

PPMI Status Update

Ken Marek

**WW-ADNI
July 11, 2013**



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Play a Part in Parkinson's Research



Disclosure

- **Co-founder on Molecular Neuroimaging LLC – PET and SPECT imaging services**
- **Consultant –BMS, GEHC, Lilly, Merck, Navidea, Piramal**
- **Pfizer, Sanofi,**

Parkinson Progression Marker Initiative

- 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
 - Stratification into PD sub-types
 - Correlation with clinical signals

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



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PPMI Study Synopsis

Study population	<ul style="list-style-type: none"> ▪ 400 <i>de novo</i> PD subjects (newly diagnosed and unmedicated) ▪ 200 age- and gender-matched healthy controls ▪ 70 SWEDD ▪ 100 Prodromal - Olfactory/RBD/LRRK2 ▪ 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	<ul style="list-style-type: none"> ▪ Motor assessments ▪ Neurobehavioral/cognitive testing ▪ Autonomic, Olfaction, Sleep ▪ DaTSCAN, VMAT, Amyloid imaging, DTI/RS MRI
Biologic collection/	<ul style="list-style-type: none"> ▪ 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	<ul style="list-style-type: none"> ▪ Lead biologic candidates to be tested: <ul style="list-style-type: none"> • Alpha-synuclein (CSF) • DJ-1 (CSF and blood) • Urate (blood) • Abeta 1-42 (CSF) • Total tau, Phospho-tau (p-181) (CSF)



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PPMI Sites

PPMI SITES IN THE UNITED STATES:

- Arizona PD Consortium (Sun City, AZ)
- Baylor College of Medicine (Houston, TX)
- Boston University (Boston, MA)
- Cleveland Clinic (Cleveland, OH)
- Emory University (Atlanta, GA)
- Institute of Neurodegenerative Disorders (New Haven, CT)
- Johns Hopkins University (Baltimore, MD)
- Northwestern University (Chicago, IL)
- Oregon Health and Science University (Portland, OR)
- The Parkinson's Institute (Sunnyvale, CA)
- PD & Movement Disorders Center at Boca Raton (Boca Raton, FL)
- University of Alabama at Birmingham (Birmingham, AL)
- University of California at San Diego (San Diego, CA)
- University of Cincinnati (Cincinnati, OH)
- University of Pennsylvania (Philadelphia, PA)
- University of Rochester (Rochester, NY)
- University of South Florida (Tampa, FL)
- University of Washington (Seattle, WA)

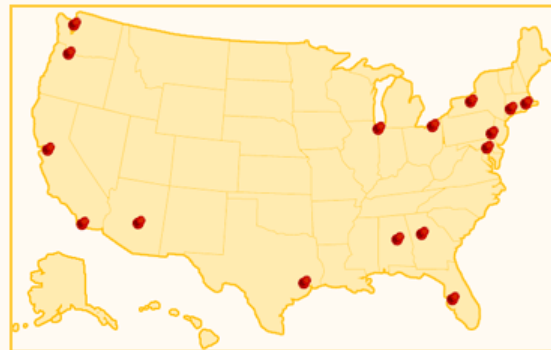
PPMI SITES IN EUROPE:

- Imperial College (London, UK)
- Innsbruck University (Innsbruck, Austria)
- Paracelsus-Elena Clinic Kassel/University of Marburg (Kassel and Marburg, Germany)
- University of Napoli (Naples, Italy)
- University of Tübingen (Tübingen, Germany)

PPMI SITES IN AUSTRALIA:

- Macquarie University (Sydney, Australia)

Sites to enroll LRRK2 and synuclein subjects will be added.



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PPMI SC and Study Cores

Steering Committee	PI-K Marek, C Tanner, T Foroud, D Jennings, K Kieburtz, W Poewe, B Mollenhauer, T Simuni, (core leaders, MJFF, ISAB), S Lasch
Clinical Coordination Core	<ul style="list-style-type: none"> University of Rochester's Clinical Trials Coordination Center PI: Karl Kieburtz, irina Lazurenko, Alice Rudolph, Cindy Casaceli
Imaging Core	<ul style="list-style-type: none"> Institute for Neurodegenerative Disorders; PI: John Seibyl, Norbert Schuff,
Statistics Core	<ul style="list-style-type: none"> University of Iowa PI: Chris Coffey
Bioinformatics Core	<ul style="list-style-type: none"> Laboratory of Neuroimaging (LONI) at UCLA PI: Arthur Toga, Karen Crawford
BioRepository	<ul style="list-style-type: none"> Coriell/BioRep PI: Alison Ansbach, Paola Casalin,
Bioanalytics Core	<ul style="list-style-type: none"> University of Pennsylvania PI: John Trojanowski, Les Shaw
Genetics Core	<ul style="list-style-type: none"> National Institute on Aging/NIH PI: Andy Singleton
RBD Core	<ul style="list-style-type: none"> Hephata Hessisches Diakoniezentrum e. V. PI: Geert Mayer
Olfactory Core	<ul style="list-style-type: none"> Institute for Neurodegenerative Disorders PI: Danna Jennings
Genetics Coordinating Core	<ul style="list-style-type: none"> Indiana University PI: Tatiana Foroud



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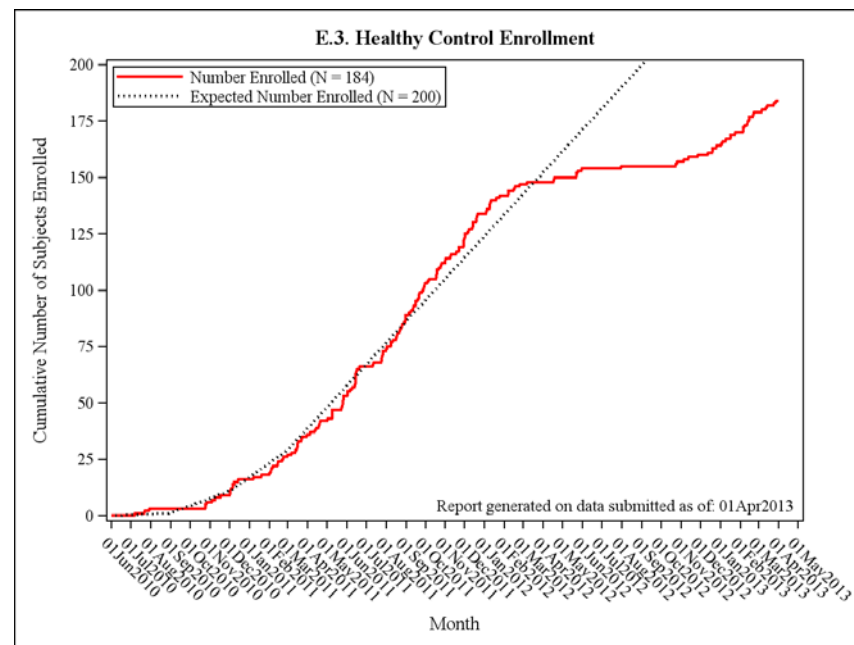
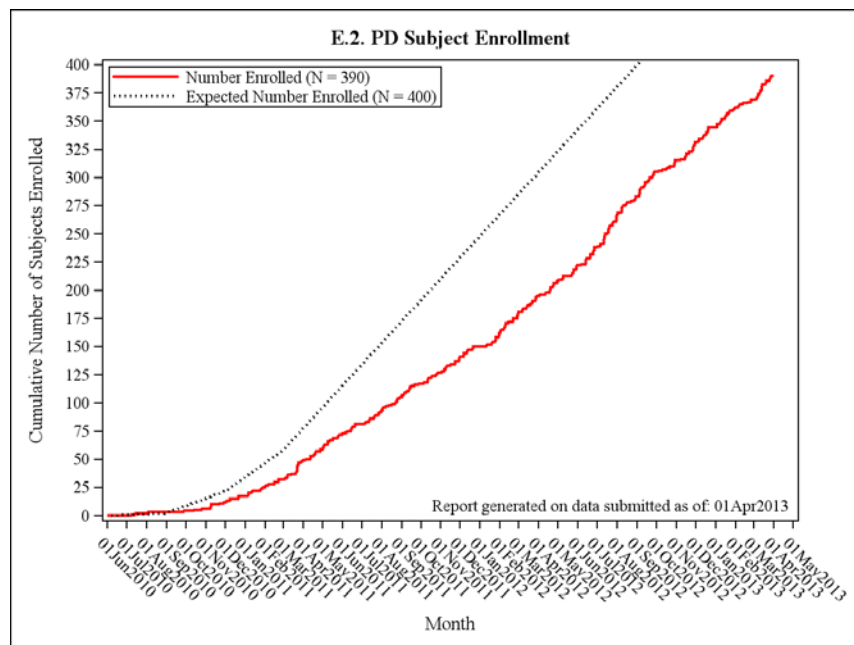
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PPMI is sponsored and partially funded by The Michael J. Fox Foundation for Parkinson's Research. Other funding partners include a consortium of industry players, non-profit organizations and private individuals.



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ENROLLMENT



- **Enrollment** – 419 PD 191 HS 59 SWEDD **669 subjects**
- **Retention** – 413 PD 183 HS 58 SWEDD - **654 subjects**



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Baseline Demographics and Motor Characteristics

Baseline Assessment	PD Subjects (N = 423)	Healthy Controls (N = 196)	SWEDD Subjects (N = 64)	PD p-value relative to HC	PD p-value relative to SWEDD
Mean Age (Range)	61.7 (33 - 85)	60.8 (31 - 84)	60.9 (38 - 79)	0.33	0.58
Gender (M %/F %)	277 (65%) / 146 (35%)	126 (64%) / 70 (36%)	40 (63%) / 24 (37%)	0.79	0.67
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	1.2	14.3	<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



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Baseline Non-motor Characteristics

Baseline Assessment	PD Subjects (N = 423)	Healthy Controls (N = 196)	SWEDD Subjects (N = 64)	PD p-value relative to HC	PD p-value relative to SWEDD
MOCA Total Score	27.1	28.2	27.1	<0.01	0.94
SCOPA AUT Total Score	9.5	5.9	113.8	<0.01	<0.01
GDS	2.3	1.3	3.3	<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.

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MoCA Cut-off Scores

MoCA	Frequency	Percentage	Cumulative Frequency	Cumulative Percent
17	1	0.26	1	0.26
19	1	0.26	2	0.52
20	2	0.52	4	1.04
21	5	1.30	9	2.34
22	8	2.08	17	4.43
23	13	3.39	30	7.81
24	13	3.39	43	11.20
25	36	9.38	79	20.57
26	49	12.76	128	33.33
27	64	16.67	192	50.00
28	68	17.71	260	67.71
29	70	18.23	330	85.94
30	54	14.06	384	100.00

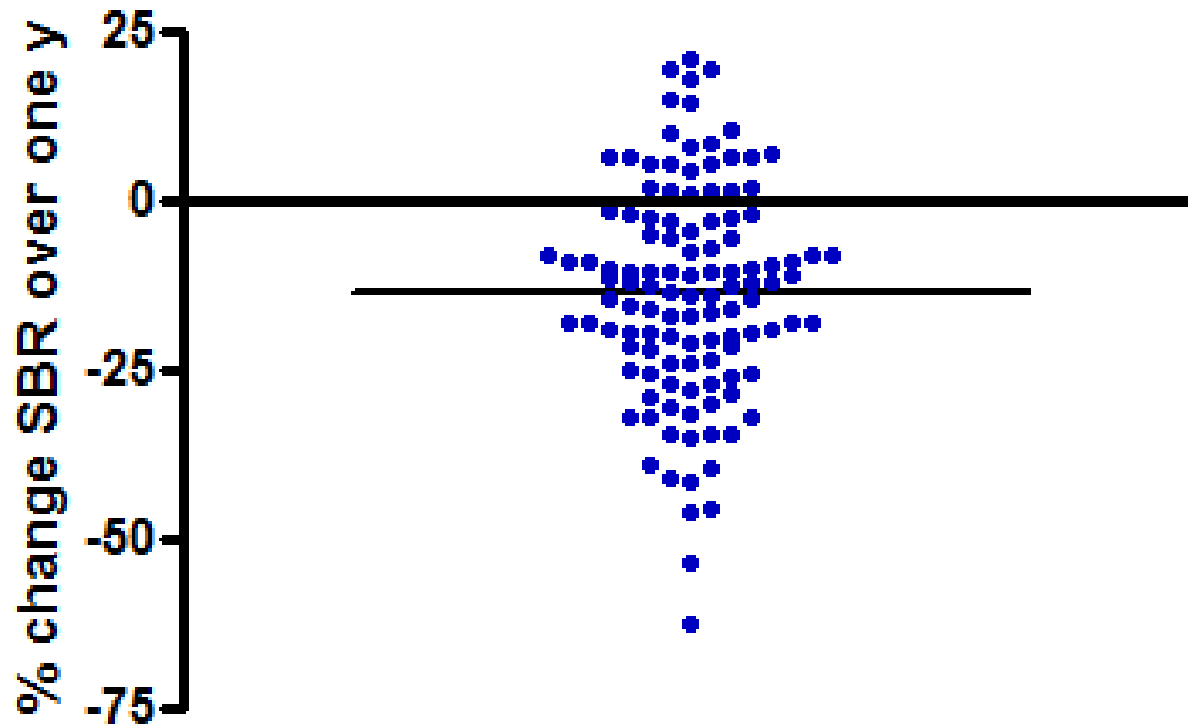
Consistent with research reporting 15-20% of de novo PD patients have MCI.



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Longitudinal DAT



N= 117

Mean 13.3% \pm 16.0%

78.6% going down at yr 1



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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

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%



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CSF Pilot Baseline Data

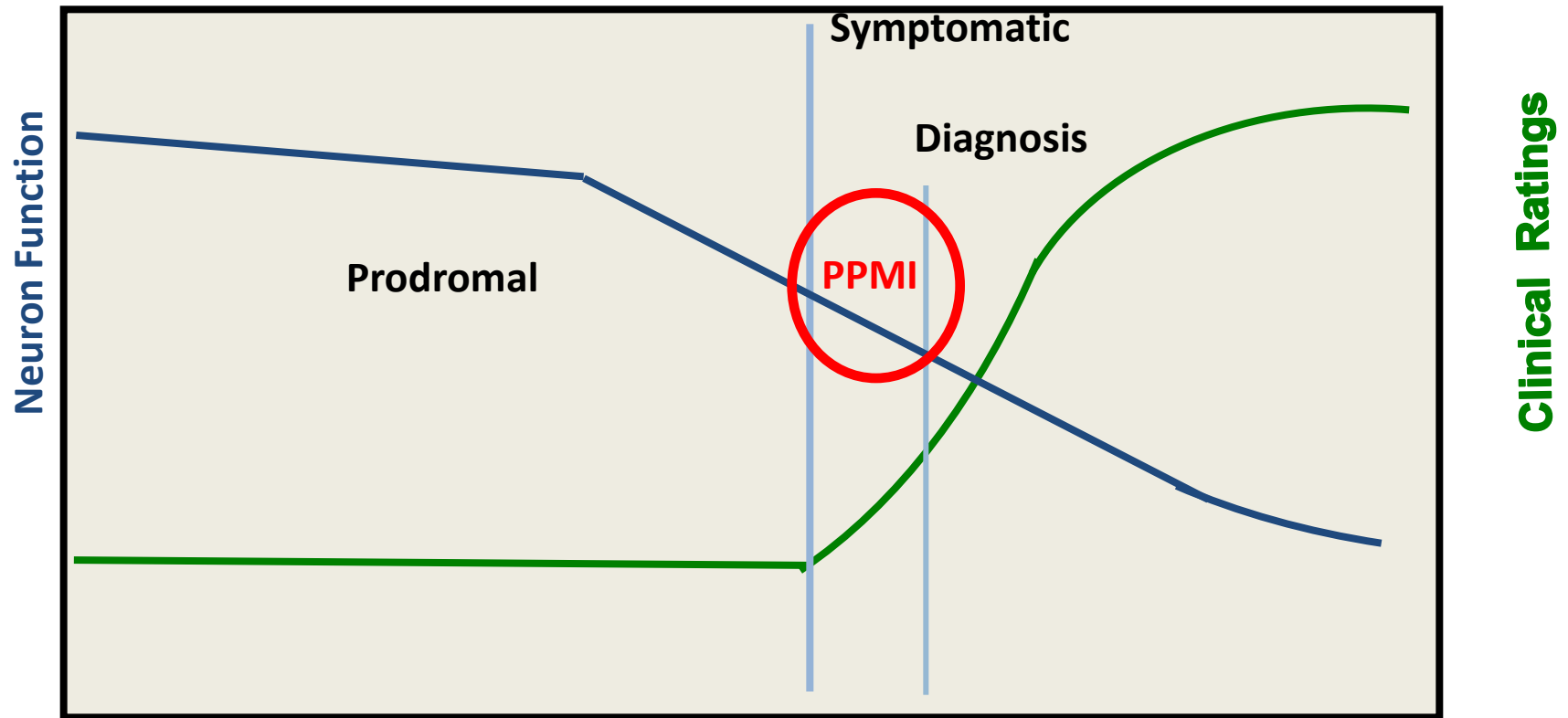
	HC (N = 39)	PD (N = 63)	P value [#]
Aβ₁₋₄₂ (pg/mL)	242.8 \pm 49.95 (226.7 – 259.0)*	228.7 \pm 45.63 (217.2 – 240.2)	0.0466
t-tau (pg/mL)	53.9 \pm 19.33 (47.6 – 60.1)	46.1 \pm 24.71 (39.8 – 52.3)	0.0276
p-tau₁₈₁ (pg/mL)	24.9 \pm 8.45 (22.2 – 27.6)	21.0 \pm 7.83 (19.0 – 23.0)	0.0093
t-tau/Aβ₁₋₄₂ ratio	0.240 \pm 0.141 (0.195 – 0.286)	0.215 \pm 0.157 (0.176 – 0.255)	0.0451
p-tau₁₈₁/Aβ₁₋₄₂ ratio	0.113 \pm 0.075 (0.089 – 0.138)	0.099 \pm 0.063 (0.084 – 0.115)	0.1482
p-tau₁₈₁/t-tau ratio	0.491 \pm 0.160 (0.439 – 0.543)	0.543 \pm 0.263 (0.477 – 0.609)	0.6820
α-syn (pg/mL)	1264 \pm 425.7 (1126 – 1403)	1082 \pm 611.1 (928 – 1235)	0.0120



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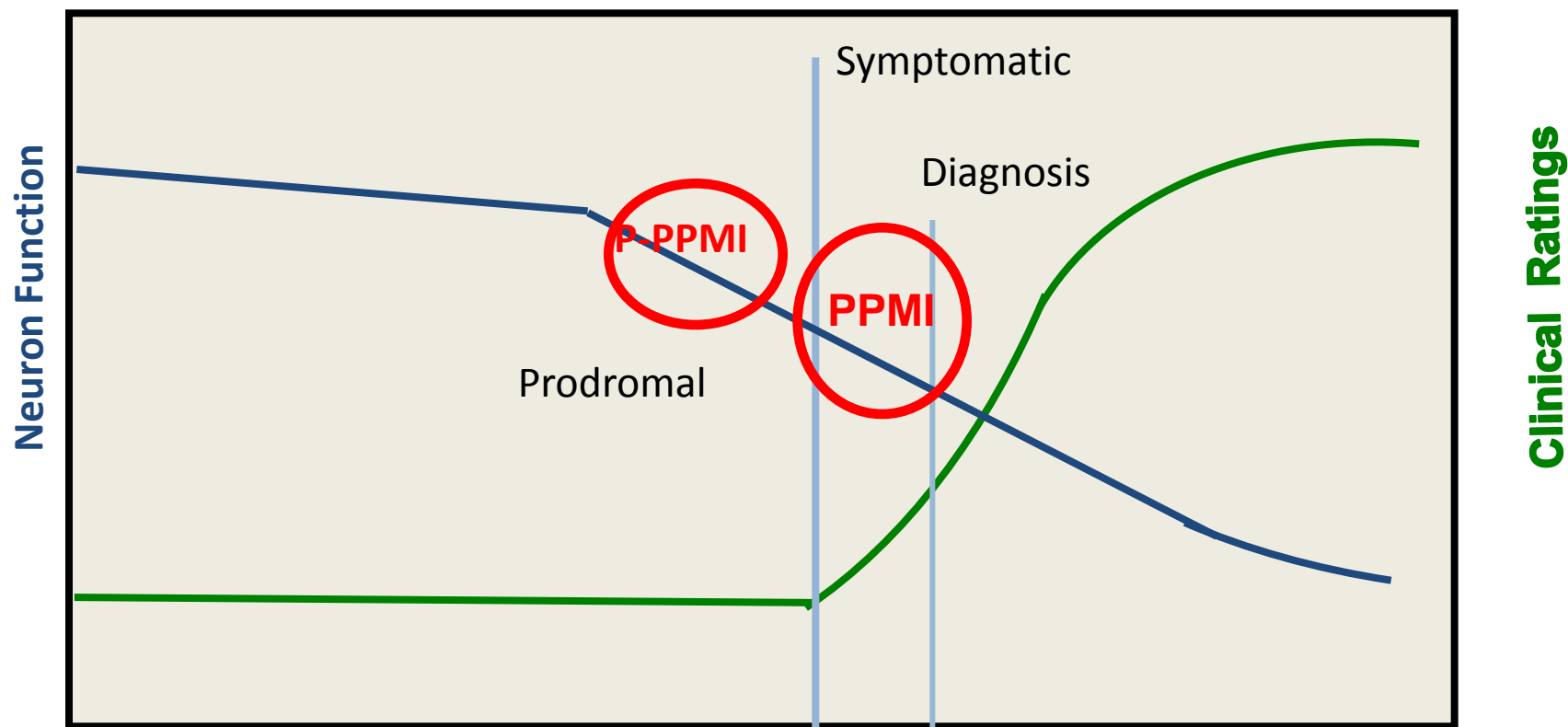
Natural history of Parkinson's disease



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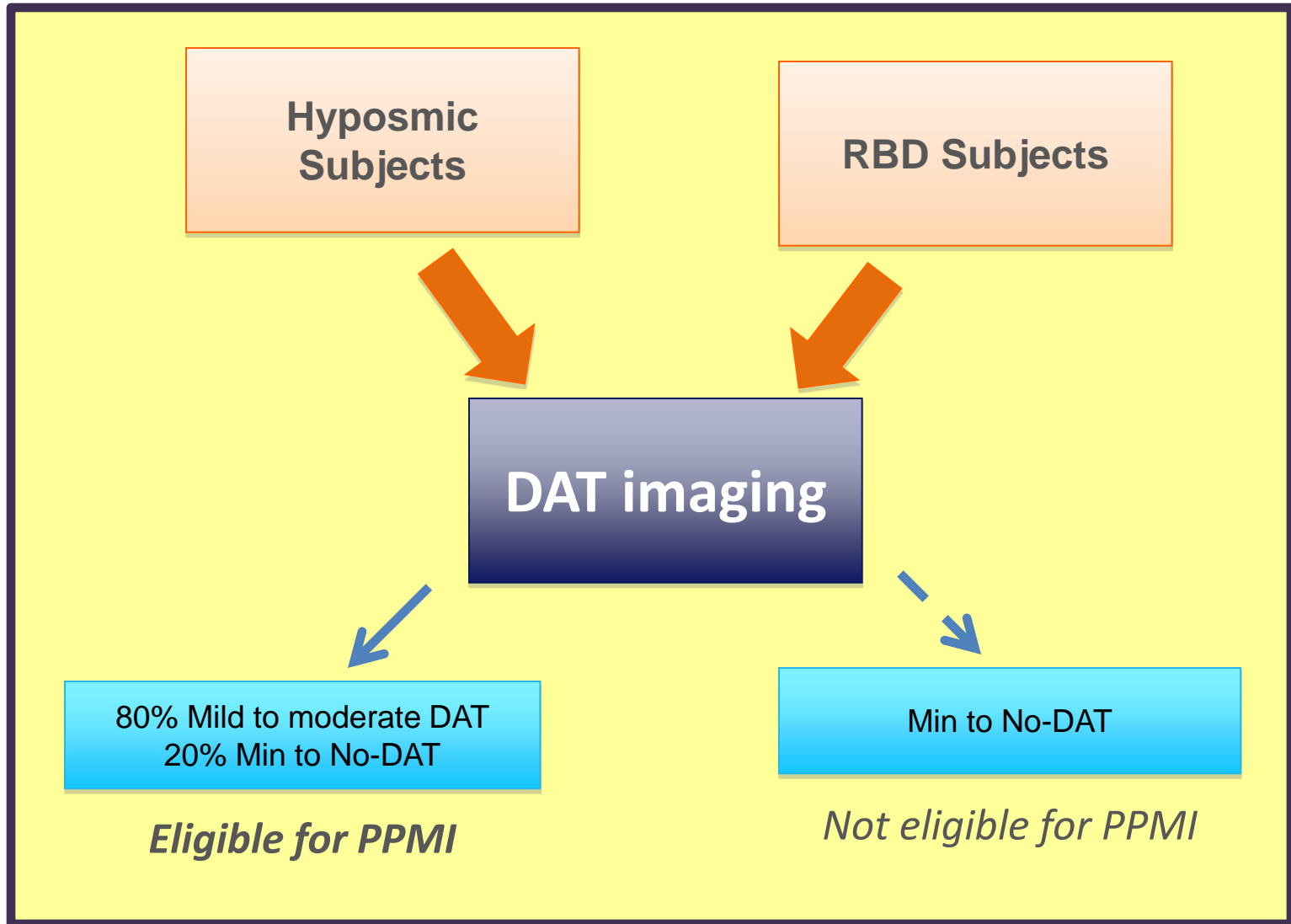
Natural History of Parkinson disease



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Eligibility for P-PPMI

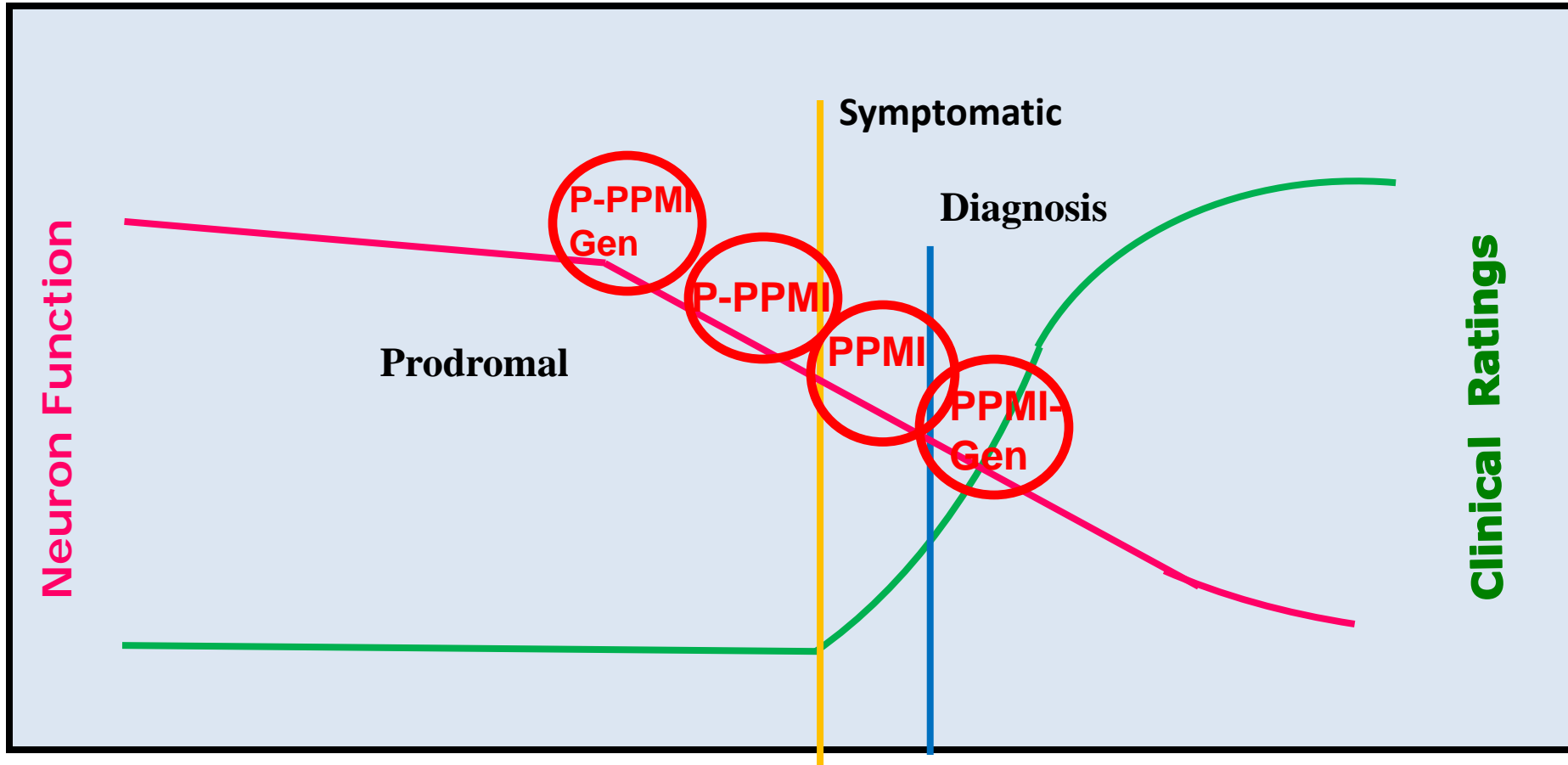


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PPMI - Cohorts

Stage of PD



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PPMI-LRRK2/SNCA

- **Leverage existing PPMI infrastructure and add sites with existing expertise and experience with LRRK2 patients and families.**
- **Enroll 250-300 LRRK2/SNCA + PD and 250-300 LRRK2/SNCA + unaffected family members with and intensive longitudinal clinical assessment protocol.**
- **Follow PD and unaffected family members for for 3-5 years**
 - **Establish pre-motor biomarker signature**
 - **Define phenoconversion**
- **Maintain PPMI database structure and commitment to rapid access to data**

Current Status

- **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 - >70000 data downloads >20 biologic specimen requested.**
- **PPMI Prodromal and Genetic cohorts incorporated to assess prodromal PD biomarkers**



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PPMI ↔ ADNI

- **Data Mining**
- **Imaging core – Amyloid imaging, DAT imaging, Tau, Inflammatory**
- **CSF– Tau, pTau, Amyloid, alpha-synuclein**
- **Cognitive outcomes**
- **Genetics – full sequence data**
- **Prodromal cohorts – ethical issues**



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