

# PPMI Status Update

**Ken Marek**

**PPMI Genetics Kickoff  
Sept 16, 2013  
New York, NY**



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# PD patient

MAY 2011

- **67 yo right handed WF in excellent general health**
- **History**  
**6 month history of poor tennis play**  
**Note 1-2 years – mild constipation**  
**2 months intermittent R UE tremor while reading the newspaper, or if in stressful situation**
- **Exam**  
**Mild R UE resting tremor**  
**Reduced R arm swing**
- **PD DIAGNOSIS – 1 MONTH AGO**
- **“IF THE SYMPTOMS REMAIN AS THEY ARE NOW – I COULD DEAL WITH THIS”**

Sept 2013

Two years + progression

**History**

**Continue to work, all activities**

**Requires sinemet 100 mg tid**

**Worried about future**

**Exam**

**Mild R UE> L UE resting tremor**

**R brady UE>LE**

**PD DIAGNOSIS – 29 MONTH AGO**

**“THESE SYMPTOMS ARE ANNOYING AND I WORRY THAT THEY ARE GETTING WORSE.”**



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## PPMI- Prodromal

- **64 yo right handed WM painter in excellent general health**
- Noticed no longer bothered by smell of paint x 2-3 years
- Wife reports episodic jumping off bed during sleep
- Maybe balance not quite as good on ladders

**Exam**

**Normal**

- **Can PPMI track the prodromal period in individuals at high risk for PD – P-PPMI**

## PPMI- Genetics

**74 yo right headed retired WF journalist in excellent general health. The subjects is of Ashkenazi Jewish dissent**

**Her brother developed PD at age 63 and her father had resting tremor and walking trouble before he died at age 71 of cardiac disease**

**Exam**

**Normal**

**Can PPMI identify and track the prodromal period in individuals at high risk for PD due to specific mutations–PPMI - Genetics**



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# Parkinson's Progression Markers Initiative

- Disease modifying PD therapeutics remain a major unmet need
- A major obstacle to current phase 2/3 neuroprotection studies is the lack of biomarkers for
  - Disease mechanism
  - Drug mechanism
  - Dosage determination
  - Study eligibility
  - Stratification into PD sub-types
  - Correlation with clinical signals

Requirements for Biomarker Infrastructure

## Specific Data Set

- Appropriate population (early stage PD and controls)
- Clinical (motor/non-motor) and imaging data
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## Standardization

- Uniform collection of data and samples
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## Access/Sharing

- Data available to research community → data mining, hypothesis generation & testing
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# PPMI Genetic Kickoff

- **Goals of PPMI – Genetic Cohort/Registry –**
  - Identify progression biomarkers that would inform therapeutic development for PD
  - Identify a cohort that might participate in clinical studies.
- **Goal of the meeting**
  - Review PPMI genetic Cohort/Registry recruitment, enrollment and study conduct
  - Integrate the new PPMI sites into the PPMI study – goals, standardization, training, data, culture
  - Review PPMI progress and continue to focus on subject retention, prodromal enrollment, data acquisition, data reporting



# PPMI Genetic Cohort - Challenges

- Subject pool in limited
  - Creative strategies for recruitment
  - Modify eligibility to be more inclusive
- Mutations have implication for families – not just individuals
- Varied strategies at sites
  - Different population – mutations
  - Different cultures – approach to genetic disorders
  - Different approach to disclosure
- Focus on confidentiality in data
- Integration into PPMI – ensure comparability to other cohorts

**Risks to PPMI – subject retention, site fatigue, infrastructure**



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# PPMI Genetic Cohort - Opportunity

- Collaboration of investigators with experience and expertise – sum greater than the parts
- Focused Pharma drug development - requires biomarkers and cohorts
- Clinical data can inform the science
- PPMI infrastructure – sites, cores, databases, funding, collaborative culture
- Building on PPMI success
  - Enrollment
  - Comprehensive Assessment– CSF, imaging
  - Open data access
  - Comparison cohorts
  - Established culture – collaboration and innovation



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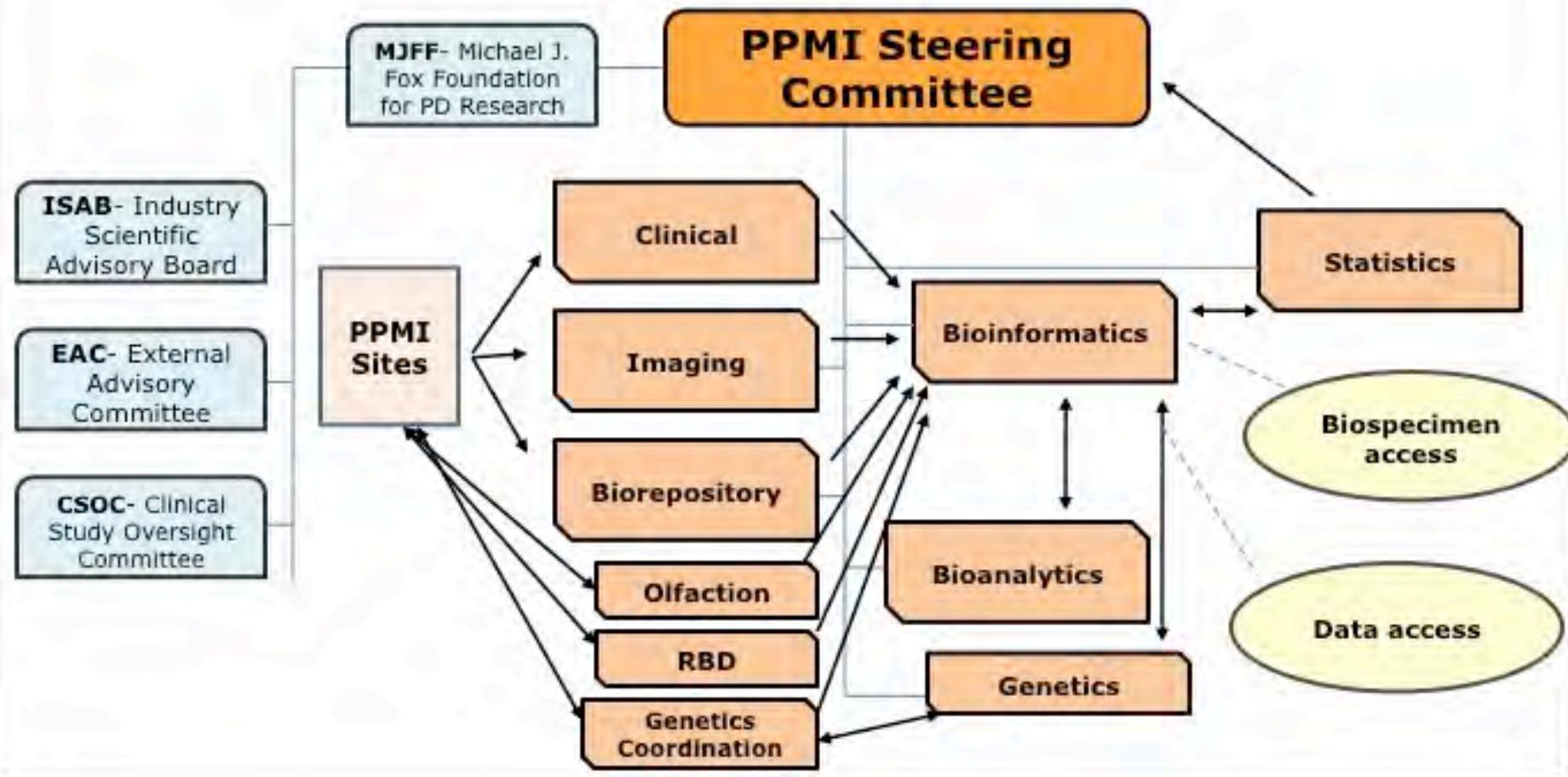


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# PPMI Study



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# PPMI Sites

## PPMI SITES IN THE UNITED STATES:

- Arizona PD Consortium (Sun City, AZ)
- Beth Israel Medical Center (NY, NY)
- Baylor College of Medicine (Houston, TX)
- Boston University (Boston, MA)
- Cleveland Clinic (Cleveland, OH)
- Columbia University (NY, NY)
- Emory University (Atlanta, GA)
- Institute of Neurodegenerative Disorders (New Haven, CT)
- Johns Hopkins University (Baltimore ,MD)
- Northwestern University (Chicago, IL)
- Oregon Health and Science University (Portland, OR)
- The Parkinson's Institute (Sunnyvale, CA)
- PD & Movement Disorders Center at Boca Raton (Boca Raton, FL)
- University of Alabama at Birmingham (Birmingham, AL)
- University of California at San Diego (San Diego, CA)
- University of Cincinnati (Cincinnati, OH)
- University of Pennsylvania (Philadelphia, PA)
- University of Rochester (Rochester, NY)
- University of South Florida (Tampa, FL)
- University of Washington (Seattle, WA)

## PPMI SITES IN EUROPE:

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

## PPMI SITES IN AUSTRALIA:

- Macquarie University (Sydney, Australia)

## PPMI SITES IN Israel:

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

# PPMI SC and Study Cores

Steering Committee	PI-K Marek, C Tanner, T Foroud, D Jennings, K Kieburtz, W Poewe, B Mollenhauer, T Simuni, S Lasch, (core leaders, MJFF, ISAB),
Clinical Coordination Core	<ul style="list-style-type: none"><li>▪ University of Rochester's Clinical Trials Coordination Center</li><li>• PI: Karl Kieburtz, Ray Dorsey irina Lazurenko, Lisa de Blieck, Alice Rudolph, Cindy Casaceli</li></ul>
Imaging Core	<ul style="list-style-type: none"><li>• Institute for Neurodegenerative Disorders;</li><li>• PI: John Seibyl, Norbert Schuff,</li></ul>
Statistics Core	<ul style="list-style-type: none"><li>▪ University of Iowa</li><li>• PI: Chris Coffey</li></ul>
Bioinformatics Core	<ul style="list-style-type: none"><li>▪ Laboratory of Neuroimaging (LONI) at UCLA</li><li>• PI: Arthur Toga, Karen Crawford</li></ul>
BioRepository	<ul style="list-style-type: none"><li>▪ Coriell/BioRep</li><li>• PI: Alison Ansbach, Paola Casalin, Dorit Berlin</li></ul>
Bioanalytics Core	<ul style="list-style-type: none"><li>▪ University of Pennsylvania</li><li>• PI: John Trojanowski, Les Shaw</li></ul>
Genetics Core	<ul style="list-style-type: none"><li>▪ National Institute on Aging/NIH</li><li>• PI: Andy Singleton</li></ul>
RBD Core	<ul style="list-style-type: none"><li>▪ Hephata Hessisches Diakoniezentrum e. V.</li><li>• PI: Geert Mayer</li></ul>
Olfactory Core	<ul style="list-style-type: none"><li>▪ Institute for Neurodegenerative Disorders</li><li>• PI: Danna Jennings</li></ul>
Genetics Coordinating Core	<ul style="list-style-type: none"><li>▪ Indiana University</li><li>• PI: Tatiana Foroud</li></ul>

# PPMI MJFF team

- **Sohini Chowdhury, PPMI Overall Project Manager**
- **Mark Frasier, Biologics (Biorepository selection; biologic collection SOPs, assay identification and optimization)**
- **Claire Meunier, Recruitment/Retention Strategies**
- **Vanessa Arnedo, Contracting, study coordination**
- **Jamie Eberling, Imaging core**
- **Katie Forsberg, Study coordination**



# PPMI Committees

- **Biologics**
  - John Trojanowski
  - Les Shaw
- **Imaging**
  - John Seibyl
  - Norbert Schuff
- **Neuropsych /Neurobehavior**
  - Dan Weintraub
- **Sleep**
  - Wolfgang Oertel
- **Genetics**
  - Andrew Singleton
- **LRRK2**
  - Tatiana Foroud
  - Susan Bressman
- **Statistical**
  - Chris Coffey
- **ISAB**
  - Bernard Ravina
- **Biospecimen review**
  - Gene Johnson
- **Data and publication**
  - David Standaert
- **Ancillary study**
  - Carlie Tanner
- **Recruitment/Retention**
  - Danna Jennings
- **Patient Advisory**
  - Danna Jennings
  - Ken Marek
- **Website**
  - Carlie Tanner
- **CSOC**
  - Ron Pfeiffer



PPMI is sponsored and partially funded by The Michael J. Fox Foundation for Parkinson's Research. Other funding partners include a consortium of industry players, non-profit organizations and private individuals.



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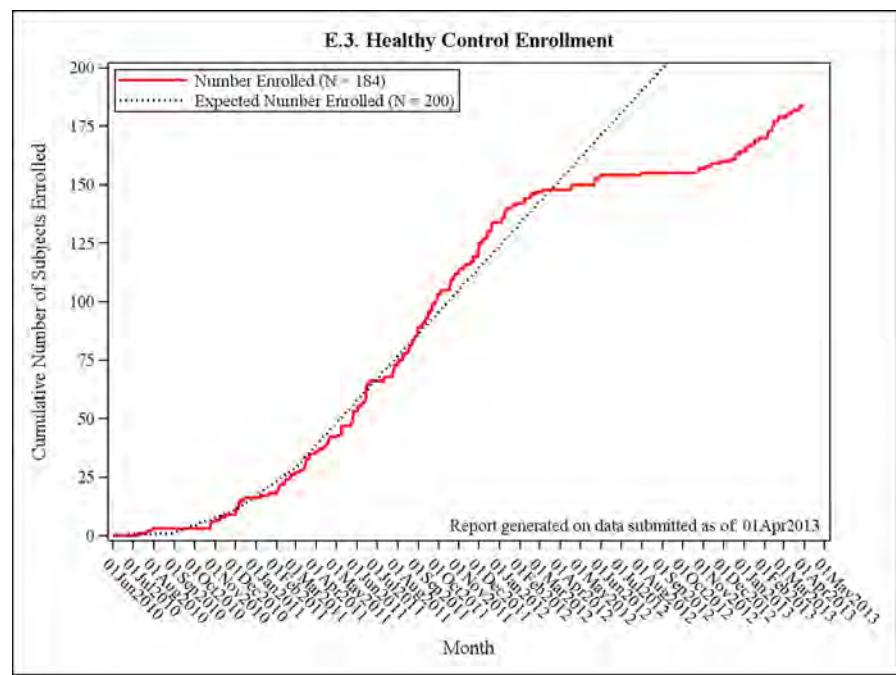
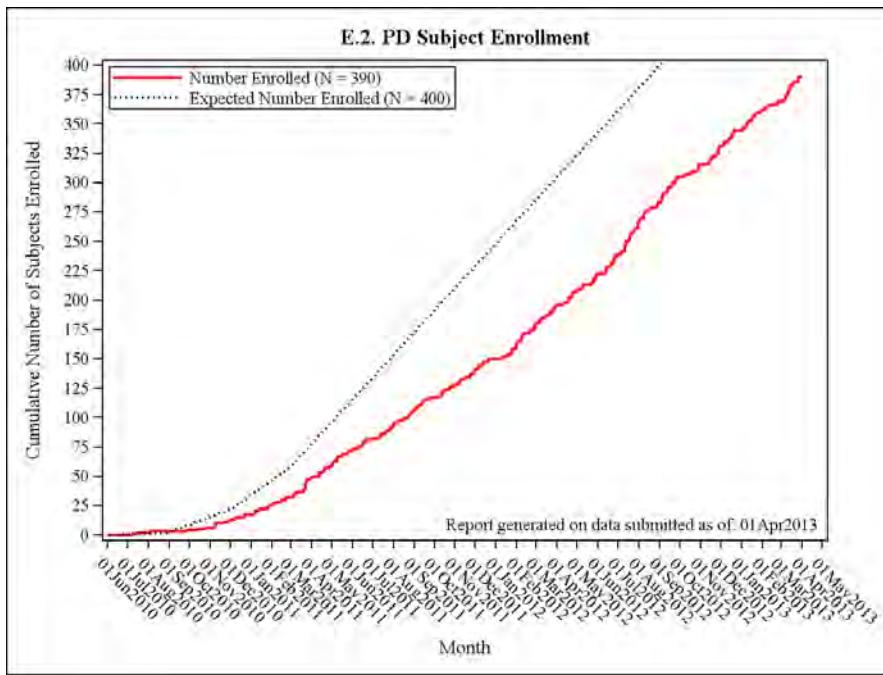
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# PPMI Study Synopsis

Study population	<ul style="list-style-type: none"><li>▪ <b>400 de novo PD subjects (newly diagnosed and unmedicated)</b></li><li>▪ <b>200 age- and gender-matched healthy controls</b></li><li>▪ <b>70 SWEDD</b></li><li>▪ <b>100 Prodromal - Olfactory/RBD/LRRK2</b></li><li>▪ <b>500 LRRK2 - PD manifest and non-manifesting family members</b></li><li>▪ <b>100 Synuclein - PD manifest and non-manifesting family members</b></li><li>▪ Subjects will be followed for 3 to 5 years</li></ul>
Assessments/ Clinical data collection	<ul style="list-style-type: none"><li>▪ Motor assessments</li><li>▪ Neurobehavioral/cognitive testing</li><li>▪ Autonomic, Olfaction, Sleep</li><li>▪ DaTSCAN, AV133, Amyloid, DTI/RS MRI</li></ul>
Biologic collection/	<ul style="list-style-type: none"><li>▪ DNA collected at screening</li><li>▪ Serum and plasma collected at each visit; urine collected annually</li><li>▪ CSF collected at baseline, 6mo 12 mo and then annually</li><li>▪ Samples aliquotted and stored in central biorepository</li></ul>
Initial Verification studies	<ul style="list-style-type: none"><li>▪ Lead biologic candidates to be tested:<ul style="list-style-type: none"><li>• Alpha-synuclein (CSF)</li><li>• DJ-1 (CSF and blood)</li><li>• Urate (blood)</li><li>• Abeta 1-42 (CSF)</li><li>• Total tau, Phospho-tau (p-181) (CSF)</li></ul></li></ul>



# Enrollment of PD/HS/SWEDD



- Enrollment – 423 PD 196 HS 64 SWEDD 683 subjects
- Retention – 413 PD 188 HS 62 SWEDD - 663 subjects



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# Recruitment – Lessons learned

- Recruitment at anticipated rate (1 PD/month, 1 control/2 months) – Note delay at startup
- Multiple strategies to enhance recruitment are necessary
  - Local media, referral groups
  - Central Fox salons, Fox Trial Finder
- Comprehensive longitudinal assessment were acceptable – including CSF and imaging  
**How to utilize experience for Prodromal and Genetic cohorts**



# Retention - moving forward

- Longitudinal data are study focus
  - Continued participation in all assessments
  - Longitudinal data
    - Need for meds
    - Participation in clinical trials
- Retention strategies are crucial
  - Site recruitment events
  - Provide study data and info to subjects
  - New cohorts – PPMI subjects assist in recruitment
  - Prevent PPMI fatigue



# Subject Enrollment and Sample Collection

**Recently Collected Samples per Visit (from May 2012 – May 2013)**

**(Total Number of Samples Collected as of May 2013)**

Visit		BL	PW	SC	ST	U01	U02	V01	V02	V03	V04	V05	V06	V07	Total
CSF Serum Plasma	Recent*	279	1	0	65	-	0	223	213	234	246	204	76	11	1552
	Total PLA	672	1	82	110	-	1	527	409	373	346	215	76	11	2823
	Recent*	279	1	0	65	-	0	223	213	234	246	204	76	11	1552
	Total SER	672	1	82	110	-	1	527	409	373	346	215	76	11	2823
	Recent*	268	-	-	39	-	-	2	184	-	211	2	61	-	767
	Total CSF	671	1	-	92	1	-	8	404	-	344	2	74	-	1597

\* The top row per biofluid type indicates the samples collected within the past year (from May 2012 thru May 2013).



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# LUMBAR PUNCTURE COMPLETENESS

Group	Baseline # Expected (% Complete)	6 Months # Expected (% Complete)	1 Year #Expected (% Complete)	2 Year #Expected (% Complete)	3 Year #Expected (% Complete)
PD Subjects	423 (98%)	357 (82%)	256 (78%)	89 (74%)	2 (100%)
Healthy Controls	196 (97%)	166 (82%)	149 (81%)	70 (67%)	2 (50%)
SWEDD Subjects	64 (92%)	55 (67%)	38 (79%)	7 (57%)	N/A

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



# Parkinson's Progression Markers Initiative

## Requirements for Biomarker Infrastructure

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# **Standardization of data acquisition/analysis**

- **Manuals/SOPs for all data acquisition**
- **Training for**
  - **Data entry**
  - **UPDRS - MDS UPDRS certification**
  - **Neuropsych/Neurobehavioral**
  - **Biologics - Collection/Aliquoting/Shipping/Storage**
  - **Imaging – Acquisition**
- **Quality control of clinical data, biosamples, imaging data at study cores**



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# Data/Biosample Access/Sharing

[www.ppmi-info.org](http://www.ppmi-info.org)

- > 80,000 Data Download via website
- >25 BRC requests – 2 successful
- Query tool to facilitate download



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# Ancillary Studies

- Assessments
  - Motor
    - TAP-PD
  - Non-Motor
    - Cognitive categorization
    - Exercise history
  - Imaging
    - AV133
    - DTI
    - RS
    - Amyloid
  - Biospecimen
    - Whole Blood
    - Skin bx for IP cells

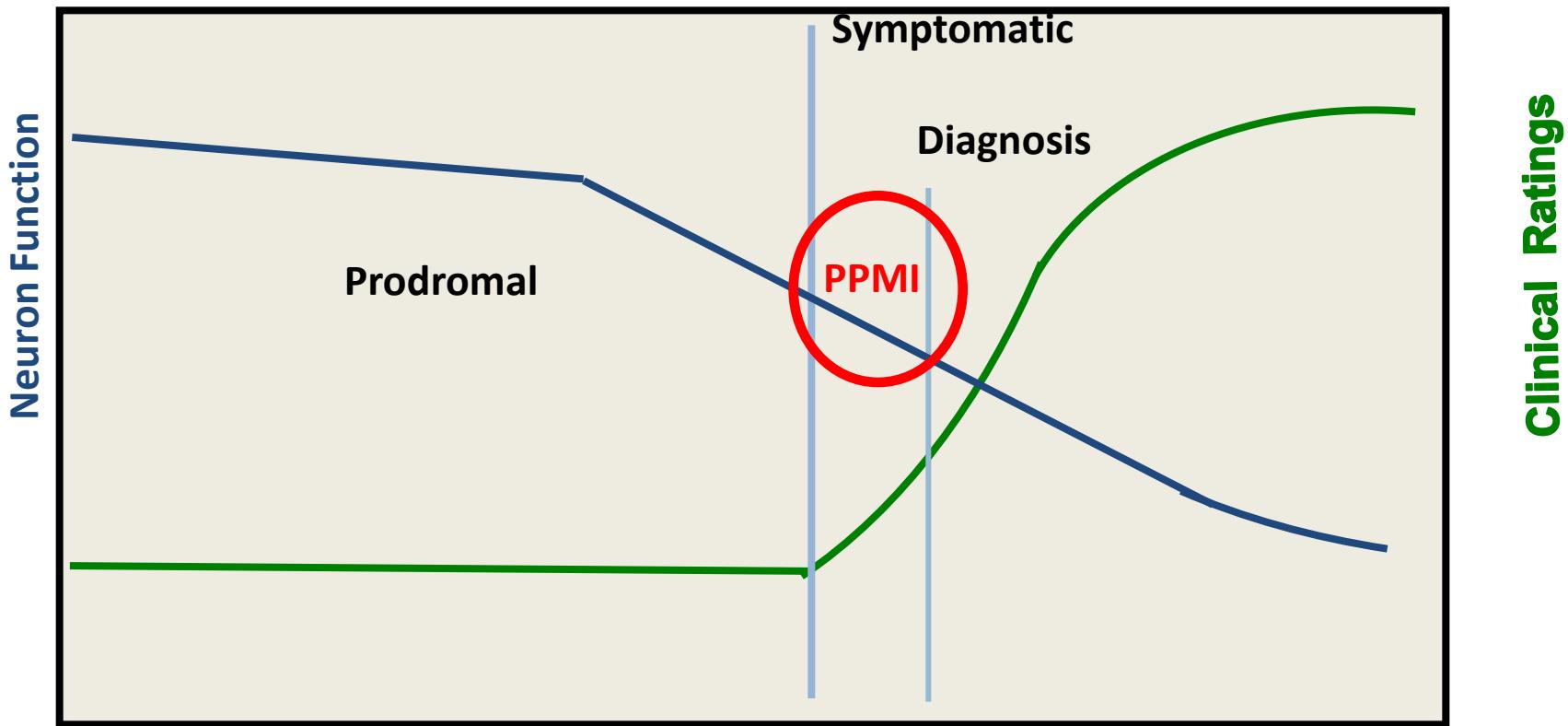


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# Natural history of Parkinson's disease

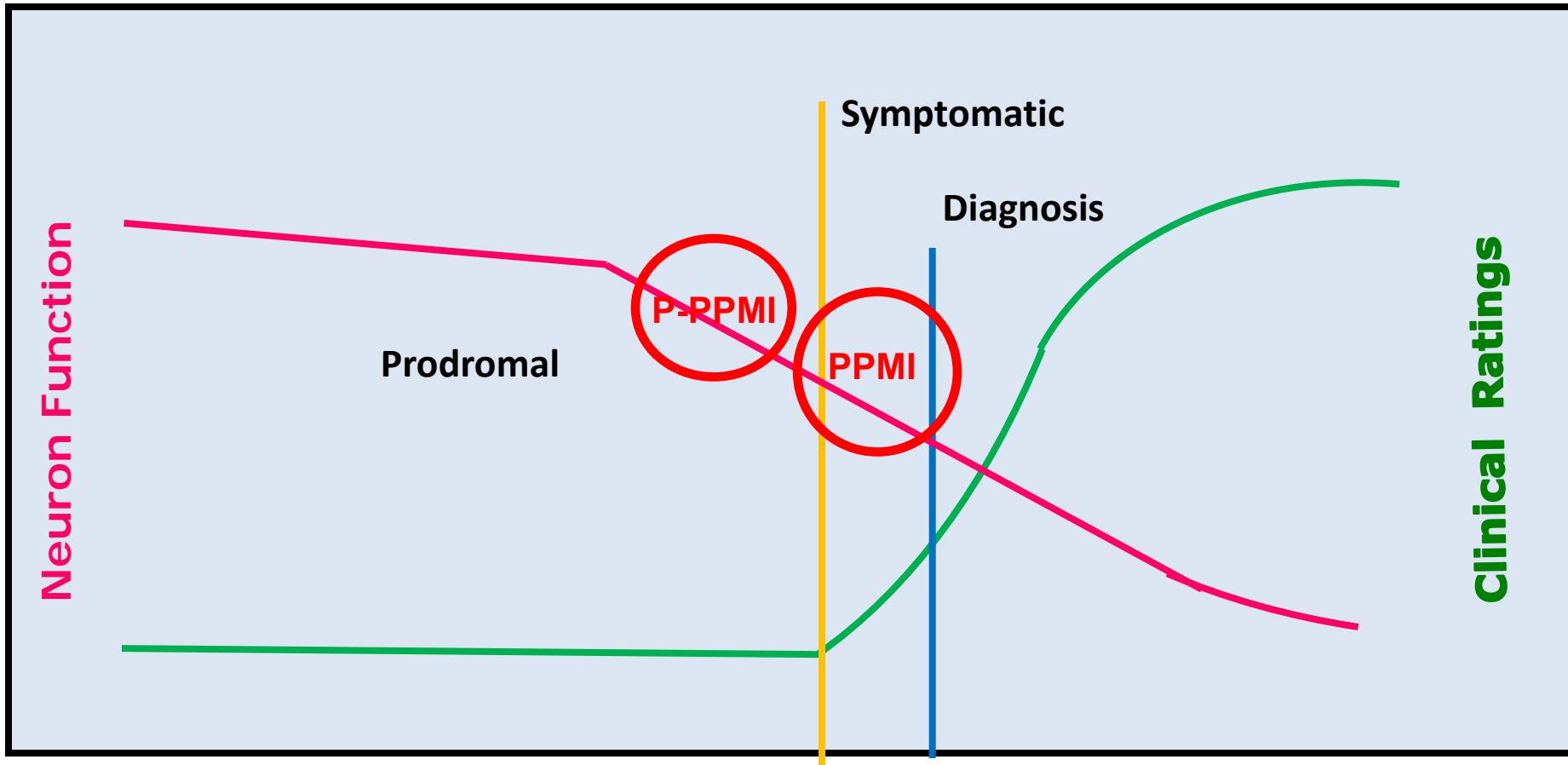


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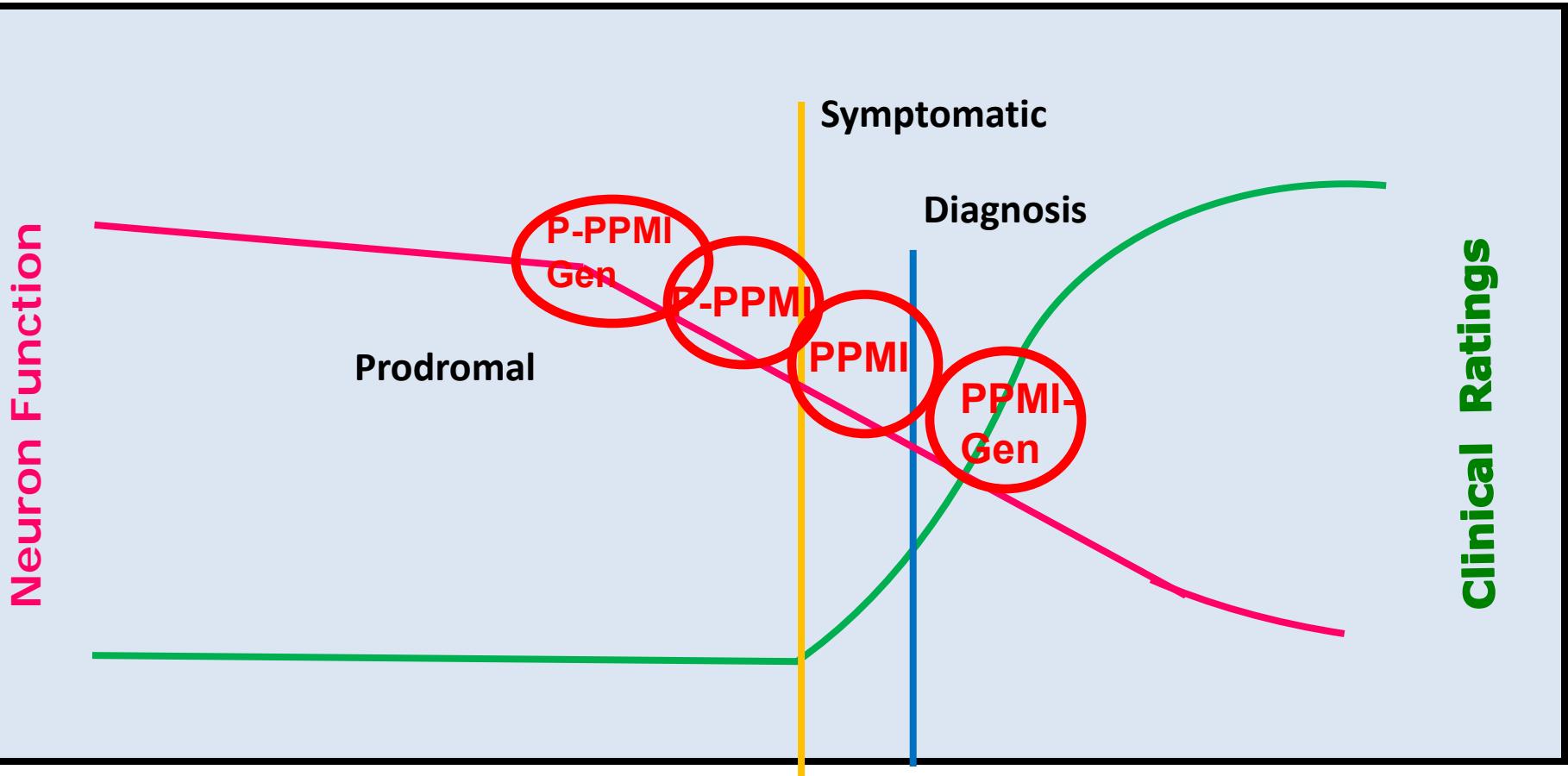
# Natural history of Parkinson's disease



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# Natural history of Parkinson's disease



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# PPMI Genetic Kickoff Meeting

## Sept 16-17, 2013

### AGENDA

<b>Monday September 16, 2013</b>		
All sessions unless otherwise noted will be held in [name] Room		
1:00-1:20 pm	<b>Welcome and Introductions</b>	Marek, Chowdhury, All
1:20-1:35 pm	<b>PPMI Goals &amp; Update – Genetics, New sites, Prodromal</b> <ul style="list-style-type: none"> <li>Goals and Study Governance</li> <li>Baseline cohort – PD, HS, SWEDD</li> <li>Prodromal cohort – RBD, Hyposmic</li> <li>Start-up of Genetic cohort/registry</li> </ul>	Marek
1:35-1:50 pm	<b>Bioinformatics Core Review</b> <ul style="list-style-type: none"> <li>Data flow and data access</li> </ul>	Toga, Lasch
1:50-3:10 pm	<b>PPMI Assessments &amp; Cores – Lessons for the Genetic Cohort</b> <ul style="list-style-type: none"> <li>Clinical</li> <li>Motor/Non-motor assessments</li> <li>Imaging</li> <li>Biologics</li> </ul>	de Blieck/Cascaeli, Simuni, Marek/Mendick, Frasier/Berlin/Shaw
3:10-3:30 pm	<b>Break</b>	All
3:30-3:45 pm	<b>Overview of LRRK2/SCNA Genetics</b>	Foroud
3:45-5:00 pm	<b>Genetic Cohort – Amendment 6</b> <ul style="list-style-type: none"> <li>Genetic cohort/Genetic registry</li> <li>Genetic Testing/Counseling</li> <li>Review of eligibility</li> <li>Genetic Coordination Core</li> </ul>	Foroud/Jackson/Marek
5:00-5:15 pm	<b>Good Clinical Practice/Study Site Monitoring</b>	de Blieck
5:15-5:25 pm	<b>Safety Reporting and Monitoring</b> <ul style="list-style-type: none"> <li>Adverse Events</li> <li>CSOC</li> </ul>	Lazurenko
5:25-5:30 pm	<b>Closing Remarks – Preparation for Tomorrow</b>	Marek
5:30-6:15 pm	<b>Coordinators Session</b> <ul style="list-style-type: none"> <li>Recruitment, retention, study logistics</li> </ul>	Coordinators
5:30-6:15 pm	<b>Investigators Session</b> <ul style="list-style-type: none"> <li>Defining phenoconversion</li> </ul>	Investigators Jennings/Tanner
6:30 pm	<b>Cocktails and Dinner</b> Delmonico's Restaurant 56 Beaver Street (at South William Street)	All

<b>Tuesday September 17, 2013</b>		
All sessions except for Breakouts will be in the [name] Room		
7:30-8:00 am	<b>Breakfast</b>	All
8:00-8:20 am	<b>Recruitment &amp; Retention Update</b>	Jennings, Meunier
8:20-9:15 am	<b>Recruitment Strategies – Genetic Cohort/Registry</b> <ul style="list-style-type: none"> <li>Participant screening</li> <li>Participant enrollment</li> <li>Family expansion</li> </ul>	Jennings, Meunier, Foroud
9:15-10:00 am	<b>Models of Subject Identification/Enrollment</b> <ul style="list-style-type: none"> <li>The Boca Raton experience</li> <li>Recruiting Asyn subjects in Greece</li> <li>Recruiting LRRK2 subjects in Norway and Israel</li> </ul>	Isaacson, Stefanis/Stamelou, Aasly, Mirelman
10:00-10:30 am	<b>Prodromal recruitment &amp; enrollment – Lessons learned for Genetic Cohort</b>	Jennings, Factor, Simuni
10:30-10:45 am	<b>Break</b>	All
10:45-11:10 am 11:15-11:40 am 11:40-12:05 pm	<b>Breakout Groups (25 minutes each – 5 minutes between each)</b> <ul style="list-style-type: none"> <li>Subject identification and recruitment</li> <li>Recruiting families</li> <li>Biospecimen training and LP overview</li> </ul>	Room TBD Room TBD Room TBD
12:15-1:15 pm	<b>Lunch</b>	All
1:15-1:45 pm	<b>Summary of Breakout Sessions</b>	All
1:45-2:00 pm	<b>Communications/Reports</b> <ul style="list-style-type: none"> <li>Enrollment verification</li> <li>Activity reports</li> <li>Reportable events</li> <li>Notifications</li> </ul>	Lazurenko
2:00-2:10 pm	<b>Financial Overview</b> <ul style="list-style-type: none"> <li>Sub-contracts</li> <li>Site payments and schedule</li> <li>Meeting reimbursement</li> </ul>	Arnedo
2:10-2:25 pm	<b>Ancillary Studies</b> Upcoming Amendment 7	Tanner
2:25-2:40 pm	<b>Break</b>	All
2:40-3:00 pm	<b>Statistics Core – Planned Data Analyses</b>	Coffey
3:00-3:30	<b>Study Policies</b> <ul style="list-style-type: none"> <li>Data access</li> <li>Publications</li> </ul>	Marek
3:30-3:45 pm	<b>Closing – Summary and Timelines</b>	Marek
4:00 pm	<b>Departure for airport/train stations</b>	All

# Break



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# Schedule of Activities- Genetic Cohort

- **Comprehensive and uniformly collected set of clinical data, imaging, and biological samples**
- **Lay foundation for future efforts to measure and modify progression**

**Note Genetic registry - minimal f/u**



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# Challenges

- **Recruitment and Retention**
- **Frequency of assessments**
- **Intensity of assessments**
- **Training and consistency**
- **Meticulous sample collection/processing**
- **Data and sample quality/completeness**



# Assessments

## Who performs what?

- **Investigator Only**
  - Neurological Exam
  - MDS-UPDRS Part Ia: Non-motor experiences of daily living (nM-EDL)
  - MDS-UPDRS Part III (Motor)
  - MDS-UPDRS Part IV (Motor complications)
  - Hoehn & Yahr Stage
  - Modified Schwab & England ADL
  - Primary Diagnosis



# Assessments

## Who performs what?

- **Subject Completed (self-administered)**
  - MDS-UPDRS Part I b (nM-EDL)
  - MDS-UPDRS Part II (Motor EDL)
  - Symbol Digit Modalities
  - Epworth Sleepiness Scale
  - REM Sleep Behavior Questionnaire
  - Geriatric Depression Scale
  - State-Trait Anxiety Scale



# Screening Visits (SC) Procedures

- Two step Informed Consent process for PPMI – Genetics -  
Consent for genetic testing –  
Consent for PPMI study- Cohort or Registry

## Note

Subjects already tested can be consented for PPMI and information confirmed by GCC

Screening should be conducted within 45 days of the Baseline visit:



# SC Visit- PPMI Genetic Cohort

- Assess inclusion/exclusion criteria
- Collect medical history and demographic information
- Assign CTCC unique ID number
- Determine prior and current medications
- Measure vital signs
- A complete physical and neurological exam
- Clinical Diagnosis Assessment
- Administer MoCA
- Administer MDS-UPDRS, Hoehn & Yahr)
- Collect blood sample for clinical lab assessments, including for females of child-bearing potential, a urine pregnancy test
- Collect blood sample for DNA
- Conduct DAT or VMAT(Australia) imaging scan
  - Females of childbearing potential; urine preg test results prior to scan



# Baseline Visit (BL) – Day 0

- **Collect vital signs**
- **Collect blood and urine sample for storage and future research purposes**
- **Conduct cognitive and neuropsychological assessments, including:**
  - Smell testing (UPSIT)
  - Epworth Sleepiness Scale
  - REM Sleep Behavior Questionnaire
  - Geriatric Depression Scale
  - State-Trait Anxiety Inventory
  - SCOPA-AUT (autonomic dysfunction)
  - Questionnaire for Impulsive-Compulsive Disorders
  - Dementia Rating Scale
  - Letter Number Sequencing
  - Hopkins Verbal Learning Test
  - Symbol Digit Modalities
  - Line Orientation
  - Animal Fluency



# BL Visit (continued)

- Administer MDS-UPDRS, Hoehn & Yahr
- Assess activities of daily living
- Complete a structural MRI (MRI with DTI and selected sites only)
- Complete a lumbar puncture for collection of cerebral spinal fluid (CSF)
- Review inclusion/exclusion criteria and confirm eligibility
- Complete RANDOM page in EDC / enroll subject into study

# Follow Up In-Person Visits

- Return every 6 months
- Clinical Diagnosis Assessment annually
- Full set of cognitive/neuropsychological assessments completed annually
- Research blood samples collected each visit up to month 24 (urine collected every other visit) and annually thereafter
- DAT imaging conducted month 24 and 48
- LP conducted annually
- MRI with DTI at selected sites month 24 and 48

# Symptomatic Therapy (ST) Visit

- Purpose: to obtain assessments and biomic samples at furthest point into study before starting dopaminergic meds
- Follow protocol and operations manual guidelines to determine activities that should be conducted



# PD Subjects Only

- If levodopa or dopamine agonist is being taken:
  - MDS-UPDRS Part III and Hoehn & Yahr conducted in practically defined off
  - Repeated 1 hour after medication dosing in clinic
  - Subjects will need to be reminded to hold meds on day of visit (if applicable)

# SC/BL Visit- PPMI Genetic Registry

- Assess inclusion/exclusion criteria
- Collect medical history and demographic information
- Clinical Diagnosis assessment
- Assign CTCC unique ID number
- Determine prior and current medications
- Measure vital signs
- A complete physical and neurological exam
- Administer MoCA
- Administer MDS-UPDRS, Hoehn & Yahr
- Collect blood sample for clinical lab assessments
- Collect blood sample for DNA

**Repeat visit every 24 months**

**Phone visit to review diagnosis every 6 months**



# Order of Activities

- Site dependent
- May take place over more than one day
- Assessments, samples should be collected at similar times over course of study



# MDS UPDRS

**4 parts – 50 Items (65 scores vs. 55 on UPDRS)**

**I: Non-motor Experiences of Daily Living**

13 items: Interview (6) Questionnaire (7)

**II: Motor Experiences of Daily Living**

13 items all patient questionnaire

**III: Motor Section - 18 items by examiner**

**IV: Motor Complications**

6 items: Interview: dyskinesias (3);  
fluctuations (3)



# MDS UPDRS (Cont)

- Training and certification from MDS – required for PPMI investigators - [www.movementdisorders.org/updrs/](http://www.movementdisorders.org/updrs/) Note this is for non-profit category
- All scores are anchored to clinical statement:
  - 0 = normal
  - 1 = slight-present but without functional consequence
  - 2 = mild-present with modest functional consequence
  - 3 = moderate-present and affecting several aspects of function
  - 4 = severe-present and prevent the activity or function
- More emphasis on early/mild disease: slight vs mild
- Direct involvement of patient in Questionnaire (Part I and Part II)
- Translation available or in progress



# BASELINE CHARACTERISTICS

Group	PD Subjects (N = 423)	Healthy Controls (N = 196)	SWEDD Subjects (N = 64)
Males	277 (65%)	126 (64%)	40 (63%)
Age (mean)	62	61	61
Education < 13 yrs	77 (18%)	29 (15%)	18 (28%)
Hispanic/Latino	9 (2%)	3 (2%)	2 (3%)
Caucasian	391 (92%)	182 (93%)	61 (95%)
Family Hx of PD	102 (24%)	10 (5%)	21 (32%)

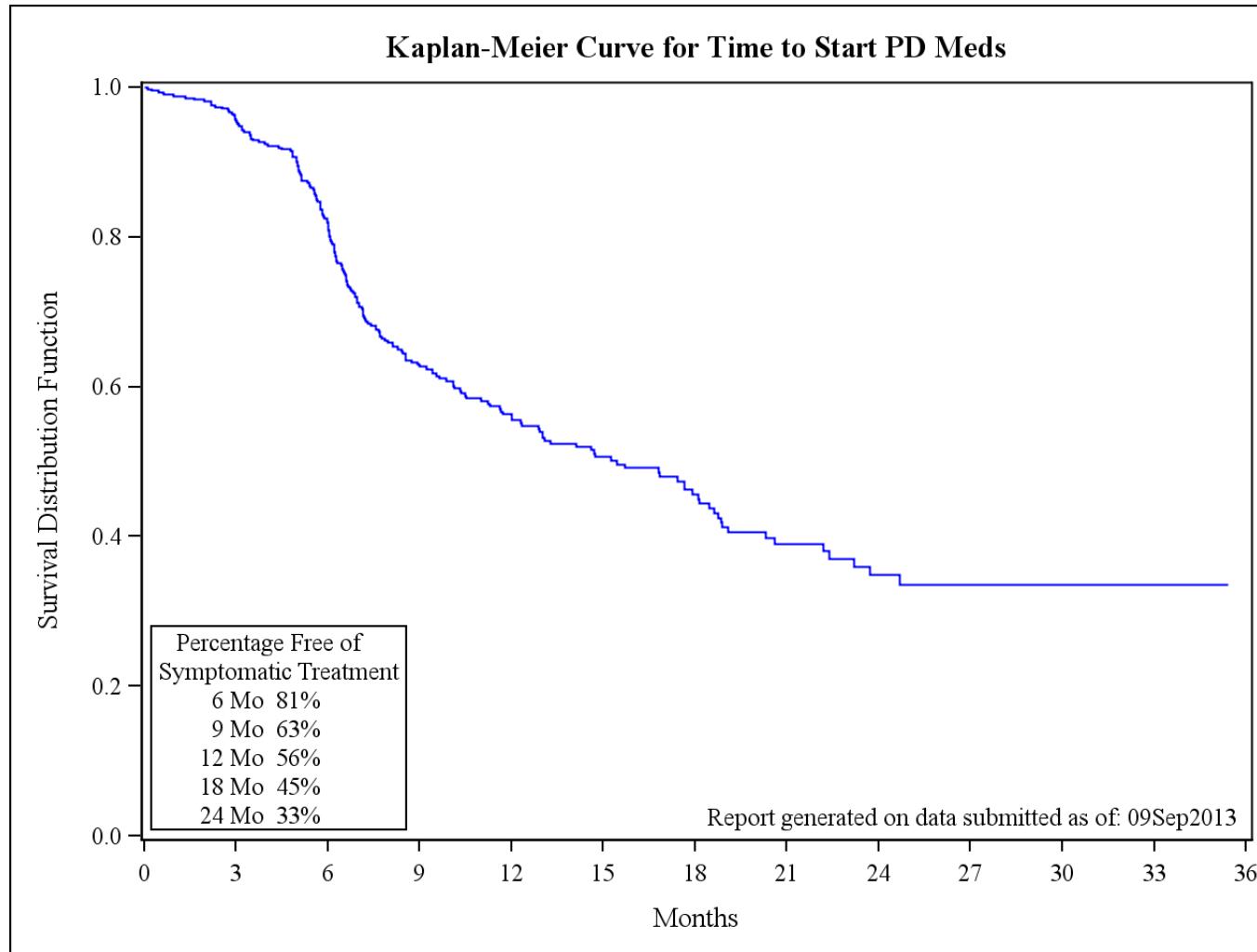


# BASELINE CHARACTERISTICS

Group	PD Subjects (N = 423)	Healthy Controls (N = 196)	SWEDD Subjects (N = 64)
<b>MDS-UPDRS Score</b>			
- Total Score	32.4 (13.1)	4.6 (4.5)	28.2 (17.4)
- Part I	5.6 (4.1)	2.9 (3.0)	8.3 (6.5)
- Part II	5.9 (4.2)	0.5 (1.0)	5.7 (5.1)
- Part III (Motor Exam)	20.9 (8.9)	1.2 (2.2)	14.3 (9.4)
<b>Hoehn &amp; Yahr</b>			
- Stage 0	0 (0%)	193 (99%)	0 (0%)
- Stage 1	186 (44%)	2 (1%)	37 (58%)
- Stage 2-5	237 (56%)	0 (0%)	27 (42%)
<b>Modified Schwab</b>	93.2 (5.9)	N/A	94.8 (6.0)
<b>Duration of Disease (months)</b>	6.7 (6.5)	N/A	7.4 (7.9)



# TIME TO START PD MEDICATIONS



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# Break



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# **PPMI - Genetic Timeline**

**Draft Amendment 6 – Complete**

**Site visits and Approvals – Complete**

**Site Contract July /Nov 2013**

**Site submission to IRB/Ethical committee –July/Nov 2013**

**Subject enrollment August 2013**

**All sites enrolling – Nov-Dec 2013**

**Enrollment complete – Dec 2015**

**Completion of 3 year f/u on all subjects – Dec 2018**



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# PPMI Data & Informatics Core

Shirley Lasch

Arthur Toga



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# Parkinson's Progression Markers Initiative

Requirements for Biomarker Infrastructure

## Specific Data Set

- Appropriate population (early stage PD and controls)
- Clinical (motor/non-motor) and imaging data
- Corresponding biologic samples (DNA, blood, CSF)

## Standardization

- Uniform collection of data and samples
- Uniform storage of data and samples
- Strict quality control/quality assurance

## Access/Sharing

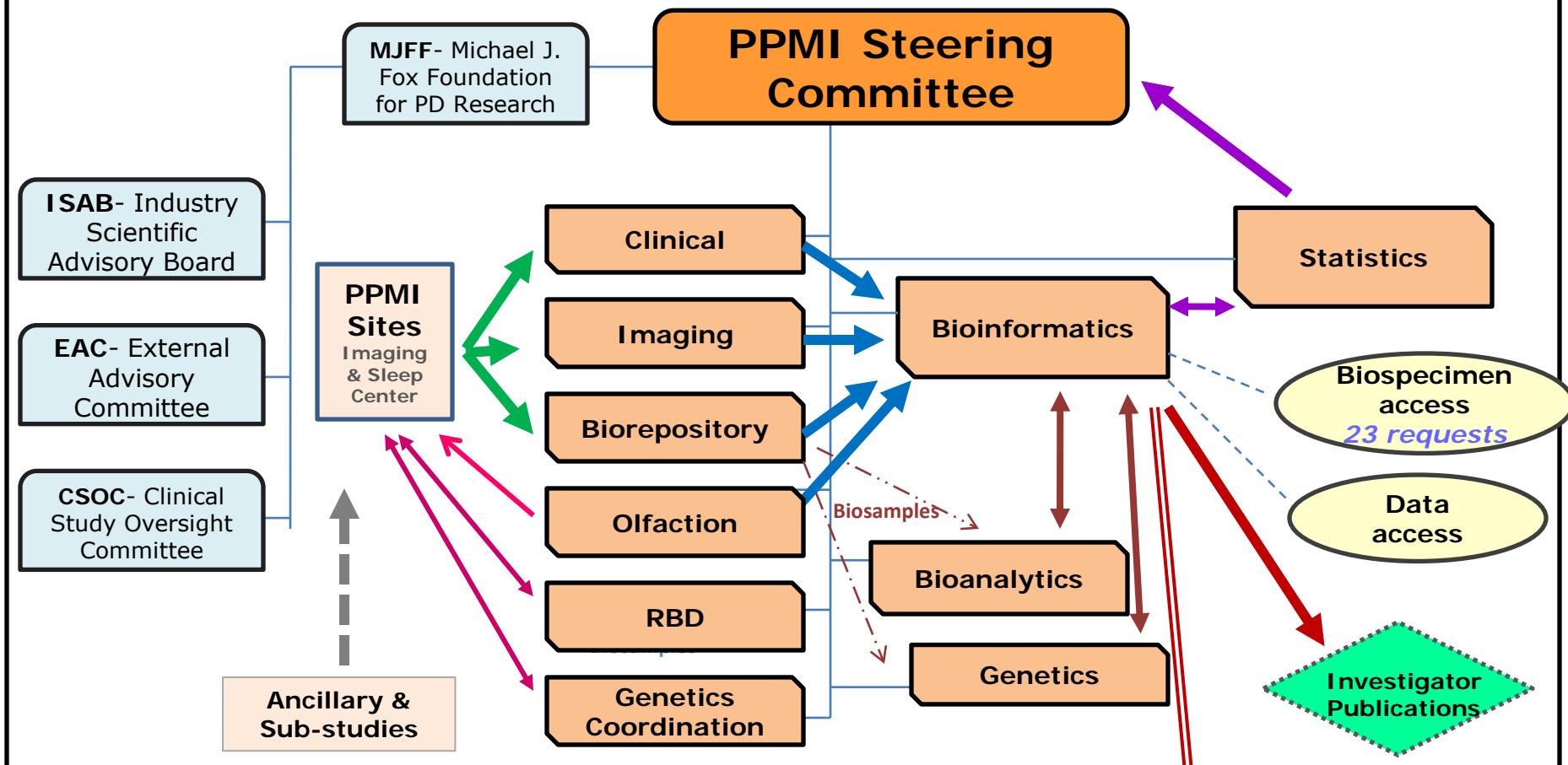
- Data available to research community → data mining, hypothesis generation & testing**
- Samples available for studies**



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# PPMI Study Data Flow and Access 2013



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# Apply for PPMI Data Access & Download

Parkinson's Progression Markers Initiative

Subscribe: News

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About PPMI Study Design Assess Data & Specimens PPMI News Get Email Updates

OUR MISSION

The mission of PPMI is to identify one or more biomarkers of Parkinson's disease progression, a critical step in the development of new and better treatments for PD. This study is being sponsored by **The Michael J. Fox Foundation for Parkinson's Research**.

Subscribe to PPMI e-news

Enter email address

WELCOME

Welcome to the Parkinson's Progression Markers Initiative (PPMI), a landmark observational clinical study to comprehensively evaluate a cohort of recently diagnosed PD patients and healthy subjects using advanced imaging, biologic sampling and clinical and behavioral assessments to identify biomarkers of Parkinson's disease.

DOWNLOAD DATA REQUEST

**DOWNLOAD DATA**

**DOWNLOAD DATA**

Through this Web site, qualified researchers may obtain access to all clinical, imaging and biomarker data collected in PPMI. This includes raw and processed MRI and SPECT images. All data are de-identified to protect patient privacy.

New Users Apply Now:

Investigators seeking access to PPMI data must submit an online application, which requires signing the **Data Use Agreement** and Compliance with the study **Publications Policy**. Applications for data access are reviewed by the Data and Publications Committee within one week of receipt.

APPLY FOR DATA ACCESS

Registered Users:

Investigators who have been granted access to PPMI data can enter their email and password below.

Email:   
Password:

Forgot your login and password? [Click here.](#)

LOG IN

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# PPMI Data Access & Download

The screenshot shows the PPMI@LONI website. At the top, there's a navigation bar with links for 'PPMI @ LONI', 'PROJECTS', 'SEARCH', 'ARCHIVE', 'DOWNLOAD', 'EXPLORE', 'MANAGE', and 'LONI Home'. Below the navigation is a banner for 'Parkinson's Progression Markers Initiative' with a yellow background and text. A blue box highlights the 'PROJECTS' and 'SEARCH' buttons. To the right is a logo for 'PARKINSON'S PROGRESSION MARKERS INITIATIVE' and another for 'LONI DATA ARCHIVE'. The main content area has a heading 'Getting Started' and text about the repository. It features a large chart titled 'Participant Research Group and Age Distribution'. The chart includes a bar chart showing the number of subjects by age group (30-39, 40-49, 50-59, 60-69, 70-79, 80-89) and a pie chart showing the distribution by research group (Control, PD, SWEDD) and gender (Male, Female).

Age Group	Number of Subjects
30-39	10
40-49	25
50-59	62
60-69	99
70-79	37
80-89	8

Research Group	Count
Control	159
PD	217
SWEDD	43

Gender	Count
Female	152
Male	267

<http://www.ppmi-info.org/>

This diagram illustrates the PPMI website structure. It shows a main page with a central title 'Parkinson's Progression Markers Initiative' and a 'Getting Started' section. Three arrows point from the text 'data containing tabs' at the bottom to three specific tabs in the navigation bar: 'Home' (highlighted in blue), 'Baseline Summary' (highlighted in orange), and 'Participant Age' (highlighted in green). The navigation bar also includes 'PROJECTS', 'SEARCH', 'ARCHIVE', 'DOWNLOAD', and 'EXPLORE'.



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# PPMI Study Enrollment – Study Data

Group	Consented	Enrolled	Withdrawn	Active	Complete
PD Subjects	487	423	10	413	0
Healthy Controls	241	196	8	188	0
SWEDD Subjects	83	64	2	59	3
Prodromal Cohort	20	1	0	1	0

**684 Total Subjects  
Enrolled**

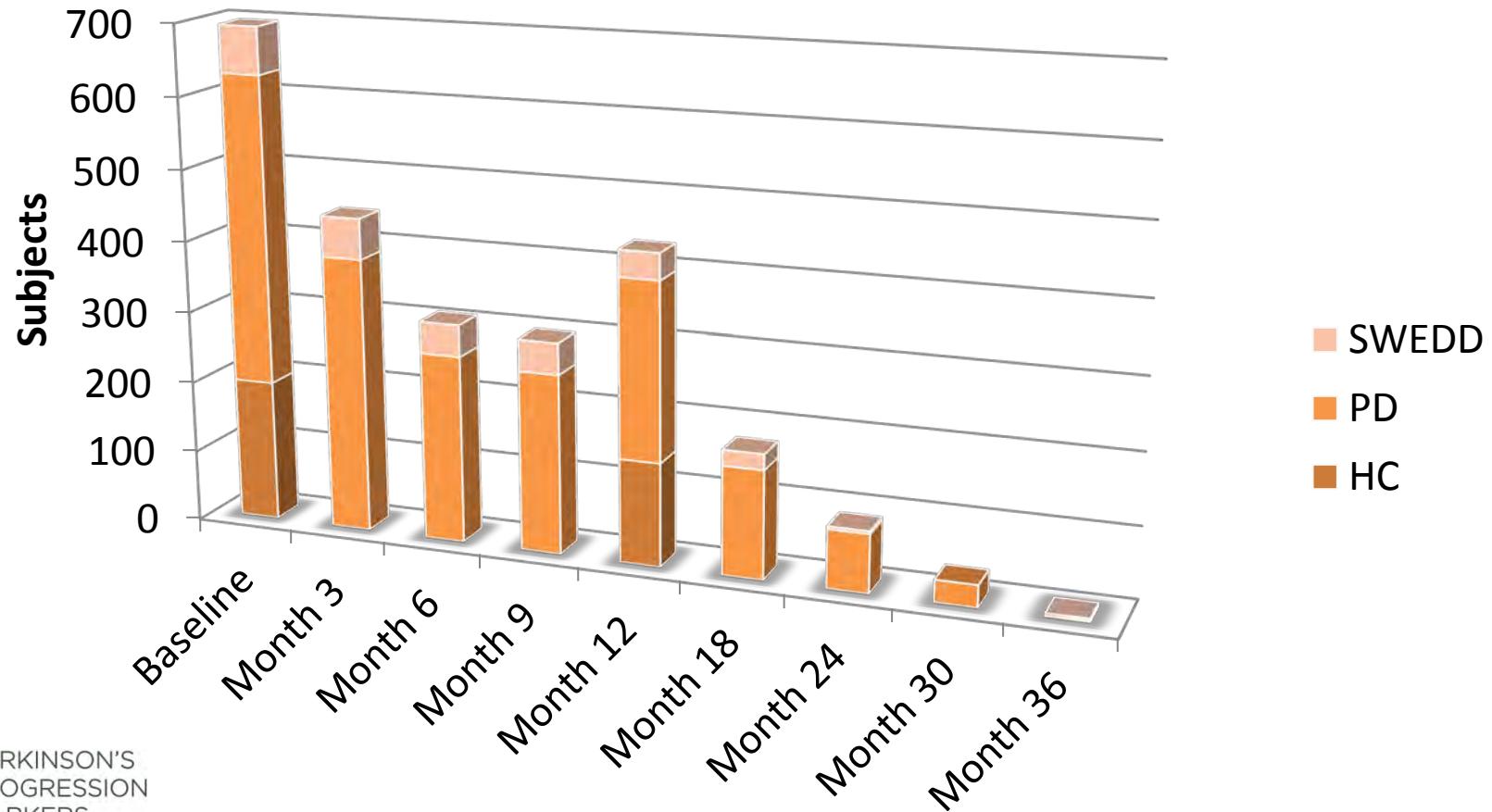


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# PPMI longitudinal Clinical Data

Subject Characteristics • Biospecimen • Enrollment • Imaging Metadata • Incidents & Notifications • Medical History • Motor Assessments • Non-motor Assessments



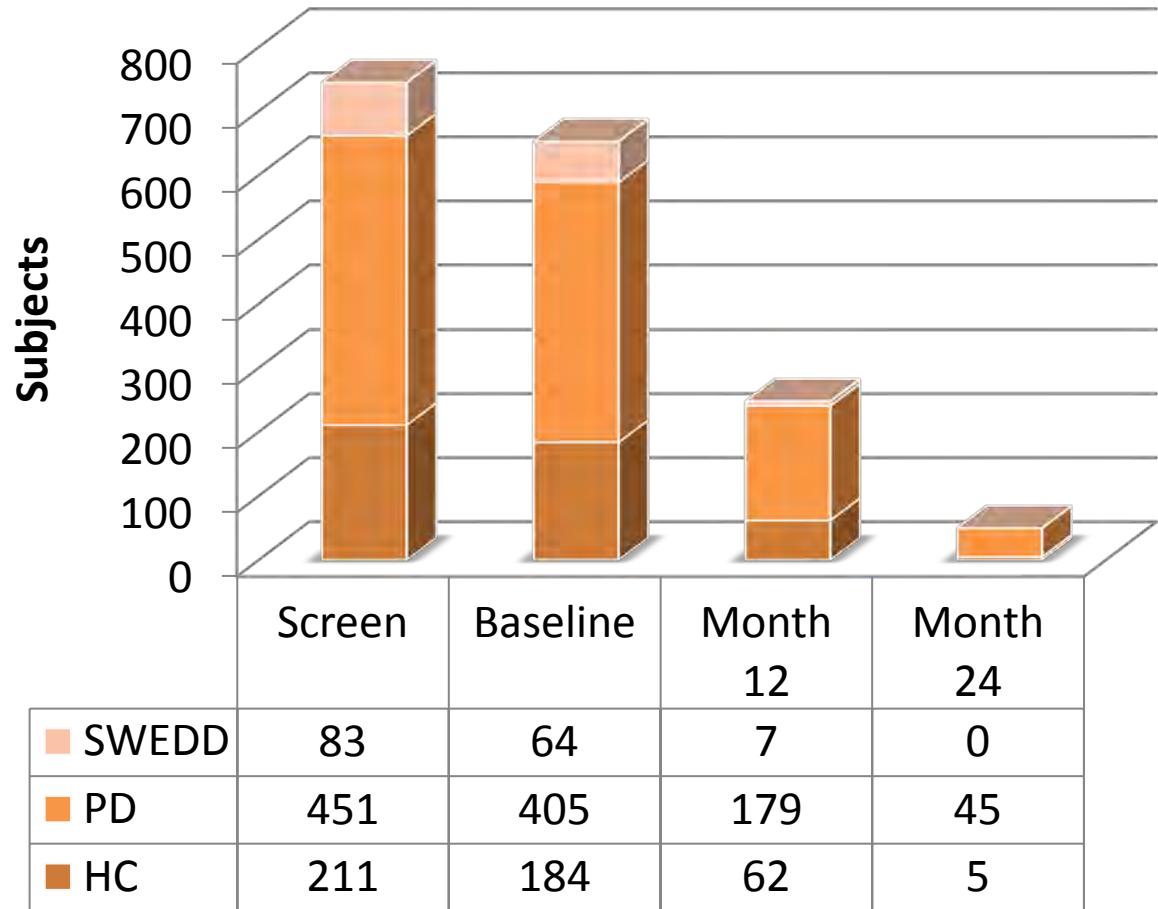
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# PPMI longitudinal Image Data

- SPECT
- PET
- Structural MRI
- rsfMRI
- Diffusion MR (raw)
- Diffusion MR (processed):
  - FA Maps
  - MD Maps
  - Eigen Vectors



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# Informatics Core

Arthur Toga  
September 2013



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# Informatics Core Status

- News
- Website
  - News and Activity
- Data Repository
  - News and Activity



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# LONI News

- LONI has moved to USC
- The move has been difficult
- Systems are back online



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# Website

New webpage about PPMI study cohorts showing enrollment progress.  
Also summarized on the homepage as bar graphs.

The screenshot shows the PPMI homepage with the following sections:

- OUR MISSION:** Describes the mission to identify biomarkers of Parkinson's disease progression and the discovery of a biomarker as a critical step in treatment development.
- LATEST NEWS FROM PPMI:**
  - MJFF hosts September funding conference call as deadline approaches.
  - PPMI to host Genetics Cohort Kick-Off meeting in New York, NY in September.
  - MJFF CEO discusses PPMI in guest post on Forbes.com.
  - Imaging Inventory: what's in the PPMI database.
- PPMI ENROLLMENT STATUS:** Shows enrollment counts for different participant groups:
  - Prodromal Participants: 10%
  - De Novo PD Participants: 100%
  - Control Participants: 100%
  - Subjects with SWEDD: 100%
- WELCOME:** A general welcome message for the PPMI study.
- FOR RESEARCHERS:** A section for researchers with a yellow icon.
- FOR INDUSTRY PARTNERS:** A section for industry partners with a yellow icon.
- FOR ENROLLED PARTICIPANTS:** A section for enrolled participants with a yellow icon.
- FOR PROSPECTIVE PARTICIPANTS:** A section for prospective participants with a yellow icon.
- REQUEST SPECIMENS:** A button to request specimens.
- DOWNLOAD DATA:** A button to download data.

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# Website

Parkinson's Progression Markers Initiative

Subscribe: News

Enter search keyword

Contact Us Home Login

**PARKINSON'S PROGRESSION MARKERS INITIATIVE**

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About PPMI Study Design Access Data & Specimens Publications & Presentations PPMI News

Research Documents & SOPs Study Cohorts Stats Forum Ancillary Studies

**STUDY COHORTS**

The following groups of subjects are being followed in the PPMI study.

**DE NOVO PD SUBJECTS**

Enrollment Goal: 400	Actual Enrollment: 423	Status: Completed April 2013
Subjects with a diagnosis of PD for two years or less who are not taking PD medications.		

**CONTROL SUBJECTS**

Enrollment Goal: 200	Actual Enrollment: 196	Status: Completed April 2013
Control subjects without PD who are 30 years or older and who do not have a first degree blood relative with PD.		

**SUBJECTS WITH SWEDD**

Enrollment Goal: TBD	Actual Enrollment: 64	Status: Completed April 2013
Subjects consented as PD subjects who have DaTscans that do not show evidence of a dopaminergic deficit.		

**PRODROMAL SUBJECTS**

Enrollment Goal: 100	Enrollment Status: Recruiting
Subjects without Parkinson's disease who have at least one of the following characteristics: Hyposmia, REM Sleep Behavior Disorder, LRRK2 genetic mutation.	

To see current enrollment statistics for all PPMI cohorts, view the charts on [www.ppmi-info.org](http://www.ppmi-info.org).

To learn more about the specific inclusion and exclusion criteria for all PPMI cohorts, [review the Study Protocol](#).

for PROSPECTIVE PARTICIPANTS  
 for ENROLLED PARTICIPANTS  
 for INDUSTRY PARTNERS  
 for RESEARCHERS

# Repository News

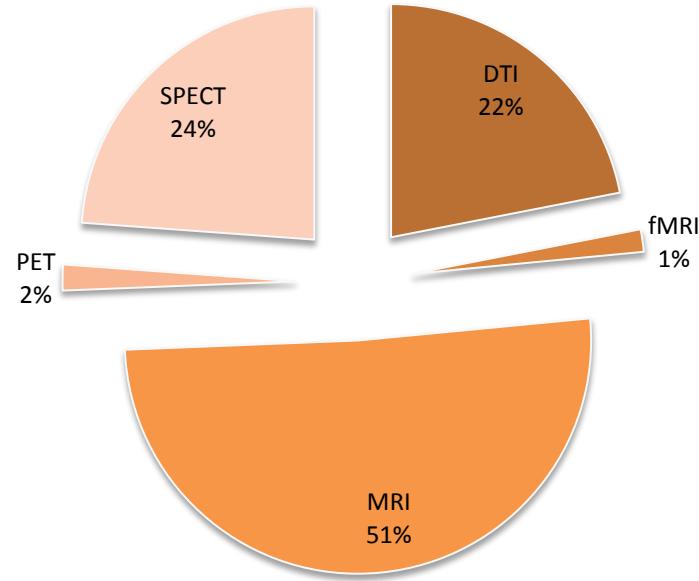
System changes for storing and distributing additional image and data types have been made and these data are now flowing into and out of the IDA

- Resting State fMRI
  - ✓ Scans Arriving in Repository
  - ✓ QA Data Arriving in Repository
- AV-133 PET
  - ✓ Scans Arriving in Repository
- SNP Genotyping Data
  - ✓ Available in Repository



# Image Inventory

3,917 Image Series



PET & fMRI are recent so low #'s for now



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# Biospecimen Results Data

Project	PI	Institution	Test	Count
101	Les Shaw	University of Pennsylvania	Total tau	120
			p-Tau181P	120
			Abeta 42	120
102	Peggy Taylor	Covance	CSF Hemoglobin	492
103	Peggy Taylor	Covance	CSF Alpha-synuclein	120
104	Andrew Singleton	National Institutes of Aging	ApoE Genotype	304

Listing of the different types of biospecimen results in the archive.  
These are post QC and available for download. Count= subjects



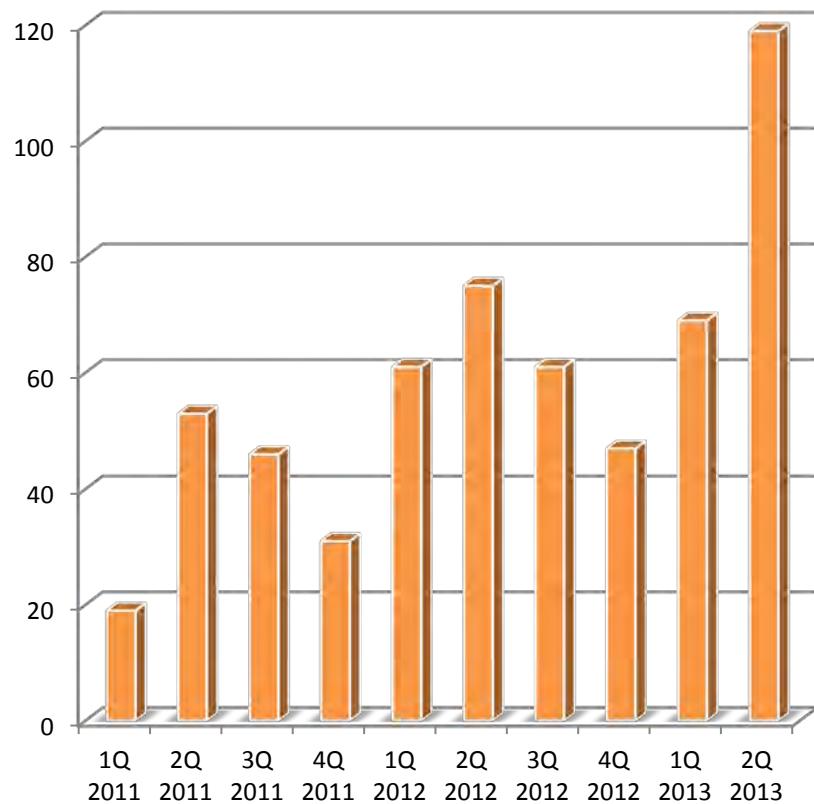
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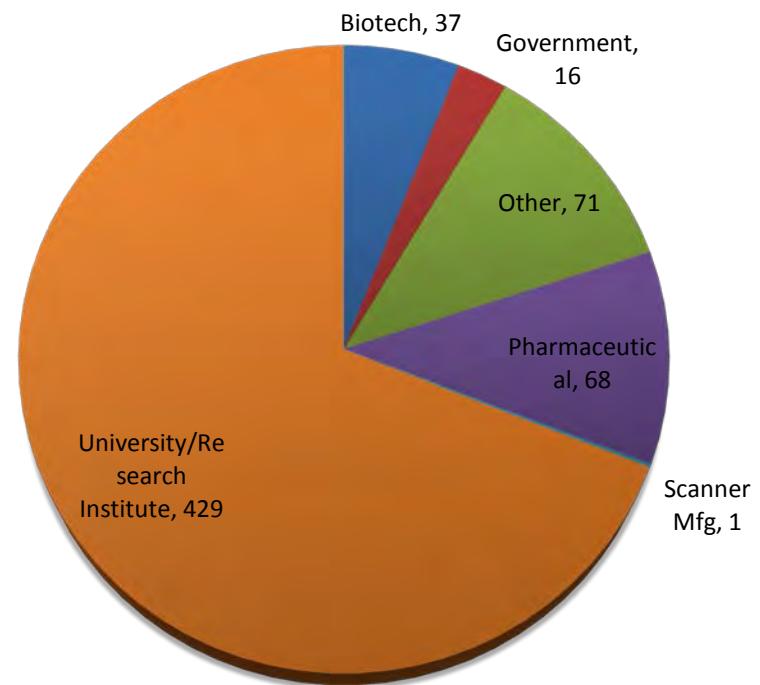


# Data Use Applications

Applicants by Quarter



Applicants by Sector



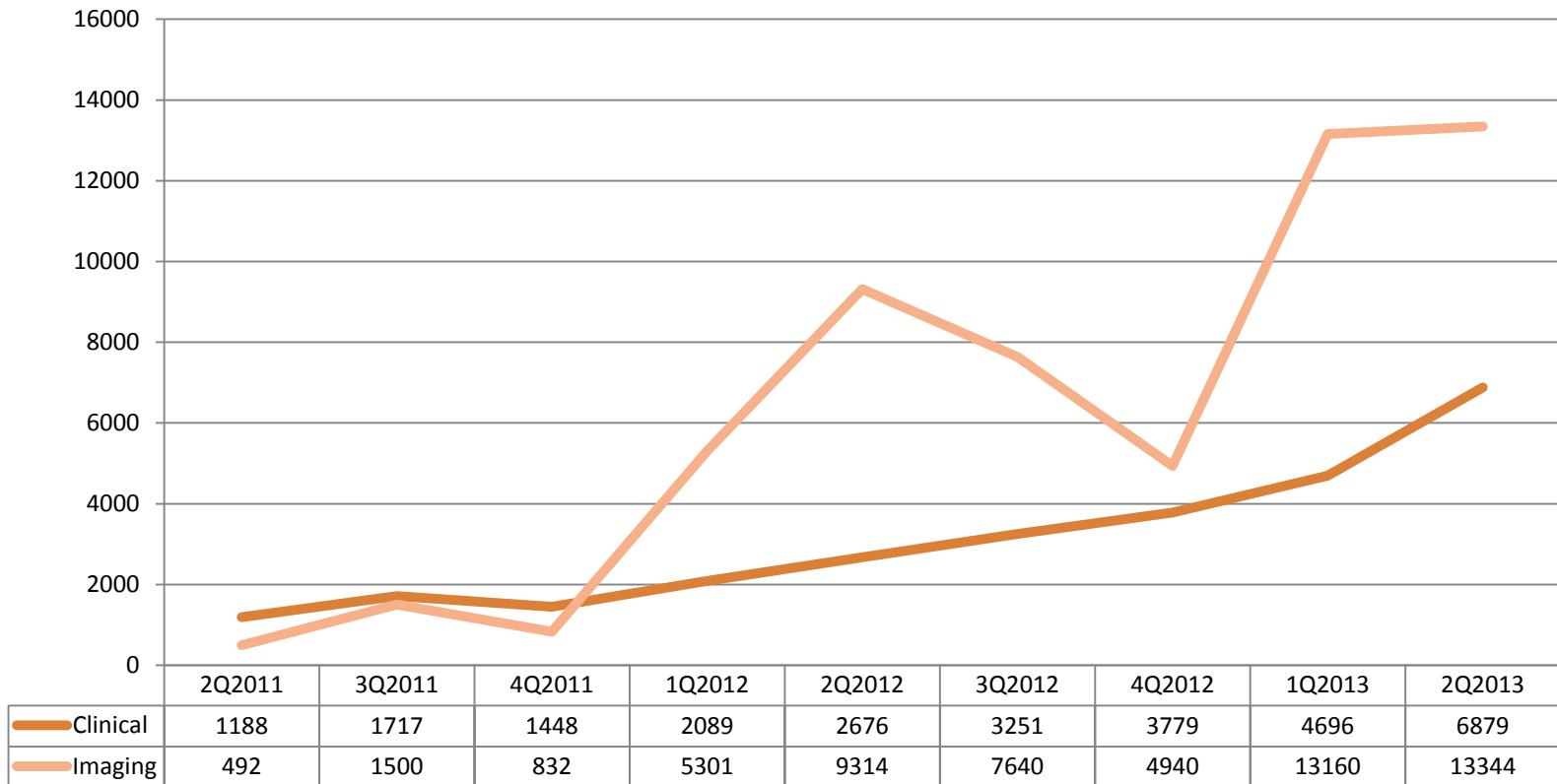
Recent upsurge in applications. Total 628 investigators.



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## Data Download Activity



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Cumulative image downloads: 64231  
Cumulative clinical downloads: 32213

# Visual Interrogation System

- An interactive tool for exploring, visualizing and downloading data
- Features
  - Define populations of subjects
  - Compare data across populations
  - Download data



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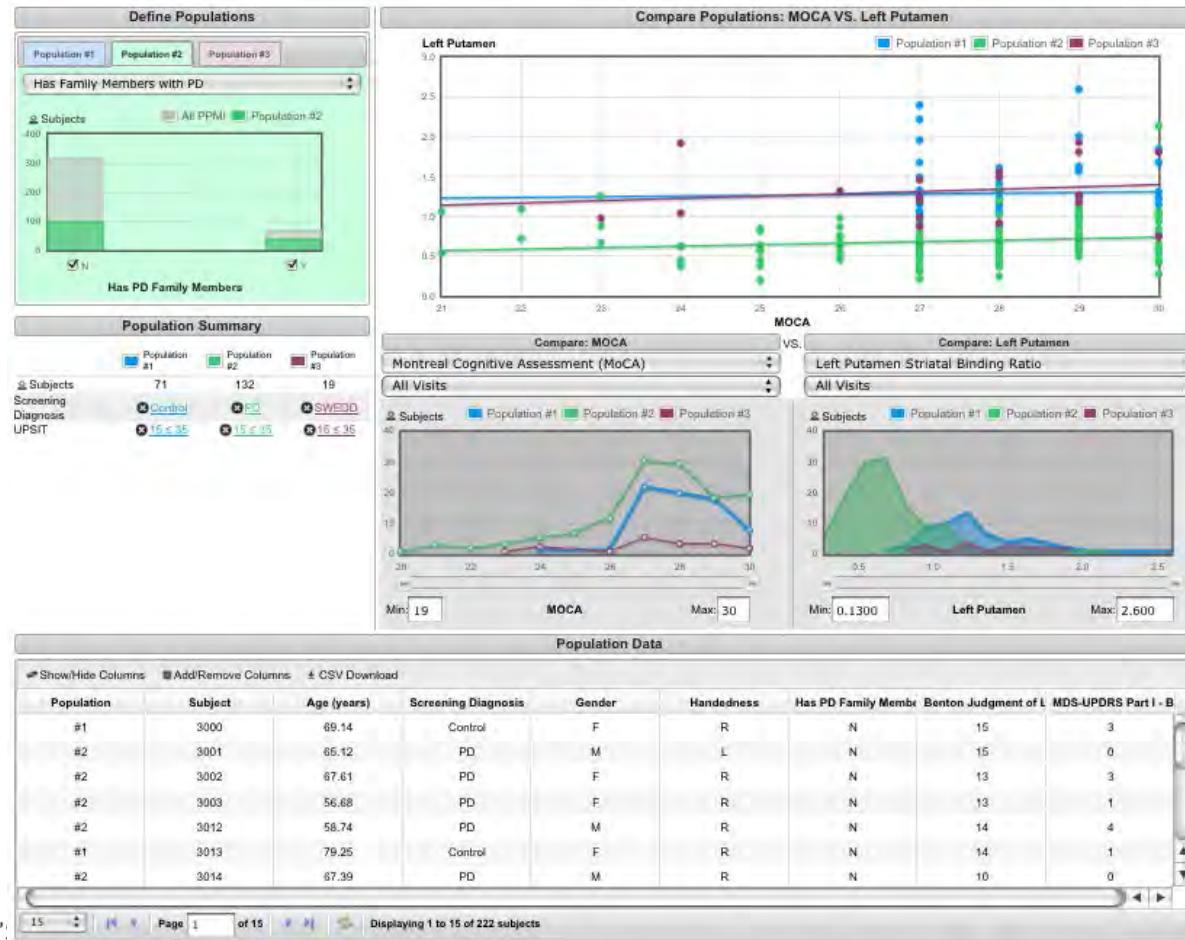


# Visual Interrogation System

The screenshot shows the homepage of the Parkinson's Progression Markers Initiative (PPMI) website. The header features a yellow background with the PPMI logo (a stylized orange square) and the text "PARKINSON'S PROGRESSION MARKERS INITIATIVE". Below the logo, a call-to-action button says "Play a Part in Parkinson's Research". On the right side of the header is a "POWERED BY LONI IMAGE DATA ARCHIVE" badge with a small brain icon. The main navigation menu includes "PPMI @LONI", "PROJECTS", "SEARCH", "ARCHIVE", "DOWNLOAD", "EXPLORE" (which is highlighted with a large blue circle), and "LONI Home". A secondary navigation bar below the main menu includes "Home" and "Baseline Summary".

This is a smaller screenshot or a separate footer section of the PPMI website. It includes the PPMI logo and the text "PARKINSON'S PROGRESSION MARKERS INITIATIVE". Below this is a "Play a Part in Parkinson's Research" button. To the right is a vertical color bar consisting of yellow and orange squares.

# Visual Interrogation System

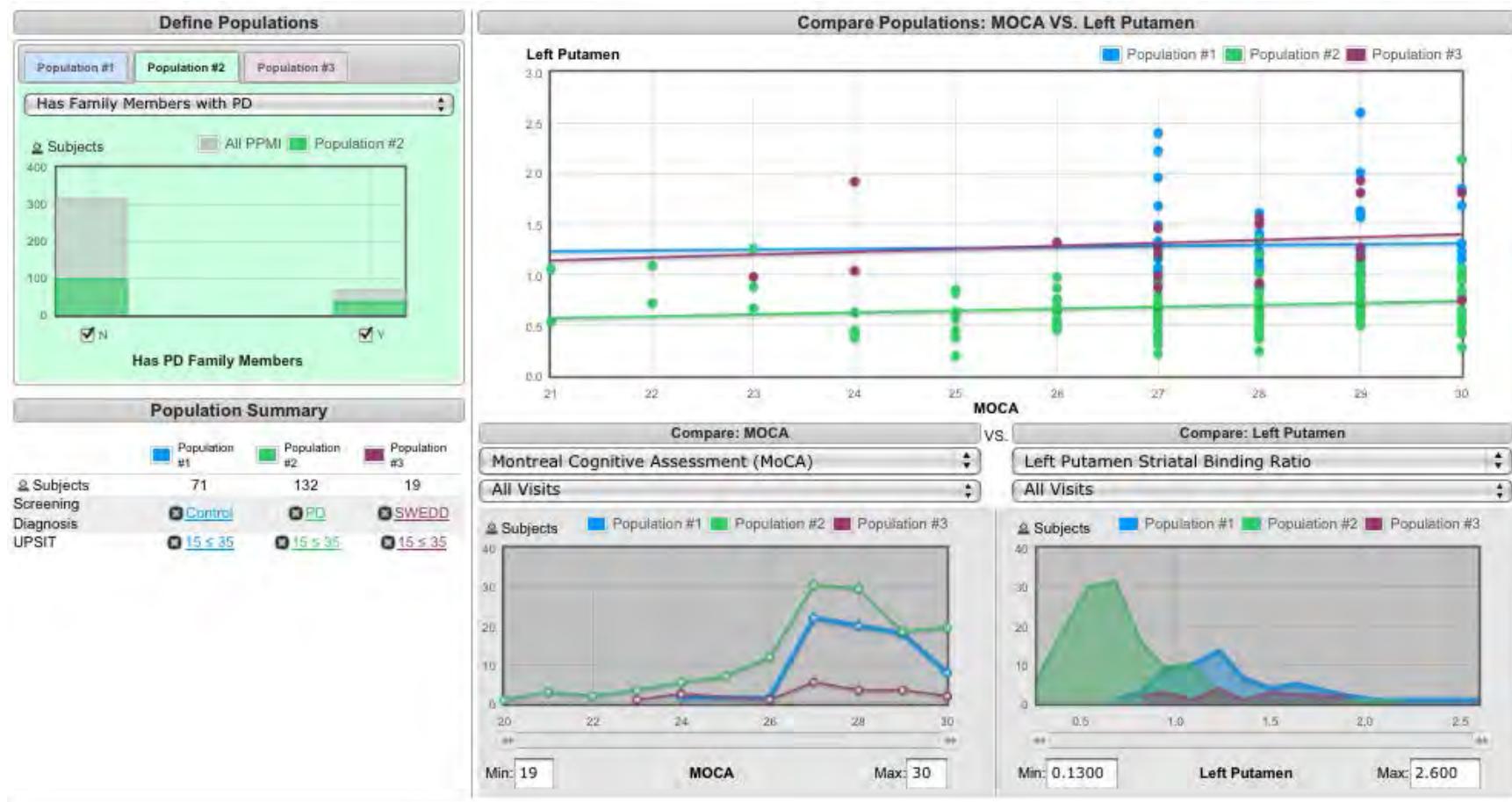


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Interactively define and compare populations of interest.  
Download attributes for defined populations.

# Compare User Defined Groups



Three populations defined: Control, PD and SWEDD all with UPSIT score between 15 – 35. Plotting MOCA score versus Left Putamen

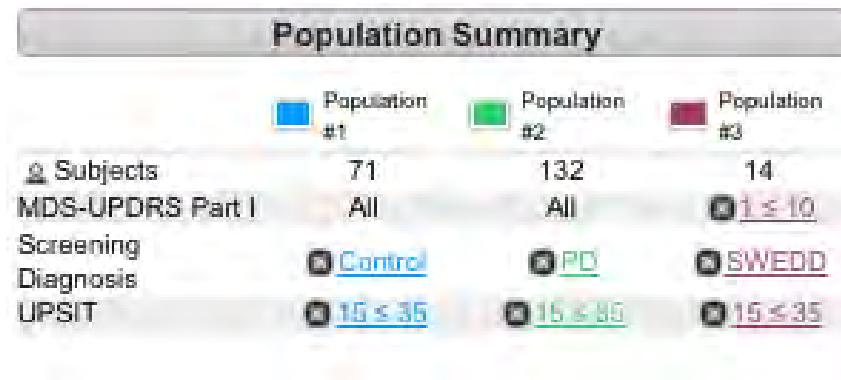
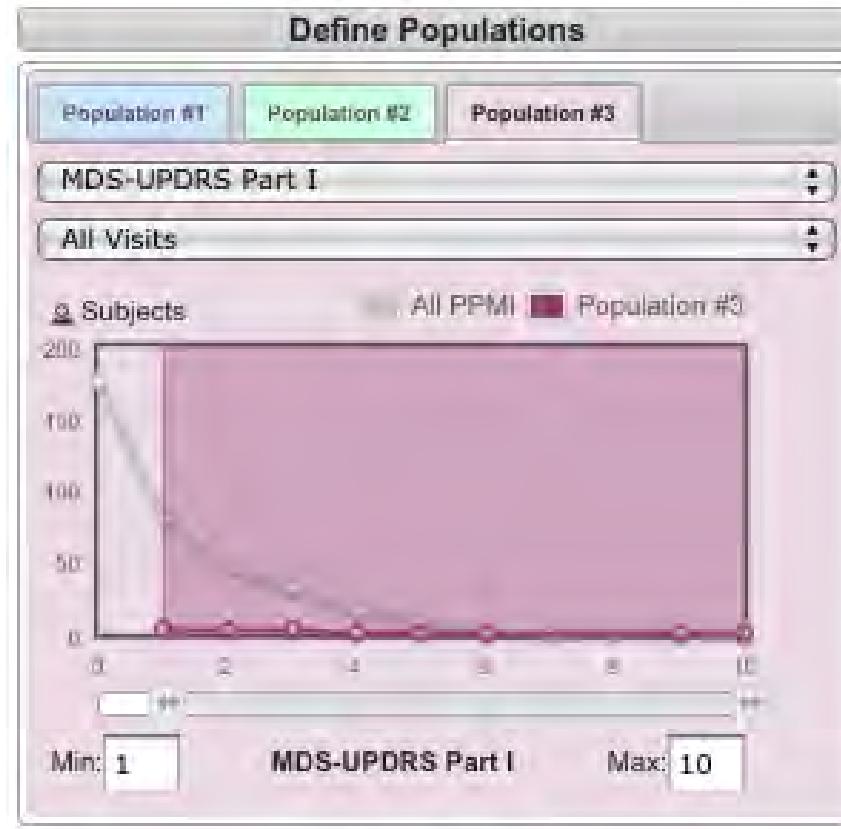


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# How to define populations:

- Select attributes from menu
- Set filters using graphs
- Graphs show distribution of selected population compared with overall population
- Use controls (sliders) to choose ranges



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# Tabular Data

Population Data									
Population	Subject	Age (years)	Screening Diagnosis	Gender	Handedness	Has PD Family Memb	Benton Judgment of L	MDS-UPDRS Part I - B	
#1	3000	69.14	Control	F	R	N	15	3	
#2	3001	65.12	PD	M	L	N	15	0	
#2	3002	67.61	PD	F	R	N	13	3	
#2	3003	56.68	PD	F	R	N	13	1	
#2	3012	58.74	PD	M	R	N	14	4	
#1	3013	79.25	Control	F	R	N	14	1	
#2	3014	67.39	PD	M	R	N	10	0	
#3	3050	51.42	SWEDD	F	R	N	14	3	
15	25	Page 1 of 15	Displaying 1 to 15 of 222 subjects						

Sortable, movable columns containing data from each defined population.  
Add/remove columns + Export data.

# Table – Add Columns

■ Add/Remove Columns

Main

Age at Screening  
 Diagnosis at Screening  
 Duration of Disease at Screening  
 Gender  
 Handedness  
 Has Family Members with PD  
 Years of Education

Assessments

	Screening Visit	Baseline Visit	Visit 01 (Month 3)	Visit 02 (Month 6)	Visit 03 (Month 9)	Visit 04 (Month 12)	Visit 05 (Month 18)
<input type="checkbox"/> Benton Judgment of Line Orientation Score	<input checked="" type="checkbox"/>						
<input type="checkbox"/> Geriatric Depression Scale (GDS)		<input type="checkbox"/>		<input type="checkbox"/>			
<input type="checkbox"/> HVLT Delayed Recognition False Alarms		<input type="checkbox"/>					
<input type="checkbox"/> HVLT Delayed Recognition Hits		<input type="checkbox"/>					
<input type="checkbox"/> HVLT Immediate Recall		<input type="checkbox"/>					
<input type="checkbox"/> Hoehn & Yahr Post-Dose		<input type="checkbox"/>			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Hoehn & Yahr Pre-Dose	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Letter Number Sequencing Raw Score		<input type="checkbox"/>					
<input type="checkbox"/> MDS-UPDRS Part I		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> MDS-UPDRS Part I - Patient questionnaire		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> MDS-UPDRS Part II - Patient questionnaire		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> MDS-UPDRS Part III Post-Dose					<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> MDS-UPDRS Part III Pre-Dose		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> MDS-UPDRS Total Post-Dose					<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> MDS-UPDRS Total Pre-Dose		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Modified Schwab & England ADL		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Montreal Cognitive Assessment (MoCA)		<input type="checkbox"/>					
<input type="checkbox"/> QUIP Positive-Buying		<input type="checkbox"/>		<input type="checkbox"/>			
<input type="checkbox"/> QUIP Positive-Eating		<input type="checkbox"/>		<input type="checkbox"/>			
<input type="checkbox"/> QUIP Positive-Gambling		<input type="checkbox"/>		<input type="checkbox"/>			
<input type="checkbox"/> QUIP Positive-Hobbies		<input type="checkbox"/>		<input type="checkbox"/>			
<input type="checkbox"/> QUIP Positive-Punding		<input type="checkbox"/>		<input type="checkbox"/>			
<input type="checkbox"/> QUIP Positive-Sex		<input type="checkbox"/>		<input type="checkbox"/>			
<input type="checkbox"/> QUIP Positive-Walking or driving		<input type="checkbox"/>		<input type="checkbox"/>			
<input type="checkbox"/> SCOPA-ALUT		<input type="checkbox"/>		<input type="checkbox"/>			
<input type="checkbox"/> Semantic Fluency Total Score		<input type="checkbox"/>					
<input type="checkbox"/> Symbol Digit Modalities Score		<input type="checkbox"/>					
<input type="checkbox"/> University of Pennsylvania Smell Identification Test (UPSIT)							

Measurements

	Screening Visit	Visit 04 (Month 12)
<input type="checkbox"/> Left Caudate Striatal Binding Ratio	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Left Putamen Striatal Binding Ratio	<input type="checkbox"/>	<input type="checkbox"/>

# Visual Interrogation System

- Future Developments
  - Integration of more data attributes
  - Link with other related data (imaging, laboratory, etc.)



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# SNP Genotype Data

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POWERED BY LONI IMAGE DATA ARCHIVE

PPMI @LONI PROJECTS SEARCH ARCHIVE DOWNLOAD EXPLORE MANAGE LONI Home

Study Data Image Collections Genetic Data

## Download Genetic Data

*Reminder: The PPMI Data Use agreement prohibits unauthorized sharing of these data, posting to public databases and any attempt data to identify individuals using these data. By downloading these data you acknowledge our [Terms and Conditions](#).*

**Genotyping**

Data Documentation [ALL](#) [ALL](#)

**Genotyping: ALL**

*PPMI SNP genotyping was performed using Illumina Innunochip and analyzed withing Genome Studio v1.9.4*

**Data** [SNP Genotyping Data](#) Version:1 .PLINK format

**Documentation** [Immunochip genotyping Method](#) Version:1 .PDF format

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New UI for obtaining SNP data.

# Sharing Data

- Now
  - Images → User chooses format
  - Clinical → CSV files and PDFs
  - SNP Genotype → PLINK
- Future
  - Whole Genome Sequencing Data
  - Requires different distribution model

Users have a choice of file format when selecting images; clinical data is in the form of comma separated value files. Currently the SNP data is only available in PLINK but that will change as more genetic data is generated.



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# WGS

Data	Description	Size/Sample
Assembly	Raw genome assembly output	90 GB
Consensus	SNP level consensus and quality per base	2.3 GB
Genotyping	Genotyping chip output	0.15 MB
Variations	SNPs & Indels	90 MB

# WGS Data Delivery Options

- SNP & Indels (VCF): download via web
- BAM files: send disk drives to be filled



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# PPMI Data Access & Download

*Thank you ! Thank you !*

Karen Crawford & LONI Team

PPMI Sites

PPMI Imaging Centers

PPMI Cores

PPMI Data Flow and Integration Group

PPMI Working Groups

PPMI Steering Committee

Michael J. Fox Foundation

Industry sponsors and donors

PPMI data users and research community

*& most importantly*

**PPMI study participants !**



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# Overview of Clinical Core

Lisa de Blieck MPA CCRC  
Irina Lazurenko  
Clinical Trials Coordination Center/  
Center for Human Experimental Therapeutics  
University of Rochester Medical Center



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UNIVERSITY of  
**ROCHESTER**  
MEDICAL CENTER



# Clinical Trials Coordination Center (CTCC) Mission

To generate and convey new knowledge leading to treatments that improve health or quality of life of patients and families.



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# CTCC Role in PPMI

Clinical Core for PPMI study

Liaise and partner with study PI & PPMI SC,  
Sponsor, PPMI Cores, PPMI sites & study  
monitors

- CTCC Leadership (Kieburtz, Dorsey, Casaceli)
- Project Management (Lazurenko, Rudolph, de Blieck)
- Data Management (Bennett, Eaton)
- Clinical Monitoring (Sharma)
- Site Monitoring



# CTCC Support for PPMI Sites

## Clinical Core for PPMI study

- Primary contact & support for PPMI sites
- Provides clinical study support
  - Study documents, CRFs & clinical assessments
  - Shared resources on eClinical portal
  - Subject ID numbering and biospecimen labels
  - Protocol training
  - Clinical and Site monitoring
  - Regulatory documentation oversight & tracking
  - Dissemination of centralized communications



# Support for PPMI Sites

- **Study documents & clinical assessments**
  - CTCC mails instruments & assessments that cannot be downloaded from eClinical to sites (UPSIT, JoLO, STIA, etc.)
    - **Sites should notify CTCC when a restock of these assessments are needed**
- **Subject IDs and biospecimen labels**
  - CTCC provides dedicated blocks of subject IDs to sites and matching preprinted biospecimen labels
    - Genetic Cohort and Genetic Registry subjects will receive 5-digit subject IDs. Site to assign PPMI subject ID at consenting
    - Site should notify CTCC if they need more subject IDs
- **Distribution of centralized site communications**
  - CTCC will distribute study communications to sites



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# CTCC Support for PPMI Sites

Who at CTCC should sites contact

- **Protocol questions (Project Manager)**
- **Data questions (Information Analyst)**
- **Safety concerns (Clinical Monitor)**



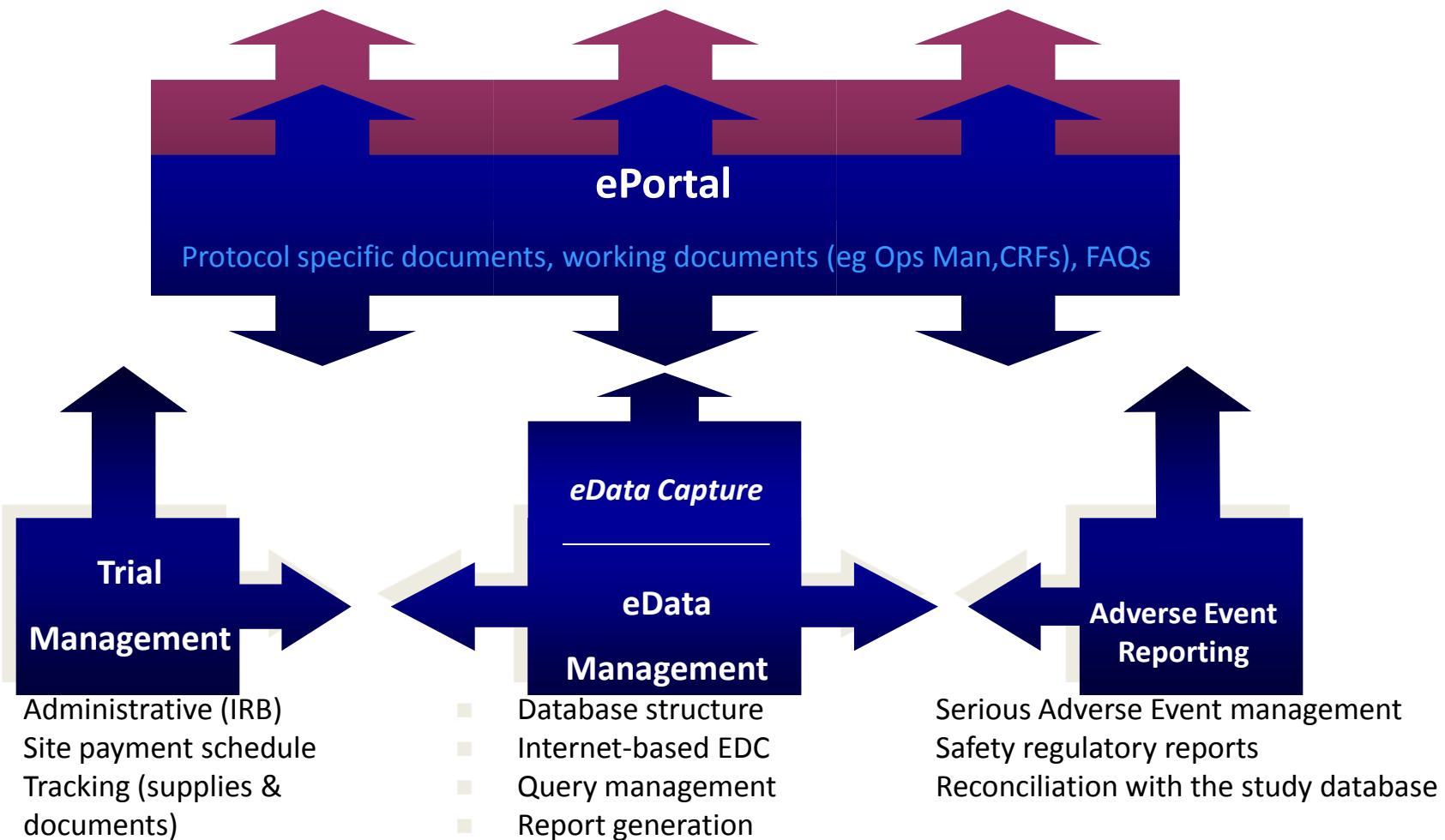
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# eClinical System

## Research Sites & Collaborators



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# eClinical End User Expectations

- eClinical Training (new user, refresher)
- Data entry timeline (**<14 days of visit**)
- Data query resolution timeline (weekly)
- Investigator electronic signatures
  - Attests to oversight of data accuracy and attention to subject safety
  - **Enables data availability for nightly transfer to Laboratory of Neuroimaging (LONI)**



# eClinical – Electronic Data Capture System



EXPeRT Clinical

**Sign In**

Login

Password

[Forgot Password?](#)

**Clinical Trials Coordination Center  
University of Rochester**

265 Crittenden Blvd. CU 420694  
Rochester, NY 14642

Phone: 1-888-406-6704 (toll-free) or 1-585-275-3893

Hours of Operation:  
Monday - Friday  
8:30 am - 9:00 pm ET  
Also visit: <http://support.ctcc.rochester.edu>

Website LINK :

<https://trials.ctcc.rochester.edu/edc/web/guest/home>

SUPPORT LINE: 1-888-406-6704 or 585-275-3893

**PLEASE REMEMBER TO LEAVE A MESSAGE**

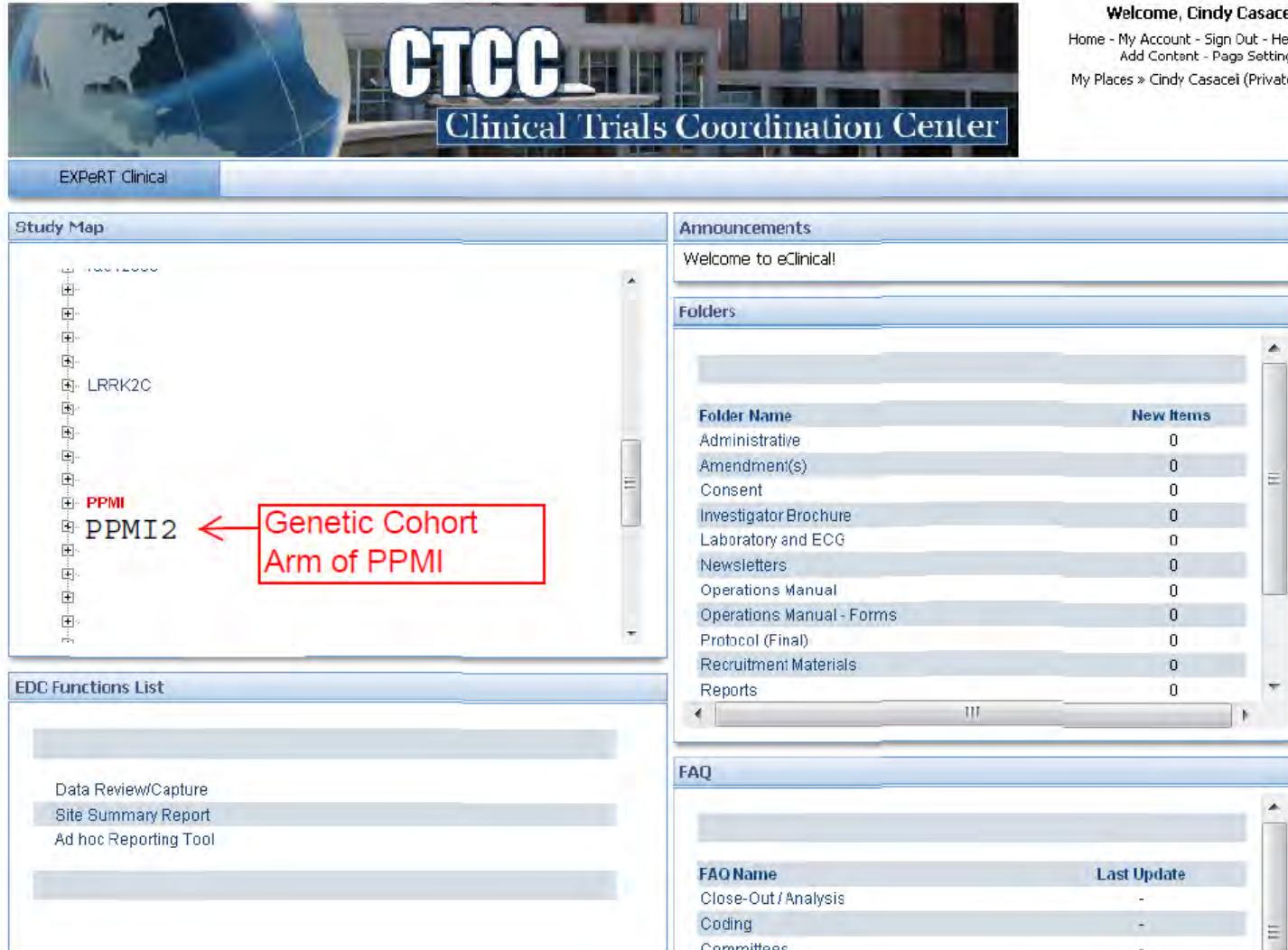


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# eClinical – Portal Screen



The screenshot shows the eClinical Portal Screen. At the top right, it says "Welcome, Cindy Casaceli" and provides links to "Home - My Account - Sign Out - Help", "Add Content - Page Settings", and "My Places » Cindy Casaceli (Private)". The main interface includes:

- Study Map:** A tree view showing study branches. A red box highlights "PPMI2" with the annotation "Genetic Cohort Arm of PPMI".
- EDC Functions List:** Includes "Data Review/Capture", "Site Summary Report", and "Ad hoc Reporting Tool".
- Announcements:** "Welcome to eClinical!"
- Folders:** A list of items with their counts:

Folder Name	New Items
Administrative	0
Amendment(s)	0
Consent	0
Investigator Brochure	0
Laboratory and ECG	0
Newsletters	0
Operations Manual	0
Operations Manual - Forms	0
Protocol (Final)	0
Recruitment Materials	0
Reports	0
- FAQ:** A list of items with their last update dates:

FAQ Name	Last Update
Close-Out / Analysis	-
Coding	-
Committees	-

PA  
PR  
MA  
INI

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**Data Capture** User ID: SITEINV1

**1. Click in Investigator signature box**

**2. Save Page**

**3. Enter password used to log into eClinical and Save Changes**

# PPMI Unique Page Status

Current Page Statuses

	<input type="checkbox"/> Completed
	<input type="checkbox"/> Reviewed
	<input checked="" type="checkbox"/> Source Verified (JCOLOSI   05092011 1)
	<input checked="" type="checkbox"/> Coordinator Signature (CBISHOP   02022)
	<input type="checkbox"/> Investigator Signature
	<input checked="" type="checkbox"/> Entry Complete (CBISHOP   01242011 1)



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# Electronic Signatures

Investigator electronically signs within eClinical on the **INVESTIGATOR SIGNATURE** page

- Equivalent to a handwritten signature.
- Must be present on all INVESTIGATOR SIGNATURE pages for each visit/contact
- As mentioned, electronic Signature needs to be present for payment of visit



# Back up slides

## Overview of Clinical Core

Lisa de Blieck MPA CCRC  
Irina Lazurenko  
Clinical Trials Coordination Center/  
Center for Human Experimental Therapeutics  
University of Rochester Medical Center

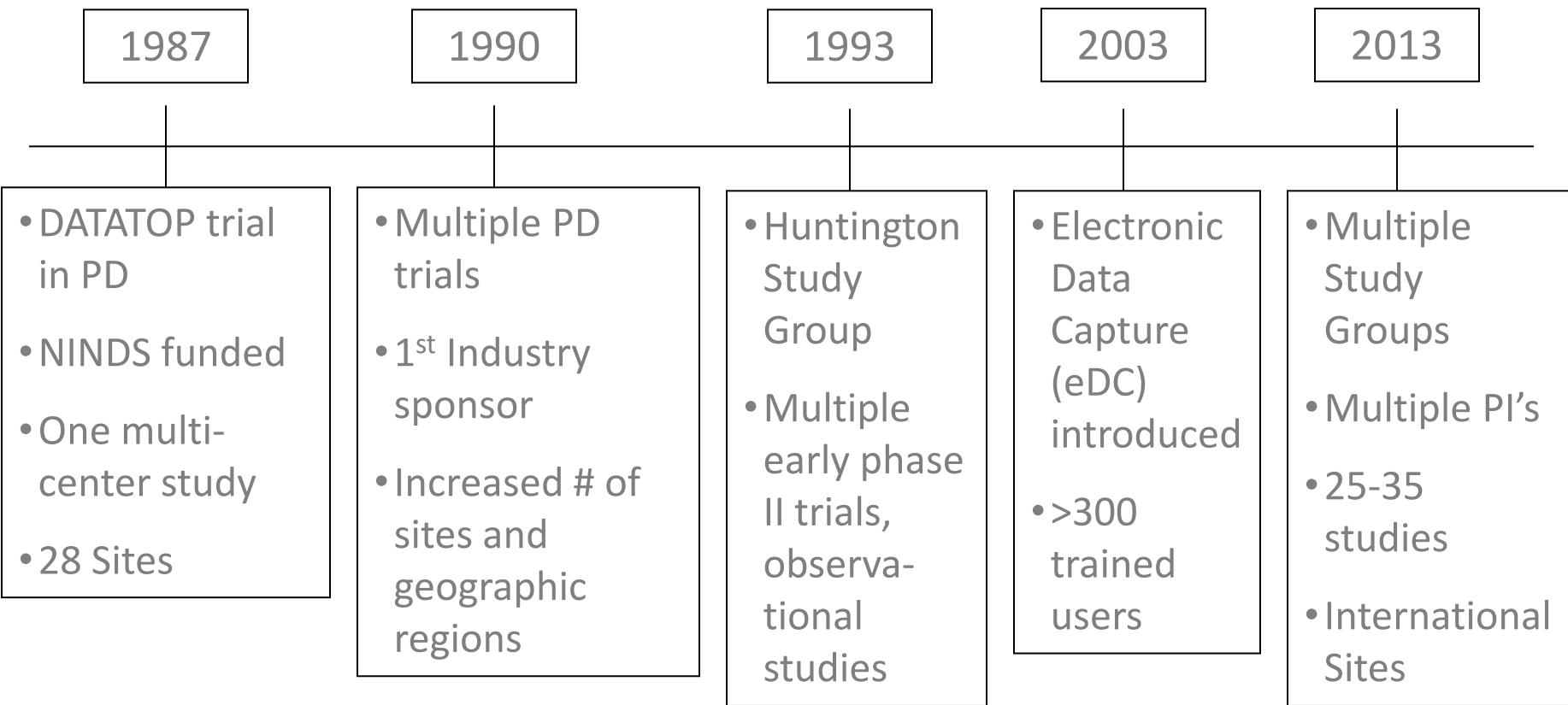


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# CTCC Historical Timeline



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# CTCC Collaborations

- Multiple study groups and investigators
- Collaboration with academics, industry, foundations, government agencies
- Over 100 studies completed with more than 30,000 study participants
- Participation in the development of five successfully approved compounds to date in the US



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# CTCC Team Model

- Clinical Project Manager(s)
- Clinical Monitor
- Database Manager/Programmer
- Information Analyst(s)
- Finance and Administrative Support
- Site Monitor(s)
- Biostatistical Programmer
- Sponsor Representatives



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Funding  
established

# Life Cycle of a Clinical Trial

Primary  
Publication

## Orientation Meeting

- Preparatory phase
  - Protocol finalized
  - Model ICF finalized
  - Sites selected
  - Operations manual completed
  - CRFs finalized
  - IRB/IEC approvals obtained
  - Site subcontracts in place
  - Build database
  - Study drug packaging/labeling
  - Vendor setup
- Protocol Synopsis finalized
- Schedule of Activities finalized

- Study launch/active phase
  - Distribution of study drug to sites
  - Recruitment and enrollment
  - Advise re protocol/data ?s
  - Intake of reportable events (e.g., SAEs, PWs)
  - Data query process
  - Oversee monitoring
- Ongoing data QA
- Close/lock database
- Transfer database to Biostatistics

Database closed,  
transferred to Biostatistics

- Perform primary/secondary analysis
- Communication of results (sites/subjects)
- Submit abstract
- Submit manuscript
- Post-hoc analysis
- 1 month post publication, deactivate conflict-of-interest obligation

**CONCEPTUAL**

**PLANNING**

**IMPLEMENTATION**

**ANALYSIS/ PUBLICATION**

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# CTCC Resources

- Regulatory compliant electronic data capture system (21 CFR part 11) - *eClinical/eDC*
  - Real-time data availability
  - Expanded access to data, including sponsors
  - Time to database lock greatly reduced over paper studies
- System support
  - Web-based informatics support site
  - Telephone support
- >60 Standard Operating Procedures and Guidelines with documented training of staff



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# Review of Non-motor Assessments

Tanya Simuni, MD  
Northwestern University  
September 16, 2013

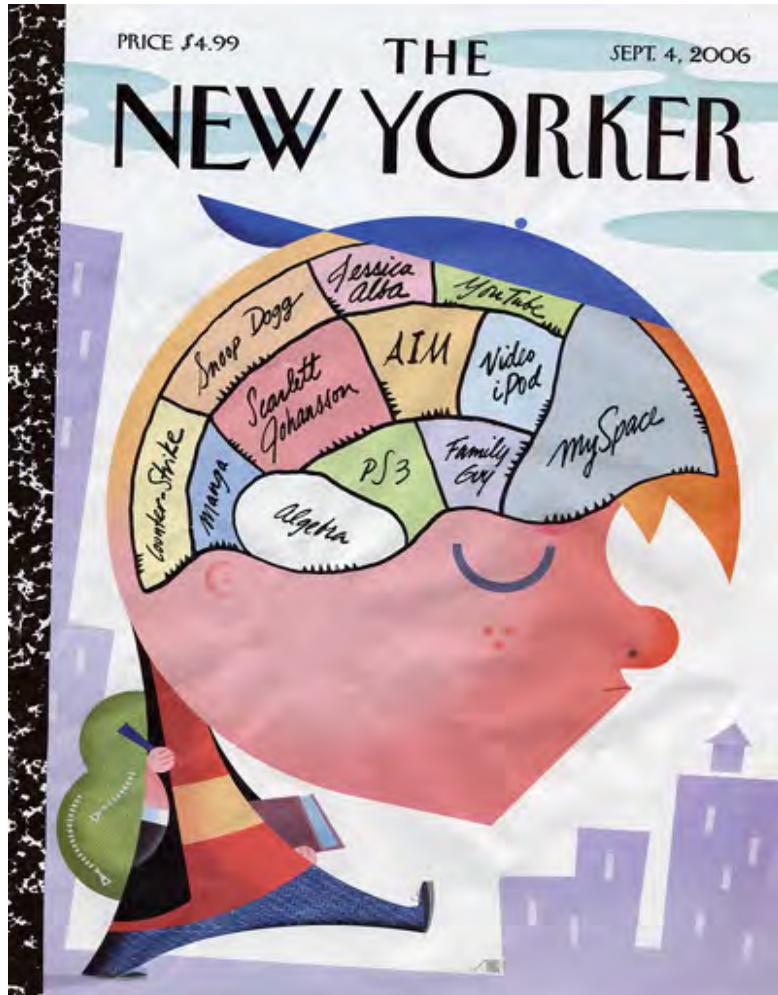


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# Background and rationale for the PPMI Non-motor assessments



- Sensitive to cognitive and non-cognitive behavioral aspects
- Relatively brief
- Repeatable
- Not require extensive formal training

**PPMI is a biomarker study!!**

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Play a Part in Parkinson's Research  New Yorker and other clip are courtesy of Dr. Siderowf

# Review of non-motor tests

- MDS-UPDRS Part I
- Cognitive and behavioral battery
- UPSIT
- Epworth Sleepiness Scale
- RBD Questionnaire
- Geriatric Depression Scale (GDS-15)
- State-Trait Anxiety Inventory (STAI)
- Impulse control (QUIP)
- SCOPA-AUT
- Physical activity scale for the elderly ( PASE)



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# University of Pennsylvania Smell Identification Test (UPSIT)

- 40 forced-choice items
- Odorants like “pizza”, “lilac” and “motor oil”
- Higher scores indicate better olfaction
- Score of 18 indicates anosmia
- Administered at baseline only



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From Doty et al, Physiology and Behavior 1984.

# Sleep Scales

- Sleep disturbances are common in PD
  - Disrupted night sleep
  - Daytime drowsiness
  - Restless leg syndrome
- REM sleep behavior disorder (RBD) is the strongest pre-motor marker of PD



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# Epworth Sleepiness Scale

- 8 items, very brief
- Score of  $\geq 10$  indicate significant daytime drowsiness
- Pre-motor risk factor for PD
- Greater motor and cognitive severity and medications are risk factors
- Very limited data in de novo PD population

## Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations?  
Answer considering how you have felt over the past week or so.

- 0 = Would never doze  
1 = Slight chance of dozing  
2 = Moderate chance of dozing  
3 = High chance of dozing

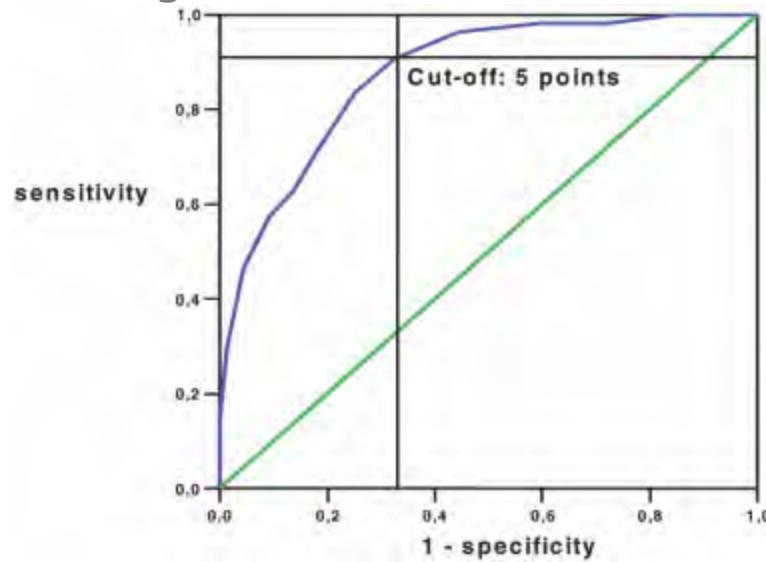
1. Sitting and reading	<input type="text"/>
2. Watching TV	<input type="text"/>
3. Sitting inactive in a public place (e.g., theater or meeting)	<input type="text"/>
4. As a passenger in a car for an hour without a break	<input type="text"/>
5. Lying down to rest in the afternoon when able	<input type="text"/>
6. Sitting and talking to someone	<input type="text"/>
7. Sitting quietly after a lunch without alcohol	<input type="text"/>
8. In a car while stopped for a few minutes in traffic	<input type="text"/>

# REM Sleep Disorder Questionnaire

- 10 items, 5 minutes
- Self-report questionnaire
- Validated in RBD patients vs controls ( 54PD and 160 controls )
- Maximum score is 13
- RBD patient score = 9.5  
control score= 4.6
- Cut off score = 5
  - Sensitivity= 0.96
  - Specificity= 0.56 /  
PPV= 0.66
- Limitations
  - RBD requires PSG confirmation

Q1.I sometimes have vivid dreams

Q6.I have or had the following phenomena during my dreams: speaking, shouting swearing, laughing loudly, sudden limb movements, “fights”



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From Staisny-Kolster, Movement Disorders, 2007

# Geriatric Depression Scale (GDS-15)

- 15 items, 5 minutes
- Self-administered
- Validated in PD
- Score of  $\geq 5$  indicates depression (Weintraub)
- Free (optional donation)
- Widely translated
- [www.stanford.edu/%7Eyesavage/GDS.html](http://www.stanford.edu/%7Eyesavage/GDS.html)

Date / /	Please tick ✓	
1. Are you basically satisfied with your life?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2. Have you dropped many of your activities and interests?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
3. Do you feel that your life is empty?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
4. Do you often get bored?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
5. Are you in good spirits most of the time?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
6. Are you afraid that something bad is going to happen to you?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
7. Do you feel happy most of the time?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
8. Do you often feel helpless?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
9. Do you prefer to stay at home, rather than going out and doing things?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
10. Do you feel you have more problems with memory than most?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
11. Do you think it is wonderful to be alive now?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
12. Do you feel pretty worthless the way you are now?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
13. Do you feel full of energy?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
14. Do you feel that your situation is hopeless?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
15. Do you think that most people are better off than you?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
TOTAL SCORE		



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Brink TL, Yesavage JA, Lum O, Heersema P, Adey MB, Rose TL: Screening tests for geriatric depression. *Clinical Gerontologist* 1: 37-44, 1982.

# State-Trait Anxiety

- 40 item scale (20 state/20 trait)
- Some questions reverse response order—need to check
- Scores range from 20–80 for both scales
- Scores above 40 on the state scale indicates significant anxiety
- <http://www.theaaceonline.com/stai.pdf>



Charles D. Spielberger, Ph.D

A number of statements which people have used to describe themselves are given below. Read each statement and then mark the appropriate choice to the right of the statement to indicate how you feel *right now*, that is, *at this moment*. There are no right or wrong answers, but give the answer which seems to describe your present feelings best.

	Not at All	Somewhat	Moderately So	Very Much So
1. I feel calm	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. I feel secure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. I am tense	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. I feel strained	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. I feel at ease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. I feel upset	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. I am presently worrying over possible misfortunes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. I feel satisfied	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. I feel frightened	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. I feel comfortable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

# Impulse Control Disorders (QUIP)

- 13 item ICD screening questionnaire
  - 2 Qs each for eating, buying, sex and gambling
  - 3 Qs for other behaviors
  - 2 Qs for medications use
- 5 minutes to complete
- Score of 1 or higher on any item indicates presence of an ICD
  - sensitivity = 0.96,  
specificity = 0.73,
  - PPV = 0.62/ NPV = 0.98



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Weintraub et al, Movement Disorders, 2009

# SCOPA-AUT

- 26 item, self administered scale, about 10 minutes
- Domains: gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillomotor, skin, respiratory, and sexual
- All but sexual dysfunction correlate with disease severity
- <http://www.scopa-propark.eu/index.php?language=eng>



## SCOPA-AUT

By means of this questionnaire, we would like to find out to what extent in the past month you have had problems with various bodily functions, such as difficulty passing urine, or excessive sweating. Answer the questions by placing a cross in the box which best reflects your situation. If you wish to change an answer, fill in the 'wrong' box and place a cross in the correct one. If you have used medication in the past month in relation to one or more of the problems mentioned, then the question refers to how you were while taking this medication. You can note the use of medication on the last page.

1. In the past month have you had difficulty swallowing or have you choked?  

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
never	sometimes	regularly	often
2. In the past month, has saliva dribbled out of your mouth?  

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
never	sometimes	regularly	often
3. In the past month, has food ever become stuck in your throat?  

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
never	sometimes	regularly	often
4. In the past month, did you ever have the feeling during a meal that you were full very quickly?  

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
never	sometimes	regularly	often



# Physical activity scale for the elderly (PASE )

- Objective
  - Pilot data
  - Assess exercise habits of PPMI subjects
  - Correlate with the other clinical measures and biomarkers
  - Brief, self administered scale

PASE Score

PASE Activity	Score	PASE weight	PASE score
Muscle strength/endurance*	h/d	30	
Strenuous sports*	h/d	23	
Moderate sports*	h/d	23	
Light sports*	h/d	21	
Job involving standing/walking*	h/d	21	
Walking*	h/d	20	
Lawn work or yard care		36	
Caring for another person		35	
Home repairs		30	
Heavy housework		25	
Light housework		25	
Outdoor-gardening		20	
PASE Total			

\* determine the average number of hours/day (h/d) over the 7-day period

1= engaged in activity during the previous 7 days

0= did not engage in activity during the previous 7 days



# Cognitive Battery Purpose

- Cohort and sub-sample characterization
- Identification of the early cognitive changes
- **Correlation with biomarkers**
- Correlation with other clinical features
- Characterization of disease subtypes
- Prediction of course (e.g., rapidity of change, eventual phenotype)
  - cognitive risk factors for particular outcomes
- Documentation of cognitive course & course variants



# Neuropsychological Test Selection Rationale

Attempt to balance competing objectives:

- **Sensitivity to PD relevant cognitive domains**
- **Provide some data in a common/known metric**
  - i. e. a clinically interpretable global score
- **Brevity**
- **Relatively easy to administer & score**
  - Maximize reliability across examiners, sites, & time.
  - Minimize examiner judgment.
- **Test selection by Steering Committee**
  - Guided by the recommendations of the Movement Disorders Task Force: Dubois, B.; Burn, D. et al. (2007) Movement Disorders, 22 pp. 2314-2324
  - Revised based on the recommendations of the Movement Disorders Task Force on MCI in PD: Litvan, Goldman, et al (2011) Mov Disorders Aug 15;26(10):1814-24.



# PPMI Neuropsychological Battery

Domain	Test		Normative Data	Time
Global	MoCA	X	—	10
Memory	Hopkins Verbal Learning-Free Recall (Trials 1-3)	X	Yes	5
	Hopkins Verbal Learning-Free Recall (Delayed)	X	Yes	3
	Hopkins Verbal Learning-Recognition	X	Yes	2
Executive	Letter-Number Sequencing	X	Yes	5
Attention-Working Memory	Symbol-Digit Modalities Test	X	Yes	3
Visuospatial	Benton's Judgment of Line Orientation (15-item)	X	Yes	5
Language	Semantic Fluency (animals, fruits, vegetables)	X	Yes	5
<b>TOTAL TIME</b>				<b>38</b>

<sup>a</sup>Propose to use all 3 versions of MoCA moving forward; <sup>b</sup>Proposed to include BHR as alternate to FAS from the start

# PPMI Behavioral Battery

Symptom/Disorder	Test	Current	Self or Rater Administered	Time (current)
Depression	GDS-15	X	Self	3
Anxiety	STAI	X	Self	7
Impulse control disorders	QUIP	X	Self	3
<b>TOTAL TIME</b>				<b>13</b>

(\* 9 items chosen from original SAPS: auditory hallucinations, voices conversing, somatic or tactile hallucinations, visual hallucinations, global rating or severity of hallucinations, persecutory delusions, delusions of jealousy, delusions of reference, and global rating of severity of delusions)



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## MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :  
Education :  
Sex :Date of birth :  
DATE :

<b>VISUOSPATIAL / EXECUTIVE</b>						<b>POINTS</b>				
				Draw CLOCK. (Ten past eleven) (3 points)						
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		/5			
<b>NAMING</b>										
			<input type="checkbox"/>				<input type="checkbox"/>		<input type="checkbox"/>	
							/3			
<b>MEMORY</b> Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.			<input type="checkbox"/>	FACE	VELVET	CHURCH	DAISY	RED	No points	
1st trial										
2nd trial										
<b>ATTENTION</b>			Subject has to repeat them in the forward order <input type="checkbox"/> 2 1 8 5 4							
			Subject has to repeat them in the backward order <input type="checkbox"/> 7 4 2							
Read list of letters. The subject must tap with his hand at each letter A. No points if $\geq 2$ errors <input type="checkbox"/> F B A C M N A A J K L B A F A K D E A A A J A M O F A A B										
Serial 7 subtraction starting at 100			<input type="checkbox"/> 93	<input type="checkbox"/> 86	<input type="checkbox"/> 79	<input type="checkbox"/> 72	<input type="checkbox"/> 65			
			4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt.							
<b>LANGUAGE</b>			Repeat: I only know that John is the one to help today. <input type="checkbox"/> The cat always hid under the couch when dogs were in the room. <input type="checkbox"/>							
			Fluency / Name maximum number of words in one minute that begin with the letter F <input type="checkbox"/> (N $\geq$ 11 words)							
<b>ABSTRACTION</b>			Similarity between e.g. banana - orange = fruit <input type="checkbox"/> train - bicycle <input type="checkbox"/> watch - ruler							
<b>DELAYED RECALL</b>			Has to recall words <input type="checkbox"/> WITH NO CUE	FACE <input type="checkbox"/>	VELVET <input type="checkbox"/>	CHURCH <input type="checkbox"/>	DAISY <input type="checkbox"/>	RED <input type="checkbox"/>	Points for UNCLUED recall only	
<b>Optional</b>			Category cue <input type="checkbox"/>							
<b>ORIENTATION</b>			<input type="checkbox"/> Date	<input type="checkbox"/> Month	<input type="checkbox"/> Year	<input type="checkbox"/> Day	<input type="checkbox"/> Place	<input type="checkbox"/> City		/6
			© Z.Nasreddine MD Version 7.1 <a href="http://www.mocatest.org">www.mocatest.org</a> Normal $\geq 26 / 30$ TOTAL <input type="checkbox"/> /30							
			Administered by: _____						Add 1 point if $\leq 12$ yr edu	

## Schedule of Activities – Parkinson Disease (PD) Subjects

Visit Number	SC	BL	V01	V02	V03	V04 <sup>b</sup>	V05 <sup>b</sup>	V06 <sup>b</sup>	V07 <sup>b</sup>	V08 <sup>b</sup>	V09 <sup>b</sup>	V10 <sup>b</sup>	V11 <sup>b</sup>	V12	PW	ST	Unsch. Visit	
Visit Description	Months (-30 days)	-45 days	0	3	6	9	12	18	24	30	36	42	48	54	60	--	--	--
Written Informed Consent		X																
Review Inclusion/Exclusion Criteria		X	X															
Medical & Family History/Demographics		X																
Physical Examination		X																
Neurological Examination		X					X		X		X		X		X	X	X <sup>k</sup>	X <sup>e</sup>
Vital Signs		X	X <sup>c</sup>	X	X	X	X <sup>c</sup>	X	X <sup>c</sup>	X	X							
Blood Sample for DNA		X																
Clinical Laboratory Assessments		X					X		X		X		X		X	X	X <sup>k</sup>	X <sup>e</sup>
Biomic blood sample			X <sup>f</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>	*X <sup>f</sup>	X <sup>f</sup>	
MDS-UPDRS (including Hoehn & Yahr) <sup>a</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Modified Schwab & England ADL		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Diagnosis Assessment(s)		X					X		X		X		X		X	X	X	X
MDS-UPDRS Repeat Part III/Hoehn & Yahr <sup>j</sup>							X		X		X		X		X	X	X	
Physical Activity Scale for the Elderly (PASE)							X		X		X		X		X	X	X	
Hopkins Verbal Learning Test – Revised		X					X		X		X		X		X	X	X <sup>k</sup>	
Benton Judgment of Line Orientation		X					X		X		X		X		X	X	X <sup>e</sup>	
Semantic Fluency		X					X		X		X		X		X	X	X <sup>k</sup>	
Letter Number Sequencing		X					X		X		X		X		X	X	X <sup>k</sup>	
Symbol Digit Modalities Test		X					X		X		X		X		X	X	X <sup>k</sup>	
Montreal Cognitive Assessment (MoCA)	X						X		X		X		X		X	X	X <sup>k</sup>	
Epworth Sleepiness Scale		X		X			X		X		X		X		X	X	X	
REM Sleep Behavior Questionnaire		X		X			X		X		X		X		X	X	X	
Geriatric Depression Scale (GDS-15)		X		X			X		X		X		X		X	X	X	
State-Trait Anxiety Inventory for Adults		X		X			X		X		X		X		X	X	X	
QUIP		X		X			X		X		X		X		X	X	X	
SCOPA-AUT		X		X			X		X		X		X		X	X	X	
Cognitive Categorization		X		X			X		X		X		X		X	X	X <sup>k</sup>	
Olfactory Testing (UPSiT)		X																
MRI (structural)		X																
MRI (DTI) <sup>e</sup>		X					X		X				X			~X		
DAT imaging <sup>m,o</sup>	X						X		X				X			~X	X <sup>k</sup>	
VMAT-2 imaging <sup>m,o,f</sup> (see companion protocol)	X <sup>p</sup>						X		X				X			~X	X <sup>k</sup>	
Lumbar puncture (CSF collection)		X		X			X		X		X		X		X	*X	X <sup>k</sup>	
Adverse Events <sup>a</sup>	X	X		X			X		X		X		X		X	X	X	
Current Medical Conditions Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

<sup>a</sup> Adverse events assessed at the visit and by phone 7 to 10 days following LP and/or DaTSCAN injection.<sup>b</sup> Telephone consent will occur at Months 15, 21, 27, 33, 39, 45, 51 and 57.<sup>c</sup> Height and weight also collected.<sup>d</sup> Diffusion tensor MRI scan and resting state sequences conducted at selected sites.<sup>e</sup> Biomimic urine sample also collected.<sup>f</sup> Conduct as clinically indicated – see protocol Sect. 5.3.17.<sup>g</sup> Part IV once subject has started PD medication.<sup>j</sup> Repeat assessment 1hr post treatment for subjects on levodopa or dopamine agonist.<sup>k</sup> Not conducted depending on when ST visit completed – see protocol Sect. 5.3.19.<sup>m</sup> DAT completed at all sites except Australia; VMAT completed in Australia and selected U.S. sites.<sup>o</sup> Urine pregnancy test prior to injection for women of childbearing potential.<sup>p</sup> Serum pregnancy test prior to injection day for women of childbearing potential; ECG for all subjects.<sup>r</sup> Subject's enrolled in U.S. may agree to initial VMAT imaging scan at YR01 rather than Screening.

ST = Symptomatic Therapy

PW = Premature Withdrawal (\*if not done in last 3 mths; ^if not done in last 12 mths)

# Cognitive Categorization of PPMI Subjects

- Documentation of cognitive decline – A determination of cognitive decline is necessary for a diagnosis of mild cognitive impairment (PD-MCI) and dementia (PDD).
  - Ideally determination of gradual cognitive decline from pre-PD baseline abilities should be based on (1) subject report; (2) informed other report, if available; and (3) physician impression.
- Operationalization of cognitive impairment – Review of standardized scores for the 5 PPMI neuropsychological tests (6 test scores) across 4 cognitive domains<sup>a</sup>.
  - For PD-MCI, impairment will require *at least 2 test scores > 1.5 SD below the standardized mean*.
  - For PDD, impairment will require *at least 1 test score from 2 domains > 1.5 SD below the standardized mean*.
- (Performance on the MoCA will be considered as a complement to the detailed neuropsychological battery, with scores
  - $\geq 26$  suggestive of PD-NC,
  - 21-25 suggestive of PD-MCI,
  - $\leq 20$  suggestive of PDD.



# Cognitive Diagnostic Categories

<b>Normal Cognition ( PD-NC)</b>	<b>Cognitive complaints</b>	<b><u>Mild Cognitive Impairment (PD-MCI)</u></b>	<b><u>Dementia (PDD)</u></b>
<u>X</u> / Report cognitive decline	<u>✓<sup>b</sup></u> / Report cognitive decline	<u>✓</u> Report cognitive decline	<u>✓</u> Report cognitive decline
<u>X</u> / Cognitive impairment	<u>X</u> / Cognitive impairment	<u>✓</u> Cognitive impairment	<u>✓</u> Cognitive impairment
<u>X</u> / Functional impairment	<u>X</u> / Functional impairment	<u>X</u> Functional impairment	<u>✓</u> Functional impairment



# AND THE DATA ...



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**Table 2. Summary Clinical Scores**

Variable	Enrolled Subjects		
	PD Subjects (N =423)	Healthy Controls (N =196)	p-value (PD vs. HC)
<b>MOCA Total Score</b>	<0.01		
Mean	27.1	28.2	
(Min, Max)	(17, 30)	(26, 30)	
Missing	0	0	
<b>GDS Total Score</b>	<0.01		
Mean	2.3	1.3	
(Min, Max)	(0, 14)	(0, 15)	
Missing	0	0	
<b>SCOPA AUT Total Score</b>	<0.01		
Mean	9.5	5.9	
(Min, Max)	(0, 39)	(0, 20)	
Missing	0	1	
<b>State Trait Anxiety Score</b>	<0.01		
Mean	65.3	57.1	
(Min, Max)	(40, 137)	(40, 105)	
Missing	1	0	
<b>QUIP</b>	0.77		
Mean	0.3	0.3	
(Min, Max)	(0, 4)	(0, 5)	
Missing	1	0	
<b>UPPSIT Raw Score</b>	<0.01		
Mean	22.4	34.0	
(Min, Max)	(1, 40)	(11, 40)	
Missing	0	0	
<b>Epworth Sleepiness Scale</b>	0.28		
Not Sleepy (9 or below)	357 (84%)	171 (38%)	
Sleepy (10 or above)	66 (16%)	24 (12%)	
Missing	0 (0%)	1 (1%)	
<b>REM Sleep Disorder</b>	<0.01		
Negative (less than 5)	263 (62%)	157 (30%)	
Positive (5 or above)	160 (38%)	39 (20%)	
Missing	0 (0%)	0 (0%)	

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Table 3c. Demographics and Clinical Predictors of MOCA &lt;26 vs. 26 or Greater in PD Subjects

Variable	Enrolled PD Subjects		Univariate p-value	Multivariate p-value
	MOCA <26 (N = 93)	MOCA 26+ (N = 330)		
<b>Age</b>			<.01	<.01
Mean	64.2	60.9		
(Min, Max)	(33.7, 84.9)	(33.5, 81.8)		
Missing	0	0		
<b>Race</b>			0.11	0.07
White	81 (87%)	310 (94%)		
Black/African-American	3 (3%)	3 (1%)		
Asian	4 (4%)	4 (1%)		
Other	5 (5%)	13 (4%)		
Missing	0 (0%)	0 (0%)		
<b>Family History</b>			0.55	-
Family Members w/PD	20 (22%)	82 (25%)		
No Family Members w/PD	73 (78%)	247 (75%)		
Missing	0 (0%)	1 (0%)		
<b>MDS-UPDRS Mean Score &amp; Sub Scores</b>				
MDS-UPDRS Total Score	34.6	31.7	0.07	N.S.
MDS-UPDRS Part I	5.9	5.5	0.36	-
MDS-UPDRS Part II	5.7	6.0	0.59	-
MDS-UPDRS Part III (Motor Score)	22.9	20.3	0.01	-
Missing	0	1		
<b>Modified Schwab &amp; England Activities of Daily Living</b>			0.01	0.01
Mean	91.8	93.5		
(Min, Max)	(80.0, 100.0)	(70.0, 100.0)		
Missing	0	0		
<b>Duration of Disease</b>			0.37	-
Mean	7.2	6.5		
(Min, Max)	(0.9, 24.6)	(0.4, 35.8)		
Missing	0	0		
<b>TD/PIGD Classification</b>			0.39	-
TD	67 (72%)	232 (70%)		
PIGD	19 (20%)	57 (17%)		
Indeterminate	7 (8%)	40 (12%)		
Missing	0 (0%)	1 (0%)		
<b>Side Most Affected</b>			0.93	-
Left	38 (41%)	142 (43%)		
Right	54 (58%)	179 (54%)		
Symmetric	1 (1%)	9 (3%)		
Missing	0 (0%)	0 (0%)		

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**Table 3d. Demographic and Clinical Predictors of MOCA in PD Subjects**

Variable	Univariate p-value	# Observations Missing	Multivariate p-value
Age	<.0001	0	<.0001
Gender	0.0073	0	0.0168
Education	0.8663	0	-
Ethnicity	0.1822	0	N.S.
Race	0.0314	0	0.0089
Family History of PD	0.8748	1	-
UPDRS Total Score	0.0106	1	N.S.
Hoehn & Yahr	0.2192	0	-
Modified Schwab and England Activities of Daily Living	0.0096	0	0.0138
Duration of Disease	0.1305	0	N.S.
TD/PIGD Classification	0.4744	1	-
Side Most affected	0.8299	0	-

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Table 6. PPMI Non-Motor II: Non-Neuropsychological at Baseline

Variable	Enrolled Subjects				
	PD Subjects (N = 423)	Healthy Controls (N = 196)	SWEDD Subjects (N = 64)	p-value (PD vs. HC)	p-value (PD vs. SWEDD)
<b>MOCA Total Score</b>				<0.01	0.94
Mean (Min, Max) Missing	27.1 (17, 30) 0	28.2 (26, 30) 0	27.1 (17, 30) 0		
<b>Benton Judgment of Line Orientation Score</b>				0.05	0.94
Mean (Min, Max) Missing	12.8 (5, 15) 1	13.1 (4, 15) 0	12.8 (5, 15) 0		
<b>HVLT Immediate Recall</b>				<0.01	0.92
Mean (Min, Max) Missing	9.7 (4, 12) 1	10.2 (6, 12) 0	9.7 (5, 12) 0		
<b>HVLT Delayed Recognition</b>				<0.01	0.04
Mean (Min, Max) Missing	11.2 (0, 12) 2	11.5 (8, 12) 0	10.8 (0, 12) 0		
<b>HVLT Delayed False Alarms</b>				0.18	0.05
Mean (Min, Max) Missing	1.2 (0, 6) 2	1.1 (0, 6) 0	1.6 (0, 6) 0		
<b>Letter Number Sequencing Raw Score</b>				0.22	0.05
Mean (Min, Max) Missing	10.6 (2, 20) 1	10.9 (2, 20) 0	9.9 (4, 15) 0		
<b>Semantic Fluency Total Score</b>				<0.01	0.03
Mean (Min, Max) Missing	48.7 (20, 103) 1	51.8 (22, 80) 0	45.2 (23, 81) 0		
<b>Symbol Digit Modalities</b>				<0.01	0.96
Mean (Min, Max) Missing	41.2 (7, 82) 1	46.8 (20, 83) 0	41.3 (19, 71) 0		
<b>Animal Fluency</b>				0.01	0.03
Mean (Min, Max) Missing	21.0 (8, 41) 1	22.1 (10, 37) 0	19.3 (8, 38) 0		
<b>Vegetable Fluency</b>				0.02	0.04
Mean (Min, Max) Missing	14.2 (3, 40) 1	15.1 (4, 27) 0	13.0 (5, 22) 0		
<b>Fruit Fluency</b>				<0.01	0.25
Mean (Min, Max) Missing	13.5 (3, 29) 1	14.6 (4, 26) 0	12.9 (7, 22) 0		

# PPMI Non-motor data analysis in progress. **Get involved!**

- Baseline cognitive and behavioral characterization of the PPMI cohort
  - Weintraub, cognitive working group
- Correlation of the clinical variables of cognitive performance and biomarkers
  - Weintraub, cognitive working group
- Prevalence and biological correlates of sleepiness in early PD
  - Simuni, sleep working group
- Prevalence and biological correlates of RBD in early PD\*
  - Sleep working group



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# PPMI Imaging Core

**Ken Marek  
Susan Mendick**

**PPMI Genetics Kickoff  
Sept 16, 2013  
New York, NY**



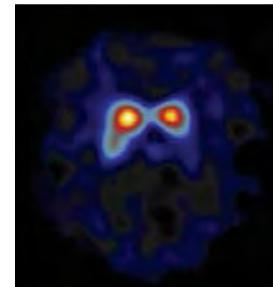
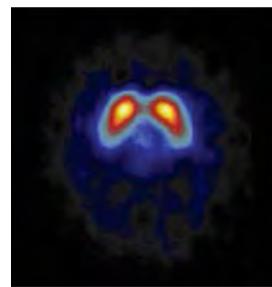
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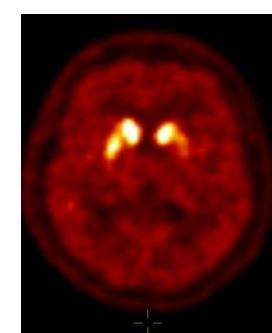
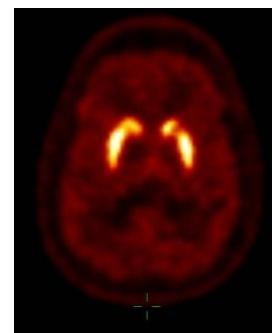


# PPMI Imaging

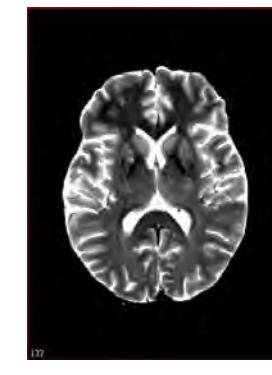
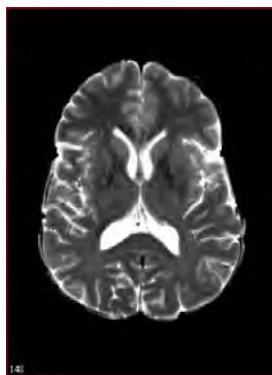
**$^{123}\text{I}$  FP-CIT-  
DAT**



**$^{18}\text{F}$  AV-133-  
VMAT2**



**DTI**



Healthy

Parkinson disease



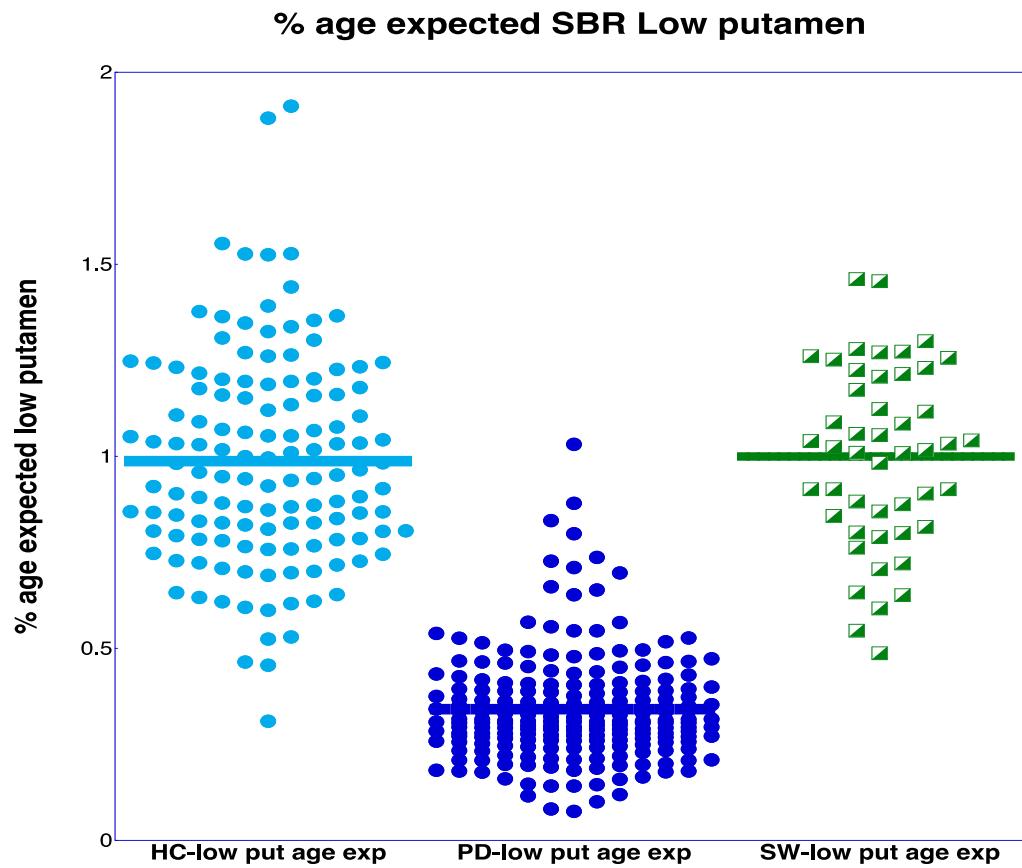
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# Baseline DAT Data

● HC-low put age exp  
● PD-low put age exp  
■ SW-low put age exp



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# Imaging - Schedule

- DAT/VMAT(australia)  
SC/24mo/48mo
- MRI SC
- MRI DTI SC/24mo/48mo

**DAT imaging is not an inclusion criteria for the Genetic Cohort**



# Imaging - Info provided

- PD - DAT/VMAT at SC – consistent with DAT/VMAT deficit or not consistent with DAT/VMAT deficit
- Unaffected – No information until completion of the study

**DAT imaging is not an inclusion criteria for the Genetic Cohort**



# Imaging Biomarkers –Beyond DA

Modality	Ligand	Target	PPMI Plans
SPECT	DaTSCAN	Dopamine Transporter	Use at all sites – eligibility criteria and progression marker
MRI	DTI/RS	Fractional anisotropy (FA)	Sub-study defined by camera – exploratory data for disease progression
PET	DTZB, AV133	VMAT2	Monoamine marker –Limited availability for multi-site

## SOME DATA IN PD, POSSIBLE VALUE IN PPMI

PET	FDG	Glucose Metabolism	Possible progressive changes in cognitive and motor patterns
Ultrasound	Substantia Nigra		Likely not progression marker
PET	Flutemetamol, Florbetaben, Florbetapir	Amyloid	Possible progressive changes in cognitive
SPECT	MIBG	Cardiac sympathetic function	Likely not sensitive progression marker
PET/SPECT	PBR06, PBR111, PK11195	PBR	Inflammatory changes
Optical coherence tomography (OCT)	Retinal morphology		Limited data for PD, none of progression
<b>Early development</b>			
PET/SPECT		alpha-synuclein	Early development
PET/SPECT		Tau	Early development
PET/SPECT		LRRK2	Early development



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# Imaging Core Lab (ICL)

- Assist with image acquisition and analysis
- Provide training and ongoing help to PPMI sites to assist with availability of the radiotracer and to ensure image data quality



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# Imaging Core Lab (ICL) Responsibilities

- Assess site technical capabilities
- Perform SPECT technical site visits (for centers new to PPMI)
- SPECT and AV-133 data:
  - QC data
  - Provide Visual Interpretation (Genetic Cohort—PD Only)
  - Analyze data
  - Provide data for inclusion in study database



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# ICL Responsibilities

- Structural MRI data
  - QC data
  - Provide data for inclusion in study database
- DTI/RS MRI data
  - QC data
  - Provide data for inclusion in study database and subsequent analysis



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# DaTSCAN Imaging Day Activities

- Urine pregnancy test for women of childbearing potential
- Administration of thyroid protection prior to injection
- 5 mCi (+/- 10%) DaTSCAN Injection
- SPECT acquisition 4 hours (+/- 15 minutes) post injection
- Adverse event assessment during imaging day and 7 days ( $\pm$  3 day) telephone call



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# AV-133 Imaging Day Activities

- Urine pregnancy test for women of childbearing potential.
- No fasting required prior to 18F-AV-133 injection.
- Obtain the subject's weight.
- Vital signs before and after administration.
- Physician or designee needs to see subject prior to injection and prior to discharge
- Injection of  $6 \text{ mCi} \pm 10\%$  18F-AV-133 as a single bolus within 6 seconds
- 2 scanning sessions: 50-60 and 80-90 minutes p.i.
- Adverse event assessment during imaging day and 2 days telephone call



# DaTSCAN Ordering

- US sites: order directly through GE pharmacy or through ICL
- EU sites:
  - **HIGHLIGHT** that the vials are to be free of charge patient vials for the PPMI study.
  - GE's customer service teams have been notified to expect and authorize free of charge vials to your center.



# Imaging Lessons Learned

- Provide correct subject ID to imaging center
- Ensure data is transferred to ICL
- Assist ICL with outstanding queries
- For DaTSCAN orders mark as research vials/PPMI study



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# Questions?

Susan Mendick

203-401-4337

[smendick@indd.org](mailto:smendick@indd.org)



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# PPMI Biorepository Update

Genetic Kick-Off Meeting

September 16-17, 2013      New York, NY

Dorit S. Berlin, PhD

Principal Investigator, PPMI Biorepository  
Coriell Institute for Medical Research



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# Outline

- Submissions summary
- Lessons learned
- Genetic cohort/registry expansion
- Specimen distribution



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# SUBMISSIONS RECEIVED



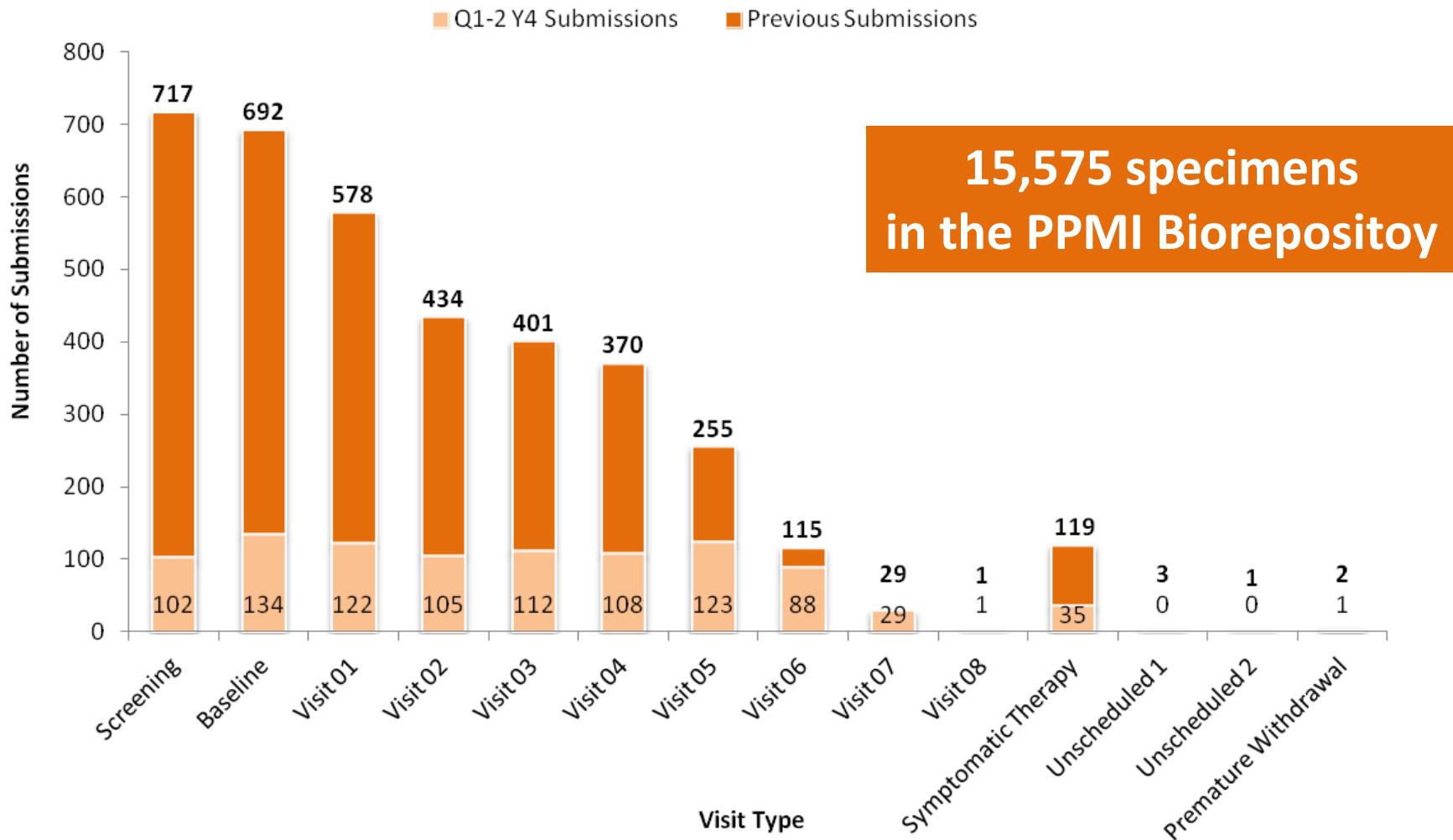
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# PPMI Sample Submission Summary

3,717 visits from 780 unique subjects

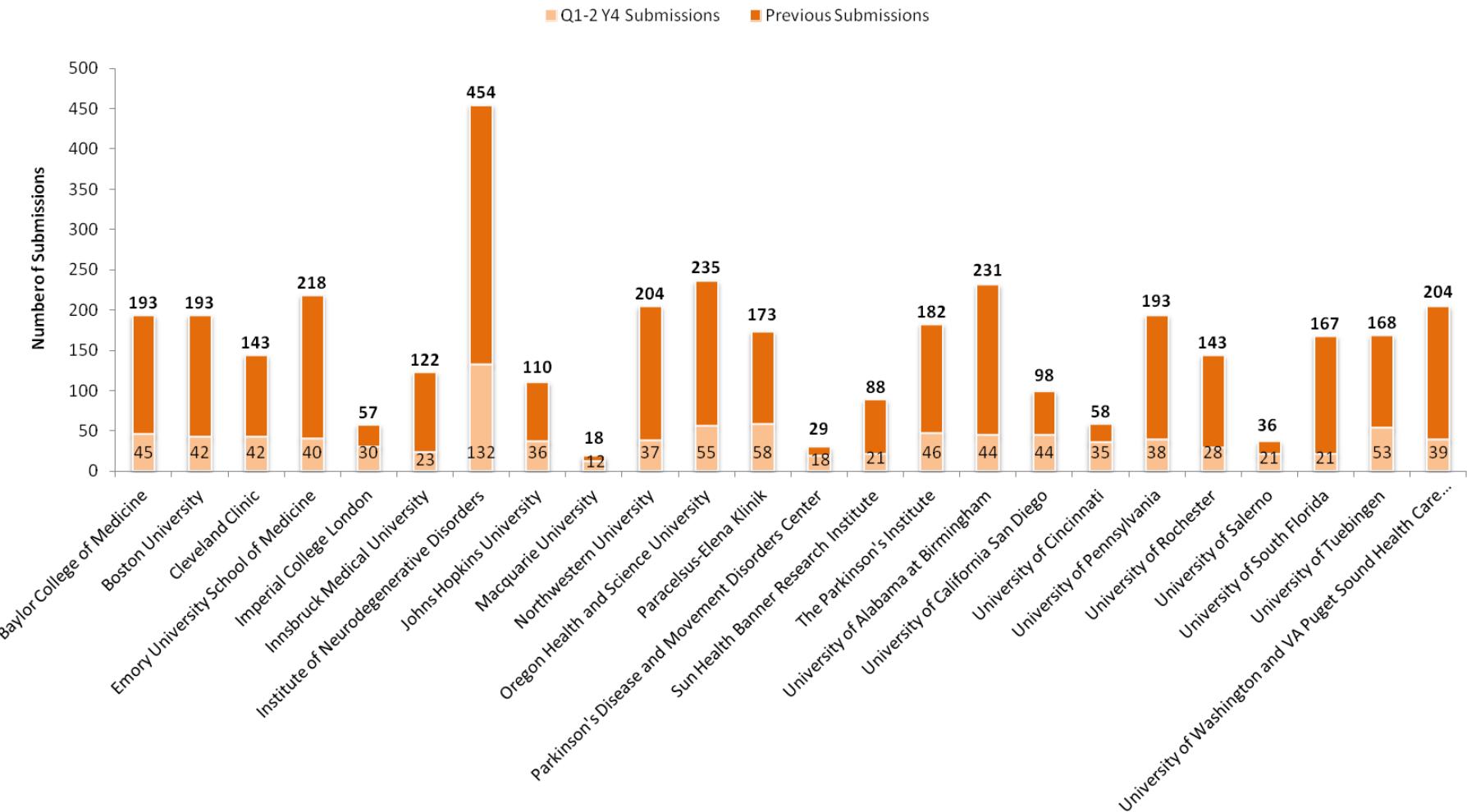


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# PPMI Submissions per Clinical Site



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# SPECIMEN PROCESSING & QC

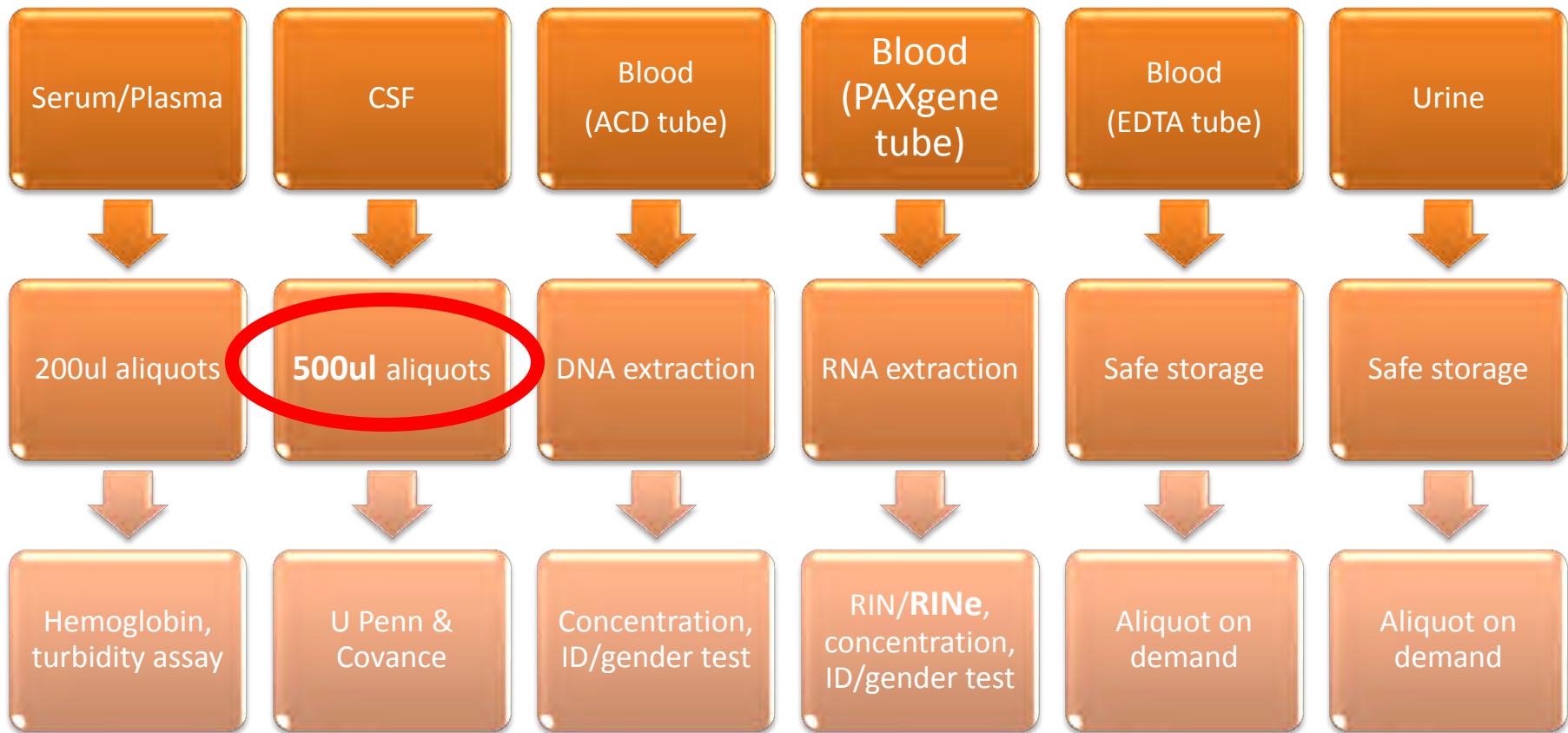


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# Sample Processing Overview

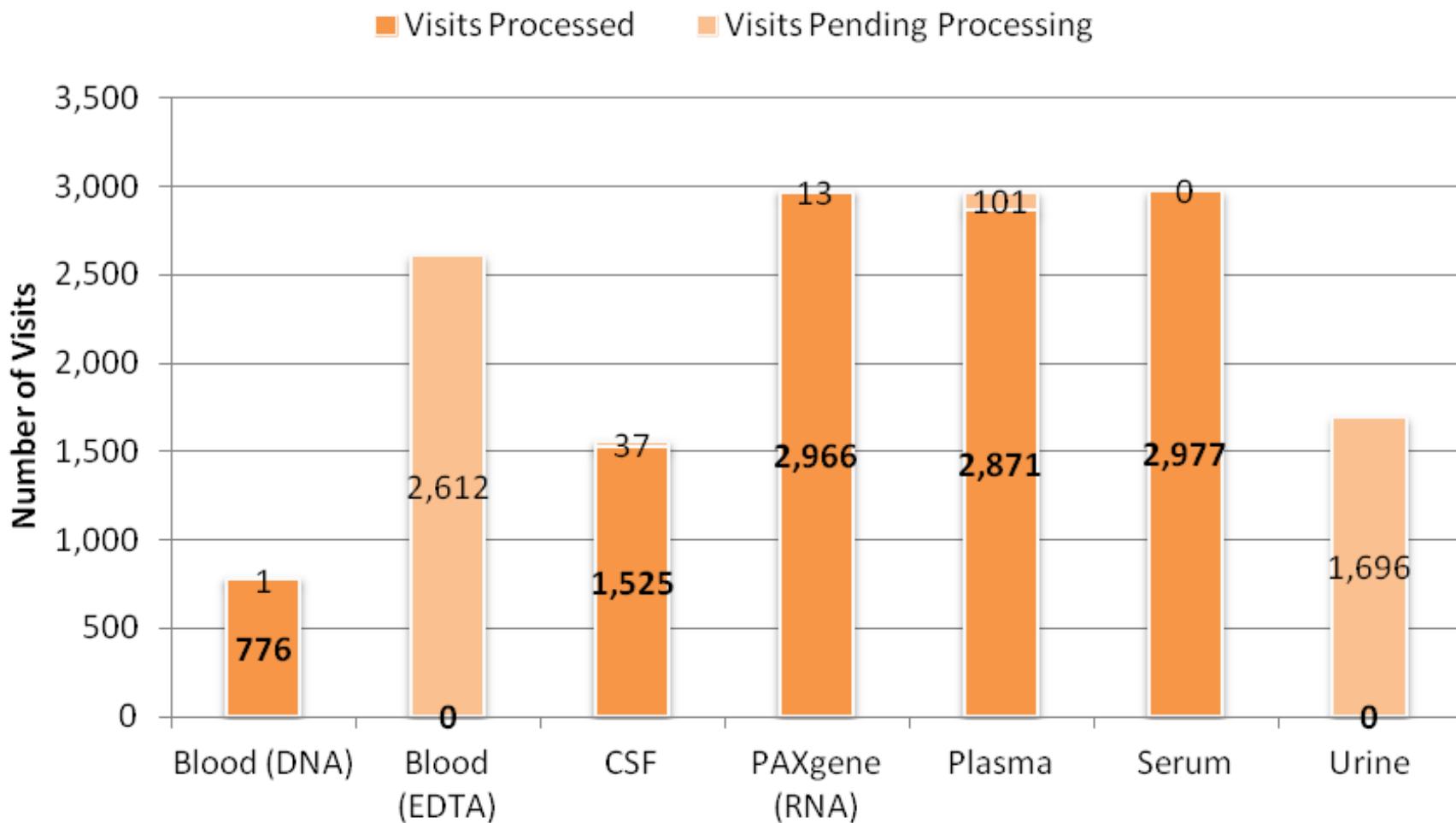


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# Submission Processing Summary



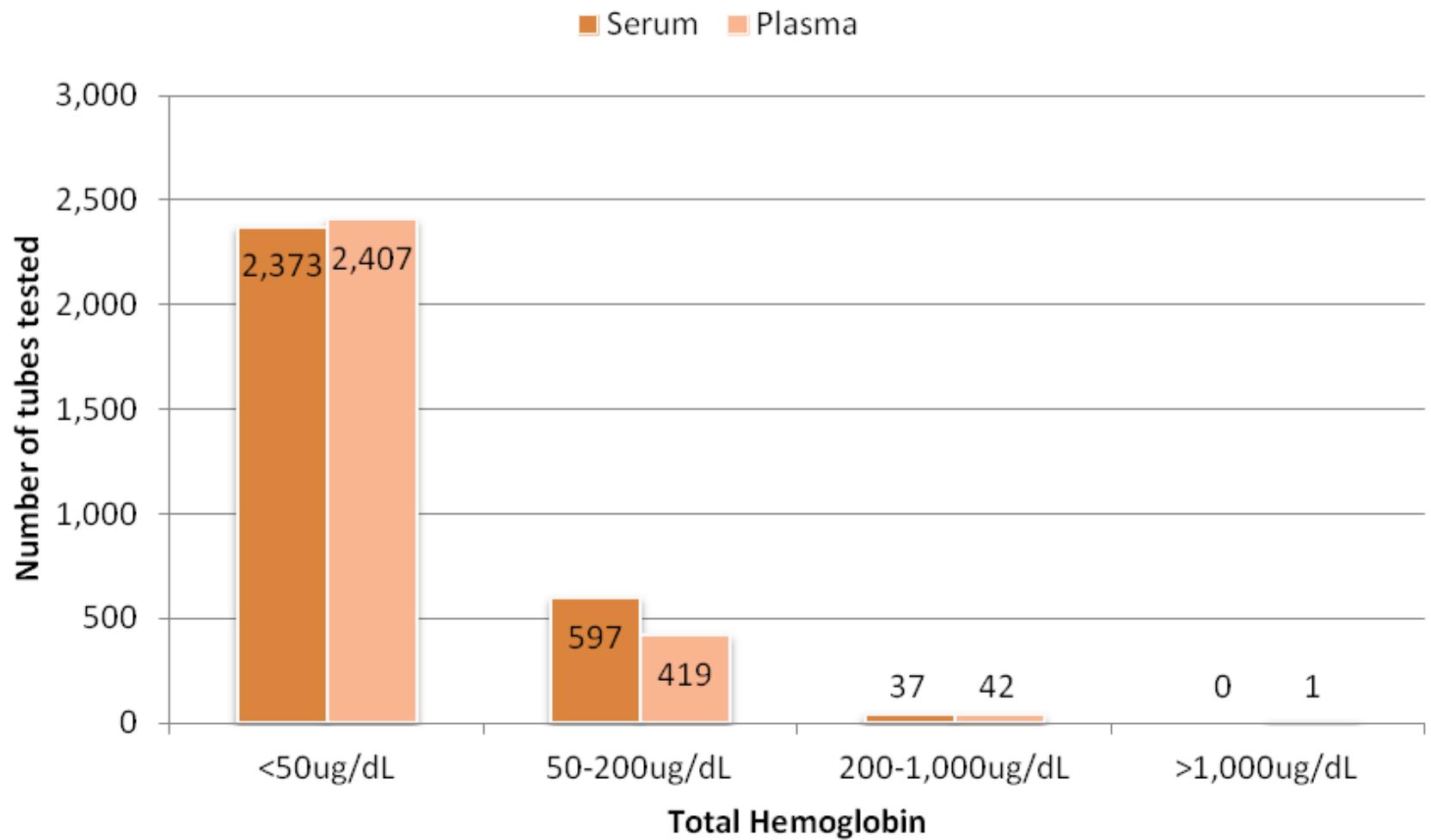
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# Serum & Plasma Total Hemoglobin



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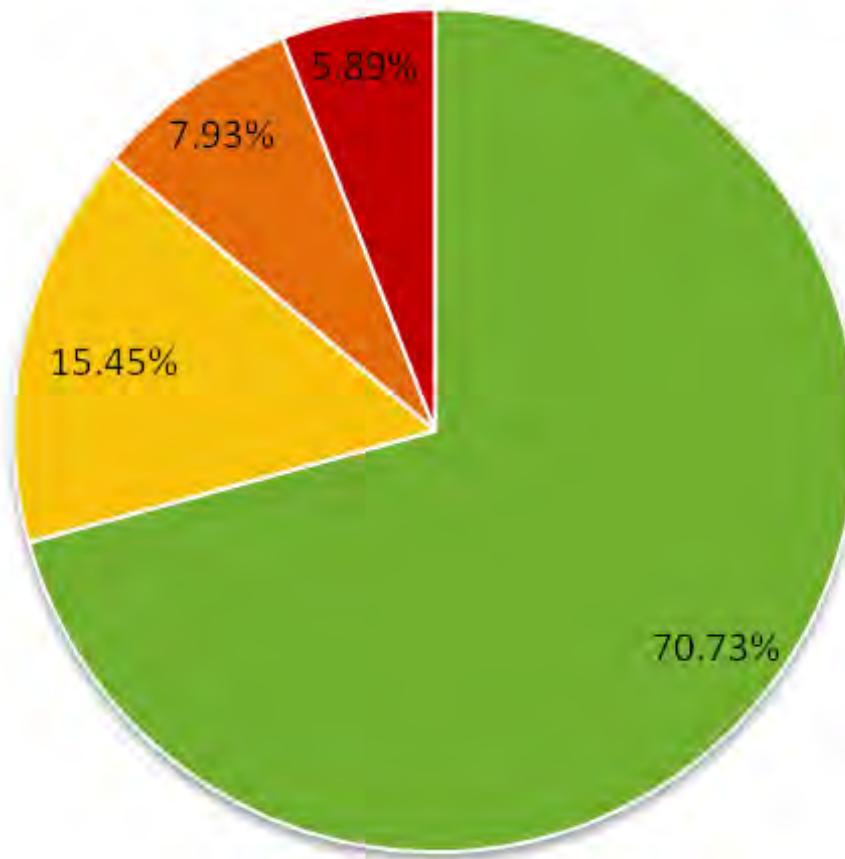
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As of 6/30/13



# CSF Total Hemoglobin

■ ≤30 ng/ml ■ 30-250 ng/ml ■ 250-1,000 ng/ml ■ >1,000 ng/ml



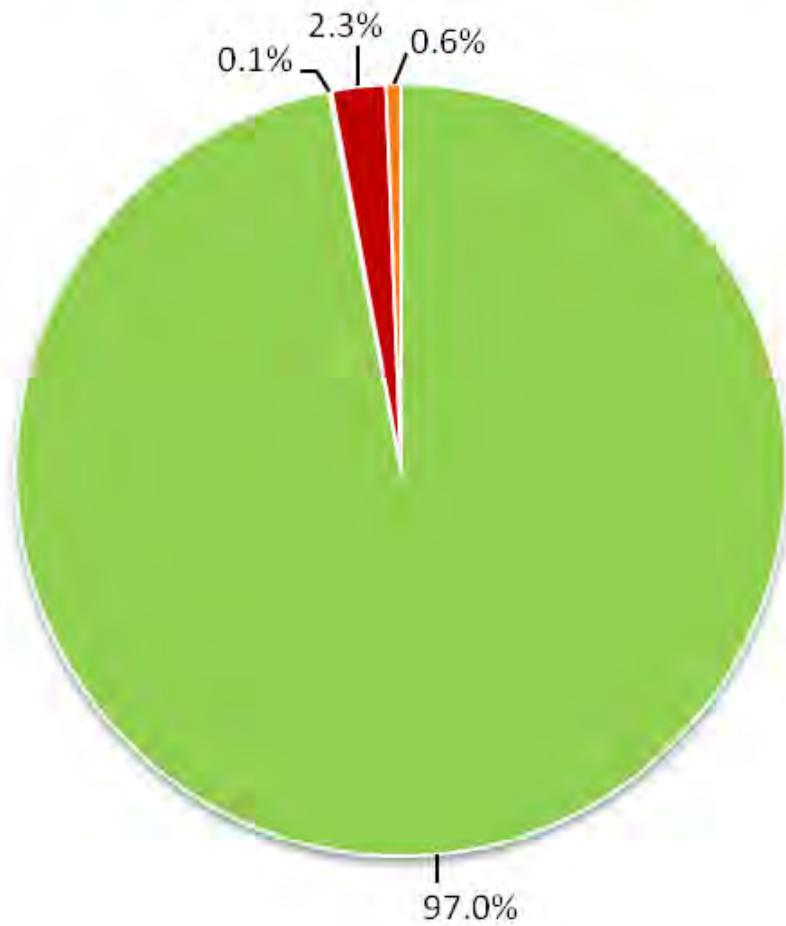
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As of 6/30/13  
Data obtained from LONI

# DNA Extraction Progress

■ QC completed ■ QC in progress ■ QC failed ■ Discarded upon receipt



Average 260/280: 1.87  
Average conc: 0.31 µg/µl  
Average total yield: 186.06 µg

As of 6/30/13

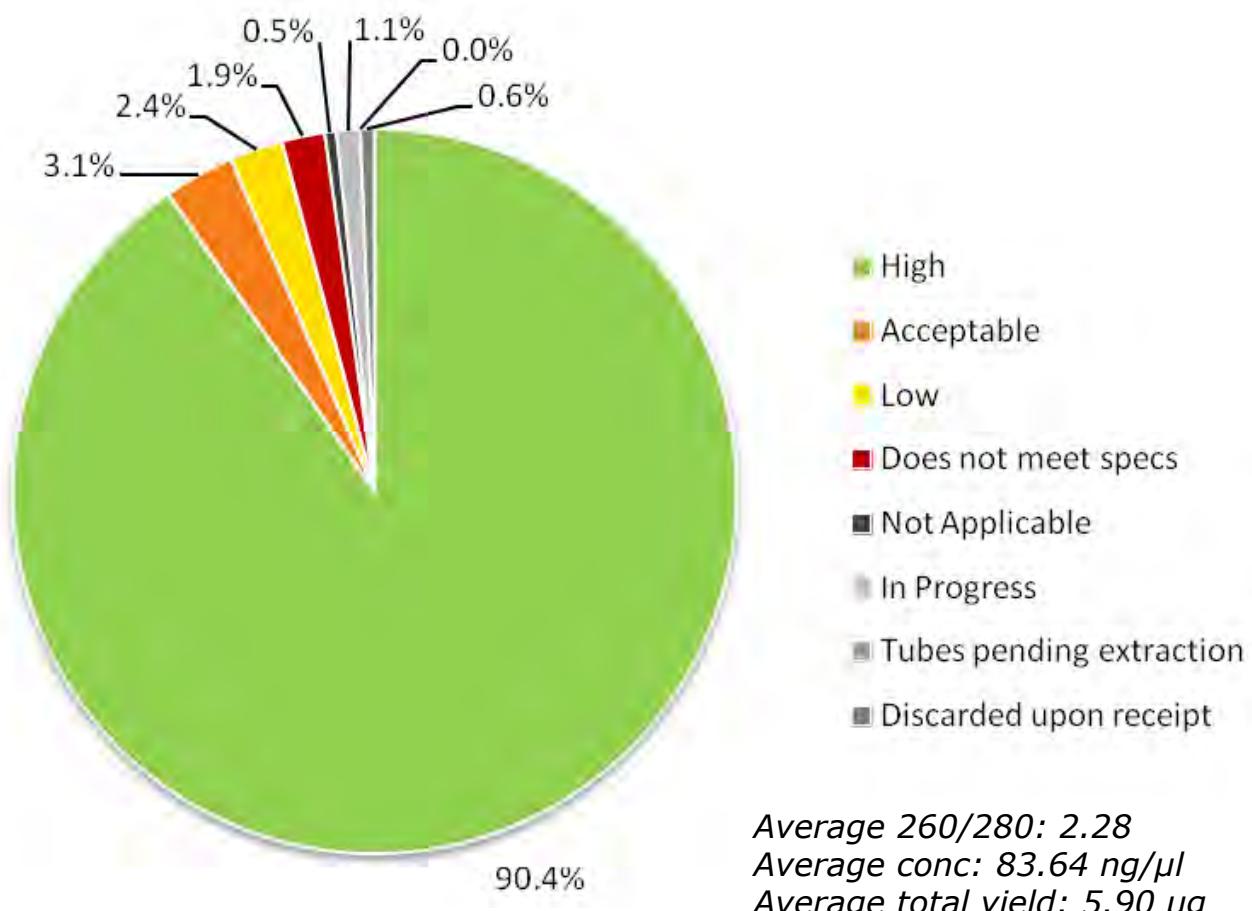


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# PAXgene RNA Extractions

High	DNA passes QC RIN $\geq 6$
Acceptable	DNA passes QC RIN 3.0-5.9
Low	DNA passes QC RIN <3 but rRNA $\geq 1$
Does not meet specs	DNA passes QC RIN <3 and rRNA <1
Not applicable	DNA fails QC



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As of 6/30/13

# LESSONS LEARNED



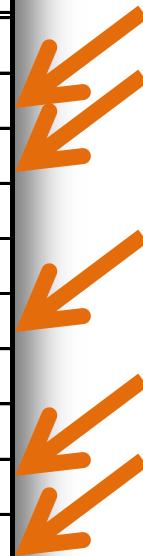
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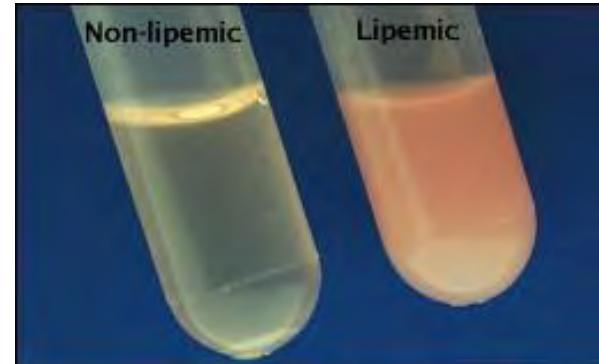
# PPMI Sample Submission Non-Conformance Report Summary

	Q1-2 Y4	Cum Total*
<b>Submissions received</b>	960	3,622
<b>Submissions requiring non-conformance report</b>	157	506
<i>Submissions with single issue</i>	116	392
<i>Submissions with multiple issues</i>	41	114
<b>Percent submissions requiring non-conformance report</b>	16%	14%
<b>Details (may be &gt;1 issue per submission)</b>		
<i>Advance notice not received, or incomplete/inaccurate</i>	46	153
<i>Submission form not included in package, or incomplete/inaccurate</i>	45	93
<i>Package shipped for weekend/holiday delivery</i>	0	10
<i>Samples improperly packaged</i>	18	86
<i>Samples received damaged</i>	33	59
<i>Frozen submissions received thawed</i>	1	10
<i>Samples improperly collected: non-standard tube/s used</i>	7	12
<i>Samples improperly collected: unlabeled/mis-labeled tubes</i>	26	113
<i>Samples improperly collected: low volume received</i>	23	61
<i>Samples improperly collected: samples discolored</i>	20	70
<i>Samples improperly collected: other (blood in EDTA tube separated)</i>	0	2



# Lipemia May Interfere with Downstream Assays

- Light scattering may falsely increase absorbance readings of some analytes
- Volume displacement may falsely decrease values of some analytes
- Hemolysis of erythrocytes is enhanced in the presence of lipemia



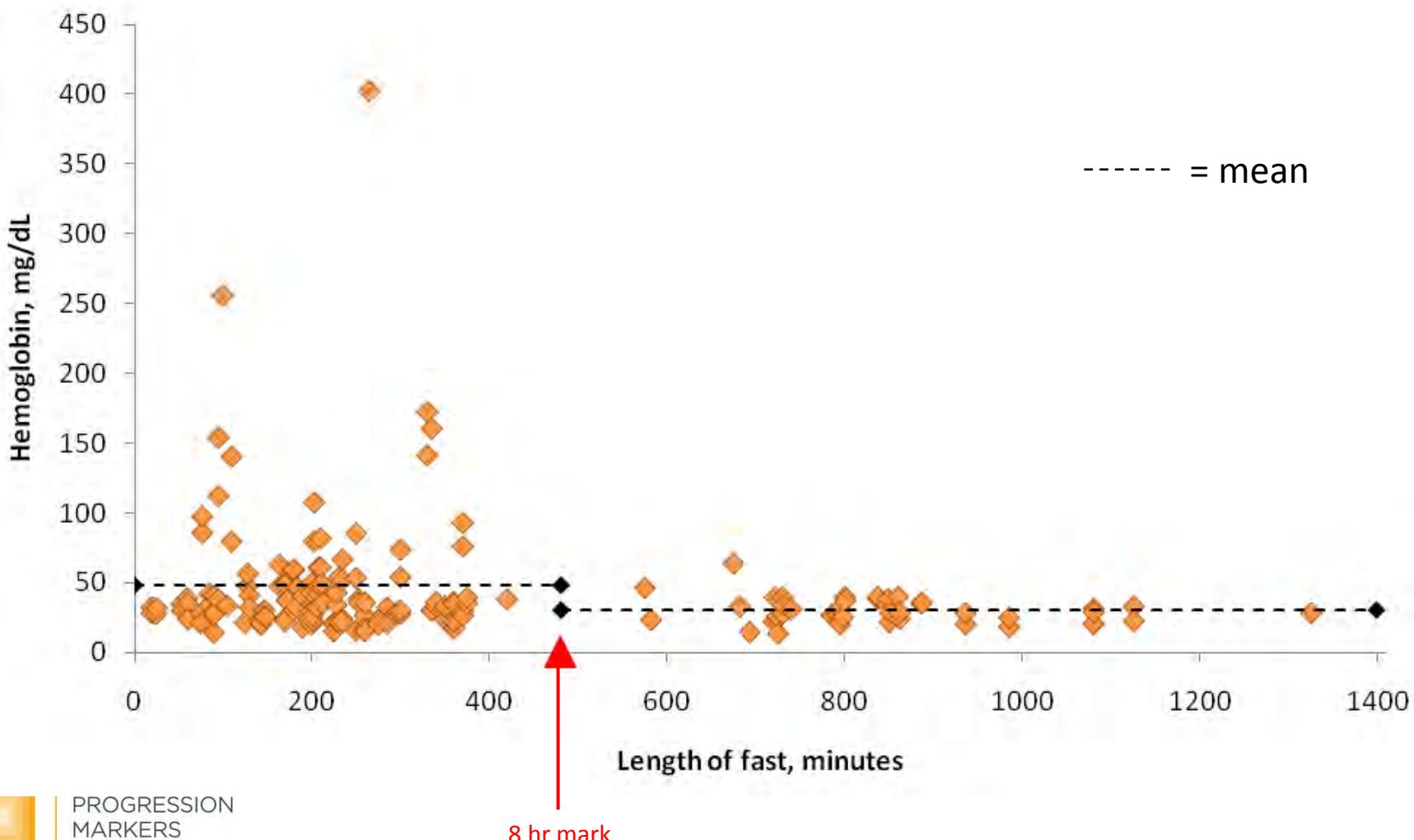
<http://www.studydroid.com/printerFriendlyViewPack.php?packId=48088>



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# Hemoglobin Level vs. Length of Fast (data from 2011)



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# **PPMI EXPANSION: GENETIC COHORT/REGISTRY**



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# PPMI Biospecimen Collection Schedule

SWEDD Subjects  
end at V06

		Visit Number	Screening	Baseline	V01	V02	V03	V04	V05	V06	V07	V08	V09	V10	V11	V12
		Months ( $\pm 30$ days)	(-45 days)	0	3	6	9	12	18	24	30	36	42	48	54	60
PD & Healthy Control Subjects	DNA (1x 8.5 ml ACD tube)		X													
	Plasma (3x 1.5 ml aliquots)			X	X	X	X	X	X	X	X	X	X	X	X	X
	Serum (3x 1.5 ml aliquots)			X	X	X	X	X	X	X	X	X	X	X	X	X
	RNA (2x 2.5 ml PAXgene tubes)			X	X	X	X	X	X	X	X	X	X	X	X	X
	Whole Blood (1x 6 ml EDTA tube)				X	X	X	X	X	X	X	X	X	X	X	X
	CSF (10x 1.5 ml aliquots)					X		X		X		X		X		X
	Urine (1x 15 ml tube)				X		X		X		X		X		X	
Prodromal Subjects	Visit Number	Screening	Baseline	V01	V02	V03	V04	V05	V06	V07	V08	V09	V10	V11	V12	
	Months ( $\pm 30$ days)	(-45 days)	0	3	6	9	12	18	24	30	36	42	48	54	60	
	DNA (1x 8.5 ml ACD tube)			X												
	Plasma (3x 1.5 ml aliquots)				X	X	X	X	X	X	X	X	X	X		
	Serum (3x 1.5 ml aliquots)				X	X	X	X	X	X	X	X	X	X		
	RNA (2x 2.5 ml PAXgene tubes)				X	X	X	X	X	X	X	X	X	X		
	Whole Blood (1x 6 ml EDTA tube)				X	X	X	X	X	X	X	X	X	X		
Genetic Cohort PD Subjects	Visit Number	Screening	Baseline	V01	V02	V03	V04	V05	V06	V07	V08	V09	V10	V11	V12	
	Months ( $\pm 30$ days)	(-45 days)	0	3	6	9	12	18	24	30	36	42	48	54	60	
	DNA (1x 8.5 ml ACD tube)		X													
	Plasma (3x 1.5 ml aliquots)				X		X	X	X	X	X	X	X	X	X	X
	Serum (3x 1.5 ml aliquots)			X		X		X	X	X	X	X	X	X	X	X
	RNA (2x 2.5 ml PAXgene tubes)			X		X		X	X	X	X	X	X	X	X	X
	Whole Blood (1x 6 ml EDTA tube)			X		X		X	X	X	X	X	X	X	X	X
Genetic Registry Subjects	Visit Number	Screening	Baseline	V01	V02	V03	V04	V05	V06	V07	V08	V09	V10	V11	V12	
	Months ( $\pm 30$ days)	(-45 days)	0	3	6	9	12	18	24	30	36	42	48	54	60	
	DNA (1x 8.5 ml ACD tube)			X												
	Plasma (3x 1.5 ml aliquots)			X						X				X		
	Serum (3x 1.5 ml aliquots)			X						X				X		
	RNA (2x 2.5 ml PAXgene tubes)			X						X				X		
	Whole Blood (1x 6 ml EDTA tube)			X						X				X		
	CSF (10x 1.5 ml aliquots)															
	Urine (1x 15 ml tube)			X				X		X		X		X		X

# SPECIMEN DISTRIBUTION



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# Distribution of PPMI Biospecimens

Institution	Research Intent	Specimen Type	Subjects	Visits
University of Pennsylvania	Biomarker Analysis	CSF	312	836
Covance	Biomarker Analysis & Hemoglobin Testing	CSF	471	1,102
National Institute on Aging, NIH	Genotyping	DNA	763	763
Brigham & Women's Hospital	Biomarker Analysis	RNA	341	341
<b>TOTAL</b>		<b>ALL</b>		<b>3,042</b>



# CSF Distribution to Penn and Covance

(planned for Sept. 2013)

Visit Sets	Sets to each recipient	Visits to each recipient
BL	357	357
BL,V02,V04	257	771
BL,V02,ST(V04)	7	21
BL,V04,ST(V02)	45	135
V01,V02,V04	4	12
V02,V04,UN1	1	3
<b>TOTAL</b>	<b>671</b>	<b>1,299</b>

Batch	Status	Ship From	Planned Ship Date	Est Delivery Date	Type of sets included	Sets	Visits	Aliq Vol	Qty to Penn	Qty to Covance
A	SCHEDULED	BioRep	9/16/2013	By 9/20/13	BL BL,V02,V04 BL,V04,ST(V02) V01,V02,V04	74 39 1 1	74 117 3 3	500ul 500ul 500ul 500ul	1 1 1 1	1 1 1 1
									<b>TOT VIALS TO SHIP</b>	<b>197</b>
B	PENDING	Coriell	10/1/2013	10/2/13	BL	283	283	500ul	1	1
									<b>TOT VIALS TO SHIP</b>	<b>283</b>
C	DELIVERED	Coriell	9/10/2013	9/11/13	BL,V02,V04	100	300	500ul	1	1
									<b>TOT VIALS TO SHIP</b>	<b>300</b>
D	IN PREP	Coriell	9/17/2013	9/18/13	BL,V02,V04	100	300	500ul	1	1
									<b>TOT VIALS TO SHIP</b>	<b>300</b>
E	PENDING	Coriell	9/24/2013	9/25/13	BL,V02,V04 BL,V02,ST(V04) BL,V04,ST(V02) V01,V02,V04 V02,V04,UN1	18 7 44 3 1	54 21 132 9 3	500ul 500ul 500ul 500ul 500ul	1 1 1 1 1	1 1 1 1 1
									<b>TOT VIALS TO SHIP</b>	<b>219</b>

671 1,299



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# Status of Biologics Review Committee

- Committee
  - Eugene Johnson, PhD (Chair), Washington University
  - Mark Cookson, PhD, National Institute of Aging
  - Un Jung Kang, MD, University of Chicago
  - Ken Marek, MD, Institute for Neurodegenerative Diseases
  - Howard Schulman, PhD, Stanford University
- Bi-monthly calls to evaluate proposals
  - 23 LOIs submitted
  - 4 Full Proposal Invited:
    - Scherzer (RNA transcripts)
    - Schwarzschild (serum and CSF urate)
    - Chen-Plotkin (plasma ApoA1 & EGF)
    - Desplats (epigenetic analysis of baseline samples)



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# Approved PPMI Biosample Analyses

Principal Investigator	Institution	Title of Analysis	Sample type	Data Available
Scherzer	Harvard University	Validation of PD-linked transcripts in PPMI	RNA	October 2013
Chen Plotkin	UPenn	Plasma Apolipoprotein A1 Level as a Biomarker in Parkinson's Disease	Serum	October 2013



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# Acknowledgments

## Coriell

Alison Scutti, MS  
Senior Project Manager

Johnathan McCullough  
Project Manager

Victoria Kelly, PhD  
Molecular Biology Group  
Leader

Steve Madore, PhD  
Director, Biobanking

Dara Kusic  
Application Developer

## BioRep

Paola Casalin, PhD  
Giulia Malferrari, PhD  
And Team

## MJFF/CTCC

Mark Frasier, PhD  
Irina Lazurenko  
And Team



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# THE END



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# PPMI Biofluid Summary

## Bioanalytics Core



# Subject Enrollment and Sample Collection

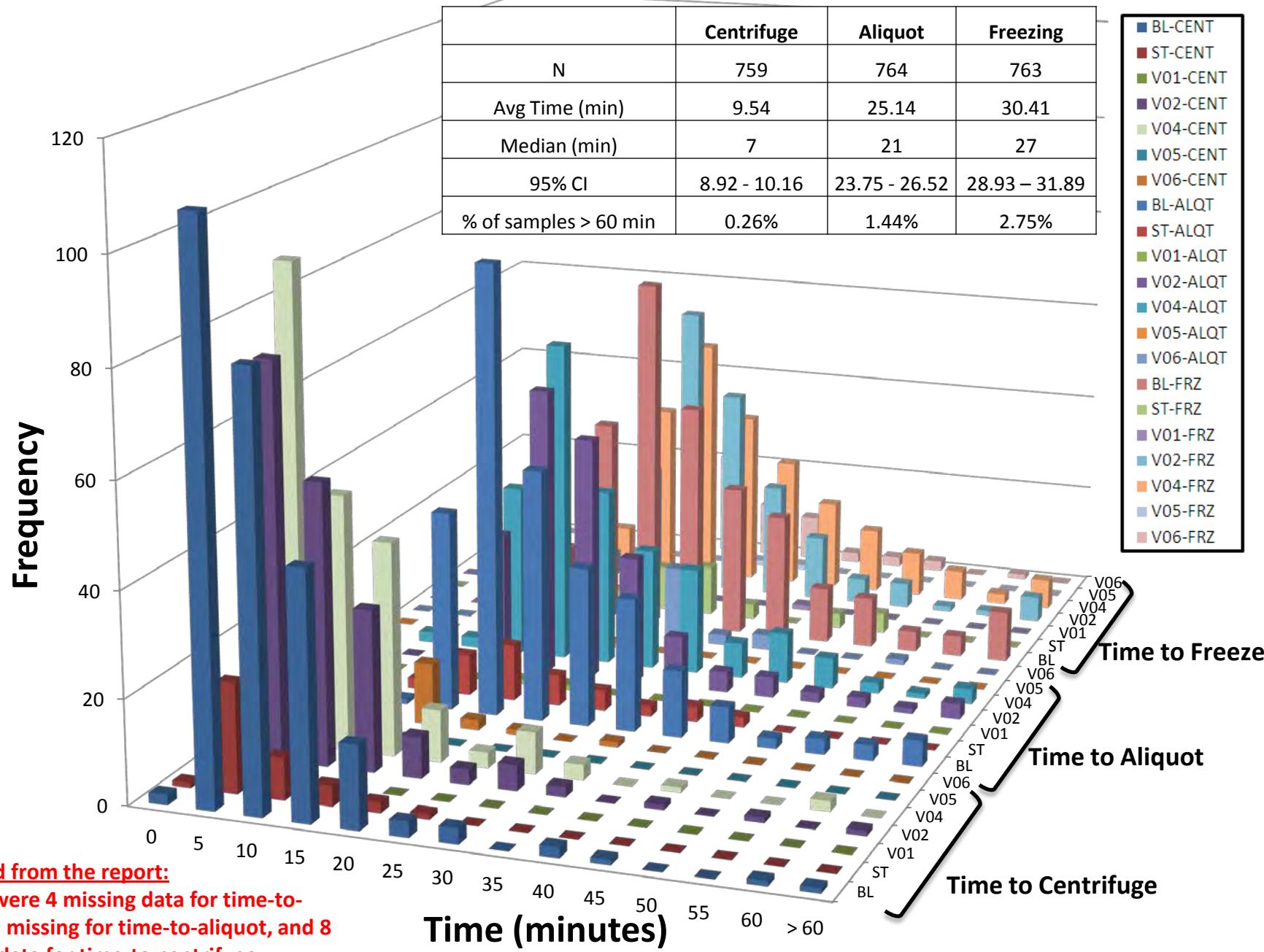
Recently Collected Samples per Visit (from May 2012 – May 2013)

(Total Number of Samples Collected as of May 2013)

Visit		BL	PW	SC	ST	U01	U02	V01	V02	V03	V04	V05	V06	V07	Total
CSF Serum Plasma	Recent*	279	1	0	65	-	0	223	213	234	246	204	76	11	1552
	Total PLA	672	1	82	110	-	1	527	409	373	346	215	76	11	2823
	Recent*	279	1	0	65	-	0	223	213	234	246	204	76	11	1552
	Total SER	672	1	82	110	-	1	527	409	373	346	215	76	11	2823
	Recent*	268	-	-	39	-	-	2	184	-	211	2	61	-	767†
	Total CSF	671	1	-	92	1	-	8	404	-	344	2	74	-	1597

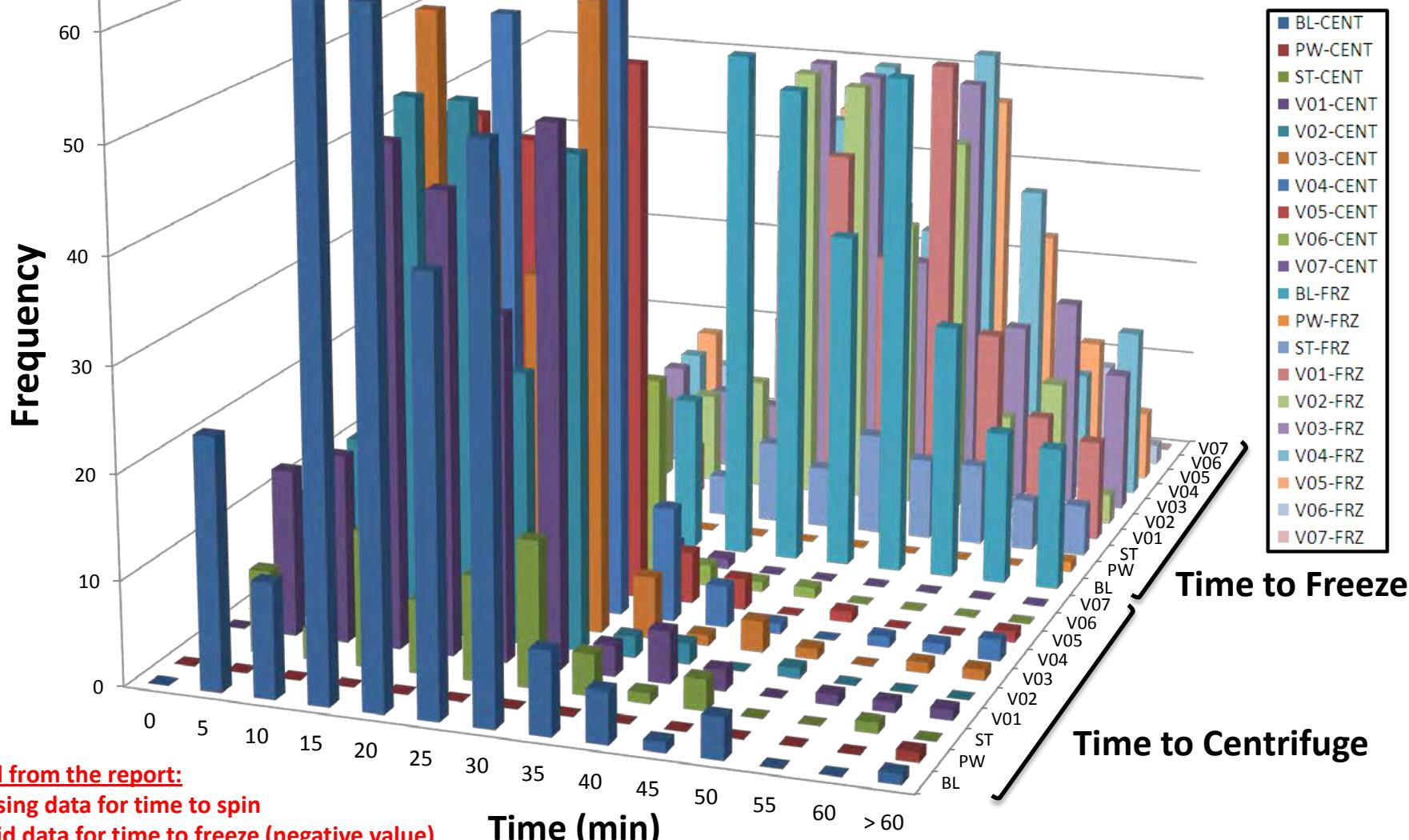
\* The top row per biofluid type indicates the samples collected within the past year (from May 2012 thru May 2013).

# Time to: Centrifuge, Aliquot, Freeze for PPMI CSF samples



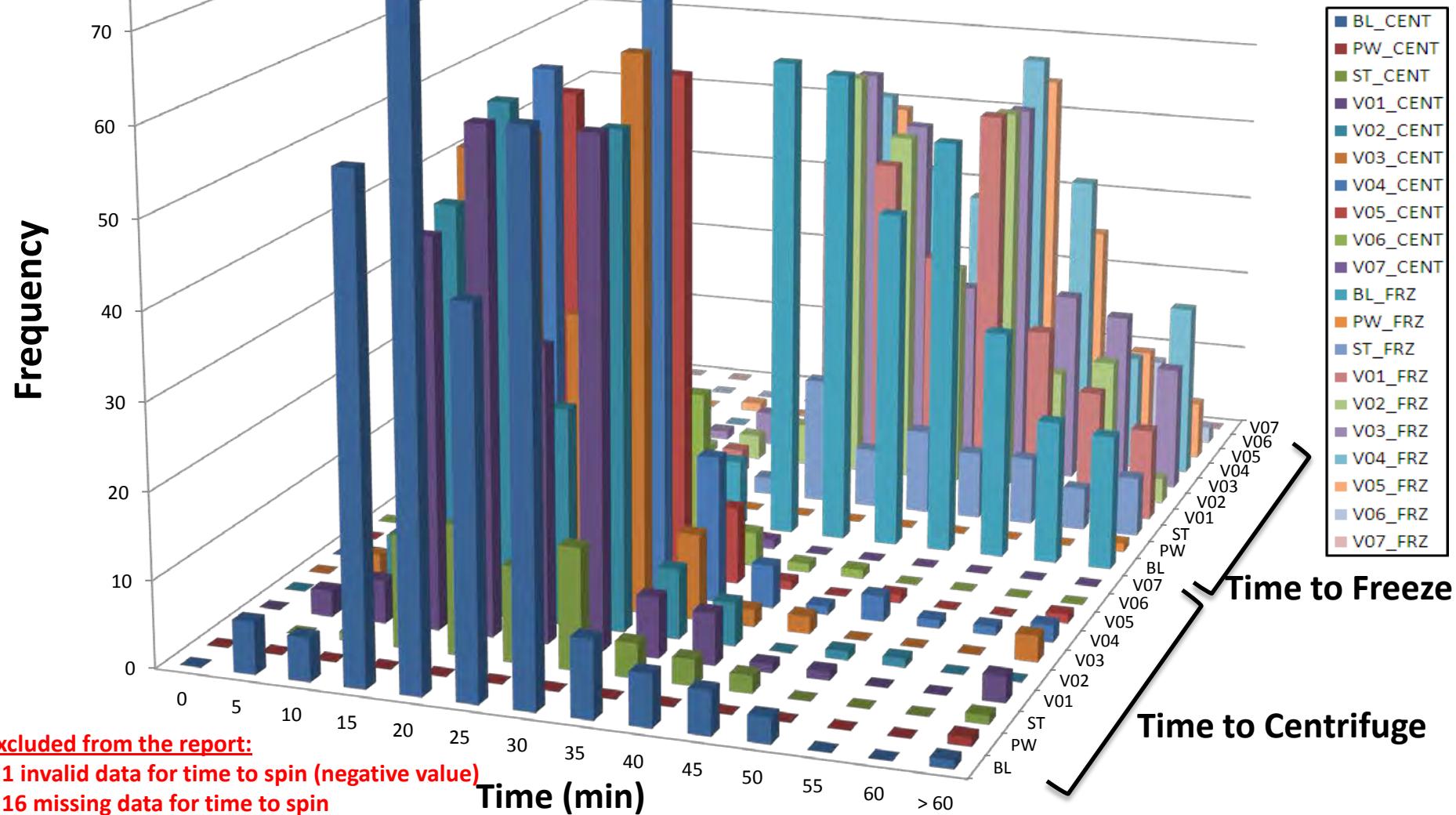
# Time to: Centrifuge and Freeze for PPMI Plasma

	Centrifuge	Freezing
N	1537	1534
Avg Time (min)	20.55	43.34
Median (min)	20	42
95% CI	20.04 – 21.05	42.49 – 44.19
% of samples > 60 min	0.46%	4.76%



# Time to: Centrifuge and Freeze for PPMI Serum

	Centrifuge	Freezing
N	1535	1532
Avg Time (min)	23.02	45.87
Median (min)	21	44
95% CI	22.39 - 23.66	44.92 - 46.81
% of samples > 60 min	0.78%	5.42%



# Summary

		Time (min) to spin	Time to Aliquot	Time to Freezing	Volume (ml) after spin	Number of ALQ
<b>Plasma</b>	Total Mean (Median)	20.55 (20)	-	43.34 (42)	4.32 (4.5)	2.97 (3)
	% CV	49.00%	-	63.35%	12.92%	9.44%
<b>Serum</b>	Total Mean (Median)	23.02 (21)	-	45.87 (44)	3.84 (4)	2.78 (3)
	% CV	55.29%	-	41.14%	18.70%	16.11%
<b>CSF</b>	Total Mean (Median)	9.54 (7)	25.14 (21)	30.41 (27)	14.05 (15)	9.31 (10)
	% CV	91.24%	77.41%	68.41%	22.27%	18.93%

Data for time to aliquot not available for plasma and serum.

%CV = SD/Mean

# Summary

Specimen		Mean time of procedures (minutes)									
Plasma	Visit	BL	PW	ST	V01	V02	V03	V04	V05	V06	V07
	Mean time to Spin	20.11	75	21.2	20.21	19.23	21.19	21.66	20.48	20.22	19.73
	Mean time to Freeze	42.51	98	42.62	42.40	40.87	44.31	46.05	43.50	43.30	46.36
Serum	Mean time to Spin	22.37	75	23.84	24.19	22.13	22.67	24.22	22.31	22.50	21.09
	Mean time to Freeze	44.62	98	46.03	46.01	43.11	46.13	49.43	45.38	45.58	47.73
CSF	Mean time to Spin	9.61	-	6.97	12.50	10.01	-	10.00	9.00	7.74	-
	Mean time to Aliquot	26.57	-	22.45	22.50	24.62	-	25.15	22.00	22.25	-
	Mean time to Freeze	32.05	-	27.55	32.50	29.77	-	30.48	29.50	26.67	-

There is only 1 PLA/SER sample at visit PW.

There are 2 CSF samples at visits V01 and V05.

# Centrifugation: Compliance with protocol

CENTRIFUGATION		Time (Duration of spin)	Temperature	Force
<b>Plasma</b>	Protocol Condition	15 min	4°C	1500×g
	Per protocol (%)	1533/1538 (99.67%)	1455/1538 (94.6%)	1248/1538 (81.14%)
<b>Serum</b>	Protocol Condition	15 min	4°C	1500×g
	Per protocol (%)	1535/1537 (99.87%)	1454/1537 (94.6%)	1246/1537 (81.07%)
<b>CSF</b>	Protocol Condition	10 min	R.T. (18-30°C)	2000×g
	Per protocol (%)	No data	729/764† (95.42%)	590/764† (77.23%)

- 14 missing data points for PLA (duration of centrifugation time, temperature, force) were excluded, resulting in a total of 1538
- 15 missing data points for SER (duration of centrifugation time, temperature, force) were excluded, resulting in a total of 1537
- +3 missing data points for CSF (temperature range and force) were excluded, resulting in a total of 764

Compliance to the force of centrifugation for plasma (81.14%, May 2012 to May 2013) and serum (81.07%, May 2012 to May 2013) remain relatively similar to the previous set of samples for plasma (82.2%, July 2010 to April 2012) and serum (81.6%, July 2010 to April 2012). While the compliance to the force of centrifugation for CSF (77.23%, May 2012 to May 2013) may have dropped slightly compared to the previous set of samples (80%, July 2010 to April 2012), overall compliance to protocol is excellent.



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### Original Investigation

# Association of Cerebrospinal Fluid $\beta$ -Amyloid 1-42, T-tau, P-tau<sub>181</sub>, and $\alpha$ -Synuclein Levels With Clinical Features of Drug-Naive Patients With Early Parkinson Disease

Ju-Hee Kang, MD; David J. Irwin, MD; Alice S. Chen-Plotkin, MD; Andrew Siderowf, MD; Chelsea Caspell, MS;  
Christopher S. Coffey, PhD; Teresa Waligórska, MS; Peggy Taylor, ScD; Sarah Pan, MPH; Mark Frasier, PhD;  
Kenneth Marek, MD; Karl Kieburtz, MD, MPH; Danna Jennings, MD; Tanya Simuni, MD;  
Caroline M. Tanner, MD, PhD; Andrew Singleton, PhD; Arthur W. Toga, PhD; Sohini Chowdhury, MA;  
Brit Mollenhauer, MD; John Q. Trojanowski, MD, PhD; Leslie M. Shaw, PhD;  
and the Parkinson's Progression Markers Initiative

*JAMA Neurol.* doi:10.1001/jamaneurol.2013.3861

Published online August 26, 2013.



# Accessioning and statistical analyses of PPMI CSF biomarker dataset

- Simultaneous download of PPMI data for the first 106 study subjects 6/30/2012 by IU and UPenn
- Agreed upon a statistical analysis plan
- Statistical analyses done at UPenn, SAS script sent to IU for replication
- All results in concordance following this process and exchanges of detailed analyses
- Data assembly, incorporation into draft manuscript
- Manuscript circulated amongst the primary authors and the study site investigator/authors for suggestions, edits, further discussions of the data

# MDS-UPDRS Subsection used to classify Tremor or PIGD-dominant phenotype

- ✓ Mean tremor score (11 items)
  - : UPDRS II – 1) Tremor
  - : UPDRS III – 2, 3) Postural tremor (both upper extremities), 4, 5) Kinetic tremor (both upper extremities), 6-10) Resting tremor (4 extremities and lip/jaw), 11) Rest constancy
- ✓ Mean Postural Instability & Gait Disturbance (PIGD) score (5 items)
  - : UPDRS II – 1) Walking and balance, 2) Freezing
  - : UPDRS III – 3) Gait, 4) Freezing of gait, 5) Postural stability
- ✓ Tremor dominant (TD), or PIGD dominant phenotype
  - Ratio of tremor/PIGD score  $\geq 1.15$ : Tremor dominant
  - Ratio of tremor/PIGD score  $\leq 0.90$ : PIGD dominant
  - $0.90 < \text{Ratio of tremor/PIGD score} < 1.15$ : Intermediate type
  - If PIGD score is 0, but tremor score  $> 0$ : Tremor dominant

# CSF biomarkers according to clinical phenotype in PD patients

Biomarkers	PIGD-PD (N=14)	TD-PD (N=43)	p value*	HC (N =39)	IND-PD (N=6)
A $\beta$ <sub>1-42</sub> (pg/mL)	211.4 ± 45.0 <sup>#</sup>	236.2 ± 46.8	0.0323	242.8 ± 50.0	215.5 ± 25.0
t-tau (pg/mL)	39.3 ± 28.27 <sup>#</sup>	50.3 ± 24.01	0.0527	53.9 ± 19.33	31.2 ± 9.97
p-tau <sub>181</sub> (pg/mL)	18.0 ± 6.74 <sup>#</sup>	22.5 ± 8.17	0.0387	24.9 ± 8.45	17.7 ± 4.97
$\alpha$ -syn (pg/mL) <sup>a</sup>	892.8 ± 542.4 <sup>#</sup>	1185 ± 649.6	0.0587	1264 ± 425.7	782.6 ± 150.1
$\alpha$ -syn (pg/mL) <sup>b</sup>	766.3 ± 446.3 <sup>#</sup>	1122 ± 451.8	0.0286	1267 ± 443.5	775.9 ± 184.8
t-tau/A $\beta$ <sub>1-42</sub> ratio	0.211 ± 0.213	0.225 ± 0.145	0.1089	0.240 ± 0.141	0.151 ± 0.072
p-tau/A $\beta$ <sub>1-42</sub> ratio	0.093 ± 0.059	0.104 ± 0.068	0.2247	0.113 ± 0.075	0.083 ± 0.026
p-tau/t-tau ratio	0.617 ± 0.398	0.513 ± 0.217	0.7597	0.491 ± 0.160	0.588 ± 0.164

\*PIGD vs. TD; Mann-Whitney U test

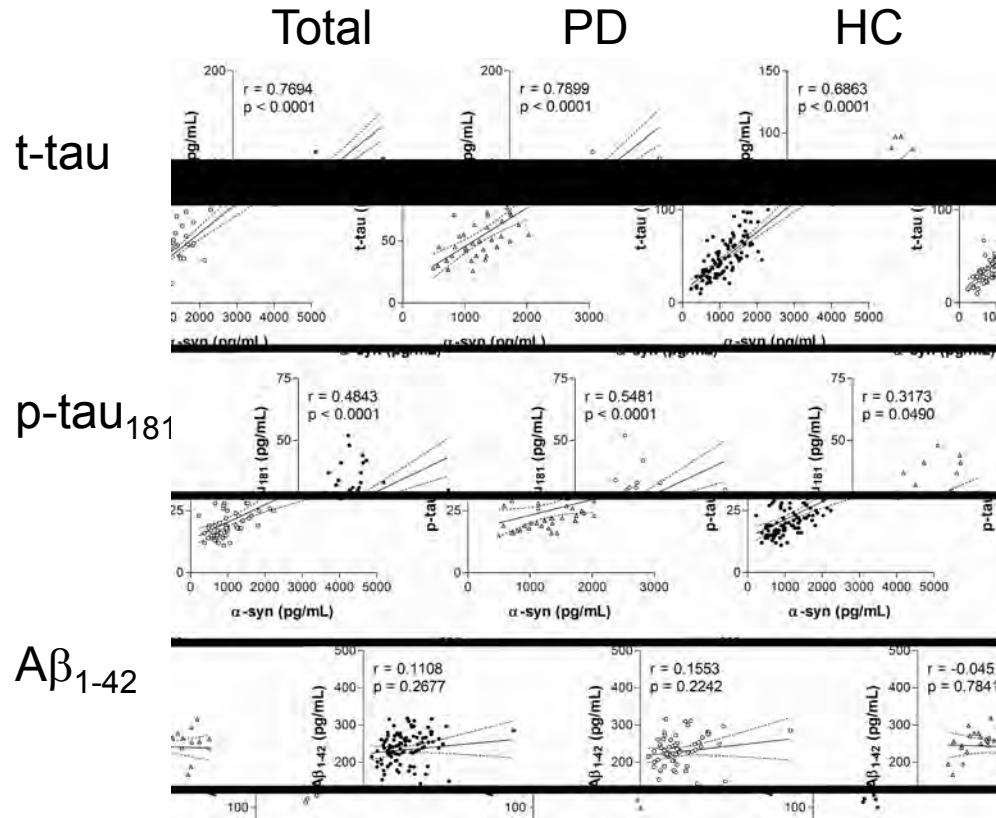
# P<0.05 versus HC by Kruskal-Wallis test with Dunn's multiple comparison

<sup>a</sup> $\alpha$ -syn was measured in total subjects, or <sup>b</sup>subjects with CSF hemoglobin level of < 200 ng/mL

# Summary of multivariate regression analyses

- Multivariate regression analysis: A $\beta$ <sub>1-42</sub> ( $p=0.0383$ ) and p-tau<sub>181</sub> ( $p=0.0015$ ) are significantly associated with PD diagnosis, but other biomarkers or their ratios are not.
- For clinical variables in PD, t-tau ( $p=0.0424$ ) and  $\alpha$ -syn ( $p=0.0081$ ) are significantly associated with MDS-UPDRS III motor score.
- We found that lower levels of CSF A $\beta$ <sub>1-42</sub> and p-tau<sub>181</sub> were significantly associated with a higher PIGD risk.

## Correlation between AD biomarkers and $\alpha$ -synuclein:



# **Association of cerebrospinal fluid A $\beta$ <sub>1-42</sub>, t-tau, p-tau<sub>181</sub> and $\alpha$ -synuclein levels with clinical features of early drug naïve Parkinson's disease patients**

J-H Kang, DJ Irwin, AS Chen-Plotkin, A Siderowf, C Caspell, CS Coffey, T Waligórska, P Taylor, S Pan, M Frasier, K Marek, K Kieburtz, D Jennings, T Simuni, CM Tanner, A Singleton, AW Toga, S Chowdhury, B Mollenhauer, JQ Trojanowski, LM Shaw and the Parkinson's Progression Marker Initiative\*

**Results:** Significantly lower concentrations of all measured CSF biomarkers and t-tau/A $\beta$ <sub>1-42</sub> ratio were seen in PD compared to HC, lower  $\alpha$ -syn was associated with a higher risk of PD and decreased CSF p-tau<sub>181</sub> associated with increased UPDRS motor score. Notably, lower CSF A $\beta$ <sub>1-42</sub> was associated with the postural instability-gait disturbance-dominant phenotype which associates with a more rapid cognitive decline and poor prognosis compared to tremor-dominant patients.

**Interpretation:** We demonstrate that CSF A $\beta$ <sub>1-42</sub>, t-tau, p-tau<sub>181</sub> and  $\alpha$ -syn have value for diagnosis and assessment of disease progression in early-stage PD. Further investigations will test the predictive performance of CSF biomarkers for disease progression.

# Bioanalytics Core 2013

- Analyses of the entire PPMI BASELINE CSFs, and CSFs for those subjects whose 6 month & 12 month CSFs are collected
- AlzBio3 immunoassay for A $\beta_{1-42}$ , t-tau and p-tau<sub>181</sub> at UPenn and  $\alpha$ -SYN by ELISA at Covance
- Data analyses, qc, data upload expected by 4th quarter, 2013.
- Statistical analyses will test hypotheses based on the pilot study

# Genetics of LRRK2 and SNCA

Tatiana Foroud, Ph.D.  
Indiana University



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# LRRK2

- Mutations in LRRK2 are the most common genetic cause for late onset PD
- Autosomal dominant inheritance
  - Equal numbers of males and females affected

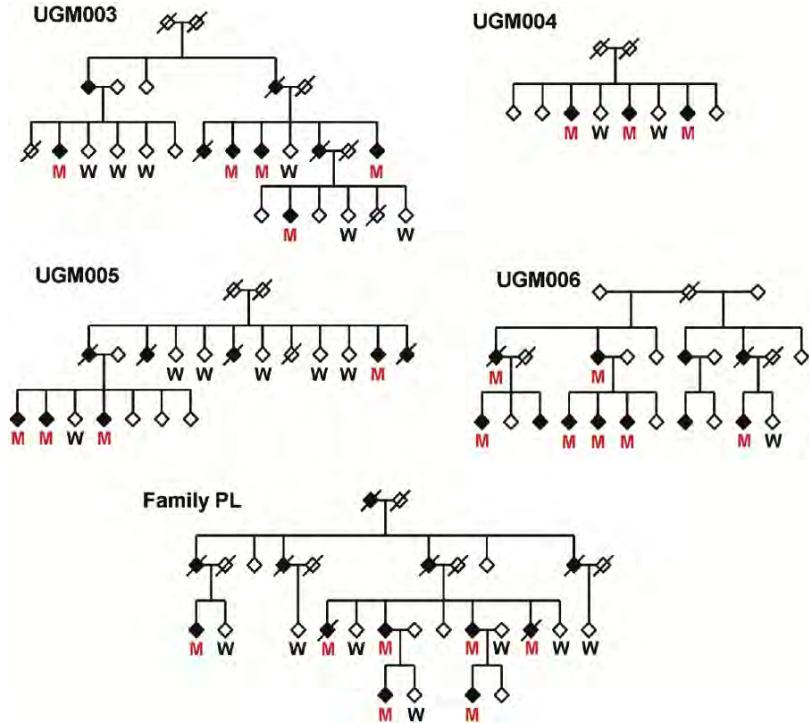


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# Early LRRK2 Families



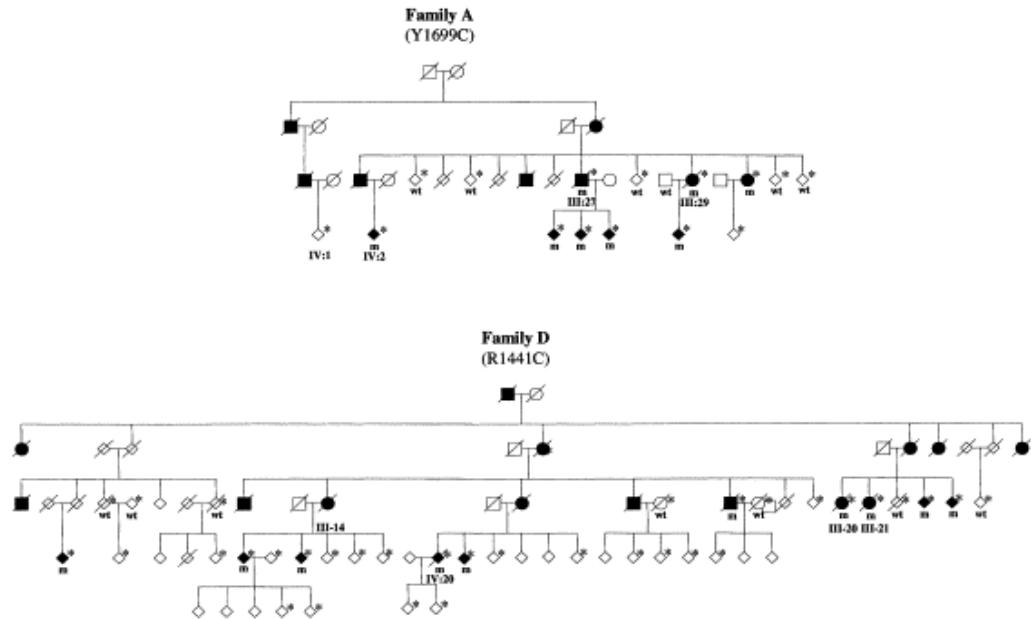
Paisan-Ruiz et al, 2004

Zimprich et al, 2004



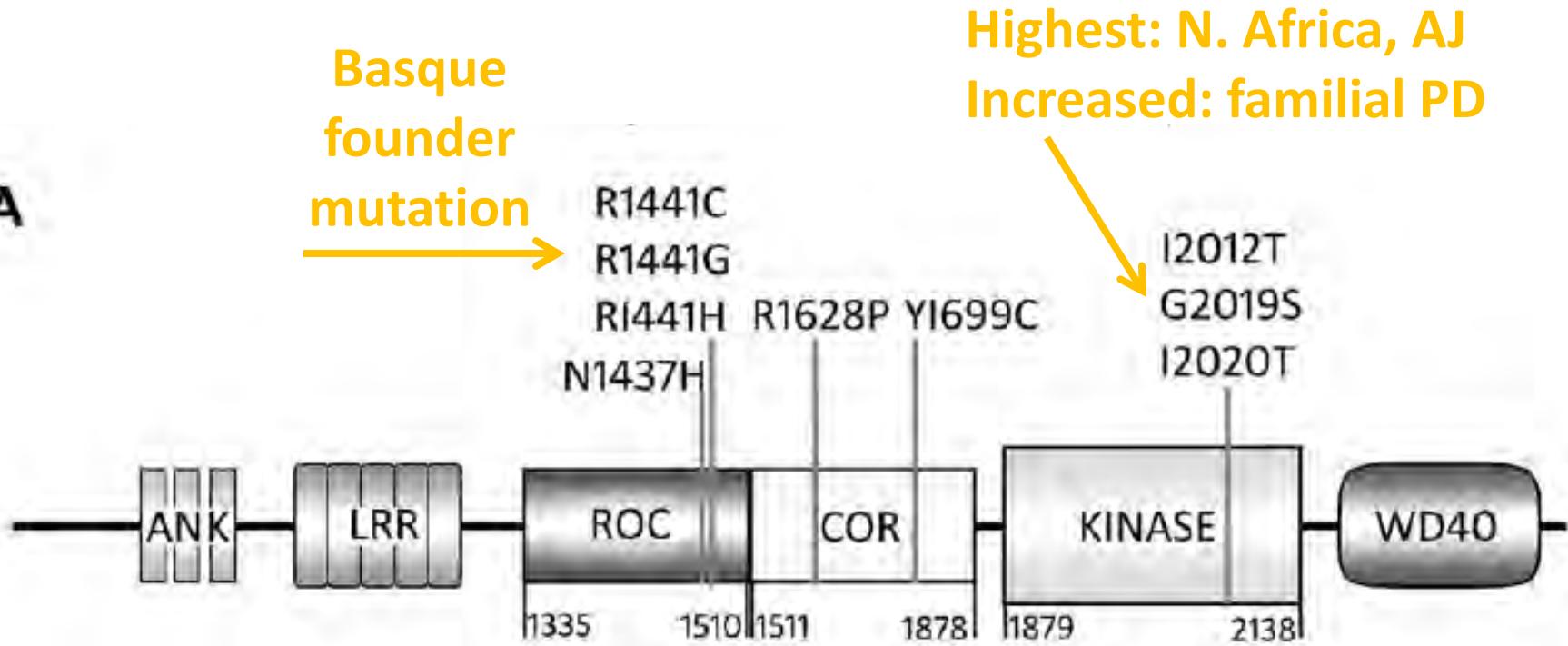
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# Distribution of Causative Mutations within the LRRK2 Gene

A



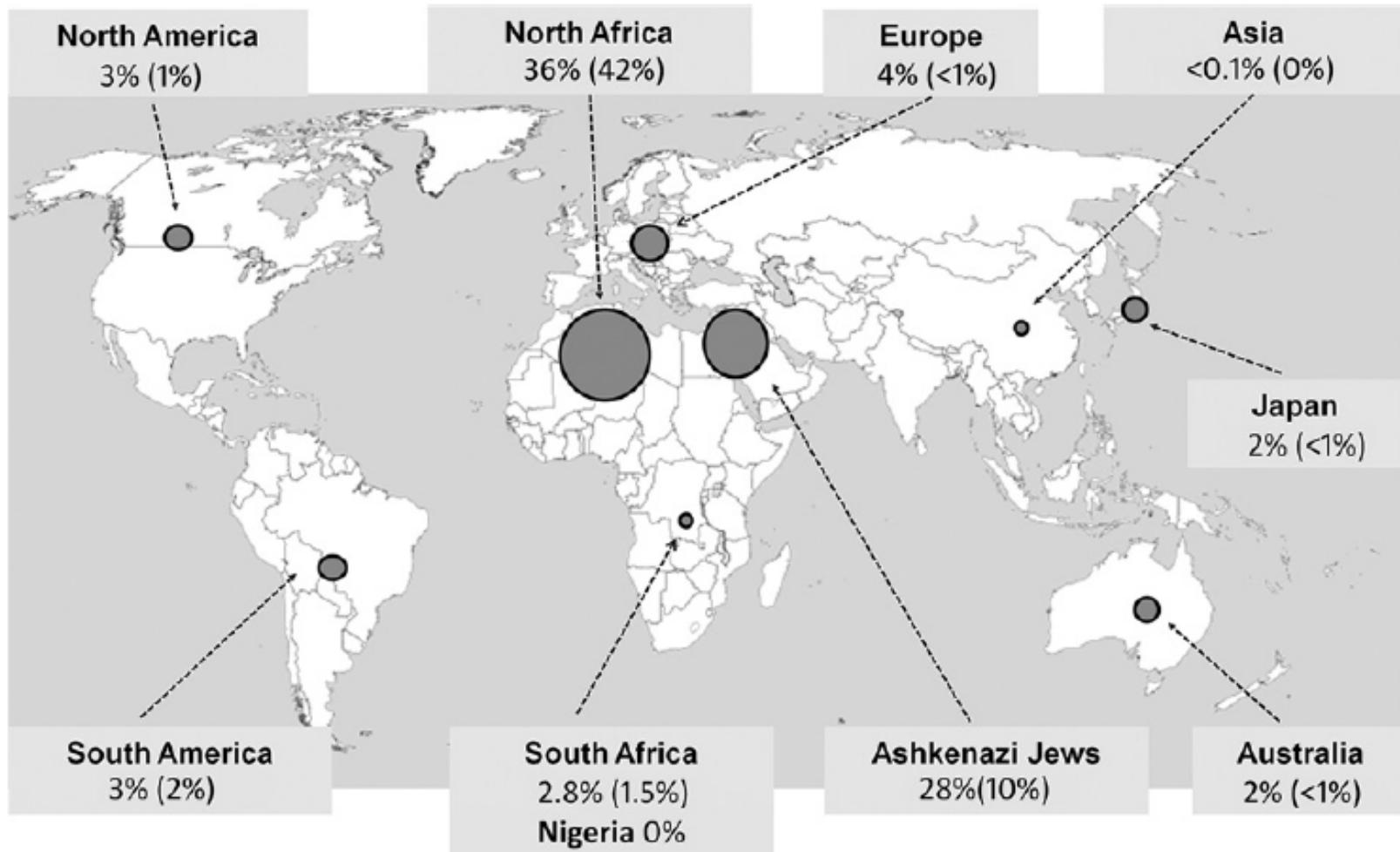
Bardien, Lesage, Brice, Carr, 2011



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# Worldwide Distribution of LRRK2 G2019S Mutation



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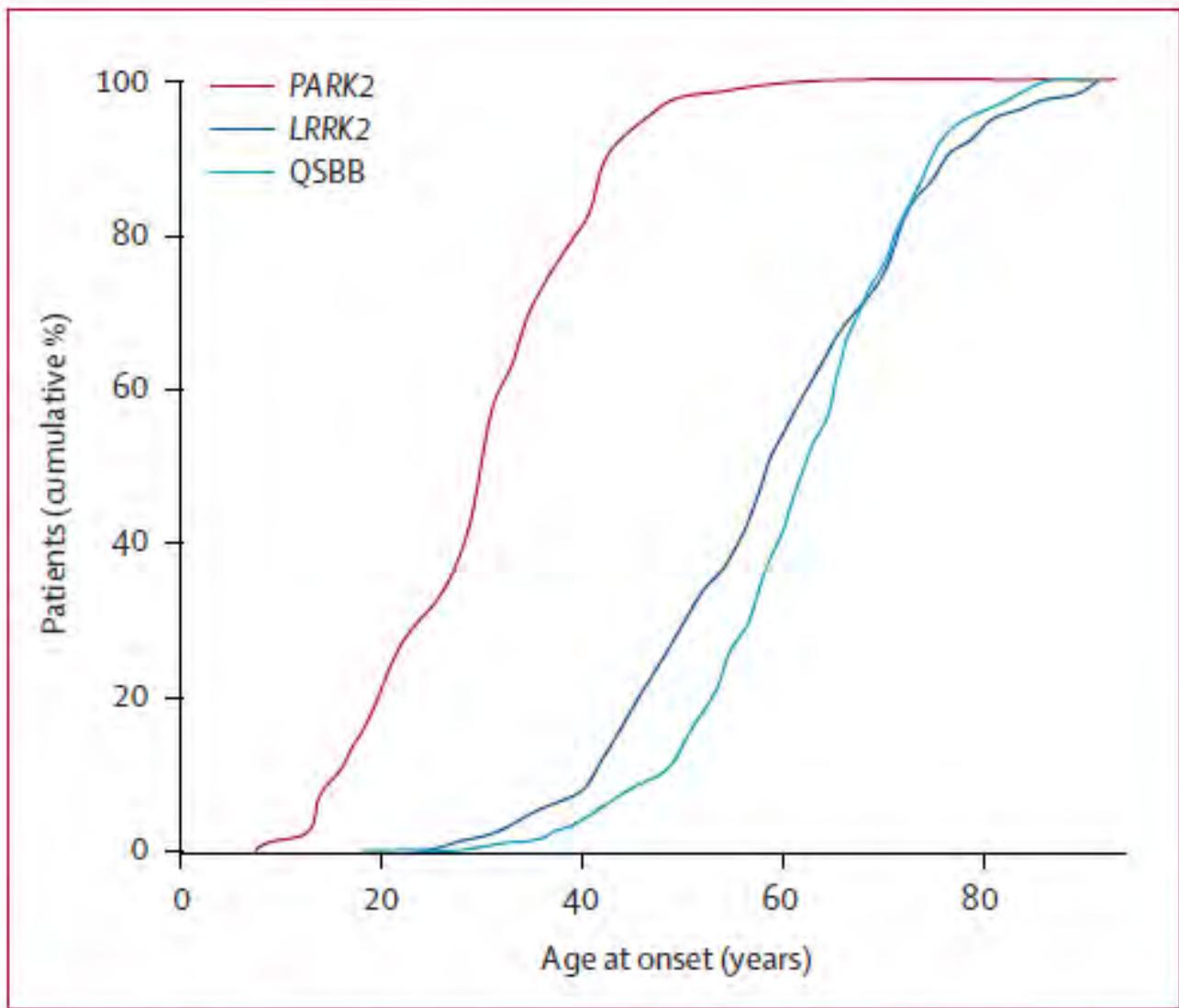
Bardien, Lesage, Brice, Carr, 2011

Familial (Sporadic) Frequency

	Patients with sporadic PD		Patients with hereditary PD		Controls	
	N	Patients with mutations (%)	N	Patients with mutations (%)	N	Patients with mutations (%)
North African Arabs	56	22 (39%)	143	51 (36%)	739	4 (<1%)
Ashkenazi Jews	259	25 (10%)	78	22 (28%)	410	4 (1%)
Portuguese	307	13 (4%)	85	12 (14%)	100	0 (0%)
Chilean*	137	4 (3%)	29	1 (3%)	153	0 (0%)
Spanish	806	22 (3%)	283	14 (4%)	544	0 (0%)
Swedish*	200	4 (2%)	127	0 (0%)	200	0 (0%)
French	300	5 (2%)	174	5 (3%)	348	0 (0%)
Italian and Sardinian	2516	37 (2%)	633	26 (4%)	1040	1 (<1%)
North American (white)	2606	26 (1%)	1450	45 (3%)	4934	1 (<1%)
British	1145	9 (1%)	192	4 (2%)	1786	0 (0%)
Norwegian	371	3 (1%)	64	6 (1%)	572	0 (0%)
Russian*	157	1 (<1%)	10	0 (0%)	126	0 (0%)
Irish	236	1 (<1%)	35	1 (3%)	212	0 (0%)
Greek*	235	1 (<1%)	0	0 (0%)	0	0 (0%)
German and Austrian	803	2 (<1%)	231	3 (1%)	436	0 (0%)
Australian*	578	2 (<1%)	252	6 (2%)	0	0 (0%)
Japanese*	526	1 (<1%)	60	1 (2%)	372	1 (<1%)
Indian*	718	1 (<1%)	82	0 (0%)	1200	0 (0%)
Serbian*	47	0 (0%)	51	2 (4%)	161	0 (0%)
Cretan	174	0 (0%)	92	1 (1%)	0	0 (0%)
Chinese*	1360	0 (0%)	973	1 (<1%)	938	0 (0%)
Basque	117	0 (0%)	41	0 (0%)	425	0 (0%)
Korean*	436	0 (0%)	17	0 (0%)	0	0 (0%)
Polish*	153	0 (0%)	21	0 (0%)	190	0 (0%)
Total white	10714	126 (1%)	3690	123 (3%)	10913	2 (<1%)
Total worldwide	14253	179 (1%)	5123	201 (4%)	14886	11 (<1%)

PD was subdivided into those with an affected first-degree relative (hereditary) and those without a family history of PD (sporadic/singleton). \*No clinical data were received from these populations; estimates are based on published data.

Healy et al,  
2007)



**Figure 1:** Age of PD onset plotted against the cumulative percentage of patients in the PARK2, LRRK2, or QSBB series  
QSBB=Queen Square brain bank.

Healy et al, 2007



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# Penetrance Estimates of LRRK2 G2019S Mutation

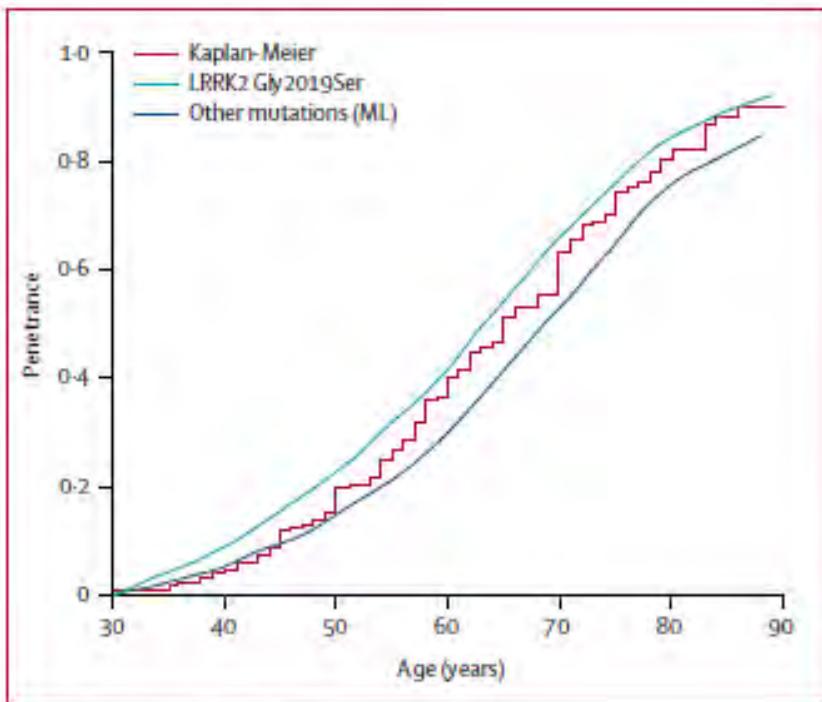


Figure 3: Age-specific risk of PD

Risk is estimated with the Kaplan-Meier method for the whole sample and with the maximum-likelihood estimation (ML) for all patients with mutations in LRRK2 combined.

Healy et al, 2007

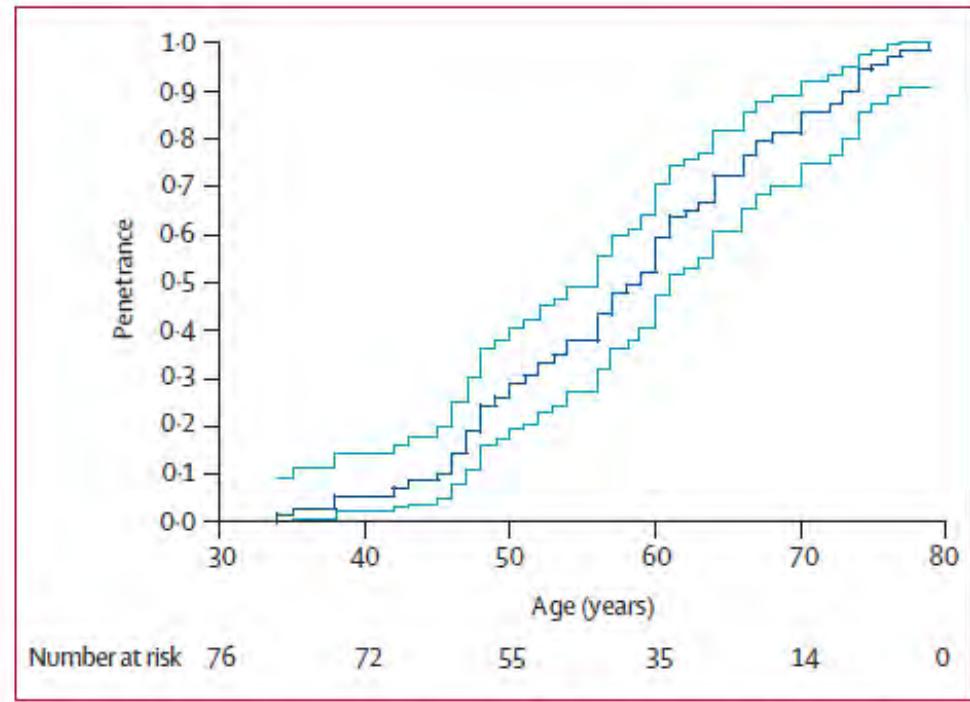


Figure: Kaplan-Meier curve of age-associated penetrance of PD in carriers of LRRK2 Gly2019Ser

Dark blue line shows penetrance; 95% CIs are shown in light blue.

Hulihan et al, 2008



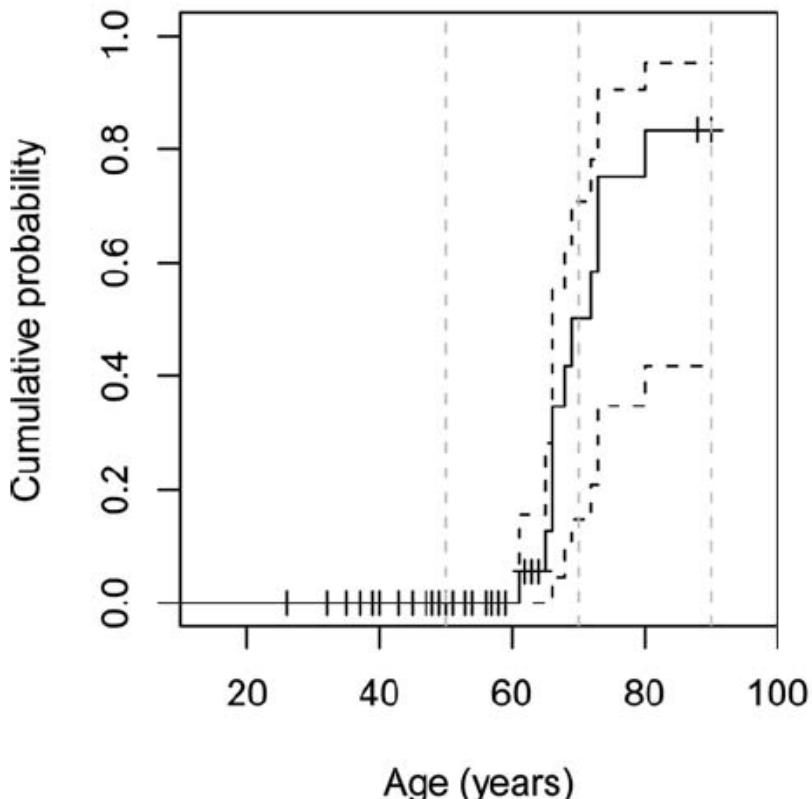
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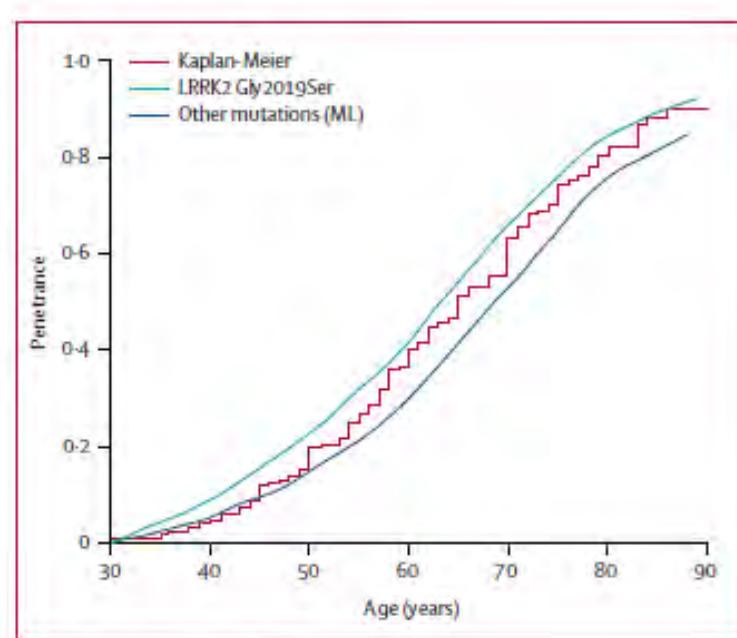


# Penetrance Estimates of LRRK2 R1441G vs. G2019S Mutation

## a) Penetrance of Parkinson's Disease



Ruiz-Martinez et al, 2010



**Figure 3: Age-specific risk of PD**  
Risk is estimated with the Kaplan-Meier method for the whole sample and with the maximum-likelihood estimation (ML) for all patients with mutations in LRRK2 combined.

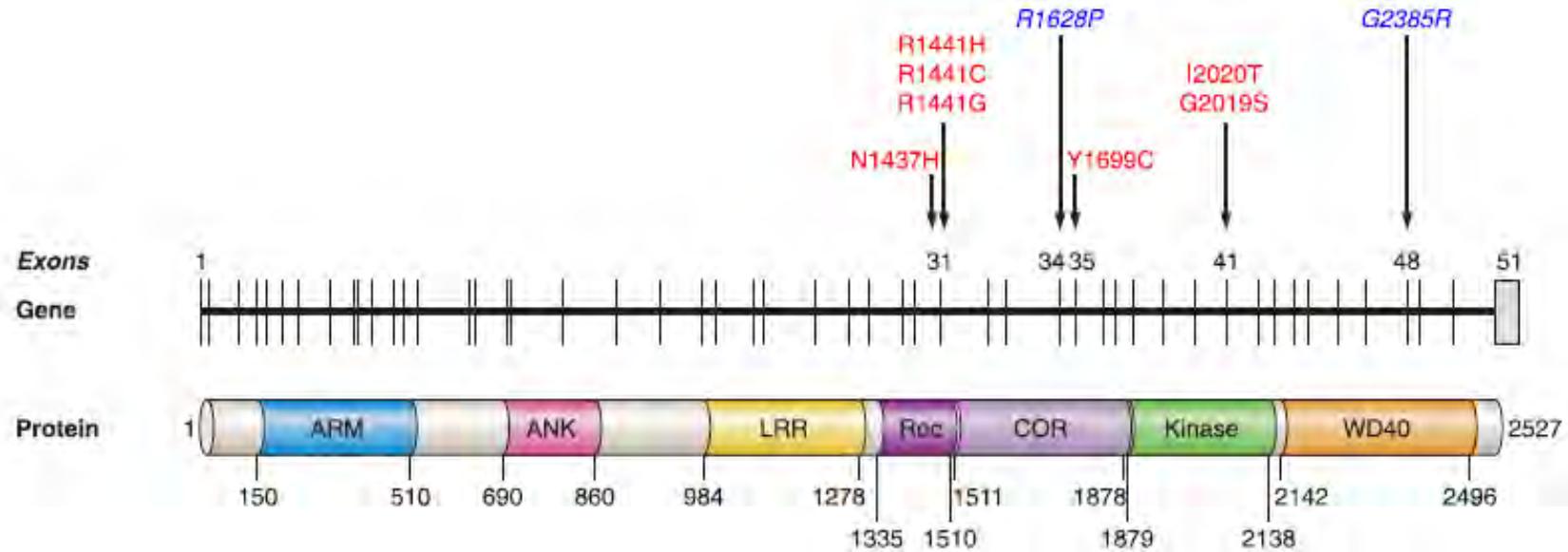
Healy et al, 2007



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# LRRK2 Gene



**Red – Causative Mutations**

**Blue – Asian-specific risk factors (not causative)**

# Implications for PPMI

- In some populations, focus on LRRK2 G2019S
  - Some populations, focus on other LRRK2 mutations
- Reduced penetrance observed with all mutations
- Focus on typical onset PD (60's)
  - Look at ancestry
  - Look at family history (autosomal dominant)



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# SNCA

- Mutations in SNCA are a very rare cause of PD
- Age of onset is typically 30's, 40's, 50's
- Autosomal dominant inheritance
  - Equal numbers of males and females affected

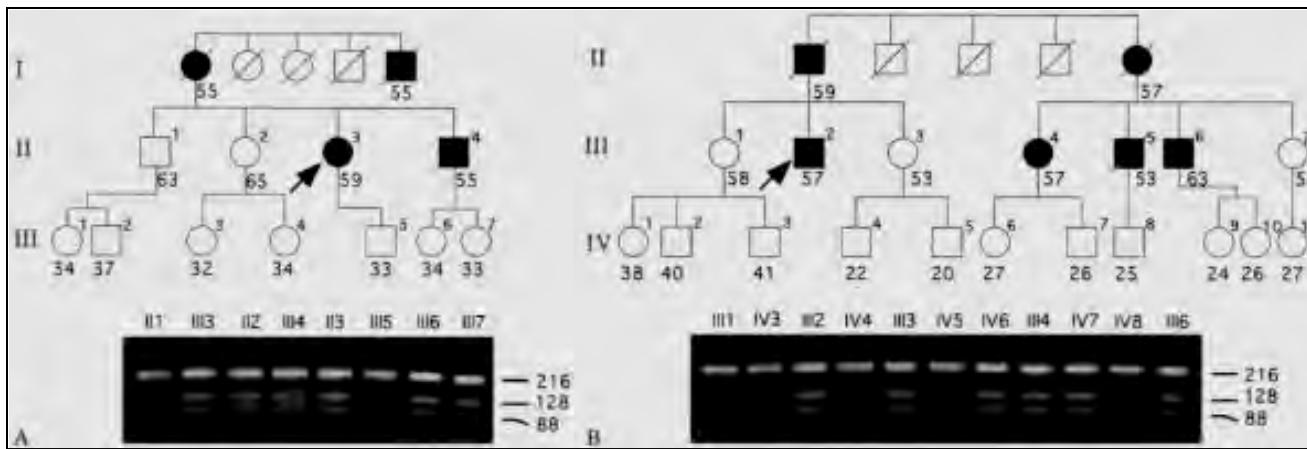


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# SNCA Pedigrees



Papadimitriou et al, 1999



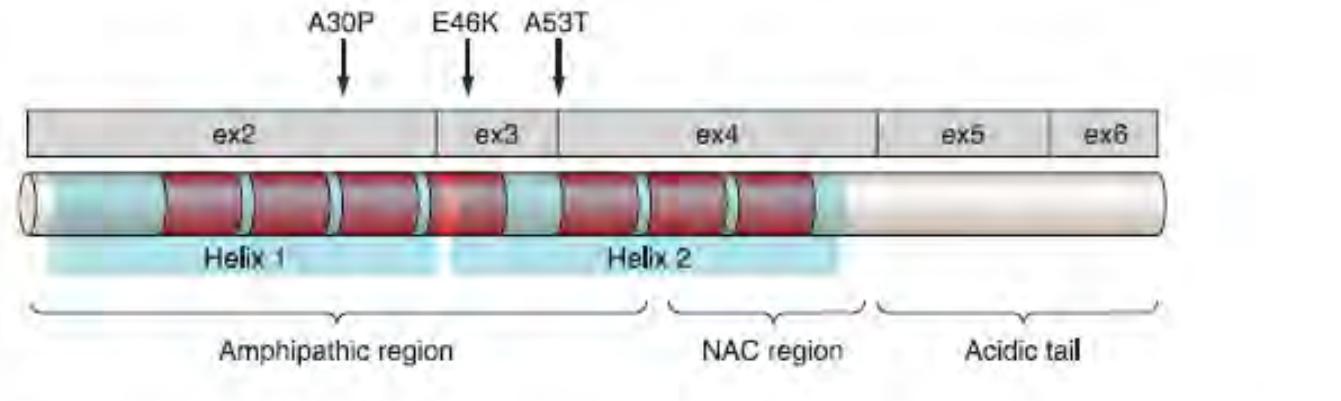
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# Distribution of Causative Mutations within the SNCA Gene

Point mutations



KTKEGV repeats

Genomic  
duplications or  
triplications of  
different sizes  
(0.4–4.5 Mb)

Cori, Lesage, Brice, 2011

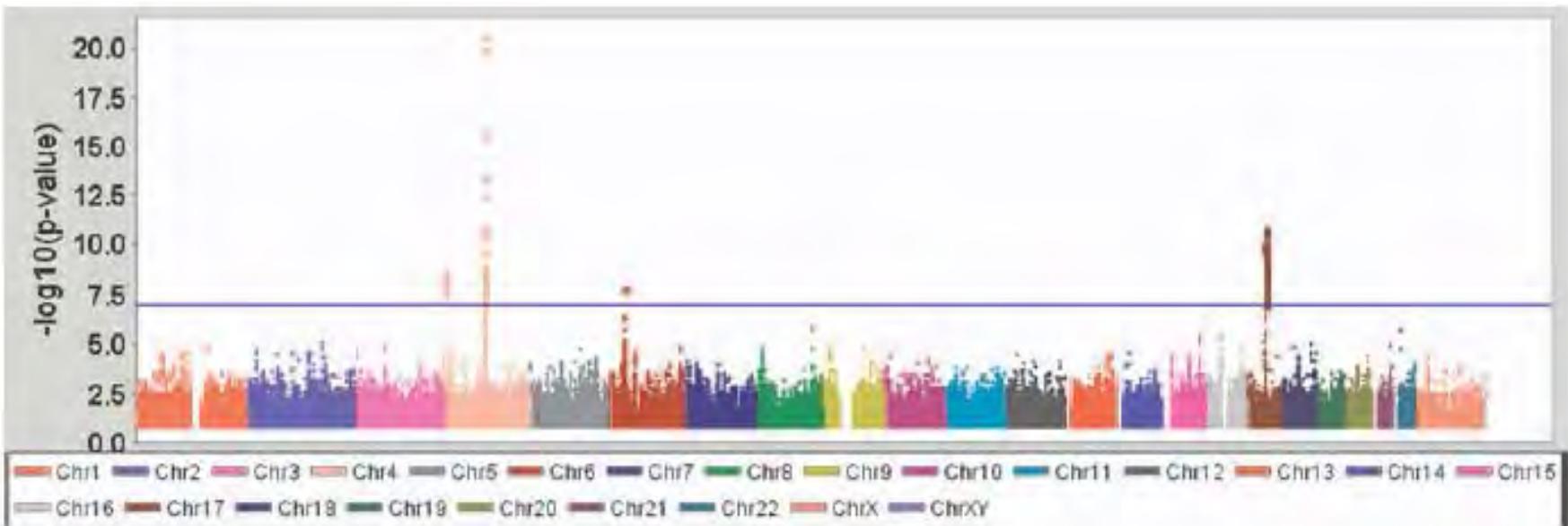


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# SNCA as a Risk Factor



**FIGURE 1: Genome-wide association results for PD susceptibility.**

Pankratz et al, 2012



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# Implications for PPMI

- SNCA mutations rare and seen in particular populations
- Focus screening in those populations
- SNCA both causative mutations and risk factor for PD
  - Confusion in molecular reporting



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# PPMI Genetics Cohorts

**Ken Marek**

**PPMI Genetics Kickoff  
Sept 16, 2013  
New York, NY**

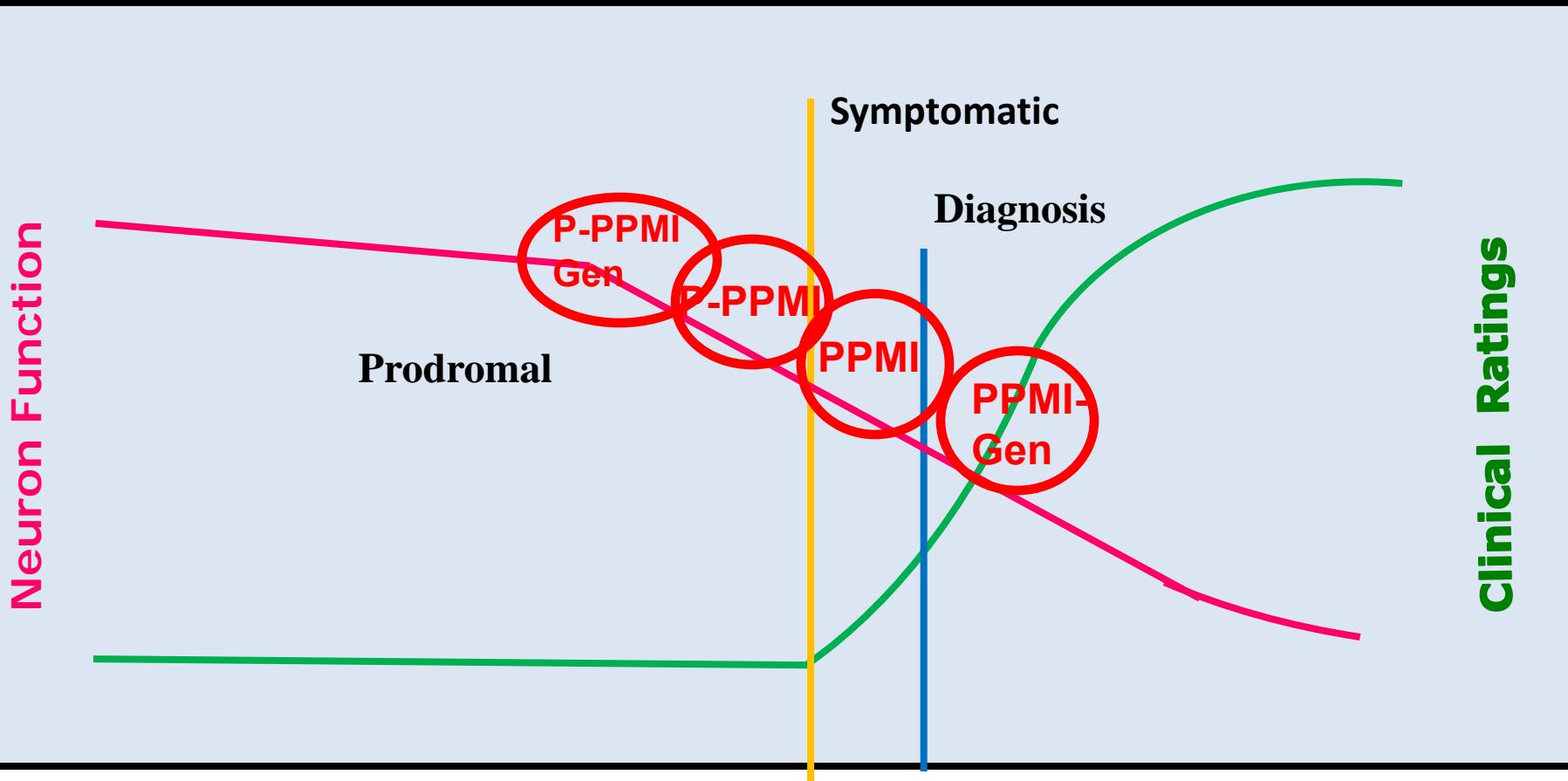


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# PPMI Genetic Cohort/Registry



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# PPMI-Genetics

- To identify progression biomarkers across the spectrum on prodromal to manifest PD that could be used in therapeutic trials
- To establish a well characterized cohort that might participate in clinical trials
- To compare PD the biomarker signature in LRRK2 and SNCA mutation subjects with prodromal PD and manifest PD without these mutations
  - To examine the prodromal biomarker signature and further define phenoconversion



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# 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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# PPMI-Genetics

## How?

- How do we identify unaffected and PD subjects with these mutations
- How do we enroll these subjects in PPMI - an intensive biomarker study
- How do we manage family members in this complex study



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# PPMI-Genetics - Plan

- **Collaboration of experts and experience**
- **Utilize PPMI infrastructure and experience – sites, recruitment experience, cores**
- **Innovative strategies for subject identification, enrollment and retention**
- **Establish Genetic Coordination Core to guide enrollment**
- **Flexible enrollment eligibility to expand from PPMI cohort**
- **Opportunity to participate in the registry for family members**



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# How Do We Identify Subjects with a LRRK2 or SNCA Mutation

Identify PD patients at  
↑ risk for  
LRRK2/SNCA mutation



Identify Unaffected relatives at ↑ risk for LRRK2/SNCA mutation  
*Known Proband with PD*

- Populations at high risk
  - Ashkenazi Jewish, African Berber or Basque populations (LRRK2); Greek/Italian populations for SNCA
- 1st degree relatives of someone who is mutation +

Identify Unaffected relatives at ↑ risk for LRRK2/SNCA mutation  
*NO Known Proband with PD, but history of PD*



- 1st degree relatives of someone who is mutation +

Populations at high risk -  
Ashkenazi Jewish, African Berber or Basque populations (LRRK2); Greek/Italian populations for SNCA with family history of a 1st degree blood relative who has/had PD

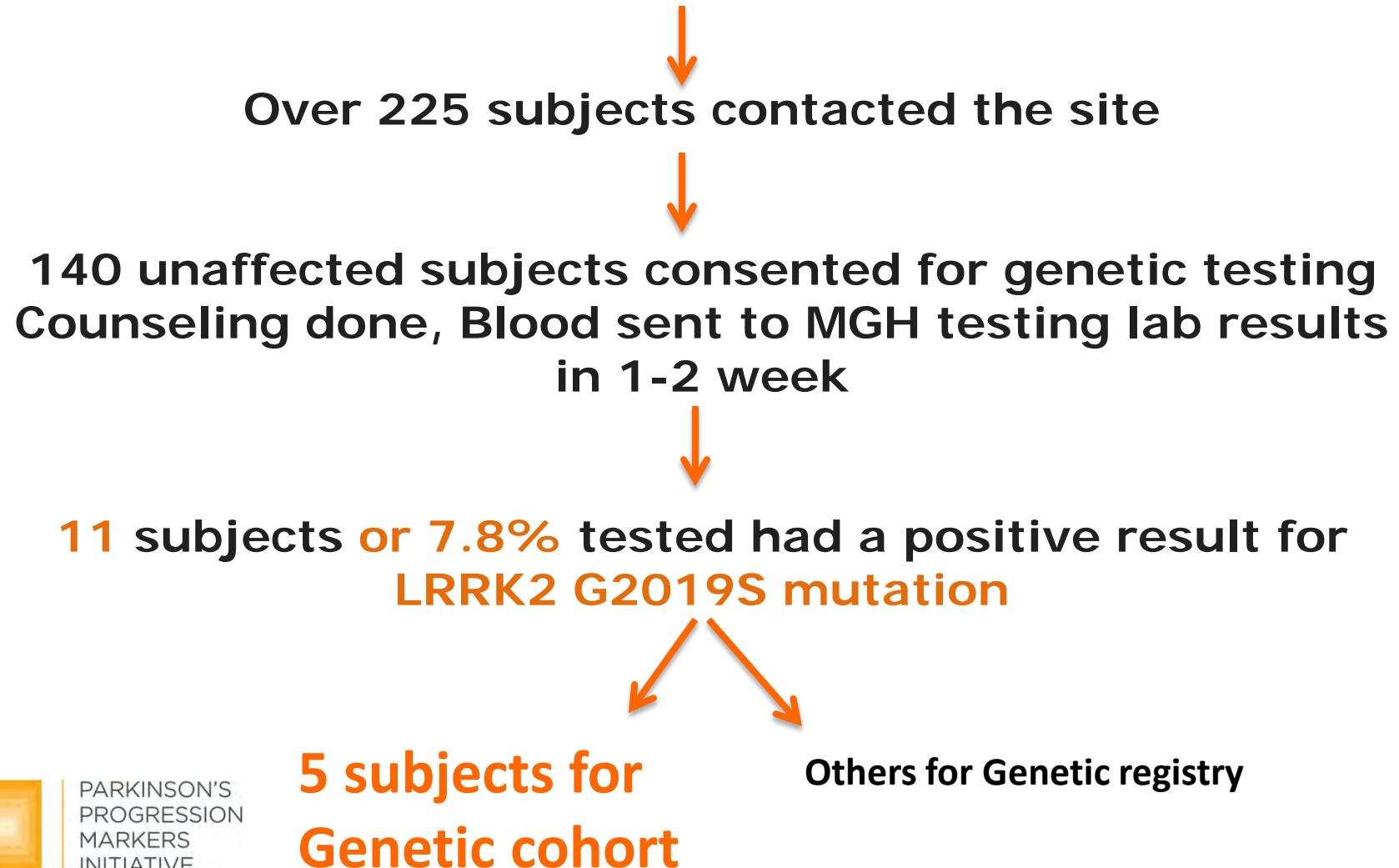


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# Screening a LRRK2 Population

Outreach to identify persons >60, AJ dissent, history of 1<sup>st</sup> degree family member with PD



# Two Stage Enrollment/Consenting–

- 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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# Inclusion criteria

## Genetic Cohort – PD Subjects

- ❖ 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
- ❖ Parkinson disease diagnosis for  $\leq$  7 years at Screening
- ❖ Hoehn and Yahr stage < 4 at Baseline.
- ❖ Age > 18 years at Baseline.
- ❖ Confirmation of causative LRRK2 or SNCA mutation (*willingness to undergo genetic testing as part of the prescreening or documentation from a CLIA approved lab*)
- ❖ **DAT or VMAT is NOT an inclusion criteria**
- ❖ Ability to provide written informed consent in accordance with Good Clinical Practice (GCP), International Conference on Harmonization (ICH), and local regulations.
- ❖ Willing and able to comply with scheduled visits, required study procedures and laboratory tests.
- ❖ Women who are pregnant or lactating will not undergo DaTSCAN and/or 18F-AV-133 imaging assessments. (The imaging assessments that would have occurred during this time will be waived)
  - Includes a negative urine pregnancy test on day of Screening scan prior to injection (DaTSCAN™ and/or 18F-AV-133).
  - Includes a negative serum pregnancy test prior to Screening scan injection (18F-AV-133 only).

# Exclusion criteria

## Genetic Cohort – PD Subjects

- ❖ A **clinical diagnosis of dementia** as determined by the investigator
- ❖ Subjects participating in VMAT-2 PET imaging have received any of the following medications that might interfere with 18F-AV-133 PET imaging:  
neuroleptics, metoclopramide, alpha methyldopa, methylphenidate, reserpine, or amphetamine derivative, within 2 weeks prior to the Screening 18F-AV-133 injection.
- ❖ Current **treatment with anticoagulants** (e.g., coumadin, heparin) that might preclude safe completion of the lumbar puncture.
- ❖ **Condition that precludes the safe performance of routine lumbar puncture,**
- ❖ Any other **medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.**
- ❖ Previously obtained **MRI** scan with evidence of **clinically significant neurological disorder** (in the opinion of the Investigator).



# Inclusion criteria

## Genetic Cohort – Unaffected Subjects

❖ LRRK2 - age ≥ 50 years or older at baseline with a LRRK2 mutation and/or a first degree relative with a LRRK2 mutation

OR

❖ SNCA ≥ age 30 years or older at baseline with a SNCA mutation and/or a first degree relative with a SNCA mutation

❖ Willing to undergo genetic testing, but may choose either to be informed of the results or remain unaware of the results

❖ Women who are pregnant or lactating will not undergo DaTSCAN™ and/or 18F-AV-133 imaging assessments. (The imaging assessments that would have occurred during this time will be waived)

- Includes a negative urine pregnancy test on day of Screening scan prior to injection (DaTSCAN™ and/or 18F-AV-133).
- Includes a negative serum pregnancy test prior to Screening scan injection (18F-AV-133 only).



# Exclusion criteria

## Genetic Cohort – Unaffected subjects

- ❖ A clinical diagnosis of PD
- ❖ A clinical diagnosis of dementia as determined by the investigator
- ❖ **GDS score greater than or equal to 10 (GDS score of 5 – 9 requires Investigator discretion to enter study).**
- ❖ **STAI Form Y-1 greater than or equal to 54 requires Investigator discretion to enter study.**
  
- ❖ Current **treatment with anticoagulants** (e.g., coumadin, heparin) that might preclude safe completion of the lumbar puncture.
- ❖ Condition that **precludes the safe performance of routine lumbar puncture**, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.
- ❖ **Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.**
- ❖ **Previously obtained MRI scan with evidence of clinically significant neurological disorder** (in the opinion of the Investigator).



# Inclusion Criteria Genetic Registry Subjects

- ❖ Male or female **age 18 years or older.**
- ❖ Individual with a **LRRK2 or SNCA mutation** or with a **first degree relative having a LRRK2 or SNCA mutation**
- ❖ **Willingness to undergo genetic testing**, but may choose either to be informed of the results or remain unaware of the results
- ❖ Ability to provide written informed consent in accordance with Good Clinical Practice (GCP), International Conference on Harmonization (ICH), and local regulations.
- ❖ Willing and able to comply with scheduled visits, required study procedures and laboratory tests.

**The registry will enroll both of  
PD and Unaffected subjects**

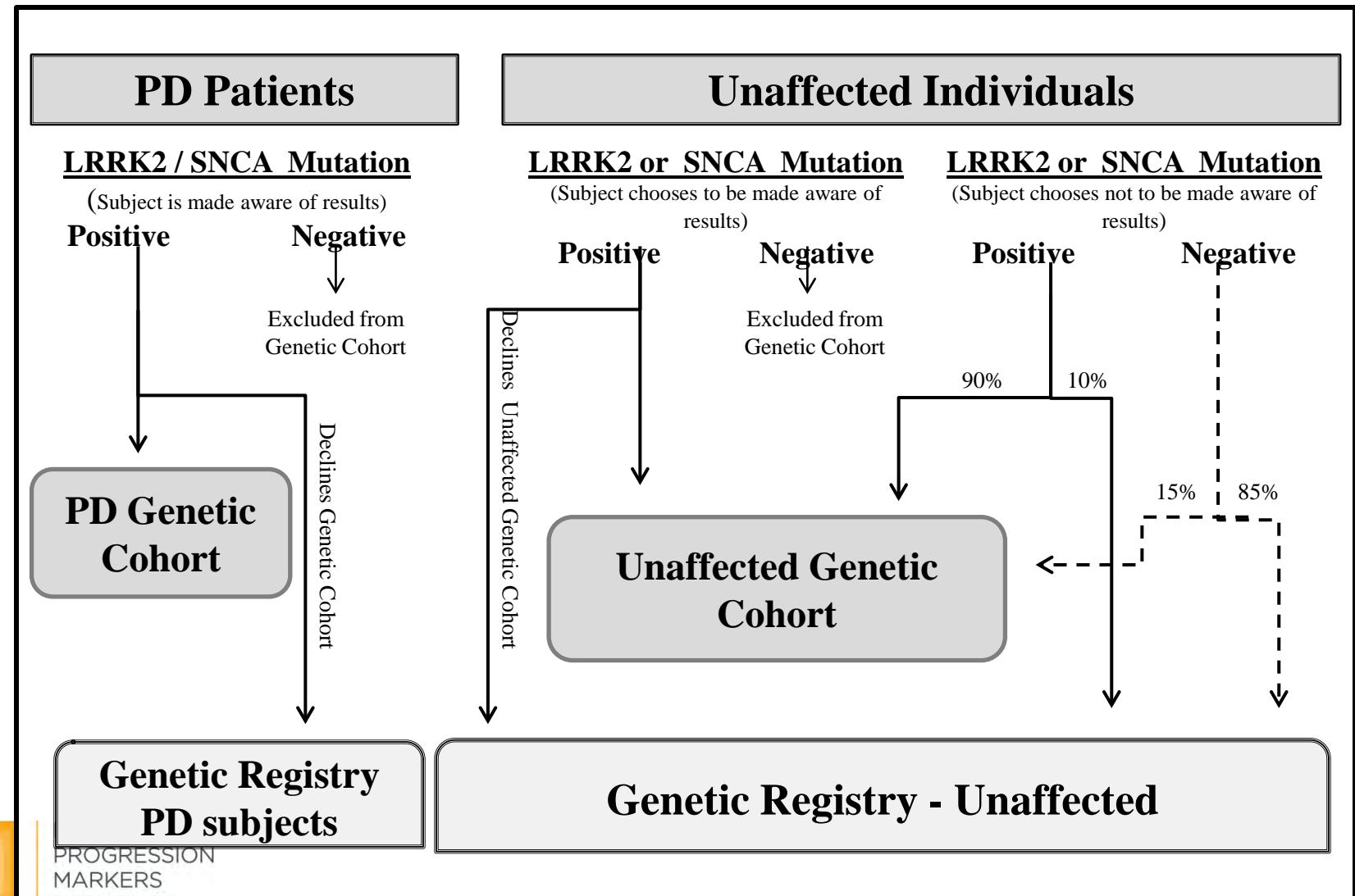


# Exclusion criteria Genetic Registry Subjects

- ❖ A **clinical diagnosis of dementia** as determined by the investigator (Appendix 1).
- ❖ Any other **medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.**
- ❖ **Previously obtained MRI scan with evidence of clinically significant neurological disorder** (in the opinion of the Investigator).



# Enrolling Individuals with a LRRK2 or SNCA Mutation



**Genetic Registry  
PD subjects**

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**Genetic Registry - Unaffected**

# Genetic Coordination Core (GCC)

- Developed in response to the new PPMI initiative to enroll and follow individuals both unaffected and with PD with a LRRK2 or SNCA mutation
  - Located at Indiana University, Indianapolis



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# Goals of the GCC

- Assist sites in screening and enrolling subjects with a mutation (LRRK2 or SNCA)
- Work with the sites to determine/confirm genetic cohort eligibility for genetic cohort and registry.
- Track related individuals in PPMI (Family History Substudy)

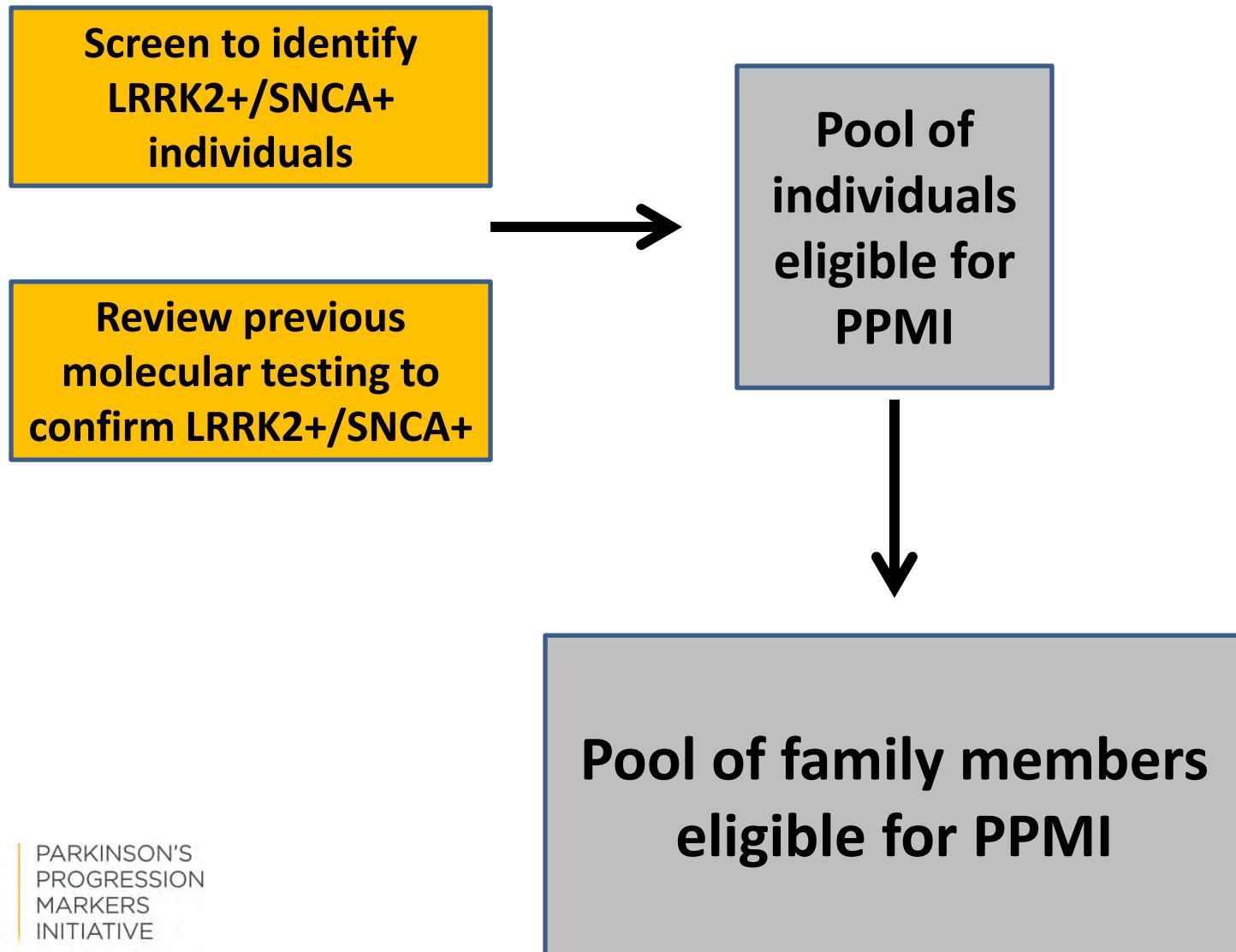


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# Recruitment and the GCC



# Breaking Apart the Process

Identifying Individuals with a LRRK2 or SNCA Mutation



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# How Do We Identify Subjects with a LRRK2 or SNCA Mutation

Identify PD patients at ↑ risk for LRRK2/SNCA mutation

Identify Unaffected relatives at ↑ risk for LRRK2/SNCA mutation

Populations at ↑ risk (LRRK2)

- Ashkenazi Jewish
- African Berber
- Basque

Populations at ↑ risk (SNCA)

- Greek/Italian

1st degree relatives of someone who is LRRK2/SNCA+

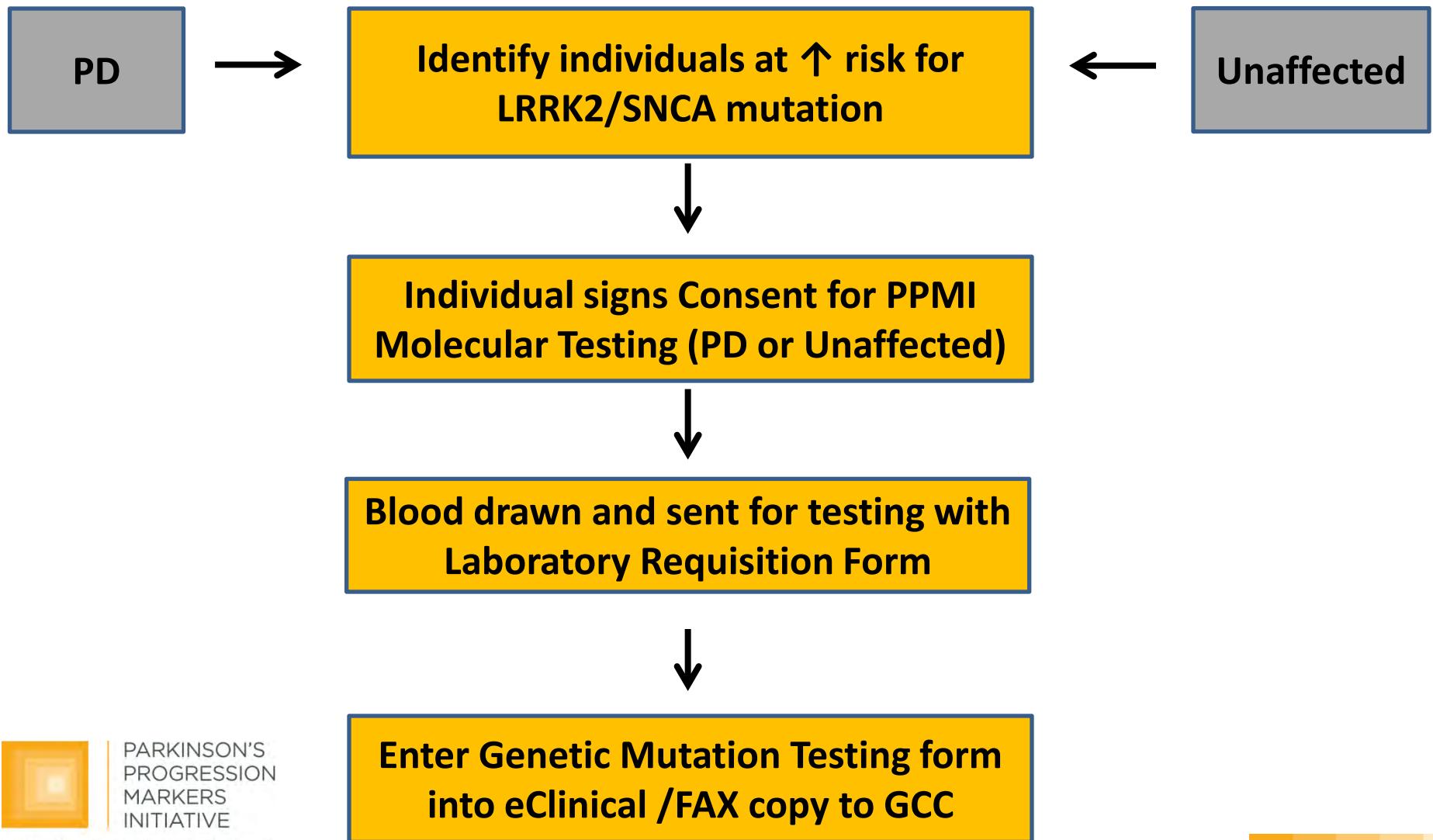


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## Prescreening

# Finding Individuals at Increased risk of a LRRK2/SNCA Mutation: Overview



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# Genetic Testing Disclosure

- Individuals with a PD diagnosis who participate in PPMI must learn the results of their genetic testing
- Unaffected individuals who participate in PPMI can choose whether they want to obtain the results of their genetic testing



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# PD Patients at Increased Risk for LRRK2/SNCA mutation

**Many ways to identify people at increased risk**

**PPMI2**  
**GUIDE FOR MOLECULAR SCREENING**  
(This form should be retained at PPMI site)

This guide can be used by PPMI sites to identify individuals who have an increased risk for a LRRK2 mutation. Individuals with multiple family members having PD and/or those who are of Ashkenazi Jewish ancestry are at increased risk of a LRRK2 G2019S mutation.

A positive response to question 1b or 3 - triggers a request for subject to enroll in the PPMI study to obtain a blood sample for LRRK2 testing. A positive response to question 2a triggers a request for subject to share a copy of their genetic testing results.

## Two risk factors

- PD patient with a family history of PD
- PD patient of Ashkenazi Jewish ancestry



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# Family History of PD

**PPMI2**  
**GUIDE FOR MOLECULAR SCREENING**  
(This form should be retained at PPMI site)

1a. Does the subject have a family history of PD?

Yes       No       Unknown

1b. If Yes, please check all that apply (must be 1st degree relative below - no half siblings):

Father       Mother       Siblings  
 Children



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# Ashkenazi Jewish Ancestry

**PPMI2**  
**GUIDE FOR MOLECULAR SCREENING**  
(This form should be retained at PPMI site)

3. Is the subject of Ashkenazi Jewish Ancestry?

Yes

No

Unknown



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# Unaffected Individuals at Increased Risk for LRRK2/SNCA mutation

- Group events with communities at increased risk
  - Fox will help organize these events and provide recruitment materials
- Very successful in Boca Raton
  - 8% of those screening had a LRRK2 mutation



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# Genetic testing for PD Patient or Unaffected Subjects

- Subject signs the Consent for Molecular Testing
- Molecular testing:
  - For sites in the US, samples will be sent to Massachusetts General Hospital (MGH) for testing
  - For sites in the EU, samples may be sent to MGH or a comparable EU lab



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# Genetic testing for PD Patient or Unaffected Subjects

- Blood drawn (prescreening)
  - Manual available with procedures, guidelines, shipping information, supply list and requisition forms
  - Sites will need to order supplies for blood draws
- Site fills out lab requisition form and ships sample to testing lab
- Site completes Genetic Mutation Testing form and faxes copy to the GCC with cover sheet/enters data into eClinical at CTCC



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# PPMI Laboratory Requisition Form for genetic testing



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## PPMI Laboratory Requisition Form Fax#: 617-724-9620

To:  
Massachusetts General Hospital  
Neurogenetics DNA/  
Biochemical Diagnostic Lab  
Center for Human Genetic Research  
CPC Building North, Suite 5300  
185 Cambridge Way  
Boston MA 02114  
Phone: 617-726-5721  
Email: [kaburke@partners.org](mailto:kaburke@partners.org)

From:  
Institution:  
Address:  
Address:  
City, State, Zip:  
Contact Name:  
Phone:  
Fax:  
Email:

Site#:

PPMI Subject ID:      MGH#:  Ref#/Client#:   
Completed by MGH

Male  Female  Year of Birth:

Date Sample Collected: \_\_\_\_\_

DNA Test Requested:  LRRK2 G2019S  Other: \_\_\_\_\_ Sample Type: Whole Blood

### Billing Information:

Institution: Michael J Fox Foundation for Parkinson's Research  
Address: Grand Central Station, P O Box 4777  
City, State, Zip Code: New York, NY 10163-4777  
Contact Name: Sohini Chowdhury  
Phone: 212-509-0995 X 206 Fax: 212-509-2390  
Email: [schowdhury@michaeljfox.org](mailto:schowdhury@michaeljfox.org)

Comments:



PPMI2

1 5 4

0 1

**GENETIC MUTATION TESTING FORM**

SUBJECT ID

VISIT NO  G  M  U

INITIALS

SITE NO

VISIT DATE

MM

DD

YYYY

If subject has not had previous genetic testing, complete questions 7 - 9

7. Date of blood draw

7.   MM   DD    YYYY

8. Volume drawn

8.    ml.

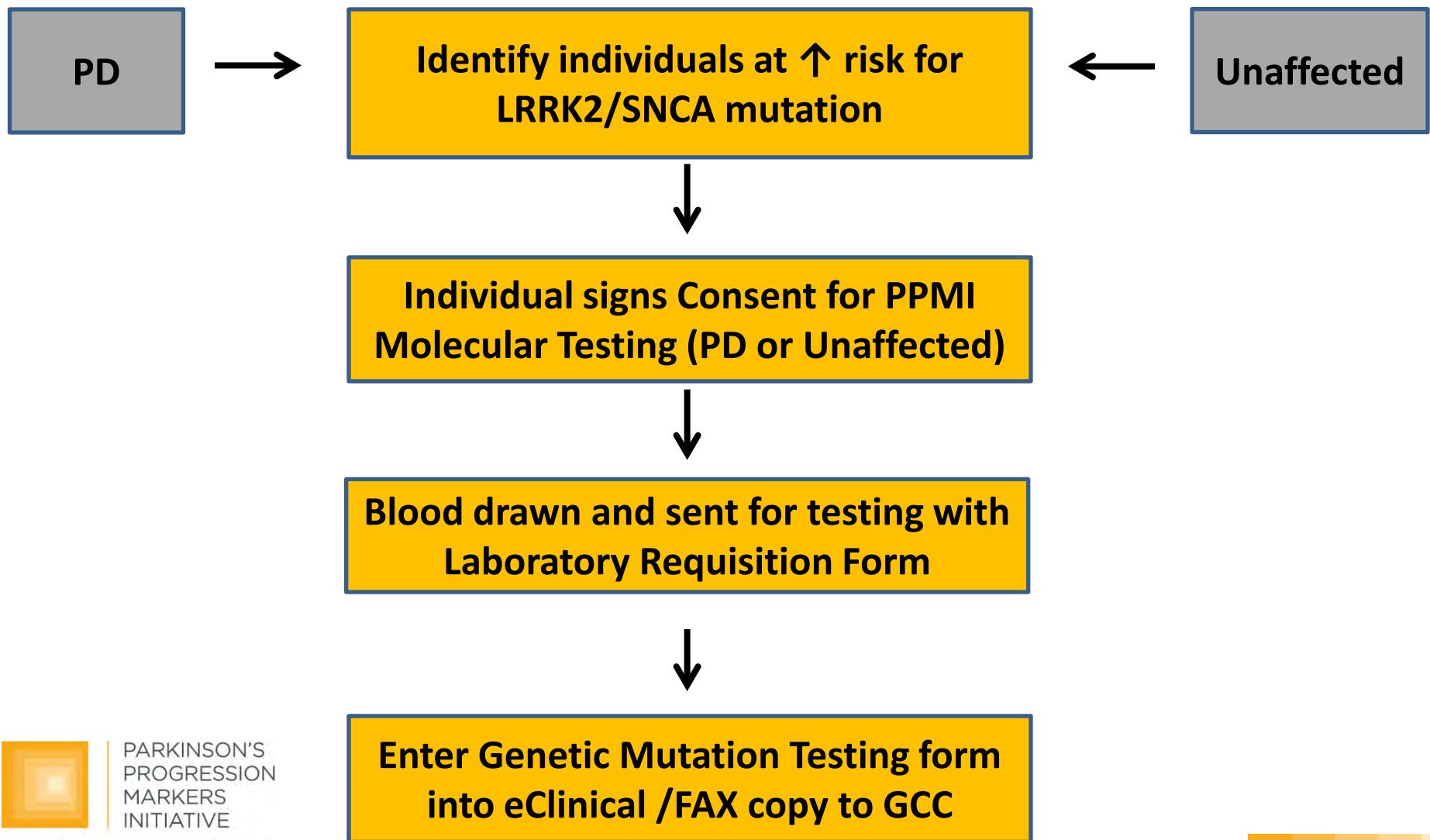
9. Sample is being shipped to

- a. Massachusetts General Hospital
- b. Other, specify \_\_\_\_\_

9.

Comments:

# Finding Individuals at Increased risk of a LRRK2/SNCA Mutation: Recap



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# Breaking Apart the Process

Individual with Previous Molecular Testing



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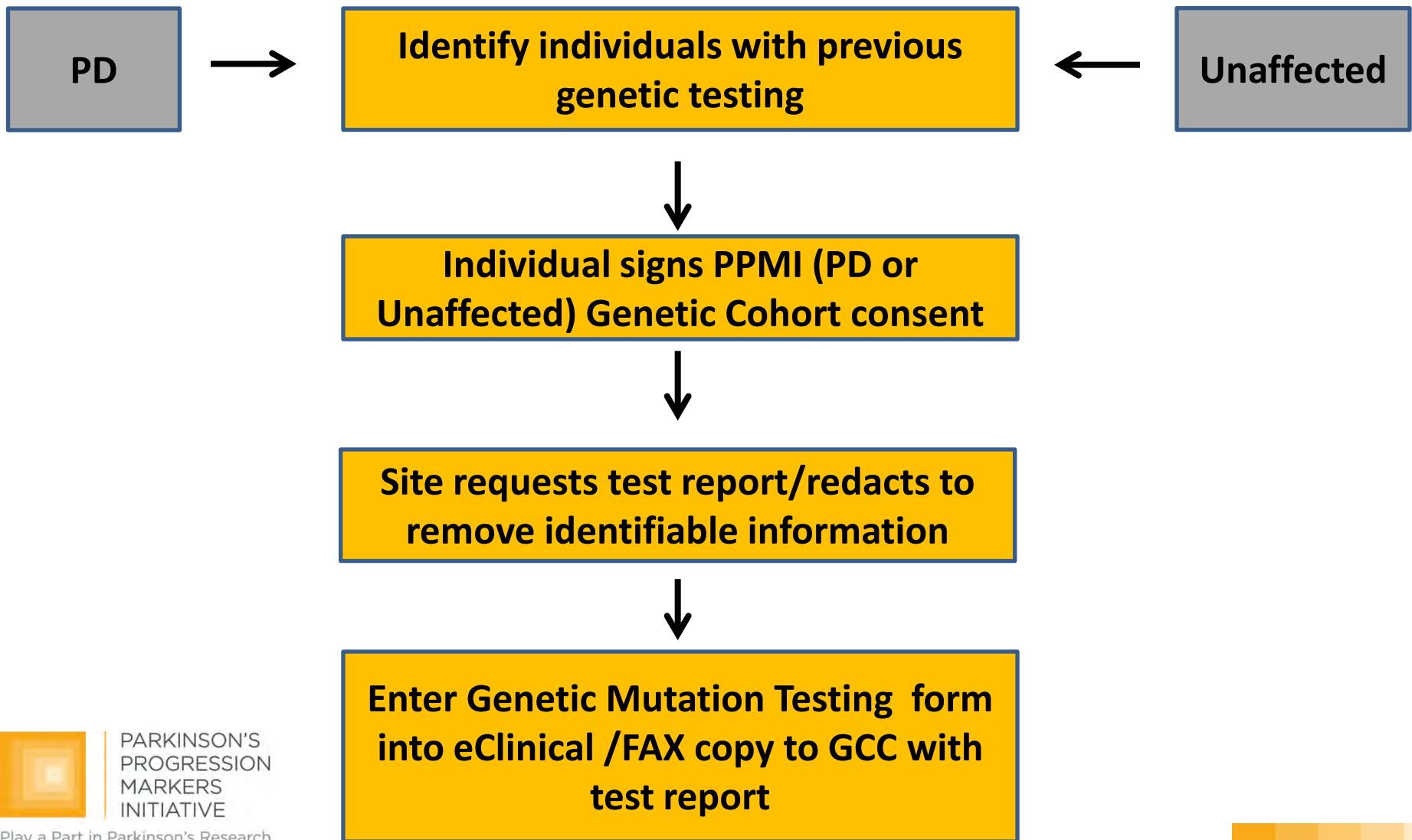


# Speeding up the Process

- One approach will be to screen large numbers of individuals who are at increased risk of carrying a mutation
- Some people may have had previous testing and KNOW they carry a mutation!
  - We want to be sure we don't miss these people



# Individuals With Previous Genetic Testing: Overview



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# Individual with Previous Genetic Testing

## PPMI2 GUIDE FOR MOLECULAR SCREENING

(This form should be retained at PPMI site)

2a. Has the subject had genetic testing for PD mutations?\*\*

- Yes       No       Unknown

2b. If Yes, where was the test performed?

- 23andMe     Other \_\_\_\_\_

**At community events, ask if individuals have genetic testing results**

**\* It is expected that a limited number of subjects will fall into this category**



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# Typical 23andMe Report

## disease risk

### Parkinson's Disease

Established Research report on 5 reported markers, updated April 28th, 2011.

Your Data | How It Works | Resources | Technical Report

Next  
Parkinson's Disease: P...

#### Technical Report

#### G2019S

GG: no mutation (LRRK2-)  
GA or AA: carry mutation  
(LRRK2+)

Gene or region: LRRK2  
SNP: rs34637584

SNP used	Genotype	Adjusted Odds Ratio*
[REDACTED] rs34637584	GG	European: 0.98 Asian: NA (not applicable)

\* Odds ratios are reported for all available ethnicities.

Mutations in the LRRK2 gene are one of the most common known genetic causes of Parkinson's disease (PD).

More than 50 variants are known in the LRRK2 gene. Several of these have been associated with PD. This variant reported by 23andMe, rs34637584, also known as the G2019S mutation, is the best-studied LRRK2 SNP related to Parkinson's in individuals with European ancestry.

Parkinson's is a fairly rare disease. The average person has a 1-2% chance of developing the disease during his or her lifetime. The chance that a person with the G2019S mutation will develop Parkinson's is much higher than average and increases with age. One recent study found that people who carry the G2019S mutation have a 28% chance of developing Parkinson's by the age of 59, 51% by the age of 69 and 74% by the age of 79. However, estimates of PD risk due to the G2019S mutation vary greatly. While it is well established that the mutation's effect is very strong, there is no consensus about its exact magnitude.

Of all people with Parkinson's, few have the G2019S mutation, but it is present at high levels in patients from some ethnic groups. Up to 40% of people with PD who are of Arab-Berber ancestry and 20% of Ashkenazi Jewish people with PD have this mutation.

Scientists do not know why only some people with the G2019S mutation get PD. There may be unknown effects due to other genes or environmental factors.



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# Typical 23andMe Report

Gene or region: SNCA

SNP: rs356220

SNP used	Genotype	Adjusted Odds Ratio*
[REDACTED] rs356220	CC	European: 0.8 Asian: 0.7

\* Odds ratios are reported for all available ethnicities.

This SNP is located near the SNCA gene, which encodes a protein called  $\alpha$ -synuclein. Rare mutations in this gene were previously found to cause familial forms of Parkinson's disease. Researchers aren't yet sure how common variants in SNCA increase susceptibility to Parkinson's, but preliminary evidence suggests that the mechanism may have something to do with increased levels of the protein.

Multiple studies have established an association between this SNP and Parkinson's disease in both European and Asian populations. In Europeans, the less common T version of the SNP is associated with slightly increased risk for Parkinson's disease. In Asians, the T version is slightly more common, and so the C version is considered slightly protective against PD. The association has not been studied in populations with African ancestry.

**Says SNCA - but this is a test for SNCA  
risk factor NOT a causative mutation**



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# PPMI Informed Consent

- Use the PPMI informed consent to consent subject to allow information to be sent to GCC
- This will consent the subject for the PPMI Protocol
- Enter cohort assignment only after confirmation from GCC



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# Genetic Testing Results

- Provide subject with a stamped envelope to send site a copy of previous genetic testing results
- Receive test results
  - Redact all identifying information on form
- Enter Genetic Mutation Testing form into eClinical
- Fax results and Genetic Mutation Testing form to GCC



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PPMI2

1 5 4

0 1

**GENETIC MUTATION TESTING FORM**

SUBJECT ID

VISIT NO  G  M  U

INITIALS

SITE NO

VISIT DATE

MM

DD

YYYY

6. Did the subject have previous genetic testing from which a copy of the results were provided to the site? (0 = No, 1 = Yes) 6.

6a. If q6 is 1 = Yes, where was the testing completed?

6a.

(1 = MGH, 2 = 23andMe, 3 = Other \_\_\_\_\_)

6b. If q6 is 1 = Yes, were de-identified testing results sent to GCC? (0 = No, 1 = Yes) 6b.

6c. If q6b is 1 = Yes, date results sent

6c.      
MM DD YYYY

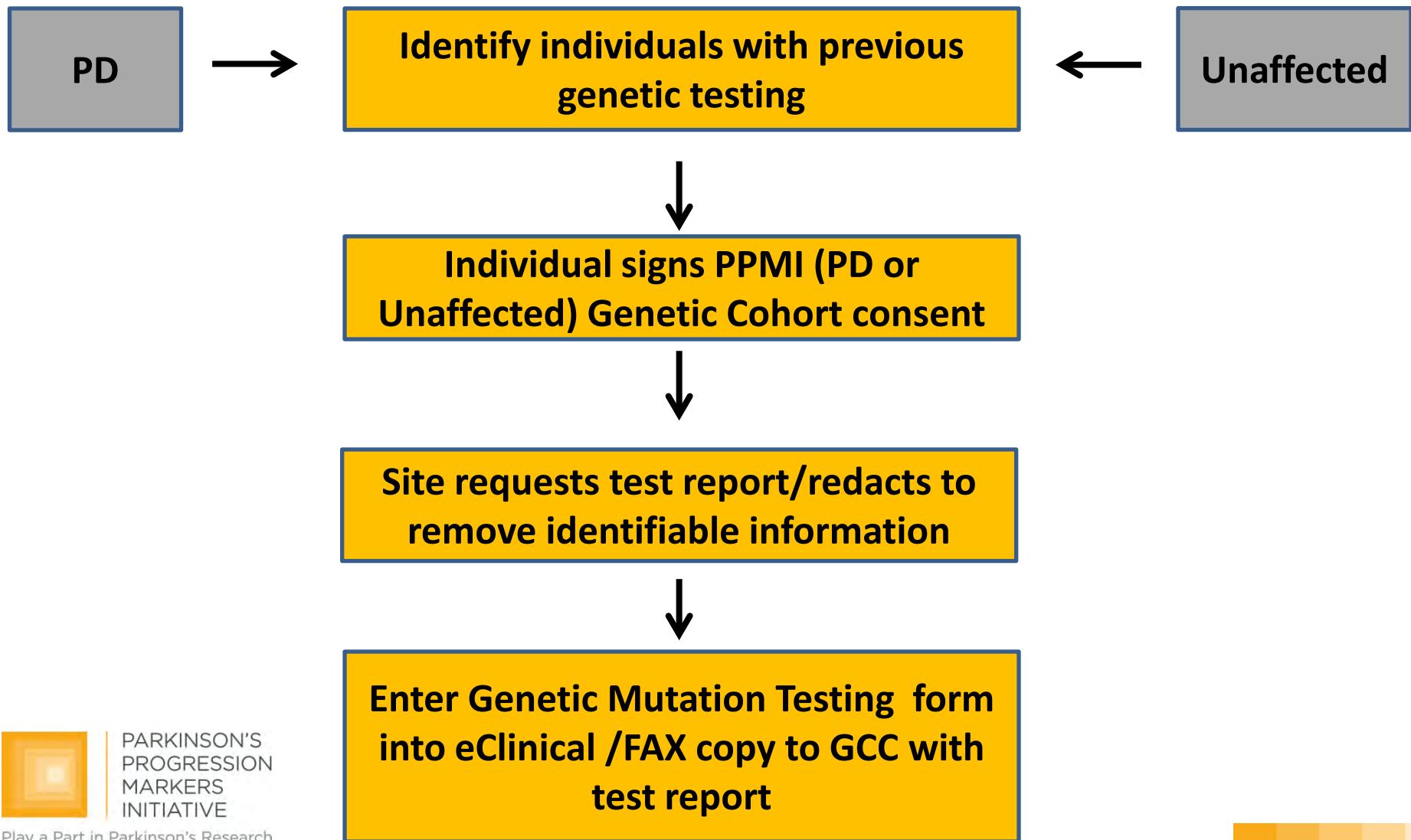


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# Individuals With Previous Genetic Testing: Recap



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# Breaking Apart the Process

## Genetic Counseling

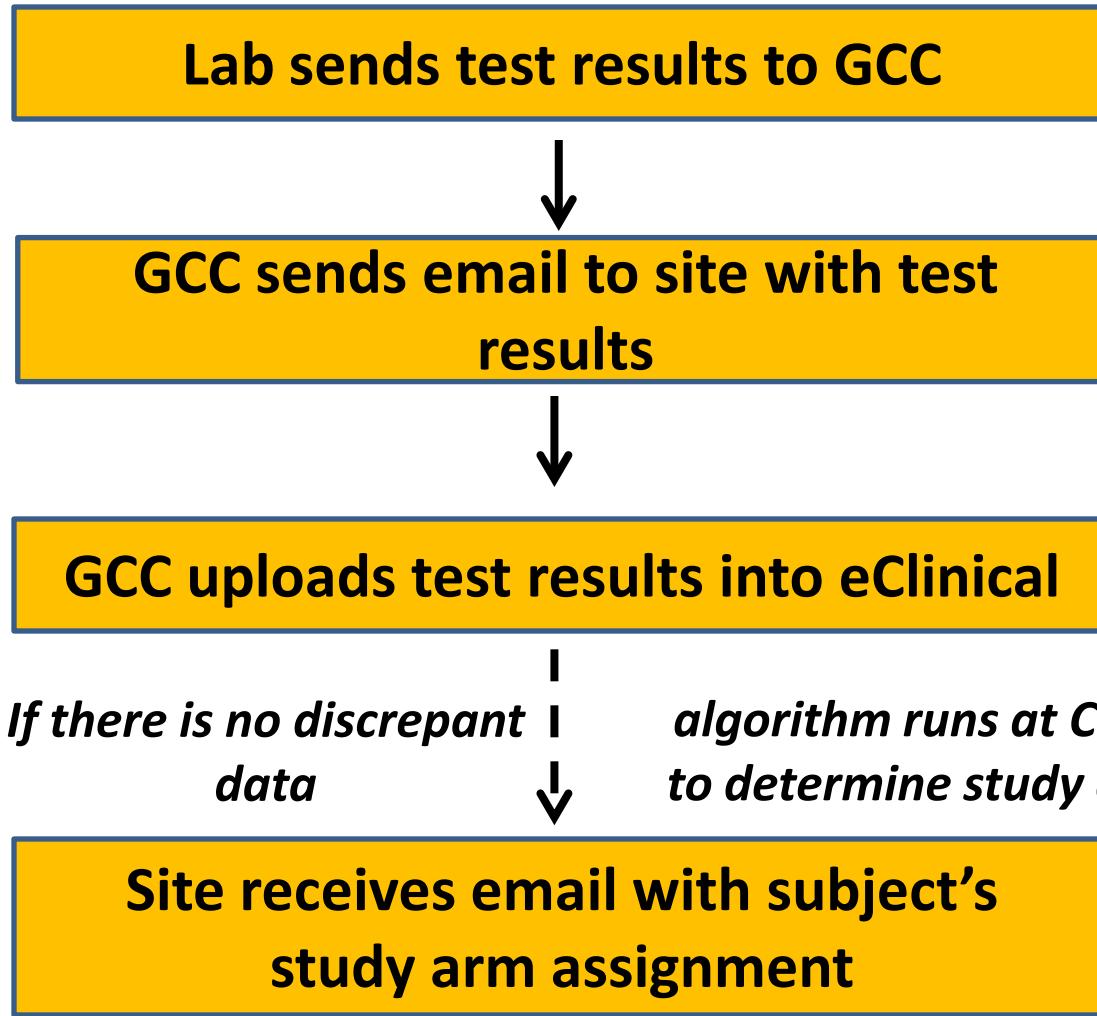


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# Transfer of Genetic Testing Results



# Genetic Counseling

- Genetic counseling will be provided to subjects
  - Individuals can receive genetic counseling from relevant professionals, and the practices change across countries/institutions
  - Genetic counseling is provided to those who are having blood drawn for testing as well as those with previous molecular results, if requested



# Genetic Counseling

- Genetic counseling will
  - Explain genetics of LRRK2 and/or SNCA
  - Explain risk to individual and family members
  - Used as a way to begin the discussion of recruiting other family members for PPMI



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# Genetic Testing Disclosure

- Individuals with a PD diagnosis who participate in PPMI must learn the results of their genetic testing
- Unaffected individuals who participate in PPMI can choose whether they want to obtain the results of their genetic testing



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# Breaking Apart the Process

## Assigning a Study Arm



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# Study Arms

## Genetic Cohort

- Comparable to other PPMI cohorts
- Ongoing biomarker assessments
- Assessment of Phenoconversion
- Visits every 6 months – comprehensive clinical, imaging and biologic assessments

## Genetic Registry

- Minimal follow-up to maintain contact
- Limited biomarker assessment and longitudinal follow-up
- Phone interviews every 6 months
- In person visit at year 2 and year 4 – limited assessment

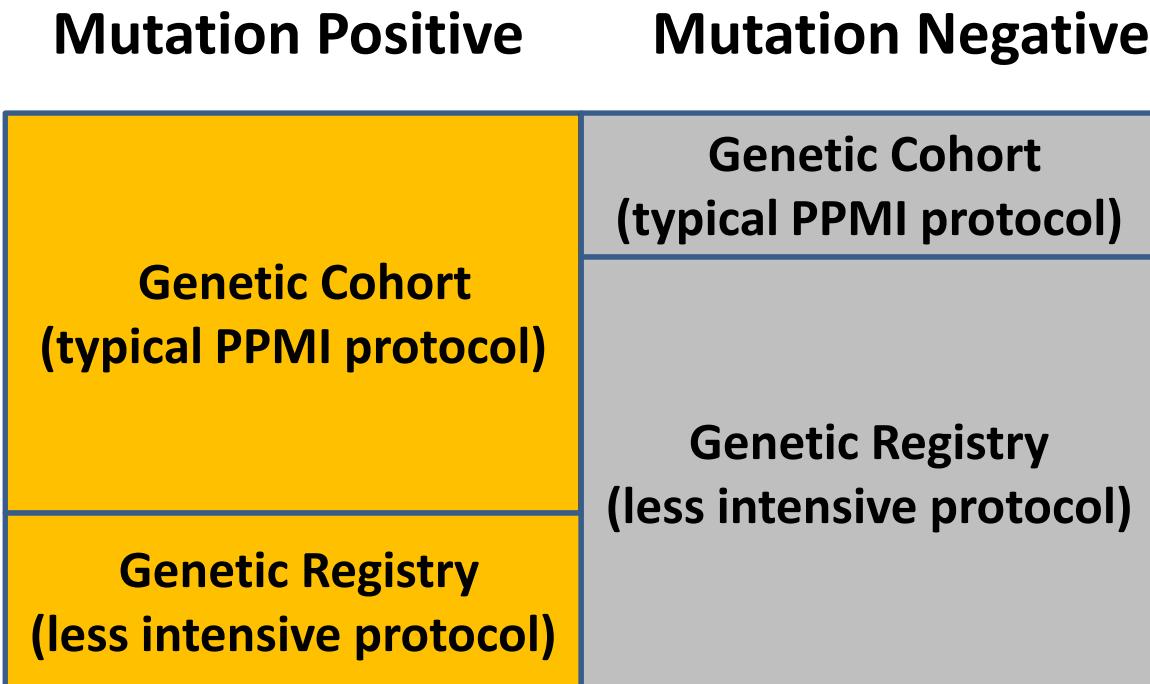


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# Relationship between Study Arm and Gene Testing Results: Overview

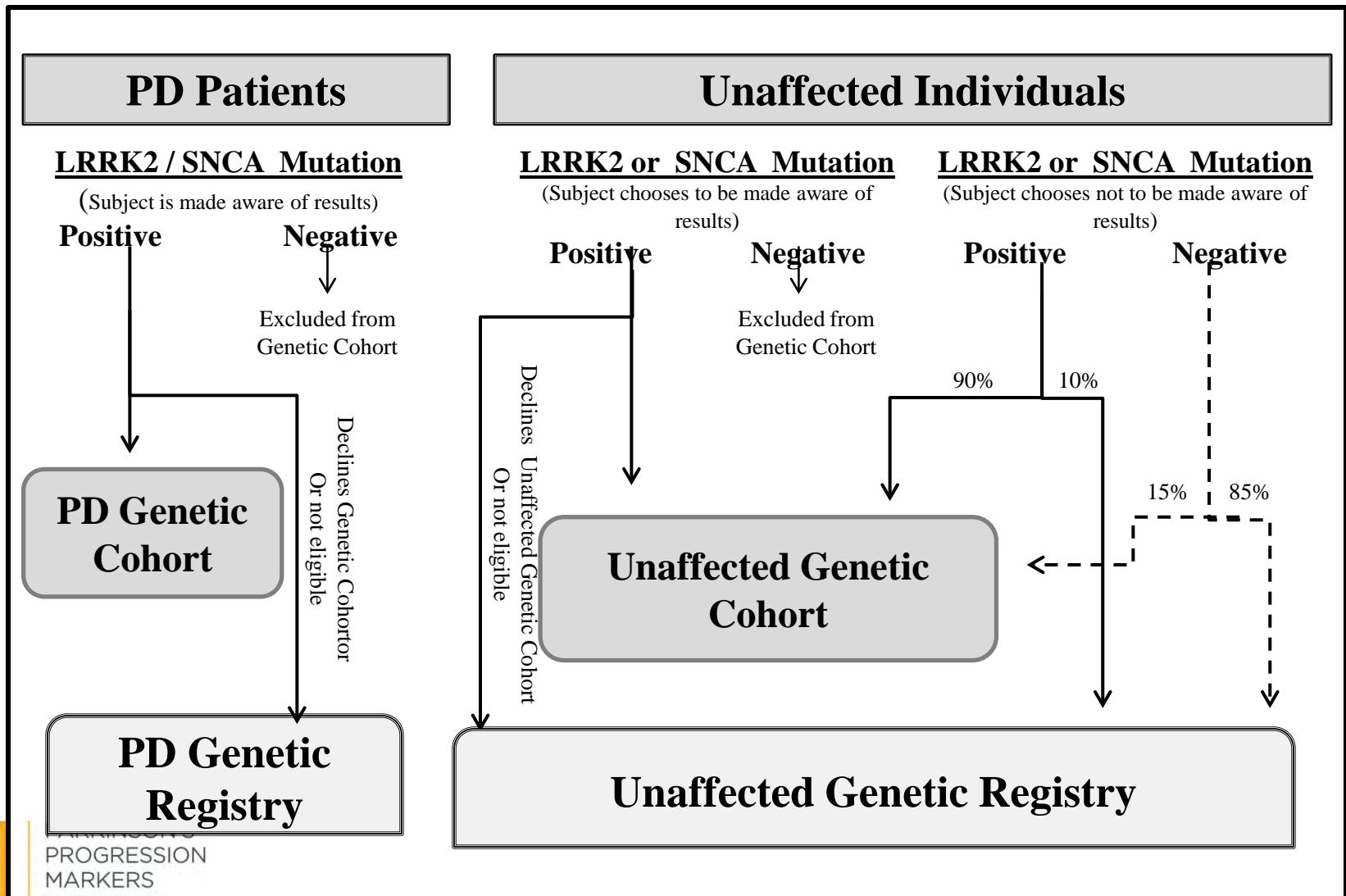


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# Identifying Individuals with a LRRK2 or SNCA Mutation – Protocol Schema



# Study Arm Assignment: PD

PD Status	Know or what to know gene status	Gene Status	Mutation	Disease Duration	Age	Study Arm
PD	Yes	+	LRRK2 or SNCA	$\leq 7$ y	$\geq 18$ y	Genetic Cohort
PD	Yes	+	LRRK2 or SNCA	$> 7$ y	$\geq 18$ y	Genetic Registry
PD	Yes	-	None	N/A	N/A	Excluded

***All individuals with a PD diagnosis must receive their genetic testing results***



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# Study Arm Assignment: Results Disclosed

PD Status	Know or what to know gene status	Gene Status	Mutation	Disease Duration	Age	Study Arm
PD	Yes	+	LRRK2 or SNCA	≤ 7 y	≥ 18 y	Genetic Cohort
PD	Yes	+	LRRK2 or SNCA	> 7 y	≥ 18 y	Genetic Registry
PD	Yes	-	None	N/A	N/A	Excluded
Unaffected	Yes	+	LRRK2	N/A	≥ 50 y	Genetic Cohort
Unaffected	Yes	+	SNCA	N/A	≥ 30 y	Genetic Cohort
Unaffected	Yes	-	None	N/A	N/A	Excluded



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## Study Arm Assignment

PD Status	Know or Want to Know Gene Status	Gene Status	Mutation	Disease Duration	Age	Study Arm
PD	Yes	+	LRRK2 or SNCA	≤7 years	≥ 18	Genetic cohort
PD	Yes	+	LRRK2 or SNCA	≥7 years	≥ 18	Genetic registry
PD	Yes	-	Not applicable	Not applicable	Not applicable	Excluded
Unaffected	Yes	+	LRRK2	Not applicable	≥ 50	Genetic cohort
Unaffected	Yes	+	SNCA	Not applicable	≥ 30	Genetic cohort
Unaffected	Yes	-	Not applicable	Not applicable	Not applicable	Excluded
Unaffected	No	+	LRRK2	Not applicable	≥ 50	90% Genetic cohort 10% Genetic registry
Unaffected	No	+	SNCA	Not applicable	≥ 30	90% Genetic cohort 10% Genetic registry
Unaffected	No	+	LRRK2	Not applicable	< 50	Genetic registry
Unaffected	No	+	SNCA	Not applicable	< 30	Genetic registry
Unaffected	No	-	LRRK2	Not applicable	≥ 50	85% Genetic registry 15% Genetic cohort
Unaffected	No	-	SNCA	Not applicable	≥ 30	85% Genetic registry 15% Genetic cohort
Unaffected	No	-	LRRK2	Not applicable	< 50	Genetic registry
Unaffected	No	-	SNCA	Not applicable	< 30	Genetic registry

# Changes in Arm Assignment

- Some subjects may decline the study arm to which they are assigned
  - Decline Genetic Cohort and request Genetic Registry
  - Record the study arm into which the subject actually consents on the Screening/Demographics CRF
- Our goal is to enroll individuals into their original study arm assignment
  - Subjects with mutations are most valuable in the Genetic Cohort



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# Changes in the Arm Assignment

PPMI2		
1	5	4
SCREENING/DEMOGRAPHICS		
SUBJECT ID <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		
SITE NO <input type="text"/> <input type="text"/> <input type="text"/> 0 2		

C. Indicate the category for this subject:  
(5 = Genetic Cohort, 6 = Genetic Registry)

C.



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# Study Visit

- Once the subject signs the PPMI Study IC, they can continue their study visit or be scheduled to return to complete the study visit
- Different consents available
  - PD Genetic Cohort
  - Unaffected Genetic Cohort
  - Genetic Registry



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# Questions



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# Good Clinical Practice

Lisa de Blieck MPA CCRC  
Clinical Trials Coordination Center



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# Good Clinical Practice (GCP)

- An international standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials
- Provides public assurance that the data and the reported results are credible and accurate = **quality data**
- Ensures the rights, integrity, and confidentiality of subjects are protected = **Ethics**

**Quality Data + Ethics = GCPs**



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# Compliance in Clinical Research

- GCP in clinical research refers to compliance with specific regulations and guidelines that govern human medical research
- Requires adherence to all the trial-related requirements, GCP requirements, and applicable regulatory requirements



# Importance of Compliance

- Ensures protection of human subjects
- Meets legal and ethical requirements
- Protects the integrity of the trial outcome
- Avoids any compromise of professional integrity



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# GCP Guidelines

- Can't be found in a single document
- Are based on several regulations and guidances
  - The PPMI study will adhere to ICH, FDA and country-specific regulations
- Define standards for clinical trial conduct, and
- Define roles, responsibilities for investigators, sponsors, and IRBs



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# GCP: Shared Responsibility

- Involves all stakeholders (e.g., IRB, sponsor, investigators)
- Investigator Responsibilities
  - International Conference on Harmonization (ICH) Guidelines (E6 – Good Clinical Practice)
  - 21CFR312 Subpart D



# Principles of GCP per ICH

1. Ethical principles (origin Declaration of Helsinki)
2. Risks, benefits, alternatives must be weighed
3. Rights, safety, and well being of subjects must prevail over interests of the study, science and society
4. The proposed study should be based on sound scientific data
5. ICF prior to initiating trial procedures
6. IRB/IEC approval prior to beginning study
7. Medical care given/medical decisions made by a qualified, licensed physician



# Principles of GCP per ICH

8. The Investigator is responsible for maintaining a well trained medical research staff
9. Informed consent by subjects must be freely given prior to conducting trial procedures
10. All trial information should be recorded, handled, and stored in a manner permitting its accurate reporting, interpretation and verification
11. Privacy and confidentiality of subject records must be maintained
12. The IP must be appropriately secured, stored and used only per protocol
13. Quality assurance systems must be in place to assure the quality of every aspect of the trial



# Investigator (per 21 CFR 312.3(a))

- “...qualified by training and experience as the appropriate expert to investigate the study in humans.”
- ...responsible for the conduct of the clinical trial at a research site
- ...is the responsible leader of the team



# Investigator Responsibilities

- Adhere to protocol: No changes to research without IRB/IEC approval except to remove immediate hazard
- Personally conduct and supervise the study, including delegated responsibilities
- Obtain informed consent prior to initiating trial activities
- Ensure initial/continuing IRB/IEC review and approval
- Report all adverse events



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# Investigator Responsibilities

- Maintain protection of subject and data confidentiality
- Handle investigational products appropriately
- Read/understand Investigator's Brochure content, including risks and side effects
- Prepare and maintain adequate and accurate source information; permit monitoring
- Promptly report changes in research, unanticipated risks
- Inform all individuals assisting with study of obligations in meeting these commitments



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# Regulatory Authorities May Ask:

- Source of study subjects?
- Did they have the disease under study?
- Did they meet inclusion/exclusion criteria?
- Was the protocol precisely followed?
- Were AEs reported appropriately?
- What was communicated between investigator and IRB/EC?



# Formula for Successful Compliance

- Regulations and responsibilities are defined
  - Learn/understand them
  - Refer to them often
  - Respect them
- Train on GCP / Practice GCP
- Follow the protocol
- Keep accurate records
  - Remember, if it's not documented, it didn't happen!



# Addressing Non-Compliance

If findings of non-compliance are communicated,

- Institute and document corrective actions
- Retrain as necessary
- Establish an ongoing re-assessment
- Carefully review data queries requested
- Promptly execute follow-up for actions identified during monitoring visits



# GCP References

- Code of Federal Regulations and ICH Guidelines
  - [www.clinicalresearchresources.com/books/bookstore.html](http://www.clinicalresearchresources.com/books/bookstore.html)
- Guidance Documents
  - <http://www.clinicalresearchresources.com/books/books tore.html>
- Guidance for Industry—Investigator Responsibilities—Protecting the Rights, Safety, and Welfare of Study Subjects
  - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf>



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# Safety Reporting and Monitoring

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Center for Human Experimental Therapeutics  
University of Rochester Medical Center



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# Adverse Events (AE)

- An AE is any untoward medical occurrence in a subject enrolled in a study after informed consent has been obtained
- Examples of AEs include:
  - Any reaction from injection of imaging tracer or lumbar puncture (e.g., pain, headache, dizziness)
  - Injury or accident during 7 day reporting period following DAT scan or LP
  - Development of intercurrent illness during 7 day reporting period following DAT scan or LP



# Adverse Events

- Adverse events are determined by subject report as well as by clinical judgment of the investigator
- Assessed on day of visit of a DAT scan and/or lumbar puncture
- Assessed also by phone 7 ( $\pm 3$ ) days following DAT or LP procedure



# Recording Adverse Events

- Document on the Adverse Event Log
- Data form includes:
  - Description of AE
  - Severity
  - Seriousness (AE vs. SAE)
  - Relationship to the study
  - Relationship to study procedure



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**PPMI**  
**ADVERSE EVENT LOG**

1	3	2
---	---	---

6	8
---	---

SUBJECT ID 

--	--	--

INITIALS 

--	--	--

SITE NO 

--	--	--

Record all adverse events that occur during the study visit or the 7 day follow up period following an LP or DaTSCAN. Record disease entity as AE only if it worsens beyond what investigator expects is within normal range of fluctuation for this subject. Elicit adverse event data by asking an open-ended question, e.g., "What unusual symptoms or medical problems have you experienced since the last visit?" Record any new or change in ongoing sign or symptom as well as any event that has resolved since last evaluation. Enter each change in "severity" on new line. Date: Please specify if the Start and Stop dates are ACTUAL or ESTIMATED. If the exact date is unknown, please enter your best reasonable estimate of the date and specify which part(s) are estimated. IF EVENT IS A SERIOUS ADVERSE EVENT, please refer to the Operations Manual for reporting guidance.

AE # (e.g., 1, 2, etc.)	Adverse Event (Record diagnosis if known)	START DATE (MM/DD/YYYY)	STOP DATE (MM/DD/YYYY)	Severity	SAE	Relationship to Study*	Related to Study Procedure			Complete when resolved or at Final Visit	
							DaTSCAN	LP	Other	Primary Outcome	AE Status at Final Visit
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

\* If 3, 4 or 5 are selected, complete "Related to Study Procedure".

<input type="text"/>	<input type="text"/>	<input type="text"/>
----------------------	----------------------	----------------------

INVESTIGATOR'S SIGNATURE

DATE

STAFF CODE

# AE Severity

- Based on the Investigator's clinical judgment and graded as follows:
  - **Mild** – usually transient in nature and generally not interfering with normal activities
  - **Moderate** – sufficiently discomforting to interfere with normal activities
  - **Severe** – prevents normal activities



# AE Relationship to Study

- As determined by the Investigator
- Indicating whether there is a reasonable possibility of a relationship between the AE and a study procedure (e.g., LP or DaTSCAN™)
  - \*Possible
  - \*Probable
  - \*Definite
  - Unlikely
- No reasonable possibility of such a relationship
  - Unrelated



# AE Relationship to Study

Relationship to Study*	Related to Study Procedure 0 = No 1 = Yes			
		DaTSCAN	LP	Other
1 = unrelated 2 = unlikely 3 = possible 4 = probable 5 = definite		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If Relationship determined as:

3 = Possible

4 = Probably

5 = Definite

Investigator must assess whether event is related to DaTSCAN™, LP and/or another study procedure.



# AE Follow Up

- All documented AEs should be evaluated at each subsequent visit until the event or its sequelae resolve or stabilize at an acceptable level
  - Enter follow-up information on the AE Log
- Any ongoing AE at the final 7 day reporting telephone call should be followed until resolution or stabilization



# Serious Adverse Events

## SAE

- An SAE is any AE that results in any of the following outcomes:
  - Life-threatening adverse event
  - Hospitalization or prolongation of existing hospitalization
  - A persistent or significant disability/incapacity
  - A congenital anomaly/birth defect
  - Death



# Reporting Serious Adverse Events

- SAEs must be reported to the CTCC project manager as soon as possible and **within 24 hours** of awareness
- Complete the MedWatch form and email to the CTCC project manager
- Updates/modifications to initial report must also be made within 24 hours of site awareness
- Sites to notify IRB/Ethics Committee according to local institution and regulatory requirements





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# Study Monitoring



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# Clinical Monitoring

- CTCC oversight of clinically related study activities (adverse events, labs, medications)
- Monthly review of medications, AEs, current medical conditions
- Advise on eligibility or clinically related study questions
- Assist with review and processing of SAEs
- Report significant issues or trends to the SC



# Site Monitoring

- Monitors will conduct an on-site monitoring visit after a minimum of 2 subjects are enrolled
- Subsequent visits will be annual (or on as needed bases)
- Monitoring responsibilities for the study include:
  - Review regulatory documentation,
  - Ensure protocol compliance and subject safety,
  - Source verification,
  - Review records for DaTSCAN™



# Site Monitoring

## Coordination of Visits/Contacts:

- Monitors are responsible for arranging site visits with Site Coordinator and Investigator
- Site visit communications will be documented through the following:
  - Pre-visit confirmation letter to site with list of activities planned (e.g., records to review)
  - Interaction during the visit with an update on progress and identification of any action items necessary
  - Follow-up letter with documentation of findings, issues and concerns



# Site Monitoring

- At each annual Periodic Monitoring Visit, the monitor will:
  - Review Regulatory Binder documentation, including study-related training records for staff involved
  - Review informed consents for all
  - Review screening/enrollment procedures
  - Complete source document verification
  - Review accountability and management of the DaTSCAN™ (first and last visit only)



# Questions?



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