PPMI Status Update

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Movement Disorders Society
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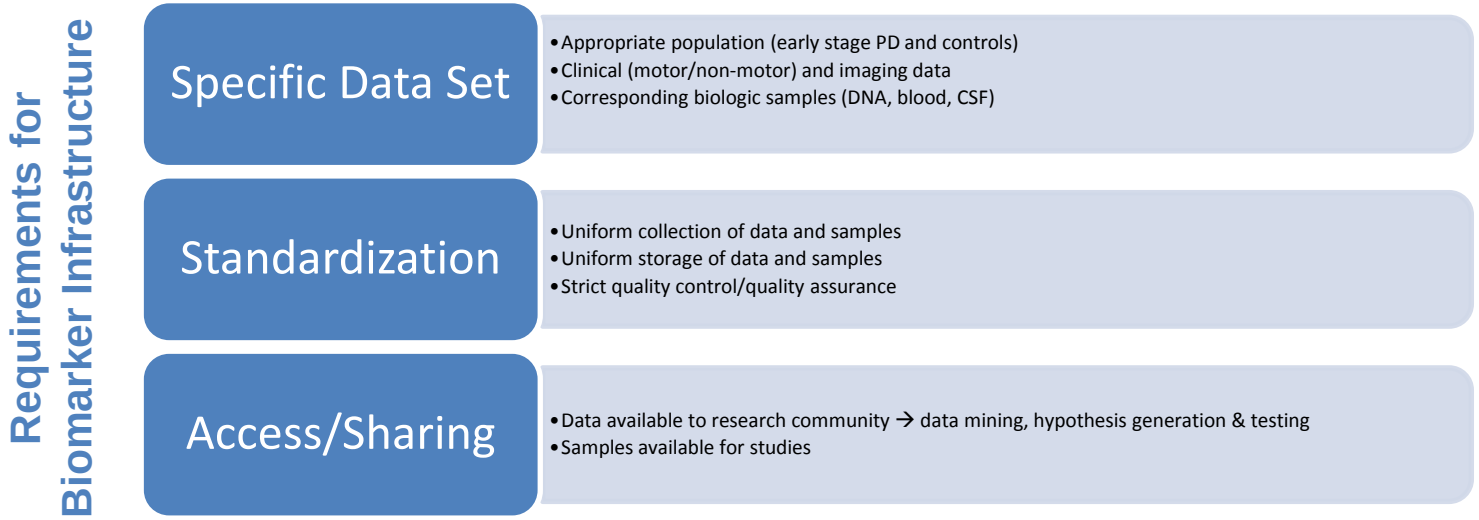
Sydney, Australia

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

Parkinson Progression Marker Initiative

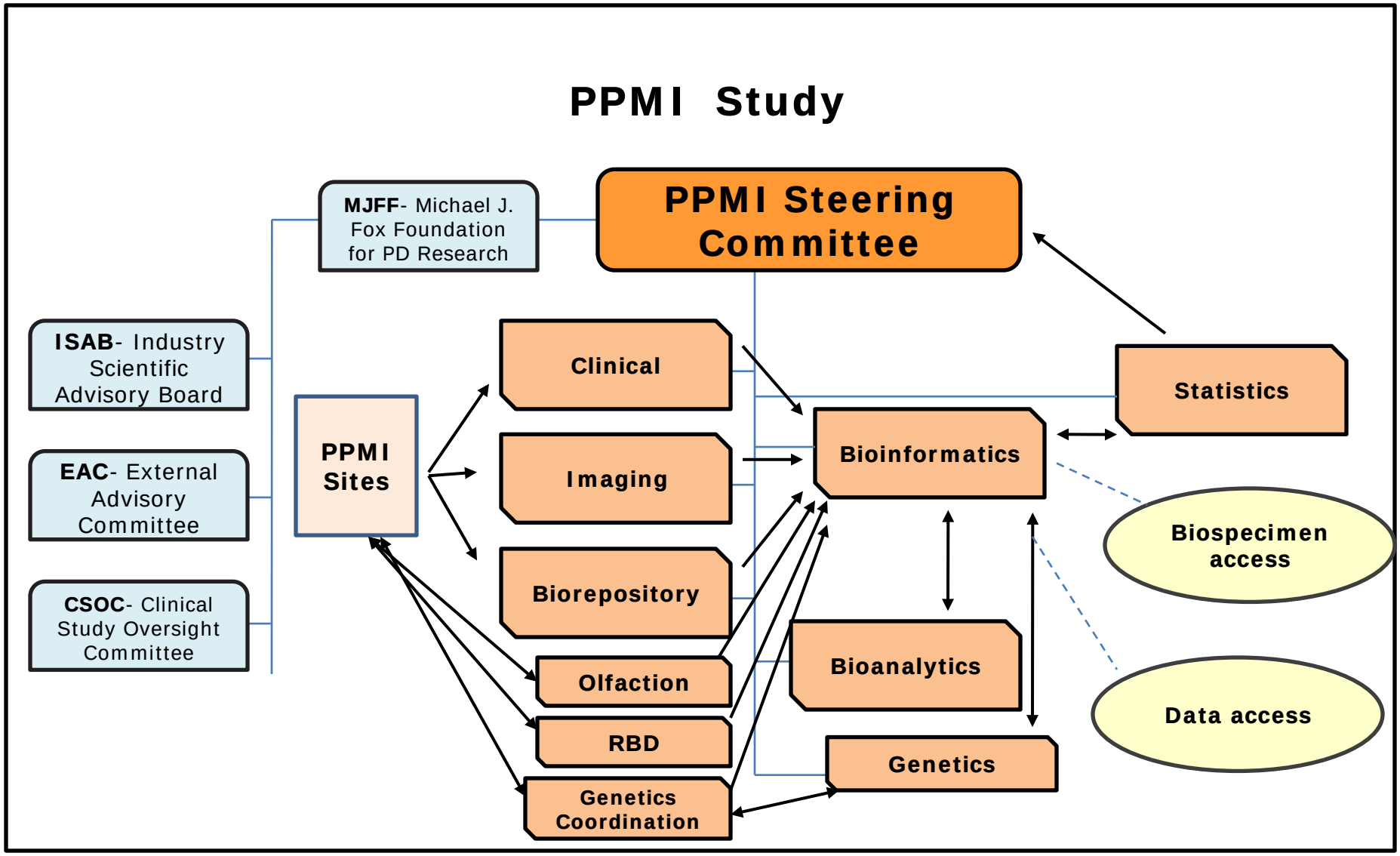
- **Disease modifying PD therapeutics remain a major unmet need**
- **A major obstacle to current phase 2/3 neuroprotection studies is the lack of biomarkers for**
  - **Disease mechanism**
  - **Drug mechanism**
  - **Dosage determination**
  - **Study eligibility**
  - **Stratification into PD sub-types**
  - **Correlation with clinical signals**



PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

PPMI Study



PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

PPMI Study Details: Synopsis

Study population	▪ 400 *de novo* 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	▪ Motor assessments ▪ Neurobehavioral/cognitive testing ▪ Autonomic, Olfaction, Sleep ▪ DaTSCAN imaging, DTI/RS 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)

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)

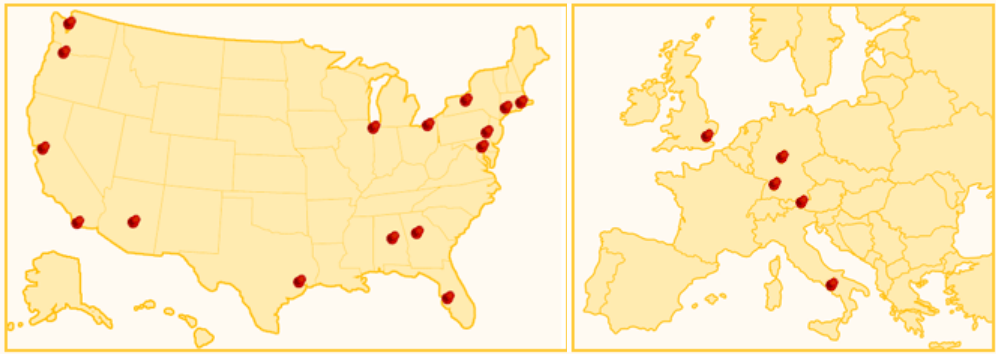
PPMI SITES IN EUROPE:

- 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.



PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

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	▪ University of Rochester's Clinical Trials Coordination Center • PI: Karl Kieburtz, irina Lazurenko, Alice Rudolph, Cindy Casaceli
Imaging Core	• Institute for Neurodegenerative Disorders; • PI: John Seibyl, Norbert Schuff,
Statistics Core	▪ University of Iowa • PI: Chris Coffey
Bioinformatics Core	▪ Laboratory of Neuroimaging (LONI) at UCLA • PI: Arthur Toga, Karen Crawford
BioRepository	▪ Coriell/BioRep • PI: Alison Ansbach, Paola Casalin,
Bioanalytics Core	▪ University of Pennsylvania • PI: John Trojanowski, Les Shaw
Genetics Core	▪ National Institute on Aging/NIH • PI: Andy Singleton
RBD Core	▪ Hephata Hessisches Diakoniezentrum e. V. ▪ PI: Geert Mayer
Olfactory Core	▪ Institute for Neurodegenerative Disorders • PI: Danna Jennings
Genetics Coordinating Core	▪ Indiana University • PI: Tatiana Foroud

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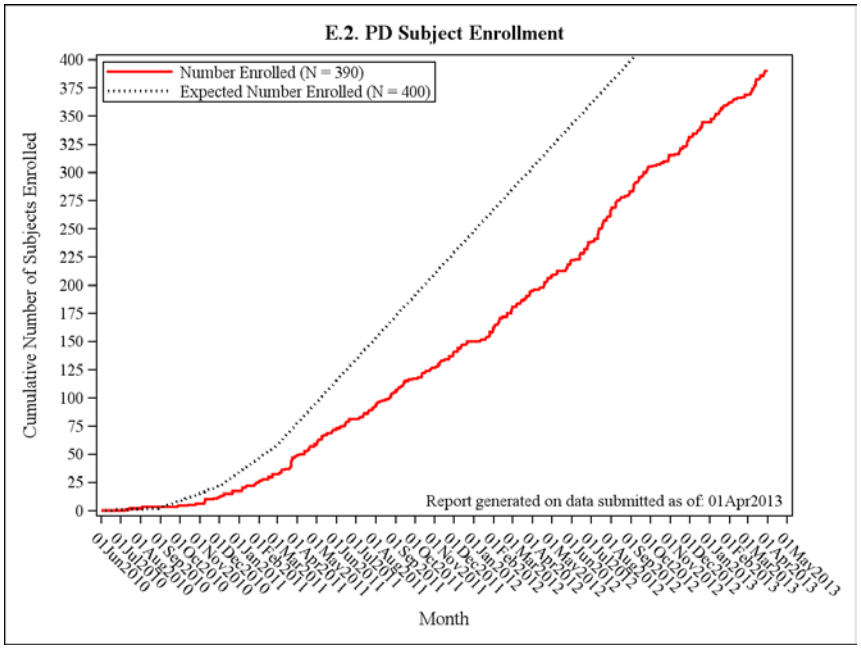
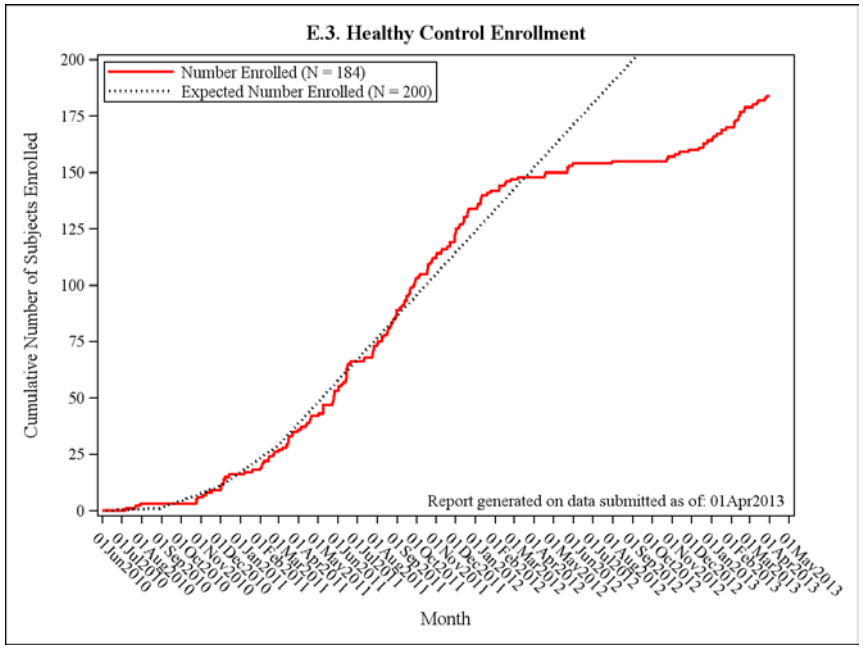
ENROLLMENT





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

PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

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

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	27.1	<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%)		

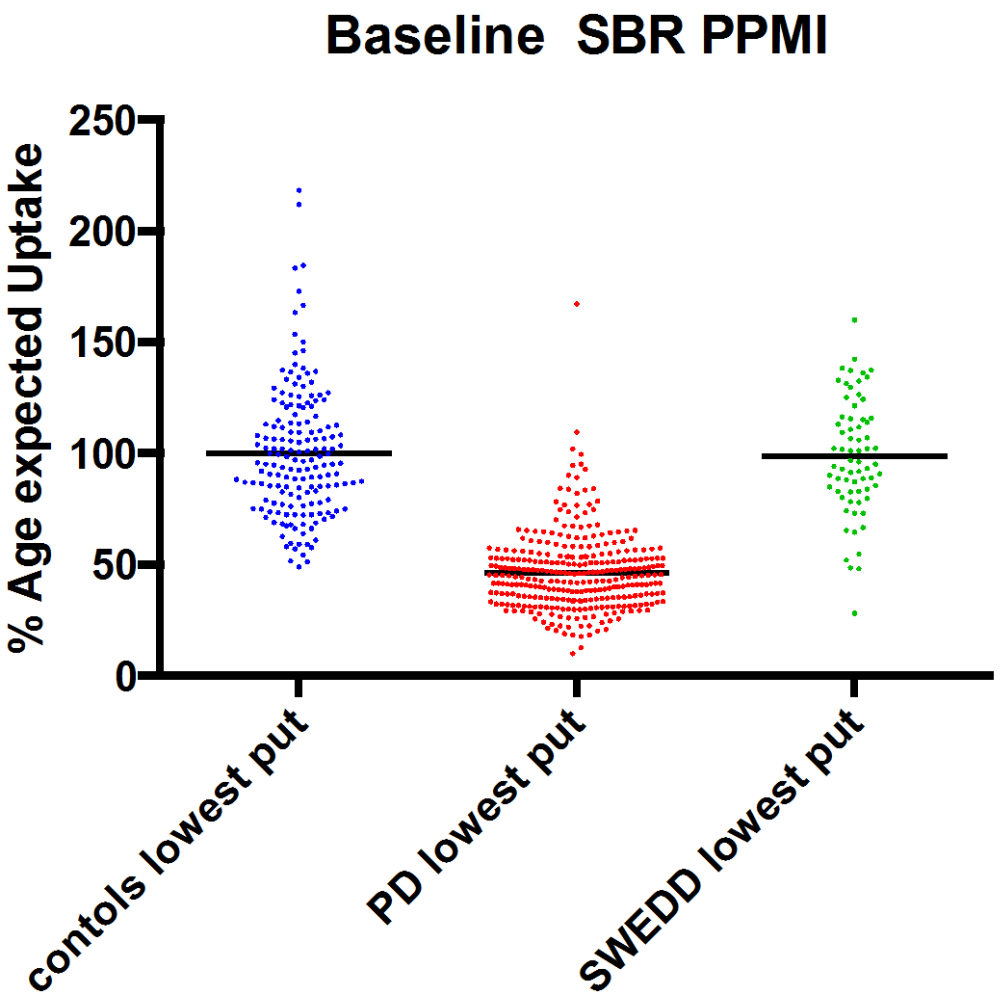
Tables Generated on Data Submitted to PPMI as of: 01MAR2013.

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.

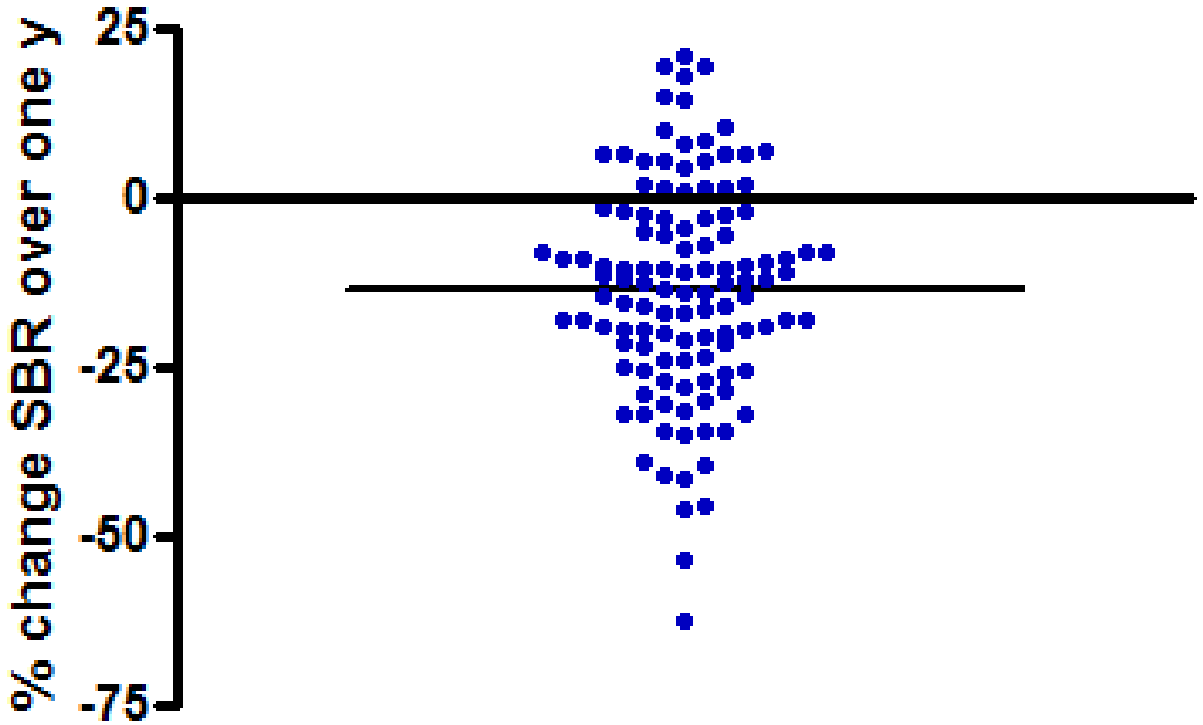
Baseline DAT Data



PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

Longitudinal DAT



N= 117
Mean 13.3% ± 16.0%
78.6% going down at yr 1

CSF Acquisition

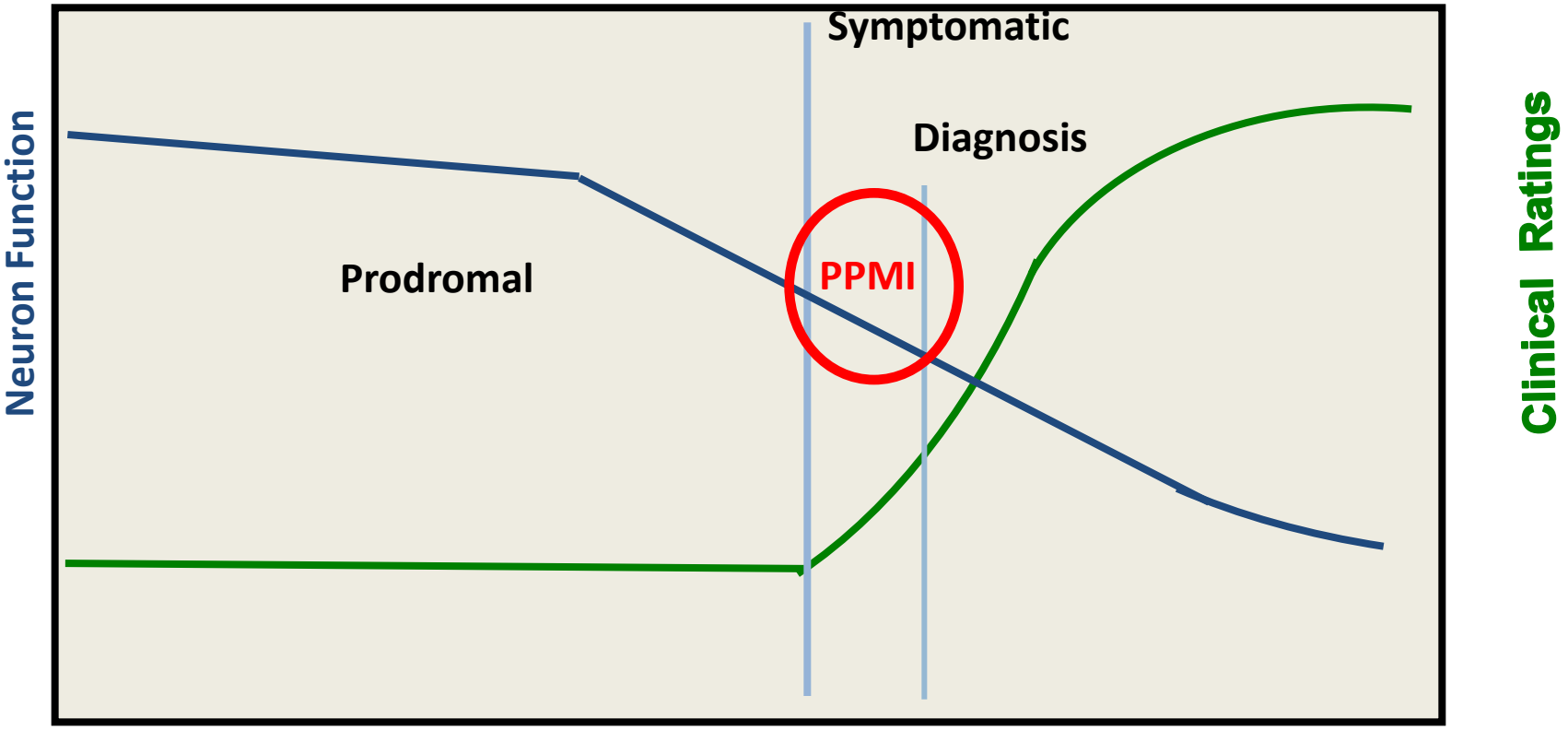
Group	Visit (months)			
	0 Baseline	6	12	24
PD	401 (98%)	275 (91%)	171 (87%)	29 (83%)
Healthy controls	184 (97%)	146 (87%)	140 (84%)	25 (80%)
SWEDD	59 (92%)	36 (89%)	25 (84%)	N/A

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%

CSF Pilot Baseline Data

	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-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-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-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**

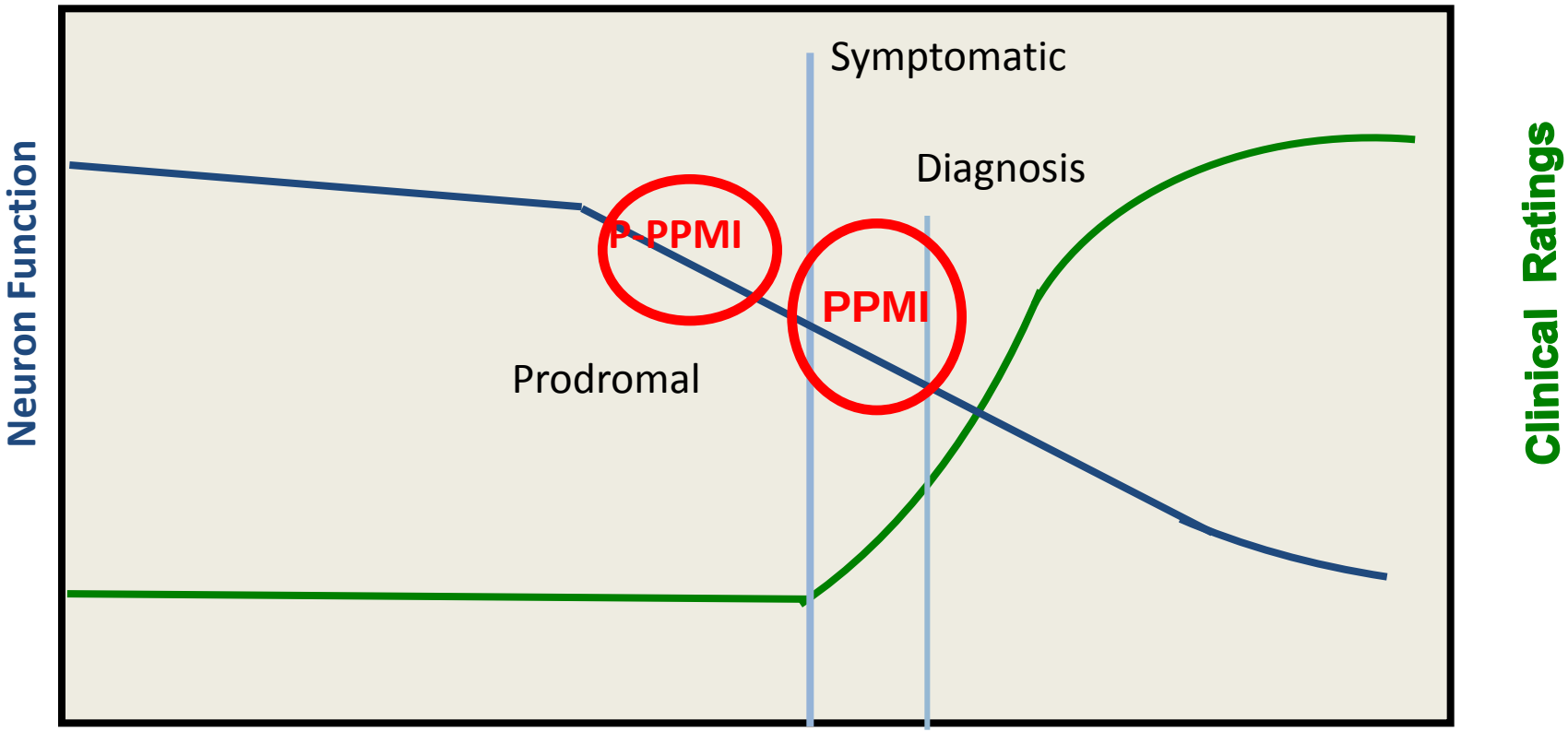
Natural history of Parkinson's disease



PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

Natural History of Parkinson disease



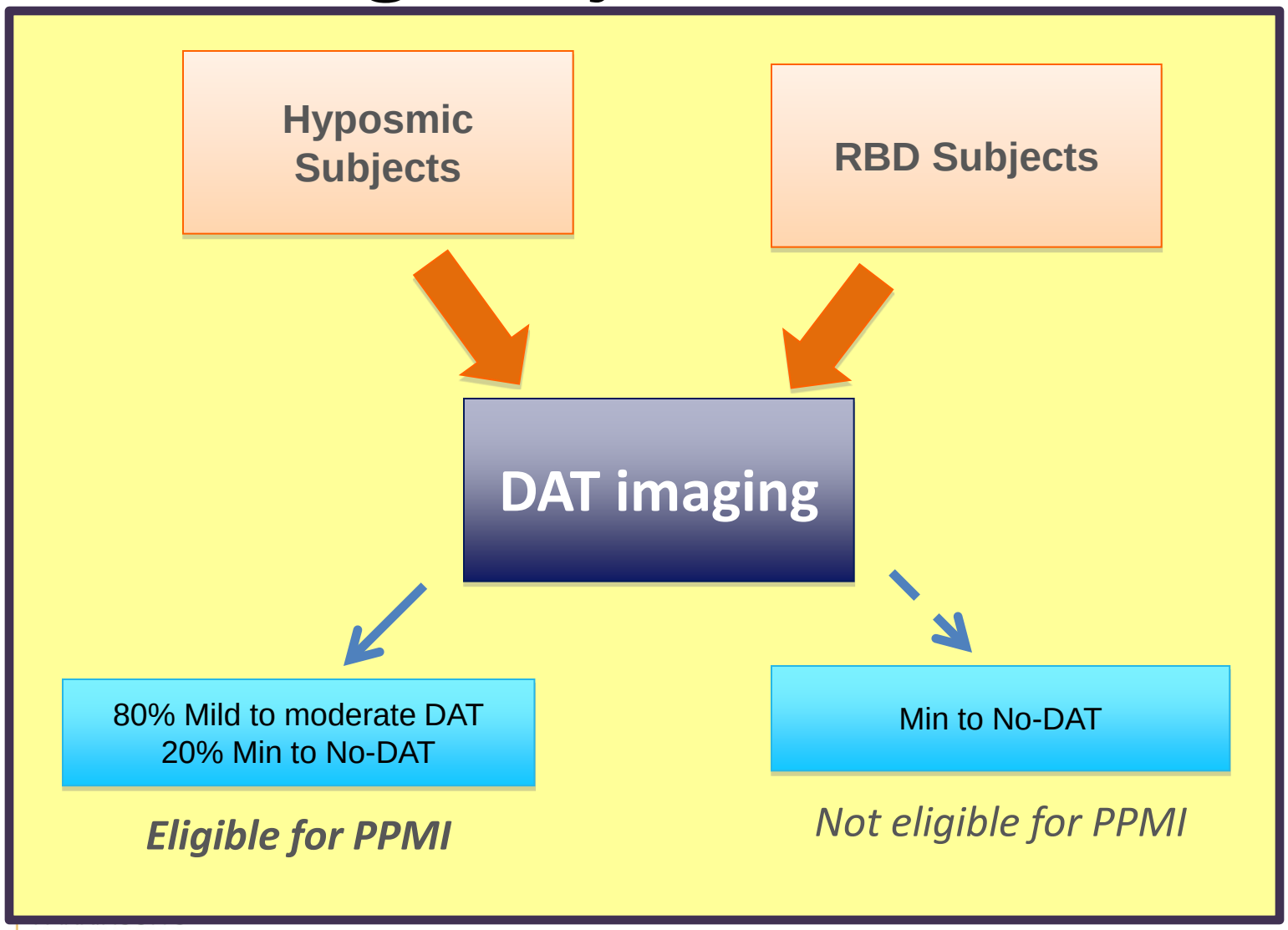
PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

Prodromal PPMI cohort

- **Enroll subjects at risk for PD proximate to conversion to motor PD**
- **Sequential biomarker strategy to identify subjects with olfaction and/or RBD, plus DAT deficit**
- **Enrollment DAT deficit (80%) and no DAT deficit (20%) group**
- **Follow group with DAT deficit and normal DAT for approx 4-5 years (n=100)**
  - **Establish prodromal biomarker signature**
  - **Define phenoconversion**

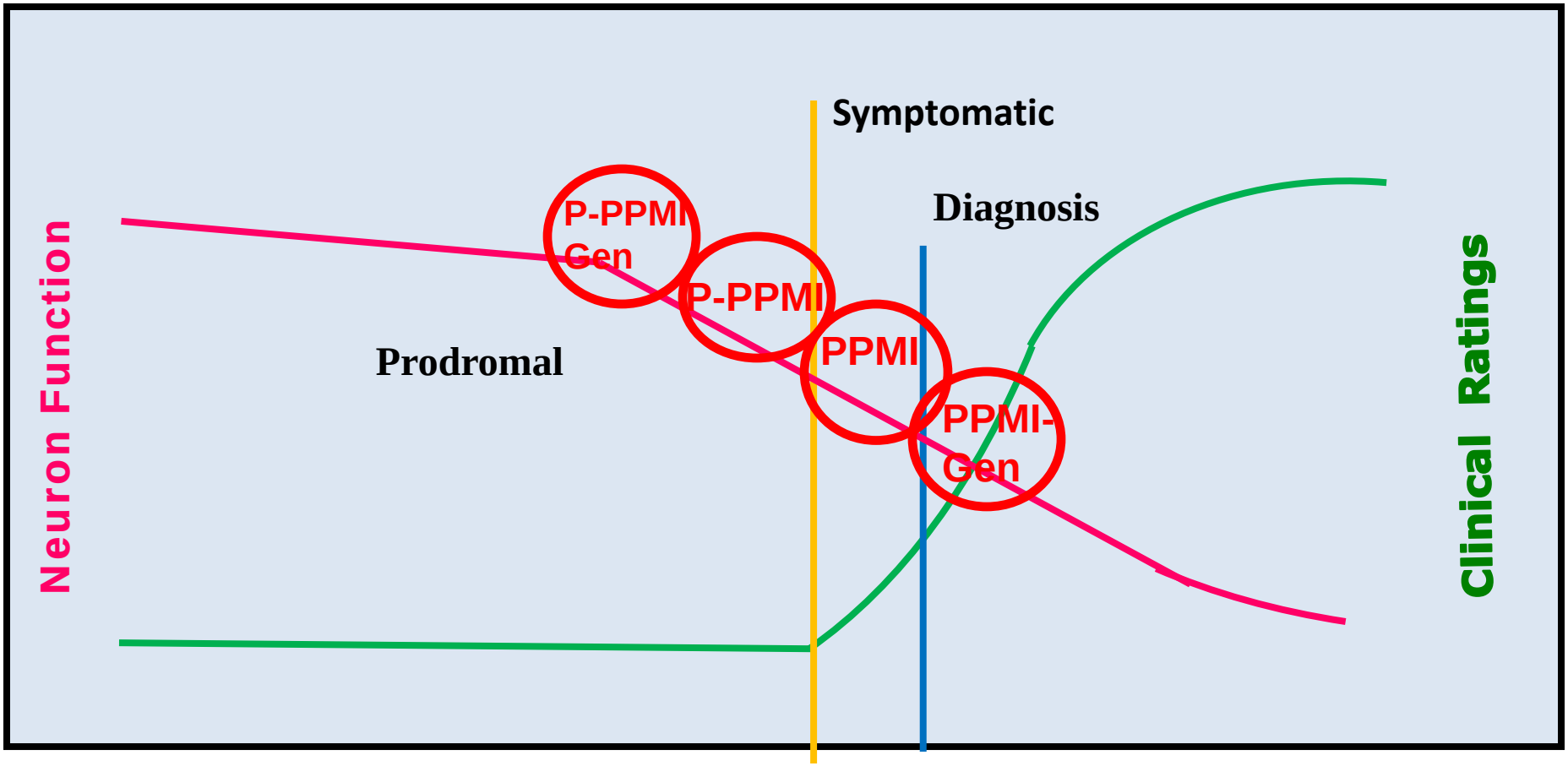
Eligibility for P-PPMI



PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

Natural history of Parkinson's disease



PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

PPMI-LRRK2

- **Leverage existing PPMI infrastructure and add sites with existing expertise and experience with LRRK2 patients and families.**
- **Enroll 200 -250 LRRK + PD and 200-250 LRKK2 + 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**

PPMI-Synuclein

- **Leverage existing PPMI infrastructure and add sites with existing expertise and experience with Synucelin patients and families.**

- **Enroll 50 synuclein + PD and 50 synuclein + unaffected family members (duplication, triplication, point mutation) in 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**

Two Stage Enrollment – Genetic PPMI

- **Consent 1 – Genetic testing/counseling (MGH genetics lab)**
  - **For PD – LRRK2/Syn +/eligible -**
  - **For non-PD - Results provided but not required - informed that PPMI intensive biased to mutation carrier and registry biased to non-mutation carrier**

GENETIC COORDINATING CORE – Allocates subjects

- **Consent 2 – PPMI - PPMI Cohort vs registry**
  - **All LRRK2/Syn pos PD eligible - PPMI intensive**
  - **Unaffected family members**
    - **LRRK2/Syn pos- PPMI cohort>>> registry**
    - **LRRK2/Syn neg - PPMI cohort<< registry**

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 - >68,700 data downloads >20 biologic specimen requested.**
- **PPMI Prodromal and Genetic cohorts incorporated to assess prodromal PD biomarkers**