson, Arizona 85718

Janet Woodcock, M.D.
Director, CDER
U.S. Food and Drug Administration

Subject: Biomarker Letter of Support



Dopamine deficiency consistent with Parkinson's

ANNOUNCEMENTS

RELATED PC

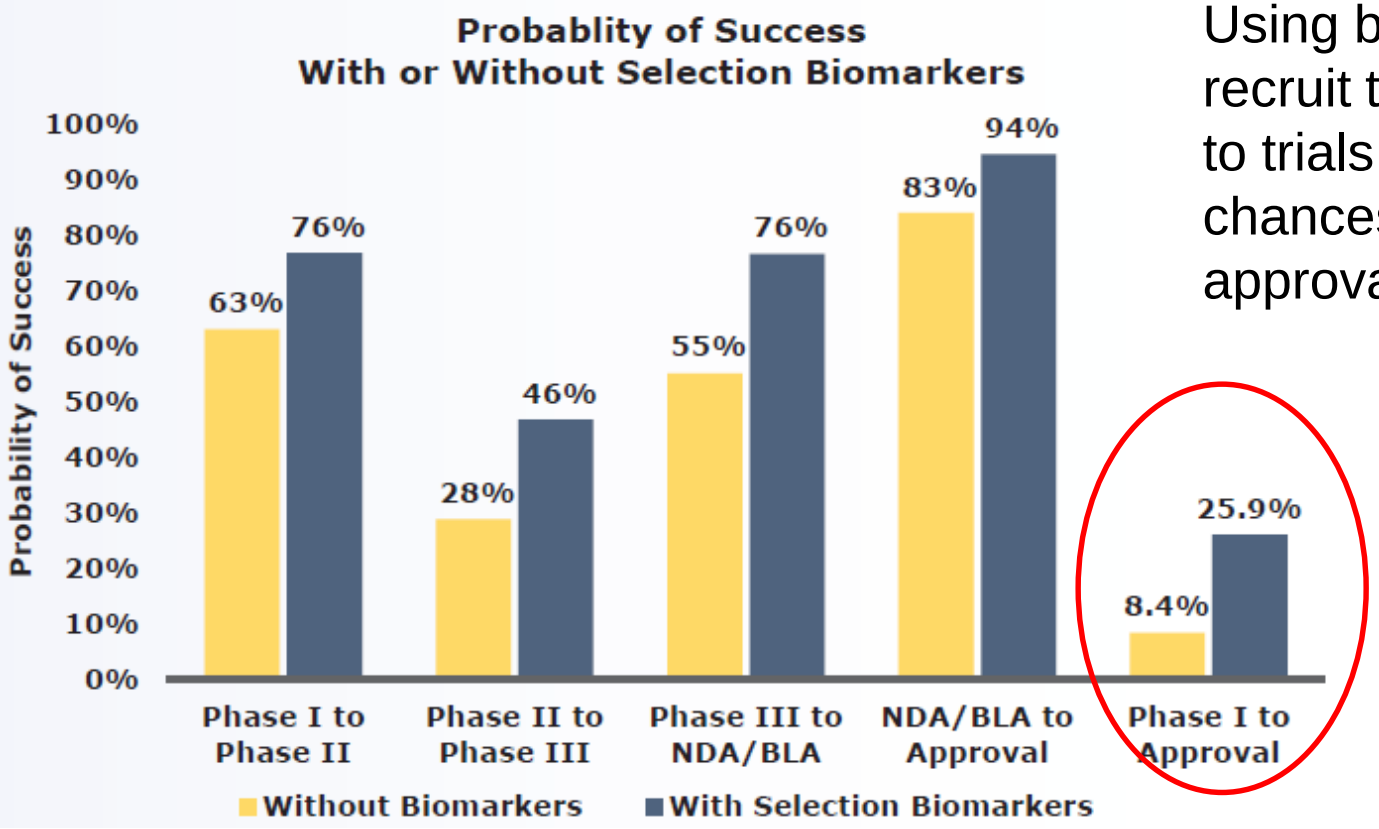
July 26, 2018

PRINT PDF

First-ever biomarker qualified for Parkinson's is a vital step toward improved clinical trials

CPP CRITICAL PATH INSTITUTE

What Impact Could This Make?

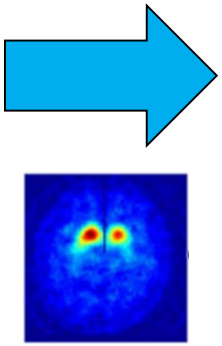


Using biomarkers to recruit the right people to trials increases chances of drug approvals.

Amplion/BIO report, 2016

Critical Path for Parkinson's is Enabling Precision Medicine Strategies

Before



Now

Selecting more appropriate subjects for clinical trials will reduce the numbers needed and make trials more efficient.

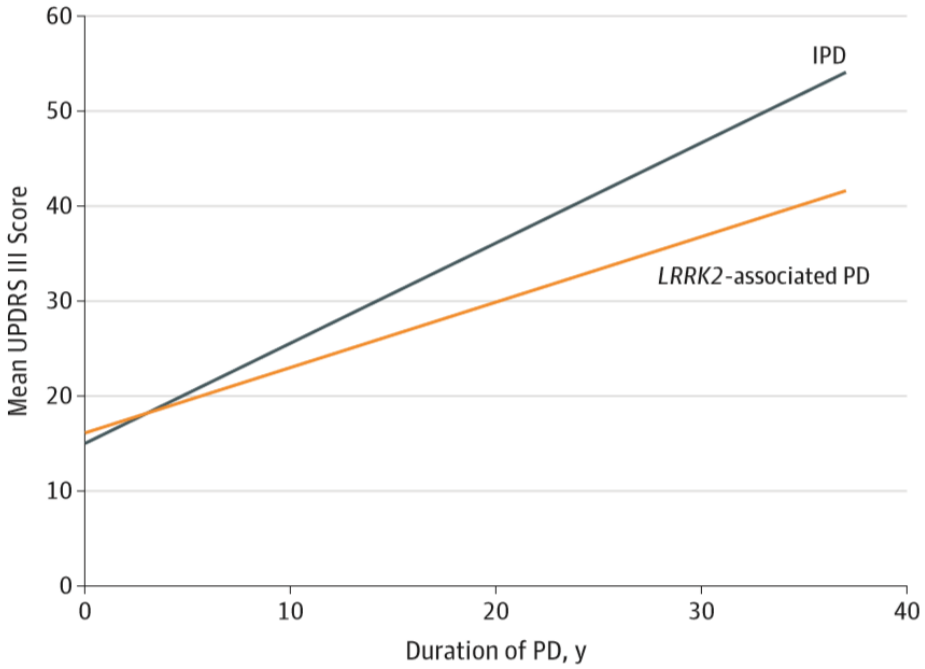
CPP Integrated Database Contains Rich Genetic Information

Gene	Study				
	CamPaIGN	ICICLE	Oxford	Tracking-PD	PPMI
APOE	n = 125	n = 292	n = 732	n = 1831	n = 619
COMT	n = 129	n = 293	n = 729	n = 1831	n = 915
GBA	n = 114	n = 236	n = 727	n = 1831	n = 922
LRRK 2	n = 139	n = 293	n = 725	n = 1831	n = 1184
MAPT	n = 128	n = 291	n = 735	n = 1831	n = 922
SNCA	n = 125	n = 293	n = 729	n = 1831	n = 923

Total number of subjects with genetic information: ~4180

Genetic Data Can be Used to Define PD Endophenotypes with Distinctive Progression Rates

Figure 1. Longitudinal Trajectories of Mean Unified Parkinson's Disease Rating Scale III (UPDRS III) Scores for Patients With Parkinson Disease (PD) Who Carry the Leucine-Rich Repeat Kinase 2 (*LRRK2*) Mutation Compared With Patients With Idiopathic PD (IPD)

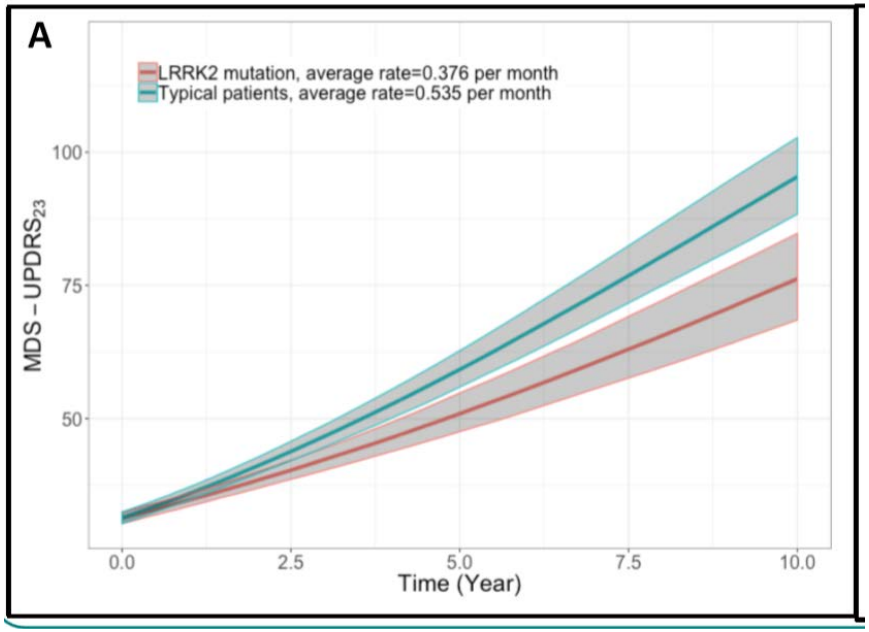


Saunders-Pullman, R., et al., (2018). Progression in the *LRRK2* -Asssociated Parkinson Disease Population. *JAMA Neurology*, *75*(3), 312.

Disease Progression model platform to inform efficient clinical trial design for Parkinson's Disease

Malidi Ahamadi, Merck Research Laboratories

Presentation at 9th American Conference on Pharmacometrics (ACoP9), San Diego, CA

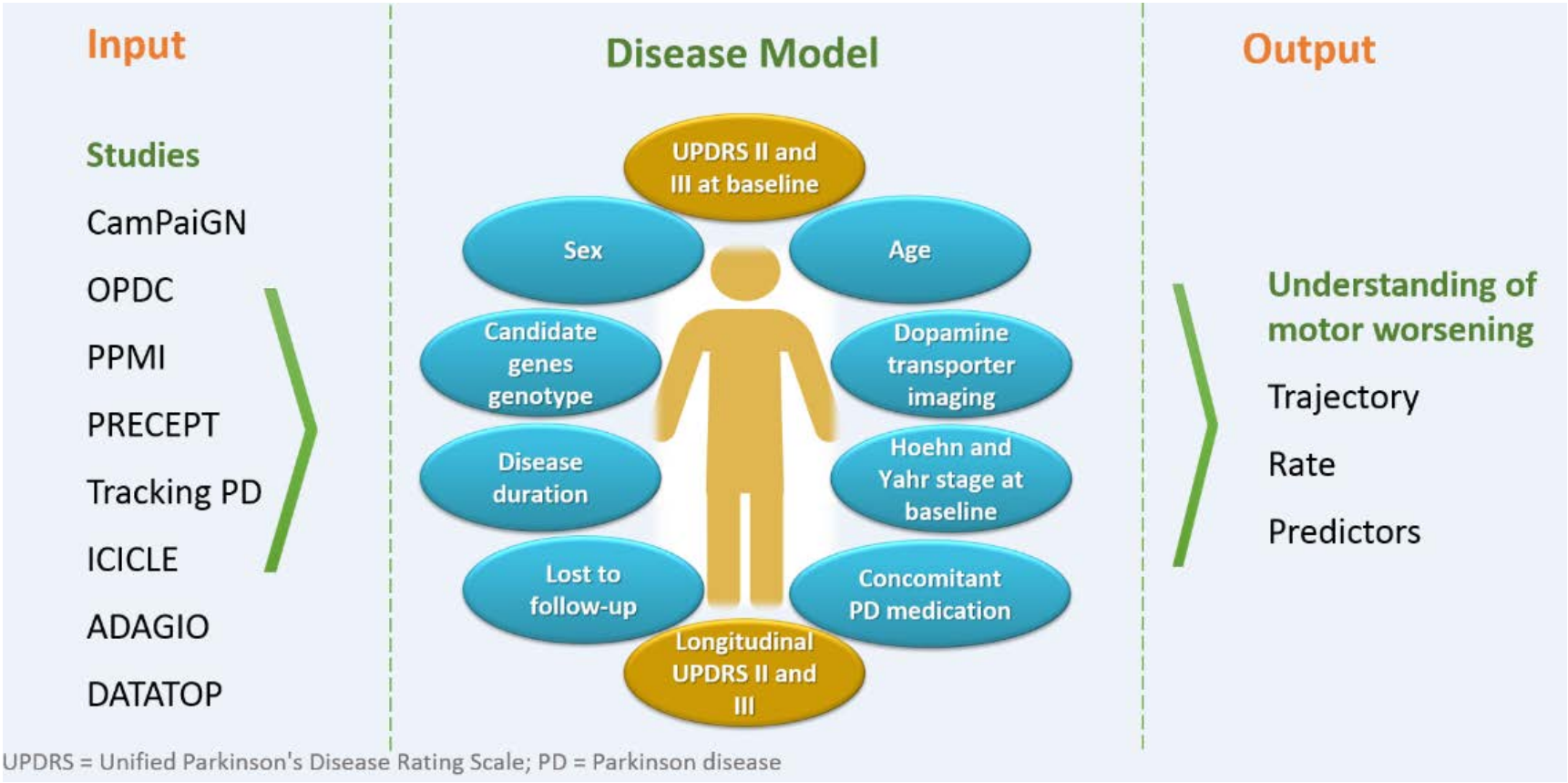


On behalf of Malidi Ahamadi, Merck And the CPP modeling and simulation team

Development of PD Drug-Disease-Trial Model

Model Informed Drug Development

- Using computerized models to simulate different 'what if' scenarios aimed at identifying the ***right drug, right patient at the right time***



UPDRS = Unified Parkinson's Disease Rating Scale; PD = Parkinson disease

The Future: A Trial 'Flight Simulator'?

This Has Been Achieved for Alzheimer's Disease: *Other Diseases are Waiting*

CPP PARKINSON'S CONSORTIUM CRITICAL PATH INSTITUTE

The Future Is Now: Model-Based Clinical Trial Design for Alzheimer's Disease

Clin Pharmacol Ther.
2015 Mar;97(3):210-4

K Romero[1], K Ito[2], JA Rogers[3], D Polhamus[3], R Qiu[2], D Stephenson[1], R Mohs[4], R Lalonde[2], V Sinha[5], Y Wang[5], D Brown[6], M Isaac[6], S Vamvakas[6], R Hemmings[6], L Pani[6], LJ Bain[1], B Corrigan[2], for the Alzheimer's Disease Neuroimaging Initiative* for the Coalition Against Major Diseases**

"Model-based drug development was one of the goals defined in FDA's 2004 Critical Path Initiative report, and this new tool sets the stage for applying new technologies to accelerating medical product development,"
Janet Woodcock, FDA

THE WALL STREET JOURNAL.

JOURNAL REPORTS: HEALTH CARE

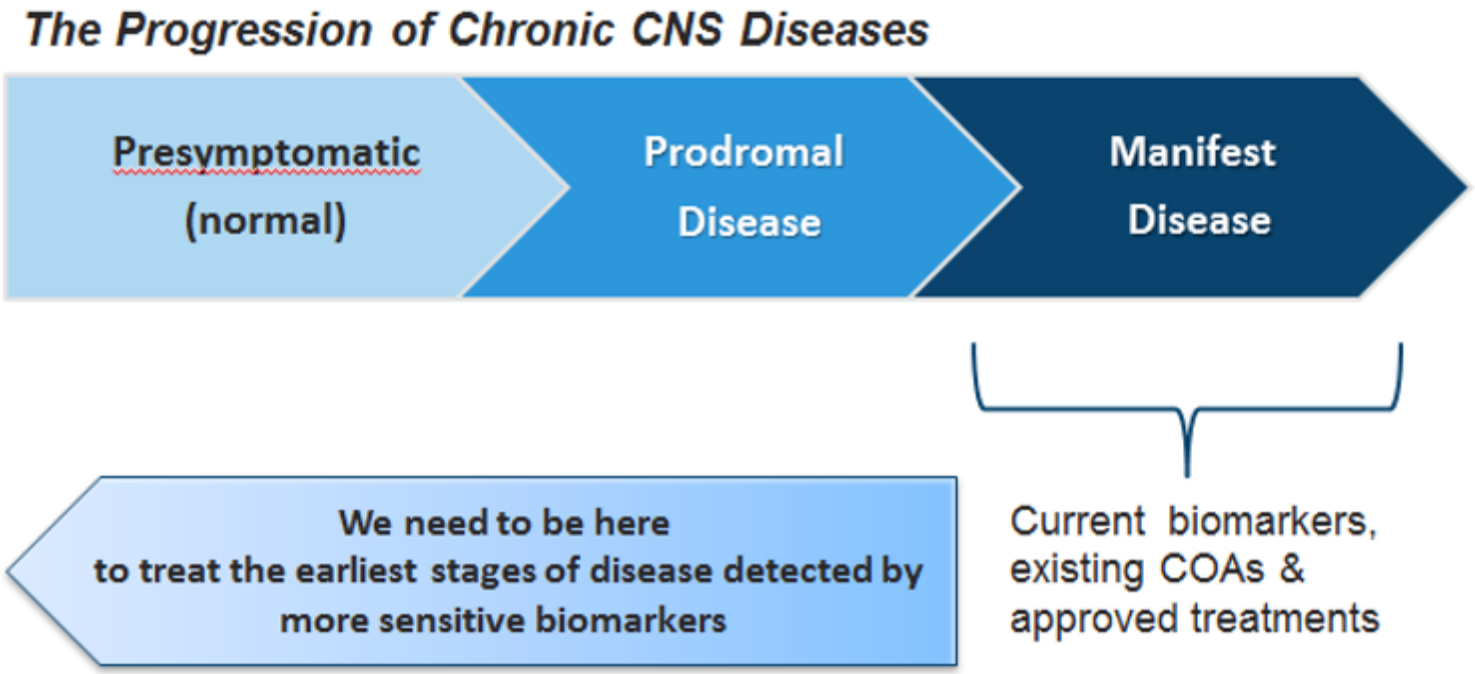
Simulators Help Build a Better Drug Trial

Pharmaceutical firms start to use powerful computer programs to improve human testing

By JONATHAN D. ROCKOFF

Nov. 17, 2013 4:07 p.m. ET

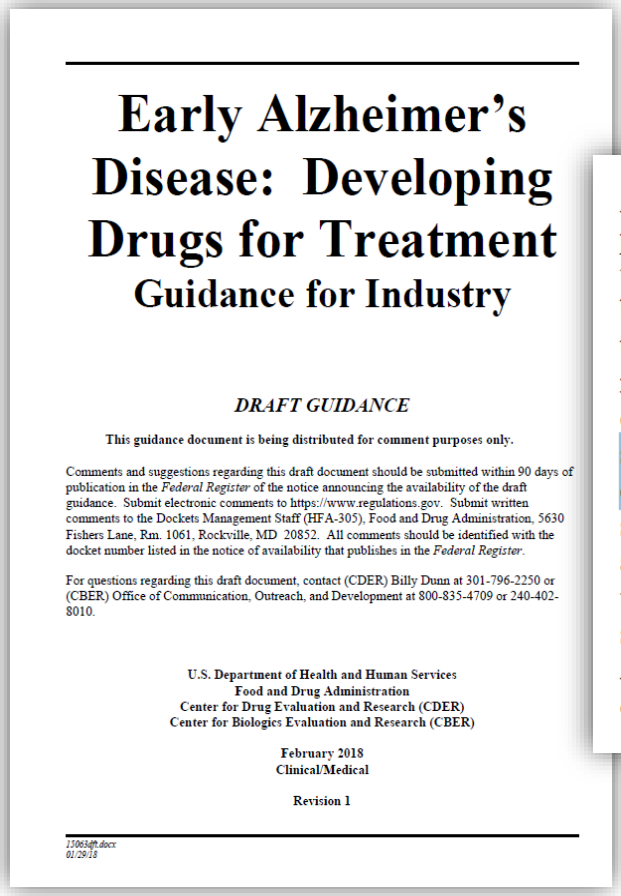
The Future Vision for Treating Nervous System Disorders



Stephenson and Arneric,
Translational Medicine in CNS Drug Development
In press (Elsevier, Feltner and Nomikos Eds)

*COA = clinical outcome assessments

FDA Early Alzheimer's Disease Guidance



Early Alzheimer's Disease: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Billy Dunn at 301-796-2250 or (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2018
Clinical/Medical

Revision 1

1306dft.docx
01/29/18

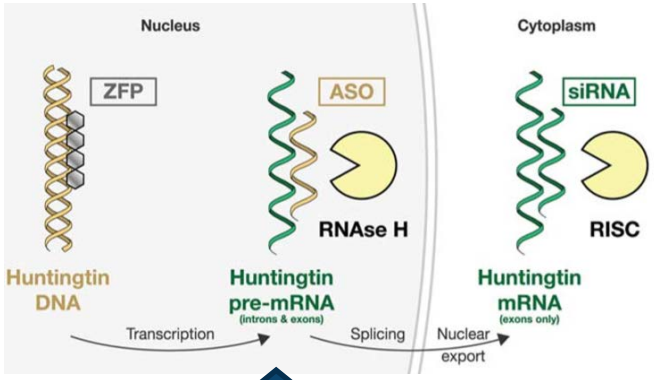
FDA U.S. FOOD & DRUG ADMINISTRATION

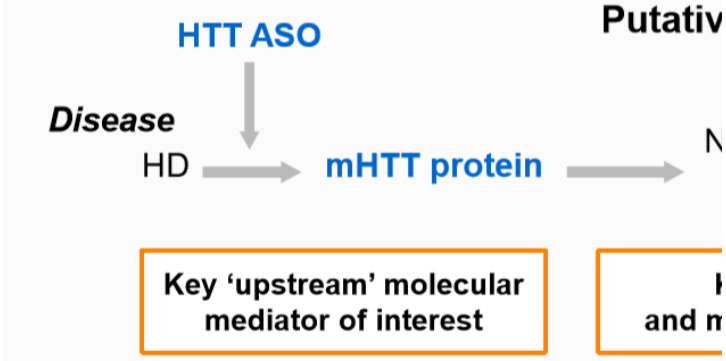
Although the issues and approaches discussed above for Stage 2 patients are relevant for Stage 1 patients, there is unfortunately at present no sufficiently reliable evidence that any observed treatment effect on such biomarker measures would be reasonably likely to predict clinical benefit (the standard for accelerated approval), despite a great deal of research interest in understanding the role of biomarkers in AD. FDA strongly supports and encourages continued research in this area and stresses its potential importance in the successful development of effective treatments appropriate for use in the earliest stages of AD. Precompetitive structured sharing across the AD scientific community of rigorously collected standardized data is a crucial component of this research. While research pursues the development of evidence sufficient to support the use of biomarker measures as the primary evidence supporting an accelerated approval, or perhaps a full approval if the fundamental understanding of AD evolves sufficiently to establish surrogacy, a possible approach to Stage 1 patients might be to conduct a study of sufficient duration to allow the evaluation of the measures discussed above for Stage 2 patients. As patients transition to Stage 2 during participation in the trial, the principles applicable to outcome assessment for Stage 2 would apply.

February 15, 2018

Remarkable Advances in Huntington's Disease:

A Flagship Disease for Early Intervention





Features

DRUG DEVELOPMENT

C&EN April 2017

A new day for Huntington's disease

First agents to possibly slow or even reverse the disease enter clinical trials

TABLE 1 | SELECT LIST OF POTENTIALLY DISEASE-MODIFYING HUNTINGTON DRUGS IN DEVELOPMENT

Drug	Sponsor	Properties	Status
RG6042	Roche/Ionis Pharmaceuticals	HTT-lowering antisense	Phase III
WVE-120101	WAVE Life Sciences/Takeda	mHTT-lowering antisense	Phase I/II
WVE-120102	WAVE Life Sciences/Takeda	mHTT-lowering antisense	Phase I/II
AMT-130	uniQure	HTT-lowering miRNA	IND
VY-HTT01	Voyager Therapeutics/Sanofi/CHDI Foundation	HTT-lowering miRNA	IND in 2019
HTT Program	Exicure	HTT-targeted spherical nucleic acids	Preclinical
VX15	Vaccinex	Anti-semaphorin 4D mAb	Phase II

ognitive,
oral and
measures
, digital
easures

om S. Schobel
entation
nd Tabrizi, 2014

C-Path's Newest Consortium
Huntington's Disease Regulatory Science Consortium

CRITICAL PATH INSTITUTE
collaborate · innovate · accelerate

CHDI
Accelerating therapeutic development for Huntington's disease

IBM
Ixico
NeuraMetrix
Prilenia
Pfizer
PTC
Roche
Sanofi
Takeda

HD-RSC
HUNTINGTON'S CONSORTIUM
CRITICAL PATH INSTITUTE

Coordinating Committee

Teva
uniQure
Wave
Vaccinex
Voyager
Academia
HSG/EHDN
HDSA/HSC/EHA
FDA/EMA

DATA
HD Modeling
Biomarkers (Biofluid & Imaging)
Clinical Outcome Assessments
Regulatory Science Forum

Progress in HD will Inform Therapeutics Across Neurodegenerative Diseases

REVIEWS

Therapeutic approaches to Huntington disease: from the bench to the clinic

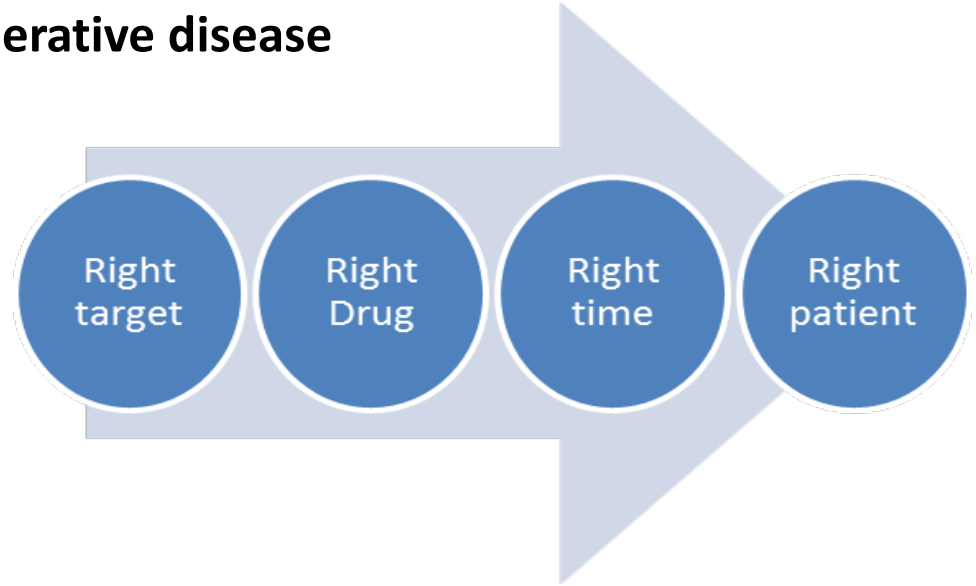
Nicholas S. Caron[1], E. Ray Dorsey[2] and Michael R. Hayden[1,3,4]*

Nat Rev Drug Discovery

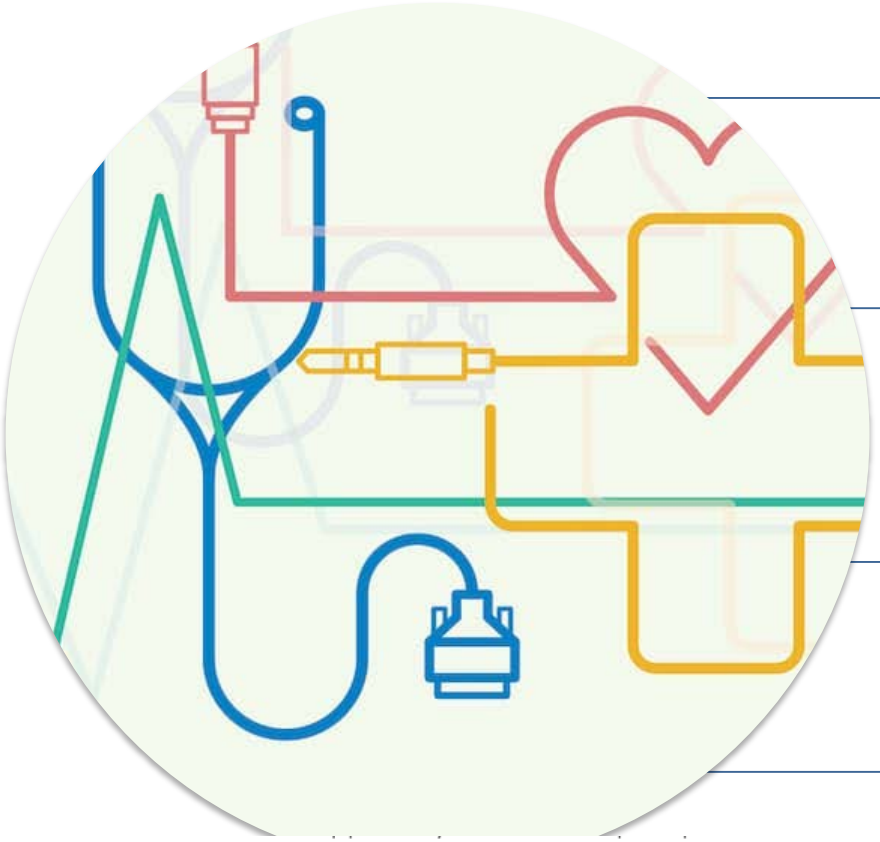
"With clinical trials for many of these approaches imminent or currently ongoing, the coming years are promising not only for HD but also for more prevalent neurodegenerative disorders, such as Alzheimer and Parkinson disease, in which many of these pathways have been similarly implicated."

Call to Action!

- **Collaboration around the world and data is urgently needed to speed the path to effective treatments and embrace personalized medicine for Neurodegenerative disease**



CPP Turns Attention to Digital Technologies



Replace Poor Endpoints

Reduce Patient Burden and Cost

Increase measurement accuracy

Validate to regulatory standards

Viewpoint – Review

The First Frontier: Digital Biomarkers for Neurodegenerative Disorders

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Digit Biomark 2017;1:6–13

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Jesse Cedarbaum, CPP Industry Co-director

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FIND A CURE.
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Critical Path for Parkinson's Consortium
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CHDI
Accelerating therapeutic development for Huntington's disease

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