Developing a Translational Toolbox for Parkinson disease: The Parkinson Progression Marker Initiative

AAIC
July 2013

Disclosure

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

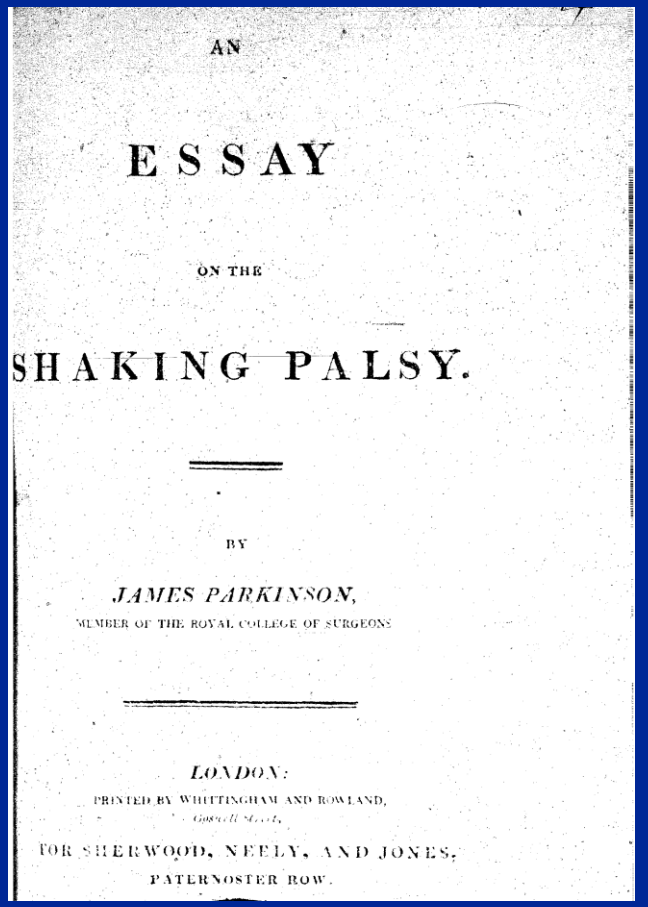
  Pfizer, Sanofi,

MNI Molecular NeuroImaging

Institute for Neurodegenerative Disorders

Parkinson's Disease (PD)

- Progressive neurologic disorder
- Clinical characteristics: resting tremor, bradykinesia, rigidity, and postural instability
- Widespread non-motor symptoms
- Pathological characteristics:
  - Loss of dopaminergic neurons in substantia nigra
  - Lewy bodies and Lewy neurites
- Cause – unknown – oxidative stress, mitochondrial disorder, inflammation, protein folding/aggregation, neurotropic failure.
- Mean age of onset early 60s, 1% of pop > 60
- 2nd most common neurodegenerative disorder


AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

Non-motor Symptoms

Cognitive/ Behavioral

- Cognitive impairment
- Anxiety
- Depression
- Fatigue
- Hallucinations
- Sleep dysfunction

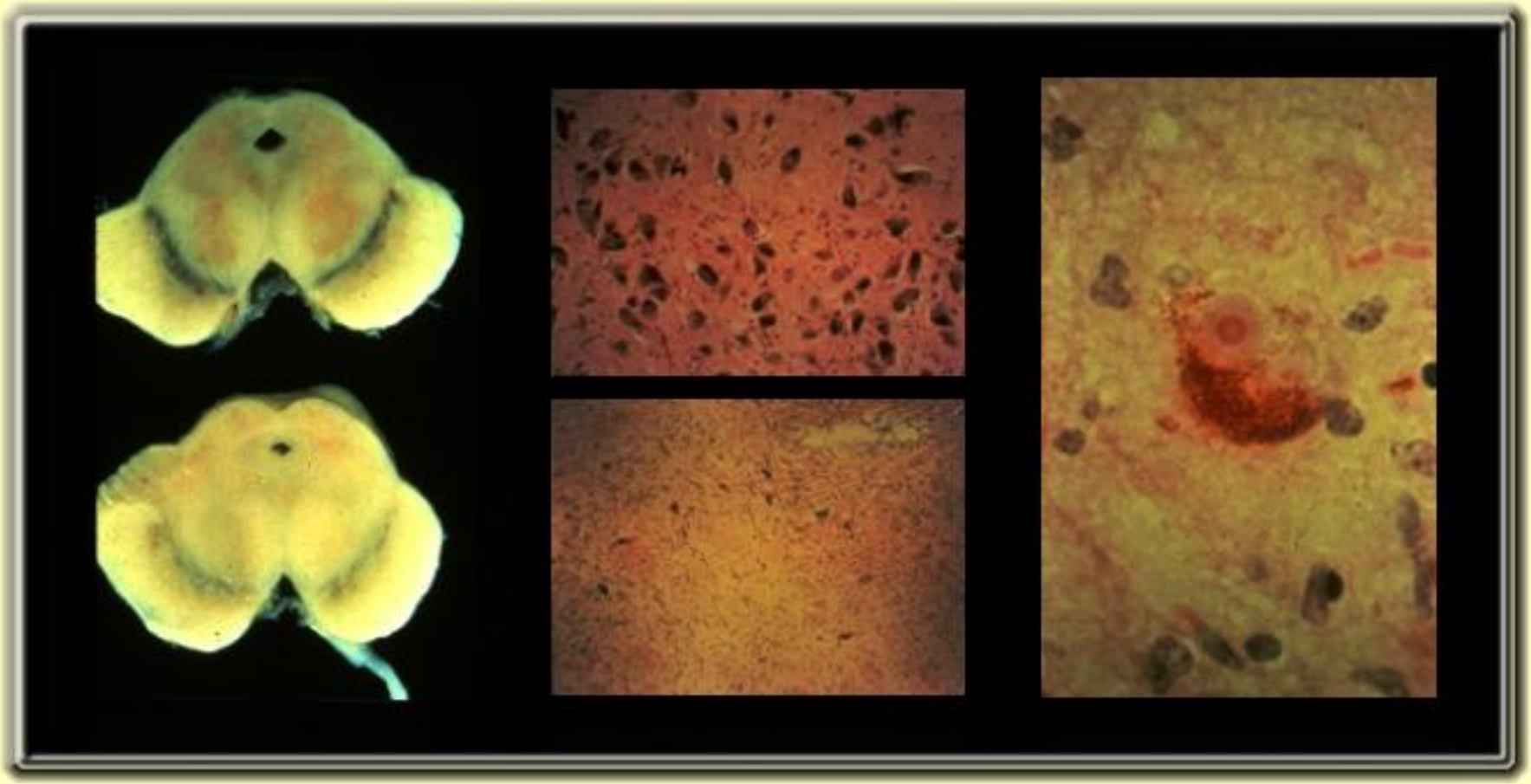
Autonomic

- Orthostatic hypotension
- Constipation
- Urinary urgency
- Sexual dysfunction
- Seborrhea
- Drenching sweats
- Dyspnea

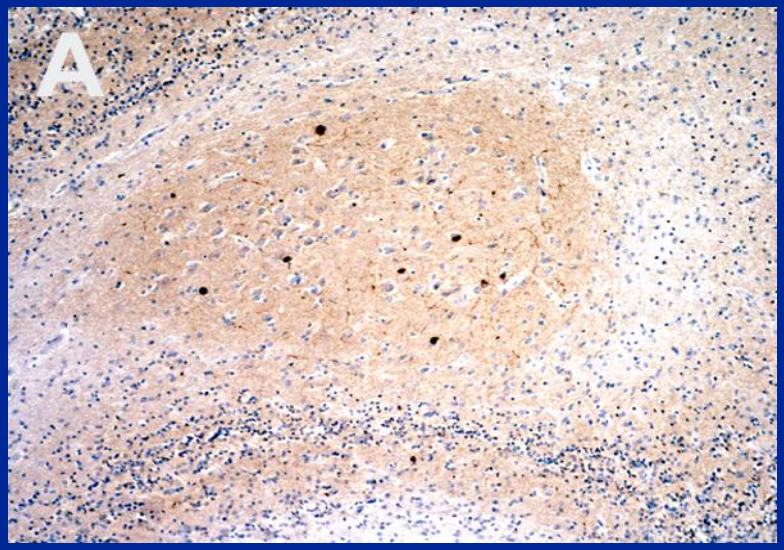
Sensory/ Pain

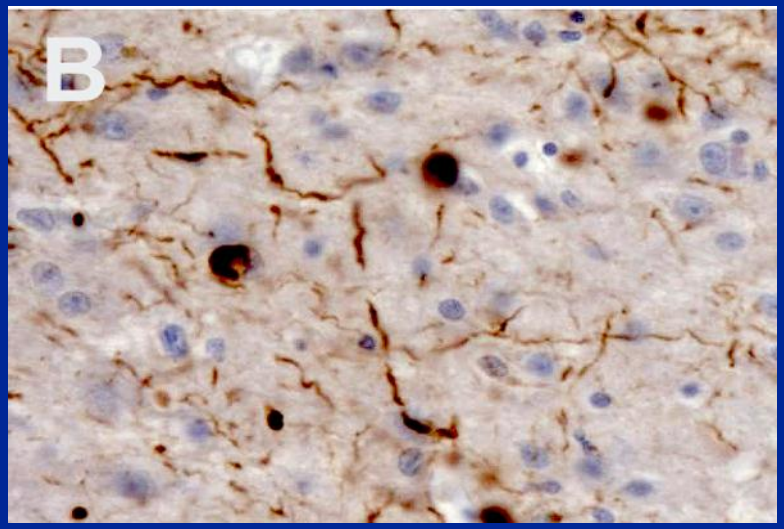
- Olfactory deficit
- Akathisia
- Diffuse pain
- Tingling sensation

Pathology of Parkinson's Disease



Lewy Pathology in the Olfactory Bulb

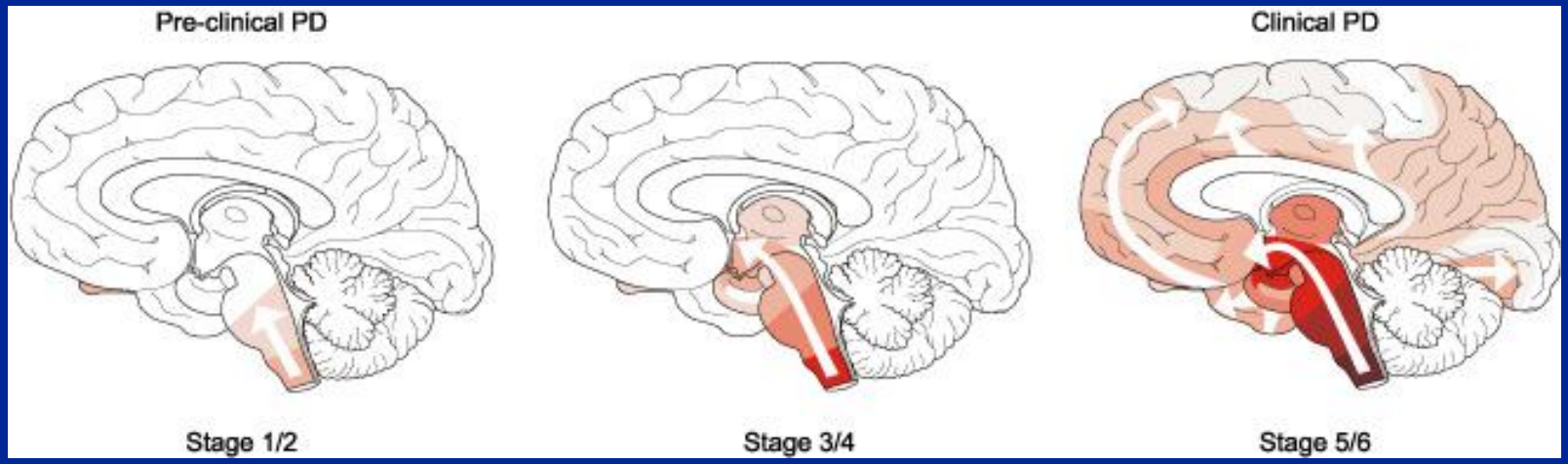




α-Synuclein immunostaining reveals Lewy pathology, including Lewy bodies and Lewy neurites in the olfactory bulb of patients with incidental Lewy body pathology. Low power magnification (Panel A) reveals Lewy pathology concentrating in the anterior olfactory nucleus and plexiform layers of the olfactory bulb while higher magnification (Panel B) of the anterior olfactory nucleus in a different individual reveals abundant Lewy bodies and Lewy neurites.

(Courtesy of John Duda, MD, and J. Noorigian, MPH).

Braak – Ascending Synuclein pathology



Staging of brain pathology related to sporadic Parkinson's disease. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E, Neurobiol Aging. 2003 197-211.

PD patient vignette

- 67 yo right handed WF in excellent general health
- History

  6 month history of poor tennis play

  Note 1-2 years – mild constipation

  2 months intermittent R UE tremor while reading the newspaper, or if in stressful situation
- Exam

  Mild R UE resting tremor

  Reduced R arm swing
- PD DIAGNOSIS – 1 MONTH AGO

- "IF THE SYMPTOMS REMAIN AS THEY ARE NOW – I COULD DEAL WITH THIS"

Neuroprotection Studies

NO CHANGE

- DATATOP – SELEGILINE/VITE
- LAZABEMIDE
- RULIZOLE
- TCH-346
- NEURO-IMMUNOPHILIN
- GPI 1485
- CALM-PD
- MINOCYCLINE
- CAFFEINE
- REAL-PET – ROPINIROLE
- ELLDOPA
- ASA/NSAID
- SR57667B
- PRECEPT – CEP1347
- GREEN TEA
- PROUD – PRAMIPEXOLE
- *QE-2/CO-Q10/QE3*

UNCERTAIN

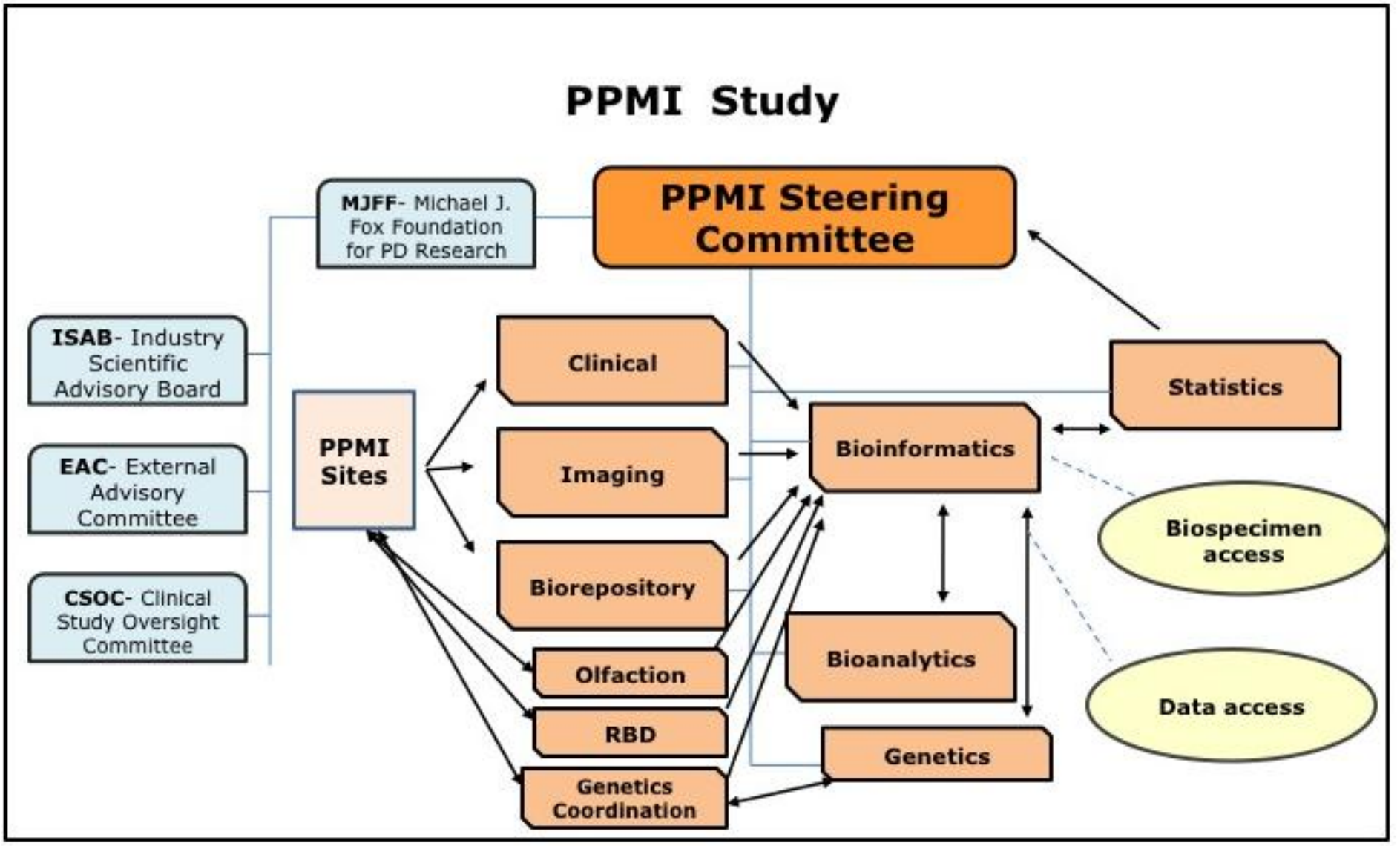
- *ADAGIO – TEVA*
- *NET PS LS1 – CREATINE*
- *ISRADIPINE*
- *SURE-PD*

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


PPMI Study
MJFF- Michael J. Fox Foundation for PD Research
PPMI Steering Committee
ISAB- Industry Scientific Advisory Board
EAC- External Advisory Committee
CSOC- Clinical Study Oversight Committee
PPMI Sites
Clinical
Imaging
Biorepository
Olfaction
RBD
Genetics Coordination
Statistics
Bioinformatics
Bioanalytics
Genetics
Biospecimen access
Data access

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 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)

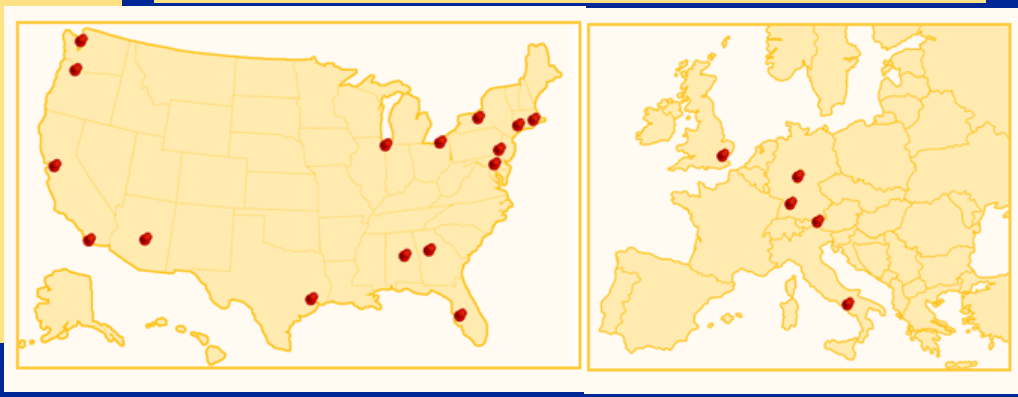
PPMI SITES IN EUROPE:

- 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.



PPMI SC and Study Cores

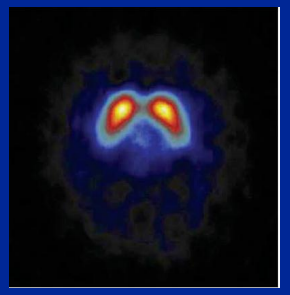
Steering Committee	PI-K Marek, C Tanner, T Foroud, D Jennings, K Kieburtz, W Poewe, B Mollenhauer, T Simuni, (core leaders, MJFF, ISAB), S Lasch
Clinical Coordination Core	▪ University of Rochester's Clinical Trials Coordination Center • PI: Karl Kieburtz, irina Lazurenko, Alice Rudolph, Cindy Casaceli
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

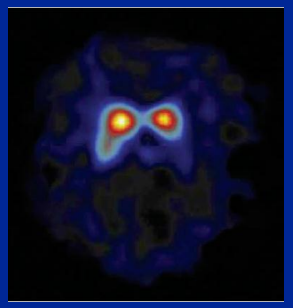
PPMI Study Details: Synopsis

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, AV133, Amyloid, 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)

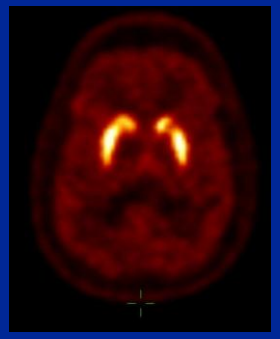
Pre-synaptic Dopaminergic Imaging

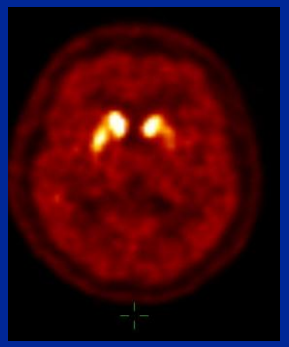
^{123}I ß-CIT-DAT



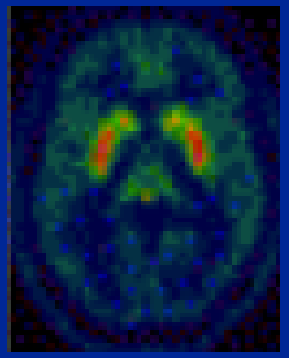


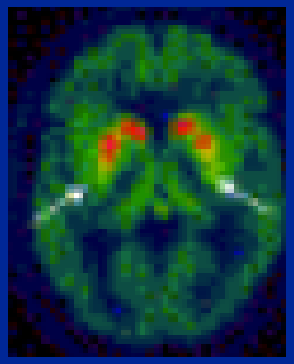
^{18}F AV-133-VMAT2





^{18}F-DOPA-AADC

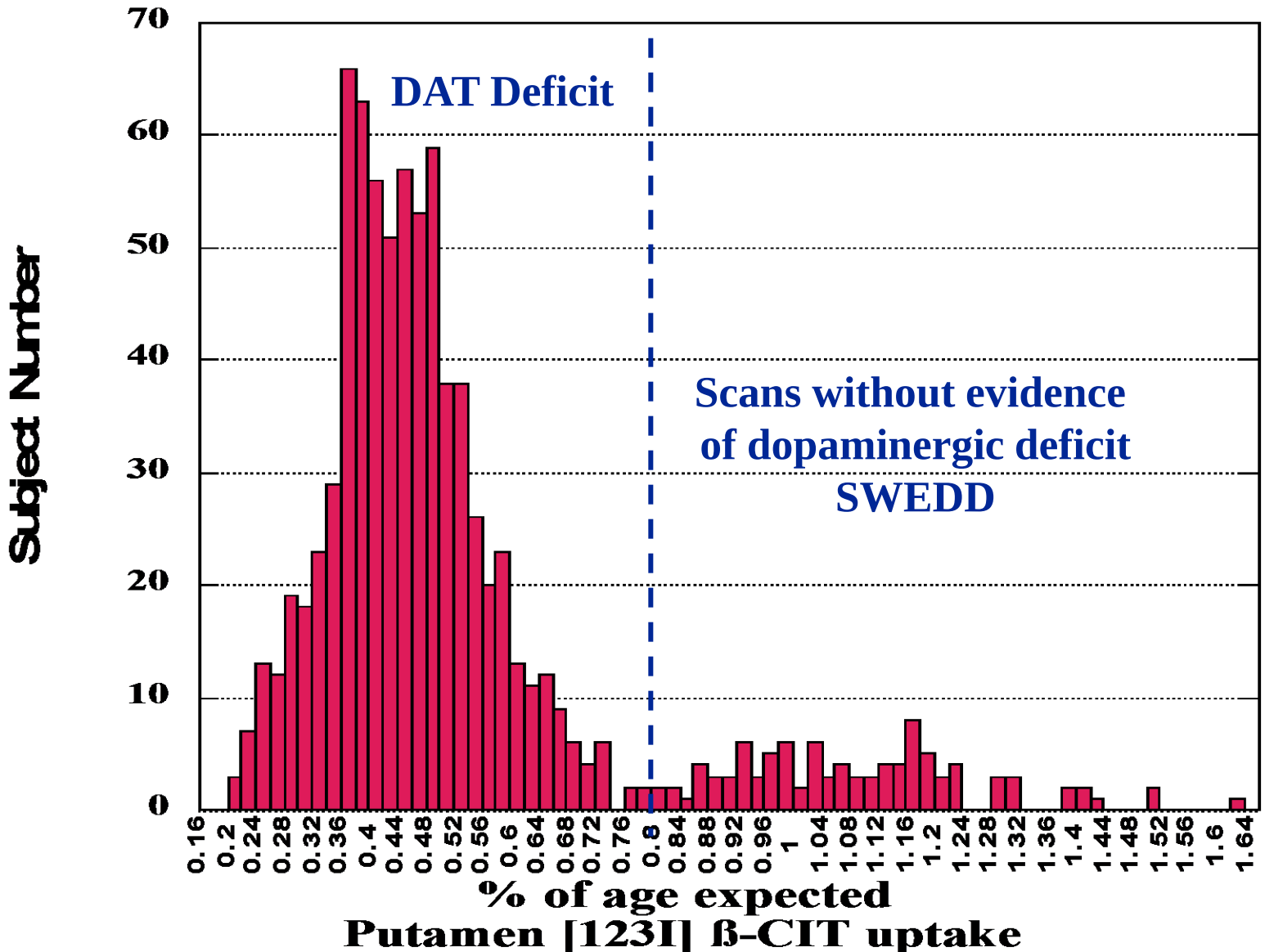




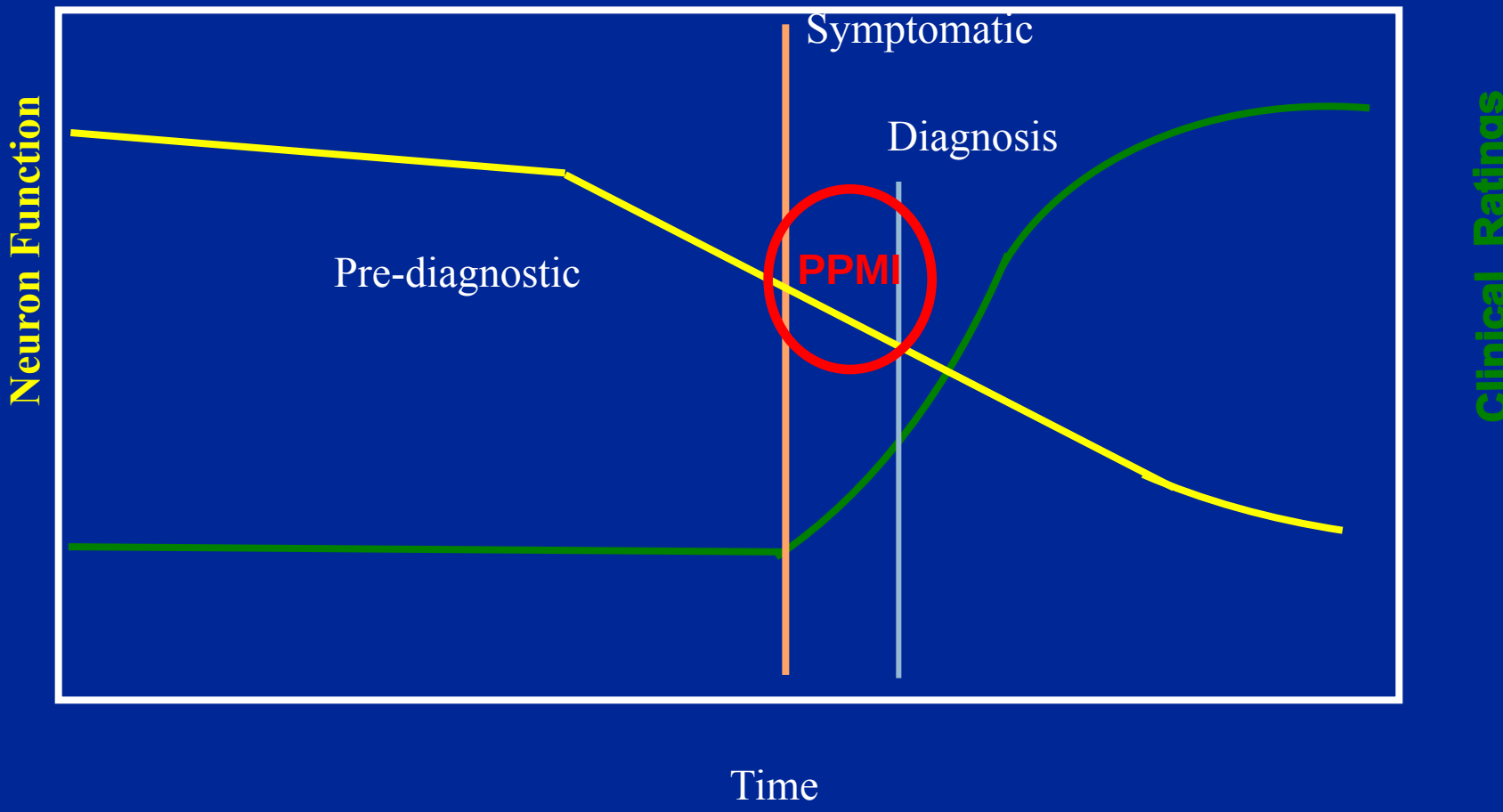
Healthy

Parkinson disease

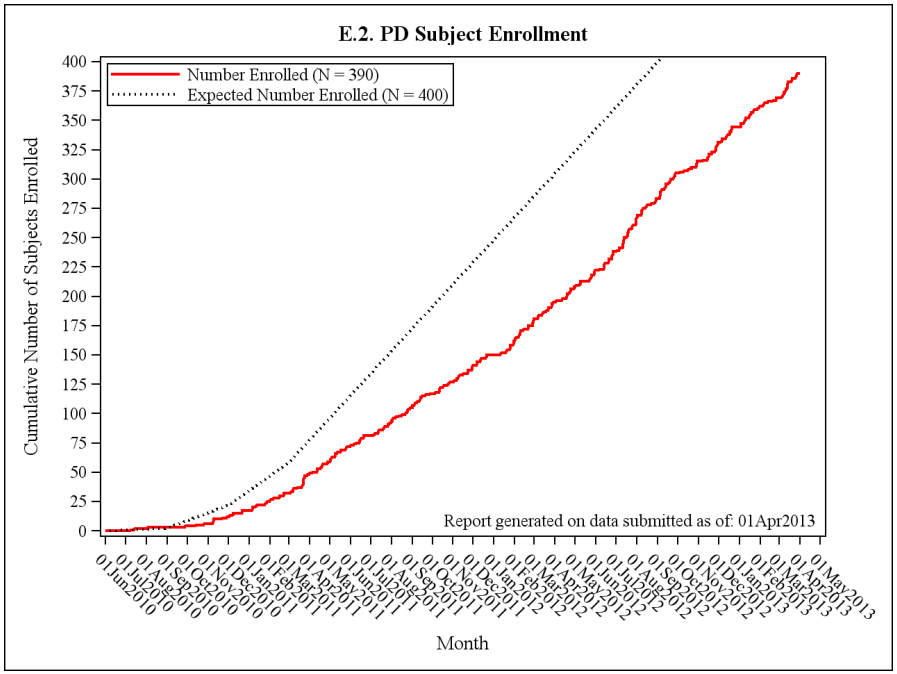
Baseline PRECEPT - % Age expected Putamen [123I] ß-CIT uptake

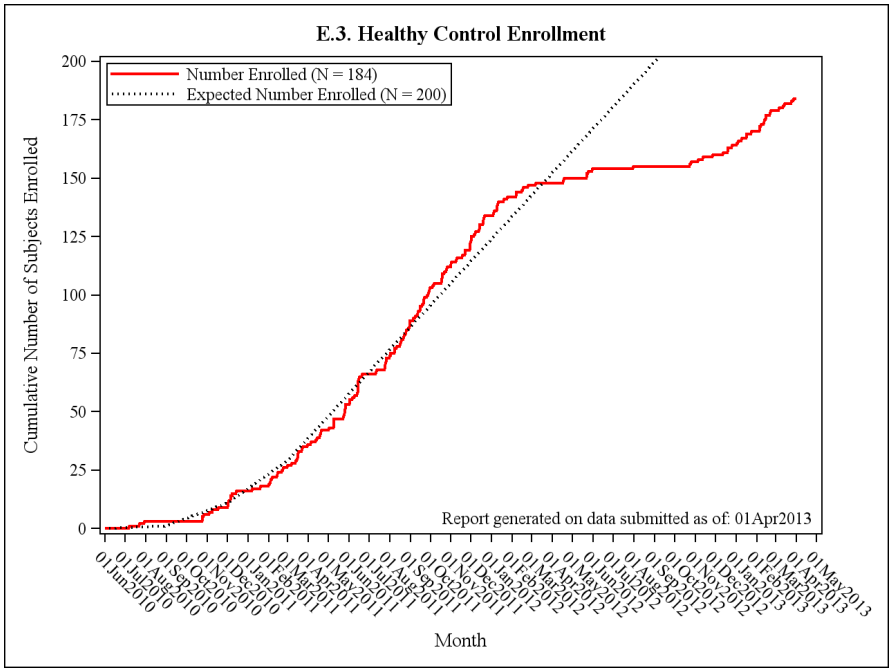


Natural History of Parkinson disease



ENROLLMENT





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

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	**32.4**	**4.8**	**28.2**	<0.01	0.03
MDS-UPDRS Part I	**5.6**	**2.9**	**8.3**	<0.01	<0.01
MDS-UPDRS Part II	**5.9**	**0.5**	**5.7**	<0.01	0.67
MDS-UPDRS Part III (Motor Exam)	**20.9**	**1.2**	**14.3**	<0.01	<0.01
Hoehn & Yahr N(%)					
Stage 0	**0 (0%)**	**193 (98%)**	**0 (0%)**	<0.01	0.11
Stage 1	**186 (44%)**	**2 (1%)**	**37 (58%)**		
Stage 2	**235 (56%)**	**0 (0%)**	**27 (41%)**		
Stage 3-5	**2 (1%)**	**0 (0%)**	**0 (0%)**		
Modified Schwab & England (mean)	**93.2**	**NA**	**94.8**	NA	0.03
First degree family Member with PD (%)	**55 (13%)**	**0 (0%)**	**15 (23%)**	<0.01	0.14
Mean Duration of Disease (months)	**6.7 (0.4 - 35.8)**	**NA**	**7.4 (0.5 - 37)**	NA	0.38
Initial Symptoms*					
Resting Tremor	**331 (78%)**	**NA**	**53 (83%)**	NA	0.40
Rigidity	**321 (76%)**	**NA**	**37 (58%)**	NA	<0.01
Bradykinesia	**348(82%)**	**NA**	**51 (80%)**	NA	0.62
Postural Instability	**29 (7%)**	**NA**	**8 (13%)**	NA	0.11
Other	**71 (17%)**	**NA**	**9 (14%)**	NA	0.58

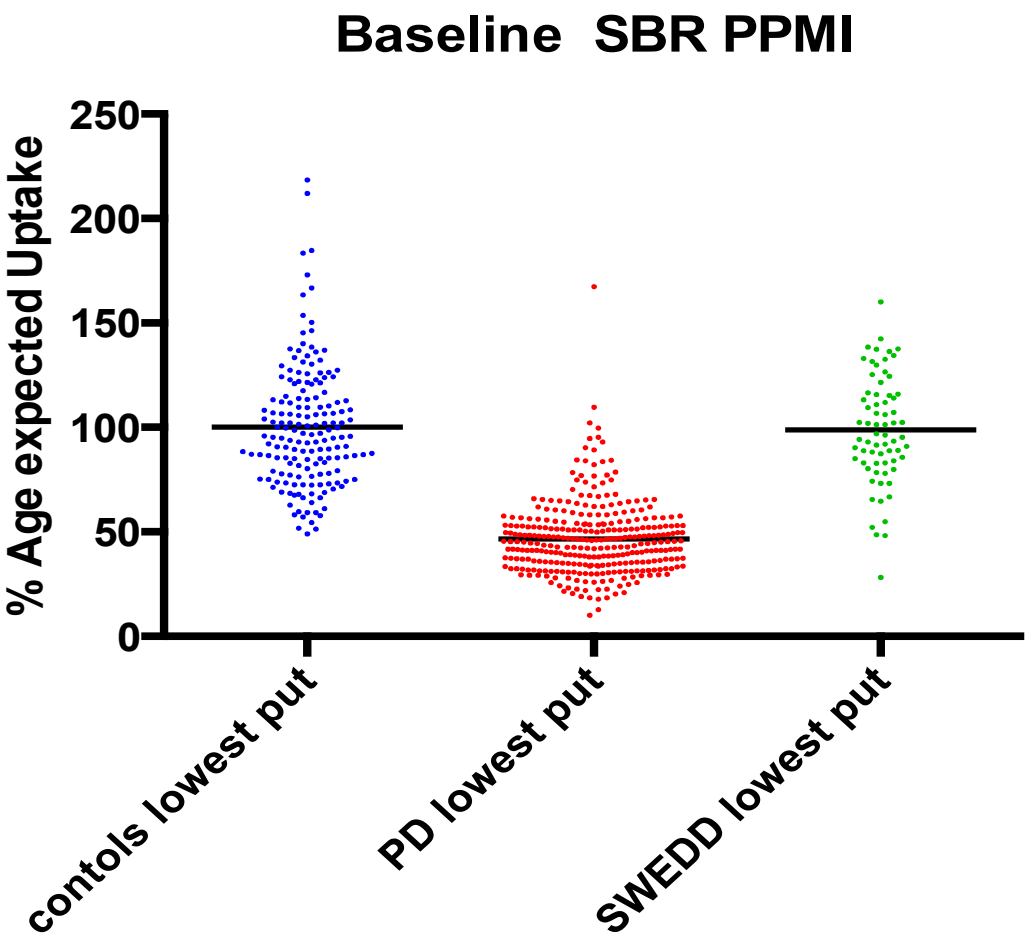
Baseline Non-motor Characteristics					
Baseline Assessment	**PD Subjects (N = 423)**	**Healthy Controls (N = 196)**	**SWEDD Subjects (N = 64)**	**PD p-value relative to HC**	**PD p-value relative to SWEDD**
MOCA Total Score	**27.1**	**28.2**	**27.1**	<0.01	0.94
SCOPA AUT Total Score	**9.5**	**5.9**	**13.8**	<0.01	<0.01
GDS	**2.3**	**1.3**	**3.3**	<0.01	<0.01
State Trait Anxiety Score	**65.3**	**57.1**	**69.8**	<0.01	0.07
QUIP	**0.3**	**0.3**	**0.6**	0.77	<0.01
Benton Judgment of Line Orientation Score	**12.8**	**13.1**	**12.8**	0.05	0.84
HVLT Immediate Recall	**9.7**	**10.2**	**9.7**	<0.01	0.92
HVLT Delayed Recognition	**11.2**	**11.5**	**10.8**	<0.01	0.04
HVLT Delayed False Alarms	**1.2**	**1.1**	**1.6**	0.18	0.05
Letter Number Sequencing Raw Score	**10.6**	**10.9**	**9.9**	0.22	0.06
Semantic Fluency Total Score	**48.7**	**51.8**	**45.2**	<0.01	0.03
Symbol Digit Modalities (SDM)	**41.2**	**46.8**	**41.3**	<0.01	0.96
UPSIT Raw Score	**22.4**	**34**	**31.4**	<0.01	<0.01
Epworth Sleepiness Scale (ESS)					
Not Sleepy (9 or below)	**357 (84%)**	**171 (88%)**	**43 (67%)**	<0.01	<0.01
Sleepy (10 or above)	**66 (16%)**	**24 (12%)**	**21 (33%)**		
REM Sleep Disorder					
Negative (< 5)	**263 (62%)**	**157 (80%)**	**38 (59%)**	<0.01	0.68
Positive (5 or greater)	**160 (38%)**	**39 (20%)**	**21 (41%)**		

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

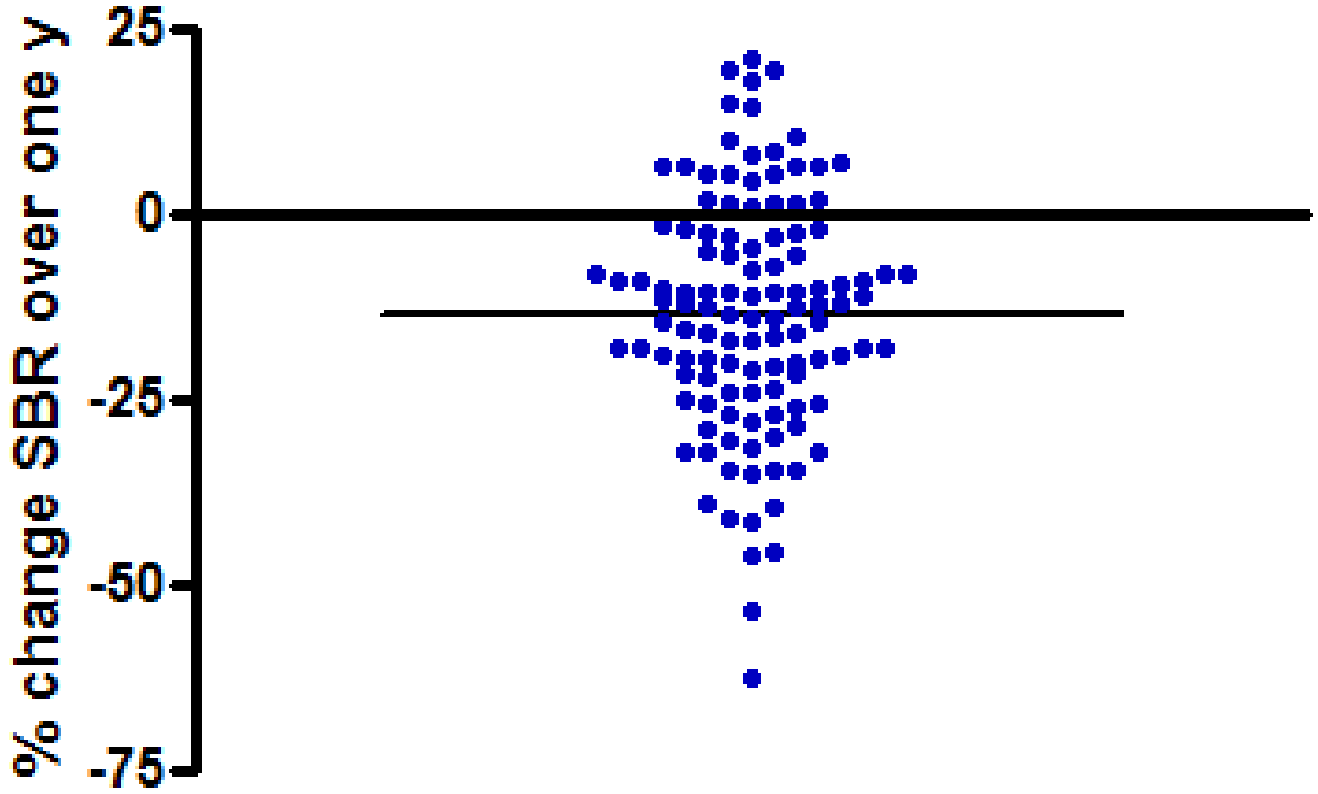
Consistent with research reporting 15-20% of de novo PD patients have MCI

Baseline DAT Data



Note that PPMI eligibility determined by visual assessment

Longitudinal DAT Imaging

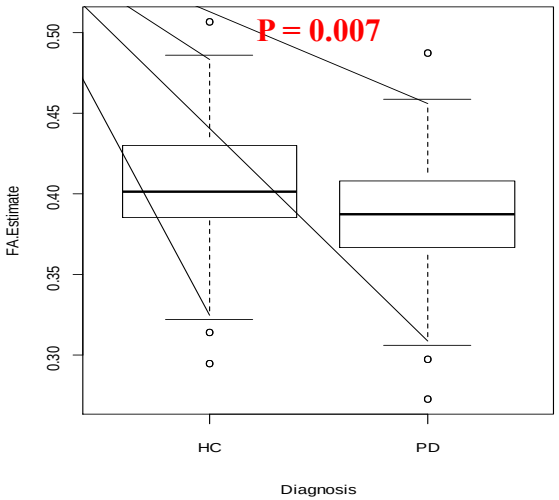


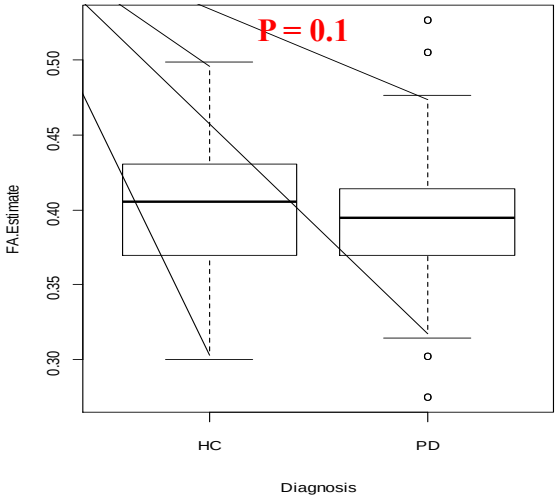
N= 117

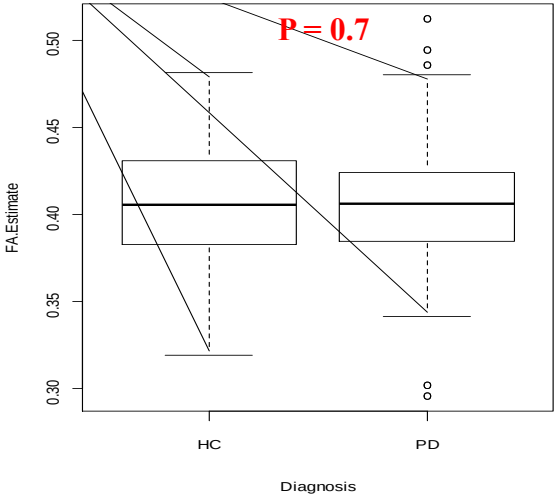
Mean 13.3% ± 16.0%

78.6% going down at yr 1

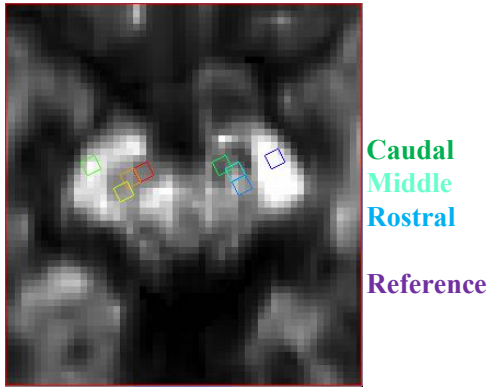
Fractional Anisotropy Of Substantia Nigra







PD (n=132); Control (n=69)
Analysis adjusted for side of symptom onset



CSF Acquisition

Group	Baseline	Month 6	Month 12	Month 24
PD	423 (98%)	296 (89%)	194 (87%)	59 (90%)
Healthy	196 (97%)	149 (87%)	141 (84%)	36 (79%)
SWEDD	62 (92%)	42 (86%)	30 (80%)	N/A

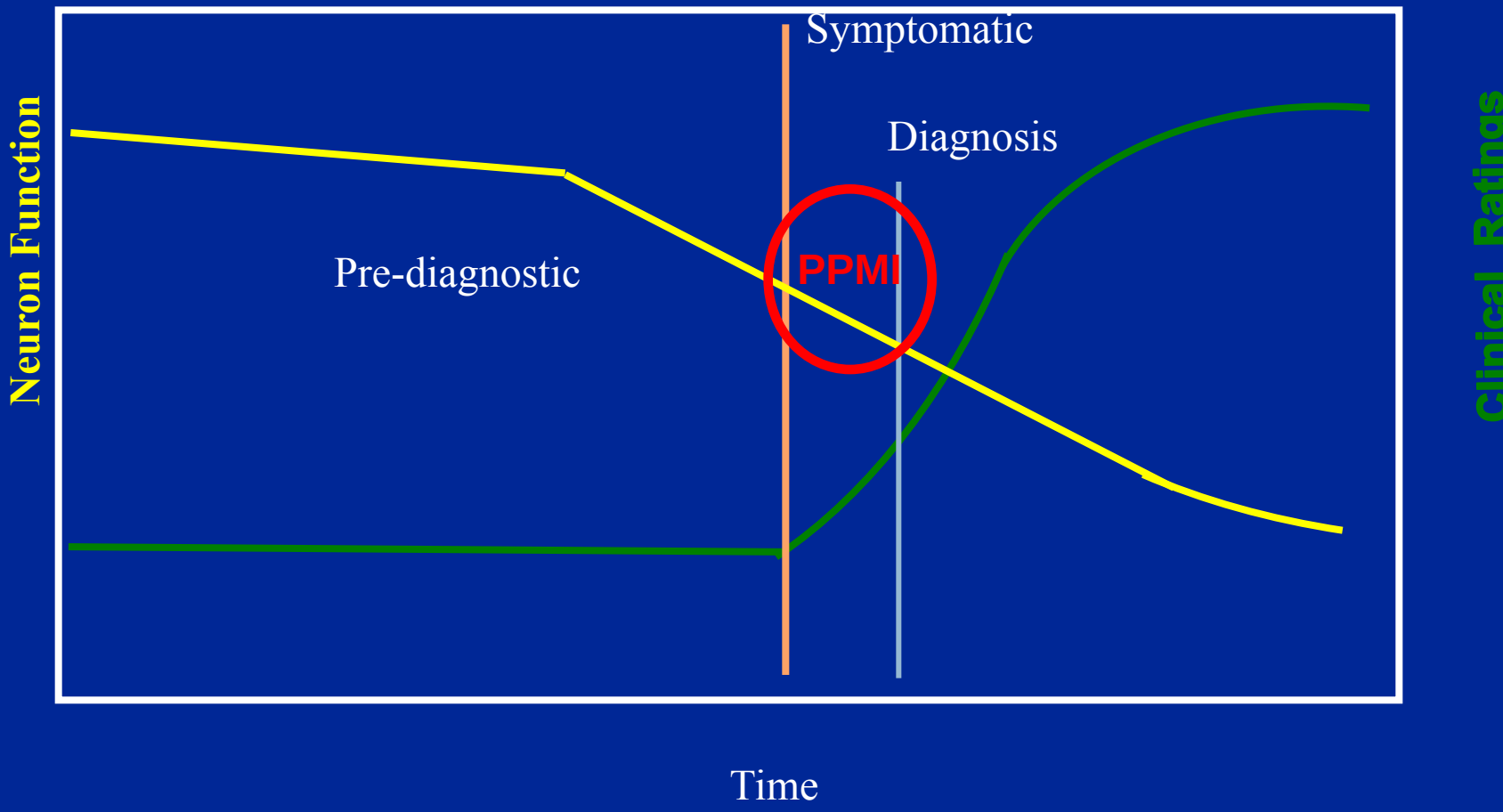
LP well tolerated – HA – 4-7%
CSF Volume collected 15.25 (mean)
Sprotte needle used in 82%
Syringe suction 63%
Sitting position in 63%
Flouroscopy in 5%

CSF Pilot Baseline Data

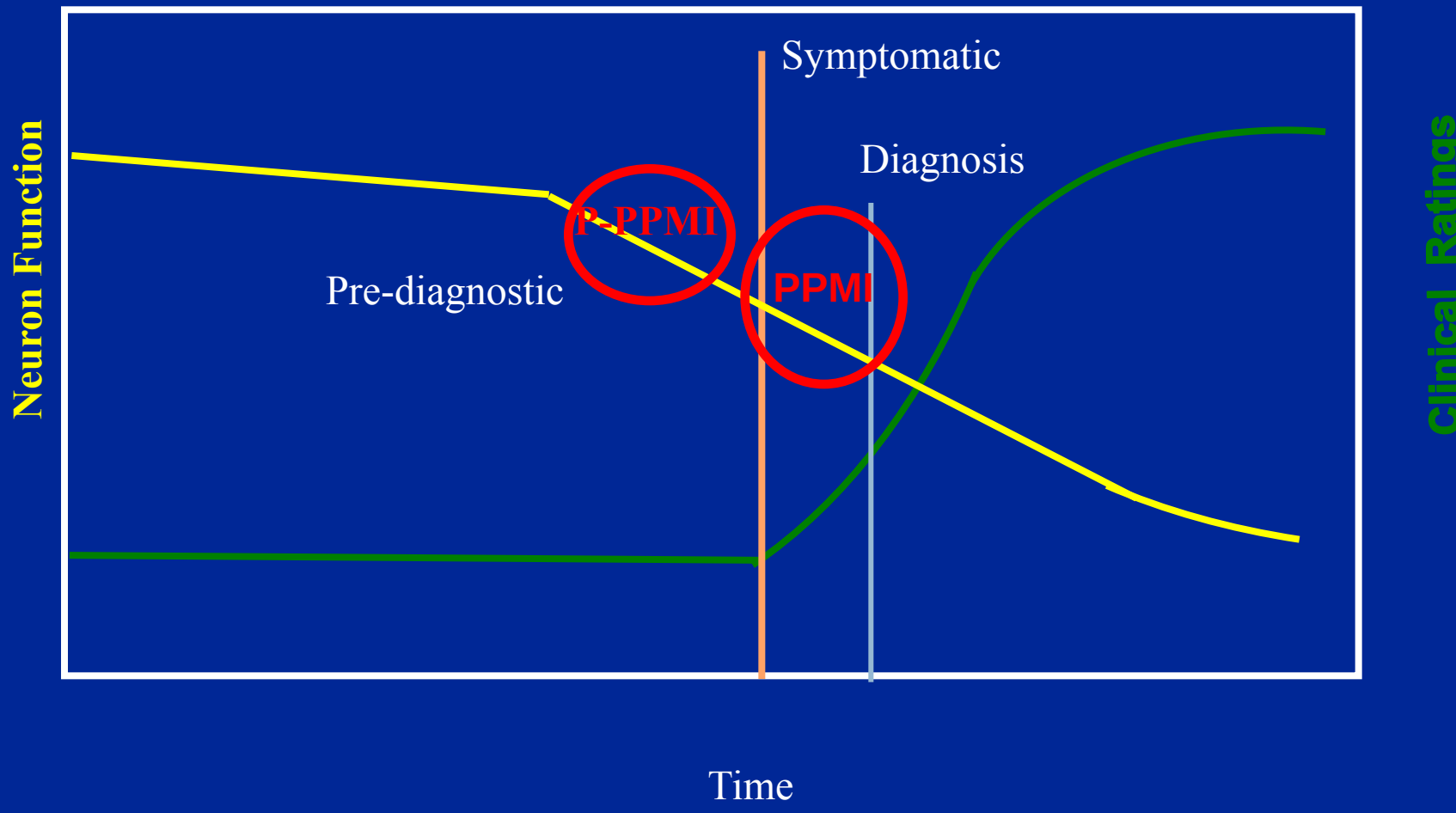
	HC (N = 39)	PD (N = 63)	*P* value#
$A\beta_{1-42}$ (pg/mL)	242.8 ± 49.95 (226.7 – 259.0)*	228.7 ± 45.63 (217.2 – 240.2)	**0.0466**
t-tau (pg/mL)	53.9 ± 19.33 (47.6 – 60.1)	46.1 ± 24.71 (39.8 – 52.3)	**0.0276**
$p\text{-}tau_{181}$ (pg/mL)	24.9 ± 8.45 (22.2 – 27.6)	21.0 ± 7.83 (19.0 – 23.0)	**0.0093**
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**

Ju-Hee Kang, et al and the Parkinson's Progression Marker Initiative
Association of cerebrospinal fluid Ab1-42, t-tau, p-tau181 and alpha-synuclein levels with clinical features of early drug naïve Parkinson's disease patients; a cross-sectional study.
JAMA Neurology, in press

Natural History of Parkinson disease



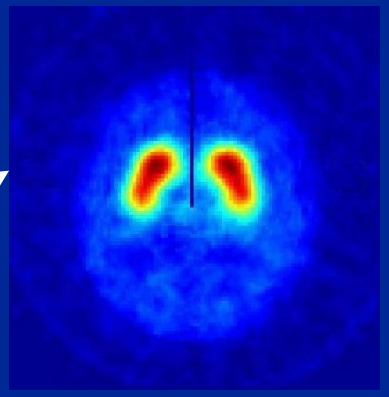
Natural History of Parkinson disease



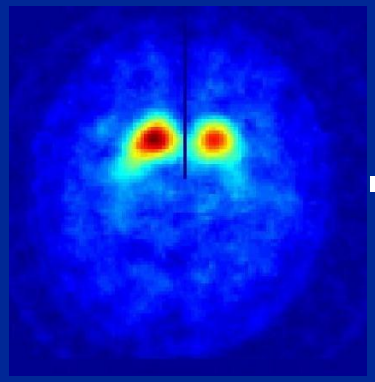
How to define Prodromal PD

- Enrich a population
- Combine Biomarkers
- Assess biomarker change
- Develop high risk cohort for phenoconversion

PARS: study scheme



PD

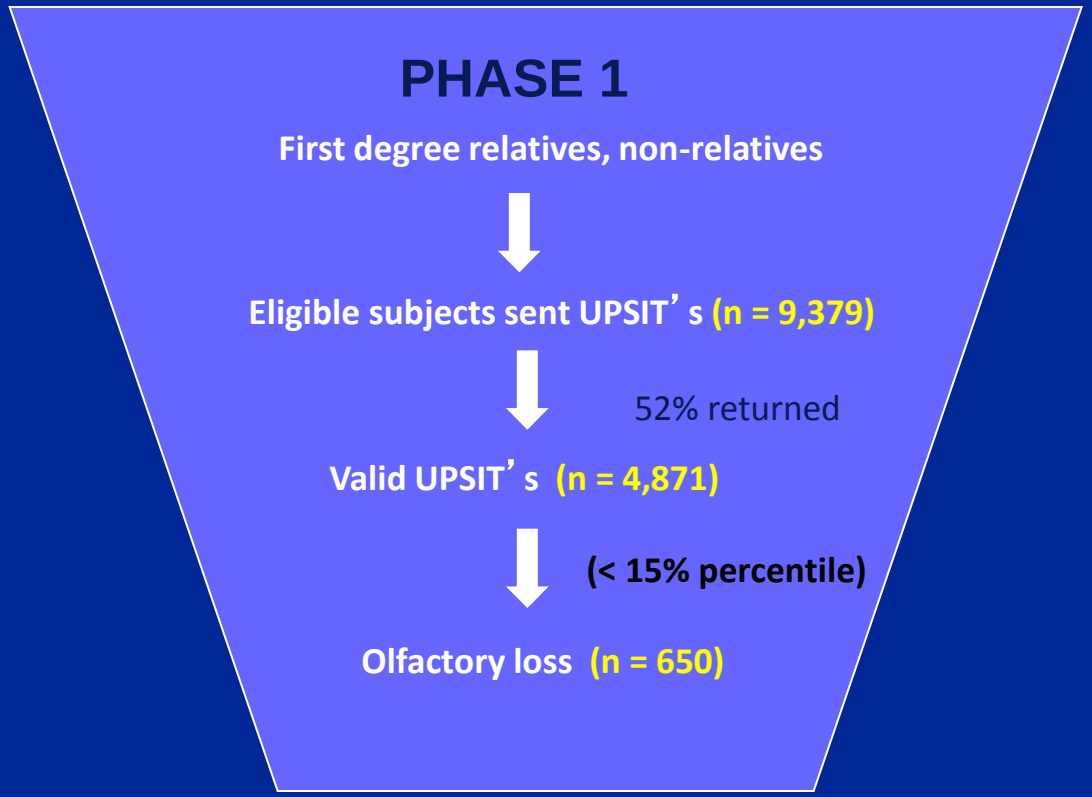


PD

PARS baseline –

Sequential and increasingly intensive biomarker assessment

PARS



PHASE 2

Clinic visit - 385

1. UPDRS
2. Diagnostic form
3. SCOPA-aut
4. Non-motor review
5. Neuropsych assess

Imaging visit- 303

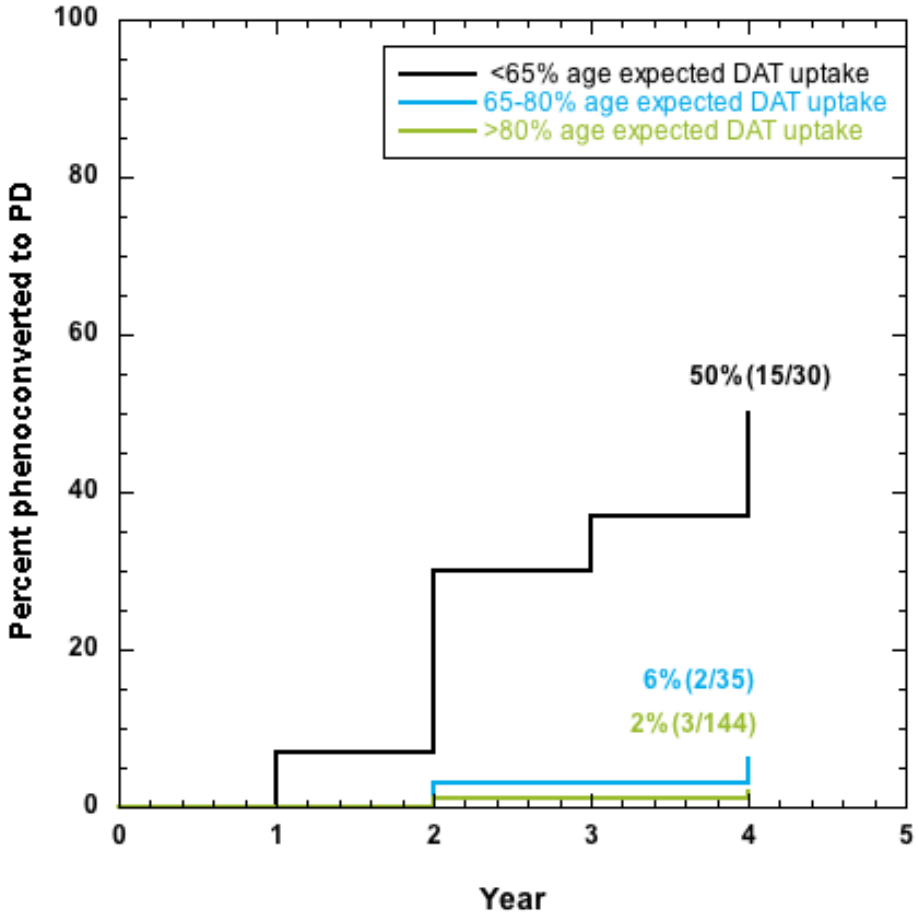
1. **DAT imaging**
2. HRV
3. Blood, CSF sampling

PARS baseline DAT IMAGING -

	HYPOSMIC (≤15%) N=203		NORMOSMIC (>15%) N=100		
Age expected Putamen DAT density	N	Percent of cohort	N	Percent of cohort	
≤65% (DAT deficit)	23	11.3%	1	1.0%	p<.01
65% - ≤80% (Indeterminate)	35	17.2%	7	7.0%	p<.05
>80% (NO DAT deficit)	145	71.5%	92	92.0%	

- Hyposmia enriches for DAT deficit (28.5% compared to 8%)
- Severe DAT deficit highly enriches for DAT deficit (11.3% compare to 1%)

Longitudinal PARS

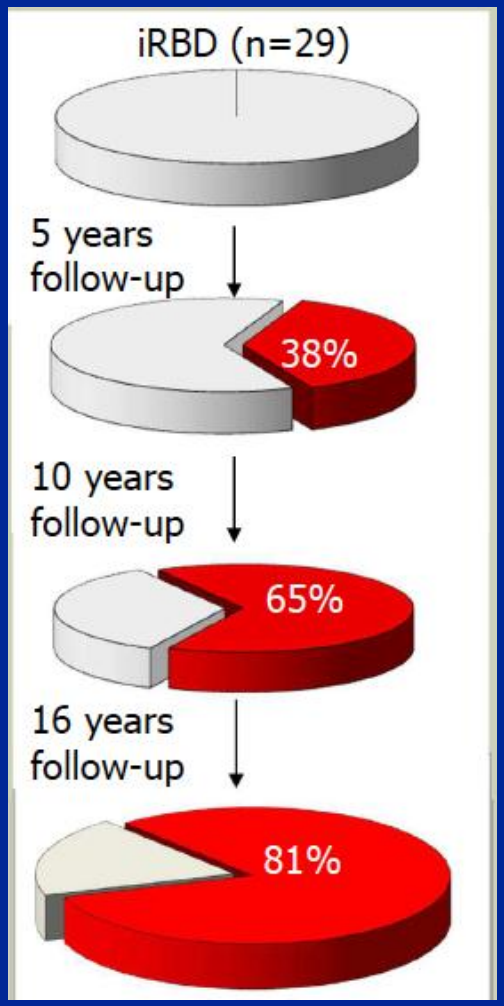


Phenoconversion rate is 50% at 4 years for subjects with a severe DAT deficit (<65% of age expected DAT uptake).

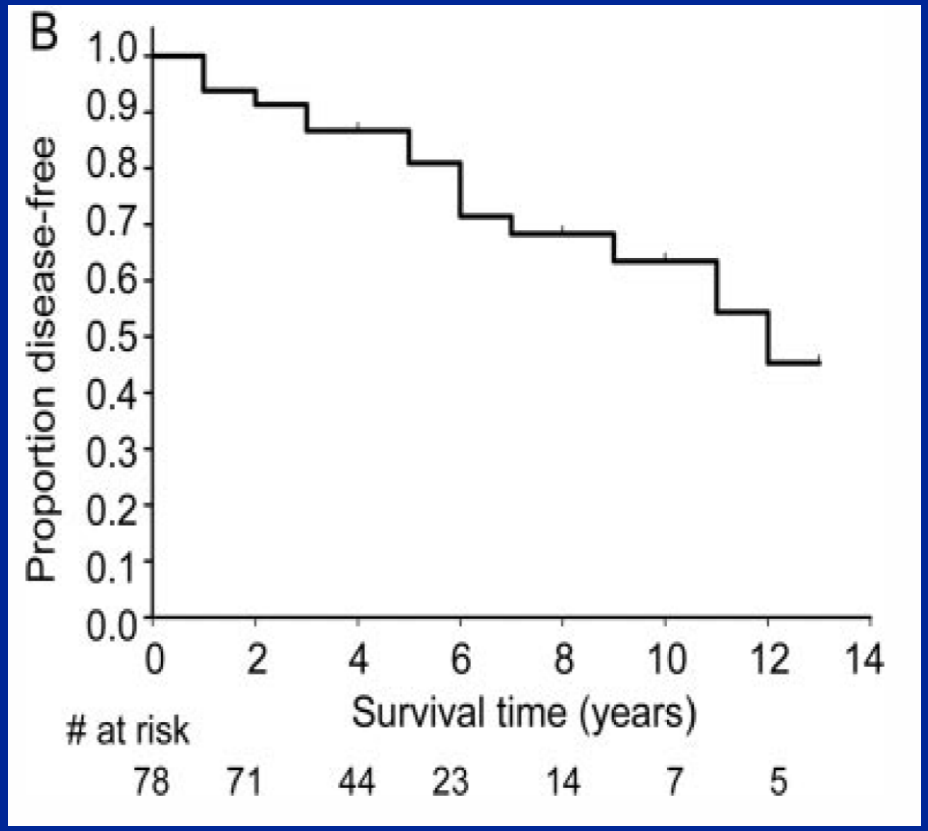
Few phenoconverters among subjects in the indeterminate (65-80% age expected uptake)

No DAT deficit (>80% age expected uptake) groups.

RBD and Risk of PD



Schenck et al., 1996, 2003, 2007, 2013



- Risk of PD in patients with idiopathic RBD is about 5%/yr
- Increased risk extends for 10-20 years from RBD diagnosis

From Postuma, Neurology 2009

Decreased striatal dopamine transporters uptake and substantia nigra hyperechogenicity as risk markers of synucleinopathy in patients with idiopathic rapid-eyemovement sleep behaviour disorder: a prospective study

A. Iranzo, F Lomeña, H Stockner, F Valldeoriola, I Vilaseca, M Salamero, JLMolinuevo, M Serradell, J Duch, J Pavía, J Gallego, K Seppi, B Högl, E Tolosa, Werner Poewe, J Santamaria, for the Sleep Innsbruck Barcelona (SINBAR) group

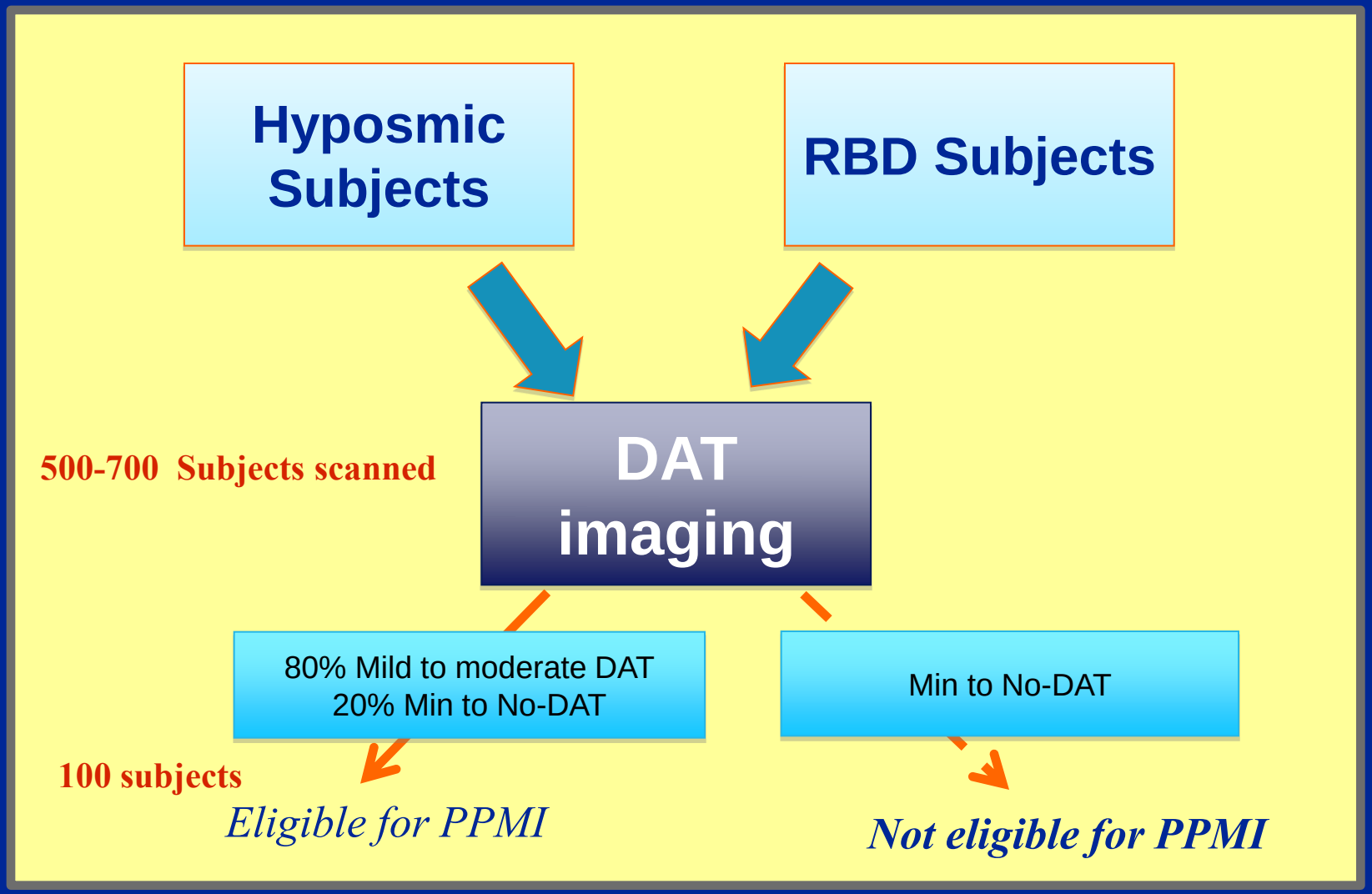
Lancet, **2010**

17 of 43 RBD subjects demonstrate reduced DAT uptake

Putamen > caudate reduction

6/17 developed PD or DLB within 2.5 years

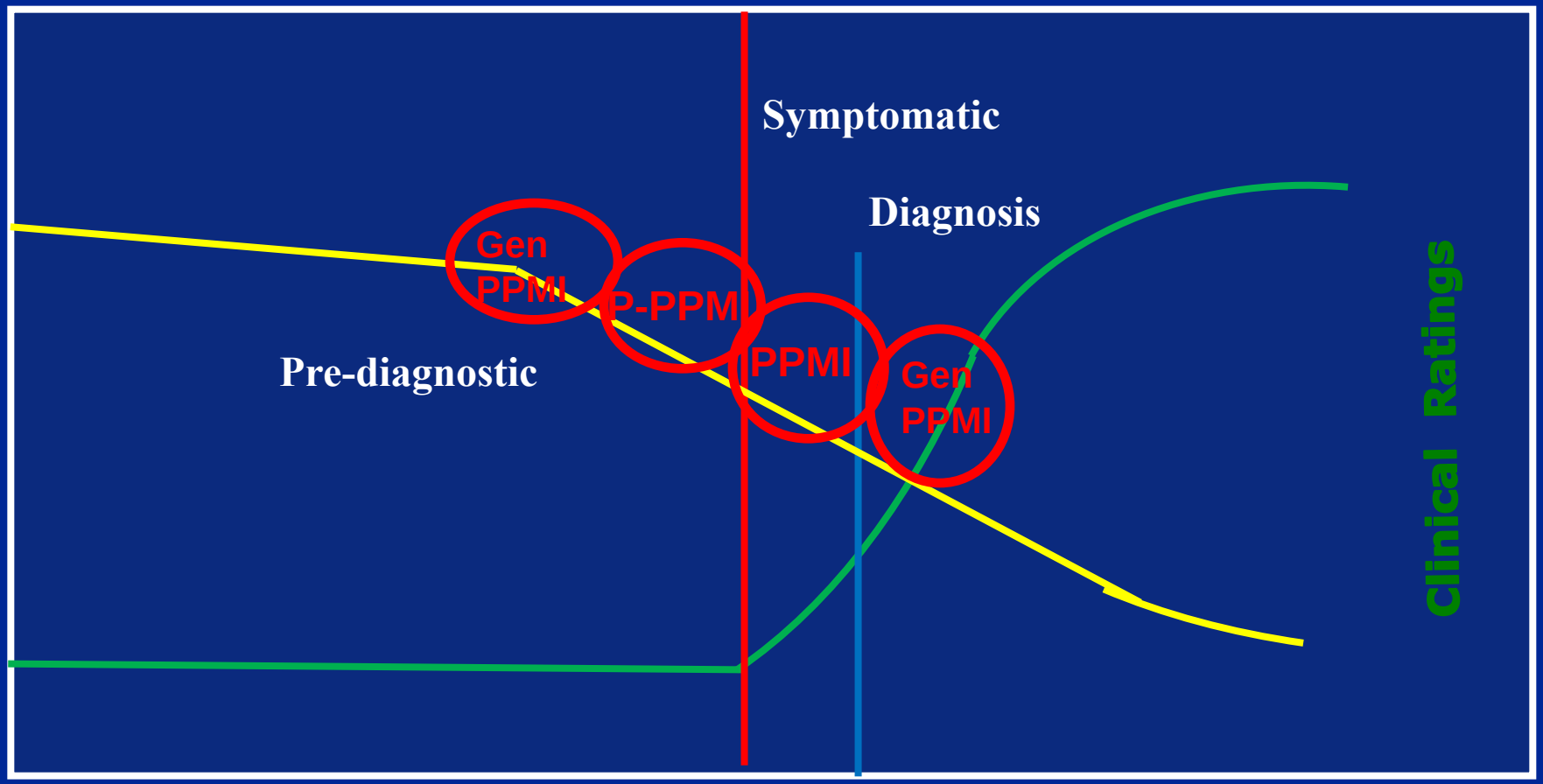
Eligibility for P-PPMI



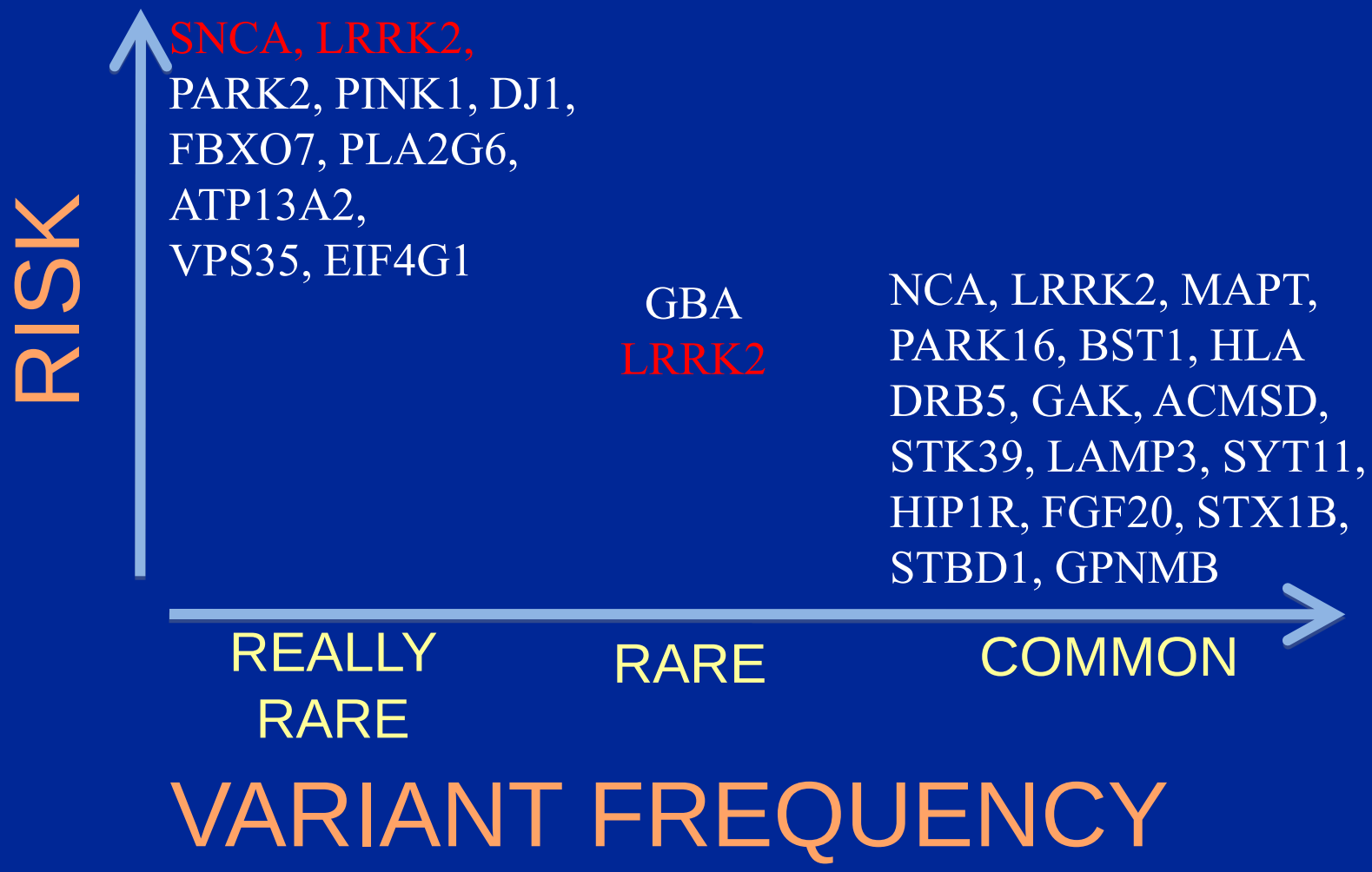
P-PPMI Outcome measures

- Change in biomarker signature – Clinical, Imaging, biologic
  - Exploratory comparison of P-PPMI to PD Healthy, SWEDD
- Phenoconversion to motor PD
  - BBB modified criteria
  - Data driven definition

Natural history Parkinson's disease

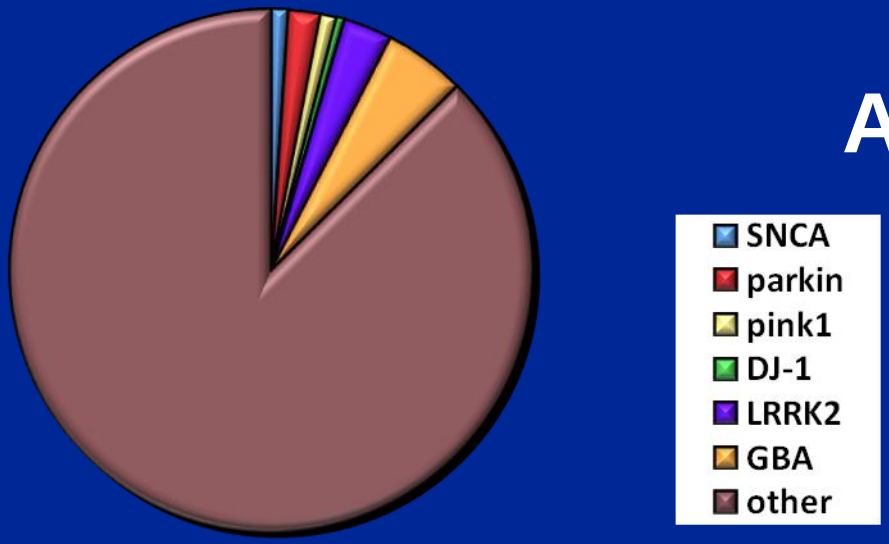


Landscape of Genetics in PD

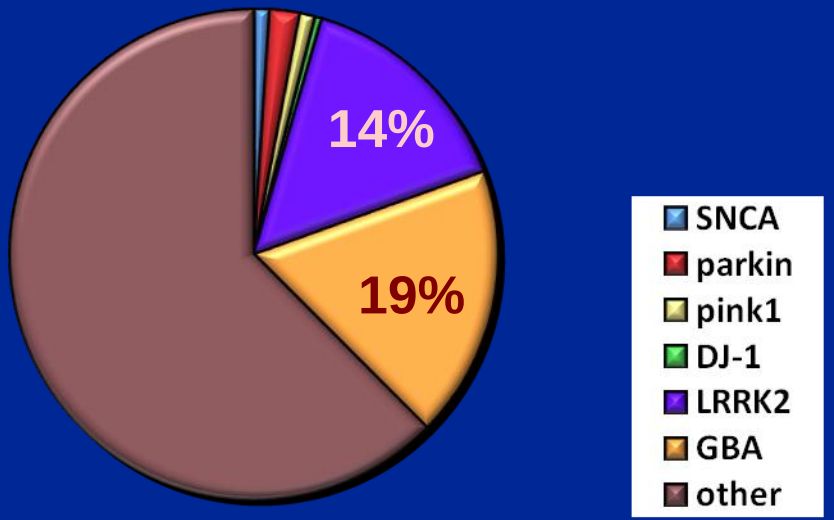


The frequency of mutation associated PD

World wide



Among Ashkenazi Jews



PPMI-LRRK2 arm in 2013

- **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 four years**
  - **Establish pre-motor biomarker signature**
  - **Define phenoconversion**

- **Maintain PPMI database structure and commitment to rapid access to data**

PPMI-Synuclein arm in 2013

- **Leverage existing PPMI infrastructure and add sites with existing expertise and experience with LRRK2 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 four 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 enrolled and standardized procedures for acquisition and analysis of all study data establishd
- 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

PPMI ⟷ ADNI

- Cognitive outcomes
- Imaging outcomes – Amyloid imaging, DAT imaging, Tau, Inflammatory
- CSF– Tau, pTau, Amyloid, alpha-synuclein
- Genetics – full sequence data
- Prodromal cohorts – prevention trials, ethical issues