

PPMI Status Update

Ken Marek

PPMI Investigators Meeting
May 7, 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”**

MAY 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 – 25 MONTH AGO

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



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PPMI-PD

62 yo right handed WM lawyer in excellent general health

History

9 month history of slowly worsening R UE tremor

6 month history of R shoulder pain

3 months voice less reliable in public speaking

Exam

Mild R UE resting tremor

Mild R bradykinesia

PD DIAGNOSIS – 3 MONTH AGO

“PPMI is attractive because no meds and I can do something that will help research”

PPMI-Control

- **62 yo right handed WF school principal in excellent general health**

- **History**

- Husband has PD for 17 years**

- No previous participation in clinical research**

- Exam**

- Normal**

- **“PPMI is something I can do for my husband even if he can’t join the study”**



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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

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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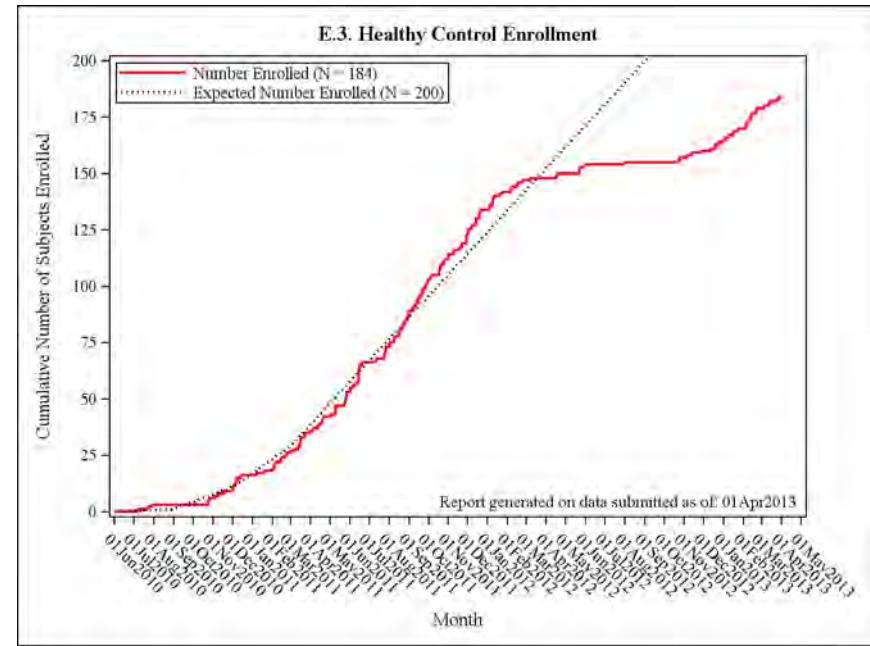
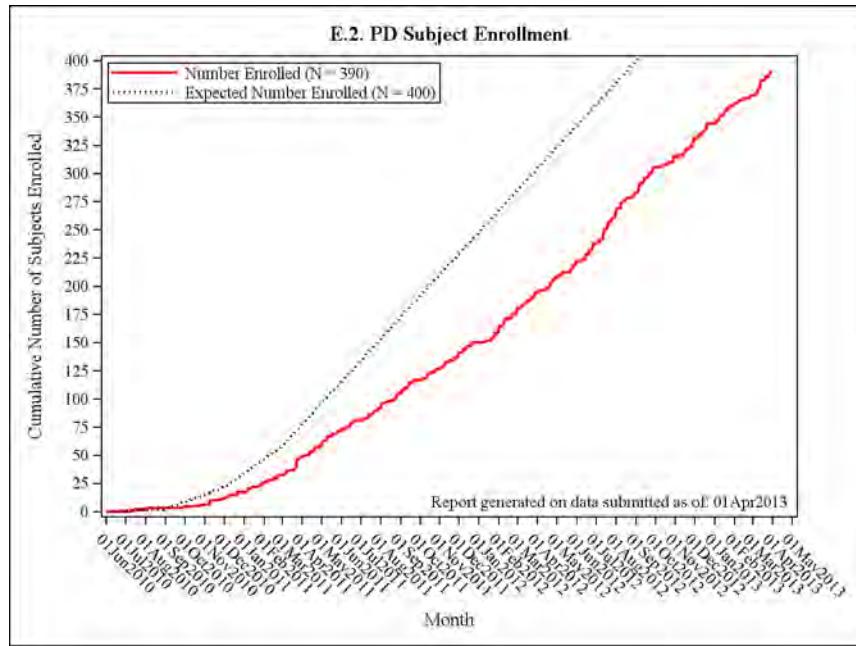


Establish a Specific Data Set

- **Enrollment – 419 PD 191 HS 59 SWEDD 669 subjects**
- **Retention – 413 PD 183 HS 58 SWEDD - 654 subjects**
- **Study Infrastructure – SC, Study cores, Working groups and committees, Sites**
- **Data flow from sites to Study Cores to LONI. Outstanding success in collection of study data and compliance with study visits and assessments**
- **Ancillary studies**
- **Prodromal and Genetic Cohorts**



ENROLLMENT



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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
- How to utilize experience for Prodromal and Genetic cohorts



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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

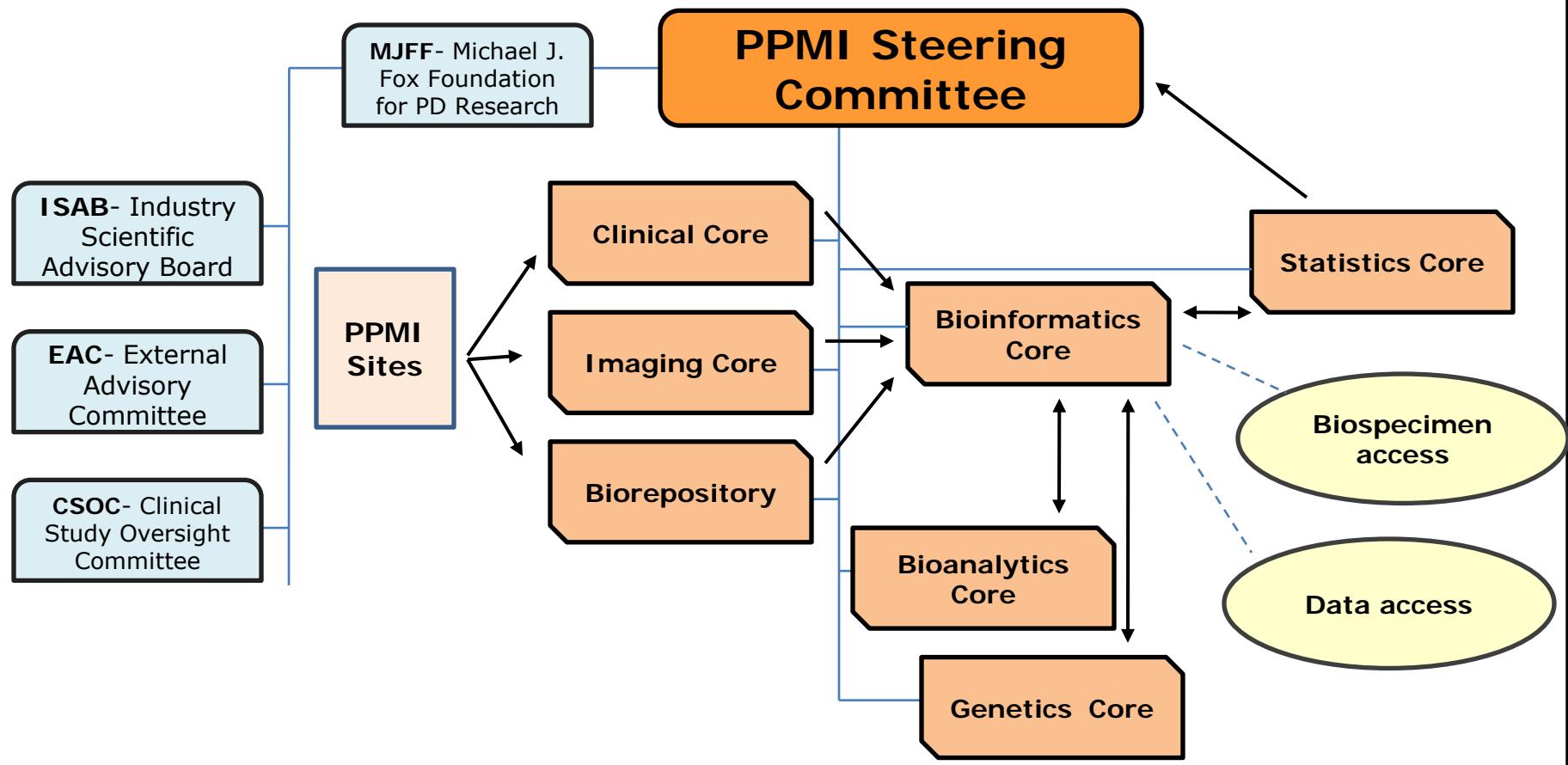


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PPMI Study



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Data Flow

- Clinical data sent to LONI from CTCC weekly
- Imaging data - > 800 DAT scans, >350 DTI
- Biospecimen -
- Genetics
- Reconciliation of different data streams



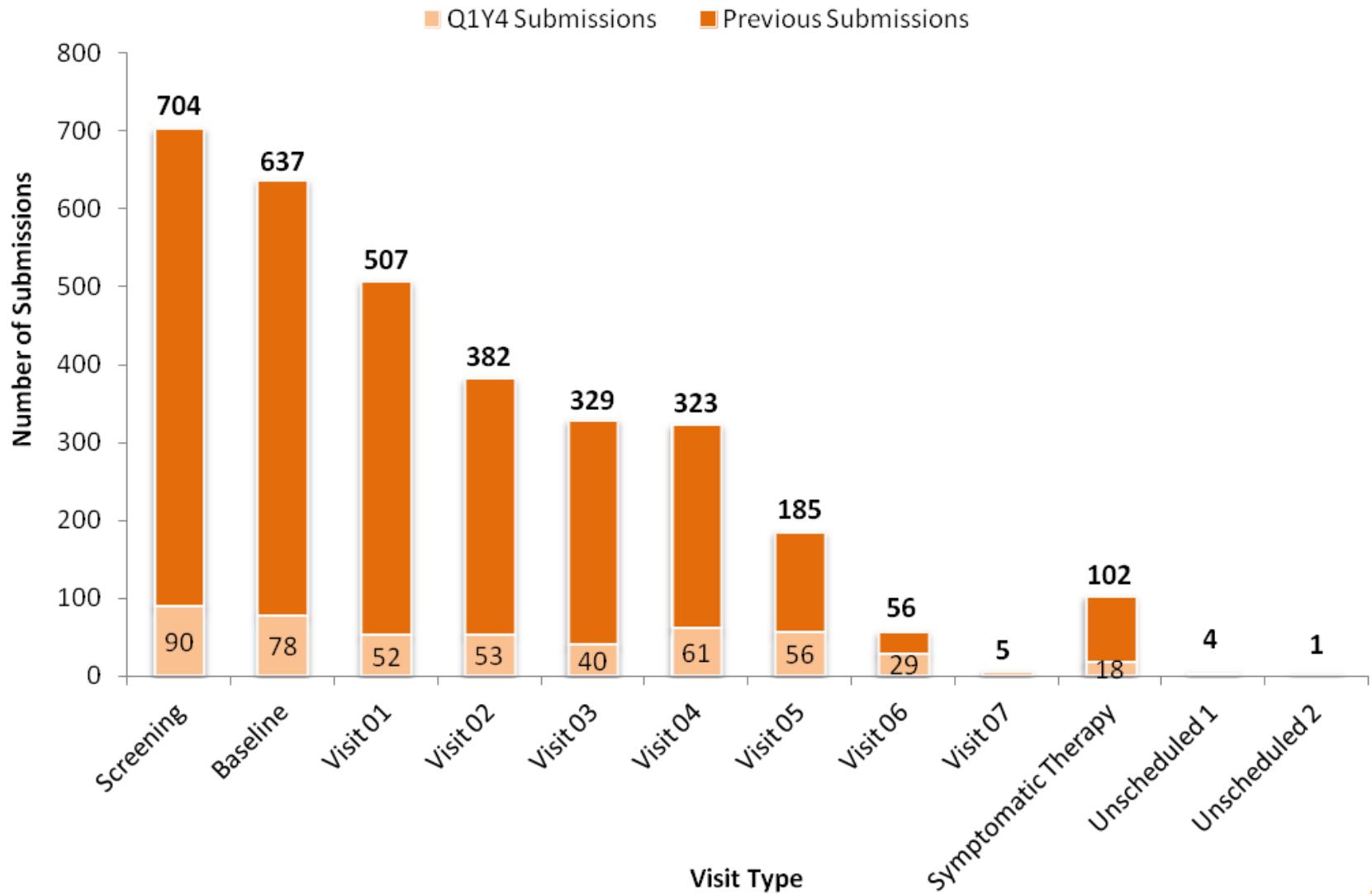
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PPMI Sample Submission Summary

3,235 submissions from 764 unique subjects



LUMBAR PUNCTURE COMPLETENESS

Group	Baseline # Expected (% Complete)	Month 6 # Expected (% Complete)	Month 12 #Expected (% Complete)	Month 24 #Expected (% Complete)
PD Subjects	383 (97%)	274 (88%)	168 (82%)	30 (70%)
Healthy Controls	182 (97%)	152 (84%)	141 (82%)	23 (74%)
SWEDD Subjects	57 (91%)	41 (76%)	21 (81%)	N/A



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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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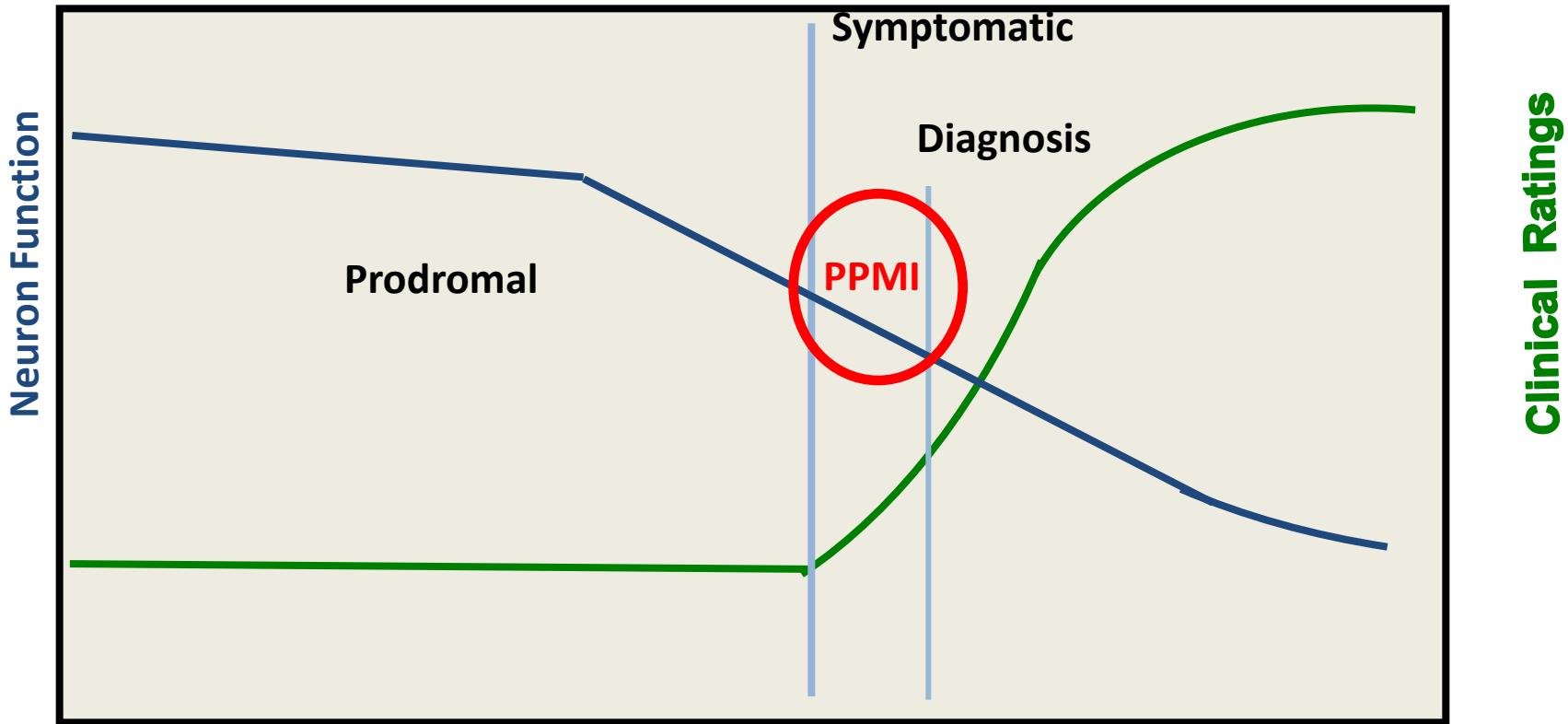


PPMI Study Details: Synopsis

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



Natural history of Parkinson's disease

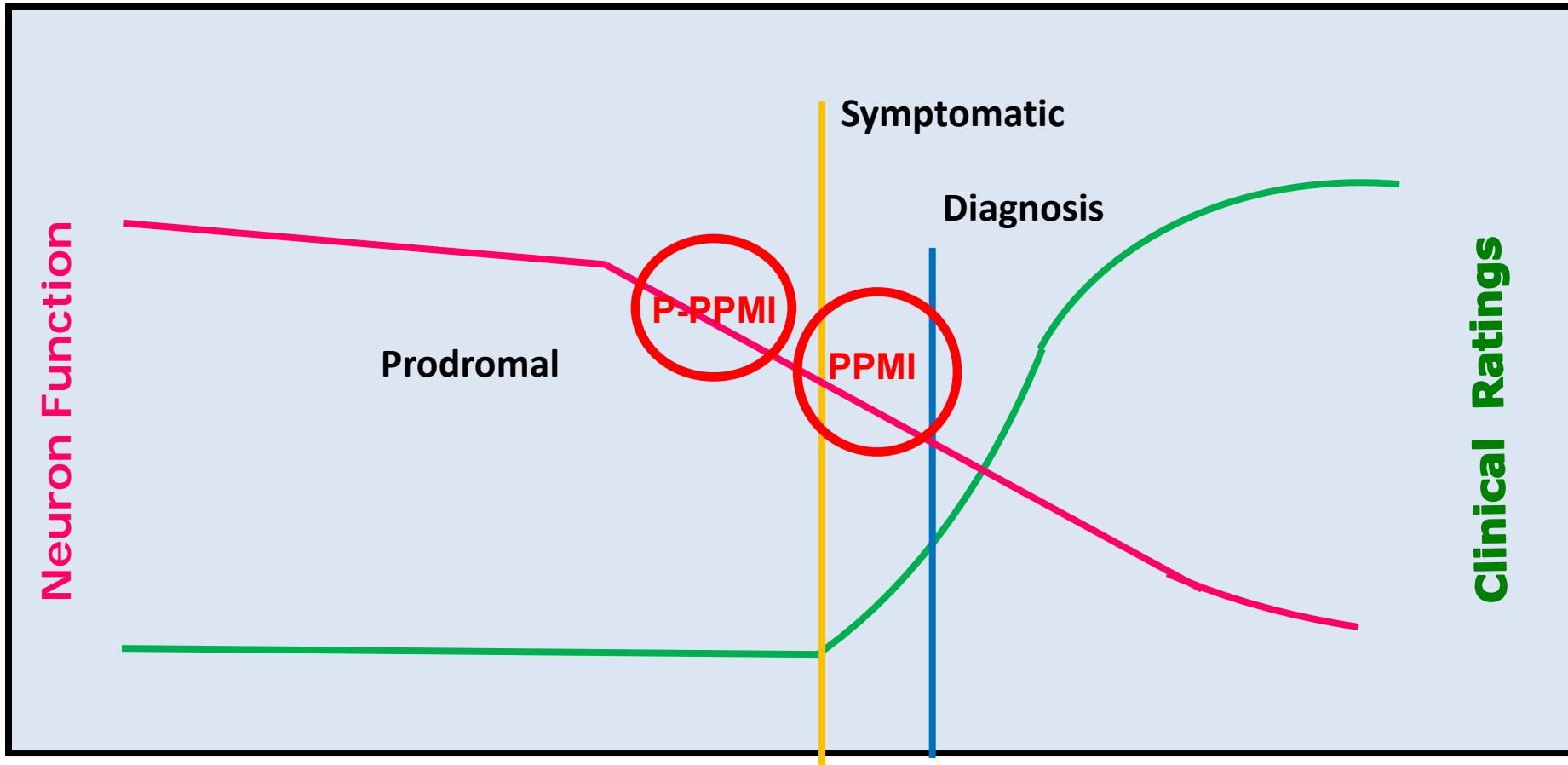


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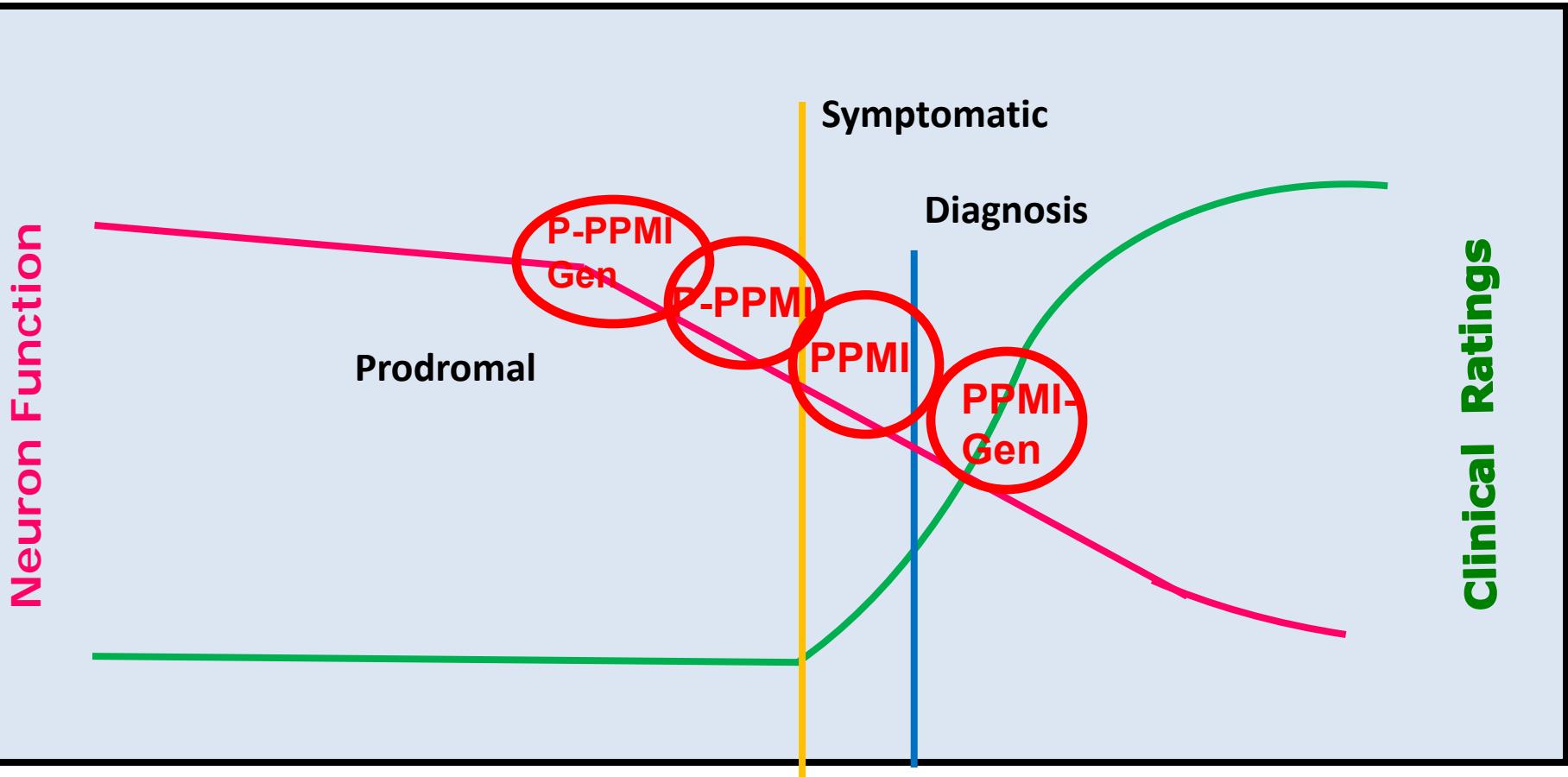
Natural history of Parkinson's disease



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Natural history of Parkinson's disease



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Standardization of data acquisition/analysis

- **Manuals/SOPs for all data acquisition**
- **Training for biosample collection and shipping, UPDRS, neuropsych, imaging acquisition and data transfer, clinical data entry.**
- **Quality control of biosamples, imaging data**



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Data/Biosample Access/Sharing

www.ppmi-info.org

- > 60,000 Data Download via website
- >20 BRC requests – 2 successful
- Query tool to facilitate download

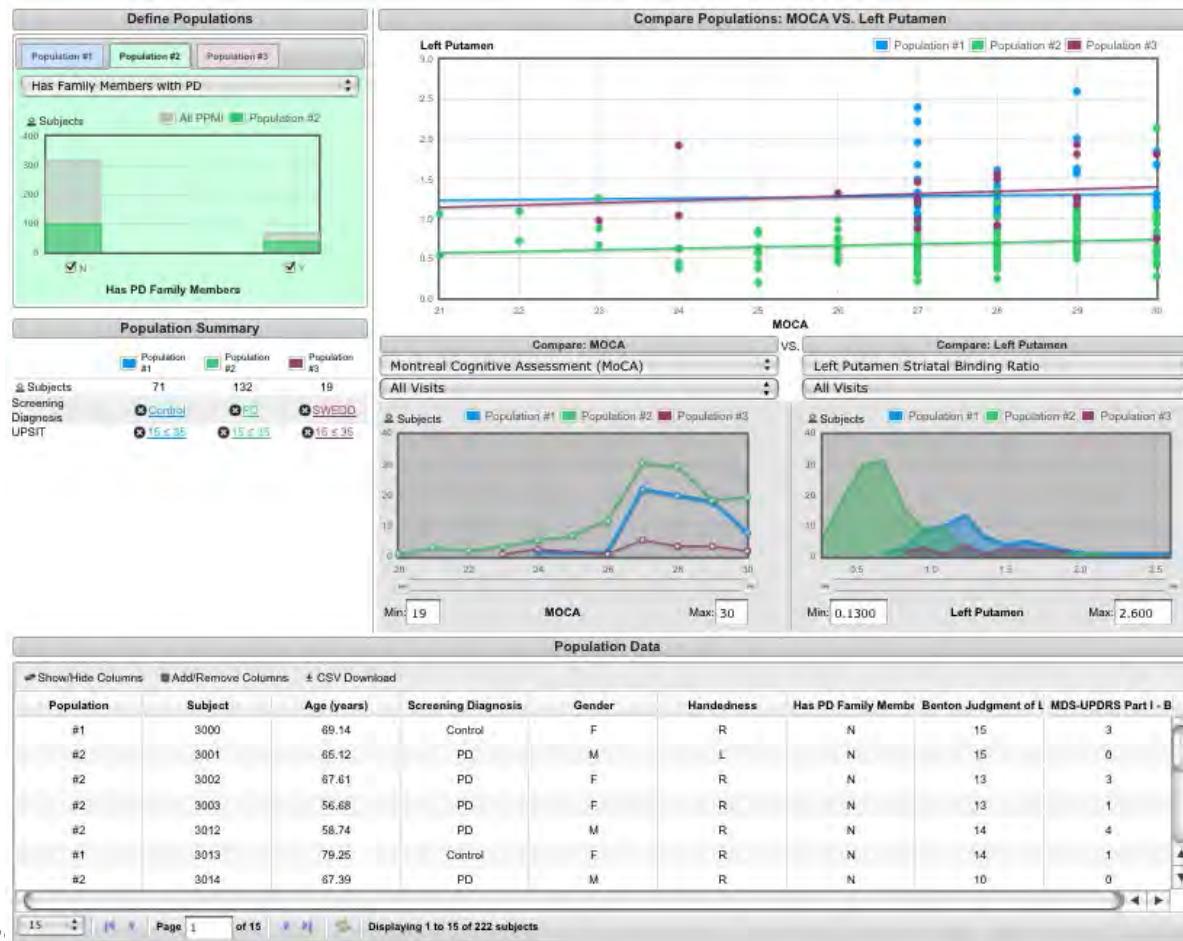


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Visual Interrogation System



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PPMI – Publication and Presentations

- PPMI publications
- Revised Publication policy and plans

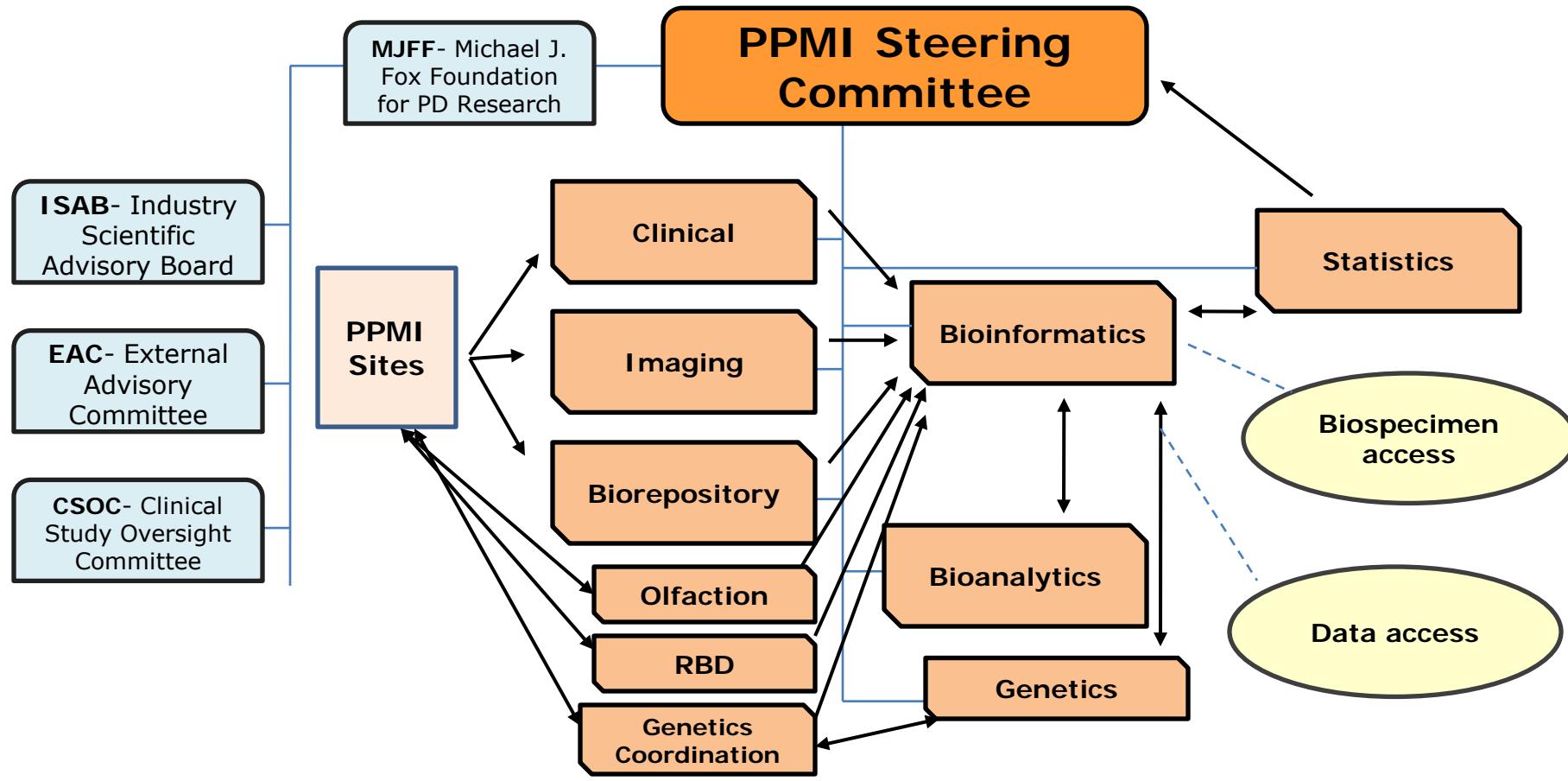


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PPMI Study



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PPMI SC and Study Cores

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



PPMI MJFF team

- **Sohini Chowdhury, PPMI Overall Project Manager**
- **Mark Frasier, PhD, Biologics (Biorepository selection; biologic collection SOPs, assay identification and optimization)**
- **Claire Meunier, Recruitment/Retention Strategies**
- **Vanessa Arnedo, Contracting, study coordination**
- **Jamie Eberling, PhD, Imaging Core and imaging SOPs**
- **Todd Sherer, PhD, MJFF CEO**
- **Debi Brooks, Industry partnership development, Media Strategies**



Industry Scientific Advisory Board (ISAB)

biogen idec

COVANCE.

Abbott
A Promise for Life

Avid
Radiopharmaceuticals

élan

GE Healthcare

Genentech
A Member of the Roche Group

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GlaxoSmithKline

Lilly

MERCK

Pfizer

Roche

ucb



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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 Sites

PPMI SITES IN THE UNITED STATES:

- Arizona PD Consortium (Sun City, AZ)
- Baylor College of Medicine (Houston, TX)
- Boston University (Boston, MA)
- Cleveland Clinic (Cleveland, OH)
- 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:

- Imperial College (London, UK)
- Innsbruck University (Innsbruck, Austria)
- Paracelsus-Elena Clinic Kassel/University of Marburg (Kassel and Marburg, Germany)
- University of Napoli (Naples, Italy)
- University of Tübingen (Tübingen, Germany)

PPMI SITES IN AUSTRALIA:

- Macquarie University (Sydney, Australia)

Sites to enroll LRRK2 and synuclein subjects will be added.



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Meeting Goals

- Review study success
 - Completed enrollment, outstanding retention
 - Clinical, Imaging, biospecimen assessments as per protocol – compliance and standardization
 - PPMI infrastructure
 - Data and Specimen available
 - New cohort and ancillary studies added
- Identify study challenges
 - Subject Retention – Longitudinal assessment
 - Enroll Prodromal
 - Establish and Enroll Genetic cohort
 - Data Quality
- Plan PPMI future – iterative study -
 - Novel analytes, imaging tools, clinical assessments, analyses
 - Prodromal implementation
 - Genetic cohort implementation
 - Publication of baseline data
 - Implement pathology core
 - Model outcomes for clinical trials



Annual Investigators Meeting

May 7/8, 2013

AGENDA

Tuesday May 7, 2013		
11:00-12:00 pm	Recruitment and Retention Meeting Rusack Room	Coordinators
<i>All sessions as of 1:00 will be held in the Matthews Room</i>		
12:00-1:00 pm	Lunch	All
1:00-1:20 pm	Welcome and Introductions	Marek, Sherer, All
1:20-1:40 pm	PPMI Status Update <ul style="list-style-type: none"> Baseline cohort Lessons learned Planned cohorts 	Marek
1:40-3:00 pm	PPMI Data <ul style="list-style-type: none"> Sites and enrolment Demographic and motor data Neuropsych/neurobehavior data LP safety/compliance 	Lazurenko, Kieburz, Coffey, Weintraub, Frank
3:00-3:15 pm	Break	All
3:15-4:30 pm	PPMI Data <ul style="list-style-type: none"> Imaging data – DaTSCAN/DTI/rsMRI Biospecimen Data – Collection, Biospecimen Review Committee, Qualification Study, CSF data and genetics 	Seibyl Scutti, Frasier, Shaw, Singleton
4:30-5:00 pm	Data Sharing/Website	Toga
5:00-5:30 pm	Ancillary Studies <ul style="list-style-type: none"> Process TAP-PD Additional assessments for prodromal phase 	Tanner, Jennings, Mirelman
5:30-6:00 pm	Report from Industry Scientific Advisory Board	Ravina
6:00 pm	Closing Remarks – Preparation for Tomorrow	Marek
6:30 pm	Cocktails and Dinner Moran's Restaurant 146 Tenth Avenue (between 19 th and 20 th streets)	All

Wednesday May 8, 2013 <i>All sessions except for Breakouts will be in the Matthews Room</i>		
7:30-8:15 am	Breakfast	All
8:15-9:00 am	Recruitment and retention <ul style="list-style-type: none"> Summary of recruitment strategies Site examples of success Approaches and challenges to retention 	Jennings, Meunier
9:00-10:00 am	Prodromal PPMI <ul style="list-style-type: none"> Status of Prodromal arm of PPMI Olfaction Process RBD Process Recruitment 	Marek, Jennings, Mayer
10:00-10:15 am	Break	
10:15-11:15 am	Inclusion of genetic cohorts in PPMI <ul style="list-style-type: none"> Plan to integrate LRRK2 and Asyn cohorts Adding family indicator Example of current data on LRRK2 and Asyn cohorts 	Marek, Foroud, Giladi, Stamelou
11:15-12:00 pm	Breakout Groups <ul style="list-style-type: none"> Biologics Imaging Neuropsych/Neurobehavior Sleep Recruitment/Retention 	Room Assignments TBD
12:00-1:00 pm	Lunch – With Breakout Groups	
1:00-2:30 pm	Report from Breakout Groups <ul style="list-style-type: none"> Biologics Imaging Neuropsych/Neurobehavior Sleep Recruitment/Retention 	
2:30-3:30 pm	Publication and planned analyses <ul style="list-style-type: none"> Publication policy Review of planned publications New analyses 	Marek
3:30-3:50 pm	Goals/Plans/Timelines	Marek
3:50-4:00 pm	Closing	Marek
4:00 pm	Departure for airport/train stations	All

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PPMI Status Update

Sites and Enrolment



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PPMI Site Status

- PPMI is global with 24 participating sites!
 - 18 in the United States
 - 2 in Germany
 - 1 in Austria
 - 1 in England
 - 1 in Italy
 - 1 in Australia



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New Since 2012

Amendment 5

- Prodromal
 - Hyposmia
 - RBD
 - LRRK2

Amendment 6

Coming soon

- LRRK2
- Synuclein
- New Sites



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PPMI Study Status

PD/HC/SW enrollment completed

PD – 430 / HC – 196 / SW - 62*

** when all baseline data is entered !*

CONGRATULATIONS



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Baseline Data Entry Status

16 sites have entered all existing screening & baseline data within 2 weeks

Sites with pending data entry	Number of Subjects with Missing pages	Total Number of Missing Pages for the site
	4	5
	1	1
	9	150
	1	23
	7	34
	1	24
	4	7
	1	2



Data Management Timelines and Tips

May 17

Screening & Baseline data

Screening & Baseline queries

Tip: Do not save pages with partial entry.

- Results in additional queries
- Results in additional work

Database/Data Entry Questions – Contact Susan Bennett

Phone: 585-273-4234 Email: susan.bennett@chet.rochester.edu



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Contact for CTCC

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Alice Rudolph

Assistant Project Manager

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Susan Bennett

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Phone: 585-273-4234

Email: susan.bennett@chet.rochester.edu



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THANK YOU!!

- To the site staff for your time, your patience, your hard work and dedication!
- To the participants for volunteering, for their time, for their contributions to research!



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PPMI Data Overview

Christopher S. Coffey
The University of Iowa

Karl Kieburtz
The University of Rochester

PPMI Investigators Meeting
May 7, 2013
New York, NY



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OVERVIEW

Source of data for this presentation:

- Information comes from:
 - Tables produced for CSOC report
 - Tables produced for monthly review by steering committee
- All data comes from a data freeze based on data obtained from the LONI website on 04/01/2013



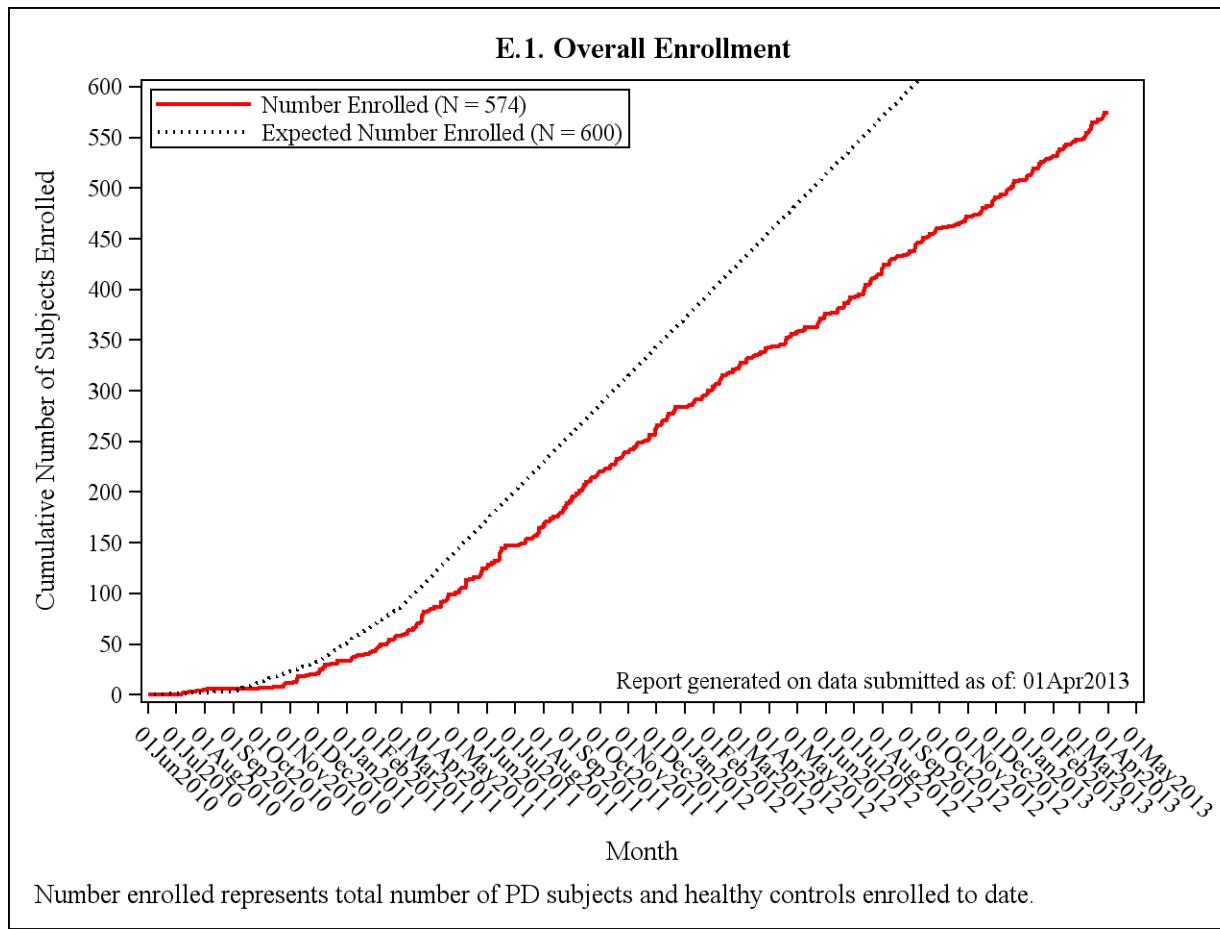
ENROLLMENT

Group	Consented	Enrolled	Pending	Excluded/ Declined
PD Subjects	478	390	32	53
Healthy Controls	229	184	6	39
SWEDD Subjects	78	58	3	17

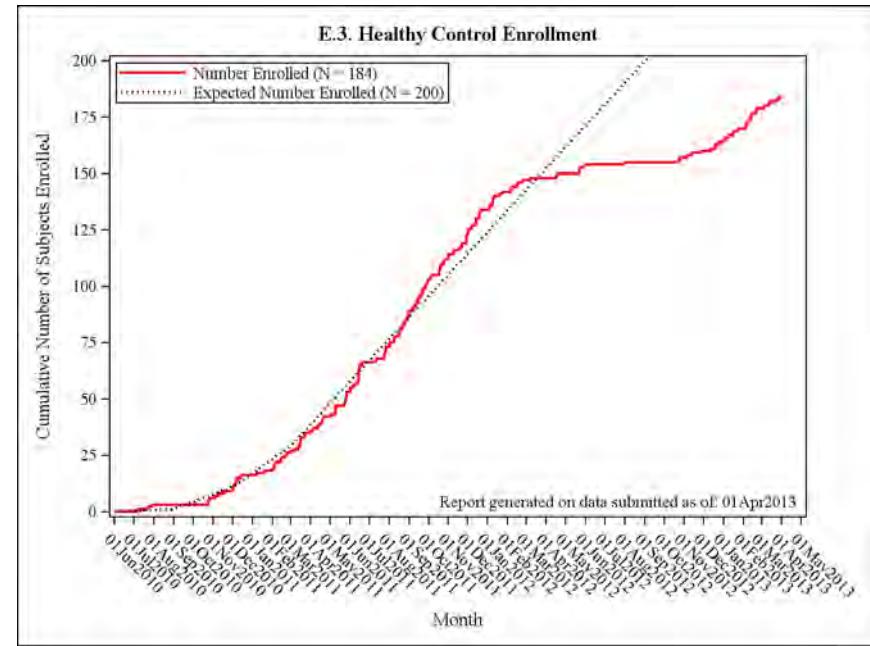
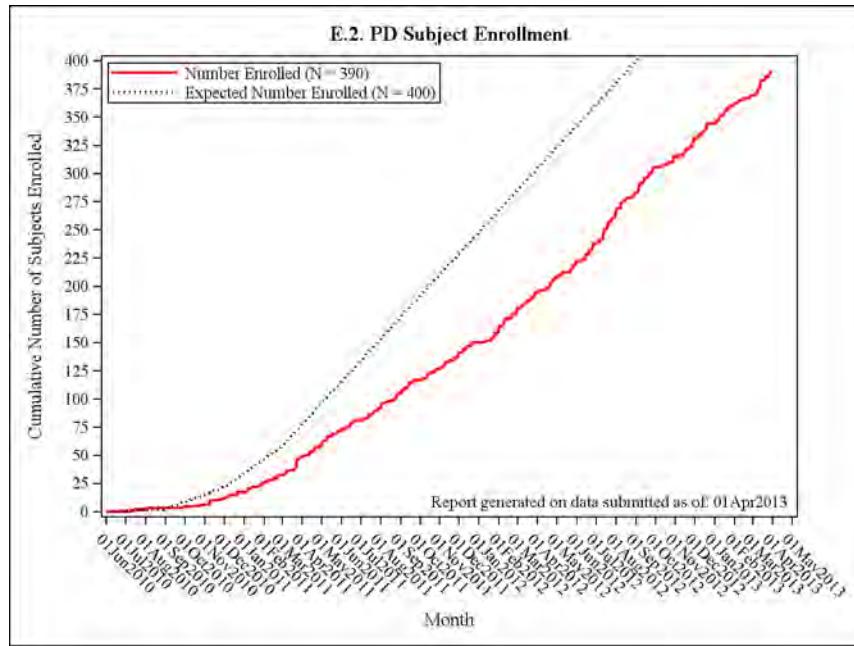
632 Total Subjects
Enrolled



ENROLLMENT



ENROLLMENT



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DaTSCAN AVAILABILITY ISSUES

For some subjects, a DaTSCAN was not performed at the same time as the baseline clinical assessments.

Reasons:

- DaTSCAN was unavailable in the United States from 01/27/2011 to 06/23/2011
- German sites did not obtain Radiation safety approval to proceed with scans for healthy controls until March 2012.



DaTSCAN AVAILABILITY ISSUES

For PD and SWEDD subjects, CSOC agreed that the scan could be counted as complete ***if conducted within 4 months of baseline.***

For HC subjects, CSOC agreed that the scan could be counted as complete ***if conducted within 12 months of baseline.***



BASELINE DATA COMPLETENESS

- 527 (83%) have all baseline information entered into the publicly-accessible database
 - 624 (99%) have cognitive testing
 - 617 (98%) have a blood sample
 - 617 (98%) have all clinical forms entered
 - 614 (97%) have a urine sample
 - 611 (97%) have a DaTSCAN
 - 599 (95%) have a lumbar puncture
 - 578 (91%) have an MRI

Actual numbers likely higher – important for all baseline data entry to be completed ASAP.



GENDER/AGE DISTRIBUTION

Healthy Controls and SWEDDs Vs PD Enrollment:

Group	PD Enrolled	Healthy Enrolled	HCs Expected Based on PD Enrollment*	SWEDD Enrolled	SWEDDs Expected Based on PD Enrollment **
Male / <56	61	31	28.8	12	9.1
Male / 56-65	93	49	43.9	8	13.8
Male / >65	101	38	47.7	15	15.0
Female / <56	43	24	20.3	10	6.4
Female / 56-65	49	25	23.1	8	7.3
Female / >65	43	17	20.3	5	6.4

* p-value 0.72

** p-value 0.41



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DEMOGRAPHIC CHARACTERISTICS

	PD Subjects (N = 390)	Healthy Controls (N = 184)	SWEDD Subjects (N = 58)	
Males	255 (65%)	118 (64%)	35 (60%)	
Age (mean)	62	60	60	p = 0.11
• <56 years	104 (27%)	55 (30%)	22 (38%)	
• 56-65 years	127 (33%)	67 (36%)	12 (21%)	
• >65 years	159 (41%)	62 (34%)	24 (41%)	
Hispanic/Latino	9 (2%)	3 (2%)	2 (3%)	
Race				
• Caucasian	361 (93%)	171 (93%)	54 (93%)	
• African-American	4 (1%)	9 (4%)	1 (2%)	
• Asian	7 (2%)	1 (1%)	1 (2%)	
• Other	18 (4%)	3 (2%)	2 (3%)	



BASELINE CHARACTERISTICS

	PD Subjects (N = 390)	Healthy Controls (N = 184)	SWEDD Subjects (N = 58)
UPDRS Part III	21.1	1.3	14.6
MOCA Total	27.1	28.2	26.9
GDS Total	2.2	1.3	3.5
SCOPA AUT	9.5	5.8	14.1
REM Sleep disorder (Positive: 5 or above)	38%	20%	41%
UPSIT Raw Score	22.2	33.9	31.2



MOTOR CHARACTERISTICS

	PD Subjects (N = 390)	Healthy Subjects (N = 184)	SWEDD Subjects (N = 58)
Family Hx of PD	97 (25%)	10 (5%)	17 (29%)
Mn duration of disease	7 months	N/A	8 months
Mn MDS-UPDRS score			
• Total score	32.5	4.7	29.2
• Part I	5.5	3.0	8.7
• Part II	5.9	0.4	6.0
• Part III (Motor Exam)	21.1	1.3	14.6
Mn Modified Schwab	93	N/A	95
Hoehn & Yahr			
• Stage 1	168 (43%)	179 (97%)	34 (59%)
• Stage 2	216 (55%)	2 (1%)	24 (41%)
• Stage 3-5	2 (1%)	0 (0%)	0 (0%)



VISIT COMPLIANCE

Group	Month 6 # Expected (% Seen)	Month 12 # Expected (% Seen)	Month 24 # Expected (% Seen)
PD Subjects	274 (95%)	168 (94%)	30 (83%)
Healthy Controls	152 (96%)	141 (98%)	23 (91%)
SWEDD Subjects	41 (85%)	21 (100%)	N/A



LUMBAR PUNCTURE COMPLETENESS

Group	Baseline # Expected (% Complete)	Month 6 # Expected (% Complete)	Month 12 #Expected (% Complete)	Month 24 #Expected (% Complete)
PD Subjects	383 (97%)	274 (88%)	168 (82%)	30 (70%)
Healthy Controls	182 (97%)	152 (84%)	141 (82%)	23 (74%)
SWEDD Subjects	57 (91%)	41 (76%)	21 (81%)	N/A



PROTOCOL DEVIATIONS

PD Subjects: 55 protocol deviations (in 49 subjects)

- 28 due to eligibility criteria
- 12 due to DaTSCAN (dosage)
- 5 due to Lumbar Puncture
- 3 due to research specimen(s)
- 3 due to MRI not done
- 2 due to clinical labs
- 2 due to 'Other' (CSF testing for hemoglobin)



PROTOCOL DEVIATIONS

Controls: 44 protocol deviations (in 38 subjects)

- 18 due to eligibility criteria
- 14 due to DaTSCAN (dosage)
- 5 due to lumbar puncture
- 3 due to research specimen(s)
- 2 due to clinical labs
- 1 due to MRI not done
- 1 due to PET Scan



PROTOCOL DEVIATIONS

SWEDD Subjects: 10 protocol deviations
(in 10 subjects)

- 4 due to eligibility criteria
- 3 due to DaTSCAN (dosage)
- 1 due to lumbar puncture
- 1 due to MRI not done
- 1 due to “Other”



EARLY STUDY TERMINATIONS

PD Subjects: 5 early study terminations

- 2 due to adverse event
(headache, exasperation of PD symptoms)
- 2 due to ‘other’
 - “patient decided to take anti-parkinsonian medication today”
 - “patient decided not to continue in study due to job and time commitment”
- 1 due to withdrawn consent

Healthy Controls: 6 early study terminations

- 2 withdrew consent
- 2 deaths
- 1 lost to follow-up
- 1 due to ‘other’ (unwilling to comply with lumbar puncture)



REPORTABLE EVENTS

PD Subjects: 164 reportable events (158 subjects)

- 152 due to starting PD meds
- 6 due to early withdrawals
- 5 due to starting another study
- 1 due to an SAE

Healthy Controls: 17 reportable events (14 subjects)

- 8 due to early withdrawal
- 5 due to change of diagnosis
- 3 due to death
- 1 started another study



REPORTABLE EVENTS

SWEDD Subjects: 26 reportable events (26 subjects)

- 25 due to change of diagnosis
- 1 due to starting PD meds

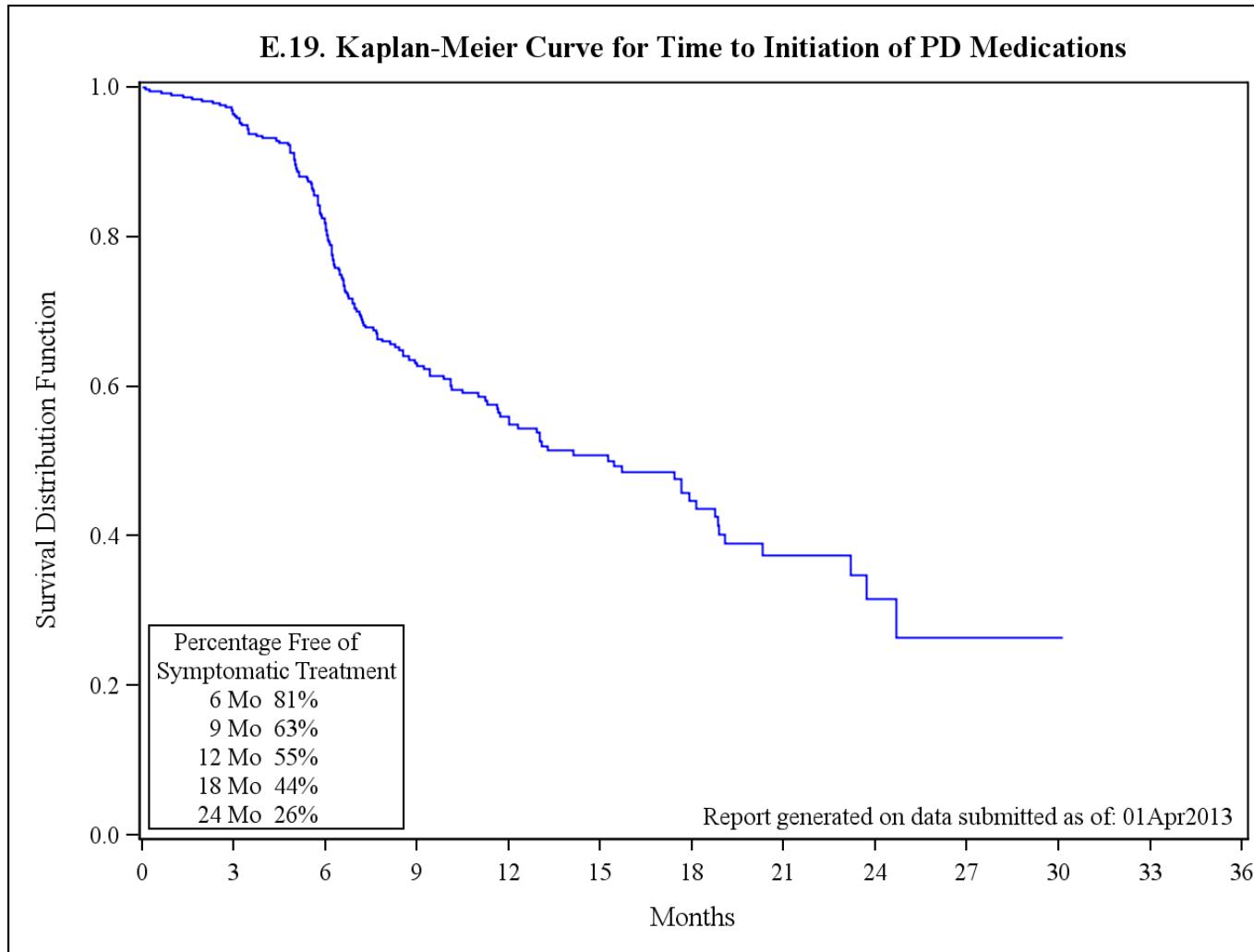


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TIME TO START PD MEDICATIONS



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ADVERSE EVENTS

PD Subjects: 189 adverse events (in 109 subjects)

- 153 LP-related AE's
 - 49 occurrences of "Headache"
 - 35 occurrences of "Injection Site Pain"
 - 21 occurrences of "Post Lumbar Puncture Syndrome"
 - 10 occurrences of "Back Pain"
- 4 DaTSCAN-related AE's

Healthy Controls: 131 adverse events (in 67 subjects)

- 110 LP-related AE's
 - 36 occurrences of "Headache"
 - 24 occurrences of "Injection Site Pain"
 - 13 occurrences of "Back Pain"
 - 12 occurrences of "Post Lumbar Puncture Syndrome"
- 7 DaTSCAN-related AE's



ADVERSE EVENTS

SWEDD Subjects: 29 adverse events (in 18 subjects)

- 23 LP-related AE's
 - 9 occurrences of "Headache"
- 3 DaTSCAN-related AE's



ADVERSE EVENTS PD vs HC

➤ Subjects with an AE:

- PD Subjects – 109/390 (28%)
- Healthy Controls – 67/184 (36%)
- RR = 0.77, 95% CI: (0.60, 0.99)

➤ Subjects with an LP-related AE:

- PD Subjects – 97/390 (25%)
- Healthy Controls – 64/184 (35%)
- RR = 0.72, 95% CI: (0.55, 0.94)

**Control Subjects
More Likely to Report
LP-Related AEs**

➤ Subjects with a DaTSCAN-related AE:

- PD Subjects – 4/390 (1%)
- Healthy Controls – 5/184 (3%)
- RR = 0.37, 95% CI: (0.10, 1.36)



ADVERSE EVENTS PD vs. SWEDD

- Subjects with an AE:
 - PD Subjects – 109/390 (28%)
 - SWEDD Subjects – 18/58 (31%)
 - RR = 0.90, 95% CI: (0.59, 1.36)
- Subjects with an LP-related AE:
 - PD Subjects – 97/390 (25%)
 - SWEDD Subjects – 16/58 (28%)
 - RR = 0.90, 95% CI: (0.57, 1.41)
- Subjects with a DaTSCAN-related AE:
 - PD Subjects – 4/390 (1%)
 - SWEDD Subjects – 3/58 (5%)
 - RR = 0.19, 95% CI: (0.04, 0.83)

**SWEDD Subjects
More Likely to Report
DaTSCAN-Related
AEs**



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SERIOUS ADVERSE EVENTS

PD Subjects: 2 serious adverse events (in 1 subject)

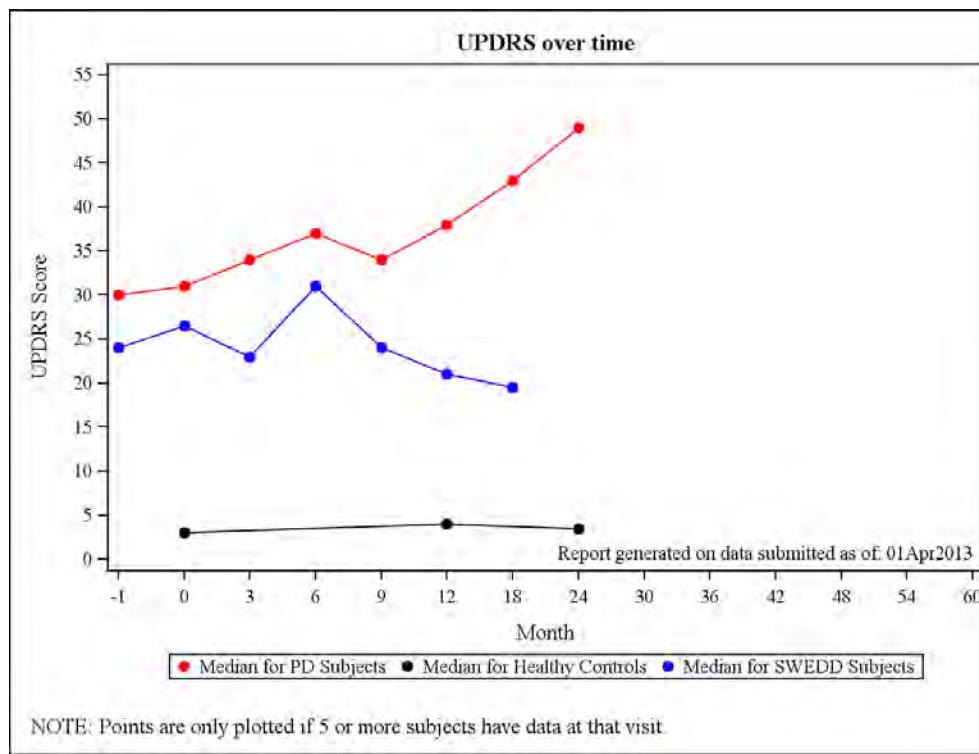
- 1 'Colitis' and 1 'Pancreatitis'
- None related to LP or DaTSCAN

Healthy Controls: No serious adverse events to date

SWEDD Subjects: No serious adverse events to date



UPDRS OVER TIME



Group	Baseline Median (N) (Min, Max)	Month 3 Median (N) (Min, Max)	Month 6 Median (N) (Min, Max)	Month 9 Median (N) (Min, Max)	Month 12 Median (N) (Min, Max)	Month 18 Median (N) (Min, Max)	Month 24 Median (N) (Min, Max)
PD	31 (384) (7, 72)	34 (320) (7, 79)	37 (268) (8, 94)	34 (175) (9, 89)	38 (167) (12, 89)	43 (103) (8, 101)	49 (40) (21, 86)
HC	3 (181) (0, 20)	N/A	N/A	N/A	4 (139) (0, 25)	N/A	3.5 (24) (1, 14)
SWEDD	26.5 (58) (4, 91)	23 (45) (6, 62)	31 (35) (4, 105)	24 (33) (2, 77)	21 (26) (3, 75)	19.5 (6) (12, 35)	N/A

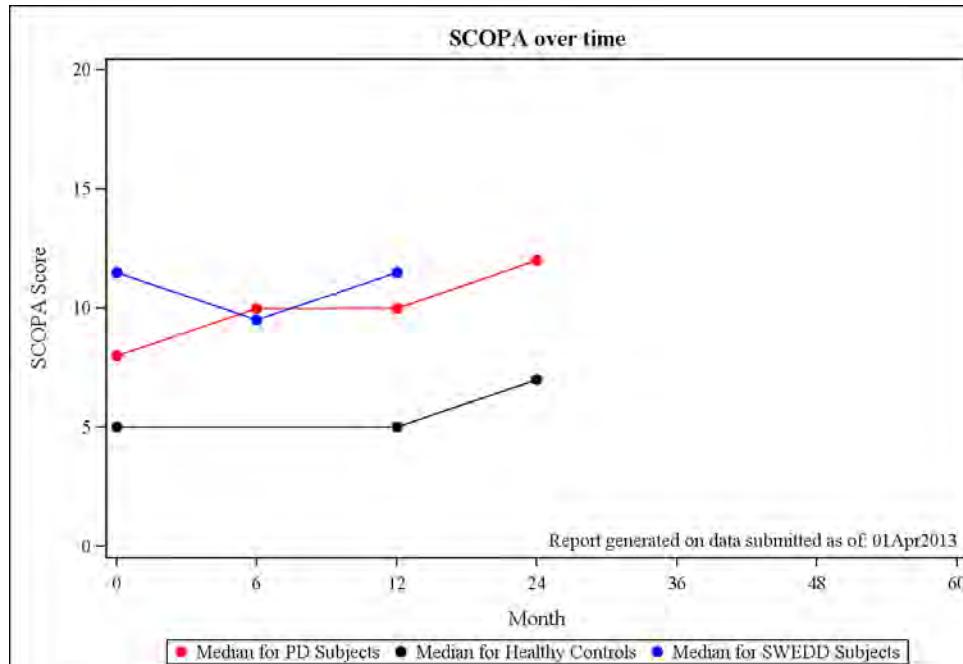
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SCOPA-AUT OVER TIME

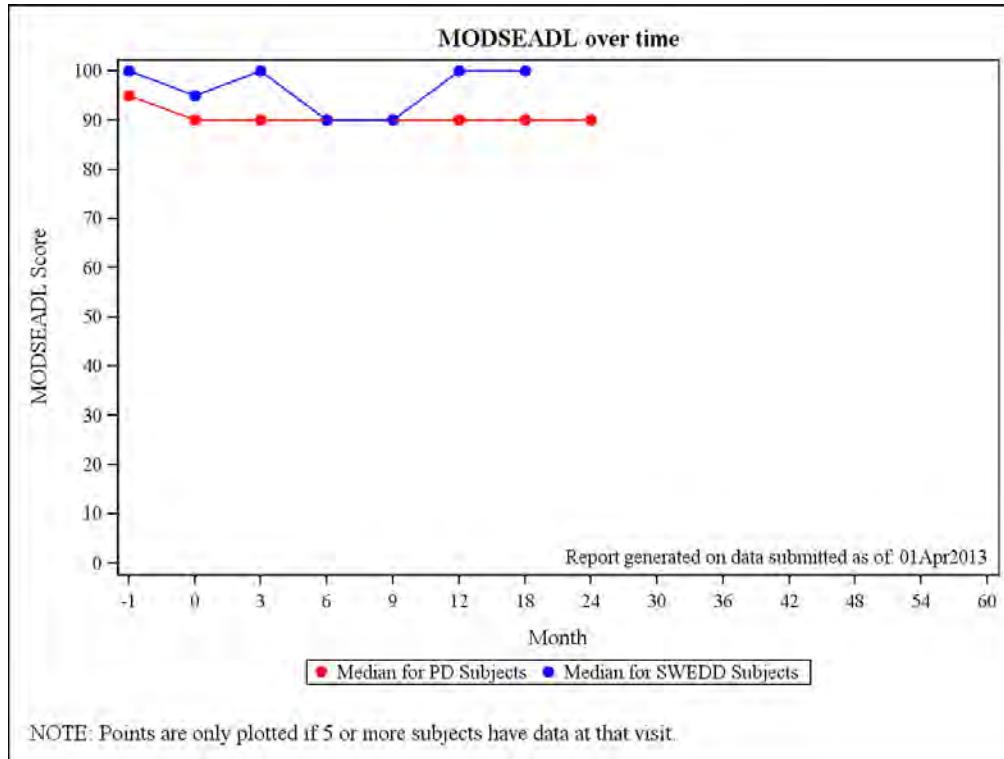


NOTE: Points are only plotted if 5 or more subjects have data at that visit.

Group	Baseline Median (N) (Min, Max)	Month 6 Median (N) (Min, Max)	Month 12 Median (N) (Min, Max)	Month 24 Median (N) (Min, Max)
PD	8 (386) (0, 39)	10 (284) (0, 34)	10 (175) (0, 30)	12 (41) (2, 32)
HC	5 (181) (0, 20)	N/A	5 (139) (0, 22)	7 (24) (0, 18)
SWEDD	11.5 (58) (2, 44)	9.5 (36) (0, 39)	11.5 (26) (2, 42)	N/A



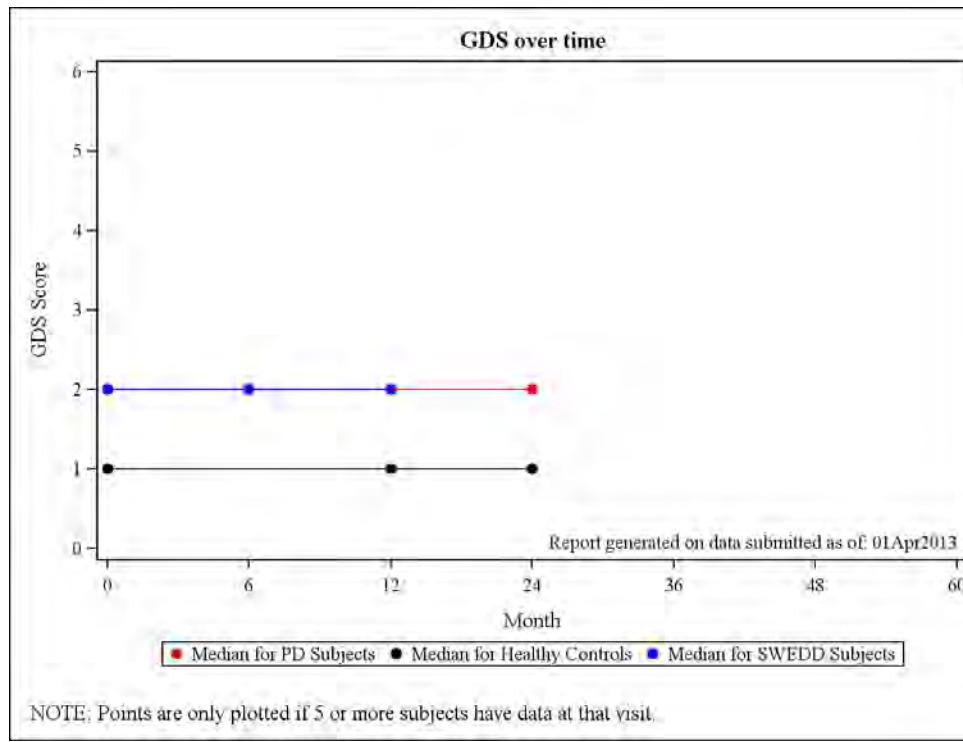
MODSEADL OVER TIME



Group	Baseline Median (N) (Min, Max)	Month 3 Median (N) (Min, Max)	Month 6 Median (N) (Min, Max)	Month 9 Median (N) (Min, Max)	Month 12 Median (N) (Min, Max)	Month 18 Median (N) (Min, Max)	Month 24 Median (N) (Min, Max)
PD	90 (386) (70, 100)	90 (322) (70, 100)	90 (268) (60, 100)	90 (174) (60, 100)	90 (170) (70, 100)	90 (101) (70, 100)	90 (39) (65, 100)
SWEDD	95 (58) (75, 100)	100 (45) (80, 100)	90 (36) (70, 100)	90 (33) (60, 100)	100 (26) (70, 100)	100 (6) (90, 100)	N/A

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GDS OVER TIME



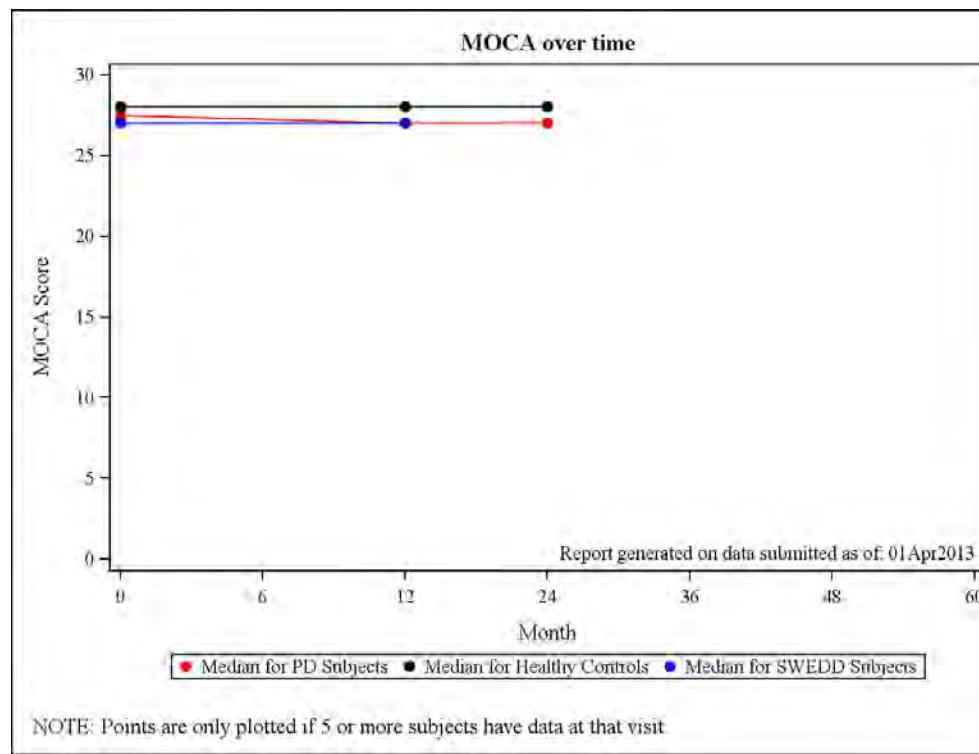
Group	Baseline Median (N) (Min, Max)	Month 6 Median (N) (Min, Max)	Month 12 Median (N) (Min, Max)	Month 24 Median (N) (Min, Max)
PD	2 (385) (0, 14)	2 (284) (0, 15)	2 (175) (0, 14)	2 (41) (0, 10)
HC	1 (182) (0, 15)	N/A	1 (139) (0, 15)	1 (24) (0, 3)
SWEDD	2 (58) (0, 14)	2 (36) (0, 14)	2 (26) (0, 11)	N/A



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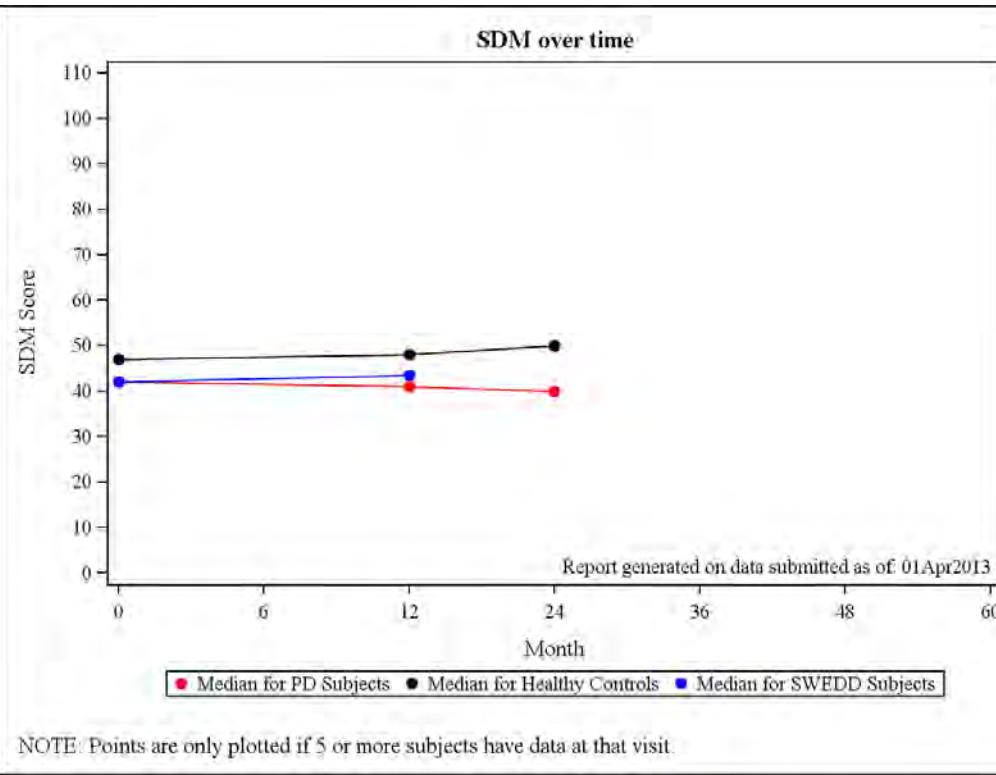
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MOCA OVER TIME



Group	Baseline Median (N) (Min, Max)	Month 12 Median (N) (Min, Max)	Month 24 Median (N) (Min, Max)
PD	27.5 (384) (17, 30)	27 (172) (15, 30)	27 (37) (14, 30)
HC	28 (184) (26, 30)	28 (139) (20, 30)	28 (24) (22, 30)
SWEDD	27 (58) (17, 30)	27 (26) (21, 30)	N/A

SDM OVER TIME



Group	Baseline Median (N) (Min, Max)	Month 12 Median (N) (Min, Max)	Month 24 Median (N) (Min, Max)
PD	42 (385) (7, 82)	41 (175) (11, 70)	40 (38) (18, 60)
HC	47 (182) (20, 83)	48 (139) (25, 83)	50 (24) (29, 70)
SWEDD	42 (58) (19, 71)	43.5 (26) (19, 59)	N/A



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COMPARISONS W/ STARTING PD MEDS

Examine risk factors for starting PD medications after baseline:

	Started Meds (N = 152)	Did Not Start Meds (N = 238)	
GDS Score	2.33	2.16	
MODSEADL	91.35	94.20	p < 0.001
SCOPA	9.66	9.44	
UPDRS Total	36.22	30.00	p < 0.001
MoCA Score	27.01	27.24	
SDM Score	41.53	41.15	



COMPARISONS W/ STARTING PD MEDS

Examine risk factors for starting PD medications after 6 months:

	Started Meds (N = 93)	Did Not Start Meds (N = 133)	
GDS Score (6 mos)	2.53	2.36	
MODSEADL (6 mos)	90.60	93.87	p = 0.02
SCOPA (6 mos)	10.74	9.57	
UPDRS Total (6 mos)	42.28	33.45	p < 0.001

PPMI Cognitive-Behavioral Working Group



Membership

Daniel Weintraub – WG Chair

Tanya Simuni – Steering Committee

Shirley Lasch – IND

Chris Coffey, Eric Foster – Statistics Core

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Alastair Reith

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Michael Ward

Paolo Barone

Regan Fong

Doug Galasko

Sandeep Gupta

Susanne Ostrowitzki

Thomas Comery

Tony Wei-hsiu Ho

William Cho

John Sims

Michelle York



Organization

- Study assessments and outcome measures
- Preliminary results
- Analysis and publication plan



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Study Assessments and Outcome Measures



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PPMI Behavioral Assessments

- Geriatric Depression Scale (GDS-15)
- State-Trait Anxiety (STAI)
- Impulse control disorder (ICD) symptoms (QUIP)
- Olfaction (UPSIT)
- Daytime sleepiness (ESS)
- RBD (REM Sleep Disorder Questionnaire)
- Autonomic symptoms (SCOPA-AUT)



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PPMI Cognitive Assessments

- Global - Montreal Cognitive Assessment (MoCA)
- Memory - Hopkins Verbal Learning Test (HVLT)
- Visuospatial - Benton Judgment of Line Orientation (JOLO)
- Working memory - Letter-Number Sequencing (LNS)
- Executive - Semantic fluency (animals, fruits, vegetables)
- Attention - Symbol-Digit Modalities Test (SDMT)



Addition of Cognitive Diagnosis

- Initially unable to diagnose mild cognitive impairment (MCI) or dementia in PPMI
- These diagnoses of clinical relevance in PD
 - Categorization more clinically meaningful than change in cognitive test score
- MDS recommended criteria for both PD dementia (2007) and MCI (2012) now exist



MDS Criteria for MCI and Dementia

MCI (Level 1)

- Report of cognitive decline from premorbid status
- Impaired cognitive performance
 - At least 2 test scores 1-2 SD below the standardized mean
 - Single or multiple domains
- *No significant* functional impairment resulting from cognitive decline

Dementia

- Report of cognitive decline from premorbid status
- Impaired cognitive performance
 - Impairment in at least 2 cognitive domains
- *Significant* functional impairment resulting from cognitive decline



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Steps for Determining Annual Cognitive Diagnosis in PPMI

1. Investigator determines presence of cognitive decline from pre-PD state based on clinical interview and knowledge of patient
2. Investigator determines presence of *significant* functional impairment due to cognitive deficits interfering with routine instrumental activities of daily living (IADLs)
3. Subject has neuropsychological testing at study visit
4. Categorization of normal cognition, MCI, or dementia made centrally based on steps #1, #2 and #3



CRF for Cognitive Decline and Functional Impairment

PPMI COGNITIVE CATEGORIZATION											
SUBJECT ID	<input type="text"/>	<input type="text"/>	<input type="text"/>	VISIT NO	<input type="text"/>	<input type="text"/>	<input type="text"/>				
INITIALS	<input type="text"/>	<input type="text"/>	<input type="text"/>	SITE NO	<input type="text"/>	<input type="text"/>	<input type="text"/>	VISIT DATE	<input type="text"/>	<input type="text"/>	<input type="text"/>
					MM	DD	YYYY				

Determining Report of Cognitive Decline

Based on information provided by the subject, the informant, or based on the site Investigator's knowledge of the subject, determine whether or not the subject has experienced a decline in cognition compared with pre-morbid abilities (i.e., pre-PD). Do not review cognitive testing results for this assessment; base the determination just on the clinical interview. The following cognitive abilities should be considered:

<u>Attention:</u>	Ability to sustain and direct attention, lapses
<u>Memory:</u>	Registration, recall of recent events or important dates, new learning ability, misplacement of items, forgetting items
<u>Orientation:</u>	Forgetting appointments, estimating time, spatial or geographical orientation
<u>Executive abilities:</u>	Reasoning ability, making decisions, following instructions, difficulty with calculations
<u>Praxis:</u>	Constructional or mechanical cognitive ability, such as use of tools and appliances
<u>Language:</u>	Word finding problems, problems with naming or comprehension).

1. Does the subject have presence of cognitive decline? (0 = No, 1 = Yes)

Determining Functional Impairment

Based on information provided by the subject, the informant, or based on the site Investigator's knowledge of the subject, determine whether or not the subject has experienced a decline in functional abilities (*from a cognitive standpoint*) to the extent of demonstrating impairment in performing instrumental activities of daily living, examples of which include: driving, managing finances, managing medications, shopping, food preparation, participation in hobbies and employment.

2. Does the subject have presence of functional impairment? (0 = No, 1 = Yes)

Impairment on Cognitive Testing

4 domains and 6 test scores:

Memory (HVLT (# words and recognition discrimination))

Visuospatial (JOLO (correct responses))

Working Memory-Executive (LNS (correct responses) and semantic fluency (# words))

Attention-Processing Speed (SDMT (correct responses))

MCI – At least 2 test scores >1.0 SD (16th %ile) below the standardized mean, regardless domain(s)

Dementia – At least 1 test score from any 2 domains >1.5 SD (7th %ile) below the standardized mean



Assigning Cognitive Diagnosis

Normal Cognition (PD-NC)

X / ✓^b Report cognitive decline

X / ✓^b Cognitive impairment

X / ✓^b Functional impairment

Mild Cognitive Impairment (PD-MCI)

✓ Report cognitive decline

✓ Cognitive impairment

X Functional impairment

Dementia (PDD)

✓ Report cognitive decline

✓ Cognitive impairment

✓ Functional impairment

^b PD-NC should be based on not meeting criteria for either PD-MCI or PDD.



Preliminary Results



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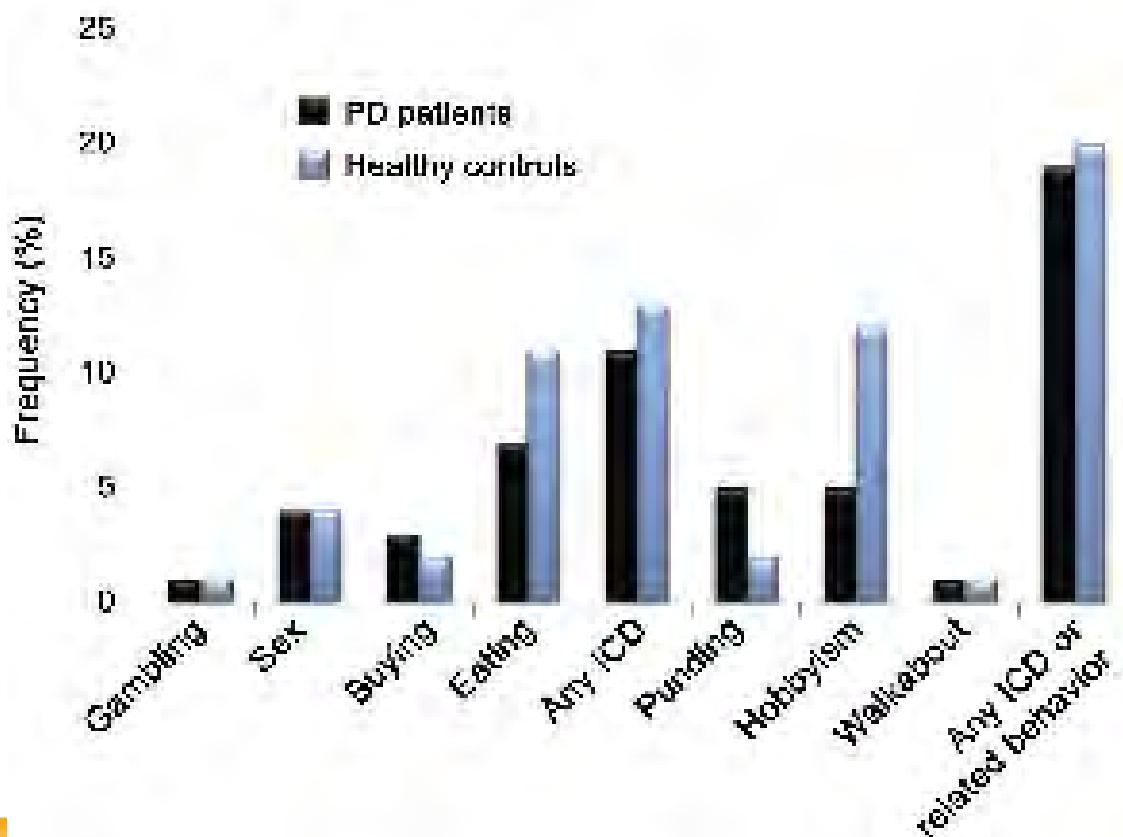
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Screening for impulse control symptoms in patients with de novo Parkinson disease

Case-control study

Daniel Weintraub, MD
Kimberly Papay, BS
Andrew Siderowf, MD,
MSCE
For the Parkinson's
Progression Markers
Initiative



There were no statistically significant differences found for frequencies of ICD or related behavior symptoms between PD patients and HCs ($p \geq 0.05$), except for hobbyism, which was more common in HCs ($p=0.04$).

Preliminary Baseline Results - MoCA

	PD	HC	SWEDD	p value
MOCA Total Score				<0.01
Mean	27.1	28.2	26.9	
(Min, Max)	(17, 30)	(26, 30)	(17, 30)	
Missing	6	0	0	



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MoCA Cut-off Scores *in PD*

MoCA	Frequency	Percentage	Cumulative Frequency	Cumulative Percent
17	1	0.26	1	0.26
19	1	0.26	2	0.52
20	2	0.52	4	1.04
21	5	1.30	9	2.34
22	8	2.08	17	4.43
23	13	3.39	30	7.81
24	13	3.39	43	11.20
25	36	9.38	79	20.57
26	49	12.76	128	33.33
27	64	16.67	192	50.00
28	68	17.71	260	67.71
29	70	18.23	330	85.94
30	54	14.06	384	100.00

Consistent with research reporting 15-20% of de novo PD patients have MCI.



Preliminary Baseline Results – Neuropsychological Battery

Variable	Enrolled Subjects			
	PD Subjects (N = 390)	Healthy Controls (N = 184)	SWEDD Subjects (N = 58)	p-value (PD vs. HC)
MOCA Total Score	<0.01			
Mean	27.1	28.2	26.9	
(Min, Max)	(17, 30)	(26, 30)	(17, 30)	
Missing	6	0	0	
Benton Judgment of Line Orientation Score	0.03			
Mean	12.7	13.1	12.8	
(Min, Max)	(5, 15)	(4, 15)	(5, 15)	
Missing	5	2	0	
HVLT Immediate Recall	<0.01			
Mean	9.7	10.2	9.7	
(Min, Max)	(4, 12)	(6, 12)	(5, 12)	
Missing	6	2	0	
HVLT Delayed Recognition	<0.01			
Mean	11.2	11.5	10.8	
(Min, Max)	(0, 12)	(8, 12)	(0, 12)	
Missing	7	2	0	
HVLT Delayed False Alarms	0.20			
Mean	1.2	1.1	1.7	
(Min, Max)	(0, 6)	(0, 6)	(0, 6)	
Missing	7	2	0	
Letter Number Sequencing Raw Score	0.07			
Mean	10.5	11.0	9.8	
(Min, Max)	(2, 20)	(4, 20)	(4, 14)	
Missing	5	2	0	
Semantic Fluency Total Score	<0.01			
Mean	48.6	51.9	44.7	
(Min, Max)	(20, 91)	(22, 80)	(23, 81)	
Missing	5	2	0	
Symbol Digit Modalities	<0.01			
Mean	41.3	47.0	40.7	
(Min, Max)	(7, 82)	(20, 83)	(19, 71)	
Missing	5	2	0	

Preliminary Baseline Results – GDS

Table 4 Time-dependent Cox regression model of time to investigator determined need for symptomatic therapy for Parkinson disease

Predictor	(Adjusted) hazard ratio	95% CI	p-value
GDS	Age, y	0.99 (p = 0.13)	(0.98, 1.00)
Meas	Male gender	1.16 (p = 0.34)	(0.85, 1.59)
(Mis)	GDS-15 ≥ 5 (0 = No, 1 = Yes)	1.83 (p = 0.0012)	(1.27, 2.63)
Mis	Total UPDRS change from baseline (higher score is worse)	1.14 (p < 0.0001)	(1.12, 1.16)
	RBANS change from baseline (higher score is better)	1.05 (p = 0.0006)	(1.02, 1.07)
Mo	PD N (%)	HC N (%)	p-value
cha	GDS ≥ 5	50 (12.8%)	0.045

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Ravina et al. Neurology 2007;69:342-347.

Preliminary Baseline Results – STAI*

	PD	HC	SWEDD	p value
State Trait Anxiety Score				<0.01
Mean	64.9	57.3	70.7	
(Min, Max)	(40, 121)	(40, 105)	(40, 113)	
Missing	5	3	0	

*Results represent combined trait and state anxiety scores (score range 40-160), can be subdivided.



Preliminary Baseline Results – QUIP

QUIP Positive	PD	HC	SWEDD	p value
Gambling	4 (1%)	1 (1%)	0 (0%)	1.00
Sex	12 (3%)	5 (3%)	2 (3%)	1.00
Buying	9 (2%)	4 (2%)	5 (9%)	1.00
Eating	34 (9%)	17 (9%)	14 (24%)	0.88
Hobbies	27 (7%)	17 (9%)	7 (12%)	0.40
Punding	21 (5%)	3 (2%)	6 (10%)	0.04
Walking or Driving	2 (1%)	1 (1%)	2 (3%)	1.00



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Preliminary Baseline Results – Other

Variable	Enrolled Subjects			
	PD Subjects (N =390)	Healthy Controls (N =184)	SWEDD Subjects (N = 58)	p-value (PD vs. HC)
UPSiT Raw Score	<0.01			
Mean	22.2	33.9	31.2	
(Min, Max)	(1, 40)	(11, 40)	(12, 39)	
Missing	5	2	0	
Epworth Sleepiness Scale	<0.01			
Not Sleepy (9 or below)	322 (83%)	158 (87%)	40 (69%)	
Sleepy (10 or above)	64 (17%)	23 (13%)	18 (31%)	
Missing	4 (0%)	3 (0%)	0 (0%)	
REM Sleep Disorder	<0.01			
Negative (less than 5)	241 (62%)	147 (80%)	34 (59%)	
Positive (5 or above)	149 (38%)	37 (20%)	24 (41%)	
Missing	0 (0%)	0 (0%)	0 (0%)	

Preliminary Baseline Results – UPDRS I

Variable	Enrolled Subjects			
	PD Subjects (N = 390)	Healthy Controls (N = 184)	SWEDD Subjects (N = 58)	p-value (PD vs. HC)
MDS-UPDRS Part I - Apathy	< 0.01			
0	322 (84%)	172 (95%)	44 (76%)	
1	56 (15%)	8 (4%)	10 (17%)	
2	7 (2%)	1 (1%)	3 (5%)	
3	0 (0%)	0 (0%)	1 (2%)	
4	0 (0%)	0 (0%)	0 (0%)	
Missing	5 (0%)	3 (0%)	0 (0%)	
MDS-UPDRS Part I - Hallucinations	< 0.01			
0	372 (97%)	180 (99%)	56 (97%)	
1	13 (3%)	1 (1%)	2 (3%)	
2	0 (0%)	0 (0%)	0 (0%)	
3	0 (0%)	0 (0%)	0 (0%)	
4	0 (0%)	0 (0%)	0 (0%)	
Missing	5 (0%)	3 (0%)	0 (0%)	

Recognition that cognitive impairment, psychosis, and RBD can occur at PD onset further blurs the boundary between PD and DLB.



Analysis and Publication Plan



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Paper #1 – Clinical Characteristics

- Cognition
 - Compare PD (only those with MoCA score >26) with HCs on cognitive tests
 - Within PD group only
 - Present % at different MoCA cut-off scores
 - Present % with impairment on cognitive tests
 - Present % with MCI (eventually dementia too)
 - Models to predict MoCA score or cognitive diagnosis
- Behavior
 - Compare PD with HCs on depression, anxiety, ICD symptoms, and UPDRS Part I
 - Models to predict raw score or categorization



Paper #2 – Neurobiological Correlates

- Association between cognitive and psychiatric measures with
 - Integrity dopamine system (DaTSCAN)
 - Brain atrophy (structural MRI)
 - Brain white matter abnormalities (DTI)
 - AD biomarkers (CSF A β , tau)
 - Genetics (COMT, MAPT, APOE, neurotransmitter receptors, etc.)
 - Other (urate)



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Feasibility and Safety of Lumbar Punctures in the Parkinson Progression Marker Initiative

Presented at AAN 2013



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Authors

- Samuel Frank
- Chelsea Caspell
- Liz Uribe
- Shirley Lasch
- Danna Jennings
- Ken Marek
- and the Investigators of Parkinson Progression Markers Initiative



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Introduction

- Lumbar Punctures (LPs) are a routine clinical test that may be useful in research in biomarker development in PD and other neurodegenerative diseases.
- The safety of LPs in the research setting has not been systematically studied in subjects with PD.
- There are multiple types of needles, positions, methods and sites that may be considered when performing an LP.
- The purpose of this analysis, is to determine the feasibility, safety and tolerability of LPs in early Parkinson disease (PD), healthy volunteer (HV) and SWEDD participants in PPMI.



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Methods

- All subjects enrolled in PPMI undergo LP at baseline, 6, 12 months and yearly (7 total).
- Baseline data as of 1 Apr 2013 was used.
- Preferred study LP technique:
 - Seated position.
 - L4-5 interspace
 - 24 gauge Sprotte needle
 - Acquisition of at least 15 mls CSF
- The small gauge needle requires aspiration of CSF, permitted by the atraumatic nature of the Sprotte needle.
- Subjects were instructed to remain horizontal for at least 30 minutes following the procedure and minimize intense physical activity for 24 hours.
- Adverse events were monitored by phone contact one week after LP completion.
- In addition to descriptive data, multivariate analysis was used to determine factors that contributed to AEs related to LPs.



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Baseline Data

Variable	Enrolled Subjects			
	All Subjects (N = 632)	PD Subjects (N = 390)	Healthy Controls (N = 184)	SWEDD Subjects (N = 58)
Age				
Mean	61.16	61.68	60.23	60.57
(Min, Max)	(30.6, 84.9)	(33.5, 84.9)	(30.6, 83.7)	(38.3, 78.8)
Missing	0	0	0	0
Weight				
Mean	81.33	81.51	79.74	85.13
(Min, Max)	(40.8, 142.4)	(40.8, 135.0)	(43.2, 124.0)	(47.3, 142.4)
Missing	14	11	3	0
CSF Volume collected				
Mean	15.25	15.54	14.65	15.23
(Min, Max)	(1.5, 90.0)	(1.5, 90.0)	(2.4, 30.1)	(6.9, 40.0)
Missing	47	28	11	8
BL Lumbar Puncture N (%)				
Partial or Completed	604 (95.6%)	375 (96.2%)	177 (96.2%)	52 (89.7%)



Fluoroscopic-Guided LPs

Variable	Subjects with Completed BL LP			
	All Subjects (N = 604)	PD Subjects (N = 375)	Healthy Controls (N = 177)	SWEDD Subjects (N = 52)
Fluoroscopy N (%) Completed	28 (4.6%)	18 (4.8%)	7 (4.0%)	3 (5.8%)



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AE rates

Column 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Adverse Event	Enrolled Subjects												RR (95% CI)	
	PD Subjects (N = 390)				Healthy Controls (N = 184)				SWEDD Subjects (N = 58)					
	# of Subjects	% of Subjects	# of Events	Rate	# of Subjects	% of Subjects	# of Events	Rate	# of Subjects	% of Subjects	# of Events	Rate	PD vs. HC	PD vs. SWEDD
Total	49	12.6%	63	.012	36	19.6%	48	.015	8	13.8%	11	.016	0.64 (0.43, 0.95)	0.91 (0.45, 1.82)
Ear														
Tinnitus	1	0.3%	1	.000	0	0.0%	0	.000	0	0.0%	0	.000	.	.
Gastrointestinal														
Nausea	2	0.5%	2	.000	0	0.0%	0	.000	0	0.0%	0	.000	.	.
Vomiting	1	0.3%	1	.000	0	0.0%	0	.000	0	0.0%	0	.000	.	.
General														
Fatigue	1	0.3%	1	.000	1	0.5%	1	.000	0	0.0%	0	.000	0.60 (0.04, 9.54)	.
Injection site pain	14	3.6%	14	.003	8	4.3%	9	.003	2	3.4%	2	.003	0.84 (0.36, 1.97)	1.06 (0.25, 4.54)
Injection site reaction	0	0.0%	0	.000	1	0.5%	1	.000	0	0.0%	0	.000	.	.
Pain	1	0.3%	1	.000	0	0.0%	0	.000	0	0.0%	0	.000	.	.
Musculoskeletal														
Arthralgia	0	0.0%	0	.000	1	0.5%	1	.000	0	0.0%	0	.000	.	.
Back pain	2	0.5%	2	.000	7	3.8%	7	.002	2	3.4%	2	.003	0.13 (0.03, 0.62)	0.15 (0.02, 1.04)
Muscle spasms	0	0.0%	0	.000	1	0.5%	1	.000	1	1.7%	1	.001	.	.
Muscle tightness	0	0.0%	0	.000	1	0.5%	1	.000	0	0.0%	0	.000	.	.
Musculoskeletal discomfort	3	0.8%	3	.001	2	1.1%	2	.001	0	0.0%	0	.000	0.73 (0.12, 4.33)	.
Musculoskeletal stiffness	3	0.8%	3	.001	0	0.0%	0	.000	0	0.0%	0	.000	.	.
Pain in extremity	1	0.3%	1	.000	0	0.0%	0	.000	0	0.0%	0	.000	.	.
Nervous System														
Dizziness	3	0.8%	3	.001	2	1.1%	2	.001	0	0.0%	0	.000	0.73 (0.12, 4.33)	.
Headache	18	4.6%	19	.004	14	7.6%	17	.005	6	10.3%	6	.009	0.61 (0.31, 1.20)	0.45 (0.19, 1.09)
Intracranial hypotension	0	0.0%	0	.000	1	0.5%	1	.000	0	0.0%	0	.000	.	.
Loss of consciousness	1	0.3%	1	.000	0	0.0%	0	.000	0	0.0%	0	.000	.	.
Presyncope	0	0.0%	0	.000	1	0.5%	1	.000	0	0.0%	0	.000	.	.
Radicular pain	1	0.3%	1	.000	0	0.0%	0	.000	0	0.0%	0	.000	.	.
Sciatica	1	0.3%	1	.000	0	0.0%	0	.000	0	0.0%	0	.000	.	.
Procedural Related Injuries														
Contusion	1	0.3%	1	.000	0	0.0%	0	.000	0	0.0%	0	.000	.	.
Post lumbar puncture syndrome	8	2.1%	8	.002	4	2.2%	4	.001	0	0.0%	0	.000	0.95 (0.29, 3.11)	.

Factors Contributing to AEs

Variable	Subjects with Completed BL LP			
	All Subjects (N = 604)	PD Subjects (N = 375)	Healthy Controls (N = 177)	SWEDD Subjects (N = 52)
CSF Needle Type				
Quincke	100 (16.6%)	67 (17.9%)	23 (13.0%)	10 (19.2%)
Sprotte	496 (82.1%)	303 (80.8%)	152 (85.9%)	41 (78.8%)
18g	8 (1.3%)	5 (1.3%)	2 (1.1%)	1 (1.9%)
Missing	0	0	0	0
CSF Collection Method				
Gravity	224 (37.1%)	140 (37.3%)	62 (35.0%)	22 (42.3%)
Syringe Suction	380 (62.9%)	235 (62.7%)	115 (65.0%)	30 (57.7%)
Missing	0	0	0	0
LP Site				
L2-L3 interspace	30 (5.0%)	20 (5.3%)	6 (3.4%)	4 (7.7%)
L3-L4 interspace	410 (67.9%)	239 (63.7%)	134 (75.7%)	37 (71.2%)
L4-L5 interspace	129 (21.4%)	89 (23.7%)	33 (18.6%)	7 (13.5%)
Unknown / Missing	35	27	4	4
LP Position				
Sitting, leaned over	376 (62.3%)	226 (60.3%)	115 (65.0%)	35 (67.3%)
Lying, curled up on side	210 (34.8%)	137 (36.5%)	58 (32.8%)	15 (28.8%)
Unknown / Missing	18	12	4	2



Non-Significant Factors

- Weight
- CSF volume
- Needle type
- Collection type (aspiration vs. gravity)
- LP site
- Having PD, SWEDD (but NOT HC!)



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Significant Factors

- Site
 - Higher rate of AEs when performed at L4-5 (vs. L3-4 or L2-3, $p=0.0339$)
- Position
 - Higher rate of AEs when performed in the seated position ($p=0.0003$)
- Experience
 - Higher risk for the **first 10 LPs** compared to the subsequent LPs when at least 20 LPs were completed [RR=2.05 (CI 1.29, 3.27)]
- Sex & Age
 - In female (but not male) subjects with PD, there was a higher age in those with AEs vs no AEs (60.9 vs. 56.5 years, $p=0.0139$).
- Based on a multivariate analysis of LP collection methods, adjusted for age and gender, incidence of post-LP headaches was significantly higher in **younger** subjects, **females**, and subjects who were in a **sitting** position during their LP.



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Position

Variable	Subjects with Completed BL LP			
	All Subjects (N = 478)		Healthy Controls (N = 151)	
	AE (N = 68)	No AE (N = 410)	AE (N = 35)	No AE (N = 116)
LP Position				
Sitting, leaned over	68 (73.1%)	308 (60.3%)	31 (86.1%)	84 (59.6%)
Lying, curled up on side	24 (25.8%)	186 (36.4%)	5 (13.9%)	53 (37.6%)
Unknown / Missing	1	17	0	4



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Other Results

- No SAEs
- Mean duration of HA=4.4 days
- Pending analysis
 - AEs by site
 - Retention
- Transient HA during procedure not reported
 - Report of up to 17% of subjects during LP with 4% post-LP HA rate

(Linker et al Neurology 2002)



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Conclusions

- Obtaining CSF in a cohort of newly diagnosed PD and HV subjects with a mean age about 60 years is safe and feasible.
- Specific LP techniques (gauge and type of needle, subject position and level of insertion) may reduce the overall incidence of AEs.
- Incidence of AEs was highest in the HC cohort, but still lower than other published reports using cutting-type needles.
- Among all cohorts, incidence of headaches was significantly higher in younger subjects, females, and subjects who were in a sitting position during their LP.
- There was no association of weight or volume of CSF and any LP-related AE, including headache.
- With experience, there appears to be a reduced risk of AEs.



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How We Compare: Peskind et al 2005

TABLE 3. Number and Frequency (%) of Adverse Events

Adverse Event	Young Normal (78 LPs)	Middle-Aged Normal (119 LPs)	Older Normal (144 LPs)	AD/MCI (87 LPs)
Mild headache*	4 (5.1%)	4 (3.4%)	10 (6.9%)	1 (1.1%)
Moderate headache†	1 (1.3 %)	3 (2.5%)	2 (1.4%)	0 (0%)
Severe post-LP headache (PLPHA)‡	1 (1.3%)	1 (.8%)	2 (1.4%)	0 (0%)
Mild low back soreness§	2 (2.6%)	2 (1.7%)	5 (3.5%)	2 (2.3%)
Moderate low back soreness§	1 (1.3%)	0 (0%)	1 (.7%)	0 (0%)
Vasovagal symptoms	2 (2.6%)	2 (1.7%)	0 (0%)	0 (0%)
Mild nausea¶	0 (0%)	2 (1.7%)	0 (0%)	1 (1.1%)
Other#	0 (0%)	1 (.8%)	0 (0%)	0 (0%)
Any adverse event**	11 (14.1%)	14 (11.8%)	18 (12.5%)	4 (4.6%)
Clinically significant adverse events††	5 (6.4%)	7 (5.9%)	5 (3.5%)	0 (0%)



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AAN Survey

- 3901/7798 surveys returned (56%)
- 2% use atraumatic needle
- Ref: Birnbach et al Headache 2001

Feature	Type of Spinal Needle		<i>P</i>
	Atraumatic (n=45 [2.0])	Standard (n=2242 [98.0])	
Practice setting			NS
Academic	19 (2.5)	741 (97.5)	
Private	26 (1.7)	1501 (98.3)	
Age of neurologist, y			NS
≤40	7 (1.3)	543 (98.7)	
>40	38 (2.2)	1692 (97.8)	
Gauge			.001
18-20 (large bore)	16 (35.6)	1342 (59.9)	
22+ (small bore)	29 (64.4)	900 (40.1)	
Lumbar punctures per month			.047
≤10 (low frequency)	41 (1.8)	2176 (98.2)	
>10 (high frequency)	4 (5.7)	66 (94.3)	
PDPH			.0014
≤10% ("low" occurrence)	42 (93.3)	1481 (66.3)	
>10% ("high" occurrence)	3 (6.7)	753 (33.7)	

No Need to Re-Invent the Wheel

A consensus protocol for the standardization of cerebrospinal fluid collection and biobanking

ABSTRACT

There is a long history of research into body fluid biomarkers in neurodegenerative and neuroinflammatory diseases. However, only a few biomarkers in CSF are being used in clinical practice. One of the most critical factors in CSF biomarker research is the inadequate powering of studies because of the lack of sufficient samples that can be obtained in single-center studies. Therefore, collaboration between investigators is needed to establish large biobanks of well-defined samples. Standardized protocols for biobanking are a prerequisite to ensure that the statistical power gained by increasing the numbers of CSF samples is not compromised by preanalytical factors. Here, a consensus report on recommendations for CSF collection and biobanking is presented, formed by the BioMS-eu network for CSF biomarker research in multiple sclerosis. We focus on CSF collection procedures, preanalytical factors, and high-quality clinical and paraclinical information. The biobanking protocols are applicable for CSF biobanks for research targeting any neurologic disease. *Neurology®* 2009;73:1914-1922



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Consensus Recommendations: Collection

Preferred volume	At least 12 mL; first 1-2 mL for basic CSF assessment (see issue 33); last 10 mL for biobanking
	Record volume taken and fraction used for biobanking
Location	Vertebral body L3-L5
If bloody	Do not process further
	Criteria for bloody: more than 500 red blood cells/ μ L
	Record number of blood cells in diagnostic samples
Type of needle	Atraumatic
Type of collection tube	Polypropylene tubes, screw cap, volume 1-2 mL
Time of day of withdrawal and storage	Preferably standardized within each center, allowing for intercenter differences in local logistics
	Record date and time of collection

AAN 2000 Therapeutics & Technology Assessment Subcommittee

Recommendations.

1. Class I and Class II data in the anesthesiology literature and either Class I or Class II data in the neurology series show that smaller needle size is associated with reduced frequency of PLPHA (Type A). The actual choice of needle size will be influenced by balancing other considerations, such as ease of use, the need to measure pressures, and the flow rate, with the desire to prevent PLPHA.
2. Class I data in the anesthesiology literature show that, when using a cutting needle, ensuring that the bevel direction is parallel to the dural fibers reduces the frequency of PLPHA. (Type A)
3. Class I data using a noncutting needle show that replacement of the stylet before the needle is withdrawn is associated with lower frequency of PLPHA. (Type A)
4. For spinal anesthesia, Class I data show that noncutting needles reduce the frequency of PLPHA (Type A). However, for diagnostic LPs, the data are inconclusive.
5. Class I and Class II data have not demonstrated that the duration of recumbency following a diagnostic LP influences the occurrence of PLPHA.
6. There is no evidence that the use of increased fluids prevents PLPHA.



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PPMI Imaging Core Update

John Seibyl, MD

7 May 2013



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PPMI Imaging Core Update

1. PPMI status update: enrollment, demographics, compliance
2. DAT analyses
 - baseline and initial progression data
 - phantom corrections
3. DTI studies



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PPMI Imaging Studies In-house at IND Core Lab

SPECT scans received: 738

PD Year 1 scans = 192

PD Year 2 scans = 49

PET AV-133 received: 17

Structural MRI Baseline: 367

DTI Baseline: 271

DTI Year 1: 128

DTI Year 2: 15

MRI Baseline resting state studies: 45

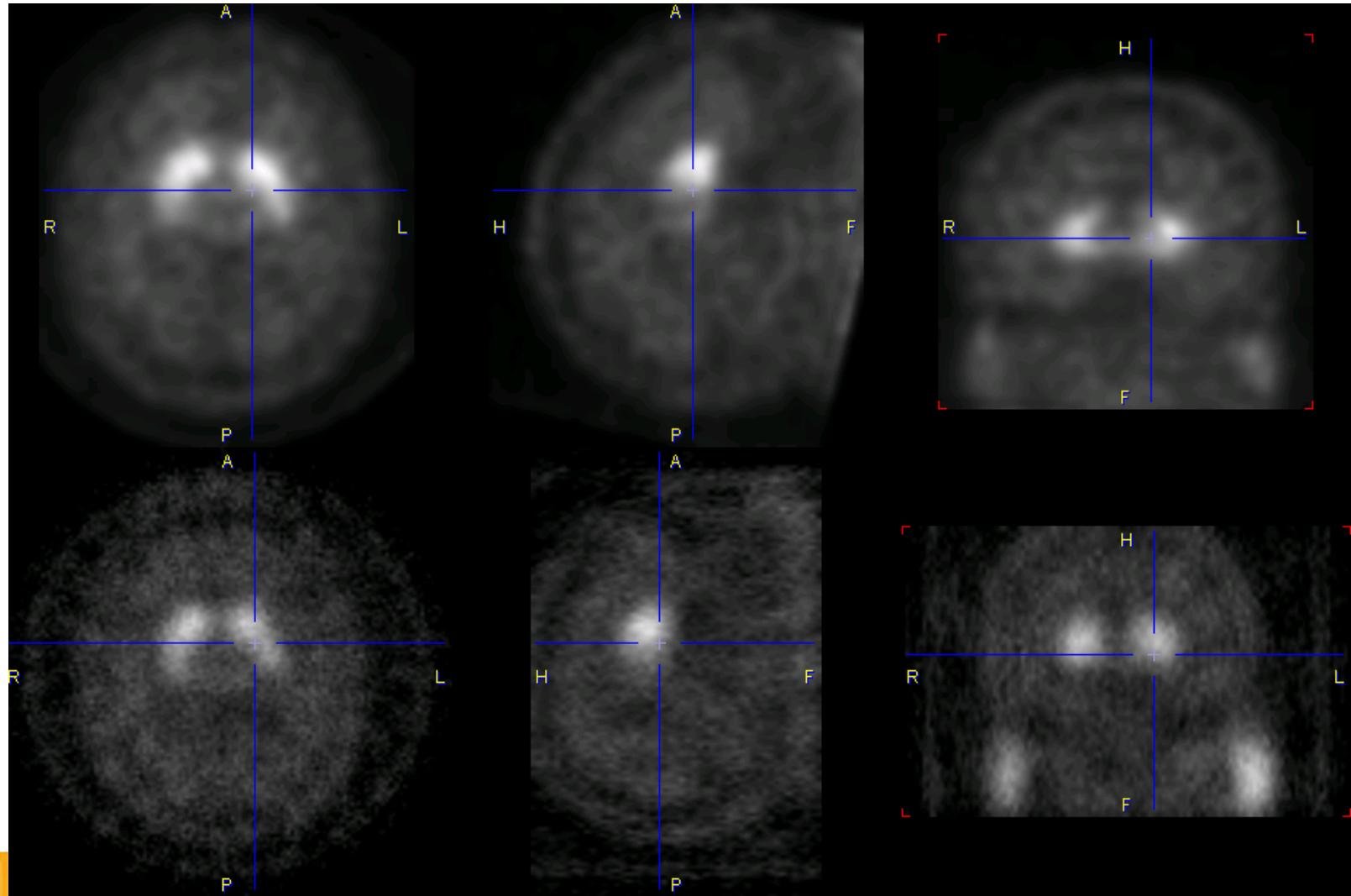
As of 5 May 2013



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Baseline DAT QC



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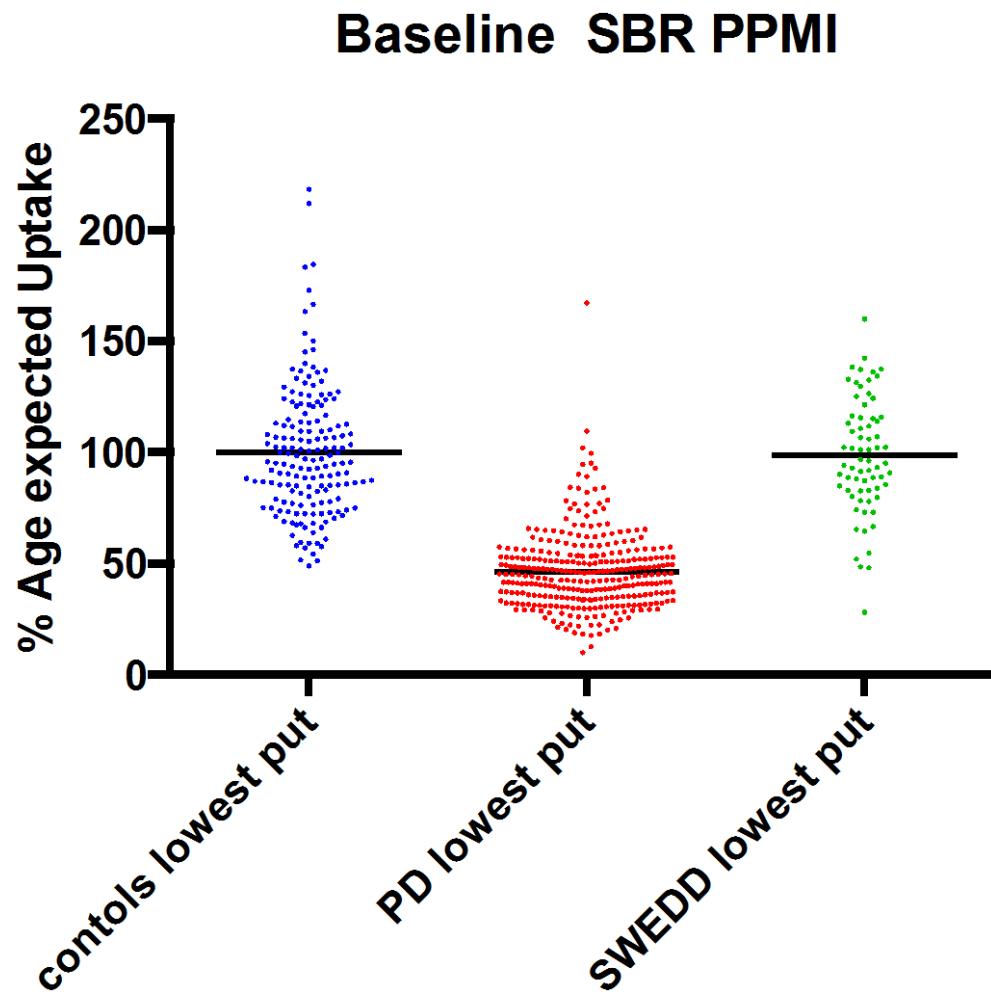


Quality Control

- Of first 527 DatScan images, visual quality ratings:
 - Good quality = 424 (80.4%)
 - Adequate quality = 90 (17.1%)
 - Low quality, but useable = 11 (2.1%)
- Two scans failed quality control (gross motion artifacts, inadequate injected dose)



Baseline DAT Data



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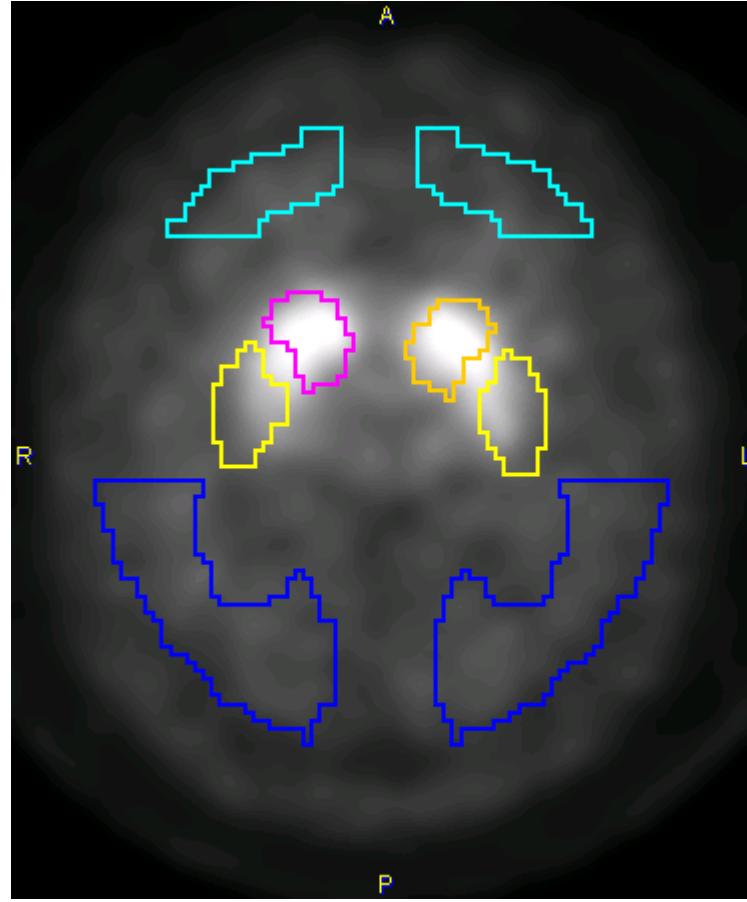
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Baseline DAT data

Variable	Enrolled Subjects		
	PD Subjects (N =378)	Healthy Controls (N =182)	p-value (PD vs. HC)
Lowest Caudate	1.21	1.89	<0.001
Lowest Putamen	0.57	1.27	<0.001
Mean Caudate	1.32	1.94	<0.001
Mean Putamen	0.65	1.33	<0.001
Mean Striatum	0.98	1.63	<0.001
Ipsilateral Caudate	1.41	1.89	<0.001
Ipsilateral Putamen	0.73	1.27	<0.001
Contralateral Caudate	1.22	1.99	<0.001
Contralateral Putamen	0.58	1.40	<0.001
Caudate Asymmetry Index	15.96	5.27	<0.001
Putamen Asymmetry Index	26.48	10.20	<0.001
Striatum Asymmetry Index	36.86	8.72	<0.001
Ipsilateral CDR	2.05	1.56	<0.001
Contralateral CDR	2.23	1.47	<0.001

Volume of Interest Strategy

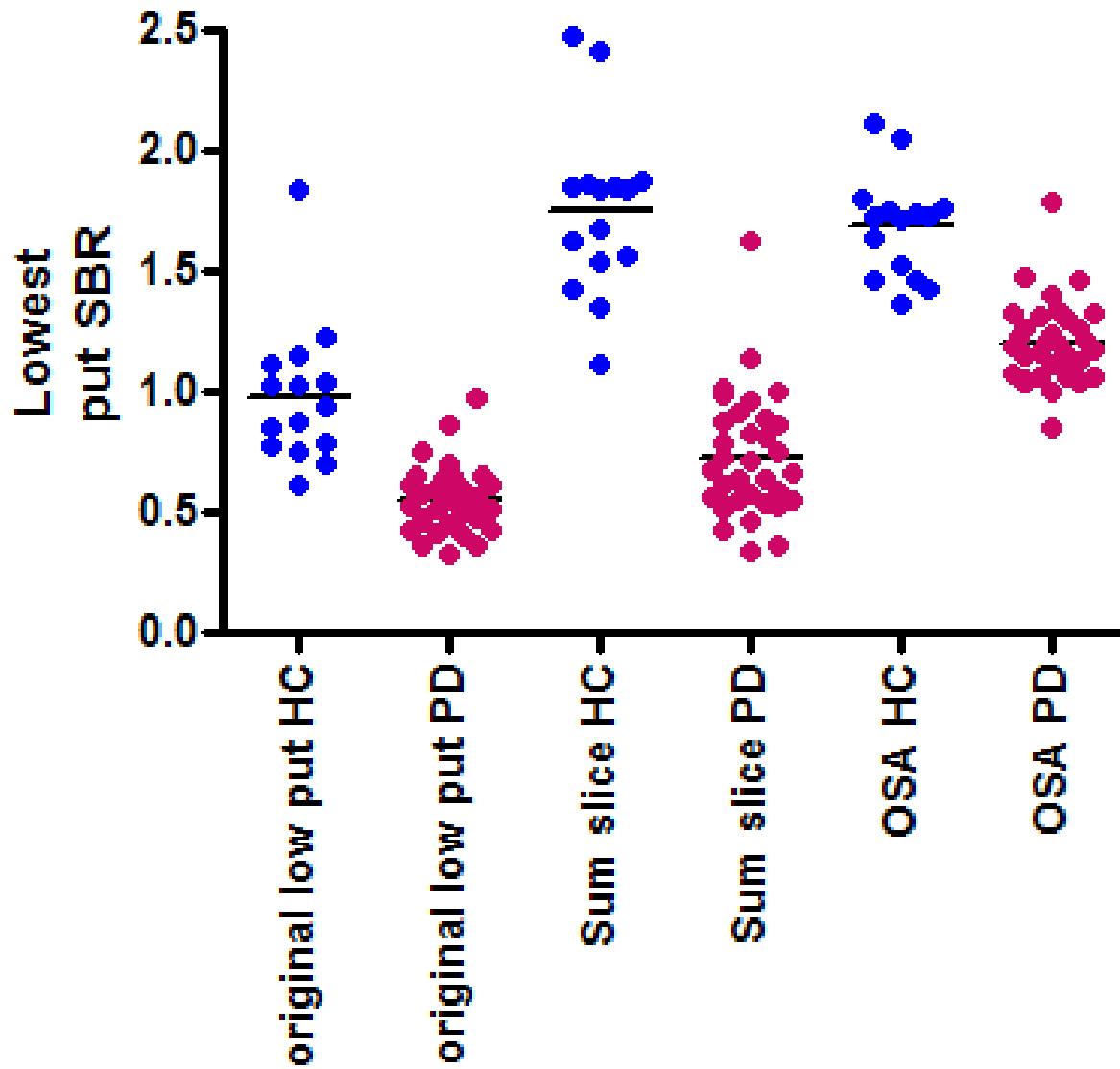


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Different VOI strategies

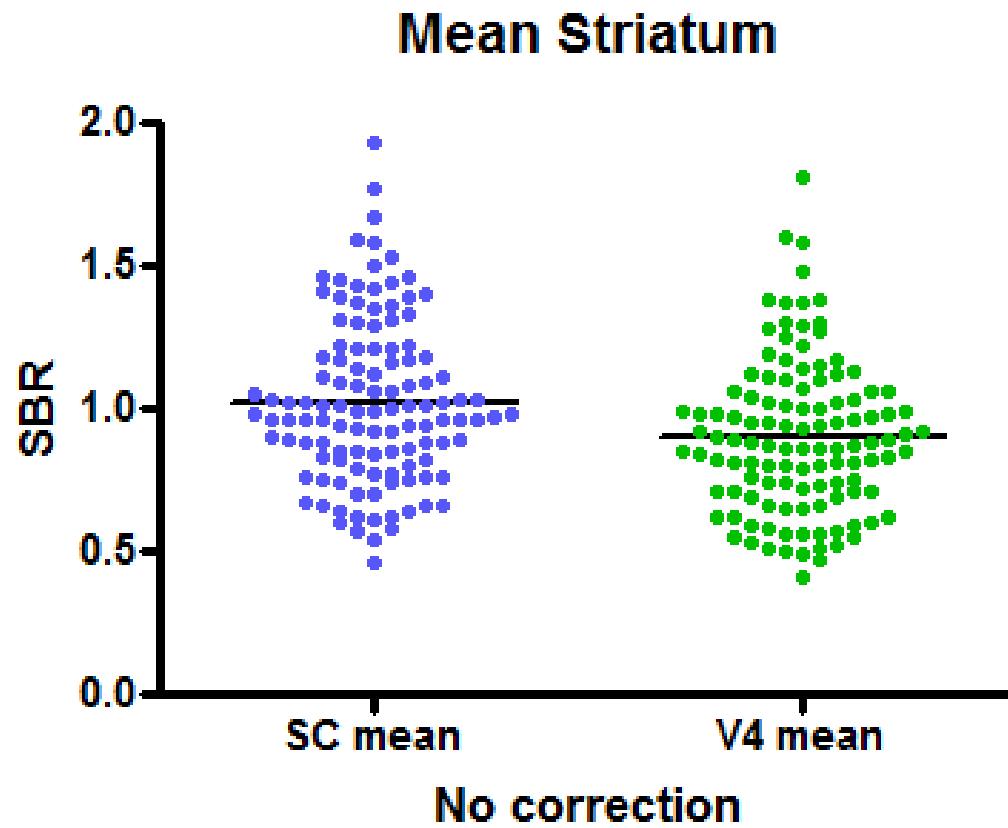


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Longitudinal Data DAT



N= 117 PD

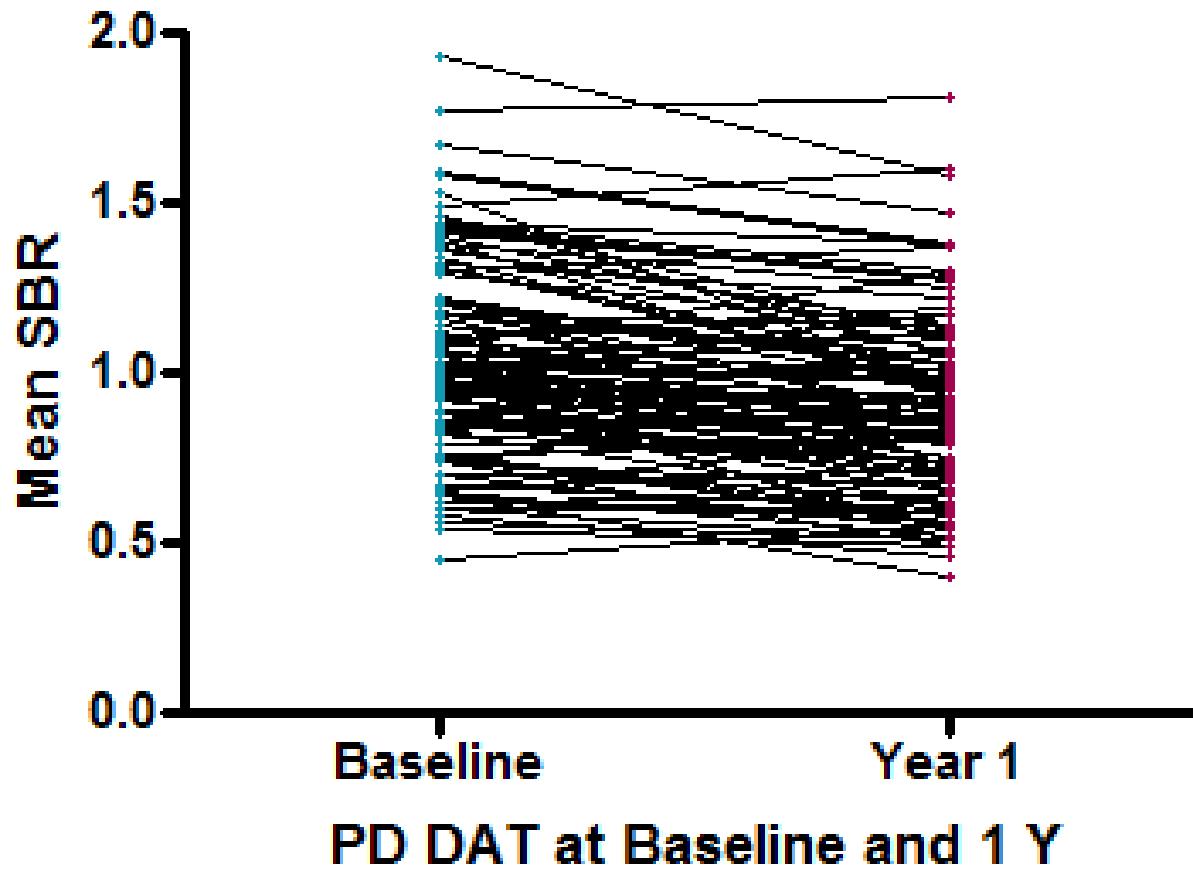


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Longitudinal Data DAT



N= 117 PD

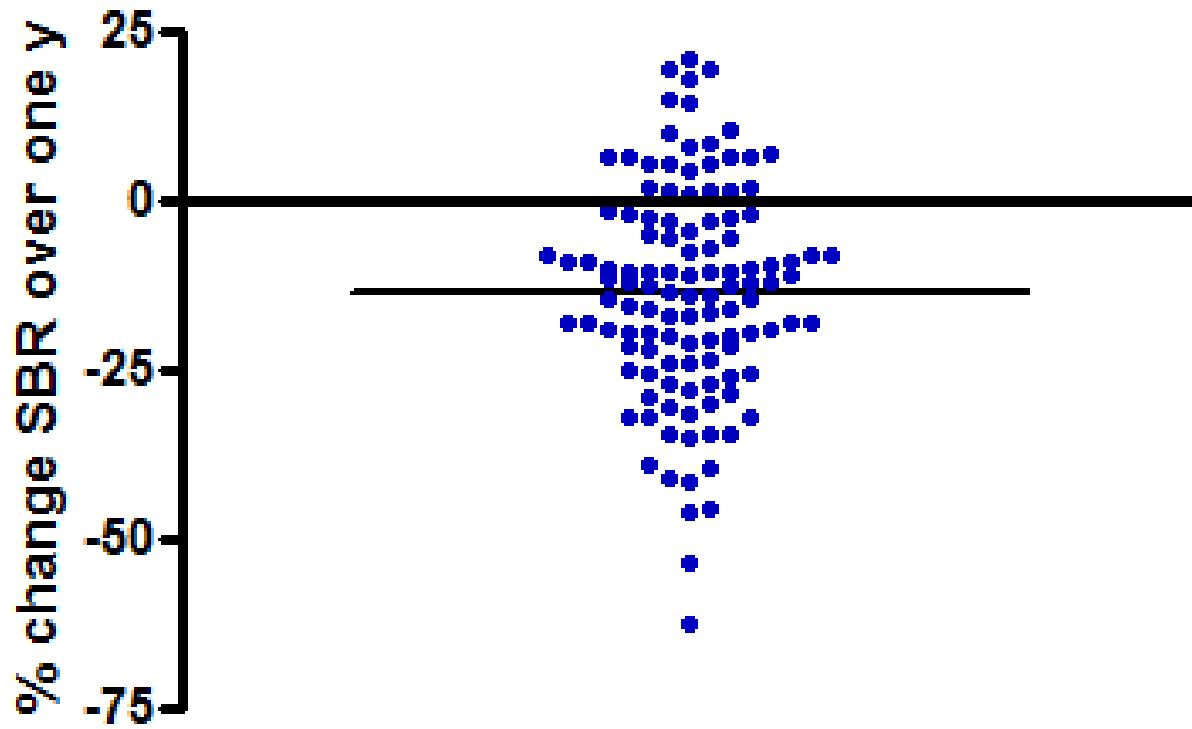


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Longitudinal DAT



N= 117

Mean $13.3\% \pm 16.0\%$

78.6% going down at yr 1



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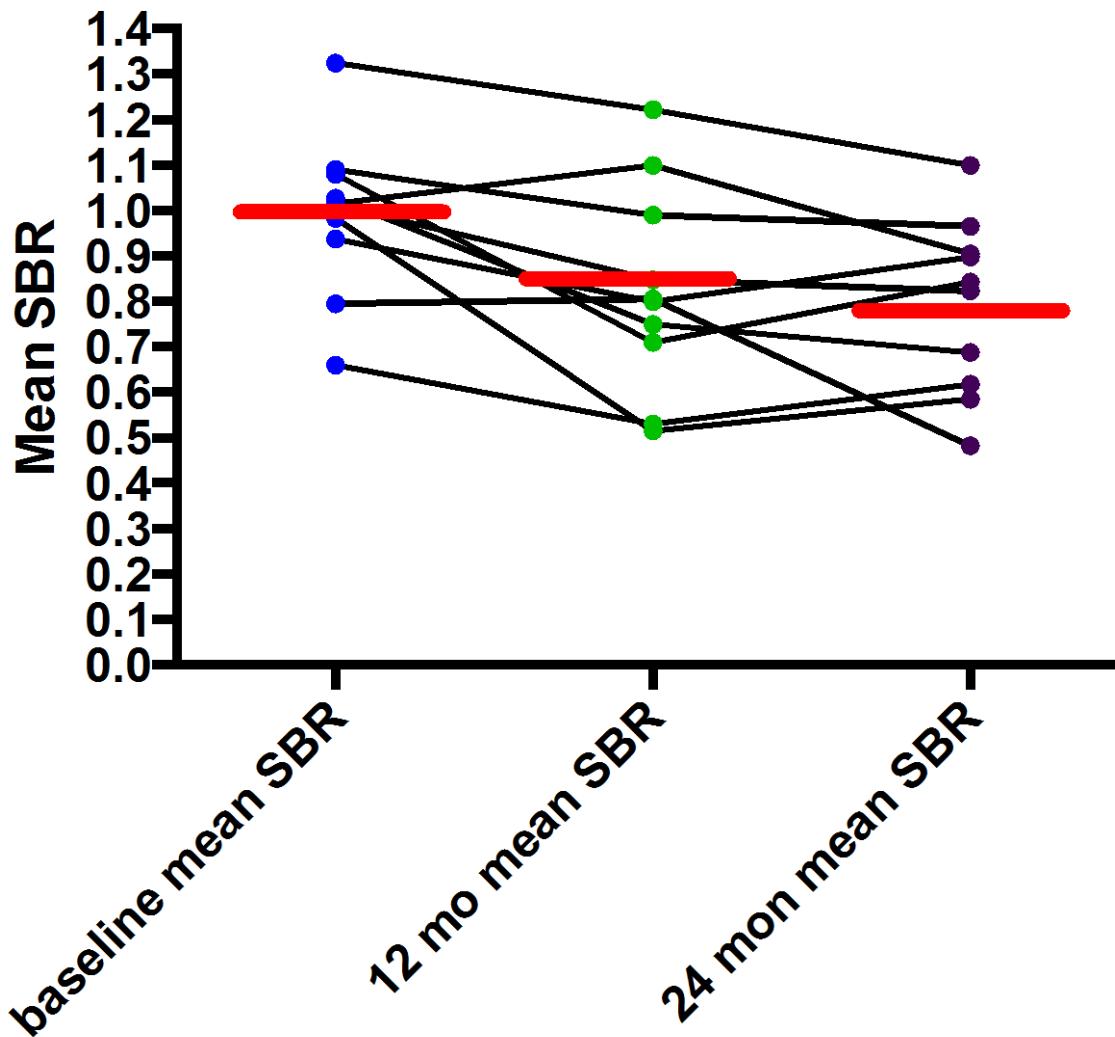


Rate of DAT change

- Identical to % signal loss in the PROUD study with DatScan
 - mean change was -15.5% for early ($n=57$) and -14.2% for delayed ($n=58$) pramipexole cohorts
- Faster than PRECEPT cohort with β -CIT ($\times 2$)



Longitudinal PD SBR

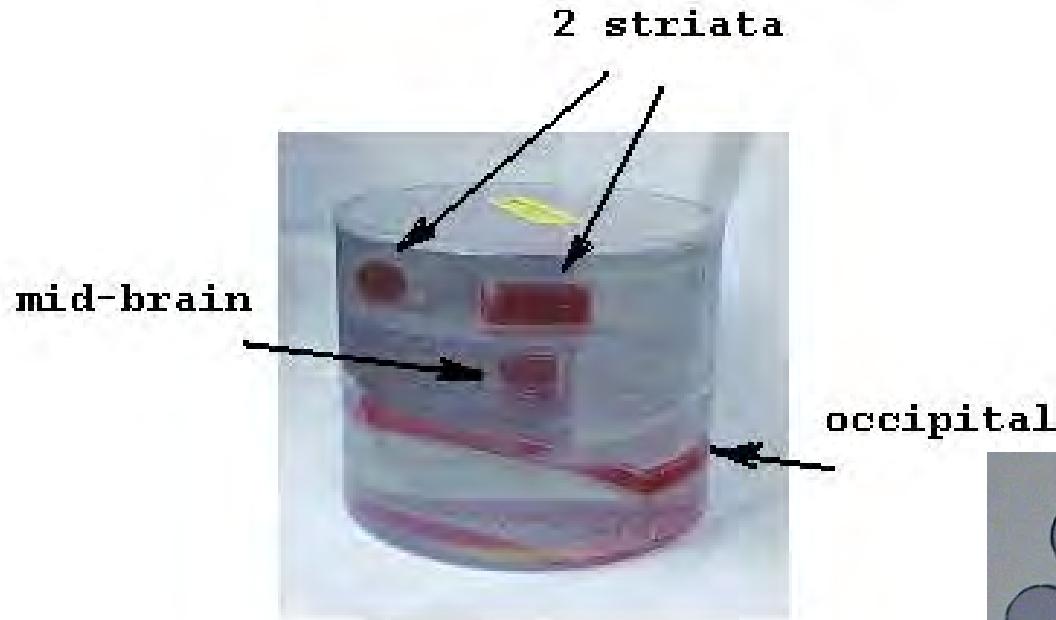


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57-Co Striatal Phantom

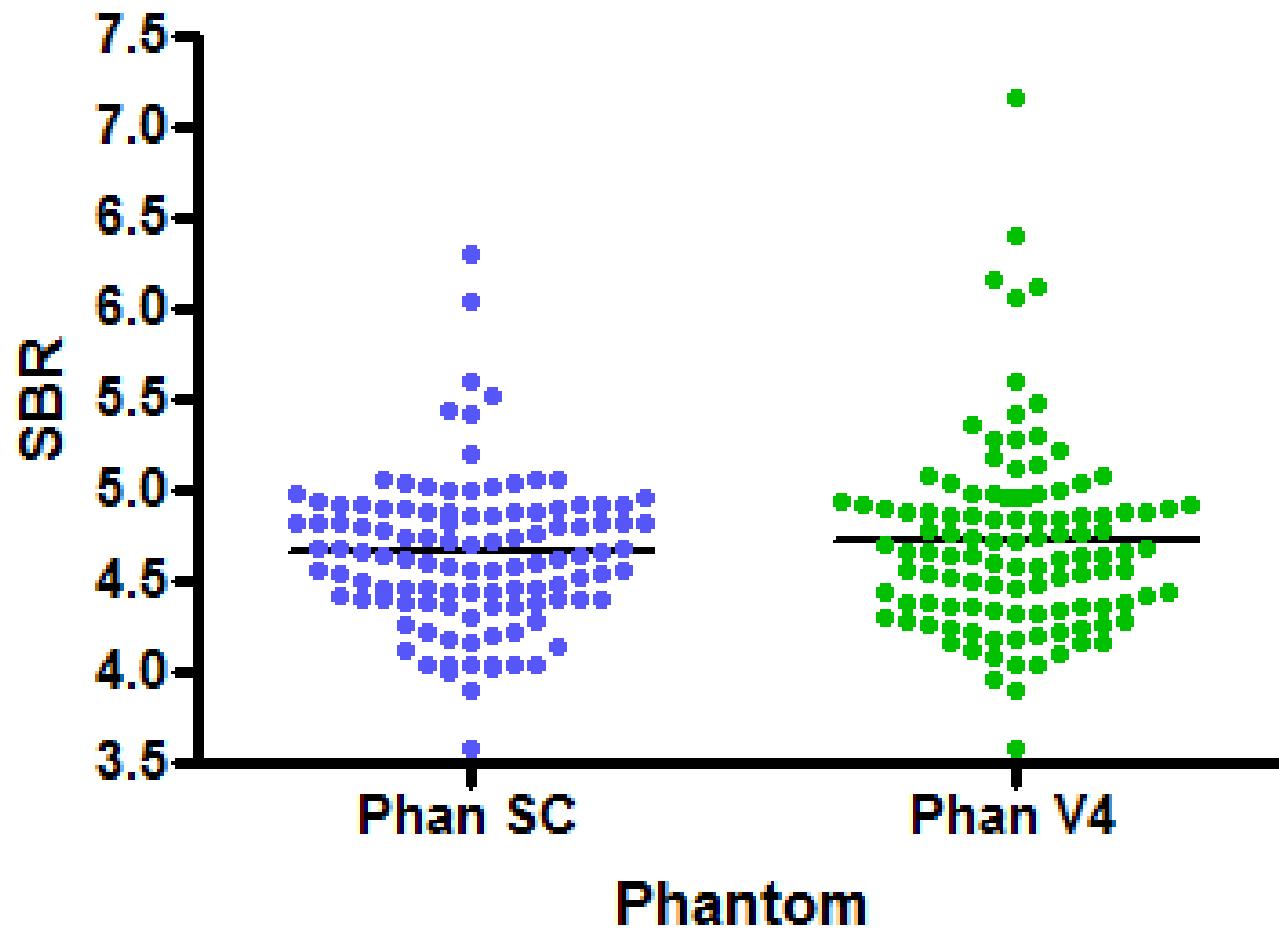


SBR phantom correction

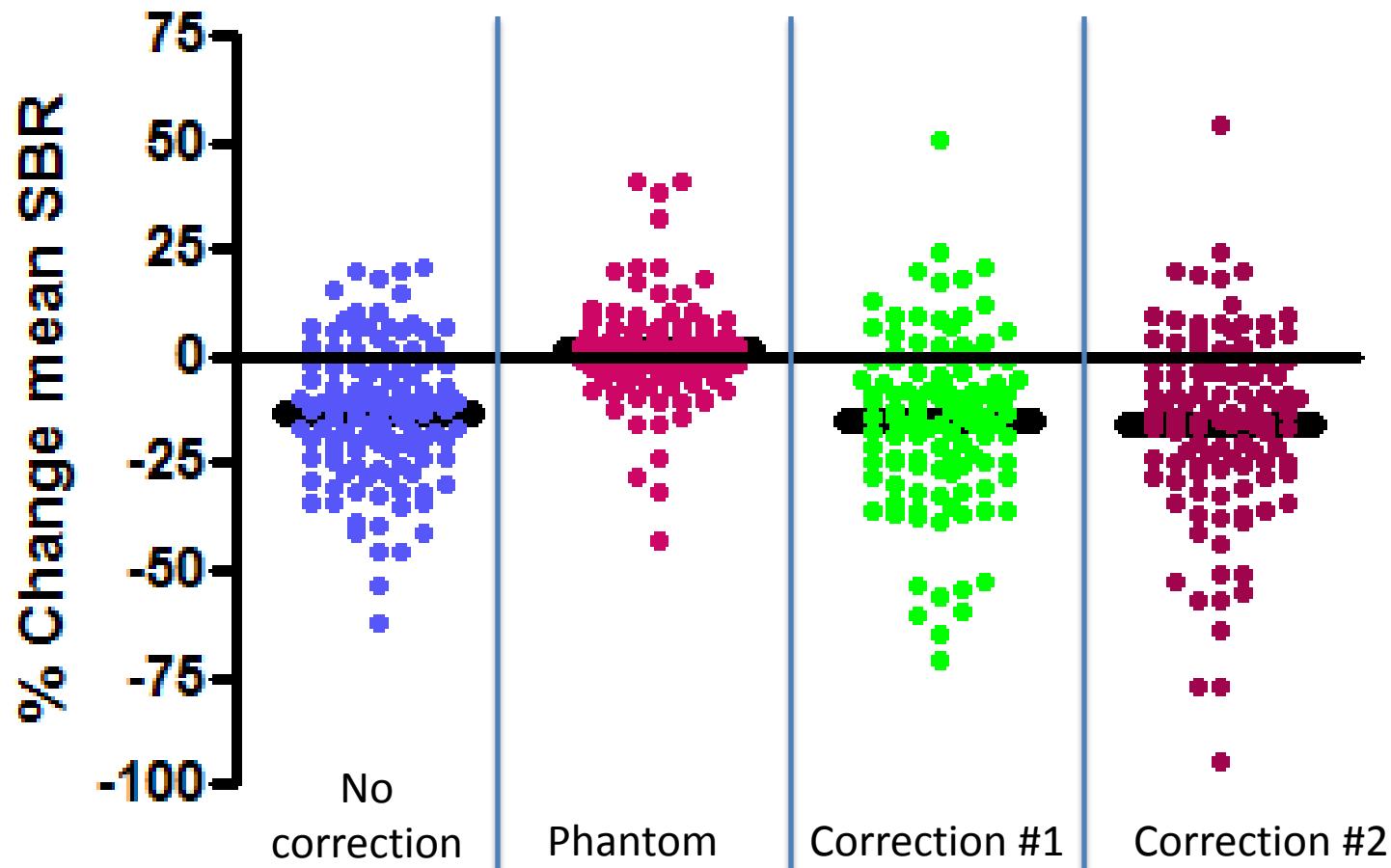
Approach #1 (Scaling) Normalize each DAT study (mean SBR) to the phantom (mean SBR) acquired on the imaging day, e.g., set the ^{57}Co SBR at 100% and multiply through the subject scan using the phantom normalizing factor then calculate percent change on the phantom-normalized subject SBRs

Approach #2 For longitudinal change, calculate the % change for ^{57}Co mean SBR and subtract this change as the “technical” component of the change from baseline to follow-up

Mean Striatum



% Change- Different corrections



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		Baseline mean SBR	Y1 mean SBR	% change
No Correction	Mean	1.02	0.90	-13.26
	SD	0.29	0.27	15.96
	%COV	28.0	29.8	-120.3

		Baseline mean SBR	Y1 mean SBR	% change
Scaling Correction	Mean	22.33	19.50	-14.90
	SD	6.71	6.13	20.04
	%COV	30.1	31.5	-134.5

		Baseline mean SBR	Y1 mean SBR	% change
Subtractive Correction	Mean	1.03	0.90	-15.78
	SD	0.29	0.28	22.35
	%COV	27.9	31.4	-141.7

Pending Analyses

Review phantom analysis outliers, some seem to be “anti-correcting”

Evaluate other SBR measures- lowest putamen, mean putamen

Manuscripts

- Baseline DAT characteristics of PPMI cohorts
- Methodology- technical standardization of SPECT, PET, and MRI
- Methodology- VOI strategies for monitoring disease progression, cohort discrimination and correction strategies



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Diffusion Tensor Imaging: Update Image Processing & Analysis

Norbert Schuff

VA Medical Center & University of California,
San Francisco

Acknowledgement of the people who do the hard work

Katherine Wu (SF)

Shannon Buckley (SF)

Dr. Yu Zhang (SF)

Susan Mendick (Yale)



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Objectives

- Data Processing
 - Perform quantitative QA
 - Align DTI to anatomical MRI
 - Compute DTI and tractography maps
- Data Analyses
 - Measure DTI alterations in PD
 - Identify DTI changes as marker of PD progression
 - Explore novel analysis strategies
 - Tractography
 - Multivariate whole brain analyses using machine learning



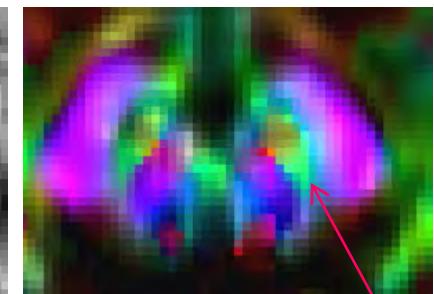
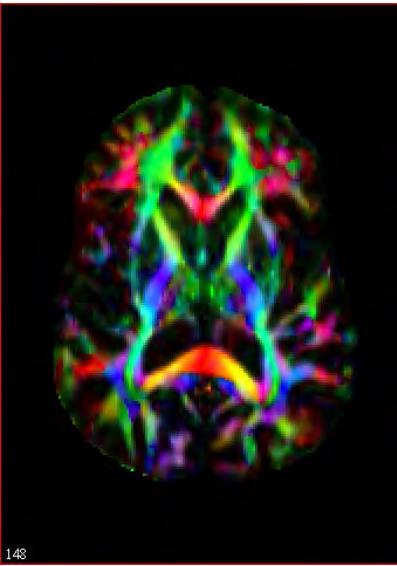
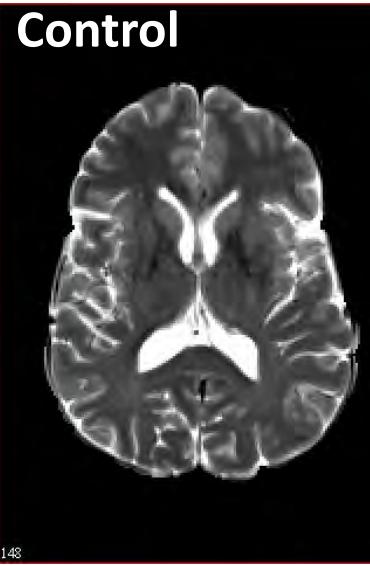
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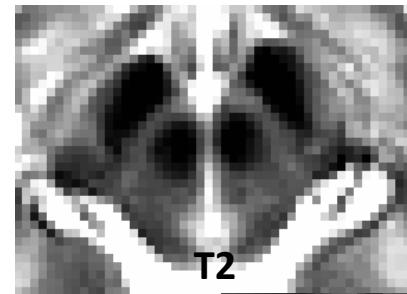
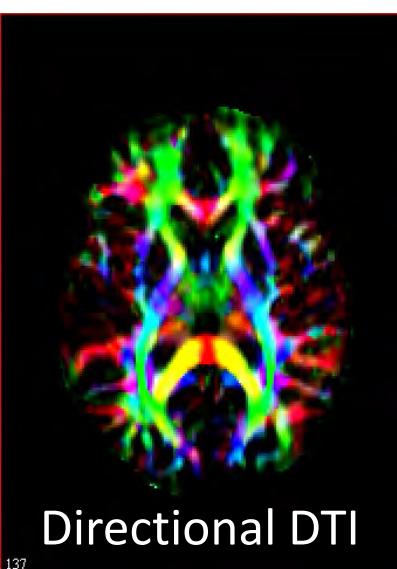
Representative DTI & T2 Maps

Control



Substantia nigra

PD

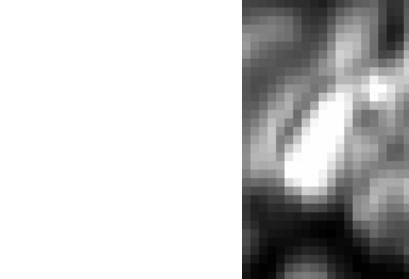


Directional

T2

Directional DTI

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FA



DTI Processing Update (as of 5/1/2013)

Time point	Control	PD	SWEDD	Total Received	Total Processed	Total Excluded
Baseline	68	144	34	246	219	16
12m	55	51	3	109	88	6
24m	0	2	0	2	1	0
Totals	123	197	37	357	308	22 (6%)*

•(*) Percent of total received

- Note: most subjects have 2 DTI scans per session . Thus the number of processed scans Is nearly double the number of subjects

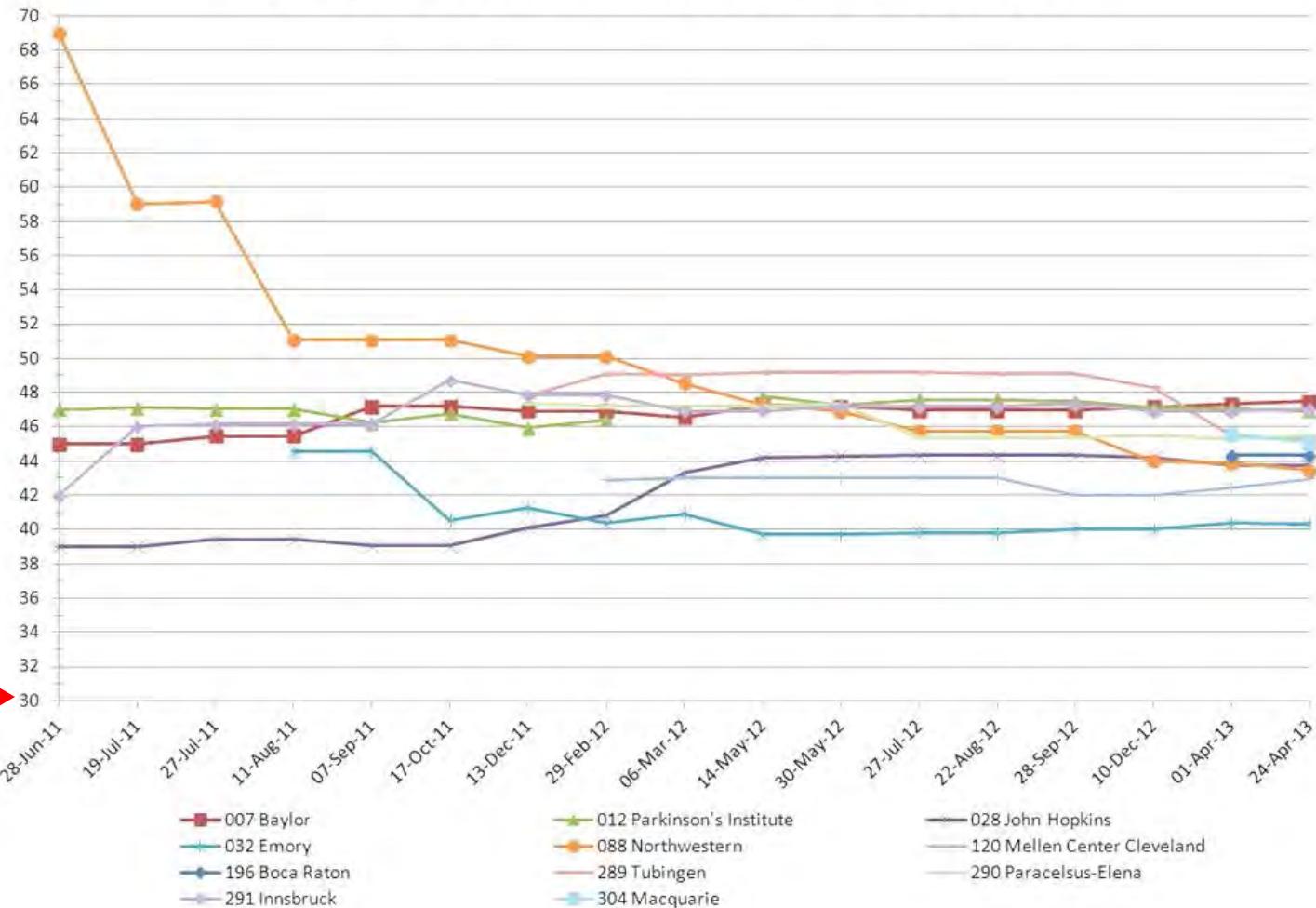


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PPMI Site Quality (DTI Signal-to-Noise over time)



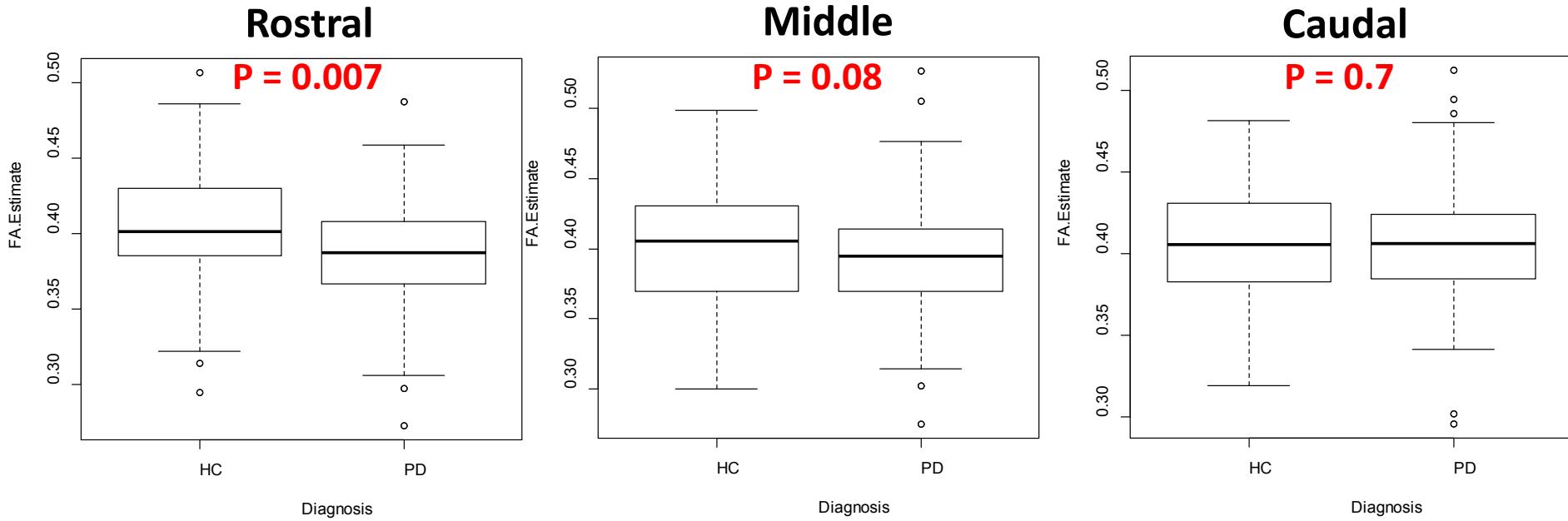
Cutoff
SNR=30



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FA Of Substantia Nigra (Manual ROI)



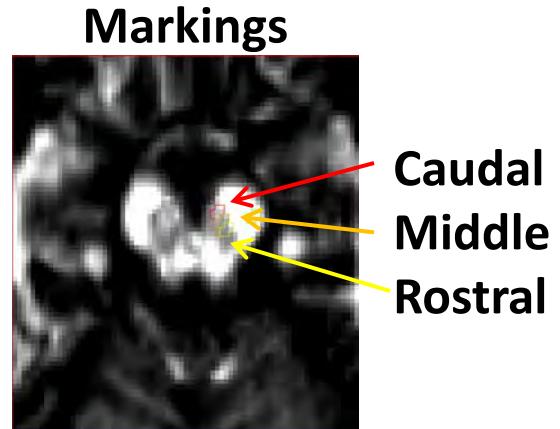
PD=100, Control= 52

100Analysis:

By diagnosis and side of symptom onset.

Statistics:

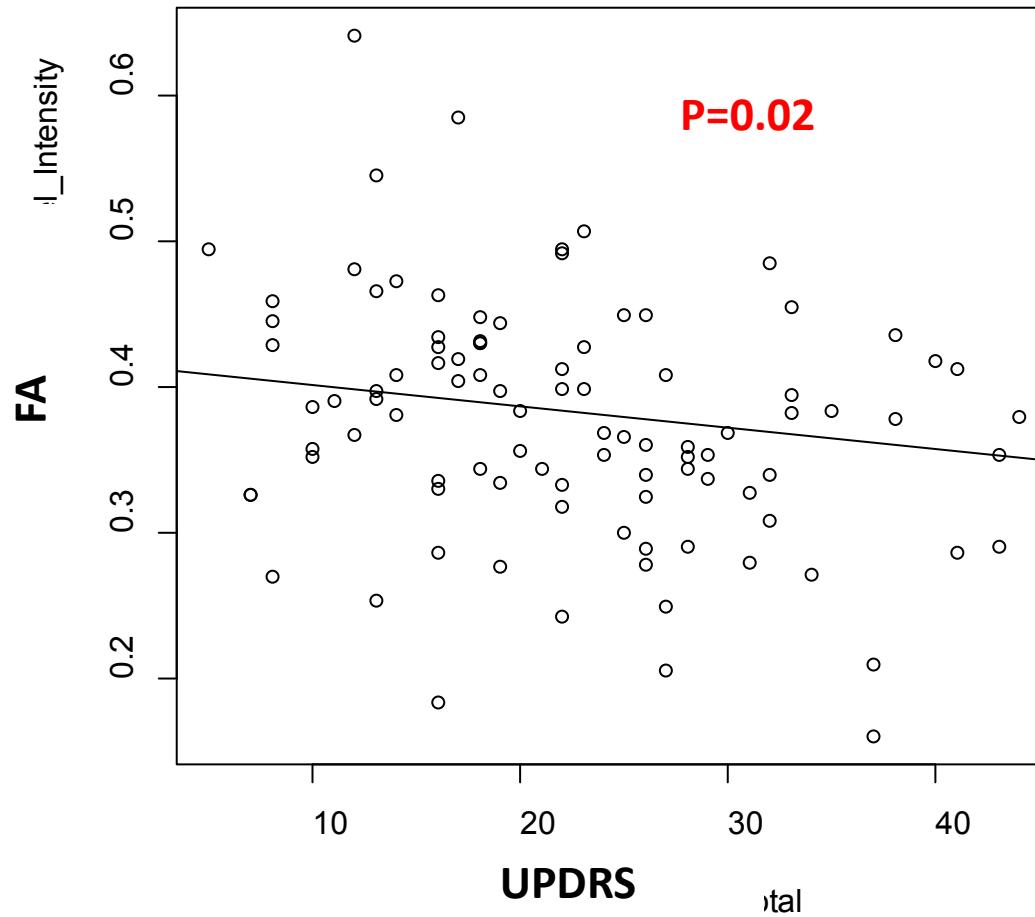
Using permutations to approximate a t-distribution



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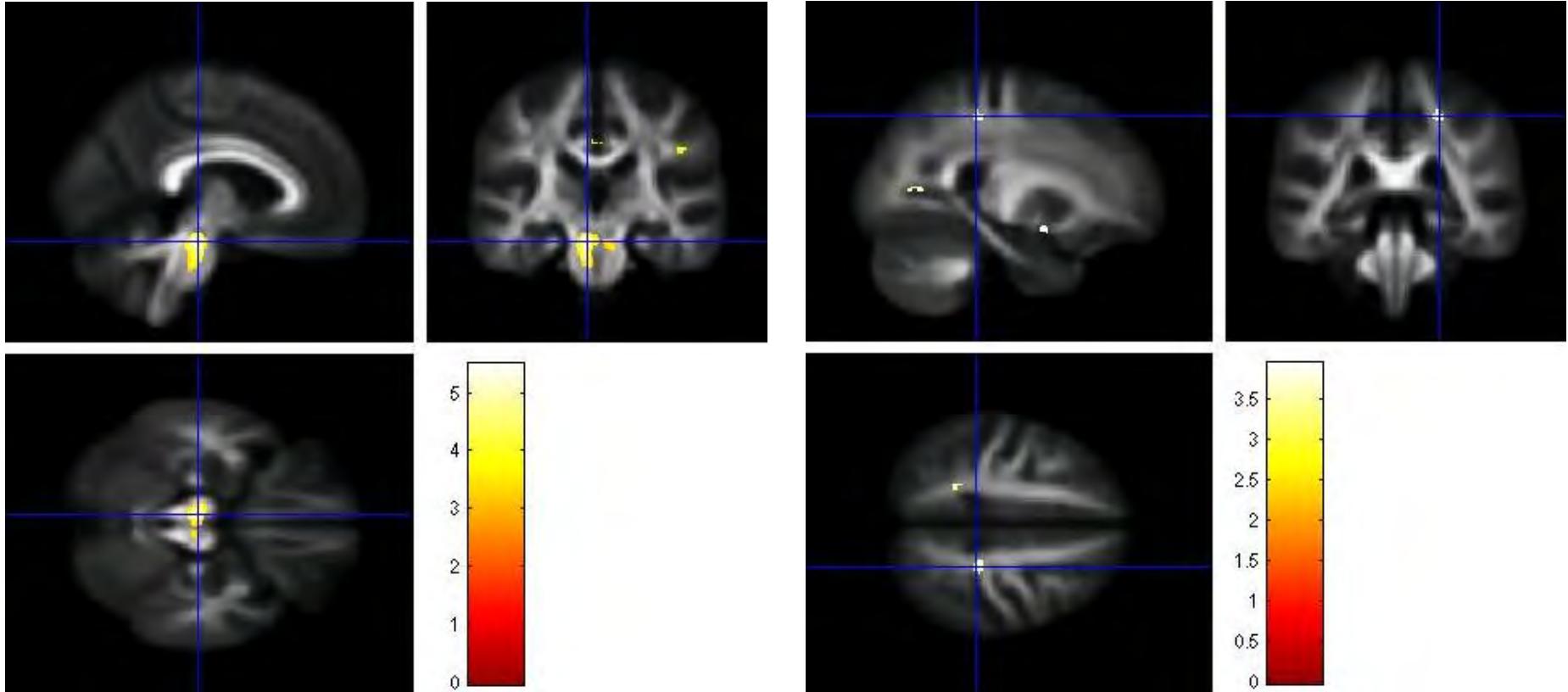
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FA Of Substantia Niagra vs UPDRS.III



Regional Reduction Of FA In SWEDD vs PD*

102 PD and 21 SWEDD (* accounting for differences in motor severity and age



SWEDD < PD

covariates: age, sex, **UPDRSIII**

$p_{\text{FWE-corr}}$ 0.003
 p_{uncorr} 0.000
 $q_{\text{FDR-corr}}$ 0.022

SWEDD > PD

covariates: age, sex, **UPDRSIII**

$p_{\text{FWE-corr}}$ 0.459
 p_{uncorr} 0.000
 $q_{\text{FDR-corr}}$ 0.203



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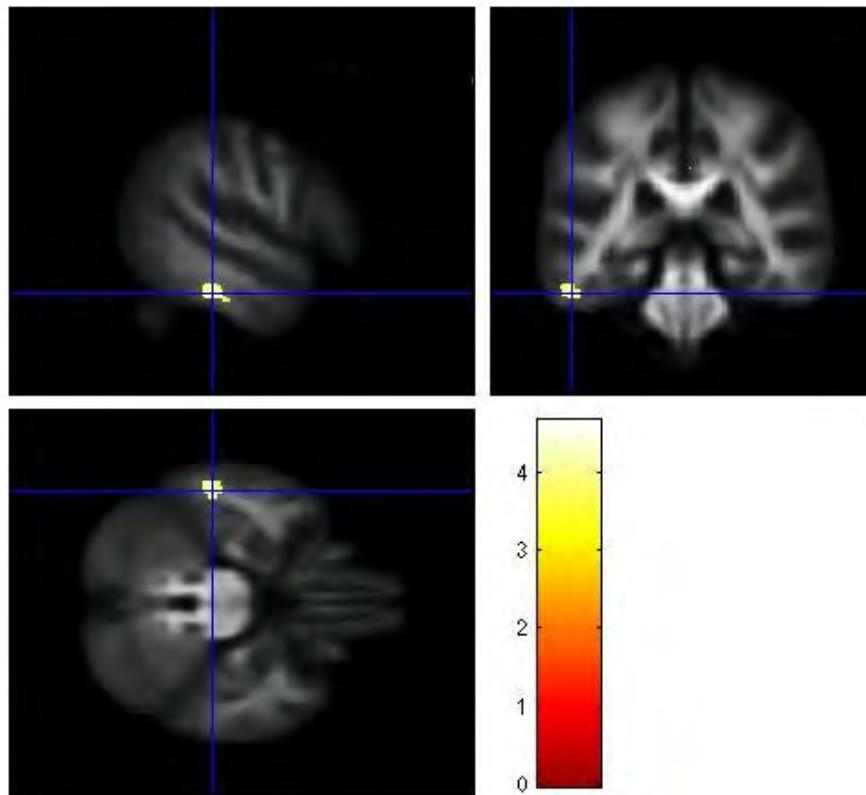
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Height threshold: T=3.16, p=0.001 (0.995)

Height threshold: T=3.16, p=0.001 (0.995)

Regional Reduction Of FA In SWEDD vs Control*

21 SWEDDs and 55 Controls



SWEDD < HC

covariates: age, sex

$p_{\text{FWE-corr}}$	0.146
p_{uncorr}	0.000
$q_{\text{FDR-corr}}$	0.176

Height threshold: T=3.21, p=0.001 (1.000)



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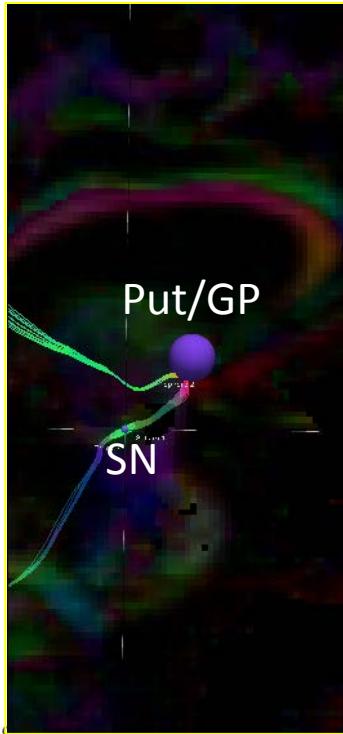


New Analysis: Tractography Of Striato-Nigral Tract

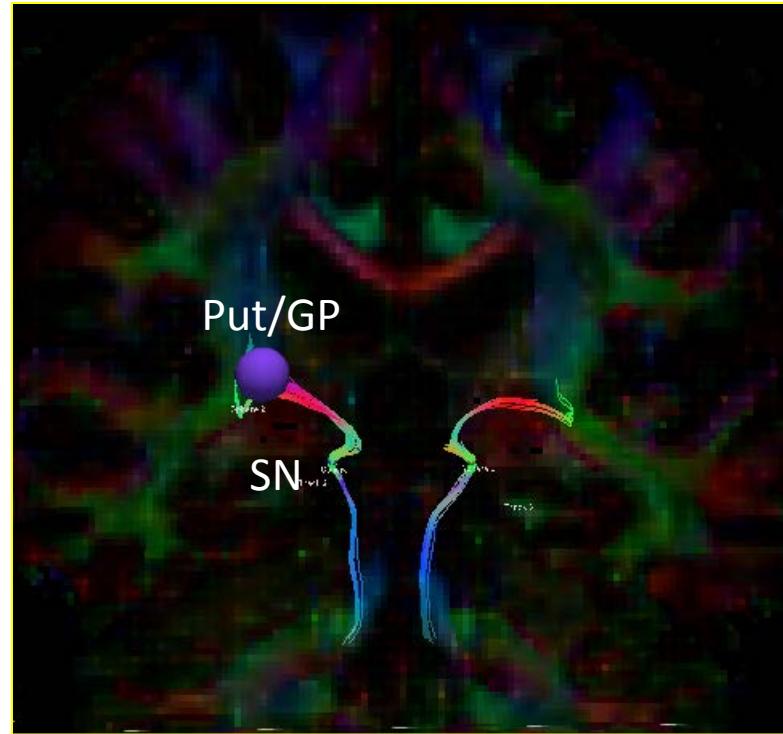
Tracing the nigro-striatal fibers

Seeding in post Putamen

Automated fiber tracking ends in SN pars compacta



Sagittal View



coronal

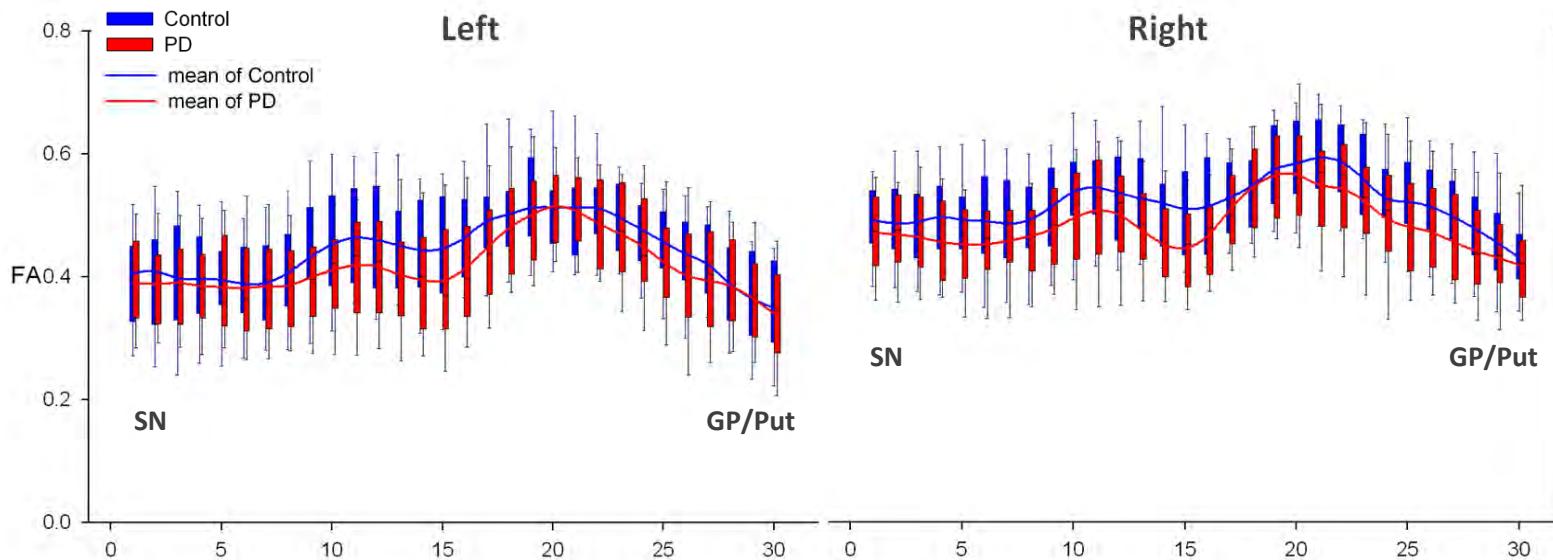


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FA Profile Along Striato-Nigral Tract



27 control 51 PD)

	Control	PD	p value
Fractional Anisotropy	0.45 ± 0.04	0.42 ± 0.04	0.002
Axial Diffusivity [$10^{-3}\text{mm}^2/\text{s}$]	1.21 ± 0.09	1.26 ± 0.10	0.05
Radial Diffusivity [$10^{-3}\text{mm}^2/\text{s}$]	0.58 ± 0.08	0.63 ± 0.10	0.02
Mean diffusivity [$10^{-3}\text{mm}^2/\text{s}$]	0.79 ± 0.08	0.84 ± 0.09	0.02

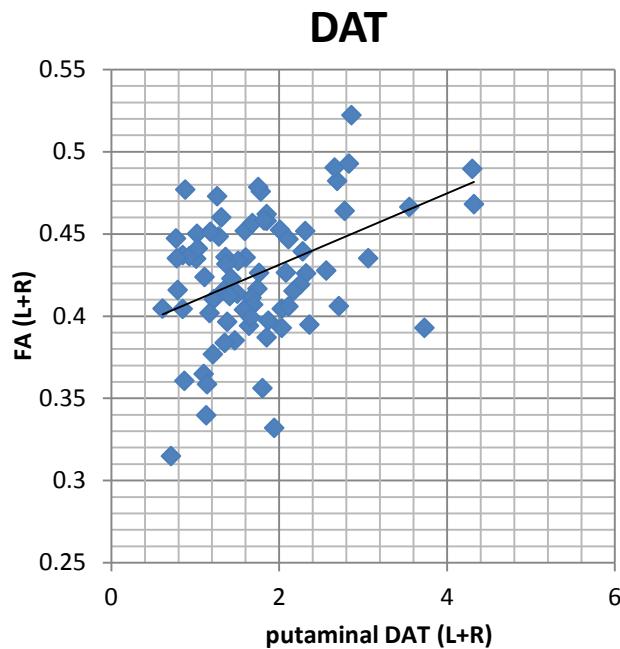


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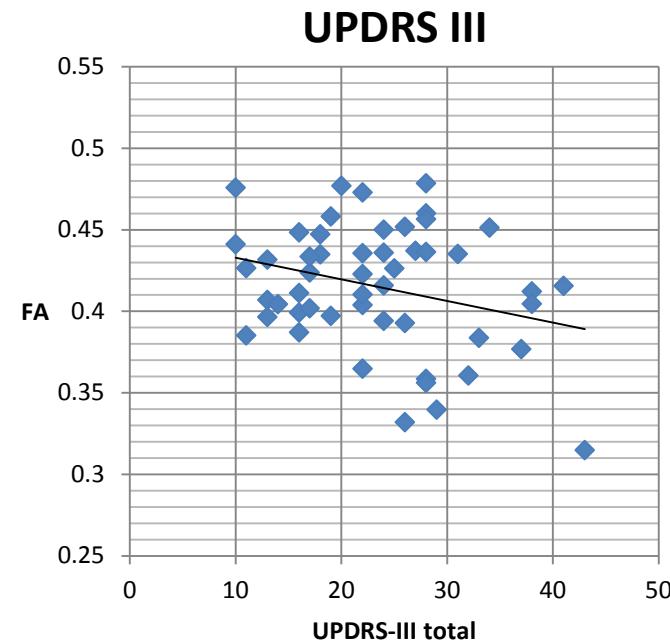
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Relation Between Radial Diffusivity Along The Tract And DAT/UPDRS



$$r = -0.42, \ p = 0.0001$$



$$r = -0.29, \ p = 0.04$$



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Conclusions

- I. Replication Of Reduced FA of the SN in PD
- II. Finding of reduced FA in SWEDD relative to PD suggests DTI is potentially more sensitive than DAT for detecting neural pathology
- III. A tract-based analysis is potentially more sensitive than a conventional ROI-based one for capturing DTI alterations in PD



Plans

- I. Papers in prep
 - I. DTI of substantia nigra
 - II. Voxelwise DTI analysis of SWEDD
 - III. FA Profile of the Striato-nigral fiber tract
 - IV. Methods Paper, multicenter DTI QC and reproducibility
- II. Proceed with longitudinal DTI analysis
- III. Multivariate (whole brain) analyses using supervised (e.g. SVM) and unsupervised (e.g. LLE) statistical learning methods
- IV. DTI Analysis of the structural connectome (network)



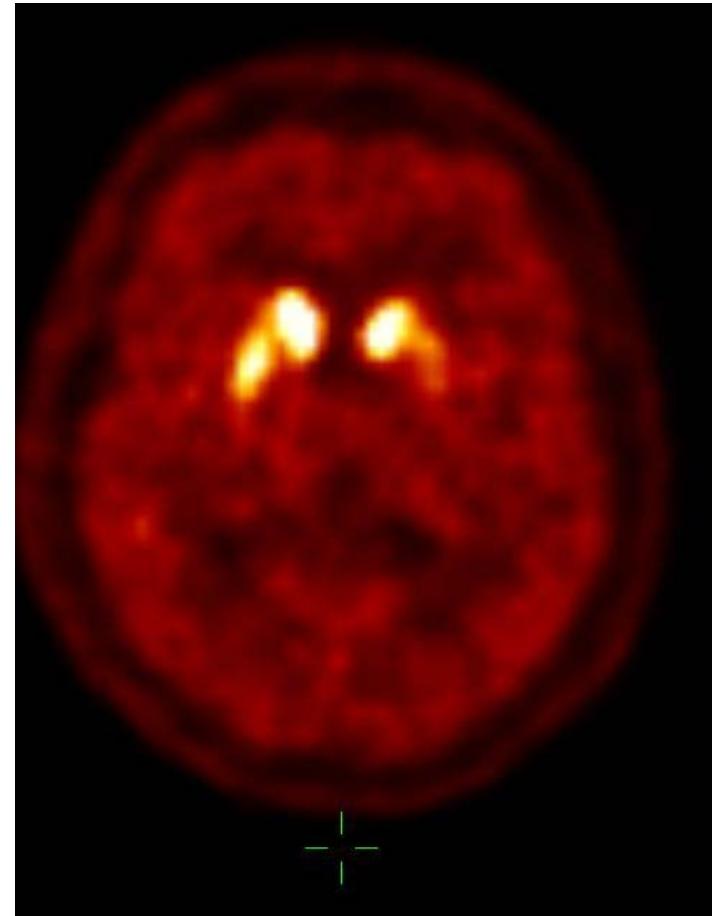
18F-AV-133: Targets VMAT2



Healthy Subject

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Mean putamen binding ratio = 3.52



Parkinson's Subject

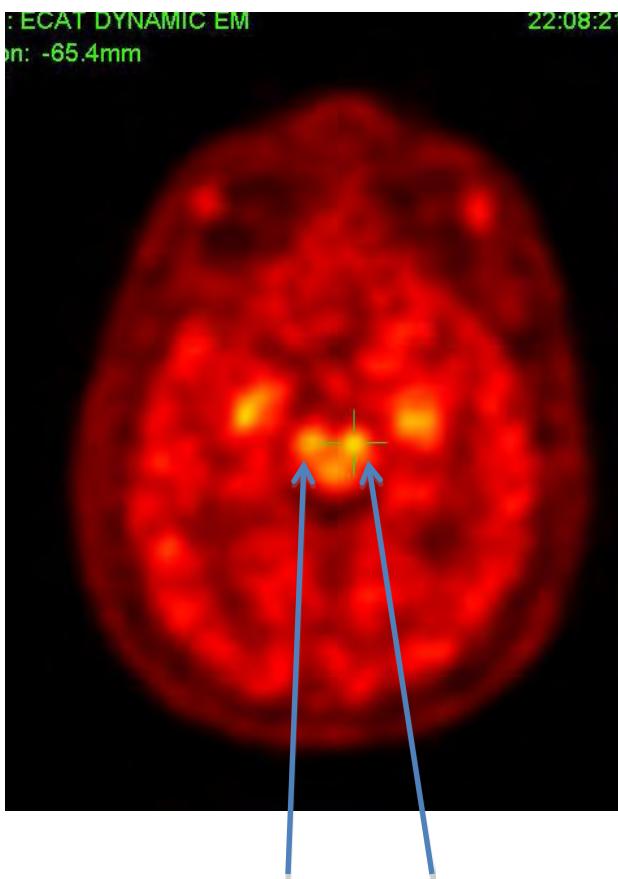
Mean putamen binding ratio = 1.36



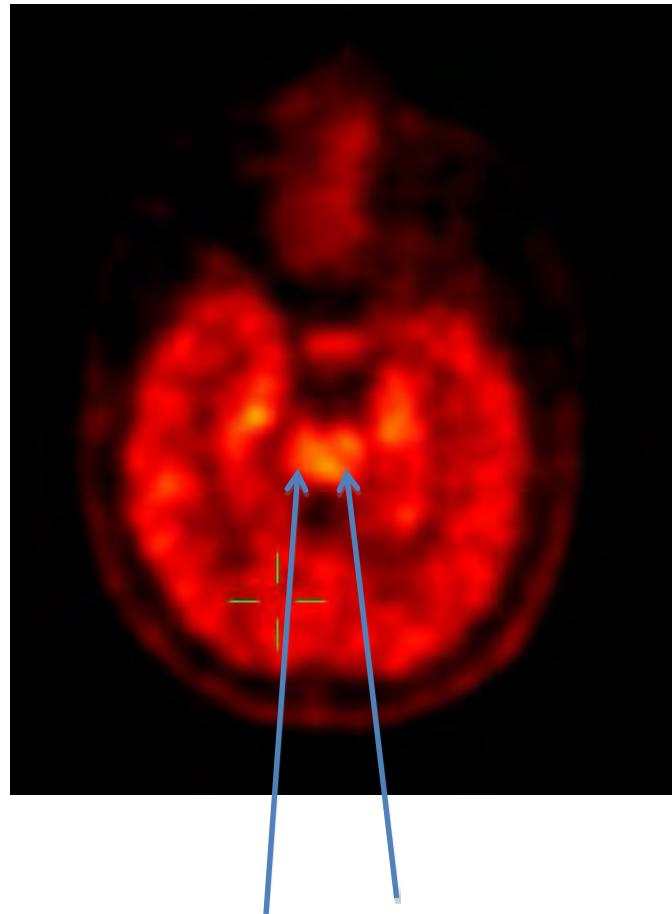
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18F-AV133 PET: possible to image the substantia nigra directly

Healthy Subject



PD Subject



Substantia nigra
SN ratio = 1.59

Substantia nigra
SN ratio = 0.91



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Extra Slides



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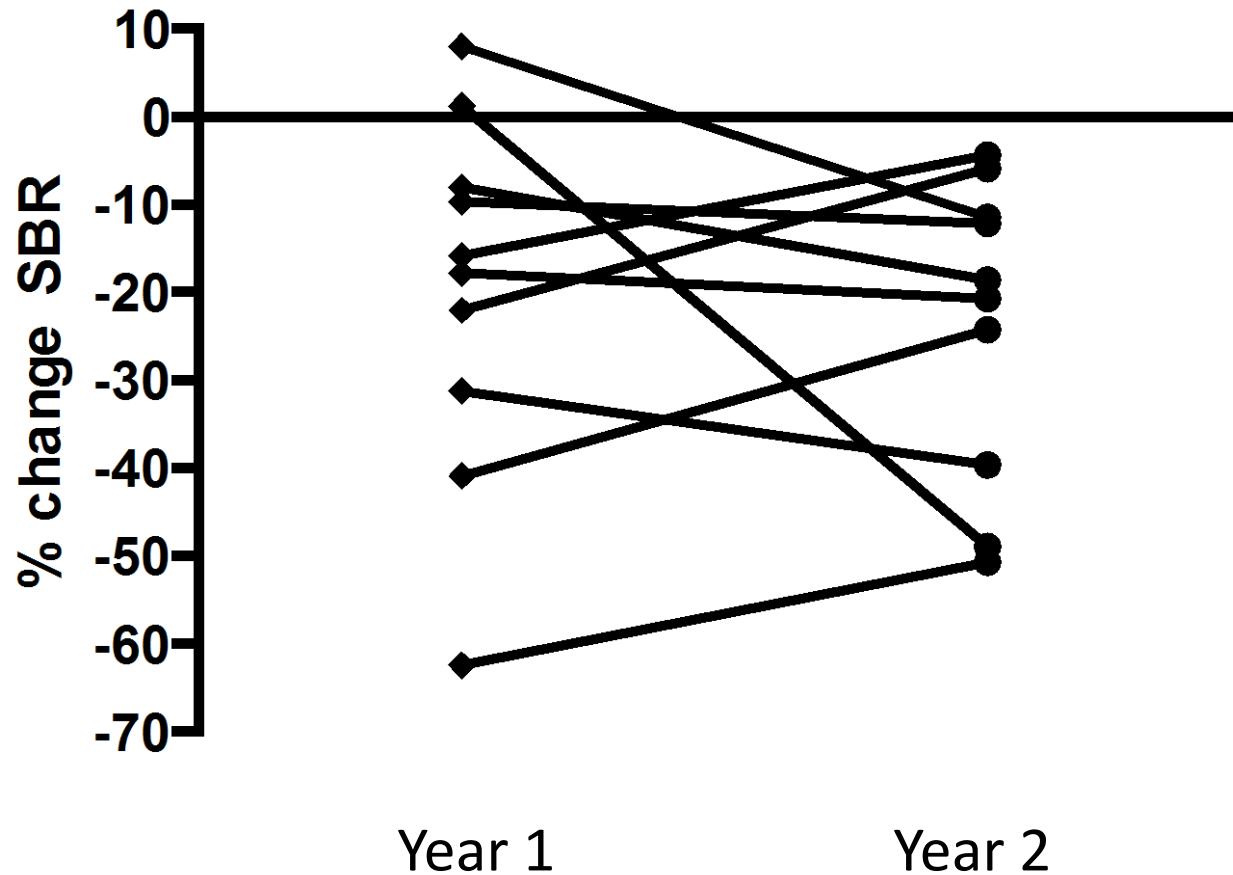
Discriminant function analysis

Number of Observations Classified into each Diagnosis			
True Diagnosis	Diagnosed As		Total
	Parkinson's Disease	Non-Parkinson's Disease	
Parkinson's Disease	240 (93.02%)	18 (6.98%)	258
Healthy Control	9 (6.57%)	128 (93.43%)	137
Total	249	146	395

Number of Observations Classified into each Diagnosis			
True Diagnosis	Diagnosed As		Total
	Parkinson's Disease	Non-Parkinson's Disease	
Parkinson's Disease	85 (95.51%)	4 (4.49%)	89
Healthy Control	10 (35.71%)	18 (64.29%)	28
Total	95	22	117



Percent Change from Baseline at Year 1 and Year 2



PPMI Study

Resting State sub-study

Darren Gitelman & Xue Wang
Northwestern University

Alen Zamanyan, Ivo Dinov, & Karen Crawford
Laboratory of Neuroimaging (LONI), UCLA



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Project goal and specific aims

- The primary goal of this sub-study is to acquire rsfMRI data on a subset of PPMI participants with Parkinson's disease and Controls, and to release this data to the scientific community.
- Specific Aims:
 - Scan 30 PD patients and 30 controls at either study entry or 1 year follow-up.
 - Perform QC measures on phantom data obtained on the same day as subject scanning in order to assess scanner noise and stability.
 - Perform QC measures on human subject data to assess subject specific factors (e.g., movement) affecting data quality.
 - Repeat scanning of PD patients over the next 3-4 years



Recruitment

- Parkinson's disease: 30
- Controls: 30

Group	Good	Bad	Questionable	Total
PD	13	2	7	23
Control	3	0	1	4
SWEDD	1	0	1	2
Total	17	2	9	29



QC pipelines

- Two QC pipelines implemented in LONI
 - Phantom QC: examine the basic imaging parameters and the scan quality of the MR scanner of the same day of the human scan
 - Human QC: examine the basic imaging parameters and the human related artifacts (eg motion)



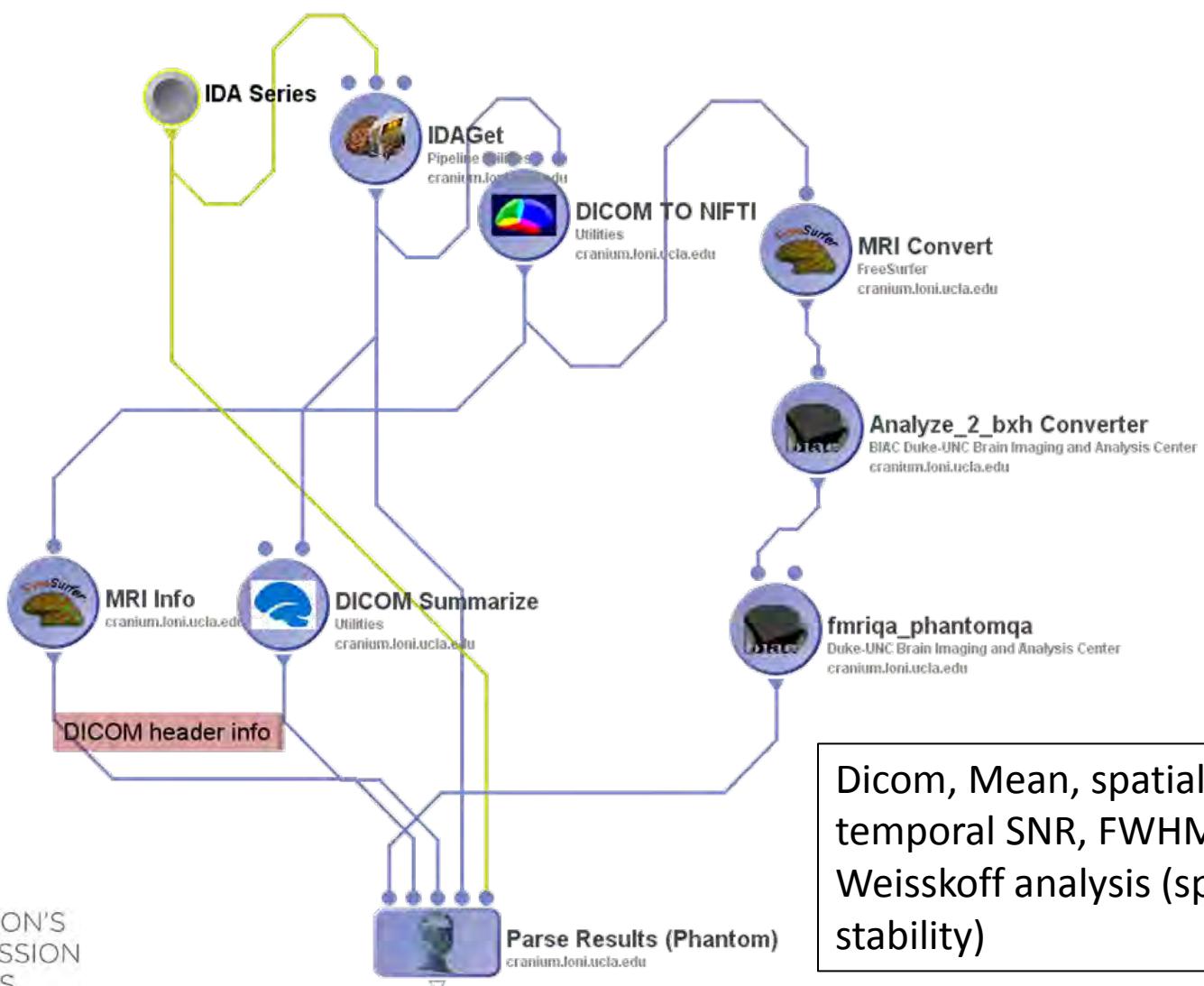
LONI Pipeline



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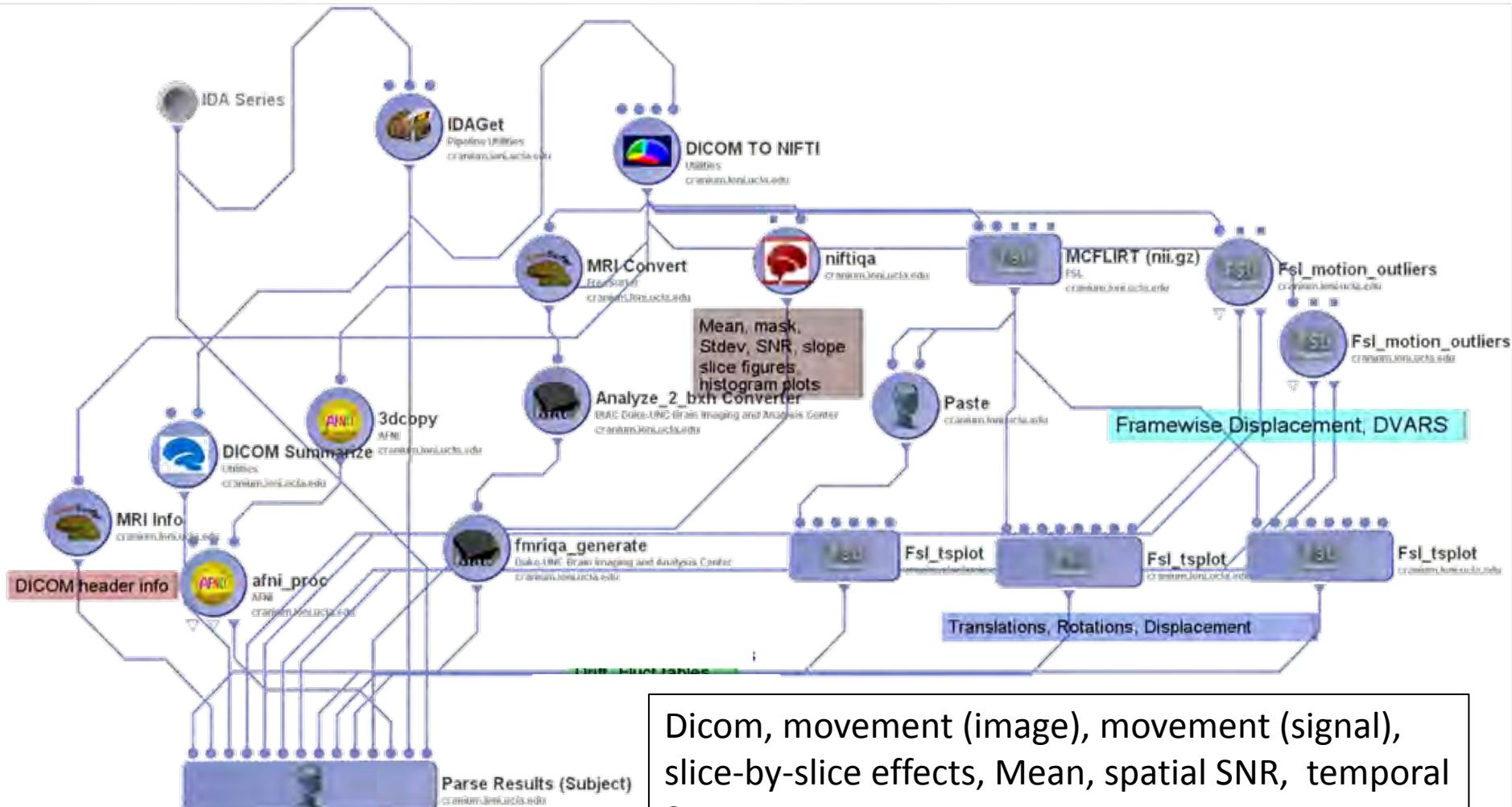
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Phantom QC pipeline

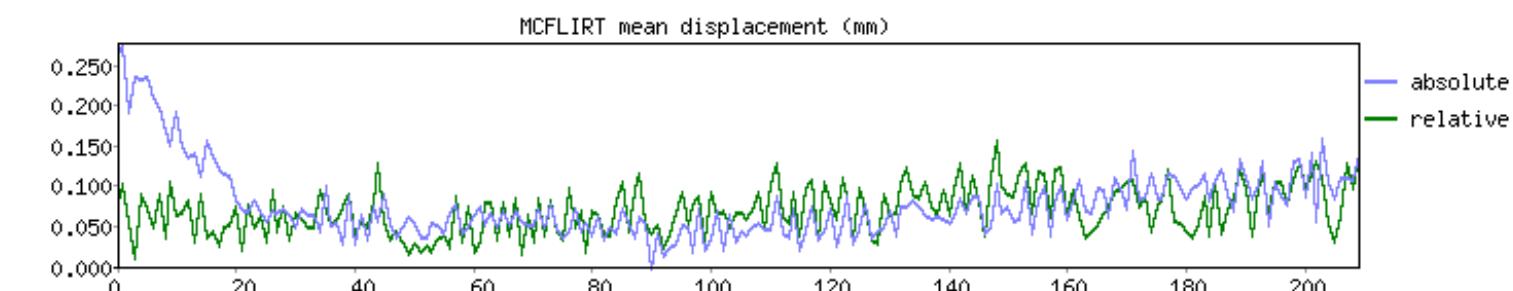
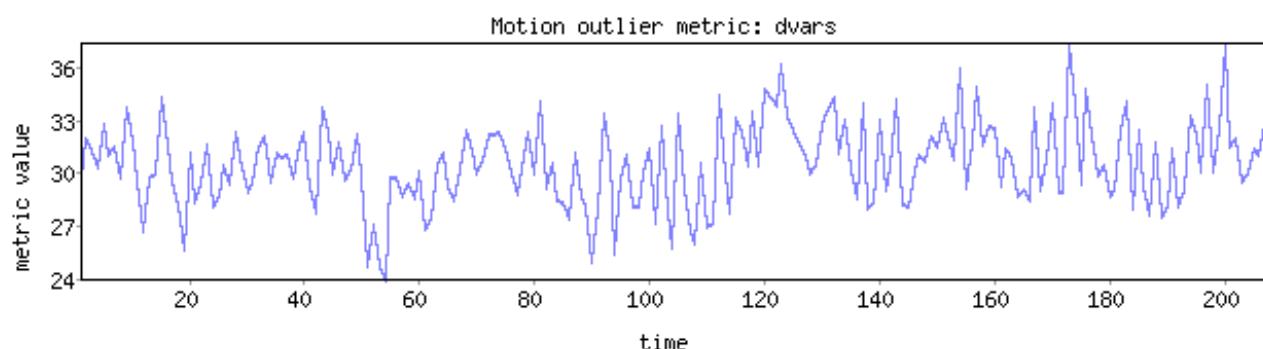
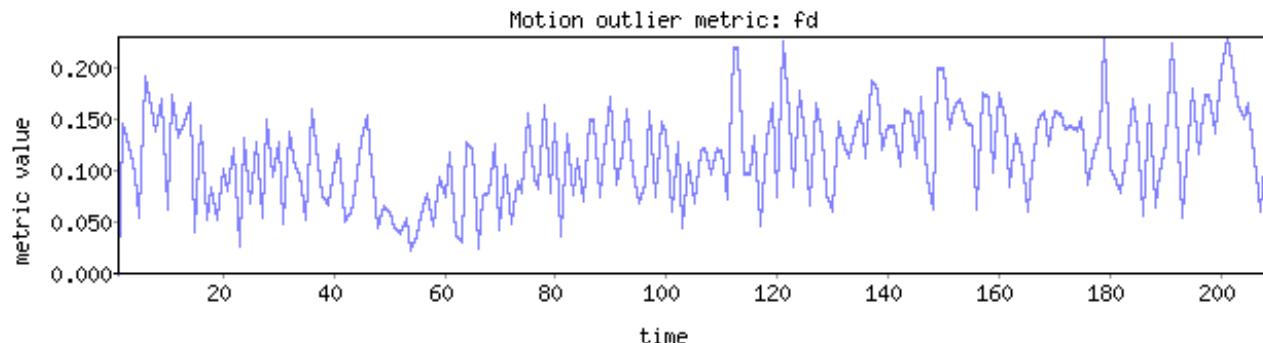


Dicom, Mean, spatial SNR,
temporal SNR, FWHM,
Weisskoff analysis (spatial
stability)

Human QC pipeline

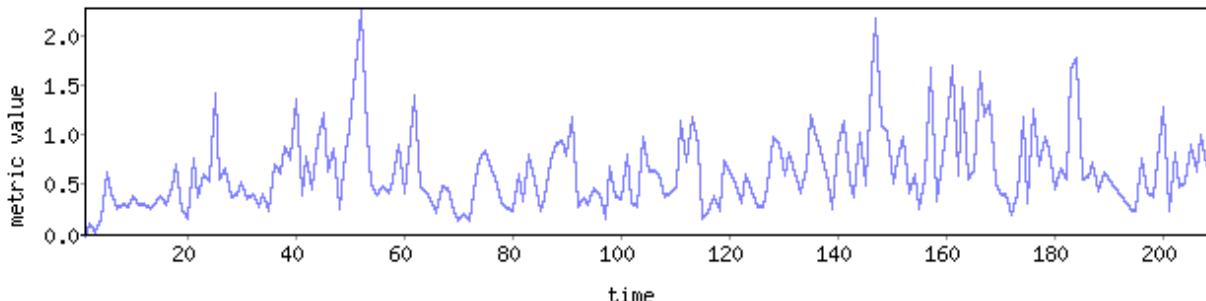


Good data: 351070

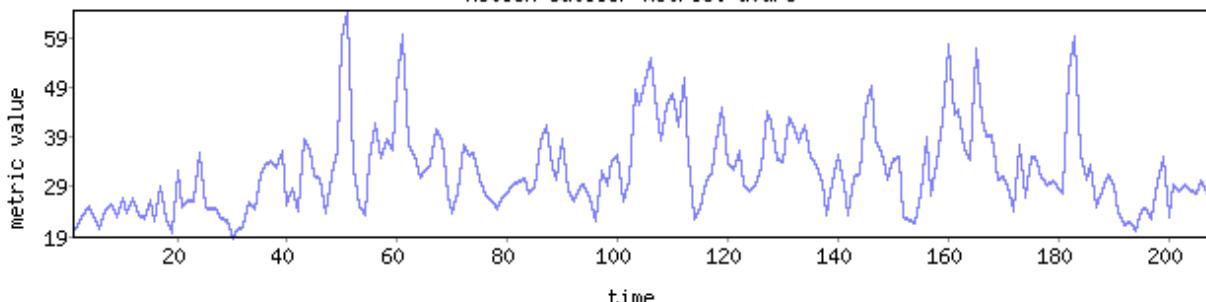


BAD Data: 362647

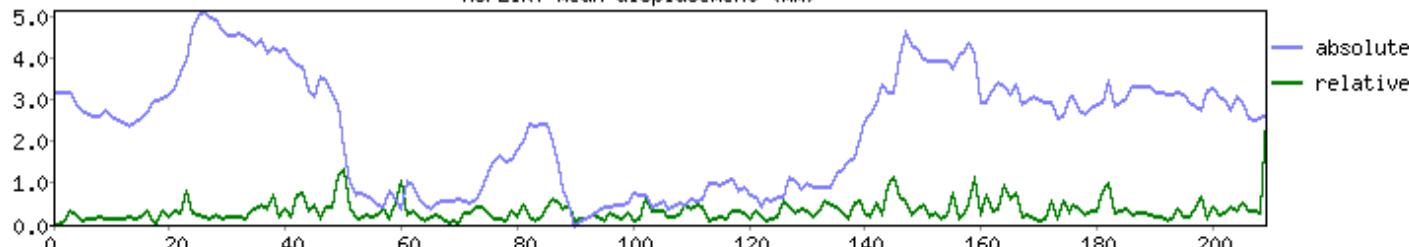
Motion outlier metric: fd



Motion outlier metric: dvars



MCFLIRT mean displacement (mm)



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Resting state data quality

1. BAD data: Repetitive, non-random movements
>1-2 mm, and any movement >3 mm.
2. Make participants as comfortable as possible
3. Instruct participants to keep as still as possible
4. Instruct subjects to avoid repetitive movements
(oral movements, blinking, etc.)
5. Constrain head movements: calipers, pads, etc.
6. Run resting state scan as the 2nd or 3rd sequence



PPMI Biorepository Update

PPMI Annual Meeting

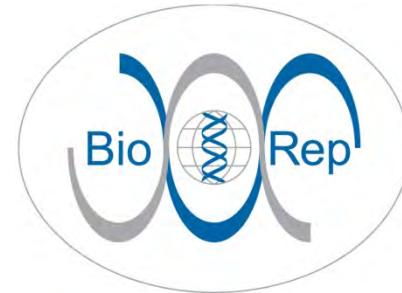
May 7-8, 2013

Alison Scutti, MS

Coriell Institute for Medical Research



CORIELL INSTITUTE
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SUBMISSIONS (VISITS) RECEIVED



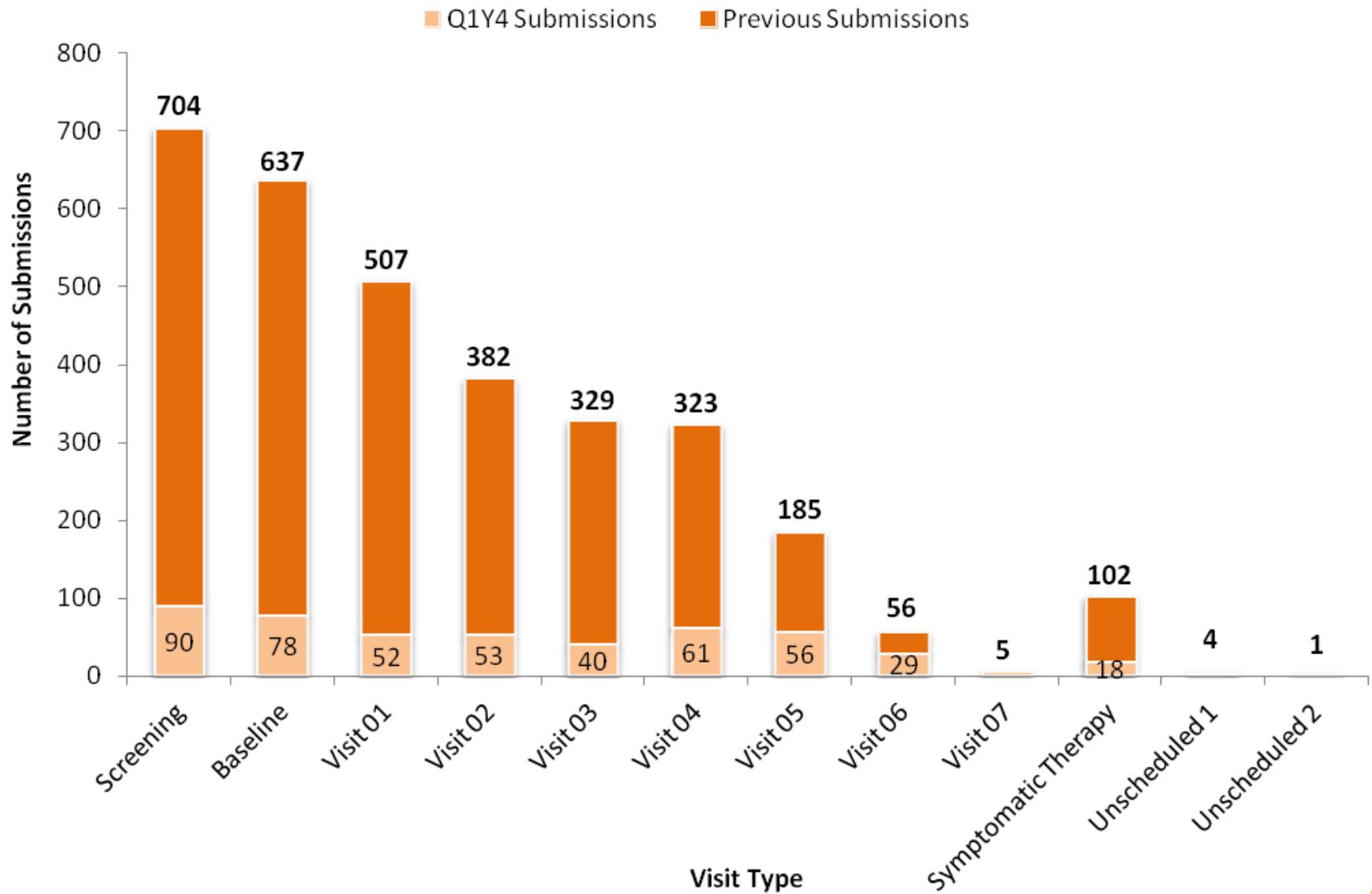
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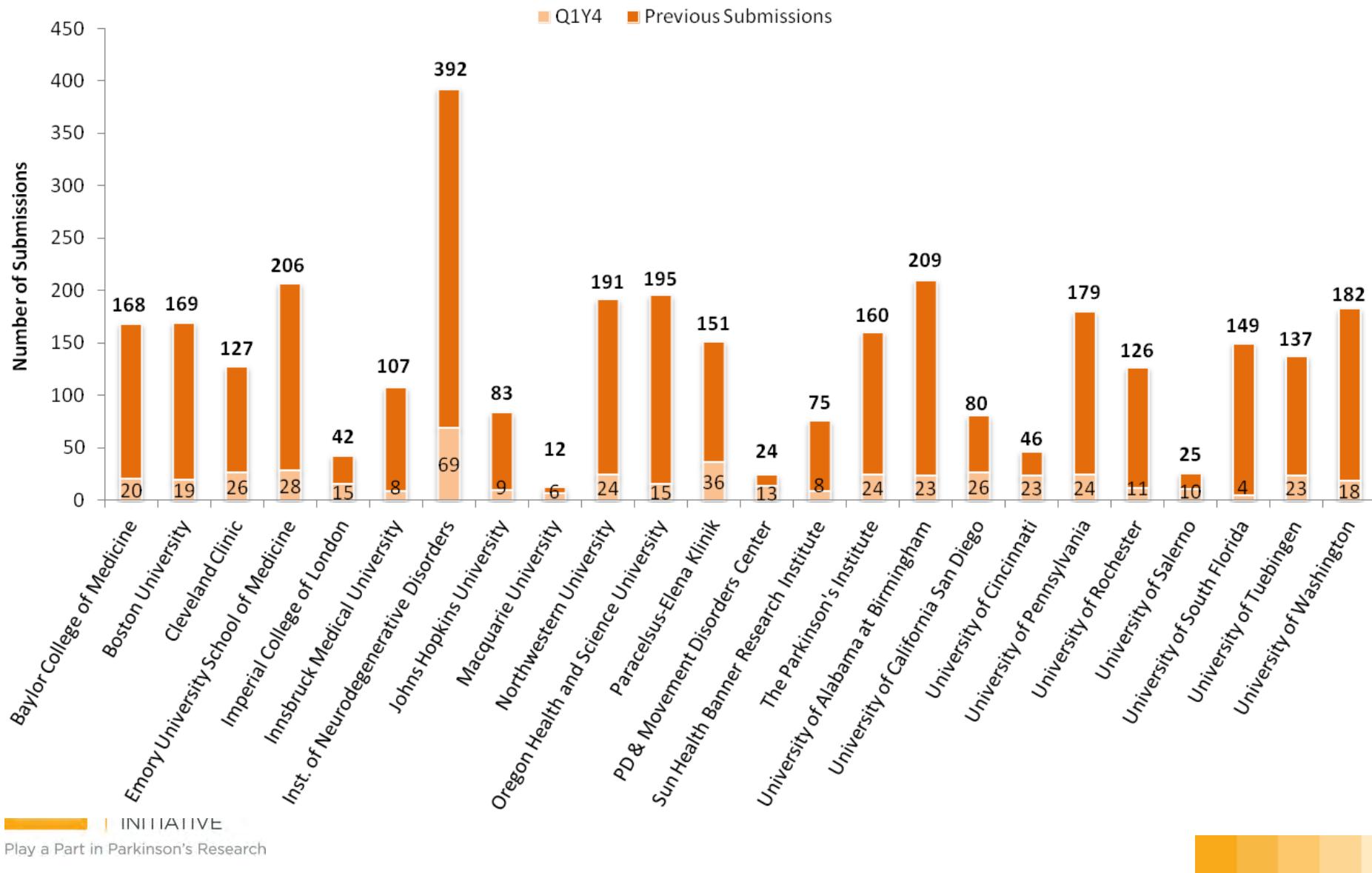


PPMI Sample Submission Summary

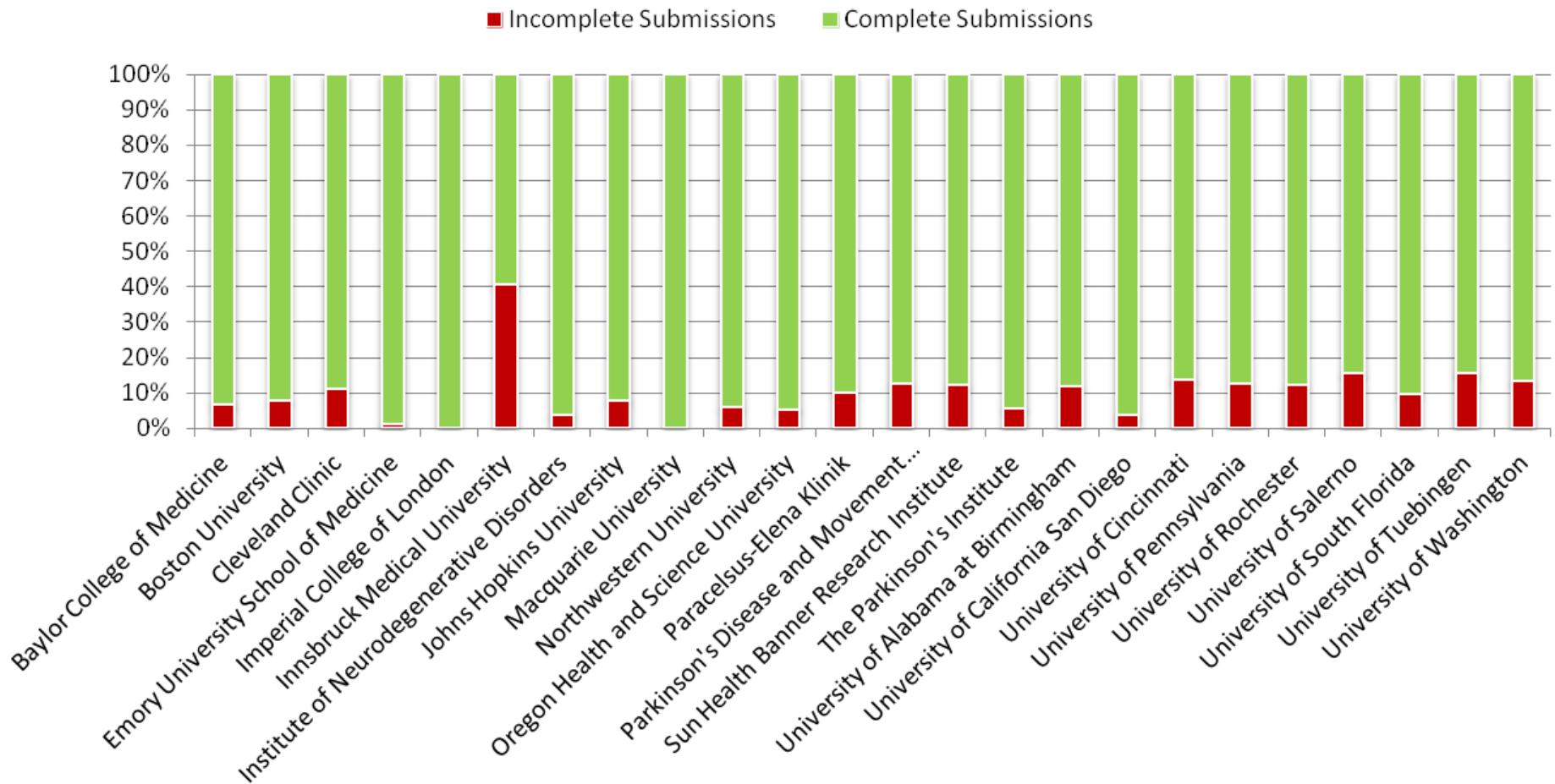
3,235 submissions from 764 unique subjects



PPMI Submissions per Clinical Site



Complete Submissions per Site



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SPECIMEN PROCESSING & QC

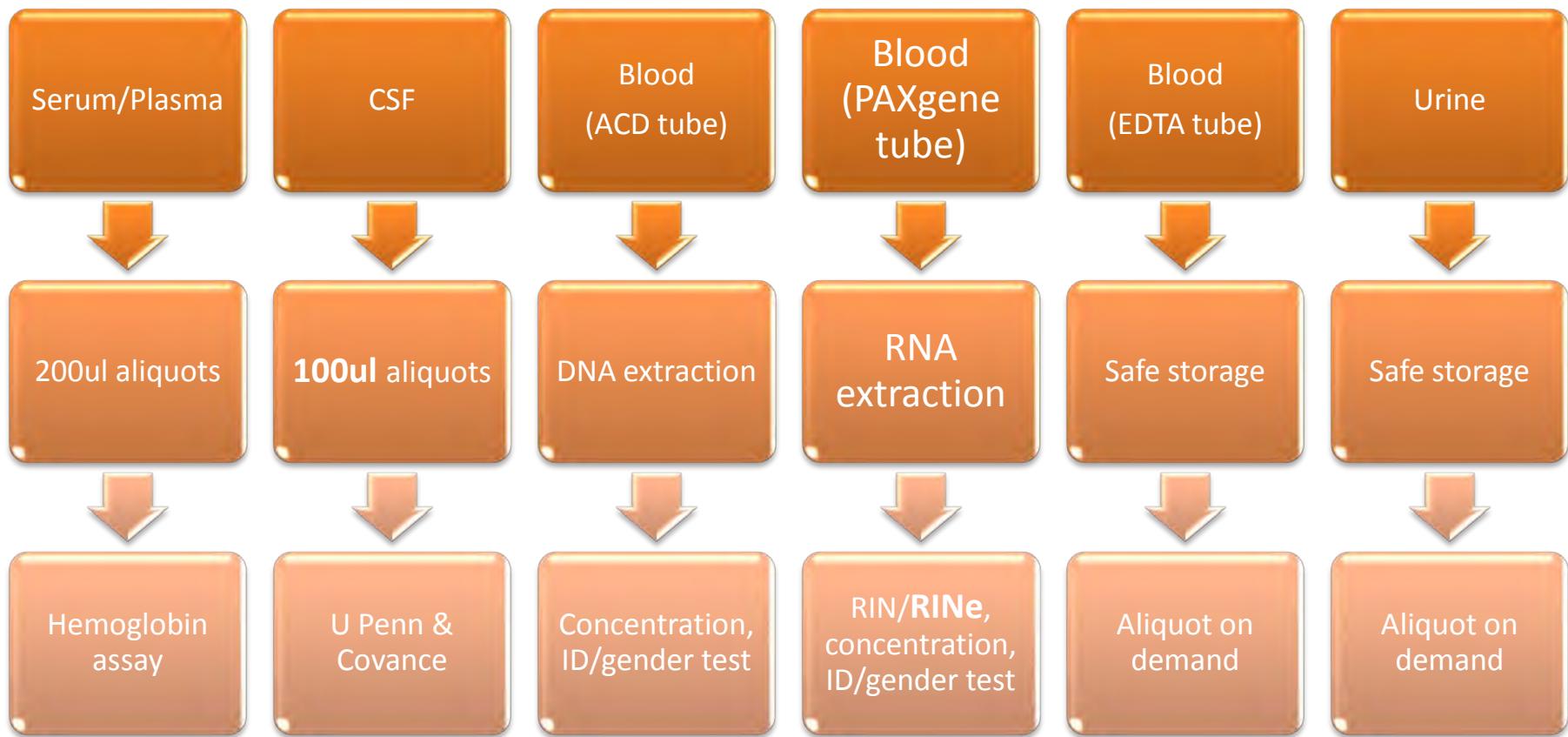


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Sample Processing Overview

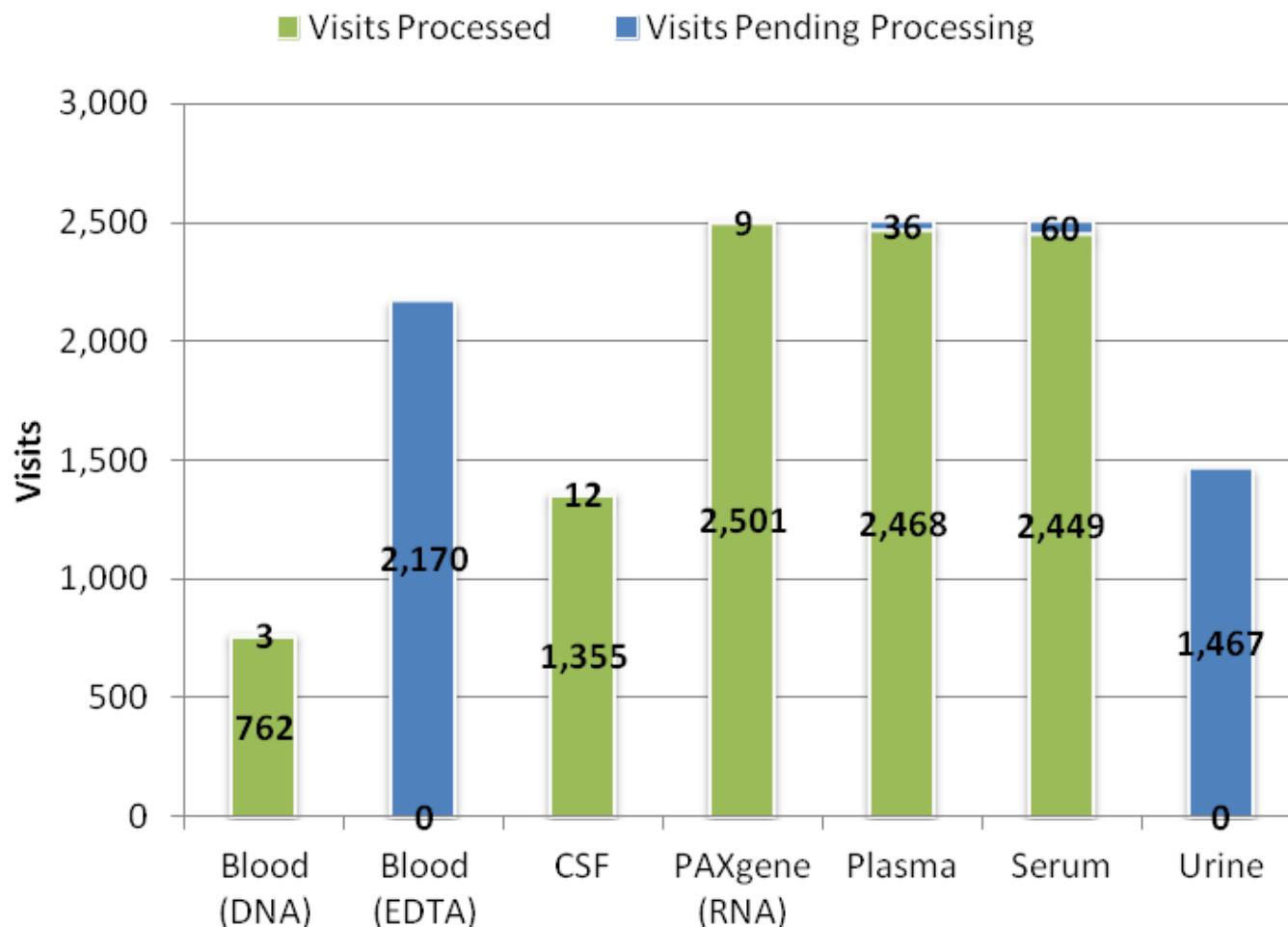


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Sample Processing Summary

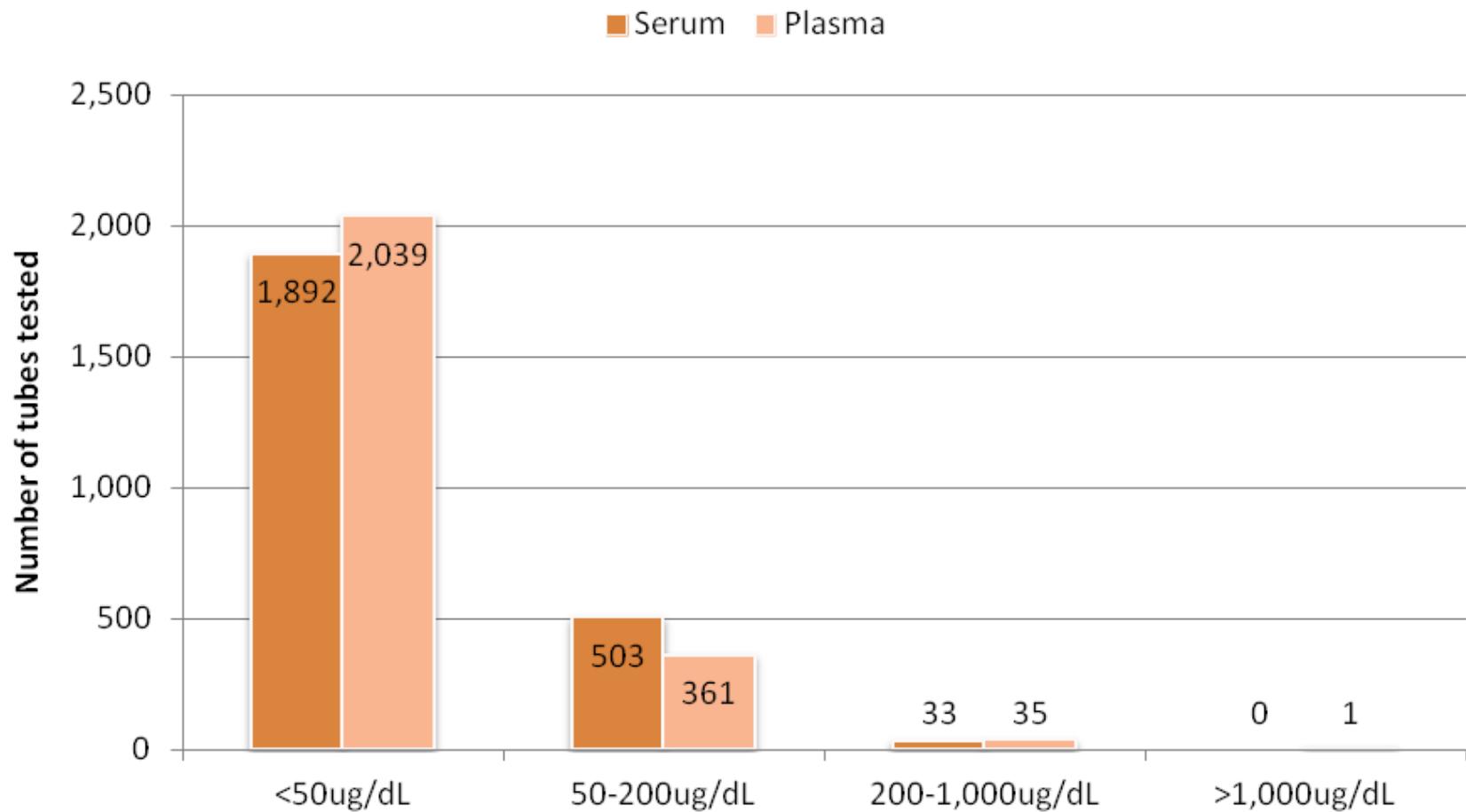


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Serum & Plasma Total Hemoglobin

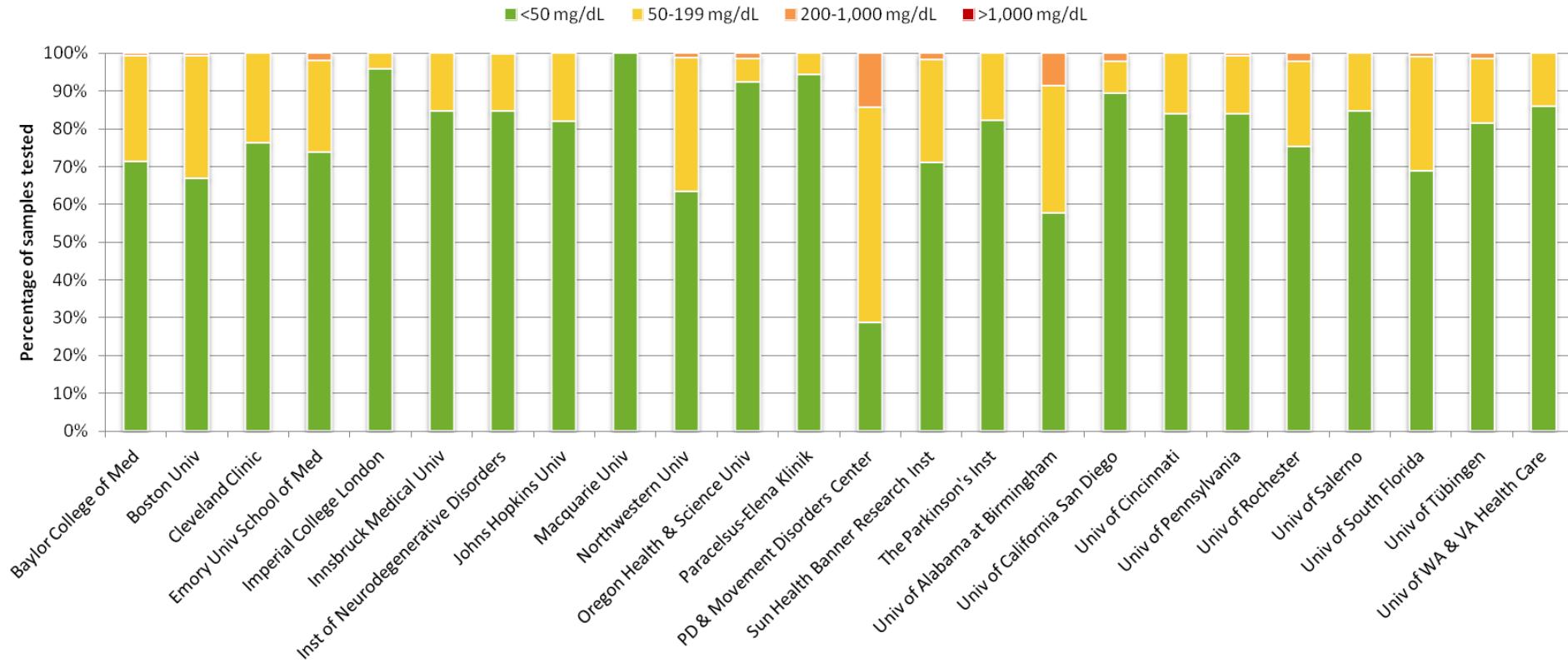


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Serum & Plasma Total Hb per Site

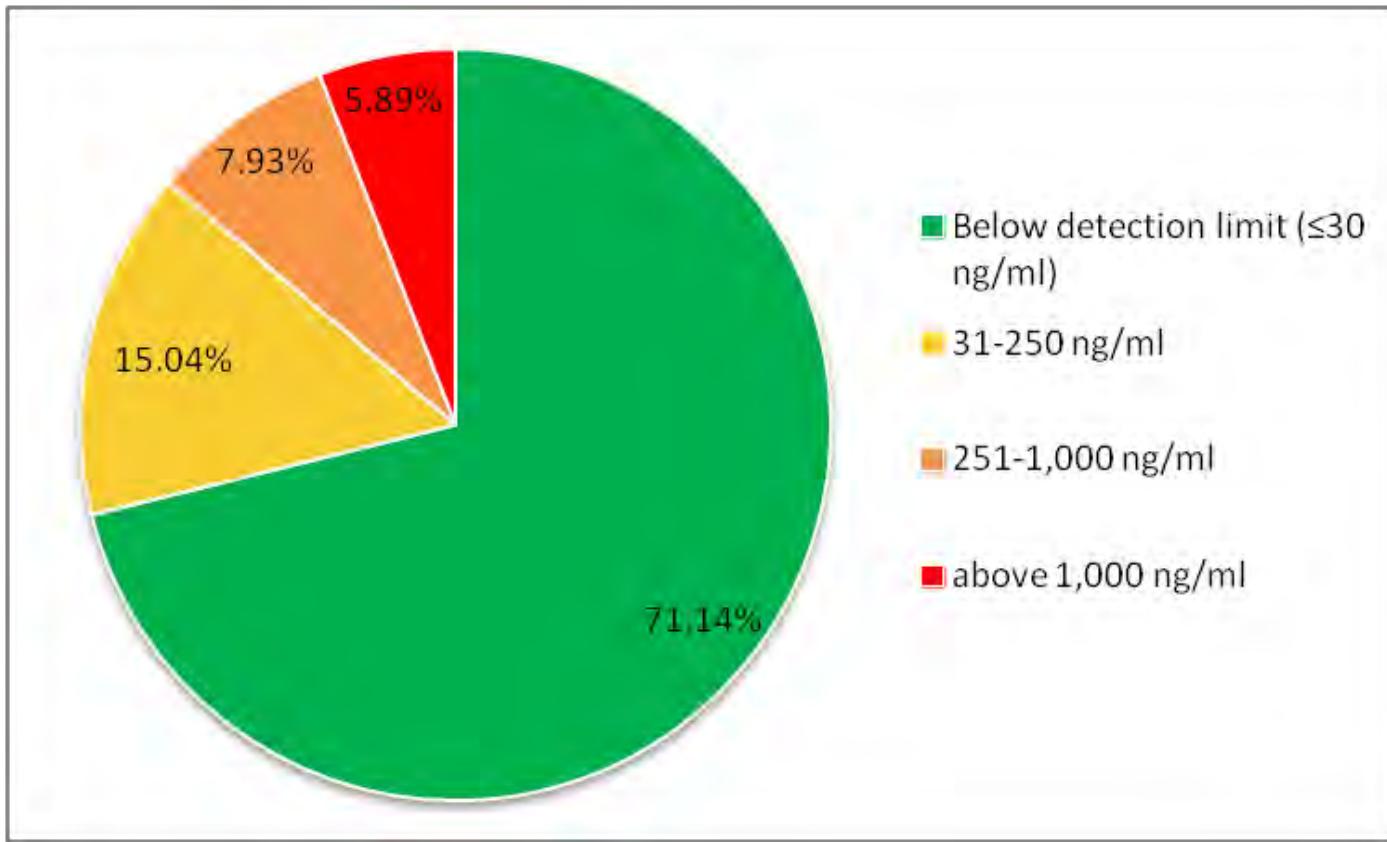


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CSF Total Hemoglobin

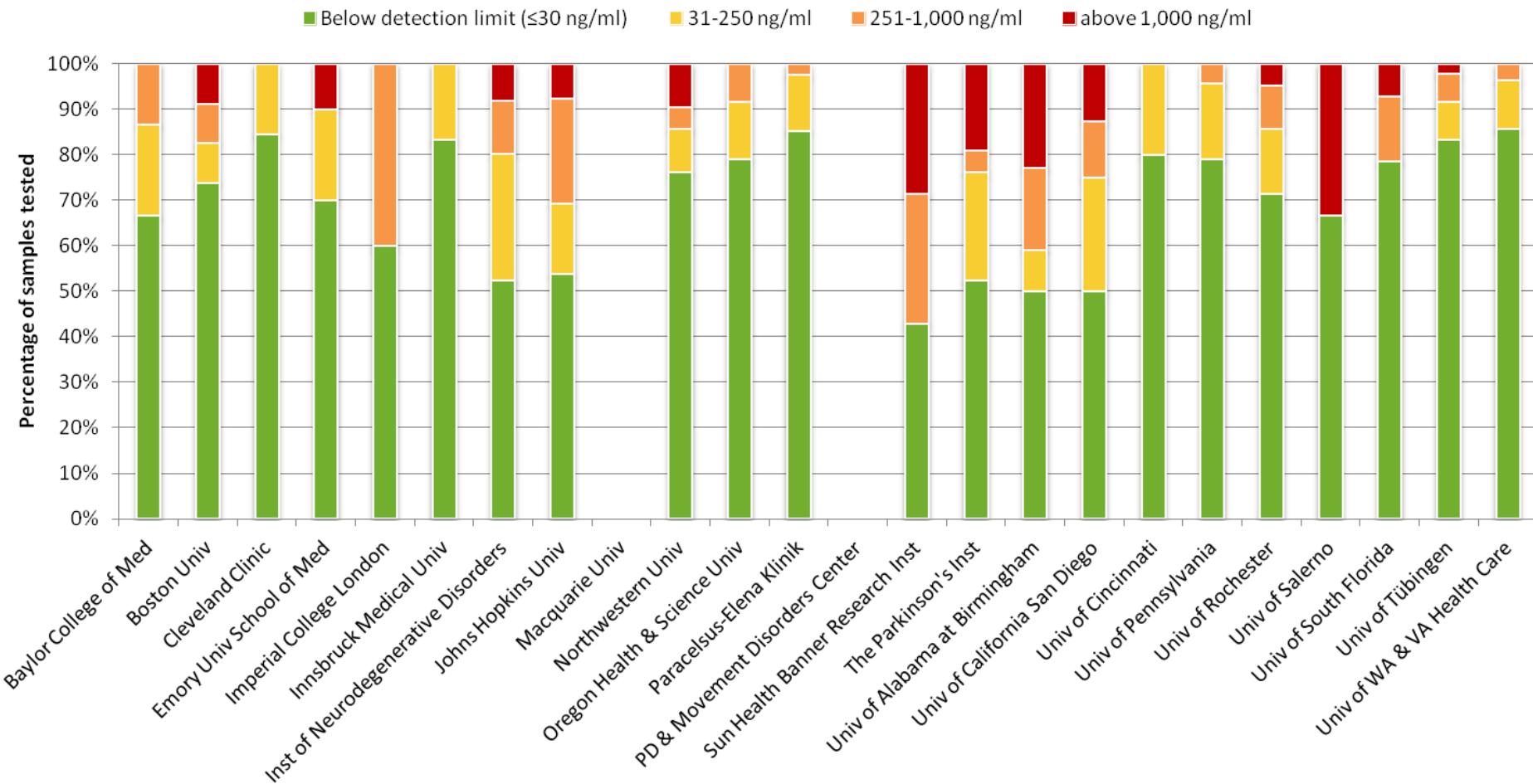


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CSF Total Hemoglobin per Site

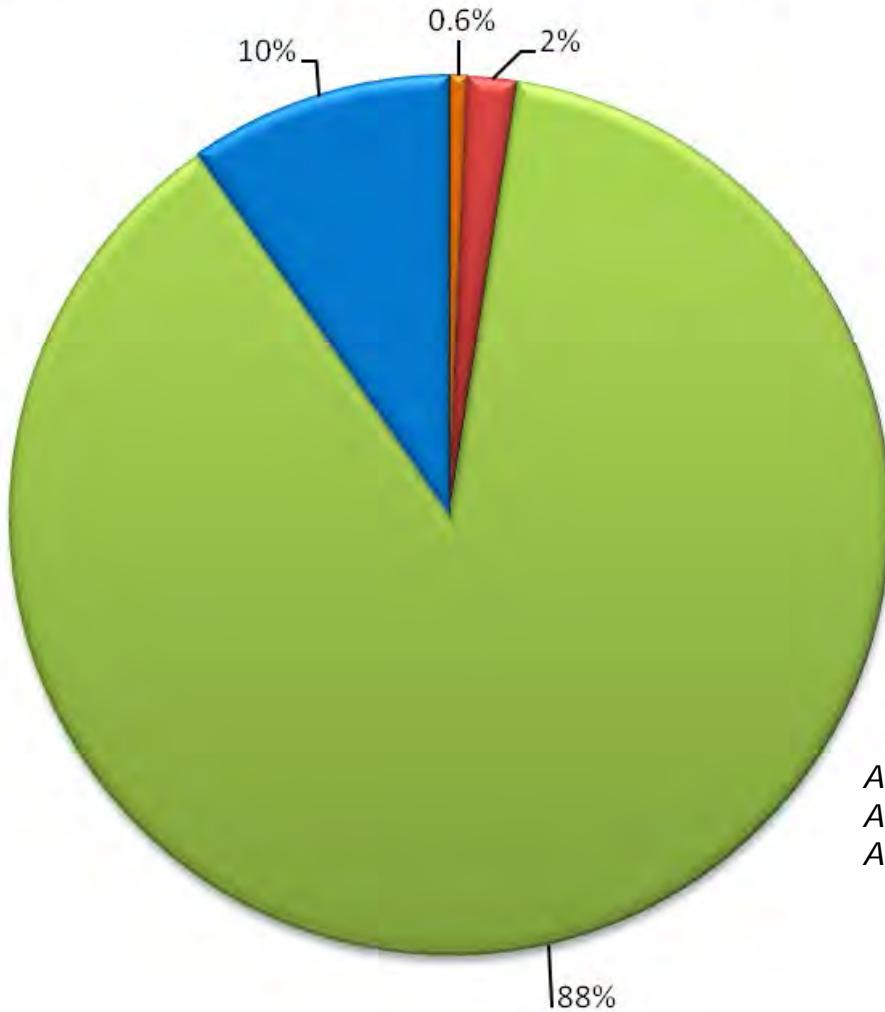


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DNA Extraction Progress

■ Discarded Upon Receipt ■ QC Fail ■ QC Complete ■ QC In Progress



*Average 260/260: 1.86
Average conc: 0.31 ug/ul
Average total yield: 188.12 ug*

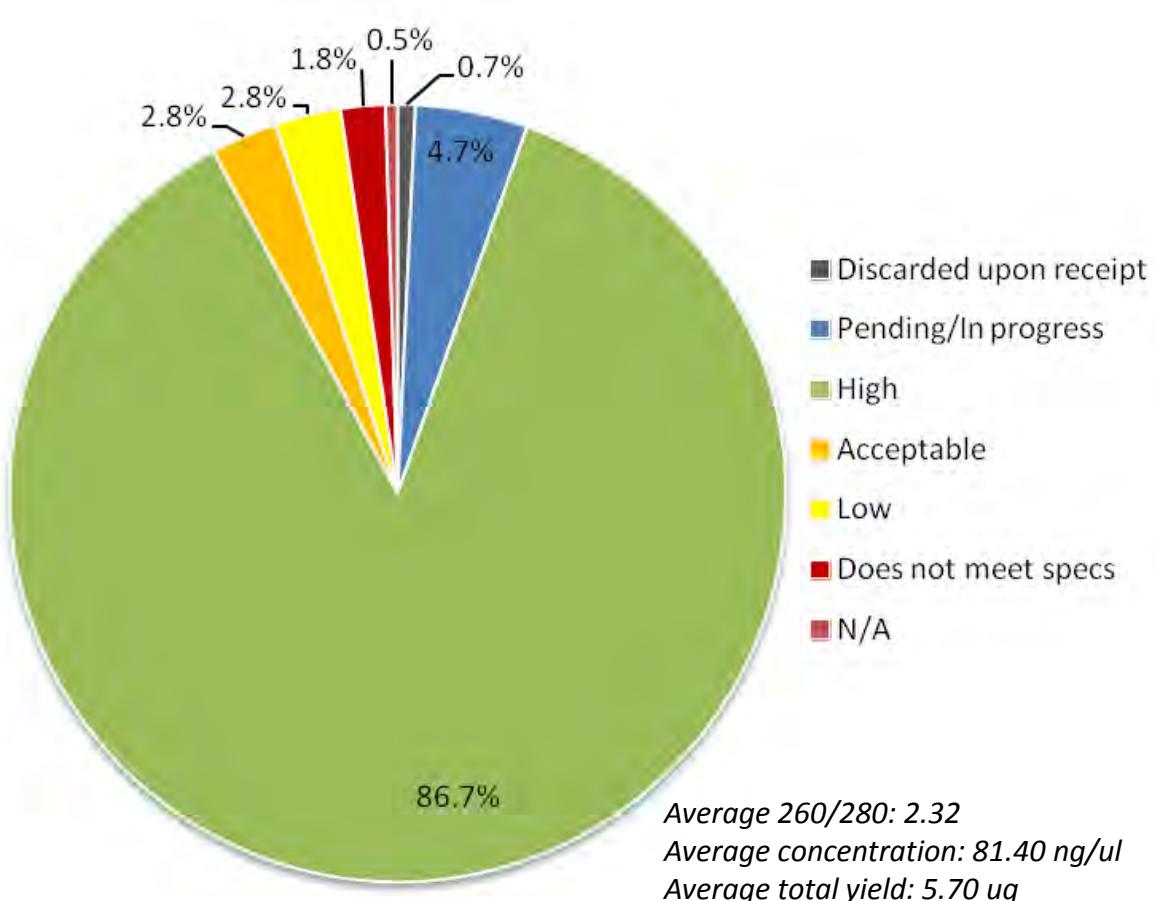
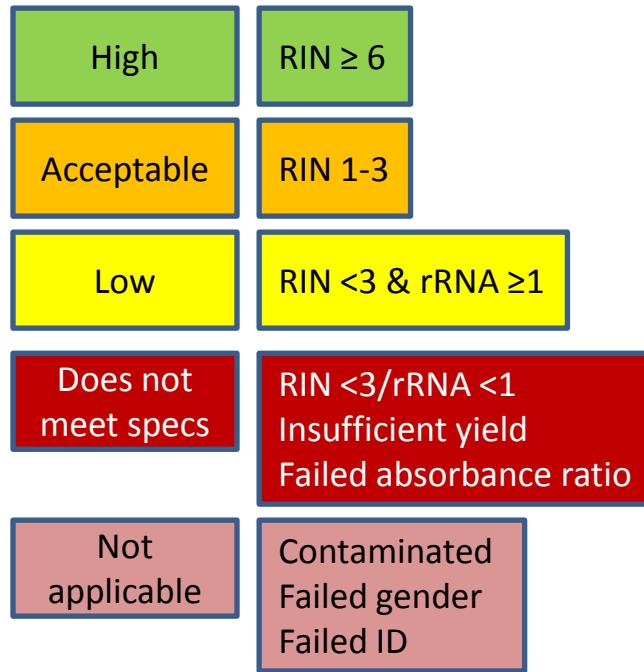


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PAXgene RNA Extractions



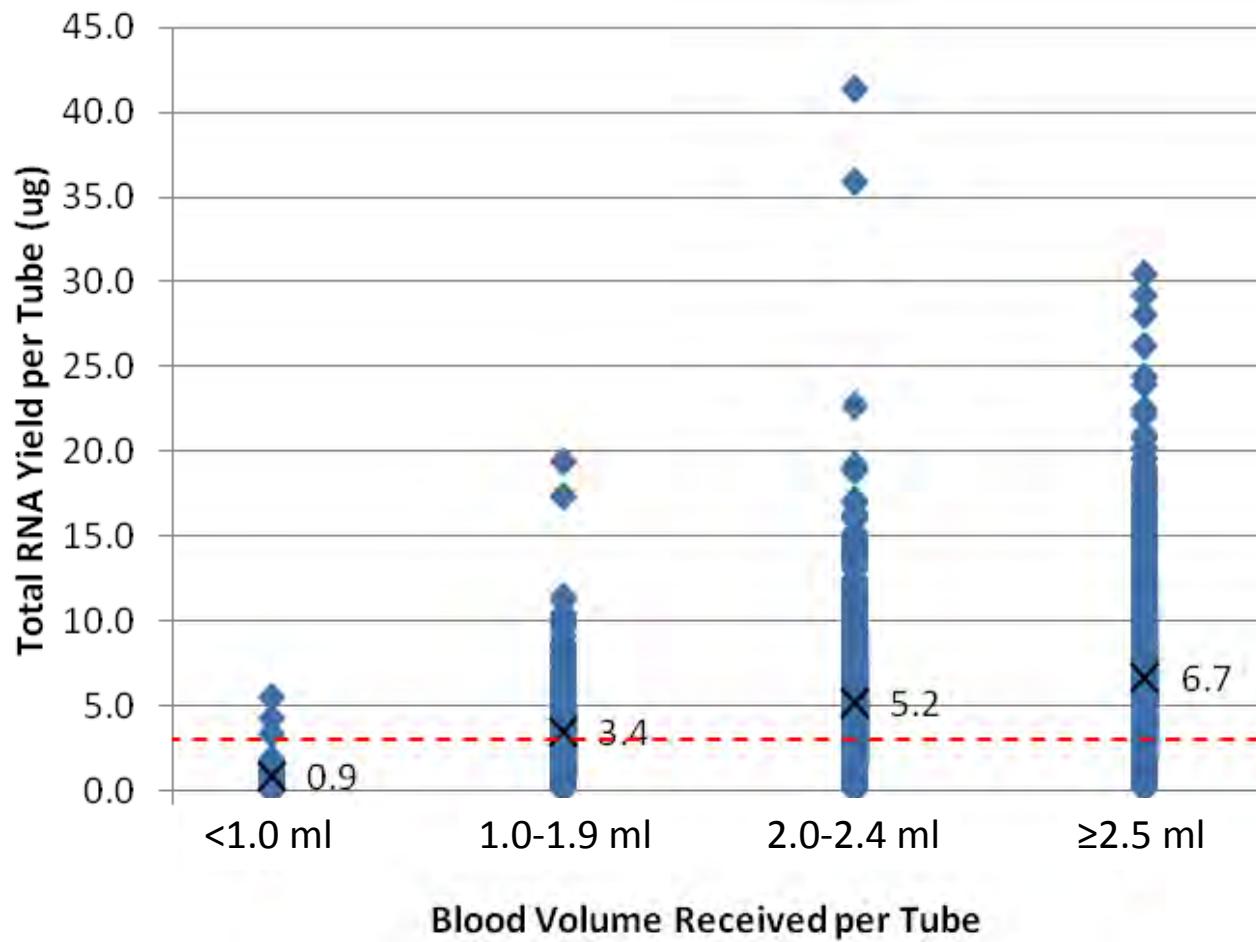
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PAXgene Blood Volume vs Total RNA Yield

Expected yield per manufacturer = ≥3ug RNA per 2.5ml of blood



Blood Volume	≥3ug Yield
<1ml (n=55)	6%
1-1.9ml (n=547)	50%
2-2.4ml (n=1,881)	78%
≥2.5ml (n=2,509)	90%



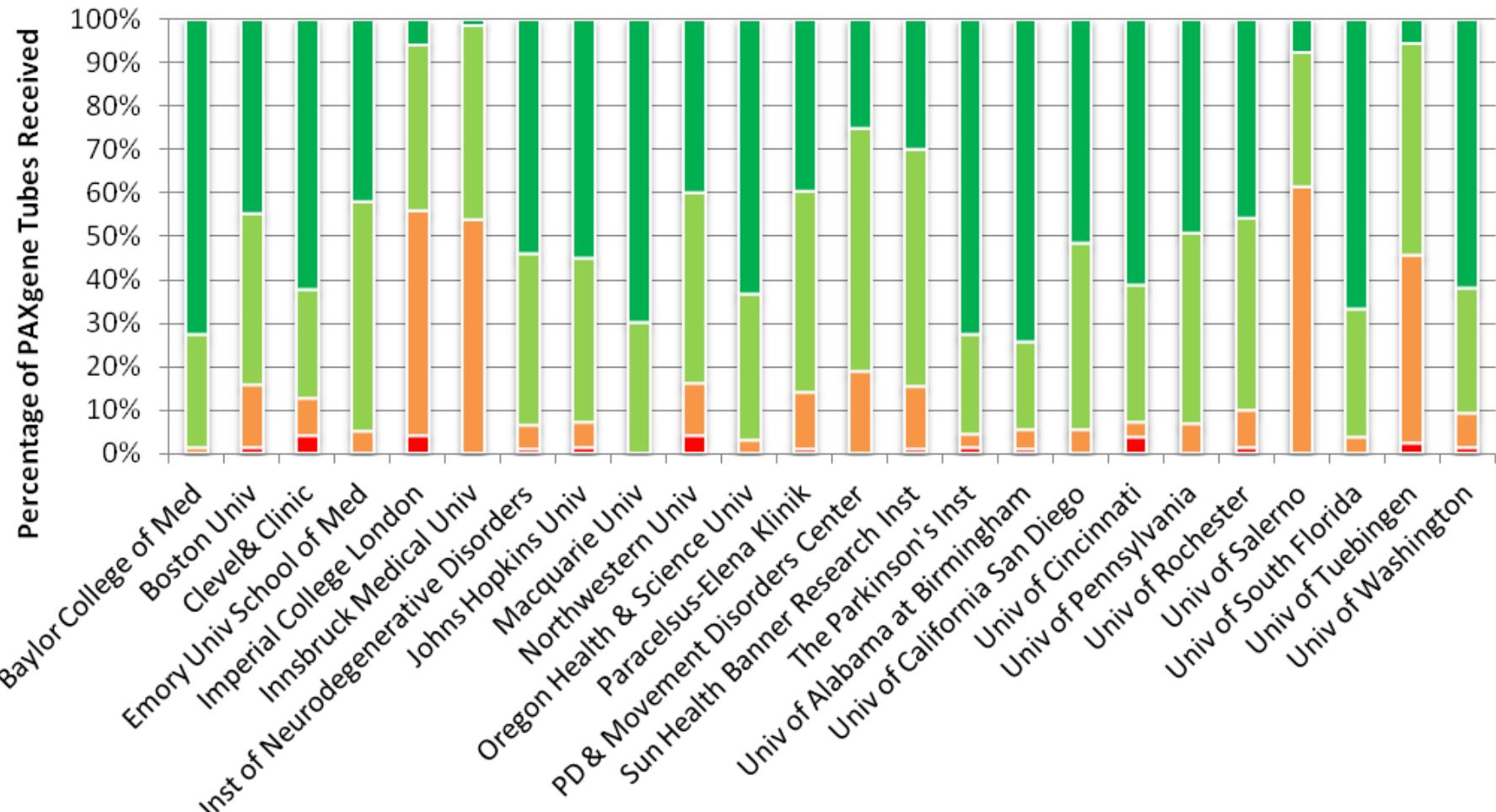
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PAXgene Blood Volume vs Total RNA Yield per Site

■ <1ml ■ 1-1.9ml ■ 2-2.5ml ■ ≥2.5ml



SPECIMEN DISTRIBUTION



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Distribution of PPMI Biospecimens

Institution	Research Intent	Specimen Type	Subjects	Visits
University of Pennsylvania/Covance	Biomarker Analysis	CSF	266	583
National Institute on Aging	Genotyping	DNA	561	561
Brigham & Women's Hospital	Biomarker Analysis	RNA	340	340



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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
 - 20 LOIs submitted
 - 4 Full Proposal Invited



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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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Genetics in PPMI

Andrew Singleton



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Andrew Singleton: singleta@mai.nih.gov



- Susan Bressman
- Marcel van der Brug
- Stuart Factor
- Tatiana Foroud
- Spyros Papepetropoulos
- Andrew Singleton*
- Dave Stone
- Mark Frasier (MJFF)



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Genetics in PPMI

- Probably not used as a discovery cohort for genetics by itself
- Mutation identification and risk profiling
- Most useful as a covariate in the biomarker studies
- Incredibly valuable with other studies on disease subtype (progression etc)
- Immediate availability of data a boon

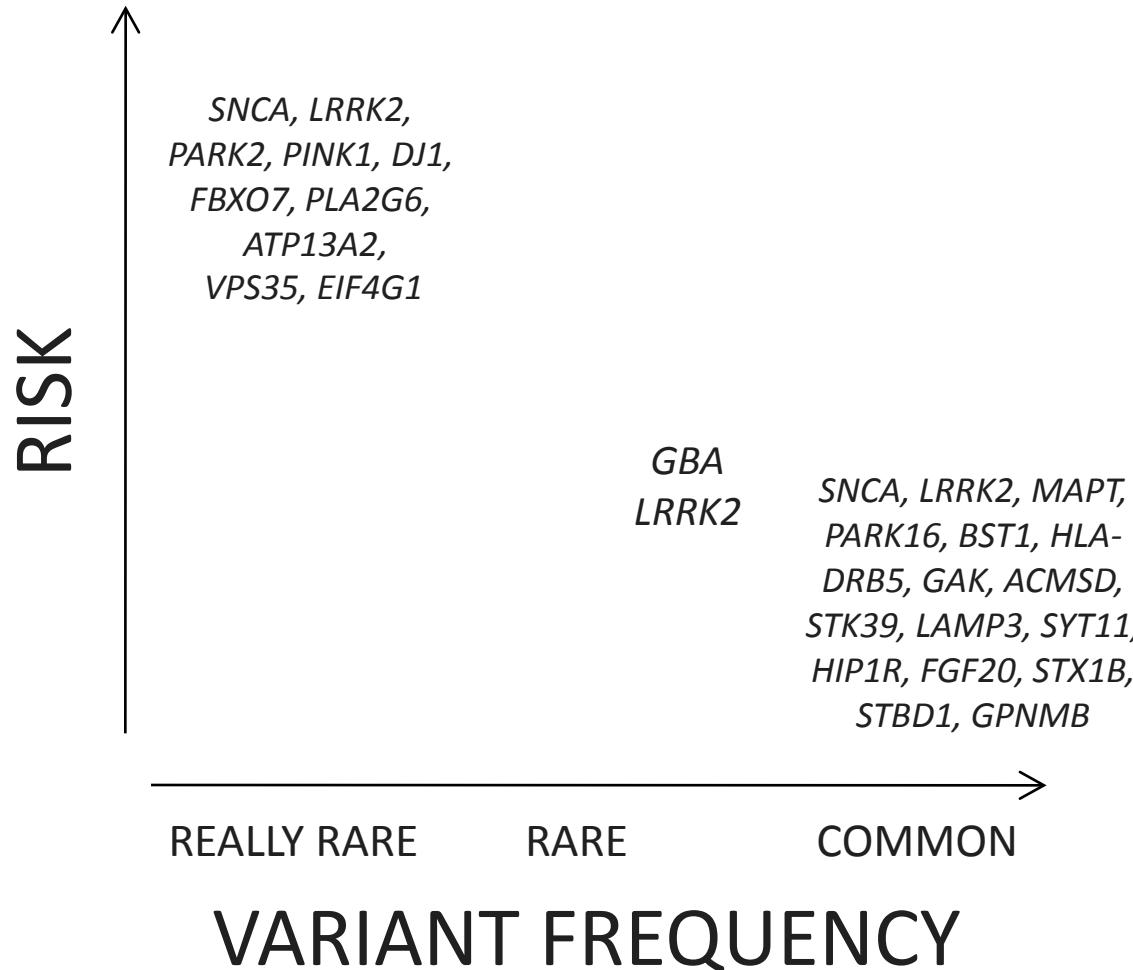


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Genetic Architecture of PD

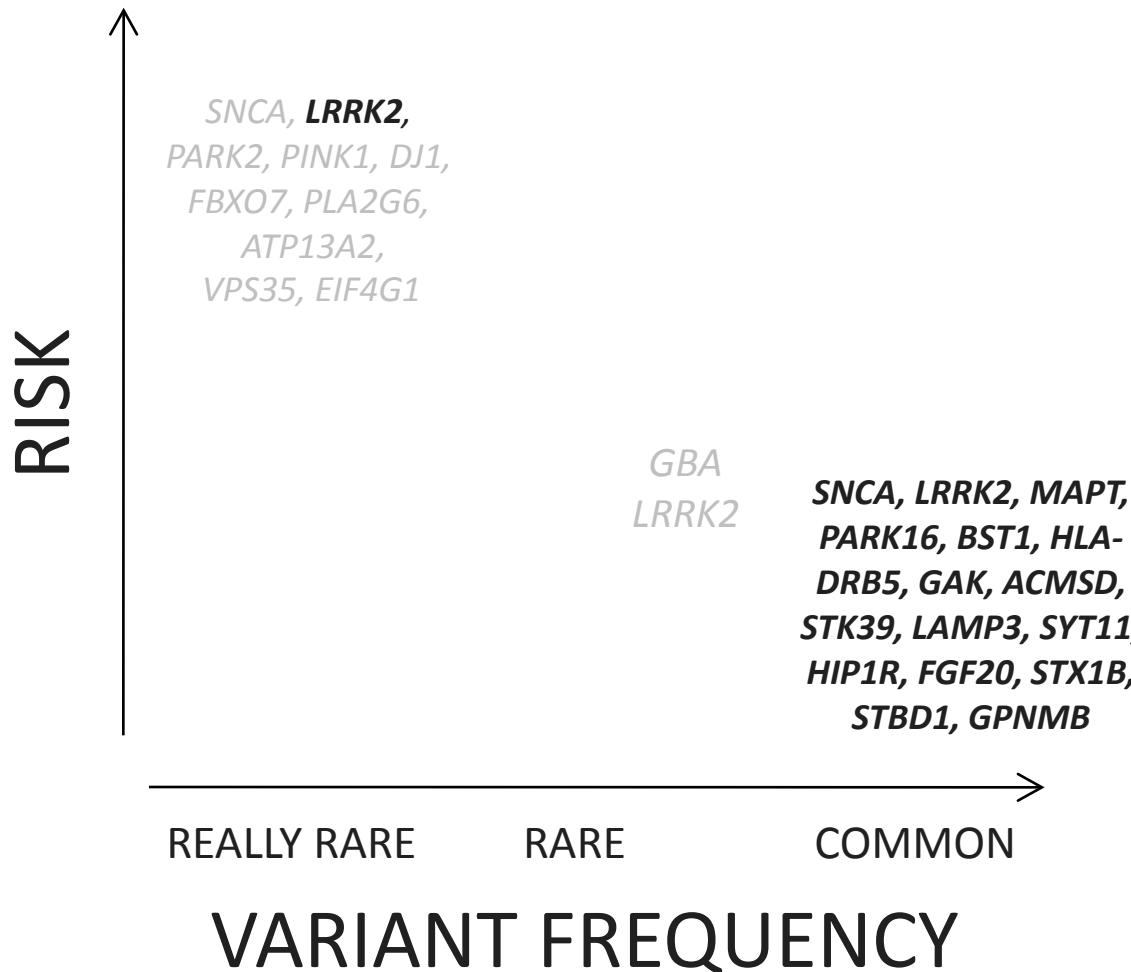


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ImmunoChip



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Data so far

- 518 samples received in early 2013
- Initial DNA QC performed
- 288 samples run on the ImmunoChip
- Sample success rate – 100%
- Genotype success rate – 98.7%
- Data being uploaded to LONI this week (following extensive QC)
- G2019S cases
- APOE genotyping performed in first 288 samples

all proceeding as planned



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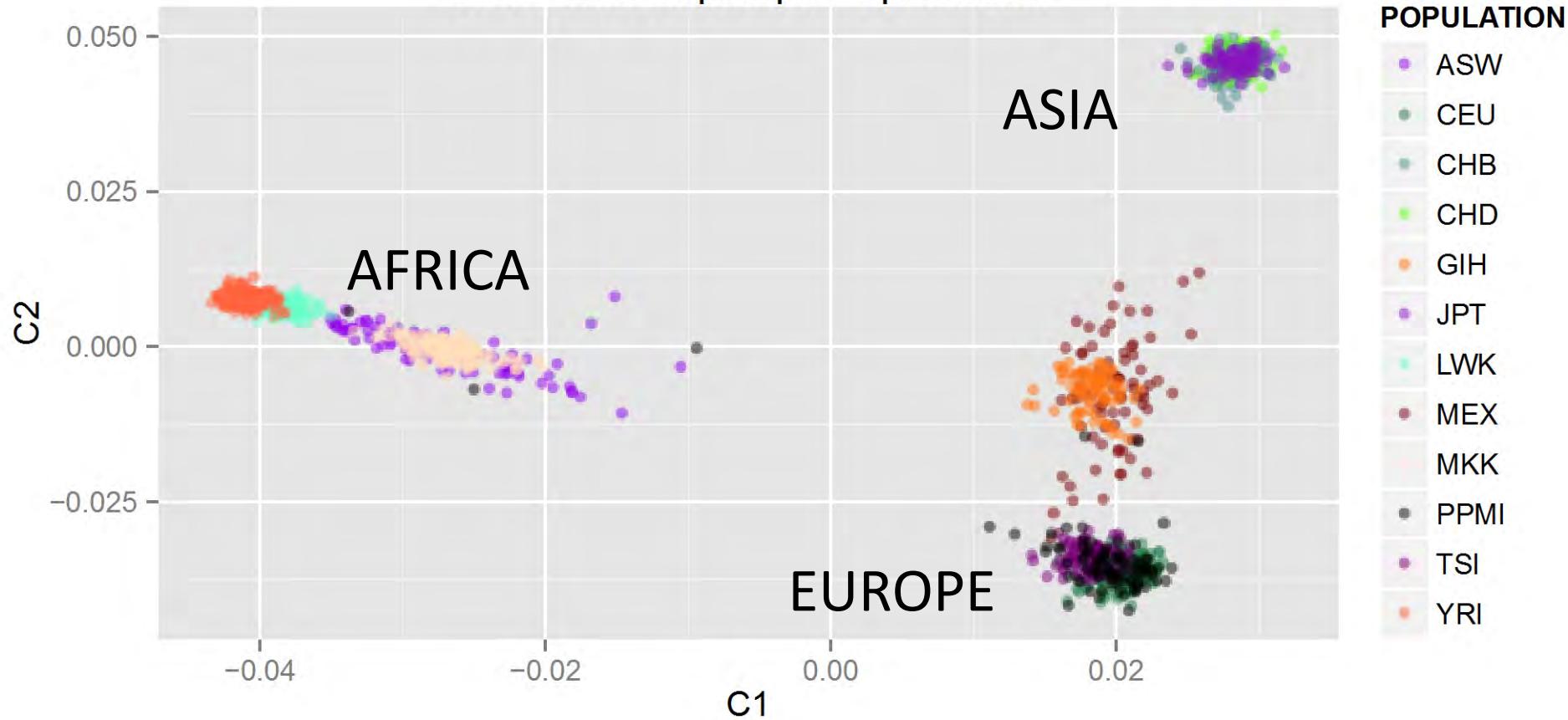
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Population by genetics

PPMI with HapMap3 Populations



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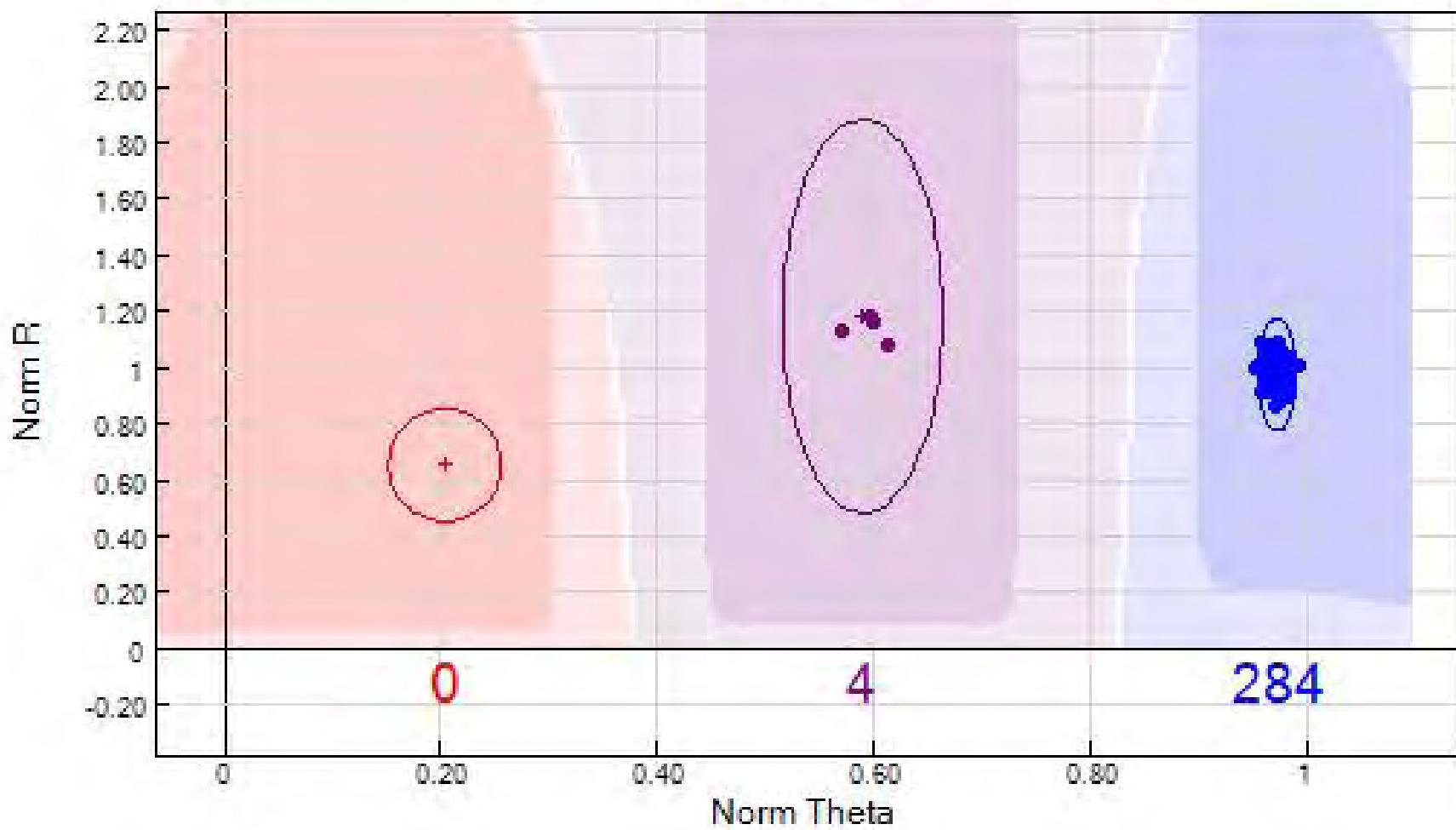
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chr12_39020469



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Genetic data

https://ida.loni.ucla.edu/pages/access/studyData.jsp?categoryId=7&subCategoryId=15

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Biospecimen: Biospecimen Sample Analysis
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- ▶ Motor Assessments
- ▶ Non-motor Assessments
- ALL

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Next Steps

- Will continue with ImmunoChip through all samples in hand
- NeuroX genotyping



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NeuroX

- Applied this to ~30,000 samples for various diseases
- NeuroX
 - Exome Chip + 30k Custom Design
 - PD variants
 - AD variants
 - PSP variants
 - ALS variants
 - FTD variants
 - QTL
 - Neurological Disease Mutations
- Made this available for others to use



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On track to finish baseline genetics in
the next few months



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Bioanalytics Core

Leslie M Shaw

PPMI Annual Investigators Meeting, NYC

May 8, 2013



Bioanalytics Core-2013

- Pilot study manuscript accepted for publication in JAMA Neurology
- Preparations for analyses of CSF A β ₁₋₄₂, t-tau and p-tau₁₈₁ in PPMI baseline samples, and baseline, 6 and 12 month longitudinal samples using validated xMAP AlzBio3 immunoassay (all longitudinal samples on same 96 well plate)
- Aliquot comparisons; compare current lot of immunoassay reagents with that used in 2012



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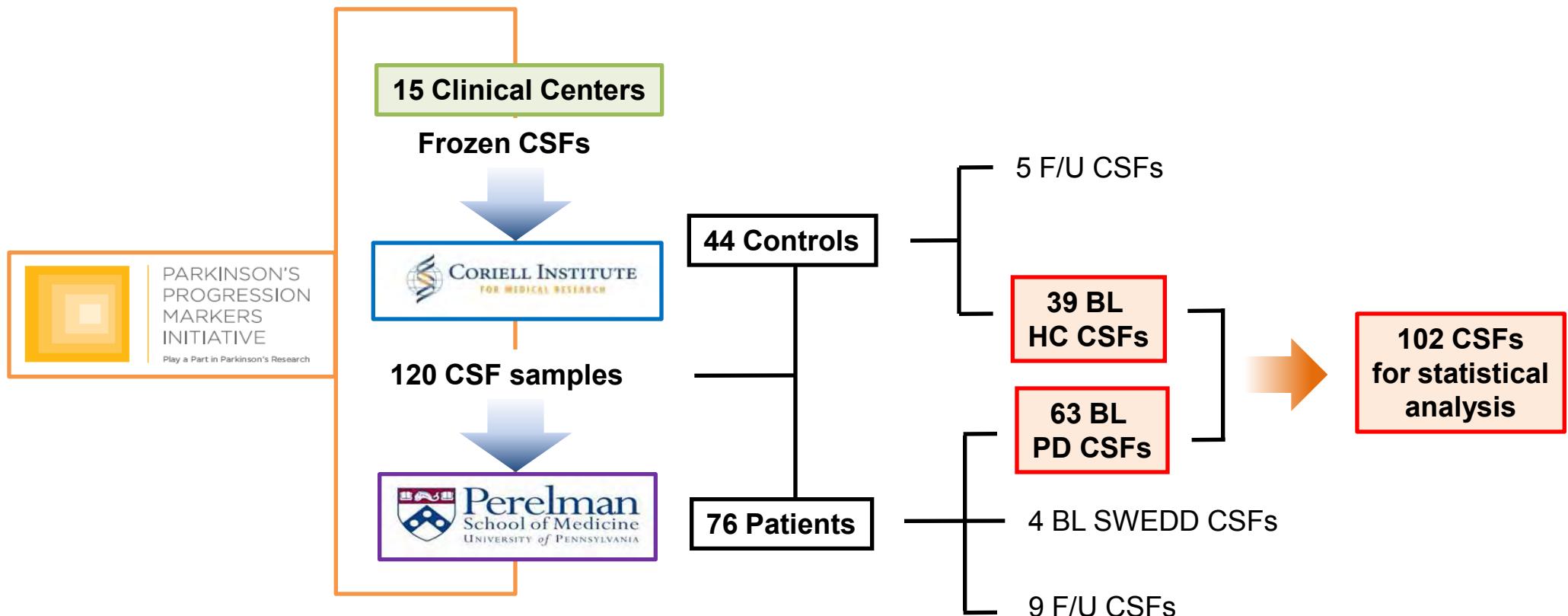
**Association of cerebrospinal fluid Ab₁₋₄₂, t-tau, p-tau₁₈₁ and alpha-synuclein levels
with clinical features of early drug naïve Parkinson's disease patients; a cross-
sectional study**

By

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

Transfer of PPMI CSFs

(Initial 102 CSF samples for statistical analysis)



Association of cerebrospinal fluid A β ₁₋₄₂, t-tau, p-tau₁₈₁ and α -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*

Objective: Evaluate baseline characteristics and relationship to clinical features of CSF A β ₁₋₄₂, t-tau, p-tau₁₈₁ and α -SYN in PD patients and matched healthy controls (HC) enrolled in PPMI.

Methods: CSF biomarkers were measured by xMAP-Luminex platform and ELISA in HC (N=39) and PD (N=63).

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

Statistical Analyses

- Software: SAS ver. 9.3
- Group comparison
 - Mann-Whitney U test (2 groups)
 - Kruskal-Wallis test with Dunn's multiple comparison (3 groups)
- Association of CSF biomarker levels and clinical variable
 - Multiple linear or logistic regression model (stepwise selection) with adjustment for confounders (Age, Gender and Education)
- Chi-square test for difference in percentage of subjects
- Pearson correlation

Demographics of the PPMI subjects

	HC (N = 39)	PD (N = 63)	P value
Age, years (95% C.I.)	58 ± 13 (54 – 63)	62 ± 10 (59 – 64)	0.2390*
Sex, F/M (% of Male)	18/21 (53.8)	24/39 (61.9)	0.4216#
Education, years (95% C.I.)	16.8 ± 2.4 (16.0 – 17.6)	16.4 ± 2.5 (15.8 – 17.0)	0.1517*
Age at diagnosis, years (95% C.I.)	-	61.1 ± 10.0 (58.6 – 63.7)	-
Disease duration, median years (range)	-	0.4 (0.0 – 2.6)	-
Number of subjects with CSF Hgb > 200 ng/mL	6	18	0.1271#

*Mann-Whitney U test; #Chi-square test for HC vs. PD.

Clinical characteristics of the PPMI subjects[#]

	HC (N = 39)	PD (N = 63)	p value*
H & Y stage	0.03 ± 0.16	1.65 ± 0.51	< 0.0001
UPDRS III motor score	1.6 ± 2.7	22.6 ± 7.6	< 0.0001
Mean tremor score	0.05 ± 0.13	0.53 ± 0.32	< 0.0001
Mean PIGD score	0.01 ± 0.04	0.24 ± 0.26	< 0.0001
UPSIT score	35.1 ± 3.4	21.9 ± 8.1	< 0.0001
Striatal binding ratios (Mean values)	PR†/PL/CR/CL 1.38/1.39/2.06/2.05	PR/PL/CR/CL 0.62/0.64/1.35/1.34	<0.0001
MoCA (95% C.I.)	28.4 ± 1.0 (28.0 – 28.7)	27.2 ± 2.0 (26.7 – 27.7)	0.0054
Semantic fluency	53.8 ± 12.1	49.5 ± 10.6	0.0565
WMSIII-LNS\$ test score	12.1 ± 2.8	11.0 ± 2.0	0.0510
SDMT	48.6 ± 11.2	41.9 ± 8.9	0.0051
HVLT-R total recall	9.0 ± 1.6	8.2 ± 1.5	0.0077
HVLT-R delayed recall	9.9 ± 2.3	8.3 ± 2.3	0.0004

#Data were updated based on PPMI database (06.30.2012)

*Mann-Whitney U test

†PR: Right putamen, PL: Left putamen, CR: Right caudate, CL: Left caudate, N=39 for HC, N=62 for PD

Comparison of CSF Biomarker levels between HC and PD [#]

	HC (N = 39)	PD (N = 63)	P value [#]
A β ₁₋₄₂ (pg/mL)	242.8 ± 49.95 (226.7 – 259.0)*	228.7 ± 45.63 (217.2 – 240.2)	0.0466
t-tau (pg/mL)	53.9 ± 19.33 (47.6 – 60.1)	46.1 ± 24.71 (39.8 – 52.3)	0.0276
p-tau ₁₈₁ (pg/mL)	24.9 ± 8.45 (22.2 – 27.6)	21.0 ± 7.83 (19.0 – 23.0)	0.0093
t-tau/A β ₁₋₄₂ ratio	0.240 ± 0.141 (0.195 – 0.286)	0.215 ± 0.157 (0.176 – 0.255)	0.0451
p-tau ₁₈₁ /A β ₁₋₄₂ ratio	0.113 ± 0.075 (0.089 – 0.138)	0.099 ± 0.063 (0.084 – 0.115)	0.1482
p-tau ₁₈₁ /t-tau ratio	0.491 ± 0.160 (0.439 – 0.543)	0.543 ± 0.263 (0.477 – 0.609)	0.6820
α -syn (pg/mL)	1264 ± 425.7 (1126 – 1403)	1082 ± 611.1 (928 – 1235)	0.0120

*Mean ± S.D. (95% confidence interval); #Mann-Whitney U test.

#Data were updated based on PPMI database (06.30.2012)

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 ≥ 1.15 : Tremor dominant
 - Ratio of tremor/PIGD score ≤ 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 β ₁₋₄₂ (pg/mL)	211.4 ± 45.0#	236.2 ± 46.8	0.0323	242.8 ± 50.0	215.5 ± 25.0
t-tau (pg/mL)	39.3 ± 28.27#	50.3 ± 24.01	0.0527	53.9 ± 19.33	31.2 ± 9.97
p-tau ₁₈₁ (pg/mL)	18.0 ± 6.74#	22.5 ± 8.17	0.0387	24.9 ± 8.45	17.7 ± 4.97
α -syn (pg/mL) ^a	892.8 ± 542.4#	1185 ± 649.6	0.0587	1264 ± 425.7	782.6 ± 150.1
α -syn (pg/mL) ^b	766.3 ± 446.3#	1122 ± 451.8	0.0286	1267 ± 443.5	775.9 ± 184.8
t-tau/A β ₁₋₄₂ ratio	0.211 ± 0.213	0.225 ± 0.145	0.1089	0.240 ± 0.141	0.151 ± 0.072
p-tau/A β ₁₋₄₂ 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

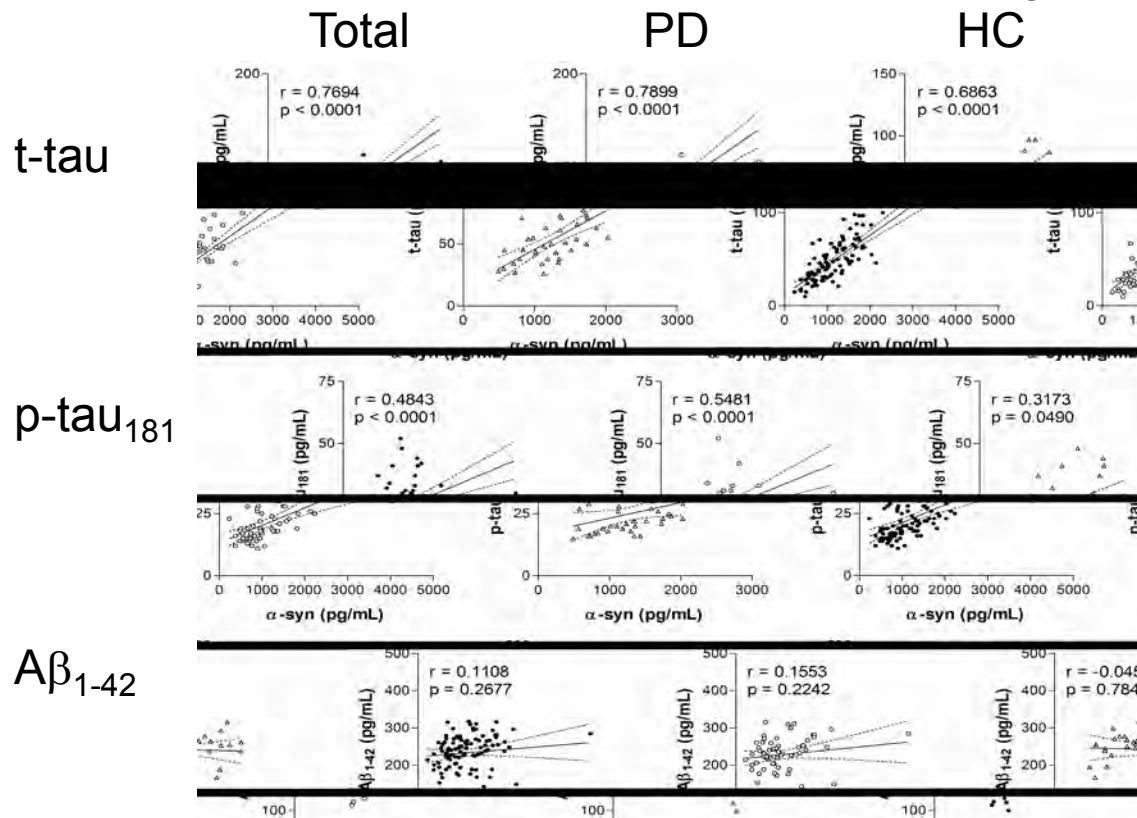
P<0.05 versus HC by Kruskal-Wallis test with Dunn's multiple comparison

^a α -syn was measured in total subjects, or ^bsubjects with CSF hemoglobin level of < 200 ng/mL

Summary of multivariate regression analyses

- Multivariate regression analysis: lower A β ₁₋₄₂ ($p=0.0383$) and p-tau₁₈₁ ($p=0.0015$) are significantly associated with PD diagnosis, but other biomarkers or their ratios are not.
- For clinical variables in PD, α -syn ($p=0.0081$) was significantly associated with the MDS-UPDRS III motor score and t-tau was marginally associated ($p=0.0424$).
- We found that lower levels of CSF A β ₁₋₄₂ and p-tau₁₈₁ were significantly associated with a higher PIGD risk.

Correlation between AD biomarkers and α -synuclein:



Association of cerebrospinal fluid A β ₁₋₄₂, t-tau, p-tau₁₈₁ and α -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 β ₁₋₄₂ ratio were seen in PD compared to HC, lower α -SYN was associated with a higher risk of PD and decreased CSF p-tau₁₈₁ associated with increased UPDRS motor score. Notably, lower CSF A β ₁₋₄₂ 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. There is a significant correlation between α -SYN and t-tau & p-tau in PD and HC subjects.

Interpretation: We demonstrate that CSF A β ₁₋₄₂, t-tau, p-tau₁₈₁ and α -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, n=645 and CSFs for those 223 subjects whose 6 month & 12 month CSFs are collected
- AlzBio3 immunoassay for A β ₁₋₄₂, t-tau and p-tau₁₈₁ at UPenn and α -SYN by ELISA at Covance
- Data analyses, qc, data upload expected by mid to late summer, 2013.
- Statistical analyses will test hypotheses based on the pilot study

Acknowledgements: John Trojanowski and the Penn PPMI Bioanalytics Core members Ju Hee Kang, Teresa Waligorska and Sarah Pan, our PPMI study participants, and the amazing PPMI Team!

Progress in Neurobiology 95 (2011) 629–635



Contents lists available at SciVerse ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio



The Parkinson Progression Marker Initiative (PPMI)

Kenneth Marek, Danna Jennings, Shirley Lasch, Andrew Siderowf, Caroline Tanner, Tanya Simuni, Chris Coffey, Karl Kieburtz, Emily Flagg, Sohini Chowdhury, Werner Poewe, Brit Mollenhauer, Paracelsus-Elena Klinik, Todd Sherer, Mark Frasier, Claire Meunier, Alice Rudolph, Cindy Casaceli, John Seibyl, Susan Mendick, Norbert Schuff, Ying Zhang, Arthur Toga, Karen Crawford, Alison Ansbach, Pasquale De Blasio, Michele Piovella, John Trojanowski, Les Shaw, Andrew Singleton, Keith Hawkins, Jamie Eberling, Deborah Brooks, David Russell, Laura Leary, Stewart Factor, Barbara Sommerfeld, Penelope Hogarth, Emily Pighetti, Karen Williams, David Standaert, Stephanie Guthrie, Robert Hauser, Holly Delgado, Joseph Jankovic, Christine Hunter, Matthew Stern, Baochan Tran, Jim Leverenz, Marne Baca, Sam Frank, Cathi-Ann Thomas, Irene Richard, Cheryl Deeley, Linda Rees, Fabienne Sprenger, Elisabeth Lang, Holly Shill, Sanja Obradov, Hubert Fernandez, Adrienna Winters, Daniela Berg, Katharina Gauss, Douglas Galasko, Deborah Fontaine, Zoltan Mari, Melissa Gerstenhaber, David Brooks, Sophie Malloy, Paolo Barone, Katia Longo, Tom Comery, Bernard Ravina, Igor Grachev, Kim Gallagher, Michelle Collins, Katherine L. Widnell, Suzanne Ostrowizki, Paulo Fontoura, Tony Ho, Johan Luthman, Marcel van der Brug, Alastair D. Reith, Peggy Taylor

The Parkinson Progression Marker Initiative¹



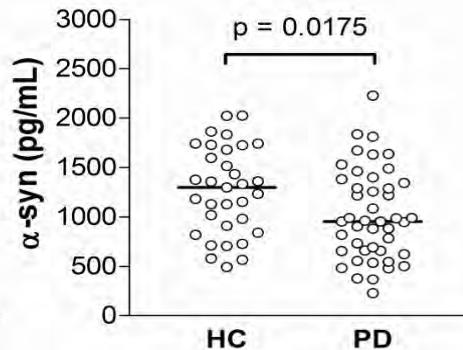
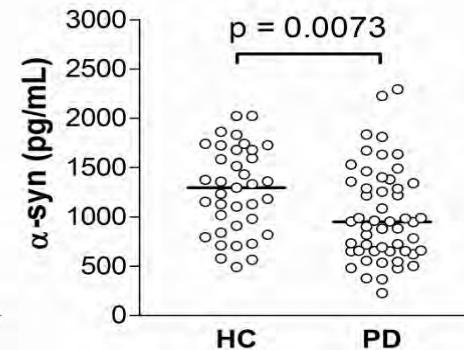
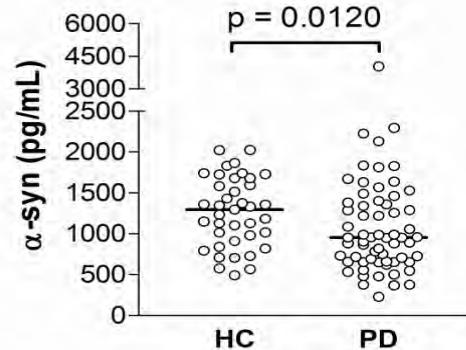
PPMI Funding Partners

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

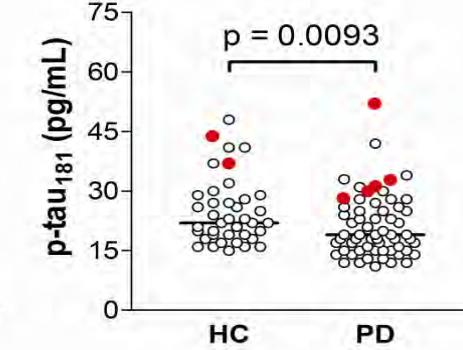
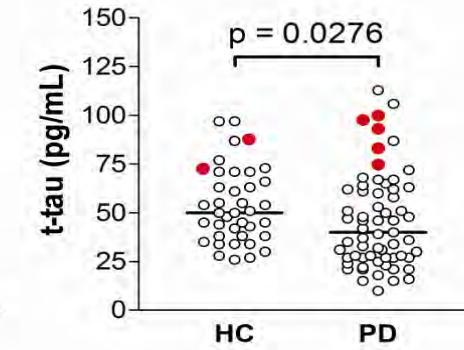
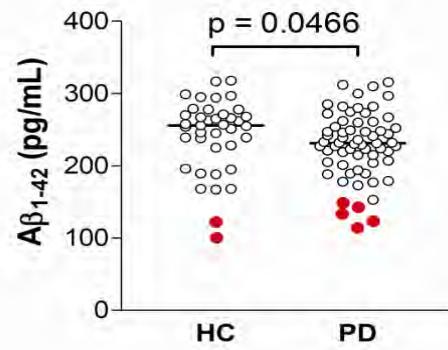


Scatter plots of CSF biomarker levels in PD vs. HC

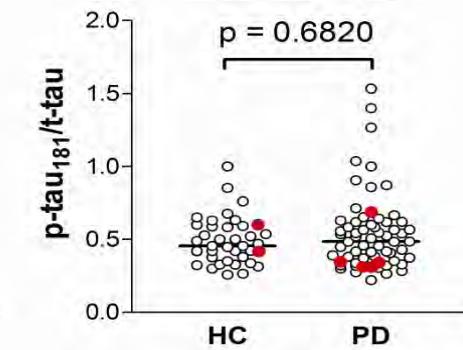
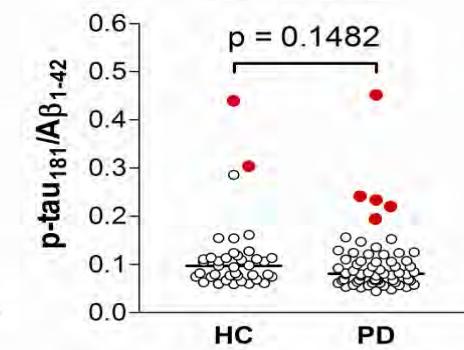
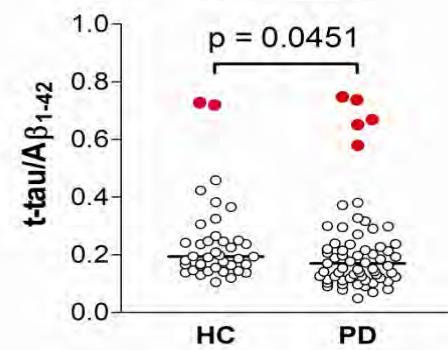
α -syn



$A\beta_{1-42}$
 t -tau
 p -tau₁₈₁



Ratios



Informatics Core

Arthur Toga
May 2013



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Informatics Core Status

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



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Website

- New Features
 - Fileshare
 - Publications & Presentations
 - Data & Biospecimen Investigator Info
- Website Analytics



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Parkinson's Progression Markers Initiative

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	PPMI Committees and Working Groups	10/11/2012 2:20 PM	Folder	
	PPMI Data	10/11/2012 2:21 PM	Folder	

BRC Calls (Limited Access)

Type	Name	Modified	Modified By
	Call agendas, documents, and minutes	10/16/2012 6:44 AM	Reena Vanjani

Calendar

April, 2013

S	M	T	W	T	F	S
31	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27

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Groups

- Approvers
- Biologics Working Group
- Biospecimens Review Committee
- Designers
- Hierarchy Managers
- Home Owners
- PPMI Administrators
- PPMI Members
- Records Center Web Service Submitters
- Restricted Readers
- Style Resource Readers

Links

- Parkinson's Progression Markers Initiative Homepage

Add new link

Play a Part in Parkinson's Research

- PPMI Committee members login to Sharepoint server
- Launched Sept 2012
- Features: file sharing, calendar, limited access groups

Publications & Presentations

- PPMI investigators can submit and browse publications and presentations online

The screenshot shows the PPMI website's Publications & Presentations section. At the top, there is a navigation bar with links for About PPMI, Study Design, Access Data & Specimens, Publications & Presentations (which is the active tab), PPMI News, and Get Email Updates. Below the navigation bar, there are two tabs: Presentations and Publications. The Publications tab is selected. A sub-section titled "PUBLICATIONS & PRESENTATIONS" contains text about the study's goal of publishing results and a link to the Publications Policy. Below this, there is a "Publications" section with a "SUBMIT A PUBLICATION" button and links to "View PPMI Publications" and "Presentations". To the right, there are four orange call-to-action boxes: "DOWNLOAD DATA", "REQUEST SPECIMENS", "for PROSPECTIVE PARTICIPANTS", and "for ENROLLED PARTICIPANTS". The footer of the page includes the PPMI logo and the tagline "Play a Part in Parkinson's Research".

PPMI Publications

Parkinson's Progression Markers Initiative

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PPMI PUBLICATIONS

Publications using PPMI data and specimens are published frequently. According to the [PPMI Publications Policy](#), all publications must be submitted to the Data and Publications Committee for administrative review. Individuals who wish to submit a publication for review can [click here](#). A complete list of PPMI publications can be found below.

Search

Displaying 2 publication(s).

Title	Author(s)	Citation	PMID
Screening for impulse control symptoms in patients with de novo Parkinson disease: a case-control study.	Weintraub D; Papay K; Siderowf A; Parkinson's Progression Markers Initiative;	Neurology 2013 Jan;80(2):176-80	23296128
The Parkinson Progression Marker Initiative (PPMI).	Parkinson Progression Marker Initiative;	Prog. Neurobiol. 2011 Dec;95(4):629-35	21930184

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76,928 site visitors

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PPMI Presentations

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Title	PPMI AAN Poster 2013
International Conference on Alpha-Synuclein in Parkinson's Disease 2013: Parkinson's Progression Markers Initiative (PPMI)	
MDS 2012 Poster: Association between CSF biomarkers and clinical phenotype in early Parkinson's disease in the Parkinson's Progression Markers Initiative (PPMI)	
MDS 2012 Poster: Frequency of Non-Motor Symptoms in De Novo PD Patients and Healthy Controls	
MDS 2012 Poster: Baseline Neuroimaging Characteristics of the Parkinson's Progression Markers Initiative (PPMI) Parkinsons and Healthy Control	
2012 PPMI Annual Meeting	

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Presentation

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Title:

[Parkinson's Progression Markers Initiative](#)

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[Presentations](#) [Publications](#)

PPMI PRESENTATIONS

Select presentations made using PPMI data and specimens are catalogued here. Individuals making PPMI presentations who wish to share them through the website can contact us with information about the presentation for consideration for inclusion.

Displaying 13 presentation(s).

Title	Author(s)	Date	Meeting/Venue	Abstract
PPMI AAN Poster 2013	Ken Marek & PPMI Senior Leadership	2013-03-23	San Diego, CA	Ultimate goal of PPMI to develop PD progression markers that could be utilized to accelerate research on disease modify...
International Conference on Alpha-Synuclein in Parkinson's Disease 2013: Parkinson's Progression Markers Initiative (PPMI)	John Q. Trojanowski, M.D., Ph.D.	2013-03-03	Dubai, UAE	Biomarkers for the early diagnosis of Parkinson Disease (PD) and to map PD progression as well as to monitor target enga...
MDS 2012 Poster: Association between CSF biomarkers and clinical phenotype of early Parkinson's disease in the Parkinson's Progression Markers Initiative (PPMI)	Ju-Hee Kang, Chelsea Caspell, Chris Coffey, Peggy Taylor, Mark Frasier, Kenneth Marek, John Q. Trojanowski, Leslie M. Shaw, and the Parkinson's Progression Marker Initiative	2012-06-17	Dublin, Ireland	Background: There is substantial heterogeneity in the onset and progression of clinical phenotypes of Parkinson's dise...

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PPMI Ongoing Analysis

The screenshot shows the 'Ongoing Analysis' section of the PPMI website. At the top, there's a navigation bar with links like 'About PPMI', 'Study Design', 'Access Data & Specimens', 'Publications & Presentations', 'PPMI News', 'Request Specimens', 'Download Data', 'Ongoing Analysis' (which is the active tab), 'Data & Specimens FAQ', 'PPMI Qualification Studies', and 'Usage Stats'. Below the navigation is a search bar with a 'Search' button. The main content area is titled 'DATA ANALYSIS' and contains a sub-section for 'Approved Investigators'. It lists 25 investigators with their names and institutions. To the right of this table is a vertical sidebar with five orange buttons, each featuring a small icon and text: 'DOWNLOAD DATA', 'REQUEST SPECIMENS', 'for PROSPECTIVE PARTICIPANTS', 'for ENROLLED PARTICIPANTS', 'for PRACTITIONERS', 'for INDUSTRY PARTNERS', and 'for RESEARCHERS'.

Investigator	Institution
Harsha A	Northern Illinois University
Abby Agbulos	Avid Radiopharmaceuticals
Shaheen Ahmed	Emory University
Raquel Alves	FEUP
Seong An	Gachon University
Beau Ances	Washington University in Saint Louis
Tatiyana Apanasovich	Thomas Jefferson University
Alberto Ascherio	Harvard School of Public Health
Scott Ayton	Florey Institute of Neuroscience and Mental Health
Mrs.Venkatalakshmi B	Velammal Engineering College
Bhavani Bagepally	National Institute of Mental Health And Neurosciences (NIMHANS)
Rachit Bakshi	Massachusetts General Hospital
Mr.Ranjith Balakrishnan	Velammal Engineering College
Mike Barlow	myHealthPal
Matthew Barrett	University of Virginia
Raymond Bartus	Ceregene
Aylin BASKIN	Ankara Training and Research Hospital, Ministry of Health
Mirza Faisal Beg	Simon Fraser University
Mahanand Belathur Suresh	Sri Jayachamarajendra College of Engineering
Jay Bergeron	Pfizer

- Data Analysis Investigators Database
- *NEW* Specimen Request Investigators Database



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Specimen Analysis

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

Request Specimens Download Data Ongoing Analysis Data & Specimens FAQ PPMI Qualification Studies Usage Stats

SPECIMEN ANALYSIS

Researchers apply to the PPMI Biospecimen Review Committee (BRC) to request PPMI samples for biomarker verification studies. Research studies approved for the use of these samples are included below. Search the PPMI specimen analysis projects by entering your terms below.

Search

Project Title	Principal Investigator	Institution	Specimen Used
Evaluation of PD-linked Transcripts in PPMI	Clemens R. Scherzer, M.D.	Harvard University	RNA
Plasma Apolipoprotein A1 Level as a Biomarker in Parkinson's Disease	Alice Chen-Plotkin, MD, MSc	University of Pennsylvania	Plasma

 **DOWNLOAD DATA**

 **REQUEST SPECIMENS**

 **for PROSPECTIVE PARTICIPANTS**

 **for ENROLLED PARTICIPANTS**



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Website Metrics



- 19,299 people visited the site from Mar 30, 2012-Apr 29, 2013

Country / Territory	Visits	Pages / Visit	Avg. Visit Duration	% New Visits	Bounce Rate
1. United States	12,459	3.32	00:02:51	55.82%	51.34%
2. United Kingdom	1,101	4.52	00:02:32	60.94%	55.04%
3. Italy	637	3.27	00:02:07	71.90%	51.33%
4. Germany	491	3.42	00:02:07	65.58%	62.53%
5. Japan	468	3.20	00:02:51	28.63%	57.48%
6. India	456	3.33	00:02:50	49.78%	43.64%
7. Canada	426	3.00	00:02:24	66.20%	57.28%
8. Australia	424	3.14	00:02:48	79.95%	45.05%
9. France	258	3.30	00:02:50	64.34%	44.19%
10. Belgium	204	3.44	00:03:58	38.73%	59.31%

Data Repository

- Overview
- New Data Flows & Data
- Usage Info



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Data Input

Acquisition → Repository



Imaging
Acquisition



Imaging Core (IND)

Quality Control
Image Pre-processing



Clinical
Acquisition



Clinical Core (CTCC)

Quality Control
Study Management

Biological Acquisition



Biorepository Core (Coriell)

Sample Storage

Biological Samples



Biosample Analysts (Various)

ppmi-info.org



- Study Information
- Data Access
- Investigator Resources
- Data Sharing Tools
- Biospecimen Access
- Publications



Inventory

Results

Data Transfer & Validation
Sample-Subject Relinking

What's New

- New Developments
 - fMRI
 - ✓ De-identification and upload programs complete
 - ✓ fMRI image data received
 - ✓ fMRI QA workflows complete
 - ✓ QA data received
 - AV-133 PET
 - ✓ De-identification and upload programs complete
 - ✓ AV-133 data received



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New Data

- Diagnostic features
- Clinical cognitive categorization
- Normative scores for:
 - Hopkins Verbal Learning Test, Symbol Digit Modalities Text, Semantic Fluency, Letter-Number Sequencing (PD)
- AV-133 scans & metadata
- fMRI scans & metadata

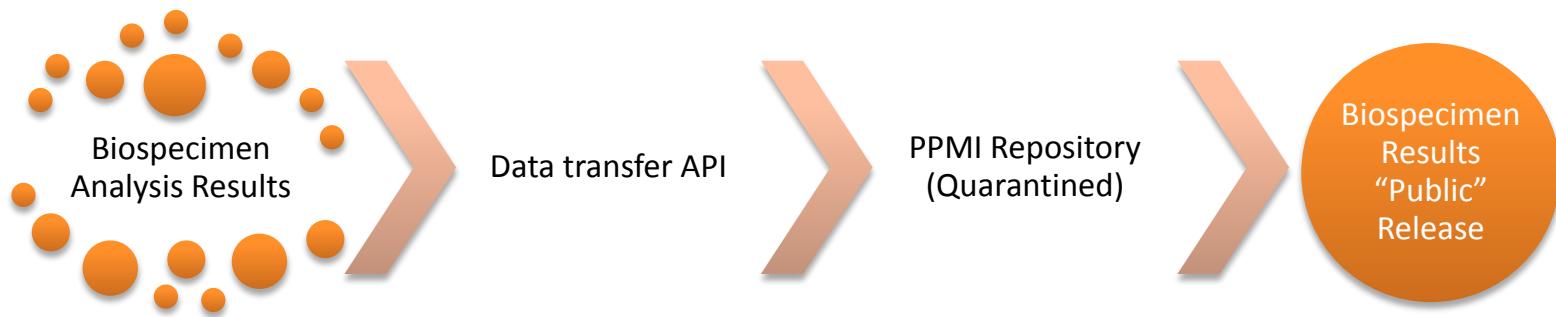


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Biospecimen Data Flow



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Biospecimen Results Data

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



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fMRI Data Flow

- Semi-automated quality control workflow developed in LONI Pipeline



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Module Groupings: fMRI.qc.full.v16.human

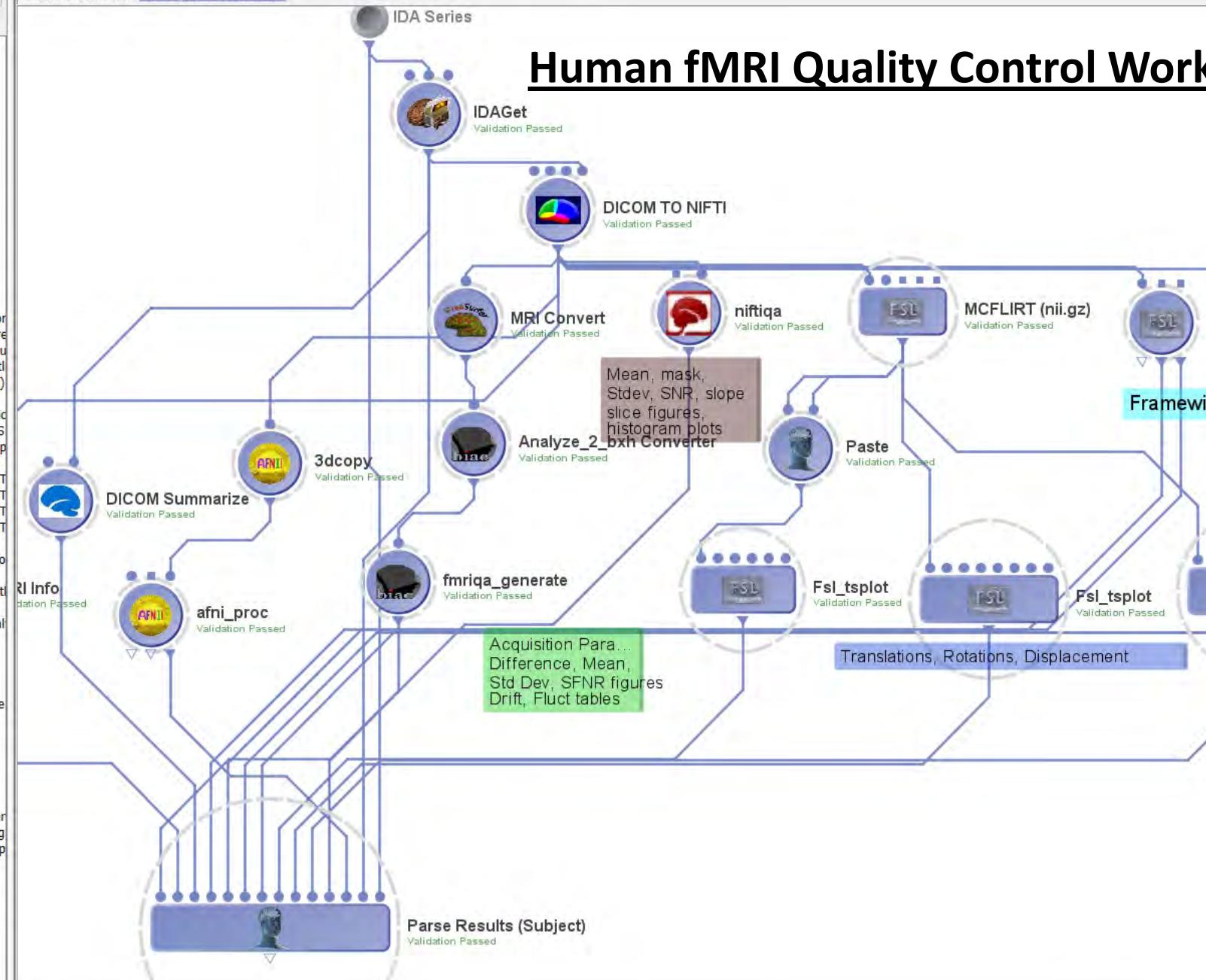
Search

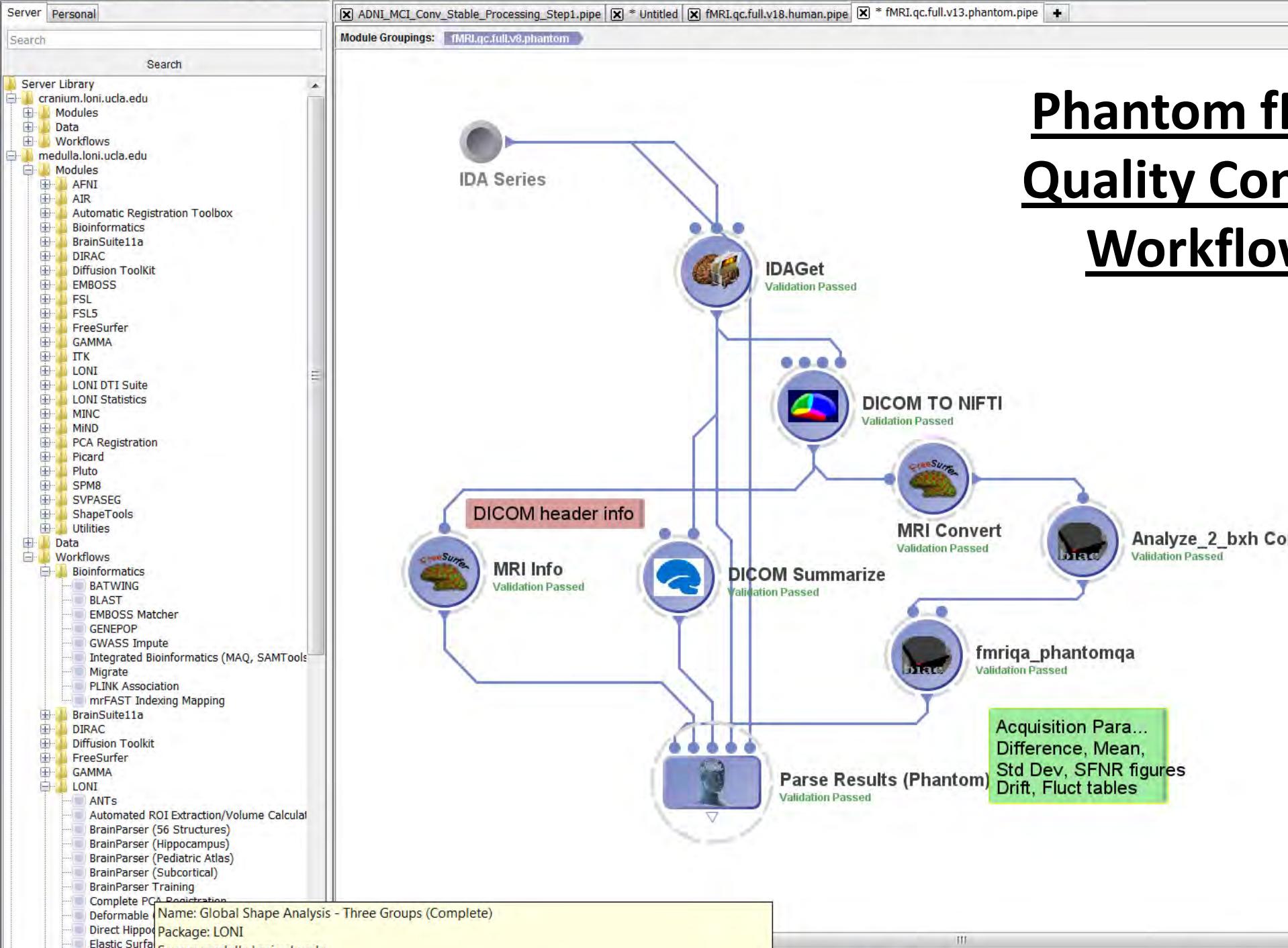
Search

Server Library

- cranium.loni.ucla.edu
- Modules
- Data
- Workflows
- medulla.loni.ucla.edu
- Modules
- Data
- Workflows
- Bioinformatics
- BrainSuite11a
- DIRAC
- Diffusion Toolkit
- FreeSurfer
- GAMMA
- LONI
- ANTs
- Automated ROI Extraction
- BrainParser (56 Structure)
- BrainParser (Hippocampus)
- BrainParser (Pediatric Atl)
- BrainParser (Subcortical)
- BrainParser Training
- Complete PCA Registratio
- Deformable Organisms S
- Direct Hippocampal Mapp
- Elastic Surface Warping
- Global Shape Analysis - T
- Global Shape Analysis - T
- Global Shape Analysis - T
- IRMA
- LONI Statistics - Two Gro
- Local Shape Analysis
- Local Shape Analysis Wit
- R-Script Example
- Rat Brain Functional Anal
- SSMA Module
- SSMA Workflow
- LONI DTI Suite
- Legacy
- Minimum Distance Template
- Mouse Workflows
- Pluto
- SPM8
- SPM8 Workflow
- Structural Analysis
- Training
- AIR-BrainSuite Heteroge
- Basic fMRI PreProcessing
- BrainSuite MNC Skullstrip
- BrainSuite Processing
- DSI_workflow
- DTI_workflow
- Registration Using AIR
- Skullstripping
- WAIR
- fMRI

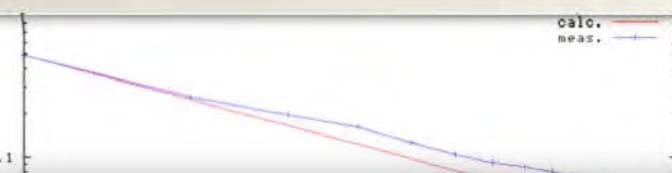
pws.loni.ucla.edu





QC Results

Acquisition Parameters



qa_relstd
Select one: Good Questionable Bad

Additional Summary Statistics			
Mean	1627.1	Select one:	<input checked="" type="radio"/> Good <input type="radio"/> Questionable <input type="radio"/> Bad
SNR	197.1	Select one:	<input checked="" type="radio"/> Good <input type="radio"/> Questionable <input type="radio"/> Bad
SFNR	206.7	Select one:	<input checked="" type="radio"/> Good <input type="radio"/> Questionable <input type="radio"/> Bad
Standard Deviation	1.00	Select one:	<input checked="" type="radio"/> Good <input type="radio"/> Questionable <input type="radio"/> Bad
Percent Fluctuation	0.06	Select one:	<input checked="" type="radio"/> Good <input type="radio"/> Questionable <input type="radio"/> Bad
Drift	0.90	Select one:	<input checked="" type="radio"/> Good <input type="radio"/> Questionable <input type="radio"/> Bad
RDC	8.0	Select one:	<input checked="" type="radio"/> Good <input type="radio"/> Questionable <input type="radio"/> Bad
Voxel Size	3.2941, 3.2941, 3.3000	Select one:	<input checked="" type="radio"/> Good <input type="radio"/> Questionable <input type="radio"/> Bad
FOV	224.000 x 217.504	Select one:	<input checked="" type="radio"/> Good <input type="radio"/> Questionable <input type="radio"/> Bad
TR	2400.0 msec	Select one:	<input checked="" type="radio"/> Good <input type="radio"/> Questionable <input type="radio"/> Bad
TE	25.0 msec	Select one:	<input checked="" type="radio"/> Good <input type="radio"/> Questionable <input type="radio"/> Bad
TI	NA	Select one:	<input checked="" type="radio"/> Good <input type="radio"/> Questionable <input type="radio"/> Bad
Flip Angle	80.0 degrees	Select one:	<input checked="" type="radio"/> Good <input type="radio"/> Questionable <input type="radio"/> Bad
Matrix	68x66	Select one:	<input checked="" type="radio"/> Good <input type="radio"/> Questionable <input type="radio"/> Bad
Slices	40	Select one:	<input checked="" type="radio"/> Good <input type="radio"/> Questionable <input type="radio"/> Bad
Number of Frames	210	Select one:	<input checked="" type="radio"/> Good <input type="radio"/> Questionable <input type="radio"/> Bad
Enter open comments here...		Apply the following selection to all of the above fields (Additional Summary Statistics): <input type="radio"/> Good <input type="radio"/> Questionable <input type="radio"/> Bad	
Overall Evaluation			
Select one: <input checked="" type="radio"/> Good <input type="radio"/> Questionable <input type="radio"/> Bad	Enter overall comments here...		
Check 1 Initial XW	Date 2013-03-12		
Check 2 Initial DRG	Date 2013-04-09		
<input type="button" value="Save Only"/>	<input type="button" value="Save & Submit"/>		

Supercomputers and High Availability Storage



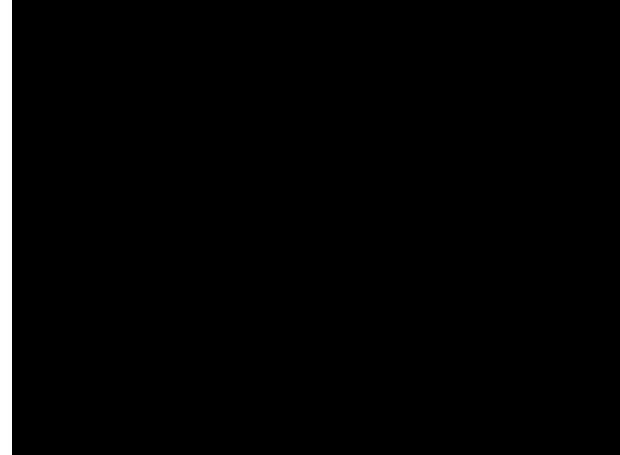
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Data Resources

- Storage
 - Fault-tolerant storage area network
 - 800 megabytes per second data throughput
 - Near 24/7 availability
- Protection
 - Daily & weekly on-site backup
 - Monthly off-site backup



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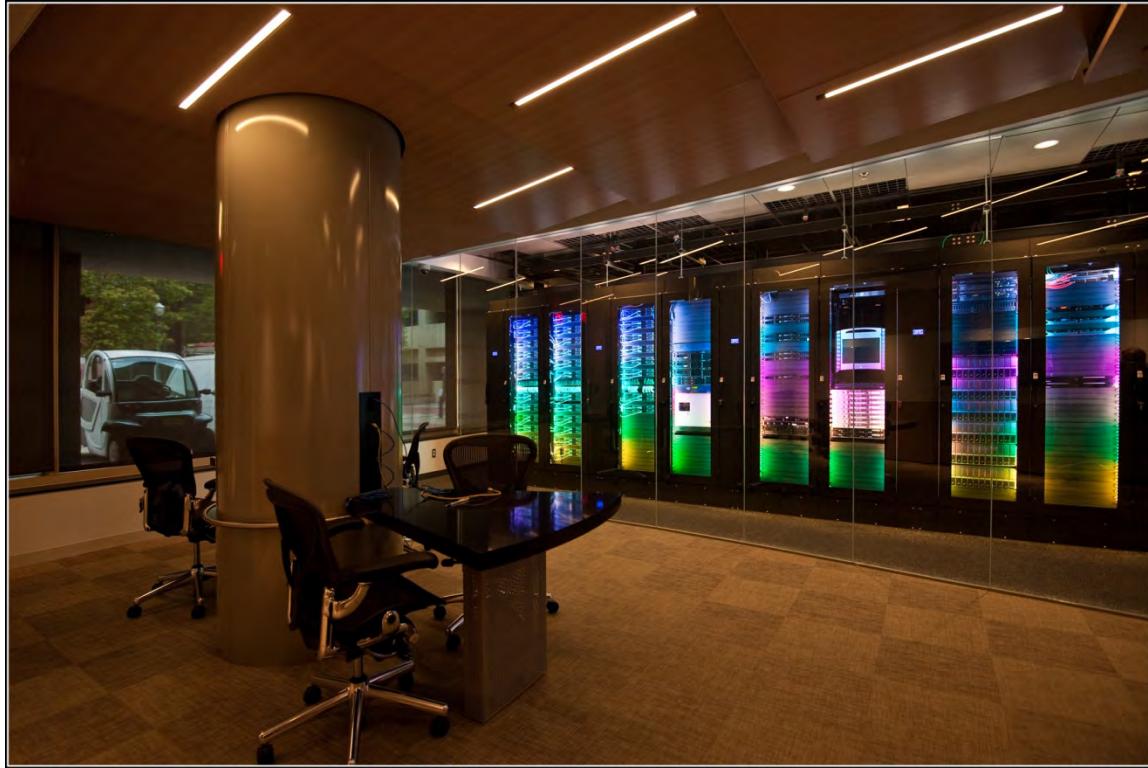




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Data Sharing

- Investigator activity
 - Average # of visits with downloads: 4.26 (per investigator)
 - Average # of clinical downloads: 64
 - Average # image downloads: 175



Investigator Activity

	Average	High
# of visits investigator downloaded data	4.26	72
# of clinical downloads	64	1476
# of image downloads	175	4632
# of all downloads	210	5690

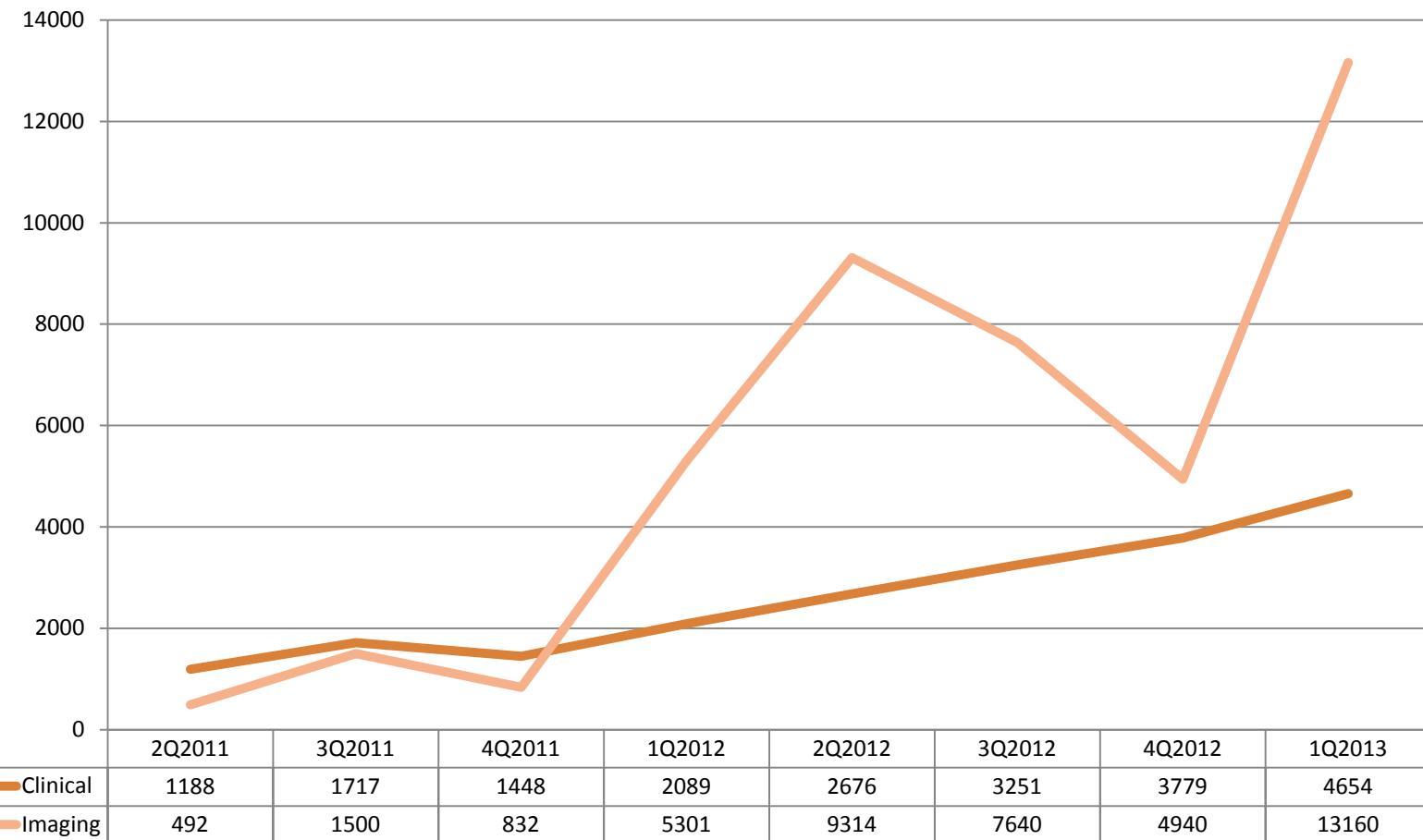


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Data Download Activity

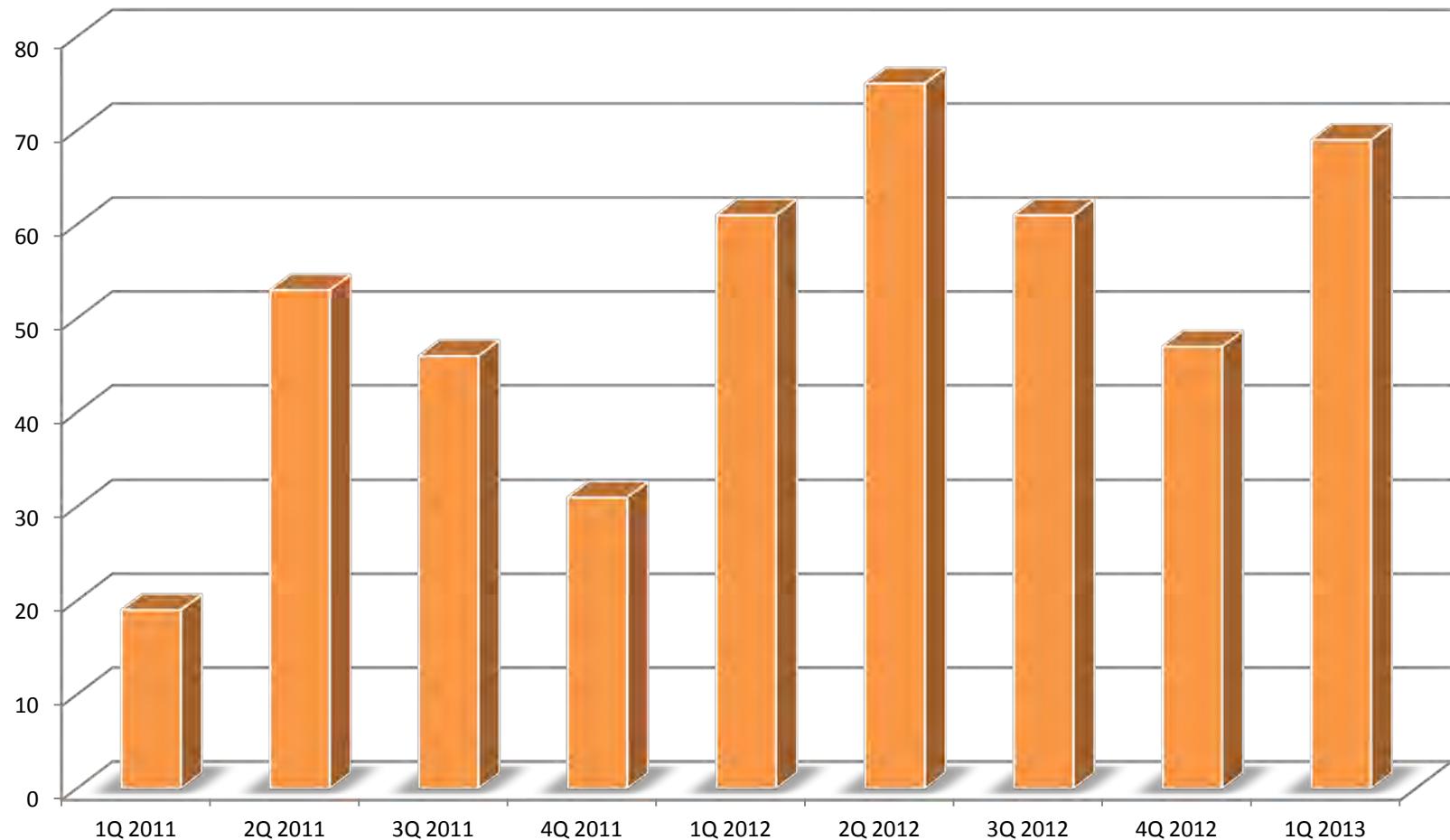


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Data Applicants by Quarter

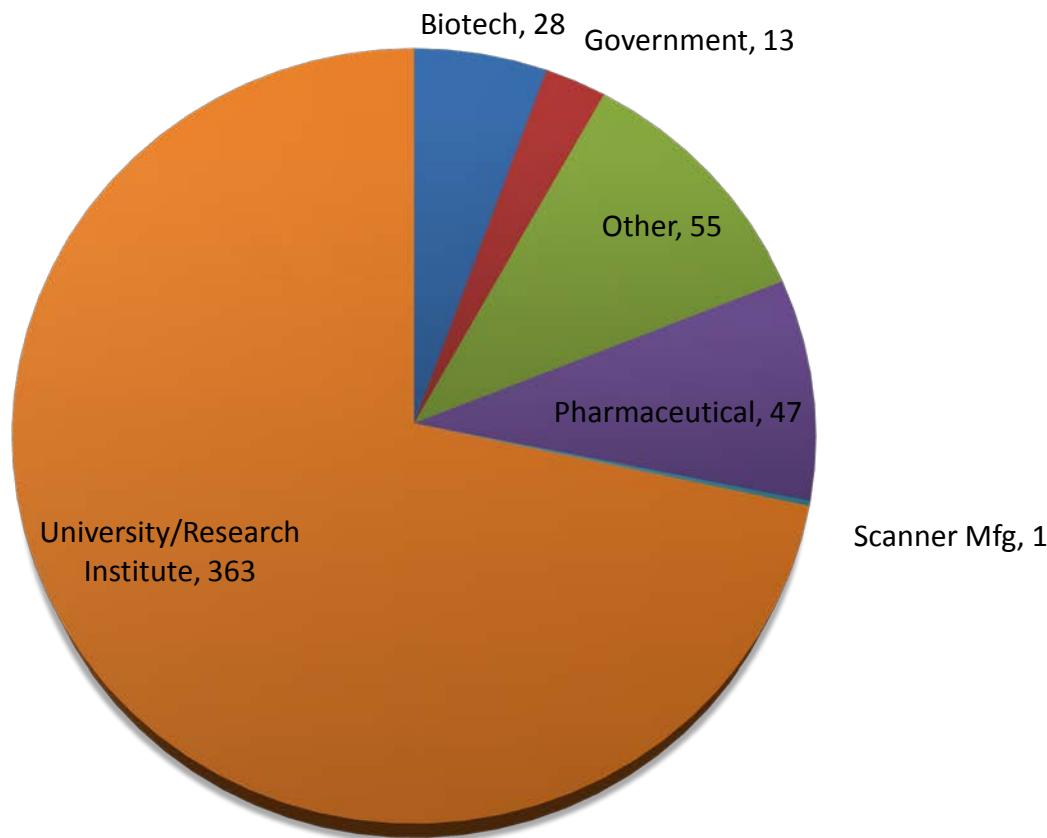


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Applicants by Sector



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Ancillary Studies



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PPMI Ancillary Study Proposals

- Easy access e-Form located on PPMI study website
- Preliminary 2 page proposal
- Screening review
- Full proposal by invitation
- Review by Ancillary Studies Committee

The screenshot shows the PPMI website with a focus on the 'Ancillary Studies' section. At the top, there is a navigation bar with links for 'Subscribe', 'News', 'Contact Us', and 'Home'. Below the navigation, there is a search bar and a 'Study Design' button. The main content area is titled 'ANCILLARY STUDIES' and contains several sections:

- Investigators interested in proposing sub-studies for PPMI are invited to do so by completing the form below.** These sub-studies may include either analysis of the existing dataset or additional study assessments and may involve all or a subset of PPMI participants. Proposals are accepted on a rolling basis.
- Proposals will be reviewed based on the following criteria:** The scientific merit of the proposal, Value added to PPMI, Additional burden to the subject, clinical site and central administration of PPMI, and, feasibility within the PPMI timeline.
- Proposals will be reviewed by the PPMI Ancillary Studies committee on a rolling basis and will go through two stages.** Additional details about the submission process are provided in the [Investigator-Initiated Ancillary Studies – Application & Review Process](#).
- The first stage of the submission process requires applicants to submit a Letter of Intent (LOI), which should include a brief description, specific goals, background and rationale, preliminary data to support the proposal, proposed additional or modified assessments, estimated sample size (including special characteristics of the population), additional resources available and/or required to complete the proposal and any potential or available source of funding for the proposal. The LOI should not exceed 2 pages.** Applicants will be notified via email within two weeks of submitting the LOI as to whether they are invited to submit a Full Proposal. Full Proposals will be reviewed by the PPMI Ancillary Study committee within 8 weeks of submission date.

Ancillary Studies Proposal Form

To begin the first stage of Ancillary Studies submission process, complete the form below. * required field.

Principal Investigator First Name*

Principal Investigator Last Name*

Suffix

Position Title

Institution*

Department

Sector
Please select one

Street Address

City*

Country*

State*

On the right side of the form, there are five orange buttons with icons and text:

- DOWNLOAD DATA**
- REQUEST SPECIMENS**
- for PROSPECTIVE PARTICIPANTS**
- for PRACTITIONERS**
- for INDUSTRY PARTNERS**
- for RESEARCHERS**



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PPMI Ancillary Study Proposal

Review Criteria

- Scientific Merit of the proposal
- Consistent with & furthers the overall PPMI goals of developing biomarkers for the progression, prognosis or diagnosis of PD?
- Sufficient preliminary data to justify using PPMI cohort?
- Does not add undue subject burden or detract from the main PPMI protocol
- Expertise, resources and environment of investigator(s)
- Willing to comply with PPMI policies including Publication and Intellectual property
- Data generated from analyses of PPMI data returned; public access



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PPMI Ancillary Studies Committee

Committee members:

Chris Coffey
Tom Comery
David Hewitt
Emily Flagg
Danna Jennings
Shirley Lasch
Ken Marek
Andrew Siderowf
Tanya Simuni
Caroline Tanner (Chair)
Eduardo Tolosa



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PPMI Ancillary Studies

- Longitudinal follow-up of screen failures due to scans with evidence of dopaminergic deficit (SWEDDs)
- Feasibility & reliability of in-home testing with the OPDM-dexterity measure (TAP-PD)
- Assessment of dementia and MCI in PPMI
- Physical Activity (measured using PASE)
- ¹⁸F AV-133
- Resting state MRI



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PPMI Ancillary Studies Proposals – Other Approaches

- Refer for review by Biologics Committee
- Ancillary study status not appropriate
(Examples:
 - data analysis using data published on website
 - proposed study not aligned with design of PPMI)
- Study application pending (Example: seeking funding prospects)



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UPDATES



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Home dexterity testing study TAP-PD

Primary objective

To assess the feasibility of incorporating home dexterity testing using the OPDM-Dexterity measure into a longitudinal observational study of progression of Parkinson's disease (PPMI)

Secondary objectives

- To assess the reliability of home dexterity testing over repeated short-term administrations
- To assess the validity of home dexterity testing relative to examiner-based measures (e.g. UPDRS)
- To assess the sensitivity to change of dexterity testing by comparing scores at baseline and year 1.

Home dexterity testing study

Subjects

- Goal: 15 PPMI PD subjects at 3 sites (OHSU, INDD, UPenn) total of 45 subjects
- Status to date: 31 subjects consented; 10 completed 1 withdrawn; 20 in process

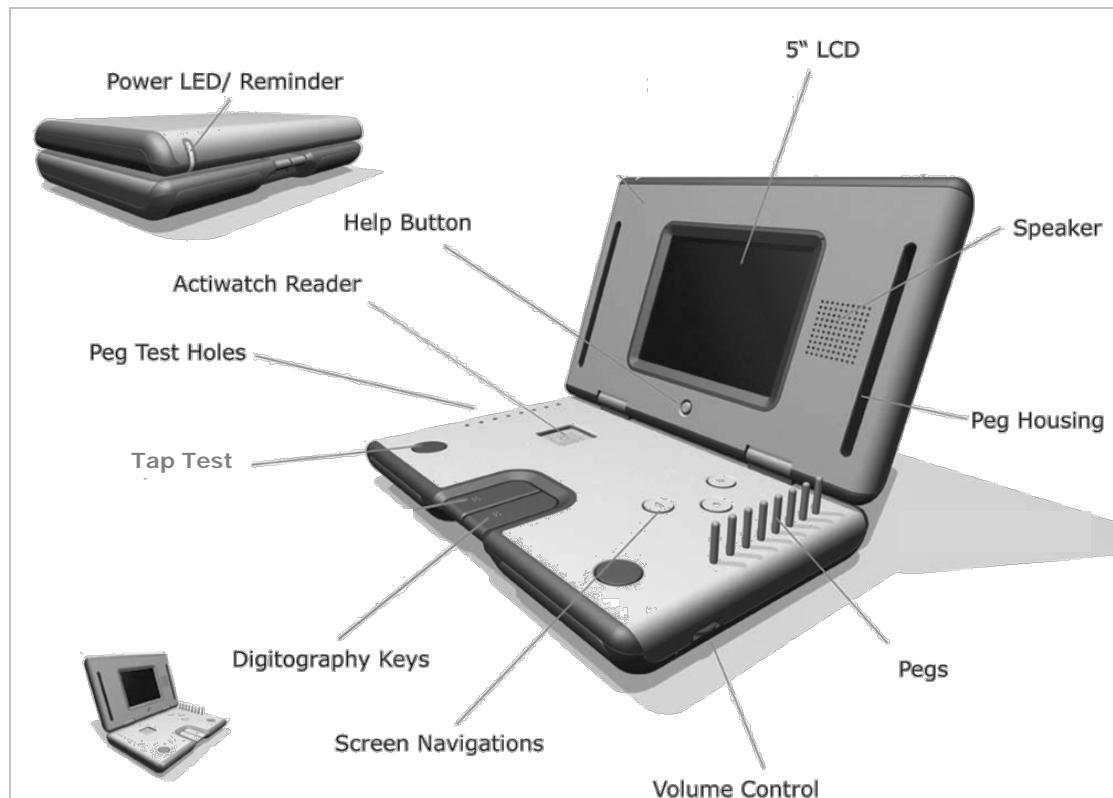
Assessments

- Home testing with OPDM dexterity device at least 3 times a month for 3 months
- In person OPDM testing at clinic visits at baseline, 3 months, 6 months and 12 months
- Comparison to UPDRS assessments collected during normal PPMI visits

Home dexterity testing study

Tests -Using OPDM device 3 test are preformed

- Digitography (keyboard test)
- Paced Keyboard Test
- Pegboard



TAP-PD baseline demographics

Characteristic	Population (PD)	Males	Females
Number of subjects consented	31	20 (65%)	11 (35%)
Mean Age - Years (range)	60.8 (33.5-84.5)	62.3 (37.2-84.8)	58.3 (33.5-81.8)
Duration of disease - months (range)	5.6 (1- 16)	6.0 (1- 13)	5.1 (1- 16)
Education - Years (range)	16.3 (12- 22)	16.2 (12- 21)	16.4 (14- 22)

TAP-PD baseline demographics

Questions	Response options	Subject Responses (n= 26)
Difficulty with understanding the directions	Not at all	25 (96%)
	A little	1 (4%)
	Moderately	0
	Very	0
Confidence in doing the tasks correctly	Not at all	0
	A little	0
	Moderately	1 (4%)
	Very	25 (96%)
Adding TAP-PD to at-home schedule	Easy	17 (65%)
	A little trouble	5 (19%)
	Moderately difficult	2 (8%)
	Very difficult	2 (8%)
How often did you need a reminder to complete the tasks at home	Not at all	17 (65%)
	Rarely	7 (27%)
	Sometimes	1 (4%)
	Often	1 (4%)
Did TAP-PD effect attitude about participating on Main PPMI study	A lot more negative	1 (4%)
	A little more negative	0
	No change	21 (81%)
	A little more positive	1 (4%)
	A lot more positive	3 (21%)

TAP-PD summary

- Positive response from participants
 - Easy to understand instructions and successfully complete the tapping procedures
 - Improved or had no impact on attitude re study
 - Reportedly easy to add to schedule by majority
- Plans for data analysis
 - Comparison to HC
 - Longitudinal evaluation
 - Treatment effects on outcome measure
- Plans for incorporating tapping device and possibly other devices in the prodromal cohort