

# **Motor symptoms in prodromal Parkinson's disease**

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Tel Aviv Medical Center  
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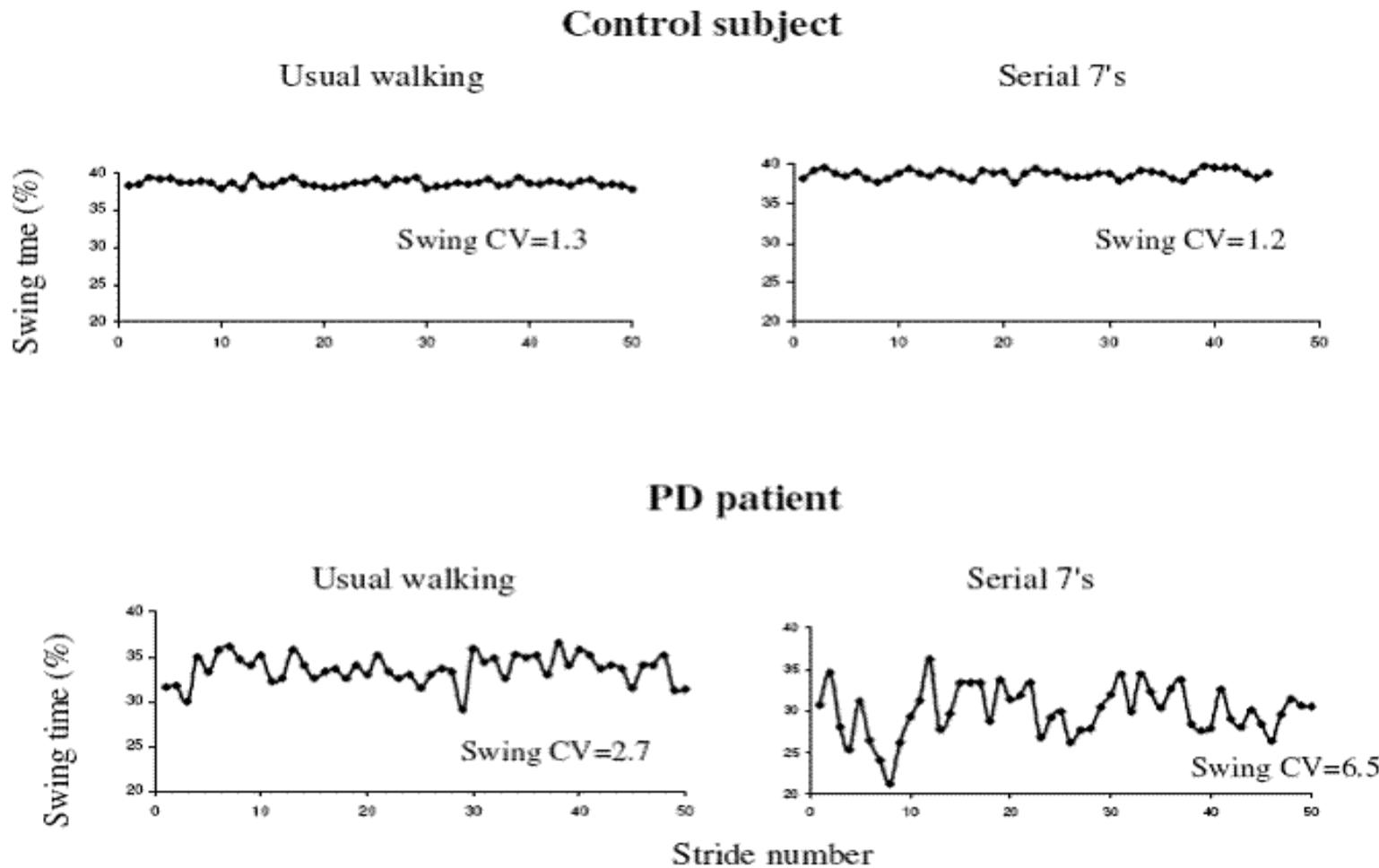
Prodromal ≠ pre-motor

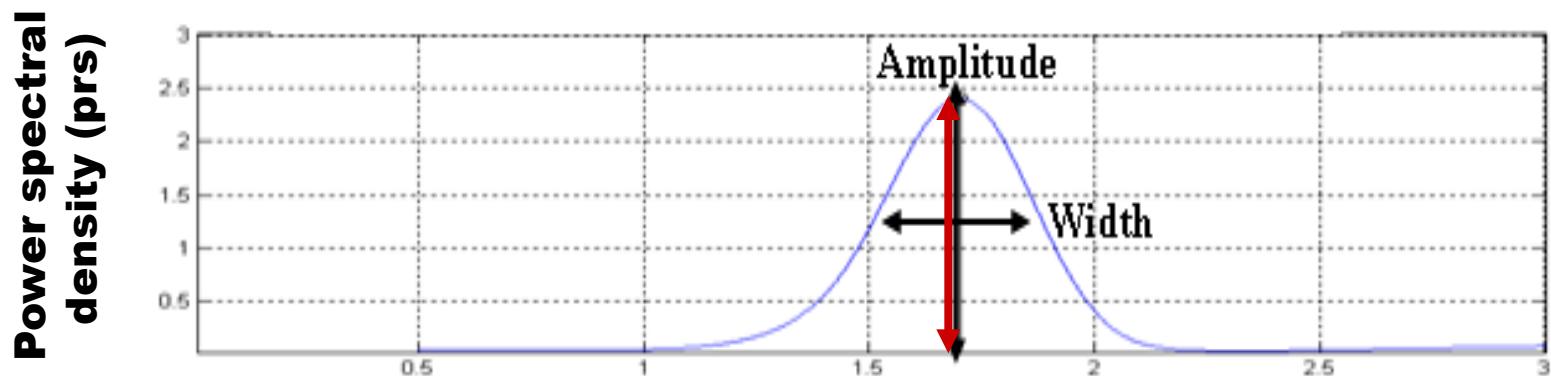
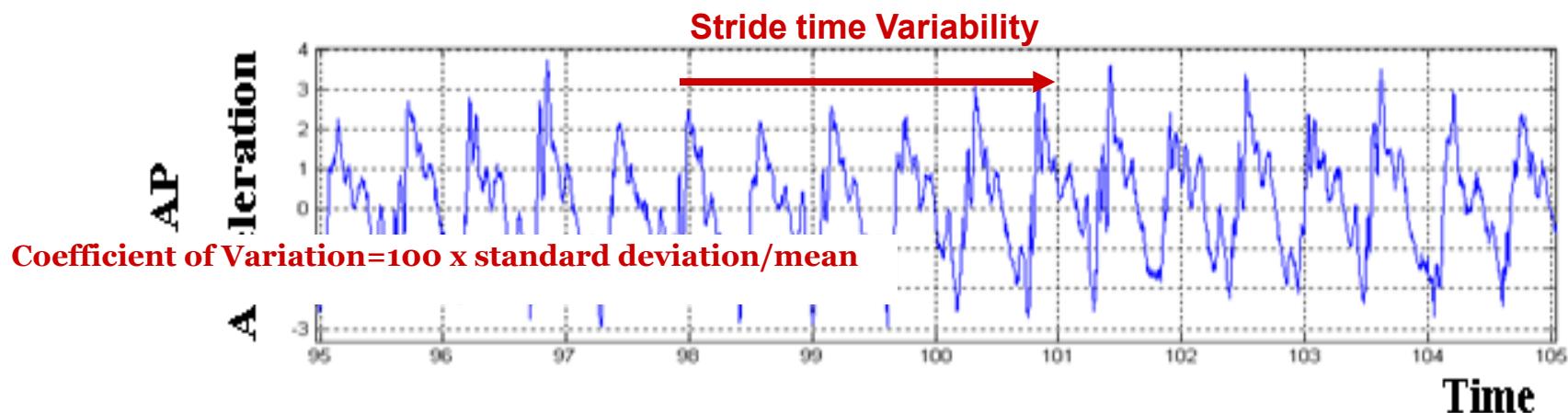
*Pre-diagnosis*

# Rationale

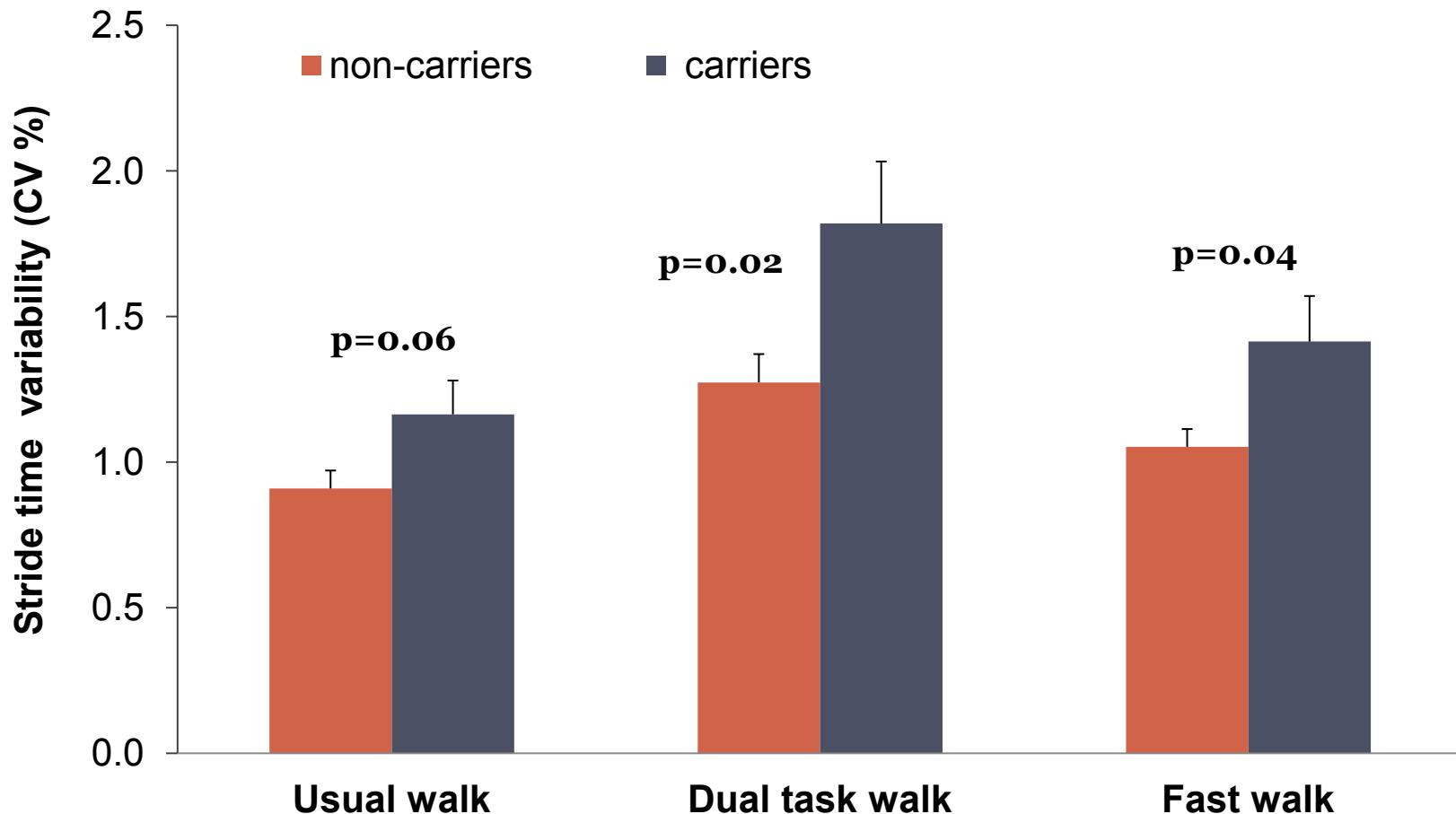
- Gait disturbances play a major role in the motor manifestation of PD.
- Gait changes frequently observed include decreased stride length and an increased stride time variability even early in the disease.
- Increased stride time variability has been reported as one of the hallmarks of gait in PD
- Stride time variability is especially sensitive to challenging conditions

# Gait Changes in PD





# Gait variability in healthy subjects at risk



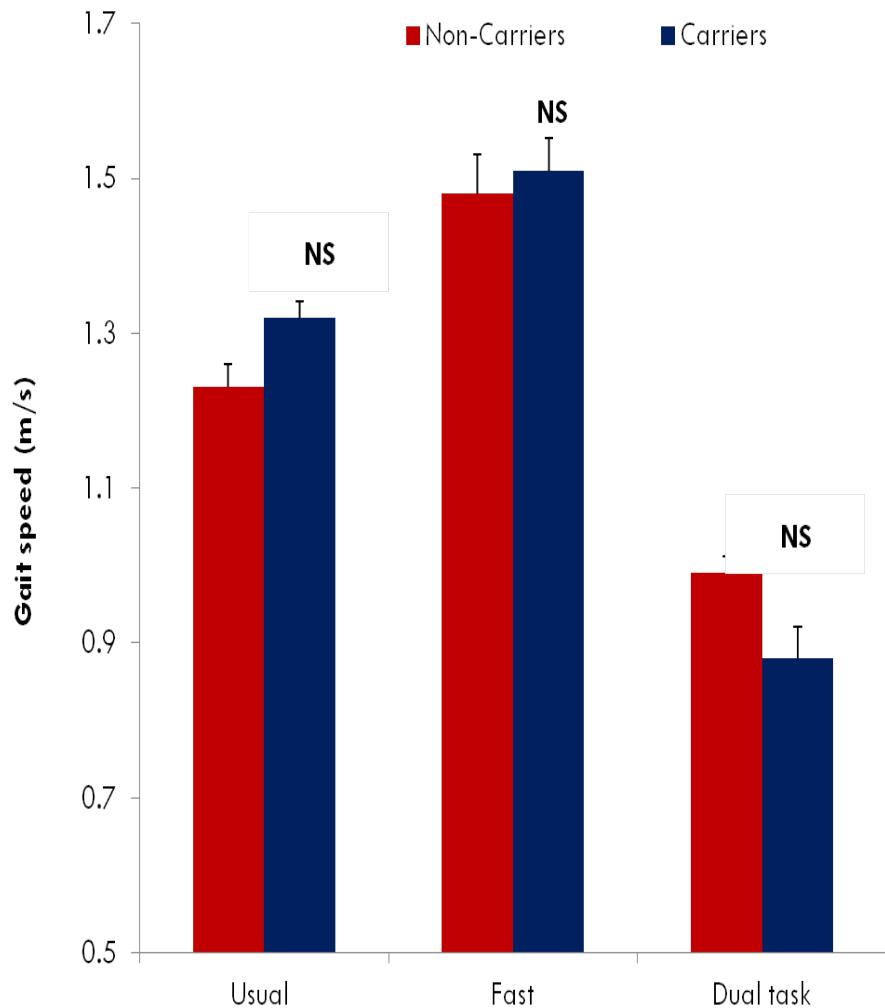
Non carriers = 25, carriers = 25

Mirelman et al. Annals of Neurology 2011

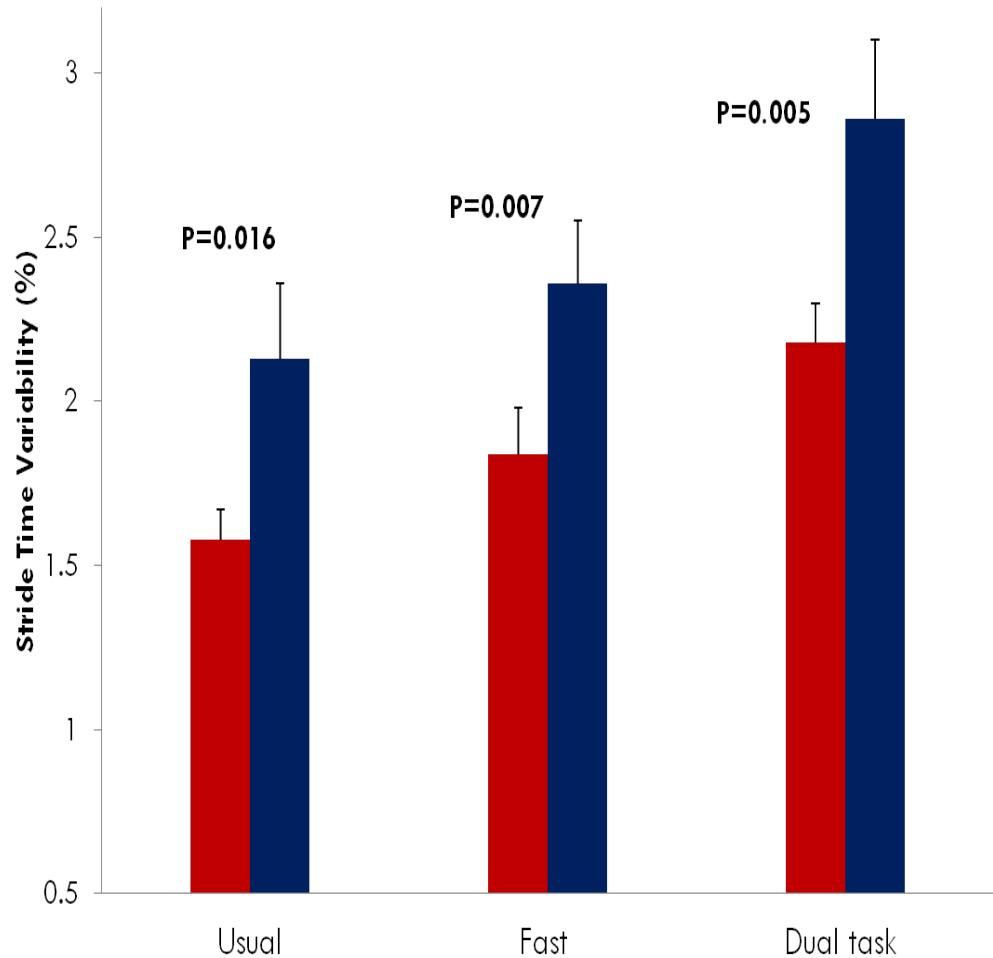


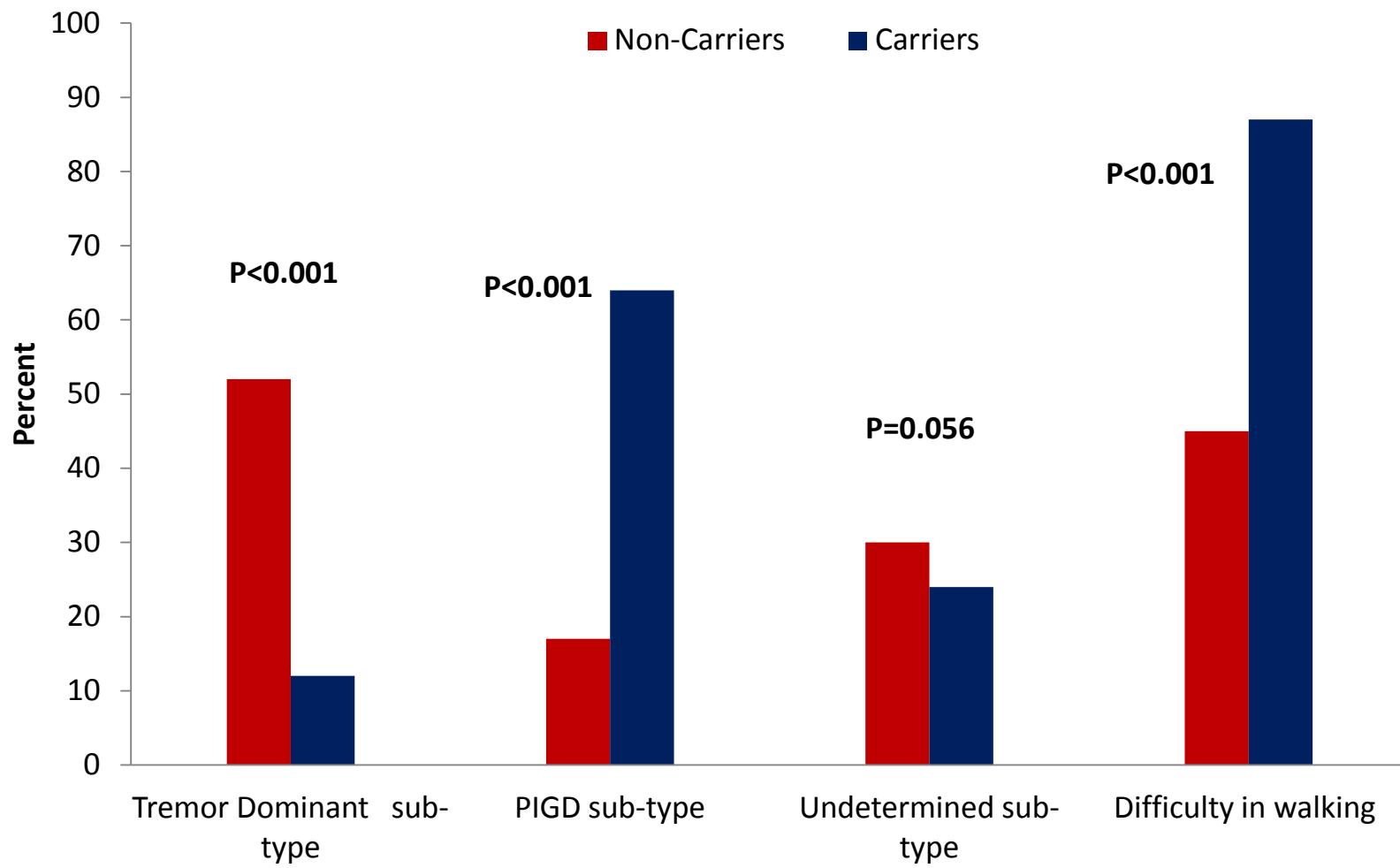
**Are these changes related to disease or  
are they an endophenotype of LRRK2?**

# Gait in PD



PD Carriers N =50, PD Non-Carriers N= 50

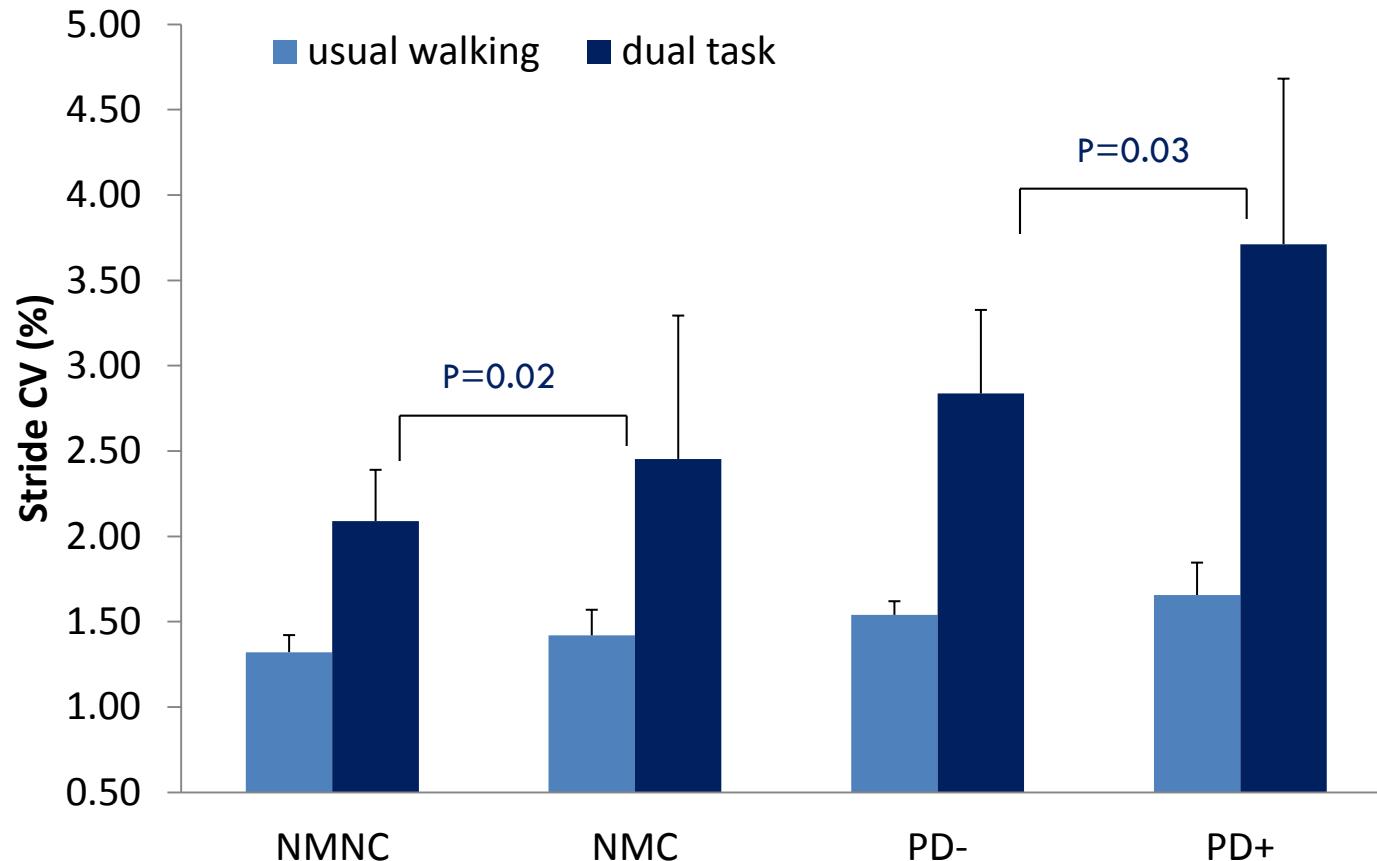




PD Carriers N =50, PD Non-Carriers N= 50

Mirelman et al in press MDJ

# Stride time variability under challenging conditions



NMNC=61 , NMC=62, PD-= 50, PD+=50

# Summary

- Differences in motor performance can be detected between carriers and non-carriers of G2019S LRRK2 mutation.
- Evidence exists to support subtle motor changes in the prodromal phase of PD, exposed in challenging conditions
- Motor decline changes with course of disease progression
- It is likely that there is a specific motor phenotype that can be related to G2019S LRRK2
- Creating a motor index could help in diagnosing early motor markers

# The team

## Tel Aviv Medical Center, Israel

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Lucien Cote  
Cheryl Waters  
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Stanley Fahn  
Oren Levy  
Ernest Roos

## Gait Consortium

Jan Aasly-Trondheim, Norway  
Daniela Berg- Tubingen, Germany  
Eduardo Tolosa- Barcelona, Spain  
Bill Chen- Beijing, China  
AJ consortium

# *Thank you!*



# **Prodromal PPMI**

**Ken Marek**

**PPMI Investigators Meeting**  
**May 8, 2013**  
**New York, NY**

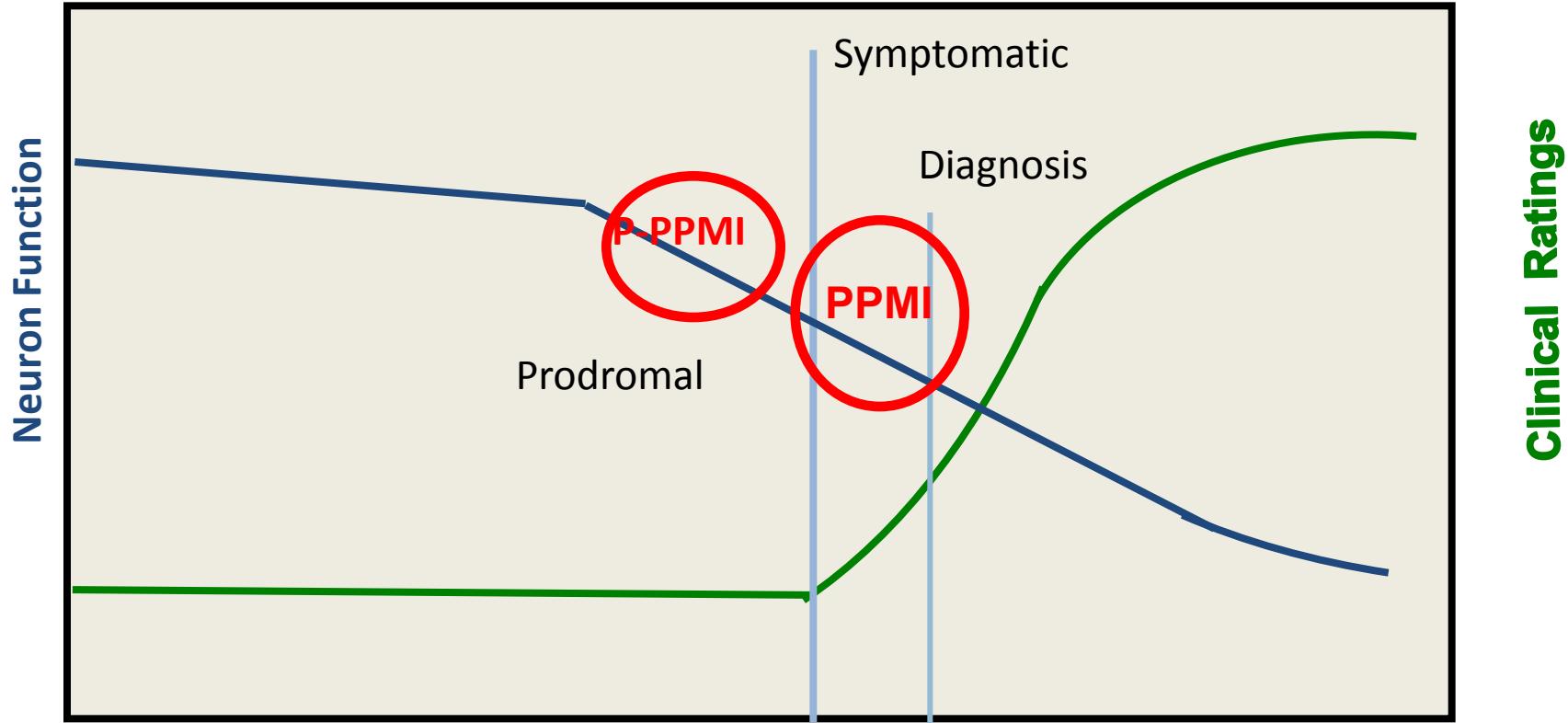


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# Natural History of Parkinson disease



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# 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



# 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



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# Prodromal PPMI cohort

- Utilize existing PPMI infrastructure
  - Sites
  - Cores
  - Database
  - Website
- Establish olfactory and RBD core
- Develop processes to identify ‘at risk’ subjects and refer to PPMI sites for enrollment

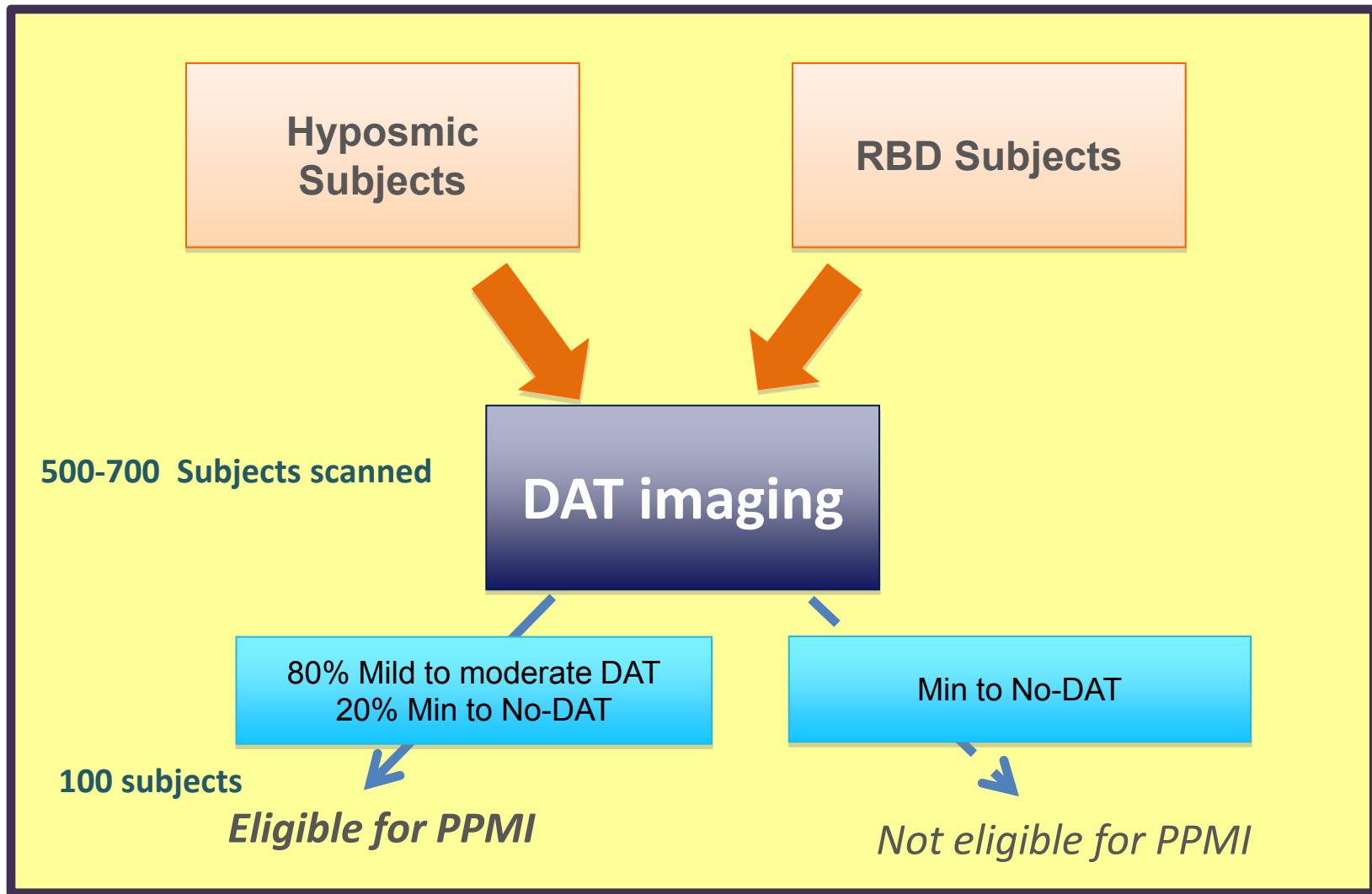


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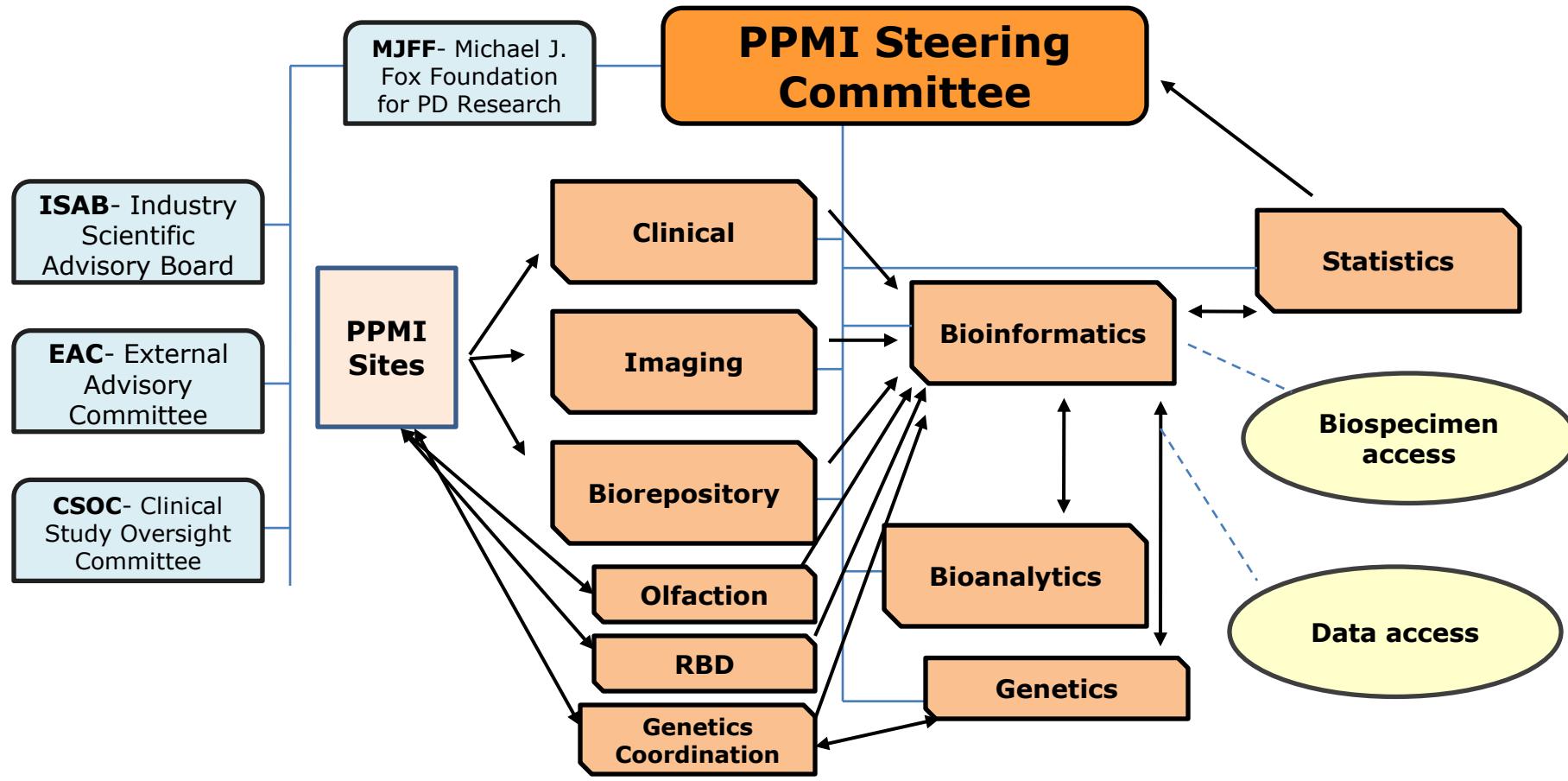
# Eligibility for P-PPMI



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# PPMI Study



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# Olfaction



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# **Prodromal Cohort: Olfaction Process**

Danna Jennings, MD  
PPMI Olfactory Core

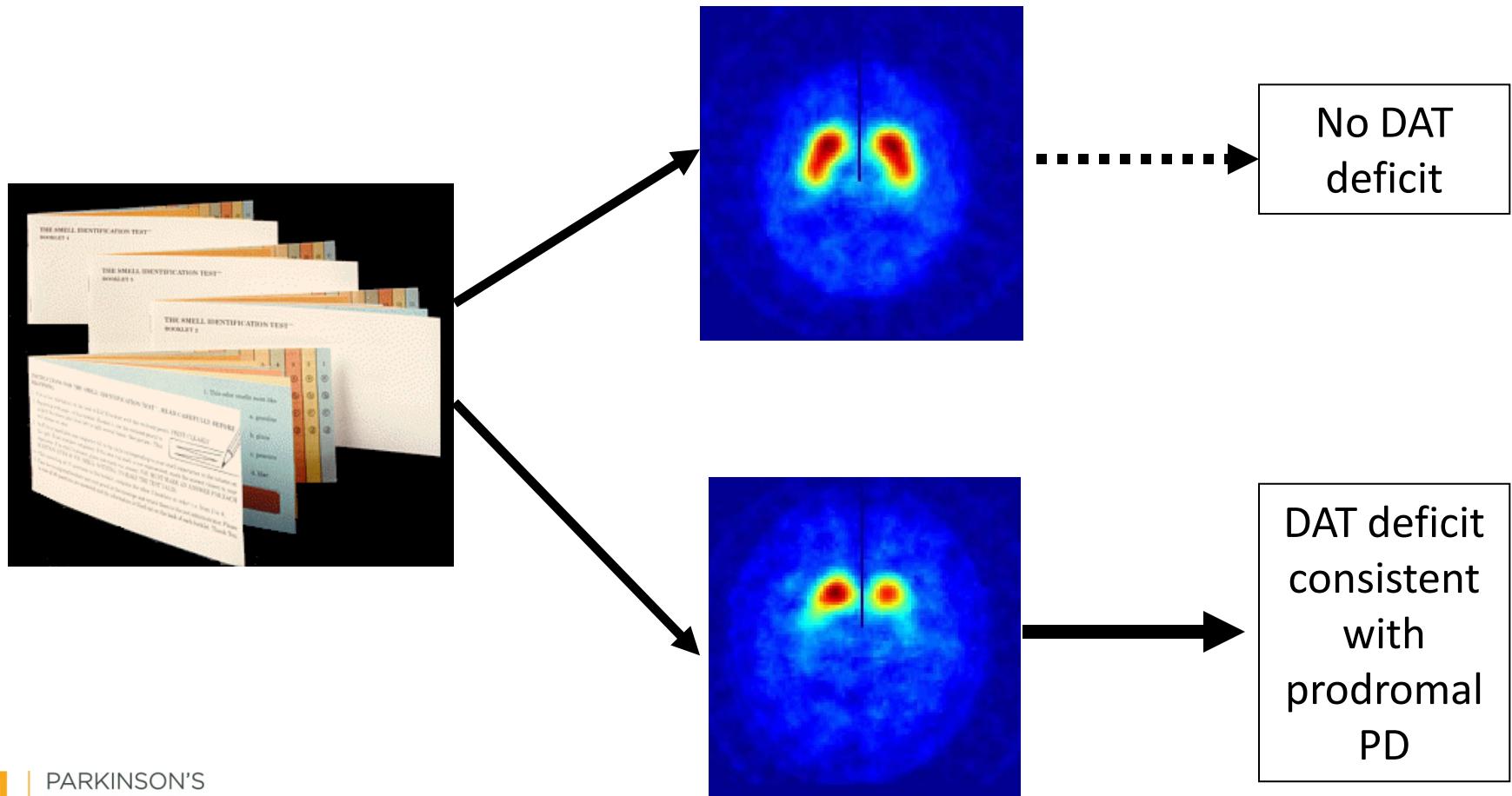


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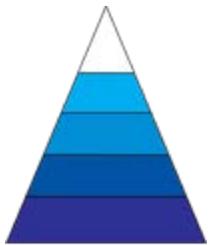
# Prodromal: Olfactory Process



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# PARS

## Sequential biomarker assessment

### PHASE 1

First degree relatives, non-relatives



Eligible subjects sent UPSITs ( $n = 9,379$ )



52% returned

Valid UPSITs ( $n = 4,871$ )



(< 15% percentile)

Olfactory loss ( $n = 650$ )



Hyposmic participants ( $n = 203$ )



DAT deficit ( $n = 23$ )

### PHASE 2

Clinic and Imaging visits

$n=303$

1. UPDRS
2. Diagnostic form
3. SCOPA-aut
4. Non-motor review
5. Neuropsych assess
6. DAT imaging
7. HRV
8. Blood, CSF sampling

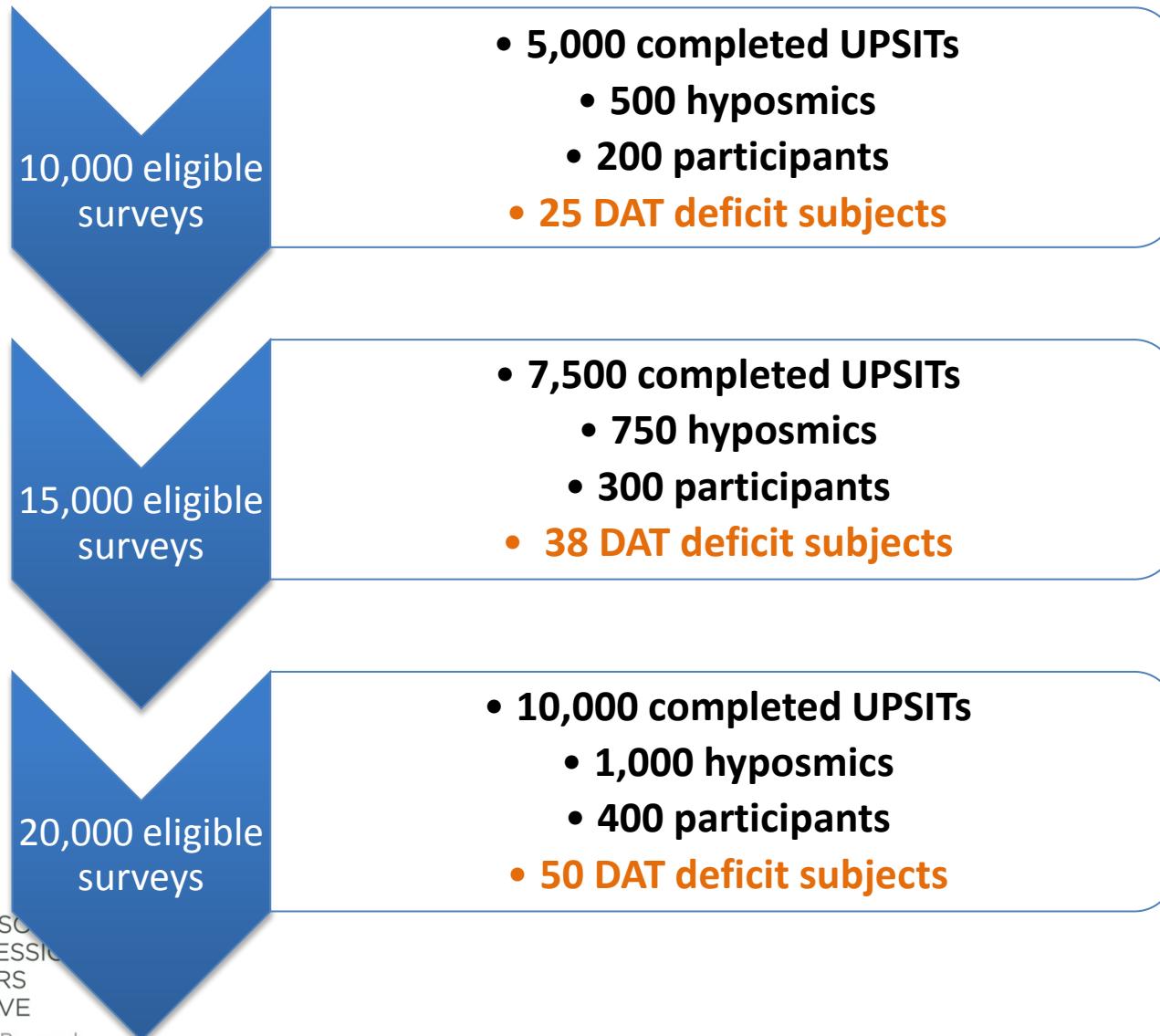


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# Hyposmia recruitment...it's all about numbers

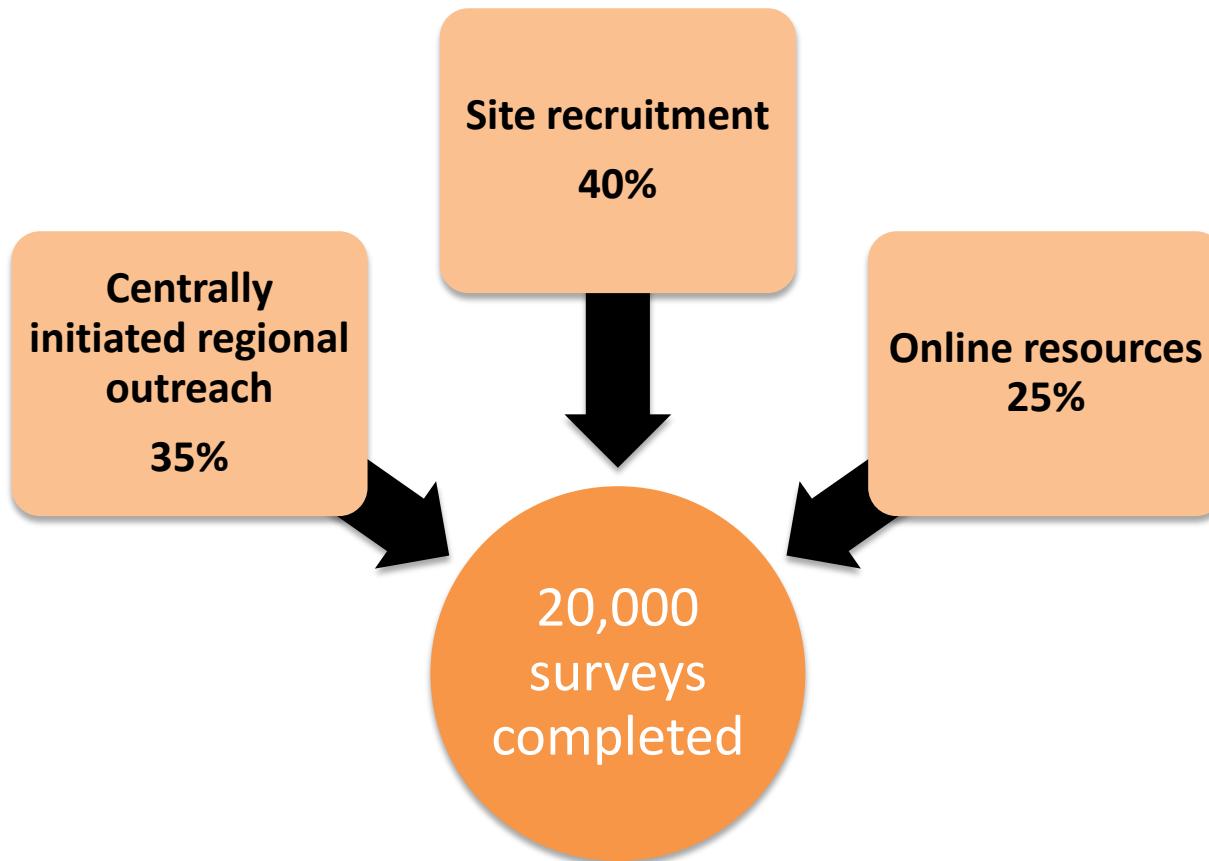


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# P-PPMI Olfaction Referral Sources



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# P-PPMI Olfaction Recruitment Sources

## Site recruitment

40%

Distribute surveys to patients, family friends

Engage institutional resources to distribute surveys

## Centrally initiated local outreach

35%

Mass emails to people within site vicinity

MJFF to engage local media

## Internet resources

25%

Google ads, MJFF website link

FTF - reach out to HC population

# Site recruitment goals

- Sites to identify 40% of olfactory cohort ( $20,000 \times 0.4 = 8,000$ )
- Recruitment period - 10 months
- 365 returned eligible surveys/site (22 sites)
- Approx 730 need to be distributed to get 365 returned
- Goal: distribute roughly 75/month



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# Olfaction: site outreach

- Packets of surveys in waiting rooms/clinic rooms for family to complete
- Packets of surveys for a PD patient to mail to family and friends—study coordinators and MDs to offer this to all patients
- Identify point person in your clinic to:
  - Remind neurologists/coordinators/nurses to approach all patients in clinic
  - Make sure clinic is stocked with surveys
- Reconnect with people interested in the original PPMI who were 1<sup>st</sup> degree relatives – ask them to take the survey
- Share info with other coordinators/departments within institution (i.e. geriatrics)
- Materials to share and present at local support groups and community outlets (slides, newsletter stories, etc)
- Engage a Parkinson advocate in your area

# Olfaction Process: US Sites

Identify 20,000 people to complete the olfaction survey

Eligibility evaluated by Olfactory Core

Olfactory Core sends Olf ICF, UPSIT and SRQ to eligible subjects

If UPSIT <10<sup>th</sup> percentile, referred to site. Site contacts subject to sched visit



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# Olfaction Process: EU Sites



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# Olfactory data so far.....

## Site generated surveys

Total received - Sites and other sources	330
Eligible	442
Ineligible	62
PD dx	19
AD dx	5
Age < 60	26
distance from site	20
other	2

## Online Surveys

Total received - Online sources	2561
Eligible	217
Ineligible	2344

## UPSITs

UPSITs sent	442*
UPSITs received	154
Hyposmics identified	9
Hyposmics referred	5
Hyposmic enrolled	0

\*176 sent in past week



# Online Recruitment Sources (n=217 eligible subjects)

#	%	Source
86	40%	Friend or Family Member
42	19%	MJFF Newsletter, Email, or Event
40	18%	MJFF Website
15	7%	Facebook or Social Media Outlet
13	6%	Other
11	5%	Site Referral
6	3%	Fox Trial Finder
2	1%	Doctor or Medical Care Provider
1	0%	Support Group
1	0%	Blank



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# RBD

PPMI Prodromal Cohort Training  
January 28<sup>th</sup> and 30<sup>th</sup> , 2013



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# RBD Operations

- **RBD Sleep Core**
  - **Core at Hephata Clinic in Schwalmstadt Germany**
  - **Lead Investigator for core is Geert Mayer**
- **Responsibilities**
  - **Provide standardized criteria for polysomnography (PSG)**
  - **Draft Technical Operations Manual for RBD sites**
  - **Receipt and tracking of polysomnography data for P-PPMI**
  - **QC and artifact discrimination of polysomnography data**
  - **Scoring of PSG as PPMI eligible or not eligible**
  - **Report to P-PPMI Referral Team**



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# RBD Subject Flow

## Site identifies subjects – PSG Review central

- Selected PPMI sites will conduct pre-screening activities for subjects with a diagnosis of RBD identified at Sleep centers
- Subjects with RBD identified by/referred to PPMI sites
- PPMI Investigators and Coordinators will contact patients
  - Provide more information about PPMI study
  - Get initial consent to obtain and centrally review their PSG to determine eligibility for PPMI
- PSG transferred and reviewed by RBD core
- P-PPMI Referral Team informs PPMI sites about subject eligibility.



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# RBD Screening

- Once site has received IRB or EC approval for Amendment-5
- For consented subjects PPMI site will send de-identified PSG to RBD Core for standardized evaluation
- Site will receive auto-reply confirmation of upload
- Site will receive confirmation that PSG is evaluable for PPMI (24-48 hrs post upload)
- RBD core will evaluate PSG for RBD and provide evaluation to P-PPMI referral team
- Referral team will send site RBD Eligibility report (2 business days)



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# RBD Screening RBD Subject Eligibility Report

- PPMI RBD Eligibility Report will be sent from PPMI Referral Team to sites
- Include in the subjects binder
- PPMI site to contact subject to schedule visit to enroll in PPMI
- Subjects not eligible based on PSG should be contacted by site

 P-PPMI Polysomnography (PSG) Analysis Results  
Eligibility Report—RBD

Study Name: \_\_\_\_\_ Protocol Number: \_\_\_\_\_  
Site Number: \_\_\_\_\_ Subject Number: \_\_\_\_\_  
Clinical Site Name: \_\_\_\_\_  
PSG Date: \_\_\_\_\_ (dd/mm/yyyy) PSG Read Date: \_\_\_\_\_ (dd/mm/yyyy)  
Results are related to PSG file named: \_\_\_\_\_

The PSG for the above subject was reviewed. Based upon the evaluation for RBD, the subject is:

ELIGIBLE to be consented and continue screening for the prodromal cohort of the PPMI Study  
 NOT ELIGIBLE to be consented and continue screening for the prodromal cohort of the PPMI Study

Interpretation Completed By: \_\_\_\_\_ Date Completed: \_\_\_\_\_

Please use this report in your assessment of the subject's eligibility for participation in the PPMI study and file this report in your study binder.

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Institute for Neurodegenerative Disorders

M N I D 1 2 0 3 \* V 1\_PSG Analysis Results Eligibility Report  
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MNIID1203



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# Prodromal Subject Enrollment



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# Eligibility of Prodromal Subjects

## Inclusion Criteria (Prodromal Subjects)

Subjects must meet the eligibility for at least one of the following

### *Hyposmia:*

- a) Male or female age 60 years or older
- b) Confirmation from olfactory core that olfaction as determined by UPSIT is at or below the 10th percentile by age and gender **Part of pre-screening completed by Olfactory Core**

### *REM Behavior Disorder (RBD):*

- a) Male or female age 60 years or older
- b) Confirmation from sleep core that subject's Polysomnography (PSG) meets criteria for RBD **Part of pre-screening completed by select sites in collaboration with sleep center and RBD Core**



# Eligibility of Prodromal Subjects

## Inclusion Criteria (Prodromal Subjects)

**4.2.7.2.** Confirmation from imaging core that screening dopamine transporter SPECT scan is read as eligible (see below).

About 80 subjects will have a range of DAT deficit similar to subjects with early PD (mild to moderate DAT deficit). About 20 subjects will be selected with no DAT deficit or minimal DAT deficit similar in age, gender, and risk profile to those with mild to moderate DAT deficit.

**4.2.7.3.** Ability to provide written informed consent in accordance with Good Clinical Practice (GCP), International Conference on Harmonization (ICH), and local regulations

**4.2.7.4.** Willing and able to comply with scheduled visits, required study procedures and laboratory tests.

**4.2.7.5.** Women may not be pregnant, lactating or planning pregnancy during the course of the study.

Includes a negative urine pregnancy test on day of screening scan prior to injection (DaTSCAN)



# Eligibility of Prodromal Subjects

## **Exclusion Criteria (Prodromal Subjects)**

- 4.2.8.1.** Current or active clinically significant neurological disorder or psychiatric disorder (in the opinion of the Investigator).
- 4.2.8.2.** GDS score greater than or equal to 10 (GDS score of 5 – 9 requires Investigator discretion to enter study).
- 4.2.8.3.** STAI Form Y-1 greater than or equal to 54 requires Investigator discretion to enter study.
- 4.2.8.4.** A clinical diagnosis of dementia as determined by the investigator (Appendix 1).
- 4.2.8.5.** A clinical diagnosis of Parkinson disease at the Screening visit as determined by the Investigator.

***Note: if subjects would qualify for PPMI de novo PD they are not prodromal***



# Eligibility of Prodromal Subjects

## Exclusion Criteria (Prodromal Subjects)

- 4.2.8.6.** Received any of the following drugs that might interfere with dopamine transporter SPECT imaging: Neuroleptics, metoclopramide, alpha methyldopa, methylphenidate, reserpine, or amphetamine derivative, within 6 months of Screening.
- 4.2.8.7.** Current treatment with anticoagulants (e.g., coumadin, heparin) that might preclude safe completion of the lumbar puncture.
- 4.2.8.8.** Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.
- 4.2.8.9.** Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.
- 4.2.8.10.** Use of investigational drugs or devices within 60 days prior to Baseline (dietary supplements taken outside of a clinical trial are not exclusionary, e.g., coenzyme Q10).
- 4.2.8.11.** Previously obtained MRI scan with evidence of clinically significant neurological disorder (in the opinion of the Investigator).

# Eligibility of Prodromal Subjects

## Subject Consenting:

Hyposmic, RBD (REM behavior disorder) who meet pre-screening criteria and are able and willing to enroll into PPMI all sign the same ICF

PPMI	Prodromal Informed Consent
<b>MODEL RESEARCH SUBJECT INFORMATION AND CONSENT FORM (Prodromal Research Participants)</b>	
<b>Study Title:</b> The Parkinson's Progression Markers Initiative	
<b>Sponsor Protocol No.:</b> 001	
<b>Sponsor:</b> The Michael J. Fox Foundation for Parkinson's Research (MJFF)	
<b>Study Chair:</b> Ken Marek, MD President and Senior Scientist Institute of Neurodegenerative Disorders 60 Temple St., Suite 8B, New Haven, CT 06510	
<b>Site Investigator:</b> {Investigator Name and Address}	
<b><u>INTRODUCTION</u></b>	
In this consent form, "you" always refers to the study subject. In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which the study team will discuss with you. This discussion will go over all aspects of this research: its purpose, the procedures that will be done, any risk of the procedures, and possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this consent form. This consent form contains important information and telephone numbers; so you should keep a copy to refer to as the study proceeds.	
<b><u>PURPOSE</u></b>	
You are being invited to take part in this study because you have at least one of the following: a decrease in your sense of smell, REM behavior disorder (acting out your dreams) or you have tested positive for the LRRK2 gene. These signs and symptoms may lead to an increased risk for Parkinson disease (PD) or other neurologic conditions. As part of this study, we will evaluate whether individuals with a decrease in the sense of smell, REM behavior disorder, or a positive LRRK2 gene test may be more likely to develop PD or other neurologic condition. In this research study we will collect clinical information, samples of blood, DNA, urine, cerebral spinal fluid, and brain images from people with PD and from people without PD. This information will be used to help develop biomarkers for PD. Biomarkers are indicators that can help in confirming a diagnosis and measure progression of a condition and the effects of therapy. We are working on biomarkers in PD because they may help to understand how the disease changes over time. Having good biomarkers for PD may also be useful in developing new treatments and may help to improve clinical care in the future. As part of this study we will test biomarkers that may help understand who is at increased risk for PD and other neurologic conditions. We will store	



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# **Eligibility – soft motor signs**



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# **When does prodromal become motor PD?**

- **Mild motor signs vs early PD – judgement call**
- **If subject meets criteria for PPMI PD group then not eligible for P-PPMI**
  - **Single asymmetric motor sign + DAT deficit**



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# DaTSCAN



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# Why DAT imaging?

- **DAT imaging used to determine those proximate to Phenocconversion among those at risk**
- **Evidence that Olfaction, RBD and LRRK2 studies plus DAT deficit results in approx 30% phenoconversion in 2-3 years**



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# DaTSCAN - What is abnormal?

- Percent age expected lowest Putamen -  $\beta$ -CIT
  - $\leq 65\%$  mild to mod DAT deficit
  - 65%-80% minimal DAT deficit
  - >80% no DAT deficit
- Linear discriminant function – DaTSCAN
  - Use PPMI PD and healthy subjects to identify best imaging discriminators
  - Developed simple tool - using ipsilateral striatal, Lowest striatum, asymmetry index – correctly classified >95% of PD and HC
- Visual assessment
  - Readers will assess with same visual method as in PPMI

**DAT deficit will require both quantitative and visual evidence**



# DaTSCAN - Why no DAT deficit

- **Enroll 80% mild to mod DAT deficit**
- **Enroll 20% minimal to NO DAT deficit**
  - Reduce bias regarding clinical assessments and phenoconversion
  - Note all subjects have PD risk
- **Sites will be informed whether the subjects DaTSCAN is eligible or not eligible**



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# Phenoconversion



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# P-PPMI Cohort - Outcomes

- **Define the biomarker signature during the prodromal period**
- **Assess Phenocconversion**



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# **Defining Phenoconversion to PD in the P-PPMI cohort**

- **Critical outcome for P-PPMI cohort**
- **Established phenoconversion definition not available**
- **Approach: develop a standardized diagnosis with minimal inter-rater variability**
- **Data Driven diagnosis**



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# Phenoconversion

- **Primary :**
  - Based on UK Brain Bank Criteria
  - Data mapped from the 'Diagnostic Features Questionnaire'
- **Secondary:**
  - Prodromal Diagnostic Questionnaire
    - Current most likely clinical diagnosis (Q#1)
    - Confidence level regarding motor symptoms c/w a diagnosis of Parkinsonian syndrome (Q#2)



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# **Phenoconversion- Exploratory Strategies**

- Assess conversion to PPMI diagnosis**
- Develop conversion to biomarker outcomes – DAT, CSF analytes, cognition**



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# UK PD Society Brain Bank Diagnostic Criteria

## Step 1: Diagnosis of Parkinsonism

Bradykinesia and at least one of the following:

- Muscular rigidity
- 4–6 Hz resting tremor
- postural instability not caused by primary visual, vestibular, cerebellar or Proprioceptive dysfunction

## Step 2: Features tending to exclude Parkinson's disease as the cause of Parkinsonism

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Neuroleptic treatment at onset of symptoms
- >1 affected relatives
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language and praxis
- Babinski's sign
- Presence of a cerebral tumour or communicating hydrocephalus on computed tomography scan
- Negative response to large doses of levodopa (if malabsorption excluded)
- MPTP exposure

- Vascular disease
- Family history
- Autonomic disorder
- Sleep Apnea
- Cognitive disorder



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## PRODROMAL DIAGNOSTIC QUESTIONNAIRE

SUBJECT ID     VISIT NO   INITIALS    SITE NO    VISIT DATE   MM  DD  YYYY

1. Indicate the current most likely clinical diagnosis from one of the categories listed below (choose one):

1.  

- 01 = Idiopathic PD
- 02 = Alzheimer's disease
- 03 = Chromosome-17 frontotemporal dementia
- 04 = Corticobasal degeneration
- 05 = Dementia with Lewy bodies
- 06 = Dopa-responsive dystonia
- 07 = Essential tremor
- 08 = Hemiparkinson/hemiatrophy syndrome
- 09 = Juvenile autosomal recessive parkinsonism
- 10 = Motor neuron disease with parkinsonism
- 11 = Multiple system atrophy
- 12 = Neuroleptic-induced parkinsonism
- 13 = Normal pressure hydrocephalus
- 14 = Progressive supranuclear palsy
- 15 = Psychogenic illness
- 16 = Vascular parkinsonism
- 17 = No PD nor other neurological disorder
- 18 = Spinocerebellar Ataxia (SCA)
- 23 = Prodromal non-motor PD (at least one non-motor symptom and no motor symptoms)
- 24 = Prodromal motor PD (at least one motor symptom to meet eligibility for enrollment in PPMI as PD subject)
- 97 = Other neurological disorder(s) (specify) \_\_\_\_\_



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## PRODROMAL DIAGNOSTIC QUESTIONNAIRE

SUBJECT ID

--	--	--	--	--

VISIT NO

--	--	--

INITIALS

--	--	--

SITE NO

--	--	--

VISIT DATE

--	--

MM

--	--

DD

--	--	--	--

YYYY

2. To what degree are you confident that this subject has motor signs consistent with a parkinsonian syndrome (PS) (any condition in which there is neurodegeneration of dopaminergic cells in the substantia nigra)?

2.

1 = Motor abnormalities that are signs of PS (90 - 100%)

2 = Motor abnormalities that are likely signs of PS (70 - 89%)

3 = Motor abnormalities that may be signs of PS (50 - 69%)

4 = Non-specific motor abnormalities (25 - 49%)

5 = No evidence of parkinsonian motor signs (0 - 24%)



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# Prodromal discussion

- **Best way for sites to dispense olfactory questionnaires**
- **Motor symptoms at screening?**
- **Clinical diagnosis at phenoconversion?**
- **Is DaTSCAN data provided?**



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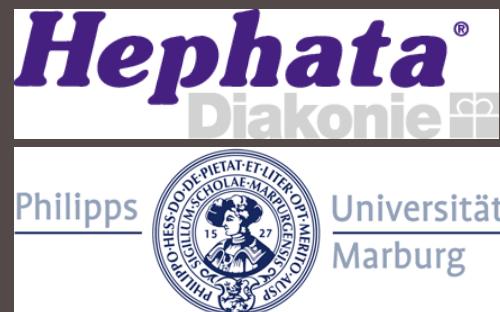


# PRODROMAL PPMI

G. Mayer

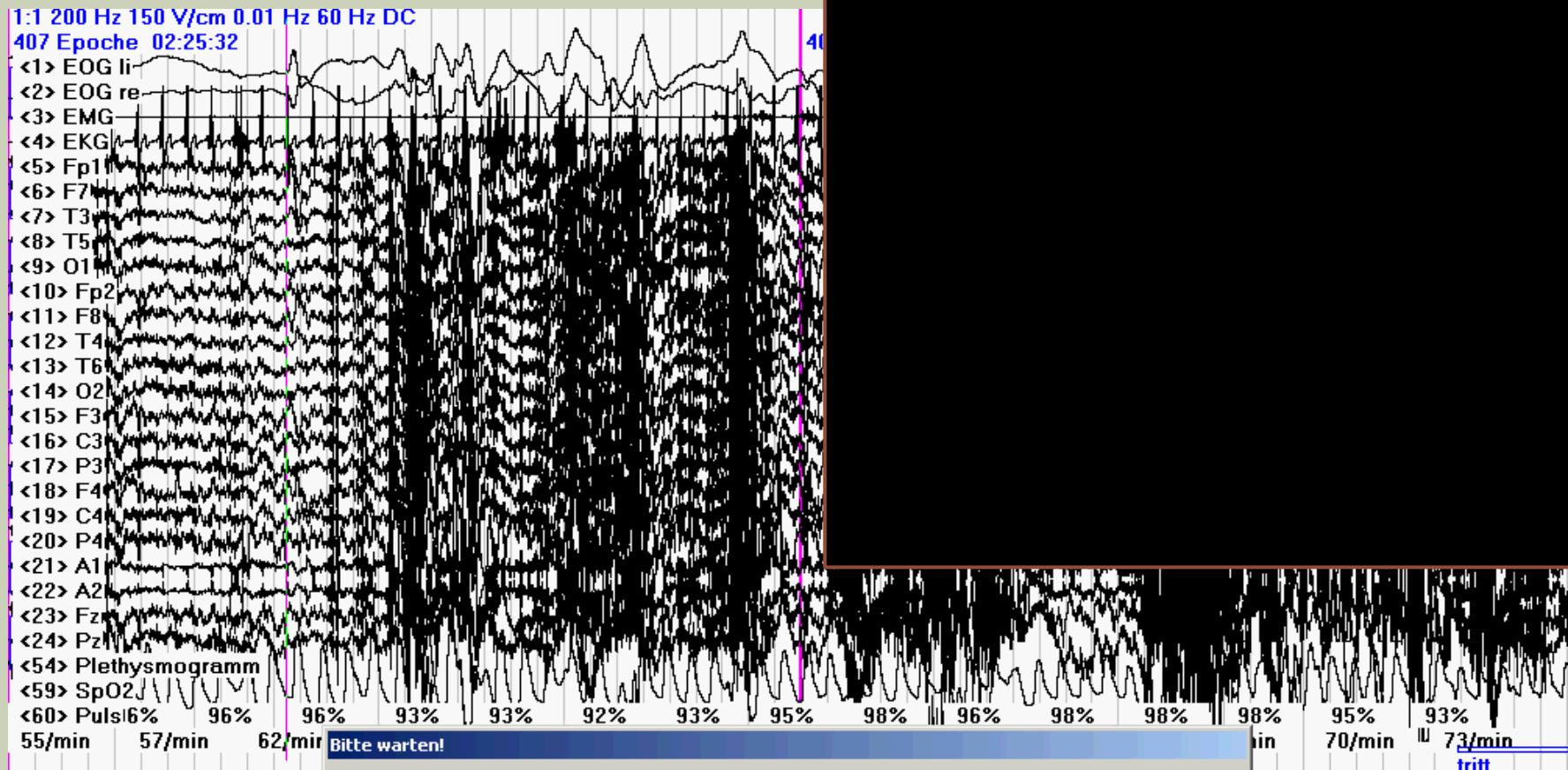
Schwalmstadt-Treysa

Philipps-Universität Marburg, Dpt. neurology



# RBD EPISODE

84Y, LIVELY DREAMS ATTACKING AND EATING UP PEOPLE  
HEAD TRAUMA, BYPASS SURGERY, HYPERTENSION, PLMD



# ICSD2

- A. Violent or injurious behavior in sleep
- B. Limb- or body movements that relate to dream contents
  - behavior (one of the following criteria):
    - Aggressive sleep behavior
    - Acting out dream contents
    - Fragmentation of sleep continuity
- C. Polysomnography
  - Excessive increase of chin EMG
  - Excessive chin EMG or limb movement
  - Complex, aggressive behavior
- D. Symptoms must not be caused by psychiatric disorders,  
association with neurological disorders (no epilepsies!)
- E. Other sleep disorders may be present but are not the cause

# EPIDEMIOLOGY

## ■ Studies

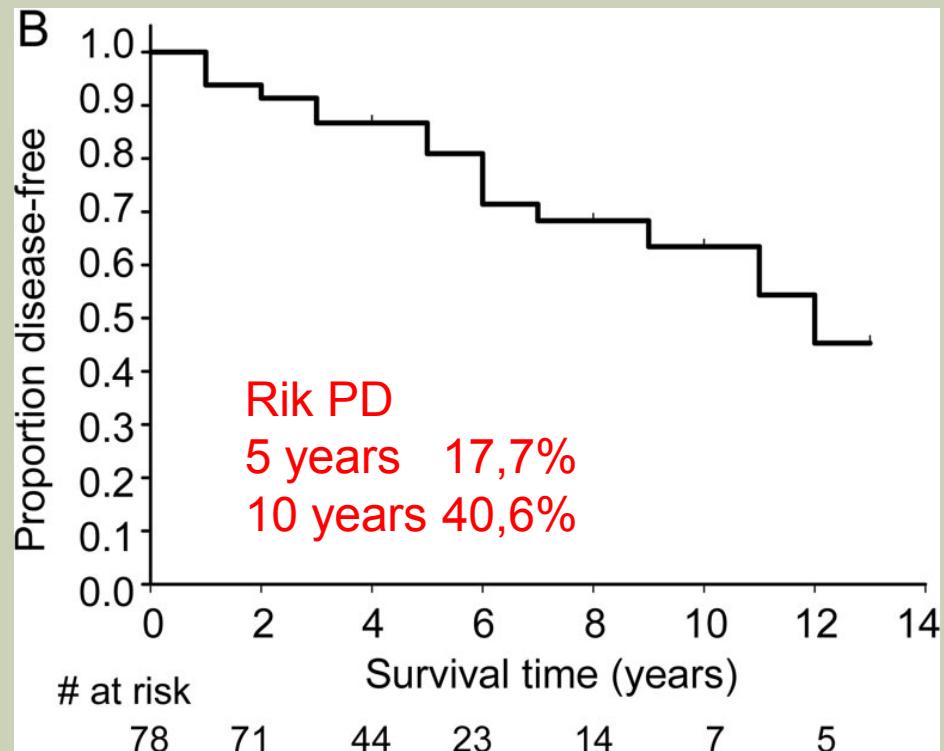
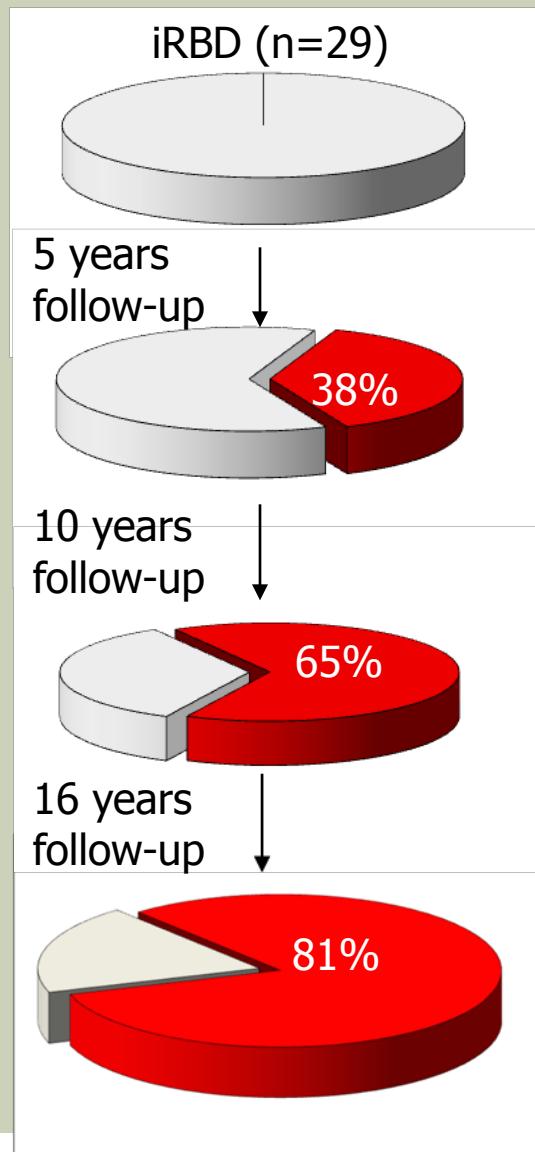
- Ohayon 1997, Ohayon & Schenck 2010: 0.5%
- Chiu 2000: Estimated prevalence in general population: 0.38%
- Boeve 2008 (PSG based, unpublished): 0,02%
- Molano 2009, Boot 2012: prevalence population >60y: 8.9%
  
- Men vs women: 9:1

# RISK FACTORS

Postuma 2012:

- Participation 13 centers worldwide: 347 iRB, 347 controls
- Questionnaire for lifestyle risk factors
- Risk factors: smoking, head injury, pesticide exposure, farming

conversion:  $14.2 \pm 6.2$



Postuma et al. 2010  
Schenck et al., 1996,  
2003, 2007, 2013

# DIAGNOSTIC STEPS

REM SLEEP BEHAVIOR DISORDER (RBD): DEVISING CONTROLLED ACTIVE TREATMENT STUDIES FOR SYMPTOMATIC AND NEUROPROTECTIVE THERAPY—A CONSENSUS STATEMENT BY THE INTERNATIONAL RBD STUDY GROUP.  
SLEEP MEDICINE 2013

- There should be at least two prior episodes of clinically reported or witnessed dream-enacting behavior supported by REM sleep without atonia recorded by PSG
- To allow for assessment of change, the minimum frequency of RBD episodes should preferably be  $\geq 2$  times weekly (with complex movements, apart from any sleeptalking), to the extent that reliable reporting is possible by a bedpartner (especially for iRBD).
- iRBD patients with “soft” neurological dysfunction (olfactory dysfunction, mild cognitive impairment...)
- video-polysomnography – REM-atonia, quantitative EMG-analysis

# PSG EVALUATION

## RBD STUDY GROUP RECOMMENDATIONS

- PSG montage for RBD evaluation: standard PSG montage according to the AASM (plus bilateral flexor digitorum superficialis muscles on the upper extremity) is encouraged.
- It is important to consider the same filter settings and impedance measures; amplification has to be stated and shown on the PSG machine. Sampling frequency should be indicated.
- EDF format should be used for data provision.
- RWA is supported by the polysomnographic findings of either: 1) Tonic chin EMG activity in > 30% of REM sleep; or 2) Phasic chin EMG activity in > 15% REM sleep, scored in 20 sec epochs
- Any (tonic/phasic) chin EMG activity combined with bilateral phasic activity of the flexor digitorum superficialis muscles in >32% of REM sleep, scored in 30 sec epochs
- Automatic analysis: Burns 2007, Ferri 2008, 2009, 2010, Mayer 2008, Kempfner 2010

# **REM SLEEP BEHAVIOR DISORDER**

## **SEVERITY SCALE (RBDSS)**

### **SIXEL-DÖRING 2011**

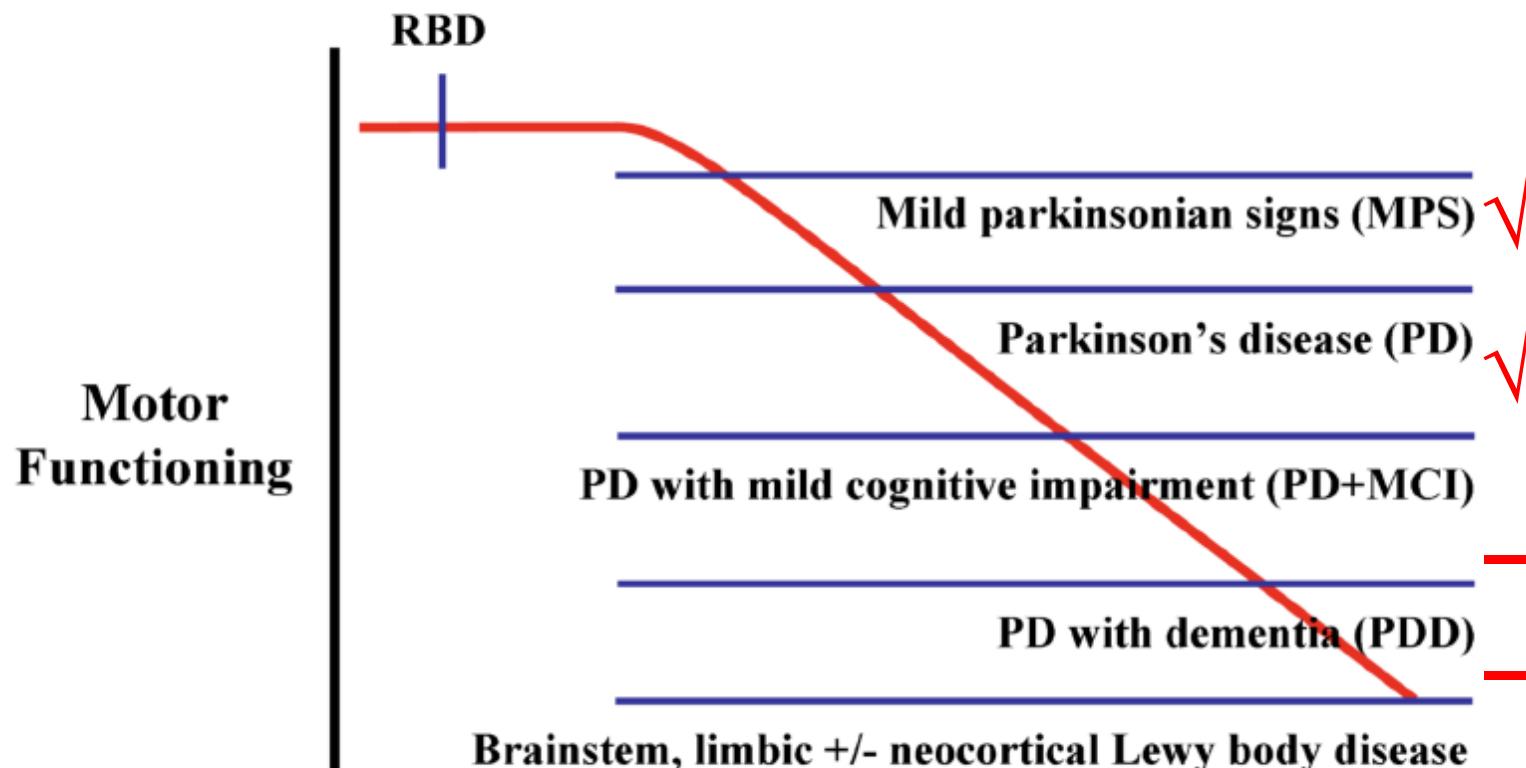
#### **Motor Event Rating:**

- **0 = no visible motor activity, RWA present**
- Only definition criteria of RWA according to ICSD are fulfilled, no other phasic muscle activity in the limbs or face is visible or obvious on recording.
  
- **1 = small movements or jerks**
- Isolated, single hand or foot movements or facial jerks visible, restricted to the distal extremities and/or face
  
- **2 = proximal movements including violent behavior**
- Single movements or series of movements including proximal extremities, no change of position
  
- **3 = axial movements including bed falls**
- Movements with axial involvement and/or change of body position, or falls

#### **Vocalization rating:**

- **0 = no vocalization**
- Snoring with some sound may be present and should be differentiated from REM-associated vocalization.

# THE GOAL



# WHERE WE ARE

- All participating centers have successfully sent test files
- Two centers have sent 2 final files each: 3 PSGs passed the requirements

# RISK FOR NEURODEGENERATION

POSTUMA ET AL NEUROLOGY, 2009

„Quantification of risk for neurodegenerative diseases in idiopathic RBD“

Longterm follow-up of 113 patients with iRBD  
**estimated risk for neurodegeneration:**

5 years: 17.7%

10 years: 40.6%

12 years: 52.4%

Majority of patients developed PD and DLB

PD + RBD: 33–46% PD; Gagnon et al., 2002; Sixel-Döring et al., 2011)

DLB: 75% ( Ferman et al., 2011)

MSA: almost 100% (MSA; Vetrugno et al., 2004).

# **PPMI**

# **Recruitment and Retention**

Update to the PPMI Annual Meeting  
May 8, 2013

*Danna Jennings, R&R Working Group Chair  
Claire Meunier, MJFF*



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# PPMI Recruitment & Retention Working Group

- Daniela Berg
- Carey Christensen
- Emily Flagg
- Hubert Fernandez
- Alexandra Gaenslen
- Katharina Gauss
- Christine Hunter
- Danna Jennings (Chair)
- Jim Leverenz
- Zoltan Mari
- Claire Meunier
- Tanya Simuni
- Carlie Tanner
- Cathi Thomas
- Karen Williams



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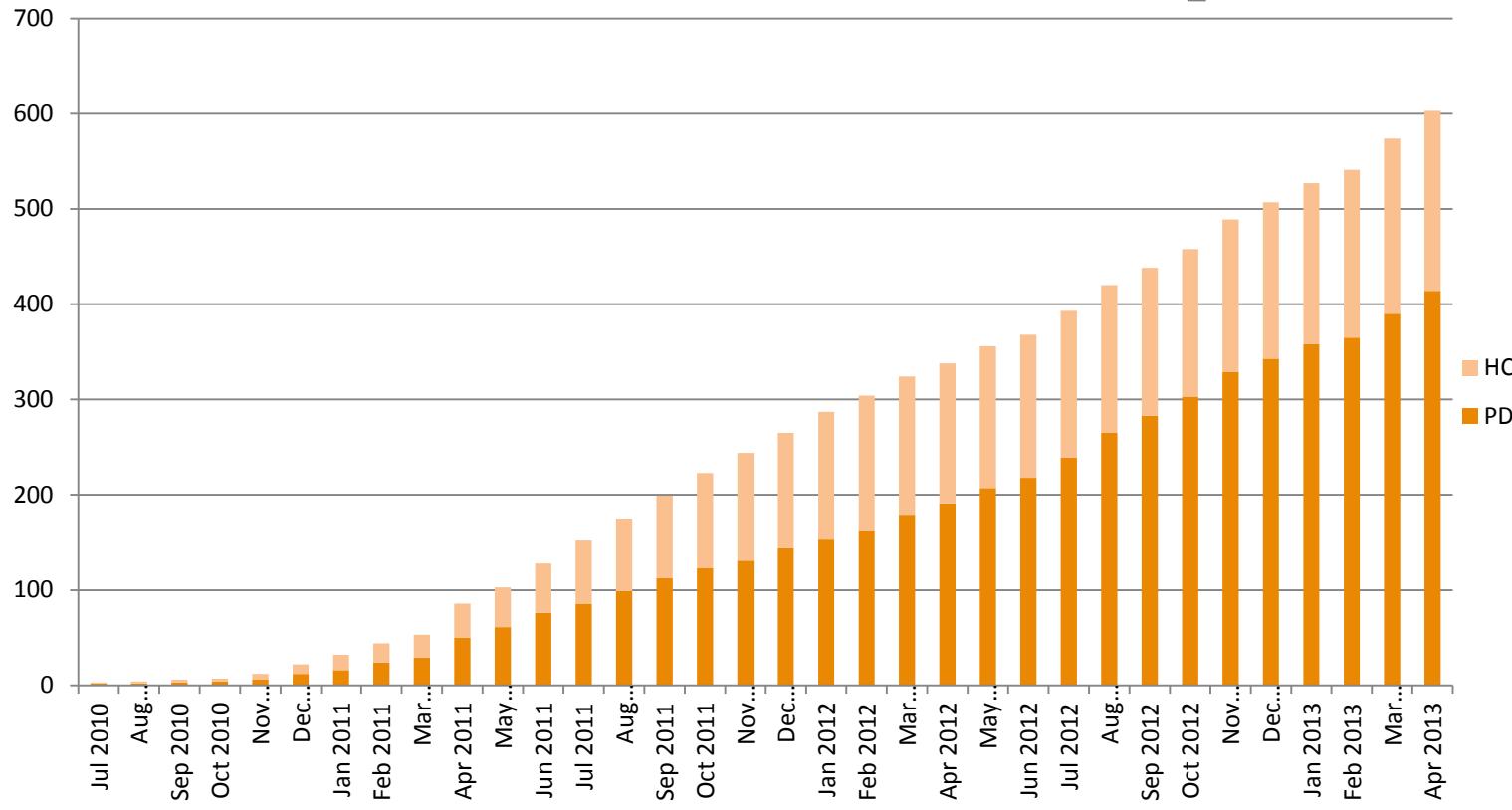


# Recap of R&R Goals

- **Recruit** 400 *de novo* and 200 control subjects
  - Site Goal: Enroll 1 PD per month and 1 control every two months
- **Retain** subjects by keeping them engaged to participate in study visits over time
  - Site Goal: Remain connected and continue to cultivate volunteers as key partners in the study



# Recruitment is complete!



- 419 PD (11 pending enrollment)
- 191 Controls (5 pending enrollment)
- 59 SWEDDs (3 pending enrollment)



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Site Name	Total PD consented	Total Controls consented	PD + SW/month	Controls/month	Subjects/month
IND	62	18	2.0	0.6	2.54
Tuebingen	27	12	1.3	0.5	1.81
Cleveland Clinic	25	11	1.2	0.5	1.74
Paracelsus-Elena Klinik	23	11	1.1	0.5	1.54
Emory	23	15	0.9	0.6	1.49
University of Alabama	22	16	0.9	0.6	1.48
U Wash/VA Puget Sound	24	15	0.9	0.6	1.46
Cincinnati	16	1	1.3	0.1	1.38
U South Florida	21	14	0.9	0.5	1.37
Northwestern	25	12	1.0	0.4	1.37
OHSU	22	15	0.8	0.5	1.31
The PI	24	13	0.9	0.4	1.31
U Penn	23	15	0.7	0.5	1.25
Boca	9	4	0.8	0.4	1.20
Imperial College	11	5	0.8	0.4	1.16
Hopkins	20	7	0.8	0.3	1.08
Baylor	25	9	0.8	0.3	1.08
Boston University	18	13	0.6	0.5	1.08
UCSD	13	9	0.6	0.5	1.06
U Rochester	19	10	0.6	0.4	0.99
Innsbruck	9	8	0.5	0.3	0.85
Salerno	12	0	0.6	0.0	0.61
Banner Health/APDC	12	4	0.4	0.1	0.51
Macquarie	6	1	0.4	0.1	0.50

# Site Awards

Drumroll, please.....



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# Sites that met the year 2 goal in less than 24 months

Site	Years to recruit 20 PD	Years to recruit 10 Controls
IND	1.12	1.08
OHSU	1.41	1.16
Tuebingen	1.41	0.87
U Wash/VA Puget Sound	1.47	0.97
Cleveland Clinic	1.51	1.28
University of Alabama	1.74	1.12
Paracelsus-Elena Klinik	1.78	0.74
The PI	1.99	1.26
Northwestern	2.00	1.04



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# Top Enrolling Sites: #1

- 58 PD, 14 controls and 6 SWEDDs were enrolled at this site
- And the winner is....



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# Top Enrolling Sites: #2

- 25 PD, 11 controls and 6 SWEDDs were enrolled at this site
- And the winner is....



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# Highest Average Number of Controls Consented per Month

- An Average of .6 controls per month were consented at this site
- And the winner is....



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# Push for Controls at the End (Since Jan 2013)

- 5 new controls consented in the last four months
- And the winner is....



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# Push for PD at the End (Since Jan 2013)

- 6 new PD subjects consented in the last four months
- And the winner is....



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# Retention Progress to Date

- Overall study retention is 97.6%
- Sites with 100% of consented subject retained:
  - OHSU
  - U Washington
  - Baylor
  - The PI
  - Boston U
  - U South Florida
  - Hopkins
  - UC, San Diego
  - U Cincinnati
  - Imperial College
  - U Salerno
  - PD Center of Boca Raton
  - Macquerie U



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# Ongoing Retention Strategies

- Giveaways
- Subject newsletters (2x per year)
- Retention events
- Subject Travel and Accommodation funding

***What other ideas should we be considering?***



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# Site Awards

Drumroll, please.....



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# 100% completion of Study Visits

- This site that has had every subject complete all of their study visits; has done 83 PPMI visits to date
- And the winner is...



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# 100% completion of LP's

- This site that has had every subject complete all of the LPs at their study visits; has done 72 LPs to date
- And the winner is...



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# The Road Ahead: Retain Retain Retain!

- Retention: Maintaining the stamina and loyalty of enrolled subjects
  - How do we keep this up?
  - How can we step this up over time?
  - What do you need at the sites to remain engaged with the study?



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# Questions?



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# **Genetic PPMI**

**Ken Marek**

**PPMI Investigators Meeting**  
**May 7, 2013**  
**New York, NY**

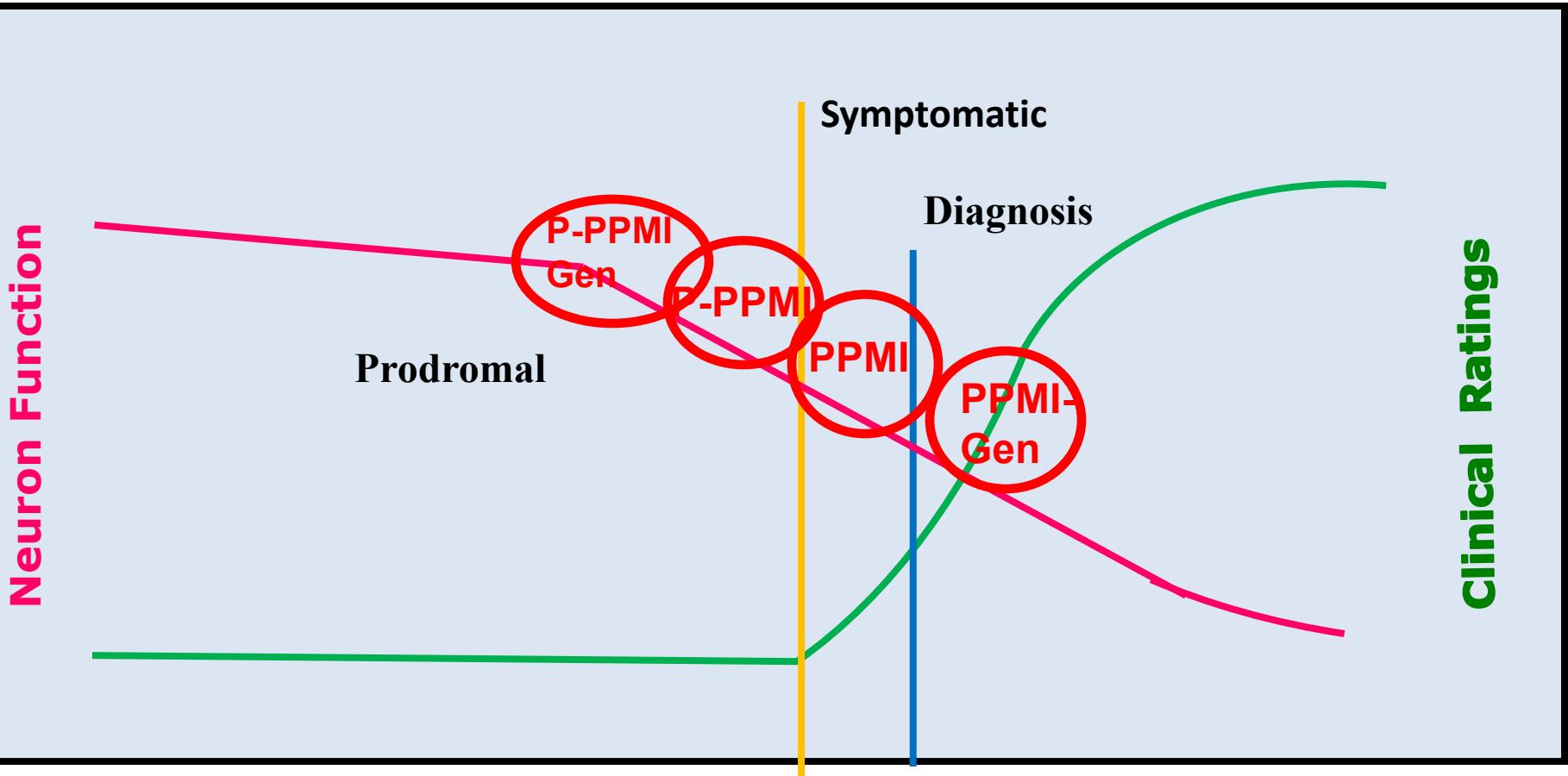


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# Natural history of Parkinson's disease



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# 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 an intensive longitudinal clinical assessment protocol.
- Follow PD and unaffected family members for four 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 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 four years
  - Establish pre-motor biomarker signature
  - Define phenoconversion
- Maintain PPMI database structure and commitment to rapid access to data



# PPMI - Cohorts

**1300-1400 Subjects Enrolled**

- **400 Parkinson disease (PD)**
- **200 Healthy controls (HC)**
- **60 subjects without evidence of dopaminergic deficit**
- **100 Prodromal**
- **200-250 Parkinson disease with LRRK2 mutation**
- **200-250 unaffected family members of LRRK2 Parkinson disease patients and/or unaffected LRRK2 mutation carriers**
- **50 Parkinson disease (PD) with a-synuclein mutation**
- **50 unaffected family members of a-synuclein Parkinson disease patients and/or unaffected a-synuclein mutation carriers**
- **600 – Registry subjects – LRRK2 PD/LRRK2 non-PD, LRRK2 family members non carriers/Synuclein PD/Synuclein non-PD, Synuclein family members non carriers**



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# Two Stage Enrollment – LRRK2

- 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 intensive vs registry
  - All LRRK2/Syn pos PD eligible - PPMI intensive
  - Unaffected family members
    - LRRK2/Syn pos- PPMI intensive >>> registry
    - LRRK2/Syn neg - PPMI intensive << registry



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# Eligibility -

## **Parkinson disease (PD) with LRRK2/Syn mutation:**

- Inclusion:
- Patients must have at least two of the following: resting tremor, bradykinesia, rigidity (must have either resting tremor or bradykinesia); OR either asymmetric resting tremor or asymmetric bradykinesia.
- A diagnosis of Parkinson disease for 10 years or less at Screening.
- Hoehn and Yahr stage < 4 at Baseline.
- Confirmation from imaging core that screening dopamine transporter SPECT scan is consistent with dopamine transporter deficit (or for sites where DaTSCAN™ is not available, that VMAT-2 PET scan is consistent with VMAT deficit).
- Male or female age 18 years or older at time of PD diagnosis.
- Confirmation of genetic mutation in LRRK2



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# **Eligibility -**

## **Parkinson disease (PD) with LRRK2/Syn mutation:**

Not Exclusion

Atypical PD syndromes degenerative diseases (e.g., MSA progressive supranuclear palsy).

Currently taking levodopa, dopamine agonists, MAO-B inhibitors (e.g., selegiline, rasagiline), amantadine or other PD medication.

Has taken levodopa, dopamine agonists, MAO-B inhibitors or amantadine within 60 days of baseline. Has taken levodopa or dopamine agonists prior to Baseline for more than a total of 60 days.

Use of investigational drugs or devices within 60 days prior to Baseline (dietary supplements taken outside of a clinical trial are not exclusionary, e.g., coenzyme Q10).



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# **Eligibility -**

**Unaffected family members of LRRK2/SYN Parkinson disease patients and/or unaffected LRRK2/Syn mutation carriers**

- **Inclusion:**
- **Male or female age 50 years or older at Screening.**
- **First degree relative of PD patients with LRRK2/Syn and/or unaffected documented LRRK2/Syn mutation carriers**
- **Willingness to undergo genetic testing for LRRK2/Syn**



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# **Eligibility -**

**Unaffected family members of LRRK2/Syn Parkinson disease patients and/or unaffected LRRK2/Syn mutation carriers**

**Not Exclusion:**

**MoCA score of 26 or less (i.e., eligible if score is 27 to 30).**

**Use of investigational drugs or devices within 60 days prior to baseline (dietary supplements taken outside of a clinical trial are not exclusionary, e.g., coenzyme Q10).**



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# Eligibility - Registry

**LRRK2/Syn PD/Unaffected family members of LRRK2/Syn Parkinson disease patients and/or unaffected LRRK2/Syn mutation carriers**

## Inclusion:

- **Male or female age 18 years or older at Screening.**
- **First degree relative of PD patients with LRRK2 and/or unaffected documented LRRK2/Syn mutation carriers or LRRK2 PD subject (note PD based on clinical dx - Willingness to undergo genetic testing)**



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# **Assessments PD and non-PD - Intensive**

Screening to assess PD/eligibility

All PD assessments

Fam History assessment

Prodromal – Phenoconversion

Prodromal - additional -

Motor

Synuclein

Timing of assessments

q 6 months



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# **Assessments PD and non-PD - Registry**

Screening to assess PD/eligibility

Baseline – UPDRS, MOCA, blood –DNA

Fam hx

Timing of assessments

q 24 months

Assessment – Phenoconversion, ?? Other reportable events



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# **Genetic Cohorts**

**All PPMI sites are recruiting sites**

**New sites – will be added to PPMI (also can participate in Prodromal)**

**F2F meeting Fall 2013?**



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# Special issues

Tracking enrollment categories

Tracking whether subjects informed regarding genetic status

Phenoconversion

Family tracking

Conversion from registry to intensive

Web site - confidentiality



# **Genetic Timeline**

**Draft Amendment 6 – May 10, 2013**

**Submission amendment 6 to central IRB – May 24, 2013**

**Site visits and Approvals –May/June2013**

**Site Contract May/June 2013**

**Site submission to IRB/Ethical committee –June-August 2013**

**Subject enrollment August 2013**



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# **PPMI** **LRRK2/SNCA Initiative**

Tatiana Foroud, Ph.D.  
Indiana University  
School of Medicine



# **What makes a family study different from a typical study?**

- Family study involves the engagement and recruitment of multiple individuals
- Knowledge of one individual's genetic status has impact on other family members
  - Some family members don't want to know their status
- Geographic distribution

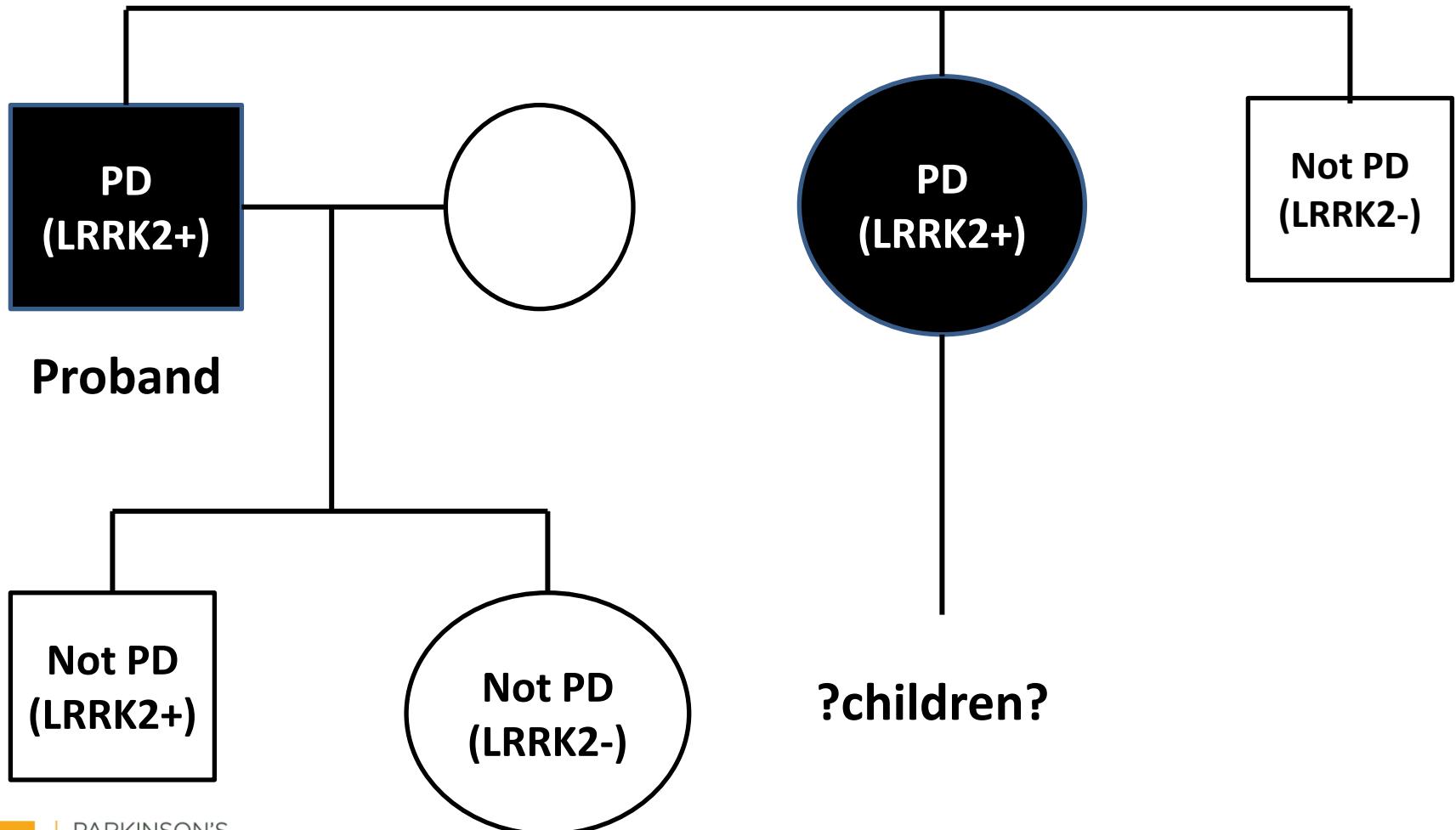


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# Typical Family



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# **Challenge: Tracking Families**

- When tracking only an individual, subject ID will suffice
- When tracking a family (multiple members) need a way to keep them together in a group with a unique identifier
  - Family ID is the most common way to do this
- Works within a site and across sites



# Challenge: Family Structure

- We can keep families together using a family ID, also need to track how they are related to each other
- Why?
  - Important in many analyses when assumptions of independence are critical
  - Can condition on relationships (when known)
  - Allows genetic transmission to be explored



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# Family Structure

- Will collect family information using Family History CRF
- Sites will need to augment this to assist in recruiting other family members
- Will confirm relationships among individuals in PPMI using DNA marker information
  - Can be used to verify paternity, half vs. full siblings, etc.



# Challenge: Distributing Genetic Information

- Genetic information often receives a higher scrutiny than other types of data
  - Concerns primarily about identification of the subject
- Many different models are used to distribute genetic data
  - Vary in the way to access the information
  - Vary in the type of information made available



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# Challenge: Distributing Genetic Information

- In PPMI, we are exploring models like those used in ADNI (AD), DIAN (AD), PREDICT (HD)
  - DIAN and PREDICT focus on Mendelian diseases with high penetrance
  - ADNI has shared deep genetic data, but not in a Mendelian disease context
- dbGaP (database of Genotypes and Phenotypes)
  - NIH solution to the sharing of genetic data



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# **Genetic Coordinating Center\***

- Located at Indiana University
- Help develop family recruitment strategies
  - Work with sites for ethics approval
  - Provide recruitment materials
  - Train coordinators to recruit families
  - Advise sites on family expansion



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# Genetic Coordinating Center

- Coordinate *LRRK2/SNCA* testing
  - Help identify who to test within a family
  - Identify appropriate *LRRK2/SNCA* testing sites
  - Review *LRRK2/SNCA* genetic results
  - Assign subjects to Intensive or Registry arm

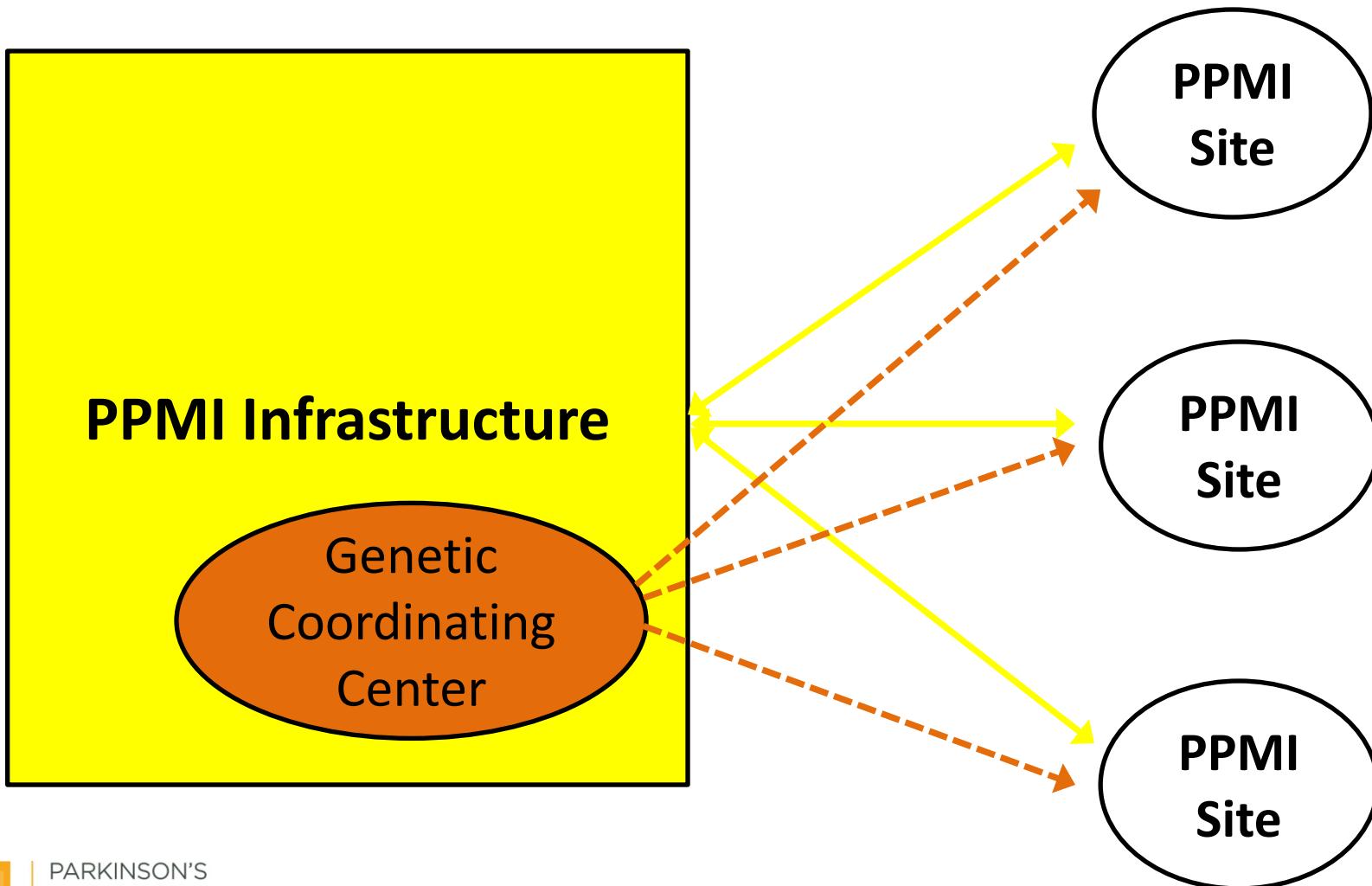


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# Partnering to Succeed



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The Tel Aviv  
Sourasky  
Medical Center



University Hospital at  
Manhattan Campus  
the Albert Einstein Co.  
of Medicine



COLUMBIA UNIVERSITY  
MEDICAL CENTER

# THE ASHKENAZI JEWS LRRK2 – G2019S MUTATION CONSORTIUM RESULTS OF THE CROSS SECTIONAL STUDY

PIs: Susan Bressman, Karen Marder, Nir Giladi, Avi Orr-Urtreger



# Frequency of mutations in the *GBA* and *LRRK2* genes in the general AJ population

Dovepress

Schulte & Gasser, 2011

Genetic basis of Parkinson's disease

**Table I** Summary of genes and loci underlying Parkinson's disease

Locus	Gene	Chromosomal location	Inheritance	Type of parkinsonism
PARK1/PARK4	SNCA	4q21	AD + risk	LOPD/EOPD, dementia
PARK2	<i>Parkin</i>	6q25-q27	AR	EOPD
PARK3	Unknown	2p13	AD	LOPD
PARK5	UCHL1	4p14	AD	LOPD
PARK6	PINK1	1p36	AR	EOPD
PARK7	DJ1	1p36	AR	EOPD
PARK8	<i>LRRK2</i>	12q12	AD + risk	LOPD
PARK9	ATP13 A2	1p36	AR	EOPD, Kufor-Rakeb syndrome
PARK10	Unknown	1p32	Unknown	LOPD
PARK11	GIGYF2	2q37	AD	LOPD
PARK12	Unknown	Xq21-25	X-linked	LOPD
PARK13	HTRA2	2p12	AD	LOPD
PARK14	PLA2G6	22q13	AR	EOPD, dystonia-parkinsonism
PARK15	FBXO7	22q12-q13	AR	EOPD, pallido-pyramidal syndrome
PARK16	Unknown	1q32	Risk	LOPD
PARK17	GAK	4p16	Risk	LOPD
PARK18	HLA	6p21	Risk	LOPD
-	EIF4GI	3q27	AD	LOPD
-	<i>GBA</i>	1q21	Risk	LOPD
-	<i>MAPT</i>	17q21	Risk	LOPD
-	<i>BST1</i>	4p15	Risk	LOPD

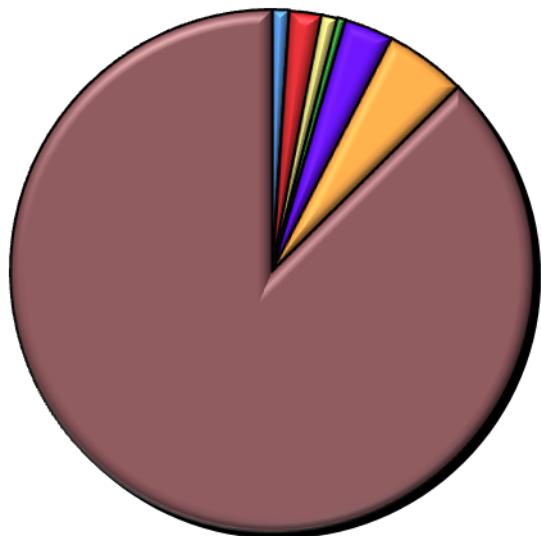
**Abbreviations:** AD, autosomal dominant; AR, autosomal recessive; EOPD, early-onset Parkinson's disease; LOPD, late-onset Parkinson's disease.

2.1% in AJ

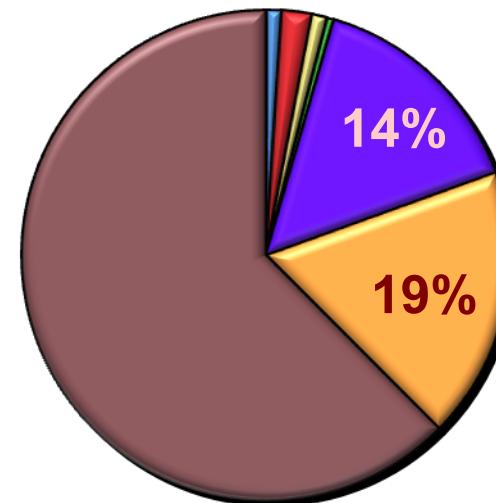
6.4% in AJ

# The frequency of mutation associated PD

World wide



Among Ashkenazi Jews



- SNCA
- parkin
- pink1
- DJ-1
- LRRK2
- GBA
- other

# “Cross-sectional”: 4 year study

- Characterize the G2019S phenotype in diagnosed PD subjects, comparing LRRK2+ to other (AJ) PD
  - Compare motor, non-motor (cognitive, autonomic, mood, olfactory, sleep) other medical (cancer) and imaging (USG, DAT)
  - Identify early, pre-diagnosis markers of LRRK2 G2019S expression /pathology
    - Compare mutation carriers without PD to non-carrier relatives and controls examining posited early alterations including DAT
- Determine G2019S penetrance of diagnosed PD by interview screens and also direct exams and genotyping
- Assess level of knowledge and attitudes toward genetic testing
- Use GWAS to identify variants associated with PD or interacting with LRRK2
- Examine LRRK2 expression by transcription profiling and pathway analyses
  - compare AJ PD with and without LRRK2 as well as LRRK2 first-degree relatives and unaffected controls

# The *LRRK2* Ashkenazi Jewish Consortium

- The study includes three stages:
  - 1) Screening evaluation of PD probands
  - 2) In-depth evaluation of carriers, and subset of non-carriers and all willing first-degree family members
  - 3) Longitudinal follow up on those recruited to the in-depth evaluation

The analyses presented here include the screening evaluation.

**2000+ AJ PD**



**Of these 225 are LRRK2 +**



**150 LRRK2+      150 LRRK2-  
In - depth exams**

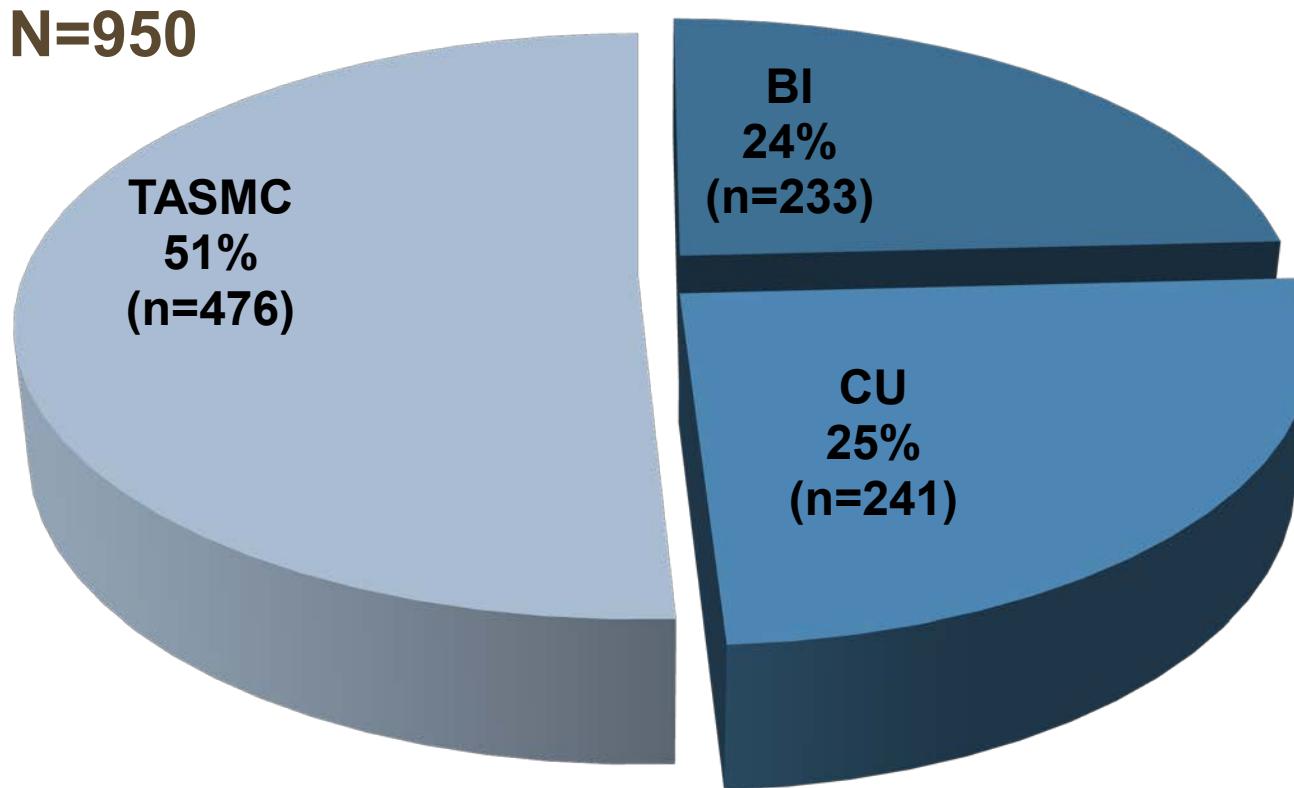
Expand families of LRRK2+  
2-2.5 per family

**100 spouse controls**

**In-depth exams**

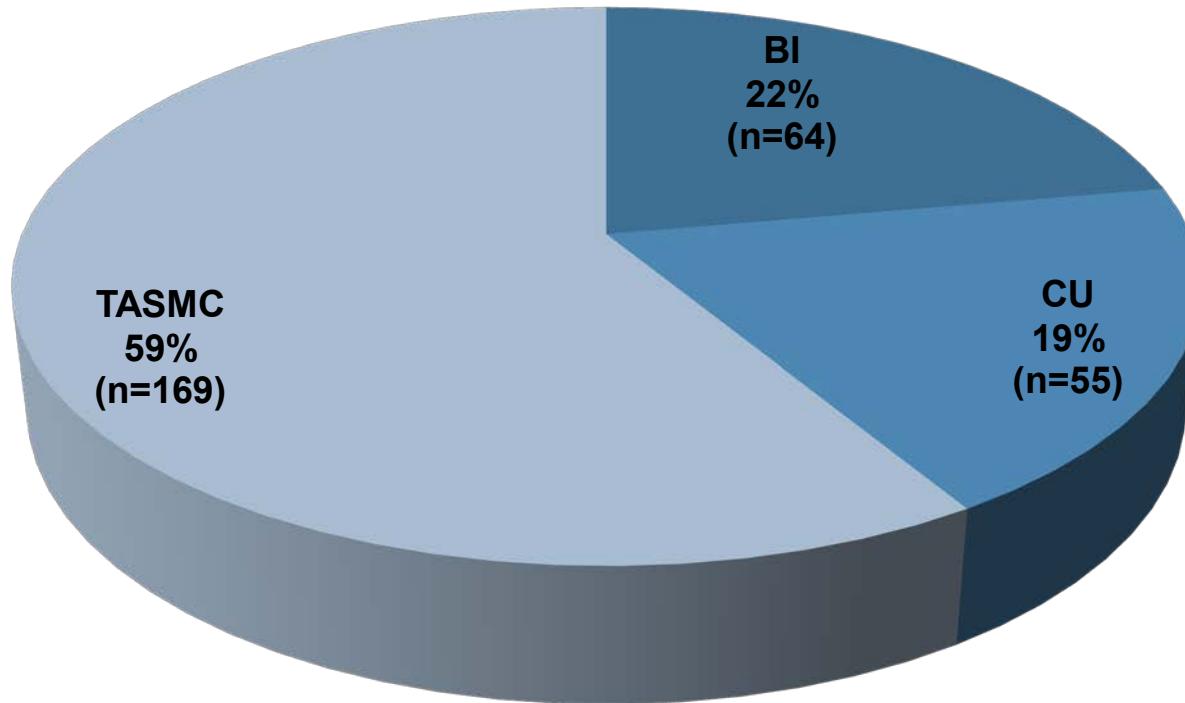
**300 1st degree relatives**  
1/2 are carriers (not diagnosed with  
PD)

# AJ consortium Total Probands Enrolled



# AJ consortium asymptomatic healthy relatives

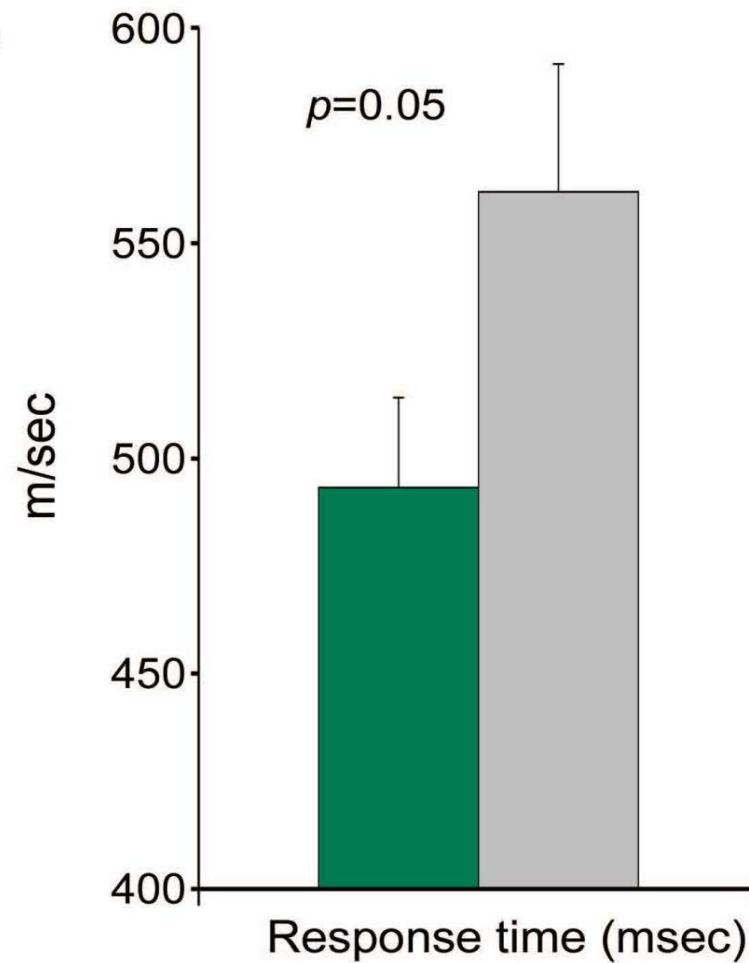
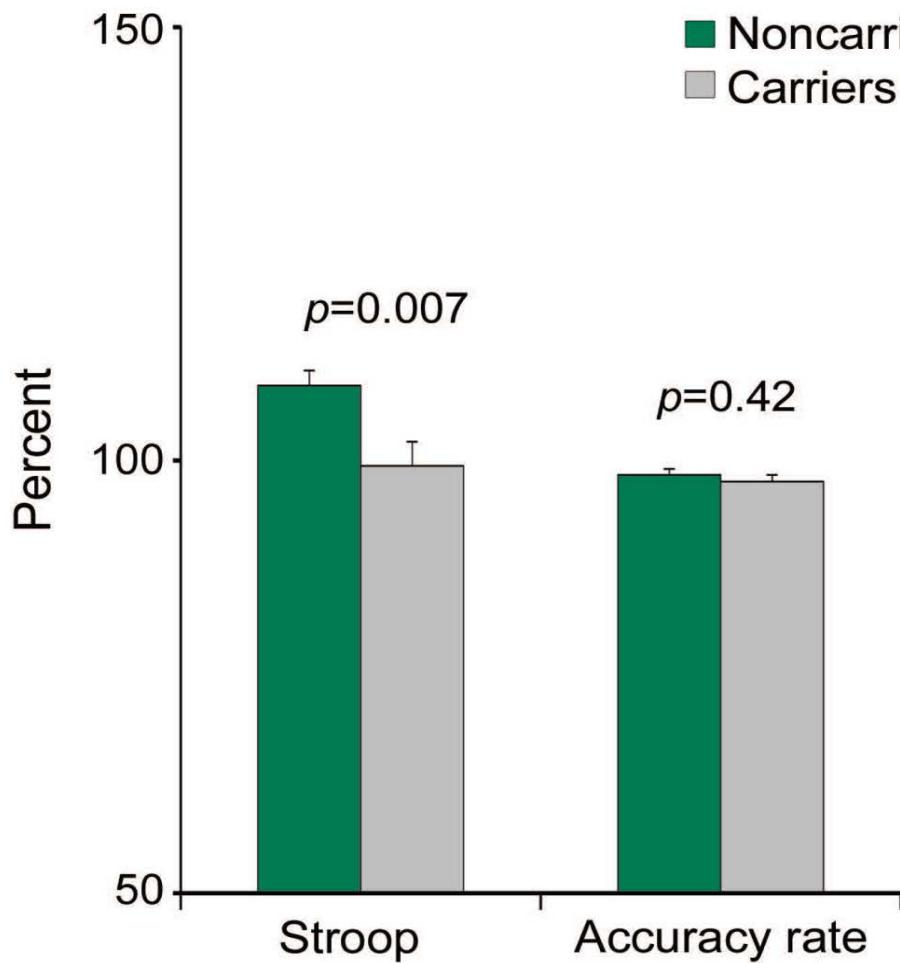
N=260



# Methods

Domain	Tool
Genotype	DNA sample from blood
Medical history	life habits and environmental questionnaires
Neurological examination	UPDRS, H&Y, S&E
Autonomic function and sleep	SCOPA-AUT, HRV, RBDQ, Epworth
Olfaction	UPSIT
Mood and affect	BDI, GDS, Spielberger trait and state anxiety
Neuropsychological evaluation	MoCA, VF, Digit span, Stroop test, TMT, computerized cognitive assessment
Motor features	BBS, TUG, gait , arm swing
Brain activation	fMRI- cognitive, motor and emotional tasks
Dopaminergic neuronal integrity	DaT scan and FDG PET

## Lower cognitive performance in healthy G2019S *LRRK2* mutation carriers





Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

**SciVerse ScienceDirect**

Journal homepage: [www.elsevier.com/locate/cortex](http://www.elsevier.com/locate/cortex)



**Research report**

**Cortex 2013**

## **Neural correlates of executive functions in healthy G2019S LRRK2 mutation carriers<sup>☆</sup>**

Avner Thaler<sup>a,b,\*</sup>, Anat Mirelman<sup>a,c</sup>, Rick C. Helmich<sup>d</sup>, Bart F.L. van Nuenen<sup>d</sup>, Keren Rosenberg-Katz<sup>b,e</sup>, Tanya Gurevich<sup>a,b</sup>, Avi Orr-Urtreger<sup>b,f</sup>, Karen Marder<sup>g</sup>, Susan Bressman<sup>h</sup>, Bastiaan R. Bloem<sup>d</sup>, Nir Giladi<sup>a,b</sup> and Talma Hendler<sup>b,e</sup>  
the LRRK2 Ashkenazi Jewish consortium

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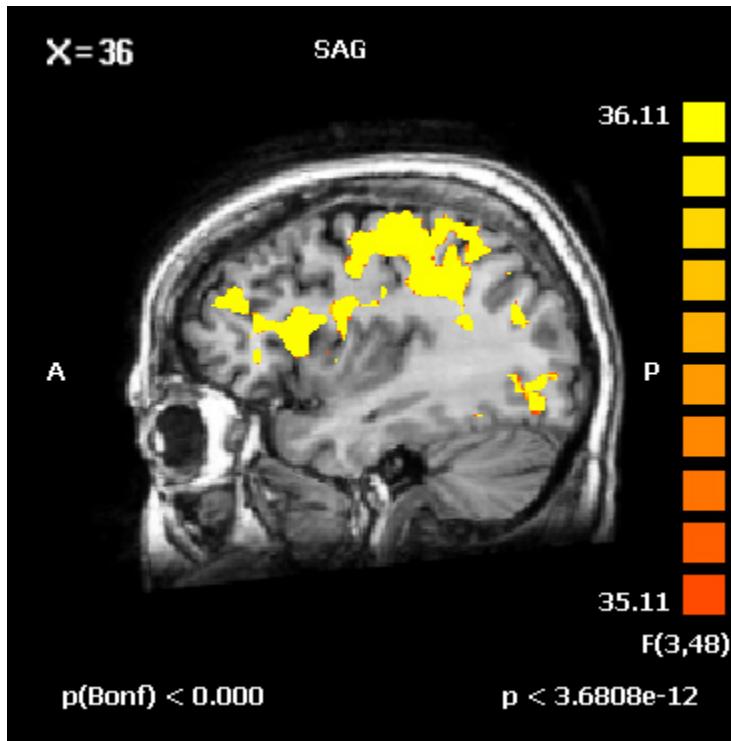
<sup>g</sup> Columbia University, Columbia University Medical Center, New York, NY, USA

<sup>h</sup> Beth Israel Medical Center, New York, NY, USA

# Activation map, stroop task

## Asymptomatic +\ G2019S mutation carriers

(N=60)

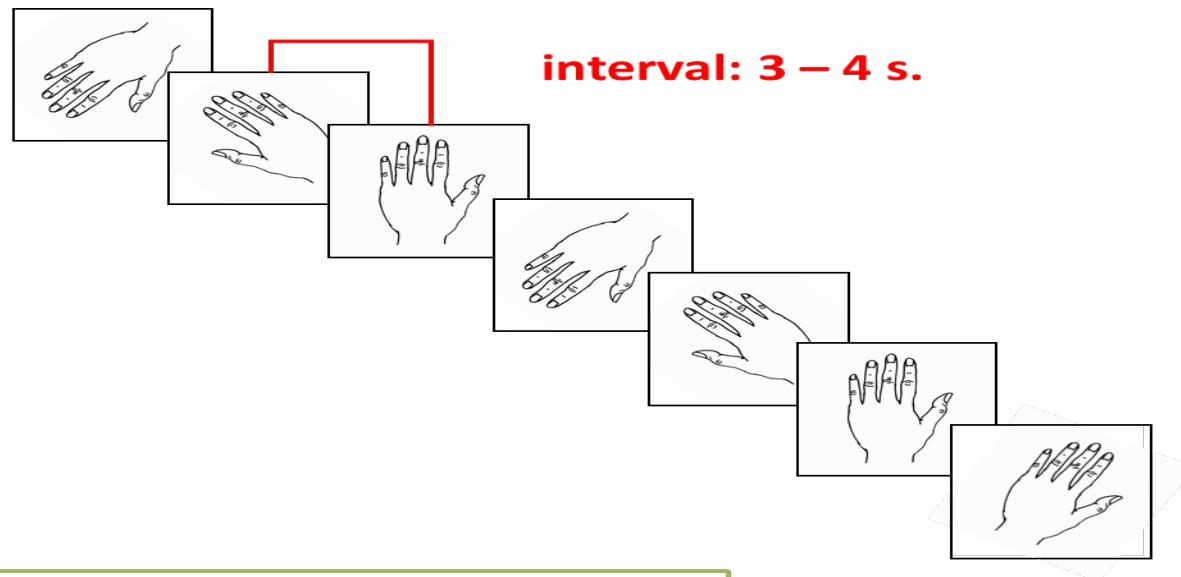


The brain areas with different activation between mutation carriers and non-carriers during the response to the stroop test

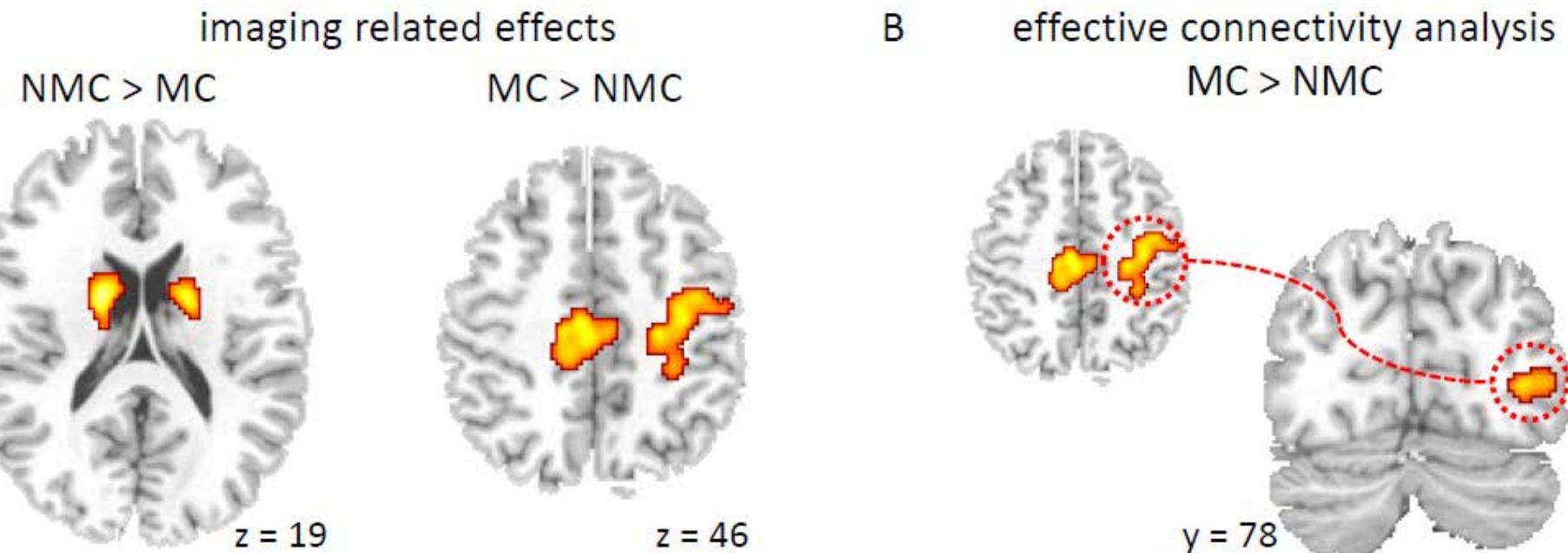
Thaler, et al, Cortex 2013

# Cerebral pathological and compensatory mechanisms in the premotor phase of leucine-rich repeat kinase 2 parkinsonism

Bart F. L. van Nuenen,<sup>1,2</sup> Rick C. Helmich,<sup>1,2</sup> Murielle Ferraye,<sup>2</sup> Avner Thaler,<sup>3</sup> Talma Hendler,<sup>3</sup> Avi Orr-Urtreger,<sup>4</sup> Anat Mirelman,<sup>3</sup> Susan Bressman,<sup>5</sup> Karen S. Marder,<sup>6</sup> Nir Giladi,<sup>3</sup> Bart P. C. van de Warrenburg,<sup>1</sup> Bastiaan R. Bloem<sup>1</sup> and Ivan Toni<sup>2</sup> on behalf of the LRRK2 Ashkenazi Jewish Consortium<sup>1\*</sup>



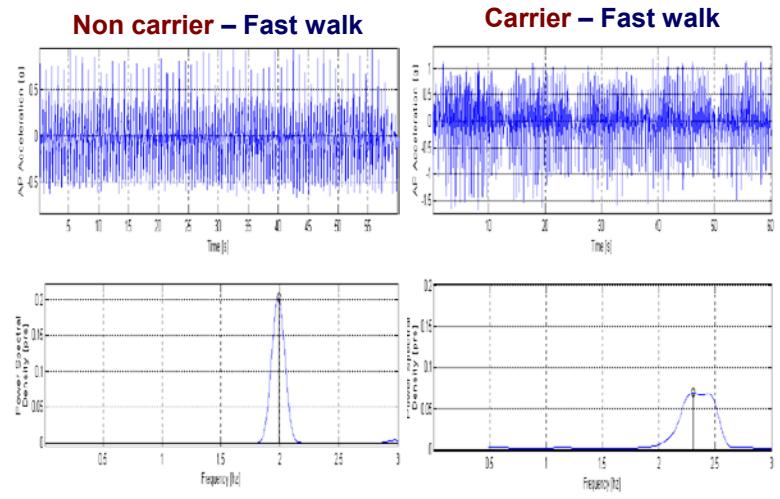
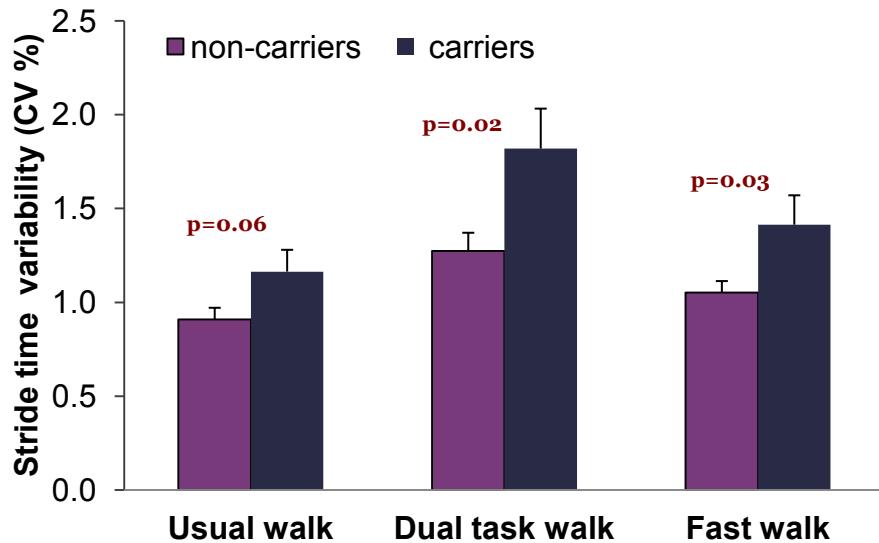
# G2019S mutation carriers use the brain differently to solve motor imagery problems



January 2011

# Gait Alterations in Healthy Carriers of the LRRK2 G2019S Mutation

***Mirelman A, Gurevich T, Giladi N, Bar-Shira A, Orr Urtreger A, Hausdorff J***



# **Future direction**

**5 years longitudinal study with 150  
1<sup>st</sup> degree subjects is on its way**

# The Ashkenazi Jewish Consortium

## Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

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Tanya Gurevich  
Jeff Hausdorff  
Avner Thaler  
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Cheryl Waters  
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Steven Frucht  
Stanley Fahn  
Oren Levy  
Ernest Roos

## Mount Sinai School of Medicine, NY, NY

Laurie Ozelius

## Yale, New Haven, CT

Ken Marrek



# PPMI Annual Meeting - MJFF

Prof Leonidas Stefanis

Dr Maria Stamelou

Second Department of Neurology

University of Athens, Greece



Science, 1997 Jun 27;276(5321):2045-7.

## **Mutation in the alpha-synuclein gene identified in families with Parkinson's disease.**

Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, Root H, Rubenstein J, Boyer R, Stenroos ES, Chandrasekharappa S, Athanasiadou A, Papapetropoulos T, Johnson WG, Lazzarini AM, Duvoisin RC, Di Iorio G, Golbe LI, Nussbaum RL.

Laboratory of Genetic Disease Research, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892-1430, USA.

### **Abstract**

Parkinson's disease (PD) is a common neurodegenerative disorder with a lifetime incidence of approximately 2 percent. A pattern of familial aggregation has been documented for the disorder, and it was recently reported that a PD susceptibility gene in a large Italian kindred is located on the long arm of human chromosome 4. A mutation was identified in the alpha-synuclein gene, which codes for a presynaptic protein thought to be involved in neuronal plasticity, in the Italian kindred and in three unrelated families of Greek origin with autosomal dominant inheritance for the PD phenotype. This finding of a specific molecular alteration associated with PD will facilitate the detailed understanding of the pathophysiology of the disorder.

# Symptomatic carriers (A53T)

N	M/F	Age of onset Mean± SD (Range)	Disease duration Mean± SD (Range)	H&Y Mean± SD (Range)
20	10/10	44.8±10.3 (30-65 years)	7.1± 4.3 (0.5-18 years)	2.4 ±1.2 (1-5)

# Symptomatic carriers (A53T) disease duration < 7 years

N	M/F	Age of onset Mean± SD (Range)	Disease duration Mean± SD (Range)	H&Y (Range)
13	6/7	46.3±11.8 (30-65 years)	4.4± 1.7 (0.5-7 years)	1-3

- Phenotypic variability between families and members of the same family

# Asymptomatic carriers

N	M/F	Age (Range)
9	1/8	51.4 ± 18 (35-90 years)

Areas where most of the current families are located



# PPMI Data Analyses

Christopher S. Coffey

The University of Iowa

Ken Marek

The Institute for Neurodegenerative Disorders

PPMI Investigators Meeting

May 8, 2012

New York, NY



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# Publication Policy

## Goals-

**High quality, rapid publication**

**Consistent with the broad PPMI collaboration**

**SC, Cores, Sites, Working Groups**

**Encourage non-PPMI community**



# Publication Policy

- **Key Primary**
- **Primary**
- **Others**
- **Abstracts for meetings**
- **Role of DPC**



# Publication Policy-Key Primary

**Key Primary Publications** - *Key Primary Publications* are defined as those reports, analyses and publications identified by the PPMI Steering Committee as fulfilling the primary objectives of the study. Examples of these reports include publications detailing the baseline or yearly data-cuts

The SC will be primarily responsible for completion of all Key Primary Publications. Key Primary publications will be authored by the Steering Committee, Investigators, Study Cores and Working Groups reflecting the contribution of those authors.



# Publication Policy - Key Primary

For KEY primary publications

“And The Parkinson’s Progression Markers Initiative\*” will be written on the author line of the manuscript with an asterisk referring to the list of names of individuals identified on the PPMI author list. The author list must be included as an appendix to ensure that all authors may be cited. The complete list of PPMI Study Investigators can be found at [www.ppmi-info.org/Authorslist](http://www.ppmi-info.org/Authorslist)

**Sent to both the PPMI Steering Committee and the PPMI Data & Publications Committee (DPC) for review prior to journal submission.**

# Publication Policy-Primary

**Primary Publications** - Primary publications are defined as reports, analyses and publications that are initiated by PPMI study members that utilize PPMI data, but which do not address the primary objectives of the study. Examples of these studies include a focus on specific biomarkers of disease progression, study infrastructure or recruitment.

Publications developed by study investigators, cores, working groups and authorship will reflect the contribution of those authors. In addition to the authors, “And The Parkinson’s Progression Markers Initiative\*” will be written on the author line of the manuscript with an asterisk referring to the list of names of individuals identified on the PPMI author list. The author list must be included as an appendix to ensure that all authors may be cited. The list of PPMI Study Investigators can be found at [www.ppmi-info.org/Authorslist](http://www.ppmi-info.org/Authorslist)



# Publication Policy-Primary

**Primary Publications - Sent to both the PPMI Steering Committee and the PPMI Data & Publications Committee (DPC) for review prior to journal submission**

# Publication Policy-Other

**Other Publications - It is expected that investigators outside of the study will conduct research and seek to publish analyses using PPMI data and specimens. These individuals are encouraged to publish novel scientific findings that result from their research using PPMI. Authorship of such a publication will not include PPMI in the author line,**

# Publication Policy-Other

PPMI personnel and PPMI funding support will be acknowledged by including the following within the manuscript:

"Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database ([www.ppmi-info.org/data](http://www.ppmi-info.org/data)). For up-to-date information on the study, visit [www.ppmi-info.org](http://www.ppmi-info.org)."

"PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including [list the full names of all of the PPMI funding partners found at [www.ppmi-info.org/fundingpartners](http://www.ppmi-info.org/fundingpartners) ]."

Make link to webpage

# Publication Policy-Other

**All other publications must be sent to the PPMI DPC for administrative review prior to journal submission. To submit to the DPC, please upload the publication for review via the PPMI website**

# Publication process - Primary

- Authors should develop data analysis plan in collaboration with Stats
- Authors should develop time-line for drafts and completion of report
- Goal is to identify authors for primary publications.



# Source and Cut of Data

- Source should be LONI data so need to submit all data
- Timing of Data cuts - Data cuts to be published by SC
  - Baseline, 6 months, 1 year, then yearly
- Definition of full data set



# Publication and Analysis plans



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# Baseline data

- Primary baseline
- Subsets
- Cognitive – domains, compare UPDRS
- Imaging - DAT, AV133, DTI, Resting state
- Biologics -CSF analytes, Urate, Genetics
- Process - Recruitment, Imaging, CSF
- Ancillary - Tap
- SWEDD



# Baseline data Papers

Paper #	Description	Contact	Status	Date of Most Recent Change to List
1	Overall Baseline Paper	Ken Marek	Preliminary Tables Reviewed	24 Apr 2013
2	Cognitive Paper	Dan Weintraub	Building Tables with Data	18 Apr 2013
3	DATSCAN Paper	John Seibyl / Ken Marek	Tables Sent to John and Ken / Feedback Pending	18 Apr 2013
4	DTI Paper	Norbert Schuff	-	24 Apr 2013
5	Biologics Paper	Les Shaw / John Trojanowski	-	18 Apr 2013
6	Urate Paper	Constantinescu Radu	Tables for an abstract sent to Radu / Feedback Pending	18 Apr 2013



# PLANNED ANALYSES

## Planned Analysis #1: Comparison of Baseline Characteristics Among Health Subjects and PD Subjects.

- Continuous variables assessed using t-test
- Dichotomous variables assessed using chi-square test
- Appropriate assumptions will be assessed for each comparison and any necessary adjustments (i.e., transformations) will be made prior to analysis



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# 12 month data

- Primary baseline
- Subsets
- Cognitive – domains, compare UPDRS
- Imaging - DAT, AV133, DTI, Resting state
- Biologics -CSF analytes
- Process – Retention,CSF
- Ancillary - Tap
- SWEDD



# PLANNED ANALYSES

## Baseline

Tabulate and compare for all subjects Demographics by diagnostic category (PD, HC, SWEDD; Compare PD vs HC; PD vs SWEDD)

Age

Gender

Education

Ethnicity

Race

Family history of PD

(From tables 3 and 4 – monthly)



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# PLANNED ANALYSES

## Baseline

Tabulate and compare for all subjects Summary clinical scores by diagnostic category (PD, HC, SWEDD; Compare PD vs HC;PD vs SWEDD)

UPDRS Total and subscore

Hoehn and Yahr

Schwab and England

Dur of Dis

MOCA total

GDS Total

SCOPA AUT total

State Anxiety

QUIP

UPSIT

Epworth

(From tables 4 and 5)



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# PLANNED ANALYSES

## Baseline

Tabulate and compare for all subjects DAT imaging SBR  
by diagnostic category (PD, HC, SWEDD; Compare PD vs HC;PD vs SWEDD)

Mean striatal

Mean putamen

Mean caudate

Ipsilateral Caudate

Contralateral Caudate

Ipsilateral Putamen

Contralateral Putamen



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# PLANNED ANALYSES

## Baseline

Tabulate and compare for all subjects CSF synuclein, amyloid, Tau by diagnostic category (PD, HC, SWEDD; Compare PD vs HC;PD vs SWEDD)

A $\beta$ <sub>1-42</sub> (pg/mL)

t-tau (pg/mL)

p-tau<sub>181</sub> (pg/mL)

t-tau/A $\beta$ <sub>1-42</sub> ratio

p-tau<sub>181</sub>/A $\beta$ <sub>1-42</sub> ratio

p-tau<sub>181</sub>/t-tau ratio

A-syn (pg/mL)

Should we include hemoglobin data?



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# PLANNED ANALYSES

## Baseline

UPDRS as an anchor: relationship between baseline UPDRS with non-motor, imaging, biologic at baseline (PD, HC, SWEDD; Focus on PD) – See Ravina et al. *Dopamine Transporter Imaging Is Associated With Long-Term Outcomes in Parkinson's Disease*

Adjusted for age, gender, duration of disease

To be compared

MOCA total

GDS Total

SCOPA AUT total

State Anxiety

QUIP

UPSIT

Epworth

DAT

A $\beta$ <sub>1-42</sub> (pg/mL)

t-tau (pg/mL)

p-tau<sub>181</sub> (pg/mL)

t-tau/A $\beta$ <sub>1-42</sub> ratio

p-tau<sub>181</sub>/A $\beta$ <sub>1-42</sub> ratio

p-tau<sub>181</sub>/t-tau ratio

A-syn (pg/mL)



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# PLANNED ANALYSES

## Baseline

DAT scan as anchor: relationship between baseline DAT with motor, non-motor biologics at baseline (PD, HC, SWEDD; Focus on PD) See Ravina et al. *Dopamine Transporter Imaging Is Associated With Long-Term Outcomes in Parkinson's Disease*

Adjusted for age, gender, duration of disease

To be compared

UPDRS

MOCA total

GDS Total

SCOPA AUT total

State Anxiety

QUIP

UPSiT

Epworth

A $\beta$ <sub>1-42</sub> (pg/mL)

t-tau (pg/mL)

p-tau<sub>181</sub> (pg/mL)

t-tau/A $\beta$ <sub>1-42</sub> ratio

p-tau<sub>181</sub>/A $\beta$ <sub>1-42</sub> ratio

p-tau<sub>181</sub>/t-tau ratio

A-syn (pg/mL)

Urate



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# PLANNED ANALYSES

## Planned Analysis #2: Comparison of Short-Term Change in Progression Endpoints.

- Examine short-term change during first six months for each progression endpoint using mixed model (continuous endpoints) or logistic regression (dichotomous endpoints)
- Initial model will include all baseline characteristics, indicator for whether healthy control or PD patient, and all possible two-way interactions
- Will utilize backwards selection to build a model for each progression endpoint



# PLANNED ANALYSES

## Planned Analysis #3: Examination of Whether Short-Term Change in Progression Endpoints is Predictive of Change in Long-Term Endpoints

- Consider only progression endpoints that show differences between healthy subjects and PD patients
- Primary focus on long-term change in UPDRS score – additional long-term endpoints may be considered as well
- Ten-fold cross-validation procedure will be used to test predictive validity of each model
- If successful, final model will provide subset of short-term progression endpoints predictive of change in long-term endpoints – suggest biomarkers for future studies of interventions in PD patient populations



# PLANNED ANALYSES

## Planned Analysis #4: Examination of PD Subsets

- Each of first three sets of analyses will be repeated comparing subsets of PD patients
- If successful, final model will determine whether some short-term progression endpoints are more predictive of long-term endpoints for some subsets of PD patients and less predictive for other subsets



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# PLANNED ANALYSES

## Planned Analysis #5: Proportion of SWEDD subjects that have a change in diagnosis over 24 month evaluation period

- Percentage and 95% confidence interval will be reported
- Other possible diagnoses will be further divided into 2 categories:
  - Other parkinsonian syndrome with a dopamine transporter deficit
  - Other condition with a dopamine transporter deficit



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# PLANNED ANALYSES

## Planned Analysis #6: Exploratory analysis of SWEDD subjects

- Important changes over time found in planned analyses 1-3 will be assessed in the SWEDD subjects
- Will help to assess whether changes over time in SWEDD subjects are similar or dissimilar to PD subjects



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# ANALYSES

- TD vs PIGD
- Meds vs no Meds
- Comparison cognitive with imaging/CSF
- Sleep assessments
- Enrollment/recruitment
- Comparison of DAT and DTI
- UPDRS vs cognitive measures



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