PPMI Paving the Way for Defining Prodromal PD

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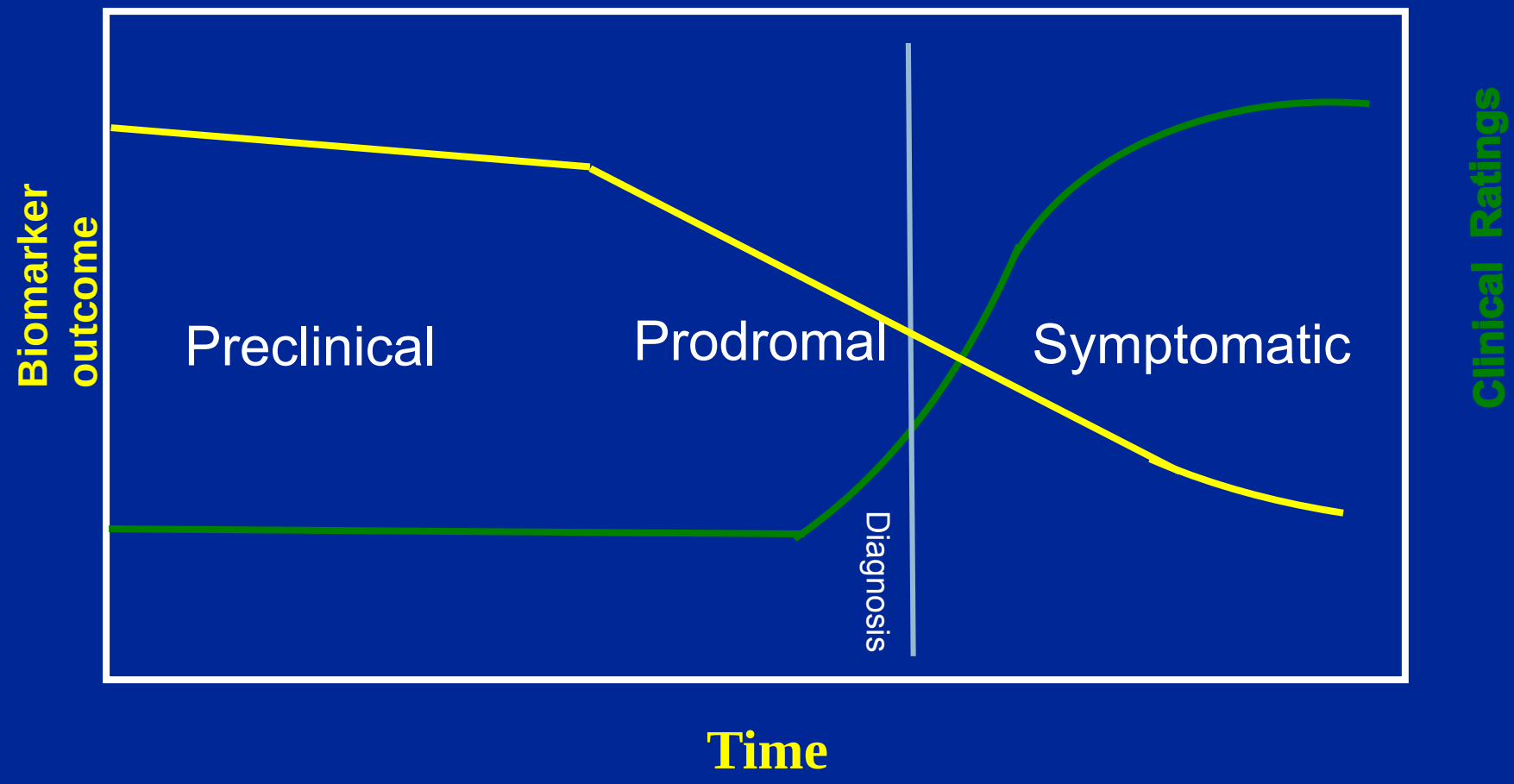
Disclosure

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

  Pfizer, Sanofi, Roche, LTI

Natural History of Neurodegenerative Disorders



Why – Prodromal/Preclinical

- Prevent Disease onset and/or progression
- Elucidate/Test therapeutic targets
  - Inflammation
  - Synuclein/GBA/LRRK2
- Enable Precision/Personalized medicine
  - Genetics/biomarkers to establish disease subsets and targeted therapies
- Reduce long-term care costs

Parkinson Progression Marker Initiative

WWW.ppmi-info.org

PPMI Biomarker Infrastructure

Specific Data Set

- Appropriate population (early stage PD and controls, prodromal, genetic PD subjects)
- 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

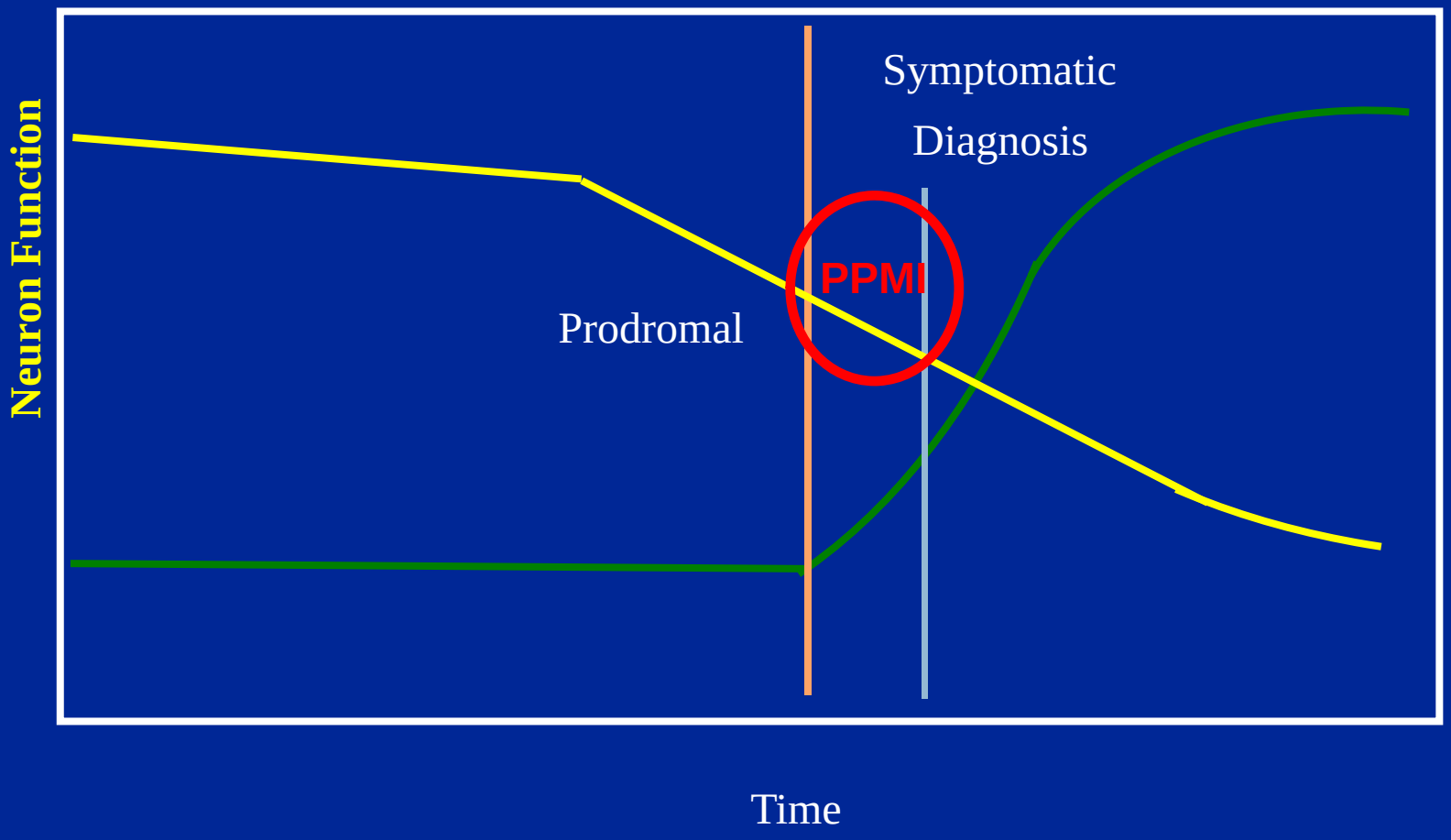
Access/Sharing

- Data available to research community → data mining, hypothesis generation & testing
- Samples available for studies
- www.ppmi-info.org

PPMI Study Details: Synopsis

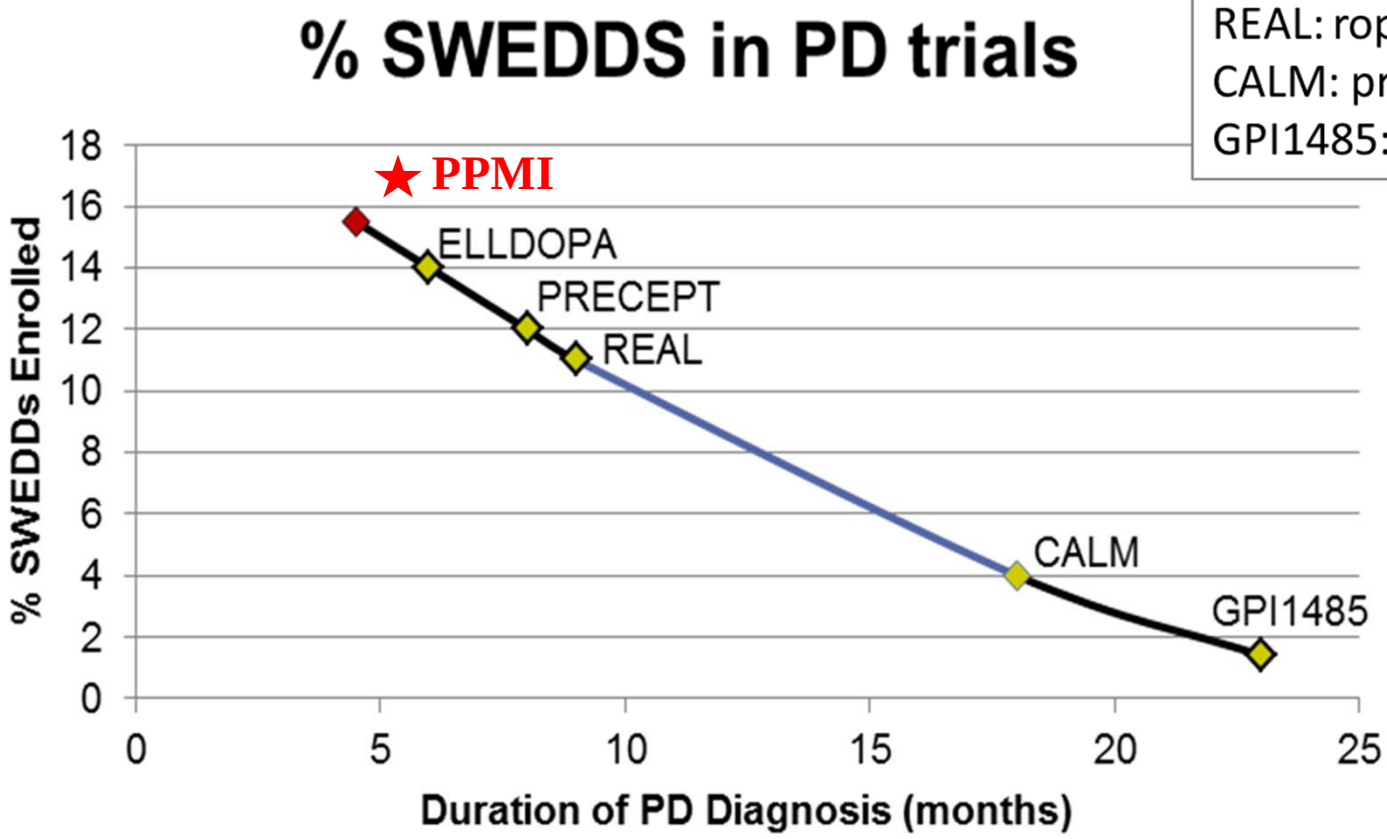
Study population	▪ 423 de novo PD subjects (newly diagnosed and unmedicated) ▪ 96 age- and gender-matched healthy controls ▪ 64 SWEDD ▪ 67 Prodromal - Olfactory/RBD ▪ *250 LRRK2 - PD manifest and non-manifesting family members* ▪ *250 GBA- PD manifest and non-manifesting family members* ▪ *100 SNCA - PD manifest and non-manifesting family members* ▪ *Subjects will be followed through 2018*
Assessments/ Clinical data collection	▪ Motor assessments ▪ Neurobehavioral/cognitive testing ▪ Autonomic, Olfaction, Sleep ▪ DaTSCAN, AV133, Amyloid, DTI/RS MRI
Biologic collection/	▪ DNA, RNA, IPSC ▪ 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	▪ > 420,000 Data downloads ▪ > 100 Sample requests via BRC ▪ Ancillary study development

Natural History of Parkinson disease

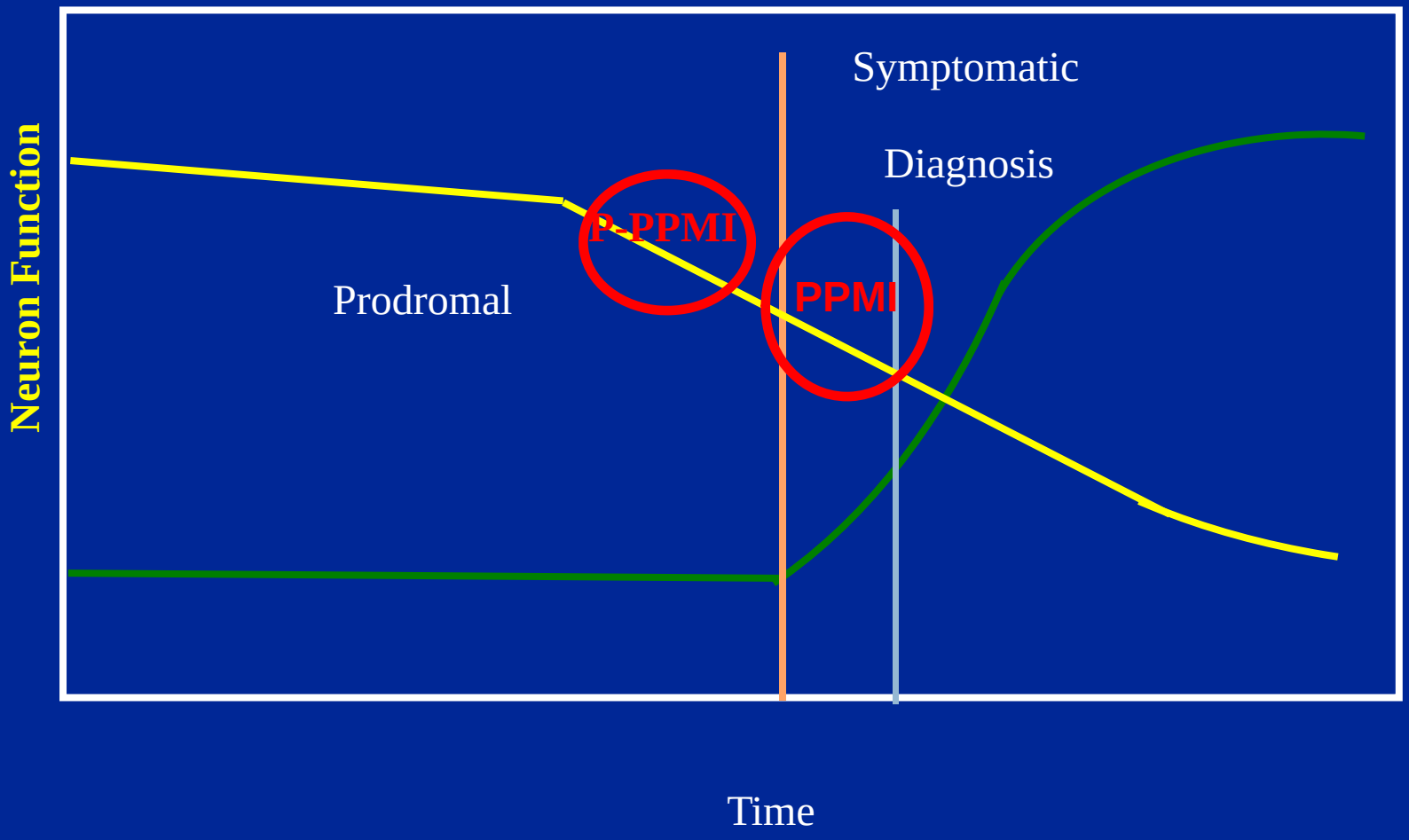


Rate of SWEDD is higher in earlier Stages of PD

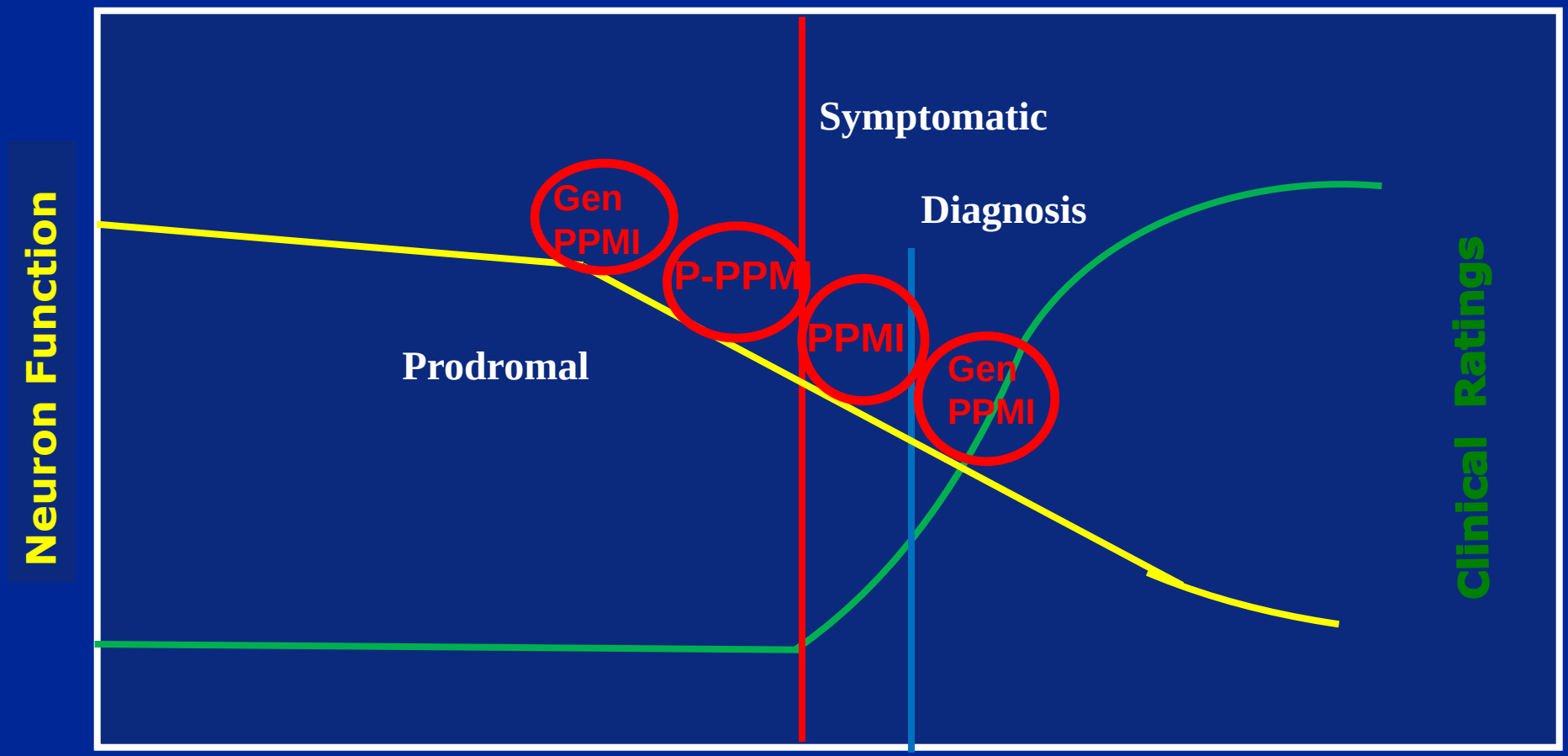
ELLDOPA: L-Dopa
PRECEPT: MLK Inhibitor CEP1347
REAL: ropinirole
CALM: pramipexole
GPI1485: immunophilin



Natural History of Parkinson disease



Natural history Parkinson's disease



Comprehensive Data and Biomarker candidates being collected and evaluated

CLINICAL MARKERS

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

IMAGING - PHENOTOMICS

- SPECT/PET- Dopamine- DAT, VMAT2
- Amyloid,
- MRI –DTI/RS, volumetrics

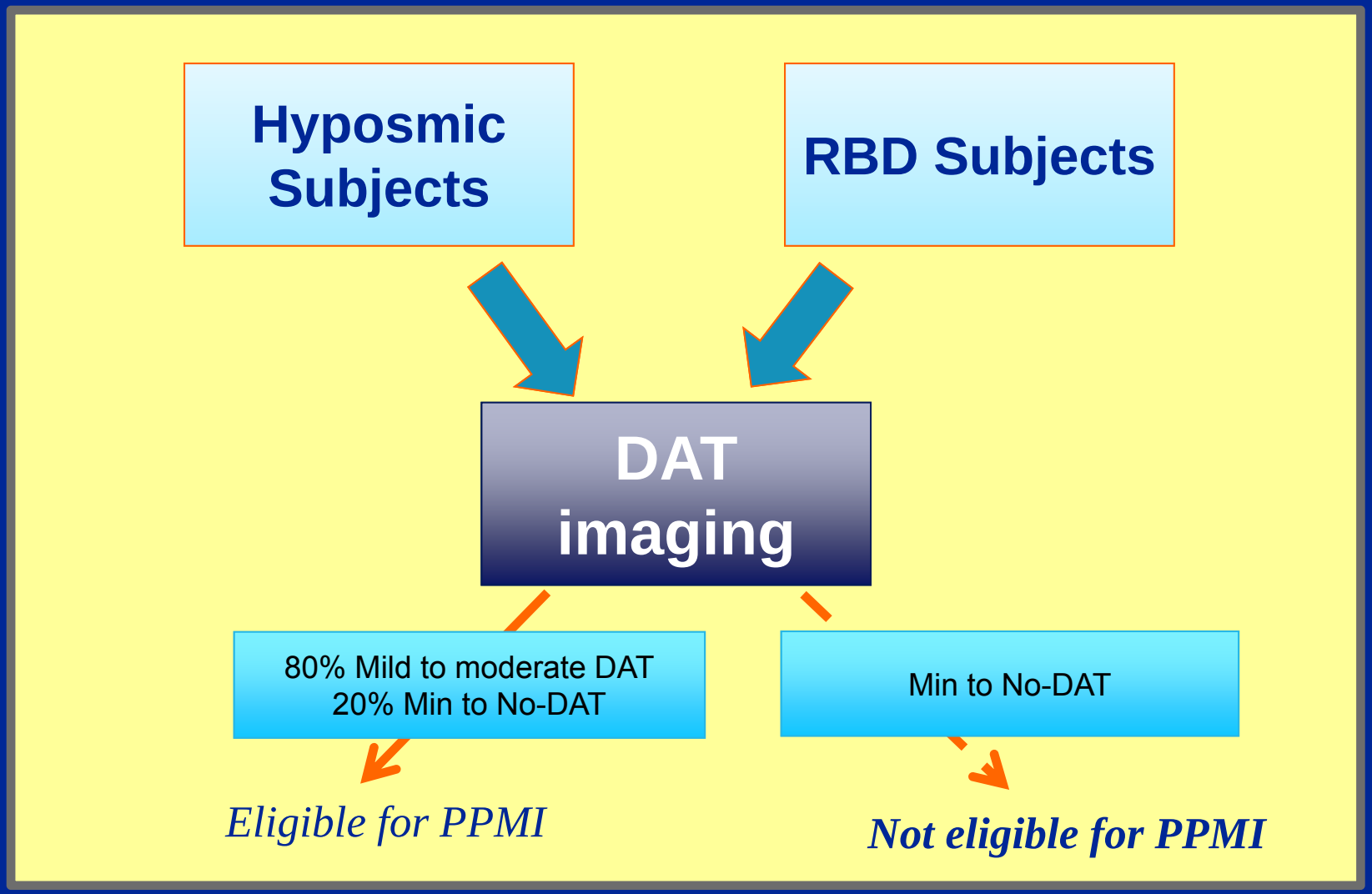
BIOLOGICS

- Blood, CSF, Urine
- Alpha-synuclein, Urate, Tau, Beta-Amyloid, EGF1, ApoA
- RNA Profiling
- IPS cells

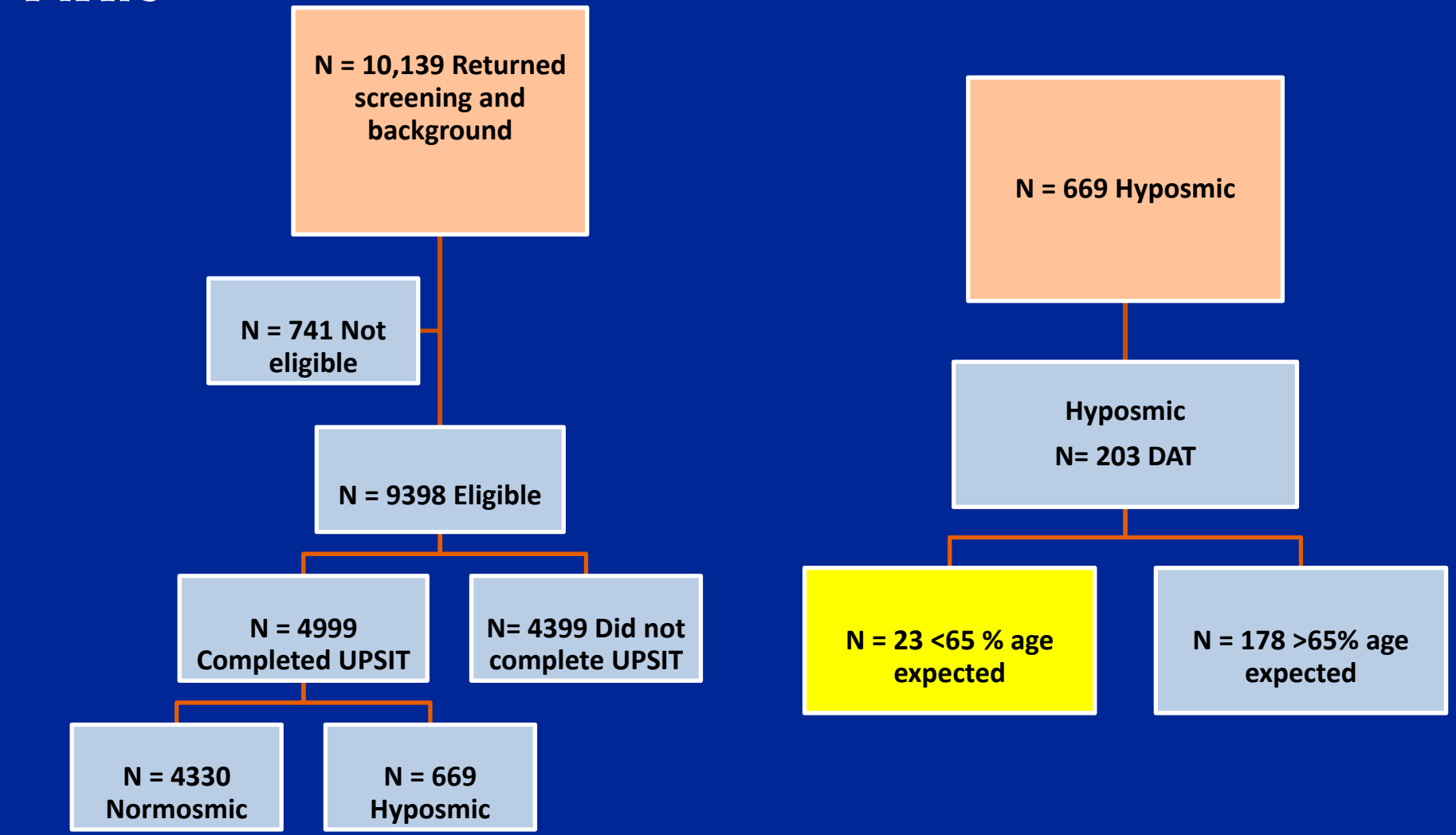
GENETICS

- Synuclein, LRRK2, Parkin, DJ-1, Pink 1, GBA, Tau
- Exome Sequencing

Eligibility for P-PPMI



Ascertainment of PARS Cohort

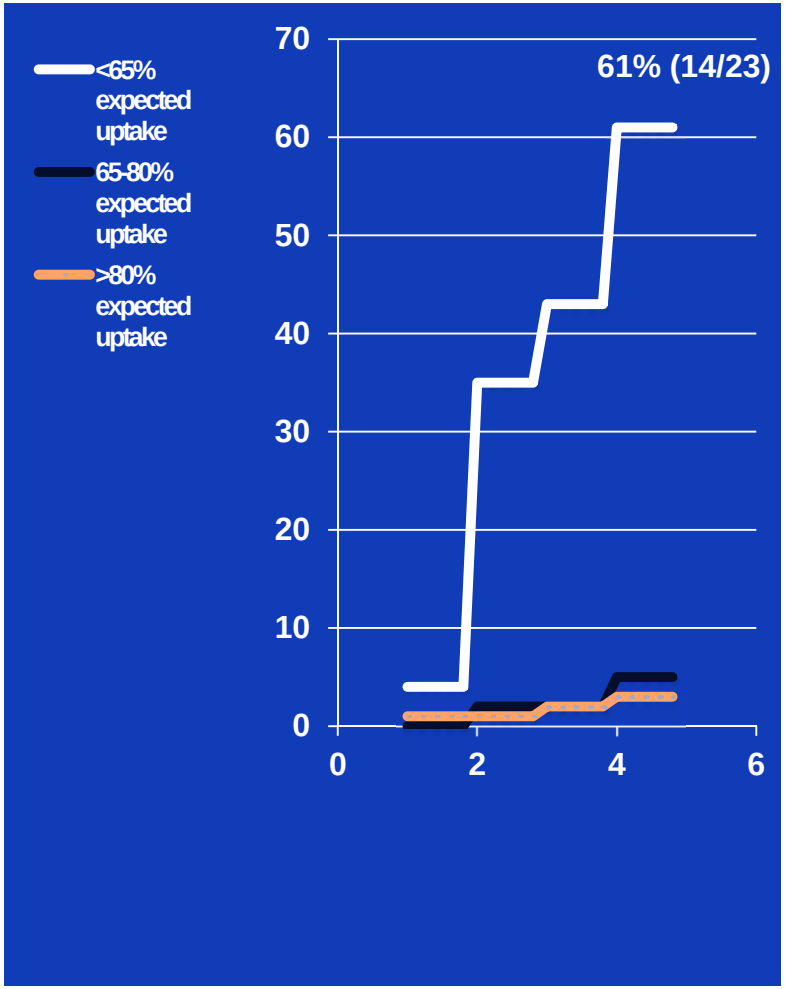


PARS 4 yr follow-up

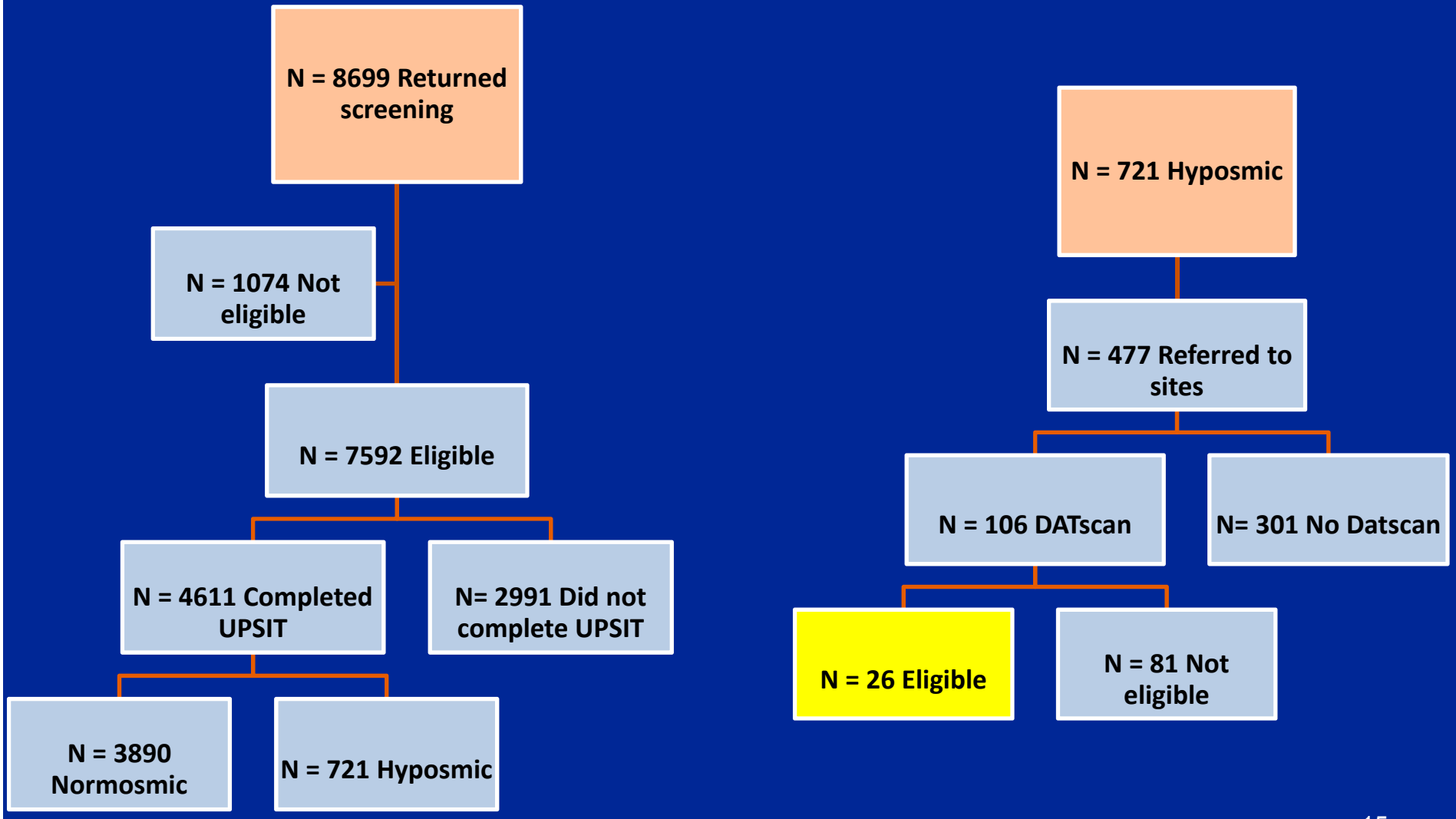
Baseline

	Normosmics	Hyposmics	P-Value
Age expected uptake in lowest putamen	N = 100	N = 203	
No DAT deficit ≥80%	92 (92%)	146 (72%)	
65 – 80%	7 (7%)	34 (17%)	
<65%	1 (1%)	23 (11%)	<0.0001
<80%	8 (8%)	57 (28%)	<0.0001

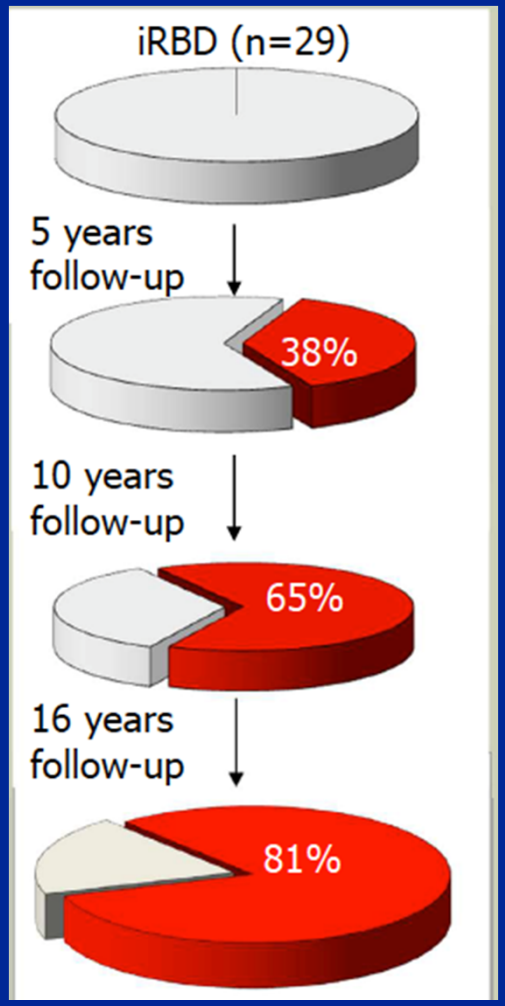
4 yr follow-up



Ascertainment of PPMI Olfactory Cohort



RBD and Risk of PD



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

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,, for the Sleep Innsbruck Barcelona (SINBAR) group

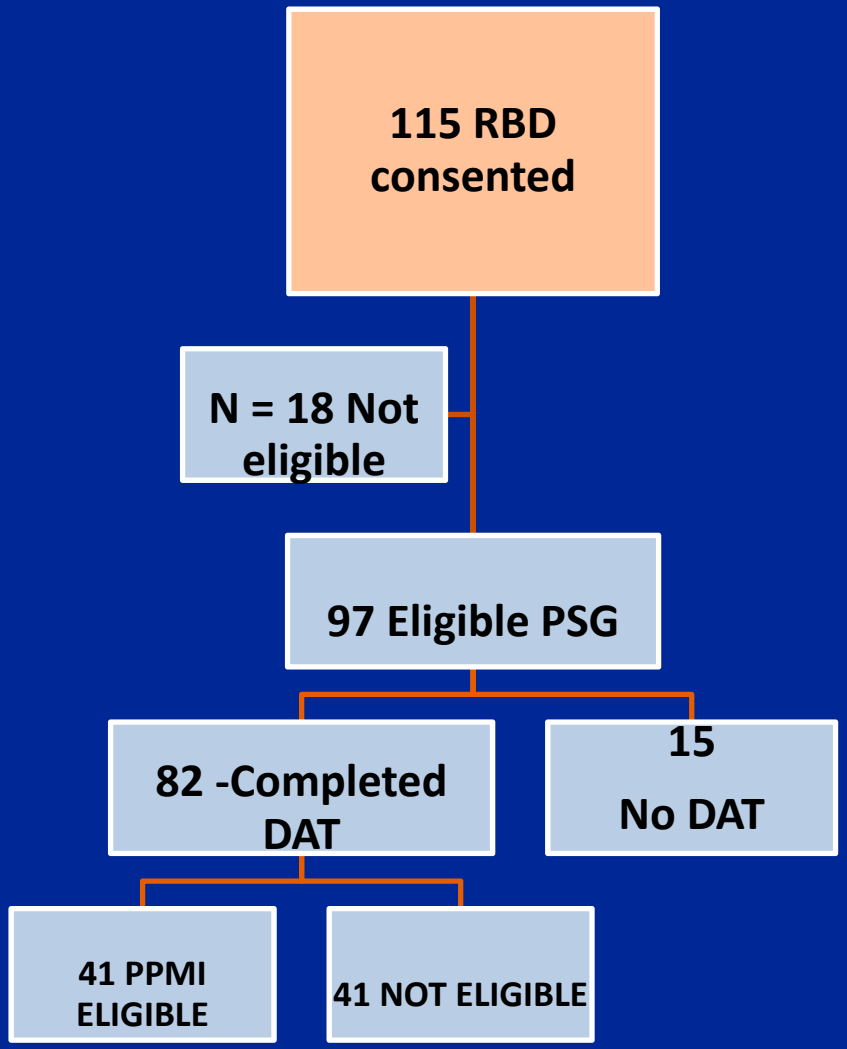
Lancet, **2010**

17 of 43 RBD subjects demonstrate reduced DAT uptake

Putamen > caudate reduction

6/17 developed PD or DLB within 2.5 years

Ascertainment of PPMI-RBD Cohort



PPMI-LRRK2/GBA/SNCA cohort

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

- **Enroll 300 LRRK/GBA/SNCA + PD and 300 LRRK/GBA/SNCA + 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**

LRRK2/GBA/SNCA Enrollment (Aug 2015)

- **PD Subjects enrolled cohort**
  - **LRRK2 83**
  - **SNCA 10**
- **Unaffected Subjects enrolled cohort**
  - **LRRK2 63**
  - **SNCA 3**

- **PD Subjects tested/pos at sites**
  - **LRRK2 708/220**
  - **SNCA 23/15**
  - **GBA 106/8**
- **Unaffected Subjects tested/pos at sites**
  - **LRRK2 359/162**
  - **SNCA 11/8**
  - **GBA 22/6**

WRI	N	%	% M	% F
Consented through WRI site, no previous testing	**2471**	100%	37%	63%
Qualified and confirmed through WRI	1664	67%	40%	60%
Did not qualify through WRI	561	23%	28%	72%
Testing for LRRK2 G2019S	**1087**	100%	45%	55%
LRRK2-	973	90%	46%	54%
LRRK2+	114	101%	38%	62%
Tested with PD	**480**	100%	59%	41%
LRRK2-	426	89%	61%	39%
LRRK2+	54	11%	46%	54%
Tested without PD	**607**	100%	33%	67%
LRRK2-	547	90%	34%	66%
LRRK2+	60	10%	30%	70%

PPMI Prodromal/Genetic Baseline Characteristics

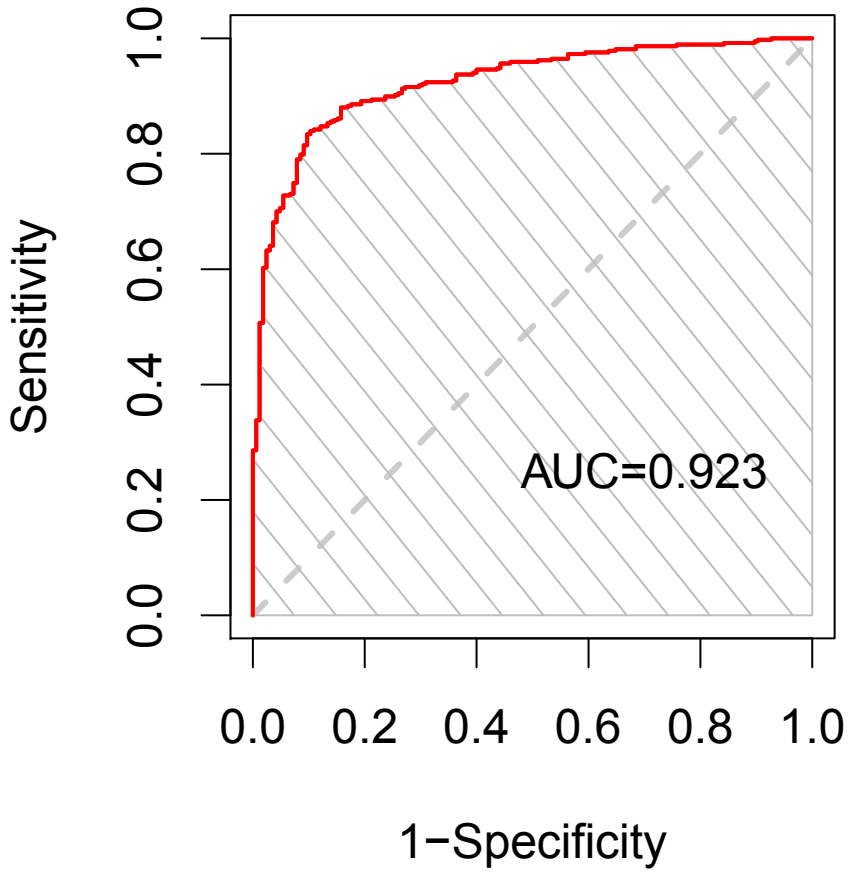
Table 3a. PPMI Demographic Characteristics by Group: Genetic and Prodromal Cohorts

Variable	Genetic Cohort		Prodromal Cohort	
	PD Subjects (N = 75)	Unaffected Subjects (N = 52)	Hyposmia Subjects (N = 26)	RBD Subjects (N = 38)
Gender				
Male	26 (35%)	21 (40%)	18 (69%)	32 (84%)
Female	49 (65%)	31 (60%)	8 (31%)	6 (16%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Age				
<56 Years	27 (36%)	14 (27%)	0 (0%)	0 (0%)
56-65 Years	20 (27%)	21 (40%)	9 (35%)	5 (13%)
>65 Years	28 (37%)	17 (33%)	17 (65%)	33 (87%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Age				
Mean (SD)	60.6 (11.1)	61.2 (8.1)	68.1 (6.2)	69.8 (5.4)
(Min, Max)	(32, 85)	(44, 81)	(61, 83)	(59, 82)
Missing	0	0	0	0
Education				
<13 Years	28 (37%)	21 (40%)	3 (12%)	14 (37%)
13-23 Years	45 (60%)	29 (56%)	23 (88%)	24 (63%)
>23 Years	1 (1%)	1 (2%)	0 (0%)	0 (0%)
Missing	1 (1%)	1 (2%)	0 (0%)	0 (0%)
Ethnicity				
Hispanic/Latino	27 (36%)	5 (10%)	2 (8%)	18 (47%)
Not Hispanic/Latino	48 (64%)	47 (90%)	24 (92%)	20 (53%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Race				
White	62 (83%)	49 (94%)	23 (88%)	34 (89%)
Black/African-American	1 (1%)	0 (0%)	0 (0%)	2 (5%)
Asian	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	12 (16%)	2 (4%)	1 (4%)	0 (0%)
Missing	0 (0%)	1 (2%)	2 (8%)	2 (5%)
MDS-UPDRS Part III				
Mean (SD)	22.8 (12.9)	2.6 (3.9)	2.9 (3.6)	4.6 (3.8)
(Min, Max)	(4, 71)	(0, 13)	(0, 13)	(0, 15)
Missing	8	4	0	1
MOCA Total Score				
Mean (SD)	25.8 (3.5)	26.3 (2.7)	27.3 (1.7)	25.4 (4.1)
(Min, Max)	(17, 30)	(19, 30)	(23, 30)	(11, 30)
Missing	5	2	0	0
GDS Total Score				
Mean (SD)	3.8 (3.3)	1.9 (2.2)	1.5 (1.5)	2.8 (2.6)
(Min, Max)	(0, 13)	(0, 8)	(0, 6)	(0, 10)
Missing	7	4	0	0
SCOPA-AUT Total Score				
Mean (SD)	14.2 (9.2)	9.0 (6.8)	9.2 (5.0)	14.9 (8.3)
(Min, Max)	(0, 40)	(1, 28)	(1, 20)	(4, 38)
Missing	5	6	0	1

Report Generated on Data Submitted as of: 01Apr2015.

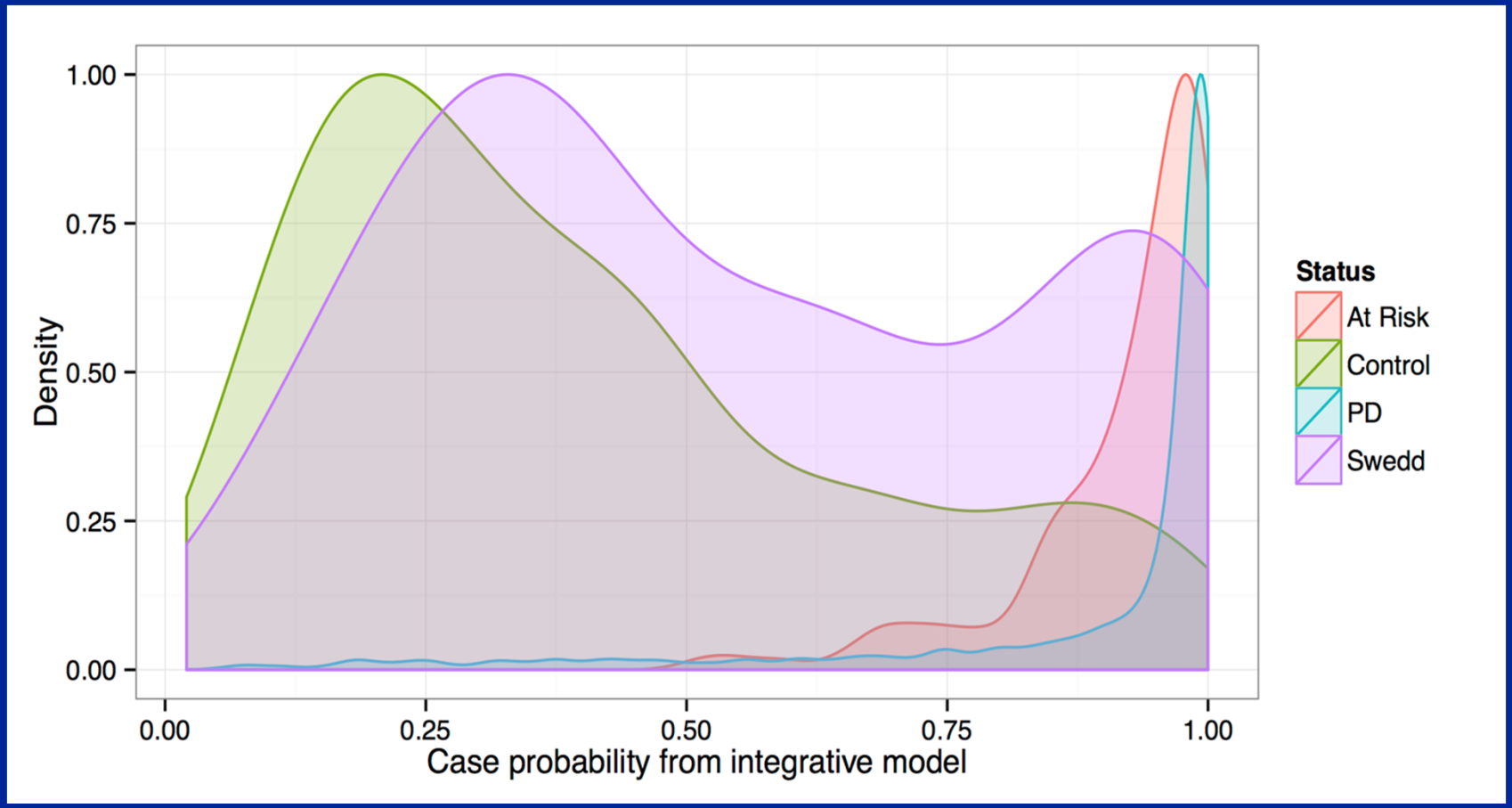
Risk Profiling- PPMI

- **Risk profiling**
  - **28 loci**
  - **p.G2019S**
  - **p.N370S**
  - **Age**
  - **Sex**
  - **Family H_X**
  - **hyposmia**



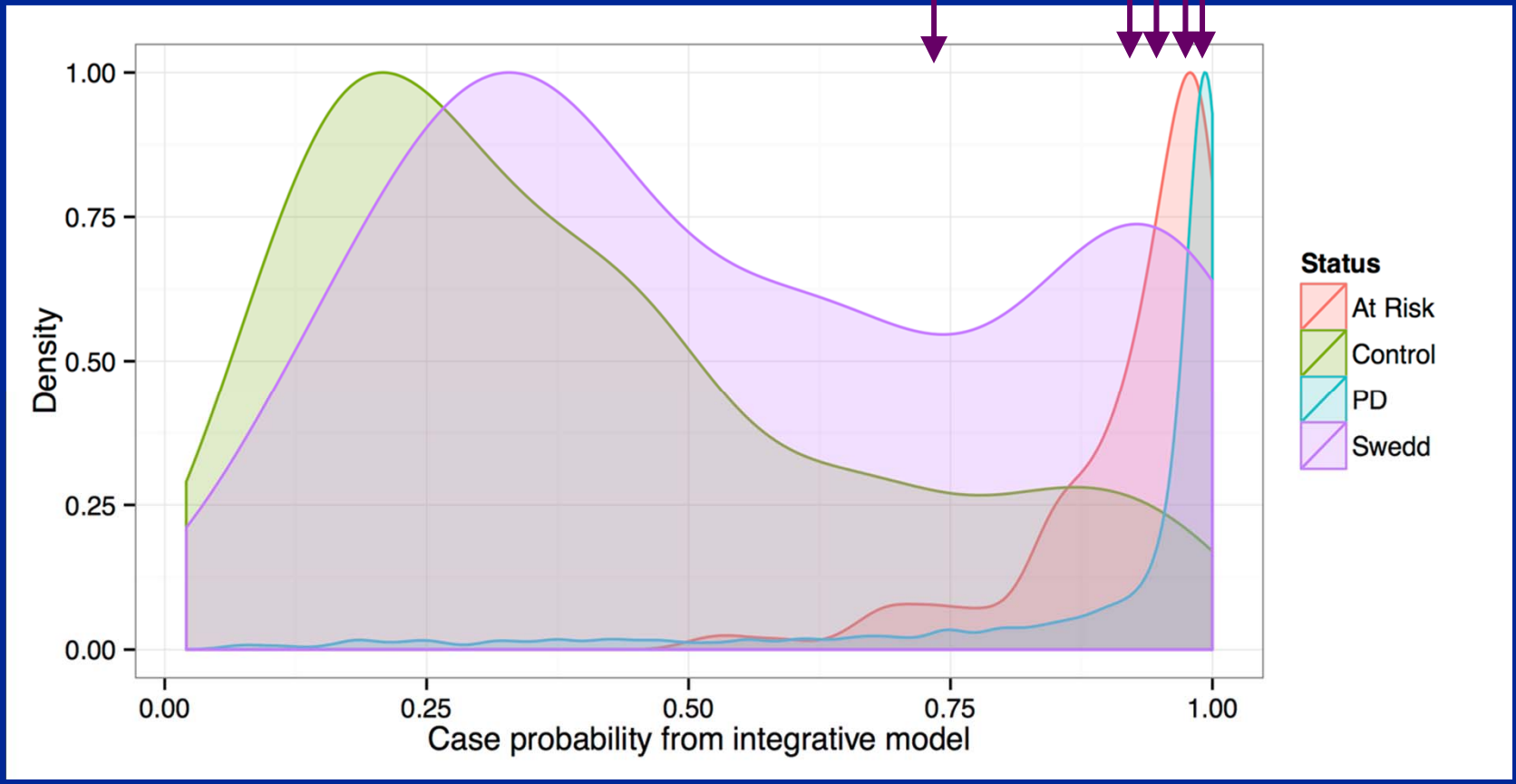
Nalls et al., Lancet Neurol. 2015

Risk Profiling –
Case probability from 5 cohorts

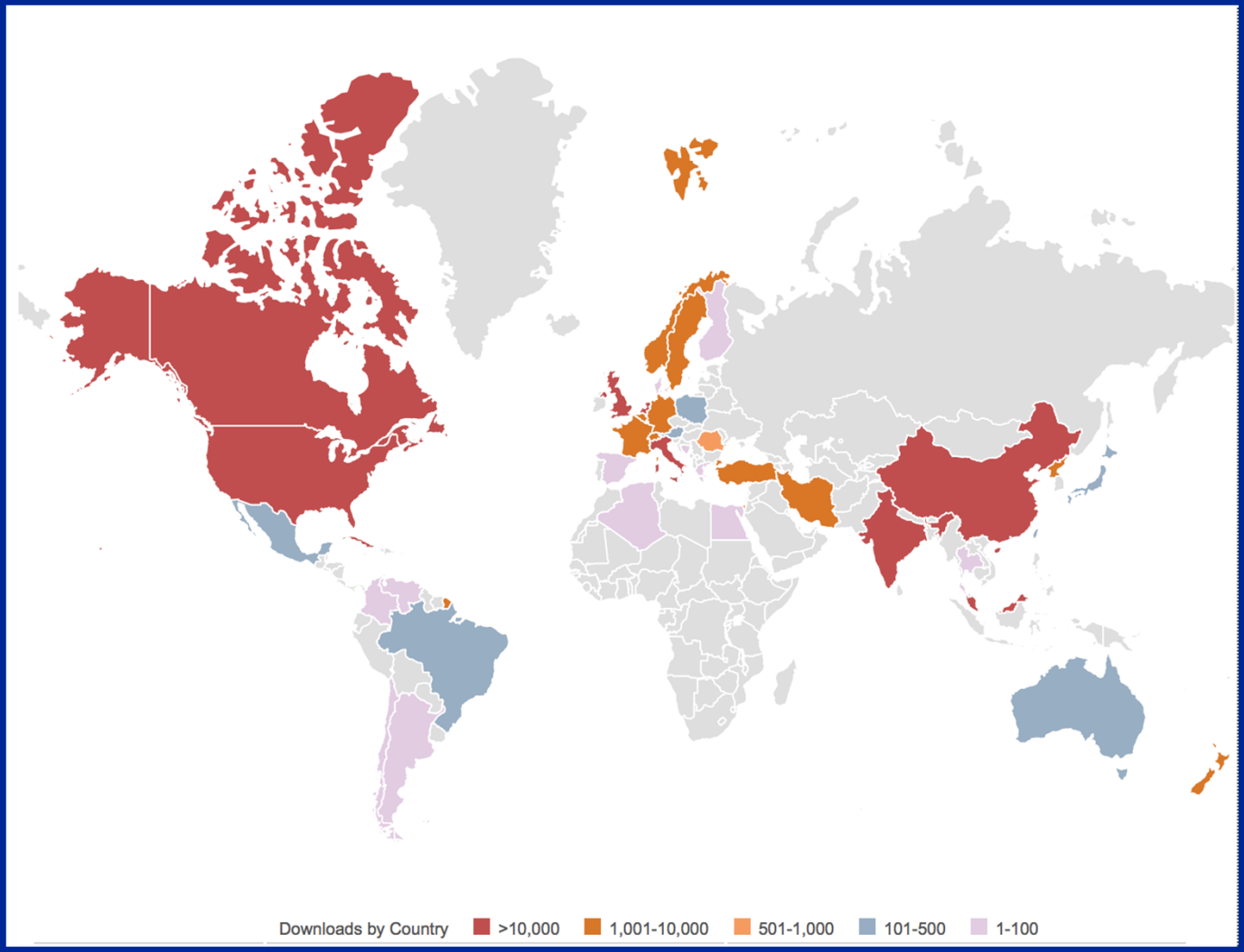


Risk Profiling –
Case probability from 5 cohorts

SWEDDS WITH ABNORMAL SCAN AT FU



PPMI Data Sharing



>450,000 Data downloads worldwide

PPMI DATA SHARING

- Papers (>50) and Presentations
- Processes and Procedures
- Data to support sample size estimates for clinical trials
- Data to establish clinical trial cohorts for prodromal/genetic studies

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 California at San Francisco (San Francisco, 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 funding partners

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