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

Keystone
March 2014

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

- **PPMI Study Rationale/Infrastructure**
- **Baseline PPMI data (baseline cohorts)**
- **PPMI new cohorts - Prodromal/Genetics**
- **Utility of Biomarkers prior to symptoms**

PD patient vignette

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

  Noted could not coordinate polls when skiing

  Note 1-2 years – mild constipation

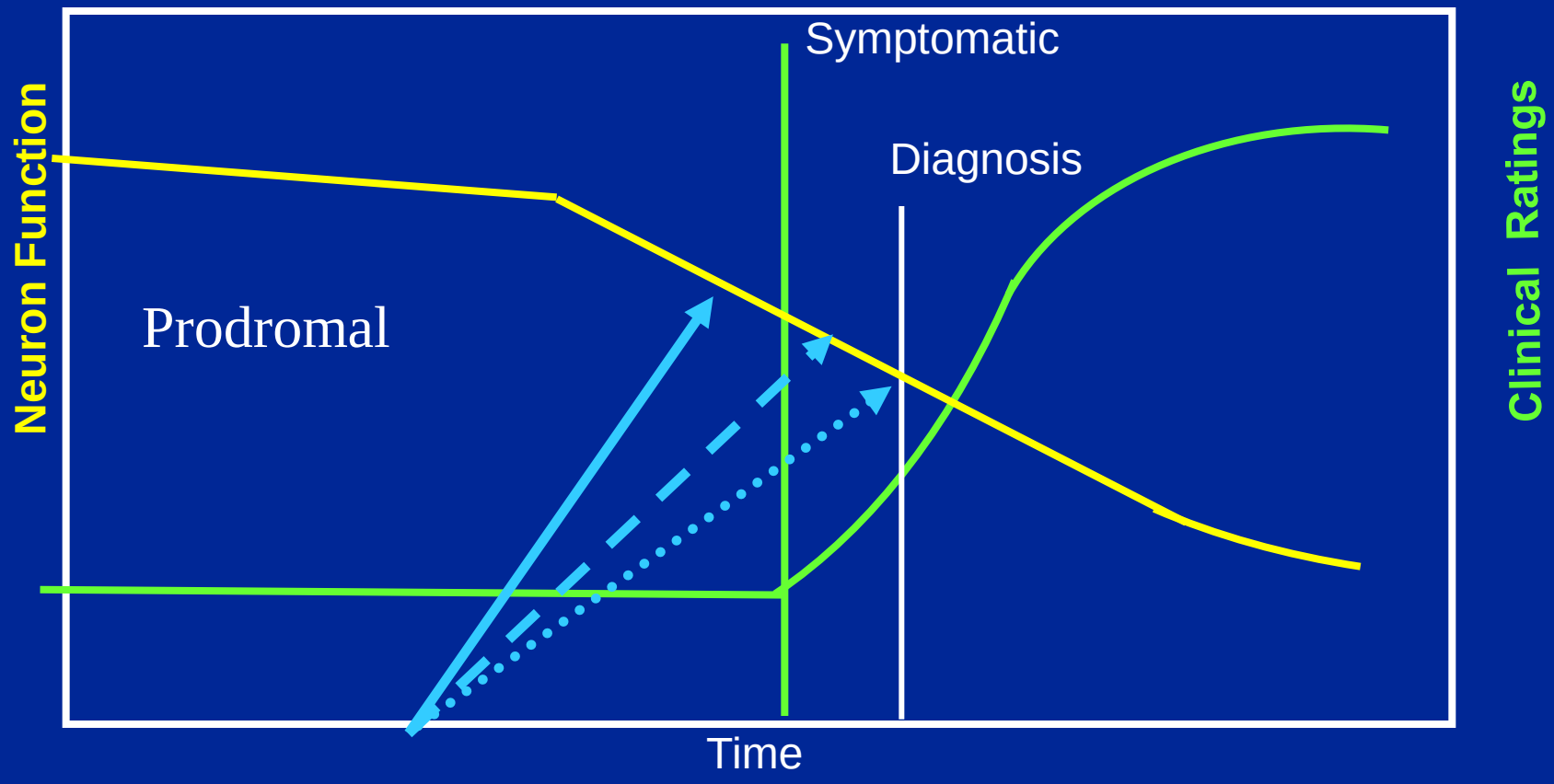
  2 months intermittent R UE tremor while reading the newspaper, or if in stressful situation
- Exam

  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"

Natural History of PD



Neuroprotection Studies

UNSUCCESSFUL

- DATATOP – SELEGILINE/VIT E
- 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*
- *NET PS LS1 – CREATINE*

UNCERTAIN

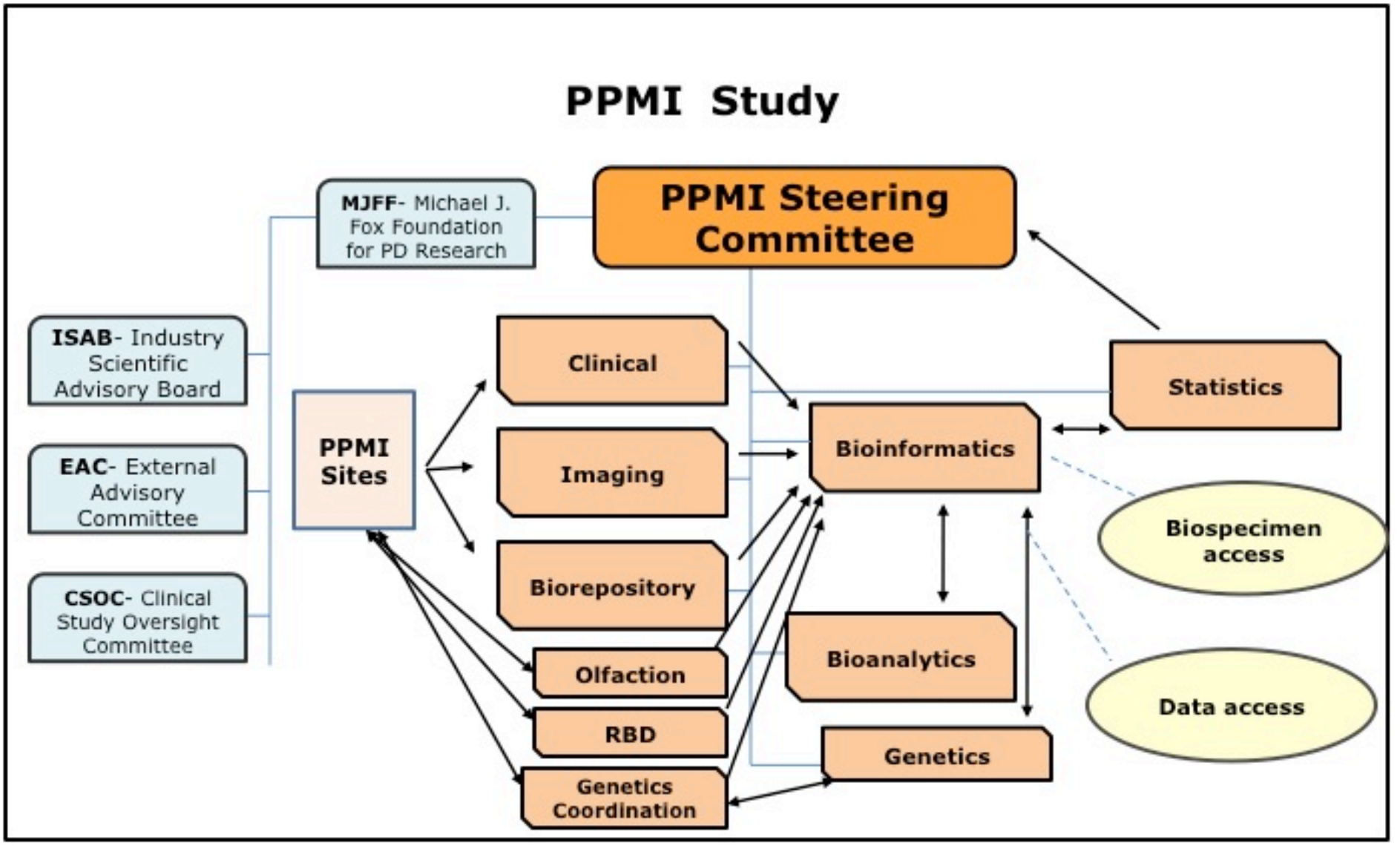
- *ADAGIO – TEVA*
- *ISRADIPINE*
- *INOSINE*

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
  - Prodromal PD detection and progression

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 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.

biogen idec

Abbott
A Promise for Life

COVANCE

Bristol-Myers Squibb

élan

Avid
Radiopharmaceuticals

GE Healthcare

Genentech
A Member of the Roche Group

gsk GlaxoSmithKline

Lilly

Lundbeck

MSD
Meso Scale Discovery

ucb

MERCK

Pfizer

Roche

PPMI Sites

PPMI SITES IN THE UNITED STATES:

- Arizona PD Consortium (Sun City, AZ)
- Beth Israel Medical Center (NY, NY)
- Baylor College of Medicine (Houston, TX)
- Boston University (Boston, MA)
- Cleveland Clinic (Cleveland, OH)
- Columbia University (NY, NY)
- 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:

- Foundation for Biomedical Research of the Academy of Athens (Athens, Greece)
- Imperial College (London, UK)
- Innsbruck University (Innsbruck, Austria)
- Norwegian University of Science and Technology (Trondheim, Norway)
- Paracelsus-Elena Clinic Kassel/University of Marburg (Kassel and Marburg, Germany)
- Pitié-Salpêtrière Hospital (Paris, France)
- University of Barcelona (Barcelona, Spain)
- University of Donostia (San Sebastien, Spain)
- University of Salerno (Salerno, Italy)
- University of Tübingen (Tübingen, Germany)

PPMI SITES IN AUSTRALIA:

- Macquarie University (Sydney, Australia)

PPMI SITES IN Israel:

- Tel Aviv Sourasky Medical Center (Tel Aviv, Israel)

PPMI SC and Study Cores

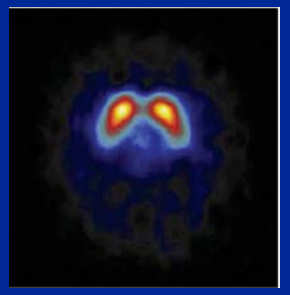
Steering Committee	PI-K Marek, C Tanner, T Foroud, D Jennings, K Kieburtz, W Poewe, B Mollenhauer, T Simuni, (core leaders, MJFF, ISAB), S Lasch
Clinical Coordination Core	▪ University of Rochester's Clinical Trials Coordination Center • PI: Karl Kieburtz, Ray Dorsey, Renee Wilson
Imaging Core	• Institute 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

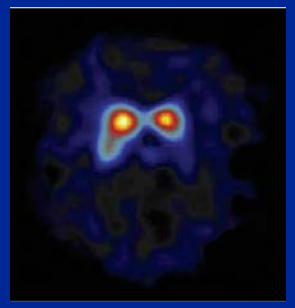
PPMI Study Details: Synopsis

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, RNA** ▪ **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**
Data and Biosamples shared on website - www.ppmi-info.org	▪ **>160,000 Data downloads** ▪ **> 35 Sample requests via BRC** ▪ **Ancillary study development**

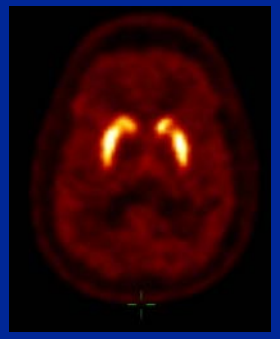
Pre-synaptic Dopaminergic Imaging

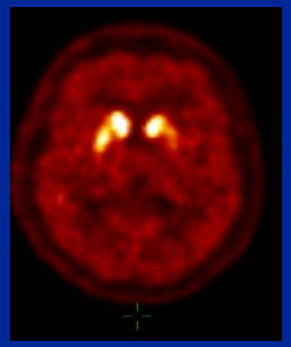
^{123}I ß-CIT-DAT



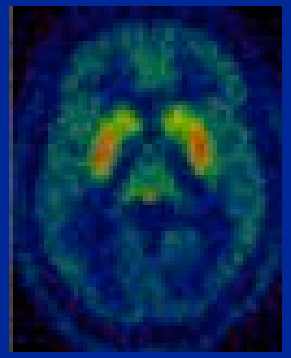


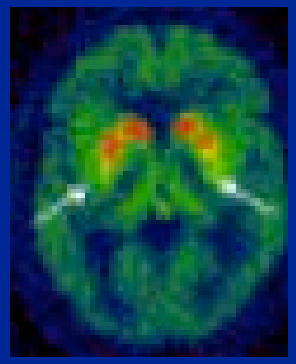
^{18}F AV-133-VMAT2





^{18}F-DOPA-AADC

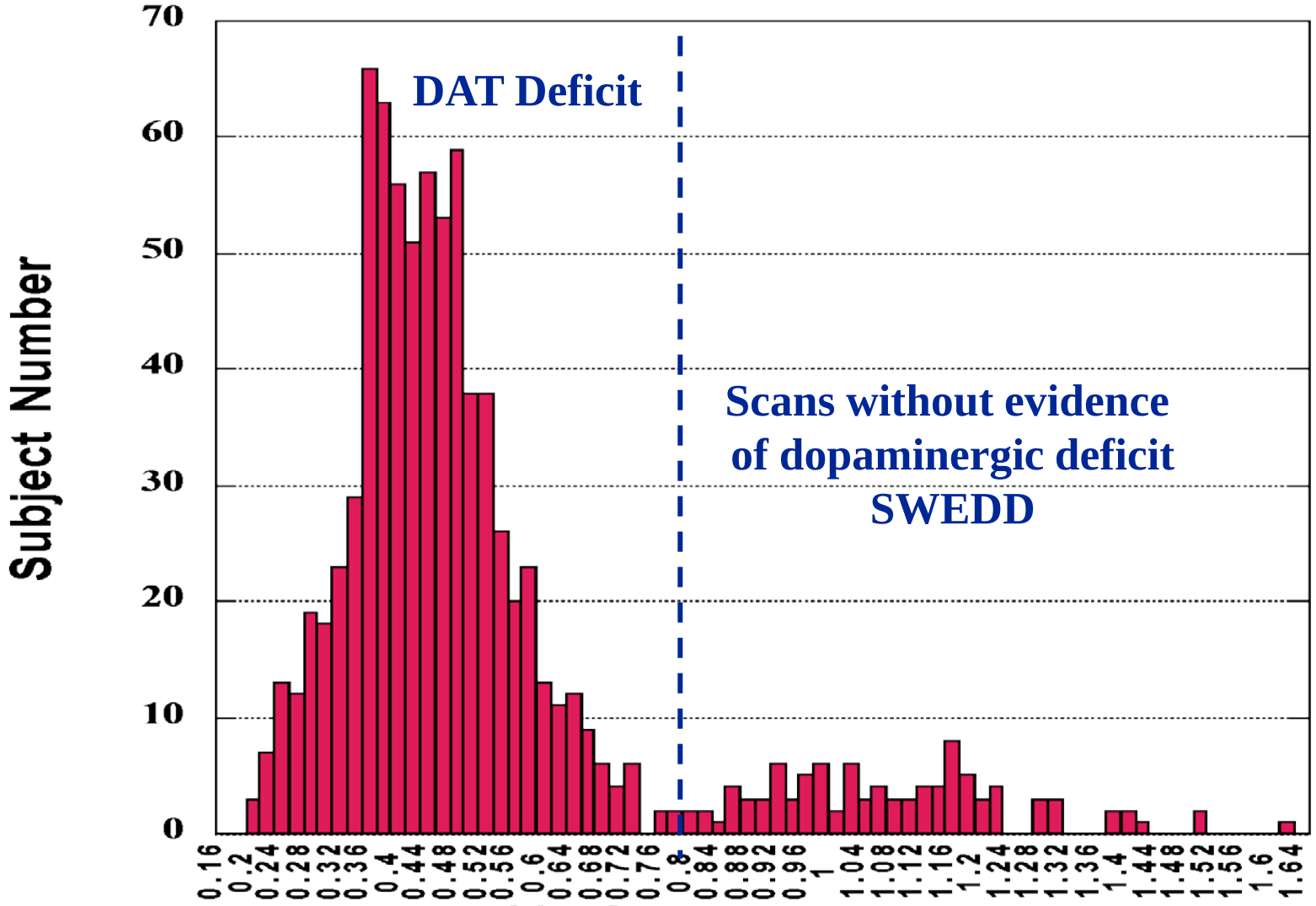




Healthy

Parkinson disease

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



PRECEPT study - FOLLOWUP IMAGING AND CLINICAL OUTCOMES BY SWEDD STATUS AT BASELINE

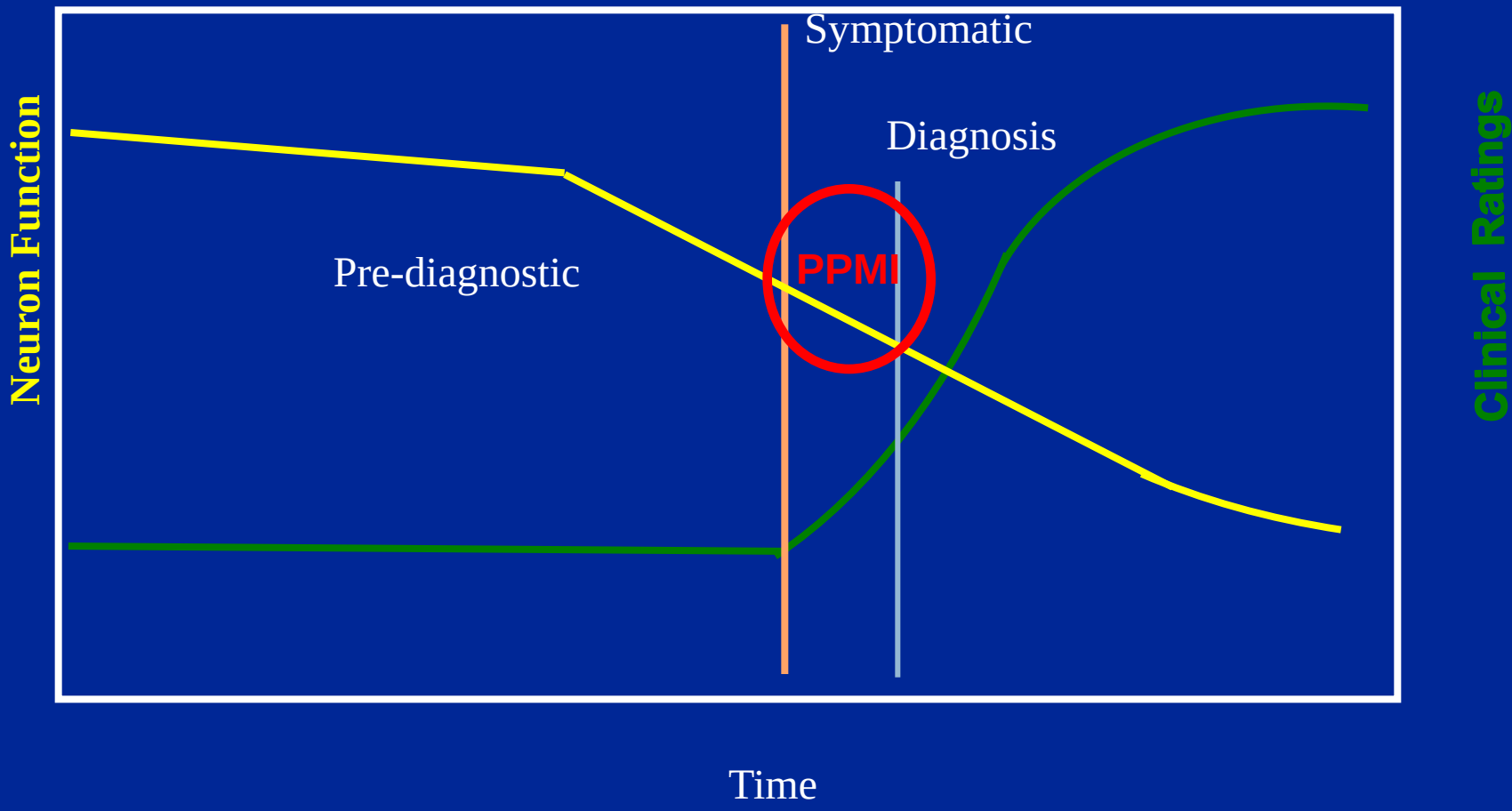
	SWEDD >80%	DAT Deficit <=80%	
% Change [^{123}I] ß-CIT	N = 72	N = 629	
Striatum:	-0.2 (12.2)	-8.5 (11.9)	*
Caudate:	1.0 (13.1)	-6.1 (12.5)	*
Putamen:	-1.9 (12.2)	-13.1 (15.1)	*
CLINICAL	N = 91	N = 708	
Change in Total UPDRS	0.5 (6.9)	10.5 (8.9)	*
Change in Motor UPDRS	-0.4 (5.0)	7.0 (6.9)	*
Need for DA treatment at 12 mo	16.7% (CI 10.2, 26.6)	50.9% (CI 47.2,54.8)	*

Mean (SD) for Change in [^{123}I] ß-CIT and UPDRS,
Percent (CI) for need for DA treatment. * indicates $p < 0.01$

SWEDD (Scans Without Evidence of Dopaminergic Deficit) in PD Trials

Study	Stage –PD	Dur DX at Baseline (mo)	% SWEDD
Elldopa-CIT	Denovo	6	21/142 (14%)
PRECEPT	Denovo	8	91/799 (12%)
REAL-PET	Denovo	9	21/186 (11%)
Calm-CIT	Start of DA Rx	18	3/82 (5%)
GPI1485	Treated Stable responder	23	3/212 (1.4%)

Natural History of Parkinson disease



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

CSF Acquisition

Group	Baseline	Month 6	Month 12	Month 24
PD	423 (98%)	390 (90%)	308 (80%)	127(83%)
Healthy	196 (97%)	181 (88%)	153 (84%)	112 (79%)
SWEDD	62 (92%)	52 (87%)	48 (83%)	11 (73%)

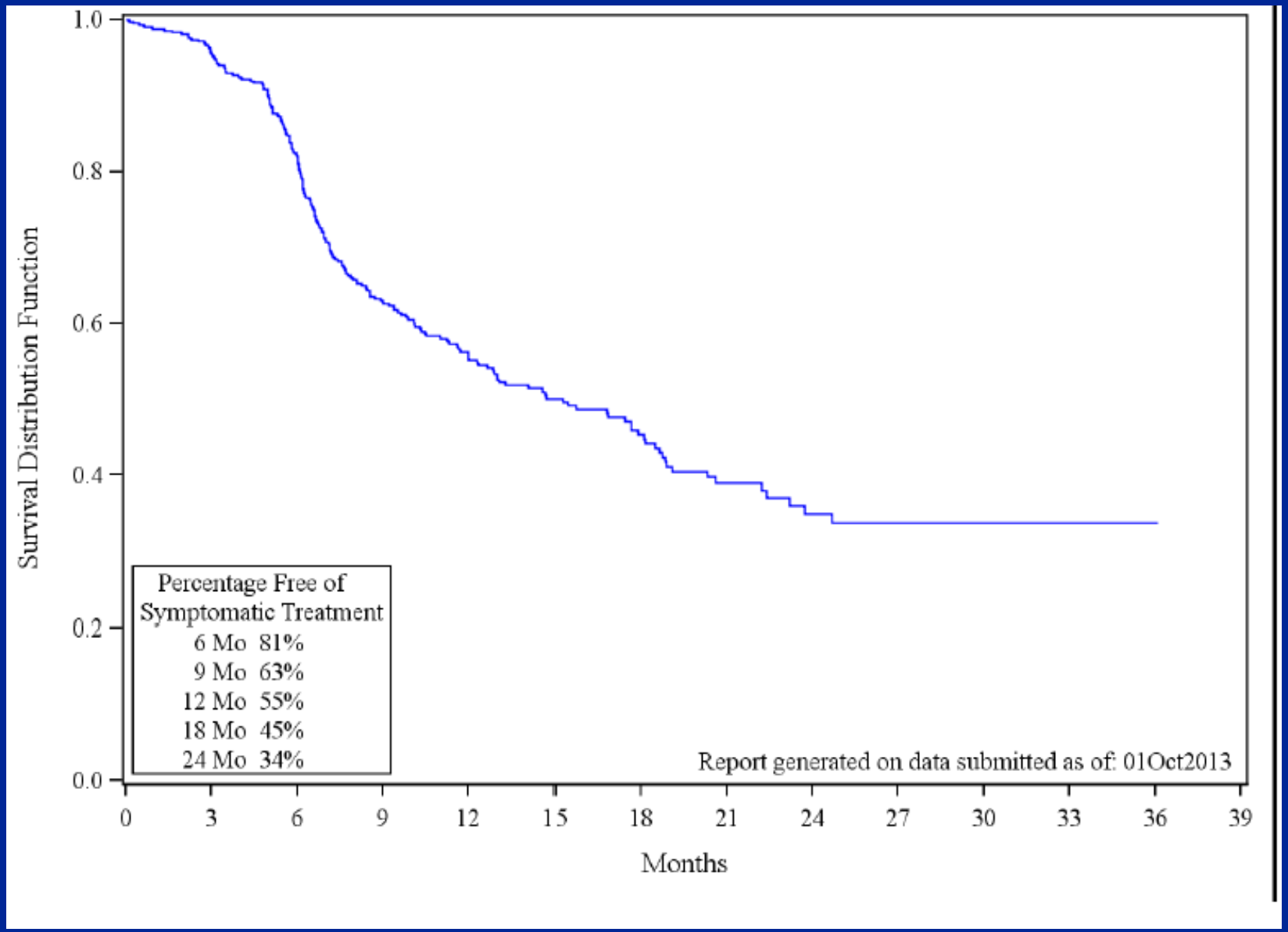
LP well tolerated – HA – 4-7%
CSF Volume collected 15.25 (mean)
Sprotte needle used in 82%
Syringe suction 63%
Sitting position in 63%
Flouroscopy in 5%

CSF Pilot Baseline Data

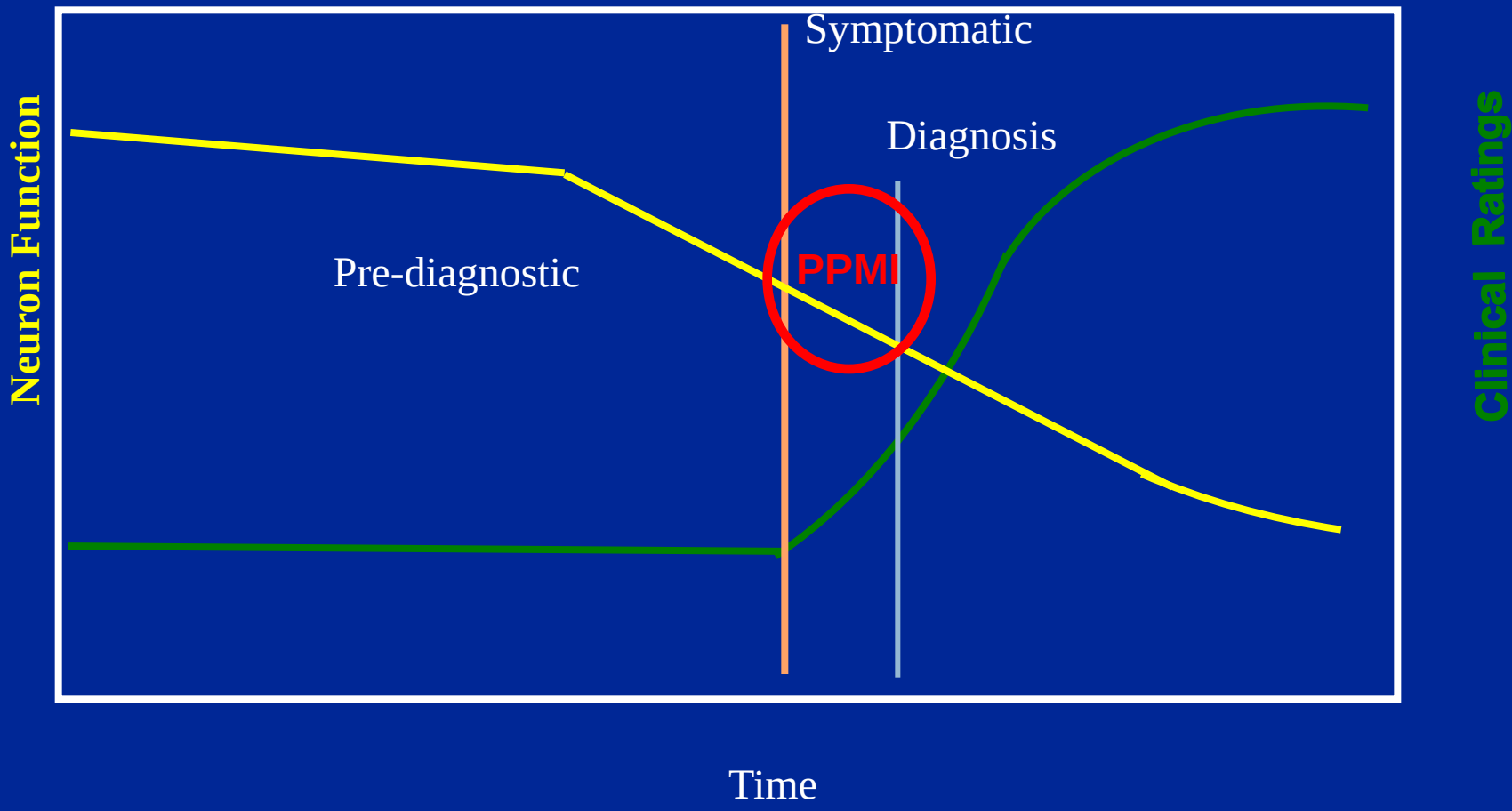
	HC (N = 39)	PD (N = 63)	*P* value#
$A\beta_{1-42}$ (pg/mL)	242.8 ± 49.95 (226.7 – 259.0)*	228.7 ± 45.63 (217.2 – 240.2)	**0.0466**
t-tau (pg/mL)	53.9 ± 19.33 (47.6 – 60.1)	46.1 ± 24.71 (39.8 – 52.3)	**0.0276**
p-tau_{181} (pg/mL)	24.9 ± 8.45 (22.2 – 27.6)	21.0 ± 7.83 (19.0 – 23.0)	**0.0093**
t-tau/$A\beta_{1-42}$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

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

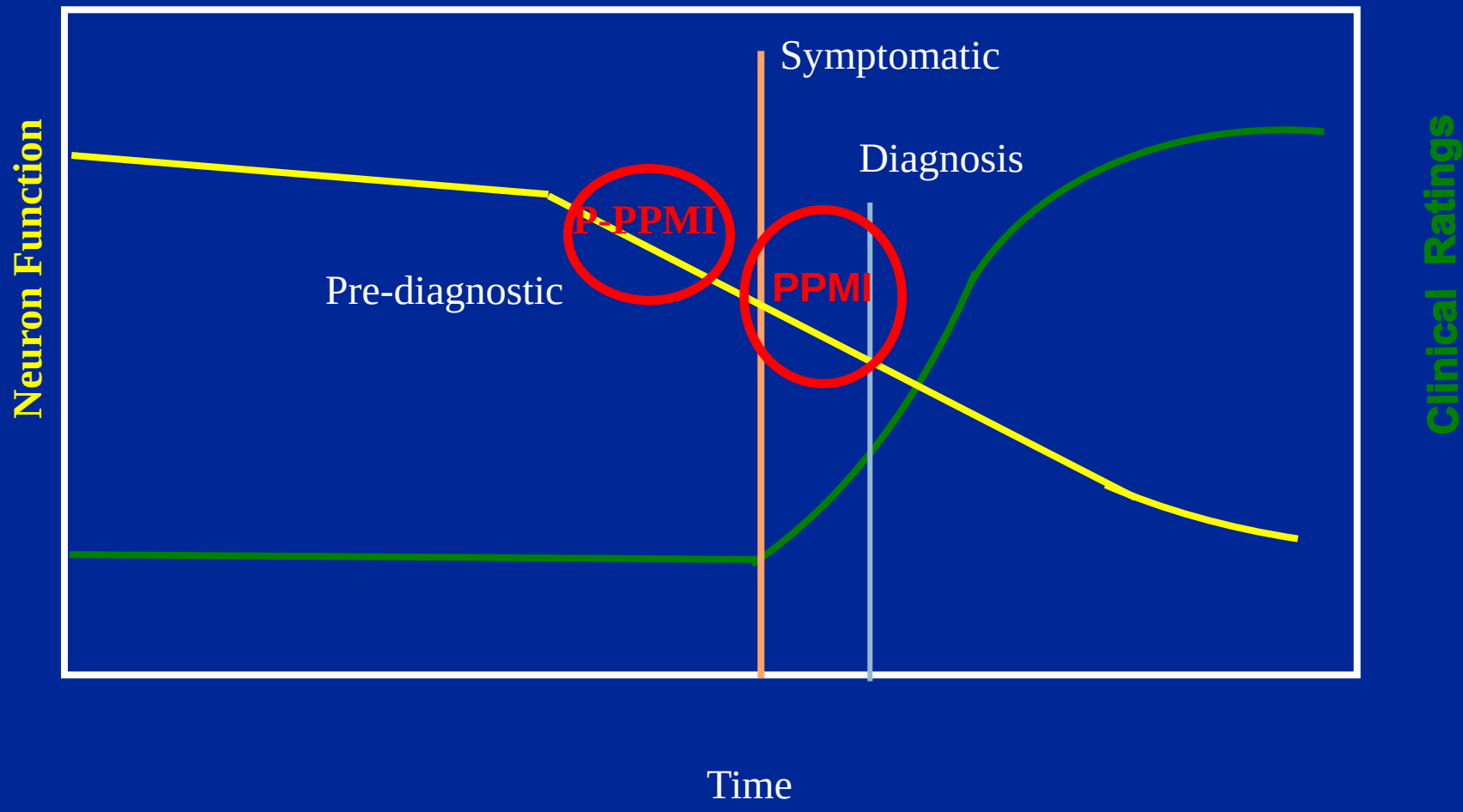
PD - Time to Start Dopaminergic Meds



Natural History of Parkinson disease



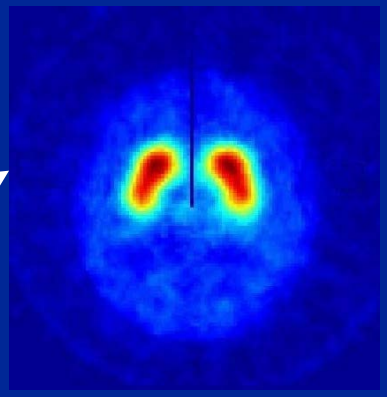
Natural History of Parkinson disease



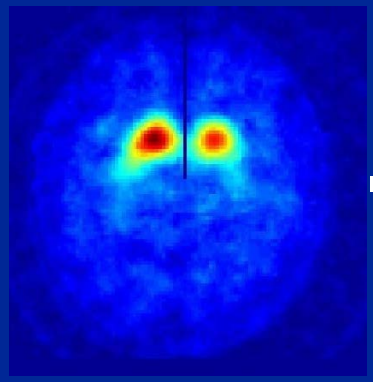
How to define Prodromal PD

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

PARS: study scheme



PD

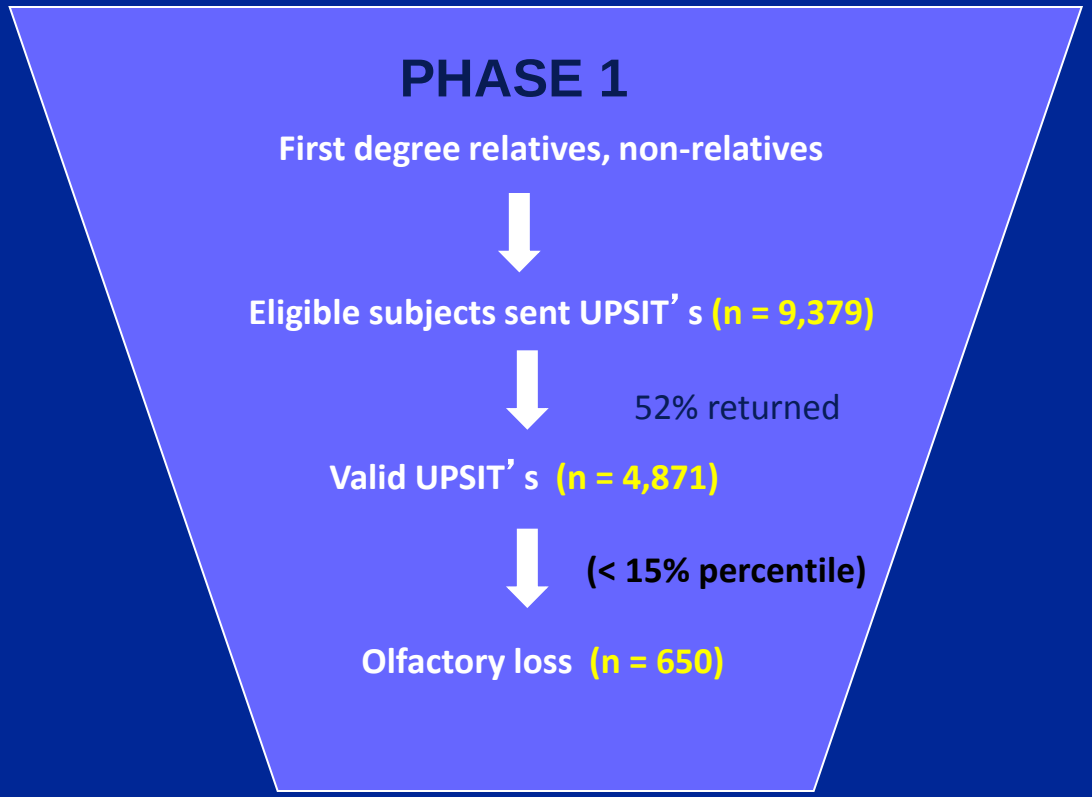


PD

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

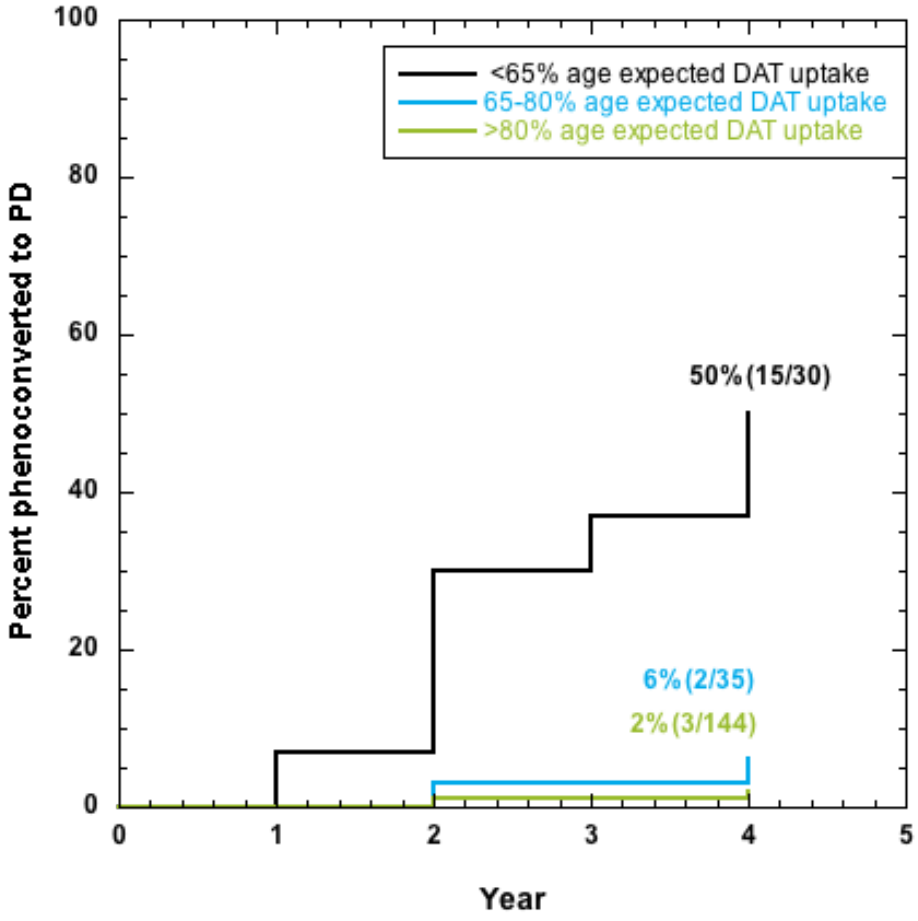
1. **DAT imaging**
2. HRV
3. Blood, CSF sampling

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

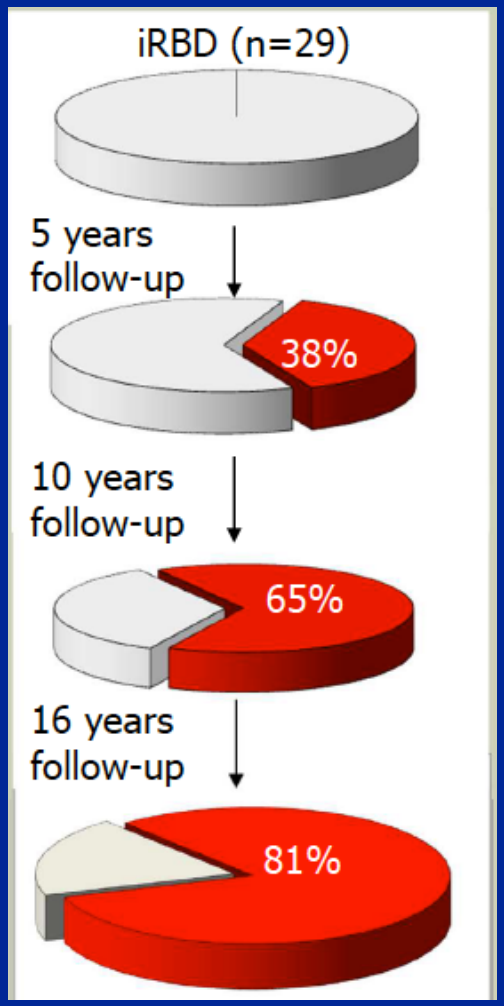


Phenoconversion rate is 50% at 4 years for subjects with a severe DAT deficit (<65% of age expected DAT uptake).

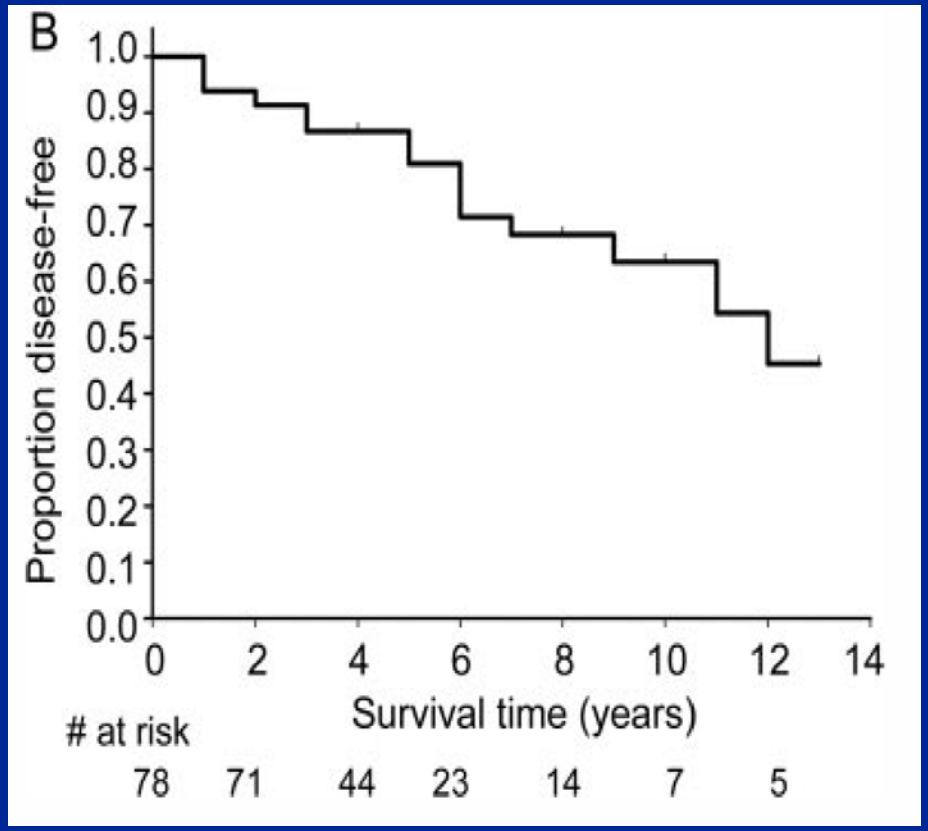
Few phenoconverters among subjects in the indeterminate (65-80% age expected uptake)

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

	Participants with IRBD (n=43)	Controls (n=18)	p value
Left putamen:occipital	2·46 (0·30)	2·68 (0·15)	0·007
Right putamen:occipital	2·42 (0·30)	2·62 (0·18)	0·012
Left caudate:occipital	2·98 (0·37)	3·17 (0·28)	0·057
Right caudate:occipital	3·01 (0·38)	3·30 (0·32)	0·008

Data are mean (SD) unless otherwise stated. IRBD=idiopathic rapid-eye-movement sleep behaviour disorder. ^{123}I-FP-CIT=^{123}I-2β-carbomethoxy-3β-(4-Iodophenyl)-N-(3-fluoropropyl)-nortropane.

Table 2: **Mean striatal ^{123}I-FP-CIT uptake ratios in participants and controls**

6/17 developed PD or DLB within 2.5 years

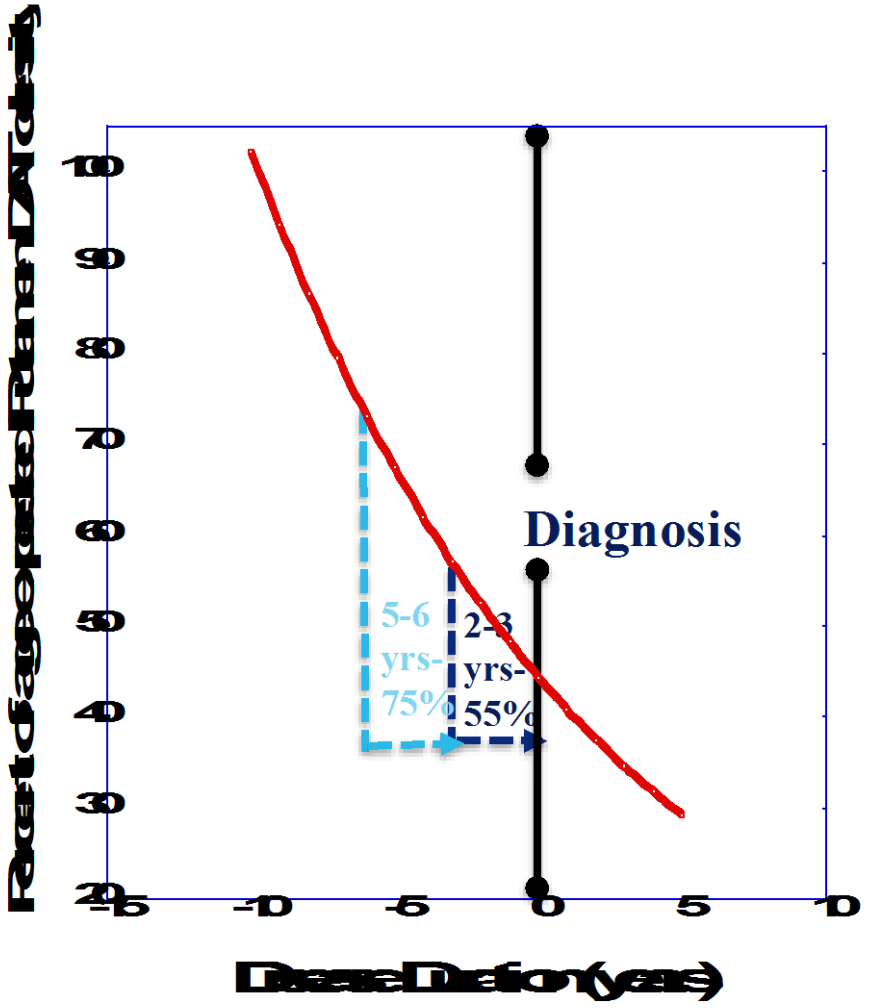
Predicting Phenoconversion

Assumptions

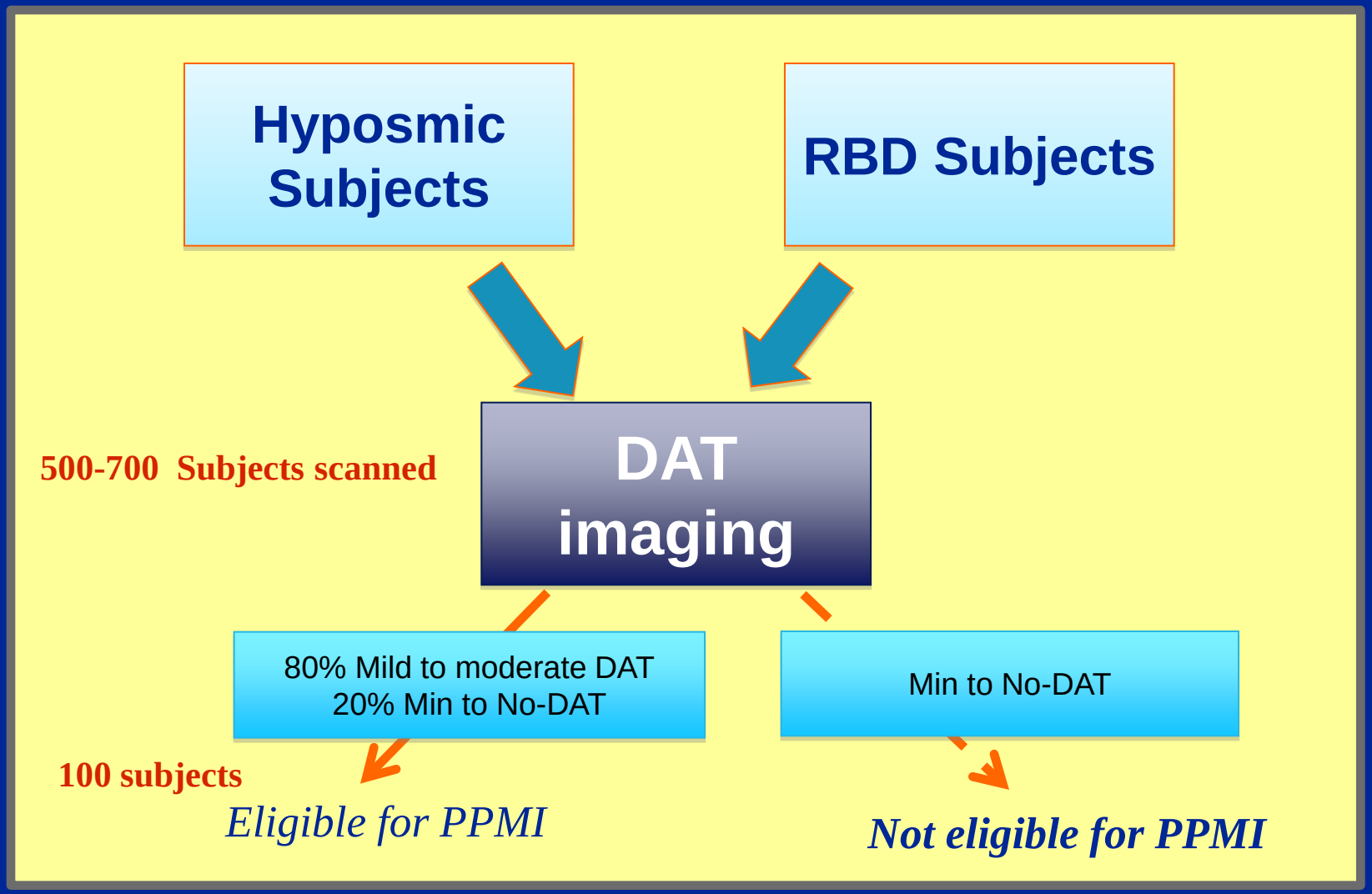
- **Similar loss of DAT in early PD and pre-diagnostic period**
- **Mean reduction in putamen 8 %/year**
- **Mean putamen % DAT density in early manifesting PD (8 months p dx) – 42%**

PHENOCONVERSION- FOR PRE-DIAGNOSTIC WITH 55% OF AGE EXPECTED DAT DENSITY = 2-3 YEARS

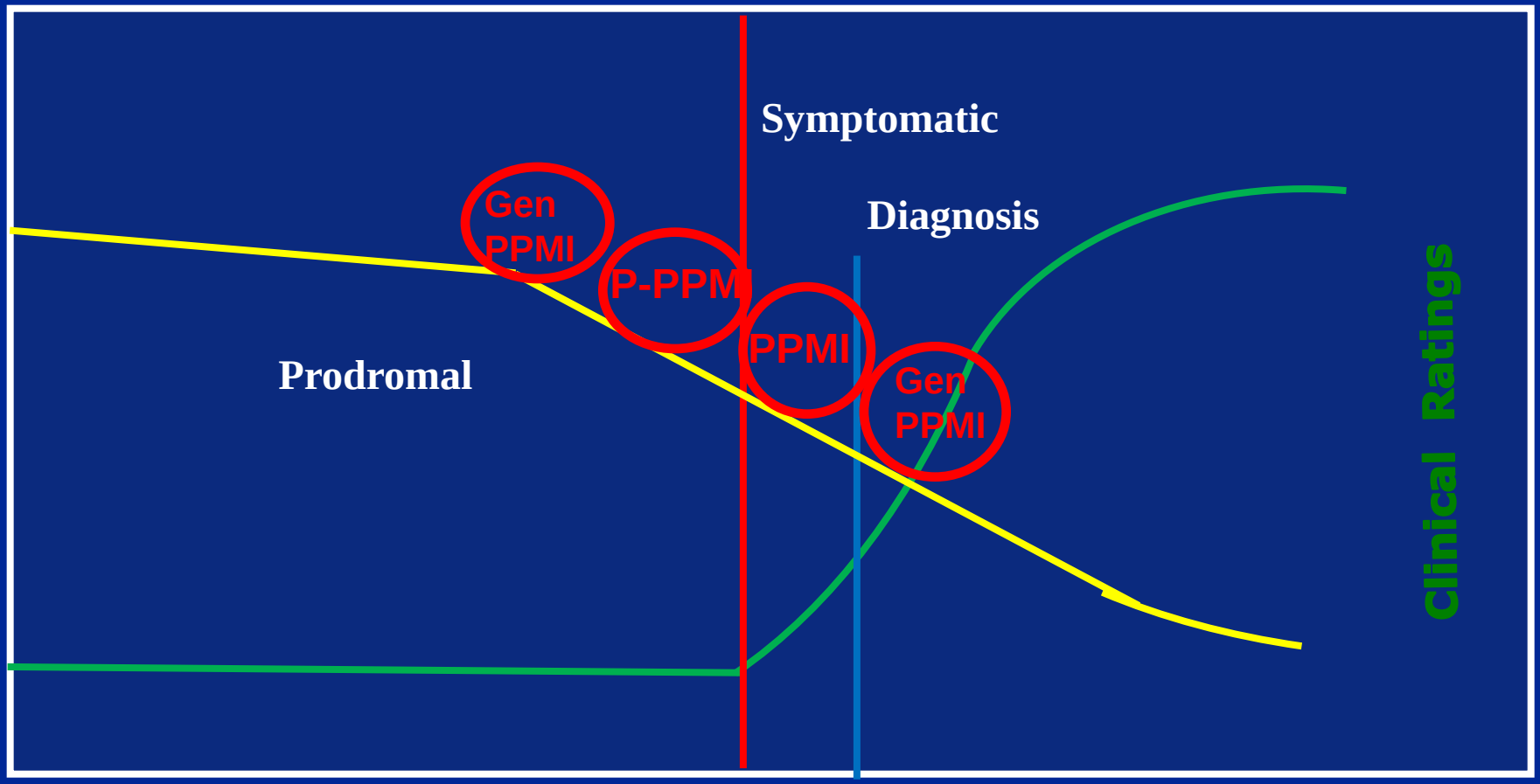
- **ESTIMATED TIME FOR START OF DAT LOSS TO DX= 9-10 YEARS**



Eligibility for P-PPMI



Natural history Parkinson's disease



PPMI-LRRK2/Synuclein Cohort

- **Leverage existing PPMI infrastructure and add sites with existing expertise and experience with LRRK2 patients and families.**

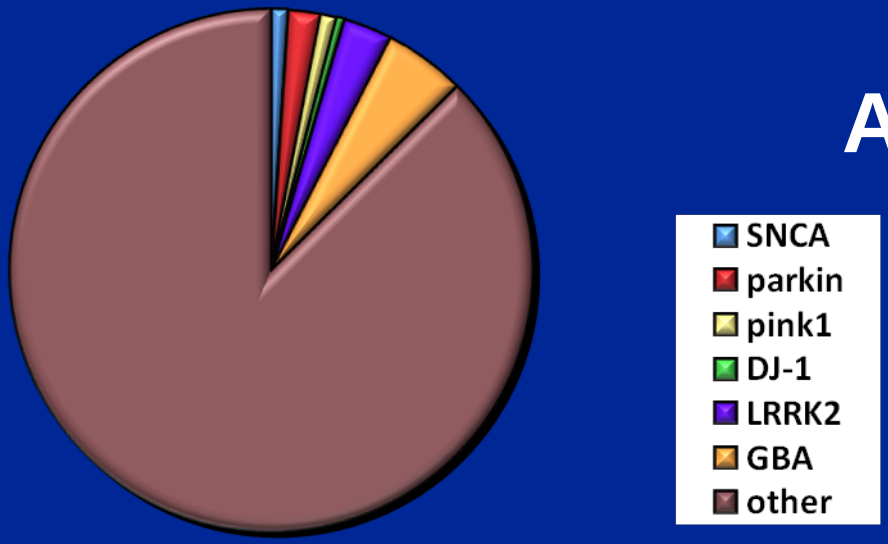
- **Enroll 250 LRRK + PD and 250 LRKK2 + unaffected family members**
- **Enroll 50 synuclein + PD and 50 synuclein + unaffected family members members with and intensive longitudinal clinical assessment protocol.**

- **Follow PD and unaffected family members for for four years**
  - **Establish pre-motor biomarker signature**
  - **Define phenoconversion**

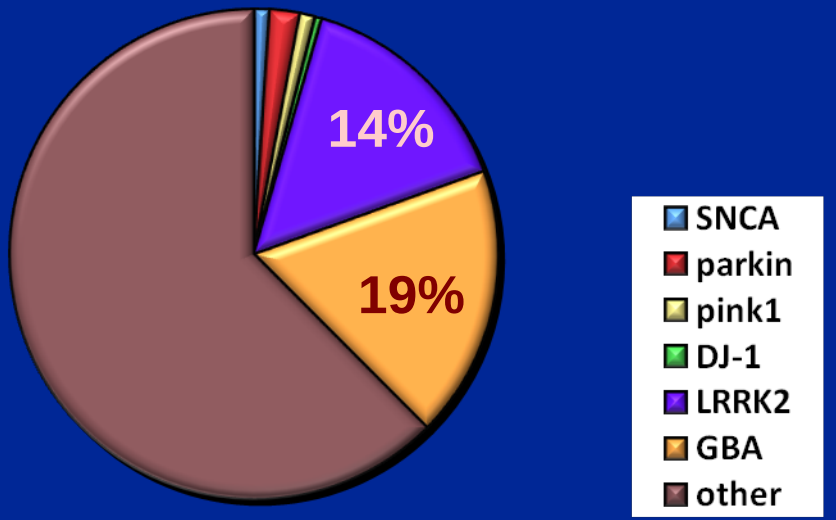
- **Maintain PPMI database structure and commitment to rapid access to data**

The frequency of mutation associated PD

World wide



Among Ashkenazi Jews



Screening a LRRK2 Population

Outreach to identify persons>60, AJ descent, history of 1st degree family member with PD

↓

Subjects consent on line and provided Saliva kit by mail

↓

Saliva sent to MGH testing lab results in 1-2 week

↓

Genetic counseling available by phone

↙

8% of subject LRRK2 + → > 50% enrolled at PPMI sites

PPMI Prodromal - Key advantages for therapeutic trials

- **Earlier is better for a neurodegenerative disorders**
- **Possible to treat longer without confound of PD meds**
- **More homogeneous populations available using biomarkers**

Temporal pattern for PD Biomarkers