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

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

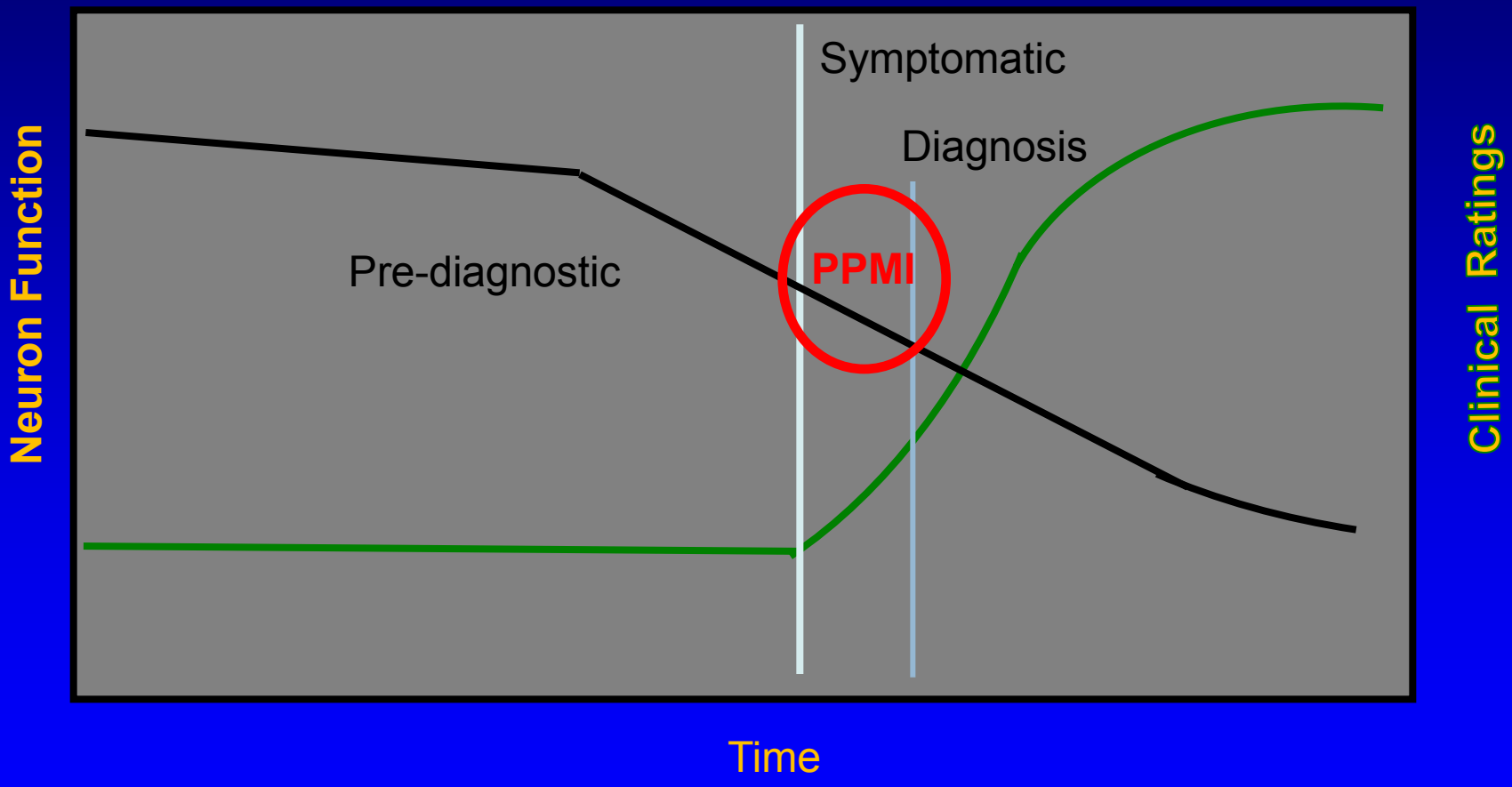
PPMI - a $50MM study - began in June, 2010 - seeks to develop PD progression markers

- 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

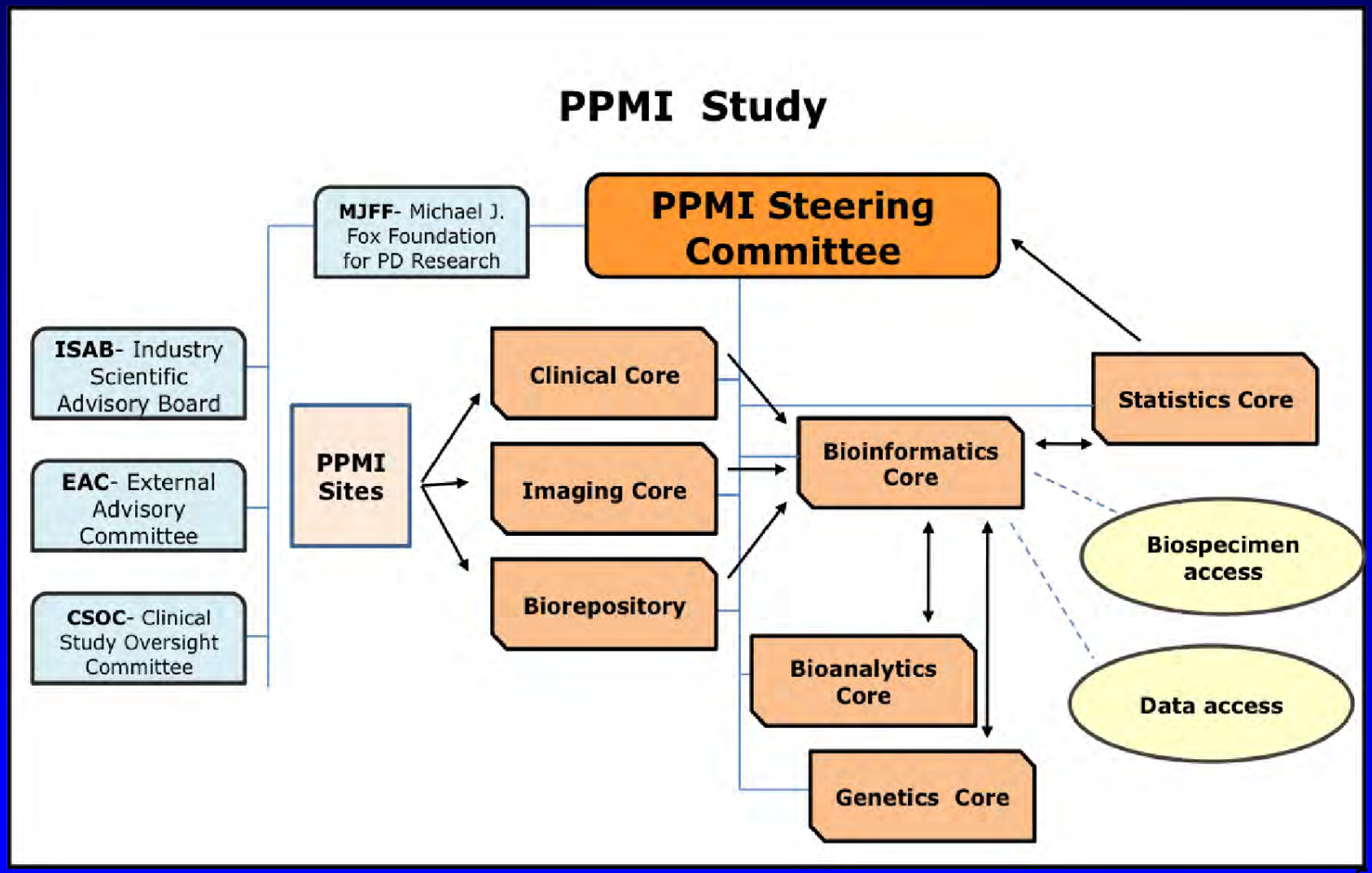
Natural History of Parkinson's Disease



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 study governance



PPMI Clinical Sites

Clinical Sites

- Arizona Parkinson's Disease Consortium (Phoenix, AZ)
- Baylor College of Medicine (Houston, TX)
- Boston University(Boston, MA)
- Emory University (Atlanta, GA)
- *Innsbruck University (Innsbruck, Austria)*
- Institute of Neurodegenerative Disorders (New Haven, CT)
- Johns Hopkins University (Baltimore, MD)
- Northwestern University (Chicago, IL)
- Oregon Health and Science University (Portland, OR)
- *Paracelsus-Elena Clinic Kassel/University of Marburg (Marburg, Kassel, Germany)*
- The Parkinson's Institute (Sunnyvale, CA)
- University of Alabama at Birmingham (Birmingham, AL)
- University of Florida – Gainesville (Gainesville, FL)
- *University of Napoli (Naples, Italy)*
- University of Pennsylvania (Philadelphia, PA)
- University of Rochester (Rochester, NY)
- University of South Florida (Tampa, FL)
- *University of Tübingen (Tübingen, Germany)*
- University of Washington (Seattle, WA)

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[c]						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

PD@LONI

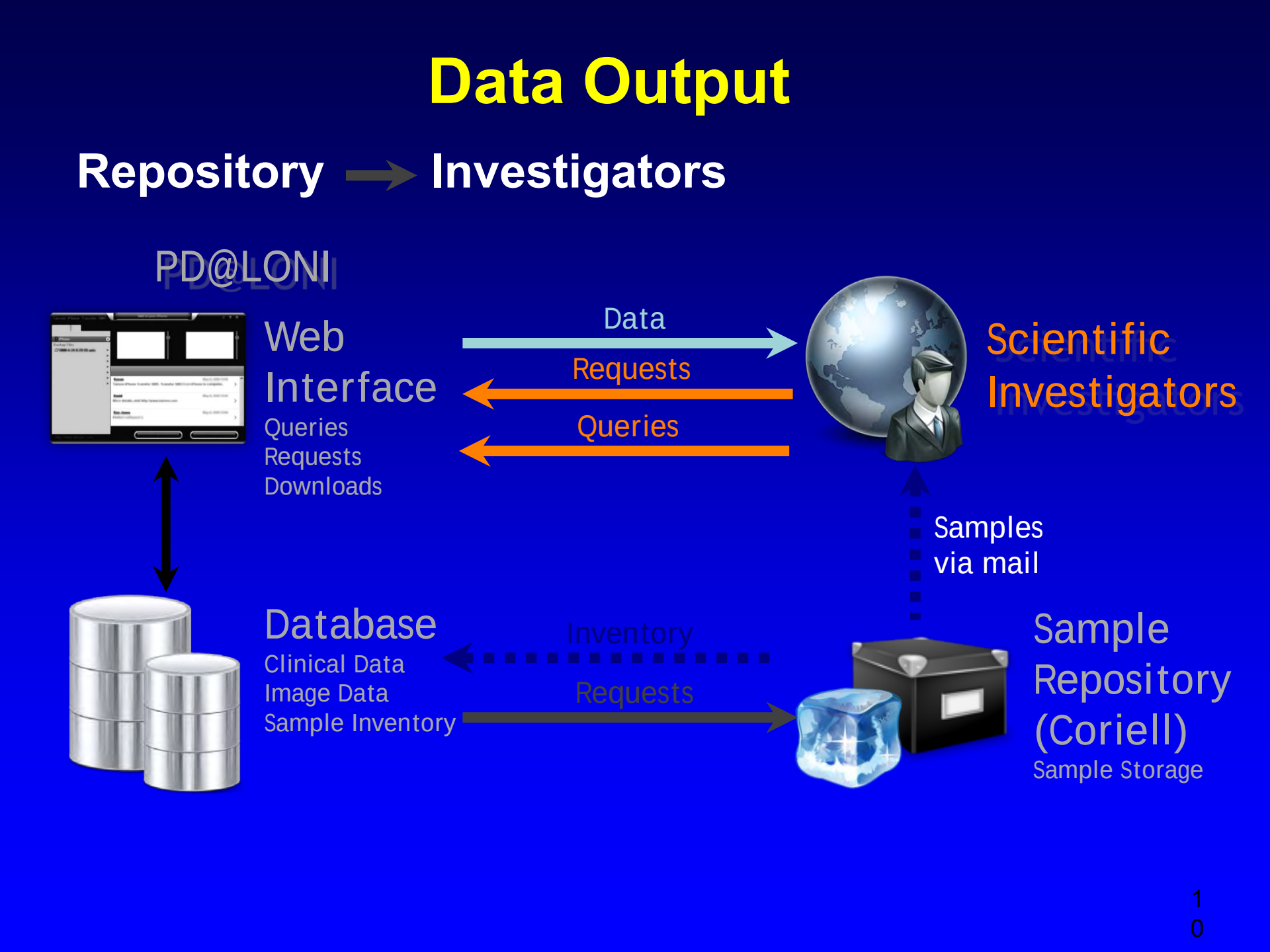
- Public Information
- Publications
- Investigator Resources
- Data Sharing Tools
- Data Access

Data Transfer & Validation

Inventory

Data Output

Repository → Investigators



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
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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

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*

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).

Demographics of the PPMI Subjects

	HC (N = 39)	PD (N = 63)	*P* value	SWEDD (N= 4)
Age, years (95% C.I.)	59 ± 13 (55 – 63)	62 ± 10 (60 – 65)	0.2781	67 ± 7 (55 – 78)
Sex, F/M (% of Male)	18/21 (53.8)	24/39 (61.9)	0.4216#	2:2 (50.0)
Education, years (95% C.I.)	16.9 ± 2.4 (16.1 – 17.6)	16.4 ± 2.5 (15.8 – 17.0)	0.1421	14.3 ± 2.1 (11.0 – 17.5)
Age at onset, years (95% C.I.)	-	59.5 ± 10.8 (56.8 – 62.2)	-	63.5 ± 8.2 (50.5 – 76.5)
Mean duration of symptoms, median years (range)	-	1.8 (0.3 – 20.8)	-	2.0 (0.0 – 2.9)
Number of subjects with CSF Hgb > 200 ng/mL	6	18	0.1271#	1

#Chi-square test

Clinical Characteristics of the PPMI Subjects#

	HC (N = 39)				PD (N = 63)				*p* value*	SWEDD (N= 4)			
H & Y stage	0.03 ± 0.16				1.65 ± 0.51				< 0.0001	1.50 ± 0.58			
UPDRS III motor score	1.6 ± 2.7				22.6 ± 7.6				< 0.0001	17.3 ± 6.2			
Mean tremor score	0.05 ± 0.13				0.46 ± 0.27				< 0.0001	0.50 ± 0.20			
Mean PIGD score	0.01 ± 0.04				0.24 ± 0.26				< 0.0001	0.00 ± 0.00			
UPSIT score	35.1 ± 3.4				21.9 ± 8.1				< 0.0001	33.0 ± 2.9			
Striatal binding ratios (Mean values)	PR	PL	CR	CL	PR¶	PL	CR	CL	<0.0001	PR	PL	CR	CL
	1.38	1.39	2.06	2.05	0.61	0.64	1.34	1.33		1.39	1.56	2.00	2.02
MoCA (95% C.I.)	28.4 ±1.0 (28.0 –28.7)				27.2 ± 2.0 (26.7 – 27.7)				0.0039	27.3 ± 2.4 (23.5 – 31.0)			
Semantic fluency	53.8 ± 12.1				49.5 ± 10.6				0.0578	40.8 ± 4.1			
WMSIII-LNS test score	12.1 ± 2.8				11.0 ± 2.0				0.0510	10.0 ± 1.4			
SDMT$	48.6 ± 11.2				41.9 ± 8.9				0.0051	44.8 ± 7.7			
HVLT_total recall	9.0 ± 1.6				8.2 ± 1.5				0.0077	7.8 ± 2.4			
HVLT delayed recall	9.9 ± 2.3				8.3 ± 2.3				0.0004	9.3 ± 4.2			

*Mann-Whitney U test

¶PR: Right putamen, PL: Left putamen, CR: Right caudate, CL: Left caudate, N=39 for HC, N=62 for PD, N=4 for SWEDD.

#Data were updated based on PPMI database (04. 12. 2012); Diagnoses of 2 patients were changed.

Comparison of CSF Biomarkers Between HC and All PD

Biomarkers	HC (N = 39)	PD (N = 63)	*P* value#	SWEDD (N =4)
$A\beta_{1-42}$ (pg/mL) (95% C.I.)	242.8 ± 49.95 (226.7 – 259.0)	228.7 ± 45.63 (217.2 – 240.2)	0.0466	276.0 ± 22.99 (239.4 – 312.6)
t-tau (pg/mL) (95% C.I.)	53.9 ± 19.33 (47.6 – 60.1)	46.1 ± 24.71 (39.8 – 52.3)	0.0276	55.0 ± 25.47 (14.47 – 95.53)
p-tau_{181} (pg/mL) (95% C.I.)	24.9 ± 8.45 (22.2 – 27.6)	21.0 ± 7.83 (19.0 – 23.0)	0.0093	23.5 ± 8.35 (10.22 – 36.78)
t-tau/$A\beta_{1-42}$ ratio (95% C.I.)	0.240 ± 0.141 (0.195 – 0.286)	0.215 ± 0.157 (0.176 – 0.255)	0.0451	0.196 ± 0.083 (0.063 – 0.329)
p-tau_{181}/$A\beta_{1-42}$ ratio (95% C.I.)	0.113 ± 0.075 (0.089 – 0.138)	0.099 ± 0.063 (0.084 – 0.115)	0.1482	0.084 ± 0.023 (0.047 – 0.121)
p-tau_{181}/t-tau ratio (95% C.I.)	0.491 ± 0.160 (0.439 – 0.543)	0.543 ± 0.263 (0.477 – 0.609)	0.6820	0.495 ± 0.230 (0.130 – 0.860)
α-syn (pg/mL) (95% C.I.)	1264 ± 425.7 (1126 – 1403)	1082 ± 611.1 (928 – 1235)	0.0120	1413 ± 750.6 (219 – 2608)
α-syn (pg/mL) (95% C.I.) *	1267 ± 443.5 (1109 – 1424)	1020 ± 456.7 (883 – 1158)	0.0175	1359 ± 909.8 (-901 – 3619)
α-syn (pg/mL) (95% C.I.) **	1269 ± 435.2 (1124 – 1414)	1019 ± 474.8 (886 – 1151)	0.0073	1359 ± 909.8 (-901 – 3619)

*Subjects with CSF Hb < 200 ng/mL. N=33 for HC, N=45 for PD, N=3 for SWEDD.
**Subjects with CSF Hb < 500 ng/mL. N=37 for HC, N=52 for PD, N=3 for SWEDD.
#Mann-Whitney U test

#Data were updated based on PPMI database (04. 12. 2012); Diagnoses of 2 patients were changed.

Comparison of CSF Biomarkers Between PIGD Vs TP PD & HC

Biomarkers	PIGD (N = 22)	Tremor (N = 18)	*p* value*	Mixed (N = 27)	HC
$A\beta_{1\text{-}42}$ (pg/mL)	213.9 ± 40.5	241.7 ± 28.1	**0.0081**	239.1 ± 55.8	**242.8 ± 49.95#**
t-tau (pg/mL)	38.7 ± 25.5	49.6 ± 16.1	**0.0187**	51.0 ± 27.7	**53.9 ± 19.33#**
p-tau_{181} (pg/mL)	19.5 ± 8.0	22.0 ± 6.6	0.1697	22.0 ± 8.4	**24.9 ± 8.45#**
α-syn (pg/mL)	905.8 ± 482.1	1149.0 ± 490.1	0.0553	1229.0 ± 758.8	**1264 ± 425.7#**
α-syn (pg/mL), CSF Hb < 500 ng/mL	857.5 ± 495.3	1068.0 ± 447.6	0.0824	1150.0 ± 517.8	**1269 ± 435.2#**
α-syn (pg/mL), CSF Hb < 200 ng/mL	778.9 ± 363.0	1098.0 ± 449.0	**0.0291**	1186.0 ± 532.9	**1267 ± 443.5#**
t-tau/$A\beta_{1-42}$ ratio	0.197 ± 0.176	0.208 ± 0.072	0.0503	0.232 ± 0.175	**0.240 ± 0.141#**
p-tau/$A\beta_{1-42}$ ratio	0.096 ± 0.052	0.092 ± 0.030	0.5960	0.105 ± 0.082	0.113 ± 0.075
p-tau/t-tau ratio	0.622 ± 0.338	0.466 ± 0.113	0.2769	0.523 ± 0.248	0.49 ± 0.16

*PIGD vs. Tremor; Mann-Whitney U test
#Significant different vs PIGD, but not vs Tremor group

Figure 1

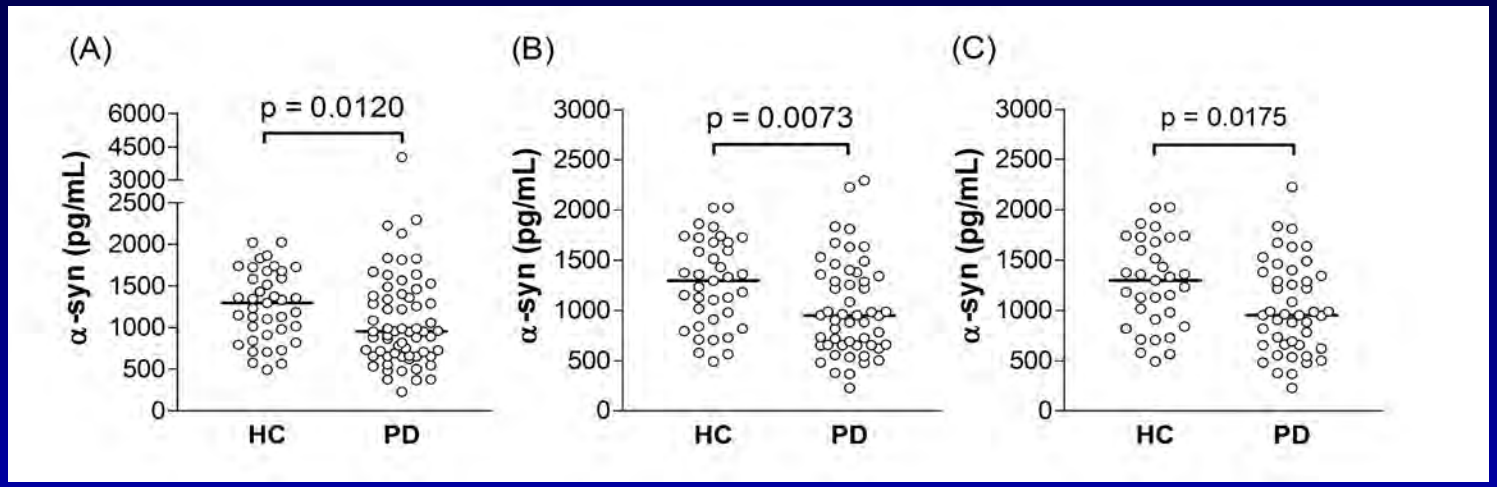
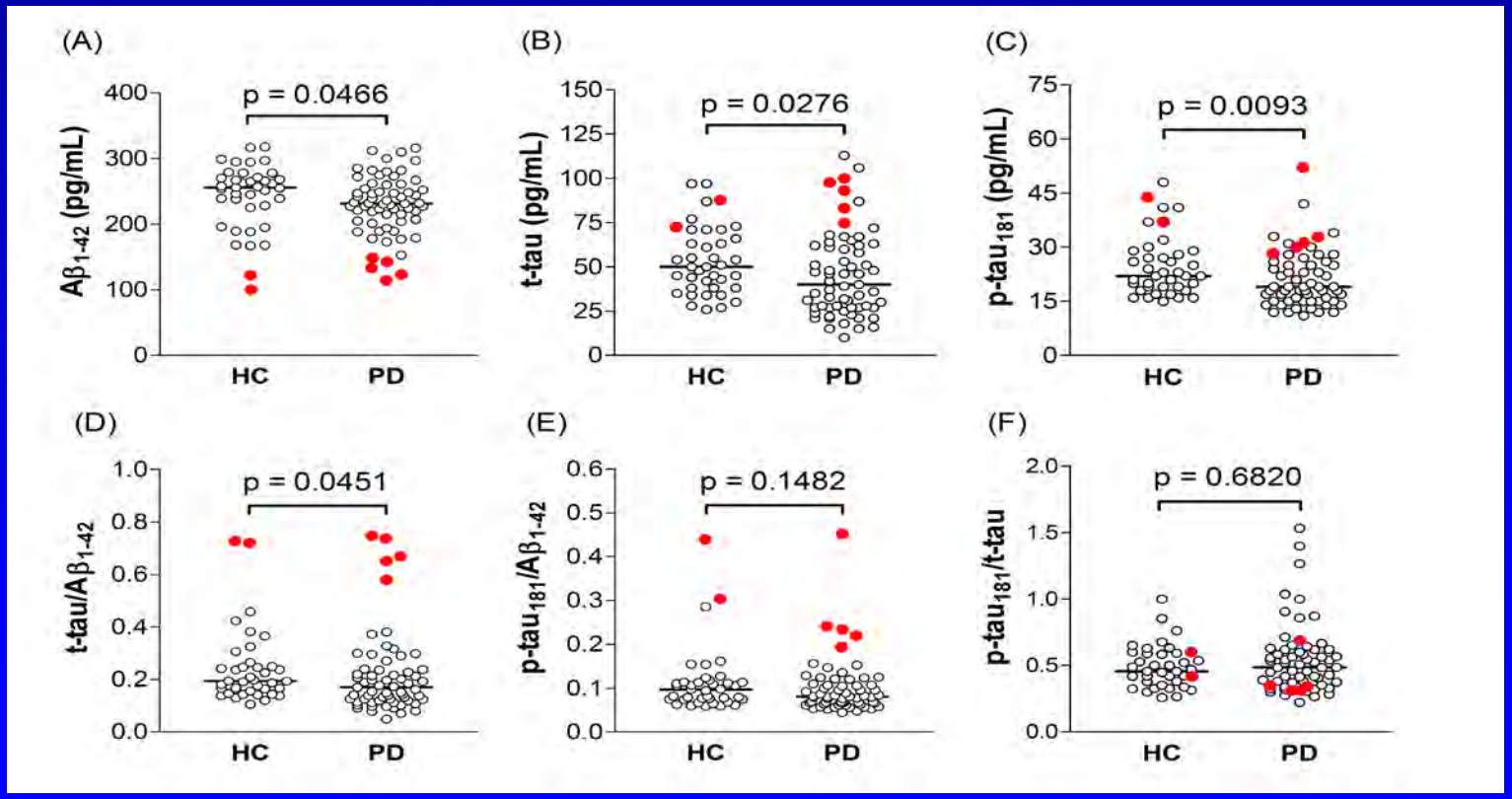


Figure 2



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

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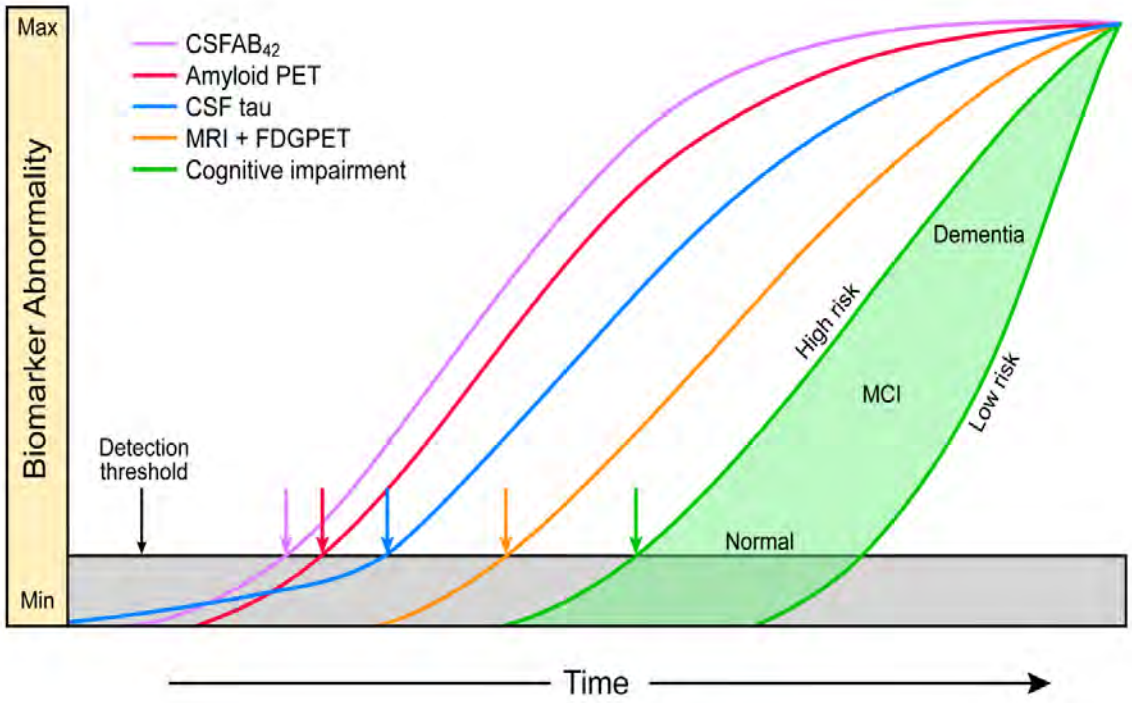
SUMMARY AND CONCLUSIONS

Results: Significantly lower concentrations of all measured CSF biomarkers and t-tau/$A\beta_{1-42}$ ratio were seen in PD compared to HC, lower α-syn was associated with a higher risk of PD and decreased CSF p-tau_{181} associated with increased UPDRS motor score. Notably, lower CSF $A\beta_{1-42}$ was associated with the postural instability-gait disturbance-dominant phenotype which associates with a more rapid cognitive decline and poor prognosis compared to tremor-dominant patients. ***Interpretation***: We demonstrate that 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. Further investigations will test the predictive performance of CSF biomarkers for disease progression.

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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The Parkinson Progression Marker Initiative[1]

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

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