Parkinson's Progression Markers Initiative (PPMI)

John Q. Trojanowski, M.D., Ph.D.

Parkinson's Progression Marker Initiative
NINDS Udall Center of Excellence For Parkinson's Disease Research,
NIA Alzheimer's Disease Core Center,
Center for Neurodegenerative Disease Research,
Marin S. Ware Alzheimer Program, Institute on Aging,
Perelman School of Medicine at the University of Pennsylvania,
Department of Pathology and Laboratory Medicine,
University of Pennsylvania, Philadelphia, PA

PPMI - a $50MM study funded by the Michael J. Fox Foundation and others- began in June, 2010 - seeks to develop PD progression markers

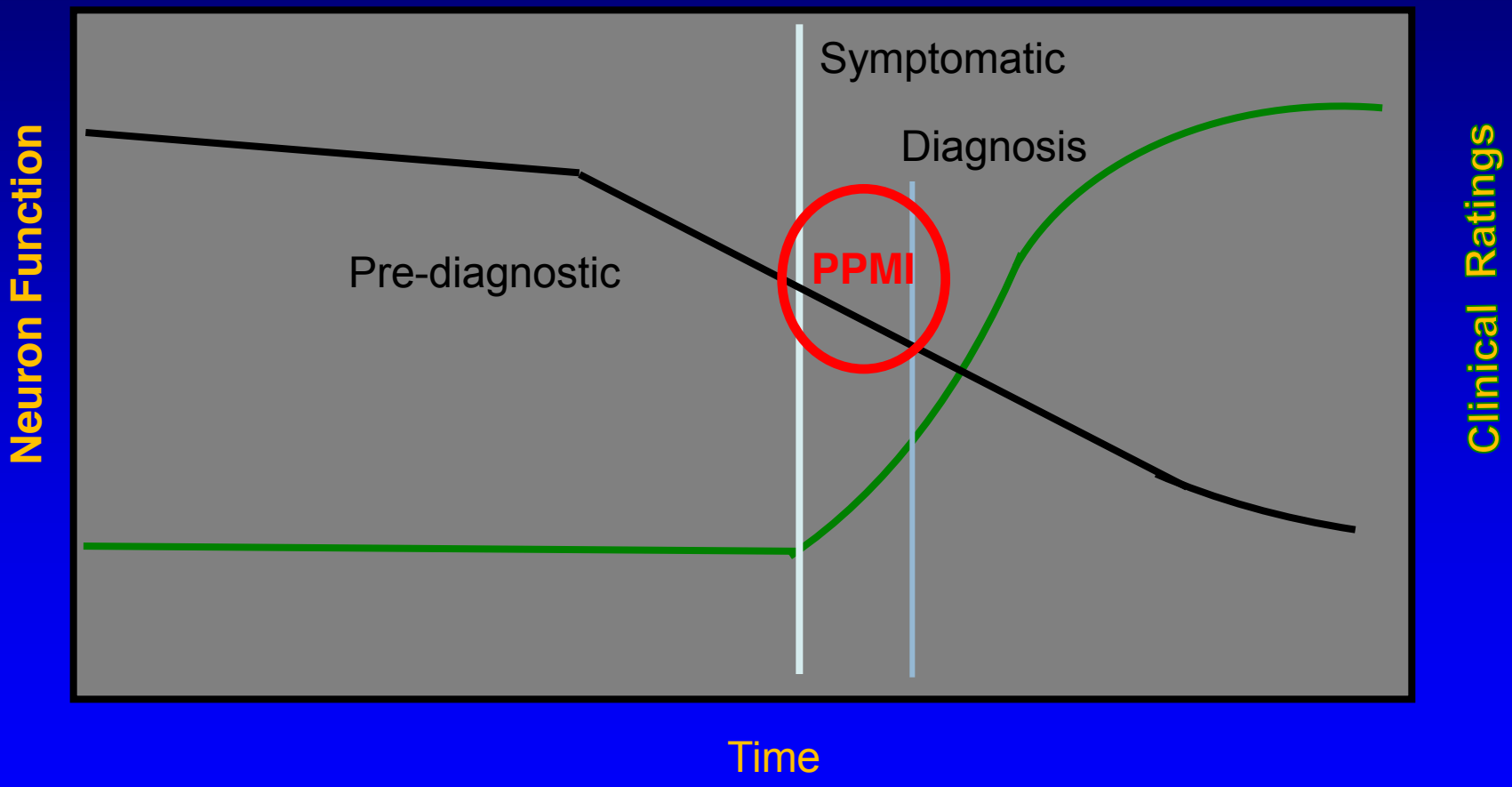
Rationale:

- Disease modifying PD therapeutics remain a major unmet need
- A major obstacle to PD clinical trials is the lack of biomarkers for
  - Disease mechanism
  - Drug mechanism
  - Dosage determination
  - Study eligibility
  - Stratification into PD sub-types
  - Correlation with clinical signals
- Biomarkers would potentially shorten study duration, reduce study sample size, limit study costs

PPMI Study Details: Synopsis

Study population	▪ 400 de novo PD subjects (newly diagnosed and unmedicated) ▪ 200 age-and gender-matched healthy controls ▪ ~70-80 SWEDD subjects ▪ Subjects followed for a minimum of 3 years and maximum of 5 years
Assessments/ Clinical data collection	▪ Motor assessments ▪ Neuropsychiatric/neurobehavioral testing ▪ Olfaction ▪ DaTSCAN imaging, MRI
Biologic collection	▪ DNA collected at screening ▪ Serum, whole blood and plasma collected at each visit; urine annually ▪ CSF collected at baseline, 6mo 12 mo and then annually ▪ Samples aliquotted and stored in central biorepository
Initial verification studies	▪ Lead biologic candidates to be tested: – Alpha-synuclein (CSF) – DJ-1 (CSF and blood) – Urate (blood) – Abeta 1-42 (CSF) – Total tau, Phospho-tau (p-181) (CSF)
PD treatment	▪ De novo for ~6 months ▪ Can participate in clinical trials (including interventional trials) after 12 months

Natural History of Parkinson's Disease



PPMI Steering Committee and Cores

Steering Committee	PI-K Marek, A Siderowf, C Scherzer, D Jennings, K Kieburtz, W Poewe, B Mollenhauer, C Tanner, B Ravina (core leaders, MJFF, ISAB)
Clinical Coordination Core	▪ University of Rochester's Clinical Trials Coordination Center • PI: Alice Rudolph
Imaging Core	▪ Institute for Neurodegenerative Disorders • PI: John Seibyl
Statistics Core	▪ University of Iowa • PI: Chris Coffey
Bioinformatics Core	▪ Laboratory of Neuroimaging (LONI) at UCLA • PI: Arthur Toga
BioRepository	▪ Coriell/BioRep • PI: Alison Ansbach, • Pasquale De Blasio, Michele Piovella
Bioanalytics Core	▪ University of Pennsylvania • PI: John Trojanowski, Les Shaw
Genetics Core	▪ National Institute on Aging/NIH • PI: Andy Singleton

PPMI Clinical Sites

Schedule of Events - PD

Visit	SC	BL	V01	V02	V03	V04[b] / ST	V05[b]	V06[b]	V07[b]	V08[b]	V09[b]	V10[b]	V11[b]	V12 / PW
Visit Description **Months (±**	**-1**	**0**	**3**	**6**	**9**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**
Written Informed Consent	X													
Inclusion/Exclusion Criteria	X	X												
Medical and Family History/Demographics	X													
Physical Examination	X													
Neurological Examination	X					X		X		X		X		X
Vital Signs	X	X[c]	X	X	X	X[c]	X	X[c]	X	X[c]	X	X[c]	X	X[c]
Clinical Laboratory Assessments	X					X		X		X		X		X
Blood Sample for DNA	X													
Montreal Cognitive Assessment (MoCA)	X													
Olfactory Testing (UPSIT)		X												
Epworth Sleepiness Scale		X		X		X		X		X		X		X
REM Sleep Behavior Disorder Questionnaire		X		X		X		X		X		X		X
Geriatric Depression Scale (GDS-15)		X		X		X		X		X		X		X
State-Trait Anxiety Inventory for Adults		X		X		X		X		X		X		X
Questionnaire for Impulsive-Compulsive Disorders		X		X		X		X		X		X		X
SCOPA-AUT		X		X		X		X		X		X		X
Dementia Rating Scale		X				X		X		X		X		X
Letter Number Sequencing		X				X		X		X		X		X
Hopkins Verbal Learning Test – Revised		X				X		X		X		X		X
Symbol Digit Modalities Test		X				X		X		X		X		X
Benton Judgment of Line Orientation		X				X		X		X		X		X
Animal Fluency		X				X		X		X		X		X
MDS-UPDRS (including Hoehn & Yahr Scale)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MDS-UPDRS Part III and H&Y[e]						X		X		X		X		X
Biomic blood sample		X	X	X	X	X	X	X		X		X		X
MRI brain (DTI)		X				X		X		X		X		X
DAT imaging	X[d]					X		X		X		X		X
Lumbar puncture (CSF collection)		X		X		X		X		X		X		X
Adverse Events	X[a]	X[a]				X[a]		X[a]		X[a]		X[a]		X[a]
Current Medical Conditions Review			X	X	X		X		X		X		X	
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Data Input

Acquisition → Repository

Imaging Acquisition

Clinical Acquisition

Biological Acquisition

Imaging Core (IND)
Quality Control
Image Pre-processing

Clinical Core (CTCC)
Quality Control
Study Management

Sample Repository (Coriell)
Sample Storage

Data Transfer & Validation

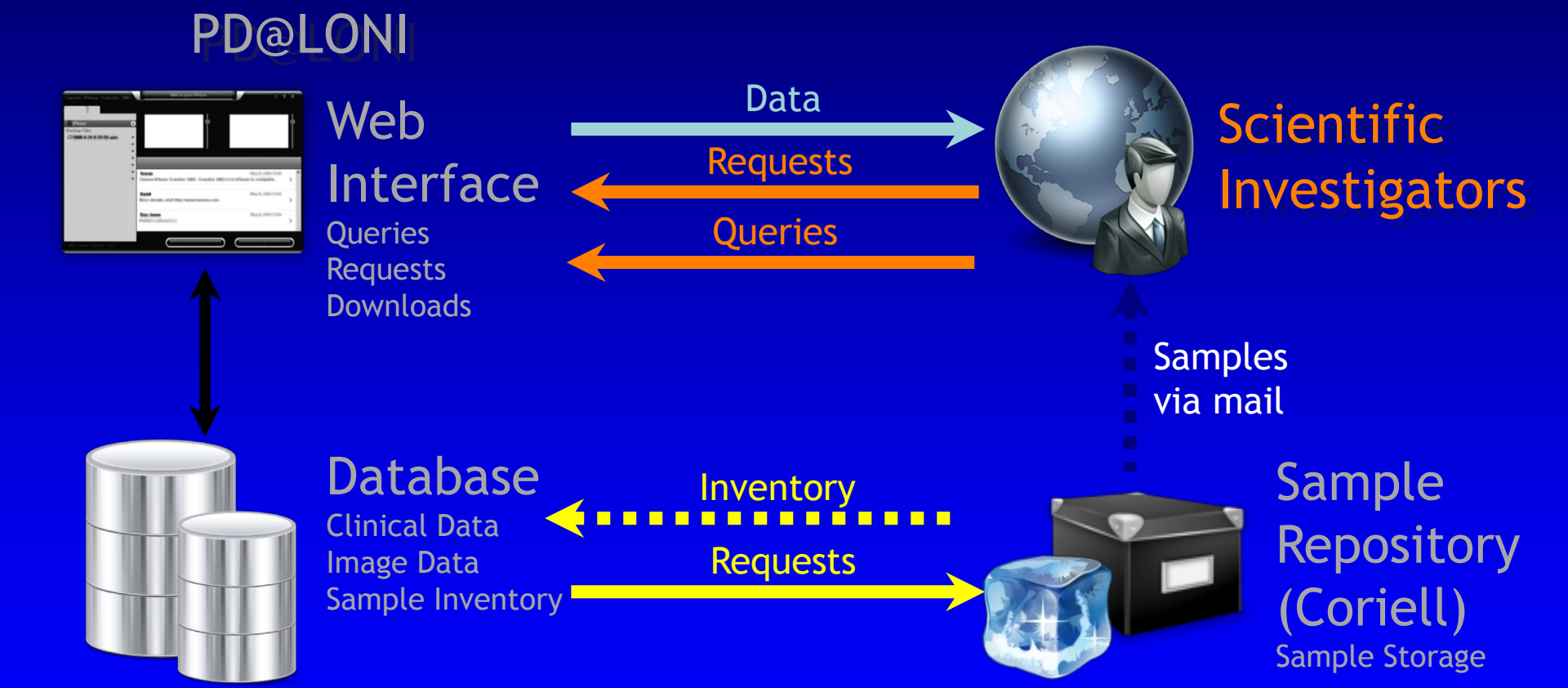
Inventory

PD@LONI

- Public Information
- Publications
- Investigator Resources
- Data Sharing Tools
- Data Access

Data Output

Repository → Investigators



PPMI Is Making Rapid Progress And Will Standardize PD Biomarkers Similar To ADNI

Hollywood star leads the way in Parkinson's research

The Michael J Fox Foundation is after the holy grail in Parkinson's research—disease-modifying treatments. They have launched Fox Trial Finder, which aims to get more patients involved in clinical trials, and are on the hunt for therapeutic biomarkers. Dara Mohammadi reports.

Lancet Neurol, 11:936-937, 2012

6 Posters on PPMI At 2012 MDS Meeting; 1st Paper Reporting On PPMI Data in 2013!

Screening for impulse control symptoms in patients with de novo Parkinson disease

A case-control study

Daniel Weintraub, MD
Kimberly Papay, BS
Andrew Siderowf, MD, MSCE
For the Parkinson's Progression Markers Initiative

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ABSTRACT

Objective: To determine the frequency and correlates of impulse control and related behavior symptoms in patients with de novo, untreated Parkinson disease (PD) and healthy controls (HCs).

Methods: The Parkinson's Progression Markers Initiative is an international, multisite, case-control clinical study conducted at 21 academic movement disorders centers. Participants were recently diagnosed, untreated PD patients (n = 168) and HCs (n = 143). The outcome measures were presence of current impulse control and related behavior symptoms based on recommended cutoff points for the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP)-Short Form.

Results: There were 311 participants with complete QUIP data. Frequencies of impulse control and related behavior symptoms for patients with PD vs HCs were as follows: gambling (1.2% vs 0.7%), buying (3.0% vs 2.1%), sexual behavior (4.2% vs 3.5%), eating (7.1% vs 10.5%), punding (4.8% vs 2.1%), hobbyism (5.4% vs 11.9%), walkabout (0.6% vs 0.7%), and any impulse control or related behavior (18.5% vs 20.3%). In multivariable models, a diagnosis of PD was not associated with symptoms of any impulse control or related behavior ($p \geq 0.10$ in all cases).

Conclusions: PD itself does not seem to confer an increased risk for development of impulse control or related behavior symptoms, which further reinforces the reported association between PD medications and impulse control disorders in PD. Given that approximately 20% of patients with newly diagnosed PD report some impulse control or related behavior symptoms, long-term follow-up is needed to determine whether such patients are at increased risk for impulse control disorder development once PD medications are initiated. *Neurology*® 2013;80:176-180

First Chemical Biomarker Study – We Are On Our Way!

Association of cerebrospinal fluid $A\beta_{1-42}$, t-tau, p-tau_{181} and α-synuclein levels with clinical features of early drug naïve Parkinson's disease patients

J-H Kang, DJ Irwin, AS Chen-Plotkin, A Siderowf, C Caspell, CS Coffey, T Waligórska, P Taylor, S Pan, M Frasier, K Marek, K Kieburtz, D Jennings, T Simuni, CM Tanner, A Singleton, AW Toga, S Chowdhury, B Mollenhauer, JQ Trojanowski, LM Shaw, & the Parkinson's Progression Marker Initiative*

JAMA Neurology , In press, 2013

Objective: Evaluate baseline characteristics and relationship to clinical features of CSF $A\beta_{1-42}$, t-tau, p-tau_{181} and α-syn in PD patients and matched healthy controls (HC) enrolled in PPMI.

Methods: CSF biomarkers were measured by xMAP-Luminex platform and ELISA in HC (N=39) and PD (N=63).

Figure 1

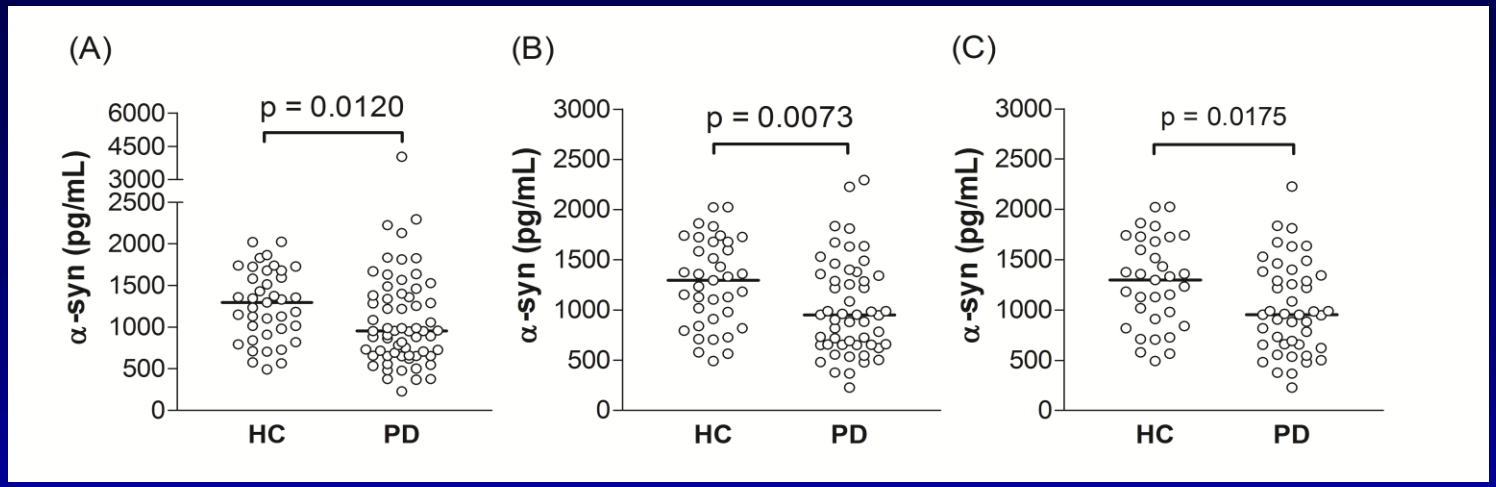
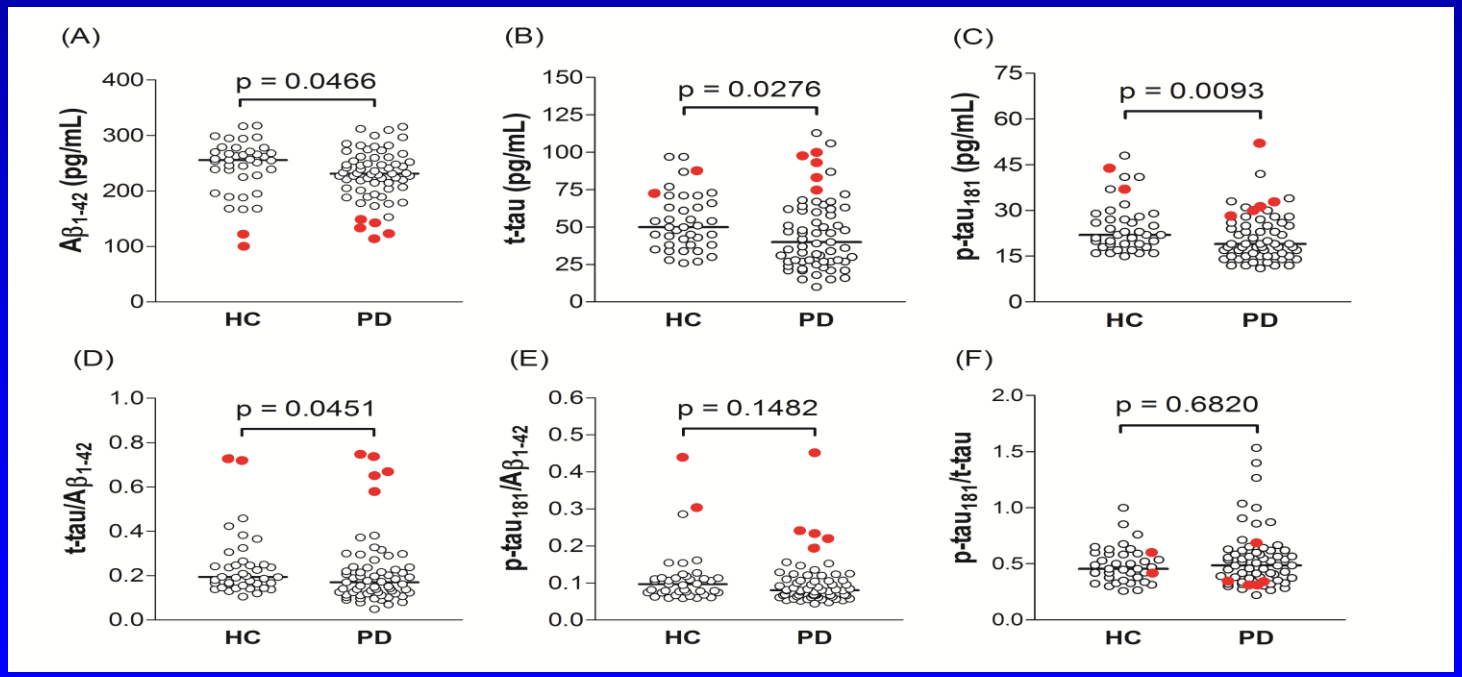


Figure 2



Red dot = subject with CSF tau and A profile

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JAMA Neurology , In press, 2013

SUMMARY AND CONCLUSIONS

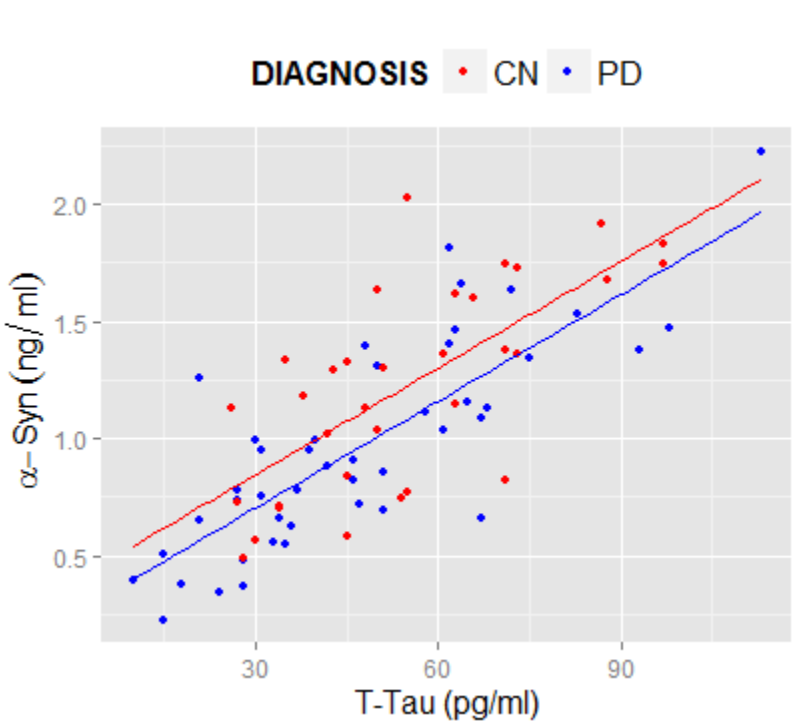
1) Significantly lower concentrations of all measured CSF biomarkers and t-tau/ $A\beta_{1-42}$ ratio in PD compared to HC.

2) Lower CSF $A\beta_{1-42}$ associated with PIGD which shows a more rapid cognitive decline and poor prognosis compared to tremor-dominant PD patients.

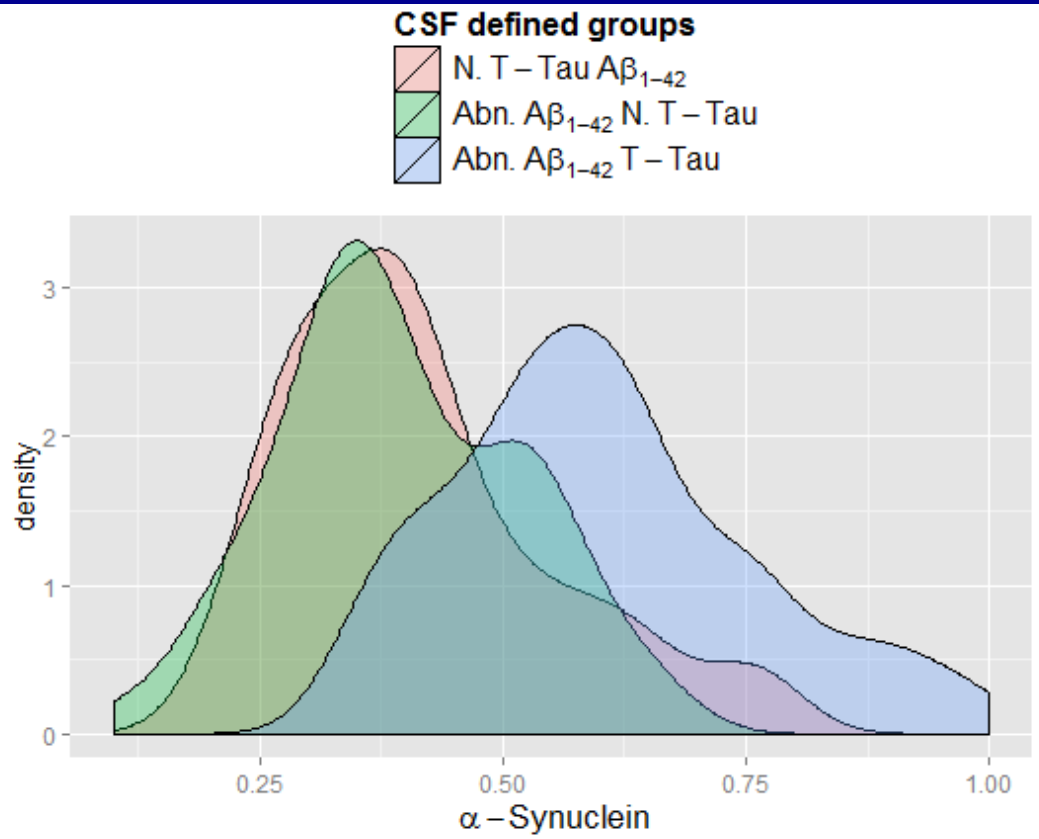
3) CSF $A\beta_{1-42}$, t-tau, p-tau_{181} and α-syn have value for diagnosis and assessment of disease progression in early-stage PD.

α-Synuclein, Tau & Aβ Levels in PPMI & ADNI

Toledo, J.B., Korff, A., Shaw, L.M., Trojanowski, J.Q., and Zhang, J. for the Alzheimer's Disease Neuroimaging Initiative.
CSF α-synuclein improves diagnostic and prognostic pfeormace of CSF tau and Aβ in Alzheimer's disease.
Acta Neuropath, In press, 2013.



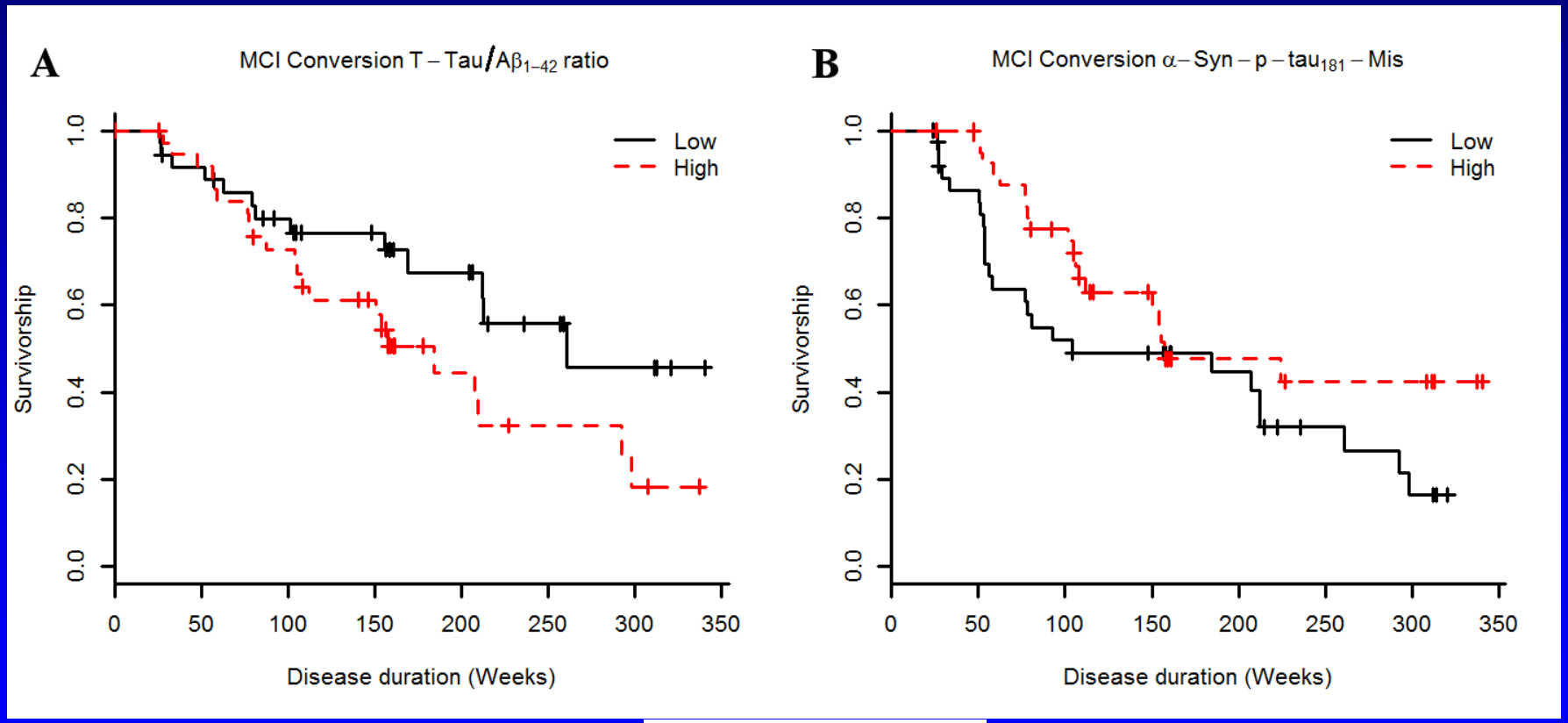
PPMI



ADNI

MCI progression to AD

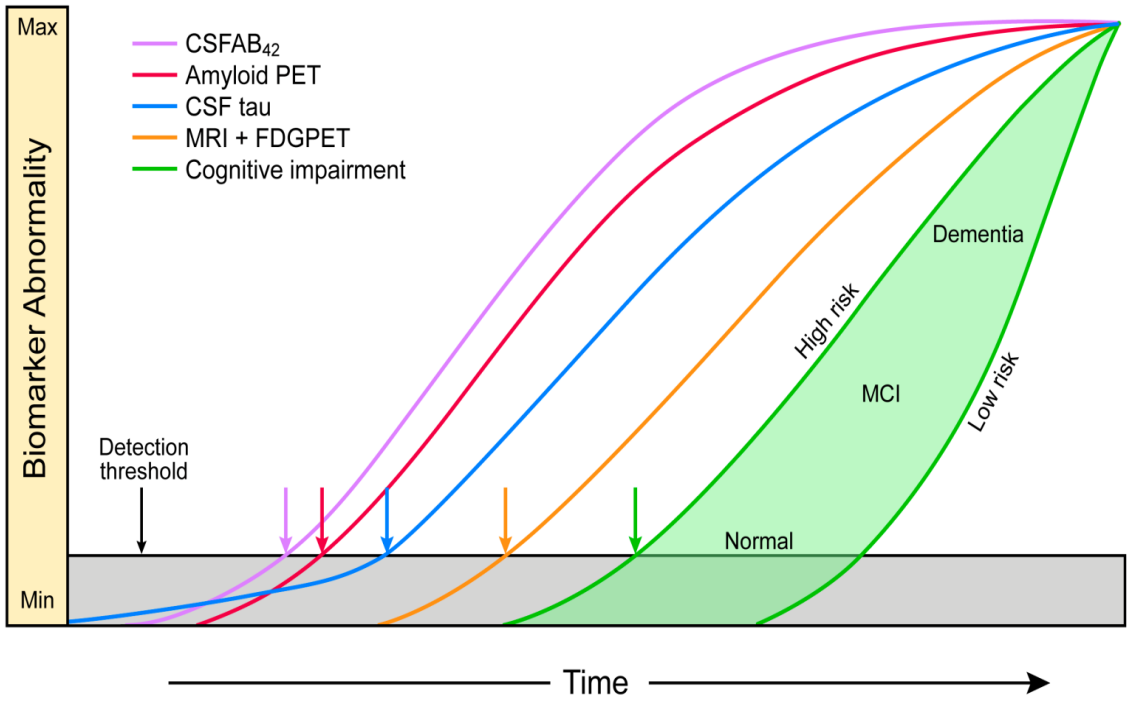
Toledo, J.B., et a; Acta Neuropath, In press, 2013.



ADNI

Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers

Clifford R Jack Jr, David S Knopman, William J Jagust, Ronald C Petersen, Michael W Weiner, Paul S Aisen, Leslie M Shaw, Prashanthi Vemuri, Heather J Wiste, Stephen D Weigand, Timothy G Lesnick, Vernon S Pankratz, Michael C Donohue, John Q Trojanowski



Lancet Neurology 2013

Temporal Ordering Of AD Biomarkers Suggests Success In Delineating A Biomarker Profile For PD That Reflects Progression Of PD In PPMI

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journal homepage: www.elsevier.com/locate/pneurobio

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The Parkinson Progression Marker Initiative[1]

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

PPMI Funding Partners

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THE MICHAEL J. FOX FOUNDATION
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