Model-Informed Biomarker Qualification:
Alzheimer and Parkinson Disease Neuroimaging Biomarkers

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Not Uncommon in AD/PD Trials

Disease Worsening

"Typical Progressor"

"Slow/No Progressor"

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”?

Neuroimaging
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.
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?

Disease Worsening

Time

“Typical Progressor”

“Slow/ No Progressor”

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.
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

**MCI ADNI-1 + ADNI-2**

**Early PD PPMI + PRECEPT**

**Baseline FreeSurfer ICV-HV**

- <= 7.46 cm³
- > 7.46 cm³

**Mean CDR-SB Score (95% CI)**

**Time (Years)**

**Mean of Observed Harmonized Motor Scores (95% CI)**

**Time (months)**

**DAT = dopamine transporter**

**DAT type of assessment = visual**

**ICV-HV = intracranial volume-adjusted hippocampal volume**

**FreeSurfer™ = an algorithm for calculating ICV-HV**

7.46 cm³ = median of the ICV-HV in dataset
Enrichment Biomarker for MCI Trials: Hippocampal Volume

MRI Healthy Control MCI


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

Healthy Control SPECT  PD SPECT  PD MRI + SPECT

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 SPECT
PD SPECT
PD MRI + SPECT

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

**Critical Path for Alzheimer’s Disease**

- AbbVie
- Biogen
- Boehringer Ingelheim
- Eli Lilly
- Johnson & Johnson
- Novartis
- Pfizer
- Takeda

**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

**UK Academic Institutions**

- University of Oxford
- 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

**Critical Path for Parkinson’s**

- Biogen
- AbbVie
- GSK
- Lundbeck
- Merck
- Pfizer
- UCB

**Persons with Parkinson’s**

- Individual Advisors

**Academic Experts**

**Government and Regulatory Agencies**

**HV = hippocampal volume; DAT = dopamine transporter**
C-Path’s Consortia Pursue Qualification of HV and DAT

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

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

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

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

PPMI or Parkinson’s Progression Markers Initiative
N = 481, observational

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:

\[
\frac{d\text{Score}_i}{dt} = r_i
\]

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


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.


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)

\[
\frac{d\text{Score}_i}{dt} = r_i \times \text{Score}_i \times \left[ 1 - \left( \frac{\text{Score}_i}{\max(\text{Score}_i)} \right)^\beta \right]
\]
Non-Linear MCI Progression: CDR-SB

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

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

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-ε4 = 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 cm³ 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

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

~ 24% reduction in sample size by enrolling only DAT deficient subjects
HV-based Enrichment Reduces MCI Trial Size

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

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

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

Clinical trial with:
- No enrichment
- Only APOE-e4 carrier subjects
- Only MMSE < median subjects
- Only ICV-HV < median subjects
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!

Draft agreed by Scientific Advice Working Party: 26 October 2017

Adopted by CHMP for release for consultation: 09 November 2017

Start of public consultation: 24 January 2018

End of consultation (deadline for comments): 07 March 2018


Consultation period for public comments has recently ended
Open Access Model-based Clinical Trial Enrichment Tool

*Simplified mockup based on hypothetical data

www.c-path.org
Huntington’s Disease: Our Newest Consortium

C&EN April 2017

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.

BioMarin Pharmaceuticals
Antisense oligonucleotide

Shire and Sangamo
Zn finger gene therapy

Wave Life Sciences
Antisense oligonucleotide (scheduled for 2017)

Basic research
Preclinical research
Clinical trials
Phase I
Phase II
Phase III
FDA approval

Spark Therapeutics
RNA interference
Sanofi and Genzyme
RNA interference
Ionis Pharmaceuticals and Roche
Antisense oligonucleotide

Courtesy of Diane Stephenson, Executive Director, HD-RSC

www.c-path.org
Promising Biomarkers for Huntington’s Disease

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

Lancet Neurol v16:601-609


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

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

RESEARCH ARTICLE

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


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- 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)

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- Alzheimer’s Drug Discovery Foundation
- CHDI Foundation

Critical Path for Parkinson’s—
Enabling Efficient Advancement of New Parkinson’s Therapies
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Alzheimer’s Drug Development Tools