The Parkinson Progression Marker Initiative (PPMI)

WW-ADNI

July 15 2011

PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

Rationale for PPMI: Challenges of disease-modifying trials

- Disease modifying PD therapeutics remain a major unmet need
- A major obstacle to current phase 2/3 neuroprotection studies is the lack of biomarkers for
  - Disease mechanism
  - Drug mechanism
  - Dosage determination
  - Study eligibility-early/accurate diagnosis
  - Pre-motor diagnosis
  - Monitoring disease progression
  - Stratification into PD sub-types
  - Correlation with clinical signals
- Biomarkers would potentially shorten study duration, reduce study sample size, limit study costs.

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Developing the Parkinson's Progression Markers Initiative

Academic, industry, government, foundation, patient constituencies worked to develop the PPMI study - process driven by the MJFF through its SAB and it unique ability to convene the interested groups

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 acquisition 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

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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 Details: Synopsis

Study population	▪ 400 *de novo* PD subjects (newly diagnosed and unmedicated) ▪ 200 age- and gender-matched healthy controls ▪ Subjects will be followed for a minimum of 3 years and a maximum of 5 years
Assessments/ Clinical data collection	▪ Motor assessments ▪ Neuropsychiatric/cognitive testing ▪ Olfaction ▪ DaTSCAN imaging, MRI
Biologic collection/	▪ DNA collected at screening ▪ Serum and plasma collected at each visit; urine collected 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 other clinical trials (including interventional trials) after 12 months

Clinical markers

Cognition

Behavioral
- Depression
- Apathy
- Anxiety
- ICD

Autonomic
- Constipation
- Bladder
- Sexual
- Cardiac

Olfaction

Sleep - RBD

Skin

Motor analysis

Speech

Biomarkers for PD

Imaging –Phenotomics

SPECT/PET-Dopamine -
DAT, F-Dopa, VMAT2

SPECT/PET-non-dopamine
FDG, MIBG, NE, 5HT, Nicotine, Ach, PBR, Amyloid, å-synuclein

MRI –DTI, Volumetrics,
Nigral Ultrasound

Biologics – Blood/CSF/Urine

Alpha-synuclein, DJ1, Urate, Tau, ß-Amyloid

'Omics' –

RNA profiling

Genetics

Synuclein, LRRK2
Parkin DJ-1, Pink1

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PPMI Schedule of Events

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

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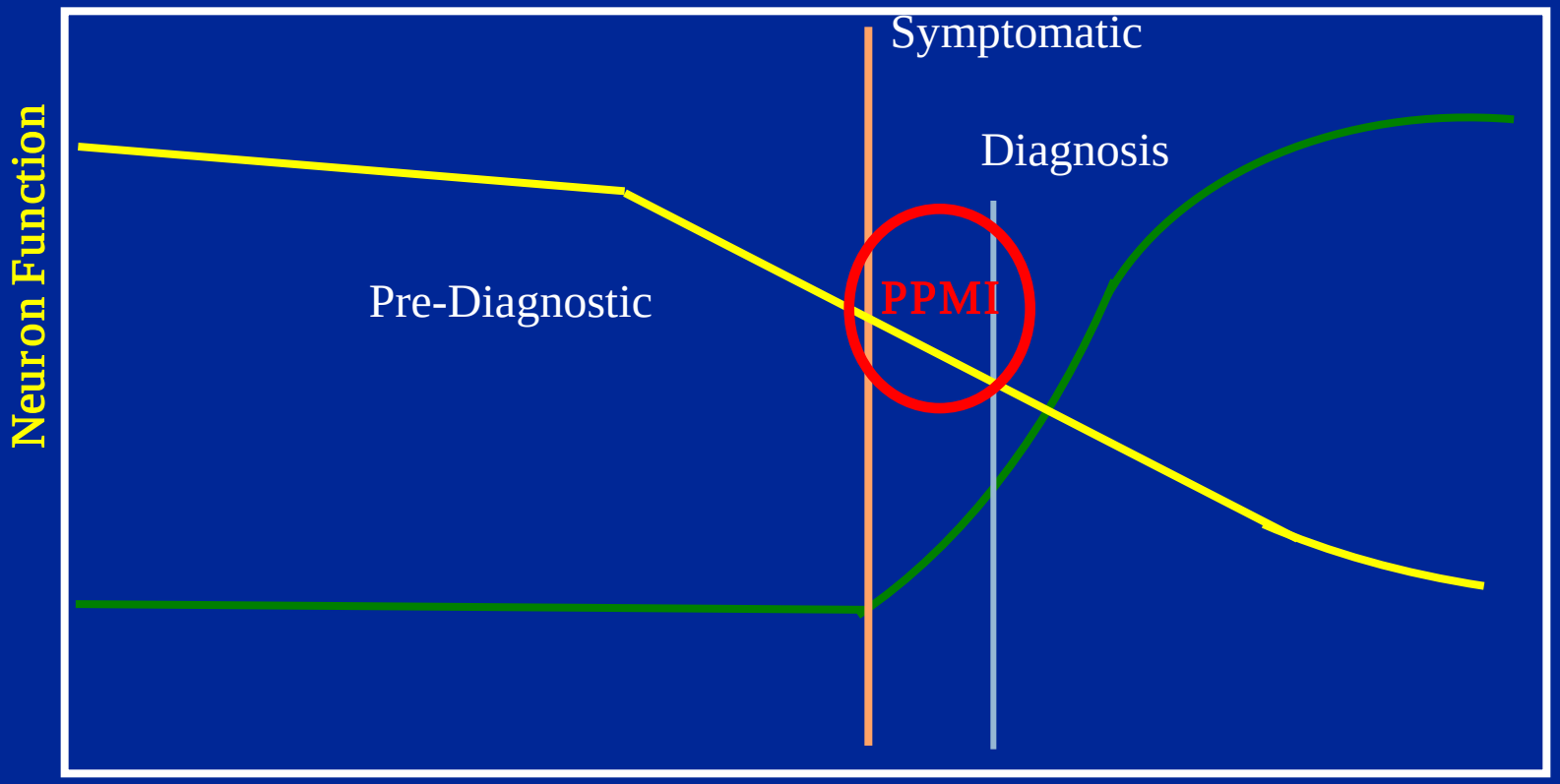
PPMI – target population



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Verification of biochemical markers

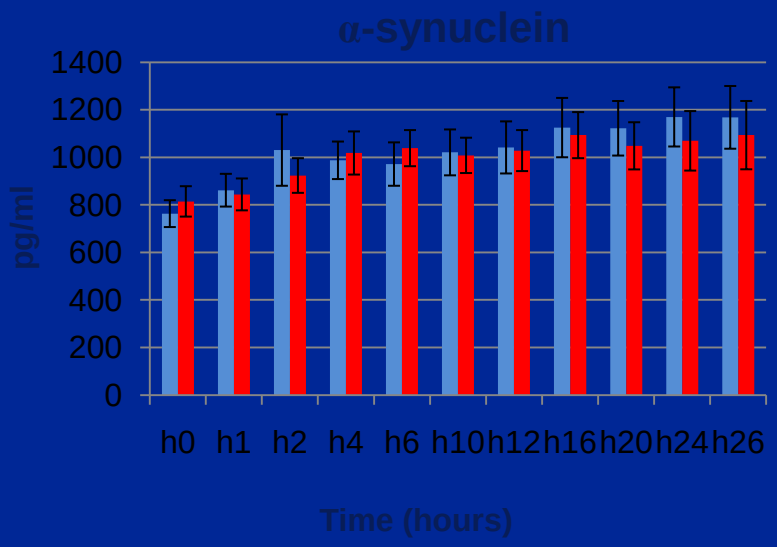
MJFF convened a biomarker taskforce, chaired by John Trojanowski, to review the state of PD biomarkers

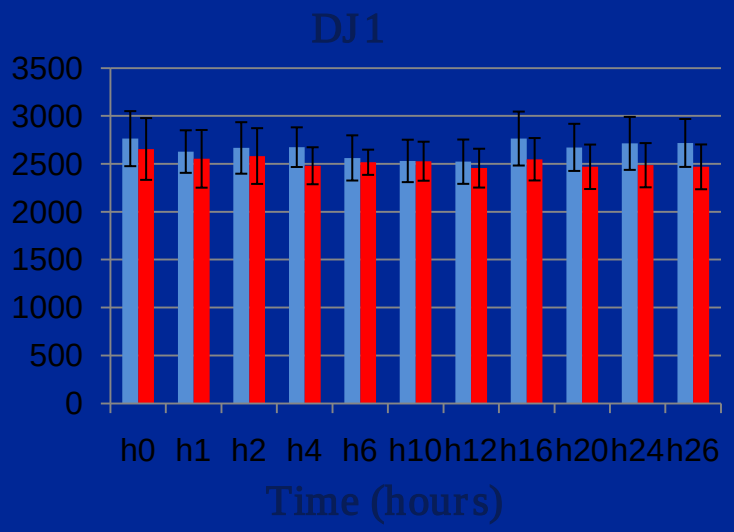
	Tier 1	Tier 2	Tier 3
Criteria	• Markers for which there is some evidence for a disease association • Preliminary data around the detection of the marker in a biochemical assay exist	• Putative markers with weak data correlating to PD • Standardized assays exist → straightforward to study in PD subjects	• Minimal data available • Relationship to PD hypotheses and mechanisms of disease exist
Candidates	• Alpha-synuclein • DJ-1 • Urate	• Cytokines • Glutamine/Glutamate • Total Tau and Phospho-Tau (p-181) • Abeta 1-42 species (INNO-BIA AlzBio3 assay)	• ST13 • J. Zhang's panel of proteins from proteomics • Glutathione • 8-OHdG

This taskforce identified several candidates to test for verification

Optimization of CSF markers

Optimization of Lead Markers	▪ RING study - synuclein assay roundrobin led by John Trojanowski and Les Shaw ▪ Multi-lab validation of existing DJ-1 assays (ELISAs)
Assay Qualification Study	▪ Collection of CSF and blood from healthy subjects to test diurnal changes and inter-subject variability of markers – CSF collected from 12 subjects over 24 hours at two different time points – A portion of CSF will be used to test samples; the rest will be banked ▪ Data from CSF collection study currently being analyzed but preliminary data suggests reliability of assays





www.ppmi-info.org

- Portal for PPMI data
- Portal for PPMI biospecimen through the biologic resource committee
- Portal for ancillary studies
- PPMI – study documents and SOPs available
- PPMI study progress
- Recruitment and retention tool

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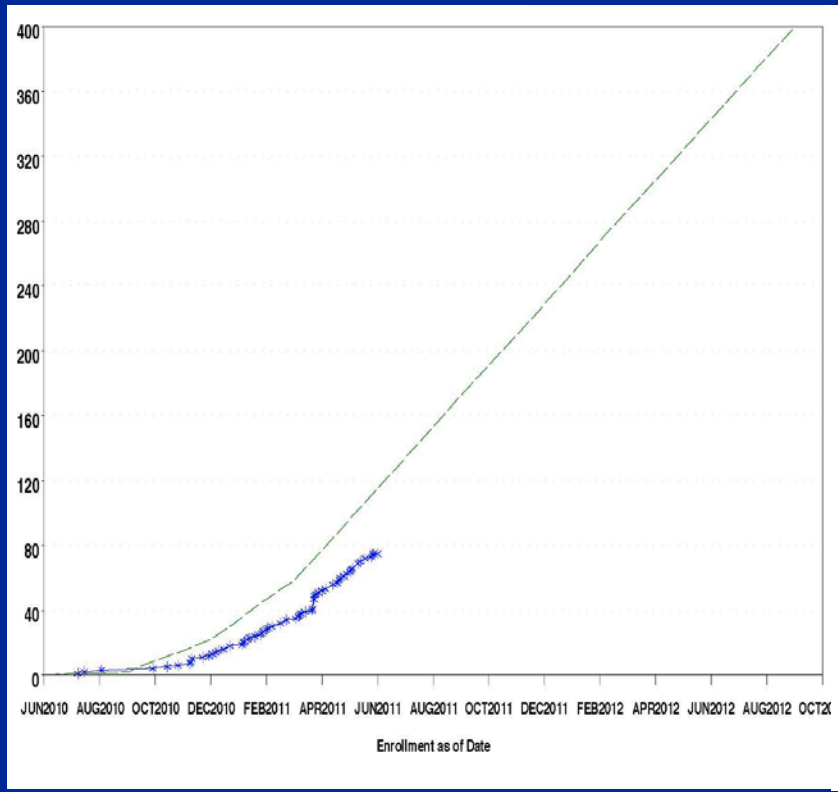
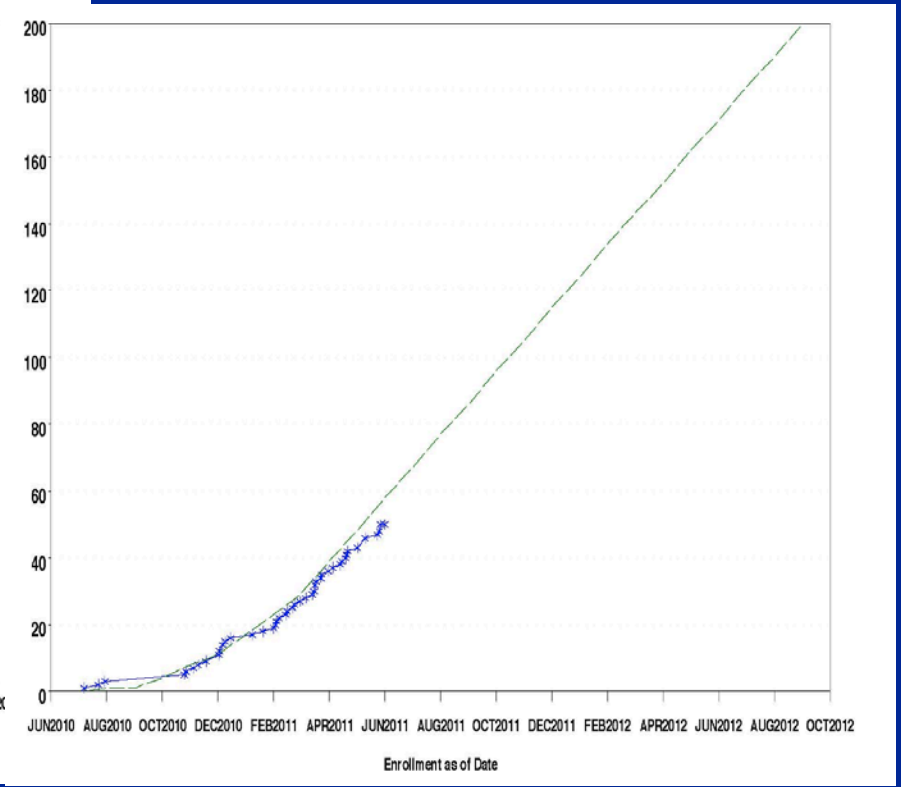
ENROLLMENT (through June 1, 2011)

PD n=75



Healthy n=50



PPMI Baseline Data

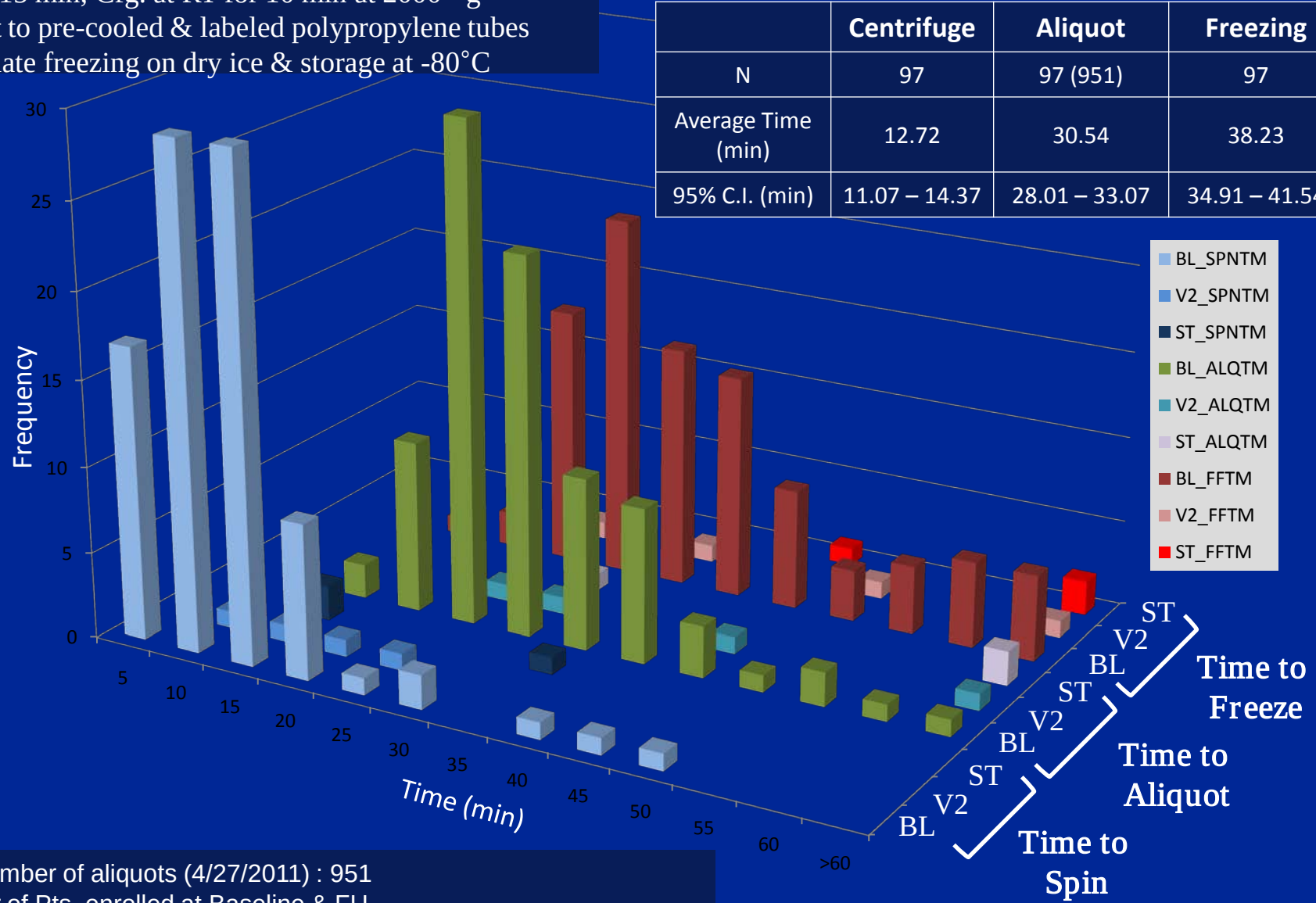
Variable	PD Subjects	HC Subjects
Female (n)	27	21
Male (n)	44	25
Subjects with family members with PD (n)	18	na
Subjects with No family members with PD (n)	52	na
Age (mean in years; range)	60.7 (35-83)	58.9 (31-80)
Year of education (mean; range)	16.1 (12-26)	16.5 (12-20)
Duration of disease (months)	8.9 (0-32)	na
Motor Evaluations		
MDS-UPDRS Total	34.0 (7-65)	4.3 (0-17)
MDS-UPDRS Part I	1.5 (0-9)	0.7 (0-5)
MDS-UPDRS Part I - Patient Questionnaire	4.8 (0-11)	2.0 (0-7)
MDS-UPDRS Part II - Patient questionnaire	6.3 (1-15)	0.3 (0-4)
MDS-UPDRS Part III	21.3 (6-39)	1.3 (0-10)
Hoehn & Yahr	1.6 (1-3)	0 (0-1)
Modified Schwab and England ADL	92.9 (80-100)	na
Non-motor Evaluations		
UPSIT - Total score	22.9 (6-39)	35 (21-40)
MoCA Score	26.9 (0-30)	28.4 (27-30)
GDS Score	2.4 (0-11)	0.8 (0-5)
SCOPA-AUT	8.3 (0-22)	5.1 (0-19)
DatSCAN Imaging Outcomes		
SBR - Caudate	1.3 (0.7-1.9)	2.1 (1.4-3.3)
SBR - Putamen	0.6 (0.3-1.0)	1.4 (0.7-2.5)

CSF Samples for PPMI

In the morning (8 am – 10 am), preferably fasted
Within 15 min, Cfg. at RT for 10 min at 2000×g
Aliquot to pre-cooled & labeled polypropylene tubes
Immediate freezing on dry ice & storage at -80°C

CSF Samples (From Collection to Freezing)

	Centrifuge	Aliquot	Freezing
N	97	97 (951)	97
Average Time (min)	12.72	30.54	38.23
95% C.I. (min)	11.07 – 14.37	28.01 – 33.07	34.91 – 41.54



Total number of aliquots (4/27/2011) : 951
Number of Pts. enrolled at Baseline & FU
: BL (90), Visit 2 (4), ST (3)
CSF was unobtainable in two patients at BL, One patient withdrawal at Visit 2

Summary of Status/Challenges

- Enrollment - 152 Subjects
- 18/21 sites activated// Plans for 3 sites in Australia
- 9 industry partners
- PPMI data flow from site to cores to LONI
- www.ppmi-info.org - Source of data, biospecimen

- Completion of recruitment
- Retention of subjects and continued data acquisition
- Adaptive design strategy - Assessment/Cohort

PPMI - ADNI

- Control populations
- Comparable clinical assessments (cognition), Bioanalysis, Imaging
- Database comparability
- Sharing of Pre-diagnostic cohorts