The Parkinson Progression Marker Initiative (PPMI)

PARKINSON'S PROGRESSION MARKERS INITIATIVE
Play a Part in Parkinson's Research

Full list of authors can be found at http://www.ppmi-info.org/

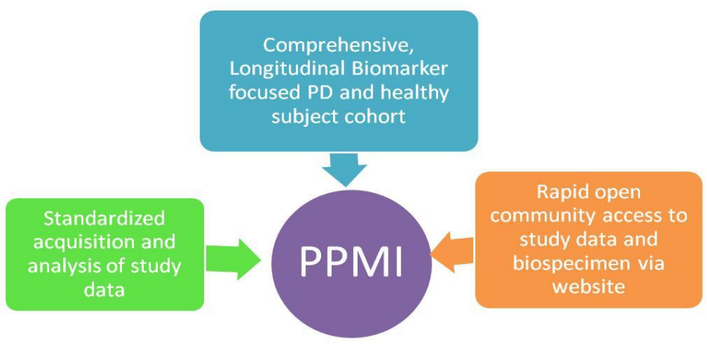
PPMI OVERVIEW

BACKGROUND / RATIONALE

PPMI is an observational international multi-center study to identify clinical, imaging and biologic markers of Parkinson disease progression

Ultimate goal of PPMI is to develop PD progression markers that could be utilized to accelerate research on disease modifying PD therapeutics.

OBJECTIVES OF PPMI



Deliverable: Identify a biomarker tool set that can be used to inform decisions at early stages of drug development and clinical testing

STUDY DESIGN

Study Population*	▪400 *de novo* PD subjects (newly diagnosed and unmedicated) ▪ 200 age- and gender-matched healthy controls ▪70 SWEDD ▪100 Prodromal - Olfactory/RBD ▪500 LRRK2 - PD manifest and non-manifesting family members ▪100 Synuclein - PD manifest and non-manifesting family members ▪ Subjects will be followed for 3 to 5 years
Assessments/Clinical Data Collection	▪ Motor assessments ▪ Neurobehavioral/cognitive testing ▪ Autonomic, Olfaction, Sleep ▪ DaTSCAN imaging, VMAT2, Amyloid, DTI/RS MRI
Biologic Collection	▪ DNA collected at screening ▪ Serum, whole blood & plasma collected at each visit; urine annually ▪ CSF collected at baseline, 6mo, 12 mo and then annually
Initial Biospecimen Studies	▪ Lead biologic candidates to be tested: – Alpha-synuclein, Abeta 1-42, Total tau, Phospho-tau (p-181) (CSF) – DJ-1 (CSF and blood) – Urate (blood)

***Study Populations in RED are complete, in Black in progress**

PPMI Clinical Sites

United States
University of Rochester – Rochester NY
Oregon Health Sciences University – Portland OR
Baylor College of Medicine – Houston TX
The Parkinson's Institute – Sunnyvale CA
University of Pennsylvania – Philadelphia PA
University of South Florida – Tampa FL
University of California San Diego - San Diego CA
Johns Hopkins University – Baltimore MD
Emory University, School of Medicine – Atlanta GA
Institute for Neurodegenerative Disorders - New Haven CT
Boston University – Boston MA
University of Alabama at Birmingham – Birmingham AL
Northwestern University – Chicago IL
Univ. of Wash & VA Puget Sound Health Care System – Seattle WA
Cleveland Clinic – Cleveland OH
University of Cincinnati – Cincinnati OH
Banner Research Institute- Phoenix AZ
Parkinson's Disease & Mov. Dis. Center of Boca Raton- Boca Raton FL

Europe
Innsbruck Medical University – Innsbruck Austria
University of Napoli – Napoli Italy
University of Tubingen – Tubingen Germany
Paracelsus-Elena Klinik – Kassel Germany
Imperial College of London – London England

Australia
Macquarie University – Sydney NSW Australia

PPMI BASELINE RESULTS

Baseline Demographics and Motor Characteristics

Baseline Assessment	PD Subjects (N = 414)	Healthy Controls (N = 189)	SWEDD Subjects (N = 59)	PD p-value relative to HC	PD p-value relative to SWEDD
Mean Age (Range)	61.7 (33 - 85)	60.4 (31 - 84)	60.7 (38 - 79)	0.17	0.49
Gender (M %/F %)	271 (65%) / 143 (35%)	121 (64%) / 68 (36%)	35 (59%) / 24 (41%)	0.78	0.38
MDS-UPDRS Mean Score & Sub Scores					
MDS-UPDRS Total Score	32.3	4.7	29	<0.01	0.08
MDS-UPDRS Part I	5.5	3	8.7	<0.01	<0.01
MDS-UPDRS Part II	5.9	0.4	5.9	<0.01	0.98
MDS-UPDRS Part III (Motor Exam)	20.9	1.3	14.4	<0.01	<0.01
Hoehn & Yahr N(%)					
Stage 0	0 (0%)	184 (97%)	0 (0%)	<0.01	0.7
Stage 1	179 (43%)	2 (1%)	35 (59%)		
Stage 2	229 (56%)	0 (0%)	24 (41%)		
Stage 3-5	2 (1%)	0 (0%)	0 (0%)		
Modified Schwab & England (mean)	93.1	NA	94.7	NA	0.05
First degree family Member with PD (%)	54 (13%)	0 (0%)	14 (24%)	<0.01	0.22
Mean Duration of Disease (months)	6.6 (0.4 - 35.8)	NA	7.9 (0.5 - 37)	NA	0.16
Initial Symptoms*					
Resting Tremor	321 (78%)	NA	50 (85%)	NA	0.23
Rigidity	314 (76%)	NA	33 (56%)	NA	<0.01
Bradykinesia	339 (82%)	NA	46 (78%)	NA	0.42
Postural Instability	29 (7%)	NA	7 (12%)	NA	0.19
Other	72 (17%)	NA	8 (14%)	NA	0.45

* Subjects may have more than one initial symptom listed.

Baseline Non-motor Characteristics

Baseline Assessment	PD Subjects (N = 414)	Healthy Controls (N = 189)	SWEDD Subjects (N = 59)	PD p-value relative to HC	PD p-value relative to SWEDD
MOCA Total Score	27.1	28.2	27	<0.01	0.63
SCOPA AUT Total Score	9.5	5.8	14.1	<0.01	<0.01
GDS	2.3	1.3	3.4	<0.01	<0.01
State Trait Anxiety Score	65.2	57	70.3	<0.01	0.04
QUIP	0.3	0.3	0.6	0.92	<0.01
Benton Judgment of Line Orientation Score	12.7	13.1	12.8	0.05	0.84
HVLT Immediate Recall	9.7	10.2	9.7	<0.01	0.84
HVLT Delayed Recognition	11.2	11.5	10.8	<0.01	0.07
HVLT Delayed False Alarms	1.2	1.1	1.7	0.2	0.02
Letter Number Sequencing Raw Score	10.5	11	9.8	0.07	0.05
Semantic Fluency Total Score	48.6	51.9	45	<0.01	0.03
Symbol Digit Modalities (SDM)	41.3	46.8	41	<0.01	0.83
UPSIT Raw Score	22.3	34	31.3	<0.01	<0.01
Epworth Sleepiness Scale (ESS)					
Not Sleepy (9 or below)	345 (84%)	163 (88%)	40 (68%)	<0.01	<0.01
Sleepy (10 or above)	65 (16%)	23 (12%)	19 (32%)		
REM Sleep Disorder					
Negative (< 5)	257 (62%)	152 (80%)	34 (58%)	<0.01	0.57
Positive (5 or greater)	157 (38%)	37 (20%)	25 (42%)		

Tables Generated on Data Submitted to PPMI as of: 01MAR2013.
Mean unless otherwise stated

❖ **PD subjects demonstrate motor symptoms and severity of illness consistent with PD clinical trials**

❖**PD subjects cognitive and behavioral scores differ from healthy subjects**
See Poster xxx Cognitive performance and psychiatric symptoms in de novo, untreated Parkinson's disease: results from the PPMI study-for more complete non-motor data

❖ **SWEDD subjects may demonstrate increased mood, anxiety and autonomic scores compared to PD and healthy subjects**

CSF Acquisition

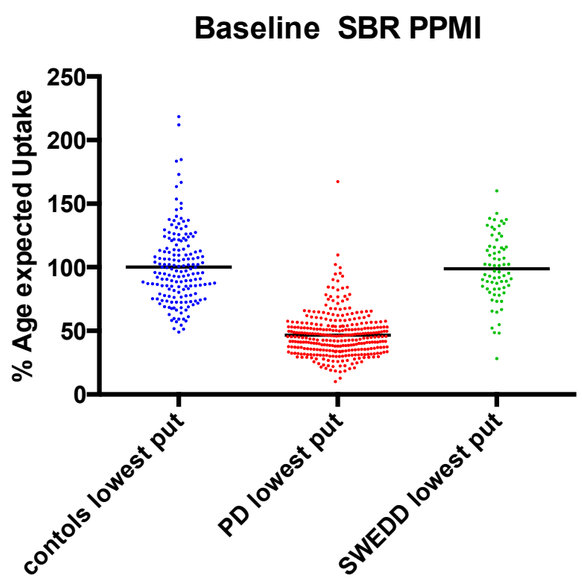
Group	Visit (months) 0 Baseline	6	12	24
PD	401 (98%)	275 (91%)	171 (87%)	29 (83%)
Healthy controls	184 (97%)	146 (87%)	140 (84%)	25 (80%)
SWEDD	59 (92%)	36 (89%)	25 (84%)	N/A

Pilot CSF

	HC (N = 39)	PD (N = 63)	*P* value#
$A\beta_{1-42}$ (pg/mL)	242.8 ± 49.95 (226.7 – 259.0)*	228.7 ± 45.63 (217.2 – 240.2)	**0.0466**
t-tau (pg/mL)	53.9 ± 19.33 (47.6 – 60.1)	46.1 ± 24.71 (39.8 – 52.3)	**0.0276**
$p\text{-tau}_{181}$ (pg/mL)	24.9 ± 8.45 (22.2 – 27.6)	21.0 ± 7.83 (19.0 – 23.0)	**0.0093**
t-tau/$A\beta_{1-42}$ ratio	0.240 ± 0.141 (0.195 – 0.286)	0.215 ± 0.157 (0.176 – 0.255)	**0.0451**
$p\text{-tau}_{181}/A\beta_{1-42}$ ratio	0.113 ± 0.075 (0.089 – 0.138)	0.099 ± 0.063 (0.084 – 0.115)	0.1482
$p\text{-tau}_{181}$/t-tau ratio	0.491 ± 0.160 (0.439 – 0.543)	0.543 ± 0.263 (0.477 – 0.609)	0.6820
α-syn (pg/mL)	1264 ± 425.7 (1126 – 1403)	1082 ± 611.1 (928 – 1235)	**0.0120**

Pilot CSF study demonstrates reduction in Tau, pTau, synuclein in PD subjects compared to healthy – Complete baseline CSF assessment is underway

Baseline DAT imaging



❖**PD subjects demonstrate 50% loss of DAT at baseline**

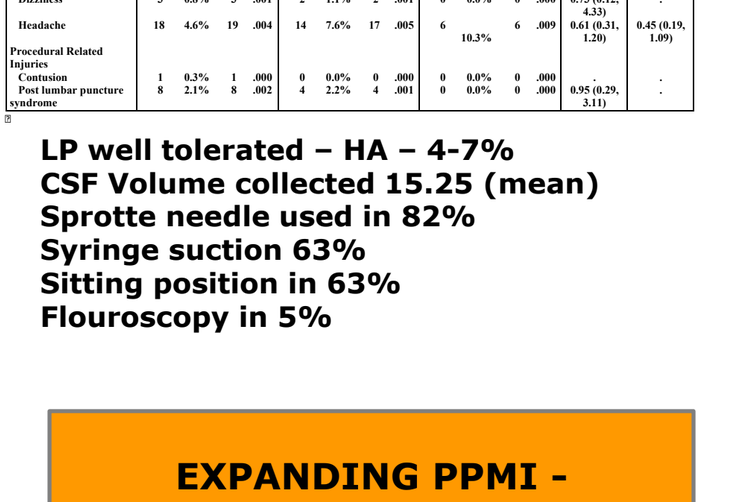
See Poster 155 123-I ioflupane SPECT measures of Parkinson's disease progression in the Parkinson Progression Marker Initiative (PPMI) trial-for more complete imaging data

CSF Safety/AE

Adverse Event	Enrolled Subjects: PD Subjects (N = 390) # of Subjects	% of Subjects	# of Events	Rate	Healthy Controls (N = 184) # of Subjects	% of Subjects	# of Events	Rate	SWEDD Subjects (N = 58) # of Subjects	% of Subjects	# of Events	Rate	RR (95% CI) PD vs. HC	PD vs. SWEDD
Total	49	12.6%	63	.012	36	19.6%	48	.015	8	13.8%	11	.016	0.64 (0.43, 0.95)	0.91 (0.45, 1.82)
General														
Fatigue	1	0.3%	1	.000	1	0.5%	1	.000	0	0.0%	0	.000	0.60 (0.04, 9.54)	.
Injection site pain	14	3.6%	14	.003	8	4.3%	9	.003	2	3.4%	2	.003	0.84 (0.36, 1.97)	1.06 (0.25, 4.54)
Musculoskeletal														
Back pain	2	0.5%	2	.000	7	3.8%	7	.002	2	3.4%	2	.003	0.13 (0.03, 0.62)	0.15 (0.02, 1.04)
Musculoskeletal discomfort	3	0.8%	3	.001	2	1.1%	2	.001	0	0.0%	0	.000	0.73 (0.12, 4.33)	.
Nervous System														
Dizziness	3	0.8%	3	.001	2	1.1%	2	.001	0	0.0%	0	.000	0.73 (0.12, 4.33)	.
Headache	18	4.6%	19	.004	14	7.6%	17	.005	6	10.3%	6	.009	0.61 (0.31, 1.20)	0.45 (0.19, 1.09)
Procedural Related Injuries														
Contusion	1	0.3%	1	.000	0	0.0%	0	.000	0	0.0%	0	.000	.	.
Post lumbar puncture syndrome	8	2.1%	8	.002	4	2.2%	4	.001	0	0.0%	0	.000	0.95 (0.29, 3.11)	.

LP well tolerated – HA – 4-7%
CSF Volume collected 15.25 (mean)
Sprotte needle used in 82%
Syringe suction 63%
Sitting position in 63%
Flouroscopy in 5%

EXPANDING PPMI - PPMI PRODROMAL and GENETIC COHORTS



❖ **Prodromal - 100 subjects with hyposmia or RBD Plus DAT eligible**

❖**Genetic Cohort: 600 subjects**
- **300 subjects with PD and a mutation in either the LRRK2 or SNCA gene**
- **300 subjects unaffected by PD who either have or are at risk to have a mutation in LRRK2 or SNCA**

ALL subjects will undergo PPMI PD assessments/followed for 3-5 years

CONCLUSIONS

- **PPMI, has successfully enrolled planned PD, healthy and SWEDD cohorts and has established standardized procedures for acquisition and analysis of all study data**
- **PPMI strategy for comprehensive biomarker acquisition including CSF has been successful.**
- **PPMI longitudinal follow-up underway-subject retention - 16/662 subjects withdrawn from the study**
- **Robust web-based access(www.ppmi-info,org) for data and biospecimen - >68,700 data downloads >20 biologic specimen requested.**
- **PPMI Prodromal and Genetic cohorts incorporated to assess prodromal PD biomarkers. -**

PPMI Funding Partners

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PPMI data is available online at http://www.ppmi-info.org/