Model-Informed Biomarker Qualification:

Alzheimer and Parkinson Disease Neuroimaging Biomarkers

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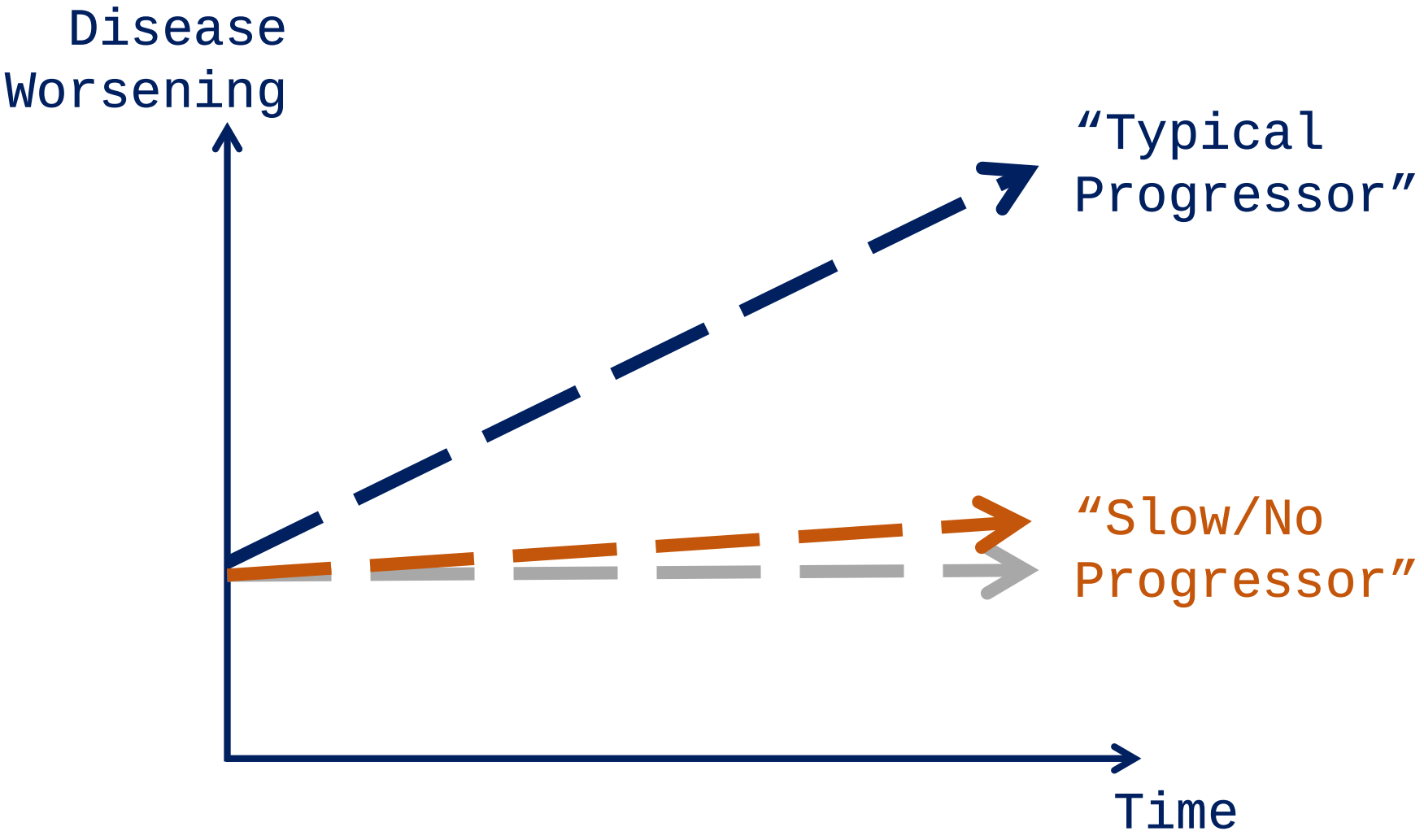
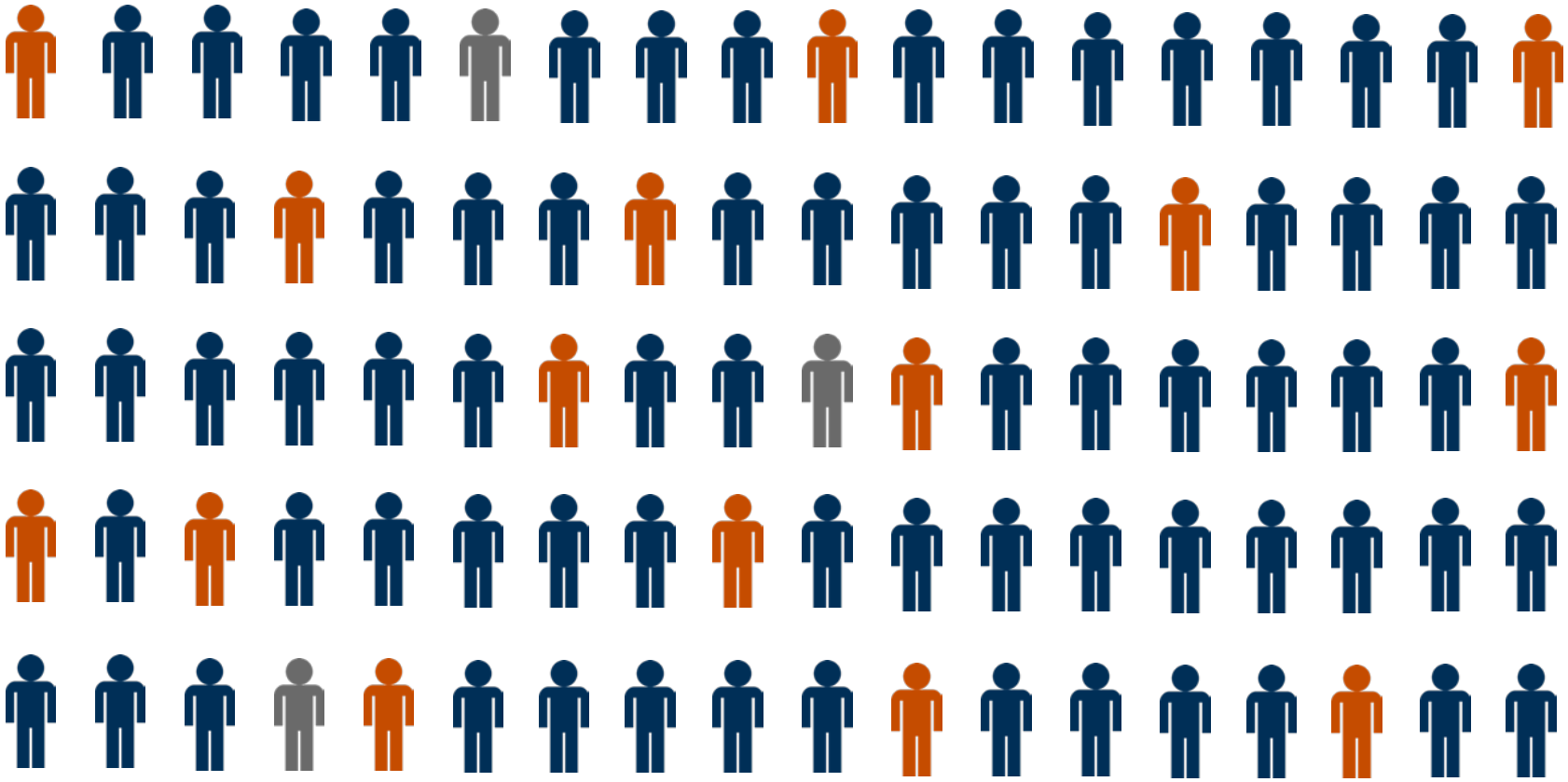
Not Uncommon in AD/PD Trials

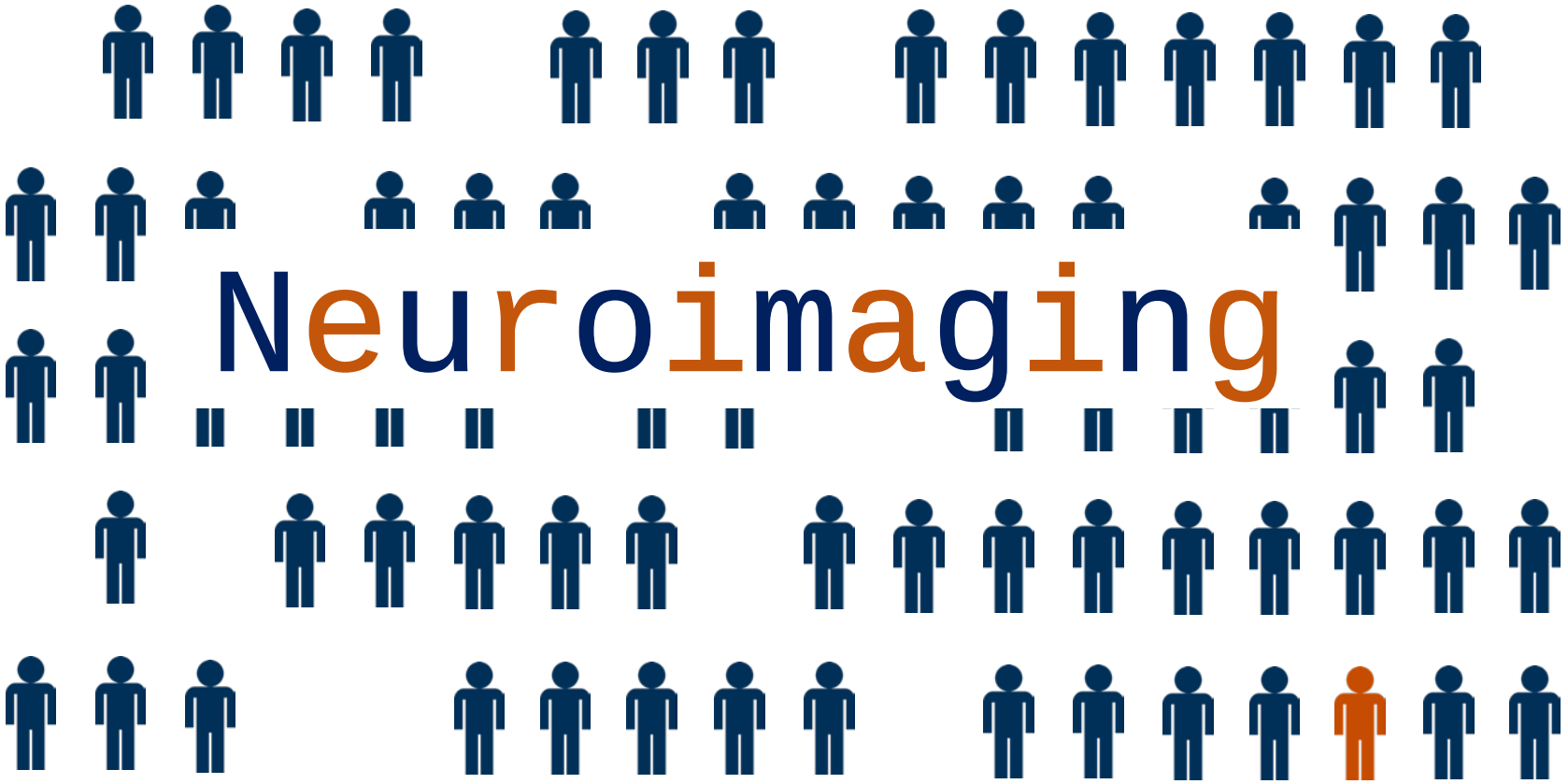


AD = Alzheimer disease
PD = Parkinson disease

How Can Clinical Trialists Know Up Front Who Will Be A "Typical Progressor"?



How Can Clinical Trialists Know Up Front Who Will Be A "Typical Progressor"?



Take-Home Messages

- Neuroimaging as a prognostic enrichment biomarker can help with AD/PD clinical trial enrollment.

- Disease progression modeling and Monte-Carlo simulations can support biomarker qualification.

Please don't leave.
We will tell you **HOW**!

AD = Alzheimer disease
PD = Parkinson disease

This Presentation

In scope

Prognostic enrichment biomarker

Out of scope

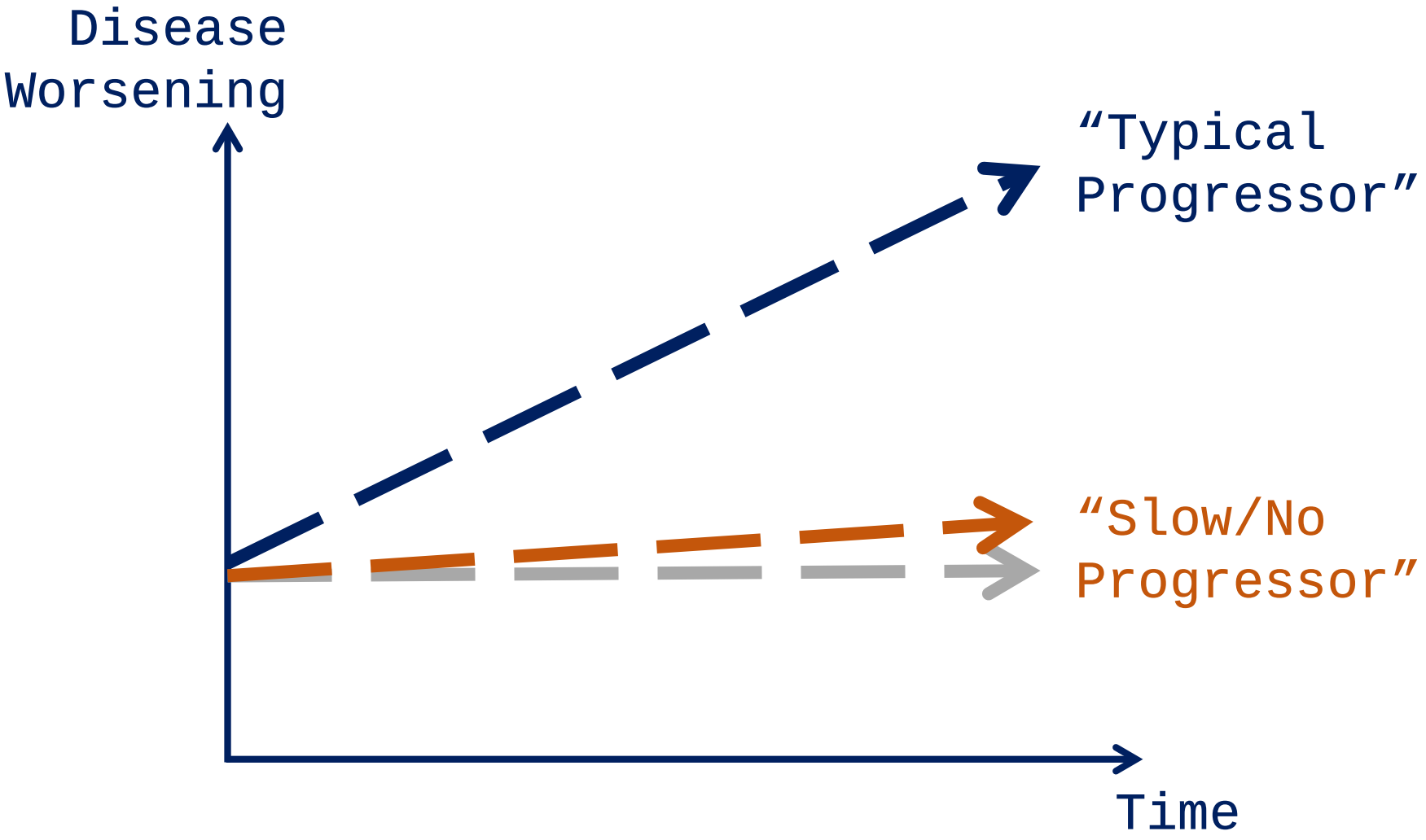
- Diagnostic biomarker
- Susceptibility/risk biomarker
- Predictive biomarker
- Safety biomarker
- Monitoring biomarker
- Pharmacodynamic/response biomarker

This Presentation

- Two examples:
  - Alzheimer disease (AD)
  - Parkinson disease (PD)

- Definition of acronyms are at the bottom of the slides

The Need in AD/PD: Why Now?



AD = Alzheimer disease
PD = Parkinson disease

The Need in AD/PD: Why Now?

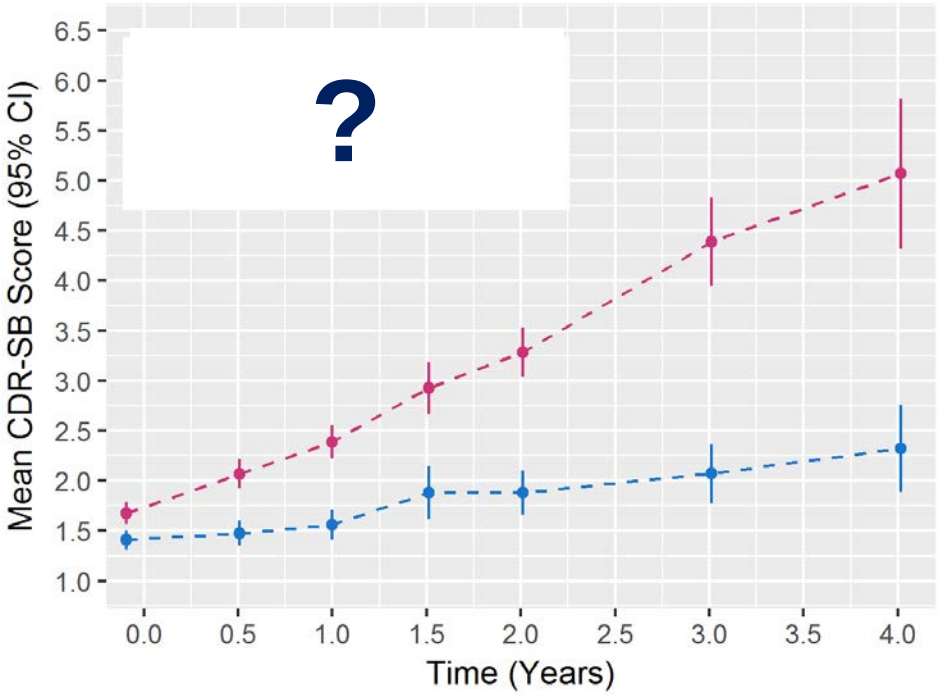
- There is an increased focus on evaluating drug candidates at earlier disease stages.

- Selection of patients in trials of early AD/PD is challenging due to pathophysiological uncertainty and patient heterogeneity.

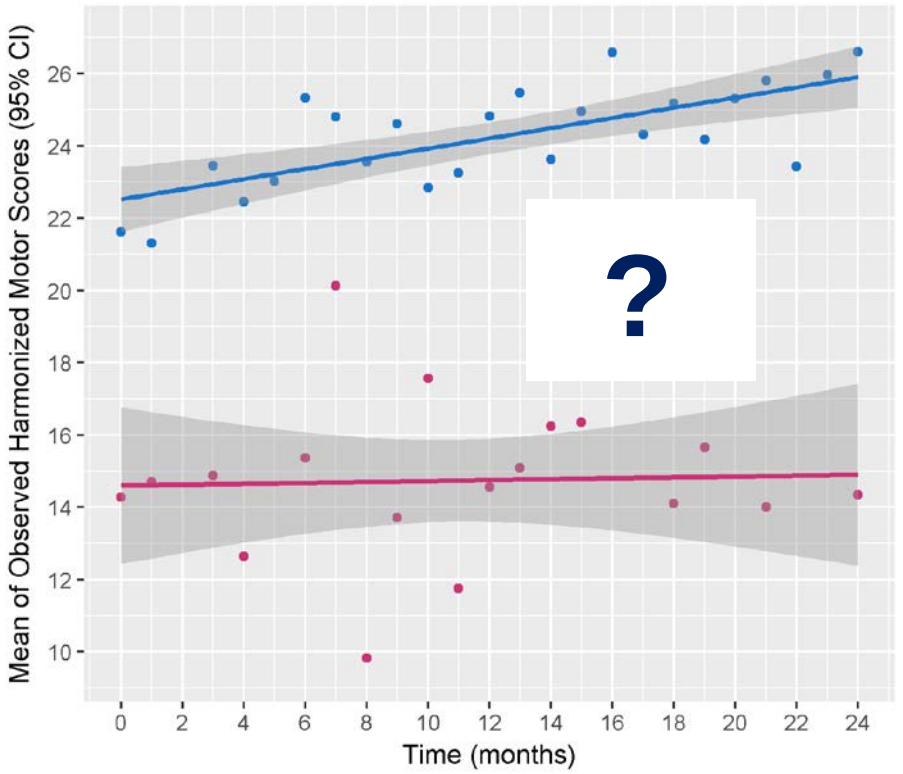
AD = Alzheimer disease
PD = Parkinson disease

Typical *vs.* Slow Progressors

MCI ADNI-1 + ADNI-2



Early PD PPMI + PRECEPT



MCI = mild cognitive impairment
PD = Parkinson disease
ADNI = Alzheimer's disease neuroimaging initiative
PPMI = Parkinson's progression marker initiative
PRECEPT = Parkinson Research Examination of CEP-1347 trial

Neuroimaging at Baseline Helps Predict Progression

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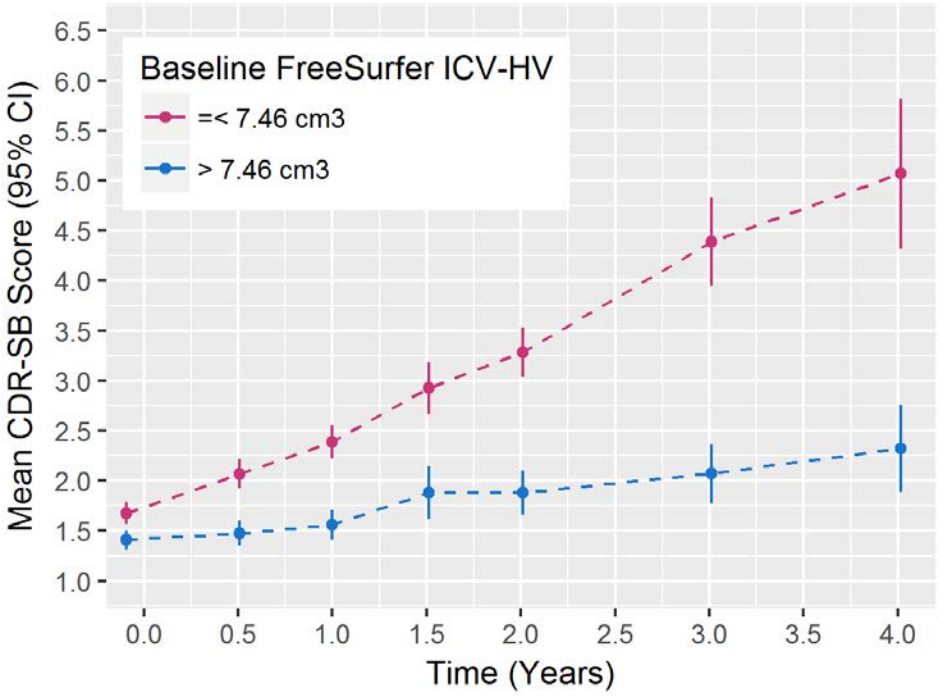
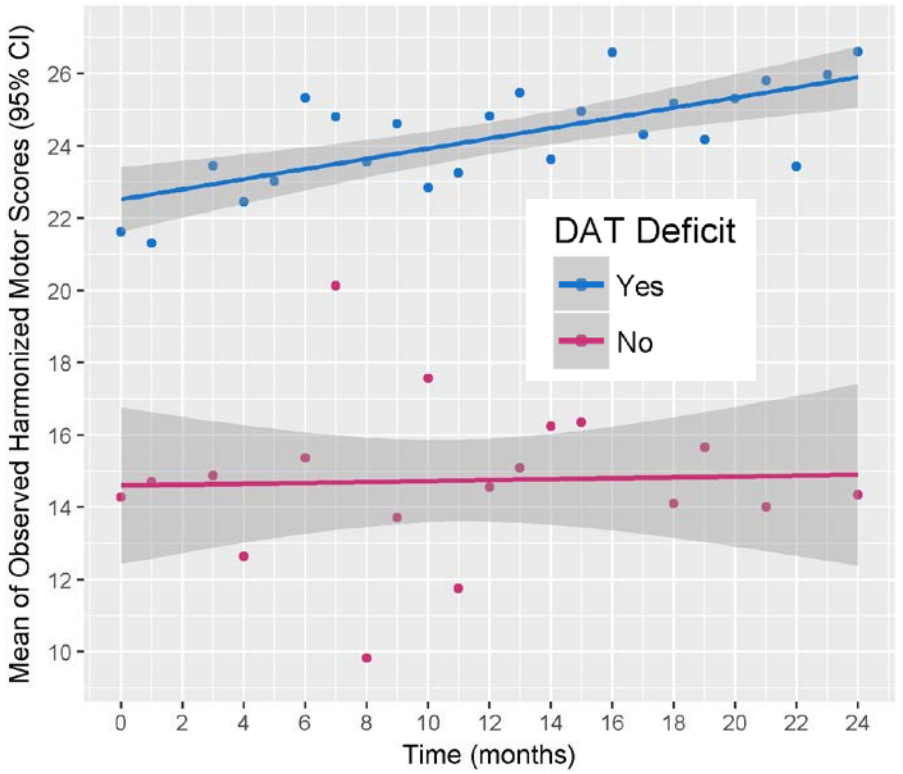
MCI ADNI-1 + ADNI-2



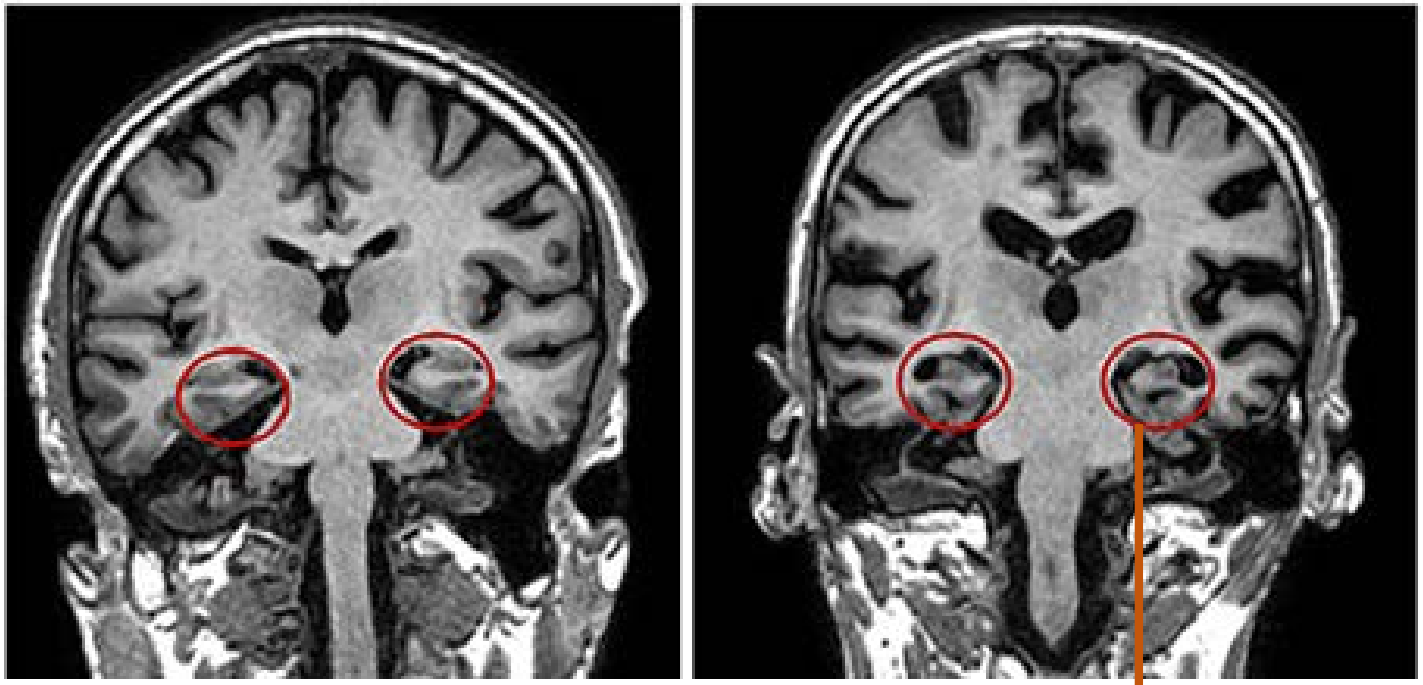
Early PD PPMI + PRECEPT



DAT = dopamine transporter
DAT type of assessment = visual
ICV-HV = intracranial volume-adjusted hippocampal volume
FreeSurfer™ = an algorithm for calculating ICV-HV
7.46 cm^3 = median of the ICV-HV in dataset

Enrichment Biomarker for MCI Trials: Hippocampal Volume

MRI Healthy Control MCI



http://journal.frontiersin.org/article/10.3389/fnins.2016.00443/full

Loss of hippocampus volume shown by a larger dark area

MCI = mild cognitive impairment
MRI = magnetic resonance imaging

Enrichment Biomarker for Early PD Trials: Dopamine Transporter

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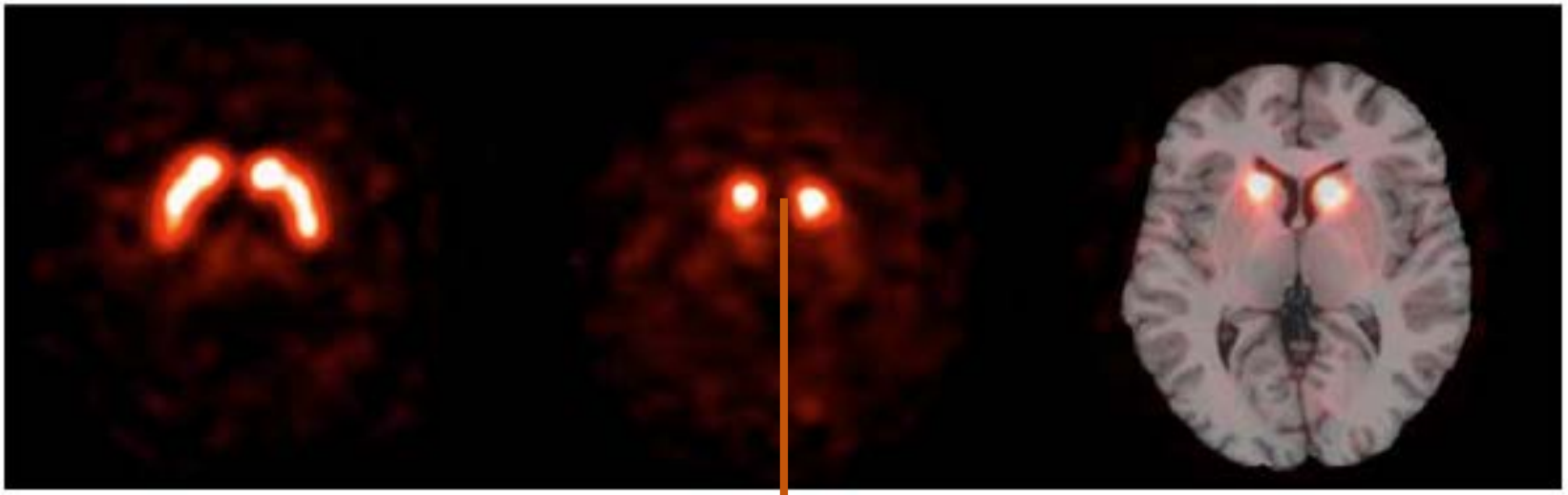
Healthy Control	PD	PD
SPECT	SPECT	MRI + SPECT



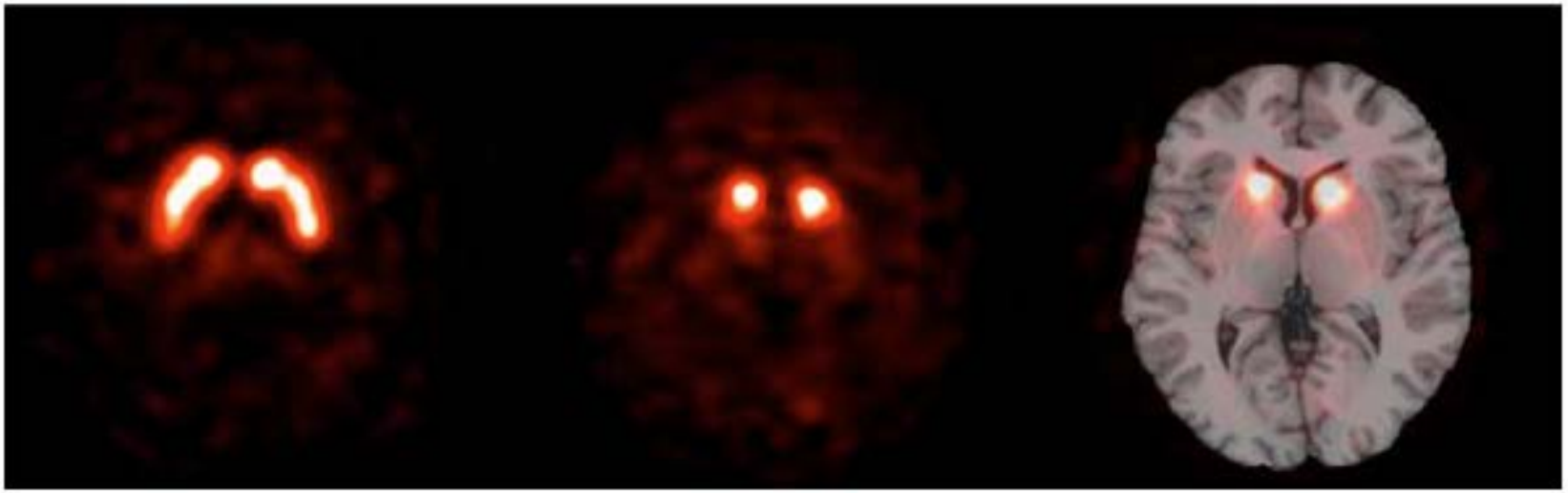
Stephenson D et al. https://c-path.org/wp-content/uploads/2016/05/ppmi_dat_poster_final_4-29-16_rev.pdf

Dopamine transporter deficiency shown by reduced binding of the ligand

PD = Parkinson disease
MRI = magnetic resonance imaging
SPECT = single-photon emission computed tomography

Enrichment Biomarker for Early PD Trials: Dopamine Transporter

Healthy Control	PD	PD
SPECT	SPECT	MRI + SPECT



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PD subjects with a scan without evidence of dopaminergic deficit = SWEDD

Pathophysiological Plausibility of the Biomarkers

- Hippocampal volume (HV) loss is implicated in the Alzheimer disease pathology.
- Dopamine transport (DAT) loss is implicated in the Parkinson disease pathology.

C-Path's Consortia Pursue Qualification of HV and DAT

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Non-profit Research Organizations
- Alzheimer's Association
- UsAgainst Alzheimer's Network
- Alzheimer's Research UK
- Alzheimer's Drug Discovery Foundation
- CHDI Foundation

Government and Regulatory Agencies
- EMA
- NINDS
- NIA
- FDA
- NIH

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- University of Cambridge
- Newcastle University
- University of Glasgow

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

HV = hippocampal volume; DAT = dopamine transporter

C-Path's Consortia Pursue Qualification of HV and DAT

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Obtain FDA qualification of HV neuroimaging as a prognostic enrichment biomarker for amnestic MCI trials

CRITICAL PATH FOR PARKINSON'S

Obtain EMA qualification of DAT neuroimaging as a prognostic enrichment biomarker for early PD trials

HV = hippocampal volume; DAT = dopamine transporter

Evaluating the Enrichment Utility of HV and DAT

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CRITICAL PATH FOR ALZHEIMER'S DISEASE

ADNI-1 or Alzheimer's Disease Neuroimaging Initiative Part 1

N = 381,observational

ADNI-2 or Alzheimer's Disease Neuroimaging Initiative Part 2

N = 321, observational

CDISC

InDDEx or Investigation into Delay to Diagnosis of Alzheimer's disease with Exelon Trial (Placebo Arm)

N = 349, clinical trial

Sample size = 1051 subjects with MCI
External validation set = InDDEx
Endpoint = CDR-SB

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PPMI or Parkinson's Progression Markers Initiative

N = 481, observational

CDISC

PRECEPT or Parkinson Research Examination of CEP-1347 Trial (Placebo Arm)

N = 191, clinical trial

Sample size = 672 subjects with early PD
Endpoint = MDS-UPDRS part III

HV = hippocampal volume; DAT = dopamine transporter; CDR-SB = Clinical Dementia Rating Scale Sum-of-Boxes; MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale

Linear Early PD Progression: MDS-UPDRS Part III

Rate of change in MDS-UPDRS Part III scores was described by a linear mixed-effects model

$$\frac{dScore_i}{dt} = r_i$$

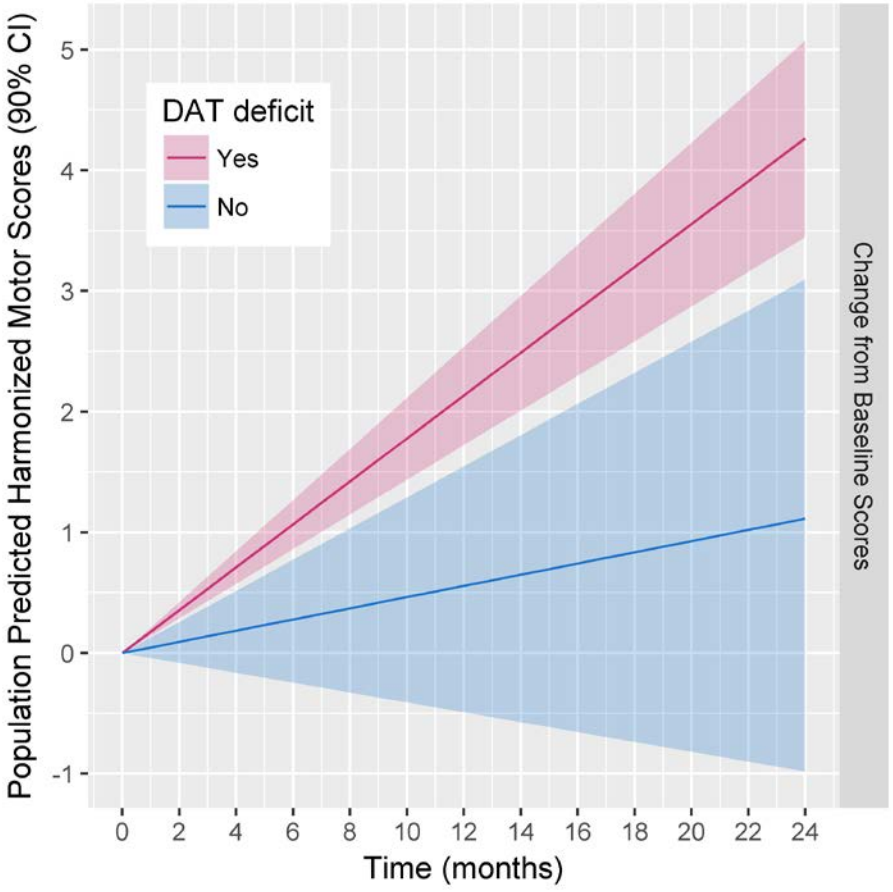
The linear mixed-effects model included as covariates:

- effect of DAT status on progression rate
- (effect of baseline on progression rate)
- effect of DAT status on baseline
- effect of age on baseline

Conrado DJ et al. Clin Transl Sci. 2018 Jan;11(1):63-70

PD = Parkinson disease; MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale

DAT Status is a Predictor of Progression Rate



Average progression in PD subjects without DAT deficit (SWEDD) is less than half of that in PD subjects with DAT deficit

Conrado DJ et al. Clin Transl Sci. 2018 Jan;11(1):63-70

CI = confidence interval
DAT = dopamine transporter

Non-Linear MCI Progression: CDR-SB

Rate of change in CDR-SB scores was described by a generalized logistic model (mixed-effects beta regression)

$$\frac{\mathrm{dScore_i}}{\mathrm{dt}} = \mathrm{r_i} \times \mathrm{Score_i} \times \left[1 - \left(\frac{\mathrm{Score_i}}{\mathrm{max(Score_i)}}\right)^{\beta}\right]$$

MCI = mild cognitive impairment; CDR-SB = Clinical Dementia Rating Scale Sum-of-Boxes

Non-Linear MCI Progression: CDR-SB

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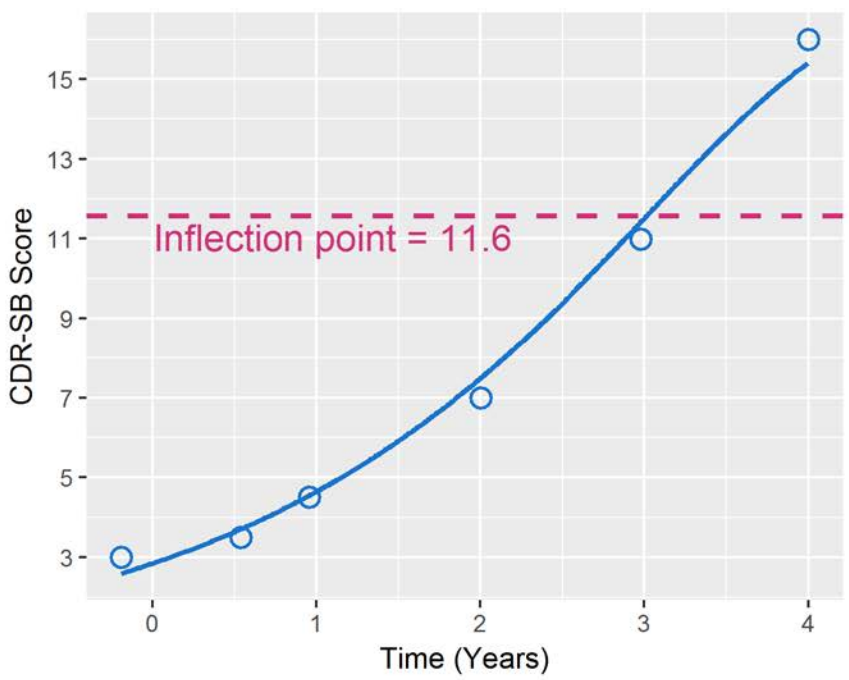
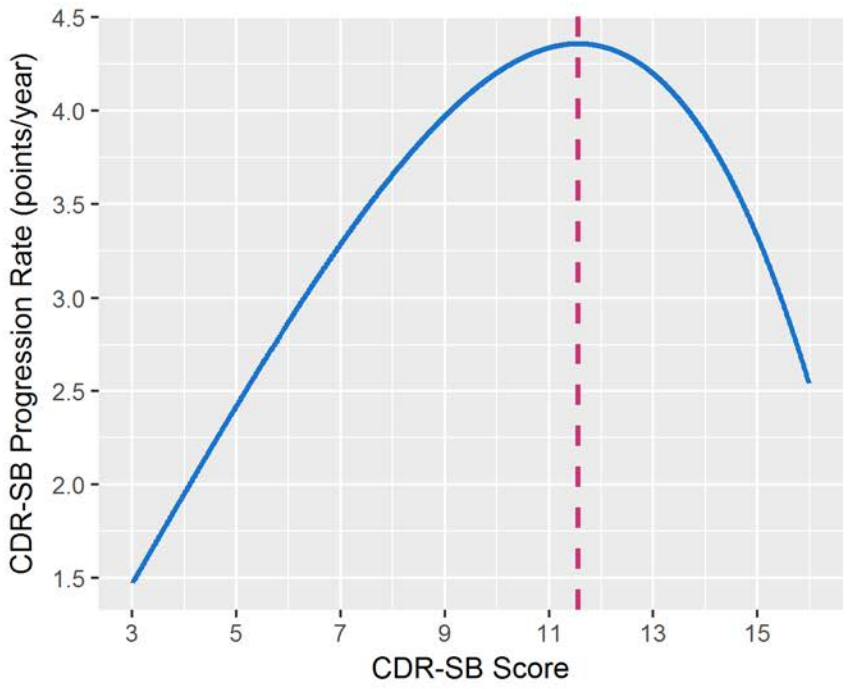
Rate of change in CDR-SB scores was described by a generalized logistic model (mixed-effects beta regression)





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Non-Linear MCI Progression: CDR-SB

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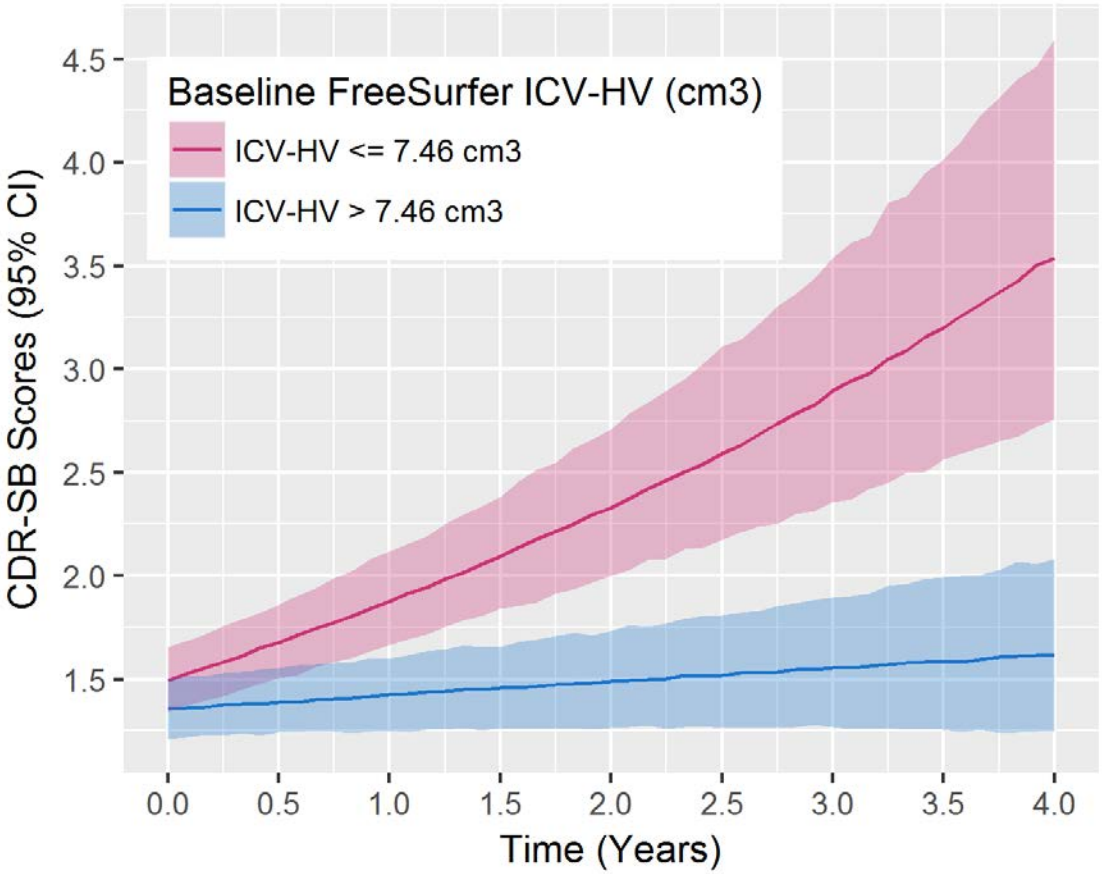
Rate of change in CDR-SB scores was described by a generalized logistic model (mixed-effects beta regression)

The nonlinear mixed-effects model included as covariates:

- effect of ICV-HV on progression rate
- effect of APOE-ε4 genotype on progression rate
- effect of MMSE on baseline and progression rate
- effect of age on progression rate
- effect of sex on progression rate

APOE-e4 = apolipoprotein E-encoding gene ϵ4 allele; MMSE = mini-mental state examination; ICV-HV = intracranial volume-adjusted hippocampal volume

HV is a Predictor of Progression Rate



An 1 cm^3 decrease in baseline ICV-HV is associated with more than 50% increase in CDR-SB progression rate

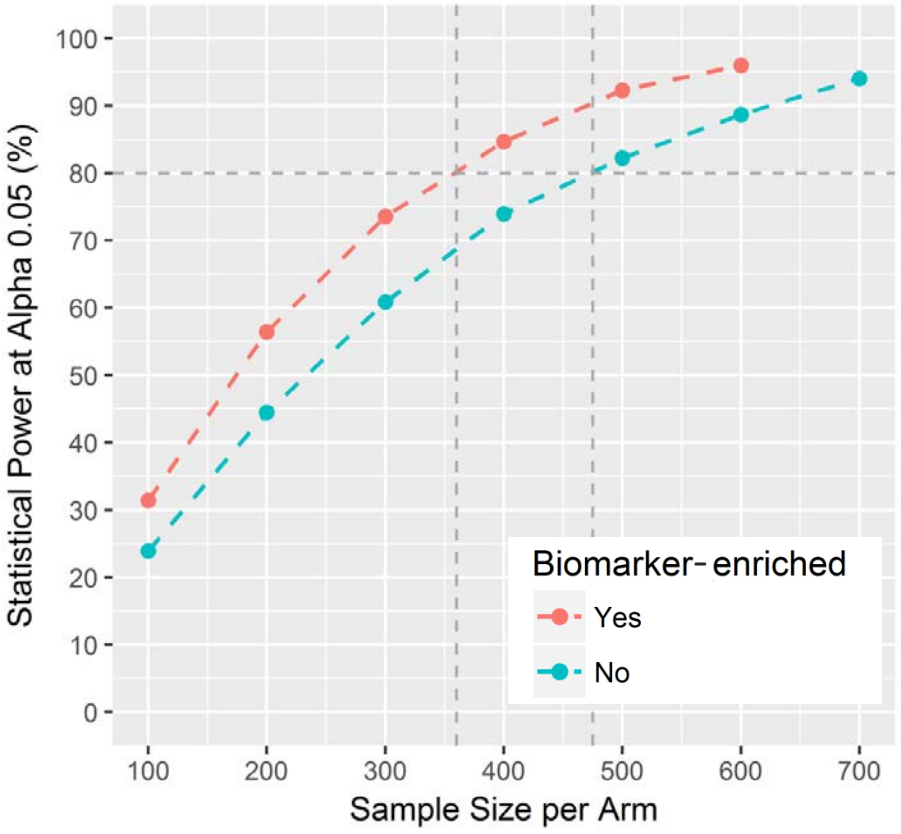
ICV-HV = intracranial volume-adjusted hippocampal volume
CDR-SB = Clinical Dementia Rating Scale Sum-of-Boxes

But That is Not Enough!

We need Monte-Carlo clinical trial simulations to show DAT/HV enrichment utility and magnitude

- Enrichment utility = ability of DAT/HV increase clinical trial efficiency, with efficiency being a measurable feature
- Enrichment magnitude = amount in which DAT/HV can increase the trial efficiency
- Metric of trial efficiency = trial size

DAT-based Enrichment Reduces Early PD Trial Size



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

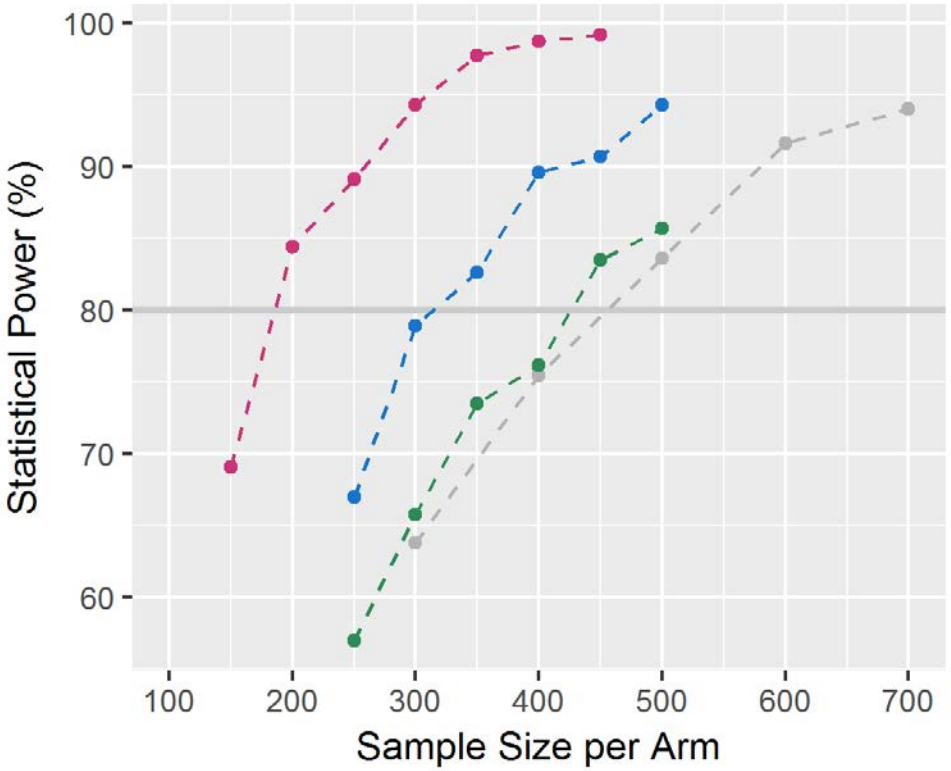
Conrado DJ et al. Clin Transl Sci. 2018 Jan;11(1):63-70

Monte-Carlo Simulation Assumptions:

- 24-month placebo-controlled parallel group trials
- 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

DAT = dopamine transporter
SWEDD = scan without evidence of dopaminergic deficiency

HV-based Enrichment Reduces MCI Trial Size



~26% and ~55% reduction of sample size with baseline ICV-HV <84.1th and <50th percentile

Clinical trial with:

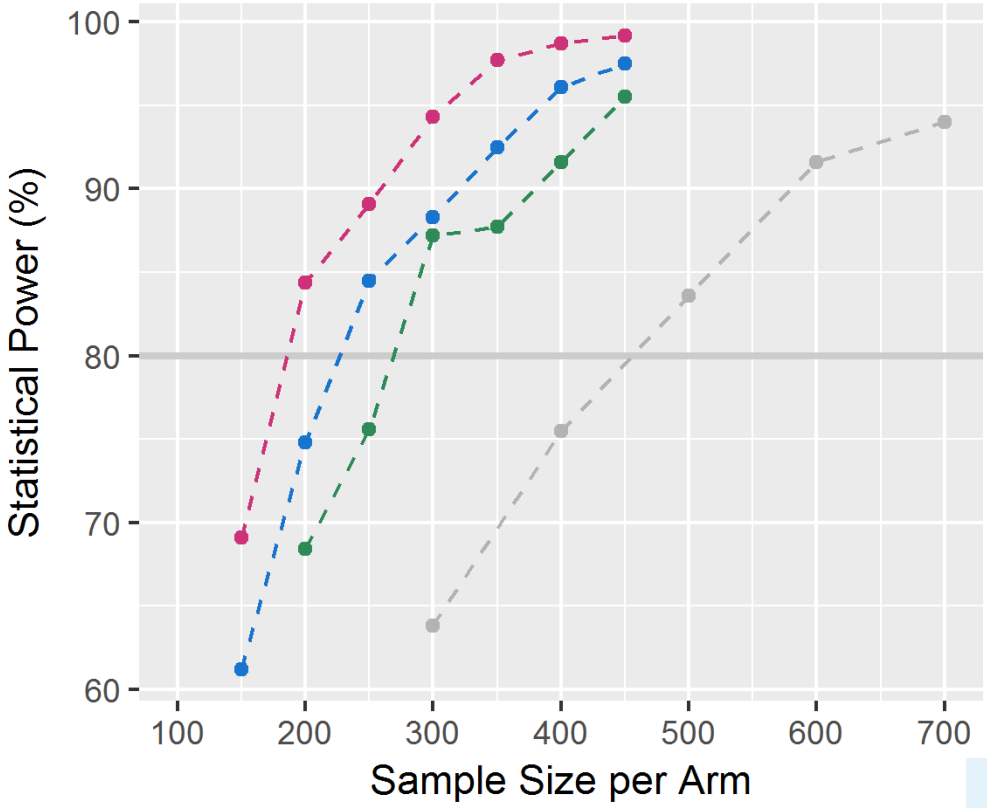
- No enrichment
- Only ICV-HV<97.7th (+2SD) subjects
- Only ICV-HV<84.1th (+1SD) subjects
- Only ICV-HV<50th (median) subjects

Monte-Carlo Simulation Assumptions:

- 24-month placebo-controlled parallel group trials
- Drug effect of 50% reduction in the progression rate
- Dropout model
- 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.

ICV-HV = intracranial volume-adjusted hippocampal volume

Enrichment with HV *vs.* Other Covariates



Clinical trial with:

- No enrichment
- Only APOE-e4 carrier subjects
- Only MMSE<median subjects
- Only ICV-HV<median subjects

Monte-Carlo Simulation Assumptions:

- 24-month placebo-controlled parallel group trials
- Drug effect of 50% reduction in the progression rate
- Dropout model
- 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.

APOE-e4 = apolipoprotein E-encoding gene ϵ4 allele
MMSE = mini-mental state examination
ICV-HV = intracranial volume-adjusted hippocampal volume

Take-Home Messages

- Neuroimaging as a prognostic enrichment biomarker can help with AD/PD clinical trial enrollment.
  - Identifies patients who are more likely to experience clinical changes, hence, benefit from an efficacious drug candidate.
- Disease progression modeling and Monte-Carlo simulations can support biomarker qualification.
  - Demonstrates biomarker enrichment utility and magnitude.

EMA Draft Qualification Opinion on DAT is Online!

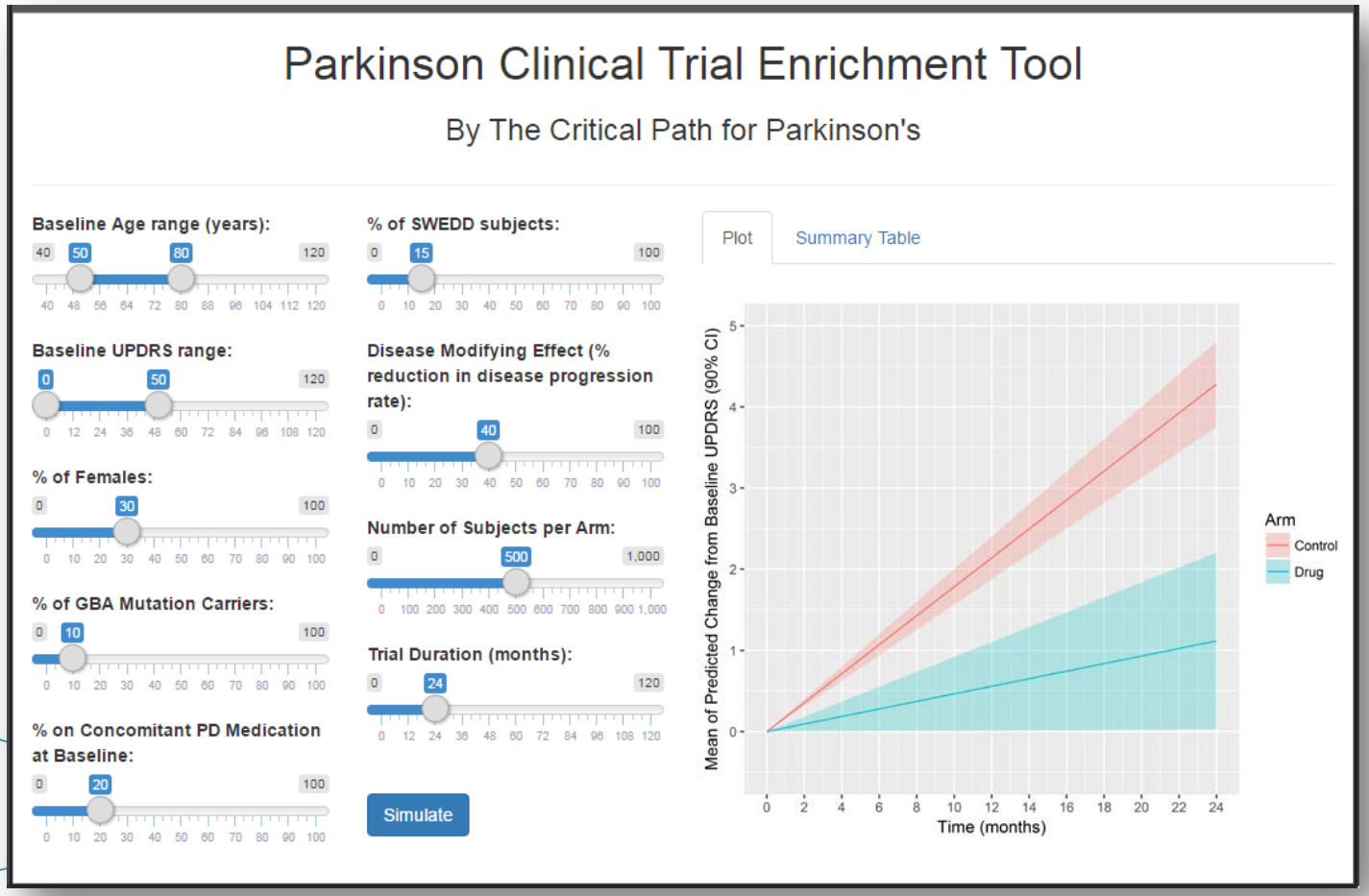
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Draft agreed by Scientific Advice Working Party	26 October 2017
Adopted by CHMP for release for consultation	09 November 2017[1]
Start of public consultation	24 January 2018[2]
End of consultation (deadline for comments)	07 March 2018[3]

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2018/01/WC500242219.pdf

Consultation period for public comments has recently ended

Open Access Model-based Clinical Trial Enrichment Tool



*Simplified mockup based on hypothetical data

Huntington's Disease: Our Newest Consortium

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Features

C&EN April 2017

DRUG DEVELOPMENT

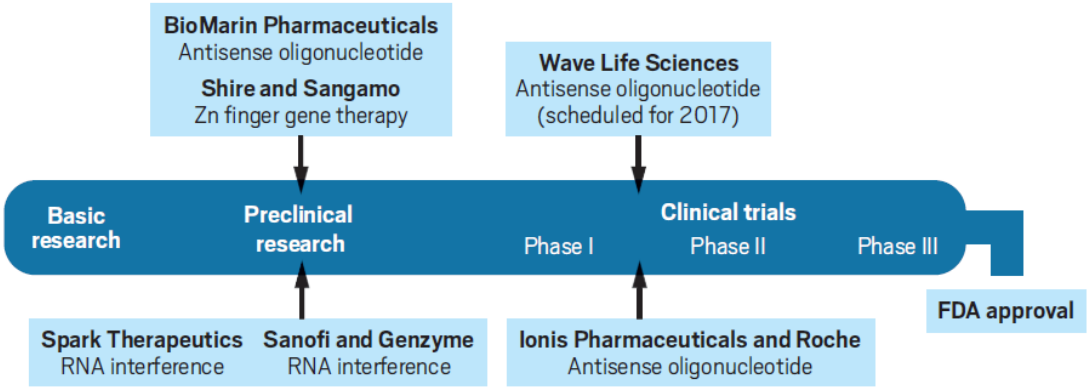
A new day for Huntington's disease

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

ERIKA GEBEL BERG, special to C&EN

The Huntington's pipeline

Several companies have disease-modifying treatments for Huntington's at various stages of the development pipeline.



CHDI

Accelerating therapeutic development for Huntington's disease

+

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Courtesy of Diane Stephenson, Executive Director, HD-RSC

Promising Biomarkers for Huntington's Disease

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Neurofilament light protein in blood as a potential biomarker of neurodegeneration in Huntington's disease: a retrospective cohort analysis

Lancet Neurol v16:601-609

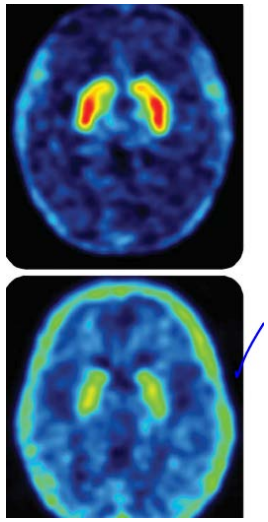
Journal of Huntington's Disease 6 (2017) 349
DOI 10.3233/JHD-170269
IOS Press

Research Report

Lauren M Byrne, Filipe B Rodrigues, Kaj Blennow, Alexandra Durr, Blair R Leavitt, Raymund A C Roos, Rachael I Scahill, Sarah J Tabrizi, Henrik Zetterberg, Douglas Langbehn, Edward J Wild

Validation of Ultrasensitive Mutant Huntingtin Detection in Human Cerebrospinal Fluid by Single Molecule Counting Immunoassay

Change in PDE10 across early Huntington disease assessed by [^{18}F]MNI-659 and PET imaging



RESEARCH ARTICLE

Movement Disorders, Vol. 30, No. 3, 2015

A Longitudinal Study of Magnetic Resonance Spectroscopy Huntington's Disease Biomarkers

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Acknowledgments

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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.....

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- Biogen
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- Eisai
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- Roche/ Genentech
- Johnson & Johnson Pharmaceutical Research & Development, LLC
- Merck, Sharp & Dohme Corp.
- Novartis Pharmaceutical
- Pfizer, Inc.
- Takeda

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- 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

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- **Jill Gallagher**, Co-Director, Parkinson's UK
- Dr. Diane Stephenson, Executive Director, Critical Path for Parkinson's Consortium, Critical Path Institute

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- **Renee Hynds, MPH**, Project Manager
- **Peggy Abbott**, Project Coordinator
- **Jackson Burton, PhD**, Associate Program Director, Quantitative Medicine

Parkinson's UK Team

- **Dr. Arthur Roach**, Director of Research
- **Prof. David Dexter**, Deputy Director of Research

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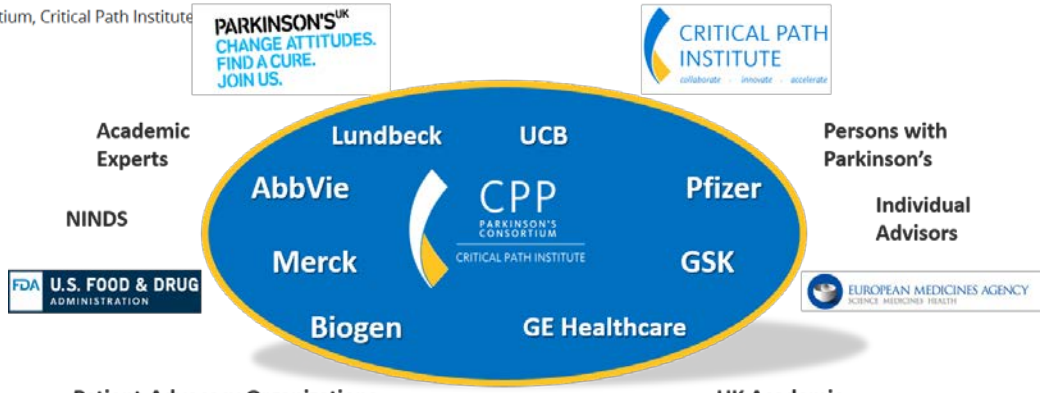

Patient-Advocacy Organizations

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

UK Academic Institutions

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

More folks:

- Emily Hartley (C-Path data scientist)
- Dan Hartley (C-Path data scientist)

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Thank You and Join Us!

NeuroCoP::DDT-AD Group

Alzheimer's Drug Development Tools

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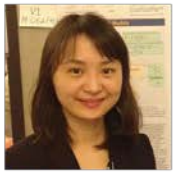
Raj


Jackson


Li Li


Jim


Sebastian


David

MERCK


Malidi

Tim Nicholas

Lilly

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