Learnings from Parkinson's disease: Critical role of Biomarkers in successful drug development

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Coalition Against Major Diseases and FDA

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Disclosure

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

MNI Molecular NeuroImaging

Institute for Neurodegenerative Disorders

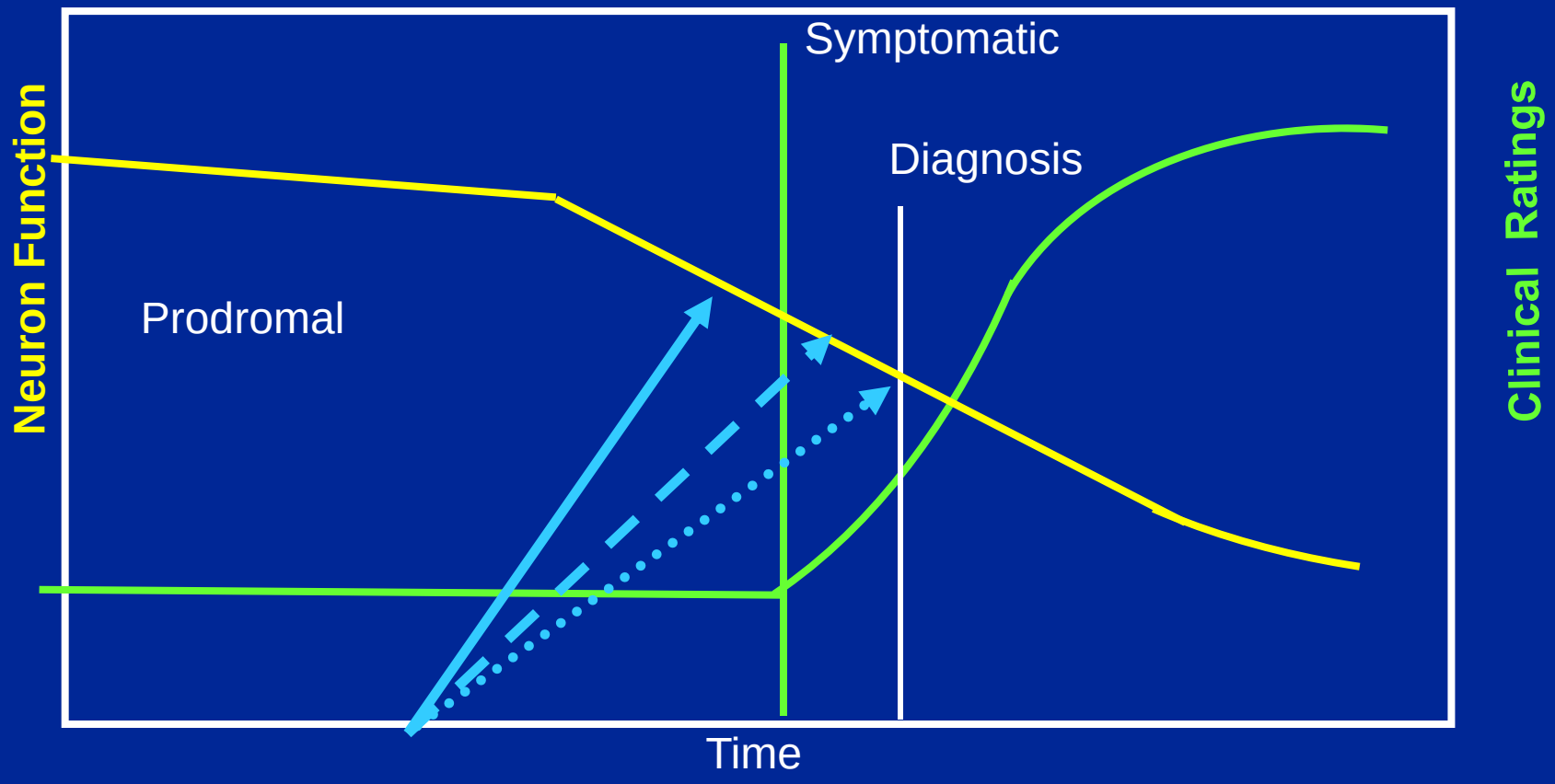
PD - Major Challenges

- **Progression in inevitable – Motor and non-motor disease features**
- **Heterogeneity is a hallmark of disease –Subsets of PD with likely different etiology, disease course, response to therapy**
- **Degeneration begins long before symptoms arise - Where does PD begin, when does PD begin, how does PD progress during the pre-diagnostic period**

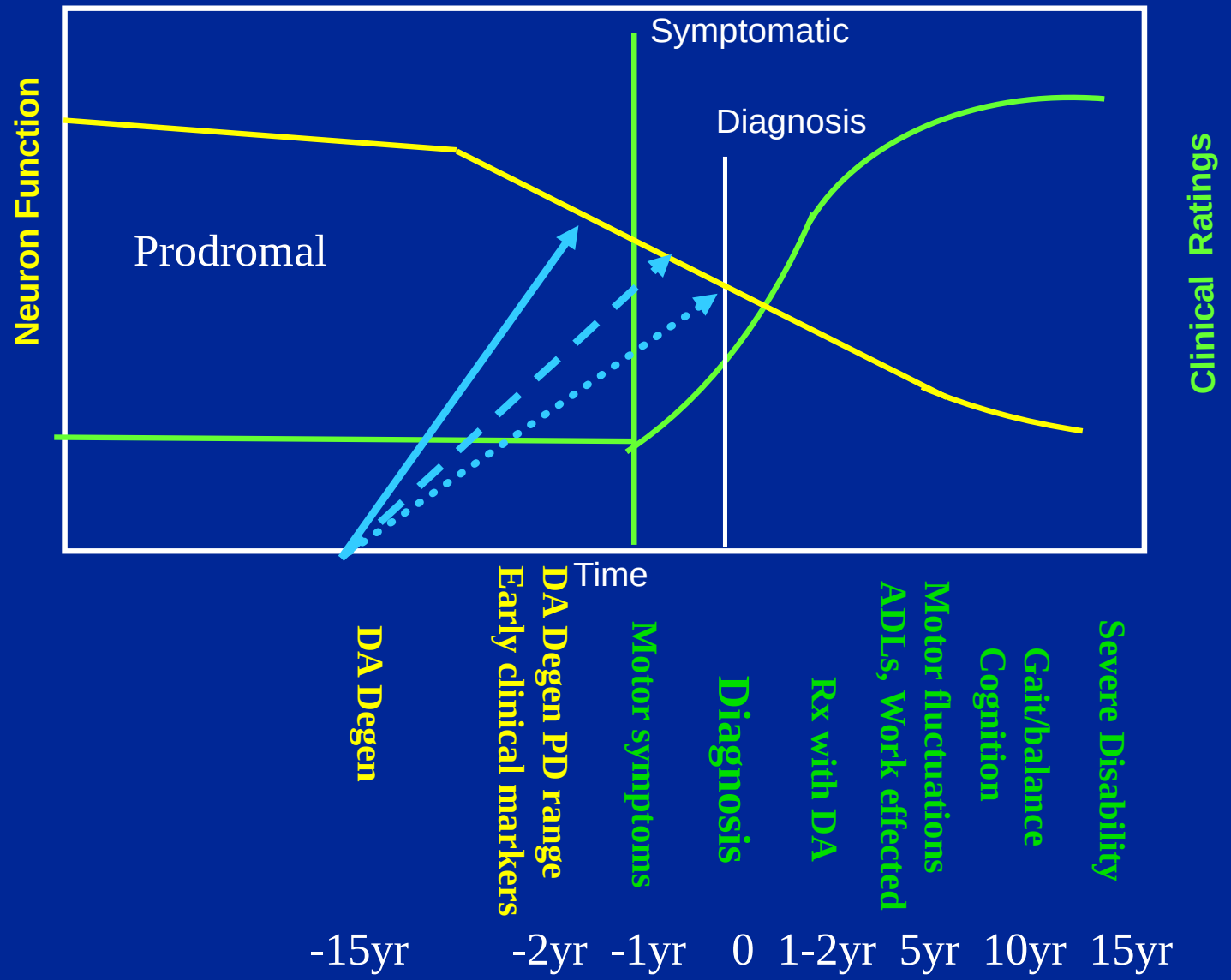
WHY BIOMARKERS

- Disease Mechanism
- Drug Mechanism/Drug dosage
- Improve diagnostic accuracy (enrich a study population)
- Identify subsets that might develop clinical outcomes
- Identify subsets that might respond to therapy
- Repeated measure to assess progression
- Eliminate confounding of symptomatic therapy
- Evaluate efficacy of disease modifying therapeutic
- Reduced sample size and more rapid assessment of effect -reduce cost and improve efficiency of clinical studies
- Assist in regulatory approvals
- Measurement prior to onset of symptoms
- Used to correlate clinical, imaging, genetic and biofluid biomarkers
- Provide objective quantitative outcomes at multiple clinical sites

Natural History of PD



Natural History of PD



PD Biomarker Candidates

CLINICAL MARKERS

- Cognition
- Behavioral
  - Depression
  - Apathy
  - Anxiety
  - ICD
- Autonomic
  - Constipation
  - Bladder
  - Sexual
  - Cardiac
- Olfaction
- Sleep- RBD
- Skin
- Motor Analysis
- Speech

IMAGING - PHENOTOMICS

- DA-SPECT/PET- Synuclein,
- MRI –DTI/RS, volumetrics
- Nigral Ultrasound

BIOLOGICS

•Blood, CSF, Urine

•Alpha-synuclein, DJ1, Urate, Tau, Beta-Amyloid, ApoA1,

'OMICS'

•RNA Profiling

•DNA exome sequencing

GENETICS

•Synuclein, LRRK2, GBA, Parkin, DJ-1, Pink 1, Tau

Pre-synaptic Dopaminergic Imaging

Nigral Dopamine loss - Face validity

Reduction in early PD 50% Put

Reduction Put>Caud

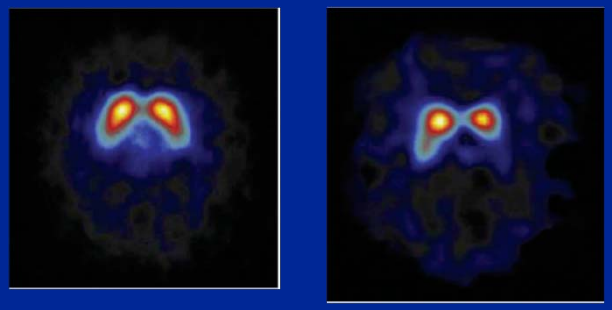
Reduction asymmetric

Correlation with severity (UPDRS)

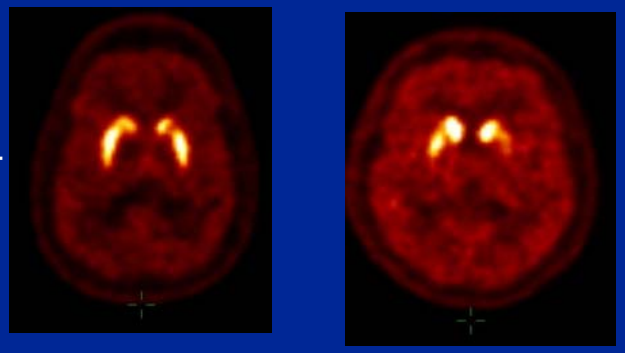
Reduction in Prodromal

Monitor PD progression

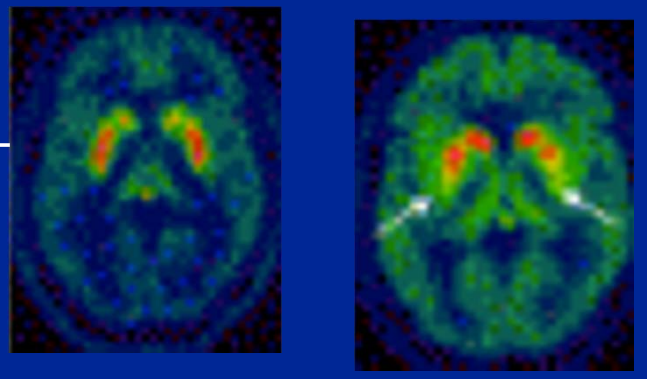
^{123}I ß-CIT-DAT



^{18}F AV-133-VMAT2

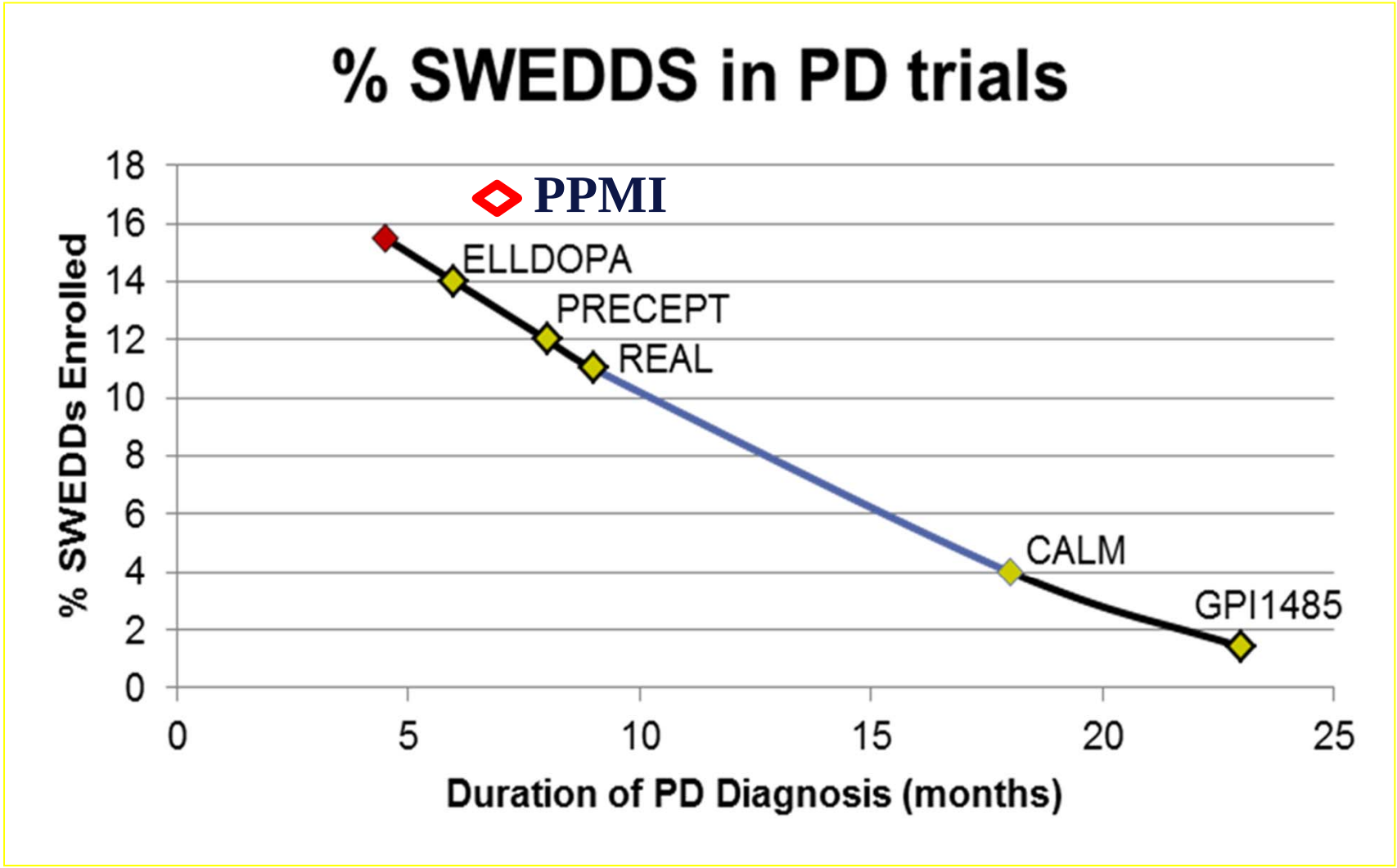


^{18}F-DOPA-AADC

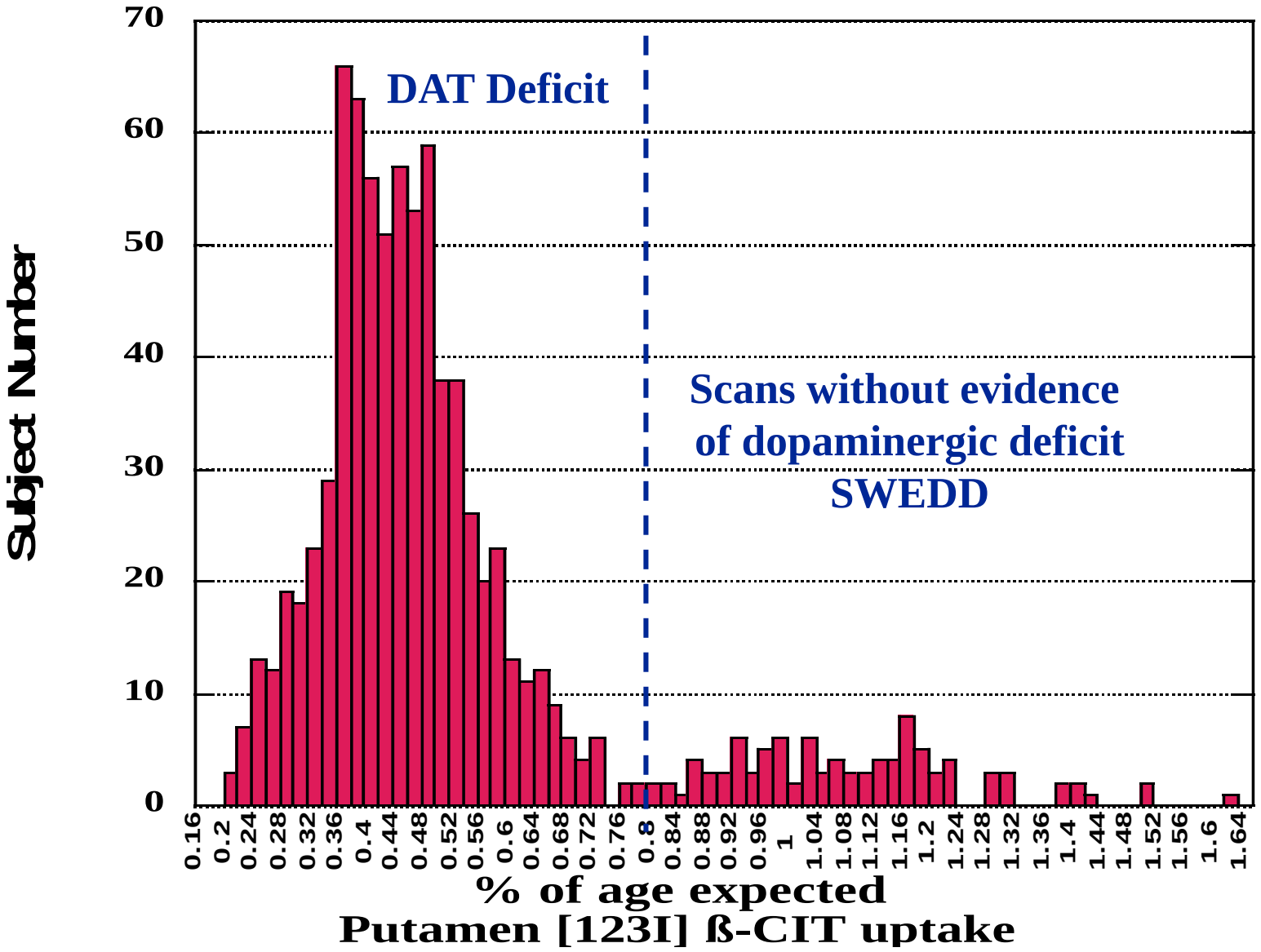


Healthy

┼Parkinson disease


% SWEDDS in PD trials
PPMI
ELLDOPA
PRECEPT
REAL
CALM
GPI1485
% SWEDDs Enrolled
0
2
4
6
8
10
12
14
16
18
0
5
10
15
20
25
Duration of PD Diagnosis (months)

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 $p < 0.01$

PRECEPT Dx at Termination

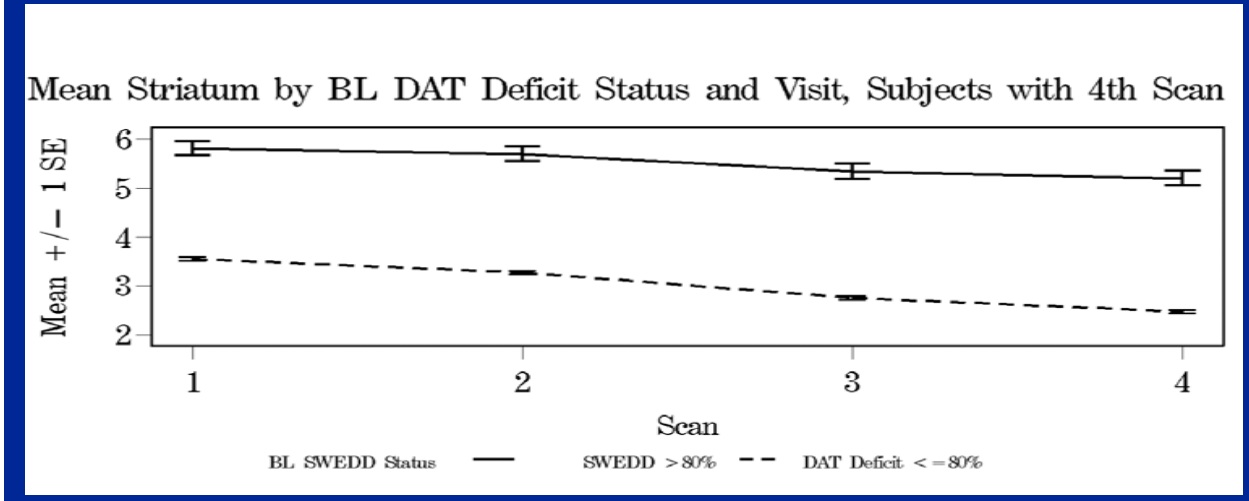
DIAGNOSIS	SWEDD Subjects	DAT DEFICIT Subjects
DAT Deficit Parkinsonism		
Confident PD	40 (44%)	609 (86%)
PD + Another	2 (2%)	11 (2%)
PSP	0 (0%)	5 (1%)
Corticobasal Degeneration	1 (1%)	2 (<1%)
Lewy Body Disease	2 (2%)	14 (2%)
Multiple System Atrophy	4 (4%)	37 (5%)
Hemiparkinson Syndrome	0 (0%)	1 (<1%)
Juvenile Parkinsonism	1 (1%)	2 (<1%)
Total	50 (55%)	681 (96%)

DIAGNOSIS	SWEDD Subjects	DAT DEFICIT Subjects
Pseudo-Parkinsonism		
Essential Tremor	15 (17%)	5 (1%)
Dopa-Responsive Dystonia	1 (1%)	1 (<1%)
Alzheimers	0 (0%)	2 (<1%)
Normal Pressure Hydrocephalus	2 (2%)	0 (0%)
Psychogenic Illness	3 (3%)	1 (<1%)
Vascular Parkinsonism	5 (6%)	13 (2%)
Other Neurological	5 (6%)	3 (<1%)
No PD or Neurological	9 (10%)	1 (<1%)
Total	40 (45%)	26 (4%)

Diagnoses of 707 DAT deficit and 90 SWEDD subjects by PRECEPT site investigators unaware of imaging data at termination (approx 21 month f/u)

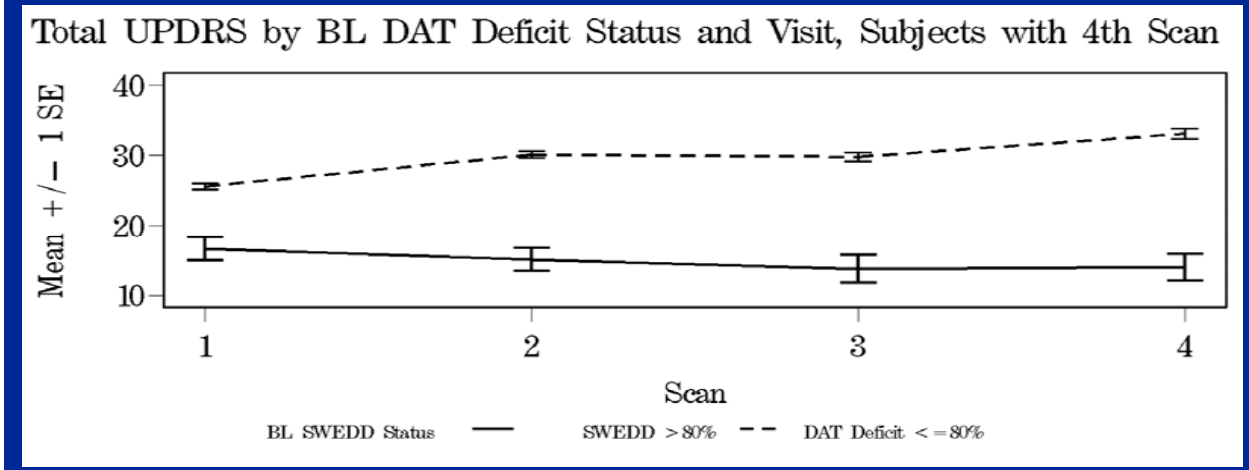
PRECEPT SWEDD 6 yr follow-

PRECEPT study – Follow up at 72 months

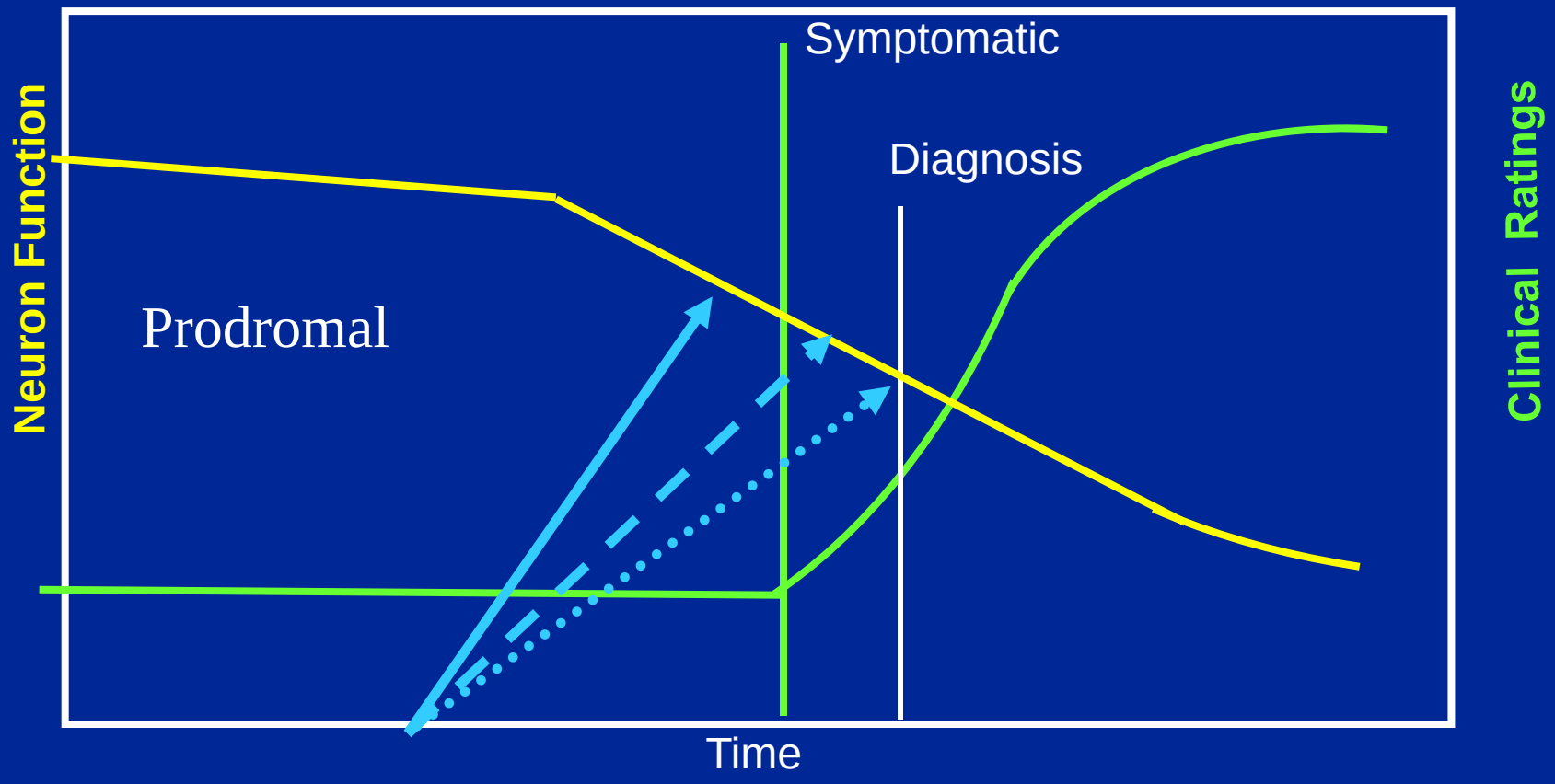


SWEDD N=42,
% Ann Change from Baseline - 1.2%

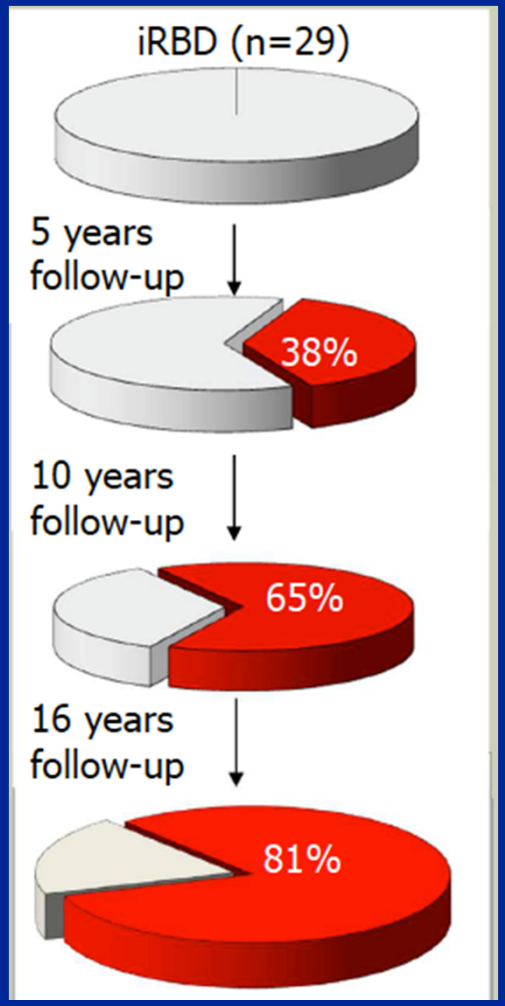
DAT Deficit N=374,
% Ann Change from Baseline - 5.1%



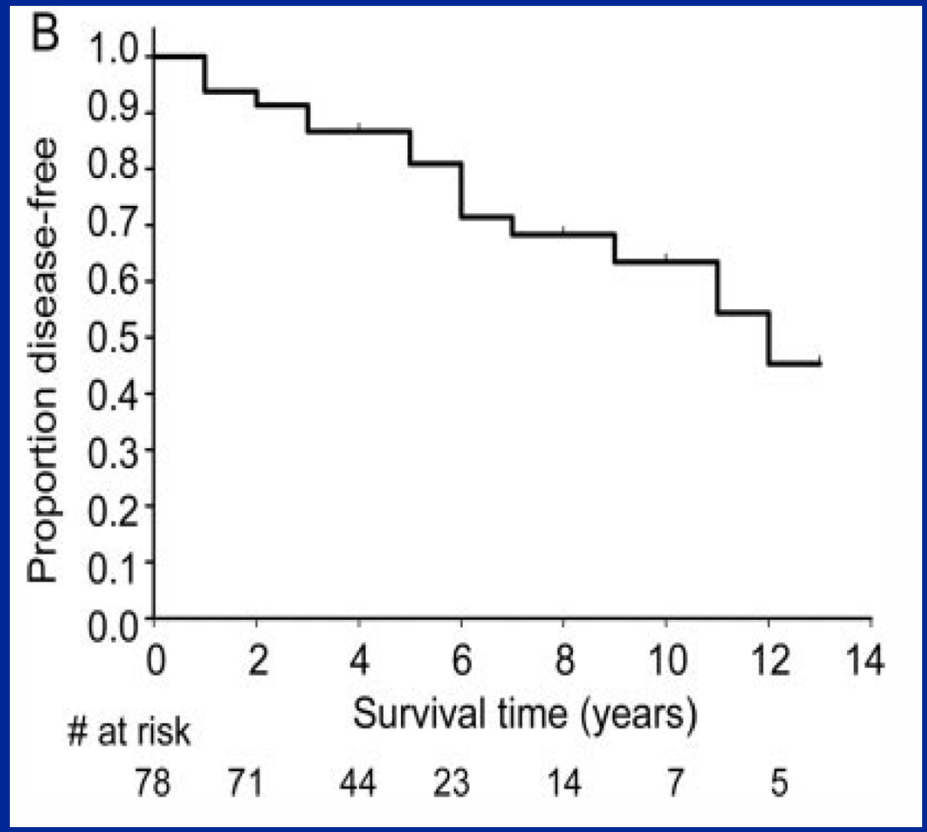
Natural History of PD



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

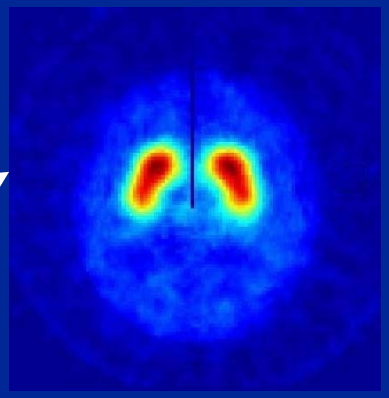
	Participants with IRBD (n=43)	Controls (n=18)	p value
Left putamen:occipital	2·46 (0·30)	2·68 (0·15)	0·007
Right putamen:occipital	2·42 (0·30)	2·62 (0·18)	0·012
Left caudate:occipital	2·98 (0·37)	3·17 (0·28)	0·057
Right caudate:occipital	3·01 (0·38)	3·30 (0·32)	0·008

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.

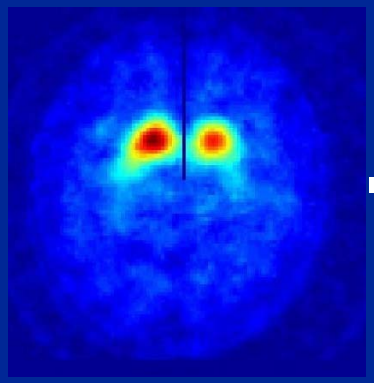
Table 2: **Mean striatal ^{123}I-FP-CIT uptake ratios in participants and controls**

6/17 developed PD or DLB within 2.5 years

PARS: study scheme



PD

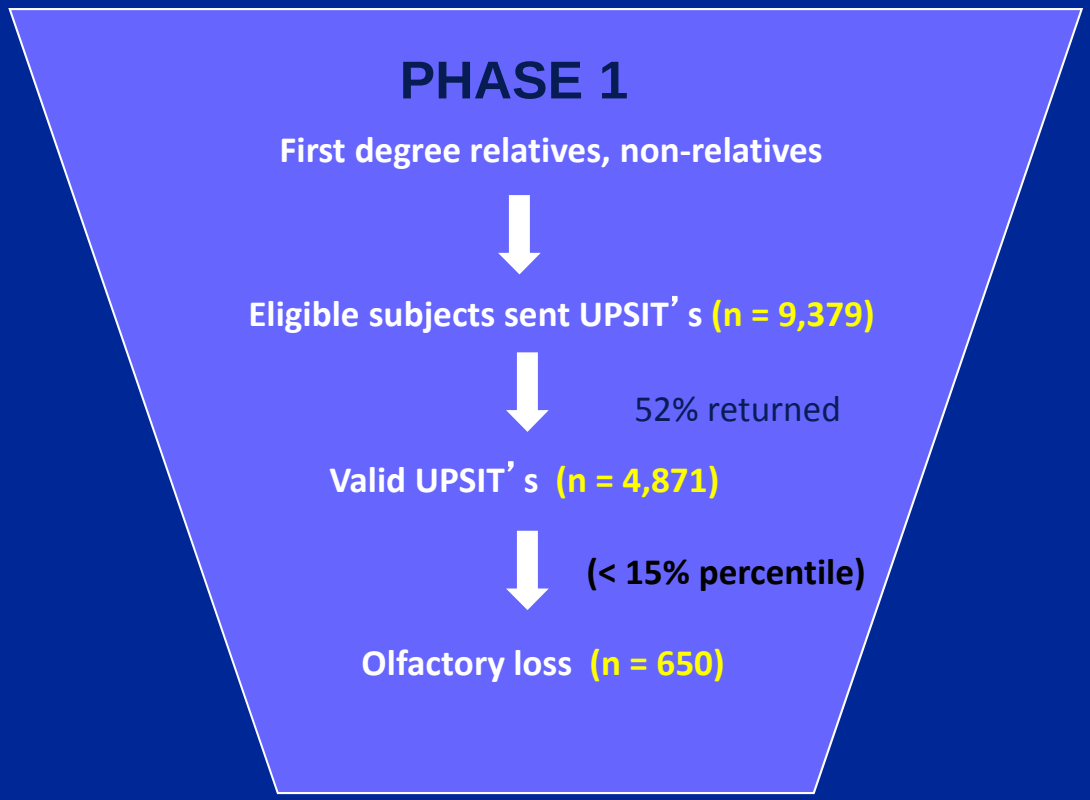


PD

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%)

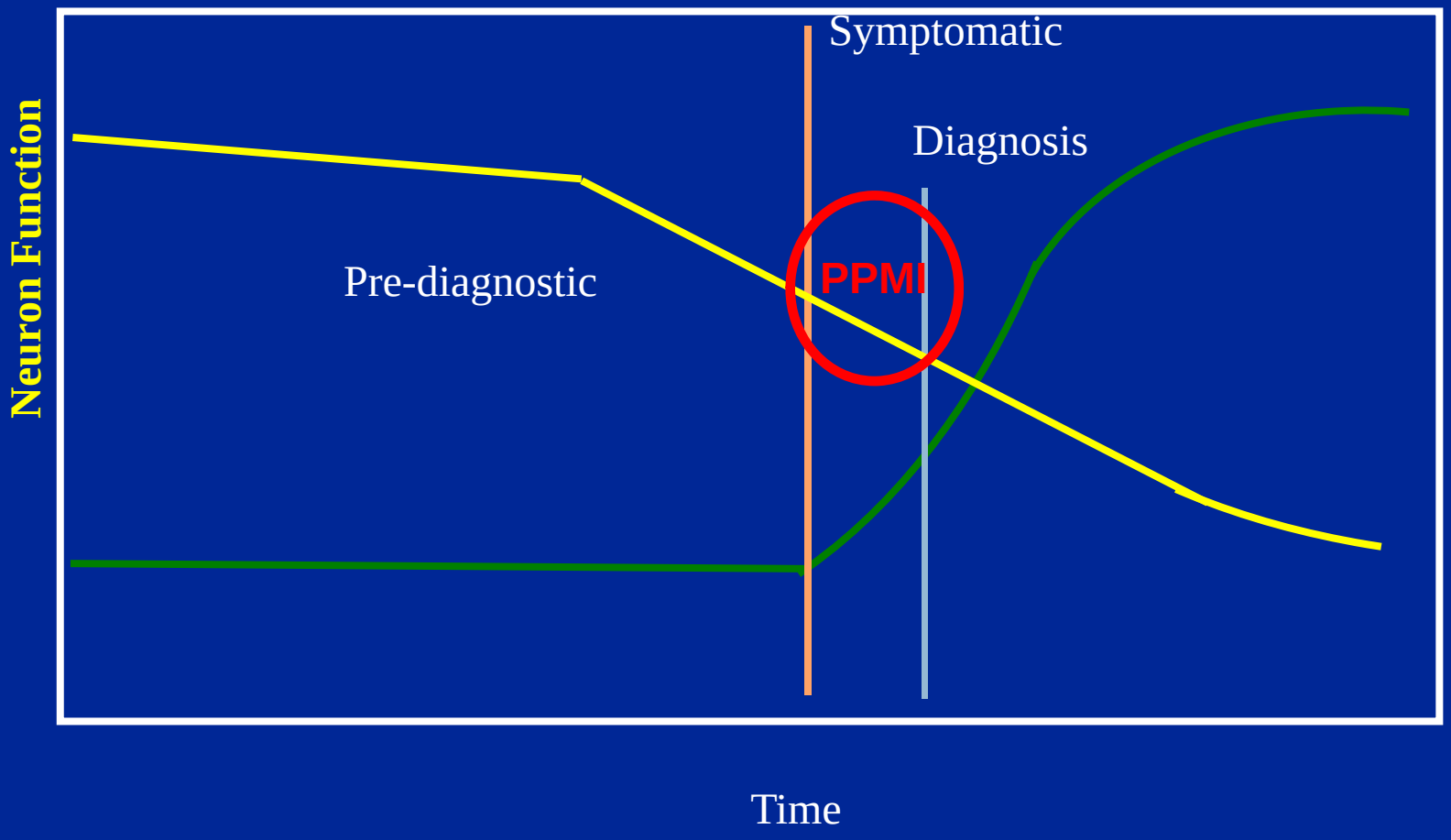
Longitudinal PARS

	DAT deficit (<65% age expected uptake) at BL			DAT deficit (<65% age expected uptake) at any scan		
Best Current Diagnosis	BL (n=23)	Yr 2 (n=23)	Yr 4 (n=23)	BL (n=23)	Yr 2 (n=30)	Yr 4 (n=37)
PD	0	8 (35%)	14 (61%)	0	10 (30%)	17 (46%)
Pre- clinical PD	7 (30%)	7 (30%)	2 (9%)	7 (30%)	8 (27%)	7 (9%)
No neuro dx	10 (43%)	6 (26%)	5 (22%)	10 (43%)	10 (30%)	13 (35%)
other	6 (26%)	2 (9%)	2 (9%)	6 (26%)	2 (7%)	0 (0%)

Phenoconversion rate is 61% at 4 years for subjects with a severe DAT deficit (<65% of age expected DAT uptake) at baseline.

Progression of DAT deficit among hyposmics increase nuber of subjects with (<65% of age expected DAT uptake)

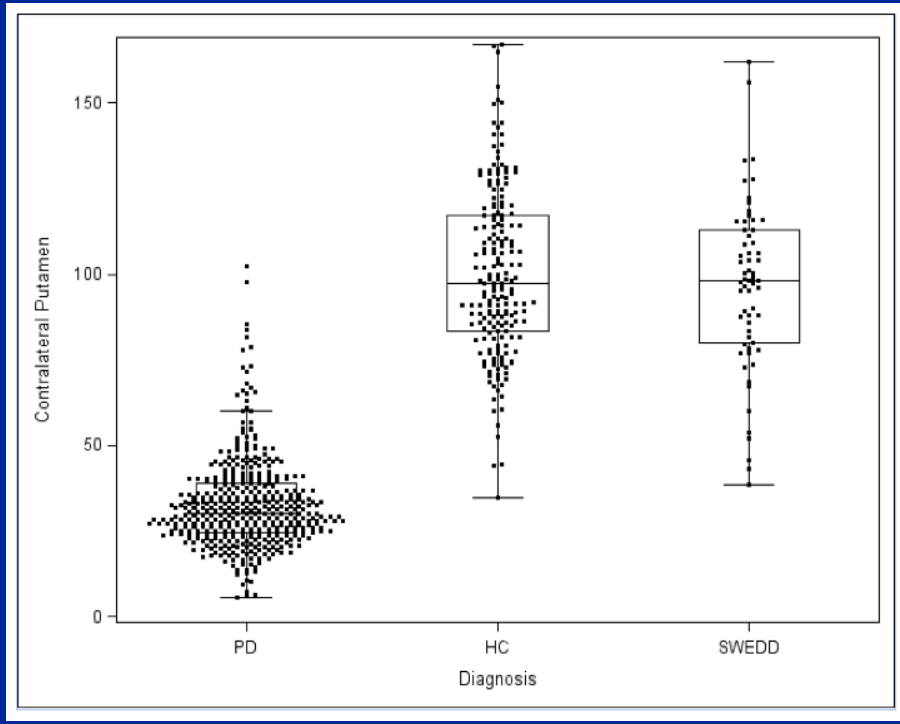
Natural History of Parkinson disease

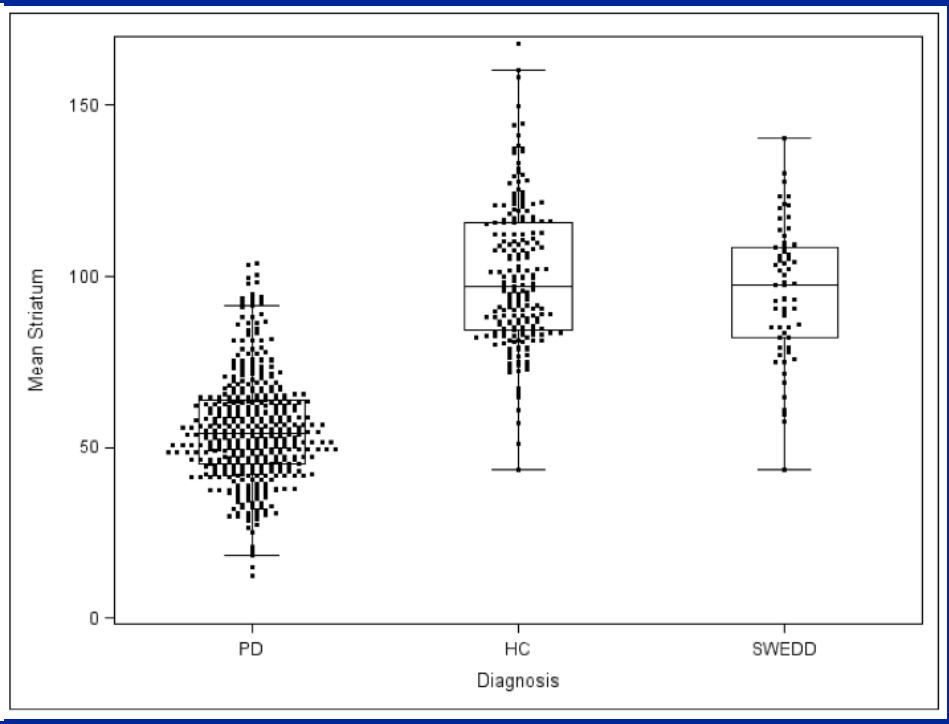


PPMI Study Details: Synopsis

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**

PPMI Baseline DAT SBR



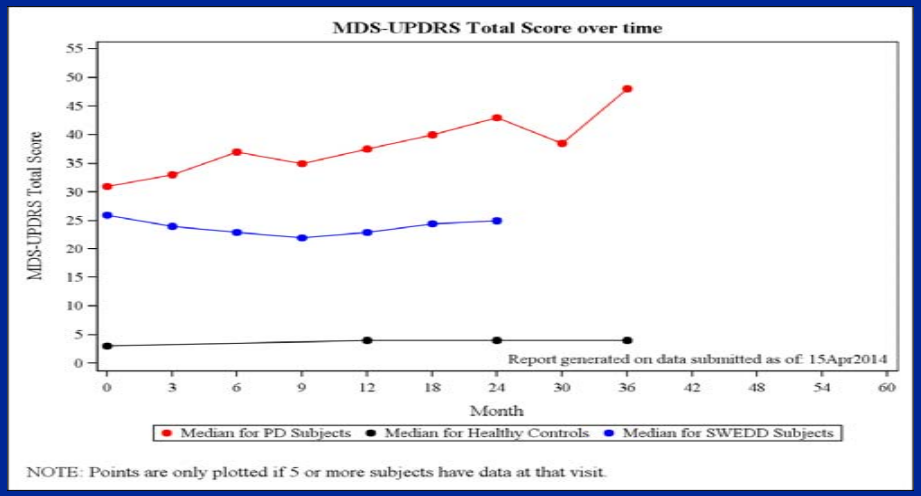


Contralateral Putamen

Mean Striatum

Comparison of PPMI PD vs SWEDD subjects

- Demographics - PD similar to SWEDD
  - Age, gender, fam hx, disease duration
- Motor assessment - PD > SWEDD at Baseline
  - UPDRS – No progression among SWEDD



- Non-Motor assessment – SWEDD > PD
  - GDS, STAI, Scopa Aut
- Biomarker measure - SWEDD similar to HS
  - Olfaction, CSF synuclein

Conclusion

- Subjects without evidence of DAT deficit do not demonstrate clinical or imaging progression.
- Subjects at risk for PD with DAT deficit have a high incidence of phenoconversion to motor PD.
- PPMI provides an opportunity to examine objective biomarkers in PD and SWEDD subjects and to further assess biomarker progression in prodromal subjects who have DAT deficit.