Parkinson's Progression Markers Initiative

Goal to promote biomarker discovery efforts, accelerate and improve biomarker verification studies, and establish biomarkers strategies for disease modifying PD trials

Requirements for Biomarker Infrastructure

Specific Data Set	• Appropriate population (early stage PD and controls) • Clinical (motor/non-motor) and imaging data • Corresponding biologic samples (DNA, blood, CSF)
Standardization	• Uniform collection of data and samples • Uniform storage of data and samples • Strict quality control/quality assurance
Access/Sharing	• Data available to research community → data mining, hypothesis generation & testing • Samples available for studies

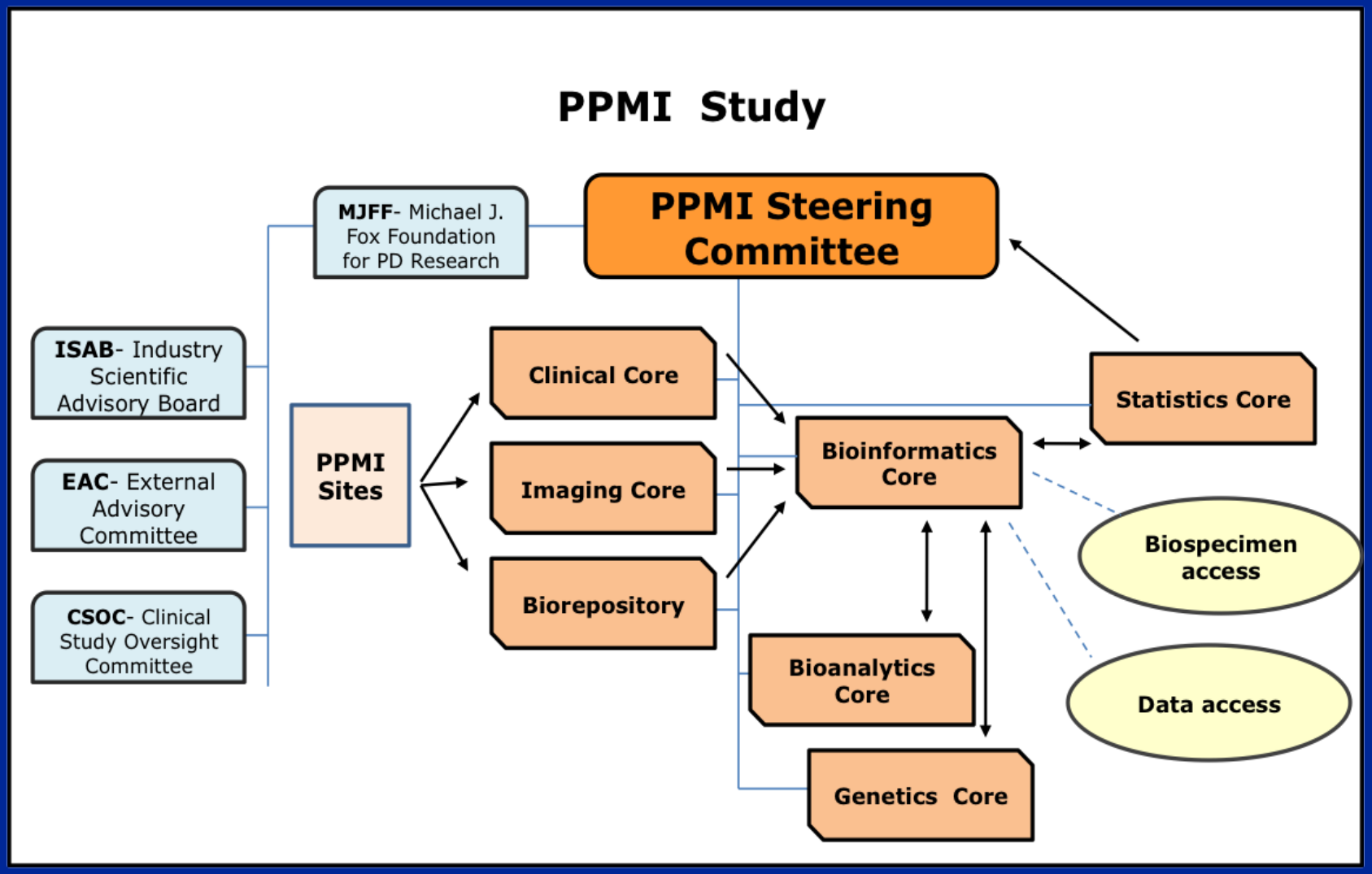
PPMI Overview

- PPMI is an observational multi-center study to assess progression of clinical features, imaging and biologic biomarkers in Parkinson's patients and healthy controls
- PPMI is a five-year natural history study of *de novo* idiopathic PD patients and healthy controls
- Subjects will be assessed at baseline and every 3-6 months thereafter
  - Clinical assessments: motor, neuropsychiatric and cognitive
  - Imaging assessment (dopamine transporter imaging, MRI)
  - Biologics collected: blood, CSF, urine and DNA
- Clinical, imaging and biological data and samples collected under standardized protocols and analyzed and stored at core facilities
- Biological samples will be used for verification of promising biomarkers
- Recognizing that biomarker development is crucial for the field at large, PPMI was designed to be a pubic-private partnership with intellectual input provided by academia, industry and MJFF and funding provided by MJFF and industry partners

PPMI Funding Partners

PPMI is sponsored and partially funded by The Michael J. Fox Foundation for Parkinson's Research. Other funding partners include a consortium of industry players, non-profit organizations and private individuals.

PPMI Study : Governance and infrastructure



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

PPMI Website (www.ppmi-info.org): Portal to study data

- **PPMI clinical and imaging data available through log-in**
- **PPMI biospecimen samples available through on-line request process**
  - **Proposals evaluated by independent Biologic Review Committee (BRC)**
- **Portal for ancillary studies: can submit though on-line submission process**
- **PPMI study documents and SOPs available and downloadable**
- **Frequent updates on PPMI study progress**
- **Recruitment and retention tool**

PPMI Baseline Data

Baseline Data Summary				
Variable	**PD Subjects**		**Healthy Controls**	
Demographics				
Female(n)	46		62	
Male(n)	109		77	
Subjects with Family Members with PD(n)	43		(n/a)	
Subjects with No Family Members with PD(n)	112		(n/a)	
	Mean	**Range**	**Mean**	**Range**
Age(Years)	61.4	35 - 83	59.1	31 - 84
Years of Education	15.8	8 - 26	16	9 - 23
Duration of Disease (Months)	8	0 - 36	(n/a)	(n/a)
Motor Evaluations	**Mean**	**Range**	**Mean**	**Range**
MDS-UPDRS Total	32.7	7 - 70	4.6	0 - 20
MDS-UPDRS Part I	1.4	0 - 9	0.7	0 - 8
MDS-UPDRS Part I - Patient questionnaire	4.5	0 - 12	2.3	0 - 11
MDS-UPDRS Part II - Patient questionnaire	6	1 - 23	0.4	0 - 4
MDS-UPDRS Part III	21	6 - 43	1.3	0 - 13
Hoehn & Yahr	1.6	1 - 3	0	0 - 1
Modified Schwab & England ADL	93	80 - 100	(n/a)	(n/a)
Non-Motor Evaluations	**Mean**	**Range**	**Mean**	**Range**
UPSIT - Total Score	21.7	5 - 39	34	11 - 40
MoCA Score*	27	0 - 30	28.3	27 - 31
GDS Score	2.3	0 - 13	1.4	0 - 15
SCOPA-AUT	9.4	0 - 39	6.1	0 - 20
DaTSCAN Imaging Outcomes	**Mean**	**Range**	**Mean**	**Range**
SBR - Left Caudate	1.4	0.6 - 2.4	2	1.3 - 3.0
SBR - Right Caudate	1.4	0.6 - 2.4	2	1.3 - 3.0
SBR - Left Putamen	0.7	0.1 - 2.1	1.4	0.8 - 2.6
SBR - Right Putamen	0.7	0.3 - 1.9	1.4	0.7 - 2.7

**MoCA and SBR values are obtained at screening visit*

Subject enrollment and sample collection

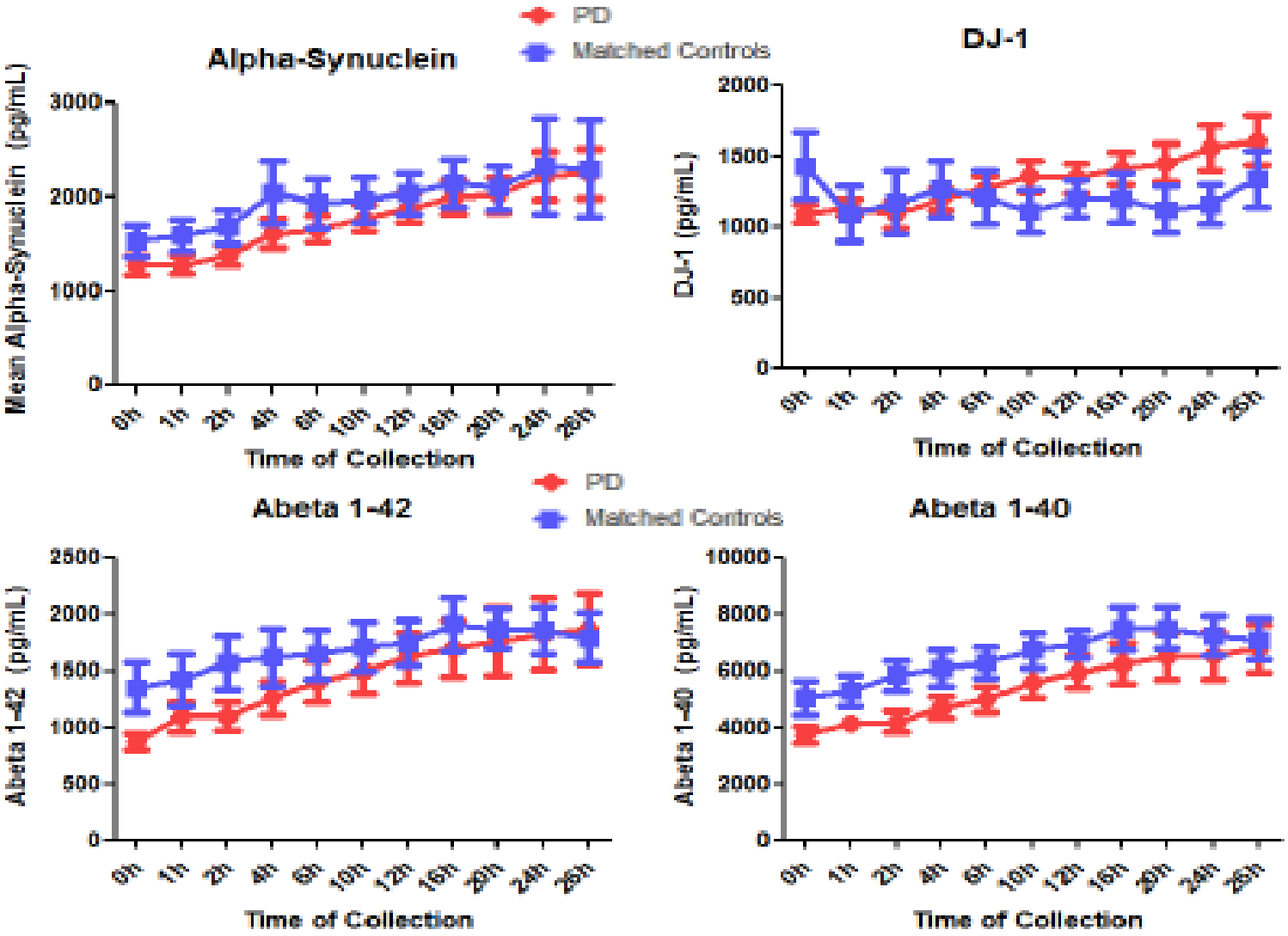
							Enrolled Patients						Collected Samples					
Plasma	Total						393						392 (99.8%)					
	BL	V1	V2	V3	V4	ST	199	116	45	13	5	15	199	115	45	13	5	15
Serum	Total						393						392 (99.8%)					
	BL	V1	V2	V3	V4	ST	199	116	45	13	5	15	199	115	45	13	5	15
CSF	Total						262						249 (95.0%)					
	BL		V2		V4	ST	198	44		5		15	192	40		4		13
Urine	Total						267						265 (99.3%)					
	BL	V1	V2		V4	ST	199	3	45	5		15	197	3	45	5		15

PPMI initial biologics analysis

	Control (N = 39)	PD (N = 67)	*P* value
Age (range)	59 ± 13.1 (31 – 82)	62 ± 9.9 (36 – 83)	0.1160
Male:Female (% of Male)	22:17 (56.4)	41:26 (61.2)	0.6286$
MoCA score			
Mean ± S.D.	28.4 ± 0.99	27.2 ± 2.0	**0.0012**
No. of subjects with score < 26 (%)	0 (0.0)	13 (19.4)	**0.0033$**
$A\beta_{1-42}$	242.8 ± 49.95	231.5 ± 45.91	0.0968
t-tau	54.0 ± 19.45	46.6 ± 24.65	**0.0361***
p-tau_{181}	24.9 ± 8.10	21.2 ± 7.82	**0.0109***
t-tau/$A\beta_{1-42}$	0.241 ± 0.142	0.215 ± 0.154	0.0494
p-tau/$A\beta_{1-42}$	0.111 ± 0.074	0.098 ± 0.060	0.1318
Alpha-synuclein	1264± 425.7	1101± 618.6	**0.0255***

* Mann-Whitney U test
$ Chi-square or Fisher's exact test

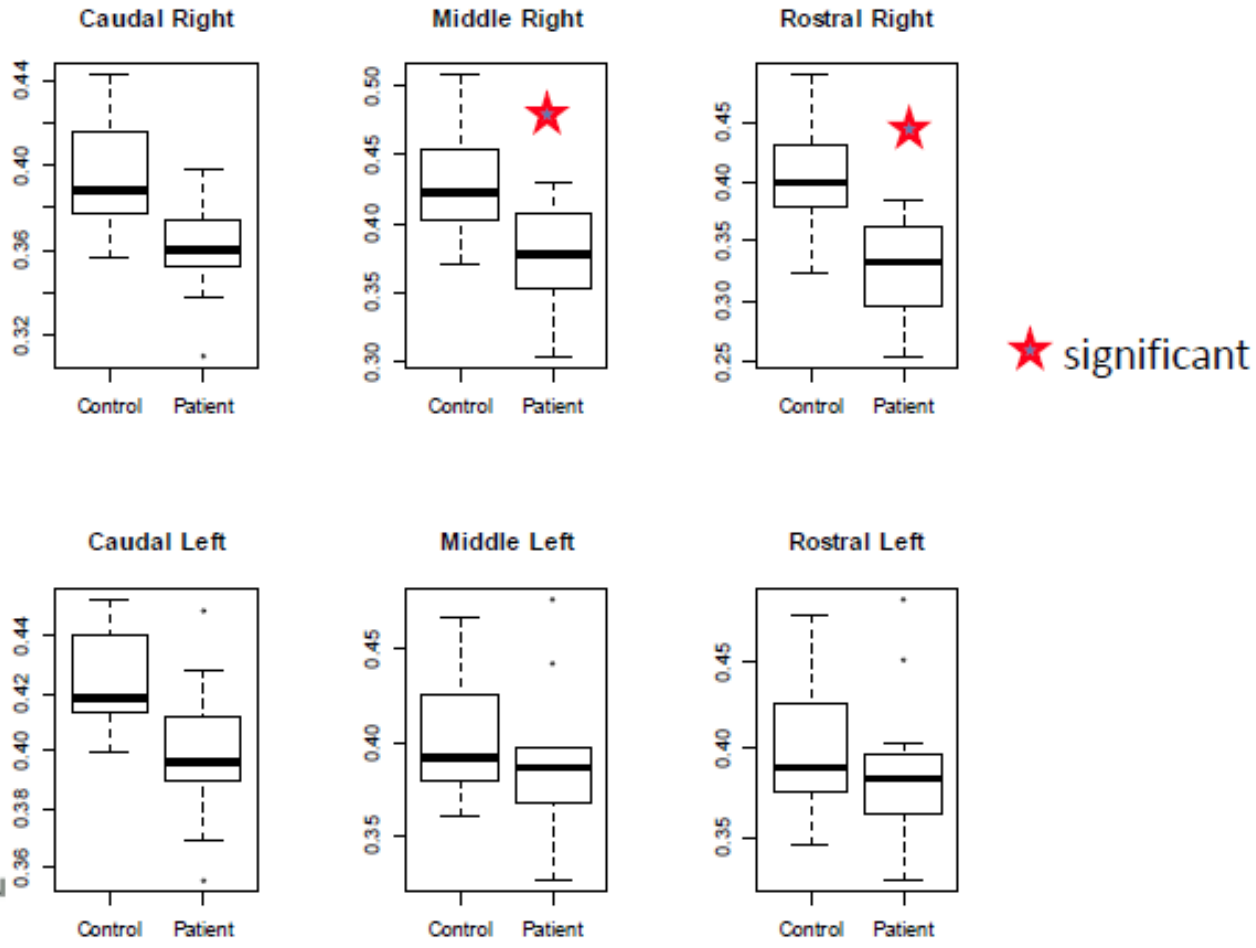
INTER SUBJECT VARIABILITY OF BIOMARKERS OVER SAMPLING PERIOD: PD vs. CONTROL



INTERSUBJECT VARIABILITY: Mean levels of biomarkers in PD group vs. Matched Controls. Alpha-synuclein, Abeta 1-42, and Abeta 1-40 increase significantly over time ($p<0.05$) while DJ-1 does not increase


Age corrected Lowest Put SBR
% age-expected SBR
250
200
150
100
50
0

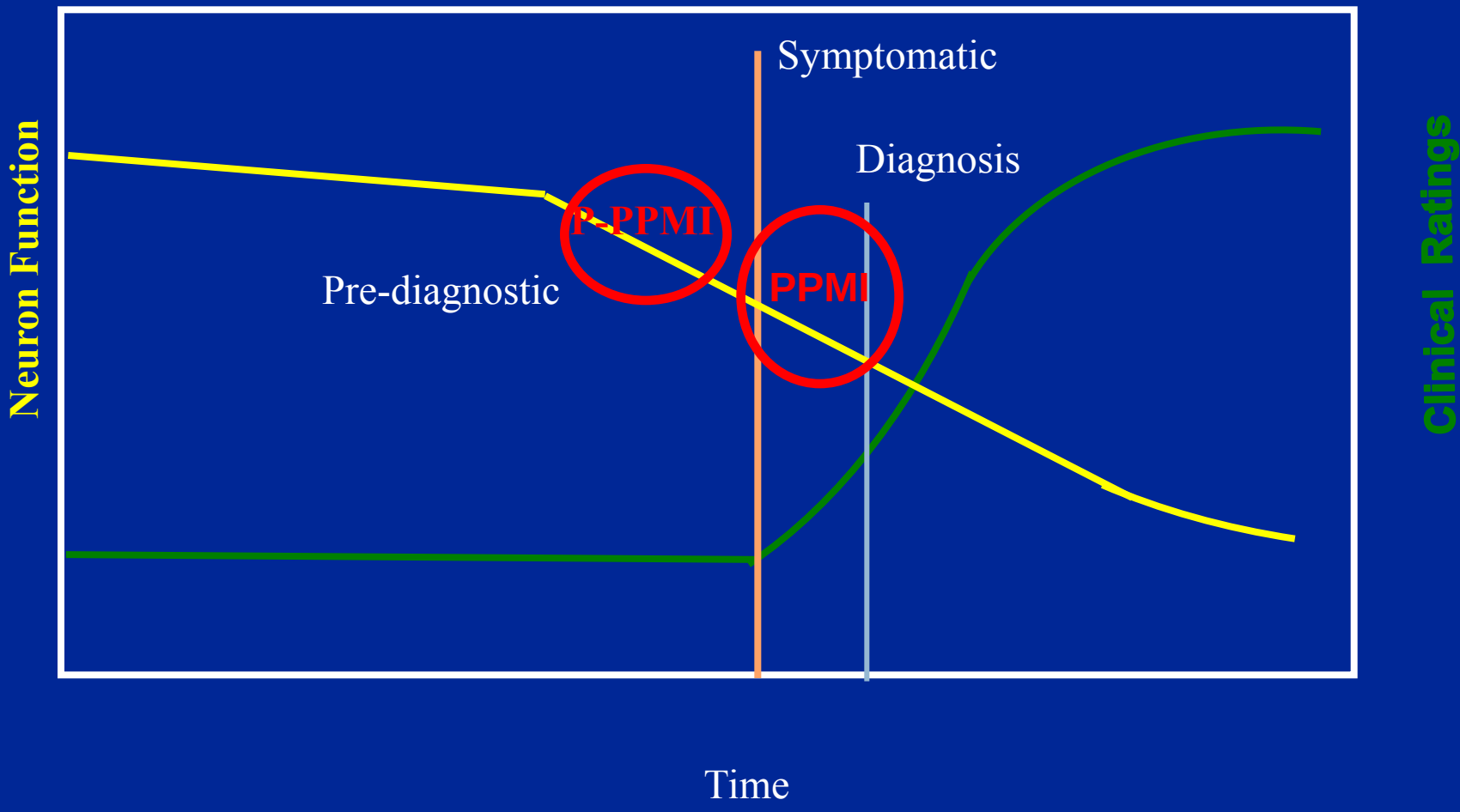
Preliminary Results: FA Variations In The Nigra



PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

Natural History of Parkinson disease



Proposal to establish pre-motor PPMI cohort define by DAT deficit

- Utilize existing PPMI infrastructure
  - Sites
  - Cores
  - Database
  - Website
- Utilize LRRK2 cohort
- Utilize Fox Trial Finder
- Utilize existing effort - olfaction, RBD as model

Proposal to establish pre-motor PPMI cohort define by DAT deficit

- Sequential biomarker strategy to identify DAT deficit cohort – olfaction, RBD, LRRK2
- Focus on subjects with < 65% expected DAT
- Develop a prodromal risk group
- Follow group with DAT deficit and normal DAT for 3-4 years (n=100)
  - Establish pre-motor biomarker signature
  - Define phenoconversion

Summary of PPMI status

- Enrollment (as of 7/1/12): 428 subjects (239 PD; 154 HS; 35 SW)
- Continued focus on subject enrollment and retention
- Plans to expand the study to Australia in early 2012
- Over 18000 data downloads to date
- Over 15 applications to BRC
- Incorporation of Pre-motor PD cohort
- Continue flexible incorporation of biomarker outcomes

PPMI ⟷ ADNI

- Study Design
- Study assessments – Tau, pTau, Amyloid, alpha-synuclein
- Healthy control cohorts
- Prodromal cohorts