Critical Path for Parkinson's Consortium

October 29, 2019

CPAD Annual Meeting

Dr. Diane Stephenson
Executive Director, Critical Path for Parkinson's
Critical Path Institute

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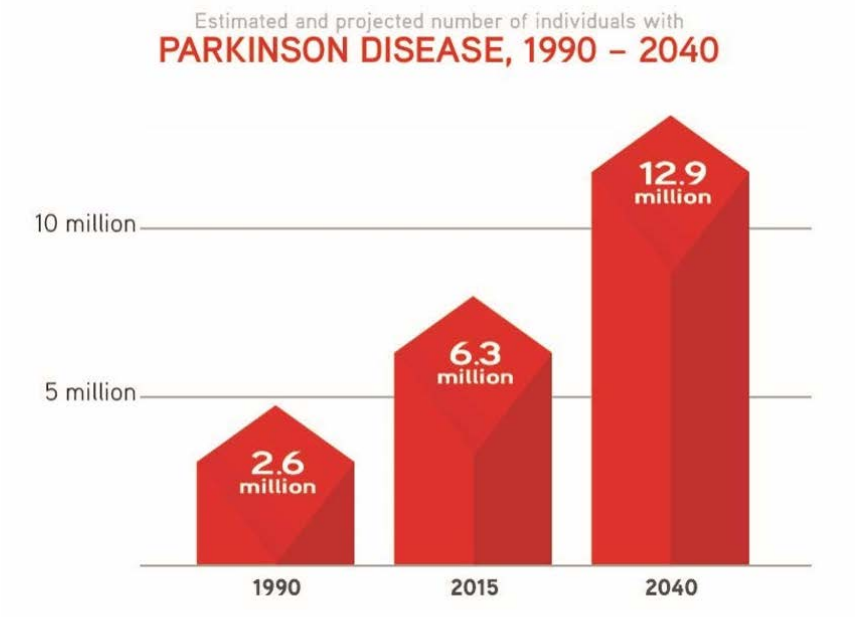
Growing Burden of Parkinson's Disease

Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016

*GBD 2016 Parkinson's Disease Collaborators**

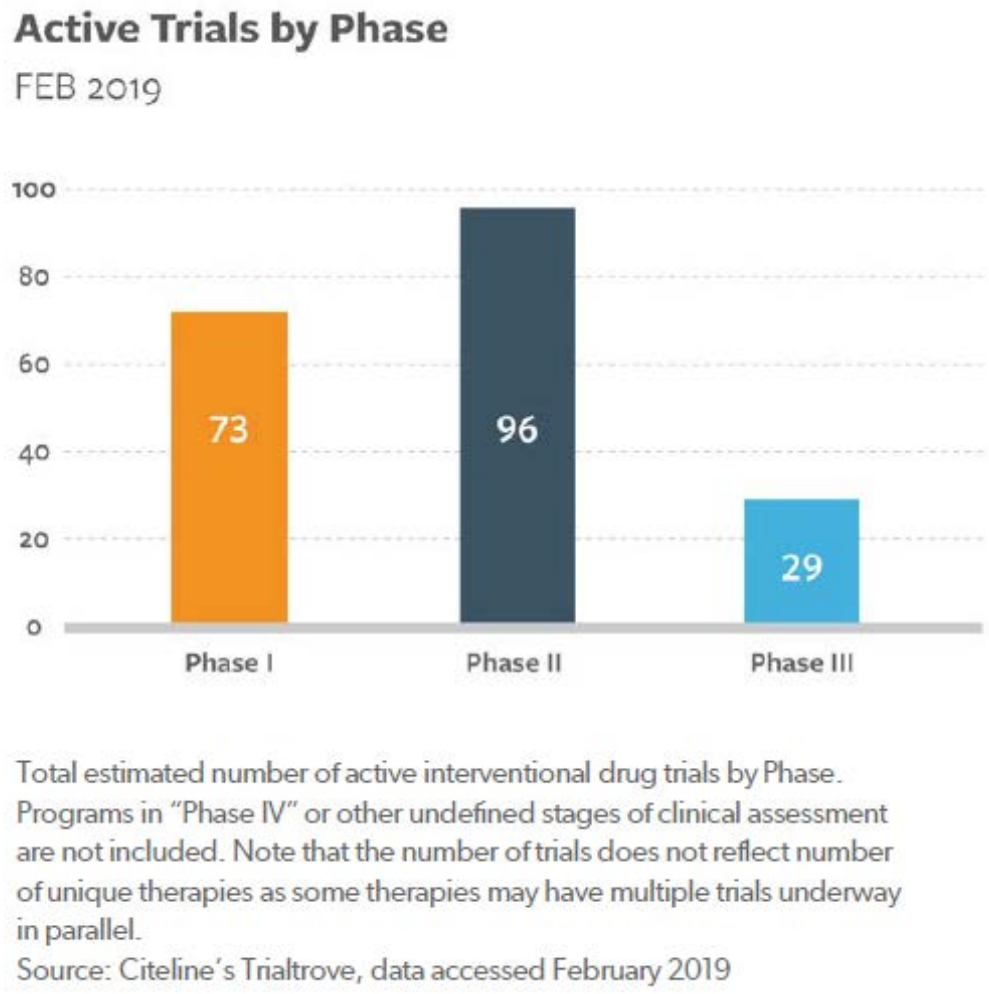


Source: Dorsey ER, Bloem BR, The Parkinson Pandemic: a call to action. *JAMA Neurology* 2017

Dorsey R. et al. Lancet Neurol 2018; 17: 939–53

"Among neurological disorders examined in the Global Burden of Disease, Injuries, and Risk Factors Study (GBD) 2015, Parkinson's disease was the fastest growing in prevalence, disability, and deaths"

The PD therapeutic pipeline is rich … yet clinical trialists face many challenges



Michael J Fox Foundation, Parkinson's Priority Therapeutic Pipeline Report, Feb 2019

Obstacles in PD Drug Development:

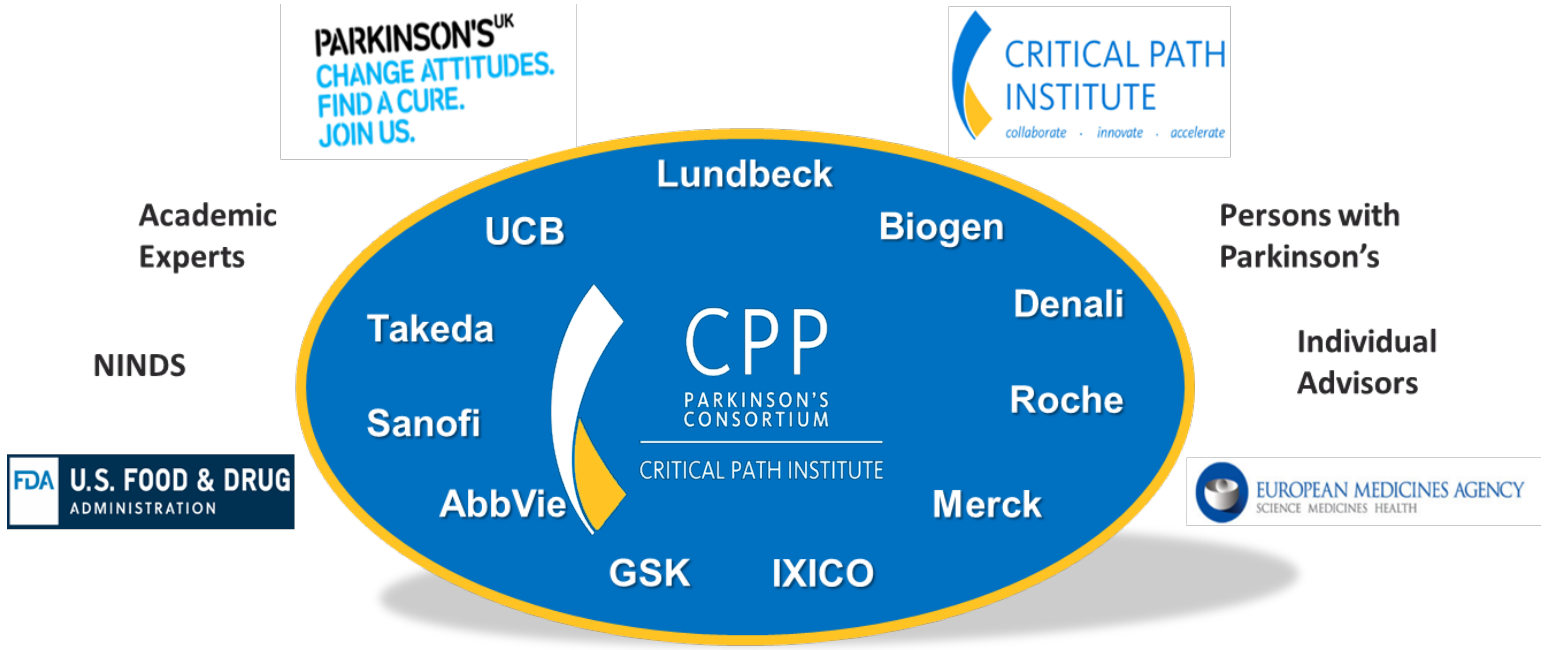
- Disease pathogenesis is unknown
- PD is characterized by phenotypic and genotypic heterogeneity
- Biomarkers that reflect disease presence, progression and severity are lacking
- Unpredictable placebo responses
- Concurrent symptomatic therapy may mask efficacy
- **Outcome measures lack precision**

Lang A. et al. Mov Disord. 2018 May;33(5):660-677

Critical Path for Parkinson's Consortium

Mission: *To serve as a leading International consortium to collectively advance data driven collaborative research under the advisement of worldwide regulatory agencies*

- CPP was launched in 2015 with a major goal to develop tools to quantify disease progression
- Successfully acquired and integrated patient level data from >9600 PD patients
- Qualification of imaging biomarker for enrichment of trials in early PD
- Current CPP focus is regulatory endorsement of PD drug disease trial model
- **Digital Drug Development Tools (3DT) team was launched under CPP with the goal of advancing regulatory readiness of digital health technologies in early PD studies**



Patient-Advocacy Organizations

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

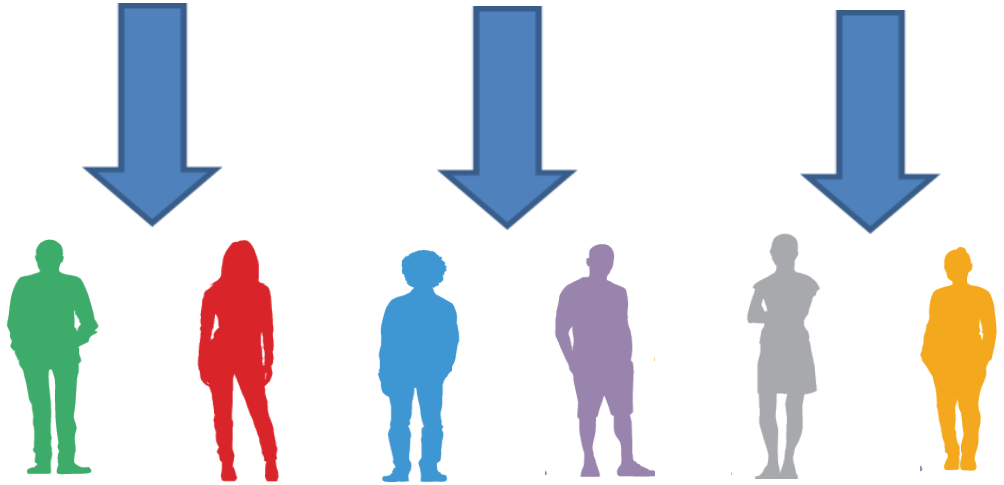
Academic Institutions

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

Future Model of Parkinson's Therapies

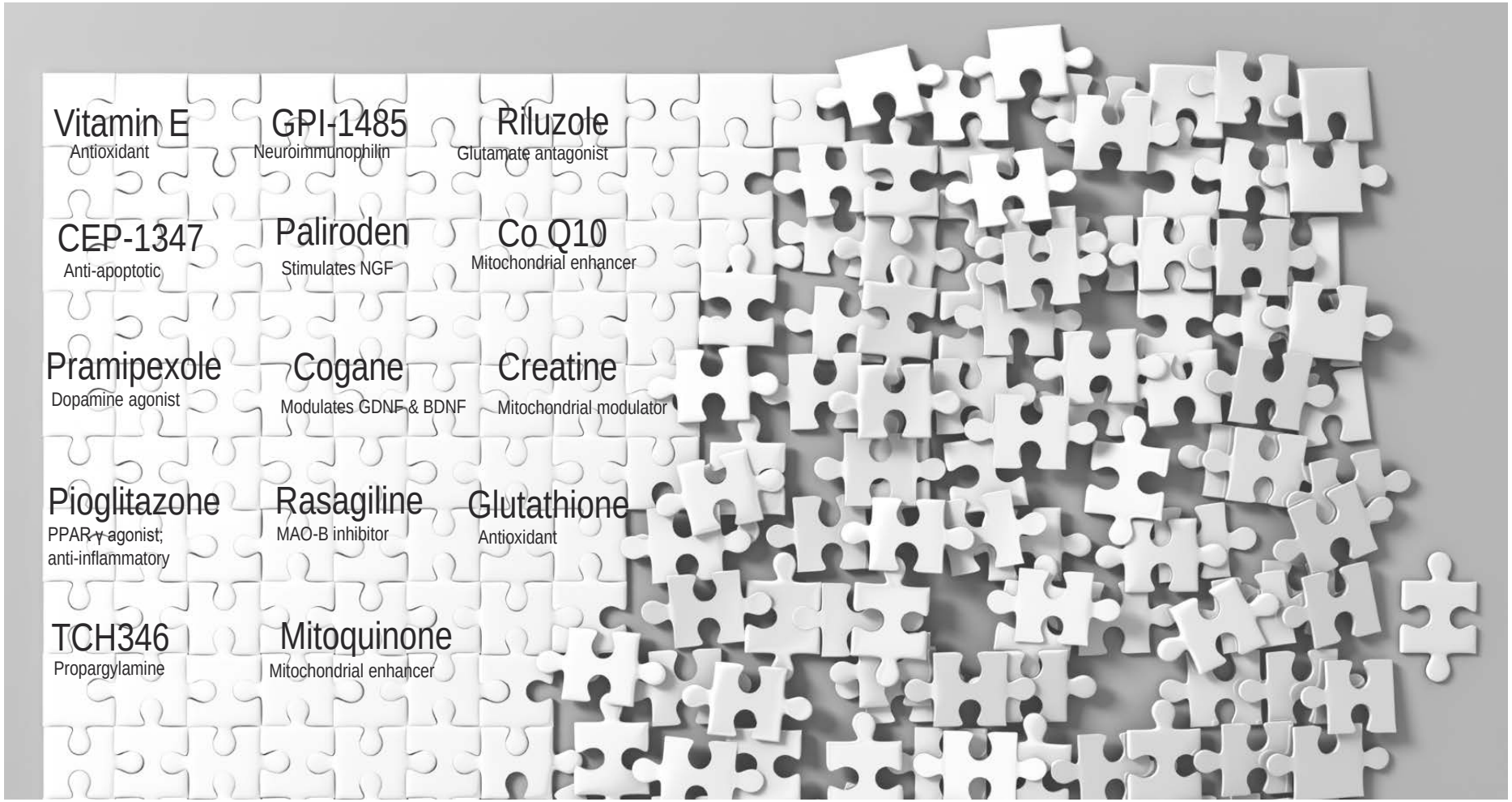
Parkinson's -
Not all one flavor

Personalized Medicine
targeted treatments



As modified from Alberto Espay

Can We Learn from Past Clinical Trials?



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CPP has Integrated Data from >10,000 People with Parkinson's From Around the World

OBSERVATIONAL COHORTS

- PPMI (n=1866)
- 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)
- CONFIDENT-PD (n=425)
- SURE-PD2 (n=75)
- SP512 (n=273)
- SP513 (n=561)

How is the CPP Database Enabling New Paths ?
Parkinson's Imaging Biomarker

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Qualification of novel methodologies for medicine development Share

Qualification opinion - Molecular neuroimaging of the dopamine transporter as biomarker to identify patients with early manifest Parkinsonism in Parkinson's disease

Qualification opinion on dopamine transporter imaging as an enrichment biomarker for Parkinson's disease clinical trials in patients with early Parkinsonian symptoms (PDF/762.14 KB)

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

EMA/765041/2017

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Drugs

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Biomarker Qualification Program

Letter of Support (LOS) Initiative

C-Path, CAMD	Molecular Neuroimaging Biomarker: Dopamine Transporter (DAT)	Exploratory Prognostic Biomarkers for Enrichment in Early Stage Parkinson's Disease Clinical Trials	3/16/2015: Letter of Support (PDF)

"We encourage the use of this biomarker in clinical trials to evaluate its utility for the identification of patients likely to show clinical progression of Parkinson's motor symptoms. We believe that sharing and Integrating data across trials can foster a more efficient path to biomarker qualification."

Sincerely,

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

DAT Imaging as an Enrichment Biomarker in Early PD Trials: *Integrated Datasets*

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Data analyzed for the qualification of the DAT neuroimaging biomarker

PPMI or Parkinson's Progression Markers Initiative
N = 481, 5-year, ongoing, multicenter, observational study

integration

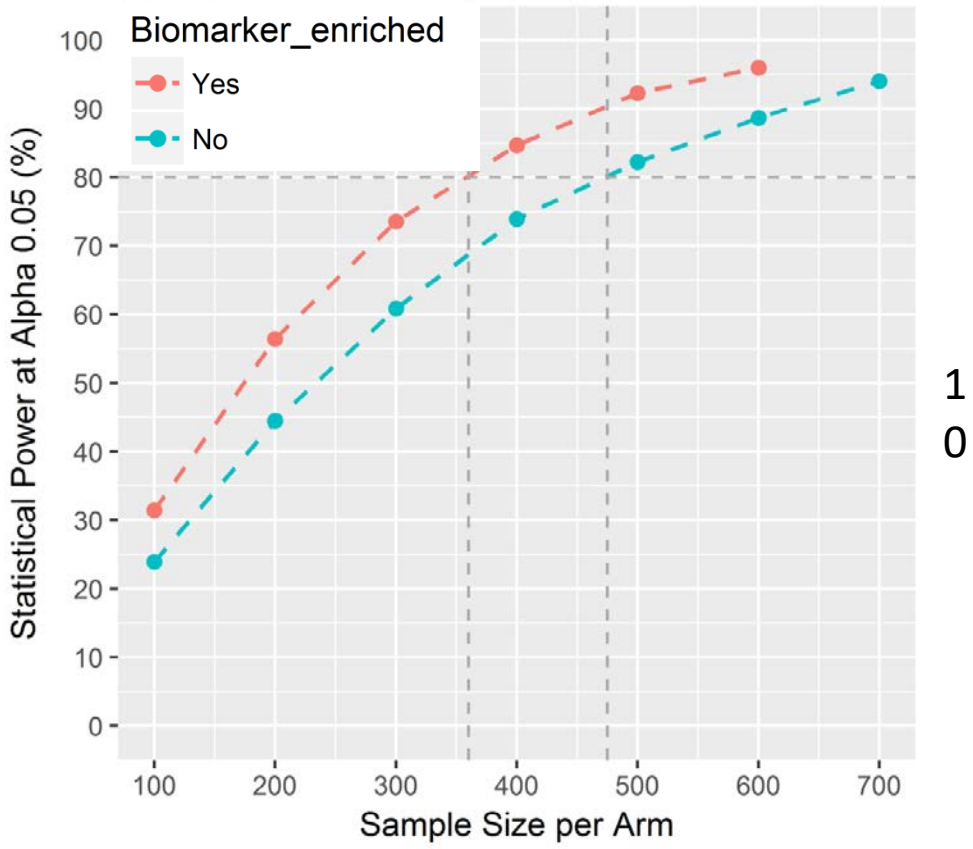
PRECEPT or Parkinson Research Examination of CEP-1347 Trial
N = 191, 2-year, multicenter, randomized, double-blind, placebo-controlled study

Total sample size: 672 subjects with early stage PD
Endpoint: harmonized MDS-UPDRS part III subtotal
DAT neuroimaging: visual assessment of DAT images at baseline

DAT = dopamine transporter

DAT Imaging as an Enrichment Biomarker in Early PD Trials:

Enrichment Allows Meaningful Reduction of Trial Size



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DAT = dopamine transporter neuroimaging;
SWEDD = scan without evidence of dopamine deficiency

~ 24% reduction in sample size by enrolling only subjects who are DAT deficient

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.

PD Clinical Trial Simulator—DAT Imaging for Enrichment

- # of subjects
- Follow up duration
- Assessment interval
- SWEDD rate
- # simulations

DAT Neuroimaging-Informed Early PD Clinical Trial Simulator - Version 1.0

Simulate clinical trials on patients with early-stage Parkinson disease

Click here for more information on this application.

Number of Subjects per Arm: 200

Duration of Subjects Follow-up (Months): 1 – 24

Assessment Interval (Months): 1 – 3 – 12

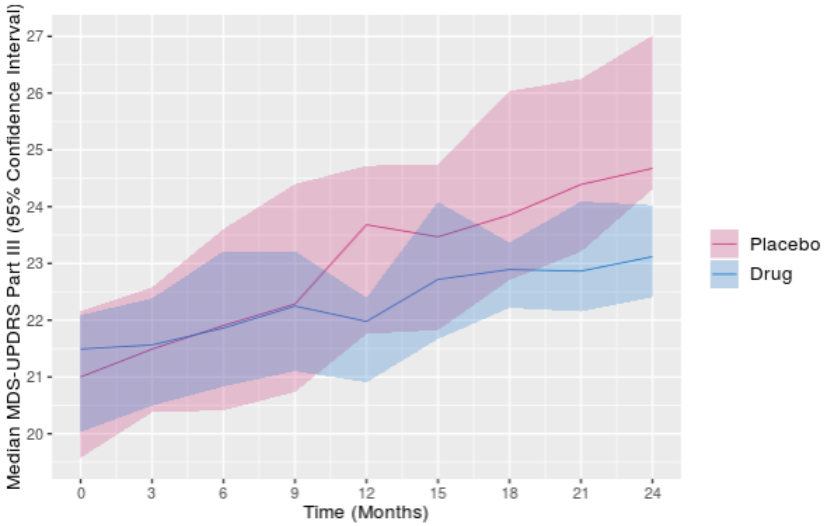
Proportion of Subjects with SWEDD (%): 0 – 14 – 28

Effect of Drug on Rate of Disease Progression (% Reduction): 0 – 50 – 100

Effect of Digital Measure on Noise of MDS-UPDRS Part III (% Reduction): 0 – 99

Number of Simulations: 10

Simulate



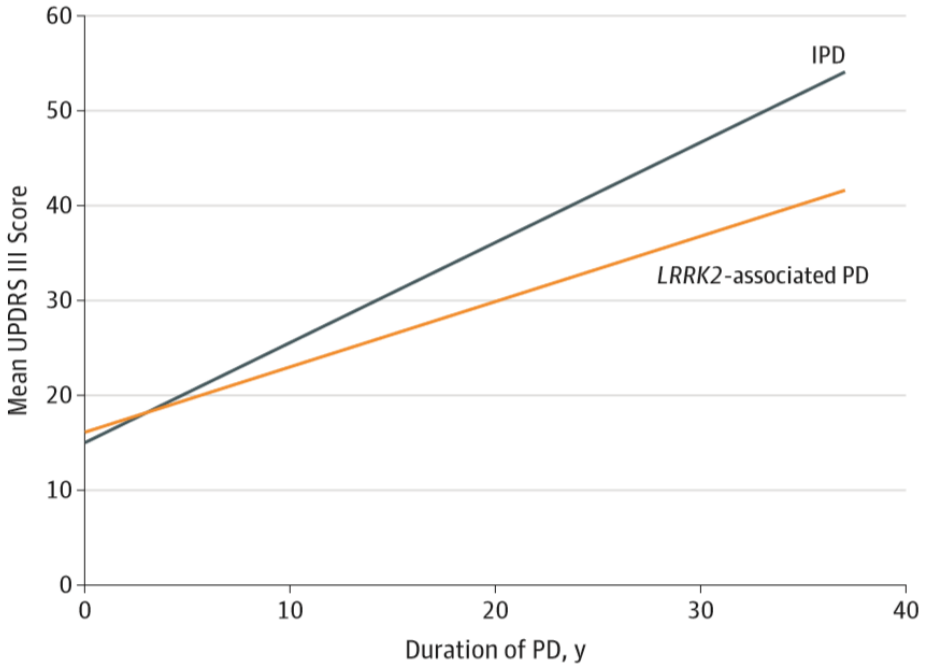
Characteristics	Values
Study Design	Placebo-Controlled Parallel Group
Total Number of Subjects	400
Study Duration (Months)	24
Assessment Interval (Months)	3
Effect of Drug on Rate of Disease Progression (% Reduction)	50
Effect of Digital Measure on Noise of MDS-UPDRS Part III (% Reduction)	0
Proportion of SWEDD (%)	14
Proportion of Female (%)	34
Median age (95% Confidence Interval) (Years)	62 (61, 63)
Number of Simulations	10
Monte-Carlo Standard Error for Calculation of Confidence Interval for Statistical Power (%)	12.6
Statistical Power (%, 95% Confidence Interval)	80 (44.4, 97.5)

By Daniela Conrado (Model and App Developer) and Jackson Burton (App Developer) on behalf of the Critical Path for Parkinson's (CPP) consortium. E-mail DConrado@c-path.org with questions or comments.

Open Source Clinical Trial Simulator

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)

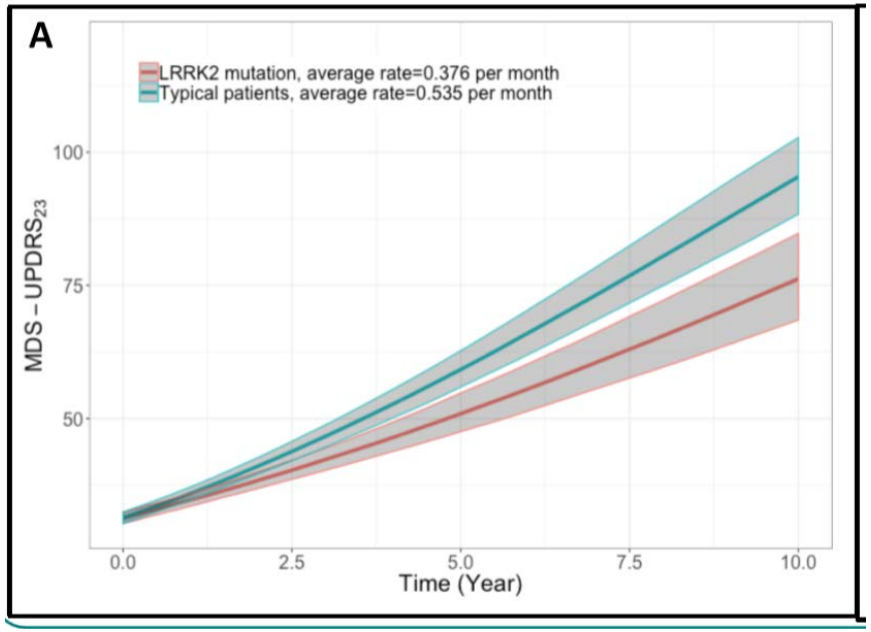


Saunders-Pullman, R., et al., (2018). Progression in the *LRRK2* -Asssociated Parkinson Disease Population. *JAMA Neurology*, *75*(3), 312.

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

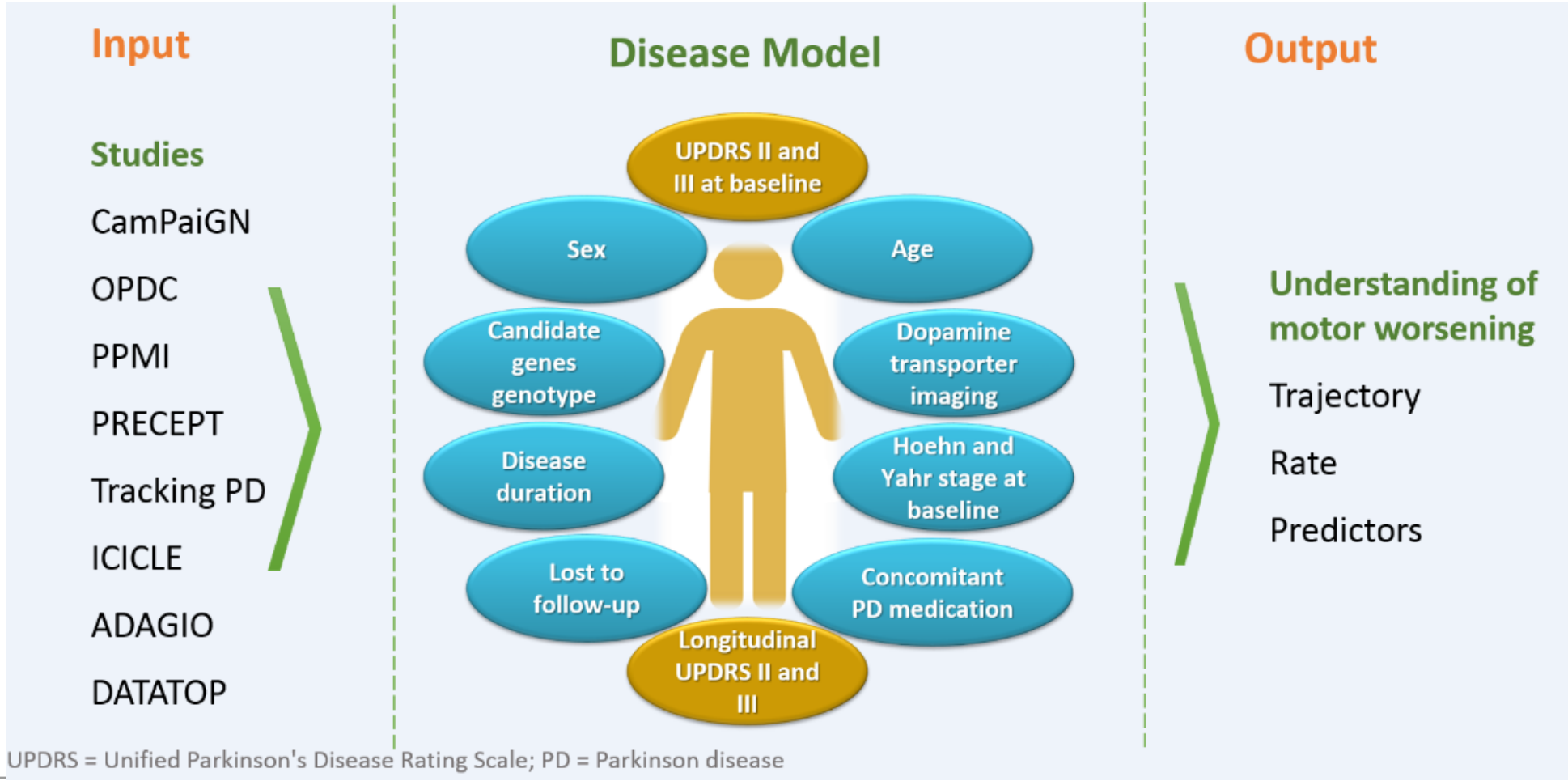


On behalf of Malidi Ahamadi, Merck And the CPP modeling and simulation team

Ahamadi Et al., Clin Pharmacol Ther. 2019 Sep 23. doi: 10.1002/cpt.1634.

Parkinson's Drug-Disease-Trial Model integrates Biomarkers, Genetics and Clinical Parameters

- 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

Current Landscape Highlights Impact of Mobile Technologies

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The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

FRONTIERS IN MEDICINE

Mobile Devices and Health

Ida Sim, M.D., Ph.D.

N Engl J Med 2019; 381:956-968 ; Sept 2019

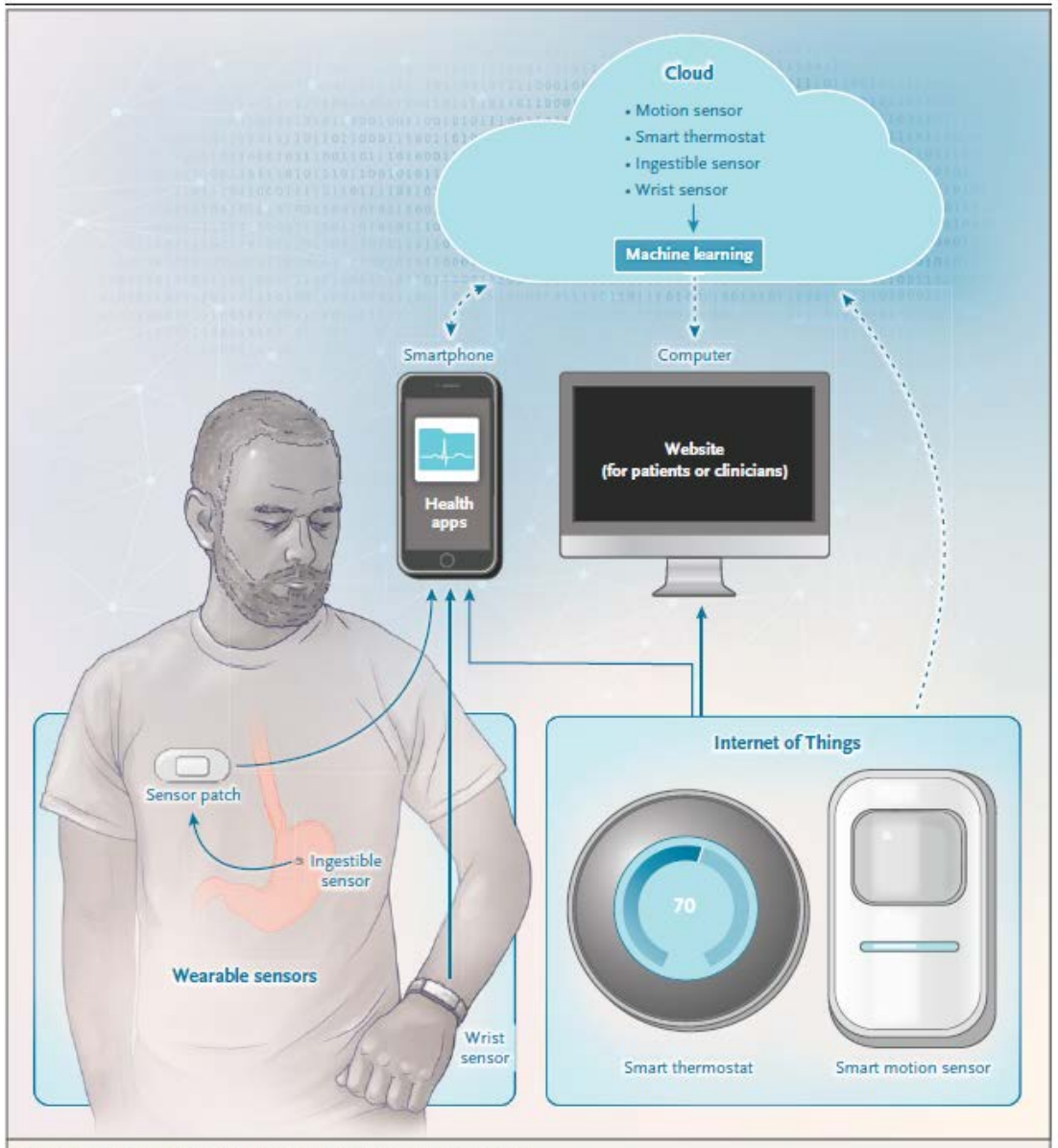

Figure 1. Data Flow of Wearable Sensors and the Internet of Things.

FDA leadership Recognizes the Potential Impact of Mobile Technologies

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Decentralized trials and mobile devices: enhancing trial feasibility and data collection

FDA

Decentralized trials

- Enabled by mobile technologies: e.g., local collection of trial endpoints, safety monitoring
- Addresses distributed pt populations, allows greater diversity of patient populations and sites of care
- *Challenges*: applying GCP and regulatory frameworks: consent, investigator and local physician roles / responsibilities, safety monitoring, drug supply, endpoints validation, security and data integrity, data traceability

Mobile technologies: wide range of possible uses in trials, such as….

- Tracking adherence
- *Novel* trial endpoints: passively (e.g., ambulation, vital signs) *or* actively assessed (e.g., timed tasks or ePROs)
- Safety monitoring
- Recruitment and retention – connecting and engaging patients

Mobile technology: wide range of sources

- Smart phones: for videos, photographs of lesions, behaviors, other findings, or collection of ePROs
- Other: accelerometers, ECGs, temp sensors, EEGs, movement sensors, GPS, glucometers, spirometers

Mobile technologies: interpretation and regulatory implications - *from data to endpoints*

- Reliability of measurements: accuracy, reproducibility, data source
- Challenges of interpretation – creating meaningful endpoints: how patients *feel and function*

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Peter Stein,
CDER
Office of New Drugs

PRO Consortium
April 2019

CPP Digital Drug Development Tools (3DT) Team

- A subset of CPP member organizations* have convened to collaborate pre-competitively with the goal of optimizing the efficiency of paths for developing digital tools for PD drug development.
- 3DT is leveraging a prospective study called WATCH-PD (Wearable Assessments in The Clinic and Home in PD), a 12-month multi-center, longitudinal, digital assessment study of PD progression in subjects with early, untreated PD as an exemplar pilot study to collect digital data in an early PD target population for the purpose of facilitating discussion and alignment with regulatory agencies.
- Face to face meetings with FDA and EMA have taken place and advice is being adopted into multiple digital device clinical studies

Biogen, Takeda, UCB, Merck, Roche, Lundbeck, GSK
Academic advisors: University of Rochester, Rush University, Parkinson's UK, Michael J Fox Foundation

Ray Dorsey,
Principal Investigator

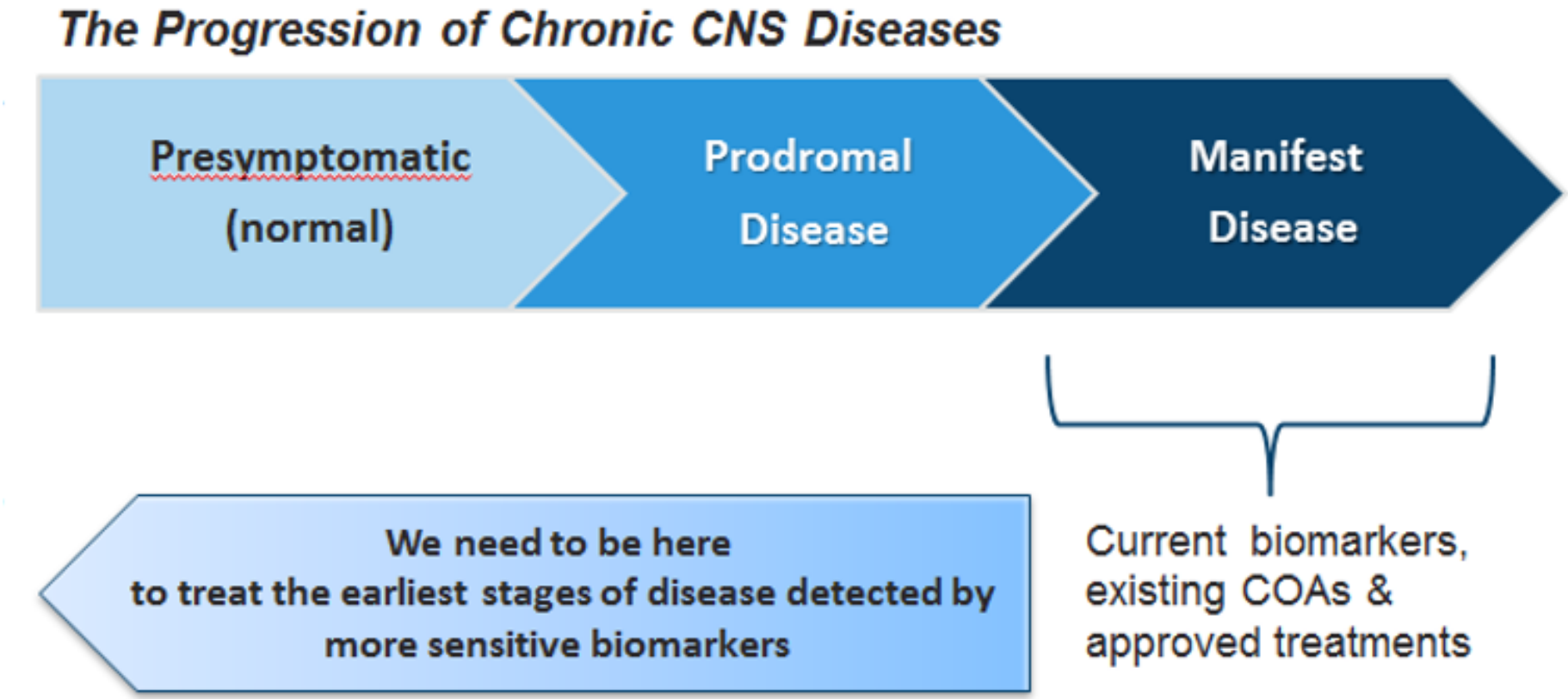
CPP's Early Interactions with FDA and EMA are Having Impact

May 14, 2019

EMA's Innovation Task Force (ITF)

July 15, 2019

The Future Vision for Treating Nervous System Disorders

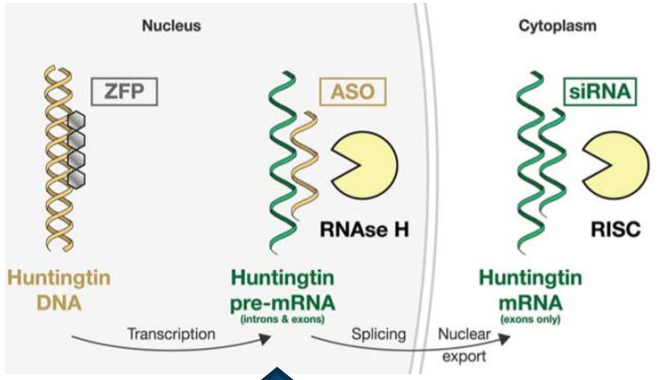


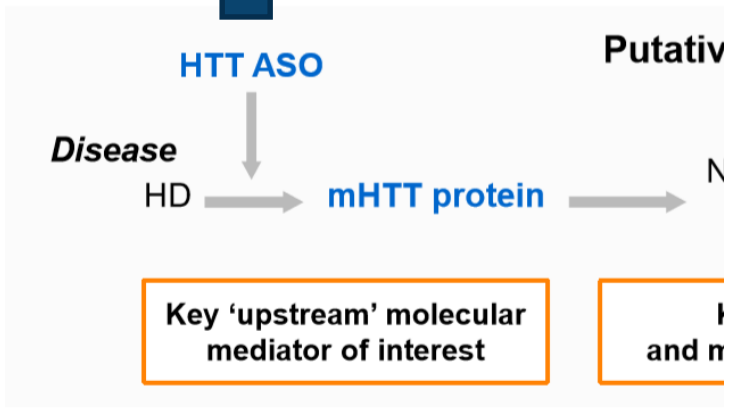
*COA = clinical outcome assessments

Stephenson and Arneric,
Translational Medicine in CNS Drug Development
V29, Chapter 20 (Elsevier, Feltner and Nomikos Eds)

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

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Huntington's Disease Regulatory Science Consortium

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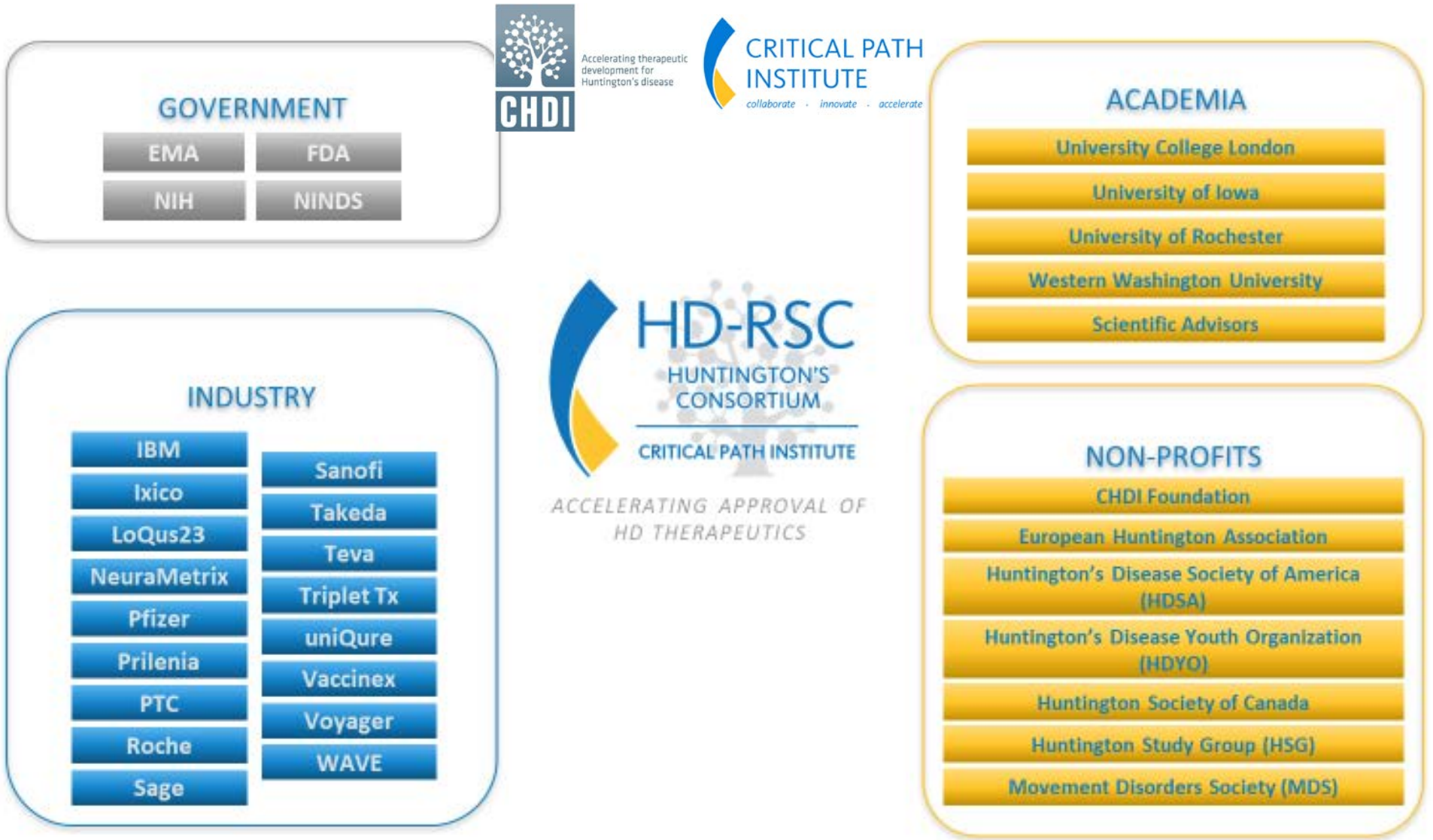

Progress in HD will Inform Therapeutics Across Neurodegenerative Diseases

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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."

Alzheimer's disease from researcher to caregiver: a personal journey and call to action

Expert Rev. Neurother. 14(5), 465–467 (2014)

Diane Stephenson

Critical Path Institute, 1730 E River Rd, Tucson, AZ 85718, USA
Tel.: +520 382 1405
Fax: +520 382 1389
Dstephenson@c-path.org

Five-year view (2014): *Still holds true today*

- it is anticipated that the explosion in data sharing, big data and innovative technologies will positively impact AD drug development.
- Increased participation of **patients** and caregivers in drug development and growing investments in PPPs will improve the sense of global commitment and alignment of efforts.
- There is an urgent need for approval of new effective treatments to support continued investments by diverse stakeholders and a global need for **aligning of efforts**.
- With this **call to action**, it is my sincere hope that 25 years from now, my own children do not have to face the helplessness that this disease brings to all.

Acknowledgements

- Critical Path for Parkinson's Consortium Members and Scientific Advisors
- Parkinson's UK
- Robert Alexander, CPP Industry Co-director Takeda
- CPP Digital Drug Development Tool Team (3DT)
  - Jesse Cedarbaum, Coeruleus Clinical Sciences (formerly Biogen)
- Michael J Fox Foundation
- Ray Dorsey, Univ Rochester
- CHDI
- FDA: Dr. Billy Dunn, Dr. Michelle Campbell, Dr. Gerald Podskalny, Dr Kevin Krudys
- EMA: Prof Maria Tome, Prof Pavel Balabanov, Prof Corrine de Vries
- Critical Path Institute: Mike Minchik, John Maciejewski, Klaus Romero, Ariana Mullin Martha Brumfield, Joseph Scheeren, Linda Restifo (U of Arizona), Derek Hill, Mike Lawton, Janice Hitchcock